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**Intracranial Self-Stimulation from the Mesencephalon
Following Intraventricular Interleukin-2 Administration
in the CD-1 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**

**Andrea Lyn Olding Hebb
Psychology Department
Carleton University**

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in the CD-1 Mouse**

submitted by

Andrea Lyn Olding Hebb

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

A handwritten signature in black ink, appearing to read "B. Jones", is written over a horizontal dashed line.

Dr. B. Jones

Chairman, Department of Psychology

A large, stylized handwritten signature in black ink is written over a horizontal dashed line.

Dr. R. Zacharko

Thesis Supervisor

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Abstract

Variations in central IL-2 activity induce neurochemical alterations and behavioral symptoms reminiscent of stress-induced pathologies and psychological disturbances, including human depression. The behavioral concomitants of increased central IL-2 activity resemble those produced by exposure to uncontrollable stressors. In particular, increased central IL-2 activity and exposure to uncontrollable stressors both serve to attenuate intracranial self-stimulation (ICSS) from mesocorticolimbic sites. There is abundant evidence suggesting that these stressor induced disruptions in ICSS performance, are precipitated by alterations of mesencephalic DA activity. In the present experiment, administration of IL-2 into the lateral ventricles was found to induce decreases in responding for ICSS from the dorsal but not the ventral aspects of the VTA. The deficits in ICSS performance from the dorsal aspects of the VTA were evident up to 168 hours following acute IL-2 administration. These results are discussed with respects to regional anatomical variations within the VTA as well as the possible mechanisms by which IL-2 interacts with DA neurons within the VTA to attenuate ICSS performance.

Acknowledgements

I would like to express my gratitude to Bob Zacharko for the considerable amount of time dedicated to the preparation of this manuscript. I would also like to thank Hymie Anisman for his help and support throughout this endeavor. Finally, an extended thanks to Ian, my parents, and everyone in the Anisman/Zacharko lab for their sensitivity, understanding, and patience during the course of this project.

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Introduction

The immune system and the central nervous system (CNS) appear to communicate through the dual actions of cytokines and neurotransmitters. The evidence for bidirectional communication is derived from the observation that modulation of central neurotransmitter activity affects immune function and conversely that modifying immune function influences central neurotransmitter turnover (Besedovsky et al, 1977; Anisman et al, 1993). The immune-CNS interaction may follow from activation of the hypothalamic-pituitary-adrenal, gonadal, or sympatho-adrenomedullary axes, peripheral catecholamine (CA) alterations or penetration of immune products into the brain (Besedovsky et al, 1977; Cross et al, 1982; Keller et al, 1991; Rivier, 1992; Anisman et al, 1993).

The three subsets of leukocytes which define immune system function include granulocytes, monocytes and macrophages, as well as lymphocytes. Lymphocytes differentiate in bone marrow (B lymphocytes or B cells) or the thymus (T-lymphocytes or T cells) into the cytotoxic, helper, and suppressor cells. T-lymphocytes are distinguished from B-lymphocytes by the presence of Thy-1 antigen on their membranes and the absence of surface immunoglobulin. B-lymphocytes produce humoral immunity with the aid of T-helper cells in the recognition and destruction of foreign antigen. The production of lymphokines including interleukin-2 (IL-2) from T-helper cells aids in the recognition of antigenic threats from T-cytotoxic cells and enables the T-cytotoxic cell to lyse

antigens. Humoral and cell-mediated immunity produce cascading immunological events in the presence of a foreign invader. These two lines of defense against pathology are interrelated, in part, through the influence of the cytokines interleukin-1 (IL-1) and IL-2. Interleukin-1, produced by macrophages in response to T-cell stimulation, causes thermoregulatory alterations and promotes growth and cell differentiation of lymphocytes. Interleukin-1 also induces release of IL-2 which activates killer T-cells, natural killer cells, and macrophages (Benjamini & Leskowitz, 1991).

Cytokines are antigen-nonspecific glycoproteins produced by T-cell activation in response to antigenic challenge. In situ hybridization has identified cytokine receptors (IL-1 and IL-2) in murine subcortical structures (Carr, 1991; Kent et al, 1992) on both neuronal tissue and astrocytes (Hopkins & Rothwell, 1995). High affinity binding sites for IL-1 were characterized in the granular cell layer and the stratum moleculare of the dentate gyrus of the hippocampus, the hypothalamus, the choroid plexus, and the anterior pituitary (Breder et al, 1988; Haour et al, 1990). Other investigators have identified IL-1 immunoreactivity in the parietofrontal cortex, olfactory tubercles, organum vasculosum laminae terminalis, meninges, brain blood vessels, and in non-neuronal cells in brain parenchyma (Ban et al, 1991; van Dam et al, 1992; Nakamori et al, 1993). The existence of IL-2 immunoreactivity and IL-2 binding sites have been identified in several discrete areas of rat brain with the highest concentrations (>0.7 ng/mg tissue) occurring in the median eminence-arcuate

nucleus, hippocampus (pyramidal cell layer and granule cell layer of the dentate gyrus), lateral septum, cerebellum, lamina IV of the cerebral cortex and the striatum (Araujo et al, 1989). Lower concentrations of IL-2 (<0.15 ng/mg tissue) immunoreactivity have been identified in the caudate, putamen, locus coeruleus, and the frontal cortex (Araujo et al, 1989; Lapchuk, 1992; Nistico, 1993). In addition, several laboratories have demonstrated that cytokines cross the blood-brain barrier (Banks et al, 1991; Waguespack et al, 1994). However, apparently less than 0.1% of systemically injected IL-1 can be detected in the brain (Hopkins & Rothwell, 1995). Although it is suspected that cytokines are produced in the brain, the nature and site of such production remain enigmatic (Hopkins & Rothwell, 1995). Interestingly, however, cytokine production appears to be influenced by central CA alterations.

Several lines of evidence suggest that changes in central dopamine (DA), serotonin (5-HT), and norepinephrine (NE) concentrations produce discernable alterations in T-cell cytokine production (Cross et al, 1980; Brooks et al, 1982; Rozman et al, 1982; Cross et al, 1982; Cross et al, 1984; Koff et al, 1986; Katayama et al, 1987). Conversely, variations in circulating interleukin level following antigen administration provoke changes in DA, NE, and 5-HT availability in the hypothalamus (Besedovsky, 1977; Carlson et al, 1987; Zalcman et al, 1991; Dunn, 1993; Mohankumar et al, 1993; Rivier, 1993; Shintani et al, 1993; Terao et al, 1993; Wan et al, 1993). For example, Mohankumar et al (1993) reported that systemic IL-1B administration increased

NE release from the paraventricular nucleus of the hypothalamus while central IL-1B administration increased 5-hydroxyindoleacetic acid (5-HIAA) release from the medial basal hypothalamus. Systemic injection of gram negative bacteria, which stimulates both IL-1 and IL-2 activity, enhanced both NE and DA turnover in the hypothalamus (Masana et al, 1990). It should be emphasized that although immunological variations have ordinarily been associated with physical pathology (e.g., acquired immune deficiency syndrome) there is considerable evidence to suggest that alterations in immune functioning may also contribute to psychological disturbances including depression (Maes et al, 1995).

Depression

Depression is a syndrome comprised of a variety of behavioral symptoms including depressed mood (melancholia), loss of motivation (anhedonia), sleep disturbances (Lauer et al, 1995), increased or decreased appetite and/or accompanying weight change, diminished concentration and self-esteem, suicidal ideation, as well as, psychomotor agitation or retardation among others (American Psychiatric Association, 1994). Numerous biological markers have been employed in the diagnosis of depression including alterations of neuroendocrine activity. Specific indices of altered hypothalamic-pituitary-adrenal (HPA) axis function in depressed patients include increased blood cortisol levels, dexamethasone nonsuppression, diminished adrenocorticotrophic hormone (ACTH) response to corticotropin-releasing factor (CRF), increased

cerebrospinal fluid (CSF) CRF concentrations, as well as, adrenal and pituitary hypertrophy (McDaniel et al, 1995). Depression has also been associated with a variety of immunologically associated disturbances, including decreased mitogen-induced lymphocyte blastogenesis, an increased ratio of T-helper to T-suppressor cells and decreased natural killer cell activity (Darko et al, 1992). The reduction in natural killer cell activity in depressed patients has been associated with decreased plasma cortisol, ACTH, B-lipotropin, and B-endorphin as well as increased levels of circulating interleukin (Darko et al, 1992). In view of the observation that IL-2 promotes killer T-cell and natural killer cell activity (Benjamini & Leskowitz, 1991), varying IL-2 levels may participate in immunological variations associated with depression (Maes et al., 1990, 1991). Consistent with this interpretation, Maes et al (1993, 1995) reported that depression was associated with elevated serum IL-2 receptor (IL-R) concentrations, increased production of cytokines IL-1B and IL-6 in mitogen-stimulated culture supernatant, as well as increased leukocyte and lymphocyte activity relative to control subjects. In contrast, Hickie et al (1993) assessed cell-mediated immunity in depressed patients by evaluating delayed-type hypersensitivity skin responses and reported that depressed patients exhibited decreased cell-mediated immunity, assessed by total induration diameter and the density of antigen responsive sites relative to control subjects. Moreover, Weizman (1994) observed a diminished capacity of peripheral blood mononuclear cells of depressed patients to produce cytokines, suggestive of

decreased cell-mediated immunity. It seems that simultaneous signs of immune activation and suppression may be detected in depression (Maes et al, 1995) reflecting the activity of multiple feedback systems. Hypersecretion of cytokines (one index of immune activation) may be required to reverse negative immune relationships (e.g., decreased NK cell activity) and to restore homeostasis. Maes et al (1995) suggested that cytokine hypersecretion and accompanying neurochemical variations, including increased CA turnover, may be linked to some of the behavioral symptoms (e.g., psychomotor retardation, anorexia, weight loss, sleep disturbances, loss of interest, lethargy, weakness and fatigue) of depression. For example, melancholia in depressed patients has in some instances been associated with increased central DA turnover (Mouret et al., 1987) and concomitant changes in cell-mediated immunity (Hickie et al, 1993; Maes et al, 1993), although alterations of central NE and 5-HT turnover have also been detected (Brown & Gershon, 1993; Dougherty et al, 1995; Maes et al, 1995). Experimental evidence to date suggests at least some of the neurochemical and immunological variations among human subjects are paralleled in some animal models of the human disorder (Zacharko & Anisman, 1991).

Dopamine and Depression

Depression is a heterogeneous clinical disorder characterized by diverse symptomatology, variable developmental course and responsiveness to therapeutic intervention. However, there is sufficient evidence to suggest that

alterations of central DA activity may be associated with some symptoms of depression including melancholia, motivational alterations and sleep disturbances (Willner, 1985; Mouret, 1987; Maes et al, 1995). Indeed, depression is likely a composite of distinct subtypes of the disorder in which abnormalities of several neurotransmitters contribute to the expression of specific clinical symptoms. Biochemical evidence supporting a DA deficiency hypothesis in depression is derived from investigations which have focused on variations in DA metabolites among depressed patients (Goodwin et al, 1973; Berger et al, 1980; Koslow et al, 1983; Asberg et al, 1984; Gjerris et al, 1987). Alterations in central DA activity have been implicated in melancholia and in depressive subtypes with psychomotor retardation (for a review see Willner, 1985). Melancholia, for example, has been associated with changes in cerebral spinal fluid (CSF) HVA, DOPAC and conjugated dihydroxyphenylactic acid levels, relative to non-melancholic control subjects (Asberg et al, 1984). In addition to lowered DA metabolite levels among depressed patients, DA receptor density may be altered as well. For example, Suhara et al (1992) reported a reduction in D1 DA receptor density in the frontal cortex of depressed patients. Interestingly, a reduction in the density of A10 DA efferent projections to the prefrontal cortex has also been detected in patients with Parkinson's disease. The loss of A8, A9, and A10 neurons has been associated with decreased initiative and motivational disturbances in Parkinson's patients (for a review see Brown & Gershon, 1993).

Antidepressants and Central Dopamine Activity

Consistent with the observation that depression may be associated with alterations in mesencephalic DA activity, some consideration has been devoted to the observation that some antidepressants exert a therapeutic effect by altering central DA transmission. Indeed, numerous clinically effective antidepressant agents appear to potentiate mesolimbic and mesocortical DA activity (McNeal & Cimbolici, 1986; D'Angio et al, 1990; Grunder et al, 1993; Brown & Gershon, 1993). While the contribution of the mesolimbic and mesocortical DA system to the pathogenesis of human depression is unclear, some antidepressant agents appear to target mesencephalic sites (Serra et al, 1990).

Some antidepressant agents may provoke a therapeutic effect by increasing DA receptor sensitivity (Muscat, Towell, & Willner, 1988; Serra et al, 1990; Brown & Gershon, 1993), increasing postsynaptic DA function at sites distal to the receptors and/or decreasing the sensitivity of DA autoreceptors (Serra et al, 1990). Tricyclic antidepressants (TCA) produce variable effects on DA activity by inhibiting DA reuptake (Mendels et al, 1975; Brown & Gershon, 1993) thereby increasing the therapeutic efficacy of DA. Furthermore, the therapeutic efficacy of pharmacological agents which increase DA availability including L-dopa and tyrosine as well as the psychostimulants methylamphetamine and methylphenidate suggest a role for DA in the etiology of depression. Recently, bromocriptine, a DA agonist, has also been found to

have therapeutic effects in depression (Brown & Gershon, 1993) while roxindole a selective autoreceptor D1 agonist, has been reported to have antidepressant properties among depressed patients with psychomotor retardation (Grunder et al, 1993). Interestingly, roxindole appears to be effective in alleviating anhedonia in some depressed patients (Grunder et al, 1993). Taken together, although the evidence for alterations of central DA activity in depression is derived from diverse sources of indirect evidence, these data cannot be ignored.

