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OPIATE RECEPTOR SUBTYPE MODULATION OF DOPAMINERGIC ACTIVITY THE EFFECTS OF MU, KAPPA AND SIGMA OPIATES ON THE DEVELOPMENT OF DOPAMINERGIC SUPERSENSITIVITY

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ON THE

DEVELOPMENT OF DOPAMINERGIC SUPERSENSITIVITY

BY

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ABSTRACT

The purpose of this research was to examine the effects of mu (μ), kappa (κ) and sigma (σ) agents namely, morphine (μ), ethylketocyclazocine (κ), SKF 10,047 (σ), pentazocine (κ, σ), cyclazocine (κ, σ) and the mu antagonists, naloxone and naltrexone on dopamine mediated behaviors and the development of haloperidol-induced dopaminergic supersensitivity (DA-SS) in the mouse. Three behavioral paradigms were utilized which are predictive of mesolimbic and/or striatal dopaminergic effects: locomotor activity (mesolimbic); apomorphine-induced stereotyped behavior (striatal) and apomorphine-induced climbing behavior (mesolimbic/striatal). Morphine, SKF 10,047, pentazocine and cyclazocine produced increases in locomotor activity suggesting increased dopaminergic activity, while naloxone and naltrexone had no effect on locomotion. Ethylketocyclazocine (EKC) induced a biphasic effect of sedation followed by an increase in locomotor activity at three hours postadministration. EKC and SKF 10,047 antagonized apomorphine-induced climbing because of motor deficits, sedation and ataxia, respectively, while the other opiates had no effect. Only EKC inhibited apomorphine-induced stereotypy, due to initial motor deficits and sedation. Thus, these compounds were not dopamine antagonists, insofar as apomorphine-induced behaviors were only antagonized at debilitating doses which incapacitated mice. Furthermore, both EKC and SKF 10,047 increased locomotion, unlike neuroleptics which generally cause motor depression.

The stimulant properties of the κ and σ opiates warranted further investigation. EKC at 5 mg/kg sc produced a biphasic effect over time

with a peak effect from 180 to 210 minutes. EKC (5 mg/kg) hyperactivity was dependent upon catecholamine synthesis and transmission since α-MPT (300 mg/kg), reserpine (5 mg/kg), tetrabenazine (5, 40 mg/kg), haloperidol (1 mg/kg), apomorphine (0.1 mg/kg), muscimol (1 mg/kg) and prazosin (2.5 mg/kg) blocked EKC-induced locomotor activity. SKF 10,047 at 40 mg/kg sc not only increased locomotor activity but also induced stereotypy and climbing behavior with an ED_{50} for climbing at 90 minutes equal to 14.6 mg/kg sc. SKF 10,047 (40 mg/kg) -induced climbing was dependent on catecholamine transmission and a direct serotonin receptor interaction since α-MPT (300 mg/kg), tetrabenazine (5, 40 mg/kg), haloperidol (1 mg/kg), apomorphine (0.1 mg/kg), muscimol (1 mg/kg), prazosin (2.5 mg/kg) and methysergide (10 mg/kg) antagonized this behavior. Both EKC-induced hyperactivity and SKF 10,047-induced climbing were not antagonized by naloxone (10, 100 mg/kg). Furthermore, naloxone, EKC and SKF 10,047 potentiated apomorphine-induced climbing.

The μ, κ, σ and mixed κ, σ agents all produced effects suggesting dopaminergic activity, i.e., locomotion, stereotypy, climbing and potentiation of apomorphine effects. Therefore, each was tested for its ability to attenuate haloperidol-induced DA-SS in the climbing and stereotyped behavior paradigms. In the acute climbing paradigm, haloperidol-induced DA-SS was dose-dependently attenuated by SKF 10,047, EKC, cyclazocine, pentazocine, naloxone and naltrexone, with morphine inactive. In the chronic (5-day) climbing and stereotypy models, only the concomitant administration of either SKF 10,047 or cyclazocine and haloperidol inhibited the development of DA-SS, while

morphine alone produced DA-SS. These results suggest differential opiate modulation of DA-SS in the acute vs. chronic paradigms. Furthermore, sigma agonists were most effective in attenuating haloperidol-induced DA-SS, presumably through dopamine agonist properties.

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I. GENERAL INTRODUCTION

Schizophrenia is a psychosis which is characterized by disordered thinking and emotions while often accompanied by delusions and auditory hallucinations. The schizophrenic fluctuates rapidly between contradictory affects, thoughts and actions (Bleuler, 1950). The original theory of schizophrenia was the dopamine hypothesis which states that schizophrenia is related to dopamine hyperactivity in the central nervous system. This theory was based on the fact that phenothiazines and butyrophenones which have effective antipsychotic and tranquilizing effects in the clinic, are dopamine-receptor blockers (Carlsson and Linquist, 1963). Furthermore, amphetamine, which releases norepinephrine and dopamine and blocks catecholamine reuptake, can elicit psychotic symptoms in chronic schizophrenics (Janowsky and Davis, 1974) and also produces a paranoid psychosis in normal individuals which closely resembles paranoid schizophrenia (Angrist and Gershon, 1970).

In recent years, experimental evidence in man and animals has shown that there is more to schizophrenia than simply an excess of dopamine activity. Studies of the neuroanatomy and physiology of the brain have revealed the dopamine system to be regulated by its own feedback mechanisms as well as by more complex interactions between this system and other neurotransmitters and neuromodulators. Recently, it was suggested that dopaminergic instability in psychosis may develop from an excess amount of feedback and modulation (King et al., 1982).

An inherent problem with chronic neuroleptic treatment in the clinic and in animal experimentation is that it leads to dopamine receptor supersensitivity, manifest as extrapyramidal side effects and tardive dyskinesias in man and enhanced responsiveness to dopamine and its analogues in animals. Many strategies have been employed in an attempt to enhance the efficacy of neuroleptic therapy while minimizing side effect liability and, in particular, the development of dopaminergic supersensitivity. Of particular interest are the reports that combined administration of antipsychotics and lithium (Gallager et al., 1978; Pert et al., 1978; Verimer et al., 1980; Seeger et al., 1981), L-dopa and other dopamine agonists (Friedhoff et al., 1977; Ezrin-Waters and Seeman, 1978; Christensen and Nielsen, 1979; List and Seeman, 1979; Seeger et al., 1981; Reches et al., 1982) and naloxone (Seeger et al., 1980) have attenuated dopaminergic supersensitivity to varying degrees.

It is possible that schizophrenia is not only associated with the dopaminergic system but may also be influenced by the opiate system. There are many dynamic interrelationships both functionally and anatomically between the dopaminergic and opiate systems (Lal, 1975). Although the endorphinergic system may not play a primary role in the etiology of schizophrenia, the opiate receptor-antagonist naloxone has no deleterious effect and may possibly improve some symptoms of this disease in the clinic (Verebey et al., 1978; Watson et al., 1978; Pickar et al., 1982; Lo et al., 1983; Blum et al., 1984). Van Ree and De Wied (1981) proposed that dopamine overactivity or imbalance in schizophrenia may be linked to a disturbance in endorphinergic

homeostasis. Moreover, extrapyramidal movement disorders may be associated with either increases or decreases in endogenous opioid activity (Sandyk, 1985). If psychosis is a result of an instability of both dopamine and endogenous opiate systems, it is of interest to investigate the effects of combined treatment of haloperidol and various opiate receptor subtype agents, namely, mu, kappa and sigma (Martin et al., 1976) on the development of dopaminergic supersensitivity. The results of the studies in this dissertation may be relevant for the clinical treatment of schizophrenia, i.e., the amelioration of psychotic symptoms and side effects, as well as a better understanding of the nature of the interactions of dopamine and opiate systems in the development of dopaminergic supersensitivity.

II. INTRODUCTION - LITERATURE SURVEY

A. The Nigrostriatal and Mesolimbic Dopamine Pathways

The major pathways of dopaminergic neurons in the central nervous system, namely, the nigrostriatal, mesolimbic and tuberoinfundibular systems, were originally mapped by histofluorescence and anterograde or retrograde degeneration techniques (Anden et al., 1965; Ungerstedt, 1971). In the study of schizophrenia, the nigrostriatal and mesolimbic areas appear to be primarily responsible for the extrapyramidal effects and the antipsychotic effects, respectively (Costall and Naylor, 1976; Crow et al., 1977).

1. The Nigrostriatal System (Figure 1)

Anatomical and histochemical studies have shown that the nigrostriatal dopaminergic cell bodies originate in the A9 DA cell group in the zona compacta of the substantia nigra and its rostromedial extension in the ventral tegmental area, ascend adjacent to the lateral hypothalamus and terminate in the neostriatum or corpus striatum, i.e., the caudate nucleus and putamen (Anden et al., 1966; Ungerstedt, 1971; Cooper et al., 1978). Also, the axons from the A8 DA cell bodies caudal to the substantia nigra join the nigrostriatal system since they show retrograde degeneration after lesions of the corpus striatum (Ungerstedt, 1971).

2. The Mesolimbic System (Figure 1)

Cell bodies in this pathway originate in the A10 cell group dorsocranial to the interpenducular nucleus of the ventral tegmental region and ascend closely but more medially with the axons of the nigrostriatal system and terminate in the nucleus accumbens, the olfactory tubercle and the prefrontal cortical area (Anden et al., 1966; Ungerstedt, 1971; Cooper et al., 1978).

B. Functional Differentiation: Mesolimbic vs. Striatal

In recent years, a generalized approach to antipsychotic effectiveness has been based on the relative effects of dopamine antagonists on the nigrostriatal and mesolimbic areas. Many of the extrapyramidal effects of neuroleptic treatment may be mediated by the effects in the basal ganglia, namely, the caudate, putamen and globus pallidus, while the antipsychotic effects may be mediated by the antidopaminergic effects in the mesolimbic and mesocortical areas. Although it is an oversimplification to state that psychosis is due to dopamine overactivity in a particular brain region such as the mesolimbic system, much research has been generated in an attempt to qualify and quantify the activity and adaptation of mesolimbic and striatal areas to dopaminergic agents.

In general, animal studies have followed two approaches: effects following either intracerebrally or extracerebrally-administered drugs. Dopamine appears to function as a mediator of various motor activities, in particular, locomotor and stereotyped

behavior. Pijnenburg and Van Rossum (1973) originally discovered that dopaminergic mechanisms within the nucleus accumbens regulate locomotor activity. Bilateral injection of dopamine (5 µg) into the nucleus accumbens of nialamide- (a monoamine oxidase inhibitor) pretreated rats resulted in a significant increase in locomotor activity compared to saline controls while noradrenaline- (5 µg) treated rats showed a slight enhancement of locomotion. On the other hand, bilateral injection of dopamine (25-100 µg) into the caudate-putamen of nialamide-pretreated rats elicited strong stereotypy, especially chewing, biting and licking, whereas lower doses (6.25, 12.5 µg) showed less intense behavior characterized by repetitive head and front limb movement and some chewing and biting (Costall et al., 1974). Furthermore, noradrenaline (100 µg) did not show hyperactivity or stereotypy in this paradigm.

Further investigations revealed subtle functional differences between structures within the mesolimbic and striatal regions. Costall and Naylor (1975) showed that bilateral injection of dopamine (1-200 µg) into the nucleus accumbens septi increased locomotor activity and caused stereotyped sniffing behavior while injections into the olfactory tubercle produced periodic hyperactivity but no stereotypy. Following pretreatment with nialamide, these effects were enhanced and biting and gnawing were observed in the olfactory tubercle-injected group. In addition, although there is a structural resemblance between the hydroxyl and nitrogen substituents of the dopamine agonist apomorphine and dopamine itself, apomorphine, which induced stereotyped biting following direct injection into the

caudate-putamen (Ernst and Smelick, 1966), did not induce hyperactivity or stereotypy following intraaccumbens injection (Pijnenberg et al., 1976; Costall et al., 1977). These results suggested differential dopaminergic mediation of stereotyped responses emanating from the nucleus accumbens versus the caudate putamen.

Additional evidence for predominant dopamine receptor mediation of hyperactivity and stereotyped behavior in the nucleus accumbens and caudate-putamen (respectively) was reported by Costall et al. (1977). Intracerebral dopamine (6.25-50 µg) dose dependently increased these behaviors in their respective areas while intraperitoneal injections of haloperidol (0.2-0.8 mg/kg) blocked these effects and 10 mg/kg of either aceperone (an alpha-adrenergic antagonist) or propranolol (a beta-adrenergic antagonist) had no effect. Interestingly, intraaccumbens injections of alpha- and/or beta-adrenergic receptor agonists such as adrenaline, noradrenaline, which augments dopamine release (Reisine et al., 1982), and isoprenaline were potent inducers of hyperactivity but to a lesser extent than dopamine (Costall et al., 1976; Vance and Blumberg, 1983) and were inhibited only by intracerebral injection of the dopamine antagonist fluphenazine and not by either the alpha antagonist, piperoxan, or the beta antagonist, propranolol (Costall et al., 1976). It was concluded that hyperactivity mediated by the nucleus accumbens may not be specific for dopamine agonists; however, this behavior is specifically antagonized by dopamine blockade.

A copious amount of data related to mesolimbic versus striatal functioning has been generated by extracerebral administration of dopaminergic agents. Since metabolic breakdown and inability to penetrate the blood-brain barrier prevents systemic administration of endogenous amines, dopamine agonists and releasers such as apomorphine and amphetamine, respectively, serve as classical drugs in animal research.

Following systemic administration, apomorphine and amphetamine induced a series of behavioral effects characterized by stereotypy and hyperactivity (Randrup and Munkvad, 1967; Costall and Naylor, 1977; Ljungberg and Ungerstedt, 1978). Drug interaction experiments were employed to ascertain the relative importance of endogenous amines in amphetamine-induced locomotor activity and stereotyped behaviors. The tyrosine-hydroxalase inhibitor, alpha-methyl-p-tyrosine, depletes brain noradrenaline and dopamine through synthesis inhibition and antagonizes amphetamine behavioral responses (Weissman et al., 1966; Stolz and Rech, 1970). However, if noradrenaline is selectively depleted by dopamine-beta-hydroxylase inhibitors, there is little or no effect on amphetamine-induced hyperactivity or stereotypy (Scheel-Kruger and Randrup, 1967; Thornburg and Moore, 1973). Furthermore, following either systemic or intraaccumbens (but not intracaudate) injection, dopamine antagonists were more efficacious than noradrenaline antagonists in blocking amphetamine-induced locomotor activity in rodents (Rolinski and Scheel-Kruger, 1973; Pijnenburg et al., 1974). Also, systemic administration of neuroleptics dose-dependently

antagonized intraaccumbens dopamine-induced hyperactivity (Costall and Naylor, 1976). In addition to antagonizing amphetamine and dopamine effects, dopamine antagonists have been shown to inhibit apomorphine-induced locomotion and gnawing (Ljungberg and Ungerstedt, 1978).

Although drug interaction experiments have provided valuable information concerning dopaminergic involvement in locomotion and stereotypy, lesioning techniques have been used to further delineate the brain areas which are functionally significant in the manifestation of these drug-induced behaviors. Basically, striatal or mesolimbic structures are destroyed by either electrolesions or 6-hydroxydopamine (6-OHDA), a chemical analog of the catecholamines which selectively destroys dopaminergic and noradrenergic nerve fibers (Uretsky and Iversen, 1970). Interpretation of lesioning studies must be guarded because varying the size of a lesion in particular areas may yield diverse results as well as varying amounts of depletion of dopamine and norepinephrine.

There is much evidence that dopaminergic neurons in the corpus striatum mediate amphetamine-induced stereotypy. Bilateral electrolytic lesions of the caudate (Divac, 1972; Fog, 1972) or globus pallidus (Costall and Naylor, 1975) and 6-OHDA lesions of either the caudate (Asher and Aghajanian, 1974; Creese and Iversen, 1974; Kelley et al., 1975), the globus pallidus (Costall and Naylor, 1977) or the substantia nigra (Creese and Iversen, 1972; 1973) all attentuate amphetamine stereotypy. On the other hand, both electrolesions and 6-OHDA lesions of the nucleus accumbens (Asher and

Aghananian, 1974; Kelley et al., 1975; Costall et al., 1979) and olfactory tubercle (Asher and Aghajanian, 1974; Costall and Naylor, 1977) had no effect on the intense forms of amphetamine stereotypy, i.e., biting, gnawing, while slightly attenuating the sniffing component of this behavior. These studies suggested a striatal mediation of amphetamine-stereotyped behavior with little or no involvement of mesolimbic structures.

The functional integrity of the mesolimbic system was essential for the expression of amphetamine hyperactivity. Both electrolytic and 6-OHDA lesions of the nucleus accumbens effectively reduced amphetamine-induced hyperactivity (Iversen et al., 1975; Kelley et al., 1975; Costall et al., 1979). By contrast, striatal lesions had little or no effect on this behavior. Electrolesions of the substantia nigra and caudate, as well as 6-OHDA lesions of the caudate, did not effect amphetamine hyperactivity (Costall and Naylor, 1973; Kelley et al., 1975; Costall et al., 1979). However, 6-OHDA lesions of the substantia nigra yielded apparently confusing results in that some groups reported no effect (Creese and Iversen, 1972; Brook and Iversen, 1975) while others found a reduction in amphetamine hyperactivity (Creese and Iversen, 1975; Roberts et al., 1975). The reduction of activity was most likely due to a dopaminergic disruption in the mesolimbic system since intranigral 6-OHDA not only reduced nigrostriatal dopamine but also mesolimbic dopamine due to the probable diffusion of drug into the A10 area following injection into the A9 cells, two areas of close proximity (Kelley et al., 1975; Costall and Naylor, 1977).

The interpretation of apomorphine-induced behaviors differs from amphetamine behaviors due to the difference in physiological responses to these drugs. Amphetamine acts presynaptically to release catecholamines and block reuptake, whereas apomorphine acts directly as an agonist at postsynaptic dopamine receptors (Ernst, 1967). 6-OHDA lesions in the nigrostriatal system may result in an enhanced or "supersensitive" response to low intensity stereotypy, i.e., sniffing but not biting induced by peripherally-administered apomorphine, although contradictory findings have been reported. 6-OHDA lesions of the caudate nucleus and substantia nigra resulted in an enhanced apomorphine-induced stereotyped behavior due to a supersensitivity of remaining intact dopamine receptors (Creese and Iversen, 1975; Kelley et al., 1975). On the other hand, 6-OHDA or electrolesions of the caudate have been reported to have no effect on apomorphine-induced stereotypy (Divac, 1972; Costall and Naylor, 1973; 1977; Asher and Aghajanian, 1974) while lesions of the substantia nigra actually reduced this behavior (Baum et al., 1971; Costall et al., 1972; Loew and Vigouret, 1975). Also, both electrolytic and 6-OHDA lesions of the globus pallidus markedly reduced apomorphine stereotypy (Costall and Naylor, 1975; 1977; Loew and Vigouret, 1975). However, when 6-OHDA was administered intraventricuarly to neonatal rats, a greater destruction of the nigrostriatal pathway resulted in an enhanced responsiveness to apomorphine-induced locomotor activity and stereotypy while amphetamine responses were abolished (Creese and Iversen, 1973). These results suggested a supersensitivity to remaining intact dopamine receptors.

Experiments involving apomorphine-induced hyperactivity following peripheral administration are even more debatable. Some investigators have reported hyperactivity following apomorphine administration (Maj et al., 1972; Iversen et al., 1975) while others showed no marked increase in locomotor activity (Costall and Naylor, 1977). Differences in the equipment used to measure hyperactivity, i.e., photocell chambers vs. electromechanical sensors, may yield conflicting results. Additionally, apomorphine has narrow dose-response and time-course "windows" for differentiating between locomotor vs. stereotyped behavior where stereotypy becomes the predominant apomorphine-induced behavior at higher dose levels.

6-OHDA lesions of the nucleus accumbens (Iversen et al., 1975; Kelley et al., 1975) and olfactory tubercle (Costall and Naylor, 1977) enhanced locomotor activity following apomorphine administration. However, Kelley et al. (1975) reported that intraaccumbens lesions resulted in a significant reduction in dopamine levels in the olfactory tubercle. Furthermore, following a more selective intraaccumbens lesion, Costall and Naylor (1977) reported no change in apomorphine-induced hyperactivity. And lastly, whereas direct injection of apomorphine into the nucleus accumbens failed to initiate hyperactivity (Pijnenberg et al., 1976), direct injection into the olfactory tubercle increased locomotor activity in rats (Pijnenberg et al., 1976; Costall and Naylor, 1977). Therefore, apomorphine-induced hyperactivity depends upon the integrity of at least the olfactory tubercle and probably to some extent an intact nucleus accumbens within the mesolimbic system.

An alternative means for measuring apomorphine effects is the climbing mouse assay. Peripheral administration of apomorphine initiated rearing and cage climbing in mice (Hester et al., 1970; Costentin et al., 1975; Protais et al., 1976; Costall et al., 1978). This behavior is specific for apomorphine since other dopamine agonists such as d-amphetamine, piribedil, amatadine and L-dopa do not induce climbing behavior (Protais et al., 1976; Nohria, 1983). Apomorphine-induced climbing is mediated by dopaminergic receptors since this behavior is specifically antagonized by neuroleptics (Protais et al., 1976; Costall et al., 1978) and GABA agonists (Dunn et al., 1980) but not by alpha- or beta-adrenergic antagonists (Costall et al., 1978).

Lesions of mesolimbic and striatal areas have generated conflicting results. Costall and associates (1979) showed that electrolytic lesions of the nucleus accumbens attenuated apomorphine-induced climbing while Protais et al. (1976) showed no effect with the same lesion (although the extent of these lesions may have differed). In contrast, intraaccumbens 6-OHDA which decreased dopamine in the nucleus accumbens and olfactory tubercle, enhanced apomorphine climbing, probably due to a supersensitive response at intact dopamine receptors in these areas (Costall et al., 1979b; 1980). Similar disagreements between these investigators were observed following lesions of the striatum. Electrolytic striatal lesions either decreased (Protais et al., 1976) or had no effect (Costall et al., 1979) on apomorphine-induced climbing while intrastriatal 6-OHDA either enhanced this behavior (Protais et al.,

1976) or had no effect (Costall et al., 1979b; 1980). Furthermore, spontaneous climbing behavior, like spontaneous locomotor activity, is reduced by either low doses of apomorphine (less than or equal to 0.1 mg/kg) which act via presynaptic autoreceptors to decrease dopamine release (Strombom, 1975; DiChiara et al., 1976; Costall et al., 1982) or by electrolesions of the caudate-putamen, nucleus accumbens or olfactory tubercle (Costall et al., 1982). Most probably, climbing behavior is modulated through mesolimbic as well as striatal dopaminergic neurons.

C. Dopaminergic Supersensitivity

Dopaminergic supersensitivity (DA-SS), i.e., enhanced responsiveness to dopamine or its analogues, is a well-established biochemical and pharmacological phenomenon following either chronic neuroleptic treatment or lesioning of dopaminergic nerve tracts (for reviews, see Owen, 1980; Rupniak et al., 1983). In man, chronic blockade of dopamine receptors in patients treated with classical neuroleptics may lead to the appearance of tardive dyskinesias (Klawans and Rubovits, 1972). Tardive dyskinesias, believed to be the result of overactive dopaminergic systems, are characterized by stereotyped, repetitive and involuntary movements of the mouth, lips and tongue, occasionally accompanied by choreiform movements of the limbs and trunk (Burki, 1979b). Various biochemical and behavioral animal models have proved to be predictive of an antipsychotic's liability for producing DA-SS.

