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Effects of Acute and Chronic Amphetamine Administration:

Behavioral and Neurochemical Specificity

Larry Kokkinidis

Dissertation presented to

the Faculty of Graduate Studies

of Carleton University

in partial fulfillment of the requirements

for the degree of Doctor of Philosophy in Psychology

The undersigned recommend to the Faculty
of Graduate Studies acceptance of the thesis
"The Effects of Acute and Chronic Amphetamine Administration:
Behavioral and Neurochemical Specificity"

submitted by

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for the degree of

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I hereby declare that I am sole author of this research. I authorize Carleton University to lend it to other institutions and individuals for the purpose of scholarly research.

Larry K. Klein

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This thesis is dedicated to Dimitra and Triantafilos.

Abstract

Several of the behavioral consequences of acute and chronic amphetamine administration were evaluated. It was observed that amphetamine produced dose-dependent variations in locomotor excitation, shock-induced reactivity, stereotypy, exaggeration of the startle reflex, rotational behavior and perseveration in a Y-maze exploratory task. These behaviors could be pharmacologically dissociated from one another. That is, reduction of norepinephrine levels via a dopamine- β -hydroxylase inhibitor, FLA-63, successfully attenuated the effects of amphetamine on startle, rotational behavior and perseveration, and also reduced somewhat shock-induced reactivity. In contrast, sensitization effects seen in the reactivity task, as well as drug-induced locomotor activity and stereotypy were not antagonized by FLA-63. In fact, stereotypy was augmented to a limited extent by the inhibition of dopamine- β -hydroxylase. The effects of amphetamine on the latter three behaviors were successfully ameliorated by reduction of dopamine levels via tyrosine hydroxylase inhibition. These data were taken to indicate that the former set of behaviors involved primarily noradrenergic activity, whereas the latter set of behaviors were dependent upon dopaminergic mechanisms.

Following chronic treatment with d-amphetamine (10 mg/kg) levels of whole brain norepinephrine were significantly reduced, and in addition those behaviors mediated by noradrenergic mechanisms were subject to tolerance. In contrast, the behaviors subserved by dopamine were either augmented or unaffected following chronic amphetamine treatment. These data were taken to support the hypothesis that tolerance occurs principally to behaviors which involve noradrenergic activity.

Several potential mechanisms which might be related to the development of tolerance were provisionally dismissed. Specifically, since cross tolerance was observed between the optical isomers of amphetamine, it was suggested that the false neurotransmitter, p-hydroxynorephedrine, did not subserve tolerance. Moreover, since tolerance was not influenced by chronic pairing of the drug with apparatus exposure, it is unlikely that conditioning factors played a role in the development of tolerance to the perseverative effects of amphetamine. The data were discussed in terms of the role played by norepinephrine, as well as by other neurotransmitters, in the development of tolerance. In addition, an hypothesis based on drug-induced changes in attentional factors was proposed in order to account for the chronic effects of d-amphetamine. Finally, several possibilities were discussed with respect to dopamine involvement in the exaggeration of some behavioral changes observed following protracted drug treatment.

Figure Captions

- Figure 1. Mean proportion of alternation responses ($\pm$ S.E.M.) over 2 consecutive days as a function of drug treatment with either scopolamine (1 mg/kg), d-amphetamine (5 mg/kg) or equipotent amounts of methylscopolamine and p-hydroxyamphetamine.
- Figure 2. Mean percent of alternation ($\pm$ S.E.M.) as a function of scopolamine or d-amphetamine treatment in pre-exposed or naive animals.
- Figure 3. Mean percent of alternation ($\pm$ S.E.M.) after concurrent injection of scopolamine (1.0 mg/kg) and d-amphetamine (3.0 mg/kg).
- Figure 4. Pattern of arm entries following intraventricular injection of d-amphetamine.
- Figure 5. Mean proportion of rotational and alternation responses ($\pm$ S.E.M.) after intraperitoneal or intraventricular injection of d-amphetamine.
- Figure 6. Effects of chronic and acute treatment of d-amphetamine on locomotor activity and spontaneous alternation. On the abscissa the upper lettering indicates the 30 day injection regimen and the lower lettering the injection on test day.
- Figure 7. Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of drug treatment (saline or 1.0, 3.0, 5.0 and 10.0 mg/kg of d-amphetamine).

- Figure 8. Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of treatment with either saline, α -MpT (125 or 250 mg/kg) or FLA-63 (20 or 40 mg/kg) 3 hr prior to administration of 5.0 mg/kg of d-amphetamine or saline.
- Figure 9. Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings after administration of 3.0 mg/kg of d-amphetamine to naive mice or to mice previously exposed to the apparatus.
- Figure 10. Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of chronic and acute d-amphetamine treatment. The upper lettering on the abscissa indicates the 5 day injection regimen and the lower lettering the injection on test day.
- Figure 11. Mean startle amplitude ($\pm$ S.E.M.) as a function of drug treatment (saline or 1.0, 3.0, 5.0 and 10.0 mg/kg of d-amphetamine).
- Figure 12. Mean startle amplitude over 25 stimulus presentations after injection of either saline or 5.0 mg/kg of d-amphetamine. Mice were tested immediately after injection.
- Figure 13. Mean startle amplitude over 10 stimulus presentations as a function of drug pretreatment (250 mg/kg of α -MpT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of d-amphetamine 3 hr after pretreatment).

- Figure 14. Mean photocell crossings ($\pm$ S.E.M.) as a function of drug pretreatment (250 mg/kg of α -MpT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of d-amphetamine 3 hr after pretreatment).
- Figure 15. Mean startle amplitude over 10 stimulus presentations as a function of 5 daily injections of either saline or d-amphetamine (10.0 mg/kg) and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).
- Figure 16. Mean number of photocell crossings collapsed over 10 min intervals as a function of drug (saline, or 1.0, 3.0, 5.0 or 10.0 mg/kg of d-amphetamine) and shock treatment.
- Figure 17. Mean stereotypy ratings collapsed over 10 min intervals as a function of drug (saline, or 1.0, 3.0, 5.0 or 10.0 mg/kg of d-amphetamine) and shock treatment.
- Figure 18. Mean number of photocell crossings collapsed over 10 min intervals as a function of drug pretreatment (saline, 250 mg/kg of α -MpT or 40 mg/kg of FLA-63), drug test treatment (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.
- Figure 19. Mean stereotypy ratings collapsed over 10 min intervals as a function of drug pretreatment (saline, 250 mg/kg of α -MpT or 40 mg/kg of FLA-63), drug test treatment (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.

- Figure 20. Mean number of photocell crossings collapsed over 10 min intervals as a function of chronic drug treatment (saline or 10.0 mg/kg of d-amphetamine), drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.
- Figure 21. Mean stereotypy ratings collapsed over 10 min intervals as a function of chronic drug treatment (saline or 10.0 mg/kg of d-amphetamine), drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.
- Figure 22. Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) following treatment with various doses of the stereoisomers of amphetamine.
- Figure 23. Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of drug treatment during the chronic phase (15.0 mg/kg of d-amphetamine or saline for either 3, 5 or 10 consecutive days) and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).
- Figure 24. Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of d-amphetamine dosage (0.0, 5.0, 10.0 or 15.0 mg/kg) during a 5 day chronic period and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).

Figure 25. Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of l-amphetamine dosage (0.0, 15.0, 30.0, 45.0 or 60.0 mg/kg) during a 5 day chronic period and drug treatment on test day (15.0 mg/kg of l-amphetamine or saline).

Figure 26. Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of drug treatment during the chronic phase (5 successive daily injections of either saline, 10.0 mg/kg of d-amphetamine or 45.0 mg/kg of l-amphetamine) and drug treatment on test day (saline, 5.0 mg/kg of d-amphetamine or 15.0 mg/kg of l-amphetamine).

Figure 27. Mean proportion of alternation responses ($\pm$ S.E.M.), mean number of arm entries ($\pm$ S.E.M.), as well as mean stereotypy scores ($\pm$ S.E.M.), as a function of prehabitation (phase 1, no-drug), drug treatment during the chronic phase (phase 2, pre-trial injection of saline or d-amphetamine 10.0 mg/kg or post-trial injection of d-amphetamine 10.0 mg/kg), and drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine).

Amphetamine has been shown to produce a wide variety of behavioral and physiological changes including pressor and bronchodilator actions, suppression of appetite, insomnia, antifatigue, deviation of mood, increased psychomotor activity, as well as enhancement of performance on intellectual tasks (Alles, 1933; Alles & Prinzmetal, 1933; Bahnsen, Jacobsen & Thesleft, 1938; Davidoff & Reifenshtein, 1937; Hartung & Munch, 1931; Nathanson, 1937; Peoples & Gutman, 1936; Sargant and Blackburn, 1936). Despite the occurrence of undesirable side effects, such as insomnia, toxicity, and behaviors resembling psychosis, amphetamines found their way into clinical pharmacology for the control of obesity, mild depression produced by barbiturates, as well as hyperkinesis (Angrist & Gershon, 1970; Bell, 1965, 1967; Connors, Eisenberg & Barcai, 1967; Edison, 1971; Ellinwood, 1967, 1969, 1972; Gittelman & Klein, 1975; Synder, 1973).

The non-medical use of amphetamines proliferated with the discovery that these agents were potent hallucinogens producing among other things euphoria and increased self-esteem (Bell, 1965, 1967). With chronic abuse of amphetamine tolerance develops to the mood altering properties of the drug (Edison, 1971; Kosman & Unna, 1968). That is, successive increases in dosage are necessary in order to achieve the desired euphoric effects. Tolerance to these behavioral effects of the drug, however, are not necessarily

accompanied by comparable tolerance to some of the undesired drug effects (e.g., psychotic-like behavior). In fact, it has been observed that upon chronic drug use these psychotic behaviors may become accentuated (Ellinwood, 1969).

Given the varied neurochemical changes induced by amphetamines, it is not particularly surprising to find that the long-term use of the drug has heterogeneous consequences. The nature of the differential effects of the drug on various behavioral patterns, however, is not well understood. Keeping this in mind, the present introduction is intended to provide an overview of research dealing with the biochemical, neurophysiological, and behavioral effects of amphetamine administration. To date, most papers dealing with the behavioral aspects of the drug's action have been restricted to two prominent behaviors, namely increased locomotor activity and stereotypy. Recently, however, a number of other behavioral effects of amphetamine have been reported, which may or may not be related to amphetamine-induced activity and stereotypy. Moreover, it is clear that when the effects of protracted, as opposed to acute amphetamine administration are considered, differential results are observed depending upon the behavior under consideration. Accordingly, an attempt will be made to assess the behavioral and neurochemical effects of both acute and chronic amphetamine treatment.

Neurochemical Changes Induced by Amphetamine

Amphetamine has profound effects on the dynamics of brain catecholamines. Inter alia, amphetamine promotes the release of the catecholamines from peripheral and central catecholaminergic nerve terminals (Carlsson, 1970; Glowinski, 1970). The release of the catecholamines has been demonstrated by perfusing this drug into brain regions rich in catecholamines, and measuring the release of tritiated norepinephrine (NE) and dopamine (DA) synthesized from labelled tyrosine. Amphetamine was found to promote release of NE from noradrenergic nerve terminals in the amygdala, hypothalamus and cerebral cortex (Carr & Moore, 1969; Chiueh & Moore, 1974; Wise & Stein, 1970), as well as from peripheral adrenergic terminals (Anden, Carlsson & Haggendal, 1969; Axelrod, 1971). Similarly, release of DA has been reported from dopamine rich areas, including the neostriatum (Chiueh & Moore, 1973, 1975). Furthermore, it has been suggested that newly synthesized NE and DA are released by amphetamine, since reserpine which depletes the primary storage pools, has no effect on the behavioral actions of amphetamine, whereas synthesis inhibition of tyrosine hydroxylase by α -methyl-para-tyrosine (α -MpT) antagonizes the central stimulant actions of d-amphetamine (Anden & Svensson, 1973; Carlsson, 1970; Lindbrink, Costa & Fuxe, 1974; Randrup & Jonas, 1967; Randrup & Munkvad, 1966; Rech, 1964; Rech & Carr, 1968; Weismann, Koe & Tenen, 1966). It is noteworthy that since amphetamine-induced behaviors were found to persist after reserpine pretreatment, several investigators suggested that amphetamine may exert a direct post-synaptic action (Proctor, Kirby, Wood, Wade & King, 1974; Smith, 1965; Van Rossum, Van Der Shoot & Hurkmans, 1962). However, the observation that synthesis inhibition produces a marked attenuation of the behavioral effects of amphetamine argues against such a notion (cf., Groves & Rebec, 1976).

Amphetamine not only elicits release of the catecholamines, but in large doses has been demonstrated to produce release of the indoleamine, serotonin (5-HT), as well. This has been demonstrated in 5-HT rich areas of the neostriatum, as well as the dorsal raphe nuclei (Fuxe & Ungerstedt, 1970; Geyer, Dawsey & Mandell, 1975). Although amphetamine produces release of 5-HT, these effects are less marked in 5-HT nerve terminals relative to that of other monoamines (Azzaro & Rutledge, 1973).

Another method by which amphetamine affects the disposition of the catecholamines is by blocking the uptake of these neurotransmitters across the neuronal membrane (Glowinski et al., 1966). It has been suggested that the presence of an α -methyl group as part of the amphetamine molecule may be responsible for the ability of amphetamine to block catecholamine reuptake (Biel, 1970; Iversen, 1967). In contrast to dopamine, which is not stereospecific, the naturally occurring l-isomer of norepinephrine was found to possess a greater affinity for reuptake at the noradrenergic synapse than d-norepinephrine (cf., Groves & Rebec, 1976). Differential effects produced by the amphetamine isomers with respect to reuptake of catecholamines have been reported as well. Specifically, it was demonstrated that in vitro d-amphetamine was ten times more potent than the l-isomer in blocking reuptake at the noradrenergic synapses, whereas the optical isomers were equipotent at dopaminergic terminals (Coyle & Snyder, 1969). On this basis, numerous investigators have employed the isomers of amphetamine in an evaluative capacity. That is, if the isomers are equipotent in eliciting

a given behavior, then the neurochemical substrate for this behavior may involve dopamine. In contrast, if the d-isomer is ten times more potent than the l-isomer, then noradrenergic mechanisms are assumed. The potency ratio has been used on studies concerned with human clinical syndromes (Angrist, Shopsin & Gershon, 1971; Arnold, Wender, McCloskey & Snyder, 1972), as well as behaviors observed in laboratory animals (North, Harek & Snyder, 1974; Taylor & Snyder, 1970, 1971). Recently, however, the efficacy of using the stereoisomers for evaluative purposes has been challenged. This opposition has come from three primary sources. First, in contrast to Coyle and Snyder (1969) it was found that both d- and l-amphetamine were equipotent in blocking the reuptake of NE in telencephalic synaptosomes, whereas the d-isomer was five times more potent than l-amphetamine in blocking the reuptake of DA into striatal homogenates (Thornburg & Moore, 1973a). Second, single unit recordings from the locus coeruleus and substantia nigra of anaesthetized or paralyzed rats revealed that d- and l-amphetamine administered intravenously were equally effective in depressing activity of NE neurons. In contrast, the d-isomer was more potent than the l-isomer in depressing activity of DA neurons (Bunney & Aghajanian, 1973; Bunney, Walters, Kuhar, Roth & Aghajanian, 1975). Finally, the third source of opposition involves the fact that the two isomers yield differential effects on stereotypy and locomotor excitation, i.e., a ratio in the magnitude of 3:1 in the former case and 10:1 in the latter (North et al., 1974). Yet, it has become apparent that both stereotypy and locomotor activity induced by amphetamine involve primarily DA mechanisms (see section on behavior). (Carlsson, 1970). As such, the use of the isomer technique as an evaluative tool in order to draw inferences towards neurochemical substrates of behavior is not warranted.

In addition to the effects of amphetamine on the release and reuptake of catecholamines, the drug has been observed to have a profound influence on turnover rate. Generally, drugs which are catecholamine agonists decrease, whereas drugs which are catecholamine antagonists increase catecholamine synthesis and neuronal activity (cf., Groves, 1977; Groves & Rebec, 1976). For example, receptor blockade by haloperidol increases the firing rate of neurons in the caudate nucleus (Bunney, 1974; Bunney, Aghajanian & Roth, 1973). This is presumably a consequence of increased tyrosine hydroxylase activity induced by DA receptor blockade. In fact, Zivkovic, Guidotti & Costa (1974) demonstrated that DA receptor blockers, such as haloperidol, promotes enhanced tyrosine hydroxylase activity. Consistent with these results, electrical stimulation of noradrenergic pathways also results in increased tyrosine hydroxylase activity (Roth, Salzman & Morgenroth, 1974). In contrast to receptor antagonists, drugs which are catecholamine stimulants, such as apomorphine (Ernst, 1967), have been shown to inhibit tyrosine hydroxylase activity (Anden, Corrodi, Fuxe & Hokfelt, 1967; Besson, Cheraing & Glowinski, 1971; Harris & Baldessarini, 1973; Javoy, Hamon & Glowinski, 1970), as well as decrease the firing rate of dopaminergic neurons in the substantia nigra (Bunney et al., 1973). Predictably, the observed depression in neuronal activity induced by amphetamine or apomorphine is reversed with the administration of DA antagonists (Bunney, 1973, 1974).

One mechanism which has been postulated to account for the regulation of catecholaminergic neuronal activity is a hypothetical neuronal feedback loop based on end-product inhibition (Carlsson, Kehr, Lindquist, 1974). Briefly, it is postulated that the rate limiting enzyme, tyrosine hydroxylase, is subject to competitive inhibition for the pteridine cofactor with DA and NE. Accordingly, increasing cytoplasmic NE and DA may result in an inhibition of tyrosine hydroxylase. This has been demonstrated both in vivo (Glowinski, 1972) and in vitro (Cooper, Bloom & Roth, 1974).

Yet another feedback loop has been posited to account for the regulation of dopaminergic activity (Aghajanian & Bunney, 1974). This post-synaptic mediated negative feedback mechanism presumably projects from the nerve terminals in the striatum to the dopaminergic cell bodies in the substantia nigra. In agreement with the hypothesized post-synaptic regulation of dopaminergic activity, transection of fibres anterior to the substantia nigra antagonized the amphetamine-induced depression of dopaminergic neuronal activity, and abolished the increased dopamine turnover ordinarily produced by a DA receptor blocker such as chlorpromazine (Anden, Corrodi, Fuxe & Ungerstedt, 1971; Bunney & Aghajanian, 1973).

Recent evidence, however, suggests that in addition to end-product inhibition and post-synaptic inhibition, dopaminergic activity is also regulated by pre-synaptic receptors (see review in Cools & Van Rossum, 1976). More specifically, inhibition of impulse flow in the nigro-neostriatal circuit, via γ -butyrolactone, produces an increase in both intraneuronal dopamine levels,

as well as increased tyrosine hydroxylase activity (Pericic & Walters, 1976; Walters & Roth, 1974). This effect cannot be accounted for by end-product inhibition, since DA synthesis increased despite a large accumulation of transmitter substance in the nerve terminals. Consistent with pre-synaptic mediation of dopamine biosynthesis, drugs which are dopamine agonists (e.g., ET-495) prevent the increase in dopamine and tyrosine hydroxylase activity observed after cessation of impulse flow by γ -butyrolactone (Morgenroth, Walters & Roth, 1976). Moreover, these effects are antagonized by dopamine receptor blocking agents (Morgenroth et al., 1976; Walters & Roth, 1974). On the basis of this evidence it was suggested that pre-synaptic DA receptors, when deprived of transmitter substance, produce an activation of dopamine synthesis resulting in increased tyrosine hydroxylase activity and subsequent increases of dopamine in the nerve terminals. Stimulation of pre-synaptic receptor sites either directly (by apomorphine) or indirectly (by amphetamine) reverse the effects of blocked impulse flow. The demand for increased production of dopamine can be reinstated by inhibiting the effects of apomorphine or amphetamine by the introduction of a dopamine receptor blocker. Whether these pharmacologic effects on pre-synaptic mediation of dopamine biosynthesis involve calcium as suggested by Roth, Walters and Morgenroth (1974), is not entirely certain.

The effects of amphetamine on the regulation of catecholamine synthesis are dependent upon the brain region under examination. For example, following amphetamine treatment synthesis of DA is not reduced in the substantia nigra (Javoy, Hammon & Glowinski, 1970) but is in the neostriatum (Aghajanian & Bunney, 1974; Bunney & Aghajanian, 1973). Furthermore, amphetamine promoted increased turnover of NE in the telencephalon, but not in the brain stem (Azzaro & Rutledge, 1973). One possibility which may account for these regional disparities may be that different forms of tyrosine hydroxylase exist, and further, these enzymes may be differentially distributed in the brain (Joh & Reiss, 1975; Kuczenski & Mandell, 1972; Segal & Kuczenski, 1974).

Finally, when injected in high doses amphetamine has been shown to be a potent monoamine oxidase (MAO) inhibitor both in vitro (Glowinski et al., 1966) and in vivo (Glowinski, 1970). It is not entirely certain whether this inhibition is specific to a particular type of MAO or alternatively a generalized inhibition. More specifically, it is well documented that there are multiple forms of MAO in the brain (Neff, Yang & Fuentes, 1974). Type A enzyme oxidatively deaminates norepinephrine and serotonin and is inhibited by clorgyline. Type B enzyme oxidatively deaminates β -phenylethylamine (PEA) and is inhibited by depr. Dopamine is a common substrate to both types of MAO. Knowledge of the existence of multiple forms of MAO has shed some light as to the neurotransmitters which may be involved in various behaviors produced by certain pharmacologic agents. For example, it is well documented that reserpine is capable of precipitating a depressive state in man (Achor, Hanson & Gifford, 1955). For

this reason, reserpine-induced depression in animals has been used as a model for naturally occurring affective disorders (Brodie, Spector & Shore, 1959; Carlsson, 1975a). Reserpine acts by promoting release of the monoamines from the storage granules, thus allowing degradation to occur via oxidative deamination (Carlsson, 1975a,b). Inhibition of MAO activity prevents amine degradation, resulting in release of monoamines, which in turn, produces behavioral excitation (Brodie et al., 1959). Moreover, this only occurs with the specific Type A MAO inhibitor, clorgyline and not with the Type B inhibitor, deprenyl (Neff et al., 1974). Since dopamine is a common substrate for both types of enzymes, but only clorgyline (the Type A inhibitor which is specific to NE and 5-HT) produced the reserpine-induced excitation, then it might be the case that norepinephrine and serotonin are responsible for the ability of MAO-inhibitors to prevent the reserpine syndrome. It would be interesting to speculate whether these neurotransmitters are also involved in the affective disorders (Weiss & Laties, 1962) observed following prolonged use of amphetamine. This is especially the case since it has been shown that in rats post-amphetamine depression was found to be highly related to decreases in both NE and 5-HT (Tonge, 1974).

BEHAVIORAL EFFECTS

Locomotor Activity

Measurement of locomotor activity is a widely used method of examining the excitatory effects of amphetamine among various infrahuman species (Stolk & Rech, 1967). Amphetamine has been reported to either increase or decrease exploratory activity or to have no effect at all, depending upon a number of factors, such as the dosage used (Bainbridge, 1970), time between injection and testing (Randrup & Munkvad, 1967), as well as the strain of animal employed (Anisman, 1976; Davis, Babbini, Pong, King & White, 1974; Ladisch, Volbeher & Matussek, 1970). Generally, low doses of amphetamine have been found to produce a decrease in locomotor activity (Boissier, Simon & Lwoff, 1964; Valzelli, 1969), whereas higher doses markedly enhance motility (Carlsson, 1970; Costa, Groppeti & Naimzada, 1972; Thornburg & Moore, 1973a). The onset of the latter effects typically is observed soon after injection (within 1-15 min) and is subsequently followed by a decrease in locomotor activity, which presumably is associated with the onset of stereotypic behaviors (see section on stereotypies) (Ellinwood & Balster, 1974; Randrup & Munkvad, 1967, 1974; Segal, 1975).

To date, there exists a substantial amount of evidence relating amphetamine-induced locomotor excitation to the drug's effects on catecholamines. Pre-treatment with α -MPT antagonized the amphetamine-induced locomotor excitation (Dingle, Owens, Norwich & Sulser, 1967; Carlsson, 1970; Hollister, Breese &

Cooper, 1974). Predictably, the locomotor excitation can be reinstated through the administration of L-DOPA in conjunction with an extracerebral decarboxylase inhibitor (Banerjee & Lin, 1973a; Bartholini, Blum & Pletscher, 1969; Bartholini & Pletscher, 1975; Groves & Rebec, 1976; Langellier, Parent & Poirer, 1972). Moreover, drugs which inhibit the inactivation of the catecholamines either by inhibition of MAO or inhibition of reuptake mechanisms, enhance the excitatory effects of amphetamine on activity (Dingle et al., 1967; Welch & Welch, 1970).

As previously discussed, depletion of the catecholamine storage pools via reserpine has no effect on locomotor activity induced by d-amphetamine, and in some instances has been shown to enhance the behavioral effects of amphetamine (Banerjee & Lin, 1973b; Rech, 1964). Whether this reflects receptor supersensitivity (see Van Rossum, 1970 for review), or an interaction between amphetamine and the substantial weight loss produced by reserpine (Campbell & Fibiger, 1971; Fibiger, Trimbach & Campbell, 1972), is not entirely certain. In any event, the fact that synthesis inhibition antagonized the stimulant actions of d-amphetamine, whereas storage pool depletion did not, has been taken to indicate that the increased locomotor activity observed following drug administration relies on a newly formed pool of catecholamines supplied by de novo synthesis.

Since d-amphetamine has profound effects on the release, reuptake and synthesis of the catecholamines, a great deal of controversy has centered around which of the catecholamines, dopamine or norepinephrine, is involved in the

stimulant actions of this drug. Support for the involvement of norepinephrine in the mediation of locomotor activity has come from two sources. The first was discussed previously, and dealt with the relative potency of the amphetamine isomers. Reiterating, it was suggested that since the d-isomer was ten times more potent than the l-isomer in eliciting locomotor activity, and a similar relationship was observed in the ability of the isomers to inhibit the reuptake of telencephalic NE, noradrenergic mechanisms were implicated in the locomotor effects produced by d-amphetamine (Coyle & Snyder, 1969; Taylor & Snyder, 1971). Recently however, the validity of using a relative potency ratio has been challenged, both from the biochemical side (Thornburg & Moore, 1973a) as well as from the physiological standpoint (Bunney & Aghajanian, 1973; Bunney et al., 1975). The second source of support for the involvement of norepinephrine in mediating the locomotor excitation comes from the use of dopamine- β -hydroxylase inhibitors. However, conclusions from these studies are at best equivocal. To be more explicit, treatment with diethyldithiocarbamate was found to reduce brain NE and inhibit locomotor excitation induced d-amphetamine (Randrup & Scheel-Kruger, 1966; Scheel-Kruger & Randrup, 1967). In contrast, treatment with either bis-(4-methyl-1-homopiperazinyl-thiocarbonyl) disulphide (FLA-63) or U-14,624 also produced a decline in brain NE levels (Carlsson, 1970; Corrodi, Fuxe, Hamberger & Ljungdahl, 1970; Thornburg & Moore, 1973b), but had little or no effect on amphetamine-induced activity (Carlsson, 1970; Corrodi et al., 1970; Hollister et al., 1974; Svensson, 1970; Thornburg & Moore, 1973b). Moreover, it has been suggested that the effects of many of

the dopamine-~~B~~hydroxylase inhibitors, such as disulfiram, U14,624, or FLA-63, on motor activity are due to non-specific irritant properties of the drug (Dolphin, Elliot & Jenner, 1976; Thornburg & Moore, 1971). Data derived from studies examining the effects of noradrenergic receptor blockers on amphetamine-induced locomotor activity are also equivocal. Generally, these studies reveal that such treatments have little or no effect on activity produced by amphetamine (Mantegazza, Naimzada & Riva, 1968; Rolinski & Scheel-Kruger, 1973). Moreover, the role of peripheral factors (Leszkovsky & Tardos, 1965), as well as alterations of MAO activity (Milmore & Taylor, 1975), produced by these drugs are not well established.

In contrast to noradrenergic receptor blocking agents, dopaminergic receptor blockers successfully antagonize the locomotor response to amphetamine (Roberts, Zis & Fibiger, 1975; Rolinski & Scheel-Kruger, 1973). Consistent with these results, selective 6-hydroxydopamine (6-OHDA) destruction of mesolimbic neurons abolished the stimulant effects of d-amphetamine or cocaine (Kelly & Iversen, 1976). Moreover, direct injection of the dopamine receptor blocker, haloperidol, into the nucleus accumbens of the rat reversed the effects of amphetamine on activity, whereas injection into the caudate nucleus had no effect (Pijneburg, Honig & Van Rossum, 1975). In contrast, selective bilateral injections of 6-hydroxydopamine into the substantia nigra abolished the locomotor response to amphetamine, whereas lesions of the dorsal or ventral

noradrenergic bundles were without effect (Greese & Iversen, 1972, 1974, 1975). Consistent with these results selective depletion (85-95%) of NE in the hypothalamus, cerebral cortices and hippocampus, failed to alter the locomotor activity observed after amphetamine treatment. However, selective depletion (92%) of neostriatal dopamine resulted in a reduction of amphetamine-induced locomotor activity (Roberts et al., 1975). Clearly, the available data suggest that dopamine plays a major role in the mediation of locomotor activity produced by d-amphetamine, and that both the mesolimbic and the nigro-neostriatal pathways play a critical role in this respect.

Although the available data suggest that NE is a secondary factor in modulating the effects of amphetamine on locomotor activity, it is not entirely certain as to whether NE elicits a synergistic or inhibitory effect on DA stimulation. To be more explicit Antelman and Caggiula (1977) maintain that norepinephrine may exert an inhibitory influence on dopaminergic mechanisms. They present data showing that norepinephrine depletion, either by synthesis inhibition or neurochemical lesions, enhanced the excitatory effects of catecholamine stimulants on locomotor activity (for review see Antelman & Caggiula, 1977). In contrast, however, there are several studies which show that NE may act synergistically with DA in mediating locomotor activity. For example, treatment with clonidine, a noradrenergic receptor stimulant (Haeusler, 1974), which results in decreased locomotor activity (Maj, Sowinska, Baran & Kapturkiewicz, 1972; Strombom, 1975, 1976) enhanced the locomotor excitation produced by apomorphine (Anden, Strombom & Svensson, 1973; Maj et al., 1972). Given these data, it certainly is possible that NE influences activity; however, these effects are dependent on the activity of DA neurons (cf., Groves, 1977; Groves & Rebec, 1976).

The presentation thus far has primarily been concerned with the excitatory effects of d-amphetamine. However, as mentioned previously, low doses of this drug may produce a depression of locomotor activity (Anisman & Cygan, 1975; Anisman, Wahlsten & Kokkinidis, 1975; Bainbridge, 1970). A decrease in responding has also been observed with low dosages of other catecholamine stimulants such as L-DOPA (Butcher & Engel, 1969; Stromberg, 1970), methylphenidate and β -phenylethylamine (Kokkinidis, unpublished observations). One possibility for the dose dependent effects on behavior may be that low dosages of these compounds promote a neurochemical rebound in order to maintain neuronal homeostasis (cf., Anisman, 1975a; Izquierdo, 1974). Support for a notion of reciprocal innervation has come from a number of sources. For example, doses of scopolamine which alone ~~do~~ not affect locomotor activity antagonize the inhibitory effects of epinephrine (Manto, 1967; Remington & Anisman, 1974). Izquierdo (1974) observed that ineffective dosages of both central and peripheral acting anticholinergics potentiate the excitatory effects of d-amphetamine. Accordingly, the suggestion was made that although amphetamine enhances performance by an excitatory effect on behavior, it also produces a parasympathetic rebound which inhibits the stimulant properties of amphetamine. A similar rebound mechanism may be involved in the biphasic behavioral effects produced by the cholinomimetic, pilocarpine. Specifically, pilocarpine induces an initial session of behavioral inhibition followed by a phase of behavioral excitation (Fibiger, Lynch & Cooper, 1971). Pretreatment with scopolamine eliminated both the inhibitory

and excitatory phases produced by pilocarpine. In contrast, administration of the anticholinergic at the onset of the hyperactive stage, resulted in a potentiation of the hypermotility. The suggestion was made that following treatment with pilocarpine there is an initial increase of acetylcholine (ACh) resulting in a decrease in locomotor activity. When pilocarpine is preceded by treatment with scopolamine, actions on ACh are blocked and the behavioral inhibition is antagonized. If, however, the initial increase in ACh occurs, a catecholaminergic rebound is initiated thus resulting in behavioral excitation. Alleviating the inhibitory effects of ACh activity at this time (via scopolamine) results in enhanced hyperactivity (Fibiger *et al.*, 1971).

These results do not necessarily imply that a catecholaminergic-cholinergic relationship alone is involved in the maintenance of activity. Rather, serotonergic manipulations also have profound effects on the behavioral consequences of amphetamine administration. For example, pretreatment with para-chlorophenylalanine (PCPA), a tryptophan hydroxylase inhibitor, enhances the locomotor effects of d-amphetamine. Moreover, this effect was reversed with the administration of 5-hydroxytryptophan (5-HTP) (Breese, Cooper & Mueller, 1974). Further to this point, lesions to the medial raphe nuclei potentiate d-amphetamine-induced locomotor activity (Jacobs & Wise, 1975). Consistent with these results, administration of PCPA, as well as destruction of serotonergic neurons via 5, 7-dihydroxytryptamine potentiate methylphenidate-induced locomotion, which in turn is inhibited by 5-HTP (Breese, Cooper & Hollister, 1975).

Stereotypic Behaviors

It has been consistently reported that catecholamine stimulants elicit stereotyped patterns of behavior (e.g., continuous sniffing, grooming, gnawing, etc.). As in the case of locomotor activity, the precise nature of the stereotypies is dependent not only upon the dosage used, the route of administration, the time between injection and behavioral evaluation, and the species under examination, but also on the specific stimulant employed (see Wallach, 1974 for review). For example, rats show a very generalized form of stereotypy which lacks the individuality observed in species higher on the phylogenetic scale. In the rat stereotypy is characterized by hyperactivity, sniffing and biting of cage wires, abnormal postural positions and dyskinetic movements (Randrup & Munkvad, 1967, 1970, 1974). The occurrence of these behaviors are temporally patterned and dose dependent. Lower dosages of amphetamine produce a marked hyperactivity without any discernible stereotypic behaviors. Higher dosages of amphetamine elicit an initial hyperactive phase (approximately 20 min after injection) followed by a phase during which stereotypies predominate (approximately 60 min after injection). Following the bout of stereotypy a second phase of hyperactivity is observed (approximately 90 min after injection), which is subsequently followed by a depression in activity (Ellinwood, 1974; Segal, 1975; Segal & Mandell, 1974).

In contrast to the stereotypies observed in rodents, species higher on the phylogenetic scale demonstrate response patterns which are individualistic and not necessarily characteristic of the species in general. For example, like rats, cats typically exhibit a restricted range of stereotypies. Most often two behavioral patterns are apparent: the first consists of sniffing, while the second has been described as a "fearful" or "paranoid like" behavior which consists of "a constant looking over the shoulder" (Ellinwood, 1969, Randrup & Munkvad, 1967; Wallach, 1974; Wallach & Gershon, 1971, 1972). Dogs clearly show an individualistic pattern of stereotypy to catecholamine stimulants. Wallach (1974), for example, reported that one dog remained motionless with only its eyes moving; a second demonstrated a pattern of behavior which consisted of "pouncing on an imaginary prey", and a third continuously ran in circles. Similar observations have been made in monkeys following administration of catecholamine stimulants. Whereas one monkey might continuously rock, a second monkey may pick at parts of its body. In humans, similar types of apparently purposeless behaviors have been reported, such as continuously polishing objects or repetitive rocking (Ellinwood, 1969).

Species differences have also been reported with respect to the amount of drug necessary to produce the desired behavioral effects. Generally it seems that less drug is needed for species higher on the phylogenetic scale. For example, in the rat, 3-10 mg/kg of d-amphetamine, 75 mg/kg of phenmetrazine or 600 mg/kg of cocaine are required to elicit stereotypic behaviors. In the dog,

2 mg/kg, 1.25 mg/kg, or 1.5 mg/kg of d-amphetamine, phenmetrazine or cocaine, respectively, are required to promote stereotypic behaviors (Fog, 1969; Randrup, Munkvad & Udsen, 1963; Wallach, Rotrosen & Gershon, 1973; Willner, Samach, Angrist, Wallach & Gershon, 1970). In addition to the dosage x species interaction in the elicitation of stereotypy, it has been argued that the route of administration also plays an important role in the occurrence of stereotypic behaviors engendered by various catecholamine stimulants. In the mouse, for example, it has been observed that amphetamine or apomorphine injected intravenously elicits stereotypies, whereas other routes of administration are incapable of producing these behaviors. In contrast, methylphenidate injected subcutaneously or intraperitoneally produced stereotypies, whereas intravenous injections had no effect (Wallach, 1974). Contrary reports, however, are frequent in this respect (see discussion in Molander & Randrup, 1974).

While the elicitation of stereotypy is a common feature of catecholamine stimulants it must be emphasized that stereotypies produced by different agents are both qualitatively and quantitatively different from one another. For example, whereas amphetamine-induced stereotypy is characterized by licking and rapid movements of the head and forelegs, methylphenidate and L-DOPA produce intense stereotyped gnawing (Pedersen, 1968; Pedersen & Christensen, 1972; Molander & Randrup, 1974), while apomorphine produces stereotypy with little evidence of gnawing (Ther & Schramm, 1962; Pedersen, 1968; Scheel-Kruger, 1970; Molander & Randrup, 1974). Recent work from this laboratory has also revealed

similar drug-induced differences in response to various catecholamine stimulants. Treatment with L-DOPA induces stereotypies which have a smaller hyperactive component relative to d-amphetamine, while apomorphine produces stereotypies but not increased activity. Methylphenidate, on the other hand, produces a marked hyperactivity with a notable absence of sniffing, gnawing or dyskinetic movements. In contrast to methylphenidate, β -phenethylamine elicits sniffing and gnawing behavior without the characteristic hyperactive component (Kokkinidis, unpublished observations).

As with amphetamine-induced locomotor activity, a great deal of research has been conducted in order to elucidate the neurochemicals which mediate stereotypic behaviors. Generally, the findings are similar to those observed with respect to amphetamine-induced locomotor activity. For example, it has been reported that reserpine has no effect and, in fact, may enhance stereotypic behavior produced by amphetamine, whereas α -MPT was observed to antagonize amphetamine-induced stereotypies, suggesting that newly synthesized catecholamines are responsible for the behavioral effects of amphetamine (Randrup & Jonas, 1967; Randrup et al., 1963; Scheel-Kruger, 1971). However, it must be remembered that since different species show varied responses to a number of pharmacologic agents, the mechanisms which subserve these behaviors are not necessarily congruent across species and drugs. Indeed, although reserpine has no effect on phenmetrazine-induced stereotypy in rats (Scheel-Kruger, 1971), it effectively antagonizes phenmetrazine-induced stereotypy in cats (Wallach &

Gershon, 1972). In rats, it seems that de novo stores of catecholamines are important in the mediation of d-amphetamine-induced stereotypies, since α -MpT antagonizes the behavioral effects of this drug, while reserpine is without effect. In contrast to d-amphetamine, stereotypies produced by methylphenidate are antagonized by reserpine, but not by α -MpT (Christensen & Pedersen, 1972; Scheel-Kruger, 1971; Wallach, 1974; Wallach & Gershon, 1972), suggesting that the main storage pools are important for the actions of methylphenidate.