Stressor-Induced Anhedonia

It will be recalled that anhedonia or motivational change, a principal symptom of clinical depression, has been argued to follow from perturbations of mesocorticolimbic DA activity (Willner, 1985; Mouret, 1987). Likewise, it has been argued that immunological challenge may induce motivational disturbances, at least in part, by modifying central DA activity (Masana et al, 1990; Zacharko & Anisman, 1991; Berkenbosch et al, 1991). Interestingly, uncontrollable stressors, like immunological challenge, may also induce motivational changes in infrahuman subjects by inducing alterations of central DA activity (Zalcman et al, 1991). In particular, while various stressor types (e.g., immobilization, footshock) influence 5-HT (Van Praag et al, 1971; Shanks et al, 1994) and NE (Weiss, 1981) turnover, the application of relatively mild, uncontrollable footshock provokes neurochemical alterations in the mesocortical and mesolimbic DA systems including the medial prefrontal cortex,

the nucleus accumbens, and the VTA (Csernansky et al, 1984; Watanabe et al, 1984; Cabib et al, 1988; Bertolucci-D'Angio et al, 1990; Keefe et al, 1990; Zacharko & Anisman, 1991; Zalcman, 1991; Cenci et al, 1992; Elbaz et al, 1994; Shanks et al, 1994) which parallel the neurochemical alterations evident in human depression. Support for similar neurochemical alterations in human depression and stress-induced pathologies is derived from studies which abolish the therapeutic efficacy of an antidepressant agent using a DA antagonist. For example, Muscat et al (1990) found that injections of raclopride, a selective D1 antagonist, reversed the restoration of sucrose ingestion in imipramine treated stressed animals. Additionally, Sampson et al (1991) reported that SCH 23390 and sulpiride, DA D1 and D2 selective receptor antagonists, abolished the restoration of sucrose consumption in desmethylinipramine or amitriptyline treated animals previously exposed to a variety of uncontrollable stressors. The efficacy of both SCH 23390 and sulpiride in abolishing one aspect of antidepressant activity is consistent with numerous studies which report that both D1 and D2 receptor antagonists decrease rewarded behavior (Kebabian & Calne, 1979; Nakajima & McKenzie, 1986; Nakajima & Baker, 1989; Nakajima, 1989).

Several lines of evidence have suggested that the neurochemical and behavioral alterations associated with stressor presentation are not attributable to the aversiveness of a stressor per se but rather to lack of controllability over the stressor (Vogel, 1985). The inability to cope with a stressor produces

prominent alterations in DA availability in the medial prefrontal cortex (Weiss, 1981) and significant but less conspicuous alterations appear in the VTA and the nucleus accumbens of infrahuman subjects (Deutch et al, 1984). It is tempting to suggest that the inability to cope with aversive life events produces comparable alterations in mesocortical and mesolimbic DA availability in human depression (Weiss, 1981; Vogel, 1985; Bertolucci-Angio et al, 1990).

It might be noted, parenthetically, that Heinsbroek (1990) assessed the impact of uncontrollable footshock on DA activity in male and female rats. Although DA turnover increased following application of the stressor in male and female subjects, increased mesencephalic dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) concentrations were more conspicuous in female subjects. In human depression, epidemiological studies have identified gender related variations in the number and the severity of reported symptoms in addition to sex dependent neurochemical alterations (Weissman, 1977; Maes, 1990-91). Taken together, these data suggest that exposure of animals to mild, uncontrollable stressors produces diverse neurochemical alterations in various mesocorticolimbic sites and such neurochemical lability may underlie various anhedonic states.

Various animal models of depression have been employed to simulate the constellation of symptoms associated with the human disorder. Such a behavioral analysis has proven to be a rather difficult one in view of the complexity of the human condition. Nevertheless, as in the human condition,

animal models of depression have revealed considerable inter- and intra-individual variability in the expression of behavioural pathology as well as the efficacy of therapeutic interventions (Shanks, 1989; Anisman & Zacharko, 1990; Zacharko & Anisman, 1991). Although some of the paradigms employed to simulate human depression have relied on alterations in shuttle escape and swim performance following exposure to an uncontrollable stressor (Willner, 1985), such tasks largely fail to provide an adequate analogue of anhedonia, one of the principal symptoms of depression (Zacharko & Anisman, 1991). In contrast, stressor induced variations in intracranial self-stimulation may be a more appropriate parallel for the motivational alterations attending clinical depression. In addition, it is of considerable advantage to demonstrate that not only are the behaviors under investigation reminiscent of the symptoms of the human condition, but also that the pharmacological interventions effective in ameliorating the clinical syndrome are also effective in alleviating behavioral alterations in the animal model. For example, uncontrollable stressors alter responding for previously rewarding brain stimulation (Anisman & Zacharko, 1990) from the ventral tegmental area (VTA)(Zacharko et al, 1990), the nucleus accumbens (Bowers et al, 1987), and the medial prefrontal cortex (Baillie et al, 1988), and chronic desmethylinipramine administration, a clinically effective therapeutic agent, antagonized stressor-induced alterations in intracranial self-stimulation from mesolimbic (Bowers et al, 1984) and mesocortical sites (Wolfe & Zacharko, 1991).

Brain Stimulation Reward and Mesencephalic Dopamine Activity

Activation of central reward neurocircuitry by intracranial self-stimulation appears to be associated with the release of a variety of neurotransmitters and putative neurotransmitters including DA (Olds & Milner, 1954; Wise, 1982; Hernandez & Hoebel, 1988; Shapovalov & Yakimovski, 1988; Nakajima, 1989; Phillips et al, 1989; Drew & Glick, 1990; Evans & Vaccarino, 1990; Cador, Taylor, & Robbins, 1991; Stamford et al, 1991). The DA hypothesis of reward (Wise, 1982) was prompted by the identification of the DA containing mesolimbic and mesocortical systems and the observation that intracranial self-stimulation could be reliably elicited along the course of these pathways (Olds & Milner, 1954). Although diverse areas of the CNS support brain stimulation reward, the VTA appears to be a focal point of central reward neurocircuitry (Bozarth, 1987). It should be considered that the anhedonia associated with major affective disorders may well follow from perturbations of central mesencephalic DA activity. Accordingly, the ensuing discussion will focus on the neurochemical, electrophysiological, and synaptic organization of the A10 region.

Cellular Composition of the VTA

The VTA is a heterogeneous mesencephalic cell population (Wang, 1981; Swanson, 1982; Oades & Halliday, 1987) bounded by the mammillary body and the posterior hypothalamus rostrally and the substantia nigra caudally. Despite such an anatomical description of the VTA, the intraregional

demarcation of the A10 region is poorly defined. To a considerable degree, the borders of the VTA are based on innervation patterns and cytoarchitectural features. The nuclei of the VTA (A10) include the paranigralis (Npn), the parabrachialis pigmentosus (Npbp), the interfascicularis (Nif), and the linearis (Nln) caudalis and rostralis (Oades & Halliday, 1987; Bunney et al, 1991). The VTA contains both DA and non-DA containing cells (Dahlstrom & Fuxe, 1964). Fluorescence histochemistry has revealed that the DA neurons of the VTA may be delineated neurochemically according to the rate of monoamine metabolism (Oades & Halliday, 1987; Trulsson et al, 1987; Bunney et al, 1991). For example, the medial cells of the Nif and Nln demonstrate higher DA turnover rate than the DA cells located in the more lateral Npn. Non-dopaminergic cells, however, predominate in the peripheral aspects of the mesencephalon (Carlsson et al, 1962; Falck et al, 1962; Oades & Halliday, 1987; Bunney et al, 1991).

Wang (1981) classified DA and non-DA containing cells in the midbrain as type 1 and type 2 respectively. Electrophysiologically, type 1 DA cells, exhibited a higher discharge rate, a longer after potential, a slower conduction velocity, typical of unmyelinated DA neurons, and a higher absolute refractory period relative to non-DA neurons. In addition, type 1 but not type 2 neurons in the VTA were sensitive to 6-hydroxydopamine (6-OHDA) and apomorphine application. It is tempting to speculate that endogenous variations in mesencephalic activity may contribute to the expression of motivational alteration in depression. Indeed, specific clusters of DA neurons identified in

subregions of the VTA display variable basal neurochemical and electrophysiological activity. In addition, as will be revealed in ensuing sections, subareas of the mesencephalon appear to be differentially sensitive to uncontrollable stressor application. Conceivably, vulnerability to specific stressors and perhaps the anhedonia of depression may be rooted in the variable responsivity of mesencephalic units. Although speculative, such an hypothesis is certainly an intriguing one and deserving of consideration.

Intrinsic Connections within the VTA and Autocrine Regulation of DA Neuronal Firing

The neurocircuitry within the VTA consists of considerable dendrodendritic, axodendritic, and somatodendritic contact (Bunney et al, 1991). The primary inhibitory modulator of mesencephalic DA function is somatodendritic release (Kalivas, 1993). Dopamine synthesis in the VTA is required for maintaining a releasable amine pool, owing to lack of vesicular storage. When dendritic DA is depleted following repeated stressor exposure, for example, DA neuronal activity within the VTA is increased. Elevated electrophysiological activity in the A10 region depletes DA stores in the terminal presynaptic projection sites of the VTA such as the prefrontal cortex and the nucleus accumbens (Deutch et al, 1985; Kalivas & Stewart, 1991). In effect, DA somatodendritic release appears to be particularly susceptible to environmental challenge (Kalivas, 1993) and dendritic field overlap produces considerable DA and non-DA interaction within the A10 region (Oades &

Halliday, 1987). Accordingly, variations in the neurochemical activity of non-DA cells may have profound effects on DA cells within the VTA, including the terminal regions associated with such projections, and may contribute to the expression of specific symptoms comprising human depression .

Efferent Projections of the VTA and Antidromic Modulation of Mesocorticolimbic Pathways

The efferent projections of the VTA include ascending projections to the forebrain (i.e., the nucleus accumbens) and medial thalamus, and descending projections to the locus coeruleus and the medial raphe nuclei (Swanson, 1982). The lateral VTA contains non-DA cells projecting to the neostriatum (Wang, 1981) and the mesolimbic/mesocortical DA system which innervates various forebrain structures including the amygdala, nucleus accumbens (Feldman & Quenzer, 1984; O'Donnell & Grace, 1993) and the cingulate and entorhinal cortices (Oades & Halliday, 1987). The most conspicuous mesolimbic projection site is the nucleus accumbens (Wang, 1981; Oades & Halliday, 1987), although the nucleus accumbens receives both DA and non-DA innervation (Wang, 1981). Lateral A10 DA neurons also project to the frontal cortex (Feldman & Quenzer, 1984; Oades & Halliday, 1987) where a dense concentration of DA and non-DA containing terminals appear (Wang, 1981; Oades & Halliday, 1987; Mitchell & Gratton, 1992). The mesostriatal, mesocortical, and mesolimbic pathways support intracranial self-stimulation but represent only a few of the VTA efferent pathways.

Neuromodulation of A10 Mesencephalic Dopamine Activity

Sensory or afferent input to the mesencephalic A10 area appears to be accomplished through the medial forebrain bundle (MFB) and the mamillary peduncle. Descending projections of the MFB split at the level of the mammillary body into dorsal and ventral components. The dorsal component enters the central gray area while the ventral component enters the VTA before branching to innervate lateral aspects of the VTA and the limbic midbrain area. The pathway arising from the mammillary peduncle originates from the medial aspects of the pons and the midbrain, including the locus coeruleus as well as the medial and dorsal raphe nuclei (Swanson, 1982). The VTA receives conspicuous innervation from the dorsal raphe (Oades & Halliday, 1987). In addition to a DA 5-HT interaction in the A10 region, the VTA is also influenced by neurotensin, noradrenergic and GABA afferents (Fluckiger, Muller, & Thorner, 1985).

In addition to MFB and peduncular afferent input into the mesencephalon, the VTA also receives mesolimbic and mesocortical innervation. For example, electrical stimulation of the nucleus accumbens resulted in the antidromic activation of type 1 cells (DA) in the Npn of the VTA (Wang, 1981). Prefrontal innervation of the VTA has also been identified (Oades & Halliday, 1987). In addition to interactions between the VTA and either mesolimbic or mesocortical terminal regions, there is sufficient evidence to suggest that DA

activity in the prefrontal cortex may also reduce DA transmission in the mesolimbic system. For example, Mitchell & Gratton (1992) demonstrated that increasing DA concentrations within the prefrontal cortex decrease DOPAC accumulation within the nucleus accumbens, presumably by altering A10 DA activity. In view of the proposal that the A10 area may be involved in the expression of the anhedonia of clinical depression, it would appear to be relevant to establish the neuroregulatory mechanisms associated with sensory input into the mesencephalon.

The Impact of Stressors on Intracranial Self-Stimulation from the Ventral Tegmental Area

It will be recalled that the VTA is a neurochemically heterogeneous area as revealed by the availability of DA and non-DA neurons. Interestingly, Deutch et al (1985) demonstrated that the VTA was not uniformly affected by stressors. Distinct populations of DA neurons within the tegmental field were differentially affected by uncontrollable stressor presentation. A subpopulation of A10 neurons, projecting to the prefrontal cortex and lacking autoreceptors, were identified which sustained their neuronal activity in response to stressors. In contrast to this neural population, continuous dendritic and axonal DA release in response to uncontrollable stressors serves to silence activity of other dopaminergic neurons within the VTA (Deutch et al, 1985). These two apparently different DA neuronal types within the VTA functionally divide the VTA into dorsal and ventral aspects. It should also be considered that the

ventral and dorsal aspects of the tegmentum innervate differential mesocorticolimbic sites, including the medial prefrontal cortex and nucleus accumbens, and have alternate responding patterns in face of stressors. For example, specific stressors have demonstrable effects on selective mesocortical and not mesolimbic neurons (Mantz et al, 1989). Furthermore, Zacharko, Kasian, MacNeil, and Anisman (1990) demonstrated that inescapable shock disrupted intracranial self-stimulation (ICSS) from the dorsal aspects of the VTA while responding from the ventral A10 region was hardly affected. The stressor induced variations in self-stimulation performance from sub-areas of the VTA were evident despite comparable acquisition latencies and stimulation parameters. While it has been suggested that variations in mesencephalic DA turnover induced by a stressor contribute to alterations in self-stimulation performance, incongruency between the behavioural and the neurochemical concomitants of stressor application suggests that non-DA systems also contribute to the expression of behavioural change. It is suspected that the presence of non-DA cell type(s) within the dorsal and ventral A10 area contributes to the ability of DA neurons to sustain neuronal activity in response to stressors. For example, Kamata et al (1986) demonstrated that pretreatment with naloxone or methamphetamine antagonized the decreased ICSS rates from the VTA exhibited in response to inescapable footshock. In addition, Maddeaux and Zacharko (1992) reported that intraventricular administration of D-Ala²-Met⁵-enkephalinamide induced rapid recovery of

responding for ICSS from the dorsal aspects of the ventral tegmentum following uncontrollable footshock. It is suspected that uncontrollable footshock may release enkephalins which facilitate DA turnover in mesolimbic or mesocortical structures and this increased mesocorticolimbic DA turnover is responsible for the attenuation of ICSS rates. Taken together, electrophysiological and neurochemical differences in A10 DA and non-DA cells may reflect the underlying relative contributions of individual cell types to behavioral pathology.