Biochemical indices for DA-SS include receptor binding studies and the measurement of dopamine metabolites. Chronic neuroleptic treatment results in an increase in striatal dopamine receptor populations (Bmax) labelled by the tritiated dopamine antagonists ^{3}H-haloperidol and ^{3}H-spiperone in rats (Burt et al., 1977; Hitri et al., 1978; Theodorou et al., 1981) and by ^{3}H-pimozide in mice (Schwartz et al., 1978). However, changes in affinity (K_D) for the dopamine receptor was controversial (probably due to differing methodologies) with a reported no change (Burt et al., 1977), decrease (Schwartz et al., 1978; Theodorou et al., 1981) and increase (Hitri et al., 1978). Also, some investigators have reported either no effect (Hitri et al., 1978) or increases (Theodorou et al., 1981; Hall et al., 1983) in mesolimbic dopamine receptor populations following chronic neuroleptic treatment. Likewise, 6-OHDA lesions of the nigrostriatal (Creese et al., 1977; Goldstein et al., 1980) and mesolimbic (Goldstein et al., 1980) systems resulted in increases of dopamine receptors in these regions.

Increase in dopamine receptor population following chronic antipsychotic treatment is directly related to compensatory changes in dopamine synthesis and release. The major indices of dopamine turnover are its principle metabolites, 4-hydroxy-3-methoxyphenylacetic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC), indicative of extraneuronal enzymatic degradation by catechol-o-methyl transferase and intraneuronal metabolism by monoamine oxidase, respectively (Roffler-Tarlov et al., 1971). Acute neuroleptic administration produced a biphasic effect in metabolite levels where initial in-

creases in striatal HVA and DOPAC levels are followed by a return to control levels at 2 to 3 days and then an eventual decrease in metabolic concentrations (Hyttel, 1977; Martres et al., 1977). In addition, 72 hours after the administration of 4 mg/kg haloperidol, there was an increased ability of apomorphine to lower HVA levels (Martres et al., 1977).

Chronic haloperidol treatment resulted in tolerance to striatal dopamine turnover as reflected by an attenuation of the large increases in HVA and DOPAC levels seen following acute treatment (Lerner et al., 1977; Burki, 1979a; Meller et al., 1980; Nicolaou, 1980; Melamed et al., 1983). However, 7 days after chronic haloperidol treatment, apomorphine still showed an increased ability to lower HVA levels (Smith et al., 1977) similar to acute treatment (Martres et al., 1977). These metabolic effects following acute and chronic haloperidol treatment have also been observed in mesolimbic areas, i.e., nucleus accumbens and olfactory tubercle (Matsumoto et al., 1983). Although, neuroleptic treatment enhances dopamine turnover, it appears that dopamine concentration remains the same due to corresponding increases in the rates of synthesis and release (Melamed et al., 1983); however, decreases in dopamine concentrations have also been reported (Hyttel, 1975).

The increase in dopamine turnover following acute neuroleptic administration is attributable to a blockade of presynaptic autoreceptors which regulate dopamine release and/or postsynaptic receptor blockade as well as negative feedback mechanisms or loops (Snyder et al., 1974; Iversen et al., 1976). Tolerance following

chronic neuroleptic treatment may be due to adaptational processes at neuroleptic sites which result from an incomplete blockade of the increased number of dopamine receptors, decreased negative feedback and effects on tyrosine hydroxylase kinetics (Lerner et al., 1977; Meller et al., 1980; Melamed et al., 1983).

The findings and conclusions of these metabolic studies were further substantiated by electrophysiological studies. Following acute neuroleptic administration, extracellular recordings of neuronal activity in the A9 (substantia nigra) and A10 (ventral tegmental area) areas of the rat brain showed an increase in both the firing rate of dopamine neurons and the number of active neurons that could be identified (Bunney et al., 1973). This increased firing rate correlates with an increase in dopamine turnover. It was postulated, similar to the metabolic studies, that this increase was due to autoreceptor blockade, postsynaptic blockade and the nigrostriatal feedback loop's attempt to maintain homeostasis. On the other hand, chronic neuroleptic treatment resulted in an almost complete absence of spontaneous firing of dopamine neurons, a silence due to the gradual development of a depolarization block (Bunney and Grace, 1978). This tonic depolarization block appeared to be mediated by the nigrostriatal feedback pathways and caused by the initial increases in the activity of dopamine neurons.

While these biochemical and electrophysiological events are occurring at the neuronal level, corresponding behavioral activities can be observed which are predictive of DA-SS. The most commonly used methods for assessing dopamine receptor hypersensitivity

involve measurement of increased locomotor activity and stereotyped behavior following administration of dopamine agonists. As earlier described, increased locomotor activity and stereotypy following chronic neuroleptic administration would be indicative of DA-SS in mesolimbic and striatal areas, respectively.

The results of supersensitivity experiments involving locomotor activity are controversial. Animals were chronically administered neuroleptics and following withdrawal, spontaneous locomotor activity and/or dopamine agonist-induced motor activity were measured. While some investigators reported increases in spontaneous motor activity in rats or mice after termination of chronic administration of "typical" neuroleptics such as haloperidol, chlorpromazine, penfluridol and alpha-flupenthixol (Jackson et al., 1975; Von Voigtlander et al., 1975; Shakian et al., 1976; Gianutsos and Moore, 1977; Gianutsos et al., 1978; Hulperin et al., 1983), others reported no difference compared to controls (Tarsy and Baldessarini, 1974; Smith and Davis, 1976; Dunstan and Jackson, 1977; Costall and Naylor, 1978; Davis et al., 1978). Also, chronic administration of the atypical neuroleptics, clozapine and thioridazine, has either enhanced (Smith and Davis, 1976) or had no effect (Gianutsos and Moore, 1977) on spontaneous motor activity.

Equally as confusing were the results when dopamine agonists or releasers were peripherally administered following chronic neuroleptic treatment. Whereas some groups found either increased apomorphine-induced locomotion (Gianutsos and Moore, 1977; Gianutsos et al., 1978; Montanaro et al., 1982; Fayle et al., 1985) or increased

d-amphetamine-induced locomotion (Von Voigtlander et al., 1975; Dunstan and Jackson, 1977; Gianutsos et al., 1978), others reported either no difference or slight decreases compared to controls (Sahakian et al., 1976; Smith and Davis, 1976; Dunstan and Jackson, 1977; Costall et al., 1978; Rupniak et al., 1983).

The most reliable model for studying locomotor activity involved direct injection of dopamine through cannulae into the nucleus accumbens. This procedure consistently showed increased locomotion in animals treated chronically with neuroleptics (Jackson et al., 1975; Davis et al., 1978; Moore et al., 1980; Halperin et al., 1983). Direct injection of dopamine yielded site-specific activity (mesolimbic supersensitivity) while peripheral injection of dopamine agonists results in a whole spectrum of peripheral as well as central nervous system effects which may mask or interfere with locomotor activity per se.

On the other hand, enhanced stereotyped behavior in response to systemic administration of dopamine agonists following chronic neuroleptic treatment showed a more consistent and robust effect reported by numerous laboratories (Klawans and Rubovits, 1972; Tarsy and Baldessarini, 1974; Sahakian et al., 1976; Costall et al., 1978; Gianutsos et al., 1978; Nielsen et al., 1978; Waddington and Gamble, 1980; Montanaro et al., 1982). In addition, Christensen and his associates (1976) reported DA-SS as measured by methylphenidate- and apomorphine-induced gnawing after a single administration of various neuroleptics. The high intensity components of apomorphine-induced stereotyped behavior included gnawing, licking and biting while the

lower intensity responses included sniffing and some locomotion. Direct injection of dopamine into the striatum and in particular, the caudate putamen, after chronic neuroleptic administration also resulted in an enhanced stereotypic response compared to controls (Jackson et al., 1975; Moore et al., 1980; Halperin et al., 1983).

In comparison, striatal DA-SS as measured by apomorphine-induced stereotyped behavior is a more consistent and reliable model than mesolimbic supersensitivity as measured by locomotor activity following chronic antipsychotic treatment. Direct injection of dopamine into either the striatum or nucleus accumbens proved to be reliable models for detection of striatal and mesolimbic DA-SS, respectively. However, these models are somewhat tedious and cumbersome.

DA-SS, as measured by the apomorphine-induced climbing mouse assay, has been shown to be a predictive model. Enhanced responsiveness to apomorphine as measured by climbing behavior was observed in all reported studies 48-72 hours following either acute (Costentin et al., 1975; Protais et al., 1976; Martres et al., 1977) or chronic (Von Voigtlander et al., 1975; Protais et al., 1976; Day and Greenblatt, 1979; Wilcox et al., 1980) neuroleptic treatment. The climbing mouse assay appears to be particularly sensitive for measurement of DA-SS since both acute and chronic dopamine receptor blockade results in an increased dopamine receptor sensitivity whereas neither locomotor activity nor stereotyped behavior has consistently shown DA-SS after acute treatment.

Thus, it appears that a consequence of neuroleptic treatment is the development of dopamine receptor supersensitivity as measured by various behavioral or biochemical techniques in animals and the physical manifestation of tardive dyskinesias in man. It was of interest to various laboratories to attempt to attenuate DA-SS by means of a concurrent treatment of certain compounds in combination with antipsychotics. It was demonstrated that chronic administration of either direct or indirect dopaminergic agonists such as apomorphine, L-dopa/carbidopa, amantadine and bromocriptine, in combination with haloperidol, significantly reversed the increase in ^{3}H-neuroleptic binding in the striatum (Friedhoff et al., 1977; List and Seeman, 1979; Allen et al., 1980; Reches et al., 1982), the increase in adenylate cyclase activity (Friedhoff et al., 1977) and the enhanced stereotyped activity induced by apomorphine (Christensen and Nielsen, 1979; Allen et al., 1980). It was also reported that the combination of L-dopa and haloperidol partially prevented the development of ventral tegmental intracranial self-stimulation (ICSS) supersensitivity (Seeger et al., 1981). Therefore, the administration of dopamine agonists counteracted the ability of dopamine antagonists to induce DA-SS.

In addition, chronic lithium in combination with haloperidol was reported to either attenuate (Pert et al., 1978) or have no effect (Staunton et al., 1982a) on the haloperidol-induced increase in ^{3}H-spiroperidol binding, decreased the enhanced effect of apomorphine-induced stereotyped behavior (Pert et al., 1978; Staunton et al., 1982b), partially prevented the development of ventral tegmental

ICSS supersensitivity (Seeger et al., 1981) and blocked the development of presynaptic DA-SS as measured either electrophysiologically (Gallager et al., 1978) or behaviorally by the low dose apomorphine-induced inhibition of locomotor activity (Verimer et al., 1980).

It has been demonstrated that neuroleptic-induced DA-SS can be attenuated by concomitant administration of dopamine agonists or lithium. Knowing that opiate systems share certain anatomical and functional properties with dopaminergic systems, might simultaneous treatment of an opiate agent with haloperidol be prophylactic in the development of DA-SS?

D. Opiate Receptor Subtypes

The concept of multiple opiate receptors (summarized in Figure 2; structures Figures 3, 4) has evolved over the years from pharmacological observations of differences seen between the various analgesic agents. The landmark studies in this area were performed by Martin and his coworkers (Gilbert and Martin, 1976; Martin et al., 1976). On the basis of neurophysiological and behavioral evidence in the dog, Dr. Martin postulated that there were three different opiate receptors in the central nervous system, namely, μ (mu), κ (kappa) and σ (sigma) receptors, represented by the prototype drugs, morphine, ketocyclazocine and N-allylnormetazocine (SKF 10,047), respectively. Although there are other endogenous opiate receptors which preferentially interact with enkephalins and endorphins, namely, delta (δ) and epsilon (ε) receptors; they will not be covered in this dissertation.

The morphine syndrome (μ) was characterized by miosis, bradycardia, hypothermia and analgesia. The ketocyclazocine and ethylketocyclazocine syndrome (κ) was associated with pupillary constriction, decreased flexor reflexes and sedation. SKF 10,047 (σ) caused mydriasis, tachypnea, tachycardia and mania or "canine delirium" which was proposed to be the equivalent of psychotomimetic effects in man.

Martin's group extended these studies and observed the ability of these agents to precipitate and suppress signs of abstinence in both morphine- and cyclazocine-dependent, chronic spinal dogs. Antagonists were 1/20 to 1/60 as potent in precipitating abstinence in the cyclazocine-, compared to the morphine-dependent dog. It was also observed that the ketocyclazocine and cyclazocine (κ, σ agonist; μ antagonist) precipitated abstinence syndromes were qualitatively similar to each other but different from the morphine abstinence syndrome. SKF 10,047 precipitated (suggesting antagonist activity at the μ receptor) while morphine suppressed the abstinence syndrome in morphine-dependent dogs. On the other hand, ethylketocyclazocine neither suppressed nor precipitated withdrawal in morphine-dependent dogs; however, it did suppress the cyclazocine abstinence syndrome. On the basis of these findings, ethylketocyclazocine could not be an agonist, partial agonist or competitive antagonist at the morphine receptor. It was inferred that both ethylketocyclazocine and cyclazocine must produce their agonistic action at another receptor. Furthermore, ethylketocyclazocine's actions were different from those of N-allylnormetazocine.

Therefore, Martin postulated the existence of 3 separate opiate receptors.

Recently, much evidence has been generated which supports this 3-receptor theory while some findings are to the contrary. In-vivo evidence obtained from antinociceptive testing in rats and mice show that when chemical agents were the nociceptive stimuli, both μ and κ agonists were effective (Tyers, 1980; Ward and Takemori, 1983). However, κ-agonists were more potent against pressure nociception than against heat nociception while the converse was true for μ-agonists (Tyers, 1980; Sewell et al., 1981; Upton et al., 1982; 1983). SKF 10,047 (σ agonist) had potent antinociceptive activity in chemically-induced writhing (Pasternak et al., 1981; Aceto and May, 1983) but was inactive against heat (Aceto and May, 1983) and pressure nociception (Dunn, unpublished observation).

The prototypic opiate compounds also have differential effects on locomotor activity. Morphine (μ-agonist), pentazocine (κ, σ-agonist, μ-antagonist), cyclazocine (κ, σ-agonist, μ-antagonist) and SKF 10,047 (σ-agonist, μ-antagonist) increased locomotor activity (Rethy et al., 1971; Holtzman and Jewett, 1972; 1973; Iwamoto, 1981) whereas ketocyclazocine and ethylketocyclazocine (κ-agonist, μ-antagonists) decreased locomotion (Tepper and Woods, 1978; Iwamoto 1981). Naloxone and naltrexone either had no effect (Parker, 1974) or slightly decreased locomotor activity (Castellano and Puglisi-Allegra, 1982). Only morphine-induced locomotion was antagonized by naloxone or naltrexone (Rethy et al., 1971; Iwamoto, 1981) while the

other agents were insensitive to the μ antagonists (Holtzman and Jewett, 1972; 1973; Iwamoto, 1981).

Interestingly, decreased brain catecholamine levels were noted following morphine-, pentazocine- and cyclazocine-induced locomotion (Rethy et al., 1971; Holtzman and Jewett, 1972; 1973). Furthermore, the catecholamine synthesis inhibitor, alpha-methyltyrosine, blocked the increased locomotor activity induced by these compounds (Buxbaum et al., 1973; Holtzman and Jewett, 1972; 1973). Also, spiperone (0.03 mg/kg), a postsynaptic dopamine-receptor blocker and apomorphine (0.1 mg/kg), a presynaptic dopamine inhibitor at this dose, attenuated morphine- and SKF 10,047-induced locomotor activity (Iwamoto, 1981). These results suggested that mu- and sigma-agonist-induced locomotor activity may be dependent on catecholamine transmission and, more specifically, dopaminergic transmission (antinociceptive and locomotor activity for opiate subtypes are summarized in Figure 5).

Characterization of three receptor subtypes was possible by concomitant testing of two in-vivo models. In the flurothyl-induced seizure test in rats, μ and σ agonists raised seizure thresholds, κ agonists had no effect, while in the rat Y-maze test, the behavioral profiles of μ and κ agonists could be differentiated from SKF 10,047 (σ) and cyclazocine (κ/σ) (Cowan, 1981). In drug discrimination models measuring generalization and antagonism, rat and monkey data generally support the three-receptor theory (Teal and Holtzman, 1980; Herling and Woods, 1981). Finally, cortical EEG spectral analysis has been employed as a sensitive tool to delineate

qualitative and quantitative similarities and differences between the μ, and opiate agents (Young et al., 1981).

Perhaps some of the more compelling evidence for the existence of μ, κ and σ receptors can be found in the in-vitro studies. In the last few years, there has been considerable controversy concerning the μ, κ and σ receptors. The type of tissue used in the assay is of utmost importance. It has been shown that rabbit vas deferens contains κ receptors exclusively and does not respond to μ or σ agonists (Oka et al., 1980). It was originally thought that the guinea pig ileum contained mainly μ receptors and the mouse vas deferens contained mainly μ and δ (delta) opiate receptors (Lord et al., 1977). It has now been shown that ethylketocyclazocine is a pure agonist in the guinea pig ileum and mouse vas deferens and effectively antagonizes selective μ agonists in the rat vas deferens (Gillan et al., 1981).

Receptor binding studies using CNS tissues have provided more concrete results. Initial sudies using ^{3}H-ethylketocyclazocine in competitive binding assays concluded there were no distinct κ receptors (Chang et al., 1980; Hiller and Simon, 1980). Chang et al. (1980) suggested that κ agonists have agonistic activity toward μ and δ receptors whereas σ agonists were agonists at σ receptors and antagonists at μ receptors. In a later study, when (D-Ala^{2}, D-Leu^{5}) enkephalin and morphiceptin were added in concentrations which occupied 98% of the enkephalin (δ) and morphine (μ) receptors, ^{3}H-diprenorphin binding was only partially inhibited (Chang et al., 1981). Therefore, a third binding site exhibited high affinity for

several benzomorphan drugs (cyclazocine, ethylketocyclazocine, SKF 10,047, etc.). Wood and coworkers (1981) identified a κ receptor in rat brain where ^{3}H-ethylketocyclazocine binding was potently displaced by κ, partial μ and agonist-antagonist analgesics while μ, δ, and σ receptor agonists were much less active at this binding site.

In a study using ^{3}H-cyclazocine, ^{3}H-ethylketocyclazocine and ^{3}H-SKF 10,047 and various other agents, competitive displacement and kinetic analysis revealed 3 cyclazocine binding sites (in order of decreasing affinity): 1) μ receptor, 2) a non-μ, non-σ binding site (which may represent the κ receptor) and 3) a putative σ receptor (Zukin and Zukin, 1981a). Other displacement studies in rat brain suggested the existence of distinct binding sites for κ- and σ-opiates which differed from morphine (μ) and enkephalin (δ) binding sites (Wolozin et al., 1982). In another series of studies, it was suggested that the σ receptor and the PCP (phencyclidine) binding site may be one in the same (Zukin and Zukin, 1981b) with the (+)-isomers of N-allylnormetazocine and cyclazocine being highly specific sigma opiate/PCP ligands (Zukin et al., 1984; Mendelsohn et al., 1985; Sircar et al., 1986). This may explain why behaviorally PCP and sigma agonists produce similar psychotomimetic effects. However, other investigators have shown a distinction between sigma and PCP binding sites in mice, rat and guinea pig brains (Su, 1982; Tam, 1983; Martin et al., 1984; Gundlach, 1985; Downes et al., 1986).

Behavioral and biochemical data suggest the existence of multiple opiate receptors. Discovery and development of specific

ligand antagonists for each receptor subtype would be beneficial in clarifying the presence, both functionally and anatomically, of specific mu, kappa and sigma receptors.

E. Similarities of Opiate and Dopaminergic Agents - Modulation of Dopaminergic Nigrostriatal and Mesolimbic Systems by Opiates

The opiate and dopaminergic systems share certain dynamic interrelationships, both functionally and anatomically, in the central nervous system and, especially in the nigrostriatal and mesolimbic systems. Functionally, both morphine and haloperidol induce catalepsy in rats which can be antagonized by apomorphine or benztropine (Lal et al., 1975). However, there was a qualitative difference in the catatonia; neuroleptic-induced catalepsy was marked by muscular hypotonia whereas hypertonia characterized narcotic-induced catatonia (Wauquier et al., 1974). Likewise, the endogenous opiates, β-endorphin, met-enkephalin and leu-enkephalin, produced sedation and catalepsy following microinjection into the periaqueductal gray in rats (Jacquet and Marks, 1976). Narcotics and neuroleptics effectively block either apomorphine or amphetamine-induced stereotypy in the rat and L-dopa and amphetamine-induced jumping in mice, as well as apomorphine-induced emesis in dogs (Lal et al., 1975). Moreover, morphine and haloperdol antagonized apomorphine-induced aggression in the rat, apomorphine- and amphetamine-induced aggression in mice and morphine withdrawal aggression in rats (Lal et al., 1975). Motivational behavior such as lateral hypothalmic self-stimulation

in rats was also effectively blocked by haloperidol and morphine (Wauquier et al., 1974).

On the other hand, whereas opiate agonists as well as neuroleptics antagonized dopamine-dependent behaviors, opiate antagonists such as naloxone potentiated apomorphine- and amphetamine-induced behaviors. Naloxone has been reported to potentiate apomorphine-induced hyperthermia in rabbits (Quock, 1977), the anticataleptic effect of L-dopa in reserpinized mice (Namba et al., 1980), the antitremor effect of L-dopa in oxotremorine-treated mice (Quock and Lucas, 1983), apomorphine-induced turning in rats with unilateral electrocoagulation lesion of the substantia nigra (Quock and Welsh, 1980), apomorphine-induced climbing in mice (Quock and Lucas, 1981; Quock et al., 1983) and apomorphine- and d-amphetamine-induced stereotypy in rats (Adams et al., 1981).

Biochemical binding techniques have shown these behaviors are probably not a result of the direct action of opiate agents on dopamine receptors since the acute administration of opiates had no effect on ^{3}H-neuroleptic binding (Burt et al., 1976; Puri et al., 1978; Carlson and Seeger, 1981; 1982). Conversely, acute haloperidol showed competitive binding to the opiate receptor similar to an opiate agonist while other butyrophenones bind and resembled antagonists or mixed agonist-antagonists (Creese et al., 1976). Hence, opiates do not directly act as antagonists at dopamine receptor sites but neuroleptics may act at opiate receptor sites.

These opiate receptor sites were biochemically demonstrated by ^{3}H-naloxone binding to be located in large amounts in rat brain with the greatest concentration in the corpus striatum (Pert and Snyder, 1973). Opiate and enkephalin receptors have been located presynaptically on dopamine neurons in the mesolimbic (Pollard et al., 1977a) and striatal (Pollard et al., 1977b) systems, respectively. In fact, the highest concentration of enkephalins was found in the globus pallidus followed by the caudate nucleus and the nucleus accumbens (Hong et al., 1977). Furthermore, biochemical (Pollard et al., 1978) and autoradiographic techniques (Murrin et al., 1980) have shown that one-third of the striatal opiate receptors are located presynaptically on dopamine neurons while two-thirds of the opiate receptors are located on intrinsic neurons with the majority of these making postsynaptic contact with dopamine neurons. Since opiate and enkephalin receptors and neurons are in close proximity and contact with dopamine neurons in the striatal and mesolimbic systems, they may serve to modulate dopaminergic transmission in these areas.

Additional evidence for opiate regulation of dopaminergic processes was reported following chronic morphine administration. Iwamoto and his associates (1973) found that following chronic morphine pellet implantation in mice, naloxone-induced withdrawal jumping behavior was accompanied by an increase in dopamine levels with the greatest elevation occurring in the corpus striatum while norepinephrine and serotonin levels remained relatively constant. Chronic morphine treatment has also led to the development of

postsynaptic DA-SS as measured by apomorphine-induced stereotyped behavior in rats (Cox et al., 1976) and guinea pigs (Carlson and Almasi, 1978); apomorphine-induced aggression in rats (Puri and Lal, 1973; Gianutsos et al., 1974); apomorphine-induced locomotion in rats (Bhargava, 1980) and apomorphine-induced climbing in mice (Baume et al., 1979; Martin and Takemori, 1986). Also, repeated intraventricular injections of beta-endorphin in rats resulted in the development of DA-SS (Bhargava, 1981).