Although stereotypy probably should not be considered in a singular fashion, the available data suggest that dopaminergic mechanisms are primarily involved in subserving stereotypic behaviors induced by catecholamine stimulants. Thus, DA receptor blockers abolish the stereotyped responses to amphetamine (Rolinski & Scheel-Kruger, 1973), whereas alpha-adrenergic blocking agents were ineffective in this respect (Christensen & Pedersen, 1972). It has been reported that a high dosage of the β -receptor antagonist, propranolol, antagonized the stereotyped behavior produced by amphetamine; however, this effect was not generalizable to other β -adrenergic receptor blocking agents (Randrup et al., 1963; Herman, 1967; Wallach, 1974). Further to this point inhibition of dopamine- β -hydroxylase had no effect on d-amphetamine-induced stereotypy (Randrup & Scheel-Kruger, 1966; Scheel-Kruger & Randrup, 1967). Recently, however, Mogilnicka and Braestrup (1976) have shown that NE may exert subtle effects on stereotypic behaviors.

Specifically, the α -adrenergic receptor blocking drug (phenoxybenzamine), dopamine- β -hydroxylase inhibitors (DDC and FLA-63) or a storage granule depletor (reserpine) decreased stereotyped sniffing elicited by apomorphine, amphetamine or β -phenethylamine. The observed decrease, however, occurred at the expense of an increase in gnawing and biting. These results suggest that NE may play an inhibitory role in the expression of certain components of stereotyped behaviors.

Further evidence for the involvement of DA in mediating stereotypy is derived from lesion studies. On the surface, these findings are in some ways enigmatic. Whereas bilateral electrolytic destruction of either the substantia nigra or the caudate putamen have been shown to have little or no effect on amphetamine-induced stereotypies (Costall & Naylor, 1974; Costall, Naylor & Olley, 1972a; Iversen, 1971; Simpson & Iversen, 1971), 6-OHDA lesions of these structures abolished the stereotyped response to amphetamine (Asher & Aghajanian, 1974; Creese & Iversen, 1972, 1974, 1975; Evetts, Uretsky, Iversen & Iversen, 1970; Iversen, 1974; Iversen & Creese, 1975; Price & Fibiger, 1974). One possibility which may account for these paradoxical effects (cf., Asher & Aghajanian, 1974; Price & Fibiger, 1974) is that following electrolytic lesions, DA depletion is insufficient, thus allowing for the amphetamine response to occur. In contrast, 6-OHDA, due to its affinity for reuptake into dopaminergic nerve terminals (cf., Sachs & Jonsson, 1975; Peters, Anisman & Pappas, 1978), provides a marked depletion of dopamines when injected directly into dopamine containing areas. Consequently, d-amphetamine induced stereotypies are abolished. Indeed, the depletion may be sufficient to induce post-synaptic supersensitivity, such that stereotypies associated with systemically injected apomorphine are enhanced.

It has been argued thus far that stereotypy is subserved primarily by dopaminergic mechanisms. Treatments which affect serotonergic and cholinergic systems, however, have also been found to modify the stereotypic response to amphetamine. In particular, increases in serotonergic activity via 5-HTP antagonized amphetamine-induced stereotypy. Conversely, methysergide, a serotonergic antagonist, potentiates the effects of amphetamine (Goetz & Klawans, 1974; Weiner, Goetz, Westheimer & Klawans, 1973). Treatment with the anticholinestrase, physostigmine, antagonized the amphetamine-induced stereotypies whereas scopolamine, an anticholinergic (antimuscarinic), had the opposite effect (Arnfred & Randrup, 1968; Fjalland & Moller-Nielson, 1974; Randrup & Munkvad, 1970). Such pharmacologic interactions are not surprising given that there are an abundance of data implicating a biochemical interaction between DA, ACh and 5-HT in the corpus striatum. Briefly, it is well documented that there is a relationship between dopaminergic terminals and cholinergic interneurons in the neostriatum (Kemp & Powell, 1971, McGeer et al., 1975; Anden, Fuxe, Hamberger & Hokfelt, 1966). The general consensus is that dopaminergic neurons tonically inhibit cholinergic activity, whereas cholinergic excitation results in an increase of dopaminergic activity (Bartholini, Lloyd & Pletscher, 1973). Accordingly, inhibition of dopaminergic activity produced an excitation of cholinergic interneurons (Bartholini, Lloyd & Pletscher, 1973; McGeer, Grewall & McGeer, 1974; Sethy & Van Woert, 1974). Thus, the increased DA activity produced by the administration of L-DOPA or amphetamine, or stimulation

of dopaminergic receptors with apomorphine serves to increase dopaminergic inhibition of cholinergic interneurons in the striatum, resulting in increased levels of ACh (McGeer et al., 1974). On the other hand, depletion of dopaminergic storage pools with the administration of reserpine, or blockade of dopamine receptor sites with haloperidol or clozapine, tend to attenuate the inhibition of cholinergic interneurons ordinarily produced by dopaminergic stimulation, thereby increasing cholinergic activity with resultant decreases in levels of acetylcholine (Consolo, Ladinsky & Garattini, 1974; McGeer et al., 1974). These findings suggest that increases in levels of dopamine, which result in various behavioral changes (e.g., activity, stereotypy) are not necessarily a direct result of the dopaminergic excitatory system per se, but rather the interaction of this system with the cholinergic inhibitory system (cf., Anisman, 1975a). Along with the acetylcholine and dopamine sensitive areas in the caudate nucleus there is evidence of a serotonergic sensitive area, as well (Cools, 1973; Cools & Van Rossum, 1970). Treatment with L-DOPA not only increased DA content in the caudate nucleus, but had a 5-HT depleting action, which was not the result of displacement, but rather appeared to be a consequence of a neurochemical interaction between these systems (Bartholini, Da Prada & Pletscher, 1968; Pletscher, 1969).

Spontaneous Alternation/Perseveration

In addition to stereotypy, numerous catecholaminergic agents have been observed to induce perseverative behavior. For example, in a simultaneous discrimination task involving two choices, animals treated with d-amphetamine tend to respond repeatedly to a single alternative (see reviews in Bignami, 1978 and Carlton, 1963). However, many types of manipulations, either pharmacological or physiological in nature, produce such perseverative effects. As such, it is necessary to determine whether a genuine perseverative bias exists (as opposed to motor changes, habituation or circling biases), and in addition, whether the bias is of the response type, stimulus type or a combination of the two.

The use of spontaneous alternation tasks has proved to be a useful tool in evaluating the nature of the bias produced by d-amphetamine. Spontaneous alternation appears to involve the ability to selectively inhibit responses to non-reinforced stimuli (Carlton, 1969; Douglas & Issacson, 1966; Drew, Miller & Baugh, 1973; Swonger & Rech, 1972). When animals are pre-exposed to a novel stimulus array, and permitted to explore, more often than not they respond to those cues least recently visited. Presumably, the rewarding properties inherent in the exploration of novel cues wane (habituation) and consequently alternative stimuli are sought out. It should be noted that there are two distinct processes in action here. The first deals with the reinforcing value inherent in the

exploration of novel situations (Williams, Hamilton & Carlton, 1975); the second deals with the inhibition of behavioral responses to those situations where the stimulus factors are no longer novel (Carlton, 1969). Conceivably, response strength could be altered either by maintaining the novelty of the situation and thus maintaining the reinforcing value of exploration, or by altering the habituation process.

Essentially, two types of alternation tasks have been employed. The more commonly used T-maze task involves placing the animal in the start arm (the main stem), and allowing the animal to respond by visiting one of the two empty compartments. The animal is then confined to the chosen alley for a predetermined period, is then removed and placed in the start arm and a second trial is initiated. Typically, the response on the second trial is directed to the opposite goal box on approximately 85 percent of the trials (Douglas, 1966, 1975; Douglas & Issacson, 1966; Squire, 1969). The second form of alternation utilizes a free running Y-maze task in which animals are placed in the maze for a set period of time and the order of arm entries is recorded. Generally, it has been observed that animals enter the least recently visited arm (alternation) approximately 60-65 percent of the time (Anisman & Kokkinidis, 1975; Swonger & Rech, 1972).

Two possibilities exist which can account for the occurrence of spontaneous alternation in both a T- or Y-maze situation. Animals may alternate on the basis of internal feedback (e.g., left-right turns), or animals emit responses to positional cues (i.e., stimulus factors). The available data suggest that stimulus factors play a more important role in determining alternation behavior (cf., Douglas, 1975). Specifically, Glanzer (1953) found that when animals are permitted the choice of alternating responses or alternating novel compartments, animals choose to alternate compartments. This distinction becomes clearer when the behaviors in the T- and Y-maze tasks are considered together. Specifically, in a T-maze task position responding and left-right responding are confounded, in that response on the second trial is always accompanied by a change in position as well as a change in directionality. If alternation were dependent upon internal feedback, then alternation between compartments would not be observed in the Y-maze situation, since under these conditions repeated left-right turns would result in alternation between two compartments only. The fact that spontaneous alternation occurs in both tasks suggests that animals alternate on the basis of position cues or stimulus factors. Further evidence to this point has been derived from studies in which it was observed that contextual or olfactory cues will increase alternation performance (Douglas, 1966).

Reiterating, when animals are placed in a symmetrical Y-maze and permitted free exploration, they tend to enter the least recently visited arm. Thus, a series of arm entries in which alternation took place would be 1, 2, 3, 1, 2, 3, etc. After treatment with d-amphetamine (5.0 mg/kg in mice) animals tend to visit primarily only 2 arms of the Y-maze (perseveration) (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a). Once a novel arm is visited, this arm is then employed in the perseverative sequence. For example, a sequence of arm entries would be 1, 2, 1, 2, 1, 2, 1, 2, 3, 2, 3, 2, 3, etc. The perseveration elicited by amphetamine is distinct from other amphetamine-induced behaviors such as locomotor activity or stereotypy. Evidence for this comes from several sources. First, apomorphine which induces stereotypy and locomotor stimulation (see earlier sections) does not elicit perseverative behavior (Kokkinidis, unpublished observations). Second, α -MPT which antagonizes amphetamine-induced locomotor activity and stereotypies has no effect on perseverative responding (Anisman & Kokkinidis, 1975). However, after pretreatment with reserpine, both tyrosine hydroxylase and dopamine- β -hydroxylase inhibition antagonized the perseverative response to amphetamine, suggesting the involvement of NE in this behavior as opposed to DA which is important for the expression of locomotor activity and stereotypy (Anisman & Kokkinidis, 1975).

Although d-amphetamine alters the response pattern in a Y-maze situation, it apparently does so without effect on habituation (cf., Kokkinidis & Anisman, 1976a, b). If the course of habituation was affected by drug administration, then response to the compartments in the Y-maze should occur on a random basis, resulting in chance level alternation (50% given two choices). However, following treatment with amphetamine response levels fall significantly below chance (e.g., 30-40%), suggesting that the drug is altering processes other than (or in addition to) habituation. Recent work from this laboratory has revealed that d-amphetamine exerts minimal effect on habituation (Kokkinidis & Anisman, 1976b). Specifically, alternation is observed to decline within a session as well as between sessions (Swonger & Rech, 1972). Thus, if a drug disrupts alternation via its effects on habituation in the drug state, then subsequent performance in the non-drug state should resemble that of naive animals. Conversely, if a drug modifies alternation without effect on habituation per se, then performance on the subsequent retest should be comparable to that of animals which had been previously exposed to the apparatus in the non-drug state. Although d-amphetamine produced perseveration in the drug state, performance in the non-drug state 24 hours later, resembled that of animals initially trained in the saline condition (see Figure 1) (Kokkinidis & Anisman, 1976b). The absence of carry-over effects observed in this experiment have been reported in other tasks which have utilized a similar carry-over procedure (Anisman, Kokkinidis, Glazier & Remington, 1976; Carlton, 1969; Carlton & Vogel, 1965).

Figure 1

Mean proportion of alternation responses ($\pm$ S.E.M.) over 2 consecutive days as a function of drug treatment with either scopolamine (1 mg/kg), d-amphetamine (5 mg/kg) or equipotent amounts of methylscopolamine and p-hydroxyamphetamine.

It is noteworthy that although habituation is not directly involved in the mediation of perseveration, this behavior appears to be dependent upon stimulus factors. We have consistently observed that pre-exposure to the apparatus prior to drug treatment enhances the perseverative tendency (Kokkinidis & Anisman, 1976a; Kokkinidis, Walsh, Lahue & Anisman, 1976). Conversely, perseveration produced by d-amphetamine is reduced substantially when the novelty value of the apparatus is increased (Kokkinidis, unpublished observations). Further support for the role of stimulus factors in the mediation of perseverative behavior is found when developmental changes in alternation are examined. It is well documented that the brain develops in a caudal-rostral fashion, and that neurotransmitters involved in midbrain structures (i.e., monoamines) are functional during the second postnatal week of development, whereas the forebrain cholinergic system is still immature (Campbell, Lytle & Fibiger, 1969; Campbell & Mabry, 1972; Douglas, 1975; Moorcroft, 1971; Thornburg & Moore, 1973c). Animals tested during this period of development exhibit a high degree of perseverative behavior in an alternation task (Egger, Livesely & Dawson, 1973). Treatment with d-amphetamine augments the perseveration, suggesting that the catecholamines may be involved in the perseverative tendencies observed in immature, undrugged animals (Remington, Kokkinidis & Anisman, unpublished report). As in adult animals the perseveration observed in immature animals is modified readily by manipulation of the external stimulus array. Increasing the novelty value of the apparatus results in increased alternation performance (Egger, 1973), whereas pre-exposure to the apparatus enhances perseverative behavior (Remington, Kokkinidis & Anisman, unpublished report).

It is apparent from data of this nature that the repetitive behavior produced by d-amphetamine reflects an approach rather than an avoidance tendency. If an avoidance tendency were exacerbated by drug treatment, then prior habituation to the Y-maze should mitigate, or at least reduce, the avoidance tendency, thus resulting in decreased perseveration (cf., Kokkinidis & Anisman, 1976a). Since pre-exposure enhances perseverative behavior, it is likely that this behavior reflects an increased responding to selective stimuli. Indeed, several investigators have suggested that the behavioral changes elicited by d-amphetamine are a result of drug-induced novel interoceptive cues (Scheaer & Moore, 1974; Schechter & Cook, 1975). Consequently, in the alternation task the response output relies upon the interaction between the tendency to persevere, which is subserved by the novel internal stimulus complex produced by drug treatment, and habituation to the external stimulus complex. Accordingly, if response strength to the external cues is reduced either by pre-exposure to the apparatus (Swonger & Rech, 1972) or by treatment with an anticholinergic which results in a diminished tendency to alternate (Carlton, 1969; Douglas & Isaacson, 1966; Kokkinidis & Anisman, 1976a; Leaton & Utell, 1970), the organism should respond primarily to the drug-induced internal cues and exhibit enhanced perseveration (Kokkinidis & Anisman 1976a). Conversely, if the stimulus novelty of the Y-maze is enhanced (Egger, 1973), or if habituation is attenuated via treatment with an anticholinestrase (Egger et al.,

1973; Kokkinidis & Anisman, 1976a; Squire, 1969), then response strength to the external stimulus complex is maintained and perseverative behavior is less pronounced (Kokkinidis & Anisman, 1976a). As can be seen in Figures 2 and 3 the effects of d-amphetamine are exaggerated by either apparatus pre-exposure or concurrent treatment with scopolamine, respectively (Kokkinidis & Anisman, 1976a).

As with locomotor activity and stereotypy, the perseveration elicited by amphetamine can be altered by pharmacologic manipulations which affect other neurotransmitter systems. For example, as previously discussed, Kokkinidis and Anisman (1976a) found that scopolamine enhanced and physostigmine reduced perseverative behavior engendered by d-amphetamine (see, however, opposite findings of Swonger & Rech, 1972 and discussion of these data in Kokkinidis & Anisman, 1976a). In the same vein, the finding that concurrent administration of LSD and d-amphetamine produces a synergistic effect on alternation clearly indicates that the monoamines act in a balanced manner in subserving spontaneous alternation (Swonger & Rech, 1972, 1978).

Finally, it needs to be pointed out that the anatomical areas involved in the mediation of spontaneous alternation are not similar to those involved in locomotor activity and stereotypic behaviors. It will be recalled that the

Figure 2 Mean percent of alternation ($\pm$ S.E.M.) as a function of
scopolamine or d-amphetamine treatment in pre-exposed or
naive animals.

Figure 3 Mean percent of alternation ($\pm$ S.E.M.) after concurrent
injection of scopolamine (1.0 mg/kg) and d-amphetamine
(3.0 mg/kg).

nigro-neostriatal, as well as the mesolimbic systems were implicated as important sites in modulating locomotor activity and stereotypy (Costall & Naylor, 1972, 1974; Creese & Iversen, 1972, 1974, 1975; Evetts et al., 1970). With respect to spontaneous alternation, the available data suggest that the hippocampus, locus coeruleus and raphe nuclei are important anatomical substrates of this behavior (Clody & Carlton, 1969; Douglas, 1975; Stevens & Cowey, 1973; Swonger & Rech, 1972, 1978; White, 1974).

Circling Behavior

After unilateral electrolytic or chemical lesions of dopaminergic cell bodies in the substantia nigra or dopamine nerve terminals in the caudate-putamen, rotational behavior ipsilateral to the side of the lesion is observed (Anden, Dahlstrom, Fuxe & Larsson, 1966; Ungerstedt & Arbuthnott, 1970; Von Voightlander & Moore, 1973). Circling behavior observed following lesions of this nature is apparently the result of a bilateral hemispheric imbalance of nigro-neostriatal dopamine (Arbuthnott & Crow, 1971; Crow, 1971; Ungerstedt, 1976; Ungerstedt & Arbuthnott, 1970). Thus, the animal rotates contralateral to the side which contains the higher dopamine content or ipsilateral to the side which is functionally least active. Rotational behavior can be re-elicited following recovery from chemical or electrolytic lesions by amphetamine administration (Christie & Crow, 1971; Iwamoto, Loh & Way, 1976; Ungerstedt, 1971a). Presumably, amphetamine induces release of dopamine from the intact side producing rotation ipsilateral to the side of the lesion. If the lesion is of a chemical nature

(i.e.; 6-OHDA), such that receptor sites are not damaged, systemic injection of either apomorphine or L-DOPA will elicit contraversive turning (Anden, 1966; Cools & Van Rossum, 1970; Van Voightlander & Moore, 1973). There exists a considerable amount of evidence suggesting that the differential drug effects on rotational behavior reflect supersensitivity of dopaminergic receptors (Ungerstedt, 1971b; Von Voightlander & Moore, 1973). To be more explicit, following 6-OHDA lesions, the lack of neurotransmitter following such lesions results in post-synaptic receptor supersensitivity (Moore, 1974; Ungerstedt, 1971b). Under these conditions increasing the amount of transmitter by L-DOPA, or direct receptor stimulation by apomorphine serves to produce functionally more dopaminergic activity on the lesioned side relative to the intact side, resulting in rotation to the side which is functionally least active, or contralateral to the lesion. Consistent with these results electrical stimulation of the substantia nigra also elicits contralateral circling behavior (Arbuthnott & Crow, 1971).

A wide variety of additional evidence bearing on the importance of the nigro-neostriatal pathway as an anatomical substrate of rotational behavior exists. Moreover, these studies have indicated that both ACh and DA are involved in the behavioral asymmetry observed following lesions to this system. Briefly, direct injections of the cholinomimetic, arecoline, or the DA receptor antagonist, haloperidol, into the caudate-putamen, globus pallidus, or substantia nigra produced circling ipsilateral to the side of injection (Costall, Naylor & Olley, 1972b). These effects were potentiated by direct

injection of an anticholinergic into these areas (Costall et al., 1972b). Conversely, unilateral chemical stimulation of dopaminergic activity in the caudate-putamen via direct application of dopamine or apomorphine produced contraversive rotational behavior (Cools & Van Rossum, 1970; Ungerstedt et al., 1969). On the basis of these data it seems that unilateral inhibition of dopaminergic activity or potentiation of cholinergic activity in the nigro-neostriatal system produces ipsilateral turning. Thus, as in the case of locomotor activity, stereotypic behaviors, and other extrapyramidal disorders, rotational behavior is subserved by a balance between DA and ACh.

Although the available data are suggestive of a DA/ACh interaction in modulating circling behavior, there are several studies which report that different unilateral brain lesions produce motor asymmetries. For example, removal of the frontal cortex induces ipsilateral rotation following amphetamine treatment; however, this only occurs 1-7 days post-operatively (Glick & Greenstein, 1973). When testing occurred 15-30 days following surgery, contralateral circling was observed. Lesions to the olfactory tubercle produced ipsilateral turning following amphetamine treatment (Yehuda & Wurtman, 1975). In contrast, contralateral turning was observed following mesencephalic reticular formation lesions, which in turn was potentiated by d-amphetamine (Marsden & Guildberg, 1973). Similar types of motor asymmetries were observed following administration of amphetamine or apomorphine to rats with lesions of the locus coeruleus (Pycock, Donaldson &

Marsden, 1975). The mechanisms involved in subserving these asymmetries are not well understood. It may be the case that extensive damage to the aforementioned areas may affect neostriatal DA/ACh activity. Indeed, Pycock et al. (1975) reported a significant increase in striatal DA ipsilateral to the locus coeruleus lesion.

Recently, Glick and his associates (Glick & Cox, 1976; Glick, Cox & Greenstein, 1975; Glick, Jerussi & Fleisher, 1976; Glick, Jerussi, Waters & Green, 1974; Glick, Zimmerberg & Greenstein, 1976; Jerussi & Glick, 1974, 1975) reported that systemic injection of amphetamine may induce circling behavior in the absence of unilateral lesions. Moreover, they suggest that the rotational behavior observed following amphetamine administration is similar to that observed following direct injections of dopaminergic agonists or antagonists to the nigro-neostriatal pathway (Ungerstedt et al., 1969). They suggest that there exists a natural imbalance of dopaminergic activity in the nigro-neostriatal system. Following systemic treatment this asymmetry apparently is exacerbated, resulting in rotational behavior (Glick et al., 1974; Jerussi & Glick, 1974).

Kokkinidis and Anisman (1977) recently argued that the circling response to amphetamine is an artifact of drug-induced stimulus perseveration rather than a genuine circling tendency observed following lesions to the substantia nigra. Specifically, after unilateral intraventricular injection of d-amphetamine

mice tend to exhibit contraversive turning (Kokkinidis & Anisman, 1977; Kokkinidis, Raffler & Anisman, 1977). In the Y-maze situation the circling produced by intraventricular administration of amphetamine produced consistent turning in a single direction at both the choice point and the ends of the arms, thus resulting in near perfect alternation (see Figure 4). Intraperitoneal injections of d-amphetamine produce comparable motor excitation as well as rotational behavior to that observed following intraventricular treatment when tested in a circular alley (see Figure 5). In contrast to intraventricular administration, however, systemic treatment with amphetamine results in stimulus perseveration (see previous section). In order for animals to persevere in the Y-maze task, consistent left-right turns must be made at the choice point. As such, these data suggest that stimulus perseveration induced by amphetamine is not an artifact of a turn bias. The possibility exists, however, that circling behavior produced by systemic drug injections may well be an artifact of stimulus perseveration. More importantly, since genuine circling (after intraventricular injection) and stimulus perseveration (after intraperitoneal injection) mimic one another in a circular runway, it may be more appropriate to evaluate rotational behavior in a Y-maze task (see discussion in Kokkinidis & Anisman, 1977).

Figure 4 Pattern of arm entries following intraventricular
injection of d-amphetamine.

Figure 5 Mean proportion of rotational and alternation responses
 ($\pm$ S.E.M.) after intraperitoneal or intraventricular
 injection of d-amphetamine.

Self-Stimulation

It is well established that animals will continuously bar press in order to receive the reinforcing value of enhanced neuronal activity elicited by electrical stimulation (see German & Bowden, 1974 for review). As such, centrally-induced self-stimulation has been thought to represent a direct activation of the brain's reward system (Deutsch, 1960; Olds, 1962; Stein, 1964a; Gallistel, 1973), and to date, a considerable amount of research has been conducted in order to elucidate the neural pathways which may subserve such a system.

Evidence for the involvement of catecholamine pathways in the mediation of intracranial self-stimulation (ICSS) has come from several sources. First, ICSS response rates are greatest and most consistent in those brain regions which have a high concentration of catecholamine neurons (cf., German & Bowden, 1974). Consistent with the notion of catecholamine systems mediating ICSS, amphetamine (Domino & Olds, 1972; Horowitz & Carlton, 1962; Horowitz, Chow & Carlton, 1962; Margules, 1969; Olds, 1959, 1970; Stein, 1964b), methamphetamine (Olds, 1959; Stein, 1964b), phenethylamine (Stein, 1964b, 1966, 1968), monoamine oxidase inhibitors (Poschel, 1969; Poschel & Ninteman, 1964) and cocaine (Crow, 1970), have been observed to increase rates of responding for brain stimulation. Conversely, drugs which reduce catecholaminergic tone such as reserpine or α -MPT predictably reduce self-stimulation behavior (Black & Cooper, 1970; Bigson, McGeer & McGeer, 1970; Stein, 1962).

As is the case concerning several behaviors previously discussed, a controversy currently exists with respect to the involvement of DA or NE systems in subserving self-stimulation. The evidence in support of a NE or DA involvement in the mediation of ICSS is listed here. It will be recognized, of course, that this listing is not exhaustive, and the reader is directed to the original reports for more detail.

Evidence Implicating Norepinephrine

1. The dorsal, ventral and periventricular noradrenergic pathways all have been shown to support self-stimulation (Crow, Spear & Arbuthnott, 1972; Ritter & Stein, 1973, 1974).
2. Dopamine- β -hydroxylase inhibition abolishes ICSS and antagonizes the amphetamine-induced potentiation of ICSS. Moreover, intraventricular administration of norepinephrine inhibits the depressant effects of disulfiram or diethyldithiocarbamate and reinstates the enhancing effects of amphetamine (Wise & Stein, 1969, 1970).
3. Intraventricular administration of phentolamine (α -NE receptor antagonist) but not propranolol (β -antagonist) blocked the facilitory effects of amphetamine (Wise, Berger & Stein, 1973).
4. Self-stimulation of the medial forebrain bundle released norepinephrine from the lateral hypothalamus and amygdala (Stein & Wise, 1969; Wise & Stein, 1970).

5. Infusion of norepinephrine via the ventricles facilitated lateral hypothalamic self-stimulation, whereas dopamine administration did not (Wise & Stein, 1970).
6. Treatment with 6-aminodopamine produced a depression in ICSS from the medial forebrain bundle with concomitant decreases in NE, whereas dopamine levels remained unchanged (Monasmith, Plotsky, Blank & Adams, 1976).
7. L-DOPA produced an excitatory effect on ICSS from either the dorsal NE bundle or the medial forebrain bundle. Moreover, pretreatment with the dopamine- β -hydroxylase inhibitor, diethyldithiocarbamic acid sodium (DEDTC), completely antagonized the excitatory effects of L-DOPA (Poschel & Ninteman, 1975).

Evidence Implicating Dopamine

1. Self-stimulation can be obtained readily from dopamine containing areas such as the substantia nigra and the caudate-putamen (Crow, 1971, 1972a, b; Phillips, Carter & Fibiger, 1976; Prado-Alcala, Kent & Reid, 1975).
2. DA receptor stimulation by apomorphine has been reported to both enhance (Liebman & Butcher, 1974; Wauquier & Niemegeers, 1973), as well as disrupt ICSS (Liebman & Butcher, 1973; St. Laurent, Le Clerc, Mitchell & Miliaressis, 1973), regardless of whether electrode sites were placed in DA or NE areas (Broekkamp & Van Rossum, 1974).
3. DA receptor blockers, haloperidol and pimozide, decrease ICSS regardless of whether electrodes are placed in dopaminergic or noradrenergic projections (Liebman & Butcher, 1974; Phillips, Brooke & Fibiger, 1975).

4. Selective DA depletion by 6-OHDA lesions in conjunction with desimipramine resulted in: a) depression of lateral hypothalamus-induced ICSS; b) enhancement of α -MPT-induced depression of ICSS, and c) antagonized the facilitation of self-stimulation produced by d-amphetamine (Breese, Cooper & Hollister, 1974; Breese, Cooper & Smith, 1973; Cooper, Colt & Breese, 1974).
5. Bilateral injections of d-amphetamine into the nucleus accumbens or the neostriatum enhanced ICSS from the ventral tegmentum (Broekkamp, Pijnenburg, Cools & Van Rossum, 1975).
6. 6-OHDA lesions of the corpus striatum suppressed electrical stimulation of the lateral hypothalamus. Moreover, direct application of both dopamine and norepinephrine reinstated the ICSS (Neill, Parker & Gold, 1975).

It seems that both DA and NE may be involved in self-stimulation behavior. However, some of the studies discussed pertaining to DA have yielded paradoxical results: (a) Drugs which are selective DA receptor blockers produce a reduction in ICSS regardless of whether self-stimulation is occurring at DA or at NE sites. (b) Dopamine receptor agonists such as apomorphine suppress as well as enhance responding, regardless of the site of stimulation. (c) Self-stimulation is disrupted by 6-OHDA in the striatum but is reinstated with microinjections of norepinephrine in the same site. (d) ICSS from the substantia nigra is diminished following either pharmacological inhibition of norepinephrine synthesis or after chemical or mechanical damage to ipsilateral NE pathways (Belluzzi, Ritter, Wise & Stein, 1975).

On the basis of data involving the effects of 6-OHDA and neuroleptics on self-stimulation from either the lateral hypothalamus or neostriatum, Phillips et al. (1976) and Fibiger et al. (1976) suggested that dopaminergic mechanisms are involved in the initiation or maintenance of operant behavior. As such, damage to dopaminergic systems results in the inability of the animal to maintain active responding (cf., Fibiger, Zis & Phillips, 1975), thus resulting in decreased ICSS (Fibiger et al., 1976). Other investigators have suggested that whereas NE is primarily involved in reinforcement, DA mediates a motivational component which may be involved in self-stimulation (Herberg, Stephens & Franklin, 1976; see also Deutsch, 1963; Gallistel, 1973). Basically, this hypothesis is not at variance with the motor deficit hypothesis and is consistent with the notion (Ungerstedt, 1971c) that dopamine is involved in the mediation of a non-specific motivational state.

Although DA and NE may affect different components of ICSS it seems that other neurotransmitters may also subserve self-stimulation behavior. For example, synthesis inhibition of tryptophan hydroxylase by PCPA enhanced self-stimulation from a number of brain sites (Poschel & Ninteman, 1971). Similarly, destruction of serotonergic nerve terminals by 5, 6-dihydroxytryptamine (5, 6-DHT) produced an excitatory effect on ICSS from several self-stimulation points in the brain, while increasing serotonergic activity via 5-HTP results in a depression of self-stimulation behavior (Poschel & Ninteman, 1975). The dorsal raphe nuclei have been reported to support self-stimulation behavior

(Liebman, Mayer & Liebeskind, 1973). However, it is likely that NE neurons were involved since ICSS from this area was affected by drugs which altered catecholamine activity, but not 5-HT activity (Margules, 1969). Changes in ICSS are not restricted to monoaminergic manipulations, in that there are data available which implicate ACh as an important neurotransmitter in subserving ICSS. Generally, increases in ACh either by a cholinomimetic or an anticholinesterase result in a depression of ICSS at several brain sites (Domino & Olds, 1968; Newman, 1972). Conversely, inhibition of ACh by antimuscarinics enhances ICSS (Jung & Boyd, 1966; Stark & Boyd, 1963).

Clearly, self-stimulation is subserved by a balance of several neurotransmitters (cf., Pradhan, 1975). It would be interesting to speculate at this point that different balances may subserve the different components of self-stimulation behavior. It will be recalled that a DA/ACh balance has been posited to mediate locomotor activity, stereotypy, as well as several extrapyramidal disorders (see earlier sections). It might be the case as suggested by Fibiger *et al.* (1975) that a similar balance is involved in the maintenance of active responding. Norepinephrine, on the other hand, was previously implicated as an important neurotransmitter in mediating reinforcement. As suggested by several investigators, the possibility exists that the reinforcing component of self-stimulation is subserved by a balance between NE and 5-HT (Holloway, 1975; Poschel & Ninteman, 1975). At present, however, firm conclusions must be held in abeyance.

Startle Response

Upon exposure to a strong stimulus (e.g., buzzer) animals typically exhibit a startle reflex. Unlike emitted responses (e.g., spontaneous alternation), habituation of this elicited reflex is preceded by a period of sensitization, i.e., increased responsiveness. The startle reaction is modifiable via catecholaminergic manipulations. For example, treatment with either d- or l-amphetamine results in an enhancement of startle amplitude, without altering within session habituation to repeated tone presentation (Davis, Svensson & Aghajanian, 1975). Consistent with the view of catecholamine involvement in startle sensitization, α -MPT produces a depression in startle amplitude (Sorenson & Davis, 1975), and antagonizes the enhancing effects of amphetamine (Davis et al., 1975).

Paradoxically, catecholamine depletion via reserpine augments startle amplitude as well (Fechter, 1974a). It is not entirely clear why depletion of the catecholamines by α -MPT and reserpine should produce such diametrically opposite results. Receptor supersensitivity following reserpine treatment cannot account for this effect, since NE receptor stimulation by clonidine antagonizes, whereas DA receptor stimulation by apomorphine is without effect on the reserpine-induced increase in startle amplitude (Fechter, 1974a). Although both reserpine and d-amphetamine affect startle amplitude, the effects are not entirely congruent. To be more explicit, reserpine enhances startle amplitude

on the first tone presentation and does not produce sensitization over repeated tone presentations. In contrast, d-amphetamine has little or no effect on the first tone presentation, but startle amplitude progressively increases with repeated stimulation. Given these differences it would not be surprising to find variations in the neurochemical substrates mediating these effects. Indeed, both L-DOPA and clonidine antagonize the reserpine-induced enhancement of startle, whereas apomorphine is without consequence, suggesting that NE is involved in the reserpine action (Fechter, 1974a). Conversely, apomorphine which mimics the effects of amphetamine on a startle task is antagonized by haloperidol (Davis & Aghajanian, 1976), indicating that dopaminergic activity may be involved in modulating startle sensitization.

In contrast to the behaviors discussed in previous sections, cholinergic manipulations have no effect on the startle response (Groves, Wilson & Boyle, 1974; Williams, Hamilton & Carlton, 1974, 1975). However, the available data suggest that 5-HT may serve in an inhibitory capacity in the mediation of the startle response. Treatment with PCPA, lysergic acid diethylamide (LSD-25) or N, N-di-methyltryptamine (DMT), all of which decrease serotonergic activity (Aghajanian, Foote & Sheard, 1970; Gallagher & Aghajanian, 1975), enhance startle amplitude (Conner, Stolk, Barchas & Levine, 1970; Davis & Sheard, 1974a, 1974b). Consistent with these results lesions to the raphe nuclei also enhance startle amplitude (Davis & Sheard, 1974c). Further to this point, p-chloro-amphetamine (PCA), which results in an initial increase in 5-HT release

(Sanders-Bush, Bushing & Sulser, 1975), followed by a rapid decrease in 5-HT and 5-hydroxyindoleacetic acid (Fuller, Hines & Mills, 1965; Miller, Cox, Snodgrass & Maickel, 1970; Pletscher, Bartholini, Bruderer & Grey, 1964), produced a similar biphasic action on the startle reflex (Davis & Sheard, 1976). That is, soon after drug treatment when 5-HT is increased, startle amplitude is inhibited. In contrast, when testing occurs at the time corresponding with 5-HT depletion, startle amplitude is exaggerated.

Reactivity. Application of foot-shock to rats or mice invariably results in a substantial reduction of locomotor activity, the extent of which is strain dependent (Anisman, 1975b, c; Wahlsten, 1973, 1974). Surprisingly, in mice the same treatment following amphetamine administration results in a motor excitation which exceeds that produced by the drug treatment alone (Anisman, 1976; Anisman & Cygan, 1975; Anisman, Kokkinidis & Wahlsten, 1975). In effect, foot-shock which ordinarily produces behavioral inhibition may, under the appropriate conditions result in behavioral excitation.

To date, this phenomena has not received extensive attention. It is known, however, that the post-shock excitation, which occurs, for example, in the A and DBA/2 strains, is absent in the C57BL/6 strain (Anisman et al., 1975). Furthermore, it appears that the occurrence of the post-shock excitation is independent of baseline levels of locomotor activity, as well as locomotor

activity elicited by d-amphetamine. That is, the F_1 between the A and C57BL/6 strains exhibits general locomotor activity after amphetamine comparable to that of the latter parent strain, but the post-shock excitation is more similar to that of the former parent strain. A somewhat similar dissociation is observed in the case of the DBA/2 x C57BL/6 cross (Anisman, 1976). Finally, unlike the locomotor excitation produced by amphetamine alone, the added excitation contributed by the shock treatment is antagonized by dopamine- β -hydroxylase inhibition (Anisman & Cygan, 1975). As such a potential role for norepinephrine might be considered.

Owing to the relative paucity of data concerning the post-shock excitation it is not clear whether the phenomena is in fact restricted to the A and DBA/2 strains, or whether it might appear in other inbred strains or non-inbred stocks, as well. Furthermore, it is not certain whether the post-shock excitation is a reflection of a sensitization effect, much like that seen upon the presentation of strong auditory stimuli. Finally, given the pervasiveness of neurochemical interactions in mediating other amphetamine-induced behaviors, it needs to be determined whether this phenomena likewise involves such interactions. At this time, the only information available

in this respect, is that cholinergic manipulations (Anisman & Cygan, 1975; Anisman et al., 1975) did not influence the post-shock excitation. In addition, it has been demonstrated repeatedly that the motor excitation induced by treatments which reduce 5-HT levels (e.g., PCPA, 5, 6-DHT) are effective exclusively or, at least, primarily following strong stimulation (Tennen, 1967; Jacobs, 1974; see review in Peters, Anisman & Pappas, 1978). Taken together, the possibility should be considered that either NE and 5-HT are jointly responsible for the post-shock excitation induced by amphetamine, or that the excitation is due to changes in 5-HT induced by amphetamine treatment.

EFFECTS OF CHRONIC AMPHETAMINE ADMINISTRATION

Neurochemical Effects

Repeated exposure to d-amphetamine results in a substantial depletion of brain catecholamines (Brodie, Cho & Gessa, 1970; Ellinwood, 1970; Lewander, 1968, 1969, 1970, 1971a, b, c, d, 1974; Segal, 1975). Although both DA and NE are affected by chronic drug treatment, studies involving the neurochemical effects of prolonged amphetamine administration have, for the most part, dealt with drug induced depletion in norepinephrine levels. The reasons for this are two-fold. First, the NE depletion produced by amphetamine is both dramatic and long-lasting (Lewander, 1974, 1970). In fact, whereas the normal half-life of amphetamine in brain tissue is approximately 2 hrs (Brodie et al., 1970; Costa & Groppetti, 1970; Maickel, Cox, Segal & Miller, 1966), NE levels are depleted for as long as 40 hrs following a single intraperitoneal

injection of 10 mg/kg of the drug in rats (Brodie et al., 1970). The second source for the concentration given to NE is related to the metabolic fate of d-amphetamine. Specifically, it has been demonstrated that the metabolite of amphetamine, p-hydroxyamphetamine (Axelrod, 1954), is a substrate of dopamine- β -hydroxylase (Creveling, Daly, Witkop & Udenfriend, 1962; Sjoerdsma & Studnitz, 1963). Moreover, the conversion of p-hydroxyamphetamine to p-hydroxynorephedrine is stereospecific to the d-isomer (Goldstein & Anagnoste, 1965). As such, the hydroxylated metabolite of d-amphetamine has been implicated as the primary source responsible for the depletion of NE following d-amphetamine administration (Brodie et al., 1970). The observation that p-hydroxynorephedrine accumulates at noradrenergic neurons (for review see Groves & Rebec, 1976), taken together with the finding that p-hydroxynorephedrine is stored and released from sympathetic nerve terminals following nerve stimulation (Lewander, 1971; Theonen, Hurlimann, Gey & Haefly, 1966) has led to the suggestion that this metabolite acts as a false neurotransmitter at noradrenergic sites (cf., Kopin, 1968, 1972).

