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THE INFLUENCE OF DOPAMINERGIC AND SEROTONERGIC
MANIPULATIONS ON COCAINE SELF-ADMINISTRATION IN THE RAT
USING A PROGRESSIVE RATIO SCHEDULE OF REINFORCEMENT

By
NICOLE RENÉE RICHARDSON

A thesis submitted to the Faculty of Graduate Studies and Research
in partial fulfillment of the requirements for the degree of
Master of Science

Department of Psychology
Carleton University
Ottawa, Ontario
September, 1991

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the Faculty of Graduate Studies and Research
acceptance of the thesis submitted by

Nicole Renée Richardson

in partial fulfillment of the requirements
for the degree of Master of Science

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Thesis Supervisor

Carleton University

September, 1991

ABSTRACT

The effects of three pharmacological agents on the self-administration of cocaine were investigated using a progressive ratio (PR) schedule of reinforcement. Pretreatment with the novel dopamine (DA) receptor antagonist, (+)-AJ 76, significantly decreased both the time animals took to self-administer their first six infusions of cocaine and the breaking points they ultimately attained. The "typical" D2 antagonist, haloperidol, similarly increased animals' rates of cocaine self-administration (ie. decreased the time from the 1st to the 6th infusion of cocaine), and although there was a trend towards a decrease in breaking point this failed to reach significance. The serotonin (5-HT) re-uptake inhibitor, fluoxetine, reduced breaking points in a dose-dependent manner, while failing to alter the rate of cocaine self-administration. The highest dose of (+)-AJ 76 tested (30 mg/kg) delayed the onset of responding for cocaine by an average of one hour; neither haloperidol nor fluoxetine had a similar effect. The present data provide additional support for the importance of DA in cocaine reinforcement. A role for 5-HT in cocaine reinforcement is also supported by the present findings, and this role appears to be aversive. Furthermore, these data suggest that all three of the drugs screened here - fluoxetine, (+)-AJ 76, and haloperidol - should undergo preliminary evaluations in humans for their clinical efficacy in treating cocaine abuse. (+)-AJ 76 appears to be an especially promising candidate in light of its apparent ability to delay an animal's desire for cocaine. Finally, the present thesis provides further support for the use of PR schedules in investigating the influence of pharmacological manipulations on drug reinforcement.

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I would like to thank my advisor David C. S. Roberts for always having his office door wide open for me to stroll in with my questions, problems, frustrations, puzzlements, and small triumphs. The love and enthusiasm he has for this research is highly infectious. I would also like to thank Gary Vickers for teaching me everything I needed to know to complete these experiments. Finally, I want to thank my lab mates for making it a pleasure to come to work everyday.

This piece of work was born of the enthusiasm and pride given me by my mother, Gabriella Richardson. I have more love, admiration and respect for her than I can possibly express here. I would also like to extend my gratitude to my dear companion, Cleo, who spent many an hour laying her head on my keyboard to closely examine my progress. Last, but certainly not least, without my fiancé and best friend, Ian Gilron, I would not be writing these acknowledgements. He was there for me every minute of the way, and for that I am forever grateful.

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include such measures as rate (eg. responses/min, infusions/h), time (eg. time from the first to the sixth infusion, time of the first infusion), pause duration (eg. inter-response interval), breaking point (eg. the ordinal value corresponding to the final infusion for which the required response criterion was satisfied), and mean drug intake (eg. the mean volume of drug administered in a 24 h period). Which dependent variable is most reliable, valid and sensitive to changes in an animal's level of motivation to receive a drug remains a controversy.

The Fixed Ratio Schedule of Reinforcement

A majority of the self-administration experiments that have been carried out to date have employed rate as the dependent variable. Rate of responding is most commonly derived from a fixed ratio (FR) schedule of reinforcement in which an animal must complete a preset number of lever responses in order to receive a drug infusion. Advocates of this practice interpret an animal's rate of responding for a drug as reflecting that animal's level of motivation to receive the drug or, stated another way, the response rate for a drug indicates the reinforcement value of that drug.

The Role of Dopamine in Stimulant Reinforcement

Dopamine was the first of the neurotransmitters to be investigated for its role in stimulant reinforcement. Specifically, the first studies of this sort examined the effect of DA antagonists on the rate of stimulant self-administration. These studies revealed that low doses of DA antagonists including chlorpromazine (Wilson and

edema, bronchitis, respiratory arrest, seizures, psychosis, paranoia, congenital malformations, and acquired immunodeficiency syndrome (AIDS) (Estroff and Gold, 1985; Pollack et al., 1989; Rowbotham and Lowenstein, 1990). Furthermore, overdoses of cocaine are usually rapidly fatal. Often, victims die from respiratory depression and seizures within minutes of administering the fatal dose. The National Institute of Drug Abuse (NIDA) (1988) reports that there were approximately 2000 cocaine-related deaths in the United States in 1985 (NIDA, 1988).

Considering the severe health risks and complications that accompany cocaine use, one cannot help but wonder why individuals continue to take it. The solution most commonly offered in response to this puzzle is that cocaine is one of the most efficacious reinforcers known to exist (Aigner and Balster, 1978; Woods et al., 1987). This fact has been demonstrated repeatedly in research. For example, strong evidence in support of cocaine's efficacy as a reinforcer comes from the fact that cocaine is self-administered by every species of animal tested. These include rats (Pickens, 1968), squirrel monkeys (Goldberg, 1973), rhesus monkeys (Aigner and Balster, 1978; Bedford et al., 1978), pigtail macaques (Young and Woods, 1980), baboons (Griffiths et al., 1975), cats (Balster et al., 1976), dogs (Risner and Jones, 1975), and humans (Fischman et al., 1990). Furthermore, in experiments that compare cocaine with other drugs, cocaine is found in nearly all instances to be more reinforcing than the drug with which it is compared (Yanagita, 1973; Griffiths et al., 1975; Bedford et al., 1978; Griffiths et al., 1978; Risner and Silcox, 1981; Risner and Goldberg, 1983).

Due to the immense reinforcing value of this stimulant, cocaine is one of the drugs of greatest national health concern. Consequently, there is a great deal of attention currently being directed towards identifying potential therapies for treating the abuse of this potent stimulant.

Pharmacotherapeutic Interventions

The first attempts at treating cocaine abuse utilized non-pharmacological therapies such as interpersonal psychotherapy (Horberg and Schnoll, 1983; Rounsaville et al., 1985), support group therapy (Ehrlich and McGeehan, 1985; Acee and Smith, 1987; Vandegaer, 1989), social network therapy (Galanter, 1987), contingency contract programs (Washton, 1988), biopsychosocial therapy (Nuckols and Greeson, 1989), vitamin/mineral supplementation (Horne, 1988), and behavioral therapy (Siegel, 1984; O'Brien et al., 1988). These non-pharmacological therapies, however, were having very limited success in promoting cocaine abstinence in cocaine abusing patients. In addition to their apparent ineffectiveness, non-pharmacological treatments were associated with high rates of patient drop-outs and recidivism. Consequently, researchers began to suspect that pharmacological interventions were what was required to combat the euphoric and addictive properties of cocaine.