Biochemically, chronic administration of morphine was similar to haloperidol in that an initial rise in HVA levels was followed by a significant decrease for several days (Baume et al., 1979). One explanation for the diminished activity of dopamine neurons was due to the increased activity of the feedback loop when the postsynaptic receptors became hypersensitive to dopamine (Martres et al., 1977). Also, apomorphine caused a greater reduction in dopamine turnover in morphine-dependent rats (Kuschinsky, 1975; Gianutoss et al., 1974; Puri et al., 1977) suggesting DA-SS and probable supersensitive presynaptic dopamine autoreceptors (Kuschinsky, 1975). Unlike haloperidol-induced DA-SS where there was an increase in dopamine receptors (Burt et al., 1977), chronic morphine treatment was reported to either decrease (Puri et al., 1978), slightly increase (Baume et al., 1979) or have no effect (Carlson and Seeger, 1982) on ^{3}H-neuroleptic binding. However, a recent study showed that chronic morphine administration in mice resulted in a significant increase in ^{3}H-spiroperidol binding sites in whole brain (Martin and

Takemori, 1986). Also, there may be an increase in affinity, although fewer binding sites (Puri et al., 1978; Bhargava, 1983).

It would appear that dopaminergic transmission is modulated to some extent by the opiate system, especially in the nigrostriatal and mesolimbic areas. Since morphine and haloperidol display some similar behavioral and biochemical effects with each capable of eliciting DA-SS, might dopamine metabolism be modified by mu antagonists and/or non-mu opiates in such a way to down regulate the dopamine system? Namely, since naloxone has been shown to potentiate certain dopaminergic mediated behaviors and because simultaneous administration of dopamine agonists with dopamine antagonists compensates for the development of DA-SS, would the concomitant administration of mu antagonists with the dopamine antagonist, haloperidol, attenuate DA-SS? What effects would the kappa agonist, ethylketocyclazocine or the sigma agonist, SKF 10,047 (agents which also possess mu antagonistic properties) have on the development of haloperidol-induced DA-SS? This disseration investigates these possibilities using both acute and chronic behavioral paradigms predictive of mesolimbic and striatal dopaminergic activity, namely locomotor activity and stereotyped behavior, respectively, as well as the climbing mouse model.

F. Hypotheses

The following hypotheses will be investigated concerning the mediation of the dopamine receptor by the opiate receptor subtype agents, particularly concerning the development of haloperidol-induced dopaminergic supersensitivity (DA-SS). The opiate receptor

subtype agents specifically investigated include: the mu agonist, morphine; the mu antagonists, naloxone and naltrexone; the mixed kappa, sigma agonists and mu antagonists, pentazocine and cyclazocine; the kappa agonist and mu antagonist, ethylketo-cyclazocine; and the sigma agonist and mu antagonist, N-allylnormetazocine (SKF 10,047).

1. Opiates are not dopamine-receptor antagonists and therefore, will not attenuate apomorphine-induced climbing and stereotyped behaviors in mice.
2. Opiates which stimulate catecholamine neuronal activity will cause either increased locomotor activity (indicative of mesolimbic activity), stereotypy (indicative of striatal activity) or climbing behavior (indicative of mesolimbic and/or striatal activity) in mice.
3. The acute and/or chronic simultaneous administration of the opiate receptor subtype agents and haloperidol will attenuate the development of dopaminergic supersensitivity as measured by apomorphine-induced climbing and stereotyped behavior in mice.

MATERIALS AND METHODS

For all experiments, male CD-1 albino mice (Charles River) weighing 20-30 g were used. They were group housed (20 per cage) in a room where the temperature was 22 $\pm$ 1° C with lights on between 6 a.m. and 6 p.m. Food and water were available ad libitum. All experiments were carried out between 10 a.m. and 4 p.m.

Acute Studies.

Following a one-hour acclimation period, compounds were administered to male mice (CD-1) and tested for their effects on either locomotor activity, stereotypy or climbing behavior.

Acute Supersensitivity Studies.

Each opiate agent was simultaneously administered sc with haloperidol ip to male mice (CD-1) 72 hours before testing. Controls were given appropriate treatments. Mice were then group housed (9 per cage) until test day under the standard laboratory conditions detailed above.

Chronic Supersensitivity Studies.

Each opiate agent was simultaneously administered sc with haloperidol ip to male mice (CD-1) for 5 days. Controls were given appropriate treatments. Mice were group housed (9 per cage) until test day, 72 hours after last dosing under the standard laboratory condtions detailed above.

Locomotor Activity Experiments.

Locomotor activity was measured on electromagnetic sensors (Stoelting Co. #13404) in sound-attenuated chambers. CD-1 male mice

were placed in opaque plastic cages (2 mice per cage) measuring 10.5" x 8" x 6" which rested upon each sensor. Following a one-hour adaptation or exploratory period where mice became acclimated to their cages, each animal was administered drug and testing commenced.

To measure the effects of individual opiate agents, mice were administered drug sc, then activity was assessed immediately after injection for 6 hours. To measure supersensitivity effects of acute and chronic pretreatment of haloperidol, apomorphine HCl was administered sc, then activity was measured for 2 hours. The combined activity of each pair of mice provided activity counts. The counts were recorded by a Data General Nova 2/10 computer within 15-minute intervals over the first 2 hours of testing, then at hourly intervals for the remaining 4 hours during the 6-hour test. These counts were transformed into square-root values to normalize the data and to make the means and variances independent, with the resulting variances homogeneous. Control scores were compared with scores from compound-treated subjects using a one-way analysis of variance (ANOVA) followed by a Dunnet's multiple comparison (Kirk, 1968) on a DEC (Digital Equipment Corporation) PDP 11/10 computer.

Apomorphine-Induced Stereotypy.

Prior to injection, CD-1 male mice were placed in clear plastic cages (2 mice per cage) measuring 10.5" x 8" x 6" and were allowed to acclimate for 60 minutes. For antagonism studies, compounds were administered ip 30 minutes before apomorphine at 1.5 mg/kg sc. For acute and chronic supersensitivity studies, 72 hours following appropriate treatments (and one hour after cage acclimation), mice

received apomorphine at 0.4 mg/kg sc. In both designs, mice were scored for stereotypy during 2-minute observation periods at 10, 20 and 30 minutes after injection. Scores were assigned according to the following rating scale modified from Costall et al. (1972): 0 -normal behavior, mice essentially the same as before injection; 1 -locomotor activity and sniffing; 2 - discontinuous locomotor activity, rearing, intense, continuous sniffing, licking and gnawing.

Stereotypy scores were individually totaled (maximum score = 6 per mouse over 3 readings) and tranformed into square-root values to normalize the data and to make the means and variances independent, with the resulting variances homogeneous. Control scores were compared to scores from compound-treated subjects by a one-way ANOVA followed by the Duncan's multiple range test by using a SAS (Statistical Analysis System) program on an IBM 3033 computer.

Apomorphine-Induced Climbing.

Prior to injection, CD-1 male mice were placed individually in wire mesh test cages measuring 4" x 4" x 10" and were allowed to acclimate for 60 minutes. For antagonism studies, compounds were administered 30 minutes before apomorphine at 1.5 mg/kg sc. For potentiation studies, compounds were administered prior to apomorphine at either 0.4 or 0.8 mg/kg sc. For acute and chronic supersensitivity studies, 72 hours following appropriate treatments (and one hour after cage acclimation), mice received apomorphine at 0.4 mg/kg sc. In both designs, mice were scored for climbing activity during observation periods at 10, 20 and 30 minutes after injection. Scores were assigned according to the following rating scale (Protais et al.,

1976): 0 - no climbing, 4 paws on bottom of cage; 1 - rearing, 2 paws clinging to the side of the cage; 2 - full climbing, 4 paws clinging to the side or top of the cage.

Climbing scores were individually totaled (maximum score = 6 per mouse over 3 readings) and transformed into square-root values to normalize the data and to make the means and variances independent, with the resulting variances homogeneous. Control scores were compared to scores from compound-treated subjects by a one-way ANOVA followed by the Duncan's multiple range test by using a SAS program on an IBM 3033 computer.

SKF 10,047-Induced Climbing Behavior.

Same as above for apomorphine-induced climbing where SKF 10,047 was administered sc. ED_{50} values with 95% confidence limits were calculated by linear regression analysis. For antagonism studies, SKF 10,047 at 40 mg/kg sc was administered 90 minutes before testing. Compounds were administered at appropriate pretreatment times.

Ethylketocyclazocine-Induced Hyperactivity.

Same as above for apomorphine-induced climbing where ethylketocyclazocine was administered sc and hyperactivity, not climbing, was measured. Hyperactivity scores were assigned according to the following rating scale: 0 - no locomotor activity, animal in resting position on the bottom of the cage; 1 - locomotion and circling, confined to the bottom of the cage; 2 - more continuous locomotion on bottom and sides of cage. For antagonism studies, ethylketocyclazocine at 5 mg/kg sc was administered at 180 minutes

before testing. Compounds were administered at appropriate pretreatment times.

Drugs.

The following drugs were used in these studies: apomorphine HCl (Merck), haloperidol (McNeil), alpha-methyl-para-tyrosine (Sigma), atropine (Sigma), bicuculline (Regis), clonidine HCl (Boehringer), cyclazocine (Sterling-Winthrop), ethylketocyclazocine (Sterling-Winthrop), methylsergide (Sandoz), muscimol (Regis), N-allyl-normetazocine (NIDA), naloxone (Endo), naltrexone (Endo), pentazocine (Sterling-Winthrop), dl-p-chlorophenylalanine methyl ester HCl (Sigma), propranolol HCl (Ayerst), phentolamine HCl (Ciba), prazosin (Pfizer), reserpine (Aldrich), tetrabenazine (Hoffman-La Roche) and yohimbine (Sigma).

Drugs which were not water soluble were suspended in distilled water and one drop of Tween 80, i.e., haloperidol, ethylketocyclazocine, dl-p-chlorophenylalanine methyl ester, prazosin and yohimbine. Cyclazocine, N-allyl-normetazocine and pentazocine were solubilized in distilled water with the addition of one drop of lactic acid and pH adjusted with 0.25 N NaOH. The final volume was prepared to account for the salt content and the dosage is expressed as 100% base. The injection volume was 10 ml/kg.

RESULTS

Apomorphine-induced behaviors. Locomotor Activity. Generally, apomorphine at 1.5 and 5 mg/kg produced slight but not significant increases in locomotor activity in mice over the first hour (14% to 21%) following subcutaneous administration with little or no effect during the second hour (Table 1, Fig. 6).

Stereotyped behavior. Apomorphine dose-dependently increased stereotyped behavior in mice at doses from 0.3 mg/kg to 3.0 mg/kg with an ED_{50} equal to 0.80 (0.76-0.84) mg/kg sc (Table 2). At the lower doses, locomotion and sniffing were prevalent while at the higher doses, discontinuous activity was marked by intense sniffing, rearing, licking and gnawing.

Climbing behavior. Apomorphine at doses from 0.3 to 3.0 mg/kg produced climbing behavor in mice characterized by elongated, deliberate and sustained verticalization in the wire mesh stick cages. The ED_{50} value for climbing was 0.58 (0.55-0.61) mg/kg sc (Table 3).

Locomotor activity of opiate subtype agents in mice. Morphine at 2.5, 5 and 10 mg/kg produced dose-dependent increases from 23% to 41% in locomotor activity, during the first hour of testing and increases from 79% to 101% during the second hour where these increases were significant (Table 4, Fig. 7). These increases in locomotion were consistently seen at higher doses (Table 5) and would correspond to the characteristic "morphine mania" observed in rodents. In general, the mu antagonists, naloxone (Table 6, Fig. 8) and naltrexone (Table 7, Fig. 9) at doses from 10 to 40 mg/kg had no effects on locomotor activity. The kappa agonist, mu antagonist ethylketocyclazocine (EKC)

at 5, 10 and 20 mg/kg showed an interesting biphasic effect on locomotor activity in mice (Table 8, Fig. 10). At 5 mg/kg, initial significant decreases in locomotion (with almost complete cessaton of activity at 30 minutes) over 75 minutes were followed by increases which peaked between three (+46%) to four hours (+85%). At the higher doses (10 and 20 mg/kg), decreased activity lasted for three hours followed by increases beginning at four hours and lasting throughout the six hours of testing. The mixed kappa and sigma agonists, mu antagonists, pentazocine and cyclazocine, enhanced locomotor activity beginning at about 30 minutes for the first two to three hours of testing (Table 9, Fig. 11 and Table 10, Fig. 12, respectively). Pentazocine at doses from 20 to 80 mg/kg increased activity by 27% to 78% while cyclazocine at doses from 2.5 to 10 mg/kg augmented locomotion by 33% to 112% compared to controls. This hyperactivity was followed by slight decreases in activity at five hours for pentazocine and at four hours for cyclazocine. On the other hand, the prototype sigma agonist, SKF 10,047 at 10 to 40 mg/kg produced an increase in locomotor activity from 15 minutes through five hours (Table 11, Fig. 13). The hyperactivity ranged from 25% to 86% over control levels of locomotion.

Effects of opiate subtype agents on apomorphine-induced climbing and stereotypy. It was of interest to determine the acute effects of opiate agents on the reliable and consistent apomorphine-induced behaviors (apomorphine did not produce reliable increases in locomotion), namely climbing and stereotypy. Morphine, naloxone, naltrexone, pentazocine and cyclazocine had no effect on apomorphine

(1.5 mg/kg) -induced climbing behavior. However, EKC at 20 mg/kg and SKF 10,047 at 40 mg/kg significantly decreased the maximal climbing induced by apomorphine at 1.5 mg/kg by 52% and 25%, respectively (Table 12). General depressive effects including ataxia and flaccidity were observed following EKC and SKF 10,047 administration, which may have interfered with the ability of the mice to climb. However, in both cases the lower doses of EKC and SKF 10,047, namely 5 and 10 mg/kg, respectively, had no significant effects on climbing. EKC and SKF 10,047 at the doses which were active in attenuating apomorphine-induced climbing, were then tested for their effects on apomorphine-induced stereotyped behavior. EKC at 20 mg/kg significantly attenuated apomorphine-induced stereotypy while SKF 10,047 at 40 mg/kg had no effect (Table 13).

The effect of 72-hour pretreatment of haloperidol (1.25 mg/kg) on apomorphine-induced locomotor activity. There was no significant effect of 72-hour haloperidol pretreatment on apomorphine-induced locomotor activity (Table 14, Fig. 14).

The effect of 72-hour pretreatment of haloperidol (1.25 mg/kg) on apomorphine-induced stereotypy. There was no significant effect of 72-hour haloperidol pretreatment on apomorphine-induced stereotyped behavior (Table 15).

The effect of 72-hour pretreatment of haloperidol (1.25 mg/kg) on apomorphine-induced climbing. Haloperidol 72 hours prior to apomorphine at 0.4 mg/kg sc significantly increased climbing (approximate two-fold increase) compared to vehicle controls (Table 16).

The effects of simultaneous administration of opiate agents and haloperidol 72 hours prior to apomorphine at 0.4 mg/kg sc in the climbing mouse assay. Since acute pretreatment (72 hours) of haloperidol produced an enhanced responsiveness or supersensitivity to apomorphine-induced climbing (CMA-SS), the effects of various opiate agents on this behavior was investigated. The concurrent treatment of these agents and vehicle (72 hours pretreatment) had no significant effects on apomorphine-induced climbing behavior (Table 17). However, every agent except morphine had a significant effect on attenuating the enhanced responsiveness to haloperidol pretreatment on apomorphine-induced climbing (Table 18). Simultaneous administration of haloperidol at 1.25 mg/kg and either naloxone at 20 mg/kg, naltrexone at 20 mg/kg, EKC at 20 mg/kg, pentazocine at 80 mg/kg, cyclazocine at 1.25 and 5 mg/kg or SKF 10,047 at 10 and 40 mg/kg significantly reduced CMA-SS by 44%, 51%, 56%, 42%, 53% and 64%, or 54% and 75%, respectively (Table 18).

Dose-response relationships were assessed for those agents which effectively attenuated haloperidol-induced supersensitivity (Tables 19 to 24). Generally, increasing doses of naloxone (Table 19), naltrexone (Table 20), EKC (Table 21), pentazocine (Table 22), cyclazocine (Table 23) and SKF 10,047 (Table 24) resulted in an increased suppression of haloperidol-induced supersensitivity in the climbing mouse assay whereas these agents alone did not significantly effect this behavior (Tables 19 to 24).

Increasing doses of naloxone (5 to 20 mg/kg) in combination with haloperidol, dose-dependently decreased (37% to 62%) the enhanced

responsiveness to apomorphine following haloperidol pretreatment (Table 19). Likewise, naltrexone at doses from 5 to 20 mg/kg dose-dependently decreased CMA-SS by 34% to 59% (Table 20). The combination of EKC with haloperidol was also effective in attenuating the enhanced responsiveness to apomorphine following haloperidol treatment alone (Table 21). Although the effects of EKC at doses from 2.5 to 20 mg/kg were variable, significant reduction of CMA-SS was seen at 5 mg/kg (-35%) and 20 mg/kg (-57%) without any observed overt depressive effects.

The mixed kappa and sigma agonists, pentazocine and cyclazocine each dose-dependently decreased haloperidol-induced CMA-SS although cyclazocine was more potent. Pentazocine at doses from 20 to 80 mg/kg decreased CMA-SS from 29% to 63% (Table 22) while cyclazocine attenuated CMA-SS at doses from 1.25 to 5 mg/kg by 32% to 55% (Table 23). The prototype sigma agonist, SKF 10,047 also effectively reduced haloperidol-induced CMA-SS by 39% to 75% at doses between 5 and 40 mg/kg (Table 24).

The effects of chronic (5-day) haloperidol (1.25 mg/kg) administration on apomorphine-induced locomotor activity. Although there was a slight increase (15%) in apomorphine (0.4 mg/kg) -induced locomotor activity during the first hour of testing following chronic haloperidol treatment, this effect was not statistically significant (Table 25, Fig. 15).

The effects of chronic (5-day) simultaneous administration of opiate agents and haloperidol 72 hours prior to apomorphine at 0.4 mg/kg sc on stereotyped behavior. Chronic treatment of haloperidol at 1.25 mg/kg per day for five days resulted in approximately twice the amount of stereotyped behavior following apomorphine at 0.4 mg/kg, compared to vehicle-treated controls (Tables 26-30, Figs. 16-20). Chronic morphine at 10 mg/kg per day for five days also produced a significantly enhanced stereotyped response (+117% compared to control) to apomorphine (Table 26, Fig. 16). However, when morphine was simultaneously administered with haloperidol, the enhanced effect (+117%) was not additive and was essentially the same as the chronic haloperidol group (+144%) and the chronic morphine-haloperidol group (+150%, Table 25). When naltrexone at 40 mg/kg was chronically administered, it had no effect on apomorphine stereotypy compared to vehicle controls (Table 27, Fig. 17). Also, naltrexone did not attenuate haloperidol-induced enhancement of apomorphine stereotypy (Table 27, Fig. 17). Likewise, chronic EKC at 20 mg/kg either alone or in combination with haloperidol had no effect in this paradigm (Table 28, Fig. 18).

On the other hand, both chronic cyclazocine and SKF 10,047 effectively attenuated haloperidol-induced supersensitivity in the stereotypy model. Apomorphine (0.4 mg/kg) -induced stereotypy was enhanced by 137% in the chronic haloperidol group and only enhanced by 58% in the cyclazocine (2.5 mg/kg) -haloperidol group when compared to the vehicle control group (Table 29, Fig. 19). In comparing the mean stereotypy scores ($\bar{x}$ of veh.-haloperidol = 5.63; $\bar{x}$ of cyclazocine-

haloperidol = 3.75), there was a 33% reduction in supersensitivity which was statistically significant (Table 29). The combination of chronic SKF 10,047 at 40 mg/kg and haloperidol was most effective in significantly reducing haloperidol-induced supersensitivity by 61% to control levels (Table 30, Fig. 20).

The effects of chronic (5-day) simultaneous administration of opiate agents and haloperidol 72 hours prior to apomorphine at 0.4 mg/kg sc in the climbing mouse assay. Chronic morphine at doses from 2.5 to 10 mg/kg resulted in an enhanced responsiveness (53% to 76%) to apomorphine in the climbing assay although this effect was not significant (Table 31). However, when morphine was simultaneously administered with haloperidol, there was no further enhancement of apomorphine-induced climbing seen after haloperidol alone (Table 31). The concurrent administration of chronic naloxone (5 to 40 mg/kg) and haloperidol had no effect on haloperidol-induced CMA-SS (Table 32). However, chronic naltrexone at doses from 2.5 to 40 mg/kg slightly decreased (11% to 46%) haloperidol-induced CMA-SS although this effect was not statistically significant (Table 33).

The chronic simultaneous administration of EKC at 5 to 20 mg/kg and haloperidol resulted in a consistent (although non-significant) suppression (40% to 49%) in the enhanced climbing response to apomorphine seen after haloperidol alone (Table 34). Five-day administration of EKC alone had variable effects on the climbing behavior (Table 34). The mixed agonist-antagonist, pentazocine (10 to 80 mg/kg) had no effect on haloperidol-induced CMA-SS (Table 35) while chronic cyclazocine at doses from 0.38 to 3 mg/kg significantly

reduced (by 38% to 49%) the enhanced responsiveness of apomorphine following chronic haloperidol to control levels (Table 36). On the other hand, chronic cyclazocine and vehicle had no effect in this paradigm (Table 36). The sigma agonist, SKF 10,047 dose-dependently attenuated haloperidol-induced CMA-SS (Table 37). At doses from 5 to 40 mg/kg, haloperidol-induced CMA-SS was decreased from 33% to 76% while chronic SKF 10,047 alone had no effect on apomorphine-induced climbing behavior in this paradigm.

Acute interaction effects of apomorphine (0.4 mg/kg) and either naloxone, EKC or SKF 10,047 on climbing behavior in mice. Naloxone alone at 1, 3 and 10 mg/kg did not induce climbing behavior in mice (Table 38). However, when naloxone at 3 and 10 mg/kg ip was simultaneously administered with apomorphine at 0.4 mg/kg sc, there was a slight potentiation in climbing from 25% climbing in the apomorphine group to 46% climbing in the apomorphine-plus-naloxone group (Table 38). EKC alone at 3 and 10 mg/kg 180 minutes after administration, produced hyperactivity after an initial depression unlike the prolonged stereotyped climbing seen after apomorphine (Table 39). This hyperactivity was not similar to either amphetamine or morphine hyperactivity in that the mice did not limit their locomotion to circling on the bottom of the cage as with amphetamine or exhibit the "running fit" of persistant circling accompanied by Straub tail as observed with morphine (unpublished observations). EKC-induced hyperactivity was characterized by quick, sporadic running up and down vertically in the cage and episodes of stereotypic rearing and sniffing. The combination of EKC and apomorphine resulted in a slight

increase in climbing behavior compared to apomorphine controls (27% climbing compared to 33% to 42%). SKF 10,047 at 10 mg/kg induced a climbing response (+33%) at 90 minutes resembling the deliberate and sustained stereotypic climbing seen after apomorphine alone (Table 40). Mice were initially ataxic for the first 30 minutes after administration, then followed stereotyped behavior characterized by vocalization, excessive grooming and sniffing, then rearing and finally climbing approximately 75 to 90 minutes post administration. The combination of SKF 10,047 (1 to 10 mg/kg) and apomorphine produced an approximate additive climbing response compared to apomorphine controls (Table 40).