Although the formation of p-hydroxynorephedrine may be responsible for the depletion of NE following chronic amphetamine treatment, there are data which suggest that this is not the sole contributing factor. For example, among guinea pigs and rabbits, where p-hydroxylation of amphetamine does not occur (Dring et al., 1970), a substantial decrease in brain NE is observed

following chronic drug treatment (Lewander, 1974). Further to this point, l-amphetamine which is not converted to p-hydroxynorephedrine also has been shown to produce a decrease in norepinephrine (Lewander, 1971a, c). Moreover, depletion of NE is observed following chronic d-amphetamine treatment in rats which were pretreated with desmethylinipramine or iprinodole in order to block the p-hydroxylation of d-amphetamine (Freeman & Sulser, 1972; Lewander, 1971a). Finally, the progressive depletion of NE associated with chronic amphetamine administration probably does not involve an inhibition of catecholamine synthesis in noradrenergic areas (Fibiger & McGeer, 1971; Javoy, Hamon & Glowinski, 1970). It is clear from data of this nature that the effects of chronic amphetamine treatment on norepinephrine metabolism are not well understood, and further work is necessary in order to elucidate the factors which may be involved in the depletion of norepinephrine induced by amphetamine.

The depletion of DA following prolonged amphetamine administration apparently does not involve the hydroxylated metabolites of d-amphetamine (Lewander, 1974). In contrast to NE, it is likely that the decrease in DA levels reflects changes in the biosynthesis of dopamine following chronic drug treatment (Segal & Mandell, 1974; Segal, 1975). Several investigators have found that the conversion of tyrosine to dopamine in the neostriatum is reduced substantially following chronic drug treatment (Fibiger & McGeer, 1971; Harris & Baldessarini, 1973). Whether the extended reduction in biosynthesis of dopamine reflects a

homeostatic adjustment to amphetamine-induced release of dopamine (Segal & Mandell, 1974; Segal, 1975) or is related to a reduced storage capacity of DA (Lewander, 1971b, 1974), is not entirely clear. In any event, the effects of chronic treatment on dopaminergic activity are not nearly as pronounced as on noradrenergic activity. The observed decrease in DA synthesis following 5 mg/kg of d-amphetamine is maximal at 2 hrs following injection which corresponds to the half-life of the drug, and remains at reduced levels for up to 12 hrs (Segal, 1975).

In contrast to the catecholamines, few data are available concerning the effects of chronic amphetamine treatment on serotonergic activity, and in fact, those data which are available, prove to be somewhat enigmatic. For example, prolonged exposure to amphetamine has been reported to cause either no change or an increase in brain concentrations of 5-HT (Garattini & Valzelli, 1965; McLean & McCartney, 1961). Diaz and Huttunen (1972) reported that chronic treatment with low dosages of d-amphetamine produced an increase in whole brain 5-HT as well as increasing turnover rate. In contrast to these reports, Lewander (1974) found a decrease in brain 5-HT, as well as depletion of 5-hydroxyindole acetic acid (5-HIAA) following chronic treatment with high dosages of d-amphetamine.

Behavioral Effects

Prolonged exposure to amphetamine in humans results in tolerance to the mood altering, and the anorexigenic and hyperthermic effects produced by the drug (cf., Kosman & Unna, 1968). In contrast, the aberrant motor and cognitive patterns associated with amphetamine intoxication are augmented with chronic use, ultimately resulting in paranoid-like symptoms (amphetamine psychosis) (Bell, 1965; Ellinwood, 1967; Griffith, Cavanaugh, Held & Oates, 1970; Snyder, 1973). As such, a considerable amount of research has been conducted with animals in order to relate the neurochemical effects of chronic amphetamine administration to the differential behavioral consequences of extended drug use. Considerable attempts have also been made to evaluate the importance of environmental or conditioning factors in determining the abatement of drug effects, or vice versa the lack of tolerance which follows protracted drug use.

With the repeated administration of amphetamine in animals, tolerance is observed to develop to the hyperthermic (Gotestam, 1976; Harrison, Ambrus & Ambrus, 1952; Lewander, 1971a), anorexigenic (Magour, Cooper & Fahdrich, 1976; Gotestam, 1976; Gotestam & Lewander, 1975; Milroy & Glick, 1976), cardiovascular (Burn & Rand, 1958; Day & Rand, 1963), adipsic (Epstein, 1959; MacPhail & Seiden, 1975), as well as to the toxic effects (Gotestam & Andersson, 1975; Lewander, 1968) of the drug.

Although prolonged amphetamine administration is known to produce a variety of neurochemical changes, several investigators have proposed that tolerance is subject to conditioning factors. Carlton and Wolgin (1971) showed that the time between amphetamine injection and food presentation was an important factor in the development of tolerance to the anorexigenic effects of the drug. That is, rats which were treated with amphetamine prior to presentation of sweetened milk developed tolerance to the disruptive effects of the drug on food intake. If animals were exposed to an equivalent dosage of the drug following the feeding sessions, tolerance was subsequently not observed. The lack of tolerance observed in this group suggests that repeated drug administration per se is not a critical factor in the development of tolerance to the anorexic effects of amphetamine. Rather, the tolerance is contingent upon drug administration occurring concomitantly with food presentation. Similar conditioning factors have been shown to play an important role in the development of tolerance to amphetamine-induced disruption of responding on a differential-reinforcement-of-low-rate schedule (DRL) for appetitive reinforcement (Campbell & Seiden, 1973).

Physiological tolerance, however, does appear to be critical so far as other behaviors are concerned. For example, chronic treatment with 10 mg/kg of d-amphetamine for 30 days abolished the perseverative effects of d-amphetamine (Kokkinidis et al.,

1976). In contrast, similar long term-treatment had no effect on the disruption of spontaneous alternation produced by 1 mg/kg of d-amphetamine (see Figure 6) (Kokkinidis et al., 1976). Moreover, preliminary data from this laboratory revealed that conditioning factors are not important in the development of tolerance to amphetamine-induced stimulus perseveration (Kokkinidis, unpublished observations), though further work is certainly critical in this respect.

As indicated previously, tolerance was observed to develop to the disruptive effects of amphetamine on a DRL schedule. Schuster, Dockens and Woods (1966) demonstrated that tolerance was dependent upon the schedule of reinforcement under examination. They found that although d-amphetamine initially increased response rates on a free-operant avoidance schedule and on a fixed schedule interval as well as on a DRL component of a multiple fixed interval 30 sec DRL 30 sec schedule, tolerance was only observed to the DRL component of the multiple fixed interval schedule. Accordingly, the suggestion was made that tolerance occurs only to those behaviors where d-amphetamine ordinarily disrupts the reinforcement requirements and not in those situations where the drug enhances or has no effect on the number of reinforcements received (Campbell & Seiden, 1973; Schuster et al., 1966). Moreover, this tolerance probably involves a behavioral adaptation to the disruptive effects of drug treatment as opposed to a physiological tolerance (Campbell & Seiden, 1973).

Figure 6 . Effects of chronic and acute treatment of d-amphetamine on locomotor activity and spontaneous alternation. On the abscissa the upper lettering indicates the 30 day injection regimen and the lower lettering the injection on test day.

PERCENT ALTERNATION

60
50
40

MEAN ARM ENTRIES

130
100
70
40

SAL
SAL

AMP
SAL

SAL
AMP

AMP
AMP

These findings, however, are not generalizable to other behaviors which also involve reinforcement. For example, Leith and Barrett (1976) showed that the facilitative effect of d-amphetamine on self-stimulation from the medial forebrain bundle undergoes tolerance following chronic amphetamine administration. Moreover, as in the case of amphetamine-induced perseveration, the development of tolerance to the facilitative effects of amphetamine on self-stimulation involves a physiological tolerance. Specifically, in the Leith and Barrett experiment chronic injections of amphetamine were not followed by behavioral testing. Rather, testing occurred 16 hrs following the last injection of d-amphetamine, thus minimizing (or precluding) the possibility of conditioning factors influencing the tolerance. In contrast to the Leith and Barrett data, the facilitative effect of d-amphetamine on self-stimulation from the substantia nigra did not undergo tolerance following chronic amphetamine treatment (Liebman & Segal, 1975). This finding, taken together with evidence implicating a noradrenergic component as being involved in the mediation of self-stimulation from the medial forebrain bundle (Holloway, 1975; Monasmith et al., 1976; Poschel & Ninteman, 1975; Stein & Wise, 1969; Wise & Stein, 1970) reinforces the notion that NE may be involved in the tolerance of the facilitative effects of amphetamine on self-stimulation.

As in the case of the effects of chronic amphetamine treatment on the substantia nigra supported ICSS, other behaviors in which dopaminergic activity in this area are known to be important do not undergo tolerance. Specifically, long-term amphetamine administration produces a progressive augmentation of locomotor activity and stereotypic behaviors elicited by d-amphetamine (Ellinwood, 1972; Ellinwood & Escalante, 1970; Lewander, 1971a; Lyon & Randrup, 1972; Segal & Mandell, 1974; Segal, 1975). While these behaviors are enhanced following chronic amphetamine intoxication it appears likely that these changes represent alterations in peak drug action. For example, an acute injection of a low dose of d-amphetamine which ordinarily produces a small effect on locomotor activity, will elicit a much larger locomotor response following chronic drug treatment (Segal & Mandell, 1974). Moreover, a moderate dosage of d-amphetamine which produces both locomotor excitation as well as stereotypic behaviors, generates enhanced stereotypies followed by an increase in locomotor activity upon repeated exposure to the drug (Segal, 1975).

Recently, several investigators have suggested that the effects of chronic amphetamine treatment on locomotor activity may depend on situational variables, and in fact, may come under stimulus control (Rech, Tilson & Marquis, 1975; Tilson & Rech, 1973). In particular, the enhanced locomotor activity observed following long-term amphetamine administration may result from the conditioning of the locomotor excitatory effects of d-amphetamine to the neutral stimuli of

the apparatus which are present after drug treatment (Rech et al., 1975). Although conditioning factors may be involved in the enhanced response to d-amphetamine following prolonged exposure to the drug, such factors are not considered sufficient to account completely for the behavioral effects of chronic amphetamine treatment. Specifically, when animals were housed in the apparatus 2 weeks prior to the initiation of the experiment, as well as throughout the duration of the experiment, thus minimizing the possibility of conditioning of the drug effects to the novel stimuli of the apparatus, dramatic increases in locomotor activity were observed following chronic drug treatment (Segal, 1975).

The data presented thus far indicate that chronic d-amphetamine treatment elicits differential effects depending on the behavior under consideration. That is, behaviors such as amphetamine-induced perseveration, as well as the facilitative effects of amphetamine on ICSS undergo a physiological tolerance, whereas the stereotypic and locomotor response to amphetamine is enhanced following chronic exposure to the drug. The possibility exists that the neurochemical concomitants of prolonged amphetamine treatment may be responsible for the differential effects on behavior. Specifically, where a physiological tolerance has been observed to develop, these behaviors appear to be influenced by noradrenergic manipulations. In contrast, those behaviors which are augmented following chronic amphetamine treatment are primarily mediated by dopamine.

Several neurochemical models have been posited to account for the differential behavioral effects of long-term amphetamine treatment. For example, attempts have been made to relate the tolerance observed following chronic drug exposure to the formation of p-hydroxynorephedrine in both central and peripheral noradrenergic neurons. However, this line of investigation has met with little success. Pretreatment with the hydroxylated metabolite antagonized the hyperthermic effects of d-amphetamine (Brodie et al., 1970; Lewander, 1971a). Somewhat surprisingly, however, this phenomenon is sex dependent. That is, p-hydroxynorephedrine will protect against the hyperthermic effect among male but not among female rats, although both sexes show tolerance to chronic d-amphetamine administration (Lewander, 1971a; Sever, Caldwell & Williams, 1974).

Schmitt and Schmitt (1970) reported that pretreatment with p-hydroxynorephedrine abolished the amphetamine-induced increase in blood pressure in pithed rats. Using another technique, however, Freeman and Sulser (1975) suggested that p-hydroxynorephedrine is not involved in the tolerance to the cardiovascular effects of amphetamine. Specifically, imipramine-like antidepressants have been shown to be potent inhibitors of aromatic hydroxylation at dosages that do not affect neuronal uptake mechanisms (Freeman & Sulser, 1972). Although both iprinodole and desimipramine are potent in vivo inhibitors of the aromatic hydroxylation of amphetamine, only the latter abolished the amphetamine-induced increase in blood pressure (Freeman & Sulser, 1975).

When other behaviors are considered, it appears that p-hydroxynorephedrine is not involved in the development of tolerance. For example, tolerance to the anorexigenic effects of amphetamine persist for up to 16 days following the last injection of d-amphetamine, a time when norepinephrine levels are normalized (Gotestam & Lewander, 1975). Moreover, pretreatment with p-hydroxyamphetamine which is β -hydroxylated into p-hydroxynorephedrine, both in the central and peripheral nervous system (Axelrod, 1954), does not alter d-amphetamine induced anorexia (Lewander, 1971a). Further to this point, tolerance is observed to develop to the anorexigenic effects of d-amphetamine, as well as to the anorexigenic effects of l-amphetamine; the latter is not converted to p-hydroxynorephedrine but still produces a depletion in NE levels (Lewander, 1971d, 1974). As would be predicted from these data, symmetrical cross-tolerance between the isomers was observed (Lewander, 1974).

In addition to p-hydroxynorephedrine, several alternative neurochemical substances (e.g., octopamine) have been implicated as possible false neurotransmitters which may accumulate at the noradrenergic site, and diminish the amount of norepinephrine released (cf., Kostopoulos & Yarbrough, 1975; see also Kopin, 1968). However, in view of the paucity of data available concerning these possible false transmitters, conclusions regarding their involvement in the development of tolerance after chronic amphetamine administration cannot be drawn at this time.

Recent studies have presented evidence demonstrating the existence of dopamine and norepinephrine sensitive cyclic 3, 5-adenosine monophosphate (cyclic AMP); which may act as a second messenger at DA and NE synapses in the mammalian brain (Goldstein, Anagnoste, Battista, Miyamoto & Fuxe, 1974; Martes, Baudry & Schwartz, 1975). It has been demonstrated that NE induced an accumulation of cyclic AMP from cortical slices in vitro. Following chronic d-amphetamine treatment, however, the NE-induced accumulation of cyclic AMP is decreased, whereas DA and 5-HT-induced accumulation of cyclic AMP remains unaltered (Martes et al., 1975). Thus, the possibility must be entertained that the observed physiological tolerance following long-term amphetamine treatment may occur at the level of the noradrenergic receptor.

Turning to the augmentation of dopamine-mediated behaviors (i.e., locomotor activity and stereotypy) following chronic amphetamine administration, Segal (1975) suggested that an increase in dopamine synthesis may result in order to compensate for the reduction in DA biosynthesis which occurs following prolonged drug treatment. Consequently, the release of newly formed DA by d-amphetamine may evoke an enhanced behavioral response. Another possibility which must be considered is that the selective augmentation of motor behavior associated with long-term amphetamine exposure reflects a change in dopaminergic receptor sensitivity. In agreement with such a notion it was found that low doses of apomorphine which had no effect on behavior, elicited a strong stereotypic response following chronic amphetamine treatment (Klawans, Crosset & Dana, 1975).

Purposes of the Present Investigation

Summarizing, the data presented thus far suggest that the catecholamines play a major role in subserving the effects of both acute and chronic amphetamine administration. Moreover, the available data suggest that those behaviors which are influenced primarily by noradrenergic manipulations undergo tolerance, whereas those behaviors mediated by dopamine are not attenuated or are enhanced following chronic amphetamine treatment. It was suggested that the prolonged depletion of norepinephrine following long-term amphetamine treatment may be responsible for the observed behavioral tolerance, whereas alterations in dopamine synthesis or dopamine receptor supersensitivity may be involved in the observed augmentation of dopamine-mediated behaviors. Clearly, more research is necessary from both the behavioral and neurochemical vantage in order to clarify further the role of DA and NE in modulating the behavioral effects of chronic amphetamine administration. Accordingly, in the present investigation a series of interrelated behaviors were evaluated in order to: a) document systematically the effects of amphetamine on several simple behavioral tasks; b) evaluate the behavioral concomitants of these phenomena, i.e., might a particular behavioral effect of the drug be a secondary consequence of some other amphetamine-induced behavior; c) determine, via pharmacological analysis, the neurochemical mechanisms which subserve these behaviors, and d) assess the mechanisms, both behavioral and physiological, which may be involved in the development of tolerance to amphetamine.

It will be recalled that evaluation of the mechanisms which subserve amphetamine tolerance are complicated not only by the fact that subtle procedural details influence the response to the drug, e.g., whether or not the drug is consistently administered in the presence of certain stimuli (Carlton & Wolgin, 1971; Tilson & Rech, 1973), but also by the fact that d-amphetamine elicits a variety of neurochemical changes (Carlsson, 1970; Welch & Welch, 1970). Some of these neurochemical changes may be more influential in the mediation of one behavior relative to another, while the converse may be true of other drug-induced neurochemical modifications (Carlsson, 1970; Creese & Iverson, 1974, 1975). As such, the possibility should be entertained that tolerance effects may be restricted to a limited subset of neurochemical changes produced by the drug, and consequently is reflected in only some of the behaviors ordinarily elicited by this treatment.

The fact that amphetamine elicits several different behavioral effects is not necessarily a drawback in assessing behavioral/neurochemical relations. Indeed, coupled with the neurochemical changes induced by d-amphetamine, the varied behavioral effects of the drug may provide a potentially useful way in which to determine the mechanisms which are involved in the tolerance. Specifically, by simultaneously or successively examining several behaviors it may be possible to draw fracture lines between the biochemical and behavioral effects of the drug treatment. Furthermore, such a procedure may be of value in differentiating between those factors which play a primary role in the development of tolerance to amphetamine and those which exert only a secondary effect (Kokkinidis et al., 1976).

Although a fairly broad range of behaviors were considered in the present investigation, it should be re-emphasized, lest there be any misunderstanding, that these behaviors were not selected in a shot-gun fashion. Rather, the behaviors were chosen on the basis that they are simple responses in the organism's repertoire, and further, their neurochemical substrates have undergone extensive evaluation both in this and other laboratories. Moreover, these behaviors are related to one another in several respects, as previously described and are, for the most part, behaviors which are often used in psychopharmacological analyses.

The present series of experiments dealt specifically with three issues. First, a number of amphetamine-induced behaviors (locomotor activity, stereotypy, rotational behavior, perseveration, startle reflex, and reactivity) were evaluated in order to elucidate the role played by DA and NE. Second, the effects of chronic amphetamine treatment on these behaviors were considered in order to determine whether the occurrence of tolerance coincided with NE mediation and conversely whether the absence of tolerance or reverse tolerance would occur to those behaviors mediated by dopamine. Finally, an attempt was made to assess several mechanisms which might underlie the development of tolerance.

ROTATIONAL BEHAVIOR

It will be recalled (see General Introduction) that systemically administered amphetamine produces a side preference in a two lever bar-pressing task (Glick, 1973; Glick et al., 1975; Glick & Jerussi, 1974) as well as consistent unidirectional turning in a rotometer or circular alleyway (Jerussi & Glick, 1974, 1976; Kokkinidis & Anisman, 1977). On the basis of behavioral and biochemical data the suggestion was made that rotational behavior following systemic injection of d-amphetamine is comparable to that observed after direct injections of dopaminergic agonists to the nigro-neostriatal pathway (Jerussi & Glick, 1974, 1976; Ungerstedt et al., 1969). Presumably, there exists a bilateral imbalance of dopaminergic activity in the nigro-neostriatal system (Glick et al., 1974; Zimmerberg et al., 1974) which is exacerbated following treatment with d-amphetamine. This imbalance, in turn, results in rotation contralateral to the side of greater stimulation (Glick et al., 1974; Jerussi & Glick, 1976).

As an alternative to this hypothesis, Kokkinidis and Anisman (1977) have argued that the rotational behavior following systemic amphetamine treatment may be an artifact of a drug-induced perseverative tendency. More specifically, as suggested by Robbins (1975), these authors have argued that amphetamine augments unconditioned responses high in the organism's repertoire. In fact, it was shown that although intraperitoneal and intraventricular amphetamine administration led

to rotational behavior in a circular alleyway, the effects of the routes of administration could be differentiated in a free-running Y-maze exploratory task. Whereas, intraventricularly treated animals exhibited consistent unidirectional turns at the ends and the choice part of the alley, resulting in consistent entries into the least recently visited arm (e.g., 1, 2, 3, 1, 2, 3), mice which received an intraperitoneal injection, exhibited a radically different response pattern. These mice showed a pronounced perseverative tendency, i.e., they consistently entered two arms of the Y-maze only (e.g., 1, 2, 1, 2, 1, 2). Such a behavioral pattern required consistent alternation of left-right turns at the choice point of the maze. In light of the aforementioned data, the suggestion was made that circling behavior produced by systemic amphetamine administration is not necessarily comparable to that seen after unilateral intraventricular injection of d-amphetamine (Kokkinidis & Anisman, 1977). Whereas circling seen after intraventricular injection is likely a reflection of a turn bias, rotational behavior following systemically administered amphetamine should more readily be considered as a reflection of drug-induced stimulus perseveration.

Experiment 1

Experiment 1 represents an attempt to evaluate further the factors which influence rotational behavior after systemic amphetamine administration. In particular, it was previously shown that although d-amphetamine-induced circling was accompanied by an increase in locomotor activity, the frequency of direction changes was either unaffected or reduced. In effect, once animals selected a direction they persisted in running in this direction. When animals changed

direction and ran in a "non-preferred" direction the number of rotations exhibited were few. The apparent relationship between circling behavior and direction changes was examined in a more refined manner in Experiment 1.

Method

Subjects

A total of 40 naive male Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. Mice were housed in groups of 4-6 in standard polypropylene cages, and permitted free access to food and water. Subjects were approximately 60 days of age at the time of testing.

Apparatus

The circular alleyways used to measure rotational behavior were made up of three identical Plexiglas chambers 27.0 cm in diameter and 10.0 cm high. The alleyway (7.5 cm wide) was divided into three quadrants of equal size by infrared photo-electric relay units placed 1.0 cm above the Plexiglas floor. The sequence (order) of photocell crossings was recorded, thus permitting the evaluation of activity (total photocell crossings). In addition, the direction of responding (i.e., consecutive photocell crossings in sequence), as well as the frequency of direction changes were recorded.

Procedure

Mice ($n = 8/\text{cell}$) received intraperitoneal (i.p.) injections of either saline, 1.0, 3.0, 5.0 or 10.0 mg/kg of d-amphetamine sulfate (salt weight) in a volume of 10.0 ml/kg. Fifteen minutes following injection mice were placed in the circular alleyway and circling behavior was evaluated over a 30 min period.

Results

The proportion of rotations were calculated on the basis of rotation to the dominant side/total number of rotations. The direction to which more turns were made was considered dominant. Thus, if a subject made more responses to the right, then the proportion of rotations was calculated by dividing the number of turns to the right by the total number of turns (right turns + left turns).

The mean proportion of individual rotations was analyzed through analysis of variance and Newman-Keuls multiple comparisons ($\alpha = .05$). In addition, separate analyses of variance were conducted on the mean number of direction changes, as well as on the mean number of photocell crossings (locomotor activity).

Consistent with previous reports (Jerussi & Glick, 1974, 1976; Kokkinidis & Anisman, 1977), treatment with d-amphetamine resulted in a marked rotational bias, $F(4, 35) = 4.56, p < .005$, (see Figure 7, Panel A). Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that mice assigned to the 5.0 and 10.0 mg/kg drug groups exhibited a significantly higher frequency of rotational responses than did saline treated animals. Neither the 1.0 nor the 3.0 mg/kg dosages significantly produced rotational behavior.

Figure 7 Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of drug treatment (saline or 1.0, 3.0, 5.0 and 10.0 mg/kg of d-amphetamine).

2

MEAN CIRCLING

A

.70
.60

MEAN DIRECTION CHANGES

B

100
75
50

MEAN PHOTOCELL CROSSINGS

C

800
600
400
200

SAL 1.0 3.0 5.0 10.0
d-AMPHETAMINE (mg/kg)

When the number of direction changes was considered, a significant main effect of Drug Treatment was observed, $F(4, 35) = 3.38$, $p < .02$. However, the dose response curve did not parallel that observed with respect to circling behavior (see Figure 7, Panel B). Specifically, although the two higher dosages of amphetamine elicited circling behavior, the number of direction changes were unaffected. Moreover, 3.0 mg/kg of d-amphetamine which had only a small effect on rotational behavior, significantly increased the number of direction changes relative to saline controls.

Finally, the analysis of variance of locomotor activity yielded a significant drug effect, $F(4, 35) = 21.83$, $p < .001$. Newman-Keuls multiple comparisons revealed that the number of photocell crossings were considerably higher among mice treated with either 3.0 or 5.0 mg/kg of the drug than among the remaining groups (see Figure 7, Panel C).

Taken together, it appears that amphetamine will elicit circling behavior and this effect was independent of changes in motor activity. To be more explicit, whereas both the 3.0 and 5.0 mg/kg dosages of the drug had comparable effects on locomotor activity, only the latter dosage produced a marked circling tendency. In the same vein, the 10.0 mg/kg dosage of d-amphetamine elicited rotational behavior, but had only a small non-significant effect on locomotor activity.

Experiment 2

As indicated earlier, it has been argued that rotational behavior induced by d-amphetamine is a consequence of a bilateral asymmetry of dopamine activity in the nigro-neostriatal pathway (Glick et al., 1974; Jerussi & Glick, 1974). In accordance with such a view, Jerussi and Glick (1976) demonstrated that dopamine receptor blockade and inhibition of tyrosine hydroxylase antagonized the amphetamine-induced rotational bias, whereas dopamine- β -hydroxylase (DBH) inhibition was ineffective in this respect. However, in the case of the former two agents the decline in circling may have been an artifact of a decrease in locomotor activity; whereas in the case of dopamine- β -hydroxylase inhibition the occurrence of circling may have been a consequence of the persistent high levels of locomotor activity.

In contradistinction to the circling data Anisman and Kokkinidis (1975) observed that amphetamine-induced perseveration, which is thought to be responsible for the rotational behavior, was modified by dopamine- β -hydroxylase inhibition. In light of the aforementioned data and the biases inherent in the Jerussi and Glick (1976) report, Experiment 2 was carried out to determine whether the effects of amphetamine in a circling task were modifiable exclusively by DA manipulations or whether, in fact, modification of NE might also influence this behavior. Moreover, given variations in circling behavior following dopamine- β -hydroxylase inhibition it needs to be determined whether variations in the frequency of direction changes would be observed.

Method

Subjects and Apparatus

A total of 80 naive male Swiss-Webster mice served as subjects in Experiment 2. All particulars concerning the subjects and apparatus were identical to those specified in the previous experiment.

Procedure

Mice received i.p. injections of either α -methyl-para-tyrosine methylester (α -MpT, 125 or 250 mg/kg), bis-(4-methyl-1-homo-piperazinylthiocarbonyl) disulphide (FLA-63, 20 or 40 mg/kg) or saline. Three hrs after initial drug treatment subjects were sub-divided ($n = 10/\text{cell}$) such that half the animals received a second injection of d-amphetamine sulfate (5.0 mg/kg), while the remaining animals received saline. Testing commenced 15 min after the second injection and was identical to that described in Experiment 1. All drugs were injected in a volume of 10.0 ml/kg. α -MpT was dissolved in saline while FLA-63 was put into solution by adding the drug to hot saline containing 2 mg/ml of acetamide (acetic acid amide).

In addition to the behavioral experiment, three separate groups of mice ($n = 6/\text{cell}$) were injected with either saline, α -MpT (250 mg/kg) or FLA-63 (40 mg/kg) in order to determine the effects of these drugs on whole brain levels of norepinephrine, dopamine and serotonin. Three hrs after injection mice were decapitated and brains quickly removed and placed in liquid nitrogen. Amine levels were determined using a modification of the hydroxindole method (Laverty & Taylor, 1968; Maickel et al., 1968).

Results

Analysis of variance of the biochemical assay data revealed significant Drug effects for both dopamine, $F(2, 15) = 76.73$, $p < .01$ and norepinephrine, $F(2, 15) = 3.88$, $p < .05$. Newman-Keuls multiple comparisons indicated that α -MpT significantly reduced both dopamine and norepinephrine, whereas FLA-63 was effective in reducing only the latter amine. In contrast to the catecholamines whole brain serotonin levels were unaffected after treatment with either α -MpT or FLA-63 (see Table 1).

Analysis of variance of the circling behavior yielded a significant Drug Pretreatment x Amphetamine treatment interaction, $F(4, 70) = 4.10$, $p < .05$. Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that among saline pretreated mice d-amphetamine elicited marked rotational behavior. In the absence of d-amphetamine treatment, α -MpT and FLA-63 did not affect circling behavior; however, in contrast to the report of Jerussi and Glick (1976), both these enzyme inhibitors effectively antagonized the circling behavior otherwise engendered by d-amphetamine (see Figure 8). The fact that FLA-63 was effective in modifying circling behavior suggests that NE may play an important role in mediating the amphetamine-induced rotation.

The relationship between circling behavior and direction changes observed previously, was evident in this experiment as well. Specifically, the analysis of variance indicated a significant Drug Pretreatment x Amphetamine treatment interaction, $F(4, 70) = 4.18$, $p < .05$. Multiple comparisons revealed that d-amphetamine reduced the frequency of direction changes, and this effect was antagonized by both α -MpT and FLA-63.

Table 1

Summary of Assays for Whole Brain Levels of DA, NE and 5-HT ($\mu\text{g/gm}$), 3 Hr
After Injection of Saline, α -MPT (250 mg/kg) or FLA-63 (40 mg/kg)

Treatment	DA concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.	NE concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.	5-HT concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.
Saline	$2.130 \pm .179$	--	$.924 \pm .183$	--	$.193 \pm .017$	--
α -MPT	$.982 \pm .173^*$	46.08 ± 8.10	$.507 \pm .051^*$	54.80 ± 5.56	$.214 \pm .010$	114.50 ± 5.99
FLA-63	$2.419 \pm .205$	113.54 ± 9.61	$.545 \pm .971^*$	53.58 ± 9.29	$.219 \pm .019$	113.37 ± 9.80

* significantly different from saline values at $p < .05$ level

Figure 8

Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of treatment with either saline, α -MpT (125 or 250 mg/kg) or FLA-63 (20 or 40 mg/kg) 3 hr prior to administration of 5.0 mg/kg of d-amphetamine or saline.

Finally, analysis of the locomotor activity data suggested that the effects of, α -MpT and FLA-63 on drug-induced rotational behavior and direction changes were not a consequence of changes in locomotor activity. Analysis of variance of the photocell crossings yielded a significant Drug Pretreatment x Test Treatment interaction, $F(4, 70) = 3.31, p < .05$. In contrast to amphetamine-induced rotational behavior, which was antagonized by either α -MpT or FLA-63 Newman-Keuls multiple comparisons ($\alpha = .05$) (see Figure 8, Panel C) revealed that pretreatment with α -MpT antagonized the amphetamine-induced locomotor excitation, whereas FLA-63 was ineffective in this respect (see also Carlsson, 1970; Groves & Rebec, 1976; Hollister *et al.*, 1974).

Experiment 3

The results of Experiment 2 indicate that rotational behavior induced by systemic d-amphetamine treatment is mediated, at least in part, by noradrenergic mechanisms. This fact alone does not suggest that the circling behavior is a reflection of a perseverative tendency, but it does question the notion that the behavior is a consequence of a DA imbalance in the two hemispheres. Experiment 3 was carried out to determine whether the circling behavior is modifiable by prior habituation to the apparatus, as is the case in the Y-maze perseverative situation. In the Y-maze task the perseveration tendency induced by d-amphetamine is limited by the "natural tendency" to explore, i.e., as reflected by high levels of alternation. Pre-exposing animals to the apparatus

reduces the alternation tendency, thereby maximizing the expression of the perseverative behavior (Kokkinidis & Anisman, 1976a). The finding that apparatus pre-exposure influences circling behavior could not, of course, be taken as evidence that circling and perseveration are one and the same; however, it would suggest that the behaviors induced by amphetamine in the two situations have common features other than that of potential NE involvement.

Method

Subjects and Apparatus

Forty naive male Swiss-Webster mice served as subjects. All subject and apparatus specifications were identical to those described in Experiment 1.

Procedure

Half the mice were placed in the circular runway for a 30 min period, while the remaining mice spent an equivalent amount of time in a holding cage. Following the pre-exposure period mice ($n = 10/\text{cell}$) received i.p. injections of either d-amphetamine sulfate (3.0 mg/kg) or saline. The dosage of d-amphetamine, it will be noted, was reduced from Experiment 2 in order to avoid a ceiling effect from precluding potential performance differences engendered by apparatus pre-exposure. Fifteen min after drug injection mice were tested in the circular apparatus for a 30 min period as described in Experiment 1.

Results

The mean proportion of circling responses, the mean number of direction changes, as well as the mean number of photocell crossings as a function of the pre-exposure and drug treatments are shown in Figure 9. Analysis of variance of the circling scores yielded only a significant Drug Treatment main effect, $F(1, 36) = 26.08, p < .001$. Although the Pre-exposure x Drug Treatment interaction did not reach statistical significance, $F(1, 36) = 2.69, p < .10$, Newman-Keuls multiple comparisons ($\alpha = .05$) were carried out on the simple effects since an a priori prediction had been made concerning the interaction (Winer, 1962). These comparisons revealed that treatment with d-amphetamine in the absence of pre-exposure increased the proportion of circling responses relative to the saline controls (Figure 9, Panel A). This finding is somewhat inconsistent with that observed in Experiment 1, in that this dosage was not previously found to produce significant levels of rotational behavior. It should be noted, however, that the magnitude of the drug effect is comparable between experiments ($\bar{x}$ rotations = .616 in Experiment 1 and .649 in Experiment 3). Among mice tested with d-amphetamine, prior habituation to the apparatus significantly enhanced the proportion of rotational responses relative to naive mice tested with the drug (see Figure 9, Panel A). In fact, these animals behaved much like those which received 5.0 mg/kg of the drug in Experiment 1.

Figure 9 Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings after administration of 3.0 mg/kg of d-amphetamine to naive mice or to mice previously exposed to the apparatus.

Consistent with the results of the previous experiment, 3.0 mg/kg of d-amphetamine substantially increased the number of direction changes, $F(1, 36) = 38.17, p < .001$. In contrast to the circling data, direction changes were decreased by apparatus pre-exposure, $F(1, 36) = 13.22, p < .01$. The fact that prior habituation to the apparatus reduced the number of direction changes and enhanced rotational behavior suggests that an inverse relationship exists between the propensity to circle and the tendency to change directions. More importantly, these data indicate that stimulus factors may be involved in the mediation of rotational behavior. In particular, behavior in the rotometer is thought to reflect the perseverative effects induced by amphetamine, coupled with a natural exploratory tendency. The exploratory tendency is presumably manifested as frequent direction changes (see also Kokkinidis & Anisman, 1977). Accordingly, after habituation to the apparatus cues the tendency to alternate directions is minimized, thereby permitting fuller expression of the drug-induced perseveration. It could be argued that upon pre-exposure to the stimulus array of the apparatus, biases pertaining to response factors are modified, resulting in the tendency to make consistent unidirectional turns. However, when the behavior in the circling and Y-maze tasks are considered jointly, it appears that pre-exposure modifies performance by affecting position cues, i.e., stimulus factors, as opposed to response feedback (turn preferences) (Kokkinidis & Anisman, 1976a, b). After all, pre-exposure to the Y-maze enhanced perseveration in this task, which entails consistent left-right turns rather than unidirectional turns seen in the circular alley.

Finally, as observed in Experiment 1, circling behavior is not an artifact of the locomotor effects of the drug. Specifically, although d-amphetamine increased the number of photocell crossings, $F(1, 36) = 109.97$, $p < .001$, pre-exposure to the apparatus resulted in negligible effects on drug-induced locomotor activity (see Figure 9, Panel C).

Experiment 4

From the vantage of both behavioral and pharmacological studies there appears to exist a similarity between amphetamine-induced circling behavior and stimulus perseveration. Specifically, both behaviors are modified readily by either prior habituation to the apparatus or by indirect pharmacological manipulation of noradrenergic activity. The purpose of Experiment 4 was to evaluate the effects of chronic amphetamine administration on drug-induced rotational behavior. As indicated earlier, behaviors mediated by DA do not undergo tolerance, and in fact, may be exacerbated with repeated exposure to the drug (Kokkinidis, et al., 1976; Lewander, 1971; Rech et al., 1975; Segal & Mandell, 1974). In contrast, the effects of the drug on behaviors which involve noradrenergic activity, e.g., stimulus perseveration (Anisman & Kokkinidis, 1975) are attenuated after chronic drug treatment (Kokkinidis et al., 1976). Since amphetamine-induced rotational behavior apparently involves noradrenergic activity and may be a reflection of drug-induced stimulus perseveration, tolerance would be expected to develop with protracted drug treatment.

Method

Subjects and Apparatus

A total of 40 male Swiss-Webster mice served as subjects. All subject and apparatus specifications were identical to those described in the previous experiments, with the exception that mice were housed individually for 1 week prior to the initiation and throughout the course of the experiment.

Procedure

Subjects were randomly assigned to two groups and treated with daily i.p. injections of either saline (10.0 ml/kg) or d-amphetamine sulfate (10.0 mg/kg) for five consecutive days. Previous work in this laboratory revealed that this schedule of chronic drug treatment resulted in tolerance to other amphetamine-induced behaviors (see also Experiments 8, 11 and 12). On test day (day 6) mice were sub-divided ($n = 10/\text{cell}$) such that half of the animals received an i.p. injection of saline, while the remaining animals were injected with 5.0 mg/kg of d-amphetamine. Fifteen min after drug treatment mice were placed in the apparatus and the proportion of rotational responses, the number of direction changes, and the number of photocell crossings were recorded for a 30 min period. Two additional groups of mice ($n = 10/\text{cell}$) were chronically injected with either saline or d-amphetamine (10.0 mg/kg) in order to determine the effects of five daily injections of d-amphetamine on whole brain levels of norepinephrine, dopamine and serotonin. Twenty-four hrs after the last injection mice were decapitated and the brain was quickly removed and placed in liquid nitrogen. Amine levels were determined using a modification of the hydroxyindole method (Laverty & Taylor, 1968; Maickel et al., 1968).

Results

Analysis of variance of the biochemical assay data revealed that chronic amphetamine administration significantly reduced norepinephrine levels by 21.2%, $F(1, 18) = 7.80$, $p < .05$, with no apparent effect on whole brain levels of dopamine or serotonin (see Table 2). Analysis of variance of the rotational responses yielded a significant Chronic Drug Treatment x Test Drug Treatment interaction, $F(1, 36) = 8.27$, $p < .05$. Newman-Keuls multiple comparisons revealed that mice chronically treated with saline and tested with d-amphetamine (5.0 mg/kg) displayed a greater proportion of rotational responses than did mice pretreated and tested with saline (see Figure 10). Although chronic treatment with amphetamine had no effect on behavior when mice were tested with saline, daily exposure to the drug for five consecutive days antagonized the amphetamine-induced circling behavior.

Analysis of variance of the direction changes yielded a Chronic Drug Treatment x Test Drug Treatment interaction which approached statistical significance, $F(1, 36) = 3.50$, $p < .07$. Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that relative to the remaining groups, mice displayed a significant increase in direction changes. These data were consistent with those of Experiment 2 in that treatments which decreased the propensity to circle resulted in an increase of direction changes.

Table 2

Summary of Assays for Whole Brain Levels of DA, NE and 5-HT ($\mu\text{g/gm}$), 24 Hr
After the Last of 5 Daily Injections of Either Saline or d-Amphetamine (10.0 mg/kg)

Treatment	DA concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.	NE concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.	5-HT concentration $\mu\text{g/g} \pm \text{S.E.M.}$	% control concentration S.E.M.
Saline	$1.216 \pm .081$	--	$.891 \pm .061$	--	$.184 \pm .009$	--
d-Amphetamine	$1.142 \pm .087$	97.75 ± 9.77	$.700 \pm .032^*$	78.84 ± 3.68	$.173 \pm .008$	93.88 ± 4.9

* significantly different from saline values at $p < .05$ level

Figure 10 Mean ($\pm$ S.E.M.) proportion of circling responses, direction changes, and photocell crossings as a function of chronic and acute d-amphetamine treatment. The upper lettering on the abscissa indicates the 5 day injection regimen and the lower lettering the injection on test day.