Uncontrollable Stressors and Corticotropin-Releasing Hormone Availability

It will be recalled that exposure of rats and mice to mild, uncontrollable stressors alters self-stimulation performance from the dorsal tegmental area, presumably by altering the integrity of mesencephalic DA and/or DA availability. Neuropeptides located in the mesencephalon may also differentially activate mesolimbic and mesocortical DA neurons in response to uncontrollable stressors (D'Angio et al, 1990). For example, corticotropin-releasing factor (CRF) is widely distributed within the mesencephalon, including the VTA (Cummings et al, 1983; Swanson et al, 1983; Webster & DeSouza, 1988; Zhang & Barrett, 1990) and there are implications of interactions between DA and CRF in the exacerbation of depressive symptoms (Dunn & Berridge, 1986; Maes et al, 1995).

Corticotropin-releasing hormone (CRH) or CRF, is a neuropeptide produced in the neurosecretory cells of the paraventricular nucleus (PVN) and is released

during stress. Approximately 50% of the neurons in the PVN which contain CRF also contain vasopressin (VP) and together CRH and VP stimulate the release of ACTH (Bartanusz et al, 1994; Matthews & Parrott, 1994). Perturbations of HPA activity have been detailed in depressed patients (Miller et al, 1993) and increased CRF and VP release is often detected in the human disorder (Willner, 1985; Dunn & Berridge, 1986; Weizman, 1994). In rodents, intracerebroventricular (ICV) injection of CRF elevates central DA turnover as revealed by significant changes in the DOPAC:DA ratio in the nucleus accumbens and prefrontal cortex (Dunn & Berridge, 1986). Bilateral injection of CRF into the VTA also increased the concentrations of DOPAC in the striatum and nucleus accumbens while concentrations of DOPAC within the prefrontal cortex decreased. The potential relevance of the CRF-induced decrease in DOPAC concentrations in the prefrontal cortex (but not the nucleus accumbens) with intra-VTA CRF injection may reflect the functional heterogeneity of the VTA. It will be recalled that the A10 area innervates the prefrontal cortex differentially and that specific stressor types which modulate prefrontal DA neuronal function may have little or no effect on other mesencephalic DA neurons. The region specific effects of stressors on mesocortical neural activity may well follow from the particular neurochemical release profile induced in that area. Taken together, the functional dichotomy within the VTA, coupled with its projection areas, is preserved both neurochemically and neuroanatomically.

In addition to modulating mesencephalic DA function, CRF also regulates the immune response (Miller et al, 1993) as CRF-receptors have been identified on secondary lymphoid organs in the mouse (Webster and De Souza, 1988; Whitnall, 1993). In effect, CRF-binding sites are structurally (and functionally) similar in the mouse whether the receptors are in the spleen, in the brain, or the pituitary. Furthermore, the relative affinities of the CRF in the CNS and pituitary of rats and primates are highly correlated. Thus, it is suspected that CRF modulates both central neurotransmitter release (e.g., DA) and central immune activation (e.g., release and/or production of cytokines including IL-2) and, consequently, regulates peripheral immune function by regulatory feedback loops (HPA). Taken together, variations in central CRF (and VP) and DA activity, as well as immunological disturbances, appear to be implicated in human depression.

Stressors and Immunity

Immunologically-based disorders (e.g., autoimmune disease) and psychological disturbance including depression, may be precipitated by stressful life events. It has been previously demonstrated that exposure to uncontrollable stressors provokes changes in central DA activity and concomitant changes in immune function. The following sections will discuss the human and animal

literature suggesting that (1) stressors provoke immune alterations (e.g., IL-2 activity) and (2) antigenic challenge activates CRF pathways via the PVN of the hypothalamus creating neurochemical (e.g., DA) and hormonal (e.g., IL-1, IL-2) alterations reminiscent of human depression.

Stressors and Immunity: Human Experimentation

The arguments in favor of a link between stressors, immune functioning, and depression have been well documented. Van Rood et al (1993) conducted a meta-analytic review of the stress-immune literature (and relaxation studies used to alleviate the stressor effects) and identified approximately 20 immune variables associated with stressor exposure. For example, a significant decrease in IL-2R expression and T-cell proliferation in response to phytohemagglutinin (PHA) was reported in stressed subjects indicating an increase in the accumulation of IL-2 produced peripherally and a decrease in natural killer cell activity. With relaxation therapy, natural killer cell activity increased (IL2-R expression was not measured in relaxation studies). Life stressors, including bereavement and examination stress, have been shown to alter other aspects of immune functioning in addition to modulating IL-2 production and IL-2 receptor gene expression (Glaser et al, 1990, 1993; Kropiunigg, 1993; Isometsa et al, 1995). For example, Zisook et al (1994) reported that depressed widows exhibited significantly reduced natural killer cell activity while Dobbin et al (1991) reported that lymphocyte responsiveness to concavalin A and pokeweed mitogen was diminished in students facing

examination stress. Moreover, Shea et al (1993) reported decreased cell-mediated immunity in response to external stressors in subjects lacking effective coping strategies. Interestingly, it will be recalled that the inability to cope with a stressor has been associated with perturbations of mesencephalic DA activity. Although intriguing, such an analysis linking immune-stress responses and concomitant changes in mesencephalic DA activity and motivational change is speculative at best.

Stressors and Immunity: Animal Experimentation

Evidence from infrahuman experimentation suggest that as in the human condition, exposure to stressful life events compromises immune function (Ader & Cohen, 1993). Karp et al (1994) observed the effects of differential housing on in vitro antigen-specific IL-2 and IL-4 production among different strains of mice. Individual housing served to increase IL-2 production among BALB/c mice (TH-2 dominant strain) or IL-4 production among C57Bl/6 mice (TH-1 dominant strain). Other types of stressors, including footshock and restraint stress, also compromise immune function in murine models. For example, Zalcman et al (1991) reported diminished natural killer cell cytotoxicity in mice exposed to footshock. Interestingly, the decreased natural killer cell cytotoxicity induced by footshock was associated with a reduction in central catecholamines (e.g., DA, NE). Furthermore, Berkenbosch et al (1991) investigated whether uncontrollable stressors (e.g., immobilization, footshock) are capable of modulating the reactivity of the immune system to an antigen.

Indeed, both restraint stress and acute footshock increased the immune response (e.g., production of splenic antibodies) to an antigen (sheep red blood cells, SRBC) but the immune response was dependent on the interval between stressor exposure and antigen presentation. The pathway for such stressor-immune responses seem to be mediated by activation of the HPA axis. In fact, CRF antibodies selectively inhibit ACTH release from the pituitary in response to immobilization stress. Exposure to stressor associated odors also activates the HPA axis (Zalcman, 1991; Cocke et al, 1993). For example, Cocke et al (1993) reported that exposure of naive animals to the odors and vocalizations of a stressed animal suppressed splenic IL-2 production and reduced natural killer cell cytotoxicity. Tumor development and progression of symptoms of autoimmune disease also increased in these odor-recipient animals. Taken together, exposure of animals to uncontrollable stressors produces changes in IL-2 activity (and other related immune disturbances) with associated changes in DA activity. Furthermore, it seems that variations in IL-2 activity are responsible, at least in part, for the changes in central DA activity associated with either exposure to an uncontrollable stressor or induction of an antigenic challenge. Such an alteration in mesencephalic DA activity with varying central IL-2 activity would induce neurochemical and behavioral alterations, similar to those exhibited in human depression and other stress-induced pathologies.

Interleukin-2 Levels Induce Behavioral Depression by Altering Mesencephalic Dopamine Activity

Interleukin-2 produces proliferation, differentiation, and recruitment of T and B lymphocytes, natural killer cells, and thymocytes. Interleukin-2 receptors have been identified in various regions of the mouse and rat brain including the arcuate nucleus, median eminence, hippocampus, medial habenula, locus coeruleus, and cerebral cortex (Araujo et al, 1989; Nistico, 1993). Although IL-2 occurs endogenously, side effects associated with increased IL-2 levels, include somnolence and depression (Whittington & Faulds, 1993; Meyers & Valentine, 1995). Indeed, intravenous IL-2 infusion among patients with metastatic melanoma provoked fatigue and mood alteration (Caraceni et al, 1992; McDaniel et al, 1995). In addition, it should be recalled that increased levels of IL-2 in melancholic depression (Maes et al, 1992) may contribute to the fatigue reported by patients. In rats, intracerebroventricular infusion of IL-2 produced marked behavioral and EEG changes which may account for the fatigue provoked by IL-2 therapy in cancer patients. For example, intracerebroventricular IL-2 administration produced dose-dependent soporific effects and electrocorticogram (ECoG) slow wave sleep in awake animals (De Sarro et al, 1990; Nistico, 1993). Naloxone application into the locus coeruleus, conversely, antagonized the behavioral and ECoG changes. It is conceivable that opioid peptides modulate the soporific effects induced by central IL-2 administration (Kim et al, 1986; DeSarro et al,

1990; Carr et al, 1991; van den Bergh et al, 1991; Rameshwar et al, 1992; Calvo et al, 1994; Ho et al, 1994). In addition, the mood alterations and concomitant motivational disturbances evident in patients receiving IL-2 therapy are also similar to the motivational disturbances symptomatic of melancholic forms of depression. It is tempting to speculate that the motivational disturbances induced by intravenous IL-2 administration are due to inhibitory effects of IL-2 on mesencephalic DA activity.

Interleukin-2 provokes DA alterations in brain regions which may contribute to CNS-immune interactions and which are known to be affected by physical and psychological stressors. Indeed, there is evidence to suggest that IL-2 release alters central electrophysiological activity and DA utilization. For example, intraperitoneal injection of IL-2 in mice reduced DA levels in the prefrontal cortex and likewise increased DOPAC:DA ratios in the same brain region (Zalcman, 1994). In a previous investigation, Alonso (1993) reported inhibitory effects of IL-2 on DA release in the mesencephalon. Interleukin-2 inhibitory effects on DA activity are not limited to the mesencephalic DA system since IL-2 has also been shown to inhibit nigrostriatal DA release (Lapchuk, 1992). In a similar vein, DA agonists are capable of blocking IL-2 production by T-cells. For example, Morikawa et al (1994) demonstrated that systemic application of bromocriptine, a DA D2 agonist with demonstrated antidepressant efficacy, to peripheral blood mononuclear cells, prevented T-cell proliferation (e.g., blocked IL-2 production) in response to a mitogen. Although

IL-2 provokes DA alterations in brain regions typically associated with uncontrollable stressor exposure, it is not clear whether increased IL-2 activity and resultant immune activation is interpreted by the brain as a stressor. Uncontrollable stressors produce a realm of neurochemical alterations, including increased release of CRF from the PVN of the hypothalamus. Thus, if the brain were interpreting increased IL-2 activity as a stressor it would seem plausible that IL-2 would also promote CRF release. However, available evidence to date suggests that IL-2 does not promote release of CRF from the PVN (Harbuz et al, 1992; Hillhouse, 1994). Although IL-2 does not provoke CRF release from the PVN, it does, however, stimulate ACTH release from the anterior pituitary (Karanth and McCann, 1991). It will be recalled that an increase in ACTH release is also evident following uncontrollable stressor application. Karanth and McCann (1991) reported that picomolar concentrations of human IL-2 increased ACTH release, not by increasing CRF release from the hypothalamus but by stimulating the anterior pituitary. Furthermore, Hillhouse (1994) reported that IL-2 stimulated secretion of VP from rat hypothalamic cells in vitro. Vasopressin, a hypothalamic neuropeptide that coexists with CRF, increases with the introduction of a stressor (Barbtanusz et al, 1993), and is capable of promoting ACTH release from the anterior pituitary. Since IL-2 promotes the release of VP from hypothalamic nuclei (Bindoni et al, 1988; Hillhouse, 1994), which, in turn, promotes ACTH release from the anterior pituitary, IL-2 may induce a stress response (e.g., similar changes in central DA activity) that is

different from that employed with conventional stressors. Indeed, IL-2 activation of hypothalamic nuclei by the release of VP, and concomitant changes in mesencephalic DA activity, may provide another means of communication between the immune and neuroendocrine systems.

The present investigation examined the influence of intraventricular IL-2 administration on self-stimulation performance from the mesencephalon. Eventually, we would like to employ immunohistochemical procedures to assess the ability of IL-2 to provoke brain region specific alterations of c-fos activity in mesocorticolimbic sites and to compare such variations to those induced by stressor exposure. In addition, it would be interesting to evaluate the profile of DA and peptide release in the mesencephalon associated with stressor associated pathology and that provoked by IL-2 administration. Ultimately such an analysis could provide an integrative description of central CA and peptide interaction to the provocation or exacerbation of psychological disturbance in general and depression in particular.

