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**Stressor Provoked Alterations in Locomotor Activity, Exploration and
Self-Stimulation from the Ventral Tegmental Area Following
Intraventricular Administration of U50,488 in the Mouse**

**A Thesis presented to the Faculty of Graduate Studies and Research
of Carleton University in partial fulfillment of the requirements for
the degree of Master of Science in Psychology**

**Rachel Dickson
1993**

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**Stressor Provoked Alterations in Locomotor Activity, Exploration and
Self-Stimulation from the Ventral Tegmental Area Following
Intraventricular Administration of U50,488 in the Mouse**

Submitted by: Rachel Dickson
in partial fulfillment of the requirements for the
degree of Master of Science

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Carleton University,
October, 1993

Abstract

Uncontrollable stressful life events have been associated with the appearance of a number of physical and psychological disorders including depression. Stressor exposure in animals provokes a variety of behavioural alterations reminiscent of the symptom profile associated with the human disorder. While stressor provoked behavioural changes were initially linked to alterations of central dopamine (DA), norepinephrine (NE) and serotonin (5-HT) activity, increasingly greater attention has been devoted to an analysis of the neuromodulatory role of endogenous neuropeptides to the provocation of pathology. The present experiments examined the effects of acute uncontrollable footshock and central κ receptor activation (U50,488 administration) on activity, exploratory behaviour (rearing & head-dipping) and reward processes as revealed by intracranial self-stimulation from the dorsal and ventral aspects of the A10 area (VTA) in CD-1 mice. Generally, the results of Experiments 1 and 2 revealed that a) all of the behavioural measures examined were affected differentially by exposure to uncontrollable footshock and/or central U50,488 administration b) the behavioural profiles depended not only upon the behaviour under consideration but also the time following administration, the dose of the agonist employed as well as the stressor history of the animal c) U50,488 was not associated with any significant behavioural alterations within the immediate post-administration interval but did exert long term changes in all behaviours except exploratory head-dipping d) U50,488 either partially or completely antagonized the stressor provoked

increases in activity and rearing scores normally observed at long term intervals e) central κ receptor activation induced stressor-like alterations in brain stimulation from the dorsal A10 region in non-shocked mice while it reversed such impairments in shocked mice and f) the rates of self-stimulation from the ventral A10 region remained unaffected by stressor exposure but were increased one week following U50,488 administration. Taken together, these data suggest that central κ receptor activation (via dynorphin) is involved in the modulation of a number of stressor induced behavioural changes. However, it appears that the behavioural consequences of such activation may depend upon a number of factors including the behaviour under consideration, the stressor history of the animal as well as the time following treatment.

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INTRODUCTION

Stressful life events have been associated with the appearance of a number of physical and psychological pathologies including heart disease (Hansen & Rupp, 1991), gastric ulceration (Weiss, 1971a) and cancer (Sklar & Anisman, 1981; Anisman & Sklar, 1982) as well as schizophrenia (Spring & Coons, 1982; Gruen & Baron, 1984) and depression (Akiskal & McKinney, 1973). Although the precise relationship between stressors and depression remains to be elucidated, some investigators have argued that stressors precipitate such disorders (Akiskal & McKinney, 1975), while others have suggested that experience with aversive life events merely exacerbates the symptoms associated with an existent disorder (Anisman & Zacharko, 1982). Nevertheless, it should be considered that the effects of stressors in humans are paralleled by data among infrahuman subjects suggesting that stressors elicit a number of behavioural, neurochemical and hormonal alterations which may be reminiscent of those associated with human disorders (Anisman, 1984; Anisman & Zacharko, 1982; Zacharko & Anisman, 1989; Anisman, Zalcman, Shanks & Zacharko, 1991).

Depression is both a behaviourally and a neurochemically heterogeneous illness. The DSM-III-R criteria for diagnosis of a major depressive episode requires identification of at least five symptoms which have persisted for two weeks (American Psychiatric Association, 1987). The primary symptom of the disorder is depressed or blunted mood and motivational loss while other symptoms of the illness may include alterations of body weight regulation, sleep disturbances, psychomotor agitation/retardation, fatigue, feelings of worthlessness/guilt, attentional disturbances and recurrent thoughts of death or suicidal ideation. Although depressive subtypes are operationally defined in accordance with the

presumed neurotic, vegetative or psychomotor aspects of the symptom profile, there is considerable variability both within and across each of these subclassifications with respect to symptomatology and effective treatments.

A number of investigators have postulated that clinical depression is associated with central neurochemical dysfunction (van Praag, 1979; Anisman & Zacharko, 1982; Schildkraut, 1965) and considerable attention has been focused on the role of catecholamines (CA) and serotonin (5-HT) in promoting the symptoms of the human disorder. The CA hypothesis of affective disorder has attributed depression to a dysfunction of central norepinephrine (NE) activity as indicated by alterations in NE metabolite concentrations (i.e., 3-methoxy-4-hydroxyphenylethylene glycol (MHPG) (Schildkraut, 1965; Bunney & Davis, 1965). Alternatively, the indoleamine (5-HT) hypothesis of depression contends that certain forms of depression follow from a deficiency of 5-HT activity as suggested by the accumulation of its metabolite 5-hydroxyindoleacetic acid (5-HIAA) (van Praag & Korf, 1971; van Praag, 1979). Finally, there is evidence to suggest that some forms of depression may be associated with alterations of central dopamine (DA) activity as revealed by variations in the levels of 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (Jimerson, 1987). Although the NE, DA and 5-HT hypotheses of depression have received considerable attention (see Thase, Frank & Kupfer, 1985; Rush, 1986; Jimerson, 1987; Siever, 1987; Stone, 1987; Meltzer & Lowy, 1987; Rothschild, 1988), a role for other central transmitters including acetylcholine (ACh) (Janowsky & Risch, 1987) and the opioid peptides (Berger & Nemeroff, 1987) among others, cannot be dismissed.

Immunohistochemical investigations have revealed that neuropeptides are colocalized with the CA and 5-HT in a number of brain regions (Pollard, Llorens, Bonnet, Costentin & Schwartz, 1977; Schwartz, 1979; Uhl, Goodman, Kuhar, Childers & Snyder, 1979; Hokfelt, Johansson, Ljungdahl, Lundberg & Schultzberg, 1980; Lundberg & Hokfelt, 1983; Hokfelt, Johansson, Holets, Meister & Melander, 1987) and relatively dense opioid receptor concentrations have been identified in limbic regions (Mansour, Khachaturian, Lewis, Akil & Watson, 1988) involved in the modulation of mood. In addition, exogenous administration of synthetic opioid peptides have been shown to modify the activity of CA containing neurons (Gysling & Wang, 1983; Bunney, 1987; Iyengar, Kim, Marien, McHugh, Wood, 1989; Manzanares, Lookingland & Moore, 1991; Yuan, Madamba & Siggins, 1992). Indeed, in considering the regional variability in transmitter distribution (Mansour et al., 1988), the colocalization of neurotransmitters (Hokfelt et al., 1987) and the cascading nature of these systems (Carlsson, 1984), it would appear more likely that depression, with its attending symptoms is associated with complex neurochemical interactions rather than dysfunction of one particular neurotransmitter system.

The observation that neuropeptides exert potent behavioural and neurochemical effects following central administration and the influence of these putative neurotransmitters on mood has prompted consideration of the clinical relevancy of some of these findings. Although such data are relatively sparse, altered enkephalin and β -endorphin levels have been reported in the cerebrospinal fluid of bipolar and unipolar depressives (see Berger & Nemeroff, 1987 for review). Furthermore, post-mortem examination of the brains of suicide victims have revealed lowered levels

of β -endorphin in the left temporal cortex, frontal cortex and caudate nucleus relative to subjects in which suicide was not the cause of death (Scarone, Gambini, Calabrese, Sacerdote, Bruni, Carucci & Panerai, 1990). In addition, some clinical trials which involved the acute administration of β -endorphin, the enkephalin analogue, FK-33-824, or opiate agonists have had rather limited success (see Berger & Nemeroff 1987 for review). Interestingly, Cohen, Cohen, Pickar, Sunderland, Mueller and Murphy (1984) reported a worsening of depressive symptoms in patients following intravenous administration of the opiate antagonist, naloxone, but not in non-psychiatric control subjects. Taken together, the relationship between central opioid concentrations and human depression has yet to be defined, and the therapeutic efficacy of neuropeptides remains to be determined.

Various animal models of depression have been developed in an attempt to simulate the behavioural and neurochemical alterations associated with the human disorder. Such attempts have typically focused on one aspect of pathology among infrahuman subjects which may be reminiscent of a specific feature observed in depression. Nevertheless, no single animal model can encompass the entire constellation of symptoms evident in human depressives and any animal analogue of depression should consider the data derived from a number of different paradigms. At least some of the symptoms of depression appear to be amenable to empirical investigation (Caldecott-Hazard, Guze, Kling, Kling & Baxter, 1991). For example, alterations of general levels of activity, sleep patterns and disturbances of appetite or body weight regulation are relatively simple variables to assess among infrahuman subjects. However, other symptoms including feelings of worthlessness, guilt or suicidal ideation are not

generally amenable to empirical verification. Nevertheless, while some cognitive disturbances are difficult to simulate in animal models of depression, some paradigms may provide useful approximations to such disturbances. For example, Anisman, Hamilton and Zacharko (1984) examined Y-maze discrimination performance among mice exposed to uncontrollable footshock. Exposure to a stressor did not interfere with associative learning, but induced perseverative tendencies and restricted response repertoires when a previously acquired response was no longer effective in removing the organism from the source of the aversive stimulation. In effect, perseverative tendencies in animals following stressor re-exposure may be reminiscent of the rather restricted cognitive repertoires which are characteristic of human depression (Weiss & Simson, 1989).

In developing an animal model of depression, one should not only consider that the symptoms be reminiscent of the human disorder but also that agents effective in treating human depression ameliorate behavioural pathology in animals. Indeed, the behavioural and neurochemical deficits in various animal models of depression may be reduced or reversed by chronic administration of agents with established therapeutic efficacy. Chronic treatment with tricyclic antidepressant agents (e.g., desipramine, imipramine) (Peroutka & Snyder, 1980; Maj & Wedzony, 1985; Janowsky & Sulser, 1987), monoamine oxidase inhibitors (MAOI) (e.g., pargyline) (Robinson & Kurtz, 1987) and atypical antidepressants (e.g., mianserin) (Svensson, 1984) as well as electroconvulsive therapy (ECT) (Fink, 1987) have been shown to alleviate some of the behavioural disturbances in infrahuman subjects and to be effective antidepressant agents in humans (Garver & Zemlan, 1986; Henninger & Charney, 1987).

Initial consideration of the relationship between transmitter alterations and depression focused on pharmacological interventions in animals which were encouraged, in part, by anecdotal clinical reports of depression among hypertensive patients treated with reserpine (Freis, 1954; Bunney & Davis, 1965; Schildkraut, 1965; Goodwin & Bunney, 1971). Some of these paradigms involved CA (e.g., reserpine, 6-hydroxydopamine (6-OHDA) (Leith & Barrett, 1980; Koob, 1989)) or indoleamine depletion (para-chlorophenylalanine (PCPA) (Kraemer & McKinney, 1979)), α -methyl-para-tyrosine administration (α -MPT) (Beaugrand & St-Laurent, 1973), withdrawal from chronic amphetamine treatment (Kokkinidis & Zacharko, 1979; Kokkinidis & Zacharko, 1980, Kokkinidis, Zacharko & Predy, 1980) or alteration of central NE and 5-HT activity (e.g., clonidine, 5-hydroxytryptamine respectively) (Herberg, Stephens & Franklin, 1975; Holloway, 1975; Cassens, 1981). Such pharmacological agents produce behavioural changes in rats and mice which may include motivational disturbances (Koob, 1989; Zacharko & Anisman, 1989; Zacharko & Anisman, 1991b), altered levels of activity (Hahn, Zacharko & Anisman, 1986) and/or appetitive alterations (see Griffiths, 1991, for review), among others. These various pharmacological models of depression, however, can be criticized for their failure to address etiology, the potential for neurotoxicity and the finding that the magnitude of the neurochemical changes induced by such interventions frequently exceed those evident in human depression.

The supposition that the aversive life events most commonly associated with depressive episodes include separation and/or loss of a loved one (Henn & McKinney, 1987) prompted some investigators to employ social separation in young organisms as an intervening variable in

the promotion of psychological disturbance. Interestingly, the use of separation in primates as an animal model of psychopathology has revealed that CA disturbances are instrumental in promoting behavioural manifestations of pathology (e.g., diminished activity, distress vocalization, reduced appetitive behaviours). However, it has been suggested that the separation induced models of depression bear greater similarity to depressive syndromes exhibited by children following maternal separation or loss rather than to adult depression (Caldecott-Hazard et al., 1991).

Some investigators have argued that the olfactory bulbectomy paradigm is a suitable model in the investigation of human depression (Stockert, Serra & De Robertis, 1988). Following surgical removal of the olfactory bulbs, a behavioural syndrome is produced which is characterized by hyperactivity, irritability and aggression. These behavioural changes have been suggested to be reminiscent of agitated forms of depression (Richardson, 1991). This model has been criticized on grounds which relate fundamentally to the sensitivity and selectivity of conventional antidepressant interventions to the reversal of behaviours induced in bulbectomized animals (Howard, Ferris, Cooper, Soroko, Wang & Pollard, 1989). Moreover, this paradigm relies on ablation and there is no evidence to suggest organicity in depression. Indeed, such a provision would preclude diagnosis of the illness as a major affective disorder (American Psychiatric Association, 1987).

A significant proportion of the data derived from animal models of depression has emerged from the use of stressor paradigms (Weiss & Goodman, 1984; Weiss, Goodman, Losito, Corrigan, Cherry & Bailey, 1981; Weiss & Simson, 1989). In general, stressor exposure may be acute or chronic and the aversive stimulus employed may include cold, noise,

light presentation, footshock, restraint, forced swim or a combination of these stressors, among others. Such manipulations have been shown to elicit a number of behavioural changes, including alterations of locomotor activity, exploratory patterns, sexual behaviours, social interactions, food intake, sleep patterns, shuttle escape performance, spontaneous alternation, perseveration and intracranial self-stimulation (ICSS). Furthermore, the behavioural changes induced by stressors and the accompanying neurochemical alterations associated with such manipulations show considerable variability. Likewise, as in the human condition, the efficacy of pharmacological interventions in reversing specific behavioural disturbances and neurochemical alterations in animals are also variable. Such variability is dependent, at least in part, upon a number of environmental, organismic and genetic factors. For example, the response of an organism to a stressor may be influenced by genetic predisposition (species, strain), organismic factors (e.g., age, sex), the nature and the qualitative aspects of the stressor (e.g., severity, chronicity, controllability, predictability), the specific behaviour under consideration, experiential factors, and the specific neurochemical systems affected by the aversive stimulation (Anisman et al., 1991).

One paradigm which is frequently employed in assessing the effects of stressors on behavioural change is the shuttle escape task. In this procedure, animals are initially exposed to a stressor in a 'yoked' paradigm. In particular, one animal of the triad can emit a response which will result in stressor termination (controllable footshock) while the 'yoked' partner (uncontrollable) has no control over the aversive stimulation. A third animal is exposed to the apparatus but receives no shock (Maier & Seligman, 1976). When animals are subsequently tested in

the shuttle escape task, those animals exposed to a controllable stressor fail to display deficits in escape performance while animals previously exposed to inescapable shock exhibit pronounced response impairments and often fail to escape from the stressor entirely (Anisman, Remington & Sklar, 1979). Accordingly, the psychological dimension of coping rather than the severity of the stressor per se appears to be instrumental to the induction of behavioural pathology in animals (Anisman & Zacharko, 1982).

Several explanations have been advanced in accounting for the behavioural alterations induced by uncontrollable stressors. According to the 'learned helplessness' position of Maier and Seligman (1976), experience with an uncontrollable stressor results in animals learning response-outcome independence. In contrast to the learned helplessness hypothesis, the neurochemical position argues that when an organism encounters a stressor, it attempts to cope through behavioural means. Concurrently, neurochemical alterations may occur which aid the organism in contending with the stressor. If the stressor is controllable, amine synthesis keeps pace with increased utilization to effect adequate transmitter levels (or in some cases induces a transient increase in amine levels). These neurochemical changes enable the organism to (a) initiate and maintain defensive strategies (b) invigorate responding to salient stimuli and conceivably (c) blunt the impact of the stressor. However, when the stressor is uncontrollable (behavioural coping is not possible) and protracted, then the burden of coping is placed on endogenous neurochemical systems. In effect, following exposure to uncontrollable footshock, amine utilization may exceed synthesis and reduced amine levels may ensue, thus rendering the organism more vulnerable to pathology (Anisman & Zacharko, 1986). Although it is clear that various

stressors may influence central neuronal activity, the magnitude and time course of such alterations may vary with the particular neurochemical system affected. For example, the DA variations induced by stressors are less widespread and exhibit greater intra-regional variability than the NE changes and it appears that 5-HT may require a more severe stressor in order to effect amine alteration (Anisman, Kokkinidis & Sklar, 1981; Zacharko & Anisman, 1984). The neurochemical alterations induced by uncontrollable stressors in the CA and 5-HT containing systems are reminiscent of the endogenous variations described in human depression. The differential regional and intra-regional sensitivities of central neurotransmitter systems to stressor exposure may provoke neurochemical variations which contribute to the expression of specific behavioural profiles in animals. Likewise in humans, the varied symptom profile of depression may be associated with the unique cascading and interactive influence of specific transmitter and putative neurotransmitter systems.

In addition to the influence of stressors on central neurochemical change, it has also been demonstrated that such variations may be subject to conditioning or sensitization effects. For example, among animals exposed to an acute stressor, subsequent re-exposure to a milder form of the same stressor, which would normally be ineffective in inducing amine alterations, or even to cues previously associated with the initial stressor influences NE concentrations and promotes accumulation of the NE metabolite, 3-methoxy-4-hydroxyphenylethyleneglycol sulphate, (MHPG) (Cassens, Roffman, Kuruc, Orsulak & Schildkraut, 1980; Irwin, Ahluwalia & Anisman, 1986). Similar conditioning or sensitization effects following acute stressor exposure have also been observed with respect to the DA (Herman, Guilloneau, Dantzer, Scatton, Semerdjian-Rouquier & LeMoal,

1982; Deutch, Tam & Roth, 1985) and endogenous neuropeptide (e.g., enkephalin) (Chance, White, Krynock & Rosecrans, 1978) systems.