Although tolerance was observed to develop to amphetamine-induced rotational behavior, tolerance to the locomotor effects of the drug was not evidenced (see Figure 10, Panel C). As observed in the previous experiments treatment with d-amphetamine on test day increased locomotor activity, $F(1, 36) = 79.89$, $p < .001$. Unlike circling behavior, this was the case regardless of the treatment administered during the chronic phase. Thus, it appears that the reduction in the proportion of rotational responses as well as the increase in the number of direction changes following prolonged exposure to d-amphetamine were unrelated to drug-induced changes in ambulation.

Discussion (Experiments 1-4)

Consistent with previous work from this, as well as from other laboratories (Jerussi & Glick, 1974; Kokkinidis & Anisman, 1977), systemically administered d-amphetamine was observed to elicit circling behavior. Contrary to earlier reports, however, the results of the present investigation, together with that of Kokkinidis and Anisman (1977), suggest that the observed rotational behavior may involve a noradrenergic component. More specifically, reduction of norepinephrine via dopamine- β -hydroxylase inhibition successfully antagonized the amphetamine-induced circling behavior. Moreover, it was observed that the proportion of circling responses and the number of direction changes were inversely related to one another. That is, the reversal of amphetamine-induced rotational behavior by α -MPT and FLA-63 was accompanied by an increase in the frequency of direction changes. These data certainly do not imply that a hemispheric imbalance of dopaminergic activity is not involved in the rotational behavior. However, they do provide evidence in favor of a role for norepinephrine in this respect.

The effects of amphetamine on circling behavior paralleled closely those seen in other behaviors which involve a noradrenergic component. For example, amphetamine-induced stimulus perseveration, which was antagonized by FLA-63 (Anisman & Kokkinidis, 1975), was also reduced after chronic exposure to amphetamine (Kokkinidis et al., 1976). Inasmuch as genuine circling behavior is thought to be subserved by the same neurochemical systems which subserve locomotor activity and stereotypy, it would have been expected that tolerance would not develop to the circling response as was the case for locomotor activity. Given the parallels between circling behavior and stimulus perseveration elicited by d-amphetamine, viz., both appear to involve noradrenergic activity, are modifiable by pre-exposure, and undergo tolerance, the possibility should be entertained that circling after systemic injection of amphetamine is a reflection of a perseverative tendency induced by the drug. As such, it may be the case, as indicated by Jerussi and Glick (1974), that the initial direction selected by the animal is determined by an asymmetrical imbalance of nigro-neostriatal dopaminergic activity. However, once locomotor activity in a particular direction is initiated, it persists owing to the perseveration invoked by the drug (cf., Kokkinidis & Anisman, 1977). The fact that tolerance was apparent to the drug-induced rotational behavior argues in favor of the notion that circling after systemic amphetamine treatment is distinct from those behaviors which are thought to involve the nigro-neostriatal dopamine system, e.g., locomotor activity, stereotypy. In addition, these data lend support to the notion (Kokkinidis et al., 1976) that tolerance to amphetamine occurs primarily to those behaviors which involve a noradrenergic component.

STARTLE RESPONSE

As described in the General Introduction, acute amphetamine administration has been reported to produce an enhanced startle reaction to auditory stimuli (Davis et al., 1975). On the basis of two sources of evidence it was suggested that this effect is mediated by dopamine activity. Reiterating, the first deals with the relative potency of the amphetamine isomers. Specifically, it was suggested that since the d-isomer was four to five times more potent than the l-isomer in augmenting startle, dopaminergic mechanisms were involved in subserving the effects of the drug (Davis et al., 1975). However, in view of the contradictory biochemical findings concerning the effects of the isomers on reuptake of norepinephrine and dopamine (Coyle & Snyder, 1969; Thornburg & Moore, 1973a), it is premature to evaluate any behavioral or neurochemical relations on the basis of the potencies of d- and l-amphetamine (cf., Bunney et al., 1975). The second source of evidence implicating dopaminergic activity in subserving the acoustic startle response was based on the finding that the DA receptor stimulant, apomorphine, enhanced startle amplitude, while the DA receptor blocker, haloperidol, antagonized this effect (Davis & Aghajanian, 1976).

The role of norepinephrine in mediating the startle reaction is not entirely clear. It will be recalled, for example, that there is some evidence which indicates that norepinephrine may exert an inhibitory influence on the startle reflex. Specifically, it was found that the noradrenergic receptor stimulant,

clonidine, attenuated the startle amplitude of reserpinized animals (Fechter, 1974a). It is not entirely certain, however, whether the effects of clonidine on the startle response are the result of stimulation of central epinephrine, or norepinephrine receptors (cf., Davis et al., 1977). In contradistinction to the data derived from the clonidine experiment, inhibition of noradrenergic reuptake produced an increase in startle amplitude (Davis et al., 1977), whereas lesions of the locus coeruleus depressed the startle reaction (Geyer et al., 1976), suggesting that NE exerts an excitatory influence on the startle reaction. If, in fact, norepinephrine plays a role in the amphetamine-induced potentiation of startle amplitude, then dopamine- β -hydroxylase inhibition should successfully antagonize this behavioral effect. Moreover, it might be expected that tolerance would develop with protracted drug treatment as is the case in other NE mediated behaviors. In contrast, if the effect of amphetamine on the startle reaction is subserved primarily by dopaminergic activity, then tyrosine hydroxylase inhibition should antagonize this effect, whereas dopamine- β -hydroxylase inhibition should be ineffective in this respect. Furthermore, the behavior should not be subject to diminution with repeated amphetamine treatment.

Experiment 5

At the behavioral level several possibilities exist which may account for the facilitation of startle amplitude following amphetamine treatment (e.g., the drug influences startle threshold or alternatively interferes with habituation).

Davis et al. (1975) have suggested that the observed augmentation of startle amplitude in the rat is the result of enhanced sensitization produced by drug treatment. Experiment 5 was carried out to determine whether d-amphetamine would augment startle amplitude, and further, to assess whether the extent of the increase would become progressively greater with successive stimulus presentations as reported by Davis et al. (1975).

Method

Subjects

A total of 50 naive male Swiss-Webster mice approximately 60 days of age and weighing between 32 and 36 g at the time of testing, served as subjects. All specifications concerning subjects were identical to that described in Experiment 1.

Apparatus

The apparatus, modified from that described by Remington and Anisman (1976), consisted of a clear Plexiglas cylinder 0.60 cm thick, 20.0 cm in diameter, and 11.50 cm high. The cylinder was situated on an 8-watt speaker measuring 7 cm in diameter, which in turn was covered by a 0.012 cm mylar sheath. The speaker was sealed between two O-rings attached to the metal frame of the speaker. Movement on the mylar sheath and the resulting fluctuation in air pressure between the taut sheath and speaker produced deflections in the speaker cone,

which in turn varied the electromagnetic flux. The speaker was connected to a Beckman type RM dynograph (A-C coupler, type 9806A; Amplifier, type 482; Rectifier, type 9852A), which was calibrated such that a 30-40 g mouse walking on the mylar did not produce a deflection of the rectifier pen, but was sensitive to a startle reaction. Consequently, levels of locomotor activity did not influence the recording of the startle response. The startle stimulus was a 2-sec, 105 dB noise produced from a buzzer (BU 24; 50-60 Hz; 4.6 A) situated in the centre of the clear Plexiglas roof. The apparatus was housed in an illuminated room with a background noise of 75 dB.

Procedure

Independent groups of mice ($n=10/\text{cell}$) received an i.p. injection of either saline or α -amphetamine sulfate (1.0, 3.0, 5.0, 10.0 mg/kg salt weight). All drugs were injected in a volume of 10 ml/kg. Ten min following injection mice were placed in the apparatus and were allowed to explore freely for a 5 min period. Following the adaptation period mice were exposed to 10 buzzer presentations with an interstimulus interval of 1 min. The amplitude of the startle response was recorded in mm on standard Beckman chart paper.

Results

The mean startle amplitude over 10 buzzer presentations for each drug dosage is depicted in Figure 11. Analysis of variance of the startle scores yielded significant main effects for Drug Dosage, $F(4, 45)=8.81$, $p<.001$, and Buzzer Presentation, $F(9, 405)=2.72$, $p<.005$. Consistent with previous

findings (Davis et al., 1975), Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that the three higher dosages of d-amphetamine (3.0, 5.0 and 10.0 mg/kg) enhanced startle amplitude relative to saline treated mice. In contrast to these reports, however, startle augmentation with repeated stimulus presentations (i.e., sensitization) was not observed. In fact, in all groups a uniform decline in startle amplitude was seen over successive stimulus presentations. One possible explanation for these discordant findings involves procedural differences between the experiments. That is, in the Davis et al. (1975) study, testing was initiated immediately following drug injection, whereas in the present experiment testing commenced 15 min after drug administration. The fact that in the Davis et al. (1975; see also Davis and Aghajanian, 1976) experiment startle amplitude was maximal 10-20 min after drug administration, a period that coincides with peak drug effect insofar as several behaviors are concerned (Kokkinidis & Anisman, 1976a; Segal, 1975), leads to the possibility that the drug-induced potentiation of startle amplitude following repeated tone presentation may represent the development of peak drug effects, and not sensitization per se. This possibility was examined in Experiment 6.

Experiment 6

Method

Sixteen naive male Swiss-Webster mice served as subjects. The apparatus and procedural specifications were identical to those described in Experiment 5, with the exception that testing was initiated immediately after injection of either saline or d-amphetamine sulfate (5.0 mg/kg) ($n = 8/\text{cell}$), and the number of buzzer presentations was increased from 10 to 25.

Figure 11 Mean startle amplitude ($\pm$ S.E.M.) as a function of drug treatment (saline or 1.0, 3.0, 5.0 and 10.0 mg/kg of d-amphetamine).

d-AMPHETAMINE mg/kg

○—○ SALINE

□—□ 1.0

●—● 3.0

■—■ 5.0

▲—▲ 10.0

MEAN STARTLE AMPLITUDE (mm)

STIMULUS PRESENTATION

1 2 3 4 5 6 7 8 9 10

Results

Figure 12 shows the mean startle amplitude as a function of drug treatment. Analysis of variance of the startle data yielded a significant interaction between Drug Treatment and Buzzer Presentation, $F(24, 336) = 3.08$, $p < .001$. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in this interaction revealed that the startle amplitude among mice treated with d-amphetamine was significantly enhanced relative to that of the saline controls. Consistent with the data reported by Davis et al. (1975) the amphetamine-induced potentiation of startle was not evident following the first buzzer presentation, but became apparent only after several stimulus presentations (see Figure 12). The finding that the startle response was potentiated with repeated stimulus presentations when testing occurred immediately after drug injection, but not when testing was carried out 15 min after injection (see Experiment 5), argues against an explanation based on drug-induced sensitization. Rather, these data suggest that the increase in startle amplitude with successive stimulus presentations is a consequence of the development of peak drug effects.

Experiment 7

The purpose of Experiment 7 was to evaluate further the role played by norepinephrine and dopamine in modulating the effects of amphetamine on the startle response. It was previously observed that inhibition of tyrosine hydroxylase, by α -MPT, effectively antagonized the effects of amphetamine on the acoustic startle reflex (Davis et al., 1975). If noradrenergic activity is involved in the amphetamine-induced potentiation of startle amplitude, then inhibition of dopamine- β -hydroxylase activity via FLA-63 should similarly attenuate the effects of the drug on the startle reflex.

Figure 12 Mean startle amplitude over 25 stimulus presentations after
 injection of either saline or 5.0 mg/kg of d-amphetamine.
 Mice were tested immediately after injection.

✓ Method

Subjects and Apparatus

A total of 108 male Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. All subject and apparatus specifications were identical to those described in Experiment 5.

Procedure

Mice received an i.p. injection of either saline, α -MpT (250 mg/kg in a 25 mg/ml solution of saline), or FLA-63 (40 mg/kg in a 4 mg/ml solution). Three hrs after initial treatment, mice in each of these groups were sub-divided ($n = 18/\text{cell}$) such that one-half the animals received an i.p. injection of d-amphetamine sulfate (5.0 mg/kg), while the remaining animals received saline. As described in Experiment 5, mice were placed in the startle apparatus 10 min following the amphetamine injection and were allowed to explore freely for a 5 min period. Testing was initiated immediately following the adaptation period.

In addition to the behavioral experiment, 18 mice received injections of either α -MpT (250 mg/kg) or FLA-63 (40 mg/kg) or their respective vehicles. Three hrs after drug administration mice were decapitated. The brains were quickly removed and stored in liquid nitrogen until fluorometric assays were carried out using a modification of the hydroxyindole method (Laverty & Taylor, 1968; Maickel et al., 1968).

Results

As was the case in Experiment 2, analysis of variance of the biochemical assay data together with Newman-Keuls multiple comparisons revealed that α -MpT (250 mg/kg) and FLA-63 (40 mg/kg) significantly decreased norepinephrine levels relative to the saline controls, $F(2, 15) = 5.84$, $p < .01$, whereas only α -MpT reduced dopamine levels, $F(2, 15) = 13.97$, $p < .001$. Whole brain levels of serotonin were not affected by pretreatment with either α -MpT or FLA-63 (see Table 3).

Analysis of variance of the startle scores revealed a significant main effect for Stimulus Presentation, $F(9, 918) = 15.49$, $p < .001$, as well as a significant Drug Pretreatment x Amphetamine Treatment interaction, $F(2, 102) = 4.82$, $p < .01$. Consistent with the results of Experiment 5, Newman-Keuls multiple comparisons ($\alpha = .05$) indicated that startle amplitude among mice pretreated and tested with saline decreased as a function of repeated stimulus exposure (see Figure 13). Treatment with d-amphetamine enhanced the startle response at all but the first buzzer presentation. Pretreatment with α -MpT three hrs prior to testing had no effect on startle when mice were tested with saline, but virtually eliminated the augmentation of the startle reflex elicited by d-amphetamine. Comparable results were observed when animals were pretreated with FLA-63 (Figure 13). If, in fact, the role of norepinephrine in mediating the startle response is inhibitory (Fechter, 1974a, b), whereas the function of dopamine is one of excitation (Davis & Aghajanian, 1976; Davis et al., 1975), then pretreatment with FLA-63 should have augmented startle and potentiated the effects of amphetamine. The fact that both α -MpT and FLA-63 antagonized the amphetamine effects on the startle reflex indicates that newly synthesized norepinephrine is important in producing the amphetamine-induced augmentation of the acoustic startle reflex.

Table 3

Whole Brain Levels of Monoamines 3 hr after Administration of
Saline, α -MPT (250 mg/kg) or FLA-63 (40 mg/kg)

Treatment	DA concentration ug/g $\pm$ S.E.M.	% control concentration $\pm$ S.E.M.	NE concentration ug/g $\pm$ S.E.M.	% control concentration $\pm$ S.E.M.	5-HT concentration ug/g $\pm$ S.E.M.	% control concentration $\pm$ S.E.M.
Saline	1.756 $\pm$.132	--	.778 $\pm$.128	--	.219 $\pm$.018	--
α -MPT	.938 $\pm$.133*	53.52 $\pm$ 7.61	.419 $\pm$.041*	53.47 $\pm$ 5.73	.209 $\pm$.021	95.43 $\pm$ 9.52
FLA-63	2.067 $\pm$.179	116.78 $\pm$ 10.20	.432 $\pm$.058*	55.09 $\pm$ 7.30	.220 $\pm$.019	100.51 $\pm$ 8.55

* significantly different from saline values $p < .05$

Figure 13 Mean startle amplitude over 10 stimulus presentations as a function of drug pretreatment (250 mg/kg of α -MPT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of d-amphetamine 3 hr after pretreatment).

MEAN STARTLE AMPLITUDE (mm)

STIMULUS PRESENTATION

10 20 30 40

1 2 3 4 5 6 7 8 9 10

PRETREATMENT

● ○ SALINE
■ □ α -MPT
▲ ▼ FLA-63

Experiment 8

The results of Experiment 7 indicate that norepinephrine is involved in mediating the effects of amphetamine on the acoustic startle response. However, the dosages necessary to produce the potentiation of startle were also observed to increase locomotor activity. Moreover, there exists an abundance of data concerning the importance of nigro-neostriatal and mesolimbic dopaminergic activity in mediating the effects of amphetamine on locomotor activity (Creese & Iversen, 1974, 1975; Kelly & Iversen, 1976). Furthermore, tyrosine hydroxylase inhibition consistently has been shown to antagonize the locomotor effects of amphetamine, whereas dopamine- β -hydroxylase inhibition is without effect in this respect (Carlsson, 1970; Hollister et al., 1974). Thus, the possibility must be entertained that the enhanced startle produced by amphetamine, as well as the reversal of the amphetamine-induced potentiation of startle amplitude following pretreatment with α -MpT, may reflect the effects of these drugs on locomotor activity.

With respect to the antagonism of the amphetamine-induced potentiation of startle by FLA-63, it is not unlikely that the behavioral effects of the dopamine- β -hydroxylase inhibitor are mediated peripherally and are due to non-specific irritant properties of the drug (Thornburg & Moore, 1973b). Accordingly, Experiment 8 was designed to determine if the effects of α -MpT and FLA-63 on amphetamine-induced locomotor excitation would parallel the effects observed in the startle task. If, in fact, FLA-63 does not affect locomotor activity, irritant properties of the drug probably do not influence startle.

Method

Subjects and Apparatus

A total of 56 male Swiss-Webster mice purchased from the Bio-Breeding Laboratories served as subjects. The activity boxes were made up of circular black anodized aluminum chambers 30 cm in diameter and 30 cm high. Six infrared photo-electric relay units placed 0.50 cm above the grid floor, were situated 7.85 cm apart about the perimeter of the cylinders, forming a 3 x 3 matrix. If the mouse broke a beam, then this beam could not be activated again until a second beam was broken, thus precluding movements such as head bobbing or tail thrashing from being recorded.

Procedure

As in Experiment 7 mice were treated with either saline, α -MPT (250 mg/kg), or FLA-63 (40 mg/kg). Three hrs following pretreatment, mice received a second injection, such that one-half of the animals ($n = 9/\text{cell}$) received saline while the remaining animals received d-amphetamine sulfate (5.0 mg/kg). Ten min following the second injection mice were placed in one of six activity chambers and allowed to explore freely for 5 min. Immediately following the 5 min adaptation period, activity (photocell counts) was recorded and printed every 2 min over a 10 min period.

Results

Analysis of variance of the photocell crossings yielded a significant Drug Pretreatment x Test Drug Treatment interaction, $F(2, 48) = 6.37$, $p < .005$. The mean photocell crossings for each group over the 10 min test period is depicted in Figure 14. Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that among saline pretreated mice d-amphetamine increased locomotor activity. In the absence of treatment with d-amphetamine, FLA-63 reduced the number of photocell crossings but owing to the large within-group variance this reduction did not reach statistical significance. Since the amphetamine effects on locomotor activity were unaffected by pretreatment with the dopamine- β -hydroxylase inhibitor, it is unlikely that the non-specific irritant property of the drug was a factor in the observed reversal of amphetamine-induced potentiation of the startle. Of course, it may be the case that the startle response is more sensitive to the toxic effects of FLA-63.

In contrast to FLA-63, pretreatment with α -MpT produced a marked attenuation of amphetamine-induced locomotor excitation (see Figure 14). The finding that α -MpT antagonized the amphetamine effects on locomotor activity, whereas FLA-63 was without effect in this respect, demonstrates the importance of dopamine in mediating locomotor activity. The fact that both α -MpT and FLA-63 were effective in reducing the amphetamine effects on startle amplitude in Experiment 7, but only α -MpT antagonized the locomotor stimulating properties of the drug, speaks to the relative independence of these amphetamine-induced behaviors.

Figure 14 Mean photocell crossings ($\pm$ S.E.M.) as a function of drug pretreatment (250 mg/kg of α -MPT, 40 mg/kg of FLA-63, or saline) and test treatment (saline or 5.0 mg/kg of d-amphetamine 3 hr after pretreatment).

MEAN PHOTOCELL CROSSINGS

Experiment 9

The results of Experiments 7 and 8 demonstrate that the effects of amphetamine on the startle reflex probably are not related to drug-induced changes in locomotor activity. Moreover, whereas locomotor activity is probably dopamine mediated, the startle reflex involves a noradrenergic component. If tolerance occurs primarily to NE mediated behaviors, then chronic administration of d-amphetamine would be expected to attenuate or diminish the excitatory influence otherwise elicited by the drug.

Method

Subjects and Apparatus

A total of 40 male Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. Mice were housed individually from the time of arrival and throughout the experiment. All other subject and apparatus specifications were identical to those described in Experiment 5.

Procedure

Mice were randomly assigned to two groups and received daily i.p. injections of either saline (10 ml/kg) or d-amphetamine sulfate (10.0 mg/kg) for five consecutive days (chronic phase). On test day (Day 6) mice were sub-divided ($n=10/\text{cell}$) such that one-half of the animals were treated with d-amphetamine (5.0 mg/kg) while the remaining mice received an equivalent volume of saline. As in Experiment 5, mice were placed in the apparatus 10 min after injection and allowed a 5-min adaptation period. As previously described, testing was initiated following the adaptation period.

Results

The mean startle amplitude as a function of stimulus presentation and drug treatments is shown in Figure 15. Analysis of variance of the startle data yielded a significant Drug Treatment (chronic phase) x Test Day Drug Treatment x Stimulus Presentation interaction, $F(9, 324) = 2.14$, $p < .05$. Consistent with the results of the previous experiments, Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that startle amplitude among mice pretreated and tested with saline declined with repeated stimulus exposure, whereas acute treatment with d-amphetamine on the test day augmented startle amplitude. Chronic treatment with d-amphetamine resulted in a diminution of the startle augmentation. As seen in Figure 15 the reduction in startle amplitude was most apparent between the second and seventh stimulus presentations ($p < .05$). Interestingly, chronic treatment with d-amphetamine produced a somewhat larger startle reaction on the first buzzer presentation (Figure 15); this difference, however, did not reach statistical significance. This finding is consistent with those involving the effects of reserpine on the startle response. Specifically, the influence of reserpine on the startle amplitude was greatest upon initial exposure to the stimulus (Fechter, 1974a). Moreover, similar findings have been reported with respect to the effects of 6-hydroxydopamine on startle amplitude (Sorenson & Davis, 1975).

Figure 15 Mean startle amplitude over 10 stimulus presentations as a function of 5 daily injections of either saline or d-amphetamine (10.0 mg/kg) and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).

Discussion (Experiments 5-9)

Presentation of an auditory stimulus (buzzer) produced a startle reaction in mice, the amplitude of which declined with repeated stimulus presentations. As reported previously (Davis et al., 1975), treatment with d-amphetamine resulted in a potentiation of the startle amplitude; however, startle sensitization with repeated stimulus presentation was not observed. The finding that startle amplitude progressively increased with successive buzzer presentations only when testing was initiated immediately following drug injection, suggests that peak drug effects may be responsible for the development of the apparent sensitization.

Unlike the effects of d-amphetamine on locomotor activity, which apparently involves the release of dopamine (Carlsson, 1970; Creese & Iversen, 1975), amphetamine-induced potentiation of startle may well be a consequence of the effects of the drug on norepinephrine release and reuptake. To be more explicit, following pretreatment with FLA-63, which depleted NE but did not affect whole brain DA, the enhanced startle produced by amphetamine was antagonized. Since FLA-63 did not influence amphetamine-induced locomotor activity, and also did not influence the stereotypic behaviors engendered by amphetamine (Carlsson, 1970; Hollister et al., 1974; Wallach, 1974), it cannot be argued that the reduction of startle was due to the emergence of competing behaviors (e.g., stereotypy).

Although the data of the present investigation suggest that NE is involved in startle reactivity, this does not exclude a role for DA in the elicitation of this behavior (Davis & Aghajanian, 1976). It is, however, important to determine

whether both catecholamines cojointly mediate startle, or alternatively, whether optimal, or at least adequate, motor abilities involving DA are necessary in order that startle arousal mediated by NE becomes manifest. Further, it is necessary to determine whether different DA and NE pathways contribute to different aspects of the startle reflex and its maintenance.

As in the case of other amphetamine behaviors involving a noradrenergic component (see introduction), the augmentation of startle amplitude was limited following chronic amphetamine treatment. It might be argued that the decline in startle amplitude was a consequence of the emergence of competing behaviors (e.g., stereotypy) following chronic drug treatment. This, however, does not appear to be the case since treatment with dosages of d-amphetamine which engender more pronounced stereotypy (10 mg/kg in Experiment 5) did not result in the diminution of startle amplitude.

ACTIVITY, REACTIVITY AND STEREOTYPY

Following the application of foot-shock mice and rats typically exhibit a pronounced decline in locomotor activity (cf., Bolles, 1970, 1971). Paradoxically, the application of foot-shock among d-amphetamine treated animals results in response excitation which exceeds that elicited by d-amphetamine alone (Anisman & Cygan, 1975; Anisman, Wahlsten & Kokkinidis, 1975). Whereas locomotor activity precipitated by d-amphetamine appears to be primarily mediated by dopaminergic neurons (Carlsson, 1970; Creese & Iversen, 1972, 1975), it has been suggested that the post-shock excitation may involve a noradrenergic component (Anisman & Cygan, 1975). Evidence for such a conclusion has been derived from several sources. First, stress has repeatedly been shown to increase turnover of NE, whereas the effects on DA activity are minimal (Anisman, 1978; Stone, 1975). Second, Javoy, Thierry, Kety and Glowinski (1968) reported that turnover of NE, which is increased following amphetamine administration, is further augmented by foot-shock. Finally, pretreatment with a dopamine- β -hydroxylase inhibitor successfully reduced the excitation elicited by amphetamine plus shock without influencing the locomotor activity produced by amphetamine alone (Anisman & Cygan, 1975).

The purpose of the present series of experiments was four-fold. First, to ascertain whether the amphetamine/shock synergism previously observed was specific to the highly inbred A/J and DBA/2J strains of mice (cf., Anisman & Cygan, 1975) or whether it would be apparent in a non-inbred strain of mouse (Swiss-Webster).

Second, to determine whether the amphetamine x shock interaction might be related to changes in other amphetamine induced behaviors. Specifically, as discussed earlier, the behavioral characteristics induced by d-amphetamine may be interdependent (Segal, 1975; Segal & Mandell, 1974). For example, the incidence and intensity of stereotypic behaviors following acute or chronic amphetamine administration may occur at the expense of the elicitation of a drug-induced locomotor response (Groves & Rebec, 1976; Segal, 1975). Thus, in the absence of objective evaluation of stereotypy, conclusions pertaining to the source for the amphetamine x shock interaction on locomotor activity must be held in abeyance. Accordingly, in the present series of experiments motor activity and stereotypy were evaluated concurrently. Third, it has been shown on several occasions that d-amphetamine will increase responsivity to strong stimuli (startle reflex), and that the magnitude of this effect increased with repeated stimulus presentations (Davis, Svensson & Aghajanian, 1975; see also Experiment 6). The present investigation sought to determine whether the post-shock excitation might similarly be modified by repeated exposure to strong stimuli, and further, whether this behavior was noradrenergically or dopaminergically mediated. Finally, the effects of d-amphetamine after chronic exposure to the drug have been found to decrease in some behavioral situations, but to increase in other instances as previously described. The data presented thus far suggest that the effects of chronic treatment are dependent upon whether the behaviors in question were primarily DA mediated or subserved by NE activity. Thus, the chronic effects of d-amphetamine were considered in light of the respective roles of DA and NE in mediating the post-shock excitation.

Experiment 10

Experiment 10 represents a replication and extension of previous work concerning the effects of foot-shock on amphetamine-induced locomotor activity. In addition, stereotypy was evaluated in order to assess the relationship between this behavior and locomotor activity in the presence or absence of shock.

Method

Subjects

A total of 80 male Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. Mice were housed in groups of 3-5 in standard polypropylene cages. Subjects were allowed ad lib. access to food and water and were tested between 60-80 days of age. Testing was carried out during the light portion of a 12 hr light-dark cycle.

Apparatus

Locomotor activity was monitored in six identical Plexiglas cylinders, 30 cm in diameter and 30 cm high as described in Experiment 8. Foot-shock of 150 μ A could be delivered through the grid floor via a 3,000 volt source. The grid floor was connected in series through neon bulbs, thereby preventing animals from escaping shock by standing on bars of the same polarity.

Procedure

Mice received a single i.p. injection of either saline, or 1.0, 3.0, 5.0 or 10.0 mg/kg of d-amphetamine sulfate in a volume of 10.0 ml/kg. Immediately after injection one-half of the animals (n= 8/cell) were placed into the activity boxes for a five min period. Following this interval photocell counts were recorded at 5 min intervals over a 140 min session. The remaining animals were treated in an identical manner with the exception that they received a 6 sec foot-shock (150 uA, 60 Hz, AC) at 5 min intervals. In addition, throughout the testing session, mice were rated for stereotypic behaviors at the midpoint of each 5 min intertrial interval. The stereotypy index was adapted from that described by Ellinwood and Balster (1974) and had previously been found to produce better than 95 percent agreement between two trained raters. Briefly, the stereotypy scale consisted of the following criteria: 1. Lying down -- eyes closed; 2. Lying down -- eyes open; 3. Normal grooming; 4. Exploration, sniffing, rearing; 5. Running movement characterized by rapid changes in position (jerky); 6. Repetitive exploration of the cage -- normal level of activity; 7. Repetitive exploration -- hyperactivity; 8. Remaining in same place with fast repetitive head and/or foreleg movement, licking, chewing and gnawing stereotypies, and 9. Backing up, jumping, seizures, dyskinetic movements, postural abnormalities.

Results

The mean number of photocell crossings and stereotypy ratings as a function of drug and shock treatment are presented in Figures 16 and 17, respectively. Analysis of variance yielded significant Drug x Shock x Block interactions for both the activity scores, $F(52, 910) = 4.67$, $p < .001$, and stereotypy ratings, $F(52, 910) = 3.14$, $p < .001$. Consistent with previous reports involving rats (Segal, 1975) inspection of Figure 16 revealed that in the absence of shock d-amphetamine elicited several distinct behavioral phases of locomotor activity. These observations were verified by Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in the interactions. The multiple comparisons indicated that amphetamine initially elicited locomotor activity which exceeded that of the saline controls. This was the case for all dosages, with 5 mg/kg producing the most notable increase of locomotor activity. The effects of the drug on ambulation were observed to decline over the first half of the test session. This phase of reduced locomotor activity (approximately 50-80 min after injection) was evident in the 5 mg/kg group and was more pronounced among mice treated with 10 mg/kg of the drug (see Figure 16). As previously reported by Segal (1975), a second phase of hyperactivity was observed to follow the phase of decreased ambulation among the 5.0 and 10.0 mg/kg groups.

The source for the temporal variations in locomotor activity after high dosages of d-amphetamine are better understood when the drug effects on stereotypy are considered. As seen in Figure 17 and confirmed by the multiple comparisons, the drug-induced stereotypic behaviors after 5.0 and 10.0 mg/kg of the drug were maximal at approximately 50-80 min after injection, that time period

Figure 16 Mean number of photocell crossings collapsed over 10 min
intervals as a function of drug (saline, or 1.0, 3.0, 5.0
or 10.0 mg/kg of d-amphetamine) and shock treatment.

Figure 17 Mean stereotypy ratings collapsed over 10 min intervals as a function of drug (saline, or 1.0, 3.0, 5.0 or 10.0 mg/kg of d-amphetamine) and shock treatment.

which coincides with the decrease in locomotor activity. Following this phase, stereotypy was observed to decrease (see Figure 17). Predictably, this decrease in stereotypic behavior corresponds with the second phase of hyperactivity (see Figure 16).

In considering locomotor activity in the shock groups, it is clear that upon inception of shock there was a marked decline in ambulation among saline-treated mice. Among mice treated with d-amphetamine (5.0 mg/kg) shock elicited a marked increase in locomotor activity (i.e., reactivity). Moreover, the excitation became increasingly more apparent with successive shock presentations (sensitization). Indeed, as seen in Figure 16, the enhanced reactivity observed after repeated shock presentations significantly surpassed the levels of activity produced by the drug alone (i.e., in the absence of shock). It is unlikely that the observed sensitization represents a peak drug effect, since the pharmacological profile of amphetamine on locomotor activity did not show a similar increase in ambulation over time. It is also unlikely that the amphetamine/shock synergism is an artifact of changes in stereotypy, since the stereotypy noted during the course of the shock-induced locomotor excitation (i.e., during that period when a sensitization effect was apparent) was not significantly different from that seen in the no-shock condition. Although shock did seem to enhance stereotypic behavior among animals in the 5.0 mg/kg condition following the sensitization phase, this difference was not reliable, in that it was not observed in subsequent experiments.

Experiment 11

The results of Experiment 10 demonstrated that foot-shock which reduced locomotor activity in the absence of drug treatment, enhanced the amphetamine-induced locomotor response. Moreover, the amphetamine/shock synergism on locomotion was neither a consequence of variations of the drug's peak time effect, nor was it related to changes in stereotypic behaviors.

Experiment 11 was carried out to evaluate further the source for the amphetamine effect on locomotor activity and stereotypy in general, and the amphetamine/shock synergism in particular. It will be recalled that responsivity to a stressor may involve NE activity (Anisman, 1978; Stone, 1975). However, recent data have implicated a role for DA in subserving response initiation and maintenance in several shock motivated situations (cf., Peters, Anisman & Pappas, 1978). Thus, in Experiment 11 an attempt was made to replicate earlier findings concerning the antagonism of the amphetamine/shock synergism by dopamine- β -hydroxylase inhibition (Anisman & Cygan, 1975), and to determine whether such a treatment would be as effective as tyrosine hydroxylase inhibition in modifying this synergism.

Method

A total of 96 male Swiss-Webster mice were used as subjects. All apparatus specifications were identical to those described in Experiment 10. Naive mice received an i.p. injection of either saline, α -MPT methyl ester (250 mg/kg) or FLA-63 (40 mg/kg), 3 hrs after which mice were treated with a second injection

of either saline or d-amphetamine sulfate (5.0 mg/kg). Immediately after the second injection one-half of the animals ($n = 8/\text{cell}$) were placed into the activity chambers for a 5 min period. Following this adaptation period photo-cell counts were recorded at 5 min intervals over a 140 min time period. The remaining animals were treated in an identical manner with the exception that they received a 6 sec foot-shock (150 μA) at 5 min intervals as described in Experiment 10. In addition, stereotypy ratings were conducted during the inter-trial intervals as described in Experiment 10.

Results

Locomotor activity and stereotypy ratings as a function of drug treatment combinations and shock treatment are shown in Figures 18 and 19, respectively. Analyses of variance of the locomotor activity and stereotypy scores yielded significant Drug Pretreatment x Amphetamine x Shock x Block interactions for both locomotor activity, $F(26, 1082) = 7.22$, $p < .001$, and stereotypy, $F(26, 1082) = 2.35$, $p < .001$. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects involved in these interactions revealed that in the absence of shock d-amphetamine elicited pronounced variations of locomotor activity and stereotypy. As observed in Experiment 10, d-amphetamine produced an initial increase of locomotor activity, followed thereafter by a decline in ambulation. Towards the end of the testing session a slight increase in locomotor activity was again observed (see Figure 18). Consistent with the results of Experiment 10, the decline in locomotor activity among amphetamine treated animals was paralleled by a substantial increase in stereotypic behavior (see Figure 19). The competitive relationship between locomotor activity and

Figure 18 Mean number of photocell crossings collapsed over 10 min intervals as a function of drug pretreatment (saline, 250 mg/kg of α -MPT or 40 mg/kg of FLA-63), drug test treatment (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.

Figure 19 Mean stereotypy ratings collapsed over 10 min intervals as a function of drug pretreatment (saline, 250 mg/kg of α -MPT or 40 mg/kg of FLA-63), drug test treatment (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.

stereotypy becomes more evident when the effects of tyrosine hydroxylase inhibition are considered. Specifically, unlike FLA-63, pretreatment with α -MpT markedly attenuated the locomotor and stereotypic effects engendered by d-amphetamine. Indeed, as evidenced in Figure 18 the effects of α -MpT on the behavioral changes varied in a temporal fashion. In particular, the enzyme inhibitor attenuated both the initial motor excitation as well as that seen during the later portion of the session; however, as reported by Segal (1975) α -MpT increased activity at the intermediate interval (40-60 min post injection) relative to amphetamine animals which received saline pretreatment. These time-dependent changes in locomotor activity after α -MpT may have been a consequence, at least in part, of the antagonism of the stereotyped behaviors ordinarily induced by d-amphetamine (see Figure 19). More specifically, by antagonizing the stereotypic behaviors, the otherwise low levels of locomotor activity seen 50-80 min after drug administration are substantially increased.

Consistent with earlier reports (Segal & Mandell, 1974), the data of the present experiment reveal the competitive relationship which exists between the locomotor and stereotypic effects induced by d-amphetamine. Moreover, it appears to be the case that both these behaviors are mediated by DA activity (see also Groves & Rebec, 1976; Wallach, 1975). At the same time, however, it should be considered that NE may play some role in mediating these behaviors. Specifically, as reported by Mogilnicka and Braestrup (1976), dopamine- β -hydroxylase inhibition was found to produce a slight increase in stereotypic behaviors among amphetamine treated animals (see Figure 19).

As observed in Experiment 10, application of foot-shock among mice pretreated and tested with saline resulted in a decline of locomotor activity, whereas among mice pretreated with saline and tested with amphetamine, an augmentation of locomotor activity was observed. The extent of the motor excitation became increasingly greater with successive shock presentations (see Figure 18). Consistent with the results of Anisman and Cygan (1975), pretreatment with FLA-63, which did not influence amphetamine-induced locomotor activity in the absence of shock, produced a significant reduction of motor activity in the amphetamine-shock group. It is of particular relevance that although FLA-63 effectively reduced motor excitation, the sensitization effect was still evident. In contrast to FLA-63, pretreatment with α -MpT not only eliminated the post-shock excitation, but also antagonized the sensitization effect. It should be borne in mind that the greater effects of α -MpT were probably due to its effects on dopamine activity, since both α -MpT and FLA-63 produced comparable depletion of NE (see Table 1). This conclusion is supported by recent data collected in this laboratory which revealed that low dosages of haloperidol (.037 - .075 mg/kg) likewise antagonized the amphetamine-shock effects (Irwin, Anisman & Kokkinidis, unpublished report). Taken together, the present data suggest that while NE likely influences the magnitude of the amphetamine-shock synergism, adequate DA activity is necessary in order that the sensitization effect appear.

Although locomotor activity and stereotypy are competitive behaviors, it appears that the post-shock excitation was independent of variations in stereotypic behavior. That is, the augmentation of locomotor activity in shocked animals was not accompanied by variations in stereotypy. Moreover, while FLA-63 and α -MpT both reduced the post-shock excitation, the latter agent initially reduced stereotypy, while the former agent had an opposite effect.

Experiment 12

The results of Experiment 11 suggest that the post-shock excitation seen among amphetamine treated mice involves both a dopaminergic and a noradrenergic component. That is, although the occurrence of the sensitization effect apparently necessitates adequate DA activity, the magnitude of the excitation is influenced by NE. The purpose of Experiment 12 was to evaluate further the relationship between amphetamine-induced stereotypy, locomotor activity and the post-shock excitation following repeated amphetamine administration. In particular, since locomotor activity and stereotypy are DA mediated, these behaviors should be either unaffected or exacerbated following chronic d-amphetamine administration. As concerns the post-shock excitation, some decline of the reactivity may be expected, given the apparent involvement of NE in this respect. However, the sensitization effect per se should be more or less unaffected since its appearance was not influenced by inhibition of NE synthesis.

Method

Subjects and Apparatus

A total of 64 male Swiss-Webster mice served as subjects. All subject and apparatus specifications were identical to those described in Experiment 10. Unlike Experiments 10 and 11, mice were housed individually for seven days prior to the initiation, as well as throughout the course of the experiment.

Procedure

Subjects were treated daily with an i.p. injection of either saline or d-amphetamine sulfate (10.0 mg/kg) for 5 consecutive days. On test day (Day 6) subjects were further sub-divided and injected i.p. with either saline or 5.0 mg/kg of d-amphetamine. One half of the animals in each group ($n = 8/\text{cell}$) were tested in the no-shock condition, while the remaining mice were tested in the shock condition as described in Experiment 10. All other procedural particulars, including stereotypy ratings, were identical to those described in Experiment 10.