Materials and Methods

Subjects

Twenty-seven, naive, male, CD-1, mice purchased from Charles River (St. Constant, Quebec) at 5 weeks of age were employed as subjects. Mice were housed 4 per cage with food and water available ad libitum. Mice were permitted to acclimatize to the laboratory for 7 weeks before being subjected to surgery.

Surgery

At 12 weeks of age, mice were anesthetized with sodium pentobarbital (Somnotol, 65 mg/kg), and a bipolar stainless steel electrode (0.5 mm tip to tip, Plastic Products; Roanoke, Virginia) and a cannula (23 gauge) were stereotactically implanted in the mesencephalon and lateral ventricle, respectively. Stereotaxic coordinates for the A10 area and the lateral ventricle were determined by preliminary histological analyses and available mouse atlases (Sidman, Angevine, & Taber-Pierce, 1971; Wahlsten, Hudspeth, & Bernhardt, 1975). Stereotaxic coordinates for the lateral ventricle: AP +0.8 mm from Bregma, L +0.7 mm from the midline, V. -2.8 to -3.0 mm from flat skull surface; A10: A.P. -3.0 to -3.1 mm from Bregma, L +0.5 mm from the midline and V. -4.7 to -4.8 mm from flat skull surface. All subjects were maintained on warm heating pads for three days postoperatively and supplemented with a wet mash diet (Sustagen, Mead Johnson) prior to returning to the main animal housing unit. All animals were allowed a 10 day recovery period before the initiation of behavioral testing.

Apparatus

The self-stimulation apparatus consisted of 30 cm (diameter) x 24 cm high white polyethylene tubs. The floor of each tub contained a 2 cm well positioned in the center of each chamber. Head-dipping through a distance of 1 cm interrupted a photobeam, resulting in the delivery of a monophasic square wave stimulation by a constant current stimulator (Schnabel Electronics, Saskatoon,

Sakatchewan).

Self-Stimulation Training and Threshold Determination

All mice were trained to respond for ICSS until stable baseline rates were achieved. Baseline was defined as three consecutive days displaying less than 15% variability in ICSS responding among days. Initially, all mice were trained to respond at 70 μ A and 80 Hz (0.3-msec pulse width, and a 0.1-sec pulse duration) for 15 min, until stable rates of responding were observed. Following this training interval, mice were trained to respond for ICSS in a variable frequency procedure which commenced at 80 Hz (70 μ A) and decreased by 10 Hz in a stepwise fashion. Each animal was tested for 3 min at each frequency. The number of responses were recorded at 80 Hz, 70 Hz, 60 Hz, 50 Hz, 40 Hz, 30 Hz, and 20 Hz. If an animal was observed to extinguish at a particular frequency, one priming pulse was initiated to allow for completion of the ascending phase of the test session. After completion of the descending phase of the test session, stimulation frequency was increased in 10 Hz steps from 20 Hz to 80 Hz. The descending and ascending phases were averaged across frequencies and a frequency-response curve was established for each subject. If necessary, current intensities were adjusted to elicit responding at these frequencies of stimulation. Any newly selected current intensity for any animal was held constant for the remainder of the experiment. Threshold was defined as the stimulation frequency which produced 50 % of the maximal response rate employed at 80 Hz. The selection of the stimulation parameters and

threshold determination employed in this experiment was predicated on pilot experimentation (See Appendix A).

Test Procedure

Following baseline ICSS, subjects received an injection of either IL-2 (Human Recombinant IL-2, R & D Systems, Inc., Minneapolis, Mn.) 5 ng / 1 ul sterile phosphate buffered saline (PBS) ph 7.2) or vehicle (1 ul PBS) intraventricularly using a Hamilton microliter syringe. All mice were placed in ICSS chambers and retested for self-stimulation thresholds immediately (15 min), 24, 48 and 168 hours following injection.

Histology

At the conclusion of behavioral testing, animals were perfused intracardially with physiological saline and 10% formalin. After excision of the brain from the cranial cavity, brains were fixated in formalin for approximately 2 weeks. The brains were subsequently frozen on a microtome and coronal sections (40um) were mounted and stained with cresyl violet for histological verification of electrode and cannulae placement.

Data Analyses

The number of responses in both vehicle (n = 9) and IL-2 groups (dorsal VTA n = 14, ventral VTA n = 4) were analyzed by ANOVA with repeated measures for the frequency and day variables (see Appendices B, C & D). Dunn's multiple comparisons ($p < .05$) were used to compare differences in treatment or frequency effects. Reward thresholds were calculated for each

animal as the frequency which approximated the half-maximal number of responses emitted at the highest pre-treatment frequency (80 Hz).

Results

Histological examination of the electrode sites revealed that the electrode tips were localized within either the dorsal or ventral aspects of the ventral tegmental area and that the cannulae were positioned in the lateral ventricles (see Figures 1a, 1b, and 1c). No grossly observable necrotic areas were apparent among animals responding for brain stimulation from the dorsal or ventral aspects of the A10 area. Likewise, intraventricular cannulation and IL-2 administration failed to produce necrosis in the surrounding tissue. The coordinates for electrode placement in the mesencephalon varied rostrocaudally; 3.0mm to 3.2mm anterior to Bregma; 0.3mm to 0.6mm medio-laterally from midline; and 4.7mm to 4.9mm ventrally from skull surface (see Figure 2).

Insert Figures 1 & 2 about here

Figure 1a. Photomicrograph of a cresyl violet stained coronal section through the VTA, depicting a typical dorsal A10 electrode placement.

Figure 1b. Photomicrograph of a cresyl violet stained coronal section through the lateral ventricles, depicting a typical cannula placement.

Figure 1c. Photomicrograph of a cresyl violet stained coronal section through the VTA, depicting a typical ventral A10 electrode placement.

Figure 2. Schematic representation (rostral-caudal) depicting electrode placements in the dorsal (▣) or the ventral (▼) aspects of the A10 area in animal receiving IL-2 intraventricularly.

The frequency-response curves among animals responding for brain stimulation from the dorsal aspects of the tegmental area in the no-injection sessions (baseline curves) were similar in both the vehicle and drug groups (Figure 3). The shape of the frequency-response curves in the vehicle group was not affected by injection of phosphate buffered saline in any mouse. In order to compare the effects of central IL-2 administration in animals with varying response profiles, the response rates at each frequency were expressed as a percentage of the maximal baseline rate found in the no-injection sessions in the same animal. The maximal rates ranged from 45 to 172 responses per minute in mice with both dorsal and ventral electrode placements. The amount of stimulation required to produce half-maximal performance was used to detect changes in the reinforcing efficacy of brain stimulation following intraventricular IL-2 administration.

Insert Figure 3 about here

Analysis of the percent change in responding from maximal baseline scores revealed that performance varied as a function of drug ($F(2,24) = 6.37; p < .01$). Intraventricular injection of IL-2 shifted the frequency-response curve in animals responding for self-stimulation from the dorsal aspects of the tegmental area down and to the right, relative to the pre-injection baseline curve and the curve for saline control (Figure 4).

Figure 3. Mean ($\pm$ S.E.M.) rate of baseline responding for ICSS from the ventral and dorsal aspects of the VTA in mice. The frequency-response curves were comparable among animals with either dorsal or ventral electrode placements.

Intraventricular injection of the same dose of IL-2 in animals responding for self-stimulation from the ventral aspects of the tegmental area shifted the frequency response curve up and to the left relative to baseline control (Figure 5). A shift in the locus of rise requires increased stimulation (dorsal VTA) or decreased stimulation (ventral VTA) to maintain the half-maximal response in each animal.

 Insert Figures 4, 5, & 6 about here

The median threshold, which produced 50% of the maximal baseline response rate, was calculated by linear interpolation in each mouse. The threshold was determined in all mice, across all 4 test periods, in both treatment groups (IL-2 5ng/1ul PBS and 1 ul PBS) and subjected to analysis of variance (Figure 6). The effect of intraventricular drug treatment was statistically significant ($F(2,24) = 16.17, p < .01$). Dunn's multiple comparisons within the simple main effect of drug administration, based on a priori predictions, revealed a significant difference between dorsal animals which received drug and vehicle ($F(1,106) = 18.8, p < .01$), and dorsal and ventral tegmental animals which received central injections of IL-2 ($F(1,106) = 33.5, p < .01$). Although there was no significant interaction between drug (BG variable) and test session (time), a priori analyses of variance revealed a significant effect of time and drug in animals with dorsal tegmental electrode

Figure 4. Mean rate of ICSS, following IL-2 administration, in a typical mouse with a dorsal VTA electrode placement. ICSS rates were recorded at three minute intervals over the range of test frequencies, in a descending and ascending fashion. Averaged rates of responding at each frequency prior to IL-2 or saline administration served as the pre-drug(saline) control for each animal. IL-2 or saline was administered only on the immediate test day 15 min before ICSS testing. ICSS rates were assessed during a 42 minute test session (i) immediately following acute intraventricular injection of IL-2 and again (ii) 24 hours (iii) 48 hours and (iv) 168 hours post injection. Intraventricular injection of IL-2 shifted the frequency-response curve down and to the right relative to the pre-injection baseline curve.

Percent of Maximum Baseline

Percent of Maximum Baseline

Percent of Maximum Baseline

Percent of Maximum Baseline

Figure 5. Mean rate of ICSS, following IL-2 administration, in a typical mouse with a ventral VTA electrode placement. ICSS rates were recorded at three minute intervals over the range of test frequencies, in a descending and ascending fashion. Averaged rates of responding at each frequency prior to IL-2 or saline administration served as the pre-drug(saline) control for each animal. IL-2 or saline was only administered on the immediate test day 15 min before ICSS testing. ICSS rates were assessed during a 42 minute test session (i) immediately following acute intraventricular injection of IL-2 and again (ii) 24 hours (iii) 48 hours and (iv) 168 hours post injection. Intraventricular injection of IL-2 shifted the frequency-reponse curve up and to the left relative to the pre-injection baseline curve.

Percent of Maximum Baseline

Percent of Maximum Baseline

Percent of Maximum Baseline

Percent of Maximum Baseline

Figure 6. Ventral tegmentum self-stimulation reward thresholds in mice with dorsal and ventral A10 electrode placements receiving either IL-2 or phosphate buffered saline intraventricularly. The acute administration of either IL-2 or phosphate buffered saline occurred on the immediate test session 15 min before retesting of ICSS reward thresholds. The reward thresholds gradually increased over the 4 test sessions in the dorsal group which received IL-2 while the ventral and vehicle group exhibited no change in reward thresholds.

placements ($F(3,72) = 2.90$, $p < .05$). Multiple comparisons within the simple main effect of time in dorsal animals receiving IL-2 intraventricularly revealed a significant increase in threshold from immediate time of testing to testing of threshold 168 hours after central injection ($F(1,106) = 8.57$, $p < .01$). Dorsal VTA self-stimulation threshold progressively increased with acute IL-2 injection relative to vehicle. There was no significant difference in threshold between ventral animals receiving IL-2 and control animals over the four test sessions presumably due to the unequal and smaller sample sizes. In addition, thresholds in vehicle-treated and ventral tegmental animals did not vary appreciably across all 4 test periods and remained at baseline level.

Discussion

The present experiment demonstrated that central administration of IL-2 attenuated self-stimulation performance from the dorsal A10 area. Such an effect from the dorsal aspects of the tegmental area, as indicated by an elevation of ICSS threshold and a shift of frequency-response curves down and to the right, developed immediately and gradually increased over the four test sessions. Central administration of IL-2 decreased the rewarding efficacy of ICSS from the dorsal A10 area, such that a higher frequency was required to produce the half-maximal response which defined reward threshold. The decline in rewarding properties of the stimulation increased over the four test periods being most pronounced at 168 hours after IL-2 administration. In contrast, self-stimulation performance from ventral aspects of the A10 area increased with

central IL-2 administration as indicated by a slight decrease in ICSS threshold and a leftward shift of the frequency-response curve. The effect of central IL-2 administration on ICSS supported from the ventral aspects of the A10 area was also apparent immediately and remained constant over the four test sessions, although only approaching statistical significance. The attenuation of ICSS from the dorsal aspects of the A10 area did not involve reward-unrelated factors (e.g., attentional or motoric), since such factors should have decreased self-stimulation performance irrespective of the brain region supporting ICSS.

The results of the present investigation are consistent with the study by Anisman et al (1994). IL-2 administered i.p. in rats attenuated ICSS from the MFB. Using a similar behavioral paradigm as employed in the present study (constant frequency and variable current intensities), a rate-intensity function as opposed to a frequency-response curve for each animal was constructed. Reward thresholds were calculated for each animal's rate-intensity function using the constant of 30 response/min (which approximated the half-maximal number of responses rats emitted at the highest current intensity). Analysis of the effects of IL-2 on ICSS and reward thresholds revealed that performance varied as a function of cytokine treatment and current intensity. IL-2 produced a rightward shift of the rate-intensity function from the MFB in rats that received 1.0 ug IL-2 i.p. IL-2 treatment did not affect responding at the higher current intensities (45-50 uA) or the lower current intensities, but a marked reduction of responding was apparent in the mid-range (35-40 uA) of

intensities. In the present study, however, no significant effect of frequency was demonstrated. IL-2 attenuated ICSS responding across all frequencies producing a total shift of the reward thresholds in dorsal tegmental animals. The presence of an IL-2 treatment effect at the higher frequencies suggested that the behavioral protocol did not employ frequencies high enough to reestablish pre-drug ICSS thresholds.