Ethylketocyclazocine-induced hyperactivity in mice. Since EKC administration produced hyperactivity after an initial decrease in locomotor activity, a time response was run over six hours to determine the duration of locomotor activity in the wire mesh stick cages. EKC was administered at 5 mg/kg sc in mice. Onset of hyperactivity occurred at 120 to 150 minutes with peak activity (47%) at 180 to 210 minutes, followed by a gradual decrease in activity to six hours (Table 41). Then EKC was administered at doses from 1.25 to 10 mg/kg and the ED_{50} for hyperactivity measured 180 minutes after administration was equal to 7.1 mg/kg sc (Table 42).

Effects of various blocking agents on EKC-induced hyperactivity. The following agents had no effect on EKC-induced hyperactivity at 5 mg/kg sc: naloxone, bicuculline, yohimbine, clonidine, propranolol, PCPA, methysergide and atropine although PCPA at 300 mg/kg antagonized the hyperactivity by 46%, it was not statistically significant (Table 43).

The following catecholaminergic blockers and depleters significantly an-tagonized EKC-induced hyperactivity (Table 43): haloperidol at 1 mg/kg (-54%), apomorphine at 0.1 mg/kg (-65%), muscimol at 1 mg/kg (-63%), alpha-methyl-para-tyrosine at 300 mg/kg (-81%), phentolamine at 10 mg/kg (-47%), prazosin at 2.5 mg/kg (-97%), reserpine at 5 mg/kg (-74%) and tetrabenazine at 5 and 40 mg/kg (-81% and -90%, respectively).

SKF 10,047-induced climbing behavior in mice. As previously described, SKF 10,047-induced a climbing response similar to that of apomorphine-induced climbing. SKF 10,047 was administered at 40 mg/kg sc and climbing was measured from 30 to 180 minutes after dosing (Table 44). Onset of climbing began at 30 minutes with peak effect at 90 minutes (72%) and then the climbing gradually waned. Then SKF 10,047 was administered at doses from 3 to 30 mg/kg and the ED_{50} for climbing determined 90 minutes after administration was equal to 14.6 mg/kg sc (Table 45).

Effects of various blocking agents on SKF 10,047-induced climbing behavior. The following agents had no effect on SKF 10,047-induced climbing behavior: naloxone, bicuculline, yohimbine, clonidine, propranolol, PCPA, atropine and reserpine (Table 46). The following blockers significantly antagonized SKF 10,047-induced climbing activity (Table 46): haloperidol at 1 mg/kg (-73%), apomorphine at 0.1 mg/kg (-64%), muscimol at 1 mg/kg (-89%), alpha-methyl-para-tyrosine at 300 mg/kg (-97%), phentolamine (-37%) and prazosin at 2.5 mg/kg (-90%), methysergide at 10 mg/kg (-66%) and tetrabenazine at 5 and 40 mg/kg (-75% and -97%, respectively).

DISCUSSION

Just as dopaminergic supersensitivity (DA-SS) is a well-established behavioral and biochemical phenomenon following dopamine receptor blockade by neuroleptics, the fact that endorphinergic agents such as morphine and endorphin are capable of inducing DA-SS (Puri and Lal, 1973; Gianutsos et al., 1974; Cox et al., 1976; Carlson and Almasi, 1978; Baume et al., 1979; Bhargava, 1981; Martin and Takemori, 1986) is an intriguing consequence of how disruption of endorphinergic homeostasis can effect dopamine-dependent behaviors. This dissertation dealt with how the various exogenous opiate receptor subtype agents, namely mu (μ), kappa (κ) and sigma (σ) agonists, influenced dopaminergic systems, specifically in the development of haloperidol-induced dopamine receptor supersensitivity.

It has also become apparent that there are two major dopamine receptor subtypes: D-1 receptors involved in the stimulation of adenylate cyclase activity and D-2 receptors which act independently of the enzyme and which, in some tissues, inhibit adenylate cyclase activity (Kebabian and Calne, 1979; Sibley et al., 1982; Creese, 1985). Clinically, effective neuroleptics such as haloperidol, possess a nanomolar potency for displacement of tritiated ligand at D-2 receptor sites and a micromolar potency at D-1 receptor sites (Creese et al., 1982). Neuroleptics also antagonize apomorphine-induced behavioral effects which primarily reflect activation of D-2 receptor sites (Randrup and Munkvad, 1974; Creese et al., 1983). However, recent evidence suggests that dopaminergic behaviors may be mediated through D-1 receptors or be expressed by complex functional interactions

between D-1 and D-2 receptors in the brain (Mailman et al., 1984; Molloy and Waddington, 1984, 1985; Pugh et al., 1985; Barone et al., 1986; Saller and Salama, 1986).

Therefore, since apomorphine is a direct dopamine-receptor agonist (Ernst, 1967), it served as a pharmacological tool for gauging dopamine receptor (D-2) sensitivity in the behavioral paradigms predictive of mesolimbic and striatal dopamine activity, i.e., locomotion, stereotypy and climbing behavior (Pijnenberg and Van Rossum, 1973; Costall and Naylor, 1975; Kelley et al., 1975; Pijenberg et al., 1976; Protais et al., 1976; Costall et al., 1979, 1980). Apomorphine's effects on these behaviors were verified in these procedures and produced especially reliable and robust effects in stereotypy (ED_{50} = 0.80 mg/kg sc; Table 2) and climbing (ED_{50} = 0.58 mg/kg sc; Table 3), while only producing slight enhancement of locomotion (Table 1; Fig. 6). However, the reason for only slight increases in locomotion is due to the fact that the stereotypic components of apomorphine's effects (even at relatively low postsynaptic doses) interferes with horizontal locomotor activity, i.e., stereotyped behavior was observed between 0.3-3.0 mg/kg (Table 2) whereas slight increases in locomotor activity occur at 1.5 and 5.0 mg/kg (Table 1).

It was of interest to determine whether the opiates were capable of blocking dopaminergic effects by antagonizing apomorphine-induced climbing and stereotyped behavior. Biochemical studies showed neuroleptics act at opiate sites (Creese et al., 1976) but opiates do not interact at neuroleptic sites (Creese et al., 1976; Puri et al., 1978). Generally, this was the case in the climbing and stereotypy

experiments. Morphine, naloxone, naltrexone, pentazocine and cyclazocine had no effect on apomorphine (1.5 mg/kg) -induced climbing behavior (Table 12). Although, ethylketocyclazocine (EKC) at 20 mg/kg and SKF 10,047 at 40 mg/kg significantly decreased climbing by 52% and 25%, respectively (Table 12), this may have been due to the initial depressive effects of EKC and the ataxia produced by SKF 10,047 which rendered the mice unable to climb. In fact, lower doses of these compounds had no effect on climbing (Table 12). Likewise, only EKC (20 mg/kg) was active in antagonizing apomorphine-induced stereotypy (Table 13), further evidence that the side effects of EKC, namely, general overt depression and flaccidity were responsible for the blockade of these behaviors, not dopamine-receptor blockade. Also, SKF 10,047 (40 mg/kg) did not antagonize apomorphine-induced stereotypy which showed that although ataxia interfered with climbing, it had no effect on stereotypy. Furthermore, in both the acute (Tables 17, 21 and 24) and chronic (Tables 28, 30, 34 and 37) supersensitivity paradigms, neither EKC nor SKF 10,047 were capable of inducing DA-SS. Therefore, the opiate receptor subtype agents do not appear to act as dopamine receptor antagonists in the two behavioral assays which are predictive for antipsychotic agents, i.e., apomorphine-induced climbing and stereotypy.

On the other hand, might these opiates act either directly or indirectly as dopaminergic agents? Inasmuch as dopamine agonists and releasers are known to induce locomotor activity in rodents (Costall and Naylor, 1977), it was important to investigate the locomotor effects of the opiate subtypes.

In the locomotor activity experiments, morphine, EKC, pentazocine, cyclazocine and SKF 10,047 all increased locomotion at some time during the six hours of testing while the pure antagonists, naloxone and naltrexone, had no effect. Opioid-induced hyperactivity has previously been implicated to be mediated by dopaminergic transmission (Buxbaum et al., 1973; Holtzman and Jewett, 1972, 1973; Kuschinsky and Hornykiewicz, 1974; Iwamoto, 1981). Morphine (μ), SKF 10,047 (σ), pentazocine and cyclazocine (κ, σ) each produced immediate increases in locomotion which generally lasted from one to three hours (Tables 4, 9, 10 and 11; Figures 7, 11, 12 and 13).

Morphine induction of hyperactivity or "morphine mania", as well as pentazocine-, cyclazocine- and SKF 10,047-induced hyperactivity have been well documented (Rethy et al., 1971; Holtzman and Jewett, 1972, 1973; Iwamoto, 1981). However, initial experiments in rats and mice (Tepper and Woods, 1978; Iwamoto, 1981) failed to show EKC-induced hyperactivity because these experiments lasted for one to two hours and hyperactivity was not evident until three hours postadministration (Table 8, Fig. 10). The results in this dissertation, along with a recent study (Gwynn and Domino, 1984) where locomotion was monitored for 6 hours showed that EKC induced a biphasic locomotor effect where an initial decrease in activity was followed at approximately 180 minutes by a significant increase in locomotion (Table 8, Fig. 10).

EKC hyperactivity was further investigated for peak effect and mechanism of action by utilizing the wire-mesh stick cages. Peak activity at 5 mg/kg sc was determined to be between 180 to 210 minutes

(Table 41). Various blocking agents at appropriate pretreats were combined with EKC at 5 mg/kg sc and hyperactivity was measured at 180 to 210 minutes (Table 43). EKC hyperactivity was clearly distinguishable from the morphine-induced "running fit" or "morphine mania" in mice. EKC hyperactivity was relatively insensitive to naloxone (Table 43) and EKC induced a sporadic running and episodes of stereotyped rearing and sniffing whereas morphine induced a "running fit" characterized by persistant circling which was antagonized by naloxone (Rethy et al., 1971). EKC hyperactivity was dependent upon catecholamine transmission since the synthesis inhibitor α-MPT (Spector et al., 1965) and the depleters reserpine (Iverson et al., 1965) and tetrabenazine (Quinn et al., 1959; Pletscher et al., 1962) blocked EKC-induced hyperactivity. Furthermore, the postsynaptic dopamine receptor blocker haloperidol, and a presynaptic autoreceptor dose of apomorphine (0.1 mg/kg) effectively antagonized the increased activity produced by EKC. Also, the GABA agonist muscimol (Beaumont et al., 1978) suppressed the EKC-induced hyperactivity suggesting GABAergic inhibition of this activity, possibly through the mediation of the dopaminergic system. In addition to dopamine mediation of EKC-induced hyperactivity, norepinephrine transmission at the alpha-1 receptor (but not alpha-2) appeared important since phentolamine and prazosin (but not yohimbine) effectively antagonized EKC-induced locomotor activity. However, there was only limited serotonergic mediation of this behavior and no cholinergic involvement (Table 43). Therefore, the kappa agonist EKC may be acting through the mesolimbic

and/or striatal system by increasing synthesis and release of catecholamines.

These experiments also revealed that the sigma agonist SKF 10,047 (Martin et al., 1976; Pasternak et al., 1981) induced a stereotypic behavior in mice which eventually culminated into a climbing response similar to that of apomorphine (Dunn et al., 1984). Following SKF 10,047 (40 mg/kg sc) administration, mice were initially ataxic for the first 30 minutes, then exhibited stereotyped behavior characterized by vocalization, excessive grooming and sniffing, then rearing and finally climbing approximately 75 to 90 minutes postadministration (Table 44) with an ED_{50} for climbing equal to 14.6 mg/kg sc (Table 45).

In addition, SKF 10,047 induced an increase in locomotor activity beginning at 15 minutes postadministration and lasting for up to five hours (Table 11; Fig. 13). This increase in locomotion was previously observed in rats (Iwamoto, 1981) and was at least partially attributed to dopaminergic activity since this activity was attenuated by spiperone (a postsynaptic dopamine receptor antagonist) and apomorphine (a presynaptic dopamine inhibitor at 0.1 mg/kg). On the other hand, the mu antagonist naltrexone, had no effect on SKF 10,047-induced locomotion except at very high doses (Iwamoto, 1981). These results were confirmed in mice in the six-hour locomotion paradigm in that haloperidol but not naltrexone effectively antagonized SKF 10,047-induced locomotion (unpublished observations).

To further elucidate the mechanism of action responsible for SKF 10,047 induction of locomotor activity, stereotypy and climbing,

interaction experiments were conducted utilizing the climbing mouse paradigm since climbing behavior is mediated by both mesolimbic (locomotion) and striatal (stereotypy) systems (Protais et al., 1976; Costall et al., 1979). SKF 10,047 was administered at 40 mg/kg sc and combined with the various blocking agents (at appropriate pretreats) and climbing behavior was scored for 30 minutes, 90 minutes post-SKF 10,047 administration (Table 46). SKF 10,047-induced climbing behavior was not mediated by the opiate system since it was not antagonized by naloxone. SKF 10,047-induced climbing behavior was dependent upon catecholamine transmission and a direct serotonin receptor interaction. Blockade of catecholamine synthesis by α-MPT completely antagonized (-97%) SKF 10,047-induced climbing while autoinhibition of dopamine systems by apomorphine, GABAergic inhibition by muscimol and dopamine-receptor blockade by haloperidol also attenuated this behavior. Furthermore, noradrenergic receptor blockade by phentolamine, specifically alpha-1 receptor antagonism by prazosin and serotonin receptor blockade by methysergide significantly antagonized SKF 10,047 climbing behavior. However, this behavior was independent of serotonin synthesis and release since PCPA had no effect on SKF 10,047-induced climbing. Interestingly, tetrabenazine but not reserpine blocked this behavior probably due to the dopamine receptor blocking properties of tetrabenazine (Reches et al., 1983) and not because of neurotransmitter depletion.

These results suggest that SKF 10,047-induced climbing is the result of an activation of catecholamine transmission and of a serotonin receptor interaction. The effect of a serotonin mediation

of this behavior is somewhat unclear since serotonin and specifically the serotonergic raphe projection to the substantia nigra and striatum are predominately inhibitory (Grabowska, 1974; Miller et al., 1975; Dray et al., 1976), although an excitatory role of serotonin based on some selective neuronal excitation cannot be excluded (Dray et al., 1976). Furthermore, serotonin inhibits dopamine mediated hyperactivity and stereotypy (Weiner et al., 1975; Pycock et al., 1978). However, SKF 10,047 effects may be similar to the 5-HT agonist, quipazine, which has been found to potentiate apomorphine-induced stereotypy (Pycock et al., 1978), possibly through inhibition of dopamine reuptake (Ponzio et al., 1981). Therefore, SKF 10,047-induced climbing behavior may result from a dopamine reuptake inhibition similar to quipazine, a selective serotonergic excitatory effect on mesolimbic and/or striatal dopaminergic neurons, as well as a direct and/or indirect effect on catecholamine synthesis and transmission.

Although both EKC and SKF 10,047 appear to have some effects on dopaminergic systems, might these agents be working indirectly to potentiate dopaminergic transmission? In order to ascertain indirect effects, these compounds were combined with a low dose of apomorphine (0.4 mg/kg) and observed in the climbing mouse paradigm. In each case, EKC and SKF 10,047 at doses from 1 to 10 mg/kg potentiated apomorphine-induced climbing from 23 to 67% (Tables 39 and 40) in an approximately additive fashion because each of these compounds alone at 3 and 10 mg/kg showed either hyperactivity (EKC) or climbing (SKF 10,047).

Since each of these compounds have in common mu antagonist properties, might this characteristic be at least partially responsible for the potentiation of dopaminergic effects? As previously reported, naloxone has augmented several dopamine-dependent behaviors (Namba et al., 1980; Quock and Welsh, 1981; Adams et al., 1981; Quock and Lucas, 1981, 1983; Quock et al., 1983; Balsara et al., 1984). Naloxone at 1 to 10 mg/kg was shown to potentiate apomorphine climbing from 17 to 83% (Table 38) while having no effect alone on either climbing or hyperactivity. These results further substantiate the hypothesis that an opiate receptor antagonist may potentiate dopaminergic effects through the blockade of opiate receptors on nigrostriatal and mesolimbic dopamine neurons, thereby releasing these neurons from the tonic inhibition of endogenous opiate production (Celsen and Kushinsky, 1974; Loh et al., 1976; Balsara et al., 1984). In addition, recent evidence has shown that newly synthesized dopamine and norepinephrine and an alpha-1 receptor interaction influence naloxone potentiation of apomorphine-induced climbing (Quock et al., 1984). Therefore, although EKC and SKF 10,047 alone induce hyperactivity and climbing, respectively, part of the potentiation of apomorphine's effect may be due to the blockade of these opiate receptors as well as either direct and/or indirect effects of these agents on dopaminergic systems.

Because of the following results suggesting dopaminergic effects: mu, kappa, sigma and kappa, sigma agonists induced locomotor activity; sigma agonist-induced stereotypy and climbing; and mu antagonists as well as kappa and sigma agonists potentiation of apomorphine effects;

all of these protypical opiate agents were tested in the acute DA-SS climbing paradigm. All of these compounds except morphine effectively attenuated acute haloperidol-induced DA-SS (Tables 18-24). It was not surprising that compounds which either directly or indirectly augment dopaminergic transmission (in the above acute models) would prevent the development of haloperidol-induced DA-SS in an acute paradigm, since it was previously reported that L-DOPA or apomorphine in combination with haloperidol blocked the development of DA-SS (Friedhoff et al., 1977; Ezrin-Waters and Seeman, 1978; Christensen and Nielsen, 1979; List and Seeman, 1979; Seeger et al., 1981).

Morphine's lack of effect in attenuating DA-SS may be due to the fact that it, unlike all of the other opiates tested, was devoid of mu antagonist properties. Quite possibly, at least in the acute model, opiate receptor blockade was the initial factor in down regulating the development of DA-SS following haloperidol administration. The importance of opiate receptor antagonism was further substantiated since naloxone and naltrexone, which lack overt dopaminergic effects, i.e., locomotion, stereotypy, climbing etc., were active in attenuating haloperidol-induced DA-SS. Blockade of opiate receptors located presynaptically on dopamine neurons or on opiate neurons synaptically connecting with dopamine neurons in the mesolimbic and striatal areas (Pollard et al., 1977a, b; 1978; Murrin et al., 1980) may be sufficient to antagonize endorphinergic and enkephalinergic inhibition of dopamine release (Celsen and Kushinsky, 1974; Subramanian et al., 1977; Loh et al., 1976). In other words, more endogenous dopamine would be released as a result of occupation of opiate receptors by mu

antagonists. The fact that the sigma and/or kappa agonist components of SKF 10,047, EKC, cyclazocine and pentazocine may be either directly or indirectly facilitating the release of dopamine may be of secondary importance to the opiate-receptor blocking properties of these compounds (and naloxone and naltrexone) in attenuating the development of haloperidol-induced DA-SS. Therefore, would these agents when administered chronically with haloperidol, prevent the development of DA-SS?

The consequences of chronic simultaneous administration of the opiate agents with haloperidol were assessed in the climbing mouse paradigm as well as the stereotypy model since chronic haloperidol treatment produced DA-SS in this model (Tables 26-30) although acute administration did not induce DA-SS (Table 15). In both models, chronic five-day morphine administration resulted in an enhanced response to apomorphine (Tables 26 and 31) while having no effect on haloperidol-induced DA-SS. These results were similar to earlier studies where morphine induced DA-SS in various paradigms (Puri and Lal, 1973; Gianutsos et al., 1974; Cox et al., 1976; Carlson and Almasi, 1978; Baume et al., 1979; Bhargava, 1980; Martin and Takemori, 1985). Since morphine does not antagonize dopamine receptors (Creese et al., 1976; Puri et al., 1978), morphine-induced DA-SS apparently results from an inhibition of dopamine release mediated by the opiate system (Celsen and Kuschinsky, 1974; Loh et al., 1976; Subramanian et al., 1977). Therefore, chronic inhibition of dopamine release would have the same effect as receptor blockade, i.e., a decrease in postsynaptic dopaminergic activation.

The opiate antagonists, naloxone and naltrexone, when chronically administered alone or with haloperidol, had no effect in either paradigm (Tables 27, 32 and 33). These results showed that while opiate receptor blockade alone was sufficient to down regulate the hypersensitivity which developed following acute haloperidol administration in the climbing paradigm, it did not effectively attenuate chronic haloperidol-induced DA-SS in either the climbing or stereotypy models. It should be noted that naltrexone showed some slight attenuation of haloperidol-induced DA-SS in the climbing assay (Table 33). This may have been due to the longer duration of antagonist activity of naltrexone compared to naloxone (Verebey et al., 1976). The kappa agonist, mu antagonist EKC, produced similar results in these models. Although chronic EKC had no effect on the development of DA-SS in the stereotypy paradigm (Table 28), it provided a consistent suppression of haloperidol-induced DA-SS in the climbing model (Table 34). It is possible that the mesolimbic system (climbing-mesolimbic and striatal mediation) was more sensitive than the striatal system (stereotypy-striatal mediation) to these long-acting agents, i.e., naltrexone as an antagonist and EKC as an antagonist and a locomotor stimulant after three hours. Although the locomotor effects of EKC appeared to be primarily due to dopaminergic activity (Table 43), the dopaminergic effects were not as robust as SKF 10,047.

The sigma agonist, mu antagonist SKF 10,047 produced the most consistent suppression of haloperidol-induced DA-SS in both chronic stereotypy and climbing models (Tables 30 and 37). Not only was this suppression statistically significant but in each case, the combina-

tion of SKF 10,047 and haloperidol effectively reduced the development of DA-SS to vehicle control levels. The dopaminergic activity of SKF 10,047 i.e., locomotor effects, stereotypy and climbing, apparently was sufficient to down regulate the dopamine-receptor blocking effects of haloperidol which lead to the development of DA-SS, similar to L-DOPA's effect in this paradigm.

Likewise, the sigma, kappa agonist, mu antagonist cyclazocine also effectively suppressed the development of haloperidol-induced DA-SS in both the chronic stereotypy and climbing models (Tables 29 and 36). However, the kappa, sigma agonist, mu antagonist pentazocine, had no effect on haloperidol-induced DA-SS in the chronic climbing paradigm (Table 35). This may be a result of the fact that cyclazocine has a much greater affinity than pentazocine for the sigma receptor (Zukin and Zukin, 1981b). Also, in drug discrimination testing, cyclazocine but not pentazocine generalized to SKF 10,047 trained rats (Shearman and Herz, 1982). These results suggested that cyclazocine had a high affinity for and high intrinsic activity at the sigma receptor while pentazocine had a much lower affinity for the sigma receptor. Therefore, in the chronic DA-SS paradigms, cyclazocine had similar effects to SKF 10,047, whereas pentazocine did not.

These results would suggest that agents with strong sigma effects, as well as mu antagonist effects, were able to suppress the development of DA-SS in both acute and chronic behavioral paradigms. Kappa agents and opiate antagonists were effective in attenuating the development of DA-SS in the acute climbing model while showing little or no effects in the chronic stereotypy and climbing models. Other

than the fact that the attenuation of DA-SS by sigma agonists in particular may be due to dopaminergic effects as manifest behaviorally by increased locomotion, stereotypy and climbing, there are other aspects of opioid pharmacology, some of which remain controversial, which might explain some of the results in this dissertation, especially opiate influence on dopaminergic systems.

First and foremost, it was crucial to establish the existence in the central nervous system (CNS) of these various opiate receptor subtypes, namely, mu, kappa and sigma (and even delta and epilsilon for enkephalins and endorphins, respectively) so that the behavioral effects could be linked to the brain. Furthermore, any drug which attenuates DA-SS must exhibit activity in the mesolimbic and/or striatal dopaminergic systems.