Results

Analysis of variance of the activity-reactivity scores yielded a Chronic Drug Treatment $\times$ Test Day Drug Treatment $\times$ Blocks interaction, $F(13, 728) = 16.67$, $p < .001$. Newman-Keuls multiple comparisons revealed that in the absence of shock, d-amphetamine treatment on test day produced increased levels of locomotor activity. Consistent with previous reports concerning the effects of chronic amphetamine treatment on locomotor activity (cf., Segal, 1975), a biphasic pattern of ambulation was evident over the course of the test session. That is, mice chronically treated with d-amphetamine and tested in the drug state, showed significantly lower levels of activity during the initial 30 min of testing relative to mice chronically treated with saline and tested with d-amphetamine. Following this phase of depressed activity, a substantial increase

in locomotor activity was observed among mice in the chronic amphetamine group (see Figure 20). Previous work involving rats indicated that the depressed phase of locomotor activity was accompanied by increased stereotypic behaviors and the subsequent phase of hyperactivity was paralleled by a decrease in stereotypy (Segal, 1975; Segal & Mandell, 1974). Unexpectedly, in Experiment 12 these changes in stereotypy were not observed. That is, amphetamine produced pronounced stereotypy, $F(1, 56) = 513.40$, $p < .01$, but the extent of the stereotypy was unaffected by the animal's previous drug history (see Figure 21). However, post hoc analysis of the data revealed that subtle differences between the acute and chronic groups were, in fact, evident. More specifically, when the frequency and initial occurrence of focussed stereotypy were considered (i.e., animals exhibiting fast repetitive head and/or foreleg movements, licking, chewing and gnawing stereotypies), it was observed that in the amphetamine-amphetamine condition 3 of the 8 mice exhibited such behaviors within the first 20 min of testing and 5 of the 8 animals showed consistent focussed stereotypy within the first 50 min. In contrast, no animal in the saline-amphetamine condition exhibited these behaviors during the initial 20 min, while 3 mice demonstrated focussed stereotypy during the initial 50 min of testing. During the latter half of the test session (approximately 80 min after testing was initiated) this pattern was reversed. None of the mice which were chronically treated and tested with amphetamine displayed pronounced stereotypy, whereas, 4 of the 8 subjects in the saline-amphetamine condition showed continuous gnawing or grooming. Thus,

Figure 20 Mean number of photocell crossings collapsed over 10 min intervals as a function of chronic drug treatment (saline or 10.0 mg/kg of d-amphetamine), drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.

Figure 21 Mean stereotypy ratings collapsed over 10 min intervals as a function of chronic drug treatment (saline or 10.0 mg/kg of d-amphetamine), drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine) and shock treatment.

chronic amphetamine treatment resulted in a temporal shift in the incidence of stereotypy. That is, among mice in the chronic amphetamine group the focussed stereotypy occurred earlier and subsequently subsided earlier than it did in the acute amphetamine group. As seen in Figure 20, this pattern coincides with the lower levels of locomotor activity early in testing and the heightened activity apparent late in testing among mice which received acute amphetamine treatment.

Returning again to the locomotor activity data, the multiple comparisons revealed that foot-shock decreased activity among mice tested with saline and increased activity among mice tested with d-amphetamine. As predicted, among shocked mice chronic treatment with d-amphetamine resulted in a small but significant reduction of locomotor activity relative to mice in the acute amphetamine group. Moreover, the occurrence of the peak effect was seen 10 min later in the chronic group. Despite the reduction of the post-shock excitation, a marked sensitization effect was still apparent following chronic amphetamine treatment. With respect to the effects of shock on stereotypic behavior, a Drug During Test x Shock Treatment x Blocks interaction was observed, $F(13, 728) = 9.26$, $p < .01$. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that shock reduced stereotypy from the 10th block onward. Consistent with Experiments 10 and 11, the shock treatment did not influence stereotypy early in training, and was apparently not responsible for the variations in the post-shock excitation.

Discussion (Experiments 10-12)

Consistent with previous reports (Segal, 1975; Segal & Mandell, 1974), the results of the present series of experiments revealed the existence of a competitive relationship between amphetamine-induced stereotypy and locomotor activity. Although appropriate dosages of amphetamine will reliably elicit both behaviors, their occurrence is temporally distinct from one another. The initial behavioral excitation elicited by the drug is associated with low levels of stereotypy. As stereotypy becomes more accentuated, the locomotor excitation declines. The competitive nature of these drug-induced behaviors becomes clearer when the effect of tyrosine hydroxylase inhibition is considered. Pretreatment with α -MPT reduced the initial amphetamine-induced locomotor excitation. However, locomotor activity during the phase ordinarily characterized by reduced ambulation and high levels of stereotypy, was increased. Not surprisingly, the increase in activity was associated with a reduction of stereotypy.

As previously reported (Anisman et al., 1975; Anisman & Cygan, 1975), the introduction of foot-shock, a treatment which ordinarily produces response suppression, enhanced the excitatory effects of d-amphetamine. Moreover, with repeated shock presentations the amphetamine/shock synergism was augmented further. It is unlikely that the sensitization represents a peak drug effect, since in the absence of shock, activity levels did not increase over the test session. Moreover, the excitation was apparently not a direct consequence of variation in stereotypy, since the latter was unaffected by the foot-shock. That is, despite the presence of pronounced stereotypy, animals did exhibit periods of sustained locomotor activity.

The fact that tyrosine hydroxylase and dopamine- β -hydroxylase inhibition modified the post-shock excitation clearly implicates catecholamine activity in the mediation of the synergistic effects observed. Yet, the possibility should be considered that DA and NE mediate different aspects of the shock/amphetamine synergism. Specifically, as reported by Anisman and Cygan (1975) pretreatment with FLA-63 reduced the excitation contributed by the shock among amphetamine treated mice; however, it is clear that the temporal changes in activity, i.e., the sensitization itself, was still evident. In contrast, pretreatment with α -MPT not only reduced the magnitude of the shock induced excitation, but in fact entirely eliminated the sensitization effect. Indeed, among animals which received the tyrosine hydroxylase inhibitor, the response suppression typically elicited by shock became apparent. As such, it appears that adequate dopamine activity is a necessary prerequisite in order for the sensitization effect to be elicited. However, NE clearly contributes to the magnitude of this effect. These results are consistent with those of Davis et al. (1975) and Davis and Aghajanian (1976), suggesting a primary role for DA in the exaggeration of the startle reflex by amphetamine. It is, however, important to bear in mind that in the aforementioned reports, as well as in the present series of experiments, activity was monitored after the introduction of a strong stimulus. However, when startle during the presentation of a stimulus is considered, an important role for NE has been demonstrated (see Experiments 5-9).

Finally, turning to the effects of chronic amphetamine treatment, it is clear that initially, general locomotor activity was slightly reduced, likely as a consequence of an increase in stereotypy. As in the case of other DA mediated behaviors, the sensitization effect was still apparent after a chronic drug regimen. However, the extent of the post-shock excitation was somewhat reduced, and the time of maximal excitation was retarded. It appears that as in the case of the startle response, the effects of prolonged amphetamine treatment paralleled the effects produced by pretreatment with FLA-63. These results suggest a role for NE in the behavioral attenuation of the amphetamine x shock interaction after chronic exposure to the drug.

SPONTANEOUS ALTERNATION/PERSEVERATION IN THE ASSESSMENT
OF p-HYDROXYNOREPHEDRINE

It is clear from the preceding experiments, as well as earlier reports cited in the General Introduction that tolerance to repeated administration of d-amphetamine will occur insofar as some behavioral and physiological measures are concerned. In contrast, a marked absence and even an enhancement of d-amphetamine effects have been reported when other measures are considered.

Evaluation of the mechanisms which subserve amphetamine tolerance are complicated not only by the fact that subtle procedural details influence the response to the drug, e.g., whether or not the drug is consistently administered in the presence of certain stimuli (Carlton & Wolgin, 1971; Tilson & Rech, 1973), but also by the fact that d-amphetamine elicits a variety of neurochemical changes (Carlsson, 1970; Welch & Welch, 1970). As indicated earlier, through the concurrent evaluation of several behaviors it may be possible to draw fracture lines between different biochemical/behavioral relations. Indeed, such a procedure may be of value in differentiating between those factors which play a primary role in behavioral tolerance and those which exert only a secondary effect (Kokkinidis et al., 1976).

The Y-maze exploratory task has proven useful as an evaluative tool in this capacity, since it permits the concurrent measurement of at least two independent behaviors. Specifically, as previously described, in a free-running Y-maze exploratory situation, naive animals tend to enter that arm which was least recently visited (spontaneous alternation) (Drew, Miller & Baugh, 1973; Swonger & Rech, 1972). Acute treatment with d-amphetamine not only increased locomotor activity, as measured by the total number of arm entries (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a), but also produced perseverative behavior, in that animals tend to visit successively only two arms of the Y-maze (Adkins, Packwood & Marshall, 1969; Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a, b).

Aside from the additional data gained by measuring two behaviors concurrently, this paradigm is particularly appealing since (1) amphetamine-induced locomotor activity does not undergo tolerance (see Experiment 12) whereas the perseverative tendency diminishes following chronic drug treatment (Kokkinidis et al., 1976); and (2) there are reasons to believe that the locomotor stimulation and perseveration engendered by amphetamine are subserved by different neurochemical mechanisms, i.e., the former likely involves DA (Carlsson, 1970; Creese & Iversen, 1974, 1975), while the latter may be subserved by NE (Anisman & Kokkinidis, 1975). These factors, together with the findings that the two behaviors are independent, i.e., manipulation of one behavior does not necessarily influence the second (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a), make it possible to assess the role of different neurochemical/behavioral relations in the development of tolerance.

On the basis that tolerance was observed to the perseverative but not to the locomotor stimulating effects of d-amphetamine led to the suggestion that tolerance might occur exclusively to behaviors involving NE activity (Kokkinidis et al., 1976; see also Experiments 1-12). Moreover, it has been suggested on several occasions (see General Introduction) that the tolerance to amphetamine might be related to the metabolic fate of this drug (Brodie et al., 1970; Lewander, 1971). In particular, a metabolite of d-amphetamine, p-hydroxynorephedrine, which has weaker receptor stimulating properties than NE (Brodie et al., 1970) may displace the transmitter from storage granules. Accordingly, following chronic d-amphetamine treatment preferential release of the false transmitter may result in diminished behavioral and physiological effects (Brodie et al., 1970; Lewander, 1971, 1975). Accordingly, only those behaviors which are greatly influenced by NE activity would be expected to undergo tolerance.

Experiments 13-16

The purpose of Experiments 13-16 was two-fold. First, to elaborate on some of the parameters necessary to induce tolerance to perseveration induced by d-amphetamine (e.g., dosage and number of treatments) and to ascertain that the tolerance previously observed was not specific to the highly inbred C57BL/6J strain (cf., Kokkinidis et al., 1976). Second, to determine whether p-hydroxynorephedrine is involved in the tolerance to amphetamine-induced perseveration. In particular, although both d- and l-amphetamine may produce perseveration (see Experiment 13), the metabolic fate of the isomers is not congruent. That is, β -hydroxylation of p-hydroxyamphetamine to p-hydroxynorephedrine is stereospecific to the d-isomer (Brodie et al., 1970). It follows that if tolerance to the perseverative effects of the drug is observed after repeated treatment with d-amphetamine, but is absent in the case of repeated l-amphetamine treatment, then the possibility needs to be entertained that this tolerance involves the formation of p-hydroxynorephedrine. Conversely, tolerance to perseveration elicited by l-amphetamine would provide prima facie evidence suggesting that p-hydroxynorephedrine is not a major contributing factor to the tolerance effect.

Experiment 13 was specifically carried out to determine the dosage of l-amphetamine which would elicit perseveration comparable to that produced by the optimal dosage (5.0 mg/kg) of d-amphetamine (Anisman & Kokkinidis, 1975). The equated dosages were necessary in order to evaluate tolerance effects in subsequent studies. In Experiments 14 and 15 the number of daily injections, as well as the dosages necessary to produce tolerance to the perseverative effects induced by d-amphetamine were evaluated. In Experiment 16 daily injections of various dosages of l-amphetamine were administered in order to determine whether perseveration induced by l-amphetamine was subject to tolerance.

Method

Subjects

A total of 420 Swiss-Webster mice, 210 female and 210 male, procured from the Bio-Breeding Laboratories at 43-48 days of age served as subjects (120, 120, 80, 100 for Experiments 13-16, respectively). Mice were housed individually in standard polypropylene cages and permitted ad lib. access to food and water. Injection commenced approximately 1 week after arrival in the laboratory. Testing was carried out between 10:00 and 14:00 hr..

Apparatus

The apparatus used to measure spontaneous alternation/perseveration and locomotor activity consisted of a symmetrical black Plexiglas Y-maze with arms 9.0 cm long, 6.0 cm wide and 7.0 cm high, and covered with a clear Plexiglas roof. The floor of the apparatus was made up of 0.25 cm stainless-steel rods spaced 1.0 cm apart. Each arm of the Y-maze had two sets of infrared photo-electric relays mounted in the side walls 1.50 cm above the floor. The first set of photocells was positioned at the entrance of the arm while the second set was placed within the arm spaced 7.60 cm from the first. The photocells were wired so that a count, as measured by a deflection of one of three pens of an Esterline Angus recorder, was triggered only after both beams were broken. Once a count was recorded, the second beam could not be triggered until the beam at the arm entrance was again broken. Thus, the animal was required to enter the chamber at least half-way into the arm in order for an arm entry to be recorded. The apparatus was housed in an illuminated room.

Procedure

Experiment 13: Mice (n= 10/cell) received i.p. injections of either saline, d-amphetamine sulfate (1.0, 3.0, 5.0 or 10.0 mg/kg) or l-amphetamine (1.0, 3.0, 5.0, 10.0, 15.0, 20.0 or 25.0 mg/kg). The drug was administered in a volume of 10 ml/kg. Fifteen minutes after injection, mice were placed into the Y-maze and permitted to explore freely. The sequence and number of arm entries were recorded over a 15 min period. Scoring of alternation/perseveration consisted of the evaluation of response sequences in which entering into the arm least-recently visited was considered as an alternation (e.g., a sequence of arm entries in this case would be 1, 2, 3 or 1, 3, 2). Non-alternation was considered to be the case when animals returned to the compartment they had been in most recently (e.g., 1, 2, 1 or 1, 3, 1). The proportion of alternations was computed by dividing the number of alternations by the total number of alternations plus non-alternations. Perseverative behavior was defined as subjects making significantly fewer alternations than could be expected at a chance level (50%). The data were analyzed by analysis of variance of the individual alternation scores, and by χ^2 analysis of the proportion of total alternations for a given group of animals. Activity levels were determined on the basis of the number of arm entries.

Experiment 14: Experiment 14 involved a 2 (drug during chronic phase) x 3 (day) x 2 (drug during test day) factorial design. Mice received daily subcutaneous injections of either d-amphetamine sulfate (15.0 mg/kg in a 1.5 mg/ml solution) or saline (10 ml/kg) for either 3, 5 or 10 consecutive days (chronic phase). The following day (test day) each group was further subdivided, such that one-half of the animals received an i.p. injection of d-amphetamine sulfate (5.0 mg/kg in a 0.5 mg/ml solution) while the remaining mice received an equivalent volume of saline (n=10/cell).

Fifteen minutes after injection on the test day, mice were individually placed in the Y-maze and permitted to explore freely. The sequence and number of arm entries were recorded over a 15 min period. Prior to drug treatment, mice were placed in the maze for a 5 min pre-exposure session. Previous research from this laboratory (Kokkinidis & Anisman, 1976a) revealed that the perseverative effects of amphetamine were maximized by prior exposure to the apparatus, thus permitting a broader range of scores in the Y-maze task. Consequently, measurement problems descending from ceiling effects were precluded.

Experiment 15: Mice received daily subcutaneous injections of either saline or d-amphetamine sulfate in a dosage of either 5.0, 10.0 or 15.0 mg/kg for five consecutive days. On the test day, one-half of the animals in each group (n=10/cell) received i.p. injections of d-amphetamine sulfate (5.0 mg/kg) while the remaining mice were treated with an equivalent volume of saline. The testing procedure was identical to that of Experiment 13.

Experiment 16: Experiment 16 was identical to Experiment 15 in all respects, except that l-amphetamine (15.0, 30.0, 45.0 and 60.0 mg/kg) or saline were used during the chronic phase. Similarly, the testing procedure was the same as that previously described, but mice were tested with either l-amphetamine (15.0 mg/kg) or saline. Experiment 13 indicated that this dosage of l-amphetamine elicited perseveration comparable to that observed after 5.0 mg/kg of d-amphetamine.

Results

Experiment 13

The mean proportion of alternation responses, and the mean number of arm entries as a function of drug treatment are depicted in Figure 22. Analysis of variance of the proportion of individual alternations revealed that the drug treatments substantially reduced the alternation levels, $F(11, 108) = 4.22$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) together with χ^2 analyses of the group proportions revealed that saline animals alternated above chance levels as did mice treated with l-amphetamine in the 1.0 and 3.0 mg/kg dosages. Treatment with d-amphetamine (1.0 mg/kg) and l-amphetamine (5.0 and 10.0 mg/kg) reduced alternation to chance levels. With higher doses, i.e., d-amphetamine (5.0 mg/kg) and l-amphetamine (15.0, 20.0 and 25.0 mg/kg), alternation fell well below chance, i.e., perseveration (see Appendix C, Table 1). As seen in Figure 22 the optimal dose of the l-isomer (15.0 mg/kg) yielded perseveration comparable to that seen after 5.0 mg/kg of d-amphetamine.

Figure 22 Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) following treatment with various doses of the stereoisomers of amphetamine.

The analysis of arm entries indicated that the drug treatments modified activity, $F(11, 108) = 3.89$, $p < .001$. As seen in Figure 22, d-amphetamine at all doses except 10.0 mg/kg produced locomotor excitation, with 5.0 mg/kg being optimal in this respect. In the case of l-amphetamine, only the 10.0 mg/kg dose enhanced locomotor activity. The optimal dose of l-amphetamine (10.0 mg/kg) elicited changes in locomotor activity comparable to that produced by 1.0-3.0 mg/kg of the d-isomer.

Experiment 14

The mean percentage of alternations and the mean arm entries for each group are shown in Figure 23. In this experiment, as well as in each of the ensuing experiments comparable alternation and activity levels were observed during the 5 min no-drug pre-exposure period. Analysis of variance of individual alternation scores revealed that performance varied as a function of the Pre-exposure Days, Pre-exposure Drug Treatment and Test Day Treatments, $F(2, 108) = 4.55$, $p < .05$. Newman-Keuls multiple comparisons ($\alpha = .05$) for the simple main effects involved in this interaction, together with χ^2 analyses of the total group alternation scores revealed that, regardless of the pre-exposure treatment, animals tested with saline demonstrated chance or slightly above chance performance (χ^2 's = 6.40, 2.88, 16.48, 11.66, 9.72, 8.02, $df = 1$, $p < .05$ among mice pretreated with saline or d-amphetamine for 3, 5 or 10 days and tested with a saline injection). In contrast, mice pretreated with saline and tested with d-amphetamine (5.0 mg/kg) alternated well below chance levels (i.e., perseveration) (χ^2 's = 31.36, 54.00, 43.64, $df = 1$, $p < .001$). As seen in Figure 23 injections of 15 mg/kg of d-amphetamine for 3 days did not alter the perseveration produced

Figure 23 Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of drug treatment during the chronic phase (15.0 mg/kg of d-amphetamine or saline for either 3, 5 or 10 consecutive days) and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).

by 5 mg/kg of d-amphetamine on test day ($\chi^2 = 49.16$, $df = 1$, $p < .001$). However, chronic drug treatment for either 5 or 10 consecutive days was sufficient to mitigate the perseverative tendency.

With respect to the activity measures, analysis of variance of the mean number of arm entries in Experiment 14 yielded a significant main effect for drug treatment on the day of testing, $F(1, 108) = 41.47$, $p < .001$. Subsequent Newman-Keuls multiple comparisons of the main effect ($\alpha = .05$) revealed that relative to saline treated mice, injection of 5 mg/kg of d-amphetamine on the test day increased the number of arm entries (see Figure 23). Consistent with a previous report from this laboratory (Kokkinidis *et al.*, 1976), pre-exposure to drug had no effect on locomotor activity.

Experiments 15 and 16

Figures 24 and 25 show the mean proportion of alternation, as well as the mean number of arm entries for the d- and l-amphetamine experiments. In both experiments analysis of variance of the alternation data yielded main effects for drug treatment on the day of testing, $F(1, 72) = 17.12$, $p < .001$ for d-amphetamine; $F(1, 90) = 76.23$, $p < .001$ for l-amphetamine. Newman-Keuls multiple comparisons ($\alpha = .05$) were carried out for the simple main effects, since an a priori prediction had been made concerning the interactions (Winer, 1971). These comparisons, together with χ^2 analyses of the group proportion data, revealed that regardless of dosage, all animals which were treated with five daily injections of either d- or l-amphetamine and tested with saline did

Figure 24 Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of d-amphetamine dosage (0.0, 5.0, 10.0 or 15.0 mg/kg) during a 5 day chronic period and drug treatment on test day (5.0 mg/kg of d-amphetamine or saline).

Figure 25

Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of 1-amphetamine dosage (0.0, 15.0, 30.0, 45.0 or 60.0 mg/kg) during a 5 day chronic period and drug treatment on test day (15.0 mg/kg of 1-amphetamine or saline).

not differ from animals which received saline during pre-exposure and test. In contrast, among mice pretreated with saline or low dosages of d-amphetamine (5 mg/kg) or l-amphetamine (15 and 30 mg/kg) significant perseveration was observed when testing was carried out in the drug state. However, tolerance to the perseverative effects of d- and l-amphetamine was evident following pre-exposure to either 10 or 15 mg/kg of d-amphetamine or 45 mg/kg of l-amphetamine. As seen in Figures 24 and 25, the tolerance observed using the l-isomer was not as pronounced as that seen after chronic treatment with d-amphetamine.

In considering locomotor activity, it was found that animals treated with d- or l-amphetamine on the test day made a greater number of arm entries than did saline mice, $F's(1, 72) (1, 90) = 21.81, 23.32, p < .001$, respectively. Moreover, tolerance to this effect was not observed in that pre-exposure to the drug did not significantly affect activity, regardless of the dosages used.

Experiment 17

Although tolerance to the perseveration elicited by the optical isomers of amphetamine was observed, it is clear that the degree of tolerance was substantially more pronounced with the d- than with the l-isomer. Given that tolerance to the effects of the l-isomer were minimal, interpretation of these data with respect to the involvement of p-hydroxynorephedrine are, at best, equivocal.

The purpose of Experiment 17 was two-fold. First, to ascertain whether the tolerance effect observed with l-amphetamine in Experiment 16 was in fact a reliable one, and second, to determine whether cross-tolerance would be observed between the optical isomers of amphetamine. Aside from its heuristic value, this data may provide prima facie evidence concerning the role of p-hydroxynorephedrine in the tolerance effect (Lewander, 1974). Specifically, p-hydroxynorephedrine is a metabolite of d- but not of l-amphetamine (Goldstein & Anagnoste, 1965). Thus, if p-hydroxynorephedrine is a major contributing factor to the appearance of tolerance, then chronic treatment with l-amphetamine should not result in tolerance to the perseverative effects of the d-isomer. In contrast, since accumulation of p-hydroxynorephedrine occurs with prolonged exposure to the d-isomer (Brodie et al., 1970; Lewander, 1971; Theonen et al., 1966), the perseveration produced by the l-isomer should be attenuated. If p-hydroxynorephedrine is not involved in the tolerance phenomena, then symmetrical cross-tolerance between the amphetamine isomers should be observed.

Method

Subjects and Apparatus

A total of 45 female and 45 male Swiss-Webster mice served as subjects. All subject specifications, as well as the apparatus employed, were the same as that previously described in Experiment 14.

Procedure

Mice received daily subcutaneous injections of either d-amphetamine sulfate (10.0 mg/kg), l-amphetamine sulfate (45.0 mg/kg) or saline (10 ml/kg) for five consecutive days. On the sixth day (test day) each of these groups were subdivided and received intraperitoneal injections of either d-amphetamine (5.0 mg/kg), l-amphetamine (15.0 mg/kg) or saline (10 ml/kg). The testing procedure was identical to that of Experiment 1.

Results

The mean number of individual alternations and mean number of arm entries as a function of drug treatments are shown in Figure 26. Analysis of variance of individual alternation scores yielded significant main effects for Chronic and for Acute Drug Treatments, F 's(2, 81). (2, 81) = 6.61, 19.80, $p < .005$, $p < .001$, respectively. The interaction approached, but did not reach a statistically significant level, $F(4, 81) = 2.14$, $p = .08$. Newman-Keuls multiple comparisons of the simple main effects together with χ^2 analysis revealed that animals treated with saline on the test day alternated at levels which exceeded chance regardless of prior drug history (χ^2 's = 11.04, 7.64, 10.96, 5.48, $df = 1$, $p < .05$, among d-amphetamine, l-amphetamine, and saline pretreated mice respectively). Moreover, performance among these groups did not differ from one another. In contrast, animals pretreated with saline and tested with either d- or l-amphetamine showed significant perseveration scores ($\chi^2 = 35.92, 54.40$, $df = 1$, $p < .001$). Although the perseverative tendency was not entirely eliminated, exposing mice

Figure 26 Mean proportion of alternation responses ($\pm$ S.E.M.) and mean number of arm entries ($\pm$ S.E.M.) as a function of drug treatment during the chronic phase (5 successive daily injections of either saline, 10.0 mg/kg of d-amphetamine or 45.0 mg/kg of l-amphetamine) and drug treatment on test day (saline, 5.0 mg/kg of d-amphetamine or 15.0 mg/kg of l-amphetamine).

to either d- or l-amphetamine for five days significantly reduced the perseveration produced by both drugs (χ^2 's = 20.76, 9.04, 11.64, 9.96, df = 1, $p < .05$).

As shown in Figure 26, symmetrical cross-tolerance was also observed in that transfer from the d- to the l-isomer and vice versa, from the l- to the d-isomer, yielded lower perseveration scores relative to that observed in mice which received pretreatment with saline and transferred to either of the amphetamine treatments on test day.

As in the previous experiments, tolerance to the locomotor stimulating properties of amphetamine was not observed. Analysis of variance of the arm entries yielded a significant effect only for drug treatment on test day, $F(2, 81) = 10.18$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) of the main effects indicated that treatment with d- or l-amphetamine on the test day produced locomotor activity which was significantly higher than that of animals treated with saline, regardless of prior drug history.

Discussion (Experiments 13-17)

The perseveration produced by d-amphetamine was significantly attenuated by pre-exposure to the drug. These results extend further the data from a previous report in which similar tolerance was observed in a highly inbred strain

of mouse (Kokkinidis et al., 1976). In addition, the results of the present investigation revealed that 10 mg/kg of d-amphetamine injected daily for five consecutive days was sufficient to produce the tolerance effect.

As in the case of the d-isomer, administration of l-amphetamine elicited perseveration. Tolerance was observed to the perseverative effects of l-amphetamine but not to the locomotor stimulating properties of the drug. In addition, symmetrical cross-tolerance (i.e., from d- to l-amphetamine and from l- to d-amphetamine) was evident. Since p-hydroxynorephedrine does not accumulate at the noradrenergic synapse following chronic exposure to the l-isomer (Goldstein et al., 1964), these data provide indirect evidence which are incompatible with the notion that p-hydroxynorephedrine is involved in the tolerance phenomenon. This finding is consistent with a recent report showing that cross-tolerance between the isomers is evident for the anorexic effects of amphetamine as well (Lewander, 1974). Although these data suggest that the formation of p-hydroxynorephedrine may not play a critical role in the tolerance observed in this investigation, further work entailing more direct evaluative techniques is necessary. Moreover, the possibility that other false transmitters such as p-hydroxyphenylethanolamine (octopamine) (Kostopoulos & Yarbrough, 1975) may be involved in the tolerance cannot be dismissed.

Tolerance to amphetamine should also be evaluated from the strictly behavioral aspect. In particular, the behavioral effects of amphetamine may be dependent upon situational variables and may come under stimulus control. That is, environmental influences or conditioning factors may also play an important role in the development of tolerance (Campbell & Seiden, 1973; Carlton & Wolgin, 1971; Rech et al., 1975; Thompson & Schuster, 1968; Tilson & Rech, 1973). Since stimulus factors are also involved in the perseverative effects of d-amphetamine (Kokkinidis & Anisman, 1976a), the possibility cannot be dismissed that such factors may play a role in the development of tolerance to d-amphetamine-induced perseveration.

SPONTANEOUS ALTERNATION/PERSEVERATION -
BEHAVIORALLY AUGMENTED TOLERANCE

As alluded to earlier, Carlton and Wolgin (1971) found that tolerance to the anorexigenic effects of d-amphetamine developed if the drug preceded presentation of sweetened milk, but not if the animals received post-trial injections of the drug. Similar findings have been reported with respect to the disruptive effects of d-amphetamine on a DRL schedule for appetitive reinforcement (Campbell & Seiden, 1973). Conditioning factors have also been proposed as a determinant for the increased locomotor excitation seen after chronic drug treatment (Rech et al., 1975). It has been argued, however, that this factor cannot entirely account for the observed variance (Segal, 1975).

An alternative, behaviorally-based approach, to explain tolerance phenomena has recently been proposed (Siegel, 1976, 1977). According to this view, a compensatory antagonistic physiological reaction is triggered by drug treatment. This compensatory reaction is stimulus bound, and as a result the apparent strength of the primary drug reaction decreases with successive treatments. In support of this position, it has been demonstrated that following tolerance to a particular drug, a single saline injection produces a behavioral response opposite in direction to that typically observed after acute drug administration (Siegel, 1977). Presumably, this reflects the elicitation of the conditioned compensatory reaction in the absence of the primary systemic effects of the

drug. Since stimulus factors appear to be involved in the perseverative effects of d-amphetamine (Kokkinidis & Anisman, 1976a), it would be of considerable interest to determine whether the development of tolerance to perseveration following chronic drug treatment involves conditioning factors.

Experiment 18

The influence of stimulus factors on the amphetamine-induced perseverative response was examined in Experiment 18. It was previously demonstrated that prior exposure to the Y-maze resulted in a marked enhancement of perseverative behavior (Anisman & Kokkinidis, 1975). Presumably, habituation to the apparatus attenuated the alternation tendency (Swonger & Rech, 1972), which ordinarily competes with perseveration, thus maximizing the perseverative response (Kokkinidis & Anisman, 1976a). Accordingly, it would be expected that changing the stimulus array of the apparatus, by making the arms of the Y-maze distinctively different from one another, would result in the course of habituation being attenuated (Egger, 1973), and thus the intensity of the perseverative response should decline.

Subjects

A total of 36 male and 36 female Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. Mice were housed in groups of 6 in standard polypropylene cages and allowed free access to food and water. Subjects were approximately 55-65 days of age at the time of testing.

Apparatus

The apparatus used to measure spontaneous alternation/perseveration and locomotor activity was the same as that described in Experiment 13. In this experiment, however, the floor of the apparatus consisted of removable black or white Plexiglas sections which completely covered the arms and choice area of the maze.

Procedure

Experiment 18 involved a 3(drug) x 4(floor arrangement) factorial design. Mice (n= 6/cell) received i.p. injections of either saline or d-amphetamine sulfate (3.0 or 5.0 mg/kg salt weight). Drugs were administered in a 10 ml/kg volume. Fifteen minutes following injection mice were placed in the Y-maze and allowed to explore freely. The floor of the apparatus was manipulated such that four possible color arrangements existed. All arms were either a single color (i.e., all white or all black) or one arm was an odd color (i.e., 1 black, 2 white or 1 white, 2 black). The position of the odd color was counterbalanced across arms.

The sequence and number of arm entries were recorded over a 15 min period. Scoring of alternation/perseveration was the same as that described in Experiment 13. The data were analyzed by analysis of variance of the individual alternation scores, and by χ^2 analysis of the proportion of total alternations for a given group of animals. The latter measure is weighted in favor of more active animals

since each arm entry is weighted equally. That is, animals which make 30 arm entries influence the χ^2 analysis to a greater degree than animals which make only 5 arm entries. The former measure, on the other hand, weights the score of each animal equally regardless of the number of arms entered. In each of the experiments reported, the proportion of alternations were comparable regardless of the method of computation, suggesting that alternation scores were not biased by the levels of activity demonstrated within groups. Activity levels were determined on the basis of the number of arm entries.

Results

The mean proportion of alternation scores as a function of drug treatment and floor arrangement are shown in Table 4. Since alternation performance was comparable among mice when the floor of the apparatus was a single color (i.e., all white or all black), and performance among mice did not vary as a function of the position of the odd color, an analysis of variance was conducted on a 3(drug) x 2(floor color; same vs. different) design ($n = 12/\text{cell}$).

This analysis revealed a significant main effect for drug treatment only, $F(2, 66) = 32.0$, $p < .001$. Newman-Keuls multiple comparisons of the simple main effects were carried out since an a priori prediction concerning the interaction was made (Winer, 1962). Together with χ^2 analyses of the total proportion data, these comparisons revealed that regardless of the floor arrangement mice in the saline groups alternated at levels which exceeded chance, $\chi^2(1) = 51.10$, 51.06 , $p < .01$ (for mice treated with saline and assigned to the same and different

Table 4

Mean Proportion ($\pm$ S.E.M.) of Spontaneous Alternation as a
Function of Drug Treatment and Floor Arrangement

	Saline	d-Amphetamine 3.0 mg/kg	d-Amphetamine 5.0 mg/kg
Same	.635 $\pm$.015	.593 $\pm$.021	.291 $\pm$.046
Different	.621 $\pm$.020	.568 $\pm$.024	.402 $\pm$.069

conditions, respectively). In contrast, treatment with d-amphetamine (5.0 mg/kg) significantly reduced spontaneous alternation to levels which were well below chance (perseveration), $\chi^2(1) = 225.3, 19.68, p < .01$ (for mice treated with d-amphetamine 5.0 mg/kg and assigned to the same and different conditions, respectively). As predicted, perseveration was more pronounced when the floor of the apparatus was a single color than when a compartment had a floor of an odd color (see Table 4).

Owing to the relatively large variability of the 5.0 mg/kg group tested with the odd floor arrangement, a partial replication of the experiment was undertaken. Consistent with Experiment 18, it was found that the effects of d-amphetamine (5.0 mg/kg) on perseverative behavior were dependent on the stimulus aspects of the maze $t(18) = 2.17, p < .05$. When the floor of the maze was homogeneous in color, marked perseveration was noted ($\bar{X} \pm \text{S.E.M.} = .324 \pm .058; \chi^2(1) = 77.16, p < .01$), whereas chance level performance was observed when the floor was heterogeneous in color ($\bar{X} \pm \text{S.E.M.} = .484 \pm .048; \chi^2(1) = .16, p > .10$).

Analysis of variance of the mean number of arm entries revealed that all arms were frequented equally, regardless of drug treatment or floor arrangement. Consistent with previous reports (Anisman & Kokkinidis, 1975), treatment with d-amphetamine (3.0 or 5.0 mg/kg) produced a marked increase in the number of arms entered, $F(2, 66) = 11.34, p < .001$ (means for saline, 3.0 and 5.0 mg/kg groups, respectively were 63.96, 98.46, 139.02). In contrast to the data involving perseveration, changes in floor color had no effect on the locomotor excitation induced by d-amphetamine. Taken together, the results of this experiment

provide further evidence as to the distinct nature of these two amphetamine-induced behaviors. Whereas perseverative behavior is dependent upon stimulus factors, changes in the stimulus array of the apparatus did not alter the locomotor excitation produced by drug treatment.

Experiment 19

As previously discussed, conditioning factors have been found to play an important role in the development of tolerance insofar as several behaviors are concerned (Campbell & Seiden, 1973). Since stimulus factors apparently are involved in perseveration, it would be of considerable interest to determine whether conditioning factors play a role in the development of tolerance to amphetamine-induced perseverative behavior. Accordingly, mice were treated chronically with d-amphetamine such that the systemic effects of the drug were either congruent with experience in the Y-maze, or occurred following exposure to the Y-maze. If conditioning factors influence the development of tolerance, then it would be expected that a greater attenuation of amphetamine-induced stimulus perseveration would occur when the drug and testing experience were temporally congruent.

The notion of conditioned tolerance (Siegel, 1976, 1977) can be tested readily using the same paradigm. If the observed tolerance to stimulus perseveration is the result of an antagonistic conditioned compensatory

reaction, then a single saline injection to tolerant animals should produce a marked increase in alternation levels relative to mice injected with d-amphetamine. Experiment 19 was designed to evaluate these possibilities. In addition, two other amphetamine-induced behaviors were assessed (i.e., locomotor activity and stereotypy). It should be noted that experiments involving these behaviors typically utilize relatively long observation periods (Segal, 1975). In the present experiment, mice were observed only for the period corresponding to spontaneous alternation testing, in order to determine whether the development of tolerance to the perseverative effects of d-amphetamine is related to changes in locomotor activity or stereotypy following chronic drug treatment.

Subjects and Apparatus

A total of 48 (24 female and 24 male) Swiss-Webster mice served as subjects. All specifications concerning subjects were the same as those described in Experiment 18, except that mice were housed individually. The apparatus was identical to that used in Experiment 18 with the exception that the Plexiglas floors were removed exposing the grid floor. The grid floor was made up of 0.25 cm stainless steel rods spaced 1.0 cm apart.

Procedure

Mice were randomly assigned to one of three groups ($n=16/\text{cell}$), and tested in the alternation task for 15 min, on 3 consecutive days. On days 4-8, mice received i.p. injections of either saline or d-amphetamine sulfate (10.0 mg/kg)

and were subsequently tested in the Y-maze 15 min following injection (pre-trial). Mice in the third group received an i.p. injection of 10 mg/kg of d-amphetamine immediately following testing (post-trial). The number and sequence of arm entries were recorded throughout training.

In addition to monitoring levels of spontaneous alternation and locomotor activity, mice were rated for stereotypy throughout the 15 min test period. The ratings were taken at 5 min intervals using the rating scale described by Ellinwood and Balster (1974) and detailed in Experiment 10. The post-trial group was rated twice, once during behavioral testing and 15 min after drug injection in the home cage. On test day (day 9) mice were sub-divided such that half the animals in each group ($n=8/\text{cell}$) received i.p. injections of either saline or 5 mg/kg of d-amphetamine. Fifteen minutes after injection mice were tested for spontaneous alternation and locomotor activity in the Y-maze for a 15 min period.

Results

Pre-habituation -- Phase I

The mean proportion of spontaneous alternation, the mean number of arm entries as well as the mean rating score for stereotypy during the three phases of Experiment 19 are shown in Figure 27. Analysis of variance of the alternation scores, arm entries, and stereotypy scores of the first phase of

Figure 27 Mean proportion of alternation responses ($\pm$ S.E.M.), mean number of arm entries ($\pm$ S.E.M.), as well as mean stereotypy scores ($\pm$ S.E.M.) as a function of prehabitation (phase 1, no-drug), drug treatment during the chronic phase (phase 2, pre-trial injection of saline or d-amphetamine 10.0 mg/kg or post-trial injection of d-amphetamine 10.0 mg/kg), and drug treatment on test day (saline or 5.0 mg/kg of d-amphetamine).

Experiment 19 (i.e., no-drug treatment) yielded a significant Days main effect, $F(2, 90) = 16.34, 25.36, 10.43, p < .001$, (for spontaneous alternation, locomotor activity and stereotypy, respectively). Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that animals showed a decline in frequency of the three behaviors over successive days.