Responding for rewarding brain stimulation was influenced over the four test sessions following acute IL-2 administration, replicating earlier cytokine and stress studies (Zacharko et al, 1991; Anisman et al, 1994). Paralleling the self-stimulation profile detected following stressor exposure, IL-2 proactively influenced the response to later responding for rewarding brain stimulation from the dorsal A10 area. Such an effect suggests that the seemingly long-term effects of central IL-2 treatment might reflect the combined effects of IL-2 coupled with immediate retesting of ICSS thresholds (an extinction-like effect) rather than actual distended effects attributable to IL-2 alone. For example, Anisman et al (1994) demonstrated that a lack of effect on ICSS from the MFB occurred when animals were injected with IL-2 and not tested until 24 hours later. In accordance with this observation, it is conceivable that the carry-over effects of IL-2 treatment may have originated from anhedonic consequences produced by IL-2 when animals were tested immediately after treatment (Anisman, 1994). Similar effects on self-stimulation performance appear among animals tested for self-stimulation immediately following stressor exposure but

not among animals in which self-stimulation is delayed (Zacharko & Anisman, 1991).

The effects of IL-2 on ICSS from the VTA in the present study are limited to the particular dose of 5ng IL-2/1ul PBS. In fact, different laboratories have reported that the effects of IL-2 on mesencephalic DA cells vary with the dose of the peptide employed. Low concentrations of IL-2 applied exogenously to mesencephalic and nigrostriatal cell cultures potentiated DA release while higher concentrations of IL-2 inhibited DA release (Alonso, 1993; Lapchak, 1992). In the present study, the use of 5ng IL-2/1ul PBS represents a fairly large dose when compared to other dosages employed in the literature. Investigators have reportedly used doses as low as 200 picograms to doses as high as 10 ng icv in rodents (Nistico, 1993). It is likely that 5ng IL-2/1ul PBS was sufficient to inhibit DA release within the mesencephalon and to provoke increased DOPAC:DA ratios within the prefrontal cortex paralleling the neurochemical effects of IL-2 previously reported (Alonso, 1993; Lapchuk, 1992; Zalcman et al, 1994). Furthermore, it is assumed that the neurochemical changes associated with IL-2 administration reported in other studies (Zalcman et al, 1994) are responsible for the attenuation of ICSS performance reported in this study.

Another consideration when comparing the effects of cytokine administration on behavior is the route of administration. Different routes of administration of exogenous IL-2 may produce varying neurochemical effects

given the multiple potential pathways for cytokines to stimulate the HPA axis and other discrete brain regions, such as the VTA. For example, intracerebral injections of interleukins (e.g., IL-1) directly into the parenchyma failed to induce an inflammatory response in the CNS parenchyma at doses which promptly produced responses when injected subcutaneously (Perry et al, 1993). It is possible that there is an intrinsic anti-inflammatory component to the CNS microenvironment such that different neurochemical responses will be produced. The CNS is partially immunologically privileged as many aspects of immune function are suppressed or downregulated compared to other sites. Inflammatory responses are seen in the ventricles, the choroid plexus and the meninges as compared to the CNS parenchyma. Variations in immune responses evident in discrete CNS compartments might be due to the differences in the vasculature and also to specializations of the resident macrophage populations. For example, in the choroid plexus and the meninges a population of macrophages exists that show an upregulated phenotype when compared to microglia and more akin to that seen in other tissues. Additionally, in the meninges, a site of prominent acute inflammation, there are vast numbers of mast cells (Perry et al, 1993).

Direct intracerebral injection of IL-2 does not affect normal neuronal or glial cells and IL-2 receptors are not induced on the cell surface of normal brain tissue nor are antibodies formed. Yamasaki et al (1989) reported that antibodies against IL-2 were produced with multiple intracerebral or intraperitoneal

injections of IL-2 but antibody production was insignificant with a single injection of IL-2. Additionally, neuronal and vascular pathological changes are not induced following intracranial rIL-2 administration. Histological examination revealed no direct toxic action of rIL-2 on normal brain tissues, although a transient, nonspecific infiltration of mononuclear lymphoid cells or a reactive gliosis was occasionally observed at the injection site (Yamasaki et al, 1989). Therefore, the behavioral concomitants induced by intraventricular injection of IL-2 in the present study are likely due to neurochemical manipulations and not to toxic effects of IL-2. In addition, although similar alterations in ICSS performance occurred with central (present study) and peripheral IL-2 administration (Anisman, 1994), the attenuation of ICSS from the dorsal A10 area and the MFB was most probably due to the activation of distinct neural mechanisms and/or pathways.

In the present study, the use of ICSS allows for the direct measurement of IL-2 effects on the activity of the VTA although the mechanism(s) by which IL-2 affects ICSS remains to be determined. The VTA is a focal point of the neurocircuitry of reward and investigators have demonstrated its involvement in reward and incentive motivation (Wise, 1978; Phillips, 1984; Bozarth, 1987; Fibiger et al, 1987). Interestingly, IL-2 receptors are not located within the VTA yet IL-2 administered intraventricularly affects ICSS from the dorsal aspects of the VTA. As indicated earlier, IL-2 administration has been shown to induce a variety of central neurochemical changes, including alterations of

hypothalamic NE and mesocorticolimbic DA turnover, as well as neuropeptide and opioid variations in discrete brain regions, including the VTA and its projection sites. Although the interrelationships are not clearly defined, central effects of IL-2 may disrupt ICSS performance by increasing DA turnover via opioid pathways. An abundance of evidence exists linking immune function with opioid availability. For example, cytokines, including IL-2, have been reported to influence the expression of numerous neuropeptides (e.g., CRH, substance P, and opioids, among others) in several brain regions (Ho et al, 1994; Rothwell & Hopkins, 1995). In addition, it is suspected that opioid peptides modulate the effects produced by central IL-2 administration, such as the soporic effects of IL-2, which have been antagonized by naloxone (Kim et al, 1986; DeSarro et al, 1990; Carr et al, 1991; van den Bergh et al, 1991; Rameshwar et al, 1992; Calvo et al, 1994). In stress research the role of neuropeptide release is well defined. The stressor-induced activation of DA neuronal activity, the behavioral concomitants of such activation and resultant accumulation of DOPAC concentrations have been linked to the activation of opioid receptors in the A10 region. In addition, pharmacological manipulations which replenish enkephalin release largely eliminate the behavioral effects of the stressor. For example, stressor-induced disruption of ICSS from dorsal aspects of the A10 region could be antagonized by administration of the opioid analogue, D-Ala²-Met⁵-enkephalinamide (Maddeaux & Zacharko, 1992). Moreover, research conducted in this laboratory has revealed that stressors

provoke marked and long-lasting reductions in ICSS from dorsal VTA. The neurochemical profile induced by IL-2 administration both peripherally and centrally resembles that produced by exposure to uncontrollable stressors (Shanks et al, 1991; Zalcman et al, 1991; & Zalcman et al, 1994) supporting the hypothesis that alterations in central IL-2 activity are perceived, centrally, as a stressor. Taken together, the findings of the present investigation suggest that central IL-2 application affects ICSS thresholds, presumably as a consequence of a decline in the motivational or reinforcing properties associated with self-stimulation.

References

- Ader, R., & Cohen, N. (1993). Psychoneuroimmunology: conditioning and stress. Annual Review of Psychology, **44**, 53-85.
- Alonso, R., Chaudieu, I., Diorio, J., Krishnamurthy, A., Quirion, R., and Boksa, P. (1993). Interleukin-2 modulates evoked release of [3H] dopamine in rat cultured mesencephalic cells. Journal of Neurochemistry, **61** (4), 1284-1290.
- American Psychiatric Association (1994). DSM-IV: Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington D.C., American Psychiatric Press.
- Anisman, H., Kokkinidis, L. & Merali, Z. (1995). Interleukin-2 influences responding for rewarding brain stimulation. Society for Neuroscience Abstracts, **20**(2), 1603.
- Anisman, H. & Zacharko, R.M. (1990). Multiple neurochemical and behavioral consequences of stressors: implications for depression. Pharmac. Ther., **46**, 119-136.
- Anisman, H., Zalcman, S., & Zacharko, R.M. (1993). The impact of stressors on immune and central neurotransmitter activity: bidirectional communication.

Reviews in the Neurosciences, 4, 147-180.

Araujo, D.M., Lapchuk, P.A., Collier, B., & Quirion, R.

(1989). Localization of interleukin-2 immunoreactivity and interleukin-2 receptors in the rat brain: interaction with the cholinergic system. Brain Research, 498, 257-266.

Arzt, E., Sauer, J., Pollmacher, T., Labeur, M., Holsboer,

F., Reul, J., & Stalla, G. (1994). Glucocorticoids suppress interleukin-1 receptor antagonist synthesis following induction by endotoxin. Endocrinology, 134(2), 672-677.

Asberg, M., Bertilsson, L., Martensson, B., Scalia Tomba,

G.P., Thoren, P., & Trasken-Bendz (1984). CSF monoamine metabolites in depression. Acta Psychiatr Scand (69), 201-219.

Baillie, P., Wolfe, C., MacNeil, G., Kasian, M., & Zacharko,

R. (1988). Antidepressant specificity in the reversal of performance deficits in intracranial self-stimulation from mesolimbic and mesocortical sites in the DBA/2J mouse strain. Society for Neuroscience Abstracts, 14, 45.

Ban, E., Milon, G., Prudhomme, N., Fillion, G., & Haour, F.

(1991). Receptors for interleukin-1 in mouse brain: mapping and neuronal localization in hippocampus. Neuroscience, **43**(1), 21-30.

Banks, W.A., & Kastin, A.J. (1991). Blood to brain transport of interleukin links the immune and central nervous systems. Life Sciences, **48**, 117-121.

Bartanusz, V., Jezova, D., Bertini, L.T., Tilders, F.J.H., Aubry, J.M., & Kiss, J.Z. (1993). Stress-induced increase in vasopressin and corticotropin-releasing factor expression in hypophysiotrophic paraventricular neurons. Endocrinology, **132**(2), 895-902.

Bartanusz, V., Aubry, J.M., Steimer, T., Baffi, J., & Kiss, J.Z. (1994). Stressor-specific increase of vasopressin mRNA in paraventricular hypophysiotrophic neurons. Neuroscience Letters, **170**, 35-38.

Benjamini, E., & Leskowitz, S. (1991). Immunology: A Short Course. Wiley-Liss, Toronto.

Berger, P.A., Faull, K.F., Kilhowski, J., Anderson, P.J., Kraemer, H., Davis, K.L., & Barchas, J.D. (1980). CSF monoamine metabolites in depression and schizophrenia. American Journal of Psychiatry, **137**, 174-180.

Berkenbosch, F., Wolvers, D. A., & Derijk, R. (1991).

Neuroendocrine and immunological mechanisms in stress-induced immunomodulation. Journal of Steroid Biochem. Molec. Biology, 40(4-6), 639-647.

Bertolucci-Angio, M., Serrano, A., Driscoll, P., & Scatton,

B. (1990). Involvement of mesocorticolimbic dopaminergic systems in emotional states. Progress in Brain Research, 85, 405-417.

Besedovsky, H., Sorkin, E., Felix, D., & Haas, H. (1977).

Hypothalamic changes during the immune response. European Journal of Immunology, "", 323-325.

Besedovsky, H.O. & del Rey, A. (1990). Interactions between

immunological cells and the hypothalamus-pituitary-adrenal axis: an example of neuroendocrine immunoregulation. Stress and the Aging Brain, Raven Press: New York.

Bindoni, M., Perciavalle, V., Beretta, S., Belluardo, N., &

Diamanstein, T. (1988). Interleukin-2 modifies the bioelectric activity of some neurosecretory nuclei in the rat hypothalamus. Brain Research, 462, 10-14.

Black, P.H. (1994). Central nervous system-immune system interactions: psychoneuroendocrinology of stress and

its immune consequences. Antimicrobial Agents and Chemotherapy, 38(1), 1-6.

Black, P.H. (1994). Immune system-central nervous system interactions: effect and immunomodulatory consequences of immune system mediators on the brain.

Antimicrobial Agents and Chemotherapy, 38(1), 7-12.

Bowers, W.J., Zacharko, R.M., & Anisman, H. (1987).

Evaluation of stressor effects on intracranial self-stimulation from the nucleus accumbens and the substantia nigra in a current intensity paradigm. Behavioral Brain Research, 23, 85-97.

Bozarth, M. (1987). Ventral tegmental reward system. Brain Reward Systems and Abuse. J. Engel and L. Oreland (eds), Raven Press, New York.

Breder, C.D., Dinarello, C.A., & Saper, C.B. (1988).

Interleukin-1 immunoreactive innervation of the human hypothalamus. Science, 240, 321-323.

Brown, A.S., & Gershon, S. (1993). Dopamine and depression.

Journal of Neural Transmission, 91, 75-109.

Brooks, W.H., Cross, R.J., Roszman, T.L., & Markesbery, W.R.

(1982). Neuroimmunomodulation: neuroanatomical basis for

impairment and facilitation. Annals of Neurology, 12, 56-61.

Brown, M.R., Fisher, L.A., Rivier, J., Spiess, J., Rivier, C., & Vale, W. (1981). CRF: Effects on the sympathetic nervous system and oxygen consumption. Life Sciences, 30, 207-210.

Bunney, B.S., Chiodo, L.A., & Grace, A.A. (1991). Midbrain dopamine system electrophysiological functioning: a review and new hypothesis. Synapse, 9, 79-94.

Butler, P.D., Weiss, J.M., Stout, J.C., & Nemeroff, C.B. (1990). Corticotropin-releasing factor produces fear - enhancing and behavioral activating effects following infusion into the locus coeruleus. The Journal of Neuroscience, 10(10), 176-183.

Cabib, S., Kempf, E., Schleef, C., Oliverio, A., & Puglisi-Allegra, S. (1988). Effects of immobilization stress on dopamine and its metabolites in different brain areas of the mouse: role of genotype and stress duration. Brain Research, 441, 153-160.

Cador, M., Taylor, J.R., & Robbins, T.W. (1991). Potentiation of the effects of reward-related stimuli by dopaminergic dependent mechanisms in the nucleus accumbens.

Psychopharmacology, **102**, 156-162.

Calvo, C.F. (1993). Substance P stabilizes interleukin-2

mRNA in activated Jurkat cells. Journal of

Neuroimmunology, **51**, 85-91.

Caraceni, A., Martini, C., Belli, F., Mascheroni, L.,

Rivoltini, L., Arienti, F., and Cascinelli, N.