Since Martin's (1976) pioneer study in dogs where he classified opiates based on neurophysiological and behavioral evidence as either mu, kappa or sigma, some controversy has surrounded the existence of these receptors in the CNS. The existence of different mu (morphine) and delta (enkephalin) binding sites in the CNS was well established (Pert and Snyder, 1973; Snyder, 1978). Autoradiographic techniques revealed a high concentration of mu receptors in the striatum and high levels of delta receptors in the striatum, nucleus accumbens and olfactory tubercle (Goodman et al., 1980). The highest concentrations of endorphins and enkephalins were located in the striatum (Llorens-Cortes et al., 1977). Furthermore, approximately one-third of striatal opiate or enkephalin receptors are located on dopaminergic neurons while one-half to two-thirds are located on neurons intrinsic

to or emanating from the striatum (Hong et al., 1977; Pollard et al., 1977b, 1978; Murrin et al., 1980). An even larger percentage (50-70%) of opiate receptors were located presynaptically on dopaminergic neurons in the mesolimbic area (Pollard et al., 1977a).

The discovery of sigma and kappa receptors in the CNS has been somewhat controversial. SKF 10,047 is the protoype sigma agonist (with mu antagonist properties) which produces psychotomimetic effects in man (Keats and Teford, 1964). Biochemical and autoradiographic studies have identified sigma receptors in mouse, rat and guinea pig brains. Since the intial report of a commonality of the sigma opiate/phencyclidine (PCP) receptor (Zukin and Zukin, 1981b), much debate has taken place in defense of these receptors being identified (Zukin, 1982; Mendelsohn et al., 1985; Sircar et al., 1986) and to the contrary, that these receptors are distinct (Su, 1982; Tam, 1983, 1985; Martin et al., 1984; Gundlach, 1985; Downes et al., 1986). The distinction between these two binding sites was based on several observations: (^{3}H) PCP binding is decreased in the presence of sodium ions but (+)-(^{3}H) SKF 10,047 binding is not; the two binding sites have different drug selectivity; the PCP binding sites show low affinity and little stereoselectivity towards SKF 10,047, EKC, cyclazocine and pentazocine whereas these drugs are highly stereoselective towards the (+)-(^{3}H) SKF 10,047 binding sites; and the regional distribution in the CNS of the sigma binding sites differs from the PCP binding sites. Moreover, biochemical and autoradiographic techniques have shown that (+)-(^{3}H) SKF 10,047 labels two sites, a high affinity site corresponding to the sigma receptor and a

low affinity site representing the PCP receptor (Gundlach et al., 1985; Downes et al., 1986). Therefore, the sigma and PCP receptors are probably different receptors which share some similar properties.

Until recently, the proof of the existence of a central kappa receptor site was difficult since kappa drugs interacted with a number of receptor sites, i.e., mu (μ), sigma (σ), enkephalin (δ) and kappa (κ) sites (Kosterlitz and Paterson, 1980; Pasternak, 1980; Snyder and Goodman, 1980; Chang et al., 1981; Garzon et al., 1984). Biochemical and autoradiographic studies showed distinct kappa opiate receptors were present in the CNS of the guinea pig (Kosterlitz et al., 1981; Wood and Charleson, 1982), mouse (Garzon et al., 1984) and human brain (Pfeiffer et al., 1982; Maurer et al., 1983). Furthermore, κ, σ, μ, and δ receptors have all been established in the striatum, midbrain and frontal cortex (Wolozin et al., 1982).

Since enkephalin-containing neurons and various opiate receptors are present in high concentrations in the basal ganglia and mesolimbic system, areas also rich in dopamine (Snyder, 1978), what effects would endogenous and exogenous opiates have on dopaminergic transmission? <u>In vitro</u> evidence from superfused striatal slices showed that morphine (Celsen and Kuschinsky, 1974), enkephalin (Subramanian et al., 1977) and β-endorphin (Loh et al., 1976) inhibited K^+ stimulated release of (^3H)-DA. However, <u>in vivo</u> evidence appears to show a species difference between rats and mice. Both mu and delta agonists elevated striatal DA synthesis but not release in the rat striatum (Wood et al., 1980; Wood and Richard, 1982), while in the mouse, there was an increase in DA synthesis and release (Wood et al., 1980; Wood and

Richard, 1982). In the rat, this initial depression of dopaminergic transmission following morphine administration was followed by a feedback activation which was probably responsible for an increased firing rate in the substantia nigra (Iwatsubo and Clouet, 1977). Also, direct injection of opiates and opioid peptides into the substantia nigra activated dopamine neurons projecting to the caudate nucleus (Iwamoto and Way, 1977). Opiate injection into the ventral tegmental region induced hyperactivity in the rat due to a release of dopamine in the nucleus accumbens (Kelley et al., 1980). Therefore, opiates activate both mesolimbic and striatal dopamine neurons. However, this appeared to be an indirect effect since iontophoretically applied morphine at the substantia nigra has no effect on dopaminergic neuron activity (Pert et al., 1979).

Morphine-induced hyperactivity appears to be mediated by both opiate and catecholamine systems since morphine-induced locomotor activity was blocked by naloxone (Rethy et al., 1971; Parker, 1974), α-MPT or reserpine (Buxbaum et al., 1973) and presynaptic (autoinhibiting) doses of apomorphine (Strombom and Svensson, 1978). Further evidence for two independent systems which mediate locomotor activity was provided by Pert and Sivit (1977) who showed that intraaccumbens morphine-induced locomotor activity was antagonized by naloxone but not haloperidol and intraaccumbens apomorphine-induced locomotor activity was antagonized by haloperidol but not naloxone. Also, other regions besides the mesolimbic system appear to be involved in morphine-induced hyperactivity since lesions of the nucleus accumbens and ventral tegmental area attenuated and delayed,

but did not completely abolish morphine-induced locomotor activity (Bunney et al., 1984).

It is unlikely that presynaptic opiate receptors are located on dopaminergic neurons in mice since lesion of the nigrostriatal pathway in mice did not result in decreased opiate binding in the striatum whereas this lesion resulted in decreased opiate binding in the rat (Wood and Richard, 1982). Because intranigral morphine induced increases in DA metabolites similar to parenteral injection in mice, it was suggested that opiate receptors on dopaminergic cell bodies and/or afferent nerve fibers innervating these neurons regulate nigrostriatal activity (Wood and Richard, 1982).

In the mouse, the initial increase in DA turnover in the striatum following morphine administration (Baume et al., 1979; Wood and Richard, 1982) lasting for six to 12 hours (Kuschinsky, 1974; Baume et al., 1979) was followed at 24 hours by a significant decrease in HVA levels following either a single dose of morphine or for several days following chronic morphine administration (Baume et al., 1979). In fact, either a single dose of morphine or chronic morphine resulted in an enhanced apomorphine-induced climbing response for days following treatment similar to haloperidol (Baume et al., 1979; Martin and Takemori, 1985, 1986) as well as DA-SS in other models (Puri and Lal, 1973; Gianutsos et al., 1974; Cox et al., 1976; Carlson and Almasi, 1978). The diminished activity of DA neurons reflected an increased activity of the feedback loop when the postsynaptic receptors became hypersensitive to dopamine (Matres et al., 1977). Chronic morphine resulted in tolerance to the increase in DA turnover from morphine and

cross tolerance to the increase in DA turnover following haloperidol administration (Baume et al., 1979). Morphine-induced DA-SS could not be attributed to an increase in dopamine receptors similar to that seen following haloperidol administration (Burt et al., 1977) since chronic morphine either decreased (Puri et al., 1978), slightly increased (Baume et al., 1979; Martin and Takemori, 1986) or had no effect (Carlson and Seeger, 1982) on ^{3}H-neuroleptic binding. However, there may be an increase in affinity, although fewer binding sites (Puri et al., 1978).

The effects of kappa and/or sigma agonists on dopaminergic transmission remains somewhat unclear and in need of more thorough investigations. Pentazocine has been reported to have either no effect on catecholamine turnover (Holtzman and Jewett, 1972) or increased the turnover of dopamine in whole brain (Sugre, 1974) and striatum (Sugre, 1974; Wood et al., 1980). Likewise, cyclazocine slightly lowered brain catecholamine levels (Holtzmann and Jewett, 1973) while increasing striatal dopamine turnover (Wood et al., 1980; Gavend et al., 1981; Snell et al., 1984) and norepinephrine and serotonin turnover in the cortex, hypothalamus, midbrain, pons and medulla (Gavend et al., 1981). Cyclazocine also inhibited stimulated acetylcholine release from striatal slices (Johnson and Snell, 1985).

The kappa agonists, EKC and ketazocine, showed a slight increase in striatal DA metabolite levels and turnover (Wood et al., 1980; Snell et al., 1984). However, animals were sacrificed 60 minutes following drug administration while stimulant activity of EKC was not apparent until three hours postadministration. If turnover studies

were run at this time point, it might be possible that there would be higher levels of DA turnover. Furthermore, EKC potently inhibited acetylcholine (ACh) release in superfused striatal slices and this effect was reversed by haloperidol (Leventer and Johnson, 1984). Since ACh release is known to be inhibited by DA, it was suggested that EKC-induced inhibition of ACh was mediated via dopaminergic neurons (Leventer and Johnson, 1984).

The sigma agonist, SKF 10,047 produced small increases in striatal DOPAC and DA that were resistant to naloxone challenge (Wood et al., 1980). It must be noted that tissue samples were analyzed at 60 minutes postadministration and quite possibly more dramatic effects may have been seen at 90 minutes after SKF 10,047. In an in vitro assay, SKF 10,047 and EKC slightly enhanced the basal efflux of (^{3}H) DA from striatal slices (Snell et al., 1984). In addition, SKF 10,047 inhibited the reuptake of DA while EKC and cyclazocine were extremely weak uptake inhibitors (Johnson and Snell, 1985). Similar to EKC, SKF 10,047 inhibited ACh release (Leventer and Johnson, 1984; Johnson and Snell, 1985), with this effect being reversed by haloperidol (Leventer and Johnson, 1984).

In addition to biochemical evidence linking sigma activity to the dopamine system, behavioral studies have also shown a sigma-dopamine interaction. Since the original observation by Martin et al. (1976) that some of the activity of the dopamine agonist apomorphine showed certain similarities to those of SKF 10,047, recent behavioral evidence has supported a dopaminergic mediation of sigma-induced behavior. In rats, SKF 10,047 and cyclazocine induced dose-related

increases in locomotion, sniffing, repetitive head movements, rearing and some ataxia (Iwamoto, 1980, 1981; French and Vantini, 1984; Contreras et al., 1986; Greenberg and Segal, 1986). SKF 10,047-induced hyperactivity was attenuated by presynaptic autoinhibition of dopamine and norepinephrine by apomorphine (0.1 mg/kg) and clonidine (0.1 mg/kg), respectively, and by postsynaptic dopamine blockade by spiperone (0.15 mg/kg) (Iwamoto, 1980, 1981). Further indication of SKF 10,047-induced dopaminergic activity in the midbrain was shown when SKF 10,047-induced hyperactivity was prevented by 6-hydroxy-dopamine (6-OHDA) lesions of both the nucleus accumbens (French and Vantini, 1984) and the A-10 region of the ventral tegmental area (French, 1986). Also, in the rat circling model (unilateral 6-OHDA lesion of the substantia nigra), SKF 10,047 causes ipsilateral turning like amphetamine, suggesting indirect activation of the intact dopaminergic pathway possibly by inhibition of dopamine reuptake, by releasing dopamine or by indirect stimulation of neostriatal pathways at the level of the cell body (Iwamoto, 1980). Further support for SKF 10,047 indirectly activating dopamine neurons was provided by electrophysiological (single-unit recording) evidence which showed that intravenously administered SKF 10,047 increased the firing rate of dopamine neurons in the ventral tegmental area (A-10) and the substantia nigra (A-9) while iontophoretically applied SKF 10,047 had no effect on these neurons (Freeman and Bunney, 1984).

Both biochemically and behaviorally, the sigma opiates may indirectly affect dopamine turnover and/or uptake. It is intriguing that antipsychotic agents such as haloperidol and other phenothiazines

have been shown to inhibit striatal and whole brain binding of (^{3}H) SKF 10,047 *in vitro* in rat and guinea pigs (Su, 1981, 1982; Tam and Cook, 1984; Tam, 1985). Also, an *in vivo* binding assay in mouse brain found haloperidol to be the most potent compound to inhibit specific (+)-(^{3}H) SKF 10,047 binding with an ID_{50} of 0.75 mg/kg i.p., followed by thioridazine (8.9 mg/kg) and chlorpromazine (19.2 mg/kg) (Ferris et al., 1985, 1986). Therefore, in both *in vivo* and *in vitro* sigma binding assays, haloperidol was the most potent displacer of (^{3}H) SKF 10,047 followed by the phenothiazines. However, the sigma and dopamine binding sites were found to be different for several reasons: Dopamine and dopamine agonists did not bind to the SKF 10,047 binding site; there was reversed stereoselectivity for butaclamol binding to the sigma and dopamine sites; and there was no direct relationship between the affinity of antipsychotic drugs for the sigma site and for the (^{3}H) spiperone binding site (Tam, 1983; Tam and Cook, 1984). However, an intricate relationship between haloperidol and SKF 10,047 was shown in whole guinea pig brain in binding assays when the order of drug potency for opiates and antipschotics in displacing these (^{3}H) ligands was similar (Tam and Cook, 1984).

(^{3}H) Haloperidol bound to two distinct receptors, namely a dopamine D-2 binding site and the sigma site. Therefore, it was proposed that some antipsychotic agents may act therapeutically by antagonizing both dopamine and sigma receptors. Furthermore, an endogenous ligand referred to as "sigmaphin" has been identified to directly interact with sigma receptors (Su et al., 1986). It was proposed that the ideal antipsychotic drug might be a specific sigma

antagonist, devoid of dopamine receptor antagonism and, therefore, more likely not to cause the undesirable extrapyramidal side effects or tardive dyskinesias. Likewise, since there appears to be a dynamic interrelationship between the sigma and dopamine systems, it is not surprising that an agent with sigma properties could interact in some way to either down regulate or compensate for the development of dopaminergic supersensitivity following haloperidol administration.

In light of what has previously been reported as well as the results of this dissertation, it would appear that the sigma agonist, SKF 10,047 has at least indirect dopamine agonist properties in the mesolimbic and striatal areas. This, in combination with its mu antagonist property which also potentiates dopamine-dependent behaviors, would appear to sufficiently stimulate release and augment dopaminergic transmission in the mesolimbic and striatal systems to compensate for and down regulate the development of DA-SS following haloperidol treatment. Cyclazocine, which is more of a sigma rather than kappa agonist (Zukin and Zukin, 1981b), also has dopaminergic effects capable of attenuating haloperidol-induced DA-SS. Kappa effects on dopaminergic transmission are somewhat unclear at this time but following an initial period of sedation, dopaminergic activity is enhanced, but not to the extent of a sigma agonist. Enhancement of dopaminergic transmission by these opiate agents was partially responsible for the attenuation of haloperidol-induced DA-SS but it is also important to note recent results concerning haloperidol's effect on endorphinergic transmission and how this effect may mediate the development of DA-SS.

Although this dissertation did not directly study endogenous opiates, enkephalins and endorphins seem to play a role in the modulation of neuroleptic effects and the eventual development of DA-SS. Chronic administration of haloperidol has been shown to increase enkephalin content in the striatum (Hong et al., 1978; Tang et al., 1983; Chou et al., 1984; Blanc et al., 1985) and the nucleus accumbens (Hong et al., 1978) due to an increase in peptide synthesis (Hong et al., 1979). Recently, it was found that haloperidol increased the biosynthesis of the mRNA for preproenkephalin which led to an increase in enkephalin synthesis (Tang et al., 1983; Blanc et al., 1985) and possibly release (Tang et al., 1980; Blanc et al., 1985). The effects of enkephalin on dopaminergic activity remain controversial. Enkephalin has been reported to have either no effect on striatal dopamine release (Loh et al., 1976), or inhibit both striatal (Subramanian et al., 1977) and retinal (Dubocovich and Weiner, 1983) dopamine release. The inhibition of dopamine release was naloxone reversible (Subramanian et al., 1977; Dubocovich and Weiner, 1983) since naloxone blocked the binding of enkephalins to endogenous opiate receptors (Pert and Snyder, 1973). Naloxone alone either had no effect on dopamine release (Loh et al., 1976; Subramanian et al., 1977; Dubocovich and Weiner, 1983) or has caused increases in striatal dopamine concentration (Costa et al., 1978).

Acute and chronic haloperidol administration also resulted in an increased release of immunoreactive β-endorphin (β-endorphin is the predominant peptide) in the blood and in the striatum (Holt and Bergmann, 1982). However, unlike the tolerance to striatal dopamine

turnover which occurs rapidly following haloperidol administration (Lerner et al., 1977), there was no tolerance to the increase in β-endorphin following haloperidol treatments (Holt and Bergmann, 1982). Although, Arbilla and Langer (1978) reported that β-endorphin had no effect on dopamine release in the striatum, others have found β-endorphin inhibited striatal dopamine release (Celsen and Kuschinsky, 1974; Loh et al., 1976) and increased dopamine reuptake (George and Van Loon, 1982) in the striatum. These effects were naloxone reversible. Interestingly, β-endorphin secretion can be inhibited by dopamine and dopamine receptor agonists (Vale et al., 1979). Therefore, β-endorphin-induced decrease of striatal dopamine release and increased reuptake decreased dopaminergic transmission. Hence, it was not surprising that behaviorally, β-endorphin-induced DA-SS (Bhargava, 1981) and chronic stress which increases the concentration of endogenous opiates (Amir et al., 1980) produced DA-SS as measured by enhanced apomorphine-induced climbing (Cabib et al., 1984). Furthermore, stress-induced DA-SS was prevented by chronic treatment with the opiate antagonist naltrexone (Cabib et al., 1984). It has become increasingly evident that the development of dopaminergic supersensitivity is a consequence of dopamine receptor blockade as well as an endorphinergic imbalance which further effects dopamine systems.

The results of this dissertation and some of the recent results of other groups has led to intriguing possibilities concerning opiate modulation of dopaminergic supersensitivity. Under normal physiological conditions, the effects of both endogenous opiates and opiate

antagonists on the inhibition of dopamine release and disinhibition of dopamine release, respectively, is small and difficult to detect. However, enhanced dopaminergic responsiveness during DA-SS, resulting from either chronic antipsychotic treatment or from chronic endogenous or exogenous opiate agonists, magnifies the effects of enkephalins, endorphins and mu antagonists on dopaminergic transmission. Therefore, chronic haloperidol administration not only blocks dopamine receptors rendering them supersensitive but also may modulate or augment DA-SS through continual increased endorphin and enkephalin synthesis and release which inhibits dopamine release and increases reuptake. Concomitant administration of opiate antagonists may disinhibit endogenous opiate influence on dopaminergic transmission by increasing dopamine release and blocking reuptake, thereby increasing the amount of synaptic dopamine. However, this antagonism alone may be insufficient to compensate for or overcome dopamine receptor blockade to attenuate DA-SS during chronic neuroleptic therapy. Furthermore, if dopaminergic transmission is stimulated and opiate receptors blocked, DA-SS can be attenuated.

L-Dopa and other dopamine agonists have been shown to attenuate haloperidol-induced DA-SS (Friedhoff et al., 1977; Christensen and Nielsen, 1979; List and Seeman, 1979; Allen et al., 1980; Seeger et al., 1981; Reches et al., 1982). These dopamine agonists, by increasing the amount of dopamine at the receptor and increasing dopamine receptor stimulation, compensate for the haloperidol receptor blockade (Friedhoff et al., 1977; Christensen and Nielsen, 1979; List and Seeman, 1979; Allen et al., 1980; Seeger et al., 1981; Reches et

al., 1982). But also, dopamine and dopamine agonists inhibit β-endorphin secretion (Vale et al., 1979), thus releasing dopaminergic neurons from endorphinergic inhibition. Therefore, at least theoretically, greater or more effective attenuation of haloperidol-induced DA-SS can be achieved by not only increasing dopamine release during receptor blockade but by antagonizing opiate receptors thereby thoroughly negating any endogenous opiate inhibition of dopaminergic transmission. Since there is no tolerance to the increased secretion of endogenous opiates during haloperidol treatment (Holt and Bergman, 1982), it is important to block the opiate receptor and thus dopamine modulation by endogenous opiates. SKF 10,047 and cyclazocine effectively attenuate haloperidol-induced DA-SS through an apparent increase in dopaminergic transmission as well as opiate receptor blockade. However, the psychotomimetic effects of sigma agonists in normal patients (Keats and Telford, 1964) may prevent the use of these drugs in schizophrenics unless there was a paradoxical effect in psychotic patients (similar to the paradoxical effect of amphetamine in hyperactive children).

The possibility of opiate agents modulating the development of dopaminergic supersensitivity is intriguing. Human studies in schizophrenic patients who received neuroleptics have shown increased β-endorphin levels in plasma (Emrich et al., 1980) and in cerebrospinal fluid (Terrenius et al., 1976; Domschke et al., 1979; Lindstrom et al., 1980). This coupled with the fact that naloxone had no deleterious effect and may possibly improve some symptoms of schizophrenia (Verebey et al., 1978; Watson et al., 1978; Pickar et al., 1982; Lo et

al., 1983; Blum et al., 1984) adds strength to the hypothesis that schizophrenia may be due to an imbalance in endorphinergic as well as dopaminergic homeostasis. The results of this dissertation add to the intriguing possibility that opiate agents may help to fine-tune dopaminergic imbalance in the treatment of schizophrenics. Hopefully, additional preclinical and clinical research in this area will lead to a better understanding of schizophrenia and a better prognosis for a schizophrenic to lead a more normal and satisfying life.

CONCLUSIONS

Hypothesis 1.

Opiates are not dopamine receptor antagonists and therefore, will not attenuate apomorphine-induced climbing and stereotyped behavor in mice.

Ethylketocyclazocine (EKC) and SKF 10,047 inhibited apomorphine-induced climbing because of motor deficits, sedation and ataxia, respectively. Only EKC inhibited apomorphine-induced stereotypy due to initial motor deficits and sedation. Therefore, these compounds were not dopamine antagonists, insofar as apomorphine-induced behaviors were only antagonized at debilitating doses which incapacitated mice. In addition, the mixed kappa, sigma agonists, pentazocine and cyclazocine, as well as morphine, naloxone and naltrexone did not antagonize these behaviors.

Hypothesis 2.

Opiates which stimulate catecholamine neuronal activity will cause either increased locomotor activity (indicative of mesolimbic activity), stereotypy (indicative of striatal activity) or climbing behavior (indicative of mesolimbic and/or striatal activity) in mice.

Morphine, SKF 10,047, pentazocine and cyclazocine produced increases in locomotor activity suggesting increased dopaminergic activity, while naloxone and naltrexone had no effect on locomotion. EKC induced a biphasic effect of sedation followed by an increase in

locomotor activity at three hours postadministration. SKF 10,047 not only increased locomotor activity but also induced stereotypy and climbing behavior. Kappa-induced EKC hyperactivity was dependent upon catecholamine synthesis and transmission since α-MPT, reserpine, tetrabenazine, haloperidol, apomorphine (at 0.1 mg/kg, a presynaptic autoreceptor dose), muscimol and prazosin blocked EKC-induced locomotor activity. Sigma-induced SKF 10,047 climbing was dependent on catecholamine transmission and a direct serotonin receptor interaction since α-MPT, tetrabenazine, haloperidol, apomorphine (0.1 mg/kg), muscimol, prazosin and methysergide antagonized this behavior. Both EKC-induced hyperactivity and SKF 10,047-induced climbing were not antagonized by naloxone. In addition, EKC, SKF 10,047 and naloxone potentiated apomorphine-induced climbing behavior.

Hypothesis 3.

The acute and/or chronic simultaneous administration of the opiate receptor subtype agents and haloperidol will attenuate the development of dopaminergic supersensitivity as measured by apomorphine-induced climbing and stereotyped behavior in mice.