Despite the complex neurochemical and behavioural manifestations evident in human depressive syndromes, a common feature of depression is anhedonia or a diminished ability to experience pleasure. Indeed, a number of behavioural paradigms have attempted to elucidate neural substrates involved in the mediation of reward/motivational processes (e.g., drug self-administration, conditioned place preference, intracranial self-stimulation). In addition, some of these tasks and the intracranial self-stimulation (ICSS) procedure in particular, have also been employed to assess potential motivational disturbances associated with aversive life events. Other investigators have attempted to reconcile behavioural alteration in shuttle escape tasks and appetitive paradigms following stressor exposure with motivational change to a limited degree. Taken together, such experimental approaches have provided a substantial amount of information with respect to the neurochemical substrates of reward processes and treatments effective in reversing motivational disturbances incurred by stressor exposure in infrahuman subjects as well as those evident in human depression.

It has been suggested that alterations in shuttle escape performance following exposure to a stressor cannot adequately assess motivational change since such information is largely inferential (Zacharko & Anisman, 1984). In addition, it has been argued that deficits in escape performance may well follow from the induction of motoric changes rather than motivational disturbances (Anisman et al., 1979). Furthermore, appetitive models are often based upon food deprivation which may serve as a stressor (Anisman & Zacharko, 1986). In attempt to circumvent this latter

problem, some investigators have focused on procedures which do not require the imposition of a food deprivation regimen (e.g., presentation of palatable substances or solutions) (see Rosellini, DeCola & Shapiro, 1982). Indeed Katz (1982) and Willner, Towell, Sampson, Sophokleous and Muscat (1987) examined alterations in the ingestion of sweetened solutions as an indicator of motivational disturbance following experience with an uncontrollable stressor. Although the central neurochemical substrates which mediate such alterations were lacking in these early investigations more recent experimental evidence suggests that DA and opioids within the mesocortical and mesolimbic systems are involved in mediating reward associated with the intake of palatable substances (see Griffiths, 1991 for review).

In contrast to the abovementioned paradigms, ICSS appears to provide a direct analysis of alterations in motivational state following stressor exposure. Some of the advantages afforded by ICSS include direct activation of the central nervous system, the sensitivity of brain stimulation to perturbations of the reward (i.e., immediacy of effect) and the ability to evaluate relatively discrete central sites (i.e., intraregional assessment). The mesocortical, mesolimbic and nigrostriatal systems have been shown to support ICSS (Fibiger & Phillips, 1988). Although these pathways are major DA containing systems, ICSS may also be elicited from brain regions largely or completely devoid of DA activity (Ott, Destrade & Ruthrich, 1980) and some pharmacological manipulations which do not influence DA systems directly may produce alterations in self-stimulation performance (Broekkamp, Phillips & Cools, 1979; Olds & Williams, 1980; Phillips & LePiane, 1980; Phillips & LePiane, 1982). As a result of such observations, it has been suggested that other transmitters or putative

neurotransmitters may also be involved in reward processes and the mediation of ICSS (Wise, 1989; Wise & Rompre, 1989). Accordingly, increasingly greater attention has been focused upon the role of endogenous neuropeptides in the modulation of mesocorticolimbic DA activity and in the mediation of reward/motivational disturbances which follow from exposure to uncontrollable stressors.

Stressor Induced Noradrenergic Alterations

Two principal NE pathways have been identified in the central nervous system (a) the ventral noradrenergic bundle (VNB) which originates in the pontine medullary (A1, A2 cell groupings) and the subcoeruleus (A5, A7 cell clusters) areas which project to various hypothalamic nuclei, the septum and the frontal cortex and (b) the dorsal noradrenergic bundle (DNB), which originates in the locus coeruleus (A4, A6 area) and innervates the hippocampus, the amygdala and the frontal cortex (Moore & Bloom, 1979). It appears that both the VNB and the DNB are sensitive to the effects of stressor presentation although (a) the magnitude and (b) the time course of the amine alterations as well as (c) the specific sites affected vary with the nature of the stressor, its severity and the previous stressor history of the organism (Anisman & Zacharko, 1982; Anisman, et al., 1991).

The effects of uncontrollable stressors on central NE turnover have been well documented and an extensive consideration of these issues need not be reiterated here in any great detail. Thierry, Javoy, Glowinski and Kety (1968) initially demonstrated that uncontrollable stressors could provoke significant alterations in the synthesis and utilization of central NE. Korf, Aghajanian and Roth (1973) as well as Kvetnansky, Mitro, Palkovits, Brownstein, Torda, Vigas and Mikulaj (1976) subsequently

localized these central NE changes to specific hypothalamic nuclei (e.g., ventromedial and dorsomedial nuclei of the hypothalamus, the supraoptic nucleus), the locus coeruleus and the frontal cortex and reported that uncontrollable stressors could also provoke a transient inhibition of monoamine oxidase activity. Anisman (1984) and Zacharko and Anisman (1984) also demonstrated that reliable and significant reductions of NE concentrations appeared in the hypothalamus, the hippocampus, cortex and the locus coeruleus. However, there was considerable variability in the effectiveness of uncontrollable footshock in provoking such neurochemical change. For example, a larger number of stressor presentations were required to promote NE alterations in the locus coeruleus relative to the hypothalamus in the mouse. Similar neurochemical effects associated with stressor exposure have also been reported by Weiss and Goodman (1984) in the rat. The hippocampus and the frontal cortex in contrast appeared to be less sensitive to the effects of a stressor than the hypothalamus as revealed by the magnitude of the NE alterations within such sites. In addition to differential sensitivities of central NE sites to uncontrollable footshock, the time course of neurochemical recovery has also been reported to vary. For example, even when a relatively severe stressor is employed, hippocampal and locus coeruleus NE concentrations return to basal levels within 3 hours following exposure to uncontrollable footshock while hypothalamic concentrations remain depressed for a relatively protracted interval. It should also be considered that a number of different laboratories have demonstrated that the neurochemical changes following stressor presentation are relatively transient. However, upon re-exposure to a milder form of the stressor which does not ordinarily induce neurochemical change or to the cues previously associated with the

stressor (Cassens et al., 1980; Iimori, Tanaka, Kohno, Ida, Nakagawa, Hoaki, Tsuda & Nagasaki, 1982; Anisman, 1984; Tanaka, Tsuda, Yokoo, Yoshida, Mizoguchi & Shimizu, 1991), increased NE turnover can be readily reinduced.

It might be added at this juncture that Abercrombie and Jacobs (1987) have demonstrated that the DNB appears to be particularly relevant to a discussion of central NE alterations following stressor exposure. In particular, Abercrombie and Jacobs (1988) reported that exposing rats to a non-noxious stimulus (e.g, food) failed to influence electrophysiological activity in the locus coeruleus. In contrast, stressful stimuli (e.g., noise, restraint) enhanced unit activity in the locus coeruleus. Such central electrophysiological activity was strongly correlated with sympathetic nervous system activation, suggesting that stressors provoke a coactivation of central and peripheral NE systems. Interestingly, Abercrombie and Jacobs (1987, 1988) also reported that the response of locus coeruleus units to stressful stimulation was prevented by administration of the α_2 receptor agonist, clonidine. In a similar vein, Weiss and Simson (1989) reported that clonidine reversed the stressor provoked alterations of locus coeruleus NE activity. These data are consistent with an earlier report by Goodman, Weiss, Ambrose, Cardle, Bailey and Charry (1983) which revealed that monoamine oxidase inhibition ameliorated the NE variations in the locus coeruleus following presentation of a stressor. Taken together, these observations are consistent with the hypothesis that stressors reduce endogenous NE concentrations in the central nervous system and the locus coeruleus in particular. Indeed, Simson and Weiss (1988) and Weiss and Simson (1989) have argued that a deficiency of NE in the DNB may

contribute to the expression of some of the symptoms associated with human depression.

Stressor Induced Dopaminergic Alterations

The effects of stressors on DA activation were initially reported in the arcuate nucleus of the hypothalamus (Kvetnansky et al., 1976) and the lateral septum (Saavedra, 1982). These reports were the first to describe DA changes in the tuberoinfundibular (A12 area representing the arcuate and periarculate nuclei) and mesolimbic systems (Fuxe, Agnati, Kalia, Goldstein, Andersson & Harfstrand, 1985) respectively. Subsequent analyses of stressor effects on DA turnover in the mesocortical and mesolimbic systems revealed considerable variability across terminal sites. For example, enhanced DA metabolism induced by footshock, restraint or immobilization as revealed by the accumulation of 3,4-dihydroxyphenylacetic acid (DOPAC) and/or homovanillic acid (HVA), was prominent in the anteromedial prefrontal cortex, less so in the nucleus accumbens and absent in the olfactory tubercle (Abercrombie, Keefe, DiFrischia & Zigmond, 1989; see Zacharko & Anisman, 1991b; Deutch & Roth, 1990 for review).

In contrast to the variations in mesocortical/mesolimbic DA activation, stressors are typically ineffective in altering nigrostriatal DA turnover (Blanc, Herve, Simon, Lisoprawski, Glowinski & Tassin, 1980; Herve, Tassin, Barthelemy, Blanc, Laveille & Glowinski, 1979). Nevertheless, a combination of cold exposure and restraint reduced DA levels and increased the DOPAC/DA ratio in the striatum (Dunn & File, 1983) and Heyes, Garnett and Coates (1988) reported that exercise stress (to exhaustion) provoked a significant elevation of DA as well as DOPAC

and HVA in the nigrostriatal system. However, *in vivo* microdialysis has revealed that in addition to DA changes in the nucleus accumbens and the prefrontal cortex, a stressor can provoke significant increases of extracellular DA in the striatum. In effect, an aversive experience may influence striatal DA concentrations although such alterations may not be detected when the responsivity of the nigrostriatal system is gauged by static measures of metabolite accumulation. Nevertheless, it is unclear whether alterations of striatal DA turnover are related to the stressor *per se* or are secondary to the motoric effects induced by the aversive experience. Inoue, Tsukada, Kobayashi, Suhara and Itoh (1991) also recently reported that the stress of cold water swim decreased D2 receptor binding in striatal tissue. Interestingly, MacLennan, Pelleymounter, Atmadja, Jakubovic, Maier and Fibiger (1989) reported that neither footshock nor tail shock promoted alterations in DA receptor binding in the striatum and Medina, Novas, Wolfman, Levi De Stein and De Robertis (1983) demonstrated that cold water swim failed to alter DA receptor binding in the frontal cortex.

Although perturbations in the activity of major ascending noradrenergic systems (dorsal and ventral noradrenergic bundles) are more readily induced by uncontrollable than by controllable stressors (Anisman, 1978), only one study examined the effects of stressor controllability on DA activity and the data appeared to be ambiguous. Cherek, Lane, Freeman and Smith (1980) reported that predictable and unpredictable stressors were equally effective in altering mesocortical DA receptor binding (both high and low affinity). However, the length of the stressor sessions (multiple eight hour sessions) may have complicated interpretation of the results. In a subsequent investigation the influence of

potential coping factors (i.e., fighting) in influencing stressor induced DA alterations were examined (Dantzer, Guilloneau, Mormede, Herman & LeMoal, 1984). Heinsbroek, van Haaren, Feenstra, van Galen, Boer and van de Poll (1990) and Heinsbroek, van Haaren, Feenstra, Boon and van de Poll (1991) recently assessed not only the issue of controllability but also the influence of sex related differences in response to stressor exposure. Both uncontrollable and unpredictable footshock increased DA and metabolite levels in the frontal cortex as well as the pontine-medullary area; an effect which was considerably more prominent in female than male rats. Heinsbroek et al. (1991) also reported that both controllable and uncontrollable footshock elevated DA turnover in the frontal cortex but the magnitude of this effect was demonstrably greater in animals exposed to an uncontrollable stressor. In addition to the possible contribution of sex related differences to stressor induced neurochemical variations, it might also be considered that Ida, Tanaka, Kohno, Tsuda, Hoaki, Nakagawa, Iimori and Nagasaki (1982) demonstrated that the increased DA turnover evident in young rats (2 months) following immobilization was no longer apparent among older animals (15 months). Since the plasma corticosterone levels of older animals were comparable to those of younger rats, it appears that it was not the stressful nature of the stimulation that changed but rather the organism's ability to contend with the aversive event (i.e., the ability to augment DA synthesis). Accordingly, controllability over a stressor as well as the age and the sex of the organism may play a role in influencing DA turnover.

It is of interest that the ability of stressors to promote DA turnover in the frontal cortex was independent of NE innervation of this region. In particular, 6-hydroxydopamine lesions of the dorsal NE bundle did not

diminish the effects of footshock on cortical DA turnover (see Deutch & Roth, 1990, cf. Maj, Mogilnicka & Klimek, 1977). However, recent investigations have revealed that depletion of DA in the frontal cortex exaggerated the magnitude of the DA turnover ordinarily evident in the nucleus accumbens following application of a stressor (Deutch, Clark & Roth, 1990) and some laboratories have reported such effects in the striatum (Carter & Pycock, 1980; Deutch, Gruen & Roth, 1989; Lecesse & Lyness, 1987). Nevertheless, it is not clear whether the hyperresponsivity of the nucleus accumbens to a stressor can be attributed solely to DA denervation of the frontal cortex. For example, Herve et al. (1979) reported that while dorsal raphe lesions were ineffective in modifying DA turnover in the frontal cortex, such 5-HT alterations were effective in promoting DA activity in the nucleus accumbens. The site of the DA-5-HT interaction appears to be the ventral tegmental area (VTA), to which the dorsal raphe has significant input (see Herve, Simon, Blanc, LeMoal, Glowinski & Tassin, 1981; Herve, Simon, Blanc, Lisoprawski, LeMoal, Glowinski, & Tassin, 1979). Indeed, a recent report by Minabe, Ashby, Schwartz and Wang (1991) has demonstrated that 5-HT₃ receptor antagonism provokes significant alterations of unit activity in the A10 region. Nevertheless, Minabe et al. (1991) acknowledge that a direct test of this hypothesis is required (e.g., iontophoretic application within the VTA) and the possibility of mesolimbic feedback (i.e., 5-HT₃) to the VTA is not precluded.

The stressor induced increases of mesocorticolimbic DA turnover appear to follow from activation of the VTA (Deutch & Roth, 1990). However, neurochemical determination of stressor induced changes in metabolite levels within the VTA have been inconsistent. For example,

Claustre, Rivy, Dennis and Scatton (1986) failed to detect DA metabolite elevations in the A10 region, while Deutch et al. (1985) reported that uncontrollable footshock provoked a significant accumulation of DOPAC in the VTA. However, Swanson (1982) demonstrated that only 35% of VTA neurons actually project to the frontal cortex and of these, only 12-17% are DA containing. In addition, Deutch et al. (1985) observed that only a subpopulation of A10 DA neurons demonstrated sustained activation in response to stressors and the magnitude of the DOPAC accumulation correlated with the size of the frontal cortex projection field described by Swanson (1982). Apparently, tegmental DA neurons are not homogeneously activated by stressors and determination of DA turnover within the A10 area may be related to the regions of the VTA examined. The responsivity of DA neurons to stressors in the mesolimbic/mesocortical system has also been linked to the electrophysiological properties of the A10 neurons innervating these sites, receptor distributions in terminal regions and the density/sensitivity of autoreceptors (White & Wang, 1985; Gariano, Sawyer, Tepper, Young & Groves, 1989; Gariano, Tepper, Sawyer, Young & Groves, 1989). Moreover, while extraneuronal deamination of DA normally favours accumulation of HVA, stressors may alter metabolic routes such that significant concentrations of 3-methoxytyrosine (3-MT) are detected. In effect, the failure to identify significant elevation of specific DA metabolites (e.g., DOPAC, HVA) in the mesocorticolimbic system may be attributable, at least in part, to modifications in DA metabolism provoked by a stressor (Spanagel, Herz & Shippenberg, 1991).

The most significant cortical projection field of the A10 area with respect to the effects of stressors on DA turnover is the frontal cortex

(anteromedial pathway which arises from medial tegmental sites). Under basal conditions, amine utilization within the frontal cortex exceeds that of other cortical areas to which the tegmentum projects (Bannon & Roth, 1983), as well as the mesolimbic and mesostriatal systems. Consistent with the results of Deutch et al. (1985) which suggested that tegmental neurons were differentially activated by stressors, Mantz, Thierry and Glowinski (1989) and Thierry, Mantz, Milla and Glowinski (1988) reported that the electrophysiological responsivity of frontal cortex neurons to stress was not uniform. The majority of these neurons responded with increased activation, while some neurons were inhibited. The marked DOPAC accumulation in the frontal cortex following stressor exposure has been linked to the absence of autoreceptors (Bannon & Roth, 1983; Deutch et al., 1985; Tam, Elsworth, Bradberry & Roth, 1990). However, the identical stressor which provoked a two fold increase of DOPAC in the frontal cortex failed to enhance metabolite accumulation within the cingulate cortex, which has also been reported to lack autoreceptors (Bannon, Wolf & Roth, 1983; Roth, Tam, Ida, Yang & Deutch, 1988). Accordingly, the absence of autoreceptors in the frontal cortex (e.g., Tam et al., 1990) as an explanatory concept for the stressor induced enhancement of DA turnover appears inadequate. Moreover, Gariano et al. (1989a,b) and Shepard and German (1984) demonstrated that impulse regulating somatodendritic DA autoreceptors may be reduced but not absent in the frontal and the cingulate cortices and frontal cortex DA terminals possess autoreceptors which regulate release (Hoffmann, Talmaciu, Ferro & Cubeddu, 1986) but not DA synthesis (Tam et al., 1990). Consequently, the contribution of these autoreceptor subtypes to the

induction of neurochemical change following stressor exposure remains to be determined (see also Kalivas & Duffy, 1990).