(1992). Neuropsychological and neurophysiological

assessment of the central effects of interleukin-2

administration. European Journal of Cancer Therapy,

29A, 1266-1269.

Carlson, J.N., Stanley, S.D., & Hinds, P.A. (1987). Changes in

d-amphetamine elicited rotational behavior in rats

exposed to uncontrollable footshock stress. Pharmacology,

Biochemi. y, and Behavior, **26**, 17-21.

Carlsson, A., Falck, B., and Hillarp, N.A. (1962). Cellular

localization of brain monoamines. Acta Physiol. Scand

56 (Suppl. 196), 1-28.

Carr, D. (1992). Neuroendocrine peptide receptors on cells

of the immune system. Chemical Immunology, K. Ishizaka

(ed.), La Jolla, California.

Carr, D., & Blalock, J.E. (1991). Naloxone administration in

vivo stereoselectively alters antigen-dependent and

antigen-independent immune responses.

Psychoneuroendocrinology, 16(5), 407-415.

Cenci, M.A., Kalen, P., Mandel, R.J., & Bjorklund, A.(1992).

Regional differences in the regulation of dopamine and noradrenaline release in medial frontal cortex, nucleus accumbens and caudate-putamen: a microdialysis study in the rat. Brain Research, 581, 217-228.

Chappell, P.B., Smith, M.A., Kilts, C.D., Bissette, G.,

Ritchie, J., Anderson, C., & Nemeroff, C.B.(1986).

Alterations in corticotropin-releasing factor-like immunoreactivity in discrete rat brain regions after acute and chronic stress. The Journal of Neuroscience, 6(10), 2908-2914.

Cocke, R., Moynihan, J.A., Cohen, N. Grotta, L.J., & Ader, R.

(1993). Exposure to conspecific alarm chemosignals alters immune responses in balb/c mice. Brain, Behavior, and Immunity, 7, 36-46.

Cross, R.J., Brooks, W.H., Roszman, T.L. & Markesbery, W.R.

(1982). Hypothalamic-immune interactions. Journal of Neuroscience, 53, 557-566.

Cross, R.J., Markesbery, W.R., Brooks, W.H., & Roszman, T.L.

(1984). Hypothalamic-immune interactions:neuromodulation

of natural killer activity by lesioning the anterior hypothalamus. Immunology, **51**, 399-404.

Cross, R.J., Markesbery, W.R., Brooks, W.H. & Roszman, T.L. (1980). The acute effects of anterior hypothalamic lesions on the immune response. Brain Research, **196**, 79-87.

Csernansky, J.G., Csernansky, C.A., & Hollister, L.E. (1984). Distinct effects of two stresses on the behavioral response to apomorphine. Life Sciences, **35**, 1513-1518.

Cummings, S., Elde, R., Ellis, J., & Lindall, A. Corticotropin-releasing factor immunoreactivity is widely distributed within the central nervous system of the rat: an immunohistochemical study. Journal of Neuroscience, **3**, 1355-1368.

Dahlstrom, A., & Fuxe, K. (1964). Evidence for the existence of monoamine containing neurons in the central nervous system II. Demonstration of monoamines in the cell bodies of brain stem neurons. Acta Physiology Scand., **62**, 55.

Darko, D., Irwin, M.R., Risch, C., & Gillin, J.C. (1992). Plasma beta-endorphin and natural killer cell activity in major depression: a preliminary study. Psychiatry Research, **43**, 111-119.

D'Angio, M.B., Serrano, A., Driscoll, P., & Scatton, B.

(1990). Involvement of mesocorticolimbic dopaminergic systems in emotional states. Progress in Brain Research, 85, 405-416.

DeKloet, E.R., Oitzl, M.S., & Schobitz, B. (1994). Cytokines

and the brain corticosteroid receptor balance: relevance to pathophysiology of neuroendocrine-immune communication. Psychoneuroendocrinology, 19(2), 121-134.

DeSarro, G.B., Masuda, Y., Ascioti, C., Audino, M.G., and

Nistico, G. (1990). Behavioral and ECoG spectrum changes induced by intracerebral infusion of interferons and interleukin 2 in rats are antagonized by naloxone. Neuropharmacology, 29 (2), 167-179.

Deutch, A.Y., Tam, S.Y., & Roth, R.H. (1985). Footshock and

conditioned stress increase 3,4-dihydroxyphenylacetic acid (DOPAC) in the ventral tegmental area but not substantia nigra. Brain Research, 333, 143-146.

Dobbin, J.P., Harth, M., McCain, G.A., Martin, R.A., &

Cousin, K. (1991). Cytokine production and lymphocyte transformation during stress. Brain, Behavior, and Immunity, 5, 339-348.

Dougherty, D.D., Sortwell, C.E., & Sagen, J. (1995).

Pharmacologic specificity of antidepressive activity by monoaminergic neural transplants. Psychopharmacology, 118, 10-18.

Drew, K.L., & Glick, S.D. (1990). Role of D1 and D2 receptor stimulation in sensitization to amphetamine-induced circling behavior and in the expression and extinction of the Pavlovian conditioned response. Psychopharmacology, 101, 465-471.

Dunn, A.J. (1993). Role of cytokines in infection-induced stress. In: Annals of the New York Academy of Sciences, 697, Corticotropin-Releasing Factor and Cytokines: Role in the Stress Response (Ed. Y. Tache and C. Rivier), 189-202.

Dunn, A.J., & Berridge, C.W. (1986). Corticotropin-releasing factor administration elicits a stress-like activation of cerebral catecholaminergic systems. Pharmacology, Biochemistry, and Behavior, 27, 685-691.

Elbaz, Z., Rochford, J., & Gratton, A. (1994). In vivo electrochemical monitoring of conditioned stress responses in nucleus accumbens and prefrontal cortex of rat. Society for Neuroscience Abstracts, 19, 1827.

- Evans, K.R. & Vaccarino, F.J. (1990). Amphetamine and morphine induced feeding: evidence for involvement of reward mechanisms. Neuroscience and Biobehavioral Reviews, 14, 9-22.
- Falck, B., Hillarp, N.A., Thieme, G., and Torp, A. (1962). Fluorescence of catecholamines and related compounds condensed with formaldehyde. Journal of Histochemical Cytochemistry, 10, 348-354.
- Feldman, R.S., & Quenzer, L.F. (1984). Fundamentals of Neuropsychopharmacology. Massachusetts: Sinauer.
- Fibiger, H.C., Lepiane, F.G., Jakubovic, A., & Phillips, A.G. (1987). The role of dopamine in intracranial self-stimulation of the ventral tegmental area. The Journal of Neuroscience, 7(12), 3888-3896.
- Fisher, L.A., Rivier, J., Rivier, C., Spiess, J., Vale, W., Brown, M.R. (1982). CRF: central effects on mean arterial pressure and heart rate in rats. Endocrinology, 11, 2222-2224.
- Fluckiger, E., Muller, E., Thorner, M.O. (1985). The Dopaminergic System, Springer-Verlag: New York.
- German, D.C., Dalsass, M., & Kiser, R.S. (1980). Electrophysiological examination of the ventral

tegmental (A10) area in the rat. Brain Research, 181, 191-197.

Gjerris, A., Werdelin, L., Rafaelsen, O.J., Alling, C., & Christensen, N.J. (1987). CSF dopamine increased in depression: CSF dopamine, noradrenaline and their metabolites in depressed patients and controls. Journal of Affective Disorders, 13, 279-286.

Glaser, R., Kennedy, S., Lafuse, W., Bonneau, R.H., Speicher, C., Hillhouse, J., & Kiecolt-Glaser, J.K. (1990). Psychological stress-induced modulation of interleukin-2 receptor gene expression and interleukin-2 production in peripheral blood leukocytes. Archives of General Psychiatry, 47, 707-711.

Glaser, R., Lafuse, W.P., Bonneau, R.H., Atkinson, C. & Kiecolt-Glaser, J.K. (1993). Stress-associated modulation of proto-oncogene expression in human peripheral blood leukocytes. Behavioral Neuroscience, 107, 525-529.

Goodwin, F.K., Post, R.M., Dunner, D.L., & Gordon, E.K. (1973). Cerebrospinal fluid metabolites in affective illness: the probenecid technique. American Journal of

Psychiatry, 130, 73-79.

Grunder, G., Wetzell, H., Hammes, E., & Benkert, O. (1993).

Roxindole, a dopamine autoreceptor agonist, in the treatment of major depression. Psychopharmacology, 111, 123-126.

Haour, F., Ban, E., Milon, G., Baran, D., & Fillion, G.

(1990). Brain interleukin 1 receptors: characterization and modulation after lipopolysaccharide injection. Progress in Neuroendocrinology, 3 (3), 196-205.

Harbuz, M.S., Stephanou, A., Knight, R.A., Chover-Gonzalez, A.J., & Lightman, S.L. (1992). Action of interleukin-2 and interleukin-4 on CRF mRNA in the hypothalamus and POMC mRNA in the anterior pituitary. Brain, Behavior, and Immunity, 6, 214-222.

Heinsbroek, R. (1990). Sex Differences in Behavioral and Biochemical Consequences of Aversive Stimulation in Rats. University of Amsterdam.

Hernandez, L., & Hoebel, B.G. (1988). Food reward and cocaine increase extracellular dopamine in the nucleus accumbens as measured by microdialysis. Life Sciences, 42, 1705-1712.

- Hickie, I. (1993). Impaired in vivo immune responses in patients with melancholia. British Journal of Psychiatry, 162, 651-657.
- Hillhouse, E.W. (1994). Interleukin-2 stimulates the secretion of arginine vasopressin but not corticotropin releasing hormone from rat hypothalamic cells in vitro. Brain Research, 650, 323-325.
- Ho, B.T., Lu, J.G., Huo, Y.Y., Fan, S.H., Meyers, C.A., Tansey, L.W., Payne, R., & Levin, V.A. (1994). Neurochemical basis of interleukin-2 modified discrimination behavior. Cytokine, 6 (4), July, 365-367.
- Hopkins, S.J. & Rothwell, N. J. (1995). Cytokines and the nervous system I: expression and recognition. Trends in Neuroscience, 18(2), 83-88.
- Irwin, M., Hauger, R.L., Brown, M., & Britton, K.T. (1988). CRF activates autonomic nervous system and reduces natural killer cytotoxicity. Clinical Center on Alcoholism, San Diego Veterans Administration Medical Center, Departments of Psychiatry and Medicine, School of Medicine, University of California, San Diego, La Jolla, California, 92162.
- Isometsa, E., Heikkinen, M., Henriksson, M., Aro, H., &

Lonqvist, J. (1995). Recent life events and completed suicide in bipolar affective disorder. Journal of Affective Disorders, 33, 99-106.

Kalivas, P.W. (1993). Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. Brain Research Reviews, 18, 75-113.

Kalivas, P. Duffy, P., & Latimer, L.G. (1987). Neurochemical and behavioral effects of corticotropin-releasing factor in the ventral tegmental area of the rat. The Journal of Pharmacology and Experimental Therapeutics, 242(3), 757-763.

Kalivas, P. & Stewart, J. (1991). Dopamine transmission in the initiation and expression of drug-and stress induced sensitization of motor activity. Brain Research Reviews, 16, 223-244.

Kamata, K., Yoshida, S., & Kameyama, T. (1986). Antagonism of footshock stress-induced inhibition of intracranial self-stimulation by naloxone or methamphetamine. Brain Research, 371, 197-200.

Karanth, S., & McCann, S.M. (1991). Anterior pituitary hormone control by interleukin-2. National Academy of Science, 88, 2961-2965.

- Karp, J.D., Cohen, N., & Moynihan, J.A. (1994). Quantitative differences in interleukin-2 and interleukin-4 production by antigen-stimulated splenocytes from individually- and group-housed mice. Life Sciences, **55(10)**, 789-795.
- Katayama, M., Kobayashi, S., Kuramoto, N., & Yokoyama, M.M. (1987). Effects of hypothalamic lesions on lymphocyte subsets in mice. Annals of New York Academy of Science, **496**, 366-376.
- Kebabian, J.W., & Calne, D.B. (1979). Multiple receptors for dopamine. Nature, **277**, 93-96.
- Keefe, K.A., Sved, A.F., Zigmond, M.J. & Abercrombie, E.D. (1993). Stress-induced dopamine release in the neostriatum: evaluation of the role of action potentials in nigrostriatal dopamine neurons or local initiation by endogenous excitatory amino acids. Journal of Neurochemistry, **61(5)**, 1943-1952.
- Keller, S.E., Schleifer, S.J., Demetrikopoulos, M.K. (1991). Stress-induced changes in immune function in animals: hypothalamo-pituitary-adrenal influences. In: Ader R, Felten, D.L. & Cohen, N. (eds); Psychoneuroimmunology. Academic Press, San Diego, 771-787.

- Kent, S., Bluthé, R.M., Dantzer, R., Hardwick, A.J. Kelley, K.W., Rothwell, N., & Vannice, J.L. (1992). Different receptor mechanisms mediate the pyrogenic and behavioral effects of interleukin 1. Neurobiology, 29(October), 9117-9120.
- Khansari, D.N., Murgu, A.J., & Faith, R.E. (1990). Effects of stress on the immune system. Immunology Today, 11(5), 170-174.
- Kim, H.S., Iyengar, S., & Wood, P.L. (1986). Opiate actions on mesocortical dopamine metabolism in the rat. Life Sciences, 39, 2033-2036.
- Koff, W.C., Fann, A.V., Dunegan, M.A., & Lachman, L.B. (1986). Catecholamine-induced suppression of interleukin-1 production. Lymphokine Research, 5(4), 239-247.
- Koslow, S.H., Maas, J.W., Bowden, C.L., Davis, J.M., Hanin, I. & Javard, J. (1983). CSF and urinary biogenic amines and metabolites in depression and mania. A controlled, univariate analysis. Archives of General Psychiatry, 40, 996-1010.
- Kropiunigg, U. (1993). Basics in psychoneuroimmunology. Annals of Medicine, 25, 473-479.