There have emerged, in the past decade, some exciting and potentially effective pharmacological treatments for the abuse of

cocaine. These pharmacotherapies attempt to alleviate cocaine abuse in a variety of different ways - (1) desmethylinipramine (DMI) or desipramine, by facilitating initial cocaine abstinence (Gawin et al., 1989b), (2) bromocriptine and amantadine, by reducing or eliminating cocaine withdrawal symptoms (Giannini et al., 1987; Tennant and Sagherian, 1987; Teller and Devenyi, 1988; Giannini et al., 1989; Pike, 1989), (3) DMI, imipramine, bromocriptine, and flupenthixol decanoate, by reducing or eliminating cocaine craving (Gawin and Kleber, 1984; Dackis et al., 1985, 1986; Gawin et al., 1989a; Jaffe et al., 1989), (4) phenelzine, by reversing the biochemical damage caused by chronic cocaine use (Golwyn, 1988), (5) bromocriptine, lithium carbonate, methylphenidate, mazindol and magnesium pemoline, by treating psychiatric disorders for which cocaine abusers might be self-medicating (Khantzian, 1983; Gawin and Kleber, 1984, 1985; Dackis et al., 1985; Weiss et al., 1985; Cocores et al., 1987; Berger et al., 1989), and (6) buprenorphine and phenelzine, by resulting in marked dysphoria and extreme physical unpleasantness in the event that cocaine is administered (Resnick and Resnick, 1984; Kosten et al., 1989).

Although one or more of the pharmacotherapeutic treatments outlined above may eventually prove to be effective in facilitating cocaine abstinence, at present, these pharmacological interventions are still in their very early stages of research and development. In fact, the research that is required to discover and evaluate pharmacotherapies is long and difficult. Clinical trials can encounter special problems. For example, they are often (1) very long and costly, (2) hard to control experimentally, and (3) viewed as ethically

questionable in the absence of abundant and sound evidence in support of their execution. In light of these difficulties, researchers often turn to animal models for use in the screening of pharmacotherapies.

The most common of the animal models used for screening pharmacotherapeutic agents is the drug self-administration paradigm. This paradigm can serve not only to evaluate potential pharmacological drug abuse treatments, but also to investigate which neural substrate(s) may be responsible for mediating the reinforcing effects of cocaine, and psychomotor stimulants in general.

The Self-administration Paradigm

According to the drug self-administration paradigm, a laboratory animal, equipped with a chronically indwelling intravenous cannula, receives infusions of drug contingent upon self-activated operant responses made on a lever mounted on the wall of its cage. A particular dependent variable is then chosen by the investigator to quantify the animal's behavior. It is assumed that the behavior of the animal (i.e. seeking out or avoiding the lever) is reflecting that animal's level of desire or motivation to receive the drug made available to it. Experimental manipulations are then carried out, and any changes in the dependent variable are interpreted as changes in the animal's level of motivation to receive the drug.

Dependent variables vary greatly among researchers and

include such measures as rate (eg. responses/min, infusions/h), time (eg. time from the first to the sixth infusion, time of the first infusion), pause duration (eg. inter-response interval), breaking point (eg. the ordinal value corresponding to the final infusion for which the required response criterion was satisfied), and mean drug intake (eg. the mean volume of drug administered in a 24 h period). Which dependent variable is most reliable, valid and sensitive to changes in an animal's level of motivation to receive a drug remains a controversy.

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Schuster, 1972; Risner and Jones, 1976), trifluoperazine (Wilson and Schuster, 1973a), pimozide (Yokel and Wise, 1975, 1976; Risner and Jones, 1976; de Wit and Wise, 1977), perphenazine (Johanson et al., 1976), (+)-butaclamol (Yokel and Wise, 1976), alpha-flupenthixol (Ettenberg et al., 1982; Roberts and Vickers, 1984), haloperidol (De La Garza and Johanson, 1982; Roberts and Vickers, 1984; Dalton et al., 1986; Roberts et al., 1987), sulpiride, metoclopramide, thioridazine (Roberts and Vickers, 1984), and SCH 23390 (Koob et al., 1987) increase the rate of stimulant self-administration.

Roberts and Vickers (1987) were the first to investigate the effects of repeated pretreatment with a DA antagonist on stimulant self-administration. They found that cocaine intake was significantly increased following haloperidol pretreatment and this response became more pronounced with repeated administrations of the neuroleptic (Roberts and Vickers, 1987).

The effects of DA agonists on stimulant self-administration has also been investigated, although to a lesser degree. Pretreatment with the direct and indirect DA agonists methamphetamine (Pickens et al., 1968), phenmetrazine (Wilson and Schuster, 1973a), apomorphine and piribedil (Yokel and Wise, 1978), cocaine (Herling et al., 1979), amphetamine (Wilson and Schuster, 1973a; Herling et al., 1979), and bromocriptine (Hubner and Koob, 1990; Kleven and Woolverton, 1990) attenuate the rate of stimulant self-administration. Furthermore, studies have shown that many of these DA agonists are self-administered by laboratory animals (Yokel and Wise, 1978; Woolverton et al., 1984; Wise et al., 1990) suggesting

that the facilitation of dopaminergic activity results in reinforcement activity.

In summary, all of the studies involving pharmacological manipulations of the dopaminergic system reviewed above clearly indicate that DA plays an important role in stimulant reinforcement.

Findings based on lesioning studies appear to support the same conclusion. Roberts et al. (1977) were the first to explore the relative importance of ascending DA systems in intravenous cocaine self-administration by lesioning various nerve regions and fiber bundles with the neurotoxin 6-hydroxydopamine (6-OHDA). Their findings suggested that DA terminals in the nucleus accumbens septi (NAS) play an important role in cocaine reinforcement (Roberts et al., 1977). Later, it was shown that while cocaine self-administration recovered in those animals with smaller depletions of DA, it never recovered in those with depletions of greater than 80 % (Roberts et al., 1980).

The importance of the NAS in cocaine reinforcement was further supported by Zito et al. (1985) who, using kainic acid lesions of the NAS, found reductions in cocaine self-administration, as well as reductions in apomorphine and heroin self-administration (Zito et al., 1985). Taken together, all of these studies point to a role for the NAS in mediating the reinforcing effects of cocaine.

Further lesioning studies have been carried out in an attempt to discover which additional structures within the mesolimbic/mesocortical pathways are necessary for cocaine reinforcement to occur. For example, Roberts and Koob (1982) showed that lesions in the ventral tegmental area (VTA) disrupted,

and for some animals even eliminated, cocaine self-administration (Roberts and Koob, 1982). In contrast, intracerebral infusions of 6-OHDA into the caudate nucleus (Roberts and Zito, 1987), the dorsal tegmentum (Roberts et al., 1977) or the prefrontal cortex (PFC) (Martin-Iverson et al., 1986) were found to produce no changes in the self-administration of cocaine.

In summary, lesioning studies have provided investigators with valuable information regarding stimulant reinforcement and the neural pathways that are responsible for its manifestation. Although there remains some controversy with regard to which specific structures within the mesolimbic/mesocortical pathways are crucial for mediating the reinforcing effects of cocaine and amphetamine, lesioning studies support the importance of the dopaminergic system in this role.

The Role of Serotonin in Stimulant Reinforcement

In the early 1980's, Lyness and coworkers began to suspect that the serotonergic system may also play a role in stimulant reinforcement. In an attempt to test this hypothesis, they first examined the effects of intracerebroventricular (ICV) injections of the neurotoxin 5,7-di-hydroxytryptamine (5,7-DHT) on amphetamine self-administration. This study revealed that rats with forebrain 5-HT depletions consistently self-administered more amphetamine than control animals (Lyness et al., 1980). Curiously, while 5,7-DHT lesions of the median forebrain bundle (MFB) similarly produced significant increases in amphetamine intake (Leccese and Lyness,

1984), 5,7-DHT lesions of the NAS had no effect (Lyness et al., 1980). Simon et al. (1980) showed that radio-frequency lesions of the anterior raphe nuclei (dorsal or median), 5-HT nuclei which project to the forebrain, increase the rate of amphetamine self-administration (Simon et al., 1980).

Consequently, findings based on studies examining the effects of 5-HT destruction on stimulant self-administration suggest that 5-HT does indeed play an important role in stimulant self-administration. Furthermore, this role is likely aversive, such that removing 5-HT activity increases the reinforcing value of the stimulant.