Enhanced responsiveness to apomorphine following the acute administration of haloperidol 72 hours prior to testing was only observed in the apomorphine-induced climbing mouse assay. In the acute climbing paradigm, haloperidol-induced dopaminergic supersensitivity (DA-SS) was dose-dependently attenuated by SKF 10,047, EKC, cyclazocine, pentazocine, naloxone and naltrexone, all of these compounds possessing mu antagonistic properties, with morphine

inactive. Chronic five-day administration of haloperidol-induced DA-SS was observed in the apomorphine-induced climbing and stereotypy paradigms, but not in the locomotor activity model. In the chronic climbing and stereotypy models, only the concomitant administration of the sigma agents, either SKF 10,047 or cyclazocine and haloperidol attenuated the development of DA-SS, while morphine alone produced DA-SS. These results suggest differential modulation of DA-SS in the acute vs. chronic paradigms. Furthermore, sigma agonists were most effective in attenuating haloperidol-induced DA-SS.

Figure Legends

Fig. 1 Dopaminergic structures in the nigrostriatal and mesolimbic systems in the mouse brain.

Fig. 2 Agonist and antagonist interaction of prototypical opiate agents at mu, kappa and sigma receptor sites.

Fig. 3 Chemical structures of morphine, naloxone and naltrexone.

Fig. 4 Chemical structures of the benzomorphans cyclazocine, pentazocine, SKF 10,047 and ethylketocyclazocine.

Fig. 5 Antinociceptive and locomotor activity of the prototypical opiate agents.

Fig. 6 The effects of apomorphine at 0.5, 1,5 and 5.0 mg/kg sc on locomotor activity over two hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 7 The effects of morphine at 2.5, 5 and 10 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 8 The effects of naloxone at 10, 20 and 40 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 9 The effects of naltrexone at 10, 20 and 40 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 10 The effects of ethylketocyclazocine at 5, 10 and 20 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 11 The effects of pentazocine at 20, 40 and 80 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 12 The effects of cyclazocine at 2.5, 5 and 10 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 13 The effects of SKF 10,047 at 10, 20 and 40 mg/kg sc on locomotor activity over six hours in mice. Locomotor activity units for each group based on four pairs of mice which were acclimated for one hour prior to dosing.

Fig. 14 The effects of acute administration of haloperidol at 1.25 mg/kg ip 72 hours prior to apomorphine at 0.4 mg/kg sc on locomotor activity over two hours in mice. Locomotor activity units for each group based on eight pairs of mice which were acclimated for one hour prior to dosing.

Fig. 15 The effects of chronic (5-days) administration of haloperidol at 1.25 mg/kg ip 72 hours prior to apomorphine at 0.4 mg/kg sc on locomotor activity over two hours in mice. Locomotor activity units for each group based on

eight pairs of mice which were acclimated for one hour prior to dosing.

Fig. 16 The effects of chronic (5-days) simultaneous administration of morphine at 10 mg/kg sc and/or haloperidol at 1.25 mg/kg ip, 72 hours prior to apomorphine at 0.4 mg/kg sc on stereotyped behavior in mice. Stereotypy scores for each group based on eight mice (maximum score for each mouse = 6) which were acclimated for one hour prior to dosing.

Fig. 17 The effects of chronic (5-days) simultaneous administration of naltrexone at 40 mg/kg sc and/or haloperidol at 1.25 mg/kg ip, 72 hours prior to apomorphine at 0.4 mg/kg sc on stereotyped behavior in mice. Stereotypy scores for each group based on eight mice (maximum score for each mouse = 6) which were acclimated for one hour prior to dosing.

Fig. 18 The effects of chronic (5-days) simultaneous administration of ethylketocyclazocine (EKC) at 20 mg/kg sc and/or haloperidol at 1.25 mg/kg ip, 72 hours prior to apomorphine at 0.4 mg/kg sc on stereotyped behavior in mice. Stereotypy scores for each group based on eight mice (maximum score for each mouse = 6) which were acclimated for one hour prior to dosing.

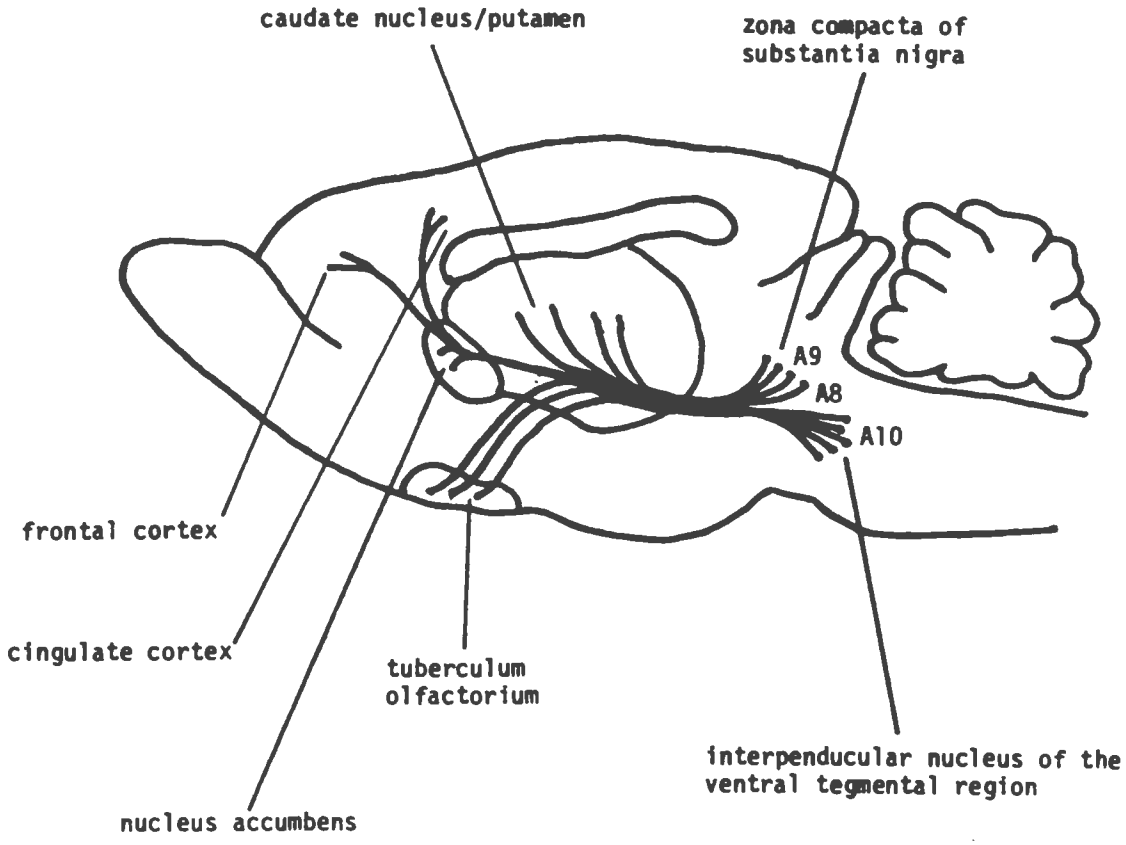
Fig. 19 The effects of chronic (5-days) simultaneous administration of cyclazocine at 2.5 mg/kg sc and/or haloperidol at 1.25 mg/kg ip, 72 hours prior to

apomorphine at 0.4 mg/kg sc on stereotyped behavior in mice. Stereotypy scores for each group based on eight mice (maximum score for each mouse = 6) which were acclimated for one hour prior to dosing.

Fig. 20 The effects of chronic (5-days) simultaneous administration of SKF 10,047 at 40 mg/kg sc and/or haloperidol at 1.25 mg/kg ip, 72 hours prior to apomorphine at 0.4 mg/kg sc on stereotyped behavior in mice. Stereotypy scores for each group based on eight mice (maximum score for each mouse = 6) which were acclimated for one hour prior to dosing.

Figure 1

NIGROSTRIATAL SYSTEM



MESOLIMBIC SYSTEM

Figure 2

Opiate Receptor Subtypes

Prototypical Agonists, Antagonists and Mixed Agonist-Antagonists

Compound	μ	κ	σ
Morphine	Ag.[1]	-	-
Naloxone, Naltrexone	Ant.	Ant.	Ant.
Ketocyclazocine, Ethylketocyclazocine	Ant.	Ag.	-
Pentazocine	Ant.	Ag.	Ag.
Cyclazocine	Ant.	Ag.	Ag.
N-allyl-normetazocine (SKF 10,047)	Ant.	-	Ag.

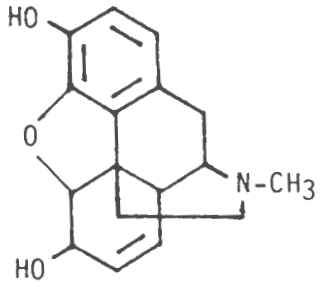
[1]Ag. = agonist, Ant. = antagonist, - = no activity

Figure 3

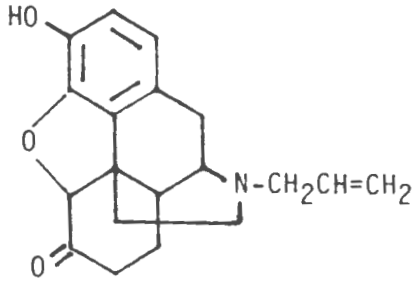
Chemical Structures of

Morphine and its Antagonists

Morphine



Naloxone



Naltrexone

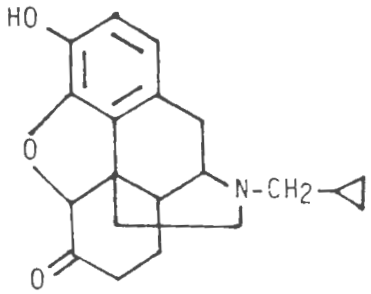
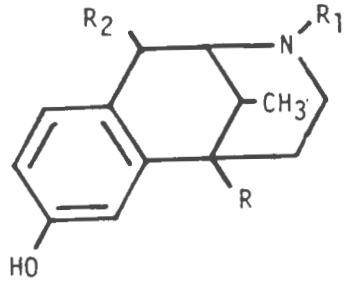


Figure 4

Chemical Structures of Benzomorphans



	Type	R	R_1	R_2
Cyclazocine	(κ, σ)	CH_3	CH_2-cyclopropyl	H
Pentazocine	(κ, σ)	CH_3	$CH_2CH=C(CH_3)_2$	H
SKF 10,047	(σ)	CH_3	$CH_2CH=CH_2$	H
Ethylketocyclazocine	(κ)	CH_3CH_2	CH_2-cyclopropyl	=O

Figure 5

Opiate Receptor Subtypes

Antinociceptive Activity - Behavioral Excitation Activity in Mice

Compound (receptor subtype)	Antinociceptive Activity	Behavioral Excitation Activity
Morphine (μ agonist)	+++[1]	↑
Naloxone, naltrexone (μ, κ , σ antagonist)	-	- (↓)
Ketocyclazocine, ethylketocyclazocine (κ agonist, μ antagonist)	+++	↓[2]; ↑
Pentazocine (κ, σ agonist; μ antagonist)	++	↑
Cyclazocine (κ, σ agonist; μ antagonist)	+	↑
N-allyl-normetazocine (σ agonist, μ antagonist)	-	↑

[1] + = positive activity; - = no activity; ↑ = increase; ↓ = decrease

[2] Initial decrease (↓) followed by increase (↑) (Dunn, 1984).

Figure 6

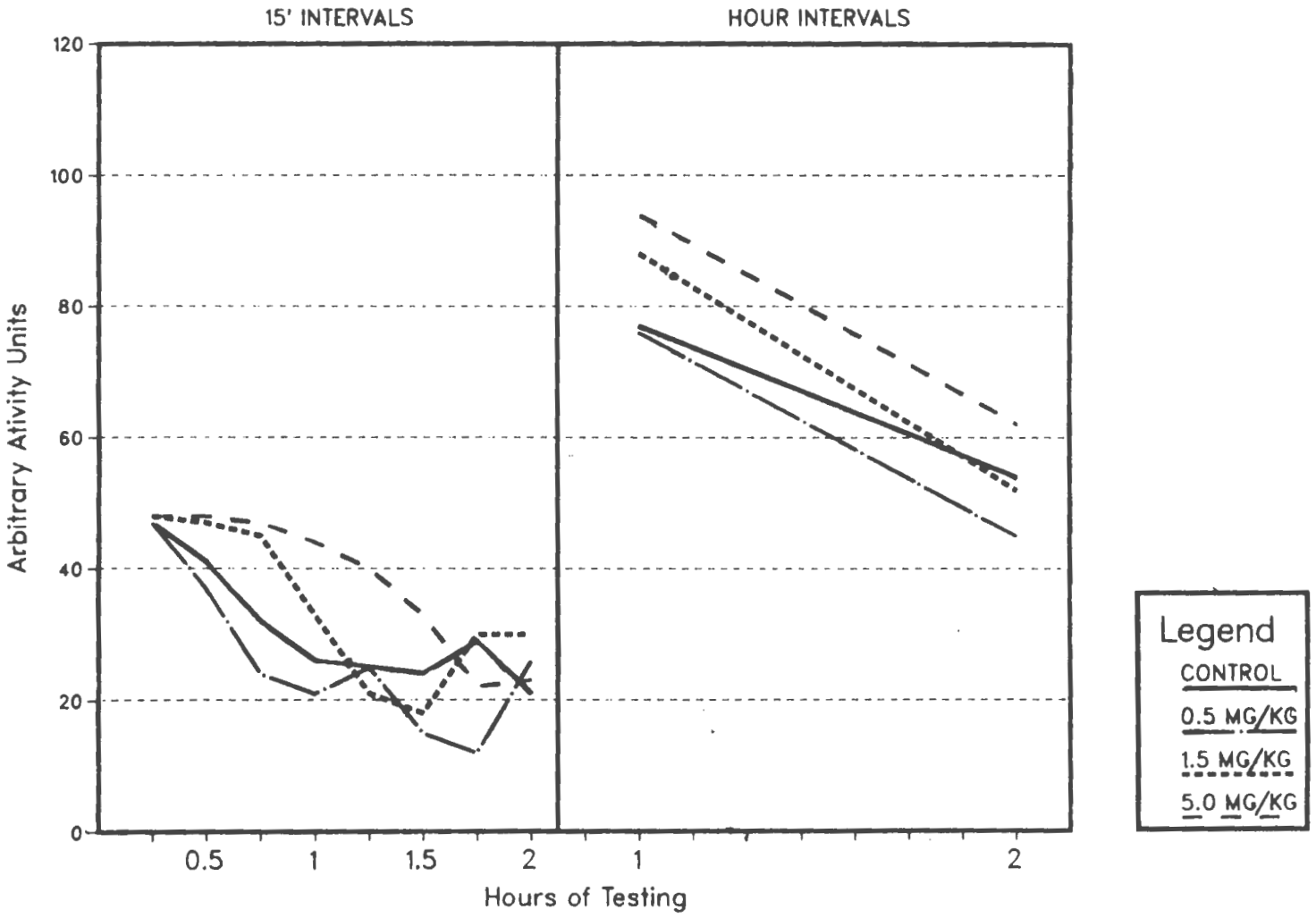

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Ativity Units
0.5
1
1.5
2
1
2
Hours of Testing
Legend
CONTROL
0.5 MG/KG
1.5 MG/KG
5.0 MG/KG

Figure 7

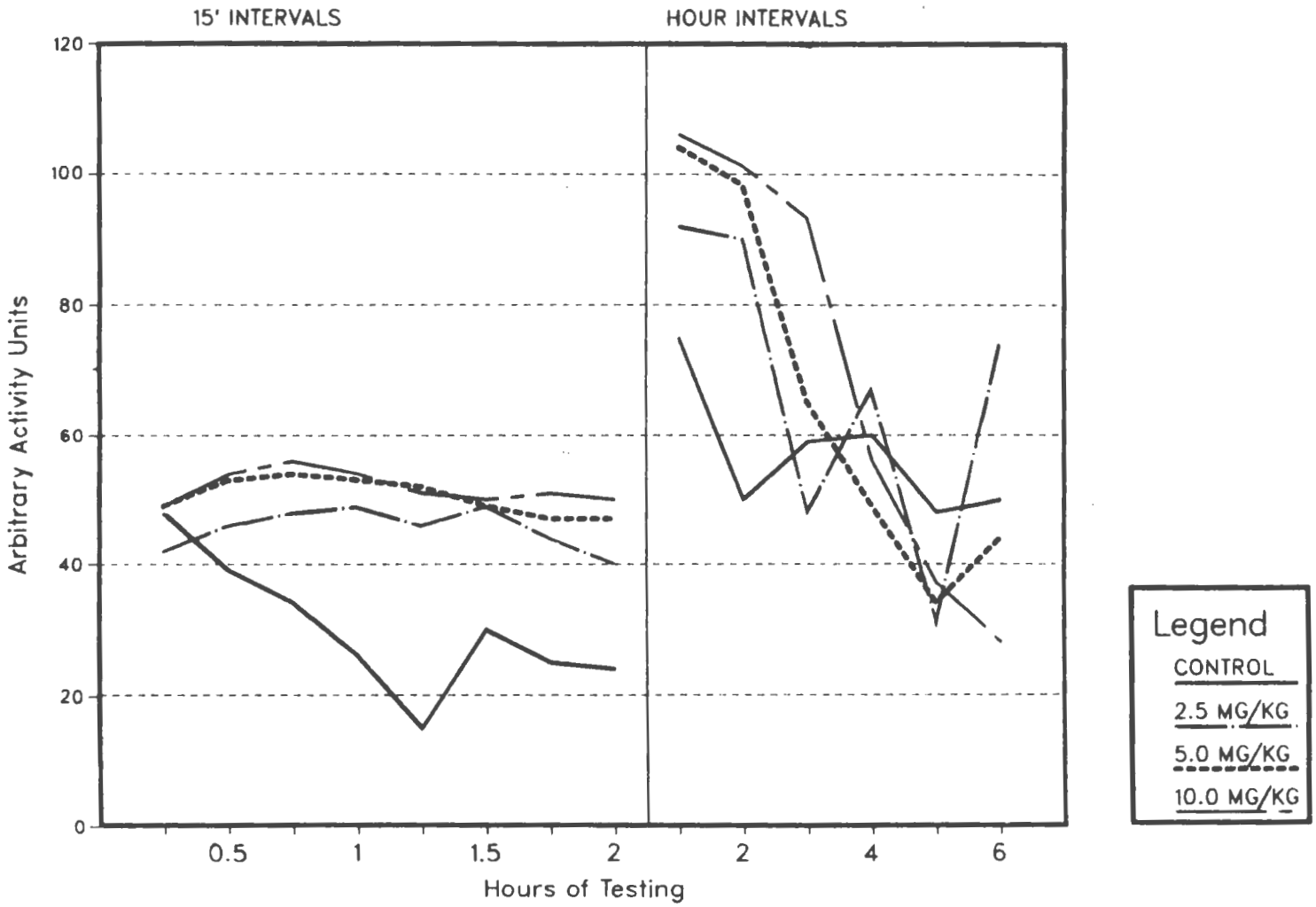

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
2.5 MG/KG
5.0 MG/KG
10.0 MG/KG

Figure 8

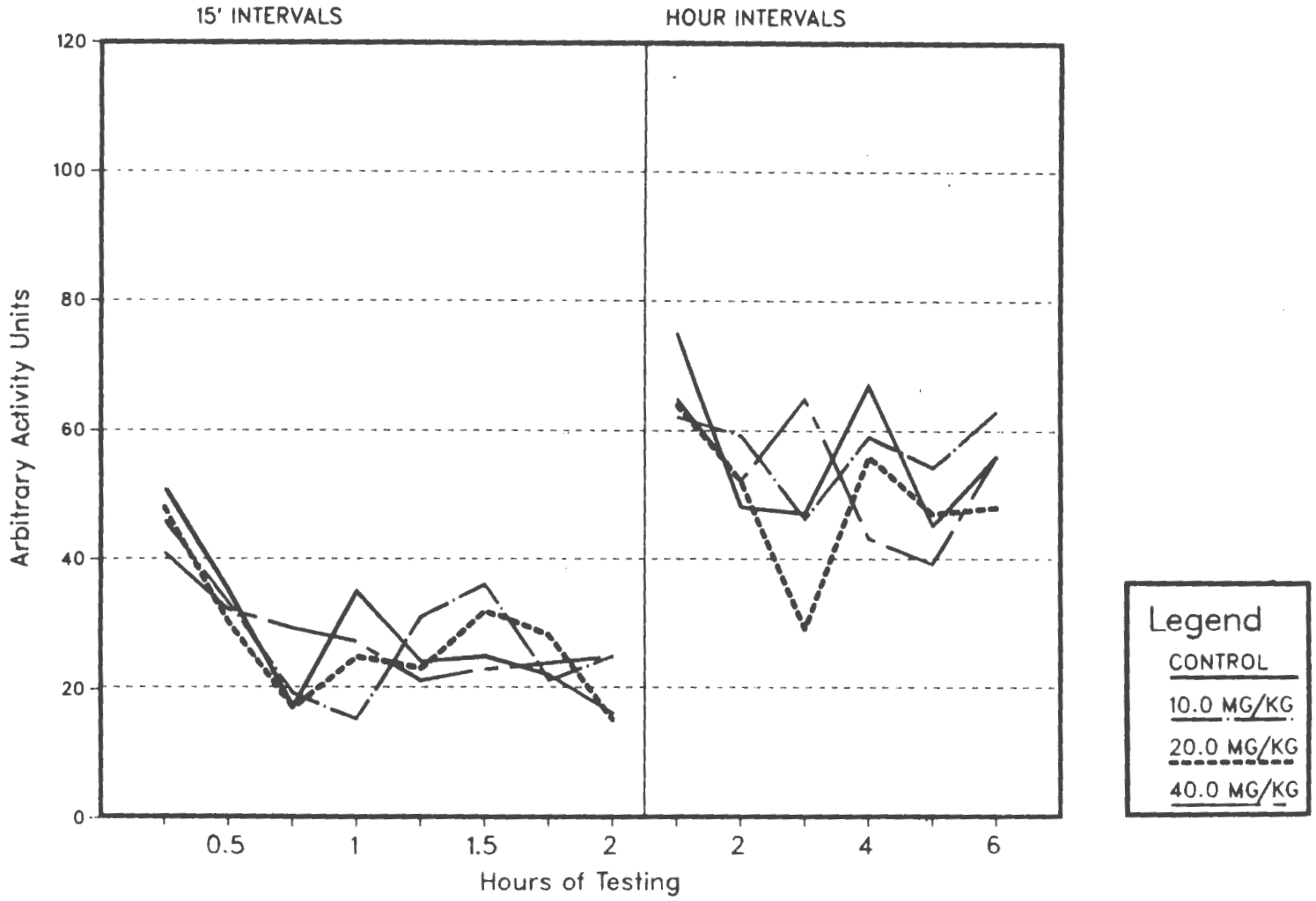

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
10.0 MG/KG
20.0 MG/KG
40.0 MG/KG