Spontaneous Alternation/Perseveration -- Phase 2

Analysis of variance of the sequence of arm entries yielded a significant main effect for drug treatment, $F(2, 45) = 8.33, p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) together with χ^2 analysis revealed that performance was at chance or just above chance levels throughout phase 2 (days 4-8) among mice treated with saline prior to testing, or injected with amphetamine following testing (post-trial). In contrast, treatment with d-amphetamine prior to testing significantly reduced alternation, such that performance was below chance levels, $\chi^2(1) = 144.2, 39.8, 27.4, 11.0, 17.42, p < .01$. As seen in Figure 27, alternation increased from day 4 to day 5. It is not entirely clear whether this increase represents tolerance, or whether the particularly low perseveration scores observed on day 4 were spurious. The latter possibility is not unlikely since previous work from this laboratory, as well as the results of Experiment 3, indicated that perseverative behavior typically ranges from 40-50 percent following 10 mg/kg of d-amphetamine (Anisman & Kokkinidis, 1975).

Locomotor Activity and Stereotypy

Analysis of variance of the number of arm entries yielded a significant Day of Testing, $F(4, 180) = 3.45$, $p < .01$, as well as Drug Treatment, $F(2, 45) = 17.46$, $p < .001$, main effect. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that regardless of the drug treatment, locomotor activity decreased with repeated testing. Treatment with d-amphetamine prior to behavioral testing significantly increased the number of arms entered (see Figure 27).

With respect to the stereotypy ratings, a significant Day of Testing x Drug Treatment interaction was observed, $F(8, 108) = 11.81$, $p < .001$. Newman-Keuls multiple comparisons ($\alpha = .05$) showed that stereotypy ratings of mice in the saline and post-trial amphetamine groups did not change with repeated testing. In contrast, pre-trial injection of d-amphetamine produced significantly higher ratings, and stereotypy was further enhanced with repeated Drug-Test pairings. Moreover, the observed augmentation in stereotypy was not situation specific. Specifically, a separate analysis carried out on the ratings of mice in the pre-trial amphetamine condition (rated in the Y-maze), and mice in the post-trial amphetamine group (rated in the home cage following drug injection), revealed that in both groups stereotypy increased over days, $F(1, 120) = 38.66$, $p < .001$, and performance was comparable between groups.

Spontaneous Alternation/Perseveration -- Test Day

Analysis of variance of the alternation data on test day yielded a significant Chronic x Acute Drug Treatment interaction, $F(2, 42) = 3.45$, $p < .05$. As seen in Figure 27, mice pretreated with saline and tested with d-amphetamine (5 mg/kg) exhibited marked perseverative behavior, $\chi^2(1) = 67.8$, $p < .01$. In contrast, mice chronically treated with d-amphetamine and tested with d-amphetamine alternated at significantly higher rates which were at or just above chance levels, $\chi^2(1) = 4.8$, 1.3 , $p < .05$ and $> .05$ (for pre-trial and post-trial groups, respectively). The finding that this was the case regardless of whether animals received drug injections prior to or following Y-maze exposure during phase II, suggests that conditioning factors are not critical for the development of the observed tolerance. Moreover, a saline injection on test day given to animals chronically treated with d-amphetamine had no effect on subsequent performance, suggesting that a conditioned compensatory reaction is not involved in the observed tolerance (see Figure 27).

Locomotor Activity and Stereotypy

In contrast to d-amphetamine-induced perseveration, tolerance was not observed to the locomotor excitation and stereotypy produced by d-amphetamine. As seen in Figure 27, mice treated with d-amphetamine on test day were more active and had higher stereotypy ratings relative to saline-treated animals, regardless of prior drug history or testing schedule, $F's(1, 42) = 20.39$, 405.4 , $p < .001$, for locomotor activity and stereotypy, respectively. In addition to

the observed main effect for drug treatment on test day, a significant Chronic Drug Treatment main effect was observed with respect to the stereotypy ratings, $F(2, 42) = 4.48$, $p < .05$. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) revealed that on test day mice in the chronic pre-trial amphetamine group displayed a small but significant increase in stereotypy relative to the pre-trial saline controls. However, the source for this effect is not well understood given that stereotypic behavior of mice in the post-trial amphetamine group was not different from that observed among mice in the pre-trial saline or amphetamine groups.

Summarizing, chronic treatment with d-amphetamine attenuated the perseverative response to the drug, whereas tolerance was not observed to amphetamine-induced locomotor excitation and stereotypy (Kokkinidis et al., 1976; Segal, 1975). Taken together, these findings suggest that the development of tolerance to the perseverative effects of the drug is not related to changes in locomotor activity or stereotypic behaviors produced by repeated drug administration. Furthermore, since pairing of drug treatment with the apparatus cues did not influence the extent of the tolerance in the case of perseveration, it is unlikely that conditioning factors play a prominent role in the occurrence of tolerance.

Experiment 20

Experiment 19 revealed that both chronic pre- and post-trial drug treatment produced tolerance to the perseveration elicited by d-amphetamine. These results argue against the involvement of conditioning factors in the development of tolerance. The absence of behaviorally augmented tolerance, however, may have resulted from the rapid development of tolerance observed with chronic drug treatment, i.e., ceiling effects prevented the influence of conditioning factors becoming apparent. Since conditioning factors did not affect performance under conditions where tolerance was apparent it might be expected that behaviorally augmented tolerance would appear when the treatment conditions were such that only limited tolerance would develop. Experiment 20 was designed to examine this possibility. Specifically, it was demonstrated in Experiment 14 that chronic drug treatment for 3 consecutive days was not sufficient to produce tolerance. If conditioning factors affect the rate at which tolerance develops, then tolerance to the perseverative effects of amphetamine might be expected to develop after only 3 daily drug-test pairings.

Subjects

A total of 20 male and 20 female Swiss-Webster mice procured from the Bio-Breeding Laboratories served as subjects. Mice were individually housed and received ad lib. access to food and water.

Apparatus and Procedure

The apparatus used in this experiment was identical to that described in Experiment 19. Mice were randomly assigned to one of five treatment conditions ($n = 8/\text{cell}$) and were tested in the spontaneous alternation task for a 15 min period on 3 consecutive days. On days 4 through 6 the injection and testing procedure for 3 of the groups (i.e., pre-trial saline and amphetamine; post-trial amphetamine) was identical to that described in phase II of Experiment 19. In addition, two separate groups were treated with 3 daily injections of either saline or d-amphetamine (10 mg/kg), and placed in a carrying cage for a 15 min period following injection. The latter two groups did not receive behavioral testing until test day (day 7). On day 7 all mice were tested in the Y-maze after a single i.p. injection of d-amphetamine (5.0 mg/kg). The testing procedure was identical to that observed in the previous experiments.

Results

As observed in Experiment 19 alternation during the non-drug phase was comparable in all groups and declined over the 3 test sessions, $F(2, 70) = 25.01$, $p < .001$. Analysis of variance of the sequence of arm entries from days 4 through 6 yielded a significant main effect for drug treatment only, $F(2, 21) = 8.74$, $p < .005$. As seen in Table 5, treatment with d-amphetamine prior to testing produced significantly lower alternation in relation to performance of mice tested in the non-drug state. Moreover, performance was observed to be stable over the 3 drug/test pairings (see Table 5).

Table 5

Mean Proportion of Spontaneous Alternation ($\pm$ S.E.M.) as a Function of Prior Habituation (Phase 1, No Drug), Chronic Drug Treatment (Saline or 10 mg/kg of d-Amphetamine) During Phase 2 (Pre-trial, Post-trial, No-test), as well as Acute Drug Treatment (5 mg/kg) on Test Day

	DAYS						
	PHASE 1			PHASE 2			TEST
	(NO DRUG)			(d-Amphetamine) 5.0 mg/kg			
	1	2	3	4	5	6	7
Saline	.658 ±.019	.583 ±.018	.587 ±.018	.530 ±.047	.522 ±.026	.563 ±.040	.349 ±.058
d-Amphetamine (pre-trial)	.702 ±.036	.636 ±.035	.570 ±.017	.426 ±.065	.411 ±.047	.446 ±.043	.362 ±.050
d-Amphetamine (post-trial)	.685 ±.026	.563 ±.027	.562 ±.015	.576 ±.021	.562 ±.016	.565 ±.021	.373 ±.044
Saline (no-test)	.640 ±.033	.556 ±.036	.563 ±.031				.351 ±.044
d-Amphetamine (no-test)	.690 ±.036	.632 ±.019	.571 ±.023				.389 ±.045

Consistent with previous observations tolerance was not evident after 3 daily injections of amphetamine. In particular, mice assigned to the 5 experimental conditions exhibited marked perseverative behavior when 5 mg/kg of d-amphetamine was administered on test day, χ^2 's(1) = 34.64, 89.2, 32.2, 30.4, 8.04, $p < .01$, for pre-trial saline and amphetamine, post-trial amphetamine, and no-test saline and amphetamine groups, respectively. Since behaviorally augmented tolerance was not observed (see Table 5), it is likely that conditioning factors do not play a major role in the development of tolerance to amphetamine-induced stimulus perseveration.

Discussion (Experiments 18-20)

The results of Experiment 19 extend previous observations concerning the effects of d-amphetamine on perseverative behavior in a Y-maze exploratory task (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a, b). The fact that differentiating the arms of the Y-maze disrupted perseveration is consistent with the notion that stimulus factors play an integral role in the elicitation of the drug-induced perseverative response. It is not clear, however, whether the attenuation of perseveration was secondary to decreased rates of habituation (Kokkinidis & Anisman, 1976a), or whether stimulus factors directly influenced the perseveration. Although stimulus factors are involved in amphetamine-induced perseveration, conditioning factors probably do not play a major role in the development of tolerance. Specifically, the development of tolerance was not augmented by pairing the chronic drug experience with Y-maze exposure, nor was

the magnitude of the tolerance effect altered by prior drug-test pairings. Furthermore, the fact that repeated amphetamine treatment did not enhance alternation when animals were tested with saline, suggests that conditioned rebound effects (Siegel, 1976, 1977) likewise do not play a major role in the development of tolerance. It must be emphasized that although the data of the present report are not in support of a role for conditioning in the development of tolerance to amphetamine-induced perseveration, this is not to say that such processes are not involved in tolerance to other amphetamine-induced behaviors. Moreover, the possibility also exists that the occurrence of perseveration and its subsequent disruption with repeated drug treatments involves variations in the response to selective stimuli. Elaboration of this notion will be held in abeyance until the General Discussion.

In contrast to stimulus perseveration, tolerance was not observed to develop to the locomotor or stereotypic effects of the drug. Taken together with previous findings (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a), these results suggest that the perseverative response is not related to drug-induced locomotor excitation or stereotypy. Similarly, although the competitive relationship between stereotypy and locomotor activity is apparent after chronic drug treatment (Segal, 1975), it is likely that the tolerance observed to stimulus perseveration is independent of changes in these behaviors following repeated drug administration.

General Discussion

Consistent with earlier reports the results of the present investigation indicated that d-amphetamine will elicit several different behavioral changes, including locomotor excitation, increased reactivity to strong stimuli, enhanced startle reflex, stereotypy, circling and perseveration. Generally speaking, these behaviors can be categorized into: (a) those primarily subserved by DA and those primarily subserved by NE; (b) parallel vs. serial drug-induced behavioral effects, and (c) behaviors which are subject to tolerance and those which are not. These dichotomies are discussed in the ensuing section.

I. EFFECTS OF ACUTE AMPHETAMINE TREATMENT

Locomotor Activity. In accordance with numerous other reports (see review in Peters et al., 1978), acute administration of d-amphetamine produced a dose-dependent increase in locomotor activity. Moreover, the locomotor excitation was found to vary in a temporal fashion. Soon after drug administration high levels of locomotor activity were observed, followed thereafter by a decline in horizontal activity. As will be seen in the section on stereotypy the phase of decreased horizontal locomotion was not indicative of motor depression but rather was a consequence of the intrusion of competing vertical movements (i.e., grooming). Whether or not these competing behaviors occurred was dependent upon the dosage employed, and the temporal patterns of motor excitation varied with

dosage as well. That is, with appropriate dosages, d-amphetamine elicited marked stereotypy which was incompatible with ambulation. Thus, with the appearance of stereotypy the horizontal locomotor activity otherwise observed was suppressed.

As indicated previously (cf., Groves & Rebec, 1976), the reduction of DA and NE via tyrosine hydroxylase inhibition successfully attenuated the locomotor excitation induced by d-amphetamine. In contrast, reduction of NE by dopamine- β -hydroxylase inhibition did not modify general locomotor activity. These data argue in favor of the notion that the motor excitation induced by d-amphetamine is subserved primarily by dopamine activity, although a role for norepinephrine cannot be entirely excluded (see discussions in Antelman & Caggiula, 1977; Hornykiewicz, 1977; Peters et al., 1978). The conclusions derived from studies involving synthesis inhibition are supported by the finding that chemical lesions of DA pathways by 6-OHDA mitigate the drug-induced excitation, whereas dorsal or ventral noradrenergic lesions are ineffective in this respect (Creese & Iversen, 1972, 1975; Roberts et al., 1975).

Although few theorists would debate the critical role of DA in mediating the amphetamine-induced locomotor excitation, it must be underlined that norepinephrine manipulations have been found to influence locomotor activity (see Peters et al., 1978). Moreover, the motor excitation induced by amphetamine has also been shown to be modifiable by serotonergic and cholinergic manipulations (cf., Groves & Rebec, 1976). Accordingly, it is premature to dismiss the potential role of NE, 5-HT and ACh in subserving the amphetamine-induced motor excitation. Indeed, when the various pharmacological interactions on locomotor activity are considered (cf., Anisman, 1975a; Anisman & Bignami, 1978), it becomes evident that even apparently simple behaviors are subject to modulation by complex neurochemical balances. Nevertheless, given the particularly potent effects of dopamine manipulations on locomotor activity, it would seem that this transmitter is essential for the drug-induced excitation to appear.

Stereotypy. Consistent with a number of other reports (cf., Antelman & Caggiula, 1977; Wallach, 1974) d-amphetamine was found to elicit pronounced stereotyped behaviors. In its extreme form the stereotypy was characterized by continuous licking, grooming, and sniffing. The occurrence of the stereotypy varied in a temporal fashion. That is, little if any stereotypy was apparent soon after injection (i.e., during the phase associated with heightened horizontal locomotor activity). However, marked repetitive behaviors were manifested 30-60 min after drug administration. This period, as previously described, was associated with relatively low levels of horizontal locomotor activity. In agreement with the speculation of Segal (1975), it appeared that the increase in stereotypy occurred at the expense of a decrease in ambulation. Predictably, modification of the stereotypy influenced the expression of the horizontal motor activity.

Consistent with reports utilizing either enzyme inhibitors (Scheel-Kruger, 1971), receptor blockers (Rolinski & Scheel-Kruger, 1973) or neurotoxins (Creese & Iversen, 1972, 1974, 1975), the stereotypy appeared to be DA mediated. That is, whereas depletion of NE did not reduce stereotypy, depletion of both DA and NE successfully antagonized this behavior. This does not imply that other transmitters do not contribute to the drug-induced stereotypy. In fact, as reported by Mogilnicka and Braestrup (1976), dopamine- β -hydroxylase inhibition accentuated the stereotypy engendered by amphetamine. Whether this represents a direct effect on stereotypy or a secondary (serial) effect owing to changes in other behaviors is not clear. Nevertheless, the fact remains that NE does seem to influence the expression of the stereotypy.

Shock-induced Reactivity. Application of footshock, which ordinarily results in response suppression (freezing), elicited pronounced motor excitation among mice treated with d-amphetamine. In fact, the motor activity observed under these conditions exceeded that seen after drug treatment alone. Unlike inbred strains of mice where the excitation is evident after a single shock (Anisman, 1976; Anisman & Cygan, 1975; Anisman et al., 1975), several shock presentations were necessary in order to elicit the excitation in the Swiss-Webster strain of mouse. Consistent with the results of Anisman (1976), the appearance of the post-shock excitation was independent of the level of general locomotor activity. That is, the excitation could be elicited even if the level of locomotor activity induced by amphetamine was relatively low (see Experiment 12). Furthermore, the post-shock excitation appeared to be independent of the stereotypic effects engendered by d-amphetamine. Specifically, the temporal changes in ambulation were not accompanied by parallel variations in stereotypic behaviors.

Despite the fact that the post-shock excitation, as well as the sensitization effect, were independent of general locomotor activity and stereotypy, this behavior seemed to be largely mediated by dopaminergic activity. This, however, is not to the exclusion of a noradrenergic contribution. To be sure, dopamine- β -hydroxylase inhibition effectively reduced the extent of the sensitization, thus implicating a noradrenergic involvement. When tyrosine hydroxylase was inhibited, the sensitization was entirely mitigated. Under these conditions the amphetamine-treated mice resembled saline animals as indicated by the decline in activity produced by footshock. Accordingly, it appears likely that although norepinephrine contributes to the shock-induced excitation, adequate dopamine activity is requisite in order that such an effect be apparent.

Startle. As reported in numerous experiments the presentation of a strong auditory stimulus will result in the elicitation of a startle reflex (cf., Davis et al., 1975). With repeated stimulus presentations the strength of this response was found to wane. Treatment with d-amphetamine resulted in the augmentation of the startle reflex. In contrast to previous reports by Davis and his associates (Davis et al., 1975; Davis & Aghajanian, 1976), the magnitude of the startle reflex did not increase with successive stimulus presentations (i.e., sensitization). If, however, testing was initiated immediately following drug administration, then an increase in response strength was noted over the course of the first fifteen stimulus presentations. It is not unreasonable to suppose that this effect was a reflection of a peak drug action as opposed to a genuine sensitization effect.

The startle reflex should be differentiated from reactivity after shock, in that the latter measure reflects activity during a protracted period following the stimulus presentation, whereas the startle response was measured during the stimulus presentation. Moreover, while a sensitization-like effect was noted in the shock-induced reactivity situation, this was not the case when the startle reflex was considered. While speculative, it may have been the case that Davis et al. were evaluating a behavior comparable to reactivity rather than startle per se.

The amphetamine elicited startle reflex can be dissociated from general locomotor activity and stereotypy. Unlike the latter behaviors, the amphetamine-induced startle was effectively antagonized by dopamine- β -hydroxylase inhibition. As a matter of fact, treatment with FLA-63 was equipotent with α -MpT in this respect. As such, it seems that norepinephrine activity is critical in the elicitation of the startle response among amphetamine treated animals. Inasmuch as locomotor activity was unaffected by FLA-63, a behavior particularly sensitive to toxic drug effects, it is unlikely that the effect of FLA-63 on startle was an artifact of the non-specific effects of the drug. However, the possibility cannot be entirely excluded that startle was more sensitive to toxic effects than was locomotor activity.

Spontaneous Alternation/Perseveration. Previous work from this laboratory (Anisman & Kokkinidis, 1975), as well as from other laboratories (Adkins et al., 1972) have revealed that the alternation tendency ordinarily seen in a T- or Y-maze exploratory task is antagonized by d-amphetamine. It has consistently been reported that with adequate doses, amphetamine will result in a perseverative tendency (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a, b, 1977). This effect is independent of changes in activity or stereotypy in that modification of (the latter behaviors will not necessarily influence the perseverative tendency (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a). Indeed, it was suggested that the perseverative tendency, unlike locomotor activity and stereotypy, involved noradrenergic activity since dopamine- β -hydroxylase inhibition modified the expression of the perseverative behavior (Anisman & Kokkinidis, 1975).

As discussed in the introduction and supported in the present report, the alternation and perseveration tendencies are largely dependent upon stimulus factors. To be more explicit, over the course of the 15 min testing session the perseverative tendency becomes progressively more pronounced, owing presumably to the decline of the competing alternation tendency (cf., Kokkinidis & Anisman, 1976a). Not surprisingly, prior habituation to the Y-maze, which likewise results in a diminution of the alternation tendency, permits the expression of the perseveration even when fairly low dosages of d-amphetamine are employed (Kokkinidis & Anisman, 1976a). Conversely, by making the arms of the Y-maze distinctive from one another, a treatment previously shown to enhance alternation (Egger, 1973), the perseverative tendency is reduced.

Rotational Behavior. Following systemic treatment with d-amphetamine, mice, like rats (Glick & Jerussi, 1974), were found to exhibit a rotational bias. While Glick and his associates (Glick et al., 1975; Glick & Jerussi, 1974; Jerussi & Glick, 1974, 1976) have argued that the circling reflects a hemispheric dopamine imbalance, similar to that produced by unilateral 6-OHDA lesions (Ungerstedt, 1971b), Kokkinidis and Anisman (1977) have provided evidence which militates against such a conclusion. These investigators have proposed that the circling produced by systemic amphetamine administration should more appropriately be considered as a reflection of a perseverative tendency (see introduction). More specifically, it is possible that the initial direction the animal selects may be a consequence of a hemispheric dopamine imbalance; however, the persistence of this behavior represents a form of stimulus perseveration.

In accordance with the view proposed by Kokkinidis and Anisman (1977), the results of the present investigation indicated that as in the case of perseveration in a Y-maze prior exposure to the apparatus enhanced the rotational behavior elicited by amphetamine. Furthermore, the rotational behavior was effectively antagonized by dopamine- β -hydroxylase inhibition, suggesting a prime role for NE in the mediation of circling. Finally, as observed in the Y-maze perseveration situation, the occurrence of circling was not related to drug-induced locomotor excitation, a behavior which seems to be primarily DA-mediated. While these data provide only prima facie evidence concerning the

relationship between circling and perseveration, when coupled with the results of Kokkinidis and Anisman (1977; see introduction) they argue strongly against the notion that circling simply reflects a turn bias. Indeed, it would seem incumbent upon theorists supporting an hypothesis based on the notion of a hemispheric dopamine imbalance, to demonstrate that perseverative tendencies, such as those seen in the Y-maze, are aligned with differential dopamine activity in the two hemispheres.

II. EFFECTS OF CHRONIC AMPHETAMINE TREATMENT

Task Differentiation. Repeated administration with d-amphetamine was found to produce behavior-specific tolerance. That is, the effects of amphetamine on perseveration, circling, startle reflex and to a lesser extent shock-induced reactivity, were reduced if mice had received previous exposure to amphetamine for 5 successive days. In contrast, locomotor activity and stereotypy, as well as the sensitization effect observed after shock, did not undergo tolerance. The initial locomotor excitation engendered by d-amphetamine was reduced in chronically treated mice; however, as reported by Segal (1975) this appeared to be a consequence of the stereotypy being intensified and occurring earlier. Indeed, owing to dissipation of the stereotypy, locomotor excitation at the mid-point of the test session increased relative to that seen among mice which received acute amphetamine treatment.

Table 6 depicts those behaviors in which tolerance was observed to develop and those in which it was not, and also indicates the behavioral consequences of α -MpT and FLA-63 on these drug-induced behaviors. As seen in the table those behaviors subject to tolerance were also attenuated by FLA-63, whereas behaviors which were not subject to tolerance were antagonized by α -MpT, but not by FLA-63. In fact, insofar as stereotypy is concerned, both chronic treatment and FLA-63 resulted in the augmentation of the behavior. Taken together, these data would suggest that tolerance occurs primarily to behaviors which principally involve a noradrenergic component. Since the chronic effects of d-amphetamine paralleled the effects of FLA-63, both in terms of its neurochemical and behavioral consequences, the suspicion should be entertained that the tolerance is a reflection of changes in noradrenergic activity. Given that a limited number of behaviors were considered in the present investigation, the conclusion of noradrenergic specificity can be considered at best as a provisional working hypothesis. Clearly, it must be determined whether, under other circumstances, tolerance might be observed to develop to other dopamine mediated behaviors.

Aside from the evidence presented in this series of experiments, there are additional data available which support the conclusions formulated here. More specifically, the increase in self-stimulation elicited by d-amphetamine is subject to tolerance when electrodes are situated in the medial forebrain bundle, a region rich in NE, but not when placed in the substantia nigra, an

Table 6

The Effects of α -MPT, FLA-63 and Chronic Amphetamine Administration on Several Behaviors Elicited by 5.0 mg/kg of d-Amphetamine

	α -MPT	FLA-63	Chronic Amphetamine
Locomotor Activity	↓ ↓	—	—
Stereotypy	↓ ↓	— or ↑	— or ↑
Shock-induced Reactivity	↓ ↓	↓	↓
Startle Reflex	↓ ↓	↓ ↓	↓ ↓
Rotational Behavior	↓ ↓	↓ ↓	↓ ↓
Perseverative Behavior	↓ ↓*	↓ ↓*	↓ ↓*

↓↓ complete antagonism

↓ partial antagonism

↑ increase

— no effect

* chance level alternation

area particularly rich in DA (Liebman, 1974; Leith & Barrett, 1976). As concerns other amphetamine-induced behaviors (e.g., anorexia and performance on time-based schedules of reinforcement (Campbell & Seiden, 1973; Lewander, 1971, 1974), there are not sufficient data available to determine the contributions made by NE and DA. As such, experiments concerning tolerance to these behaviors do not speak to the formulations derived in the present report. However, these behaviors must be differentiated from those described earlier, since these alone have been shown to be subject to behaviorally augmented tolerance, i.e., tolerance dependent upon the stimulus complex (Carlton & Wolgin, 1971; Gotesdam & Lewander, 1975).

In considering the occurrence of reverse tolerance (i.e., exaggeration of amphetamine-induced behaviors), it has been argued in the present report that such effects will occur only to behaviors mediated by dopamine. Three alternatives related to DA functioning have been proposed to account for the behavioral augmentation. One view for the increase in stereotypic behaviors following chronic exposure to the drug concerns the notion that stereotypy is due to inhibition of neuronal activity in the nigro-neostriatal pathway (Groves, 1977). With prolonged inhibition of neuronal activity following chronic exposure to the drug, the stereotypic response ordinarily observed is exacerbated (Groves, 1977). A second hypothesis is that the increased stereotypic behavior observed to develop following chronic drug treatment is due to an increase, rather than a decrease of dopamine biosynthesis. That is, following chronic

amphetamine treatment a compensatory response of increased dopamine biosynthesis would occur as a result of the initial drug-induced DA depletion (Segal, 1975). Finally, it has been argued that decreases in dopamine biosynthesis in the neostriatum and substantia nigra will result in DA depletion and consequently receptor supersensitivity (Kilbey & Ellinwood, 1977). Thus, upon subsequent amphetamine treatment the initial release of DA would result in enhanced stereotypy (Kilbey & Ellinwood, 1977). In addition to these hypotheses there remains yet another alternative, based in part on the results of the present series of studies, as well as additional data from this laboratory which have, as yet, not been published. Specifically, as indicated earlier, noradrenergic stimulation may influence the behavioral changes otherwise produced by dopamine receptor stimulation. That is, it is possible that noradrenergic stimulation inhibits the behavioral consequences induced by dopamine stimulation. As such, treatments which reduce NE, e.g., FLA-63 or chronic amphetamine treatment, result in the augmentation of dopamine mediated behaviors (see, for example, Mogilnicka & Braestrup, 1976; and Experiment 11). This notion, although speculative, warrants further consideration.

p-Hydroxynorephedrine as a False Transmitter. Several investigators (Brodie et al., 1970; Kokkinidis et al., 1976; Segal, 1975) have expressed the view that tolerance to the behavioral effects of d-amphetamine might be due to a displacement of NE by the false transmitter, p-hydroxynorephedrine. This false transmitter has been shown to accumulate in NE neurons as long as 24 hrs after the disappearance of the parent compound, d-amphetamine (Freeman & Sulser, 1972; Groppetti & Costa, 1969). Whether or not the accumulation of

p-hydroxynorephedrine is responsible for changes in DA mediated behaviors after chronic treatment cannot be deduced from the data of the present report.

However, it would seem unlikely that this pseudotransmitter is responsible for the decrease of perseverative behavior after chronic amphetamine treatment.

That is, despite the fact that p-hydroxynorephedrine is not formed from l-amphetamine, perseveration ordinarily elicited by this isomer was found to undergo tolerance, and in addition, symmetrical cross tolerance between the optical isomers was observed. The use of the isomer technique to assess the role of p-hydroxynorephedrine provides inferential evidence, and it is still necessary to evaluate the role of the false transmitter by more direct means.

Furthermore, the possibility must be considered that other false transmitters, such as octopamine, are involved in the development of tolerance to amphetamine (cf., Kopin, 1972; Kostopoulos & Yarbrough, 1975).

Behaviorally Augmented Tolerance. As described in the introduction, it has been observed frequently that the chronic effects of various drugs, including amphetamine, may be dependent upon the stimulus complex associated with drug administration. That is, the occurrence of tolerance may be potentiated if the drug is consistently administered in the locale in which testing is subsequently carried out. When perseveration, a behavior dependent upon stimulus factors, was considered, tolerance did not appear to be influenced by the association of the drug and the stimulus complex. The tolerance noted after five days of

amphetamine treatment was not enhanced by exposing mice to the Y-maze while in the drug state. Similarly, three successive days of drug administration did not result in tolerance, regardless of whether the drug was administered prior to or after daily exposure to the Y-maze. Although these data do not support a conditioned tolerance hypothesis, it must be emphasized that given a different drug regimen or a different behavioral test a conditioning effect might be observed. Accordingly, the present data must be viewed within a limited context.

Alternative Proposition. On the basis of the results described thus far, the source for the tolerance as well as for the reverse tolerance cannot be deduced. One major problem in assessing tolerance phenomenon has been the consistent attempt to evaluate the tolerance in terms of variations in neurochemical activity or in terms of conditioning factors. Much too little effort has been expended, in both this and other laboratories, in evaluating the manner by which response to the stimulus array of the environment is modified by acute and chronic drug treatment. This is somewhat anomolous, particularly since the behavioral effects of amphetamine have been consistently used as a model for evaluation of paranoid schizophrenia (cf., Hornykiewicz, 1977). Indeed, rather than attempting to evaluate attentional changes in man following amphetamine treatment, psychologists and pharmacologists alike have expended their efforts in assessing the motoric consequence of acute and chronic amphetamine treatment (see reviews in Ellinwood, 1967, 1969; Hornykiewicz, 1977).

The effect of amphetamine, inter alia, is that of increasing attention. In fact, the therapeutic efficacy of amphetamine and its analogues on hyperkinesis have recently been attributed to the drug's effects on attentional mechanisms (Barkley, 1977a, b). In considering an animal model for schizophrenia, as is frequently done in studies involving amphetamine, it might be more appropriate to evaluate behaviors dependent upon stimulus and attentional factors rather than behaviors which are exclusively motor based and involve nigro-neostriatal activity. This is not to say that the latter measure should be abandoned, but rather that the validity of an animal model would be enhanced given the evaluation of cognitive-like changes in conjunction with behaviors involving nigro-neostriatal dopamine activity.

It has been suggested that administration of amphetamine results in: a) the propagation of behaviors already high in the organism's repertoire (Robbins, 1975, 1977), and b) the elicitation of responses to biologically significant stimuli (Campbell & Randall, 1975, 1977). In considering the perseveration induced by d-amphetamine, Kokkinidis and Anisman (1976a, b) suggested that these factors may be responsible for the behavioral changes observed. Unlike anti-cholinergics, the effect of amphetamine is not one of simply disrupting alternation behavior, i.e., dishabituation (Kokkinidis & Anisman, 1976b). The occurrence of perseveration must be viewed as the elicitation of a new behavior. Given that the perseverative tendency is modifiable by the organism's prior experience to the apparatus, the notion should be entertained that this behavior represents an increase in attention to selected stimuli. Prior habituation to the apparatus enhances the perseveration, owing to the elimination of responses (e.g., exploration) which are incompatible with the attentional consequences of the drug (i.e., perseveration).

Typically, tolerance is considered as an abatement of the drug-induced behavior ordinarily produced by acute amphetamine treatment. In pharmacological terms the neuronal consequences of the drug treatment are less pronounced than they would be after acute treatment. However, in the case of perseveration the behavior of the tolerant animal does not resemble that of a non-drug animal, even when as many as 30 days of drug treatment preceded testing (Kokkinidis et al., 1976). Specifically, whereas non-drug animals show alternation behavior which exceeds chance level performance, mice which received chronic amphetamine treatment exhibit performance which does not exceed chance (see Experiments 14, 15, 17, 19 and Kokkinidis et al., 1976). In effect, the behavioral change observed after chronic amphetamine treatment is not necessarily a return to "normal state," but rather may be a reflection of either the intrusion of a competing behavior, or alternatively, the disruption of the mechanisms which mediate the behavior. If one assumes that the perseveration (or for that matter startle to external stimuli, as well as rotational behavior) is, in fact, due to enhanced selective attention, then it may be the case that the abatement of perseveration after chronic amphetamine treatment is a consequence of a breakdown in selective attention. That is, the organism suffers a deficit in terms of filtering external stimulation. Put into clinical jargon, the organism suffers from "stimulus overload." At this time there are a paucity of data available concerning the role of NE in attentional processes, other than the finding that this transmitter is involved in exploratory behavior (Robbins & Iversen, 1973; Ungerstedt, 1974). The notion proposed here is certainly highly provisional; however, it warrants further consideration and may serve as an adequate working hypothesis.

A second possibility which must be considered with respect to behavioral changes following chronic amphetamine treatment concerns the potential involvement of neurotransmitters other than the catecholamines. For example, it is well documented that dopaminergic and cholinergic activity act in a balanced fashion in mediating a number of behaviors (see introduction). Moreover, it has also been reported that in addition to catecholamines, treatment with d-amphetamine will elicit changes in ACh activity in several brain regions (see reviews in Anisman, 1975a; deFeudis, 1975). Indeed, in the case of perseveration it has been shown that an anticholinergic will enhance the amphetamine-induced perseveration, whereas an anticholinestrase will produce the opposite effect. As a matter of fact, an anticholinestrase was found to be more effective in this respect than either a tyrosine hydroxylase or dopamine- β -hydroxylase inhibition (Anisman & Kokkinidis, 1975; Kokkinidis & Anisman, 1976a). Whereas the latter treatment simply antagonized the amphetamine-induced perseveration, the anticholinestrase re-established the spontaneous alternation ordinarily observed among non-drug treated animals. In view of the fact that alternation returns to chance level performance after chronic amphetamine treatment the possibility exists that the observed tolerance involves noradrenergically-mediated mechanisms, but the drug effects on ACh activity prevent alternation from exceeding chance.

Summary

Consistent with the notion that noradrenergic mechanisms subserve the development of tolerance to the effects of amphetamine, behaviors mediated by NE were attenuated after chronic exposure to the drug, whereas this same treatment did not affect or resulted in the exaggeration of DA-mediated behaviors. Furthermore, with chronic administration of amphetamine levels of NE were found to be reduced. It is not entirely certain at this point whether false transmitters are involved in the development of tolerance; however, one major candidate, p-hydroxynorephedrine, would appear to be ruled out. As concerns other neurotransmitters, there is reason to believe that cholinergic mechanisms may interact with NE in mediating the effects of acute and chronic amphetamine treatment. From the behavioral vantage it does not appear that conditioning factors play a prominent role in the elicitation of the tolerance, though a role for stimulus factors in tolerance development cannot be excluded. Indeed, it was suggested that disruption in attentional processes, mediated by NE depletion, might be involved in the behavioral effects induced by chronic amphetamine treatment.