Lyness and colleagues continued investigating the importance of 5-HT in stimulant reinforcement through the use of pharmacological manipulations. Specifically, they demonstrated that facilitating 5-HT activity through the administration of either fluoxetine, L-tryptophan or quizapine resulted in the disruption of amphetamine self-administration (Leccese and Lyness, 1984). These manipulations, however, required intact serotonergic systems since both fluoxetine and L-tryptophan failed to alter amphetamine self-administration in 5,7-DHT lesioned animals (Leccese and Lyness, 1984).

Several, more recent studies have lent support to the earlier, pioneering work of Lyness and coworkers. For example, reductions in stimulant self-administration have been reported following acute (Porrino et al., 1989) and repeated (Yu et al., 1986; Carroll et al., 1990a) pretreatment with the 5-HT re-uptake inhibitor, fluoxetine.

Furthermore, L-tryptophan, the 5-HT precursor, has been shown to reduce both amphetamine (Smith et al., 1986) and cocaine (Carroll et al., 1990b) intake.

In accordance with those studies investigating serotonergic destruction and its effects on stimulant reinforcement, the studies which have examined the effects of direct and indirect 5-HT agonists on stimulant self-administration support the hypothesis that 5-HT systems play an important role in stimulant reinforcement. Again, the nature of that role appears to be aversive since the reinforcing value of the stimulant was attenuated through the facilitation of 5-HT activity.

The effects of pretreatment with 5-HT antagonists on the reinforcing properties of psychomotor stimulants is less clear. While cyproheptadine and methysergide, both 5-HT receptor antagonists, decreased rates of amphetamine self-administration in one study (Leccese and Lyness, 1984), metergoline, also a 5-HT receptor antagonist, increased amphetamine self-administration in another study (Lyness and Moore, 1983). Furthermore, cinanserin, a 5-HT₂ receptor antagonist, reduced rates of responding for amphetamine, but failed to alter rates of responding for cocaine (Porrino et al., 1989).

Clearly, understanding the effects of 5-HT antagonists on stimulant reinforcement proves difficult when pretreating animals with 5-HT receptor antagonists is reported to increase, decrease, and have no effect on the rate of stimulant self-administration. Further investigation is required before the nature of this puzzle can be solved.

The Role of Norepinephrine in Stimulant Reinforcement

Most researchers will agree that NE does not play a primary role in stimulant reinforcement. The noradrenergic agonist, methoxamine (Risner and Jones, 1976), and the noradrenergic antagonists, prazosin (Wooiverton, 1987), phenoxybenzamine (Wilson and Schuster, 1974; Risner and Jones, 1976; de Wit and Wise, 1977), phentolamine (Wilson and Schuster, 1974; de Wit and Wise, 1977), and propranolol (de Wit and Wise, 1977) have all failed to affect rate of stimulant self-administration.

Stimulant self-administration has similarly remained unaltered despite the destruction of noradrenergic fibers. For example, Roberts et al. (1977) found that 6-OHDA lesions of the major NE pathway extending from the locus coeruleus to the forebrain via the dorsal midbrain resulted in rates of cocaine self-administration comparable to prelesion values (Roberts et al., 1977).

In summary, while it is clear that NE does not play an important role in stimulant reinforcement, there is abundant evidence in support of the notion that DA is essential for stimulant reinforcement to occur. Recently, researchers have begun accumulating evidence which suggests that 5-HT may be involved in this capacity, as well.

The Progressive Ratio Schedule of Reinforcement

Recently, measures based on simple schedules of reinforcement, such as rate, have been criticized for being difficult to interpret. For example, increases in response rate have been

interpreted as reflecting both an attenuation (Pickens, 1968; Yokel and Wise, 1975; Johanson et al., 1976; Yokel and Wise, 1976; Roberts and Vickers, 1984) and an augmentation (Deneau et al., 1969; Wilson and Schuster, 1973b; Woolverton and Balster, 1979; Woolverton, 1987) of drug reinforcement. This ambiguity drastically limits the value of rate as a measure of drug reinforcement.

As a viable alternative to rate, several researchers have proposed the use of breaking point as a valid, reliable, and sensitive measure of drug reinforcement (Griffiths et al., 1975; Thompson, 1977; Griffiths et al., 1978; Bedford et al., 1978; Griffiths et al., 1979; Hoffmeister, 1979; Risner and Silcox, 1981; Risner and Goldberg, 1983; Koob et al., 1987; Roberts, 1989; Roberts et al., 1989a, 1989b).

Breaking point, in contrast to rate, is derived from a PR schedule of reinforcement. The PR schedule, like the FR schedule, requires that an animal complete a preset number of responses before receiving a drug infusion; however, in contrast to the FR schedule which holds the response criterion fixed, the PR schedule requires that the response criterion be systematically increased. All of the studies presented in this thesis employ a PR schedule of reinforcement which adjusts response criteria within each session in order to yield daily breaking points. This technique, originally developed by Hodos (1961), and subsequently adopted for primates (Griffiths et al., 1975) and dogs (Risner and Silcox, 1981), has recently been modified by Roberts and colleagues (Roberts, 1989; Roberts et al., 1989a, 1989b) for use with rodents.

Breaking point, as opposed to rate, is proving to be a sensitive measure of drug reinforcement. For example, while breaking point is

sensitive to (1) hormonal changes across the estrous cycle (Roberts et al., 1989a), (2) dopaminergic supersensitivity following 6-OHDA lesions of the nucleus accumbens (Roberts, 1989), and (3) 5,7-DHT lesions of the MFB and amygdala (Loh and Roberts, 1990), rate is insensitive to these experimental manipulations.

Proposed Experiments

To date, there are only four studies that have employed a PR schedule of reinforcement to study the effects of experimental manipulations on stimulant self-administration. Of these four studies, two have investigated serotonergic manipulations and two, dopaminergic manipulations.

Consistent with the earlier studies by Lyness et al. (1980), Roberts and colleagues found that ICV injections of 5,7-DHT significantly increased breaking points on a progressive ratio schedule reinforced by cocaine (unpublished data). Significant increases in the breaking points reached by rats self-administering cocaine were also observed following 5,7-DHT lesions of either the MFB or the amygdala (Loh and Roberts, 1990).

Experiment 1 of the present thesis served to examine the effects of the indirect 5-HT agonist, fluoxetine, on the self-administration of cocaine using a PR schedule of reinforcement. As far as this author is aware, this represents the first time a PR schedule has been employed to investigate the influence of enhanced 5-HT activity on stimulant reinforcement.

Koob et al. (1987) were the first to examine the effects of dopaminergic manipulation on stimulant reinforcement using a PR schedule. They found that 6-OHDA lesions of the NAS significantly reduced breaking points, suggesting a specific decrease in cocaine's reinforcing efficacy (Koob et al., 1987).

Recently, Roberts et al. (1989b) examined the effects of haloperidol on cocaine self-administration using a PR schedule of reinforcement. They found that the breaking points reached by rats self-administering cocaine were significantly reduced following pretreatment with 0.05 and 0.075 mg/kg haloperidol (Roberts et al., 1989b).

The present thesis served to examine the effects of dopaminergic manipulations on cocaine reinforcement using a PR schedule of reinforcement. In Experiments 2 and 3, respectively, rats self-administering cocaine maintained on a PR schedule were pretreated with acute administrations of (+)-AJ 76, a mixed DA agonist/antagonist, and repeated administrations of haloperidol, a DA antagonist.

Objectives

The purpose of this thesis was twofold. First, to examine several pharmacological agents using the animal drug self-administration paradigm. Specifically, three drugs - fluoxetine, (+)-AJ 76, and haloperidol - were screened for their effectiveness as pharmacotherapies for use in the treatment of cocaine abuse using a PR schedule of reinforcement. Second, to help determine what

neural system(s) are responsible for mediating the reinforcing effects of cocaine.