The cells of origin of the suprarhinal system verified along the dorsal aspects of the VTA project to the dorsal margins of the sulcal cortex. There are presently no experimental data describing the effects of stressors on DA turnover within the sulcal cortex or comparing the neurochemical sensitivity of this site with the frontal cortex. Both the piriform and the entorhinal cortices also receive significant DA input. The former system receives its innervation from the VTA as well as the medial aspects of the substantia nigra, while the latter system is derived from the lateral VTA. Mild intermittent footshock, however, was ineffective in altering levels of DA or DOPAC in either of these cortical regions in the rat (Roth et al., 1988). The lack of a stressor effect on DOPAC accumulation in the piriform cortex reported by Roth et al. (1988) contrasts with a study which revealed that the magnitude of the DA metabolite accumulation in the piriform cortex approached that observed in the frontal cortex (Bannon et al., 1983). The rat strain employed, the nature of the stressor and the parameters of stressor application were identical and reconciliation of such inter-laboratory variations are difficult. Taken together, there is considerable variability in tegmental innervation of the cortex and in the responsiveness of the VTA and its cortical projection sites to stressors. The sensitivity of some cortical subregions to stressors and to stressor related cues remains to be determined, while that of others (e.g., piriform cortex) requires additional examination.

Although footshock elevates DOPAC in the nucleus accumbens and the frontal cortex (Thierry, Tassin, Blanc & Glowinski, 1976; Fadda, Argiolas, Melis, Tissari, Onali & Gessa, 1978; Dantzer, Guilloneau,

Mormede, Herman & LeMoal, 1984; Claustre et al., 1986), increases of the metabolite are more likely to appear in the latter rather than the former region (Laveille, Tassin, Thierry, Blanc, Herve, Barthelemy & Glowinski, 1978; Kramarcy, Delanoy & Dunn, 1984; Deutch et al., 1985). However, while stressors (immobilization) may increase DOPAC levels within the frontal cortex and nucleus accumbens, the profile of the metabolite changes varied during the course of the immobilization session (Roth et al., 1988). In particular, increased DOPAC accumulation in the frontal cortex was evident within 10 minutes following initiation of immobilization, peaked within 20 minutes, and declined thereafter. In the nucleus accumbens the accumulation of DOPAC was not evident until 30 minutes of immobilization, but metabolite levels remained elevated over the course of the 120 minute immobilization session. Accordingly, the frontal cortex and the nucleus accumbens are not only differentially sensitive to a stressor but are also subject to differential rates of adaptation; data consistent with the recent experimental reports of Heinsbroek et al. (1991) and Puglisi-Allegra, Imperato, Angelucci and Cabib (1991). Heinsbroek et al. (1991) demonstrated that exposure of animals to 30 minutes of footshock was effective in increasing DA turnover in the frontal cortex but such an effect was reduced with more protracted (90 minute) exposure. Puglisi-Allegra et al. (1991) demonstrated that restraint for a protracted duration provoked a biphasic alteration in DA release (i.e., increase followed by decrease) from the nucleus accumbens of the rat. In effect, analysis of the effects of stressors on DA turnover should consider the brain region influenced by the stressor as well as the nature and duration of the aversive treatment (see also Cabib, Kempf, Schlee, Oliverio & Puglisi-Allegra, 1988).

In addition to the immediate effect of a stressor on DA lability within the mesocorticolimbic system, such variations in amine activation may be subject to sensitization/conditioning in some brain regions. For example, the stressor provoked increases of DA turnover can be reinduced by cues previously associated with uncontrollable footshock within the frontal cortex and the VTA but not the nucleus accumbens, amygdala or the olfactory tubercle (Herman et al., 1982). The magnitude of these conditioned DA changes was found to be particularly pronounced in the frontal cortex relative to the VTA. Accordingly, analysis of the behavioural effects of environmental insults need to consider not only the immediate effects of stressors, but also the long term repercussions that may be elicited by stressor related cues.

The stressor induced variations of DA turnover may be associated with the anxiety or arousal provoked by the stressor rather than the physical impact of the aversive stimulus. In particular, anxiolytic administration prevents increased DOPAC accumulation in the frontal cortex induced by a stressor or cues previously associated with aversive stimulation (Laveille et al., 1978; Ida, Tsuda, Sueyoshi, Shirao & Tanaka, 1989) and this effect can be reinstated by a benzodiazepine antagonist (Roth et al., 1988). The mechanism through which benzodiazepines attenuate stressor provoked DA turnover in the mesocorticolimbic system remains to be elucidated. However, the use of anxiogenic agents may be useful in simulating the effects of stressors on DA turnover in the mesocorticolimbic system (Ida & Roth, 1987). Moreover, Roth et al. (1988) demonstrated that methyl- β -carboline-3-carboxamide, (FG-7142), selectively increased DA synthesis and utilization in the frontal cortex and the VTA as measured by DOPA and DOPAC accumulation respectively but not in the nucleus

accumbens or the nigrostriatal system. Benzodiazepine antagonist administration, including Ro 15-1788 and CGS-8216, prevented DOPA and DOPAC accumulation in the frontal cortex. Knorr, Deutch and Roth (1989) proposed that benzodiazepines and benzodiazepine inverse agonists (β -carboline) exert their effects through a presynaptic mechanism, although the possibility that the VTA is activated directly by β -carboline was reinforced by the demonstration of benzodiazepine receptors in the A10 region of the human brain and the effects of systemic and intracranial administration of the anxiolytic, zolpidem, on DA turnover in the frontal cortex. Accordingly, it is likely that benzodiazepine agonists and inverse agonists modulate stressor provoked DA turnover by influencing terminal and impulse dependent (cell body) mechanisms, although the input of other mechanisms cannot be dismissed.

Opioids and Central Dopamine Activity

In addition to the evidence suggesting that DA turnover is altered following exposure to aversive environmental events, there are considerable data to indicate that stressors also promote release of endogenous neuropeptides which can modulate CA turnover (see Kalivas, Duffy, Dilts & Abhold, 1988 for review). Although immunocytochemical analyses have suggested a DA-opioid interface within the VTA (Johansson, Hokfelt, Elde, Schultzberger & Terrenius, 1978; Johnson, Sarr & Stumpf, 1980), attempts to identify the opioid receptor associated with the promotion of tegmental DA activity were ambiguous owing to the mixed nature of the agonists employed. For example, A10 activation induced by D-Ala²-Met⁵-enkephalinamide (DALA) affected both the μ and δ receptors. Recently developed enkephalin analogues, including Try-D-Ala-

Gly-NMe-Phe-Gly-ol (DAGO) and [D-Pen^{2,5}]-enkephalin (DPEN), which differ considerably in their relative activation of μ and δ receptors, permitted a more precise description of the mechanisms underlying the activation of the DA substrate in the tegmentum. Indeed, using such analogues it was observed that the increased activation of DA neurons, and the behavioural concomitants associated with such activation, followed from stimulation of μ rather than δ receptors in the A10 region (Latimer, Duffy & Kalivas, 1987). Furthermore, Kalivas and Abhold (1987) reported that stressors promoted release of enkephalins within the midline tegmental region, but had no effect along the lateral extent of the A10 area. Pharmacological manipulations which prevented neuropeptide release attenuated the stressor enhanced DA turnover within the nucleus accumbens and the frontal cortex. It might be added at this juncture that Jacobs and his associates (e.g., Abercrombie & Jacobs, 1988) have described a significant interaction between endogenous opioid activity and the responsivity of the locus coeruleus to aversive stimulation. This interaction appears to be channeled in part, through the A10 region (Deutch, Goldstein & Roth, 1986). The evidence in favour of this hypothesis has suggested that stressors activate the locus coeruleus NE system which results in fear and/or anxiety (Redmond, 1987). Acute stressors also effect release of endogenous neuropeptides, which may inhibit locus coeruleus activity (Abercrombie & Jacobs, 1988). It remains to be verified empirically whether controllability over stressor termination contributes to the different behavioural consequences of opioid activation.

The demonstration of an enkephalin-DA link within the A10 region appears to represent the first stage of a rather complex neuromodulatory interaction (Kelley, Cador & Stinus, 1985; Cador, Kelley, LeMoal &

Stinus, 1988; Cador, Rivet, Kelley, LeMoal & Stinus, 1989; Kelley, Cador, Stinus & LeMoal, 1989). Lisoprawski, Blanc and Glowinski (1981), for example, reported that substance P was depleted within the VTA of rats exposed to inescapable footshock, while Bannon, Elliot, Alpert, Goedert, Iversen and Iversen (1983) reported that monoclonal antibodies directed against substance P prevented activation of mesocortical DA neurons ordinarily induced by a stressor. Subsequent investigations revealed that the tachykinins, substance P and substance K (neurokinin A), appeared to be equally distributed in the VTA, although substance K was demonstrably more potent in the promotion of locomotor activity (Takano, Takeda, Yamada & Karniya, 1985). Thus, it was suggested that the neurochemical effects of substance P may actually be mediated through the substance K receptor (Kalivas, Deutch, Maggio, Mantyh & Roth, 1985). More recent investigations however have revealed that substance P and substance K do not appear to share common endogenous degrading enzymes nor do these tachykinins activate identical receptor sites (Martin, Massol, Scalbert & Puech, 1990). Finally, the identification of neurotensin (endogenous neuroleptic) in the tegmentum suggested an additional link in the stressor induced neurochemical profile (Deutch, Bean, Bissette, Nemeroff, Robbins & Roth, 1987). For example, Kalivas and Taylor (1985) observed that daily administration of neurotensin into the VTA produced a progressive elevation of DOPAC accumulation in the nucleus accumbens. Likewise, Deutch et al. (1987) demonstrated that mild footshock increased neurotensin concentration in the tegmentum; an effect which was associated with elevated levels of DOPAC in the frontal cortex.

It will be recalled that conditioning/sensitization of mesocortical DA turnover has been reported among animals re-exposed to a mild stressor or

to cues previously associated with a stressor. There is reason to suspect that such neurochemical conditioning might be influenced by endogenous opioids. Kalivas (1985) and Kalivas and Duffy (1987) reported that repeated morphine or enkephalin administration induced a progressive increase in DA turnover in the VTA, the nucleus accumbens, and the frontal cortex following challenge doses of the respective opioids. Kalivas, Richardson-Carlson and Van Orden (1986) also reported behavioural and neurochemical cross sensitization between animals subjected to daily footshock or intra-VTA DALA administration. In particular, it was demonstrated that the stressor provoked increase of DA metabolism in the nucleus accumbens was enhanced in rats that previously received DALA administration into the VTA over a 5 day period.

Stressor Induced Behavioural Change

Shuttle Escape

It will be recalled that animals exposed to uncontrollable but not controllable stressors typically exhibit pronounced response impairments and often fail to escape entirely when tested in a shuttle-escape task. Such an effect has been attributed to controllability over stressor termination rather than the physical impact of the aversive stimulus (Maier & Seligman, 1976). According to the learned helplessness position of Maier and Seligman (1976), exposure to an uncontrollable stressor results in the animal learning response-outcome independence (helplessness) which contributes to disruptions in escape performance. In contrast to a cognitive interpretation of the escape deficits following uncontrollable footshock, the neurochemical position has proposed that when an organism encounters aversive environmental stimuli over which control is not possible, the burden of coping is placed upon endogenous neurochemical systems and

neurochemical depletion may ensue (Anisman & Zacharko, 1982). Such neurochemical changes contribute to the expression of behavioural pathology. Moreover, pharmacological treatments which mimic the effects of uncontrollable stressors by reducing CA levels, influencing synthesis (α -methyl-para-tyrosine, FLA-63) or blocking DA receptors (haloperidol, pimozide) also disrupt performance (e.g., shuttle escape). These pharmacologically induced behavioural disturbances are similar to the stressor induced deficits and are only evident if the task is motorically demanding (i.e., the organism is required to sustain activity before escape is possible) (see Anisman et al., 1991 for review). Furthermore, some of the stressor induced behavioural alterations may be attenuated or reversed by repeated treatment with tricyclic antidepressants (i.e., imipramine, desmethylinipramine, amitriptyline, nortriptyline) (Zacharko, Bowers, Prince & Anisman, 1983; Zacharko, Bowers & Anisman, 1984; Sherman & Petty, 1980; Caldecott-Hazard et al., 1991) or by administration of CA precursors including l-dopa (Anisman et al., 1979). The contention that clinically effective antidepressant agents exert their effects solely through a CA or 5-HT influence is overly simplistic. Indeed, the involvement of other central transmitters such as acetylcholine and the endogenous neuropeptides to stressor induced behavioural change is not precluded. It will be also recalled that neuropeptides appear to modulate NE and DA activity, and that endogenous opioids (e.g., enkephalins, endorphins, tachykinins) are released in response to stressor exposure (Kalivas & Abhold, 1987; Deutch et al., 1987).

Although relatively few investigations have been conducted which consider the effects of opioid interventions on shuttle escape disturbance, at least one study has considered this issue. For example, Mah, Suissa &

Anisman (1980) administered morphine intraperitoneally 30 minutes prior to testing in the shuttle escape paradigm and failed to report significant alterations in escape latencies among uncontrollably stressed mice administered either saline or morphine. The failure of Mah et al. (1980) to demonstrate a morphine dependent amelioration of the escape deficits induced by a stressor appears to be at variance with recent neurochemical data. Tanaka, Ida, Tsuda, Tsujimaru, Shiroa & Oguchi (1989) demonstrated that intraventricular Met-enkephalin administration prior to immobilization reversed the stressor induced increases in MHPG concentrations within the hypothalamus, amygdala, thalamus, midbrain, hippocampus and locus coeruleus. In an earlier report, Tanaka, Kohno, Tsuda, Nakagawa, Ida, Imori, Hoaki & Nagasaki (1983) reported that morphine also attenuated immobilization induced increases in MHPG in the hypothalamus, amygdala, thalamus, midbrain and hippocampus. In addition, this blunted neurochemical effect was prevented in the hypothalamus, amygdala and thalamus following naloxone pretreatment (Tanaka, Kohno, Nakagawa, Ida, Imori, Hoaki, Tsuda & Nagasaki, 1982). In light of the apparent association between central NE alteration induced by uncontrollable stressors and behavioural change, morphine might have been expected to exert some therapeutic effect on shuttle escape performance in the investigation of Mah et al. (1980). However, it should be considered that in neither of the Tanaka investigations was behavioural change related to neurochemical alteration and in addition, the functional significance of various opioid receptor subtypes may vary between rats and mice (Yoburn, Lutfy & Candido, 1991). It should also be considered that naloxone administered 10 minutes prior to a 1 hour immobilization session was found to enhance the stressor induced increases in MHPG in the

hypothalamus, amygdala and thalamus but such an effect was not observed when animals were treated following a 2 hour exposure to the same stressor (Tanaka, Ida & Tsuda, 1988). These data are consistent with a hypothesis that endogenous opioids released in response to a stressor may attenuate the stressor induced increases in central NE and may thus alter expression of stressor induced behavioural deficits. After all, naloxone would attenuate the margin of opioid activation produced in response to the imposition of a stressor and potentially exaggerate expression of behavioural pathology. Clearly, further investigations are required in order to reach any firm conclusions regarding the relationship between stressor induced shuttle escape disturbances and opioid-NE interaction .

Locomotor Activity

Uncontrollable footshock has been shown to facilitate DA turnover in the mesocortical and mesolimbic systems as revealed by the accumulation of the DA metabolites, DOPAC and HVA (Thierry et al., 1976; Deutch et al., 1985; Anisman & Zacharko, 1990; Zacharko & Anisman, 1991a; Shanks, Zalcmán, Zacharko & Anisman, 1991). Behaviourally, such neurochemical variations have been associated with the induction of locomotor activity (Herman, Stinus & LeMoal, 1984; Kalivas, Widerlov, Stanley, Breese & Prange, 1983). Psychostimulant administration (e.g., d-amphetamine sulphate), like uncontrollable footshock, has also been shown to enhance locomotor activity and to augment DA turnover in mesocortical and mesolimbic sites (Herman et al., 1984; Hahn et al., 1986; Leyton & Stewart, 1990). Moreover, psychostimulant and stressor induced behavioural and neurochemical activation exhibit considerable cross sensitization (see below) and can be attenuated by pharmacological manipulations which block DA receptor

activity (e.g., Beninger & Hahn, 1983). Taken together, there is considerable evidence to suggest that (a) opioids modulate DA activity within the A10 region and channel such activation to both the frontal cortex and the nucleus accumbens (b) endogenous opioid systems may be activated following exposure to uncontrollable stressors or pharmacological manipulation which mimic the effects of stressors and (c) opioid-DA interactions may promote behavioural change.

Numerous immunohistochemical investigations have verified that although μ , δ and κ opioid receptors are widely distributed within the CNS, opioid receptor density is particularly conspicuous within limbic regions. In this respect autoradiographic analyses have identified μ , δ and κ opioid receptor subtypes within the VTA, nucleus accumbens and frontal cortex although the relative densities of the respective receptor sites are variable (for reviews, see Mansour et al., 1988; Adler, Goodman & Pasternak, 1990). For example, in the A10 region μ receptor labelling is particularly conspicuous, in the nucleus accumbens, μ , δ and κ binding sites are all prominent while in the frontal cortex, μ and δ receptors appear to be more densely distributed than those of κ . In addition to inter-regional variations in endogenous opioid receptor distribution, there also appears to be considerable heterogeneity in the intra-regional concentration of opioids (see Mansour et al., 1988; Adler et al., 1990, for review).