- Lapchuk, P.A. (1992). A role for interleukin-2 in the regulation of striatal dopaminergic function. Molecular Neuroscience, 3(2), 165-168.
- Lauer, C.J., Schreiber, W., Holsboer, F., & Krieg, J.C. (1995). In quest of identifying vulnerability markers for psychiatric disorders by all-night polysomnography, Archives of General Psychiatry, 52(Feb), 145-153.
- Levitt, A. (1994). Treatment guidelines for major depression. Current Canadian Psychiatry, 1(3), 9-13.
- MacNeil, G., Zalcman, S., Andrews, M., Zacharko, R., & Anisman, H. (1995). Anhedonia as a consequence of immunological challenge: differential effects of self-stimulation from the nucleus accumbens and the substantia nigra (unpublished).
- Maddeaux, C., and Zacharko, R. (1992). Intraventricular administration of D-Ala²-Met⁵-Enkephalinamide induces rapid recovery of responding for electrical brain stimulation from the ventral tegmental area following uncontrollable footshock. Brain Research Bulletin, 28, 337-341.
- Maes, M., Bosmans, E., Suy, E., Vandervorst, C., De Jonckheere, C., & Raus, J. (1990-91). Immune

disturbances during major depression: upregulated expression of interleukin -2 receptors.

Neuropsychobiology, 24, 115-120.

Maes, M., Stevens, W.J., Declerck, L.S., Bridts, C.H.,

Peeters, D., Schotte, C., & Cosyns, P. (1993).

Significantly increased expression of T-cell activation markers (interleukin-2 and HLA-DR) in depression:

further evidence for an inflammatory process during

that illness. Progress in Neuro-Psychopharmacology &

Biological Psychiatry, 17, 241-255.

Maes, M., Meltzer, H.Y., Buckley, P., & Bosmans, E. (1995).

Plasma-soluble interleukin-2 and transferrin receptor

in schizophrenia and major depression. European

Archives of Psychiatry and Clinical Neuroscience, 244,

325-329.

Maes, M., Smith, R., & Scharpe, S. (1995). The monocyte-T-

lymphocyte hypothesis of major depression.

Psychoneuroendocrinology, 20(2), 111-116.

Mantz, J., Thierry, A.M., & Glowinski, J. (1989). Effect of

noxious tail pinch on the discharge rate of

mesocortical and mesolimbic DA neurons: selective

activation of the mesocortical system. Brain Research,

476, 377-381.

Masana, M.I., Heyes, M.P., & Mefford, I.N. (1990).

**Indomethecin prevents increased catecholamine turnover in
rat brain following systemic endotoxin challenge.**

**Progress in Neuro-Psychopharmacological Biological
Psychiatry, 14, 609-621.**

Matthews, S.G., & Parrott, R.F. (1994). Centrally

**administered vasopressin modifies stress hormone
(cortisol, prolactin) secretion in sheep under basal
conditions, during restraint and following intravenous
corticotropin-releasing hormone. European Journal of
Endocrinology, 130, 297-301.**

McDaniel, J.S., Musselman, D.L., Porter, M.R., Reed, D.A., &

**Nemeroff, C.B. (1995). Depression in patients with
cancer. Archives of General Psychiatry, 52(Feb.), 89-
99.**

**McNeal, E.T. & Cimbolich, P. (1986). Antidepressants and
biochemical theories of depression.**

Psychological Bulletin, 99, 361-374.

Mendels, J., Stinnett, J.L., Burns, D., & Frazer, A. (1975).

**Amine precursors and depression. Archives of General
Psychiatry, 32, 22-30.**

Meyers, C.A., & Valentine, A.D. (1995). Neurological and psychiatric adverse effects of immunological therapy. CNS Drugs, 3(1), 56-68.

Miliaressis, E., Rompre, P.P., Laviolette, P., Phillippe, L. & Coulombe, D. (1986). The curve-shift paradigm in self-stimulation. Physiology and Behavior, 37, 85-91.

Miller, A.H., Spencer, R.L., McEwen, B.S., & Stein, M. (1993). Depression, adrenal steroids, and the immune system. Annals of Medicine, 25, 481-487.

Mitchell, J.B. & Gratton, A. (1992). Partial dopamine depletion of the prefrontal cortex leads to enhanced mesolimbic dopamine release elicited by repeated exposure to naturally reinforcing stimuli. The Journal of Neuroscience, 12(9), 3609-3618.

Mohankumar, P.S., & Quadri, S.K. (1993). Systemic administration of interleukin--1 stimulates norepinephrine release in the paraventricular nucleus. Life Sciences, 52, 1961-1967.

Mohankumar, P.S., Thyagarajan, S., & Quadri, S.K. (1993). Interleukin-1B increases 5-hydroxyindoleacetic acid release in the hypothalamus in vivo. Brain Research Bulletin, 31, 745-748.

Morikawa, K., Oseko, F. & Morikawa, S. (1994).

Immunosuppressive activity of bromocriptine on human T lymphocyte function in vitro. Clinical Experimental Immunology, **95**, 514-518.

Mouret, J., Lemoine, P., & Minuit, M.-P. (1987). Sleep

polygraphic, clinical and therapeutic markers of dopamine dependent depressions. Academie des Sciences, **305(3)**, 301-306.

Munck, A., Guyre, P.M., & Holbrook, N.J. (1984). Physiological functions of glucocorticoids in stress and their relation to pharmacological actions. Endocrine Reviews, **5(1), 25-41.**

Muscat, R., Towell, A., & Willner, P. (1988). Changes in

dopamine autoreceptor sensitivity in an animal model of depression. Psychopharmacology, **94**, 545-554.

Muscat, R., Sampson, D., & Willner, P. (1990). Dopaminergic

mechanism of imipramine action in an animal model of depression. Biological Psychiatry, **28**, 230-233.

Nakajima, S. (1989). Subtypes of dopamine receptors involved

in the mechanism of reinforcement. Neuroscience and Biobehavioral Reviews, **13 (2/3)**, 123-128.

Nakajima, S. & Baker, J.D. (1989). Effects of D2 dopamine

receptor blockade with raclopride on intracranial

self-stimulation and food-reinforced behavior.

Psychopharmacology, **98**, 330-333.

Nakajima, S., & McKenzie, G.M. (1996). Reduction of the rewarding effect of brain stimulation by blockade of dopamine D1 receptor with SCH 23390. Pharmacology, Biochemistry, and Behavior, **24**, 919-923.

Nakamori, T., Morimoto, A., Yamaguchi, K., Watanabe, T., Long, N.C., & Murakami, N. (1993). Organum vasculosum laminae terminalis (OVLT) is a brain site to produce interleukin-1 β during fever. Brain Research, **618**, 155-159.

Nemeroff, C.B. (1992). New vistas in neuropeptide research in neuropsychiatry: focus on corticotropin-releasing factor. Neuropsychopharmacology, **6(2)**, 69-75.

Nistic G. (1993). Communications among central nervous system, neuroendocrine and immune systems: interleukin-2. Progress in Neurobiology, **40**, 463-465.

Oades & Halliday (1987). Ventral tegmental (A-10) system. Brain Research Reviews, **12**, 117-165.

O'Donnell, P., & Grace, A.A. (1993). Physiological and morphological properties of accumbens core and shell neurons recorded in vitro. Synapse, **13**, 135-160.

- Olds, J. & Milner, P. (1954). Positive reinforcement produced by electrical stimulation of septal area and other regions of the rat brain. Journal of Comparative and Physiological Psychology, 47, 419-427.
- Perry, V.H., Andersson, P.B., & Gordon, S. (1993). Macrophages and inflammation in the central nervous system. Trends in Neuroscience, 16(7), 268-272.
- Phillips, A.G. (1984). Brain reward circuitry: a case for separate systems. Brain Research Bulletin, 12, 195-201.
- Phillips, A.G., Blaha, C.D., Fibriger, H.C. (1989). Neurochemical correlates of brain-stimulation reward measured by ex vivo and in vivo analyses. Neuroscience & Biobehavioral Reviews, 13, 99-104.
- Plata-Salaman, C.R. (1991). Dexamethasone inhibits food intake suppression induced by low doses of Interleukin-1B administered intracerebroventricularly. Brain Research Bulletin, 27, 737-738.
- Rameshwar, P., Gascon, P., & Ganea, D. (1992). Immunoregulatory effects of neuropeptides. Stimulation of interleukin-2 production by Substance P. Journal of Neuroimmunology, 37, 65-74.

- Rivier, C. (1992). Effect of peripheral and central cytokines on the hypothalamic-pituitary-adrenal axis of the rat. Annals of the New York Academy of Sciences, 697, 97-105.
- Rivier, C., & Rivest, S. (1993). Mechanisms mediating the effects of cytokines on neuroendocrine functions in the rat. Corticotropin-releasing Factor, Wiley, Chichester.
- Roszman, T.L., Cross, R.J., Brooks, W.H., & Markesbery, W.R. (1982). Hypothalamic-immune interactions II. The effect of hypothalamic lesions on the ability of adherent spleen cells to limit lymphocyte blastogenesis. Immunology, 45, 737-742.
- Rothwell, N.J. & Hopkins, S.J. (1995). Cytokines and the nervous system II: actions and mechanisms of action. Trends in Neuroscience, 18(3), 130-136.
- Sampson, D., Willner, P., & Muscat, R. (1991). Reversal of antidepressant action by dopamine antagonists in an animal model of depression. Psychopharmacology, 104, 491-495.
- Serra, G., Collu, M., D'Aquila, P.S., DeMontis, G.M., & Gessa, G.L. (1990). Possible role of dopamine D1 receptor in the behavioral supersensitivity to dopamine

agonists induced by chronic treatment with antidepressants. Brain Research, 527, 234-243.

Shanks, N. & Anisman, H. (1989). Strain-specific effects of antidepressants on escape deficits induced by inescapable shock. Psychopharmacology, 99, 122-128.

Shanks, N., Zalcmán, S., Zacharko, R.M., & Anisman, H. (1991). Alterations of central norepinephrine, dopamine, and serotonin in several strains of mice following acute stressor exposure. Pharmacology, Biochemistry, & Behavior, 38, 69-75.

Shanks, N., Griffiths, J., & Anisman, H. (1994). Central catecholamine alterations induced by stressor exposure: analyses in recombinant inbred strains of mice. Behavioral Brain Research, 63, 25-33.

Shapovalova, K.B. & Yakimovskii, A.F. (1988). Participation of the nigro-striatal and mesolimbic dopaminergic systems of the brain in control of learned motor responses. Fiziologicheskii Zhurnal SSR Imeni I.M. Sechenova, 73(5), 579-589.

Shea, J.D.C., Burton, R., & Girgis, A. (1993). Negative affect, absorption, and immunity. Physiology & Behavior, 53, 449-457.

Shintani, F., Kanba, S., Nakaki, T., Nibuya, M., Kinoshita,

N., Suzuki, E., Yagi, G., Kato, R., and Asai, M.

(1993). Interleukin-1B augments release of norepinephrine, dopamine, and serotonin in the rat anterior hypothalamus. The Journal of Neuroscience, 13(8), August 3574-3581.

Sidan, R., Angevine, J. & Taber-Pierce, E. (1981). Atlas of the Mouse Brain and Spinal Cord. Cambridge Mass: Harvard University Press.

Smith, K.A. (1988). Interleukin-2: Inception, impact, and implications. Science, 240, 1169-1176.

Stamford, J.A., Muscat, R., O'Connor, J.J., Patel, J., Trout,

S., Wieczorek, W., Kruk, Z. & Willner, P. (1991).

Voltammetric evidence that subsensitivity to reward following chronic mild stress is associated with increased release of mesolimbic dopamine.

Psychopharmacology, 105, 275-282.

Suhara, T., Nakayama, K., Inoue, O., Fukuda, H., Shimizu,

M., Mori, A., and Tateno, Y. (1992). D1 dopamine

receptor binding in mood disorders measured by positron emission tomography. Psychopharmacology, 106, 14-18.

- Swanson, L.W. (1982). The projection of the ventral tegmental area and adjacent regions: a combined fluorescent retrograde tracer and immunofluorescence study in the rat. Brain Research Bulletin, **9**, 321-353.
- Swanson, L.W., Sawchenko, P.E., Rivier, J. & Vale, W.W. (1983). Organization of ovine corticotropin-releasing factor immunoreactive cells and fibers in the rat brain: an immunohistochemical study. Neuroendocrinology, **36**, 165-186.
- Swiergiel, A.H., Takahashi, L.K., & Kalin, N.H. (1993). Attenuation of stress-induced behavior by antagonism of corticotropin-releasing factor receptors in the central amygdala in the rat. Brain Research, **623**, 229-234.
- Terao, A., Oikawa, M., and Saito, M. (1993). Cytokine induced change in hypothalamic norepinephrine turnover: involvement of corticotropin-releasing hormone and prostaglandins. Brain Research, **622**, 257-261.
- Trulson, M.E., Trulson, T.J., & Arastch, K. (1987). Recording of mouse ventral tegmental area dopamine-containing neurons. Experimental Neurology, **96**, 68-81

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PM-1 3½" x 4" PHOTOGRAPHIC MICROCOPY TARGET
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PRECISIONSM RESOLUTION TARGETS

- Van Dam, A-M, Brouns, M., Louisse, S., & Berkenbosch, F. (1992). Appearance of interleukin-1 in macrophages and in ramified microglia in the brain of endotoxin-treated rats: a pathway for the induction of non-specific symptoms of sickness. Brain Research, 588, 291-296.
- Van den Bergh, P. Rozing, J. & Nagelkerken, L. (1991). Opioid peptides as cytokines in T cell activation. Advances in Neuroimmunology, 1, 189-203.
- Van Praag, H.M., & Korf, J. (1971). Endogenous depressions with and without disturbances in the 5-hydroxytryptamine metabolism: a biochemical classification. Psychopharmacologia, 19, 148-152.
- Van Rood, Y.R., Bogaards, M., Goulmy, E., & Van Houwelingen, H.C. (1993). The effects of stress and relaxation in man: a meta-analytic study. Journal of Behavioral Medicine, 16(2), 163-178.
- Veening, J.G., van der Meer, M.J.M., Joosten, H., Hermus, A. R.M.M., Rijnkels, C.E.M., Geeraedts, L.M., and Sweep, C. G.J. (1993). Intravenous administration of interleukin-1B induces fos-like immunoreactivity in corticotropin-releasing hormone neurons in the paraventricular hypothalamic nucleus of the rat.