METHODS, RESULTS AND DISCUSSIONS

General Procedures

Subjects: Male Wistar rats (Woodlyn Farms, Guelph, Ont.) weighing approximately 300-330 g at the start of each experiment were individually housed and maintained on a 12 h reversed light-dark cycle (lights on: 9:30 pm - 9:30 am). With the exception of 24 h of food deprivation to facilitate learning to respond on a lever for food pellets, animals were given free access to food and water for the duration of the experiments.

Apparatus: Plexiglass boxes (25 X 25 X 25 cm) served as both housing and testing chambers. Each box was equipped with a wire grid floor, a removable response lever, a stimulus light, and a water bottle.

Animals were surgically implanted with a chronically indwelling jugular cannula, attached to tubing, encased within a protective spring, held in suspension above the animal by a swivel and counterbalance weight, and extended to a 10 ml syringe pump driven by a 5 RPM motor. All functions, including response monitoring, infusion delivery, and data recording, were controlled by an IBM-compatible computer. These methods are described in more detail elsewhere (Roberts and Richardson, in press).

Procedure: Following 24 h of food deprivation, animals were

trained to respond on a lever for Noyes food pellets maintained on an FR 1 schedule of reinforcement. Once animals exceeded 100 lever responses per food training session for a minimum of two such sessions, they were deeply anesthetized using sodium pentobarbitol (Somnotol, 60 mg/kg, IP) and implanted with a chronically indwelling jugular cannula exiting at the mid-scapular level of the back.

Following a post-operative period of not less than 24 h, animals were trained to self-administer cocaine (0.6 mg/0.12 ml saline/injection over 5 sec) maintained on an FR 1 schedule of reinforcement. All cocaine self-administration sessions were 5 h in duration and began with the introduction of a lever into the cage and a "priming" injection. The delivery of cocaine infusions coincided with the onset of a stimulus light (20 sec) during which time responses on the lever had no programmed consequence.

Once animals achieved stable responding for cocaine on an FR 1 schedule (at least three consecutive days for which the total number of infusions varied by no more than ± 2 infusions), the schedule was switched to a PR schedule of reinforcement. In accordance with this schedule, the first lever response of the session resulted in a drug infusion. Subsequent response requirements then escalated through the following exponential series: 2, 4, 6, 9, 12, 15, 20, 25, 32, 40, 50, 62, 77, 95, 118, 145, 178, 219, 268, 328, 402...

Following three days of stable baseline on a PR schedule of reinforcement (breaking points that varied by no more than ± 2 points for at least three consecutive days), animals were placed into one of three possible experiments.

Drugs: Cocaine hydrochloride was supplied by NIDA (Bethesda, MD), fluoxetine by Eli Lilly and Company (Indianapolis, IN), and (+)-AJ 76 by The Upjohn Company (Kalamazoo, MI). Haloperidol was purchased from Sigma Chemical Company (St. Louis, MI).

Cocaine hydrochloride was prepared in a vehicle solution of 0.9 % saline. Drugs for pretreatment were prepared fresh on the days of pretreatment. Fluoxetine and (+)-AJ 76 were prepared using a vehicle solution of 0.9 % saline. Haloperidol was dissolved in 100 ml of vehicle consisting of 97.5 ml of 0.9 % saline, 2.5 ml of ethanol, and two to three drops of 1 N hydrochloric acid (1 N HCL). All drugs were injected in a volume of 1.0 ml/kg of body weight.

Statistical Analyses: Three dependent variables were investigated - (1) the breaking point, or the ordinal value corresponding to the final infusion delivered to an animal prior to a 1 h period of non-reward, expressed in terms of percent of baseline scores, (2) the time from the 1st to the 6th infusion of cocaine (min) expressed in terms of percent of baseline scores, and (3) the time to the 1st infusion of cocaine (min) expressed in terms of raw scores.

Performance on the three dependent variables following pretreatment with drug and vehicle were compared by means of a two-way analysis of variance (ANOVA). While Drug served as the within subjects measure and Dose as the between subjects measure for the experiments involving acute pretreatments (Experiments 1 and 2), Days served as the within subjects measure and Drug as the between subjects measure for the experiment involving repeated

pretreatments (Experiment 3). The ANOVA was followed by a priori multiple comparisons with a Modified Bonferroni Correction to control for Type I errors (Experiment 1 and 2) or post hoc multiple comparisons (Experiment 3).

Experiment 1

The effect of acute pretreatment with the serotonin re-uptake inhibitor, fluoxetine, on the self-administration of cocaine using a PR schedule of reinforcement

Fluoxetine (Prozac) is a highly specific 5-HT re-uptake inhibitor which has only recently been introduced into clinical settings as an antidepressant. In this capacity, several research studies have found fluoxetine equally or more effective than a number of tricyclic antidepressants (i.e. doxepin, imipramine, amitryptaline), with fewer side effects (Bremner, 1984; Feighner, 1984; Feighner and Cohn, 1985; Cohn et al., 1989).

Due to the numerous positive results obtained from clinical studies investigating the treatment of cocaine abuse with DMI, an antidepressant (Gawin and Kleber, 1984; Kosten et al., 1987; Gawin et al., 1989b), a great deal of research attention is presently being directed to other antidepressants to determine if they share DMI's efficacy as a cocaine abuse treatment. Fluoxetine is one of these candidates.

To date, research regarding the effects of fluoxetine on psychomotor stimulant self-administration in animals has been scarce. Three studies, two investigating the effect of acute (Ieccese and Lyness, 1984; Porrino et al., 1989) and one investigating the effect of repeated (Yu et al., 1986) pretreatment with fluoxetine, found that the rate of self-administration maintained by amphetamine was dramatically attenuated following fluoxetine

pretreatment.

There is similarly very little information in the literature concerning the effects of fluoxetine on cocaine self-administration. Furthermore, not only is the literature limited to only a couple of studies, but the results from these studies conflict. While repeated pretreatment with fluoxetine succeeded in attenuating rates of cocaine self-administration in one study (Carroll et al., 1990a), acute pretreatment with fluoxetine failed to alter rates of cocaine self-administration in another study (Porrino et al., 1989).

Several factors may account for the apparent discrepancy between these reports. First, while one study investigated the effects of acute pretreatment with fluoxetine (Porrino et al., 1989), the other investigated the effects of repeated pretreatment with the antidepressant (Carroll et al., 1990a); second, the unit dose of cocaine self-administered by animals in the study by Carroll and colleagues (1990a) was up to 90 % lower than that used by Porrino and colleagues (1989); and third, rate was the dependent measure used by both sets of researcher. Recently, measures based on simple schedules of reinforcement, such as rate, have been criticized for being insensitive and difficult to interpret. The difficulties with the use of rate as a dependent measure were outlined earlier in this report.

The present study was designed to examine the effect of acute pretreatment with fluoxetine on the self-administration of cocaine using a PR schedule of reinforcement.

Methods

Subjects: Eighteen male Wistar rats served as subjects in this experiment. Each animal was tested under four fluoxetine dose conditions. Animals were replaced in the event of illness or cannula failure.

Pretreatment: On the day immediately following three days of stable baseline on a PR schedule of reinforcement, animals were injected with saline (0.5 ml, IP) 30 min prior to the cocaine self-administration session. The next day, these animals were injected with fluoxetine (2.5, 5.0, 10.0, or 20.0 mg/kg, IP) 30 min prior to the session. Doses of fluoxetine were administered in random order, separated by at least four days.

Results

Analysis using a two-way ANOVA revealed that fluoxetine had no significant effect on the time from the 1st to the 6th injection of cocaine (min) (data not shown). A priori multiple comparisons found no significant differences between the saline and drug means for this dependent variable at any of the fluoxetine doses tested.