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APPENDIX A

4

Table 1a

Analysis of Variance of the Mean Proportion of Rotational Responses
as a Function of Drug Treatment (Experiment 1)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	4	.17987	.0449	4.56	p < .005
S. Within Groups	35	.34498	.00985		

Table 1b

Analysis of Variance of the Mean Number of Direction Changes
as a Function of Drug Treatment (Experiment 1)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	4	.30972	7743.0	3.38	p < .02
S Within Groups	35	.80159	2290.3		

Table 1c

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Drug Treatment (Experiment 1)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	4	.328700	.821760	21.83	p < .001
S Within Groups	35	.1317400	.37640		

Table 2a

Analysis of Variance of the Mean Proportion of Circling Responses
as a Function of Drug Pretreatment (Saline, Δ -MPT or FLA-63) Three
Hr Prior to Test Drug Treatment (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	4	.07907	.0197	3.74	p < .008
Drug Test Treatment	1	.2506	.2506	47.36	p < .001
Pre x Test	4	.08682	.02170	4.10	p < .005
S Within Groups	70	.37047	.00529		

Table 2b

Analysis of Variance of the Mean Number of Direction Changes
as a Function of Drug Pretreatment (Saline, α -MPT or FLA-63)
and Drug Test Treatment (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	4	8074.6	2018.7	1.26	p < .296
Drug Test Treatment	1	35196.0	35196.0	21.90	p < .001
Pre x Test	4	26892.0	6723.0	4.18	p < .004
S Within Groups	70	112520.0	1607.4		

Table 2c

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Drug Pretreatment (Saline, Δ -MpT or FLA-63),
Three Hours Prior to Drug Test Treatment (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	4	408330.0	102080.0	3.67	$p < .009$
Drug Test Treatment	1	420720.0	420720.0	151.13	$p < .001$
Pre x Test	4	368900.0	92225.0	3.31	$p < .015$
S Within Groups	70	194870.0	27839.0		

Table 2d

Analysis of Variance of the Assay Data Involving Whole Brain Dopamine Levels ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, α -MPT or FLA-63) (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	6.9335	3.4668	16.73	$p < .001$
S Within Groups	15	3.1079	.20719		

Table 2e

Analysis of Variance of the Assay Data Involving Whole Brain Norepinephrine Levels ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, α -MPT or FLA-63) (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	.6389	.31946	3.88	$p < .04$
S Within Groups	15	1.234	.08223		

Table 2f

Analysis of Variance of the Assay Data Involving Whole Brain Serotonin Levels ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, α -MPT or FLA-63). (Experiment 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	.0023	.00118	.79	$p < .470$
S Within Groups	15	.0223	.00148		

Table 3a

Analysis of Variance of the Mean Proportion of Rotational Responses
as a Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	.19600	.196	26.08	p < .001
Pre-exposure	1	.01296	.0129	1.72	p < .197
Drug x Pre	1	.02025	.0202	2.69	p < .100
S Within Groups	36	.27058	.0075		

Table 3b

Analysis of Variance of the Mean Number of Direction Changes
as a Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	23620.0	23620.0	38.17	$p < .001$
Pre-exposure	1	8179.6	8179.6	13.22	$p < .001$
Drug x Pre	1	0	0	0	$p < 1.0$
S Within Groups	36	22279.0	618.87		

Table 3c

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	643520.0	643520.0	109.97	p < .001
Pre-exposure	1	148600.0	148600.0	2.54	p < .12
Drug x Pre	1	1345.6	1345.6	.02	p < .88
S Within Groups	36	2106600.0	58517.0		

Table 4a

Analysis of Variance of the Mean Proportion of Circling Responses
as a Function of Chronic Drug Treatment and Drug Treatment on
Test Day (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	1	.09604	.09604	7.95	$p < .008$
Drug Treatment on Test Day	1	.17956	.17956	14.85	$p < .001$
Chronic x Test	1	.1000	.1000	8.27	$p < .007$
S Within Groups	36	.43516	.01208		

Table 4b

Analysis of Variance of the Mean Number of Direction Changes
as a Function of Chronic Drug Treatment and Drug Treatment on
Test Day (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	1	5832.2	5832.2	2.05	$p < .161$
Drug Treatment on Test Day	1	12145.0	12145.0	4.27	$p < .046$
Chronic x Test	1	9954.0	9954.0	3.50	$p < .07$
S Within Groups	36	102470.0	2846.4		

Table 4c

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Chronic Drug Treatment and Drug Treatment on
Test Day (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	1	1288.2	1288.2	.04	p < .839
Drug Treatment on Test Day	1	2466600.0	2466600.0	79.89	p < .001
Chronic x Test	1	17347.0	17347.0	.56	p < .458
S Within Groups	36	1111500.0	30876.0		

Table 4d

Analysis of Variance of the Assay Data Involving Whole Brain
Levels of Dopamine ($\mu\text{g/gm}$) as a Function of Chronic d-
Amphetamine (10 mg/kg) Treatment or Saline (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	.02707	.02707	.39	$p < .543$
S Within Groups	18	1.2652	.07029		

Table 4e

Analysis of Variance of the Assay Data Involving Whole Brain Norepinephrine Levels ($\mu\text{g/gm}$) as a Function of Chronic d-Amphetamine Administration (10 mg/kg) or Saline (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	.18416	.18416	7.80	$p < .012$
S Within Groups	18	.42488	.02360		

Table 4f

Analysis of Variance of the Assay Data Involving Whole Brain Serotonin Levels ($\mu\text{g/gm}$) as a Function of Chronic d-Amphetamine Treatment (10 mg/kg) or Saline (Experiment 4)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	1	.000615	.000615	.77	p < .391
S Within Groups	18	.014319	.000795		

Table 5

Analysis of Variance of the Mean Startle Amplitude
as a Function of Drug Treatment (Experiment 5)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	4	32366.0	8091.4	8.81	p <.001
S Within Groups	45	41333.0	918.52		
<u>Within</u>					
Buzzer Presentation	9	5746.5	638.52	2.72	p <.005
Drug x Buzzer	36	7297.9	202.72	.86	p <.695
Buzzer x S Within Groups	405	94972.0	234.50		

Table 6

Analysis of Variance of the Mean Startle Amplitude
as a Function of Drug Treatment (Experiment 6)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	1	59463.0	59463.0	31.36	p < .001
S Within Groups	14	26545.0	1896.1		
<u>Within</u>					
Buzzer Presentations	24	4671.9	194.66	1.27	p < .184
Drug x Buzzer	24	11357.0	473.22	3.08	p < .001
Buzzer x S Within Groups	336	51680.0	153.81		

Table 7a

Analysis of Variance of the Mean Startle Amplitude as a Function of
 Drug Pretreatment (Saline, α -MPT or FLA-63) Three Hours Prior
 to Test Treatment (Saline or d-Amphetamine 5.0 mg/kg) (Experiment 7)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	2	6179.9	3089.9	2.28	p < .108
Drug Test Treatment	1	7904.0	7904.0	5.83	p < .018
Pre x Test	2	13063.0	6531.4	4.82	p < .010
S Within Groups	102	138350.0	1356.3		
<u>Within</u>					
Buzzer Presentation	9	24468.0	2718.7	15.49	p < .001
Pre x Buzzer	18	3709.9	206.10	1.17	p < .276
Test x Buzzer	9	2216.0	246.23	1.40	p < .182
Test x Pre x Buzzer	18	3280.9	182.27	1.04	p < .413
Buzzer x S Within Groups	918	161170.0	175.57		

Table 7b

Analysis of Variance of the Assay Data Involving Whole Brain Levels of
Dopamine ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, α -MPT or
FLA-63) (Experiment 7)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	4.080	2.04	13.97	p < .001
S Within Groups	15	2.190	.1460		

Table 7c

Analysis of Variance of the Assay Data Involving Whole Brain Norepinephrine Levels ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, FLA-63 or ~~MP~~-MpT) (Experiment 7)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	.49804	.24902	5.84	p < .013
S Within Groups	15	.63985	.04265		

Table 7d

Analysis of Variance of the Assay Data Involving Whole Brain Serotonin Levels ($\mu\text{g/gm}$) as a Function of Drug Treatment (Saline, α -MpT or FLA-63) (Experiment 7)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Treatment	2	.00046	.000230	.10	p < .903
S Within Groups	15	.0336	.00224		

Table 8

Analysis of Variance of the Mean Number of Photocell Crossings as a Function of Drug Pretreatment (Saline, Δ -MPT or FLA-63) Three Hours Prior to Drug Test Treatment (Saline or d-Amphetamine 5.0 mg/kg) (Experiment 8)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	2	1702200.0	851100.0	5.20	$p < .009$
Drug Test Treatment	1	9336700.0	9336700.0	57.04	$p < .001$
Test x Pre	2	2085800.0	1042900.0	6.37	$p < .004$
S Within Groups	48	7856600.0	163680.0		

Table 9

Analysis of Variance of the Mean Startle Amplitude as a Function of
Chronic Drug Treatment and Drug Treatment on Test Day (Experiment 9)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	1	525.55	525.55	.30	p < .586
Drug Treatment on Test Day	1	4513.8	4513.8	2.59	p < .116
Chronic x Test	1	586.86	586.86	.34	p < .566
S Within Groups	36	62808.0	1744.7		
<u>Within</u>					
Buzzer Presentations	9	8646.0	960.67	7.02	p < .001
Chronic x Buzzer	9	2788.0	309.78	2.26	p < .018
Test x Buzzer	9	2134.0	237.4	1.73	p < .081
Chronic x Test x Buzzer	9	2634.0	292.66	2.14	p < .026
Buzzer x S Within Groups	324	44341.0	136.86		

Table 10a

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Shock and Drug Treatment (Experiment 10)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	4	3147700.0	786910.0	23.28	p < .001
Shock	1	234470.0	234470.0	6.94	p < .01
Drug x Shock	4	77615.0	19404.0	.57	p < .682
S Within Groups	70	2366400.0	33806.0		
<u>Within</u>					
Block	13	1898200.0	146010.0	40.21	p < .001
Drug x Block	52	751120.0	14445.0	3.98	p < .001
Shock x Block	13	361130.0	27779.0	7.65	p < .001
Drug x Shock x Block	52	881080.0	16944.0	4.67	p < .001
Block x S Within Groups	910	3304400.0	3631.2		

Table 10b

Analysis of Variance of the Mean Stereotypy Ratings as a
Function of Shock and Drug Treatment (Experiment 10)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	4	2782.7	695.67	206.49	$p < .001$
Shock	1	117.97	117.97	35.02	$p < .001$
Drug x Shock	4	115.09	28.77	8.54	$p < .001$
S Within Groups	70	235.83	3.36		
<u>Within</u>					
Block	13	626.87	48.22	59.12	$p < .001$
Drug x Block	52	426.56	8.20	10.06	$p < .001$
Shock x Block	13	28.61	2.20	2.70	$p < .001$
Drug x Shock x Block	52	133.12	2.56	3.14	$p < .001$
Block x S Within Groups	910	742.20	.8156		

Table 11a

Analysis of Variance of the Mean Number of Photocell Crossings
as a Function of Drug Pretreatment, Drug Test Treatment and Shock
(Experiment 11)

<u>Between</u>	<u>DF</u>	<u>MS</u>	<u>SS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	2	392940.0	196470.0	7.54	$p < .001$
Drug Test Treatment	1	2557500.0	2557500.0	98.11	$p < .001$
Pre x Test	2	156380.0	78188.0	3.00	$p < .06$
Shock	1	6.2555	6.2555	0	$p < .98$
Shock x Pre	2	153490.0	76747.0	2.94	$p < .06$
Shock x Test	1	9058.0	9058.0	.35	$p < .6$
Shock x Pre x Test	2	198420.0	99210.0	3.81	$p < .03$
S Within Groups	84	2189700.0	26068.0		
<u>Within</u>					
Block	13	1427700.0	109820.0	43.10	$p < .001$
Block x Pre	26	55813.0	2146.6	.84	$p < .7$
Block x Test	13	660400.0	50800.0	19.94	$p < .001$
Block x Pre x Test	26	21034.0	809.01	.32	$p < 1.04$
Block x Shock	13	262220.0	20171.0	7.92	$p < .001$
Block x Pre x Shock	26	365330.0	14081.0	5.51	$p < .001$
Block x Test x Shock	13	386710.0	29747.0	11.67	$p < .001$
Block x Pre x Test x Shock	26	478160.0	18391.0	7.22	$p < .001$
Block x S Within Groups	1092	2782700.0	2548.2		

Table 11b

Analysis of Variance of the Mean Stereotypy Ratings as a Function of
Drug Pretreatment, Drug Test Treatment and Shock (Experiment 11)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug Pretreatment	2	704.99	352.49	112.25	$p < .001$
Drug Test Treatment	1	2300.9	2300.9	732.9	$p < .001$
Pre x Test	2	345.53	172.76	55.02	$p < .001$
Shock	1	58.96	58.96	18.78	$p < .001$
Shock x Pre	2	3.748	1.874	.60	$p < .6$
Shock x Test	1	98.317	98.317	31.31	$p < .001$
Shock x Pre x Test	2	17.17	8.586	2.73	$p < .08$
S Within Groups	84	263.78	3.1403		
<u>Within</u>					
Block	13	615.5	47.346	84.43	$p < .001$
Block x Pre	26	195.05	7.348	13.10	$p < .001$
Block x Test	13	361.08	27.77	49.53	$p < .001$
Block x Pre x Test	26	145.21	5.585	9.96	$p < .001$
Block x Shock	13	5.1201	.39386	.70	$p < .762$
Block x Pre x Shock	26	16.06	.61784	1.10	$p < .4$
Block x Test x Shock	13	132.15	10.166	18.13	$p < .001$
Block x Pre x Test x Shock	26	34.31	1.319	2.35	$p < .001$
Block x S Within Groups	1092	612.37	.5607		

Table 12a

Analysis of Variance of the Mean Number of Photocell Crossings as a
Function of Chronic Drug Treatment, Drug Treatment on Test Day and Shock
(Experiment 12)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug	1	32055.0	32055.0	.56	$p < .5$
Test Day Drug	1	5085900.0	5085900.0	89.28	$p < .001$
Chronic x Test	1	68.753	68.753	0	$p < 1.0$
Shock	1	24802.0	24802.0	.44	$p < .6$
Shock x Chronic	1	8568.4	8568.4	.15	$p < .7$
Shock x Test	1	89867.0	89867.0	1.58	$p < .3$
Shock x Chronic x Test	1	1481.7	1481.7	.03	$p < .9$
S Within Groups	56	3190200.0	56968.0		
<u>Within</u>					
Block	13	2165100.0	166540.0	30.41	$p < .001$
Block x Chronic	13	253850.0	19527.0	3.97	$p < .001$
Block x Test	13	1250100.0	96160.0	17.56	$p < .001$
Block x Chronic x Test	13	262980.0	20229.0	3.69	$p < .001$
Block x Shock	13	901810.0	69370.0	12.69	$p < .001$
Block x Shock x Chronic	13	74142.0	5703.2	1.04	$p < .5$
Block x Shock x Test	13	1186700.0	91286.0	16.67	$p < .001$
Block x Shock x Chronic x Test	13	48834.0	3765.5	.69	$p < .8$
Block x S Within Groups	728	3986600.0	5476.1		

Table 12b

Analysis of Variance of the Mean Stereotypy Ratings as a Function of
Chronic Drug Treatment, Drug Treatment on Test Day and Shock (Experiment 12)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug	1	2.26	2.26	.70	$p < .5$
Test Day Drug	1	1669.4	1669.4	513.4	$p < .001$
Chronic x Test	1	4.734	4.734	1.46	$p < .3$
Shock	1	214.13	214.13	65.86	$p < .001$
Shock x Chronic	1	3.235	3.235	1.0	$p < .4$
Shock x Test	1	.51881	.51881	.16	$p < .7$
Shock x Chronic x Test	1	.25220	.25220	.08	$p < .8$
<u>Within</u>					
Block	13	657.40	50.56	74.12	$p < .001$
Block x Chronic	13	3.3728	.25945	.38	$p < 1.0$
Block x Test	13	354.18	27.24	39.93	$p < .001$
Block x Chronic x Test	13	8.866	.6820	1.0	$p < .5$
Block x Shock	13	22.55	1.734	2.54	$p < .005$
Block x Shock x Chronic	13	2.5533	.19641	.29	$p < 1.0$
Block x Shock x Test	13	82.13	6.317	9.26	$p < .001$
Block x Shock x Chronic x Test	13	7.3809	.5677	.83	$p < .7$
Block x'S Within Groups	728	496.68	.68225		

Table 13a

Analysis of Variance of the Mean Proportion of Alternations
as a Function of Drug Treatment (Experiment 13)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	11	1.1354	.10322	4.22	p < .001
S Within Groups	108	2.6430	.024472		

Table 13b

Analysis of Variance of the Mean Number of Arm Entries
as a Function of Drug Treatment (Experiment 13)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	11	54544.0	4958.5	3.89	p<.001
S Within Groups	108	137510.0	1273.3		

Table 14a

Analysis of Variance of the Mean Proportion of Alternation Responses
as a Function of Drug Treatment during the Chronic Phase (15.0 mg/kg)
of d-Amphetamine or Saline for either 3, 5 or 10 Consecutive Days)
and Drug Treatment on Test Day (5.0 mg/kg of d-Amphetamine or Saline)
(Experiment 14)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Number of Days of Drug Treatment	2	.09165	.04582	2.18	$p < .118$
Chronic Drug Treatment	1	.22369	.22369	10.64	$p < .001$
Days x Chronic	2	.17138	.08568	4.08	$p < .02$
Test Day Drug Treatment	1	1.6453	1.6453	78.27	$p < .001$
Days x Test	2	.00962	.00481	.230	$p < .796$
Chronic x Test	1	.17856	.17856	8.50	$p < .004$
Days x Chronic x Test	2	.19109	.095546	4.55	$p < .013$
S Within Groups	108	2.2701	.21020		

Table 14b

Analysis of Variance of the Mean Number of Arm Entries as a Function of Drug Treatment during the Chronic Phase (15.0 mg/kg of d-Amphetamine or Saline for either 3, 5 or 10 Consecutive Days) and Drug Treatment on Test Day (5.0 mg/kg of d-Amphetamine or Saline) (Experiment 14)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Number of Days of Drug Treatment	2	6869.8	3434.9	1.16	$p < .318$
Chronic Drug Treatment	1	7316.4	7316.4	2.47	$p < .119$
Days x Chronic	2	3025.6	1512.8	.51	$p < .602$
Test Day Drug Treatment	1	123070.0	123070.0	41.47	$p < .001$
Days x Test	2	7123.6	3561.8	1.20	$p < .305$
Chronic x Test	1	4876.9	4876.9	1.64	$p < .203$
Days x Chronic x Test	2	4300.9	2150.4	.72	$p < .487$
S Within Groups	108	320510.0	2967.7		

Table 15a

Analysis of Variance of the Mean Proportion of Alternation Responses
as a Function of Drug Treatment During the Chronic Phase (Saline,
5.0, 10.0 or 15.0 mg/kg of d-Amphetamine for 5 Consecutive Days) and
Drug Treatment on Test Day (Saline or 5.0 mg/kg of d-Amphetamine).
(Experiment 15)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Dosage during Chronic Phase	3	.21516	.07171	2.40	$p < .075$
Drug Treatment on Test Day	1	.51248	.51248	17.12	$p < .001$
Dose x Test	3	.22039	.07346	2.45	$p < .07$
S Within Groups	72	2.1558	.02994		

Table 15b

Analysis of Variance of the Mean Number of Arm Entries as a Function
of Drug Treatment During the Chronic Phase (Dosage) and Drug Treat-
ment on Test Day (Experiment 15)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Dosage during Chronic Phase	3	2757.0	919.01	.30	$p < .823$
Drug Treatment on Test Day	1	66068.0	60607.0	21.81	$p < .001$
Dose x Test	3	2493.4	831.15	.27	$p < .844$
S Within Groups	72	218110.0	3029.3		

Table 16a

Analysis of Variance of the Mean Proportion of Alternation Responses as a Function of Drug Treatment During the Chronic Phase (15, 30, 45 or 60 mg/kg of l-Amphetamine or Saline), and Drug Treatment on Test Day (Saline or 15.0 mg/kg of l-Amphetamine). (Experiment 16)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Dosage during Chronic Phase	4	.13538	.03384	1.74	$p < .148$
Drug Treatment on Test Day	1	1.4830	1.4830	76.23	$p < .001$
Dose x Test	4	.11360	.028401	1.46	$p < .221$
S Within Groups	90	1.7510	.019456		

Table 16b

Analysis of Variance of the Mean Number of Arm Entries as a Function of Drug Treatment During the Chronic Phase (Saline or 1-Amphetamine 15.0, 30.0, 45.0 or 60.0 mg/kg) and Drug Treatment on Test Day (Saline or 1-Amphetamine 15.0 mg/kg). (Experiment 16)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Dosage During Chronic Phase	4	5295.8	1324.0	.43	$p < .786$
Drug on Test Day	1	71770.0	71770.0	23.32	$p < .001$
Dose x Test	4	12359.0	3089.7	1.00	$p < .410$
S Within Groups	90	276940.0	3077.1		

Table 17a

Analysis of Variance of the Mean Proportion of Alternation Scores as a Function of Drug Treatment During the Chronic Phase (Saline, d-Amphetamine 10.0 mg/kg or l-Amphetamine 45.0 mg/kg) and Drug Treatment on Test Day (Saline, d-Amphetamine 5.0 mg/kg or l-Amphetamine 15.0 mg/kg). (Experiment 17)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	.25023	.12512	6.61	$p < .002$
Drug Treatment on Test Day	2	.74944	.37472	19.80	$p < .001$
Chronic x Test	4	.16184	.04059	2.14	$p < .084$
S Within Groups	81	1.5328	.01892		

Table 17b

Analysis of Variance of the Mean Number of Arm Entries as a Function of Drug Treatment During the Chronic Phase (Saline, d-Amphetamine 10.0 mg/kg or l-Amphetamine 45.0 mg/kg) and Drug Treatment on Test Day (Saline, d-Amphetamine 5.0 mg/kg or l-Amphetamine 15.0 mg/kg).
(Experiment 17)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	12035.0	6017.7	.84	$p < .435$
Drug Treatment on Test Day	2	145620.0	72808.0	10.18	$p < .001$
Chronic • Test	4	13543.0	3385.8	.47	$p < .755$
S Within Groups	81	579060.0	7148.9		

Table 18a

Analysis of Variance of the Mean Proportion of Alternation Responses
as a Function of Drug Treatment and Floor Color (Experiment 18)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	2	1.0892	.54461	32.0	$p < .001$
Color	1	.01051	.01051	.62	$p < .435$
Drug x Color.	2	.06925	.03462	2.03	$p < .139$
S Within Groups	66	1.1233	.01702		

Table 18b

Analysis of Variance of the Mean Number of Arm Entries as a Function of Drug Treatment, Floor Color and Compartment Choice (i.e., Arm 1, 2 or 3). (Experiment 18)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	2	23537.0	11768.0	11.34	$p < .001$
Color	1	1098.0	1098.0	1.06	$p < .307$
Drug x Color	2	1073.4	536.68	.52	$p < .599$
S Within Groups	66	68496.0	1037.8		
<u>Within</u>					
Compartment	2	1795.3	897.67	1.09	$p < .341$
Drug x Compartment	4	3494.4	873.60	1.06	$p < .381$
Color x Compartment	2	3026.8	11513.4	1.83	$p < .164$
Drug x Color x Compartment	4	4349.0	1087.3	1.32	$p < .268$
Compartment x S Within Groups	132	109110.0	826.61		

Table 19a

Analysis of Variance of the Mean Proportion of Alternation Responses
During the No-Drug Phase (i.e., Phase 1 of Experiment 19).

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Treatment Assignment	2	.00222	.00111	.15	p < .860
S Within Groups	45	.33197	.00737		
<u>Within</u>					
Day of Testing	2	.25502	.12751	16.34	p < .001
Treatment x Day	4	.007367	.00184	.24	p < .917
S Within Groups x Day	90	.70224	.00780		

Table 19b

Analysis of Variance of the Mean Number of Arm Entries
During the No-Drug Phase (Phase 1) of Experiment 19

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Treatment Assignment	2	1852.4	926.19	1.70	$p < .195$
S Within Groups	45	24546.0	545.48		
<u>Within</u>					
Day of Testing	2	7094.7	3952.3	25.36	$p < .001$
Day x Treatment	4	234.90	58.726	.38	$p < .825$
S Within Groups x Day	90	14028.0	155.86		

Table 19c

Analysis of Variance of the Mean Stereotypy Ratings During
the No-Drug Phase (Phase 1) of Experiment 19

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Treatment Assignment	2	.0376	.0188	.37	p < .696
S Within Groups	45	2.315	.0514		
<u>Within</u>					
Day of Testing	2	1.449	.7244	10.43	p < .001
Day x Treatment	4	.19069	.0476	.69	p < .603
S Within Groups x Day	90	6.2537	.0694		

Table 19d

Analysis of Variance of the Mean Proportion of Alternation Responses as a Function of Drug Treatment for Five Consecutive Days (Experiment 19; Phase 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	2	.7712	.38558	8.33	$p < .001$
S Within Groups	45	2.082	.04626		
<u>Within</u>					
Day of Testing	4	.04195	.01048	.72	$p < .582$
Drug x Day	8	.1700	.02125	1.45	$p < .179$
Day x S Within Groups	180	2.638	.01466		

Table 19e

Analysis of Variance of the Mean Number of Arm Entries as a Function of
Drug Treatment for Five Consecutive Days (Experiment 19; Phase 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	2	110870.0	55434.0	17.46	$p < .001$
S Within Groups	45	142870.0	3175.0		
<u>Within</u>					
Day	4	9371.5	2342.9	3.45	$p < .01$
Drug x Day	8	7659.4	957.43	1.41	$p < .195$
Day x S Within Groups	180	122300.0	679.44		

Table 19f

Analysis of Variance of the Mean Stereotypy Ratings as a Function
of Drug Treatment for Five Consecutive Days (Experiment 19; Phase 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	2	812.20	406.1	709.14	$p < .001$
S Within Groups	45	25.77	.5726		
<u>Within</u>					
Day	4	4.40	1.1006	3.78	$p < .01$
Drug x Day	8	27.53	3.4418	11.81	$p < .001$
Day x S Within Groups	180	52.46	.29149		

Table 19g

Analysis of Variance of the Mean Proportion of Spontaneous Alternation
as a Function of Chronic Drug Treatment and Drug Treatment on Test Day
(Experiment 19)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	.21369	.10684	3.83	p < .05
Drug Treatment on Test Day	1	.10660	.10660	3.82	p < .06
Chronic x Test	2	.19270	.09635	3.45	p < .05
S Within Groups	42	1.1727	.02792		

Table 19h

Analysis of Variance of the Mean Number of Arm Entries as a Function of
Chronic Drug Treatment and Drug Treatment on Test Day (Experiment 19)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	771.17	358.58	.21	p < .815
Drug Treatment on Test Day	1	38251.0	38251.0	20.39	p < .001
Chronic x Test	2	1138.7	569.33	.30	p < .740
S Within Groups	42	78794.0	1876.0		

Table 191

Analysis of Variance of the Mean Stereotypy Ratings as a Function of
Chronic Drug Treatment and Drug Treatment on Test Day (Experiment 19)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	3.4579	1.729	4.48	$p < .02$
Drug Treatment on Test Day	1	156.60	156.60	405.41	$p < .001$
Chronic x Test	2	1.2163	.60813	1.57	$p < .219$
S Within Groups	42	16.224	.3862		

Table 19j

Analysis of Variance of the Mean Stereotypy Ratings of Mice Rated
in the Y-maze or Home Cage after Drug Treatment for
Five Consecutive Days (Experiment 19)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment (PRE vs. POST)	1	.3610	.3610	.45	$p < .51$
S Within Groups	30	24.335	.8112		
<u>Within</u>					
Days	4	73.337	18.334	38.66	$p < .001$
Chronic x Days	4	1.4978	.3744	.79	$p < .534$
Days x S Within Groups	120	56.913	.4742		

Table 20a

Analysis of Variance of the Mean Proportion of Alternation Responses
during the No-Drug Phase of Experiment 20 (Phase 1)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Treatment Assignment	4	.03984	.0099	1.23	p < .315
S Within Groups	35	.28304	.0080		
<u>Within</u>					
Days	2	.24001	.120	25.01	p < .001
Treatment x Days	8	.029461	.00368	.77	p < .632
Days x S Within Groups	70	.33582	.00479		

Table 20b

Analysis of Variance of the Mean Proportion of Alternation Responses as a Function of Drug Treatment for Three Consecutive Days in Experiment 20 (Phase 2)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Chronic Drug Treatment	2	.2618	.1309	8.74	p < .002
S Within Groups	21	.3146	.0149		
<u>Within</u>					
Days	2	.0083	.0041	.38	p < .689
Drug x Days	4	.0049	.0012	.11	p < .978
Days x S Within Groups	42	.46815	.0111		

Table 20c

Analysis of Variance of the Mean Proportion of Alternation Responses as a
Function of Chronic Drug Treatment and d-Amphetamine (5.0 mg/kg) on
Test Day (Experiment 20)

<u>Between</u>	<u>DF</u>	<u>SS</u>	<u>MS</u>	<u>F</u>	<u>Sig</u>
Drug	4	.0089	.0024	.11	p < .977
S Within Groups	35	.69711	.0199		

APPENDIX B

Table 1a

Mean Proportion of Circling Responses as a
Function of Drug Treatment (Experiment 1)

	<u>Drug Treatment</u>			
ne	d-amphetamine (1.0 mg/kg)	d-amphetamine (3.0 mg/kg)	d-amphetamine (5.0 mg/kg)	d-amphetamine (10.0 mg/kg)
0	.595	.616	.734	.695

mean difference necessary for $p < .05$

$$r_2 = .100$$

$$r_3 = .120$$

$$r_4 = .132$$

$$r_5 = .141$$

Table 1b

Mean Number of Direction Changes as a
Function of Drug Treatment (Experiment 1)

<u>Drug Treatment</u>				
saline	d-amphetamine (1.0 mg/kg)	d-amphetamine (3.0 mg/kg)	d-amphetamine (5.0 mg/kg)	d-amphetamine (10.0 mg/kg)
44.13	54.26	113.25	37.37	44.25

mean difference necessary for $p < .05$

$$r_2 = 48.39$$

$$r_3 = 58.20$$

$$r_4 = 64.12$$

$$r_5 = 68.35$$

Table 1c

Mean Number of Photocell Crossings as a
Function of Drug Treatment (Experiment 1)

<u>Drug Treatment</u>				
saline	d-amphetamine (1.0 mg/kg)	d-amphetamine (3.0 mg/kg)	d-amphetamine (5.0 mg/kg)	d-amphetamine (10.0 mg/kg)
181.50	181.50	737.12	861.12	325.50

mean difference necessary for $p < .05$

$$r_2 = 196.16$$

$$r_3 = 235.94$$

$$r_4 = 259.95$$

$$r_5 = 277.10$$

Table 2a

Mean Proportion of Circling Responses as a Function of
Drug Pretreatment (Saline, α -MpT or FLA-63) Three Hours
Prior to Drug Test Treatment (Experiment 2)

<u>Drug Test Treatment</u>	<u>Drug Pretreatment</u>				
	<u>Saline</u>	<u>α-MpT 125 mg/kg</u>	<u>α-MpT 250 mg/kg</u>	<u>FLA-63 20 mg/kg</u>	<u>FLA-63 40 mg/kg</u>
saline	.540	.542	.531	.542	.561
d-amphetamine (5.0 mg/kg)	.732	.670	.572	.711	.591

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .072$$

$$r_3 = .087$$

$$r_4 = .095$$

$$r_5 = .101$$

Table 2b

Mean Number of Direction Changes as a Function of Drug
Pretreatment (Saline, α -MpT or FLA-63) Three Hours
Prior to Drug Test Treatment (Experiment 2)

<u>Drug Test Treatment</u>	<u>Drug Pretreatment</u>				
	<u>Saline</u>	<u>α-MpT 125 mg/kg</u>	<u>α-MpT 250 mg/kg</u>	<u>FLA-63 20 mg/kg</u>	<u>FLA-63 40 mg/kg</u>
saline	37.50	38.75	21.25	32.0	15.62
d-amphetamine (5.0 mg/kg)	28.62	56.5	86.75	70.75	112.25

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = 39.76$$

$$r_3 = 47.12$$

$$r_4 = 52.39$$

$$r_5 = 55.66$$

Table 2c

Mean Number of Photocell Crossings as a Function of Drug Pretreatment (Saline, α -MpT or FLA-63) Three Hours Prior to Drug Test Treatment (Experiment 2)

<u>Drug Test Treatment</u>	<u>Drug Pretreatment</u>				
	<u>Saline</u>	<u>α-MpT 125 mg/kg</u>	<u>α-MpT 250 mg/kg</u>	<u>FLA-63 20 mg/kg</u>	<u>FLA-63 40 mg/kg</u>
saline	158.75	141.25	76.37	120.0	67.37
d-amphetamine (5.0 mg/kg)	700.75	382.37	434.62	682.37	656.87

mean difference necessary for $p < .05$ of the simple main effects

$$r_2 = 165.20$$

$$r_3 = 198.24$$

$$r_4 = 217.71$$

$$r_5 = 231.28$$

Table 2d

Means of Whole Brain Levels of Dopamine, Norepinephrine
and Serotonin ($\mu\text{g/gm}$) as a Function of Drug Treatment
(Saline, α -MpT or FLA-63) (Experiment 2)

<u>Drug Treatment</u>	<u>Dopamine</u>	<u>Norepinephrine</u>	<u>Serotonin</u>
saline	2.130	.924	.193
α -MpT (250 mg/kg)	.982	.507	.214
FLA-63 (40 mg/kg)	2.419	.545	.219

mean difference necessary for $p < .05$

Dopamine

$r_2 = .555$

$r_3 = .675$

Norepinephrine

$r_2 = .330$

$r_3 = .401$

Table 3a

Mean Proportion of Circling Responses as a
Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Drug Treatment</u>	<u>Pre-exposed</u>	<u>Naive</u>
saline	.545	.554
d-amphetamine (3.0 mg/kg)	.730	.649

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .0787$$

Table 3b

Mean Number of Direction Changes as a
Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Drug Treatment</u>	<u>Pre-exposed</u>	<u>Naive</u>
saline	16.60	45.20
d-amphetamine (3.0 mg/kg)	65.20	93.80

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = 22.59$$

Table 3c

Mean Number of Photocell Crossings as a
Function of Pre-exposure and Drug Treatment (Experiment 3)

<u>Drug Treatment</u>	<u>Pre-exposed</u>	<u>Naive</u>
saline	50.0	160.8
d-amphetamine (3.0 mg/kg)	841.10	974.6

mean difference necessary for $p < .05$ of the main effect
involving drug treatment

$$r_2 = 219.69$$

Table 4a

Mean Proportion of Circling Responses as a Function
of Chronic Drug Treatment and Drug Treatment on Test Day
(Experiment 4)

<u>Drug Treatment on Test Day</u>	<u>Chronic Drug Treatment</u>	
	<u>Saline</u>	<u>d-amphetamine (10.0 mg/kg)</u>
saline	.558	.560
d-amphetamine (5.0 mg/kg)	.792	.594

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .097$$

Table 4b

Mean Number of Direction Changes as a Function
of Chronic Drug Treatment and Drug Treatment on Test Day
(Experiment 4)

<u>Drug Treatment on Test Day</u>	<u>Chronic Drug Treatment</u>	
	<u>Saline</u>	<u>d-amphetamine (10.0 mg/kg)</u>
saline	50.6	43.2
d-amphetamine (5.0 mg/kg)	53.9	109.60

mean difference necessary for $p < .05$ of the simple
main effects

$r_2 = 48.24$

Table 4c

Mean Number of Photocell Crossings as a Function
of Chronic Drug Treatment and Drug Treatment on Test Day
(Experiment 4)

<u>Drug Treatment on Test Day</u>	<u>Chronic Drug Treatment</u>	
	<u>Saline</u>	<u>d-amphetamine (10.0 mg/kg)</u>
saline	198.20	167.90
d-amphetamine (5.0 mg/kg)	653.20	706.20

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment on Test Day

$$r_2 = 159.58$$

Table 4d

Means of Whole Brain Levels of Dopamine, Norepinephrine and Serotonin ($\mu\text{g/gm}$) as a Function of Chronic d-Amphetamine Treatment (10.0 mg/kg) or Saline (Experiment 4)

<u>Chronic Drug Treatment</u>	<u>Dopamine</u>	<u>Norepinephrine</u>	<u>Serotonin</u>
saline	1.216	.891	.184
d-amphetamine (10.0 mg/kg)	1.142	.700	.173

mean difference necessary for $p < .05$

norepinephrine

$$r_2 = .142$$

Buzzer Presentations

<u>Drug Treatment</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
saline	24.70 ±6.75	18.95 4.94	9.05 2.61	14.0 4.53	7.8 4.37	16.90 6.44	19.90 6.12	10.00 4.31	14.60 4.56	5.85 2.31
d-amphetamine (1.0 mg/kg)	20.95 ±6.11	13.80 6.26	12.20 4.40	9.20 4.44	9.50 5.10	14.0 6.37	15.80 6.74	4.7 2.53	10.70 4.84	9.60 4.84
d-amphetamine (3.0 mg/kg)	34.70 ±4.82	21.65 4.01	26.9 5.39	21.7 5.80	20.40 4.64	29.85 6.01	20.55 6.76	20.40 5.27	31.0 5.64	27.60 5.75
d-amphetamine (5.0 mg/kg)	29.85 ±7.98	28.40 6.70	31.50 5.34	30.95 6.19	37.25 5.67	27.20 4.76	25.01 6.06	22.81 7.48	24.90 5.91	21.60 4.99
d-amphetamine (10.0 mg/kg)	41.40 ±3.88	25.60 7.22	39.70 4.33	41.56 5.09	30.60 5.24	35.40 4.57	25.20 6.26	28.30 5.81	31.65 5.91	28.80 5.94

mean difference necessary for $p < .05$ of the main effects involving Drug Treatment and Buzzer Presentations

Between Drugs

$r_2 = 8.54$
 $r_3 = 10.26$
 $r_4 = 11.29$
 $r_5 = 12.56$

Between Buzzer

$r_2 = 5.98$
 $r_3 = 7.14$
 $r_4 = 7.84$
 $r_5 = 8.33$
 $r_6 = 8.70$
 $r_7 = 9.26$
 $r_8 = 9.48$
 $r_9 = 9.65$
 $r_{10} = 9.82$

Mean Startle Amplitude (S.E.M.) as a Function of
Drug Treatment (Experiment 6)

Buzzer Presentations

Drug Treatment	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
saline	33.25	13.75	25.0	27.37	25.62	21.25	17.75	26.5	12.25	14.00	19.75	21.75	18.12	10.5	15.5	26.62	13.87	15.5	10.12	12.37	14.5	8.25	14.12	16.62
	23.87	4.40	6.07	7.37	7.79	6.46	6.87	7.10	6.14	6.33	6.46	5.55	5.132	5.04	4.88	5.52	6.00	5.49	3.23	3.90	6.06	2.48	5.61	5.84
d-amphetamine (5.0 mg/kg)	33.0	24.37	33.75	33.12	34.5	37.37	39.62	34.5	41.37	43.37	48.87	50.12	49.87	45.62	44.0	45.12	46.5	44.75	43.12	46.42	46.65	43.25	42.50	46.62
	23.45	6.29	5.05	6.58	5.36	6.68	6.32	6.75	5.68	5.01	1.40	1.32	.666	4.01	5.0	4.24	3.5	4.65	5.07	3.42	3.17	3.20	5.02	4.09

mean difference necessary for $p < .05$ of the simple
main effects

Between Drugs (Pooled Error)

$$r_2 = 14.62$$

Between Buzzer Presentations

$$\begin{aligned} r_2 &= 12.13 \\ r_3 &= 14.49 \\ r_4 &= 15.80 \\ r_5 &= 15.89 \\ r_6 &= 17.65 \\ r_7 &= 18.26 \\ r_8 &= 18.79 \\ r_9 &= 19.22 \\ r_{10} &= 19.57 \\ r_{11} &= 19.29 \\ r_{12} &= 20.23 \\ r_{13} &= 20.49 \\ r_{14} &= 20.76 \\ r_{15} &= 21.02 \end{aligned}$$

Table 7a

Mean Startle Amplitude ($\pm$ S.E.M.) as a Function of Drug Pretreatment (Saline, Δ -MPT or FLA-63) Three Hours Prior to Drug Test Treatment (Saline or d-Amphetamine) (Experiment 7)

Drug Pretreatment	Drug Test Treatment	<u>Buzzer Presentations</u>									
		<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	<u>7</u>	<u>8</u>	<u>9</u>	<u>10</u>
saline	saline	30.33 ± 4.75	21.30 4.79	13.0 3.35	16.30 4.00	21.23 4.69	6.88 2.05	13.47 3.67	15.75 3.66	10.69 3.68	11.53 2.40
	d-amphetamine (5.0 mg/kg)	30.77 ± 4.87	31.36 4.52	35.50 4.07	38.33 3.35	27.88 4.60	28.86 4.58	26.08 4.21	31.28 4.76	22.55 5.06	27.19 4.67
	saline	33.97 ± 3.64	25.72 3.63	20.69 4.12	18.44 4.29	17.94 4.13	19.94 3.10	17.05 3.59	14.66 3.88	13.27 3.05	10.52 3.54
Δ -MPT (250 mg/kg)	d-amphetamine (5.0 mg/kg)	29.36 ± 4.38	21.38 4.48	13.5 3.81	17.25 4.06	18.44 4.64	12.50 3.94	15.66 3.97	12.11 2.97	10.47 3.36	10.50 3.23
	saline	31.27 ± 4.80	22.0 4.92	14.36 3.51	11.22 3.64	11.82 4.35	14.91 3.71	11.94 3.03	13.19 3.82	12.66 3.40	12.25 4.42
	d-amphetamine (5.0 mg/kg)	32.61 ± 4.09	22.88 3.84	23.25 4.02	18.91 3.70	20.52 4.65	20.55 4.57	18.58 4.34	20.05 3.97	15.36 4.50	16.94 4.35

mean difference necessary for $p < .05$ of the simple main effects involving the Drug Pretreatment $\times$ Drug Test Treatment interaction and of the main effect involving Buzzer Presentation

For Drug Pretreatment $\times$ Drug Test Treatment

$r_2 = 7.67$
 $r_3 = 9.20$
 $r_4 = 10.11$
 $r_5 = 10.57$
 $r_6 = 11.04$

Between Buzzer Presentation

$r_2 = 5.29$
 $r_3 = 6.32$
 $r_4 = 6.93$
 $r_5 = 7.37$
 $r_6 = 7.69$
 $r_8 = 8.19$
 $r_9 = 8.53$
 $r_{10} = 8.69$

Table 7b

Means of Whole Brain Levels of Dopamine, Norepinephrine
and Serotonin ($\mu\text{g/gm}$) as a Function of Drug Treatment
(Saline, α -MpT or FLA-63) (Experiment 7)

<u>Drug Treatment</u>	<u>Dopamine</u>	<u>Norepinephrine</u>	<u>Serotonin</u>
saline	1.756	.788	.219
α -MpT (250 mg/kg)	.938	.419	.209
FLA-63 (40 mg/kg)	2.067	.432	.220

mean difference necessary for $p < .05$

Dopamine

$$r_2 = .468$$

$$r_3 = .569$$

Norepinephrine

$$r_2 = .252$$

$$r_3 = .306$$

Table 8

Mean Number of Photocell Crossings as a Function of Drug Pretreatment (Saline, α -MpT or FLA-63) Three Hours Prior to Drug Test Treatment (Saline or d-Amphetamine) (Experiment 8)

<u>Drug Test Treatment</u>	<u>Drug Treatment</u>		
	<u>Saline</u>	<u>α-MpT (250 mg/kg)</u>	<u>FLA-63 (40 mg/kg)</u>
saline	516.66	428.55	257.22
d-amphetamine	1485.33	725.111	1486.88

mean difference necessary for $p < .05$ of the simple main effects

$$r_2 = 381.62$$

$$r_3 = 458.49$$

Mean Scatle Amplitude ($\pm$ S.E.M.) as a Function of Chronic Drug Treatment
and Drug Treatment on Test Day (Experiment 9)

Chronic Drug Treatment	Drug Treatment on Test Day	Buzzer Presentations									
		1	2	2	4	5	6	7	8	9	10
saline	saline	24.30 $\pm$ 5.73	19.85 7.32	15.70 6.62	11.80 5.15	15.90 6.37	13.35 4.99	1.35 6.91	20.25 5.87	3.40 4.66	9.50 4.71
	d-amphetamine (5.0 mg/kg)	20.0 $\pm$ 5.17	20.85 5.83	35.50 3.63	25.90 4.72	27.40 5.89	19.40 4.97	24.75 6.34	16.85 5.29	20.90 5.95	17.26 5.45
saline	saline	31.70 $\pm$ 5.64	16.55 5.00	13.60 4.40	11.50 4.25	10.80 4.60	13.70 5.75	15.05 3.55	10.15 3.51	11.50 4.20	4.55 2.17
	d-amphetamine (10.0 mg/kg)	34.40 $\pm$ 6.72	20.35 5.80	19.35 7.16	17.00 5.77	21.76 7.49	10.40 5.43	15.50 5.84	19.35 6.76	13.20 6.50	10.35 5.71

mean difference necessary for $p < .05$ of the simple
main effects

Between Drugs (Pooled Error)