Consistent with analyses which have revealed a diverse opioid receptor profile in the mesocortical and mesolimbic systems, multiple neuropeptide colocalization determinations have been identified within the mesocorticolimbic system. For example, endogenous Met- and Leu-enkephalin (e.g., methionine, leucine) (Johnson et al., 1980; Khachaturian, Lewis & Watson, 1983; Miller, 1983), neurotensin (Jennes, Stumpf &

Kalivas, 1982; Hokfelt, Everitt, Theodorsson-Norheim & Goldstein, 1984; Studler, Kitabgi, Tramu, Herve, Glowinski & Tassin, 1988) dynorphin (Fallon & Ciofi, 1990) and at least two of the tachykinins (substance P, substance K or neurokinin A) (Ljungdahl, Hokfelt, Nilsson, & Goldstein, 1978) have been identified within the VTA. With the exception of dynorphin, these putative neurotransmitters have been shown to promote behavioural activation (Kelley, Stinus & Iversen, 1980; Takano, Takeda, Yamada & Kamiya, 1985; Cador et al., 1988; DiChaira & Imperato, 1988) and increase DA turnover in the nucleus accumbens and frontal cortex following intra-VTA infusions (e.g., Latimer et al., 1987; Kalivas & Abhold, 1987). Furthermore, there is evidence to suggest that at least some of these neuropeptides (e.g., Met-enkephalin, neurotensin, substance P) (Kalivas & Abhold, 1987, Deutch et al., 1987; Bannon et al., 1983, respectively) are released within the VTA upon exposure to uncontrollable stressors.

Evidence to support the contention that stressor induced behavioural activation is attributable in part to an opioid-DA interface can be gleaned from investigations employing specific opioid and DA receptor agonists and antagonists. For example, Vezina, Kalivas and Stewart (1987) repeatedly administered the μ receptor agonists, morphine and Tyr-D-Ala-Gly-NMe-Phe-Gly-ol (DAGO) into the VTA as well as the nucleus accumbens. While both manipulations increased locomotor activity in the immediate post-administration interval, potentiation of the acute effects of opioid administration (i.e., sensitization of locomotor activity) was only observed following activation of the A10 region. In an earlier report, Kalivas et al. (1983) demonstrated that acute administration of DALA into the VTA produced both a dose-dependent increase in locomotor activity

and DOPAC concentrations in the nucleus accumbens. The behavioural and the neurochemical concomitants of mesencephalic DALA application were antagonized by neuroleptic administration into the nucleus accumbens. Daily administration of DALA into the A10 region potentiated behavioural activation and DA turnover in the nucleus accumbens (Kalivas et al., 1983) and this effect was augmented following challenge doses of either d-amphetamine sulphate administered systemically or neurotensin applied to the A10 region (Kalivas, 1985). In contrast to the sensitization effects provoked by repeated DALA administration into the VTA, comparable neuropeptide injections into the nucleus accumbens (e.g., DALA, DAGO, morphine) were only associated with a dose related increase in locomotor activity (Kalivas et al., 1983; Vezina et al., 1987). Moreover, this effect appeared independent of the mesolimbic DA system since neither neuroleptic administration into the nucleus accumbens nor 6-OHDA lesions of the mesolimbic DA system blocked the DALA induced behavioural activation (Kalivas et al., 1983; Kalivas et al., 1988). These investigations may provide some support for the proposition that behavioural sensitization observed following opiate infusion into the VTA are DA-dependent while those from the nucleus accumbens are not (Kalivas et al., 1983).

In summary, behavioural sensitization appears to follow from the promotion of A10 neuronal activity and the resultant DA turnover within the nucleus accumbens. Dopamine turnover is enhanced in both the mesolimbic system as well as the A10 region although neurochemical depletion only appears in the VTA. Although sensitization cannot be elicited from the nucleus accumbens, this brain region appears important in the promotion of locomotor activity. Finally, it would appear that the

behavioural activation induced by opioid activation within the nucleus accumbens is independent of DA activity while in the VTA the DA-opioid interface is instrumental to the induction of sensitization and the nucleus accumbens contributes to the expression of such an effect.

In addition to the sensitization of DA activity and locomotor activation following repeated administration of opioid and/or DA agonists into the VTA, several investigations have demonstrated cross-sensitization between such pharmacological manipulations and stressors. For example, Herman et al. (1984) reported that prior exposure of animals to a chronic mild footshock regimen potentiated the effects of d-amphetamine sulphate on locomotor activity relative to the performance of non-stressed amphetamine treated subjects. Such an effect was demonstrated 24 hours following stressor application at which time stressor provoked cortical and limbic DA turnover had returned to basal levels. Conceivably, a portion of this augmented behavioural activation may be attributable to environmentally induced neurochemical change, although appropriate control groups for such comparisons were not provided. Kalivas and Abhold (1987) subsequently reported that daily sessions of uncontrollable footshock in rats enhanced the motor stimulant effects to challenge doses of DALA infused directly into the A10 region. This behavioural potentiation was abolished among animals pretreated with intra-VTA naltrexone methobromide. In addition, pretreatment with the opiate antagonist attenuated the stressor induced increases of DA metabolism in the nucleus accumbens and frontal cortex. Conversely, repeated administration of DALA into the A10 DA region potentiated the effects of an acute footshock session on DA metabolism within the nucleus accumbens and septum but not the frontal cortex (Kalivas et al., 1985). Finally,

following repeated exposure to footshock, infusions of d-amphetamine sulphate but not morphine into the nucleus accumbens potentiated the stressor induced behavioural activation (Leyton & Stewart, 1990). These data support the hypothesis that opioid induced behavioural activation modulated by the nucleus accumbens may be independent of DA mechanisms (Kalivas et al., 1983). Taken together, these investigations suggest that the locomotor activation induced by stressors and opioid/DA manipulations appear to be comparable.

Daily administration of the μ and δ agonist, D-Ala²-Met⁵-enkephalinamide (DALA) into the VTA promotes behavioural activation similar to that observed following exposure of animals to an uncontrollable stressor. Such stressor or pharmacologically induced behavioural alterations are prevented by haloperidol pre-treatment (Kalivas et al., 1985), reversed by the opiate antagonists (Kalivas & Abhold, 1987) and completely abolished following 6-hydroxydopamine (6-OHDA) induced lesions of the A10 DA terminals (Kelley et al., 1980). Furthermore, the behavioural activation elicited by d-amphetamine (Kelley et al., 1980) or cocaine (DuMars, Rodger & Kalivas, 1988) may be enhanced with the simultaneous infusion of DALA into the A10 DA region. Taken together, these results suggest that DALA-induced behavioural stimulation is dependent, at least in part, upon DA activity within the VTA and may be similar to that observed following exposure to uncontrollable stressors.

Although it appears that activation of either μ or δ opioid receptors increases locomotor activity and DA metabolism in the nucleus accumbens and frontal cortex (alterations comparable to those induced by exposure to uncontrollable stressors), not all of the data are consistent with such an interpretation. For example, Ukai, Toyoshi and Kameyama (1989)

reported that intracranial administration of the δ opioid receptor agonists, D-Pen²-L-5-enkephalin (DPLPE) and D-Ala²-D-Leu⁵-enkephalin (DADL), produced demonstrably different behavioural effects. Indeed, DADL facilitated while DPLPE suppressed locomotor activity in rats. Ukai et al. (1989) attributed this differential effect to the relative affinity of DADL for μ receptors which antagonized the suppressant action of the δ receptors. Although such an hypothesis is conceivable it should also be considered that DPLPE induced suppression of activity could be attributed to the high dose of the neuropeptide employed. This latter interpretation would be consistent with the well documented demonstration of a dose dependent biphasic effect of neuropeptides on locomotor activity. In particular, low doses of either μ or δ agonists increase locomotor activity while high doses provoke a time dependent behavioural depression/activation profile (Kalivas et al., 1983; Latimer et al., 1987; Di Chiara & Imperato, 1988). Nevertheless, it might be considered that significantly higher doses of some δ agonists (e.g., DPLPE) are required to elicit comparable increases of locomotor activity provoked by μ receptor activation (Kalivas et al., 1985; Latimer et al., 1987). Clearly, additional data are required before the relative contribution of μ and δ receptor activation can be differentiated with respect to behavioural output and to the differential anatomical distribution of opioid receptors in the VTA as well as terminal regions innervated by the A10 area.

In contrast, to the enhanced behavioural activation and increased DA metabolism in the nucleus accumbens and frontal cortex following activation of μ and δ receptors, it appears that κ receptors may function to blunt DA activity in the mesocorticolimbic DA systems and suppress behavioural output. For example, Di Chiara & Imperato (1988) compared

the effects of three μ (morphine, methadone, fentanyl) and three κ (U50,488, bremazocine, tifluadom) receptor agonists on locomotor activity and DA turnover in the dorsal caudate and nucleus accumbens. Consistent with the investigations of Vezina et al. (1987) and Latimer et al. (1987), the μ opioid receptor agonists elicited a dose dependent biphasic increase in locomotor activity and such behavioural stimulation was associated with increased DA transmission in the nucleus accumbens but not the dorsal caudate. In contrast, activation of the κ receptor depressed locomotor activity in the rat and this coincided with reduced DA turnover as assessed by accumulation of the DA metabolites, HVA and DOPAC within the nucleus accumbens and dorsal caudate. Accordingly, there appears to be sufficient evidence to suggest that the behavioural and pharmacological effects of the μ and δ receptor agonists are fundamentally different from those provoked by the κ agonists. Indeed, a recent investigation has revealed that μ and κ receptors represent tonically active and functionally opposing systems in the modulation of DA release in the nucleus accumbens (Spanagel, Herz & Shippenberg, 1992). Spanagel et al. (1992) demonstrated that activation of μ receptors in the VTA increased basal DA release in the nucleus accumbens while μ antagonists reduced extracellular DA levels as revealed by in vivo microdialysis. Although the effects of A10 κ receptor activation have not been assessed with respect to DA turnover in the nucleus accumbens, selective activation of κ receptors within the accumbens reduced DA release in this region while κ antagonists enhanced DA release. Determination of the functional significance of endogenous opioid receptor activation, particularly with respect to mood/motivational processes may have profound implications for the assessment and

prediction of stressor induced behavioural pathology and ultimately the treatment of depression.

In summary, there are numerous experimental examples to illustrate similarities between stressor and pharmacologically induced behavioural activation. Data available to date suggest that stressors provoke release of endogenous opioids within the VTA which promotes neurochemical activation of terminal sites within the mesocortical and mesolimbic DA systems to favour behavioural activation. The precise mechanism(s) by which stressor induced opioid release influence(s) DA turnover and to alter behaviour remains to be elucidated. Some investigators (Kelley et al., 1980; Kalivas et al., 1985) have suggested that activation of μ or δ receptors results in presynaptic inhibition of an inhibitory (e.g., GABA) input into the A10 DA system (activation through a disinhibitory process). The net effect of such an interaction would be release of DA activity from the inhibitory influence of GABA. Conversely, it is conceivable that κ activation following stressor induced release of dynorphin may promote GABAergic activity in the VTA, inhibit DA transmission within the A10 region and affect DA turnover in terminal sites of the mesocorticolimbic system. However, Di Chiara and Imperato (1988) suggested that κ receptors may be localized on presynaptic DA terminals within the A10 region and stimulation of such autoreceptors would reduce DA turnover in the VTA and consequently attenuate DA activity in the nucleus accumbens and the medial prefrontal cortex. Finally, Spanagel et al. (1992) suggested that μ receptor activation within the VTA may inhibit κ receptors to result in a net increase in DA release from the nucleus accumbens. Conceivably, such an effect could be accomplished through non-opioid (e.g., GABA) mechanisms. Clearly, further investigations are required before any

definite conclusions can be made with respect to opioid receptor interactions in the modulation of DA activity and the resulting behavioural and/or motivational alterations.

Intracranial Self-stimulation

Intracranial self-stimulation (ICSS) was initially attributed to the activation of central NE systems and this hypothesis was supported in part, by the observation that pharmacological interventions presumed to influence NE activity (i.e., reserpine, α -mPT, disulfiram) were also reported to disrupt ICSS (see Koob, 1989 for review). However, the identification of central DA systems (i.e., mesolimbic/mesocortical, nigrostriatal) (Ungerstedt, 1971) and the demonstration that ICSS could be elicited from many DA rich brain regions which were devoid of NE, prompted a revision of the original NE theory of reward processing (Ott et al., 1980). The importance of DA in brain stimulation reward is now well recognized and responding can be elicited from regions which comprise the mesocortical (frontal cortex) and mesolimbic (nucleus accumbens, septum, amygdala) DA systems, as well as the point of origin of these pathways, the A10 region. It should also be considered that ICSS can be elicited from the nigrostriatal system which originates in the substantia nigra (SN) and innervates the caudate and putamen. The fibre tracts of the mesocortical/mesolimbic and nigrostriatal systems ascend the lateral hypothalamic area, in the region of the medial forebrain bundle (Schaefer, 1988). Finally, the tuberoinfundibular/ tuberhypophyseal system(s) which originate in the arcuate and periarculate nuclei of the hypothalamus (A12 area) terminate in the median eminence, infundibular stalk as well as the neural and intermediate lobes of the pituitary (Fuxe et

al., 1985). However, the contribution of this/these pathway(s) to central reward processing remain(s) to be determined.

While ICSS can be readily elicited and supported from specific regions which comprise the mesocorticolimbic and nigrostriatal DA systems, it appears that these reward systems are fundamentally different from one another. The mesolimbic and mesocortical systems appear to be associated with mood/motivational aspects of reward whereas the nigrostriatal system is associated with motoric/behavioural activation (Phillips, Pfaus & Blaha, 1991). Such an hypothesis is supported by investigations in which selective lesions of the VTA or the substantia nigra produce fundamentally different behavioural effects. While nigrostriatal (e.g., SN) damage will disrupt ICSS, the basis of such a disturbance can be linked to the induction of motoric impairments (Fibiger, 1978) while lesions of the mesolimbic or mesocortical systems result in motivational disturbances devoid of the profound motoric alterations (Phillips, LePiane & Fibiger, 1983). In contrast, the tuberoinfundibular and tuberhypophyseal DA systems are less well characterized but appear to be involved in the regulation of hormonal release (Moore & Wuerthele, 1979). Such DA mediated hormonal regulation may well influence motivational state.

Nakahara, Fuchikami, Ozaki, Iwasaki and Nagatsu (1992) recently demonstrated that the mesocortical and mesolimbic DA systems are activated by ICSS as revealed by in vivo microdialysis. In particular, extracellular DA release and levels of DOPAC and HVA were increased within the medial frontal cortex and nucleus accumbens following ICSS from the medial forebrain bundle. However, no changes in levels of DA or its metabolites were observed in the striatum. Similarly, Phillips, Jakobovic and Fibiger (1987) reported that ICSS from the VTA was

associated with increased DA metabolism within the frontal cortex, nucleus accumbens and to a lesser extent in the striatum. As such, it would appear that activation of the mesocorticolimbic system is associated with the promotion of DA turnover in terminal sites and the induction of behaviour patterns consistent with reward (e.g., ICSS, place preference, drug self-administration, consummatory behaviour). Conversely, destruction of the A10 region and depletion of DA in particular, produce a profound anhedonia or the abolition of motivated behaviour as expressed in the abovementioned paradigms.

In recent years the evidence that DA activity is singularly instrumental in promoting brain stimulation reward has been challenged. It will be recalled that endogenous neuropeptides appear to modulate DA activity (see previous section) and that the DA containing brain regions which support ICSS (i.e., VTA, nucleus accumbens, frontal cortex) contain moderate to high levels of opioid binding sites (see Mansour et al., 1988 for review). Furthermore, self-stimulation performance may be altered through pharmacological manipulations which alter opioid and/or DA activity (see Schaefer, 1988 for review). For example, both DA (i.e., d-amphetamine sulphate), as well as μ and δ opioid receptor agonists (e.g., morphine, D-Pen²-D-Pen⁵-enkephalin, DPDPE) administered either systemically or intracranially have been shown to increase ICSS (Jenck, Gratton & Wise, 1987; Heidbreder, Gewiss, Lallemand, Roques & Dewitte, 1992). Furthermore, these facilitatory effects are reversed with DA or opioid antagonists (i.e., haloperidol or naloxone respectively) (see Schaefer, 1988 for review). Indeed, these observations are consistent with the data derived from other paradigms presumed to measure motivational state. Rats and mice will self-administer psychostimulants (e.g., cocaine or

d-amphetamine sulphate) (Roberts, 1992; Carney, Landrum, Cheng & Seale, 1991) as well as opiates (e.g. morphine or heroin) directly into the VTA and such effects are disrupted following the administration of opiate or DA antagonists (see Wise & Hoffman, 1992 for review). Similarly, conditioned place preferences may be established following systemic or central administration of opioids (e.g., DALA, morphine) or psychostimulants (e.g., d-amphetamine, cocaine); effects which are also blocked by the administration of agents which block DA or opiate receptor activity (see Hoffman, 1989 for review). These findings parallel the neurochemical investigations which report that administration of opioid agonists such as DALA, DPLPE or morphine into the VTA are associated with the accumulation of DOPAC and HVA within the frontal cortex (Latimer et al., 1987) and nucleus accumbens (e.g., Kalivas et al., 1983) and these increases in DA activity may be blocked by the systemic administration of DA or opiate antagonists as well as lesions of the ascending DA pathways (Hoffman, 1989).

While the activation of μ and δ receptors in the VTA promote the expression of behaviours presumed to provide an indication of reward, the behavioural profile for κ agonists are demonstrably different. At least two theories of κ receptor activation have emerged leading to fundamentally different versions of the functional consequences of such stimulation. In particular, Jenck et al. (1987) have argued that two forms of reward can be elicited from or modified by the VTA. In addition to ICSS, Jenck et al. (1987) demonstrated that consummatory behaviour typically induced by lateral hypothalamic stimulation (stimulus bound behaviour) could be modified by opioid activation of the A10 region. The former behaviour appeared to be independent of κ receptor activation (e.g., failure to alter

threshold) while stimulus bound consummatory behaviour increased following administration of the selective κ agonist, U50,488 into the VTA. In addition, Mucha and Herz (1985) and Bals-Kubik, Herz and Shippenberg (1989) demonstrated that low doses of U50,488 elicited conditioned place aversion rather than preference. Interestingly, it has been suggested that the aversive properties of κ agonists follow from a κ mediated inhibition of μ receptor activity (Bals-Kubik et al., 1989) rather than aversive effects of κ receptor activation per se (Millan, 1990). Finally, unlike μ or δ agonists, rats or mice will not self-administer κ agonists (e.g., Tang & Collins, 1985). Taken together, these investigations suggest that consummatory behaviour, place preference, ICSS and self-administration may represent fundamentally different versions of motivational state, leading to unique functional outcomes following κ receptor activation.