Fluoxetine similarly failed to alter the onset of responding for cocaine (data not shown). No significant main effect or interaction was revealed by a two-way ANOVA. A priori multiple comparisons found no significant differences between the saline and drug means

for the time to the first infusion of cocaine (min) at any of the four doses tested.

Figure 1 shows the effect of fluoxetine on breaking points. When these data were submitted to a two-way ANOVA, a significant Drug by Dose interaction was revealed ($F=4.40$; $df=3,32$; $p<0.05$). Further analyses using a priori multiple comparisons indicated that the 5.0 and 20.0 mg/kg doses of fluoxetine produced significant reductions in breaking points from saline pretreatment levels ($p<0.035$, as per Modified Bonferroni Correction). Saline pretreatment failed to significantly alter breaking point values (Figure 1).

Figure 1: The effect of fluoxetine pretreatment on the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. The mean ($\pm$ SEM) breaking point values following pretreatment with fluoxetine (2.5, 5.0, 10.0, and 20.0 mg/kg) and saline (0.5 ml) are shown. Nine animals were tested at each dose. All values are expressed in terms of percent of baseline performance. An asterisk (*) indicates a statistically significant change in breaking point from saline levels ($p < 0.035$) as revealed by a priori multiple comparisons with a Modified Bonferroni Correction to control for Type I errors.

Discussion

Fluoxetine reduced breaking points in a dose-dependent manner. Specifically, pretreatment with the 5 and 20 mg/kg doses significantly reduced breaking point values from saline pretreatment levels. The breaking point data, as depicted in Figure 1, reveal a dose/response curve with the greatest decrements (~32 %) in breaking point occurring following pretreatment with the highest dose of fluoxetine, 20.0 mg/kg. The lowest dose which produced a significant effect in the present study was 5.0 mg/kg. This dose has previously been found effective in reducing rates of cocaine self-administration (Carroll et al., 1990a).

The involvement of 5-HT in cocaine reinforcement has recently been supported by another study (Loh and Roberts, 1990) in which bilateral 5,7-DHT lesions of both the MFB and the amygdala significantly increased the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. This is consistent with other 5-HT lesioning studies (Leccese and Lyness, 1984; Lyness et al., 1983) involving amphetamine. Both ICV injections of the neurotoxin 5,7-DHT (Lyness et al., 1983) and bilateral 5,7-DHT-induced lesions of the MFB (Leccese and Lyness, 1984) produced increases in rates of amphetamine self-administration.

All of the 5-HT lesioning studies cited immediately above suggest that the serotonergic system plays an important role in stimulant self-administration. It would appear that depleting 5-HT

augments the rewarding value of psychomotor stimulants. These data would imply that 5-HT exerts an aversive or antagonistic influence over the reinforcing properties of psychomotor stimulants, like cocaine and amphetamine. The present data support this hypothesis. Specifically, facilitating serotonergic activity through the administration of the indirect 5-HT agonist, fluoxetine, reduced the reinforcing effects of cocaine. This reduction in cocaine's rewarding value was reflected by a reduction in breaking points. Animals were not as motivated to continue satisfying the escalating response requirements following pretreatment with fluoxetine as they were following pretreatment with saline.

These conclusions are further supported by the fact that, in two of the four studies investigating the effects of fluoxetine on stimulant self-administration (Carroll et al., 1990a; Leccese and Lyness, 1984), a number of rats exhibited extinction-like bursts of responding following fluoxetine pretreatment. This initial increase or "bursting" followed by a sudden decline in responding resembles the behavior of an animal following substitution of saline for drug reinforcement and, therefore, suggests that fluoxetine may act to block the reinforcing effects of the psychomotor stimulants, cocaine and amphetamine.

It should be noted that the cocaine unit dose adopted in the present study (~1.5 mg/kg) is high relative to those used in other studies (Porrino et al., 1989; Carroll et al., 1990a). In the study by Carroll et al. (1990a), fluoxetine reduced responding in rats self-administering low doses of cocaine (0.1 and 0.2 mg/kg), yet had no effect at a higher cocaine dose (0.4 mg/kg). Consequently, it appears

that cocaine unit dose is an important variable to consider when examining the effects of fluoxetine on cocaine reinforcement. The cocaine unit dose used in the present study was chosen for its ability to maintain breaking points which fall on the ascending limb of the dose-response curve (Roberts et al., 1989a).

There are several alternative hypotheses which may explain fluoxetine's attenuation of breaking point in the present study. First, fluoxetine may have reinforcing effects of its own. Consequently, fewer infusions of cocaine would be required by animals pretreated with fluoxetine to achieve the level of euphoria and/or reward desired. This hypothesis is not likely, however. Although animal self-administration studies have yet to be carried out in order to determine if fluoxetine is a reinforcer, a current review of clinical studies reports no fluoxetine abuse in humans (Cooper, 1988).

Second, fluoxetine may produce a non-specific impairment of motor activity. This decrement in activity could explain why animals reached breaking points which were significantly lower following pretreatment with fluoxetine than following pretreatment with saline. While the data collected from the present study cannot rule out this hypothesis, Carroll and colleagues (1990a) report no reductions in responding for food, water, or an inactive lever following fluoxetine pretreatment. Furthermore, two other studies have reported that fluoxetine failed to alter responding for cocaine (Porrino et al., 1989) and saline (Yu et al., 1986). Finally, the information based on human reports suggests that fluoxetine is only mildly sedating, and may even be somewhat activating (Bremner,

1984; Feighner, 1985; Feighner and Cohn, 1985; Cooper, 1988; Cohn et al., 1989; Perry et al., 1989).

Third, fluoxetine alone, or in combination with cocaine, may produce illness or dysphoria, thereby, acting as a direct punishing stimulus. Alone, fluoxetine is reported to produce only mild side effects in humans (Bremner, 1984; Feighner, 1985; Feighner and Cohn, 1985; Cooper, 1988; Cohn et al., 1989; Perry et al., 1989). In fact, it is reported that fluoxetine produces fewer side effects than most other antidepressants available today (ie. imipramine, amitryptiline, and doxepin) (Bremner, 1984; Feighner, 1985; Feighner and Cohn, 1985; Cohn et al., 1989). Whether fluoxetine interacts with cocaine to produce adverse side effects is not known. In the present experiment, gross observations revealed that animals were in no apparent distress, however.

In summary, it appears that the hypothesis which best explains the present findings is that fluoxetine attenuates cocaine's reinforcing effects. It would logically follow that 5-HT plays an aversive role in cocaine reinforcement. The present findings suggest that fluoxetine may serve as an effective pharmacotherapy for use in the treatment of cocaine abuse. It remains to be determined, however, whether this is in fact the case. While human clinical trials have shown other antidepressants such as DMI (Gawin and Kleber, 1984; Gawin, 1986; Kosten et al., 1987; Gawin et al., 1989b), maprotiline (Brotman et al., 1988), and phenelzine (Resnick and Resnick, 1984; Golwyn, 1988) are somewhat effective in achieving and maintaining abstinence in cocaine abusers, fluoxetine has yet to be evaluated in this manner. Now that animal self-administration

studies, such as the present study, are indicating that the 5-HT system plays an important role in drug reinforcement. pharmacological agents which manipulate this system, such as fluoxetine, should be evaluated for their efficacy in treating cocaine abuse.

Experiment 2

The effect of acute pretreatment with the novel dopamine antagonist, (+)-AJ 76, on cocaine self-administration

Cis-(+)-(1S,2R)-5-methoxy-1-methyl-2-(n-propylamino) tetralin or (+)-AJ 76 is a mild aminotetralin stimulant possessing properties characteristic of DA antagonists. Evidence in support of (+)-AJ 76 as a DA antagonist has come almost exclusively from neurochemical studies. For example, Svensson and colleagues (1986a, 1986b) have reported that (+)-AJ 76 increases the synthesis, metabolism, and release of DA in the striatal and limbic brain regions (Waters et al., 1990). Furthermore, (+)-AJ 76 displays preferential selectivity for DA receptors, specifically the newly cloned D3 receptor subtype (Sokoloff et al., 1990).