$r_2 = 15.09$
 $r_3 = 18.03$
 $r_4 = 19.78$

Between Buzzer Presentations

$r_2 = 10.22$
 $r_3 = 12.21$
 $r_4 = 13.39$
 $r_5 = 14.24$
 $r_6 = 14.87$
 $r_7 = 15.38$
 $r_8 = 15.83$
 $r_9 = 16.49$
 $r_{10} = 16.78$

Mean Number of Photocell Crossings (t.b.E.M.) as a Function of Shock and Drug Treatment (Experiment 10)

Box

Expenditure

Solution	Within										Between (Pooled Error)									
	1	2	3	4	5	6	7	8	9	10	1	2	3	4	5	6	7	8	9	10
d-amphetamine (1.0 mg/kg)	40.06	25.75	16.06	21.91	26.35	13.61	2.50	7.37	17.62	14.21	9.81	12.56	9.25	11.31	13.31	40.93	26.56	19.92	16.66	14.66
d-amphetamine (3.0 mg/kg)	40.10	20.5	20.0	16.92	11.5	6.75	7.0	13.0	13.25	20.66	6.12	5.53	10.00	9.50	8.00	32.43	22.43	21.75	21.0	21.0
d-amphetamine (10.0 mg/kg)	33.33	8.2	7.79	4.64	2.5	1.93	1.79	4.55	5.52	5.78	3.50	1.61	2.54	3.91	3.91	8.43	11.43	11.43	11.43	11.43
d-amphetamine (1.0 mg/kg)	111.68	104.31	290.25	160.10	129.81	59.68	21.43	21.51	28.81	16.43	18.06	18.65	19.50	12.0	12.0	75.56	76.18	72.75	68.06	61.75
d-amphetamine (3.0 mg/kg)	56.34	90.13	94.43	83.55	56.83	18.82	9.27	6.19	6.16	3.82	4.64	4.96	6.91	3.96	3.96	9.70	13.16	10.86	12.43	12.43
d-amphetamine (10.0 mg/kg)	145.43	350.81	390.50	348.12	281.75	195.81	115.68	72.12	51.31	40.56	32.48	32.06	32.31	12.81	12.81	203.21	203.62	198.37	164.18	143.56
d-amphetamine (10.0 mg/kg)	22.53	24.01	24.83	22.27	41.72	18.11	18.44	15.90	13.82	19.81	8.99	10.54	7.67	5.16	5.16	16.78	16.11	18.58	22.99	16.59

mean difference necessary for $p < .05$

Belva (Page 4 Error)

R. 275.36

2, 2 49.34

14-00000

 $x_1 = 104.06$

Table 100

Mean Number of Sterility Ratings (S.I.M.) as a Function of
Dose and Drug Treatment (Experiment 10)

BLOCK

BLOCK

BLOCK

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Saline	2.75 2.34	2.75 2.34	2.0 0	2.0 0	2.35 1.64	2.0 0	2.0 0	2.1 0.6	2.0 0	2.0 0	2.0 0	2.12 1.23	2.0 0	2.12 1.23	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0
Chlorbutolone (1.0 mg/kg)	3.54 3.20	3.15 2.87	2.0 0	2.43 2.04	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.12 1.23	2.0 0	2.12 1.23	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0	2.0 0
Chlorbutolone (3.0 mg/kg)	4.31 4.16	4.36 4.44	3.12 3.07	4.01 4.13	3.0 3.33	3.0 4.12	3.0 3.33	3.0 4.12	3.0 3.33	3.0 4.12	3.0 3.33	3.31 1.89	3.0 0	3.31 1.89	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0	3.0 0
Chlorbutolone (5.0 mg/kg)	6.31 6.30	6.37 6.45	6.37 6.45	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43	6.43 6.43
Chlorbutolone (10.0 mg/kg)	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00	8.03 8.00

Mean difference necessary for $p < .05$

Within

$r_6 = 1.27$
$r_7 = 1.32$
$r_8 = 1.35$
$r_9 = 1.39$
$r_{10} = 1.41$
$r_{11} = 1.44$
$r_{12} = 1.46$
$r_{13} = 1.48$
$r_{14} = 1.50$

Between (Pooled Error)

$r_2 = .87$
$r_3 = 1.13$
$r_4 = 1.26$
$r_5 = 1.34$

Table 11a

Mean Pharmacokinetic Crossings (± S.E.M.) as a Function of Drug Treatment,
Drug Test Treatment and Blood (Experiment 11)

P.D. CROSS

P.D. CROSS

P.D. CROSS

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
Saline	35.42	34.97	34.31	33.64	9.56	9.23	13.75	19.06	9.75					5.44											
Saline	99.34	3.32	3.07	3.89	2.95	3.03	4.76	6.58	3.31					3.32											
Saline	394.06	264.23	207.0	241.31	336.56	262.68	190.34	131.68	76.67	33.50	21.62	17.67	13.57	9.63											
Saline	62.71	59.61	74.04	76.35	74.33	54.42	32.98	24.55	25.32	13.0	9.66	3.75	9.35	3.78											
Saline	13.37	6.37	7.0	3.31	3.37	13.62	2.75	7.25	1.75	3.75	2.0	6.37	2.75	1.37											
Saline	3.01	3.01	3.61	1.43	1.54	1.82	1.88	1.34	1.34	1.03	2.50	1.26	1.26	1.26											
Saline	135.75	124.62	106.43	63.06	37.93	19.37	13.56	10.06	6.87	2.62	2.01	9.75	2.18	1.18											
Saline	23.34	31.83	24.5	15.27	10.70	8.92	7.55	3.33	2.77	7.60	1.49	6.10	4.99	4.99											
Saline	41.54	43.81	34.25	30.06	19.50	24.33	20.75	23.62	9.37	21.93	14.16	14.04	12.93	13.66											
Saline	14.72	17.53	16.58	17.36	6.63	31.60	9.55	9.11	3.12	10.03	6.06	6.92	7.23	7.01											
Saline	17.56	241.18	245.5	275.01	226.31	155.5	103.07	93.5	60.45	56.68	66.3	21.04	23.83	14.96											
Saline	33.56	45.62	51.87	54.14	34.02	31.22	35.19	26.02	28.59	15.0	15.25	10.89	10.59	6.26											
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Mean difference necessary for $\alpha = 0.05$

Between (pooled error)

Within

 $r_1 = 0.41$
 $r_2 = 0.41$
 $r_3 = 0.41$
 $r_4 = 0.41$
 $r_5 = 0.41$
 $r_6 = 0.41$
 $r_1 = 0.41$
 $r_2 = 0.41$
 $r_3 = 0.41$
 $r_4 = 0.41$
 $r_5 = 0.41$
 $r_6 = 0.41$
 $r_7 = 0.41$
 $r_8 = 0.41$
 $r_9 = 0.41$
 $r_{10} = 0.41$
 $r_{11} = 0.41$
 $r_{12} = 0.41$
 $r_{13} = 0.41$
 $r_{14} = 0.41$
 $r_{15} = 0.41$
 $r_{16} = 0.41$
 $r_{17} = 0.41$
 $r_{18} = 0.41$
 $r_{19} = 0.41$
 $r_{20} = 0.41$
 $r_{21} = 0.41$
 $r_{22} = 0.41$
 $r_{23} = 0.41$
 $r_{24} = 0.41$
 $r_{25} = 0.41$
 $r_{26} = 0.41$
 $r_{27} = 0.41$
 $r_{28} = 0.41$
 $r_{29} = 0.41$
 $r_{30} = 0.41$
 $r_{31} = 0.41$
 $r_{32} = 0.41$
 $r_{33} = 0.41$
 $r_{34} = 0.41$
 $r_{35} = 0.41$
 $r_{36} = 0.41$
 $r_{37} = 0.41$
 $r_{38} = 0.41$
 $r_{39} = 0.41$
 $r_{40} = 0.41$
 $r_{41} = 0.41$
 $r_{42} = 0.41$
 $r_{43} = 0.41$
 $r_{44} = 0.41$
 $r_{45} = 0.41$
 $r_{46} = 0.41$
 $r_{47} = 0.41$
 $r_{48} = 0.41$
 $r_{49} = 0.41$
 $r_{50} = 0.41$
 $r_{51} = 0.41$
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 $r_{67} = 0.41$
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 $r_{69} = 0.41$
 $r_{70} = 0.41$
 $r_{71} = 0.41$
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 $r_{73} = 0.41$
 $r_{74} = 0.41$
 $r_{75} = 0.41$
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 $r_{77} = 0.41$
 $r_{78} = 0.41$
 $r_{79} = 0.41$
 $r_{80} = 0.41$
 $r_{81} = 0.41$
 $r_{82} = 0.41$
 $r_{83} = 0.41$
 $r_{84} = 0.41$
 $r_{85} = 0.41$
 $r_{86} = 0.41$
 $r_{87} = 0.41$
 $r_{88} = 0.41$
 $r_{89} = 0.41$
 $r_{90} = 0.41$
 $r_{91} = 0.41$
 $r_{92} = 0.41$
 $r_{93} = 0.41$
 $r_{94} = 0.41$
 $r_{95} = 0.41$
 $r_{96} = 0.41$
 $r_{97} = 0.41$
 $r_{98} = 0.41$
 $r_{99} = 0.41$
 $r_{100} = 0.41$

Mean Stereotypy Ratings ($\pm$ S.E.M.) as a Function of Drug Pretreatment,
Drug Test Treatment and Shock (Experiment II)

	INDEX										NO INDEX									
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Saline	3.50	2.25	2.25	2.25	2.0	3.125	3.0	3.125	2.125	2.0	2.0	2.0	2.0	2.0	2.0	1.62	1.07	2.0	1.67	1.25
Saline	2.109	.164	.164	.164	0	.125	0	.125	.125	0	0	0	0	0	0	.285	.295	.566	.879	.164
Saline	6.06	6.75	6.81	6.75	7.0	6.75	6.43	6.0	6.0	2.56	2.56	2.0	2.0	2.0	2.0	5.37	6.12	6.06	6.06	6.12
Saline	.144	.231	.250	.250	.189	.231	.371	.796	.824	.495	.495	0	0	0	0	.779	.460	.189	.148	.125
Saline	2.87	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	1.50	1.04	1.16	1.04	1.37
Saline	.265	0	0	0	0	0	0	0	0	0	0	0	0	0	0	.203	.061	.103	.063	.375
Saline	6.125	4.125	3.50	3.0	2.37	2.25	2.12	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	3.06	3.12	3.25	3.27	2.75
Saline	.125	.306	.327	.378	.183	.164	.125	0	0	0	0	0	0	.125	.125	.343	.387	.354	.420	.601
Saline	3.75	3.12	2.50	2.50	2.50	2.25	2.50	2.50	2.25	2.50	2.25	2.25	2.25	2.12	2.12	1.31	1.93	1.43	1.50	1.12
Saline	.250	.350	.327	.327	.327	.164	.327	.327	.250	.327	.164	.164	.164	.125	.125	.134	.383	.220	.335	.354
Saline	4.75	6.10	6.03	6.56	6.93	6.75	7.12	7.00	6.06	5.0	4.06	3.75	3.75	3.75	3.75	7.25	6.56	5.37	4.31	4.06
Saline	.211	.162	.240	.238	.199	.231	.350	.535	.700	.064	.099	.773	.750	.644	.644	.401	.667	.265	.210	.164

was difference necessary for $\lambda = .03$

WITNESSES:

Person (Poised Error)

1. 3 . 991

8.1.17

1-29

2.1

11

Table 11a

Mean Number of Photocell Crossings ($\pm$ S.E.M.) as a Function of
Circadian Drug Treatment, Drug Treatment on Test Day and Block
(Experiment 11)

BLOCKS

BLOCK

NO. PERIOD

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24			
Saline	64.8	20.0	10.0	31.07	9.43	10.93	8.37	16.37	13.01	17.12	9.43	0.0	13.37	12.43	107.93	85.93	75.13	74.37	70.04	61.31	53.54	43.12	44.01	43.0	44.32	20.0	20.23
Saline	8.54	8.15	7.15	2.07	5.5	3.75	3.62	7.05	6.02	7.55	3.46	2.54	4.37	4.40	13.31	9.51	10.54	13.71	11.46	13.25	12.14	14.01	17.11	10.65	13.92	10.98	11.31
Saline	34.0	454.75	450.54	397.10	399.81	235.93	170.01	112.31	55.54	35.76	35.93	30.04	20.04	25.12	330.93	293.43	264.43	107.12	101.93	164.56	142.31	130.31	143.23	133.07	131.12	141.43	133.31
d-amphetamine (5 mg/kg)	69.84	100.28	103.00	77.65	60.11	37.38	49.18	31.32	21.40	9.10	12.50	11.0	12.52	13.17	41.01	37.21	45.7	52.11	49.34	49.26	43.98	44.59	35.05	30.32	24.45	50.33	
d-amphetamine (10 mg/kg)	76.25	31.25	20.07	12.54	6.16	3.07	10.44	6.43	9.54	3.81	9.54	1.43	7.12	8.62	74.87	54.40	49.12	40.31	33.10	33.54	35.25	36.35	20.75	21.43	30.25	22.12	27.41
Saline	15.43	10.81	5.94	3.84	1.02	1.14	4.54	4.05	4.74	3.03	4.42	1.10	4.54	3.72	4.94	7.41	8.35	8.11	8.54	7.00	6.65	3.05	9.44	9.07	7.65	7.13	11.35
d-amphetamine (10 mg/kg)	237.10	293.54	341.23	428.5	304.43	279.54	187.54	141.23	105.01	50.50	34.18	14.0	7.07	7.04	133.01	162.5	158.93	145.31	125.54	148.01	204.75	254.43	232.70	214.62	180.01	143.07	120.15
d-amphetamine (5 mg/kg)	65.03	77.04	80.81	41.40	55.38	40.47	45.03	26.43	20.87	27.74	16.55	3.00	3.00	3.310	30.44	47.14	48.50	46.83	42.67	44.34	44.27	51.20	31.40	30.50	24.07	17.36	12.24

mean differences necessary for p < .05

TABLE

 $r_1 = 73.40$ $r_2 = 87.22$ $r_3 = 95.50$ $r_4 = 101.34$ $r_5 = 103.02$ $r_6 = 109.44$ $r_7 = 113.44$ $r_8 = 115.04$ $r_9 = 117.22$ $r_{10} = 119.35$ $r_{11} = 121.44$ $r_{12} = 122.01$ $r_{13} = 124.31$

Between (Pooled Error)

 $r_1 = 95.03$ $r_2 = 112.62$ $r_3 = 122.44$

Table 12b

Mean Stereotypy Ratings ($\pm$ S.E.M.) as a Function of Chronic
Drug Treatment, Drug Treatment on Test Day and Month
(Experiment 12)

0.015

0.015

0.015

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Saline	3.36	3.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Saline	2.14	2.37	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Saline	3.44	3.37	4.41	4.01	4.34	4.07	4.03	4.30	4.33	4.30	4.33	4.34	4.33	4.31	4.31	4.33	4.34	4.33	4.33	4.33	4.33	4.33	4.33	4.33
Amphetamine (3.0 mg/kg)	3.33	3.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Amphetamine (10.0 mg/kg)	2.30	2.44	2.12	2.12	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Saline	2.36	2.34	2.13	2.13	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amphetamine (10.0 mg/kg)	3.12	3.44	4.34	4.01	4.37	4.30	4.31	4.13	4.07	4.23	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37	4.37
Amphetamine (3.0 mg/kg)	3.39	3.39	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10	3.10

Mean difference necessary for $p < .05$

Saline (Control) Error

 $r_1 = .001$ $r_2 = 1.17$ $r_3 = 1.19$

Kritika

 $r_1 = .014$ $r_2 = .043$ $r_3 = 1.03$ $r_4 = 1.13$ $r_5 = 1.17$ $r_6 = 1.19$ $r_7 = 1.19$ $r_8 = 1.13$ $r_9 = 1.17$ $r_{10} = 1.19$ $r_{11} = 1.13$ $r_{12} = 1.19$ $r_{13} = 1.19$ $r_{14} = 1.17$

Table 13a

Mean Proportion of Alternation as a
Function of Drug Treatment (Experiment 13)

<u>D1</u>	<u>D3</u>	<u>D5</u>	<u>D10</u>	<u>L1</u>	<u>L3</u>	<u>L5</u>	<u>L10</u>	<u>L15</u>	<u>L20</u>	<u>L25</u>
.5399	.4575	.3319	.5248	.6588	.6321	.5376	.4842	.3621	.4195	.4326

mean differences necessary for $p < .05$

$$r_2 = .130$$

$$r_3 = .160$$

$$r_4 = .180$$

$$r_5 = .188$$

$$r_6 = .200$$

$$r_7 = .204$$

$$r_8 = .207$$

$$r_9 = .215$$

$$r_{10} = .219$$

$$r_{11} = .222$$

$$r_{12} = .230$$

Table 13b

Mean Number of Arm Entries as a
Function of Drug Treatment (Experiment 13)

<u>line</u>	<u>D1</u>	<u>D3</u>	<u>D5</u>	<u>D10</u>	<u>L1</u>	<u>L3</u>	<u>L5</u>	<u>L10</u>	<u>L15</u>	<u>L20</u>	<u>L25</u>
.30	70.90	85.0	111.2	53.0	57.5	46.4	35.1	78.3	43.6	35.1	47.3

mean difference necessary for $p < .05$

$$r_2 = 9.96$$

$$r_3 = 11.96$$

$$r_4 = 13.13$$

$$r_5 = 13.96$$

$$r_6 = 14.60$$

$$r_7 = 15.09$$

$$r_8 = 15.38$$

$$r_9 = 15.95$$

$$r_{10} = 16.23$$

$$r_{11} = 16.52$$

$$r_{12} = 16.80$$

Table 14a

Mean Proportion of Alternation Responses as a Function of
Drug Treatment during the Chronic Phase and Drug Treatment on
Test Day (Experiment 14)

<u>Chronic Treatment</u>	<u>Test Day Treatment</u>	<u>Number of Days of Injection</u>		
		<u>3</u>	<u>5</u>	<u>10</u>
saline	saline	.5542	.5407	.6358
saline	d-amphetamine (5.0 mg/kg)	.3383	.1994	.2590
d-amphetamine (15.0 mg/kg)	saline	.5740	.5734	.6109
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	.2867	.4956	.5049

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .130$$

$$r_3 = .151$$

$$r_4 = .166$$

Table 14b

Mean Number of Arm Entries as a Function of Drug Treatment
during the Chronic Phase and Drug Treatment on Test Day (Experiment 14)

<u>Chronic Treatment</u>	<u>Test Day Treatment</u>	<u>Number of Days of Injection</u>		
		<u>3</u>	<u>5</u>	<u>10</u>
saline	saline	44.0	34.8	49.9
saline	d-amphetamine (5.0 mg/kg)	125.5	107.2	126.8
d-amphetamine (15.0 mg/kg)	saline	36.3	45.8	38.4
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	124.7	69.0	80.7

mean difference necessary for $p < .05$ of the main effect
involving Test Day Drug Treatment

$$r_2 = 19.68$$

Table 15a

Mean Proportion of Alternation Responses as a Function of
Drug Treatment during the Chronic Phase (Dosage) and Drug Treatment
on Test Day (Experiment 15)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>
saline	.5772	.2978
d-amphetamine (5.0 mg/kg)	.6093	.3622
d-amphetamine (10.0 mg/kg)	.5786	.4996
d-amphetamine (15.0 mg/kg)	.5912	.5564

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .150$$

$$r_3 = .180$$

$$r_4 = .198$$

Table 15b

Mean Number of Arm Entries as a Function of Drug Treatment
during the Chronic Phase (Dosage) and Drug Treatment on Test Day
(Experiment 15)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>
saline	39.2	111.6
d-amphetamine (5.0 mg/kg)	48.3	89.6
d-amphetamine (10.0 mg/kg)	36.7	92.2
d-amphetamine (15.0 mg/kg)	29.1	89.8

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment on Test Day

$$r_2 = 24.36$$

Table 16a

Mean Proportion of Alternation Responses as a Function of
Drug Treatment during the Chronic Phase and Drug Treatment on Test Day
(Experiment 16)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>l-amphetamine (15.0 mg/kg)</u>
saline	.6189	.2424
l-amphetamine (15.0 mg/kg)	.5819	.3749
l-amphetamine (30.0 mg/kg)	.5559	.3432
l-amphetamine (45.0 mg/kg)	.6530	.4247
l-amphetamine (60.0 mg/kg)	.5802	.3869

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .120$$

$$r_3 = .144$$

$$r_4 = .158$$

$$r_5 = .168$$

Table 16b

Mean Number of Arm Entries as a Function of Drug Treatment
during the Chronic Phase and Drug Treatment on Test Day (Experiment 16)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>l-amphetamine (15.0 mg/kg)</u>
saline	41.70	60.90
l-amphetamine (15.0 mg/kg)	28.70	109.10
l-amphetamine (30.0 mg/kg)	31.60	72.80
l-amphetamine (45.0 mg/kg)	28.70	81.80
l-amphetamine (60.0 mg/kg)	28.90	102.90

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment on Test Day

$$r_2 = 21.95$$

Table 17a

Mean Proportion of Alternation as a Function of Drug Treatment
during the Chronic Phase and Drug Treatment on Test Day (Experiment 17)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>		
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>	<u>l-amphetamine (15.0 mg/kg)</u>
saline	.5991	.2764	.2877
d-amphetamine (10.0 mg/kg)	.5569	.4325	.4620
l-amphetamine (45.0 mg/kg)	.6111	.4456	.4749

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .120$$

$$r_3 = .144$$

Table 17b

Mean Number of Arm Entries as a Function of Drug Treatment
during the Chronic Phase and Drug Treatment on Test Day (Experiment 17)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>		
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>	<u>l-amphetamine (15.0 mg/kg)</u>
saline	31.30	158.3	130.0
d-amphetamine (10.0 mg/kg)	36.70	111.0	123.6
l-amphetamine (15.0 mg/kg)	36.70	96.0	102.2

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment on Test Day

$$r_2 = 43.20$$

$$r_3 = 51.84$$

Table 18a

Mean Proportion of Alternation Responses as a Function
of Drug Treatment and Floor Color (Experiment 18)

<u>Arm Color</u>	<u>Drug</u>		
	<u>Saline</u>	<u>d-amphetamine (3.0 mg/kg)</u>	<u>d-amphetamine 5.0 mg/kg)</u>
same	.635	.593	.291
different	.621	.568	.402

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .1067$$

$$r_3 = .1276$$

Table 18b

Mean Number of Arm Entries as a Function of Drug Treatment,
Floor Color and Compartment Choice (i.e., Arm 1, 2, or 3)
(Experiment 18)

<u>Color</u>	<u>Drug</u>								
	<u>Saline</u>			<u>d-amphetamine</u>			<u>d-amphetamine</u>		
				<u>(3.0 mg/kg)</u>			<u>(5.0 mg/kg)</u>		
	<u>ARM CHOICE</u>								
	<u>1</u>	<u>2</u>	<u>3</u>	<u>1</u>	<u>2</u>	<u>3</u>	<u>1</u>	<u>2</u>	<u>3</u>
same	19.25	20.0	22.75	35.58	35.58	35.25	46.8	32.08	75.9
different	22.0	22.42	21.5	29.67	31.58	29.25	37.25	47.25	41.75

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment

$$r_2 = 18.39$$

$$r_3 = 22.00$$

Table 19a

Mean Proportion of Individual Alternation Responses
during the No-Drug Phase (Phase 1) of Experiment 19

<u>Treatment Assignment</u>	<u>Day of Testing</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
saline (PRE)	.617	.550	.537
d-amphetamine (PRE) (10.0 mg/kg)	.640	.540	.531
d-amphetamine (POST) (10.0 mg/kg)	.635	.565	.533

mean difference necessary for $p < .05$ of the main effect
involving Day of Testing.

$$r_2 = .034$$

$$r_3 = .040$$

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Table 19b

Mean Number of Arm Entries during the No-Drug Phase
(Phase 1) of Experiment 19

<u>Treatment Assignment</u>	<u>Day of Testing</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
saline	58.87	48.0	39.4
d-amphetamine (PRE) (10.0 mg/kg)	55.18	50.0	40.3
d-amphetamine (POST) (10.0 mg/kg)	51.75	39.75	31.62

mean difference necessary for $p < .05$ of the main effect
involving Day of Testing

$$r_2 = 5.04$$

$$r_3 = 6.04$$

Table 19c

Mean Stereotypy Ratings during the No-Drug Phase
(Phase 1) of Experiment 19

<u>Treatment Assignment</u>	<u>Day of Testing</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
saline	3.906	3.787	3.656
d-amphetamine (PRE) (10.0 mg/kg)	3.900	3.900	3.606
d-amphetamine (POST) (10.0 mg/kg)	3.825	3.794	3.669

mean difference necessary for $p < .05$ of the main effect
involving Day of Testing

$$r_2 = .107$$

$$r_3 = .128$$

Table 19d

Mean Proportion of Individual Alternation Responses as a Function
of Drug Treatment for Five Consecutive Days (Experiment 19; Phase 2)

<u>Drug Treatment</u>	<u>Day of Testing</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
saline	.539	.522	.523	.537	.505
d-amphetamine (PRE) (10.0 mg/kg)	.308	.419	.427	.429	.435
d-amphetamine (POST) (10.0 mg/kg)	.530	.517	.501	.521	.544

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment

$$r_2 = .039$$

$$r_3 = .047$$

Table 19e

Mean Number of Arm Entries as a Function of Drug Treatment
for Five Consecutive Days (Experiment 19; Phase 2)

<u>Drug Treatment</u>	<u>Day of Testing</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
saline	31.87	24.68	23.31	23.37	17.43
d-amphetamine (PRE) (10.0 mg/kg)	89.0	83.12	73.0	61.93	51.68
d-amphetamine (POST) (10.0 mg/kg)	30.12	25.37	32.06	28.75	26.12

mean differences necessary for $p < .05$ of the main effects
involving Drug and Day

Between Drugs

$$r_2 = 17.42$$

$$r_3 = 20.08$$

Between Days

$$r_2 = 10.41$$

$$r_3 = 12.44$$

$$r_4 = 13.64$$

$$r_5 = 14.51$$

Table 19f

Mean Stereotypy Ratings as a Function of Drug Treatment
for Five Consecutive Days (Experiment 19; Phase 2)

<u>Drug Treatment</u>	<u>Day of Testing</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
saline	3.35	3.11	3.0	3.15	2.9
d-amphetamine (PRE) (10.0 mg/kg)	5.93	6.98	7.30	7.43	7.62
d-amphetamine (POST) (10.0 mg/kg)	3.42	3.12	3.28	3.23	3.16

mean differences necessary for $p < .05$ of the simple
main effects

Between Drugs (Pooled Error)

$$r_2 = .407$$

$$r_3 = .486$$

Between Days

$$r_2 = .371$$

$$r_3 = .443$$

$$r_4 = .486$$

$$r_5 = .517$$

Table 19g

Mean Proportion of Alternation as a Function of Chronic Drug Treatment and Drug Treatment on Test Day (Experiment 19)

Drug Treatment on Test Day

<u>Chronic Drug Treatment</u>	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>
saline	.523	.249
d-amphetamine (PRE) (10.0 mg/kg)	.535	.535
d-amphetamine (POST) (10.0 mg/kg)	.523	.513

mean difference necessary for $p < .05$ of the simple
main effects

$$r_2 = .167$$

$$r_3 = .201$$

Table 19h

Mean Number of Arm Entries as a Function of Chronic Drug Treatment
and Drug Treatment on Test Day (Experiment 19)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>
saline	24.87	73.00
d-amphetamine (PRE) (10.0 mg/kg)	29.25	80.37
d-amphetamine (POST) (10.0 mg/kg)	23.62	93.75

mean difference necessary for $p < .05$ of the main effect
involving Drug Treatment on Test Day

$$r_2 = 25.54$$

Table 191

Mean Stereotypy Ratings as a Function of Chronic Drug Treatment
and Drug Treatment on Test Day (Experiment 19)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	
	<u>Saline</u>	<u>d-amphetamine (5.0 mg/kg)</u>
saline	2.85	6.01
d-amphetamine (PRE) (10.0 mg/kg)	3.16	6.98
d-amphetamine (POST) (10.0 mg/kg)	2.71	6.56

mean differences necessary for $p < .05$ of the main effects
involving Chronic Drug Treatment and Drug Treatment on Test Day.

Chronic

Test Day

$r_2 = .438$

$r_2 = .358$

$r_3 = .527$

Table 19j

Mean Stereotypy Ratings of Mice Rated in the Y-maze or Home Cage
after Drug Treatment for Five Consecutive Days (Experiment 19; Phase 2)

<u>Chronic Drug Treatment</u>	<u>Day of Testing</u>				
	<u>1</u>	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>
d-amphetamine (PRE; rated in the Y-maze; 10.0 mg/kg)	5.93	6.98	7.38	7.43	7.62
d-amphetamine (POST; rated in home cage; 10.0 mg/kg)	5.69	7.30	7.41	7.65	7.77

mean difference necessary for $p < .05$ of the main effect
involving Day of Testing

$$r_2 = .340$$

$$r_3 = .408$$

$$r_4 = .449$$

$$r_5 = .477$$

Table 20a

Mean Proportion of Alternation Responses During the No-Drug
Phase of Experiment 20 (Phase 1)

<u>Treatment Assignment</u>	<u>Day of Testing</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
saline	.658	.583	.587
d-amphetamine (PRE) (10.0 mg/kg)	.702	.636	.570
d-amphetamine (POST) (10.0 mg/kg)	.685	.563	.562
saline (NO TEST)	.640	.556	.563
d-amphetamine (NO TEST) (10.0 mg/kg)	.690	.632	.571

mean difference necessary for $p < .05$ of the main effect
involving Day of Testing

$$r_2 = .028$$

$$r_3 = .036$$

Table 20b

Mean Proportion of Alternation Responses as a Function of Drug Treatment
for Three Consecutive Days in Experiment 20 (Phase 2)

<u>Chronic Drug Treatment</u>	<u>Day of Testing</u>		
	<u>1</u>	<u>2</u>	<u>3</u>
saline	.530	.522	.563
d-amphetamine (PRE) (10.0 mg/kg)	.426	.411	.446
d-amphetamine (POST) (10.0 mg/kg)	.576	.562	.565
saline (NO TEST)		NO TEST	
d-amphetamine (NO TEST) (10.0 mg/kg)		NO TEST	

mean difference necessary for $p < .05$ of the main effect
involving Chronic Drug Treatment

$$r_2 = .070$$

$$r_3 = .085$$

Table 20c

Mean Proportion of Alternation Responses as a Function of Chronic
Drug Treatment and d-Amphetamine (5.0 mg) on Test Day (Experiment 20)

<u>Chronic Drug Treatment</u>	<u>Test with d-amphetamine (5.0 mg/kg)</u>
saline	.349
d-amphetamine (PRE) (10.0 mg/kg)	.362
d-amphetamine (POST) (10.0 mg/kg)	.373
saline (NO TEST)	.351*
d-amphetamine (NO TEST) (10.0 mg/kg)	.389

APPENDIX C

Table 1

χ^2 Analysis of Total Number of Group Alternation
and Non Alternation Responses (Experiment 13)

	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	325	228	16.66
d-amphetamine			
1	382	327	4.12
3	445	418	.780
5	341	772	166.12
10	255	275	.680
l-amphetamine			
1	364	207	42.62
3	348	213	32.0
5	195	156	4.12
10	377	406	1.0
15	171	276	24.2
20	158	195	3.68
25	230	253	1.0

In all cases, $df = 1$

χ^2 value necessary for $p < .05 = 3.8$

χ^2 value necessary for $p < .01 = 6.6$

Table 2

χ^2 Analysis of Total Number of Group Alternation
and Non Alternation Responses (Experiment 14)

		<u>A</u>	<u>N</u>	<u>χ^2</u>
<u>3 Days of Chronic Injection</u>				
<u>Chronic Treatment</u>	<u>Treatment on Test Day</u>			
saline	saline	223	201	1.04
saline	d-amphetamine (5.0 mg/kg)	431	824	122.44
d-amphetamine (15.0 mg/kg)	saline	209	154	8.04
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	316	931	302.30
<u>5 Days of Chronic Injection</u>				
saline	saline	190	148	4.98
saline	d-amphetamine (5.0 mg/kg)	252	900	363.40
d-amphetamine (15.0 mg/kg)	saline	276	200	11.82
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	225	239	.360
<u>10 Days of Chronic Injection</u>				
saline	saline	306	177	33.92
saline	d-amphetamine (5.0 mg/kg)	347	891	238.16
d-amphetamine (15.0 mg/kg)	saline	234	152	17.00
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	329	478	27.14

Table 3

χ^2 Analysis of the Total Number of Group Alternation
and Non Alternation Responses (Experiment 15)

<u>Chronic Treatment</u>	<u>Treatment on Test Day</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	saline	227	165	9.50
saline	d-amphetamine (5.0 mg/kg)	376	740	118.08
d-amphetamine (5.0 mg/kg)	saline	290	193	19.08
d-amphetamine (5.0 mg/kg)	d-amphetamine (5.0 mg/kg)	270	598	123.2
d-amphetamine (10.0 mg/kg)	saline	217	150	11.86
d-amphetamine (10.0 mg/kg)	d-amphetamine (5.0 mg/kg)	421	501	6.76
d-amphetamine (15.0 mg/kg)	saline	173	118	10.02
d-amphetamine (15.0 mg/kg)	d-amphetamine (5.0 mg/kg)	482	387	10.16

Table 4

χ^2 Analysis of the Total Number of Group Alternation
and Non-Alternation Responses (Experiment 16)

<u>Chronic Treatment</u>	<u>Treatment on Test Day</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	saline	259	158	23.98
saline	d-amphetamine (15.0 mg/kg)	200	669	252.04
l-amphetamine (15.0 mg/kg)	saline	178	119	11.32
l-amphetamine (15.0 mg/kg)	l-amphetamine (15.0 mg/kg)	507	594	6.72
l-amphetamine (30.0 mg/kg)	saline	183	133	7.60
l-amphetamine (30.0 mg/kg)	l-amphetamine (15.0 mg/kg)	345	489	24.52
l-amphetamine (45.0 mg/kg)	saline	176	101	19.76
l-amphetamine (45.0 mg/kg)	l-amphetamine (15.0 mg/kg)	353	462	14.32
l-amphetamine (60.0 mg/kg)	saline	208	121	22.48
l-amphetamine (60.0 mg/kg)	l-amphetamine (15.0 mg/kg)	441	586	20.20

Table 5

χ^2 Analysis of the Total Number of Group Alternation
and Non-Alternation Responses (Experiment 17)

<u>Chronic Treatment</u>	<u>Treatment on Test Day</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	saline	191	121	15.26
saline	d-amphetamine (5.0 mg/kg)	416	873	161.32
saline	l-amphetamine (15.0 mg/kg)	296	986	370.3
d-amphetamine (10.0 mg/kg)	saline	205	153	9.88
d-amphetamine (10.0 mg/kg)	d-amphetamine (5.0 mg/kg)	434	680	53.88
d-amphetamine (10.0 mg/kg)	l-amphetamine (15.0 mg/kg)	566	680	53.88
l-amphetamine (45.0 mg/kg)	saline	220	145	15.00
l-amphetamine (45.0 mg/kg)	d-amphetamine (5.0 mg/kg)	440	572	16.96
l-amphetamine (45.0 mg/kg)	l-amphetamine (15.0 mg/kg)	392	498	12.38

Table 6

χ^2 Analysis of the Total Number of Group Alternation
and Non-Alternation Responses (Experiment 18)

<u>Floor Color</u>	<u>Drug Treatment</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
Same	saline	453	261	51.1
	d-amphetamine (3.0 mg/kg)	866	799	2.62
	d-amphetamine (5.0 mg/kg)	452	1078	255.3
Different	saline	510	305	51.06
	d-amphetamine (3.0 mg/kg)	803	753	2.68
	d-amphetamine (5.0 mg/kg)	641	811	19.68

Table 7a

χ^2 Analysis of the Total Number of Group Alternations
and Non-Alternations of the No-Drug Phase (Phase 1) of Experiment 19

<u>Treatment Assignment</u>	<u>Day of Testing</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	1	472	350	52.98
	2	422	347	7.12
	3	338	295	2.78
d-amphetamine (PRE) (10.0 mg/kg)	1	560	323	63.08
	2	446	354	10.36
	3	342	270	8.24
d-amphetamine (POST) (10.0 mg/kg)	1	528	300	62.24
	2	358	281	9.04
	3	267	229	2.76

Table 7b

χ^2 Analysis of the Total Group Alternations
and Non-Alternations (Experiment 19; Phase 2)

<u>Treatment Assignment</u>	<u>Day of Testing</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	1	276	234	3.30
	2	215	170	5.02
	3	201	169	2.60
	4	208	166	4.50
	5	145	134	.36
d-amphetamine (PRE) (10.0 mg/kg)	1	485	939	144.2
	2	555	765	39.8
	3	494	674	27.4
	4	458	565	11.0
	5	353	474	17.42
d-amphetamine (POST) (10.0 mg/kg)	1	255	227	1.52
	2	210	196	.42
	3	259	254	.04
	4	237	213	1.18
	5	236	194	3.90

Table 7c

χ^2 Analysis of the Total Group Alternations
and Non-Alternations (Experiment 19; Test Day)

<u>Chronic Drug Treatment</u>	<u>Drug Treatment on Test Day</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
* saline	saline	99	90	.34
	d-amphetamine (5.0 mg/kg)	192	392	67.8
d-amphetamine (PRE) (10.0 mg/kg)	saline	115	108	.16
	d-amphetamine (5.0 mg/kg)	349	293	4.8
d-amphetamine (POST) (10.0 mg/kg)	saline	100	89	.52
	d-amphetamine (5.0 mg/kg)	413	380	1.3

Table 8a

χ^2 Analysis of the Total Group Alternations
and Non-Alternations (Experiment 20; Phase 1)

<u>Treatment Assignment</u>	<u>Day of Testing</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	1	396	213	54.40
	2	252	181	11.30
	3	158	129	2.74
d-amphetamine (PRE) (10.0 mg/kg)	1	307	177	34.40
	2	225	172	7.34
	3	208	164	4.98
d-amphetamine (POST) (10.0 mg/kg)	1	304	132	67.0
	2	188	152	36.0
	3	141	116	.64
saline (NO TEST)	1	299	164	38.8
	2	197	164	18.8
	3	179	141	4.32
d-amphetamine (NO TEST) (10.0 mg/kg)	1	285	146	44.2
	2	207	125	18.8
	3	151	116	4.32

Table 8b

χ^2 Analysis of the Total Group Alternations
and Non-Alternations (Experiment 20; Phase 2)

<u>Chronic Drug Treatment</u>	<u>Day of Testing</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
saline	1	146	125	1.48
	2	173	149	1.64
	3	140	105	4.72
d-amphetamine (PRE) (10.0 mg/kg)	1	303	364	5.40
	2	194	205	.260
	3	151	178	2.38
d-amphetamine (POST) (10.0 mg/kg)	1	131	108	2.02
	2	120	90	4.0
	3	120	93	3.18
saline	NO TEST			
d-amphetamine (10.0 mg/kg)	NO TEST			

Table 8c

χ^2 Analysis of the Total Group Alternations
and Non-Alternations (Experiment 20; Test Day)

<u>Chronic Drug Treatment</u>	<u>A</u>	<u>N</u>	<u>χ^2</u>
(Test with d-amphetamine 5.0 mg/kg)			
saline	285	445	34.64
d-amphetamine (PRE) (10.0 mg/kg)	105	295	89.20
d-amphetamine (POST) (10.0 mg/kg)	303	461	32.20
saline (NO TEST)	385	555	30.40
d-amphetamine (NO TEST) (10.0 mg/kg)	321	398	8.04

END

06

02

79

FIN