Figure 9

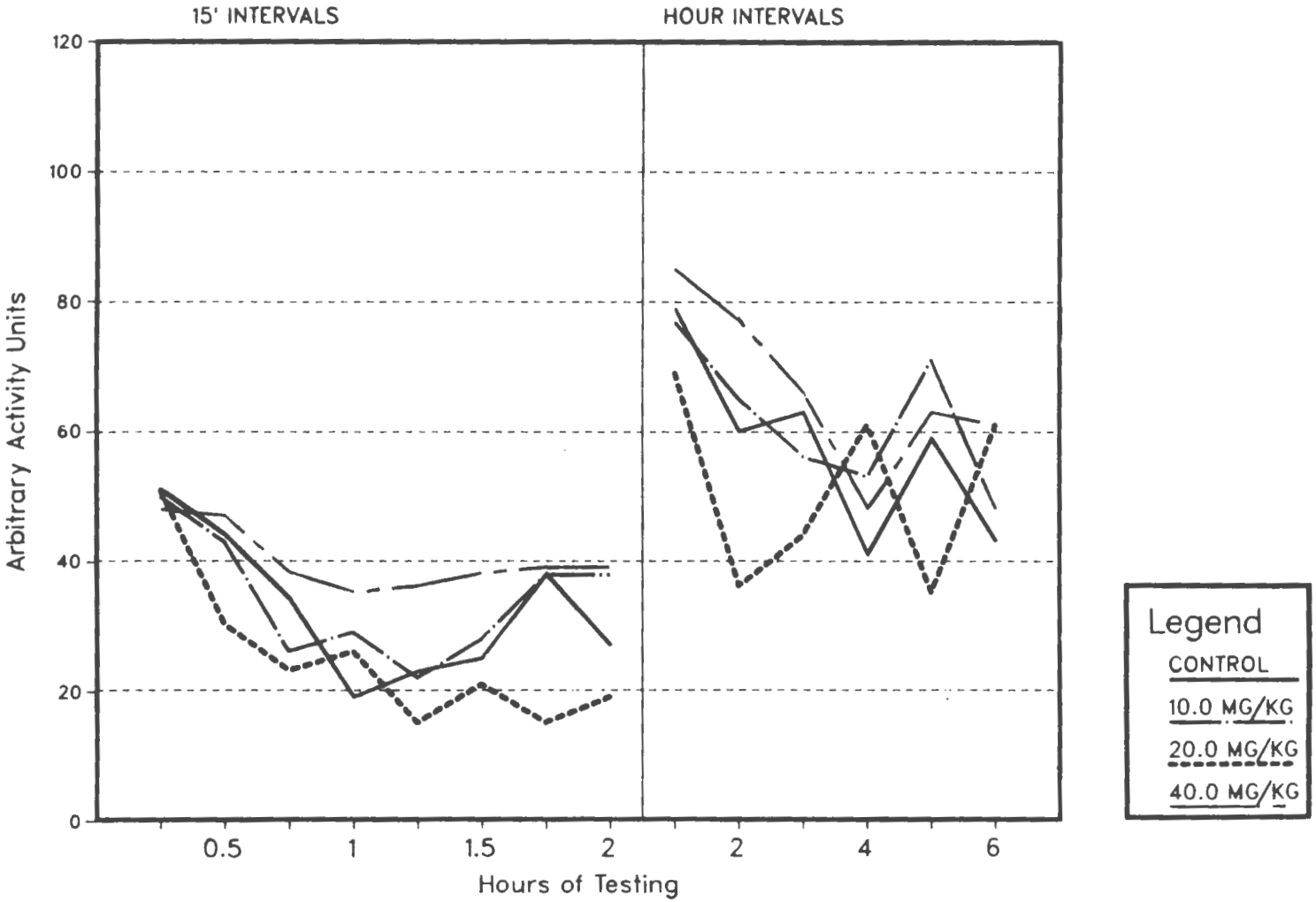

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
10.0 MG/KG
20.0 MG/KG
40.0 MG/KG

Figure 10

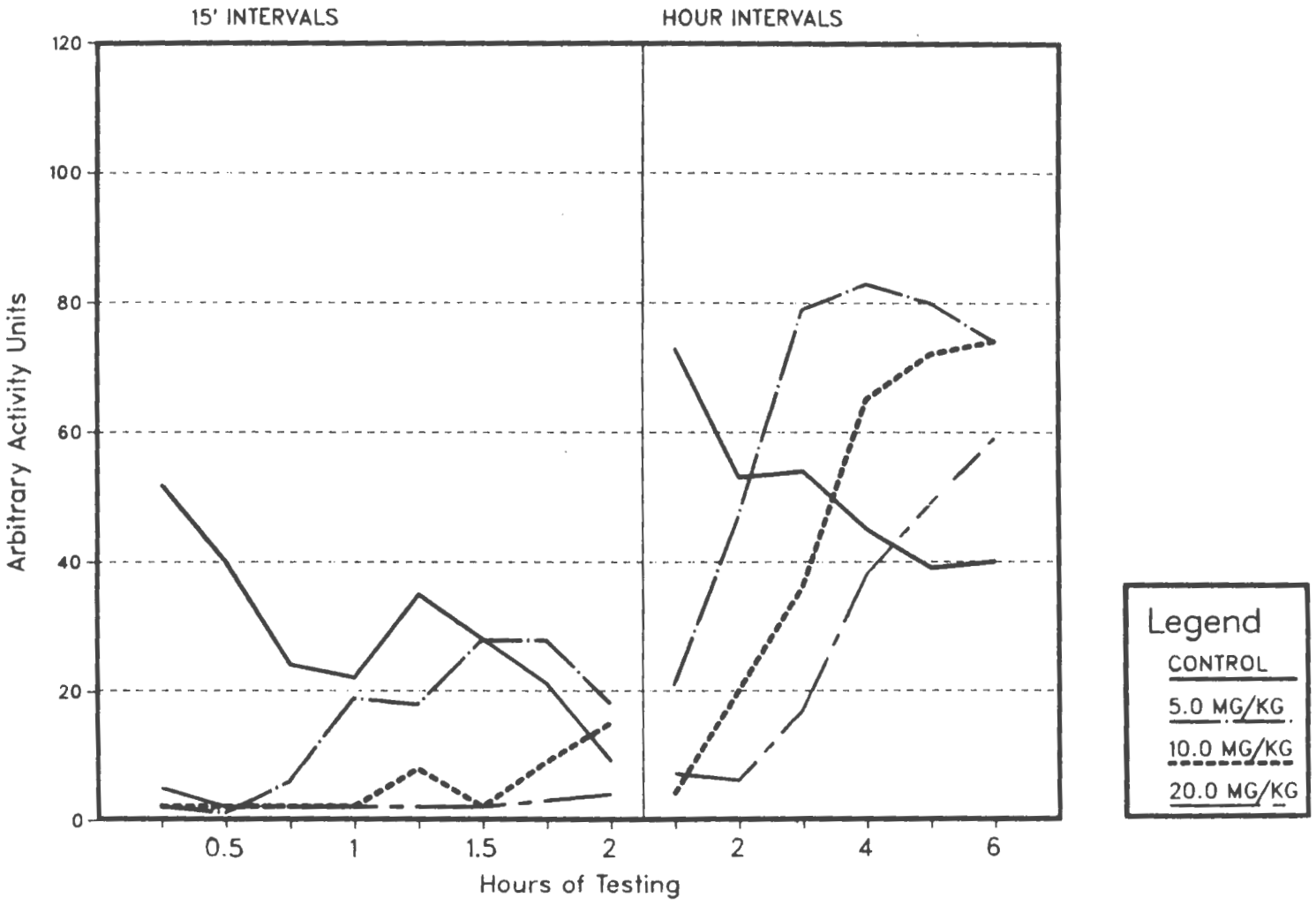

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
5.0 MG/KG
10.0 MG/KG
20.0 MG/KG

Figure 11

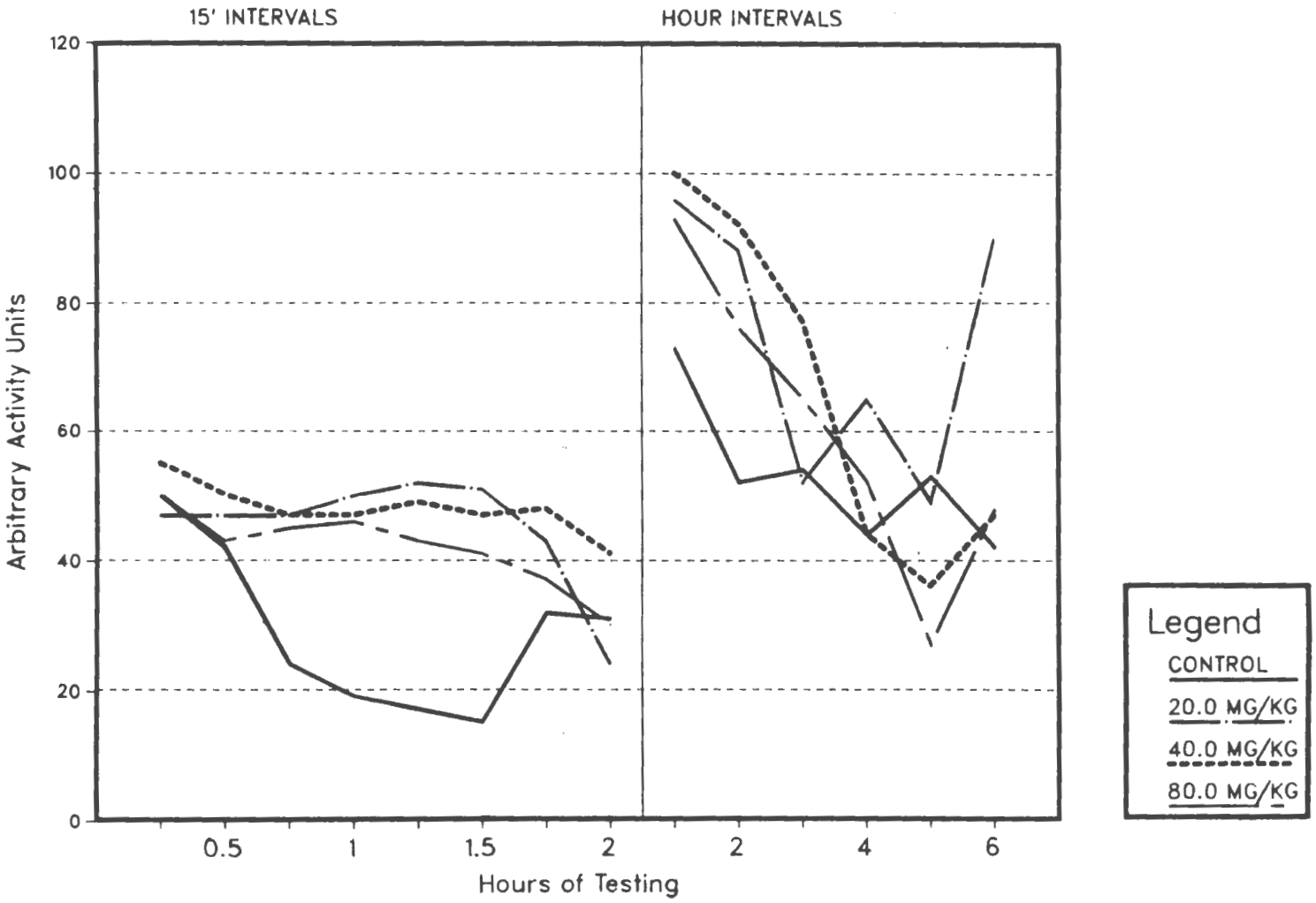

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
20.0 MG/KG
40.0 MG/KG
80.0 MG/KG

Figure 12

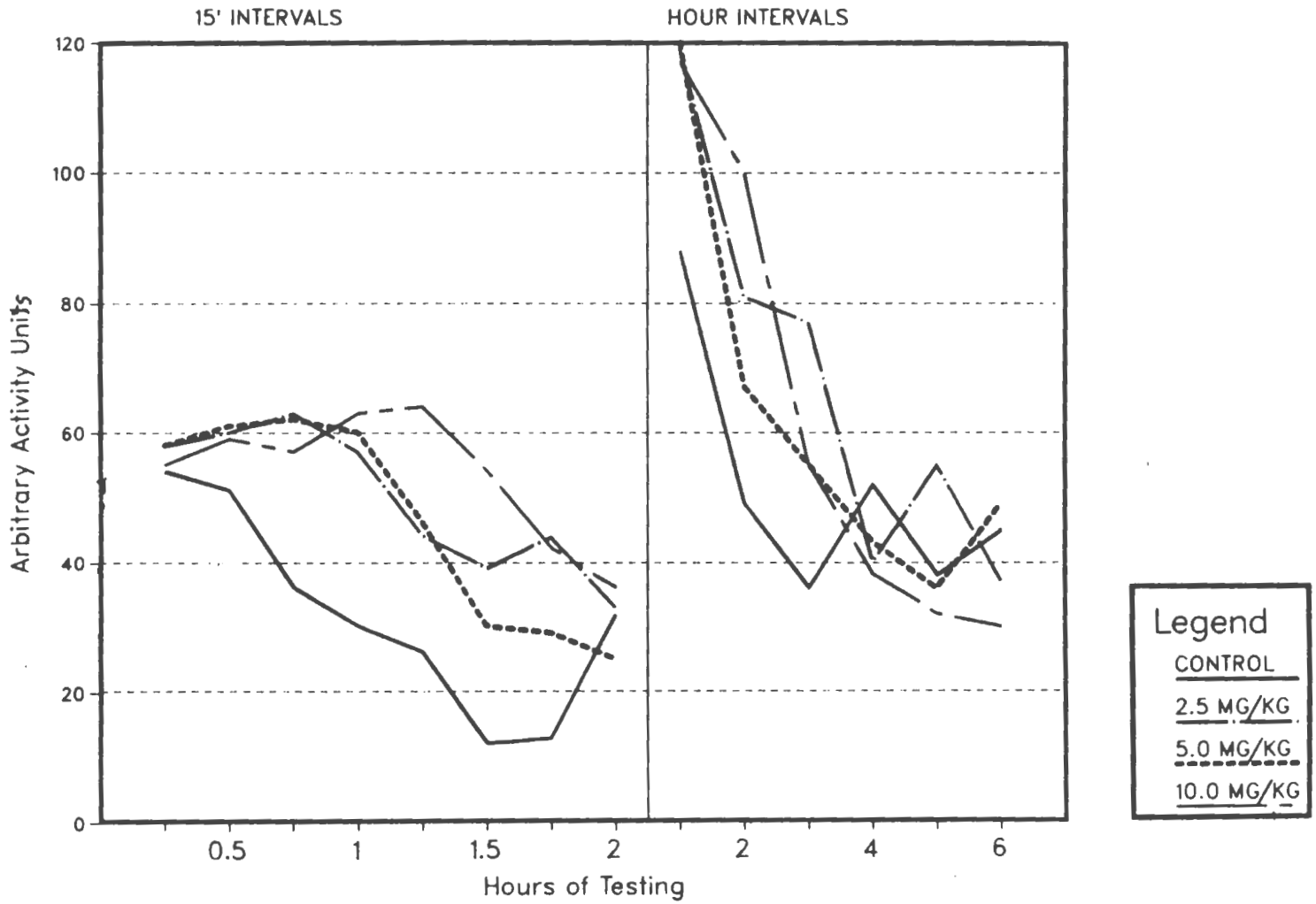
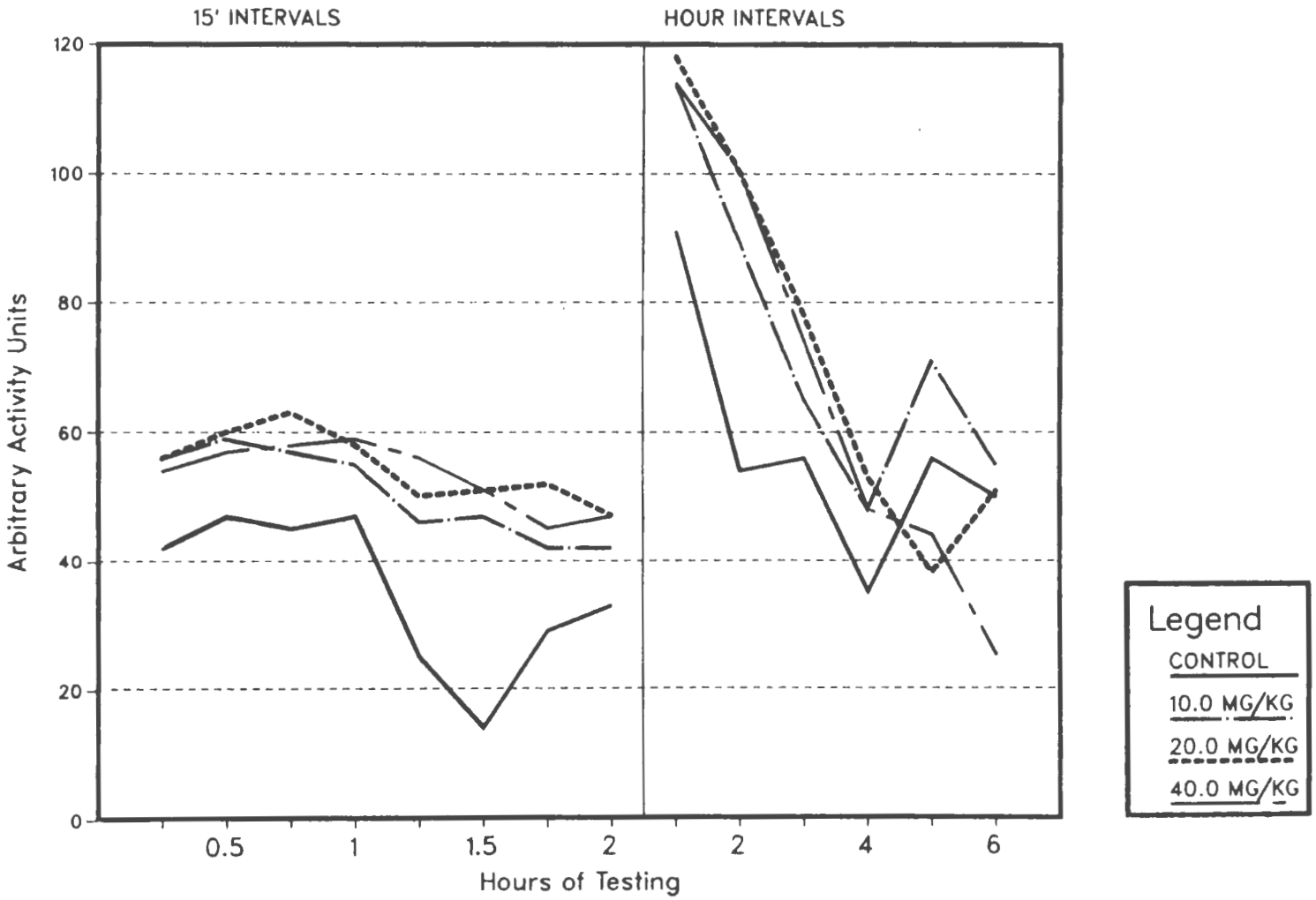

15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
2.5 MG/KG
5.0 MG/KG
10.0 MG/KG

Figure 13


15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Activity Units
0.5
1
1.5
2
2
4
6
Hours of Testing
Legend
CONTROL
10.0 MG/KG
20.0 MG/KG
40.0 MG/KG

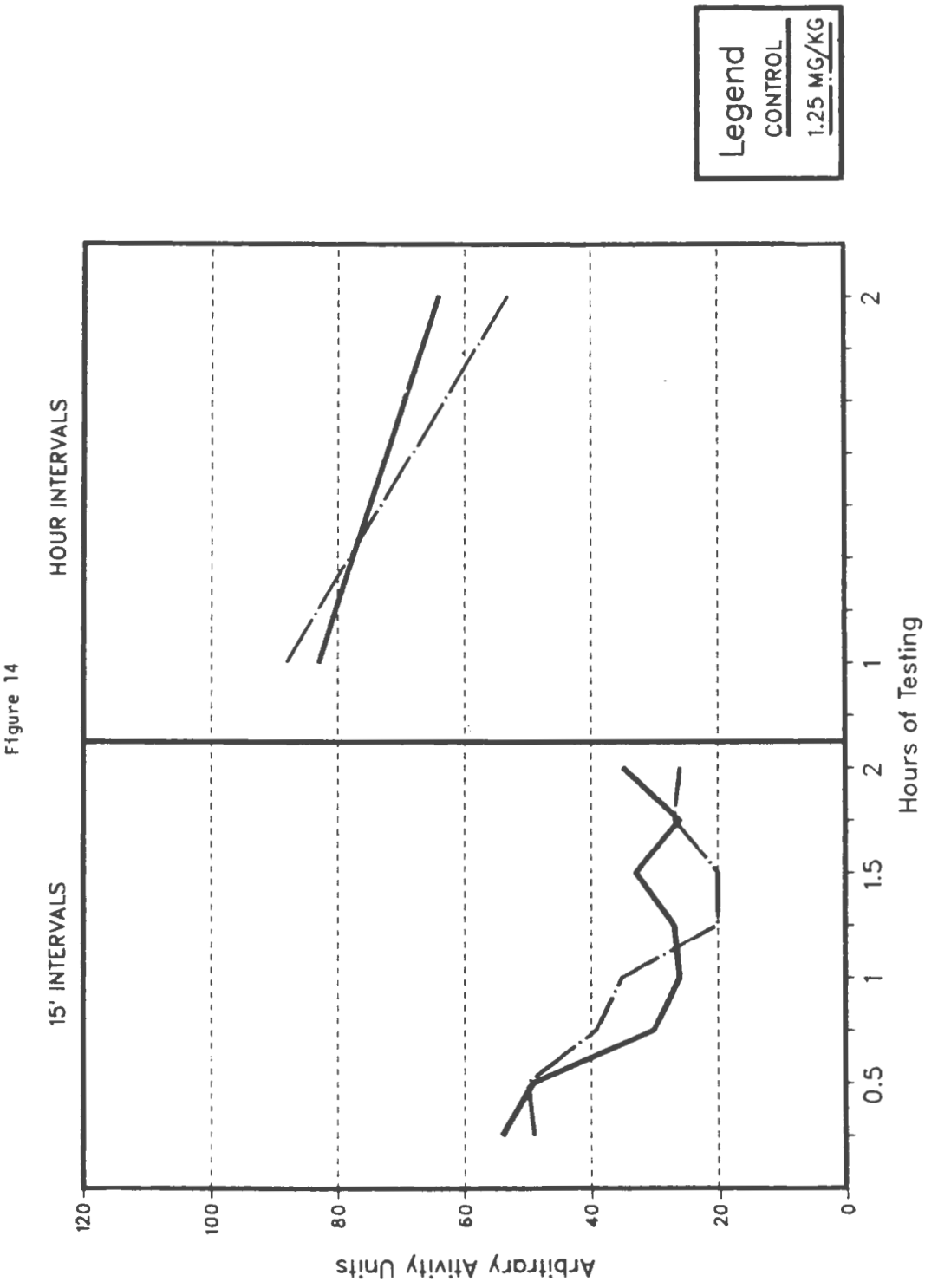
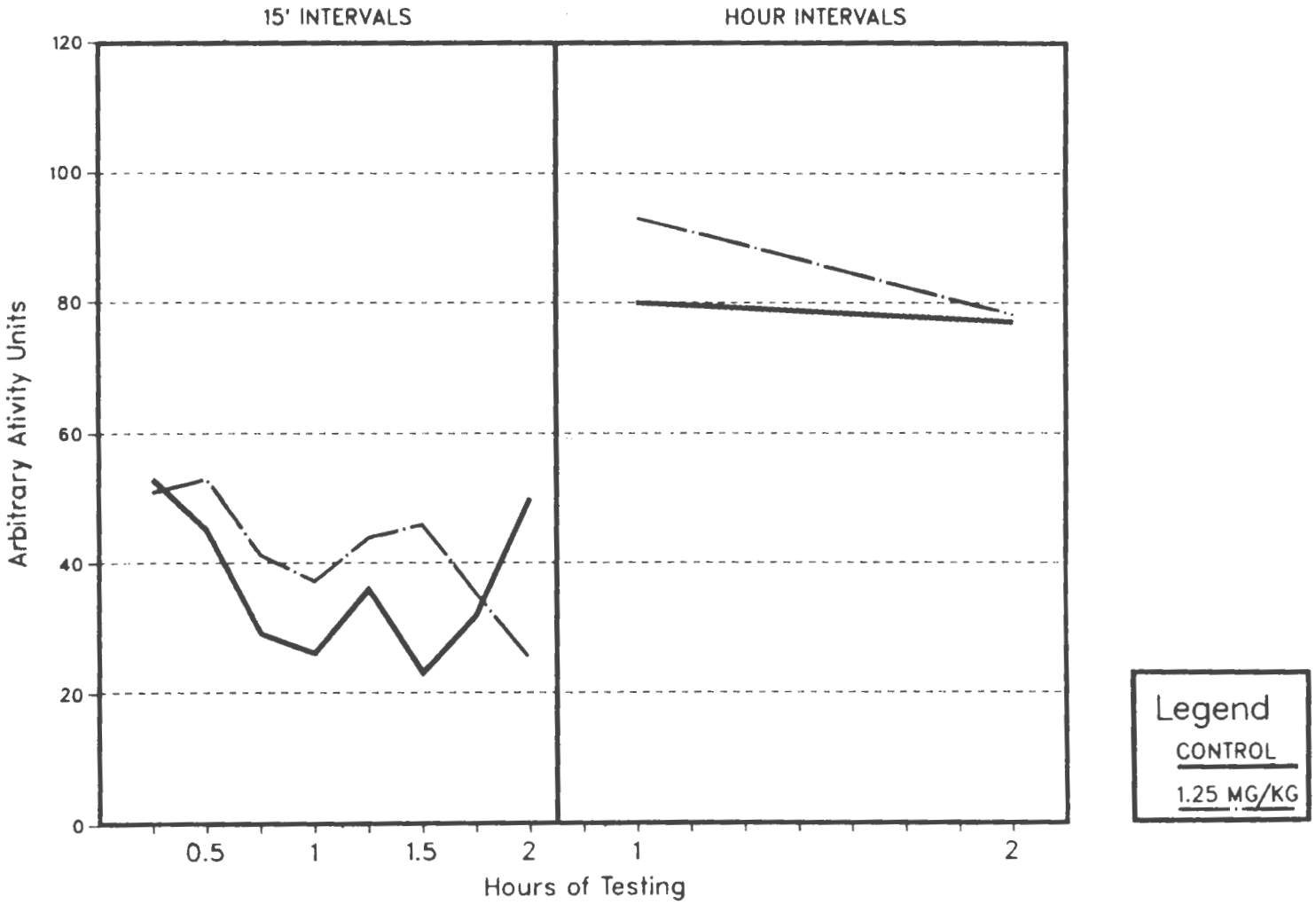