The variable behavioural consequences in the reward paradigms described above following μ , δ or κ receptor activation may be explained at least in part, by their differential effects upon endogenous DA systems. While intracerebral activation of μ or δ receptors are typically associated with increased DA activity (see previous section), such neurochemical alteration does not invariably appear across all brain sites within the mesocorticolimbic system. Although the influence of κ activation on central DA activity is less well characterized than that of either the μ or δ receptors, fundamental differences can be cited. For example, Manzanares et al. (1991) reported that following activation (i.e., haloperidol) of the nigrostriatal, mesolimbic, tuberohypophyseal, or tuberoinfundibular (i.e., prolactin) systems, systemically administered U50,488 reduced DA turnover in the nucleus accumbens, striatum, median eminence as well as the neural and intermediate lobes of the pituitary. However, in the absence

of prior activation, κ induced reductions in DA turnover were only evident in the tuberohypophyseal system (i.e, neural and intermediate lobes of the pituitary). Similarly, Di Chiara and Imperato (1988) reported that κ receptor activation was associated with reduced DA turnover in the dorsal caudate and nucleus accumbens as measured by in vivo microdialysis in freely moving rats. While locomotor activity *per se* may be effective in activating the nigrostriatal and mesolimbic systems, prior activation of central DA systems was not considered as a necessary prerequisite to the κ receptor modulation of DA activity. In summary, it appears that when activated, κ receptors may induce a decrease in central DA activity whereas μ and δ receptors appear to increase DA turnover. Furthermore, these investigations suggest that the effects of κ receptors (like those of μ and δ) on DA activity may be variable across brain regions. Such differential neurochemical profiles which follow from the activation of specific opioid receptor subtypes may be important in determining behavioural output. Finally, it should be emphasized at this juncture that opioid receptor stimulation may follow from the exogenous administration of opioid agonists or from the stressor induced release of endogenous neuropeptides.

Following exposure to uncontrollable stressors, rats and mice typically exhibit pronounced reductions in responding (or increased thresholds) for ICSS from brain regions which comprise the mesocortical /mesolimbic DA systems which are associated with reward processes. Since the rewarding value of the stimulation is reliably diminished following stressor exposure and this anhedonia is reminiscent of that prevalent in human depressives, this paradigm has been employed by several investigators as an animal model of depression (e.g., Danysz, Fowler, & Archer, 1985; Kamata, Yoshida & Kameyama, 1986; Valentino,

Dufresne & Riccitelli, 1990; McCutcheon, Rosselini & Bandell, 1991) Furthermore, these deficits in reward/motivational state may be prevented or reversed following chronic administration of clinically effective antidepressants including desmethylinipramine (DMI) (Zacharko, Bowers, Kelley & Anisman, 1984). However, there is evidence to suggest that controllability over the stressor rather than the physical impact of the aversive stimulus leads to disruptions in reward processes. For example, McCutcheon et al. (1991) reported that rats exposed to uncontrollable footshock of moderate severity exhibited increased thresholds in responding for ICSS from the posterior lateral hypothalamus 24 and 48 hours following stressor exposure while the current intensity functions of yoked animals remained unaltered. Similarly, exposure to uncontrollable but not controllable stressors are effective in reducing self-stimulation performance from the medial forebrain bundle and the nucleus accumbens in the CD-1 mouse strain (Zacharko, Bowers, Kokkinidis & Anisman, 1983). The performance alterations were marked and lasted for relatively protracted intervals as revealed by depressed rates of responding one week following initial stressor exposure. Interestingly, the appearance of the reward alterations were dependent upon the imposition of an immediate self-stimulation test following exposure to the aversive stimulation. In the absence of an immediate self-stimulation test, deficits in ICSS failed to appear from either the medial forebrain bundle or the nucleus accumbens. Such an effect may be attributed to conditioning or the imposition of stressor provoked neurochemical changes on self-stimulation performance. Conversely, neither uncontrollable nor controllable stressors were effective in influencing ICSS from the nigrostriatal system and the substantia nigra in particular. Subsequent investigations also revealed that aversive

stimulation failed to alter current intensity functions from the substantia nigra across a range of brain stimulation intensities. In contrast, uncontrollable footshock reduced responding for brain stimulation from the nucleus accumbens at the upper end of the current intensity range (Bowers, Zacharko & Anisman, 1987), while failing to alter performance at any of the other stimulation parameters.

Consistent with the effects of uncontrollable stressors on ICSS from the nucleus accumbens and the medial forebrain bundle, footshock also elicited reductions in responding for ICSS from the medial prefrontal cortex. However, it appeared that the duration of such deficits may be dependent at least in part upon the electrode placement within this brain region (i.e., medial or dorsal) since performance alterations were transient in some animals and relatively protracted in others (Wolfe & Zacharko, 1990). There is evidence to suggest that the electrophysiological response of neurons in the medial prefrontal cortex may be differentially activated following stressor exposure. For example, Mantz et al. (1989) reported that tail pinch stress provoked increases in unit activity of specific neurons within the medial prefrontal cortex while inhibiting the activity of others. Furthermore, these effects were specific to tail pinch since other forms of sensory stimulation failed to alter unit activity in the cortex. However, it is conceivable that such regional variability in the activation of the medial prefrontal cortex is due to the cortical innervation pattern provided by specific segments of the A10 area (Swanson, 1982; Oades & Halliday, 1987) which are activated upon exposure to an uncontrollable stressor (Bannon et al., 1983; Bowers, Bannon & Hoffman, 1987). Indeed, such regional specificity to the effects of stressor presentation has also been verified in the VTA (see ensuing section).

Finally, data collected in this laboratory revealed that uncontrollable footshock also reduced responding for ICSS from the A10 region. These performance alterations were apparent one week following stressor presentation and were typically of greater magnitude than those reported from the nucleus accumbens or the medial prefrontal cortex. Moreover, the induction of motivational alterations from the point of origin of the mesolimbic/mesocortical system demonstrated that the effects of stressors were not simply related to a cell body versus terminal region differentiation. In addition, as previously reported from the nucleus accumbens, deficits in ICSS were apparent in both rate dependent and current intensity paradigms. Finally, it should also be emphasized that the deficits in self stimulation performance from the VTA were region specific and reductions in responding for ICSS were only apparent when stimulating electrodes were positioned within the dorsal aspects of the VTA. Electrode placements in the ventral portion of the A10 region were not associated with performance alterations in either rate dependent or rate independent paradigms (Zacharko, Kasian, MacNeil & Anisman, 1990). Such an effect may be due in part, to the presumed neurochemical heterogeneity within the A10 region (e.g., Deutch et al., 1985; Kalivas et al., 1988; Kelley & Cadore, 1988) and the differential sensitivity of select sub-regions within the VTA to stressor exposure (Deutch et al., 1985; Kalivas & Abhold, 1987; Zacharko et al., 1990).

Taken together, it appears that DA, opioids and DA-opioid interactions influence reward systems. Likewise, exposure to uncontrollable stressors have been shown to disrupt reward/motivational processes and are associated with alterations of central DA and/or opioid activity. To date, relatively few investigations have been employed in

describing the effects of stressors on motivational state, particularly with respect to ICSS and the role of endogenous opioids. However, Kamata et al. (1986) reported that stressor induced reductions in responding for electrical brain stimulation from the VTA were antagonized by pretreatment with naloxone. In contrast, naloxone administration to non-stressed rats was without effect. In addition, met-amphetamine at a dose which did not alter the ICSS response, antagonized the stressor induced reductions in responding for ICSS.

In a recent investigation, Maddeaux and Zacharko (1992) examined the effects of the μ and δ agonist, D-Ala²-Met⁵-enkephalinamide (DALA) upon the stressor induced reductions in responding for ICSS from the VTA in the CD-1 mouse strain. It will be recalled that footshock of moderate severity typically induces pronounced and relatively protracted reductions (i.e., evident one week following stressor presentation) in responding for ICSS from the dorsal A10 region. However, when DALA was administered intraventricularly 15 minutes following exposure to uncontrollable footshock, the deficits in self-stimulation performance were attenuated in the immediate post stressor interval but this therapeutic effect did not persist 24 or 168 hours following initial stressor presentation. In contrast, the administration of DALA prior to the stressor effected only a partial antagonism of the deficits in ICSS immediately and 24 hours following uncontrollable footshock but were completely antagonized one week following stressor presentation relative to saline treated animals.

Although the precise relationship between stressor exposure, the DA-opioid interface and reward processing remains to be elucidated, it is clear that activation of μ and/or δ receptors, like uncontrollable stressors is associated with increased DA turnover within mesocorticolimbic brain

regions. It is also conceivable that eventual DA depletion may occur owing to the sustained increase of DA turnover promoted by stressor induced release of endogenous opioids. Such neurochemical alteration may come to disrupt ICSS performance. Such an hypothesis would be consistent with the reports of Kamata et al. (1986) in which manipulations that blocked endogenous opioid activity or increased DA levels were effective in masking stressor induced impairments of ICSS.

It is conceivable that DALA administered 15 minutes following stressor exposure in the investigation of Maddeaux and Zacharko (1992) produced a transient increase of DA activity which prevented detection of a deficit in ICSS in the immediate post-stressor interval. In effect, post-stressor opioid administration may activate the organism and mask expression of behavioural pathology. Intuitively, it is appealing to consider that enkephalin release within the VTA following stressor exposure may activate DA neuronal activity to protect the organism by blunting the impact of the stressor rather than to envision that opioid release and the resulting depletion is responsible for producing behavioural pathology. However, with a protracted stressor, extracellular enkephalin availability is reduced, DA levels are depleted owing to excessive activation and pathology ensues. Indeed, Kalivas and Abhold (1987) reported a time dependent decrease in the concentration of immunoreactive Met-enkephalin within the medial portion of the VTA following uncontrollable footshock in rats and enhanced DA metabolism in the medial prefrontal cortex and nucleus accumbens. Naltrexone pretreatment into the VTA was effective in attenuating such stressor induced increases in DA metabolism in terminal sites. Clearly, in order to fully understand the relationship between stressor

exposure, DA, opioids and reward/motivational processes, further investigations are required to address these issues.

The present experiments investigated the influence of central κ receptor activation to the induction of behavioural change in animals exposed to uncontrollable footshock. In particular, Experiment 1 evaluated the effects of central κ receptor activation upon exploratory behaviour as revealed by measures of locomotor activity and rearing in an open arena and head dipping in the absence of electrical brain stimulation. Experiment 2 considered the effects of U50,488 on stressor provoked motivational disturbances as revealed by ICSS from the A10 area. It remains to be determined empirically whether the consequences of κ receptor activation in the brain stimulation paradigm will produce behavioural alterations congruent with effects observed in paradigms which are independent of brain stimulation. These data, in combination with experiments currently underway in this laboratory may provide a delineation of the functional significance of specific opioid receptor subtypes to the induction of behavioural change under stressful and non stressful conditions. In addition, such findings may be fundamental in addressing issues pertinent to the etiology and pharmacological treatment of depression.

EXPERIMENT 1

As described in preceding sections, activation of the mesocorticolimbic DA system has been associated with alterations in general levels of activity as well as motivational processes. In addition, it appears as though specific neuropeptides within the VTA may play a role in the modulation of DA transmission to effect such behavioural change. Generally, μ or δ receptor activation within the A10 region is associated

with increased DA turnover in the midbrain as well as terminal sites. In addition, such manipulations are associated with behavioural activating effects (i.e., locomotor activation, rearing, head-dipping), although the μ receptor may be more potent in this respect (Latimer et al., 1987). However, there have been at least two reports which suggest that the δ receptor is associated with behavioural depression rather than stimulation (i.e., Ukai et al., 1989; Heidbreder et al., 1992). Such inconsistencies may be attributable in part, to the differential selectivities or potencies of the specific agonists employed.

In contrast to μ and δ receptors, κ receptor activation has been consistently associated with locomotor suppression (VonVoigtlander, Lahti & Ludens, 1982; Ukai & Kameyama, 1985; Jackson & Cooper, 1988) as well as reductions in DA turnover within the mesolimbic, nigrostriatal, and tuberoinfundibular systems although it appears that these systems must be activated before κ agonists exert an effect (Manzanares et al., 1991). Such differential neurochemical and behavioural consequences following from μ or δ versus κ receptor activation have been observed in a number of behavioural paradigms (See previous sections). However, due to the relatively recent development of a selective κ agonist (i.e., VonVoigtlander et al., 1982), little information has been gathered with respect to the functional consequences of κ receptor activation in the mouse, particularly in conjunction with uncontrollable stressor exposure. Experiment 1 will assess the effects of κ receptor activation upon locomotor activity, rearing and head-dipping in mice in which the mesocorticolimbic DA system has been activated by prior exposure to an uncontrollable stressor.

METHODS

Subjects: Sixty, naive, male, CD-1 mice obtained at 5 weeks of age from Charles River Laboratories (St. Constant, Quebec) were used as subjects in Experiment 1. All animals were housed in groups of 4 in polypropylene cages and allowed access to food and water ad libitum.

Surgery: Following acclimatization to the laboratory, all subjects were anesthetized intraperitoneally with sodium pentobarbital (Somnotol, 65 mg/kg) and stereotactically implanted with a guide cannula in the lateral ventricle (A.P. +0.8 mm from Bregma, L.+0.7 mm from sagittal suture and V. -2.7 mm from a flat skull surface). The guide cannulas were constructed from 23 gauge hypodermic needles cut to a length of 1.1 cm and fitted with stylettes protruding 0.5 mm beyond the guide cannula tip. Following surgery, mice were individually housed and maintained on warm heating pads for at least three days.

Procedure: Following a ten day post-operative recovery period, baseline measures of locomotor activity, rearing and head-dipping were established for all mice over a three day period. For each of these baseline days as well as the subsequent test days, all animals were handled in a manner consistent with that necessary for the intraventricular injection. Each of the behaviours were measured every three minutes over three consecutive 15 minute intervals. Locomotor activity, rearing and head-dipping were measured in black aluminum activity tubs (28 cm diameter x 32.5 cm high) (Carleton University Technology Centre). Locomotor activity was monitored by photobeams mounted 0.5 cm above the tub floor. In addition, rearing was recorded by a separate set of photobeams arranged 7 cm above the floor of the apparatus. Finally, exploratory hole board head dipping

was also assessed. The number of head-dips into one of two wells (2 cm diameter) positioned on the tub floor was determined by the interruption of a photoelectric beam positioned 0.5 cm below the floor. All three behaviours were recorded on a Macintosh computer employing a Tub Monitor programme (Schnabel Electronics, Saskatoon, Saskatchewan). Following this interval, animals were assigned to either Shock or No Shock groups matched on the basis of the abovementioned behavioural test levels ($n=30/\text{group}$).

Uncontrollable footshock was delivered in black Plexiglas boxes (30 x 40 x 15 cm). The floor of each box consisted of 0.32 cm rods spaced 1 cm apart. Footshock (150 μA , 60 x 6s) was delivered through a microcomputer controlled 3000 Volt source (Carleton University Technology Centre). Mice assigned to the No Shock control group were exposed to the shock apparatus for a comparable period of time but shock was withheld. Immediately following the stressor treatment, subjects from the Shock and No Shock conditions were further subdivided into five groups ($n=6/\text{group}$) to receive either 0.0 μg , 0.01 μg , 1.0 μg , 5.0 μg or 10.0 μg of U50,488 (Research Biochemicals Inc., MA) delivered in a 1 μl volume of sterile distilled water. Drug administration was accomplished by employing a Hamilton 1 μl syringe connected to a 30 gauge injector via polyethylene tubing. The positioned injector protruded 0.5 mm beyond the tip of the guide cannula. The κ agonist U50,488 was delivered over a one minute period and the injector left in place for an additional minute to allow for diffusion of the drug. Once intraventricular administration was complete, the stylette was replaced and all animals were placed in the activity tubs. Behavioural recording was initiated two minutes following completion of drug administration. Behavioural scoring was recorded

automatically every 3 minutes for 3 consecutive 15 minute trials 0, 24, and 168 hours following initial exposure to uncontrollable footshock.

Histology: At the end of Experiment 1, all animals were sacrificed with an overdose of sodium pentobarbital and perfused intracardially with physiological saline followed by a 10% formalin solution. Brains were then excised and soaked in 10% formalin for at least 2 days prior to sectioning. Frozen coronal sections (40 μ m) were cut using a sliding microtome and stained with cresyl violet. The brain sections were subsequently examined under a microscope for verification of the cannula placements.

Data Analysis

The data gathered for locomotor activity, rearing and exploratory head-dipping were analyzed using an analysis of variance for repeated measures followed by an analysis of the simple main effects with BMDP-4V. Newman-Keuls multiple comparisons ($\alpha=.05$) were employed where appropriate.

RESULTS

Cannula placements for all animals included in Experiment 1 were histologically verified. Acceptable lateral ventricle cannula placements were consistent with those of previous investigations in this laboratory (see Wolfe, 1990). In any instance where there was evidence of considerable necrosis or tissue distortion around the cannula, the data for that animal were excluded from the statistical analyses.

Locomotor Activity

The analysis of variance conducted to examine the differences in the levels of activity for each dose of U50,488 across the various post stressor

intervals in the Shock and No Shock conditions revealed a significant Time x Shock ($F_{14,700} = 3.27$, $p < .05$), Day x Shock ($F_{3,150} = 6.65$, $p < .05$), a Day x Drug ($F_{12,150} = 1.80$, $p = .052$) and a Day x Shock x Drug interaction ($F_{12,150} = 1.79$, $p = .054$) (Table 1, Appendix A). Since no higher order interactions involving the Time variable within each of the 45 minute test sessions were found to be statistically significant, all figures used to depict the differences between each drug level with respect to stressor exposure were collapsed over Time (i.e., even though all data were collected every 3 minutes for each 45 minute test interval).