Initially, it was believed that (+)-AJ 76 acted as a preferential DA autoreceptor antagonist (Svensson et al., 1986a, 1986b; Hoffmann et al., 1988). Evidence in favor of this hypothesis came from findings that (+)-AJ 76 antagonized the sedative effects produced by low doses of apomorphine, and completely blocked the apomorphine-induced decrease in DA synthesis rate in animals treated with gamma-butyrolactone (GBL) (Svensson et al., 1986a, 1986b). More recently, electrophysiological studies have provided evidence in support of the notion that (+)-AJ 76 antagonizes both pre- and postsynaptic DA receptors equally (Bergstrom et al., 1988; Piercey and Lum 1990).

Contrary to other DA antagonists, (+)-AJ 76 possesses properties which are characteristic of the psychomotor stimulants.

For example, (+)-AJ 76 increases locomotor activity in habituated rats (Svensson et al., 1986b), produces no apparent sedation (Svensson et al., 1986b), increases global brain energy metabolism (Piercey and Hoffmann, submitted), and produces small increases in globus pallidus neuronal firing rates (Bergstrom et al., 1988). Selective autoreceptor antagonism, and specifically terminal autoreceptor antagonism, may account for (+)-AJ 76's stimulant properties (Piercey and Lum, 1990).

The influence of the novel DA antagonist, (+)-AJ 76, on drug self-administration has yet to be investigated. Since (+)-AJ 76 possesses properties characteristic of both the psychomotor stimulants and DA antagonists, Experiment 2 served to evaluate whether (+)-AJ 76's influence on cocaine self-administration maintained on a PR schedule of reinforcement would more closely resemble that of a DA agonist or antagonist.

Methods

Subjects: Twenty-two male Wistar rats served as subjects in this experiment. Each animal was tested under five (+)-AJ 76 dose conditions. Animals were replaced in the event of illness or cannula failure.

Pretreatment: The pretreatment procedure followed here was identical to that outlined in Experiment 1 with the exception that (+)-AJ 76 (1.88, 3.75, 7.50, 15.0, and 30.0 mg/kg, IP) was

administered to the animals on treatment days (please refer to the methods section of Experiment 1 for further details).

Results

The effect of (+)-AJ 76 on the time from the first to the sixth infusion of cocaine (min) is depicted in Figure 2. These data, when submitted to a two-way ANOVA, revealed a significant effect of Drug ($F=10.05$; $df=1,22$; $p<0.05$). Further analyses using a priori multiple comparisons indicated that the 15 mg/kg dose resulted in significant reductions in the time animals took to self-administer their first six infusions of cocaine ($F=11.62$; $df=1,22$; $p<0.04$, as per Modified Bonferroni Correction). Saline produced no significant reductions in this measure (Figure 2).

Figure 3 illustrates the effect of (+)-AJ 76 on the initiation of cocaine self-administration. Analysis of log transformed data revealed a significant Drug by Dose interaction ($F=4.69$; $df=4,14$; $p<0.05$). A priori multiple comparisons indicated that the highest dose of (+)-AJ 76 tested significantly delayed the onset of responding ($F=17.51$; $df=1,14$; $p<0.04$). Saline pretreatment had no effect on the time to the first response (Figure 3).

Figure 4 shows the effect of (+)-AJ 76 on the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. When the breaking points for all five (+)-AJ 76 dose conditions were submitted to a two-way ANOVA, a significant Drug by Dose interaction was revealed ($F=2.83$; $df=4,28$; $p<0.05$). Further

analyses using a priori multiple comparisons indicated that the highest dose of (+)-AJ 76 tested produced significant reductions in breaking points from saline levels ($F=24.33$; $df=1,28$; $p<0.04$). Saline pretreatment failed to alter breaking point values to a level which reached significance (Figure 4).

Figure 2: The effect of (+)-AJ 76 pretreatment on the time taken by animals to self-administer their first six infusions of cocaine on a PR schedule of reinforcement. The mean ($\pm$ SEM) times from the 1st to the 6th infusion of cocaine (min) following pretreatment with (+)-AJ 76 (1.88, 3.75, 7.5, 15.0, and 30.0 mg/kg) and saline (0.5 ml) are shown. Between five and eight animals were tested at each dose. All values are expressed in terms of percent of baseline performance. An asterisk (*) indicates a statistically significant change from saline levels ($p < 0.04$) as revealed by a priori multiple comparisons with a Modified Bonferroni Correction to control for Type I errors.

Figure 3: The effect of (+)-AJ 76 pretreatment on the onset of responding for cocaine. All values are expressed in raw scores. Please refer to Figure 2 for further details.

Figure 4: The effect of (+)-AJ 76 pretreatment on the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. Please refer to Figure 2 for further details.

Discussion

(+)-AJ 76 influenced cocaine self-administration in a manner characteristic of DA antagonists. For example, (+)-AJ 76 significantly increased the rate of cocaine self-administration (ie. decreased the time animals took to self-administer their first six injections). This is consistent with numerous studies which have shown that DA antagonists increase the rate of stimulant self-administration (Wilson and Schuster, 1972, 1973a; Yokel and Wise, 1975, 1976; Johanson et al., 1976; Risner and Jones, 1976; de Wit and Wise, 1977; De La Garza and Johanson, 1982; Ettenberg et al., 1982; Roberts and Vickers, 1984; Koob et al., 1987; Roberts et al., 1987). Yokel and Wise (1975, 1976) have offered very convincing arguments that increases in a stimulant's rate of self-administration are the result of a partial blockade of that stimulant's reinforcing effects.

In the present study, the breaking points reached by animals self-administering cocaine were significantly reduced from saline control levels following pretreatment with (+)-AJ 76. The ability to reduce breaking points is a property recently shown to be characteristic of the "typical" DA antagonist, haloperidol (Roberts et al., 1989b). These data further suggest that (+)-AJ 76 blocks the reinforcing effects of cocaine.

Alternatively, (+)-AJ 76 may have reduced breaking points by substituting for cocaine's rewarding effects. This hypothesis has gained some support from Callahan et al. (submitted) who found that (+)-AJ 76 partially substituted for cocaine. Additional evidence in favor of this hypothesis comes from the finding that (+)-AJ 76

supports place preference in a dose-dependent manner (Richardson et al., submitted). Even so, (+)-AJ 76 was not found to be self-administered by rats in that same study (Richardson et al., submitted).

The impairment of motor ability is an interpretation commonly offered to explain the disruption of drug self-administration by DA antagonists. It is highly unlikely, however, that (+)-AJ 76 reduced animals' breaking points by impairing their motor ability since these same animals showed an augmentation in their rate of responding. Also, Callahan et al. (submitted) have reported that rats are capable of responding at high rates for water reward following the administration of comparable doses (2.5 to 20 mg/kg) of (+)-AJ 76. Furthermore, it has been reported that (+)-AJ 76 is not sedating, and in fact increases locomotor activity in habituated rats (Svensson et al., 1986b).

Finally, (+)-AJ 76 alone, or in combination with cocaine, may have produced illness or dysphoria, thereby, acting as a direct punishing stimulus. Regardless of which hypothesis is correct, the results of the present experiment suggest that (+)-AJ 76 may be a promising candidate for use in the treatment of cocaine abuse in humans. Animals appeared less motivated to self-administer cocaine following pretreatment with the mixed DA agonist/antagonist. (+)-AJ 76's ability to delay the onset of the cocaine binge provides further support for its potential as a pharmacotherapeutic agent. The identification of a drug that could delay the onset of cocaine craving possibly until peak periods of intense craving subside would be a

breakthrough in cocaine abuse therapy. Finally, (+)-AJ 76 is an especially exciting candidate for use in the treatment of cocaine abuse since it appears to lack the dysphoria and adverse side effects common to the "typical" DA antagonists that often lead to problems in patient compliance and drop outs.