Journal of Chemical Neuroanatomy, 6, 391-397.

Vogel, W.H. (1985). Coping, stress, stressors, and health consequences. Neuropsychobiology, 13, 129-135.

Waguespack, P.J., Banks, W., & Kastin, A.J. (1994).

Interleukin-2 does not cross the blood-brain barrier by a saturable transport system. Brain Research Bulletin, 34(2), 103-109.

Wahlsten, D., Hudspeth, W., & Bernhardt, K. (1975).

Implications of genetic variation in mouse brain structure for electrode placement by stereotaxic surgery. The Journal of Comparative Neurology, 162, 519-532.

Wan, W., Janz, L., Vriend, C.Y., Sorensen, C.M., Greenberg, A.H., & Nance, D.W. (1993). Differential induction of c-fos immunoreactivity in hypothalamus and brain stem nuclei following central and peripheral administration of endotoxin. Brain Research Bulletin, 32, 581-587.

Wang, R.Y. (1981). Dopaminergic neurons in the rat ventral tegmental area. Brain Research Reviews, 3, 153-165. Watanabe, H. (1984). Activation of dopamine synthesis in mesolimbic dopamine neurons by immobilization stress in the rat. Neuropharmacology, 23(11), 1335-1338.

- Webster, E.L. & De Souza, E.B. (1988).** Corticotropin - releasing factor receptors in mouse spleen: identification, autoradiographic localization, and regulation by divalent cations and guanine nucleotides. Endocrinology, **122**(2), 609-617.
- Weiss, J.M., Goodman, P.A., Losito, B., Corrigan, S., Charry, J.M. & Bailey, W.H. (1981).** Behavioral depression produced by an uncontrollable stressor: relationship to norepinephrine, dopamine, and serotonin levels in various regions of rat brain. Brain Research Reviews, **3**, 167-205.
- Weissman, M.S., Pottenger, M., Kleber, H., Ruben, H.L., Williams, D., & Thompson, W.D. (1977).** Symptom patterns in primary and secondary depression: a comparison of primary depression with depressed opiate addicts, alcoholics, and schizophrenics. Archives of General Psychiatry, **34**, 854-862.
- Weizman, R., Laor, N., Podliszewski, E., Notti, I., Djaldetti, M. & Bessler, H. (1994).** Cytokine production in major depressed patients before and after clomipramine treatment. Biological Psychiatry, **35**, 42-47.

- Whitnall, M.H. (1993). Regulation of the hypothalamic corticotropin-releasing hormone neurosecretory system. Progress in Neurobiology, 40, 573-629.
- Whittington, R., & Faulds, D. (1993). Interleukin-2: A review of its pharmacological properties and therapeutic use in patients with cancer. Drugs, 46, 446-514.
- Willner, P. (1985). Depression: A Psychobiological Synthesis. John Wiley & Sons, Toronto.
- Wise, R.A. (1978). Catecholamine theories of reward: a critical review. Brain Research, 152, 215-247.
- Wise, R.A. (1982). Neuroleptics and operant behavior: the anhedonia hypothesis. The Behavioral and Brain Sciences, 5, 39-89.
- Wolfe, C., & Zacharko, R.M. (1991). Desmethylinipramine promotes recovery of self-stimulation from the prefrontal cortex following footshock. Brain Research Bulletin, 27, 601-604.
- Yamasaki, T., Kikuchi, H., Paine, J.T., Yamashita, J., Miyatake, S., Iwasaki, K., Kobayashi, H. Naraba, Y., & Hanaoka, M. (1989). Murine intracerebral interleukin-2 injection: pathological and immunological effects. Journal of Neurosurgery, 71, 732-740.

Zacharko, R.M., Lalonde, G., Kasian, M., & Anisman, H.

(1987). Strain-specific effects of inescapable shock on intracranial self-stimulation from the nucleus accumbens. Brain Research, 426, 164-168.

Zacharko, R.M. & Anisman, H. (1991). Stressor-induced anhedonia in the mesocorticolimbic system. Neuroscience & Biobehavioral Reviews, 15, 391-405.

Zacharko, R.M. & Anisman, H. (1990). Stressor provoked alterations of intracranial self stimulation in the mesocorticolimbic system: an animal model of depression. In P. Wilner and J. Scheel-Kruger (Eds.), The Mesolimbic Dopamine System: From Motivation to Action, Wiley, London.

Zacharko, R.M., Kasian, M., MacNeil, G., & Anisman, H. (1990). Stressor-induced behavioral alterations in intracranial self-stimulation from the ventral tegmental area: evidence for regional variation. Brain Research Bulletin, 25, 617-621.

Zacharko, R.M., Gilmore, W., MacNeil, G., Kasian, M. & Anisman, H. (1990). Stressor induced variations of intracranial self-stimulation from the mesocortex in several strains of mice. Brain Research, 533, 353-357.

Zalcman, S., Kerr, L., & Anisman, H. (1991).

Immunosuppression elicited by stressors and stress related odors. Brain, Behavior, and Immunity, 5, 262-273.

Zalcman, S., Irwin, J., & Anisman, H. (1991). Stressor-

induced alterations of natural killer cell activity and central catecholamines in mice.

Pharmacology, Biochemistry, and Behavior, 39, 361-366.

Zalcman, S., Shanks, N., & Anisman, H. (1991). Time

dependent variations of central norepinephrine and dopamine following antigen administration. Brain Research, 557, 69-76.

Zalcman, S., Green-Johnson, J.M., Murray, L., Nance, D.M.,

Dyck, D., Anisman, H., and Greenberg, A. (1994).

Cytokine specific central monoamine alterations induced by interleukin (IL) -1, IL-2, and IL-6. Brain Research, (00).

Zhang, L. & Barrett, J.E. (1990). Interactions of

corticotropin-releasing factor with antidepressant and anxiolytic drugs: behavioral studies with pigeons.

Biological Psychiatry, 27, 953-967.

Zisook, S., Shuchter, S.R., Irwin, M., Darko, D., Sledge, P., & Resovsky, K. (1993). Bereavement, depression, and immune function. Psychiatry Research, 52, 1-10.

Appendix A

The purpose of the pilot experimentation was to determine the effect of central IL-2 administration on the rate of ICSS responding from dorsal and ventral aspects of the tegmentum.

Materials and Methods

Subjects

Ten, naive, male, CD-1, mice purchased from Charles River (St. Constant, Quebec) at 5 weeks of age were employed as subjects. Mice were housed 4 per cage with food and water available ad libitum. Mice were permitted to acclimatize to the laboratory for 7 weeks before being subjected to surgery.

Surgery

At 12 weeks of age, mice were anesthetized with sodium pentobarbital (Somnotol, 65 mg/kg), and a bipolar stainless steel electrode (0.5 mm tip to tip, Plastic Products; Roanoke, Virginia) and a cannula (23 gauge) were stereotaxically implanted in the mesencephalon and lateral ventricle, respectively. Stereotaxic coordinates for the A10 area and the lateral ventricle were determined by preliminary histological analyses and available mouse atlases (Sidman, Angevine, & Taber-Pierce, 1971; Wahlsten, Hudspeth, & Bernhardt, 1975). Stereotaxic coordinates for the lateral ventricle: AP +0.8 mm from Bregma, L +0.7 mm from the midline, V. -2.8 to -3.0 mm from flat skull surface; A10: A.P. -3.0 to -3.1 mm from Bregma, L +0.5 mm from the

midline and V. -4.7 to -4.8 mm from flat skull surface. All subjects were maintained on warm heating pads for three days postoperatively and supplemented with a wet mash diet (Sustagen, Mead Johnson) prior to returning to the main animal housing unit. All animals were allowed a 10 day recovery period before the initiation of behavioral testing.

Apparatus

The self-stimulation apparatus consisted of 30 cm (diameter) x 24 cm high white polyethylene tubs. The floor of each tub contained a 2 cm well positioned in the center of each chamber. Head-dipping through a distance of 1 cm interrupted a photobeam, resulting in the delivery of a monophasic square wave stimulation by a constant current stimulator (Schnabel Electronics, Saskatoon, Saskatchewan).

Test Procedure

Animals were trained at a constant current of 70 μ A across a diverse range of frequencies (70, 80, 90, and 100 Hz). Animals were allotted 10 minutes to respond at each frequency as the frequency increased in 10 Hz increments. The average number of responses over three days at each frequency served as baseline data for each animal. Animals were then given either IL-2 (5ng IL-2/1ul PBS) or 1 ul vehicle (PBS) and immediately tested for change in response rates over four test periods (immediately, 24 hours, 48 hours, and 168 hours).

Results

Animals with ventral tegmental electrode placements given IL-2 did not decrease rate of responding relative to vehicle controls, so were combined into one group (ventral drug control, $n = 4$). Animals with dorsal VTA electrode placements upon receiving central IL-2 ($n = 6$) decreased the rate of responding significantly with respect to vehicle and ventral IL-2 animals ($F(1,8) = 6.60$; $p < .05$). Refer to Figures A and B.

Insert Figures A & B about here

There was also a significant interaction between group (control vs drug) and day ($F(3,24) = 4.02$; $p < .05$). Examination of the data suggest a more pronounced decrement in performance over test periods. Rate of responding at 168 hours in dorsal animals which received IL-2 decreased dramatically in comparison to other test sessions in this group, while vehicle and ventral animals increased or remained at baseline response rates. There was no significant effect of frequency, day, or interactions among these factors. The insignificance of frequency was not suprising after examining baseline rates. Animals responded at a relatively equal rate across frequencies and thus it was suspected that the parameters chosen may represent the upper portion of the frequency-response (reward threshold) curve. In addition, since animals were tested for ICSS performance only at higher current intensities, it is not

Figure A. Mean rate of responding for intracranial self-stimulation from the dorsal VTA in a typical mouse. ICSS rates were assessed during a 40 minute test session (i) immediately following acute intraventricular injection of IL-2 and again (ii) 24 hours (iii) 48 hours and (iv) 168 hours post injection.

Rate of Responding (5 min)

Rate of Responding (5 min)

Rate of Responding (5 min)

Rate of Responding (5 min)

Figure B. Mean rate of responding for intracranial self-stimulation from the ventral VTA in a typical mouse. ICSS rates were assessed during a 40 minute test session (i) immediately following acute intraventricular injection of IL-2 and again (ii) 24 hours (iii) 48 hours and (iv) 168 hours post injection.

clear whether central IL-2 administration influenced self-stimulation from dorsal and ventral aspects of the VTA across a wide range of stimulation parameters. Therefore, decreases (increases) by 10 Hz every 3 minutes over 42 min test period was employed. Ten Hz increments were chosen since preliminary work indicated that the smaller steps did not produce discernible alterations in responding.

Table 1:
Anova Table for Change in Rate of
ICSS Responding with Central II-2 Administration

Source	Sums of Square	DF	Mean Square	F Value	P. Value
Group	20718.28	1	20718.28	6.60	.033
Error	25109.05	8	3138.63		
Freq.	368.81	3	122.94	.07	.974
Group x Freq.	1917.97	3	639.32	.38	.766
Error	40036.75	24	1668		
Day	6672.91	3	2224.30	1.50	.239
Group x Day	17822.4	3	5940.80	4.02	.019
Error	35500.80	24	1479.20		
Freq. x Day	6169.30	9	685.48	1.16	.336

Group x					
Freq. x					
Day	2269.05	9	252.12	.43	.917
Error	42673.89	72	592.69		

Appendix B**Table 2:****Anova Summary Table For Threshold Determination**

Source	Sum of Squares	DF	Mean Square	F Value	P. Value
Drug	27242.40	2	13621.20	16.17	.000
Error	20219.17	24	842.47		
Session	201.07	3	67.02	.28	.840
Drug x Session	1366.82	6	227.80	.95	.465
Error	17266.05	72	239.81		

Appendix C

Table 3:
Anova Summary Table For Percent Change in ICSS
Performance From Dorsal and Ventral VTA

Source	Sums of Squares	DF	Mean Square	F Value	P. Value
Group	178626.9	2	89313.49	6.37	.006
Error	336613.9	24	14025.58		
Freq.	13372.53	6	2228.76	1.64	.141
Freq. x Group					
	12060.65	12	1005.05	.74	.712
Error	195938.6	144	1360.68		
Day	2006.15	3	668.72	.15	.932
Day x Group					
	40689.60	6	6781.60	1.48	.197
Error	329877.3	72	4581.63		
Day x Freq.					
	7726.37	18	429.24	.69	.825

Day x					
Group x					
Freq.	27008.84	36	750.25	1.20	.203
Error	270044.1	432	625.10		

Appendix D**Table 4:**

**Anova Summary Table For Percent Change in ICSS Performance From
Dorsal VTA with IL-2 Administration**

Source	Sums of Squares	DF	Mean Square	F Value	P.Value
Group	113776.5	1	113776.5	10.67	.004
Error	223895.2	21	10661.68		
Freq.	26882.98	6	4480.50	3.26	.005
Group x Freq.	3245.43	6	540.90	.39	.882
Error	173137.8	126	1374.11		
Day	8282.27	3	2760.76	.65	.585
Day x Group	28180.61	3	9393.54	2.21	.095
Error	267259.5	63	4242.21		
Day x Freq.	10646.82	18	591.49	1.06	.388

Day x					
Freq. x					
Group	14629.85	18	812.77	1.46	.101
Error	210271.8	378	556.27		

END

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FIN