Figures 1a-1e depict the levels of locomotor activity accumulated over 45 minutes for stressed and non-stressed animals treated

 Insert Figures 1a-1e about here

Figures 1a-1e. Mean levels of locomotor activity ($\pm$ S.E.M.) for CD-1 mice exposed to uncontrollable footshock or no shock followed by 0 ug, .01 ug, 1.0 ug, 5.0 ug or 10.0 ug of U50,488 administered intraventricularly (n=6/group). Activity levels were monitored over 45 minute intervals for baseline measures as well as immediately, 24 hr and 168hr following initial stressor application.

intraventricularly with vehicle, 0.01 ug, 1.0 ug, 5.0 ug or 10.0 ug of U50,488 respectively. Subsequent Newman-Keuls multiple comparisons ($\alpha = .05$) of the simple main effects associated with the higher order interaction revealed that activity scores for mice exposed to either uncontrollable footshock or no shock conditions were comparable to one another prior to intraventricular drug treatment. Significant reductions in activity among vehicle treated mice exposed to uncontrollable footshock were not evident in the interval immediately following stressor application (Figure 1a) and at the 24- and 168-hr test intervals activity levels were significantly increased relative to No drug-No shock mice. Uncontrollably stressed mice which received intraventricular administration of .01 ug U50,488, exhibited reduced levels of activity relative to the respective no shock drug treated condition immediately but increased levels of activity at the 168 hr interval (Figure 1b). Non-stressed mice treated intraventricularly with 0.01 or 1 ug U50,488 exhibited behavioural profiles comparable to that of vehicle non-stressed mice immediately, 24-hr and 168-hr following administration of the κ agonist. However, when animals were administered 1 ug of U50,488, the behavioural profiles were comparable regardless of whether mice were previously exposed to uncontrollable footshock or no shock conditions (Figure 1c). In contrast, non-stressed mice challenged with 5 ug U50,488 exhibited increased levels of activity 24- and 168-hr following drug administration relative to non drug treated non-stressed animals, while non-stressed mice administered 10 ug of the κ agonist showed significant increases in activity scores only during the 168-hr test session. Intraventricular administration of either 5 ug or 10 ug U50,488 produced comparable behavioural profiles among

stressed animals (Figures 1d and 1e). Nevertheless, significant differences appeared relative to the drug treated non-stressed animals as a function of the interval following stressor application. In particular, 5 ug U50,488 provoked an increase in activity among non-shocked mice at the 24 hr test session while significant differences failed to appear in either the immediate or 168-hr post-stressor intervals relative to the respective drug treated shocked animals. In contrast, 10 ug of U50,488 combined with footshock provoked reductions in the levels of activity immediately but failed to discriminate between stressed and non-stressed mice 24-hr and 168-hr following stressor application and prevented the rebound increase in activity scores evident in the Vehicle-Shock and 5 ug-No Shock groups 24 hr post-stressor. The higher doses of U50,488 (i.e., 5 and 10 ug) failed to discriminate between stressed and non-stressed animals 1 week following initial stressor application.

Rearing

The analysis of variance for the rearing scores over each drug dose employed within the Shock or No Shock conditions revealed a significant Day x Shock ($F_{3,150}=6.43$, $p<.05$), Day x Drug ($F_{12,150}=2.91$, $p<.05$) Day x Shock x Drug ($F_{12,150}=2.19$, $p<.05$) as well as a Time x Shock ($F_{14,700}=4.41$, $p<.05$) and a Day x Time x Shock x Drug interaction ($F_{168,2100}=1.24$, $p<.05$) (Table 2, Appendix A).

Figures 2a-2e depict rearing scores assessed over 45 minute test intervals for stressed and

 Insert Figures 2a-2e about here

Figures 2a-2e. Mean rates of rearing ($\pm$ S.E.M) for shocked and non shocked CD-1 mice treated intraventricularly with vehicle, .01 ug, 1.0 ug, 5.0 ug or 10.0 ug of U50,488 .espectively (n=6/group). The rates of rearing were monitored over 45 minute intervals for baseline as well as immediately, 24 hr and 168 hr following stressor exposure.

non-stressed mice intraventricularly administered either 0 ug, 0.01 ug, 1 ug, 5 ug or 10 ug of U50,488 following stressor application (n=6/group). Subsequent Newman-Keuls multiple comparisons ($\alpha=.05$) revealed that rearing scores were comparable for the respective experimental groups of mice prior to pharmacological or stressor intervention. Substantial reductions in the rates of rearing (i.e., approximately 70%) were apparent in the Vehicle-Shock condition in the immediate post-stressor interval although such behavioural impairments were no longer apparent within the 24- or 168-hour test intervals. In fact, rearing scores were significantly increased relative to the respective Vehicle-No Shock control group (Figure 2a).

Mice treated with either .01 ug or 1.0 ug of U50,488 in the absence of stressor exposure exhibited similar behavioural profiles. However, upon comparison with the Vehicle-No Shock condition, some differences were apparent. In particular, animals intraventricularly challenged with .01 ug of U50,488 exhibited marginal reductions in rearing scores immediately following drug administration, while significant reductions were observed at the 24-hr test interval relative to the Vehicle-No Shock control group (Figure 2b). In contrast, non-stressed animals administered 1.0 ug U50,488 displayed significant increases within the 168 hr test interval relative to the Vehicle-No Shock control group but no significant differences were detected immediately or 24-hr following uncontrollable footshock (Figure 2c).

Stressed and non-stressed animals challenged with 1.0 ug of U50,488 exhibited comparable behavioural profiles. With the exception of the immediate post-stressor interval this was also the case for the .01 ug

treatment condition where mice exposed to uncontrollable footshock and treated with the κ agonist exhibited reduced rearing scores relative to their respective No Shock treated counterparts. Despite such similarities between stressed animals treated with either .01 or 1.0 ug and U50,488 treated-No Shock treatment conditions, both doses of the κ agonist in combination with Shock were associated with reduced levels of rearing within the 168-hr post-stressor interval relative to vehicle treated stressed animals.

In contrast to the effects of either .01 or 1.0 ug of U50,488 administered in non-stressed mice, 5 ug of U50,488 produced no immediate alteration in rearing, but provoked a significant enhancement of these scores 24- and 168-hr following drug administration in comparison to the Vehicle-No Shock condition (Figure 2d). Although the behavioural profile associated with the administration of 10 ug of U50,488 in non-shocked animals resembled that of the 5 ug treatment group, significant increases in the rates of rearing were only apparent within the 168-hr post-stressor interval relative to the 0 ug No Shock group of subjects (Figure 2e).

When administered in conjunction with footshock, both the 5 and 10 ug doses of U50,488 effected comparable drug induced behavioural profiles but substantially different effects relative to their respective No Shock-U50,488 treated mice. In particular, mice administered 5 ug of U50,488 following uncontrollable footshock exhibited rates of rearing which were significantly lower than those displayed by the non-shocked mice treated with 5 ug U50,488 immediately as well as 24- and 168-hr following initial stressor exposure. Animals which received the 10 ug dose of the κ agonist following exposure to uncontrollable footshock exhibited significantly lower rates of rearing within the immediate and 168-hr

intervals but not at the 24-hr post-stressor test session in comparison with non-stressed mice administered the 10 ug dose of U50,488. In comparison with vehicle treated stressed animals, both 5 and 10 ug of the κ agonist administered intraventricularly following uncontrollable footshock were associated with reduced rates of rearing at the 24- and 168-hr post-stressor intervals. Finally, these higher drug doses prevented the rebound increases in rearing at the 24 and 168 hr intervals associated with both the vehicle /Shock and 5 ug/ No Shock treatment conditions.

Exploratory Head-Dipping

Inspection of the exploratory head-dipping data gathered every 3 minutes over 45 minute test sessions typically revealed very low operant rates over successive 3 minute intervals. As a result, the data analyses were conducted using the mean ($\pm$ S.E.M) number of head-dips for holes A and B collapsed over the 3 minute time intervals within each 45 minute test session. The analysis of variance for these data revealed a significant Day x Shock interaction ($F_{3, 132} = 2.81, p < .05$) (Table 3, Appendix A). Since no additional significant interactions were detected, these data were collapsed across the respective drug doses employed.

Figure 3 represents the total number of head-dips for shocked ($n = 26$) and non-shocked ($n = 28$) animals over each 45 minute test session.

Insert Figure 3 about here

Figure 3. Mean rates of exploratory head-dipping ($\pm$ S.E.M) for CD-1 mice exposed to uncontrollable footshock (n=26) or no shock (n=28). The rates of head-dipping were monitored over 45 minute intervals on baseline as well as immediately, 24 hr and 168 hr following stressor application.

Head-dipping rates for all mice were equated prior to experimental manipulation. However, in the interval immediately following stressor application, the rates of head-dipping for animals exposed to uncontrollable footshock were significantly lower than those displayed by non-shocked mice. At the 24- and 168-hr test sessions, such an effect was no longer evident and head dipping rates were comparable across the shocked and non-shocked groups of mice.

DISCUSSION

Consistent with the data of previous investigations, exposure to acute uncontrollable footshock failed to alter locomotor activity in the immediate post-stressor interval (Zacharko, Bowers, Kokkinidis and Anisman, 1983). Moreover, Anisman, Kokkinidis and Sklar (1981) have previously reported that variations in activity attributable to stressor presentation are ordinarily confined to the period during which the stressor is actually applied. Nevertheless, the data of the present investigation revealed that encounter with uncontrollable footshock produced an impairment in rearing scores. These data suggest that rearing may be fundamentally more sensitive than motor activity to the influence of stressor exposure. Such a conclusion is an interesting one, especially when it is considered that rearing has also been shown to be more sensitive to pharmacological challenge of central catecholamine and/or opioid systems (e.g., Ukai & Kameyama, 1985; Michael-Titus, Dourmap & Costentin, 1989). It is conceivable that the neurochemical basis of the stressor induced differentiation between locomotor activity and rearing may likewise be attributable to such variations, particularly when it is considered that NE, DA and the opioids have been implicated in subserving some aspects of behavioural pathology

following stressor presentation (see Anisman, Zalcman & Zacharko, 1993 for review).

It should be underscored that although rearing and activity were differentially affected by uncontrollable footshock within the immediate post-stressor interval, evidence of similarities between these behaviours emerged upon subsequent testing (i.e., 24- and 168-hr post-stressor). Interestingly, rearing and locomotor activity were observed to increase (approximately 50% and 40% respectively) above that displayed by non shocked animals. Although it is conceivable that the increases in rearing may follow from the initial stressor induced behavioural suppression (i.e., a compensatory response perhaps serving to increase vigilance/arousal and thereby protect the organism from further environmental insults), such a proposal would clearly be inadequate in accounting for the augmented levels of activity. To be sure, uncontrollable footshock failed to affect locomotor activity in the immediate post-stressor period. Accordingly, it should be considered that a stressor may, in some instances, exert long-term behavioural alterations owing to its immediate consequences while in other cases long-term variations may be revealed in the absence of immediate effects. Moreover, it should be recalled that the neurochemical substrates subserving activity and rearing may be affected differentially by stressor experience and the precise behavioural profile observed may be determined, in part, by the sensitivity of such neurochemical systems.

In contrast to previous investigations which reported an immediate suppression of activity and rearing following κ receptor activation (VonVoigtlander et al., 1983; Ukai & Kameyama, 1985; Di Chiara & Imperato, 1988), the data of Experiment 1 revealed that U50,488 administered intraventricularly failed to alter either of these behaviours in

the immediate post-injection interval. Several factors may have contributed to these discrepant data. In particular, the notion that κ receptor activation is ordinarily associated with behavioural suppression is derived largely from investigations involving systemic routes of drug administration (e.g., VonVoigtlander et al., 1983; Di Chiara & Imperato, 1988). Systemic drug treatment, however, largely precludes accessibility of neuropeptides to central sites. Accordingly, such drug induced behavioural suppression is likely to result from the activation of peripheral rather than central opioid systems. In addition, there is reason to suspect that inter-species variation may also contribute to the detection of variable behavioural results following U50,488 administration. In particular, most investigations involving U50,488 have employed rats, rather than mice. Moreover, it is well documented that the density as well as the distribution of central κ receptors are not only highly variable between rats and mice but there is considerable species dependent inter- and intra-regional variability (Mansour et al., 1988; Lutz & Pfister, 1992). Finally, there is evidence to suggest that the propensity of U50,488 to influence central neurochemical change, including neurochemical variations associated with the suppression of locomotor activity (i.e., reduced DA turnover), is dependent upon prior activation of the mesolimbic, nigrostriatal and tuberoinfundibular systems (Manzanares et al., 1991). The activation of these major DA containing systems may be readily accomplished following stressor exposure (Herve et al., 1979; Dunn & File, 1983; Heyes et al., 1988), pharmacological challenge (Manzanares et al., 1991; Leyton, Rajabi & Stewart, 1992), or electrical brain stimulation (Nakahara et al., 1992).

It should be considered that all mice were handled during the period of intraventricular U50,488 challenge. Some investigators have noted that

apparently innocuous manipulations, including handling, may in fact provoke stressor-like effects and induce sensitization (Robinson, 1988). It is interesting that the "stressful" nature of the injection/handling procedure apparently failed to influence responsivity to U50,488 immediately following intraventricular administration regardless of the dose of the κ agonist employed. Either the nature of the stimulus precluded activation of the relevant DA systems or the intensity/duration of such handling was inadequate in provoking neurochemical change conducive to the expression of altered behavioural output. Alternatively, it is conceivable that adaptation to the effects of handling was already accomplished at this juncture. All mice were routinely handled for a period of at least 2 minutes over 3 baseline days. The notion of within session adaptation to the neurochemical effects of a stressor is not a novel one. Such alterations were originally demonstrated by Kvetnansky et al. (1976) with respect to the NE system following immobilization stress and subsequently extended to that of DA by Roth, Tam, Ida, Yang and Deutch (1988). In fact, casual observation revealed that intraventricular drug administration was readily accomplished in mice in the absence of significant restraint. Although speculative, such an hypothesis appears deserving of some consideration.

The data of Experiment 1 suggest that the differential effects on rearing and activity induced by κ receptor activation are dose and time dependent. It should be considered that since U50,488 was administered intraventricularly, behavioural change might be expected immediately following drug administration. The absence of such alterations in either locomotor activity or rearing and the detection of pronounced behavioural alteration on subsequent non drug test days would suggest that κ receptor activation is not directly involved in the modulation of either of these

behaviours. Nevertheless, it would appear that κ receptor activation induces a delayed behavioural response which is initially expressed as a reduction in rearing within 24 hours following drug infusion. Such drug induced suppression of rearing by low dose U50,488 administration (i.e., .01 ug) is replaced by behavioural facilitation following administration of a moderate dose of the κ agonist (i.e., 1.0 ug). Not only was the direction of behavioural change affected by increasing the dose of U50,488 in CD-1 mice, but the time course of such behavioural alteration was also altered (decrease within 24 hours of facilitation at 1 week). Interestingly, the alterations in rearing occurred in the absence of any demonstrable effects on locomotor activity at comparable doses of the κ agonist. At first glance, these data suggest that rearing and locomotor activity are subserved by fundamentally distinct neurochemical mechanisms. While such a proposition is conceivable, there is more convincing data to suggest that rearing and activity are differentially sensitive to κ receptor activation at low doses of U50,488.

In contrast to the dissociated behavioural profiles accompanying low doses of the κ agonist, higher doses provoked behavioural excitation of comparable magnitude for both activity and rearing. In both cases, onset of the drug induced behavioural activation was delayed, occurring either 24 hours or one week (i.e., 5 ug cf. 10 ug respectively) following initial drug administration. These data suggest that elevated doses of U50,488 activate a neurochemical system common to both locomotor activity and rearing. Indeed, it has been suggested that while U50,488 is a relatively selective κ agonist (VonVoigtlander et al., 1983), this peptide appears to possess some affinity for the μ receptor (Lahti et al., 1982). Accordingly, it is conceivable that high doses of U50,488 effectively saturate κ receptors,

permitting central μ receptor activation. It will be recalled that pharmacological challenge of the μ receptor site is ordinarily associated with behavioural activation, effects which are consistent with the demonstration of augmented rearing and activity in Experiment 1. Taken together, low doses of U50,488 exerted behavioural effects consistent with κ receptor activation and influenced rearing preferentially. At higher doses of the agonist, stimulation of the μ receptor may have predominated resulting in a behavioural excitation which influenced rearing and activity to a similar extent. The behavioural outcome of elevated U50,488 administration would be to mask or reverse the behavioural effects ordinarily associated with low dose U50,488 administration.

It will be recalled that a number of investigators have reported that κ receptor activation is ordinarily without effect on central DA turnover. Among animals in which the mesolimbic, nigrostriatal or the tuberoinfundibular systems have been challenged, κ agonists will reduce central DA turnover (Manzanares et al., 1991; Leyton et al., 1992). Furthermore, such alterations of central DA activity have been associated with behavioural change (VonVoigtlander et al., 1983; Di Chiara & Imperato, 1988). Such an hypothesis may be useful in accounting for the absence of immediate alterations in rearing or activity following intraventricular administration of U50,488. It will be recalled, however, that handling may act as a mild stressor (File, 1985) and such a stimulus may serve to activate the major ascending DA pathways. Although there appeared to be no immediate consequences of handling (but note previous caveats) such a stimulus may be adequate in sensitizing the organism to subsequent stressful experiences (i.e., handling re-exposure) or pharmacological challenge. Likewise, the long-term behavioural effects of

such treatment (i.e., sensitization) would vary with the magnitude of the neurochemical change initially associated with environmental challenge. Although the data gathered in the present investigation neither confirm or refute such a suggestion, the possibility that handling and/or κ receptor activation sensitizes the animal to subsequent encounters with a stressor or the cues previously associated with the stressor cannot be ignored.