Experiment 3

The effect of repeated pretreatment with the "typical" dopamine antagonist, haloperidol, on cocaine self-administration

Haloperidol (Haldol), a butyrophenone, is presently one of the most widely used antipsychotic medications. It is considered by many clinicians, and researchers alike, to be a "prototypical" neuroleptic drug. At the neuronal level, haloperidol acts as a highly specific D2 receptor blocker.

The effect of DA receptor antagonists on rates of stimulant self-administration has been investigated extensively. Low doses of DA antagonists including chlorpromazine (Wilson and Schuster, 1972; Risner and Jones, 1976), trifluoperazine (Wilson and Schuster, 1973a), pimozide (Yokel and Wise, 1975 1976; Risner and Jones, 1976; de Wit and Wise, 1977), perphenazine (Johanson et al., 1976), (+)-butaclamol (Yokel and Wise, 1976), alpha-flupenthixol (Ettenberg et al., 1982; Roberts and Vickers, 1984), haloperidol (De La Garza and Johanson, 1982; Roberts and Vickers, 1984; Dalton et al., 1986; Roberts et al., 1987), sulpiride, metoclopramide, thioridazine (Roberts and Vickers, 1984), and SCH 23390 (Koob et al., 1987) increase the rate of stimulant self-administration.

The authors of the above studies all interpreted the increase in response rate following pretreatment with low doses of DA antagonists as reflecting an attenuation of the reinforcing effects of the stimulant. This interpretation is best explained by Yokel and Wise (1975) who drew an analogy between the effects of DA

antagonists and injection dose decrements. Like DA antagonists, low doses of psychomotor stimulants maintain high rates of responding (Pickens, 1968; Goldberg et al., 1971; Dougherty and Pickens, 1973; Downs and Woods, 1974; Bedford et al., 1978). Yokel and Wise (1975) argue that the increases in rate generated by both DA antagonists and the lowering of a unit dose represent compensatory responses on the part of the animal. Specifically, an animal augments its rate of responding in an attempt to overcome a reduction in the stimulant's reinforcement value brought about in one case by the lowering of the unit dose and in the other case by the partial blockade of DA receptors.

Roberts and colleagues (1989b), using a PR as opposed to an FR schedule of reinforcement, found that breaking points were drastically reduced following haloperidol pretreatment (Roberts et al., 1989b). This study, in accordance with those studies using rate as the dependent measure, concluded from its findings that pretreatment with a DA antagonist, haloperidol in this case, results in an attenuation of cocaine's reinforcing effects. In summary, there is an abundance of evidence in support of the idea that acute pretreatment with DA antagonists reduces the reinforcing efficacy of cocaine and other stimulants.

In patients afflicted with psychosis, many of the therapeutic actions and side effects of DA antagonists can take several weeks to develop (Kane, 1989). A similar time course may be required in order to observe the full effects of DA antagonists on cocaine self-administration behavior. For this reason, studies evaluating the

effects of repeated administration of DA antagonists on stimulant self-administration are important.

Although numerous studies have investigated the effects of acute administration of DA antagonists on self-administration behavior maintained by stimulants, only one has looked at the effects of repeated pretreatment with a DA antagonist (Roberts and Vickers, 1987). This study found that an initial haloperidol pretreatment served to increase cocaine self-administration, and repeated administrations of the DA antagonist augmented this response (Roberts and Vickers, 1987).

As noted previously, rate measures are often ambiguous and difficult to interpret. Hence, in order to clearly understand the effects of repeated haloperidol on cocaine self-administration further investigations are required which use less ambiguous and more interpretable dependent measures. Experiment 3 is an example of such an investigation. In this experiment, the effect of repeated pretreatment with haloperidol on cocaine self-administration maintained by a PR schedule of reinforcement was investigated.

Methods

Subjects: In total, fourteen male Wistar rats served as subjects in this experiment. Seven subjects served in the haloperidol group and seven served in the vehicle group.

Pretreatment: Following three days of stable baseline on a PR schedule of reinforcement, animals were randomly assigned to

one of two groups - the haloperidol group (n=7) or the vehicle group (n=7). Both groups then carried out three baseline days. A baseline day consisted of a 5 h session during which the animals self-administered cocaine maintained on a PR schedule of reinforcement. No vehicle or drug pretreatment was given to either group for these three baseline days.

Immediately following the three baseline days, both groups were given five days of treatment. A treatment day was identical to a baseline day in every respect, but one. Thirty minutes prior to the start of the session, the animals in the haloperidol group were injected with haloperidol (0.05 mg/kg, IP), and the animals in the vehicle group were injected with vehicle (1.0 ml/kg, IP).

The five treatment days were immediately followed by three days of recovery. The recovery days were identical to the baseline days with no vehicle or drug pretreatment administered to either group.

Results

The times from the first to the sixth injection of cocaine for animals receiving daily pretreatment with haloperidol (n=7) or vehicle (n=7) are shown in Figure 5. This figure clearly illustrates that animals in the haloperidol group displayed mean baseline times (days 1 to 3) and mean recovery times (days 9 to 11) which were nearly identical to those displayed by animals in the vehicle group. During the treatment phase, however, while animals in the vehicle

group maintained baseline levels (ie. within 15 % of mean baseline times), animals in the haloperidol group experienced a drastic drop in this measure from baseline values. The mean times from the 1st to the 6th injection of cocaine for days 4 to 8, when submitted to a two-way ANOVA, revealed a significant overall effect of Drug ($F=8.08$; $df=1,10$; $p<0.05$).

On the initial day of treatment (day 4), haloperidol reduced mean times from the 1st to the 6th injection from baseline levels by approximately 26 %. This drop became more pronounced over days. By day 7, animals in the haloperidol group were displaying mean times that were as much as 42 % below mean baseline values. On day 8, however, the trend was broken and the haloperidol-induced drop in mean times from baseline levels (~33 %) was slightly less than that of day 7. Following treatment, animals in the haloperidol group showed immediate and complete recovery.

Both haloperidol and vehicle had no significant effect on the second dependent measure, the time to the 1st injection (min) (data not shown). Animals in both groups began responding for cocaine very quickly on days 1 through 7. On days 8 through 11, however, animals showed a great deal of variability in onset of responding. This variability is principally due to two subjects. On days 8, 9 and 11, one animal in the vehicle group (M385) delayed its responding for 193, 140 and 212 min, respectively, while on day 10, one animal in the haloperidol group (M388) delayed its responding for 221 min. Statistical analysis of these data using a two-way ANOVA resulted no significant main effects or interactions.

Figure 6 depicts the effect of pretreatment with haloperidol or

vehicle on breaking points. Both groups achieved similar breaking points during baseline (days 1 to 3). During treatment, while mean breaking points for the vehicle group diminished slightly, yet systematically over days from baseline values (within 12 % of mean baseline values), mean breaking points for the haloperidol group dropped by as much as ~33 %. As was the case with the time from the 1st to 6th injection, the effect of haloperidol on breaking point was augmented over days, and again this trend was broken on day 8. Statistical analysis of the breaking points reached by animals during the treatment phase (days 4 through 8) using a two-way ANOVA revealed a significant Days effect ($F=2.91$; $df=4,44$; $p<0.05$). In an effort to isolate the factors contributing to the Days effect one-way ANOVAs were performed separately on the breaking point data for the vehicle and haloperidol groups. This analysis yielded no significant findings ($p>0.05$).