A number of investigators have reported that dynorphin A, the endogenous ligand for the κ receptor, is involved in modulating stressor induced behavioural and neurochemical change (Fallon & Ciofi, 1990). In this respect, there is considerable evidence to suggest that dynorphin levels are altered in the mesocortex, hypothalamus, anterior pituitary as well as the spinal cord following stressor exposure (Millan, Tsang, Przewkocki, Holtt & Herz, 1981; Morley Elson, Levine & Schafer, 1982 Smith & Lee, 1988). Furthermore, Katoh, Nabeshima & Kameyama (1990) reported that intraventricular (dynorphin A₁₋₁₇) or systemic (E 2078) administration of κ agonists potentiated stressor induced behavioural change in the forced swim and conditioned suppression of motility paradigms at drug doses which ordinarily failed to provoke behavioural alterations. In contrast to κ receptor activation, μ and δ receptor agonists have been associated with an amelioration of stressor induced behavioural pathology (i.e., Katoh et al., 1990; Maddeaux & Zacharko, 1992). In addition, there is considerable evidence to suggest that the neurochemical and behavioural consequences of μ and κ receptor activation are mutually antagonistic. However such neurochemical antagonism is one of neuromodulation (Spanagel et al., 1992; Katoh et al., 1990; Dosaka-Akita, Tortella, Holaday & Long, 1993). For example, while dynorphin A₁₋₁₇ administered centrally fails to produce analgesia, it decreases the potency of morphine-induced analgesia

in naive animals while potentiating analgesia in morphine tolerant animals. Similarly, dynorphin fails to influence respiration but enhances morphine-induced respiratory depression in naive animals while reversing this effect in morphine tolerant animals. Finally, although dynorphin is associated with mild hyperthermic effects, this neuropeptide potentiates morphine induced hypothermia (see Smith & Lee, 1988 for review). As a result of such observations, it has been suggested that Met-enkephalin released in response to stressor exposure may serve to protect the organism from environmental insult while dynorphin A release may serve to antagonize or down-regulate μ receptor activation (Kato et al., 1990), possibly as a compensatory response to DA over-activation induced by stressful life events.

The data of Experiment 1 revealed that the immediate stressor-induced behavioural alterations in rearing and activity were comparable regardless of the dose of the κ agonist employed. However, rearing and activity were differentiated at more protracted intervals. It will be recalled that in the absence of pharmacological challenge a facilitation of both activity and rearing was detected following stressor application. Interestingly, administration of U50,488 either partially (i.e., 5 ug) or completely (i.e., 10 ug) antagonized such augmented increases in activity scores at the 24-hr test interval. A similar antagonism was observed with respect to rearing although the effects were more pronounced and persisted for at least one week following treatment regardless of the drug dose employed. It remains to be determined whether such antagonism in previously stressed animals serves in an adaptive capacity. It is conceivable that while activation of μ receptors in response to stressor exposure may be adaptive initially (i.e., increase vigilance/arousal), pathology (i.e.,

exhaustion, illness) may ensue with sustained and/or excessive stimulation (e.g., Maddeaux and Zacharko, 1992). Accordingly, simultaneous κ receptor activation in response to stressor application may aid the organism in conserving energy and curtail advancement of pathology.

The proposition that κ receptor activation is associated with attenuation of neurochemical change ordinarily associated with pathology may gain a margin of support from the results of Experiment 1. In particular, it is interesting to note that mice which received high doses of U50,488 in the absence of footshock exhibited subsequent increases in activity and rearing. Such effects are notably similar to those displayed by vehicle treated animals which were exposed to uncontrollable footshock. It would appear that at some drug doses, at least, high doses of U50,488 mimic the long term behavioural alterations associated with uncontrollable footshock. It will be recalled that such long term enhancement of locomotor activity induced by footshock was observed in the absence of immediate behavioural change. In contrast, increases of rearing were also observed in mice which demonstrated reduced rearing scores immediately following footshock. Likewise, the rebound increases in activity and rearing associated with κ receptor activation occurred in the absence of behavioural change in the immediate post-drug interval. The mechanisms underlying such stressor induced behavioural alteration following U50,488 administration may be available and the neuromodulatory role of dynorphin- κ receptor activation elucidated. It will be recalled that U50,488 reduces DA turnover in previously activated DA systems with attenuated DA activity apparently mediated by antagonism between the μ and κ receptor systems. Several behavioural examples of such κ receptor modulation/antagonism of μ receptor activity have already been provided

(e.g., analgesia, thermoregulation or respiratory depression). Such neuropeptide induced alterations may vary as a function of the margin of activation of the μ - κ -DA receptor system complex. In Experiment 1, levels of rearing and activity were elevated 24 and again 168 hours following initial stressor exposure in the absence of U50,488 administration. Since Met-enkephalin is released in response to uncontrollable footshock, it is conceivable that endogenous dynorphin release in response to stressful life events may serve to attenuate potential over-activation of the μ receptor system. Nevertheless, the extent of the antagonism is proportional to stressor severity, allowing for compensatory behavioural alterations to appear. One might expect, however, that prevention of endogenous κ receptor activation (e.g., employing norbinaltorphimine) would be associated with exacerbated compensatory (and perhaps maladaptive) responses following stressor exposure. Similarly, high doses of U50,488 antagonized the rebound- μ dependent behavioural increases ordinarily observed following stressor exposure. It is conceivable that exogenously applied U50,488 in combination with endogenous dynorphin release may be sufficient in partially or completely antagonizing behavioural compensatory responses. Finally, in the absence of stressor exposure, high doses of U50,488 induced such rebound increases at intervals comparable to those observed following stressor exposure (i.e., long-term effects associated with the stressor are mimicked by U50,488). With sufficiently high doses, U50,488 may saturate κ receptors and favour μ receptor activation. It is conceivable that such resulting activation (or perhaps overactivation) of the mesocorticolimbic system can provoke stressor like effects in the immediate post-infusion interval and provoke compensatory increases which are ordinarily

associated with stressor application. Low dose U50,488 administration, in contrast, would fail to activate μ receptors and correspondingly fail to provoke stressor-like facilitation of behaviour.

Interestingly, the rates of exploratory head dipping were reduced by uncontrollable footshock in the immediate post-stressor interval but such alterations were no longer evident during subsequent test sessions. The observed behavioural profile associated with head-dipping appeared to be independent of the stressor induced alterations of either locomotor activity or rearing. These data suggest that head dipping may represent a form of exploration independent of other measures of investigatory behaviour. In addition, exploratory head dipping remained unaffected by the administration of U50,488 regardless of the dose of the κ agonist employed. Such an effect was a surprising one since it will be recalled that U50,488 has been associated not only with behavioural suppression (VonVoigtlander et al., 1983; Di Chiara & Imperato, 1988) but also with centrally mediated aversive properties (Bals-Kubik et al., 1989). In any event, these data demonstrate that exploratory head-dipping remained independent of κ receptor activation while both activity and rearing were influenced at more protracted intervals. Although the mechanisms subserving these differential behavioural profiles remain to be determined, it is conceivable that head dipping was less sensitive to drug manipulation, owing to the innate aspects of this operant in the mouse repertoire (Kokkinidis & Zacharko, 1980). Head dipping also appears to represent a type of exploration which is independent of perturbations in either locomotor activity or rearing.

In summary, the results of Experiment 1 suggest that (a) the various indices of exploratory behavior are differentially influenced by uncontrollable footshock (b) κ receptor activation induces differential

effects on exploratory behaviour (c) κ receptor activation is involved in the modulation of stressor provoked behavioural change (d) the nature of the neuromodulatory role of κ receptor system appear to involve the μ receptor and (e) the extent of the modulation of the κ receptor depends upon previous stressor experience and other variables including handling and drug dose as well as the nature of the task under investigation.

EXPERIMENT 2

It will be recalled that the VTA, the point of origin of the mesocorticolimbic system, is a critical locus in central reward neurocircuitry (Phillips et al., 1991). Uncontrollable stressors have been shown to provoke selective alterations of DA turnover in the midbrain tegmental area as well as its principle innervation sites in the forebrain. Such neurochemical perturbations have been associated with alterations in self-stimulation performance from the A10 region (Zacharko & Anisman, 1991a). Although there has been considerable emphasis linking changes in DA availability to the expression of reward and anhedonia, it is clear that such an interpretation is overly simplistic. Neuropeptides identified in the VTA are released in response to stressors (Kalivas & Abhold, 1987) and enkephalin activity in the A10 region has been associated with the induction of DA turnover and the expression of anhedonia following exposure to uncontrollable footshock (Zacharko & Anisman, 1991b).

It will be recalled that μ , δ and κ receptors are densely distributed within the mesocortical and mesolimbic DA systems (Mansour et al., 1988). Intra-VTA or systemic administration of μ or δ agonists increase DA turnover, promote general levels of activity and induce sensitization (Kalivas et al., 1988). In contrast, κ receptor activation has been associated

with decreased DA turnover in the mesolimbic and tuberoinfundibular/tuberohypophyseal DA systems and the suppression of locomotor activity. Interestingly, however, κ induced neurochemical variations are predicated upon prior activation of the mesolimbic and tuberoinfundibular systems. (Manzanares et al., 1991). Moreover, it should be considered that while μ and δ receptors have been implicated in reward neurocircuitry, κ receptor activation has been linked to the induction of centrally mediated aversive states (Bals-Kubik et al, 1989; Millan, 1990).

It should be emphasized that there are sufficient data to suggest an interdependence of opioid receptor activation to the provocation of behavioural change. Indeed, κ receptors antagonize μ but not δ receptor activity (Spanagel et al, 1992). Moreover, μ agonists enhance, δ agonists inhibit, while κ agonists have no effect on substance P release. Finally, the tachykinin substance P promotes Met- but not Leu-enkephalin release. Accordingly, κ agonists (i.e., endogenous dynorphin) may attenuate Met-enkephalin activity and interfere with the modulatory influence of substance P. Under non-stressor conditions levels of dynorphin activity might be expected to be marginal. However, among animals exposed to an uncontrollable stressor endogenous activation of the dynorphin system may ensue. Experiment 2 will consider the effects of κ receptor activation upon ICSS from the dorsal VTA in mice in which the mesocorticolimbic DA system has been activated by prior exposure to an uncontrollable stressor.

METHODS

Subjects: Nineteen, naive, male CD-1 mice obtained at 5 weeks of age from Charles River Laboratories (St. Constant, Quebec) were used as subjects in the present experiment. All animals were housed in groups of 4

in standard polypropylene cages and allowed access to food and water ad libitum.

Surgery: Following acclimatization to the laboratory environment, subjects were anesthetized with sodium pentobarbital (65 mg/kg, i.p.) and a bipolar stainless steel electrode (0.15 mm, Plastic One, Roanoke, VA) was stereotaxically implanted into the dorsal VTA (A.P. -3.1 mm from Bregma, L. +0.5 mm from the sagittal suture and V. -4.7 mm from the flat skull surface). Animals were also implanted with a cannula in the lateral ventricle ipsilateral to the electrode site (A.P. +0.8 mm from Bregma, L.+0.7 mm from sagittal suture and V. -2.7 mm from flat skull surface). The guide cannula was constructed from a 23 gauge hypodermic needle cut to a length of 1.1 cm and fitted with a stylette which protruded 0.5 mm beyond the guide cannula tip. Following surgery, mice were housed individually and kept on warm heating pads for three days.

Procedure: Ten days following surgery, all animals (N=19) were trained to respond for electrical brain stimulation in the head dip task. Individual self-stimulation tests were conducted for 3 consecutive 15 minutes intervals and response rates were monitored at 3 minute intervals. The current intensity (20-25 μ A, base to peak) and frequency (90-100 Hz) of brain stimulation was adjusted to elicit stable response rates (i.e., < 10% variation over 4 consecutive days). Once stable baseline self-stimulation rates were established, animals were subdivided into the Shock or No Shock groups. Mice in the Shock condition (n=9) were exposed to inescapable footshock while the mice in the No shock treatment group (n=10) were placed in the same apparatus for an equivalent period of time but shock was withheld. The particulars related to stressor exposure were identical to those outlined in Experiment 1. Immediately following the

Shock or No Shock treatments, mice of the Shock and No Shocks conditions were further sub-divided such that half of the mice ($n=5$) of each of these groups received an intraventricular injection of 0.01 μg U50,488 delivered in a 1 μl volume while the remaining mice were administered vehicle according to the procedure described in Experiment 1. Mice were placed in the self-stimulation tubs immediately following drug administration but were not permitted access to the stimulation wells for 2 minutes. This procedure was followed to allow animals sufficient times to recover from the handling and injection procedure. Mice were then tested for self-stimulation over three consecutive 15 minute trials immediately, 24- and again 168 hours following initial stressor exposure.

Histology : Following completion of behavioural testing, all animals were sacrificed in accordance with the procedure provided earlier. All lateral ventricle cannula placements and dorsal A10 electrode placements were histologically verified. Electrode placements were subsequently plotted on a schematic diagram.

RESULTS

Cannula and electrode placements for all mice in Experiment 2 were histologically verified. The positioning of the intraventricular cannulas were consistent with the histological profile demonstrated in previous investigations in this laboratory (see Wolfe, 1990). The distribution of bipolar electrode placement within the dorsal A10 region is provided schematically in Figure 4. Typically, stimulating electrodes were verified in rostral aspects of the dorsal A10 area, along a medial plane.

 Insert Figure 4 about here

Figure 4. Schematic representation of electrode placements within dorsal portions of the VTA in CD-1 mice (n=19).

The analysis of variance conducted to determine variations in self-stimulation performance among shocked and non-shocked CD-1 mice infused intraventricularly with vehicle or U50,488 revealed a significant Day x Shock x Drug interaction ($F_{3,45}=3.16$, $p<.05$). Since the Time variable (within each 45 minute test session) failed to reach an acceptable level of statistical significance, the data was collapsed over each 45 minute test day (see Table 3, Appendix A).

Figure 5 depicts the rates of responding for ICSS from the dorsal aspects of the VTA for shocked ($n=9$) and non-shocked ($n=10$) CD-1 mice

Insert Figure 5 about here

Figure 5. Mean rates of responding ($\pm$ S.E.M) for intracranial self-stimulation (ICSS) from the dorsal VTA for shocked and non shocked CD-1 mice treated intraventricularly with vehicle or .01 ug of U50,488. The rates of responding for ICSS were monitored over 45 minute test intervals at baseline as well as immediately, 24 hr and 168 hr following initial stressor exposure.

treated intraventricularly with vehicle or .01 ug of U50,488. Subsequent Newman-Keuls multiple comparisons of the simple main effects associated with this interaction ($\alpha=.05$) revealed that Baseline self-stimulation performance was comparable for all groups of mice prior to experimental treatment. A significant reduction in self-stimulation performance among shocked mice was detected immediately following exposure to uncontrollable footshock. While similar alterations in responding were still evident at the 24 hr post-stressor interval, response rates had returned to baseline levels one week following treatment and were comparable to those displayed by non shocked animals.

Although no significant alterations in self-stimulation performance were apparent immediately or 24 hr following U50,488 administration, response rates were attenuated one week following the initial drug infusion relative to vehicle treated animals. Following exposure to uncontrollable footshock, mice administered U50,488 exhibited rates of responding for brain stimulation which were significantly increased both immediately and at the 24 hr test interval relative to vehicle-shock treated animals. Moreover, the shocked CD-1 mice treated with the κ agonist displayed elevated rates of responding at all post-drug intervals examined in comparison to their No Shock counterparts. Interestingly, subjects treated with the κ agonist in combination with stressor application were comparable to the non-shocked vehicle treated mice while non-shocked mice administered U50,488 were comparable to vehicle-shock treated mice.

MICROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS
STANDARD REFERENCE MATERIAL 1008
ANALYTICAL TEST CHART NO. 2

DISCUSSION

Consistent with data previously reported in this and other laboratories, ICSS rates from the dorsal aspects of the VTA were reduced following exposure to uncontrollable footshock (Kamata et al., 1986; Zacharko et al., 1990; Maddeaux & Zacharko, 1992). Similar disruptions in self-stimulation performance have been observed in rats and mice following stressor exposure from the point of origin and terminal sites of the mesolimbic and mesocortical (i.e., prefrontal cortex, nucleus accumbens, medial forebrain bundle/lateral hypothalamus) DA systems in both current-intensity and rate dependent paradigms (e.g., Bowers, Zacharko & Anisman, 1987; McCutcheon et al., 1991; Wolfe & Zacharko, 1991). Curiously, however, in contrast to previous investigations (e.g., Maddeaux & Zacharko, 1992) in which disruptions in ICSS performance from the dorsal A10 region persisted for at least one week following stressor application, the data of Experiment 2 revealed impairments which were restricted to the immediate and 24-hr post-stressor test sessions. Nevertheless, it should be emphasized that electrode placement, levels of self-stimulation performance and latency to acquire the operant were consistent with those routinely observed in this laboratory. It should also be emphasized that self-stimulation among shocked mice responding for brain stimulation from the dorsal A10 region was reduced by approximately 50% of the values noted among non shocked mice 168-hr following initial exposure to uncontrollable footshock. Such a depression in ICSS however, failed to reach an acceptable level of statistical significance.

Although there is relatively little information detailing the effects of κ receptor activation on intracranial self-stimulation and reward processes

in general, one investigation reported that U50,488 administered directly into the VTA failed to influence rates of responding for ICSS from the lateral hypothalamus in the rat (Jenck et al., 1987). Such an effect is somewhat surprising in view of the observation that central κ receptor activation has been associated with the induction of conditioned place aversion (Bals-Kubik et al., 1989). At the very least, it might have been expected that intraventricular infusion of the κ agonist would reduce the rewarding properties ordinarily associated with intracranial brain stimulation. Alterations in self-stimulation performance following U50,488 administration in Experiment 2 were only evident one week following intraventricular infusion. Although it is conceivable that such drug induced variations in self-stimulation might also appear from lateral hypothalamic sites, the behavioural tests conducted by Jenck et al. (1987) were restricted to the interval immediately following drug administration. Accordingly, it is not readily apparent whether such inter-laboratory variations are attributable to the species under investigation, the choice of brain site under investigation, the dose of the κ agonist employed, the route of drug administration, the differential distribution of κ receptors between rats and mice and/or the schedule of behavioural testing following drug administration. In any event, the data of Experiment 2 suggest that the influence of U50,488 on self-stimulation from the dorsal aspects of the A10 region in the mouse is delayed. It is conceivable that such variations in self-stimulation parallel emergence of cascading neurochemical/receptor alterations induced by κ receptor activation. It should also be considered that such neurochemical alterations may be initiated by the interactive influence of intraventricular U50,488 administration and that of brain

stimulation. As will be revealed in the ensuing discussion, there is some support for such a position.