Animals receiving repeated pretreatment with haloperidol recovered immediately and completely once treatment was terminated (Figure 6). On day 10 the mean breaking points for animals in the haloperidol group were ~15 % above baseline levels, and ~17 % and ~21 % above their mean breaking point values for the two other recovery days, days 9 and 10 respectively. An analysis of the breaking points reached by animals in both groups during the recovery phase (days 9 to 11) using a two-way ANOVA revealed no significant main effects or interactions. Consequently, a post hoc multiple comparison between the mean breaking point for the haloperidol group and that of the vehicle group for day 10 was not

undertaken.

Figure 5: The effect of repeated administrations of haloperidol on the time taken by animals to administer their first six infusions of cocaine on a PR schedule of reinforcement. The mean ($\pm$ SEM) times from the 1st to the 6th infusion of cocaine (min) following pretreatment with haloperidol (0.05 mg/kg) and saline (1.0 ml/kg) during baseline, treatment, and recovery phases are shown. Seven animals served as subjects in each group. All values are expressed in terms of percent of baseline performance.

Figure 6: The effect of repeated administrations of haloperidol on the breaking points reached by animals self-administering cocaine on a PR schedule of reinforcement. Please refer to Figure 5 for further details.

Discussion

Repeated pretreatment with haloperidol increased rates of cocaine self-administration (ie. decreased the time from the 1st to the 6th injection), and this response was augmented over days. These findings replicate those of an earlier study which looked at the effect of repeated administrations of haloperidol on cocaine intake (Roberts and Vickers, 1987).

The fact that rats self-administering cocaine show a reverse tolerance to haloperidol is interesting since most electrophysiological (Bunney and Grace, 1978; White and Wang, 1983), biochemical (Mellar et al., 1980; Nicolaou, 1980; Pizzolato et al., 1985), and behavioral measures show tolerance with repeated testing. In humans, while the extrapyramidal side effects of DA antagonists show tolerance, the antipsychotic actions of DA antagonists show reverse tolerance. Consequently, cocaine self-administration may be mediated by the same substrate through which DA neuroleptics are thought to achieve their therapeutic effect. This substrate is likely the mesolimbic dopaminergic pathway (Roberts and Koob, 1982).

The haloperidol and vehicle groups did not differ significantly in terms of their mean breaking points during the five treatment days (days 4 through 8). An analysis of the breaking point data from both groups did reveal a significant Days effect, however. While the breaking points for the vehicle group decreased slightly, yet systematically over the five treatment days, the breaking points for the haloperidol group declined dramatically (Figure 6).

Consequently, animals showed reverse tolerance in terms of their breaking points when administered haloperidol repeatedly. This is consistent with the time from the 1st to the 6th injection data reviewed immediately above.

The dose of haloperidol used in the present study (0.05 mg/kg) is the smallest acute dose found to alter the breaking points reached by animals self-administering cocaine (Roberts et al., 1989b). Perhaps a higher dose of haloperidol would have reduced breaking points in the present study to a level significantly lower than vehicle. Further testing is necessary in order to verify this speculation.

GENERAL DISCUSSION

The present findings (Experiments 2 and 3) support a role for the dopaminergic system in cocaine reinforcement. While acute pretreatment with the DA receptor antagonist, (+)-AJ 76, reduced breaking points and increased rates of cocaine self-administration to levels significantly different from saline, repeated pretreatment with the D2 antagonist, haloperidol, significantly increased rates of cocaine self-administration over the five days that haloperidol was administered.

These data further suggest that DA antagonists are promising candidates for use in the treatment of cocaine abuse in humans. The novel drug, (+)-AJ 76, is especially promising in light of the fact that it appears to lack the dysphoria and side effects common to the "typical" DA antagonists. (+)-AJ 76's failure to produce extrapyramidal side effects may be due to its preferential selectivity for the newly cloned D3 receptor. Further research is required to validate this hypothesis.

The present thesis revealed another interesting and exciting property of (+)-AJ 76. Specifically, the highest dose of (+)-AJ 76 tested (30 mg/kg) was able to significantly delay responding for cocaine. This ability was not displayed by haloperidol or fluoxetine in the present experiments. In fact, as far as this author is aware, this is the first time a drug has been found to disrupt stimulant self-administration in such a manner. The ability of (+)-AJ 76 to delay the onset of the cocaine binge is exciting and could prove to be a

breakthrough in cocaine abuse therapy. This phenomenon clearly warrants further investigation.

While many of the studies done in the past have examined the effects of acute drug pretreatment on drug self-administration, more and more contemporary studies are investigating the effects of repeated drug pretreatments. Repeated pretreatment studies are especially necessary when it has been established that the pretreatment drug's time course of action is lengthy. For example, the antipsychotic actions of DA antagonists often require two or three weeks to develop in humans. Consequently, it is advisable to observe the effects of DA antagonists on cocaine reinforcement over a prolonged time period. This was carried out in Experiment Three of the present thesis. It would be informative to repeat this experiment using a higher dose of haloperidol (ie. 0.075 or 0.1 mg/kg).

It would also be valuable to investigate other DA antagonists using the repeated pretreatment model. For example, this model could be used to study the effects of the promising new DA antagonist, flupenthixol decanoate, on cocaine self-administration. In clinical trials, flupenthixol decanoate has been effective in reducing and/or eliminating cocaine craving in abusers (Gawin et al., 1989a).

Depot injections or Alzet miniosmotic pumps are more appealing routes of administration for use in the repeated pretreatment model. These routes are superior to the daily IP injections used in Experiment 3 in two principle ways. (1) They require only one intervention; thereby, minimizing the distress to the animal and the risk of cannula failure, and (2) they allow for the

constant and gradual administration of drug.

In Experiment 1, the 5-HT re-uptake inhibitor, fluoxetine, reduced breaking points in a dose-dependent manner. This finding, along with several others investigating the effects of serotonergic manipulations on stimulant self-administration (Lyness et al., 1980; Lyness and Moore, 1983; Leccese and Lyness, 1984; Yu et al., 1986; Loh and Roberts, 1989; Porrino et al., 1989; Carroll et al., 1990a, 1990b), suggest that the serotonergic system also plays an important role in stimulant reinforcement.

Fluoxetine's attenuation of breaking points suggests that it may prove to be an effective pharmacotherapeutic agent for use in the treatment of cocaine abuse. In its capacity as an antidepressant, fluoxetine has been effective and well tolerated by patients. In fact, fluoxetine is reported to cause fewer side effects than a number of tricyclic antidepressants (Bremner, 1984; Feighner, 1984; Feighner and Cohn, 1985; Cohn et al., 1989). While there has been some speculation that fluoxetine triggers acute suicidal ideations in patients afflicted with major affective disorders (Teicher et al., 1990), this notion has been refuted by a large scale study which found no evidence of fluoxetine-induced suicidal ideation in 2938 patients (Cooper, 1988).

While fluoxetine reduced breaking points in the present study, it failed to alter the rate of cocaine self-administration (ie. the time from the 1st to the 6th injection of cocaine). This constitutes another example for which breaking point was sensitive to experimental manipulation, while rate was insensitive. Three other examples

(Roberts, 1989; Roberts et al., 1989a; Loh and Roberts, 1990) were discussed earlier in this thesis.

Almost twenty years ago, researchers studying drug reinforcement in primates abandoned simple schedules of reinforcement such as the FR schedule in favour of more complex schedules such as PR schedules (Griffiths et al., 1975, 1978, 1979; Bedford et al., 1978; Hoffmeister, 1979), concurrent schedules (Iglauer and Woods, 1974; Catania, 1972; Iglauer et al., 1976; Llewellyn et al., 1976), second order schedules (Kelleher and Goldberg, 1977; Johanson, 1982), choice procedures (Johanson and Schuster, 1975; Johanson and Aigner, 1981), and discrete trials (Stretch, 1977). Researchers studying drug reinforcement in rodents have yet to make the same transition from simple to complex schedules. Applying complex schedules to rodents should prove to be a valuable endeavour for future research.

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