Although administration of U50,488 was not associated with alterations in self-stimulation performance from the dorsal A10 region for at least 24 hours following intraventricular infusion, it is interesting that the performance profile of U50,488 treated animals was indistinguishable from that noted in mice exposed to uncontrollable footshock. The propensity of U50,488 to reduce self-stimulation at protracted intervals coupled with the immediate and long term depressive effects of uncontrollable stressors on ICSS suggest that the combined effects of κ receptor activation and stressor exposure may exert additive (if not synergistic) effects on ICSS performance. Such an expectation would gain some support from the observation that κ receptor activation may, in some instances, potentiate stressor-induced behavioural impairments (e.g., Katoh et al., 1990). Surprisingly, while intraventricular administration of U50,488 appeared to induce stressor-like effects in non-shocked animals, low dose administration of the κ agonist was associated with the amelioration of impairments in self-stimulation performance in mice previously exposed to uncontrollable footshock.

It will be recalled that U50,488 has been associated with a down-regulation of DA activity within the mesolimbic, nigrostriatal and/or tuberoinfundibular systems although prior activation of such systems must be elicited before the neurochemical consequences of κ receptor activation can be demonstrated (Manzanares et al., 1991; Leyton et al., 1992). In this respect, recent experimental evidence suggests that intracranial self-stimulation derived from major ascending DA systems may be adequate in producing such an effect. For example, Fibiger, LePiane, Jakubovic and

Phillips (1987) employed *in vivo* microdialysis to demonstrate that the levels of DOPAC and HVA as well as the ratios of DOPAC and HVA to DA were increased in the medial frontal cortex (MFC), nucleus accumbens (Nas) as well as the striatum following ICSS from the VTA. Similarly, Nakahara et al. (1992) reported increased levels of extracellular DA and its metabolites from terminal sites (i.e., MFC, Nas) of the mesocorticolimbic system following ICSS from the medial forebrain bundle although no alterations in striatal DA turnover were observed. These data suggest that self-stimulation may induce and is sustained by enhanced DA turnover. In this respect, intraventricular U50,488 administration likely antagonizes increased DA turnover in the mesocorticolimbic system induced by self-stimulation from the dorsal VTA and attenuates self-stimulation performance. Endogenous dynorphin release provoked by experience with uncontrollable life events may ordinarily serve to reduce DA turnover and preclude excessive neurochemical activity. Such attenuation of enhanced amine activity typically induced by uncontrollable stressors may prevent expression of pathology. In the present investigation, the behavioural parallel associated with neurochemical blunting induced by κ receptor activation might well be a reduction in reward as expressed in attenuated self-stimulation performance. Considered in this light, dynorphin release in response to stressors may exert prophylactic effects. However, uncontrollable stressors may, in some instances, produce anhedonia owing to the failure of endogenous dynorphin to attenuate central DA turnover sufficiently. Although the differentiation between blunted affect and anhedonia may be rather subtle, it should be underscored that the influence of the κ receptor on central amine activity is one of neuromodulation. It might be suggested that human depression may often be preceded by

episodes of dysphoria prior to the emergence of anhedonia (see Zacharko & Anisman, 1991a). In effect, the expression of dysphoric states might represent an adaptive behavioural response of the organism to threatening or potentially threatening environmental stimuli. Taken together, it would appear that U50,488 exerted differential effects on self-stimulation performance among stressed and non-stressed mice. The behavioural alterations apparent in the brain stimulation paradigm may be dependent, at least in part, upon the level of mesocorticolimbic stimulation effected prior to κ receptor activation. Such effects are consistent with the data of earlier reports which suggested that κ activation modulates rather than determines neurochemical/behavioural alteration.

It should be noted that verification of the site specific effects of uncontrollable footshock on brain stimulation reward was accomplished by the inclusion of additional subjects which were responding for brain stimulation from the ventral A10 area. Consistent with the data of previous investigations in this laboratory, (e.g., Maddeaux & Zacharko, 1992), uncontrollable footshock failed to alter self-stimulation performance from the ventral aspects of the VTA (see Appendix C) at any of the post-stressor intervals examined. Intraventricular U50,488 infusion, at the same dose employed for dorsal A10 sites, failed to affect self-stimulation performance either immediately or 24-hr following initial encounter with footshock. Interestingly, however, self-stimulation rates were elevated one week following initial drug treatment. Taken together, these data suggest that not only are mesocorticolimbic sites differentially sensitive to the effects of stressor presentation, but also that the effects of U50,488 administration are demonstrably different. Indeed, U50,488 provoked a depression in responding for brain stimulation among animals implanted with stimulating

electrodes in the dorsal aspects of the A10 region. In contrast, the present data suggest that U50,488 enhanced self-stimulation performance among animals responding for ICSS from ventral portions of the midbrain. These data are intriguing for several reasons. It has been suggested that the dorsal A10 area is particularly vulnerable to the effects of uncontrollable stressors. Conversely the ventral A10 region appears to be resistant to the disruptive effects of stressors on brain stimulation reward. In view of the effects provoked by U50,488 treatment it would appear that endogenous dynorphin activity might also affect these areas differentially (e.g., Fallon & Ciofi, 1990). Taken together it would appear that the effects of U50,488 on self-stimulation from the A10 area are site specific and dose dependent and apparently affected by the prior stressor history of the organism.

GENERAL DISCUSSION

Current data available from infrahuman experimentation would suggest that encounters with acute uncontrollable stressors can induce a variety of behavioural alterations which are associated with pathology. In particular, acute footshock can provoke variations in motivational processing, activity, perseverative behaviour, analgesia, consummatory behaviour and spontaneous alternation among others (Zacharko & Anisman, 1984). It is also well documented that such behavioural change appears to be influenced by stressor induced neurochemical variations. Considerable attention has been devoted to an analysis of central CA and indoleamine variations associated with stressors. In recent years it has become increasingly apparent that endogenous opioids can modulate central DA, NE and 5-HT activity and influence expression of stressor induced pathology. Research collected in this laboratory has suggested that

motivational alterations induced by uncontrollable footshock as expressed by responding for brain stimulation from the A10 area is susceptible to opioid modulation. Indeed, there is considerable data to suggest that μ and δ receptors are also intimately involved with the expression of arousal, activity and exploration. However, there is a paucity of data which outline the effects of κ receptor activation and the influence of such central neuropeptide influence on stressor induced pathology.

The data of Experiments 1 and 2 suggest that measures of activity, exploration, investigatory behaviour and motivation are modified by stressors differentially. The identification of demonstrably variable profiles of behavioural change within the same paradigm can also be reconciled with the data of previous investigations. For example, motivational blunting and the failure to induce depression in locomotor activity following footshock are compatible with the behavioural repertoire ordinarily reported in various laboratories. Although variations in exploration and investigatory behaviour might lead one to suspect that stressors depress behaviour in general, such a conclusion would be misleading. Although stressors undoubtedly produce both immediate and long term variations, failure to detect the latter effects may well stem from the data collection procedure. In any event, it is clear that fundamental variations exist in the profiles of activity, exploration, investigatory behaviour and motivation at protracted intervals following stressor experience. Moreover, it would appear that head dipping in the absence of brain stimulation is fundamentally different from brain stimulation reward. Although such data have been previously reported (e.g., Kokkinidis & Zacharko, 1979), the present data support the notion that the "rewarding" aspects of investigatory responding are fundamentally different from those

derived from activation of specific central sites. Perhaps equally important in this respect is the demonstration that "anhedonic" effects are not restricted to self-stimulation performance. It should also be noted parenthetically that the duration of the behavioural depression of investigatory head dipping was curtailed considerably relative to the effects detected in the brain stimulation paradigm. Taken together, these behavioural alterations may be reminiscent of the varying symptom profile associated with human depression in which the intensity and time course of the behavioural disturbances may represent varying degrees of pathology.

It should also be considered that uncontrollable footshock provoked increases of activity and rearing one week following initial encounter with the stressor. Such effects are remarkably similar to those detected in animals treated with high doses of U50,488. Although the enhancement of behaviour induced by stressor experience conceivably functions to prepare the animal to deal with subsequent encounters with aversive life events, the κ induced effect is a surprising one. The stressor induced behavioural alterations might well be attributed to sensitization of central neurochemical activity. It is conceivable that behavioural sensitization engendered by κ receptor activation might also be attributable to comparable variations of central neurochemical activity. Indeed, the effects of the κ agonist may well mimic the effects of an uncontrollable stressor immediately. It is tempting to suggest that handling may well provide the cue for such central neurochemical activation which may serve to sensitize the animal to subsequent environmental challenge. Nevertheless, the absence of a demonstrable stimulus for such behavioural change would make such an interpretation suspect (footshock cf handling).

Previous data collected in this laboratory have suggested fundamental differences among animals responding for brain stimulation from the dorsal and ventral aspects of the A10 area. Such variations in self-stimulation performance have been attributed to the distribution and release of neuropeptides in the mesencephalic region. The behavioural consequences of uncontrollable footshock on ICSS have been replicated in the present investigation. Surprisingly, however, the effects of the κ agonist were not predicted, since it was suspected that U50,488 would exacerbate the effects of the stressor. Moreover, it was presumed that any drug induced behavioural alteration associated with U50,488 administration would be opposed to the effects ordinarily associated with either μ or δ receptor activation. The amelioration of motivational change by U50,488 poses a dilemma for further investigations. One might suspect that activation of the endogenous κ receptor would antagonize stressor provoked alterations of μ receptor activation but the demonstration of a therapeutic outcome from the dorsal aspects of the VTA is certainly at variance with such an interpretation. However, it should also be considered that we have previously shown that the absence of a brain stimulation test immediately following footshock abrogates the anhedonic effects of footshock. Likewise, the interval at which U50,488 is administered following stressor application may be integral to the expression of behavioural change. Clearly additional research is required before such an hypothesis can be entertained. Finally, it might be noted that mice responding for brain stimulation from the ventral aspects of the A10 area demonstrated a diametrically opposed response to U50,488 relative to mice responding for brain stimulation from the dorsal A10 region. This profile is highly reminiscent of the divergent profiles previously noted in this

laboratory employing the mixed μ and δ receptor agonist DALA from these identical sites. At the very least, these data suggest that reward and anhedonia is affected differentially from the dorsal and ventral mesencephalic sites and the influence of opioids although unpredictable, in some instances, are at the very least consistent. Taken together, it is interesting to note that the various aspects of behaviour altered by a stressor can be qualitatively, quantitatively and temporally differentiated and further that the behavioural response to the various opioid peptides appear to be fundamentally distinct. The implications of these data for therapeutic interventions in depression and antidepressant administration in particular remain to be determined.

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APPENDIX A

TABLE 1

ANOVA SUMMARY TABLE FOR LEVELS OF ACTIVITY-EXPERIMENT 1

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Probability Level
S	9232	1	9232	0.09	.7675
D	369140	4	92285	0.88	.4805
S x D	263408	4	65852	0.63	.6430
Error	5221719	50	104434		
A	230356	3	767839	41.01	.0000
A x S	373332	3	124444	6.65	.0003
A x D	405156	12	33763	1.80	.0522
A x S x D	402189	12	33516	1.79	.0544
Error	2808393	150	18723		
T	2900640	14	207189	85.72	.0000
T x S	110671	14	7905	3.27	.0000
T x D	162903	56	2909	1.20	.1532
T x S x D	100110	56	1788	0.74	.9214
Error	1691950	700	2417		
A x T	127250	42	3030	2.38	.0000
A x T x S	69293	42	1650	1.29	.0981
A x T x D	209396	168	1246	0.98	.5637
A x T x S x D	225155	168	1340	1.05	.3150
Error	2675474	2100	1274		

S = Shock
D = Drug
A = Day
T = Time

APPENDIX A

TABLE 2
ANOVA SUMMARY TABLE FOR REARING DATA-EXPERIMENT 1

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Probability Level
S	68696	1	68696	2.00	.1639
D	166641	4	41660	1.21	.3181
S x D	157264	4	39316	1.14	.3475
Error	1720765	50	34415		
A	841690	3	280563	56.30	.0000
A x S	96109	3	32063	6.43	.0004
A x D	173747	12	14479	2.91	.0012
A x S x D	130886	12	10907	2.19	.0148
Error	747438	150	4983		
T	63043	14	4503	8.23	.0000
T x S	33825	14	2416	4.41	.0000
T x D	40283	56	719	1.31	.0668
T x S x D	28406	56	507	0.93	.6283
Error	383193	700	547		
A x T	26554	42	632	1.77	.0018
A x T x S	16020	42	381	1.07	.3577
A x T x D	56461	168	336	0.94	.6960
A x T x S x D	74685	168	445	1.24	.0223
Error	751197	2100	358		

S = Shock
D = Drug
A = Day
T = Time

APPENDIX A

TABLE 3

ANOVA SUMMARY TABLE FOR EXPLORATORY HEAD-DIPPING DATA
EXPERIMENT 1

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Probability Level
S	2487	1	2487	0.28	.6001
D	16871	4	4218	0.47	.7553
S x D	50646	4	12662	.42	.2433
Error	392425	44	8919		
A	152655	3	50885	18.46	.0000
A x S	23264	3	7755	2.81	.0418
A x D	45395	12	3783	1.37	.1868
A x S x D	23164	12	1930	0.70	.7489
Error	363806	132	2756		

S = Shock
D = Drug
A = Day

APPENDIX B

TABLE 1

ANOVA SUMMARY TABLE FOR INTRACRANIAL SELF-STIMULATION DATA
EXPERIMENT 2

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Probability Level
S	22361	1	22361	0.05	.8178
D	151810	1	151810	0.37	.5503
S x D	962899	1	962899	2.37	.1447
Error	6099436	15	406629		
A	519744	3	173248	4.18	.0108
A x S	77761	3	25920	0.63	.6024
A x D	82119	3	27373	0.66	.5808
A x S x D	392985	3	130995	3.16	.0336
Error	1865512	45	41456		
T	749194	14	53514	5.07	.0000
T x S	112030	14	8002	0.76	.7141
T x D	222295	14	15878	1.50	.1117
T x S x D	111850	14	7989	0.76	.7154
Error	2218181	210	10563		
A x T	574651	42	13682	1.64	.0076
A x T x S	304142	42	7241	0.87	.7071
A x T x D	325249	42	7744	0.93	.6013
A x T x S x D	313519	42	7465	0.90	.6610
Error	5251527	630	8336		

S = Shock

D = Drug

A = Day

T = Time

APPENDIX C

Figure A schematically represents electrode placements positioned within the ventral aspects of the A10 region in CD-1 mice (N=11). Animals were exposed either to uncontrollable footshock or no shock and treated intraventricularly with vehicle (n=7) or .01 ug of U50,488 (n=4). Animals were re-tested for rates of responding for ICSS immediately, 24 hr and 168 hr following stressor application. The analysis of variance revealed a significant Day x Time x Drug interaction ($F_{42,336}=1.40$, $p=.056$, See Table 1, Appendix C). Subsequent Newman-Keuls multiple comparisons revealed that the overall response rates for both groups were comparable prior to pharmacological or stressor manipulation although several of the 3 minute intervals were found to be significantly different (i.e., at 3, 30 and 33 min. into the test session). Although no significant differences were detected between groups immediately, drug treated animals did exhibit increased rates of responding at dispersed segments throughout the 24 hr post-stressor session. Interestingly, mice treated with .01 ug of U50,488 exhibited increased rates of responding throughout the 168 hr post-treatment interval relative to the vehicle treated mice (Figure B). It is also interesting to consider that the overall baseline rates of responding for ICSS from the ventral aspects of the A10 region are approximately double those typically observed from dorsal portions of the A10 area.

Consistent with previous investigations in this laboratory, stressor exposure failed to provoke impairments in ICSS from the ventral portions of the A10 region (Zacharko et al., 1990). Furthermore, these results are in contrast to those reported in Experiment 2 in which stressor-induced reductions in ICSS performance from the dorsal VTA were observed at more protracted intervals. It is also interesting to consider that U50,488 exerts opposite effects on self-stimulation performance from the dorsal and ventral portions of the A10 area. Such effects may be linked to the differential distribution of κ receptors within this brain region (Fallon & Ciofi, 1990). Although the significance of these data remains to be determined, it would appear that these effects are attributable to regional variations in neurochemical/receptor substrates within the VTA.

Figure A. Schematic representation of electrode placements positioned in ventral portions of the A10 region in CD-1 mice (n=11).

APPENDIX C

TABLE 1

ANOVA SUMMARY FOR RATES OF RESPONDING FOR INTRACRANIAL
SELF-STIMULATION FROM THE VENTRAL A10 AREA

Source	Sum of Squares	Degrees of Freedom	Mean Square	F Value	Probability Level
S	8482	1	8482	0.01	.9319
D	2495502	1	2495502	2.29	.1688
S x D	953315	1	953315	0.87	.3771
Error	8722583	8	1090323		
A	293366	3	97789	1.06	.3827
A x S	189791	3	63264	0.69	.5678
A x D	453230	3	151077	1.64	.2055
A x S x D	345924	3	115308	1.26	.3120
Error	2204905	24	91871		
T	386579	14	27613	1.67	.0726
T x S	139239	14	9946	0.60	.8598
T x D	309640	14	22117	1.34	.1982
T x S x D	396083	14	28292	1.71	.0636
Error	1855165	112	16564		
A x T	470034	42	11191	0.80	.8141
A x T x S	437415	42	10415	0.74	.8815
A x T x D	828675	42	19730	1.40	.0561**
A x T x S x D	764457	42	18201	1.30	.1126
Error	4722080	336	14054		

S = Shock

D = Drug

A = Day

T = Time

**** Note:** Due to the small number of subjects and unequal group sizes, caution should be taken when interpreting these data. These are preliminary investigations only.

Figure B. Mean rates of responding ($\pm$ S.E.M.) for intracranial self-stimulation (ICSS) from ventral portions of the A10 region in CD-1 mice treated intraventricularly with vehicle (n=7) or .01 ug of U50,488 (n=4). The rates of responding were monitored at 3 minute intervals over each 45 minute test session. ICSS performance was re-assessed immediately, 24 hr and 168 hr following drug infusion.

END

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FIN