Legend
CONTROL
1.25 MG/KG
15' INTERVALS
HOUR INTERVALS
Arbitrary Ativity Units
0
20
40
60
80
100
120
0.5
1
1.5
2
1
2
Hours of Testing

Figure 14

Figure 15


15' INTERVALS
HOUR INTERVALS
120
100
80
60
40
20
0
Arbitrary Ativity Units
0.5
1
1.5
2
1
2
Hours of Testing
Legend
CONTROL
1.25 MG/KG

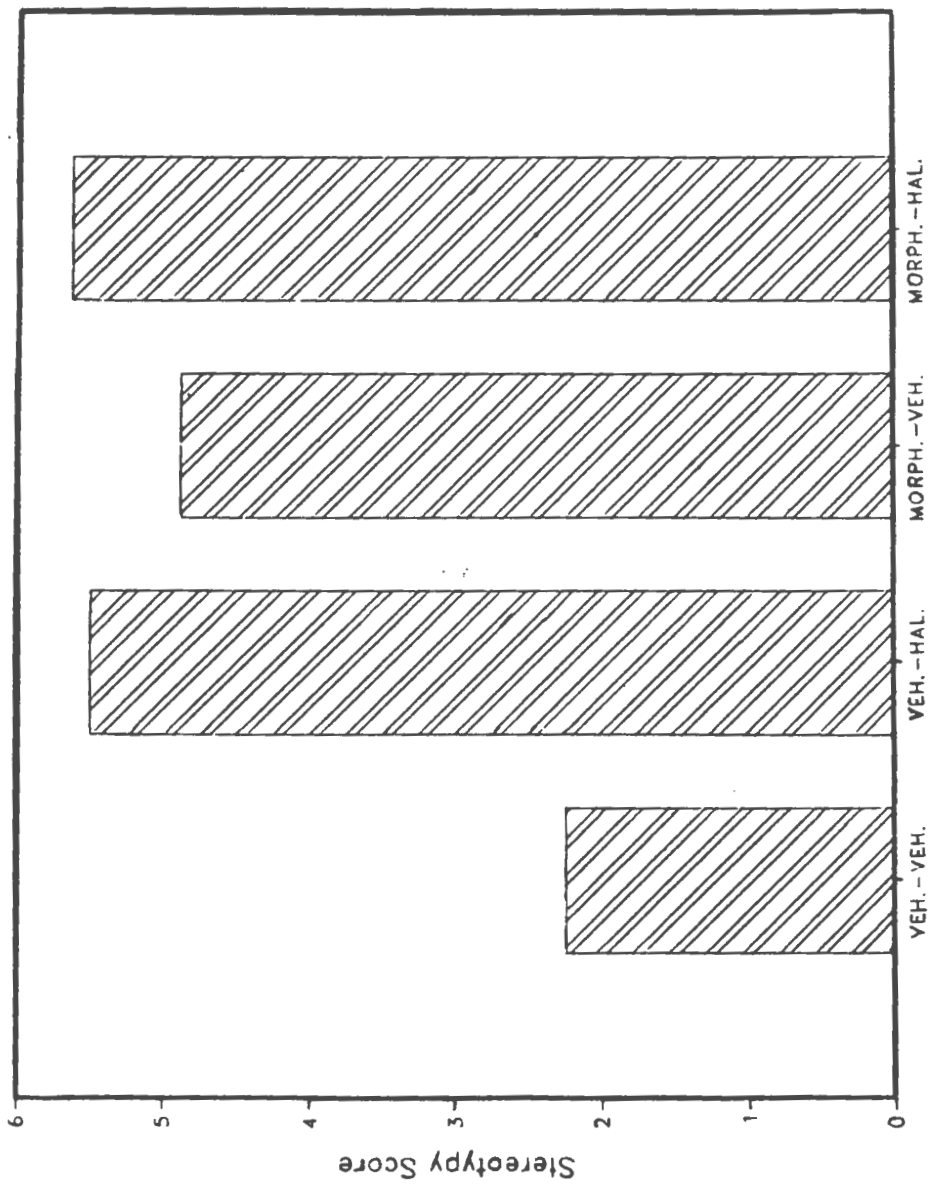

Stereotypy Score
0
1
2
3
4
5
6
VEH. - VEH.
VEH. - HAL.
MORPH. - VEH.
MORPH. - HAL.

Figure 16

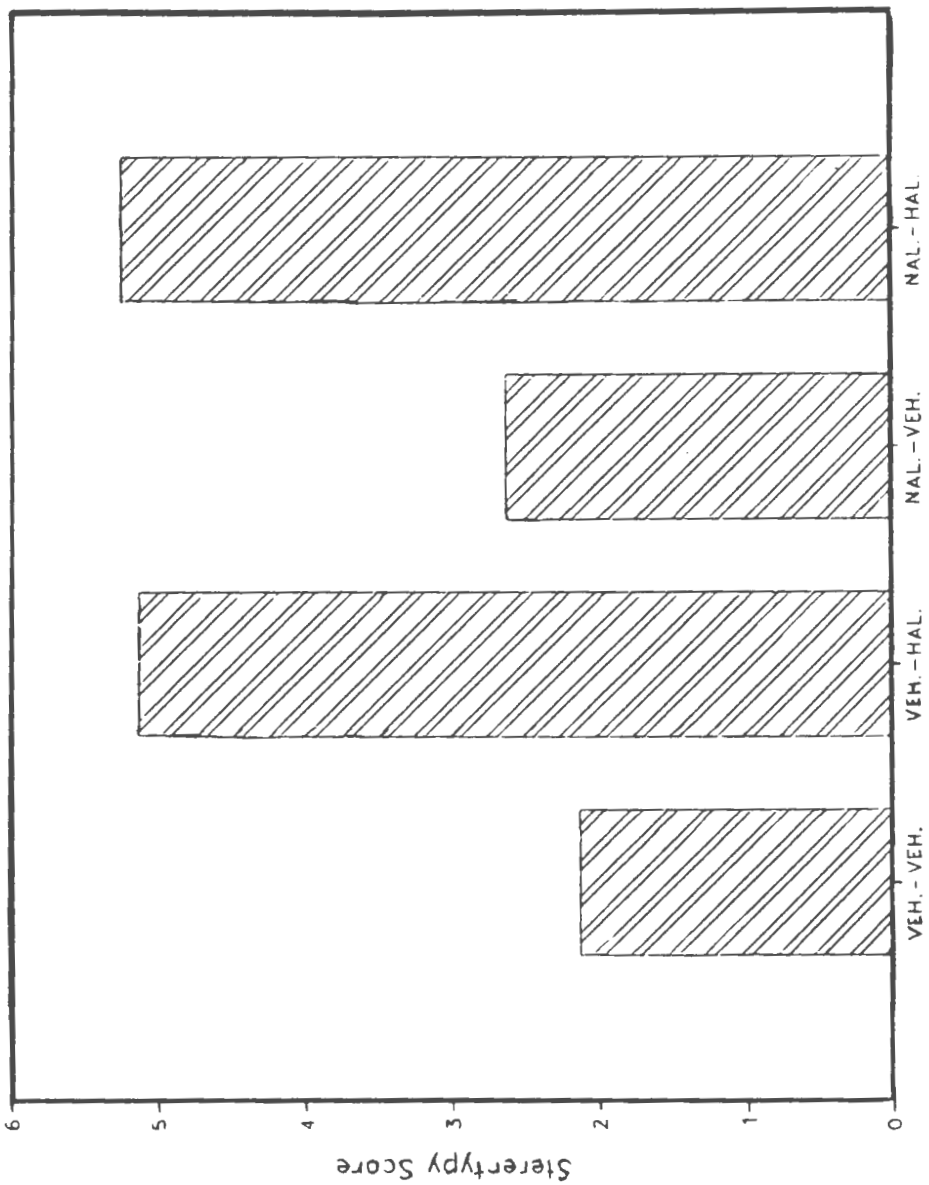


Figure 17

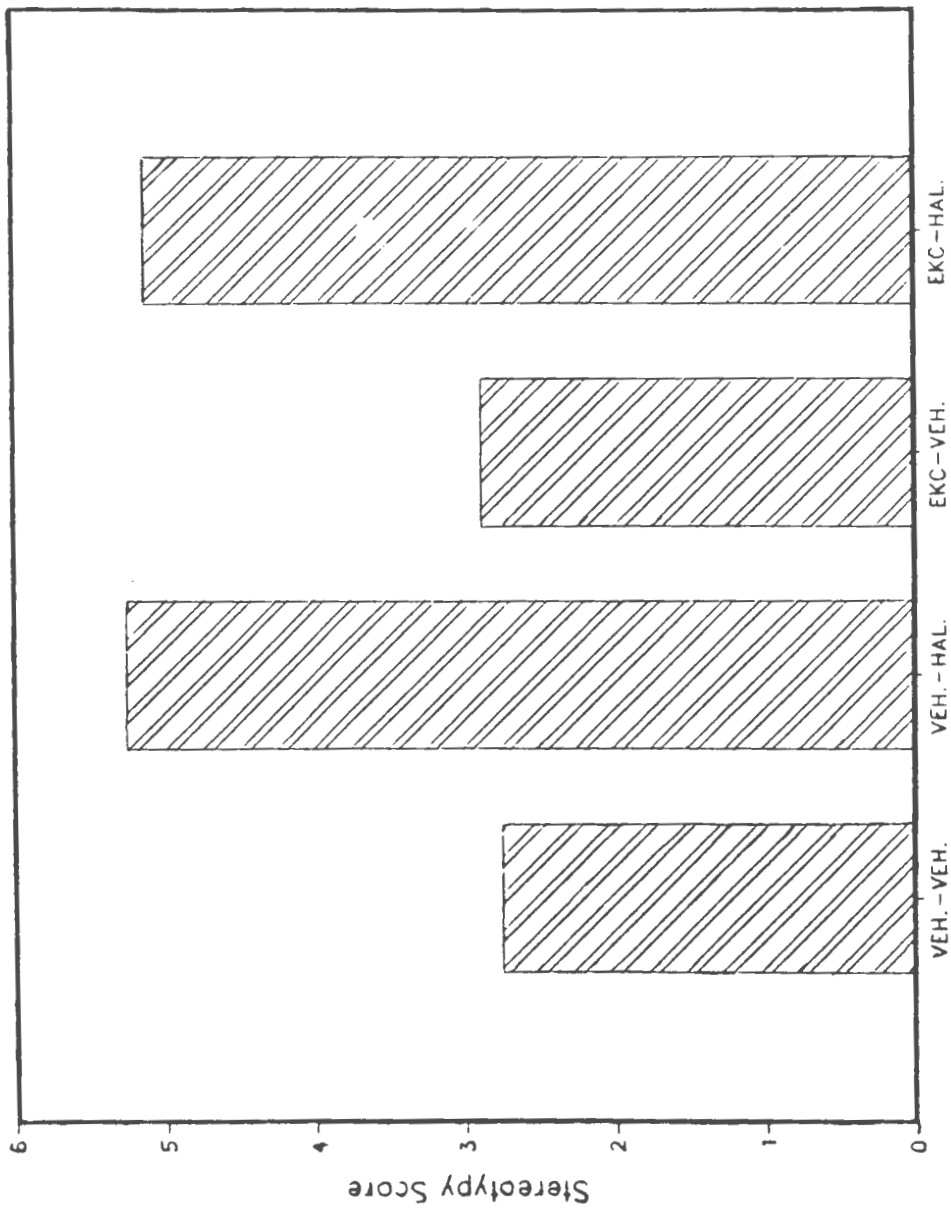


Figure 18

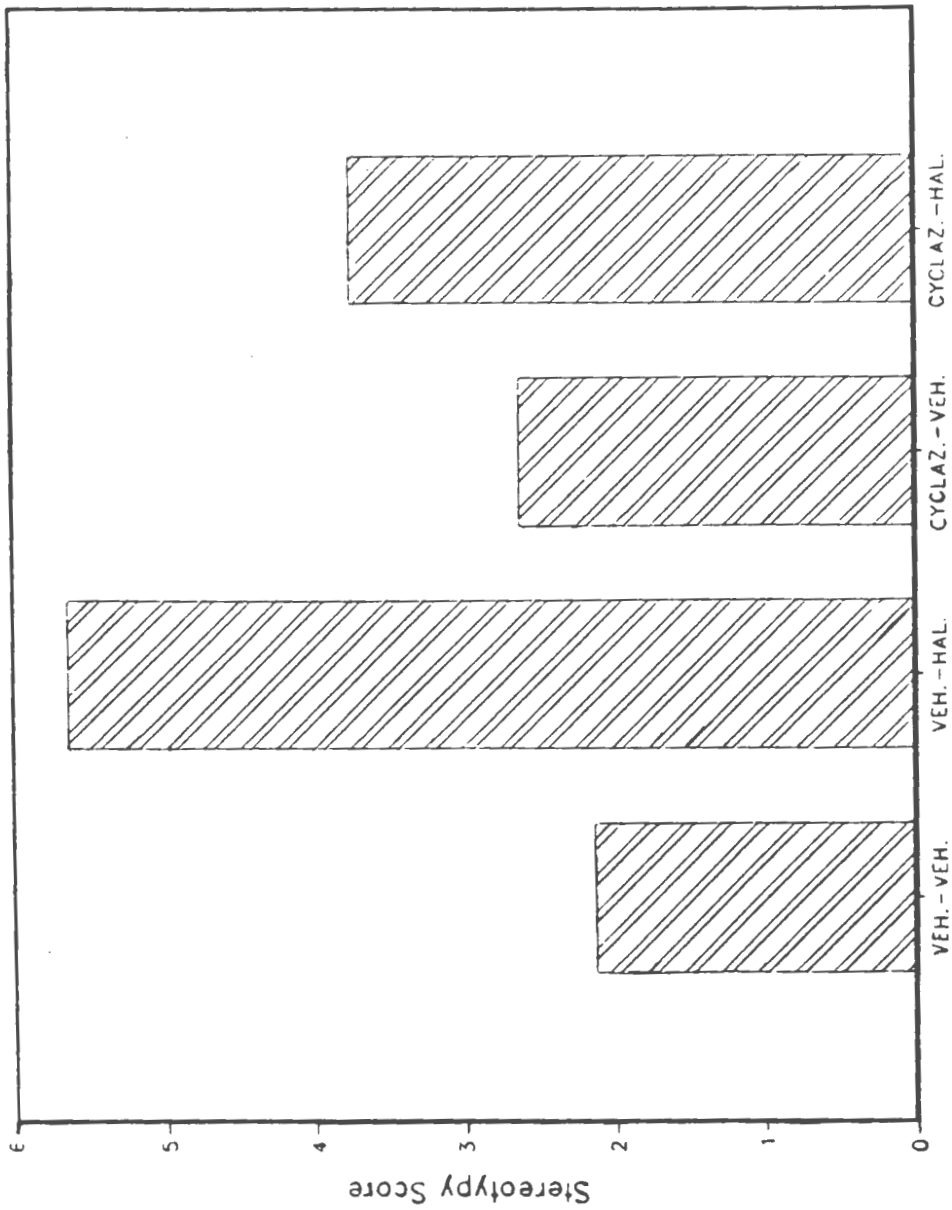

Stereotypy Score
0
1
2
3
4
5
6
VEH.-VEH.
VEH.-HAL.
CYCLAZ.-VEH.
CYCLAZ.-HAL.

Figure 19

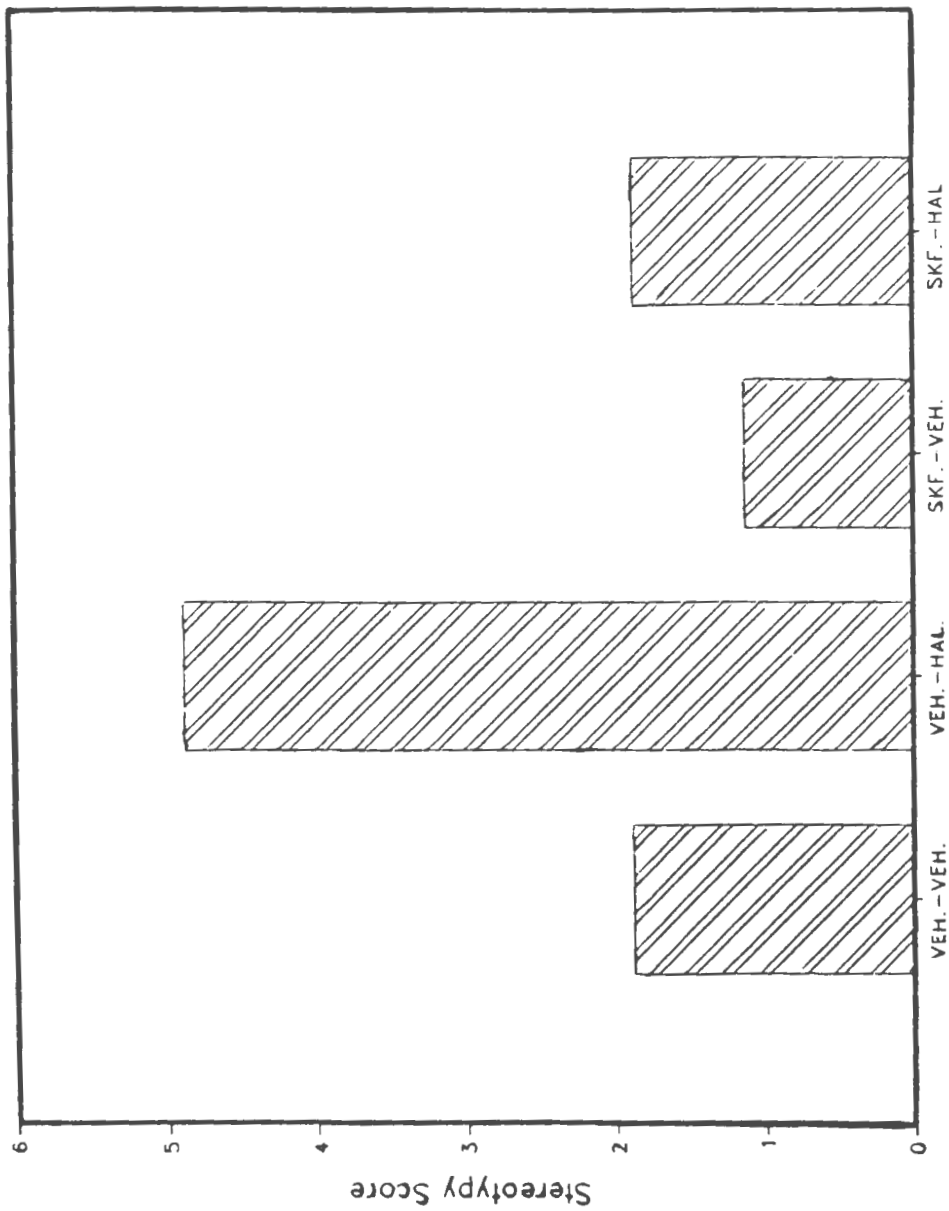


Figure 20

TABLE 1

Effects of Apomorphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	46.5 ± 1.4	40.5 ± 4.0	32.4 ± 6.0	25.8 ± 6.9	24.6 ± 7.0	24.4 ± 4.3	29.4 ± 3.7	21.0 ± 5.1
0.5	46.9 ± 0.9	37.1 ± 3.0	24.4 ± 3.1	21.3 ± 3.1	24.6 ± 3.2	14.9 ± 3.2	12.0 ± 4.0	25.5 ± 4.4
1.5	48.0 ± 0.5	47.1 ± 0.7	45.1 ± 1.2	33.1 ± 2.7	21.1 ± 3.1	17.8 ± 3.3	30.0 ± 3.5	29.6 ± 3.6
5.0	48.1 ± 1.5	47.6 ± 2.1	46.8 ± 2.6	44.0 ± 2.3	39.9 ± 2.8	32.8 ± 4.6	22.3 ± 4.8	23.0 ± 4.0

2. 60' Intervals over 2 Hours

Dose (mg/kg sc)	60'	120'
Control	77.0 ± 6.8	53.5 ± 7.4
0.5	75.7 ± 2.9	44.5 ± 2.6
1.5	87.8 ± 1.7	52.3 ± 4.3
5.0	93.5 ± 4.1	62.0 ± 6.7

[a]Mean and standard error of the square root of the activity counts of 16 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 1a

Effects of Apomorphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2170 ± 133	1751 ± 261	1289 ± 331	1001 ± 324	944 ± 352	732 ± 214	961 ± 222	624 ± 245
0.5	2195 ± 79	1427 ± 197	670 ± 149	514 ± 158	688 ± 143	298 ± 89	261 ± 135	797 ± 214
1.5	2308 ± 45	2242 ± 66	1797 ± 178	1148 ± 192	507 ± 127	383 ± 151	988 ± 203	975 ± 198
5.0	2345 ± 144	2297 ± 205	2244 ± 262	1966 ± 212	1655 ± 225	1225 ± 272	660 ± 252	636 ± 198

2. 60' Intervals over 2 Hours

Dose (mg/kg sc)	60'	120'
Control	6211 ± 999	3261 ± 791
0.5	4805 ± 367	2043 ± 228
1.5	7732 ± 301	2863 ± 446
5.0	8851 ± 800	4176 ± 868

[a]Mean and standard error of the activity counts of 16 pairs of mice.

TABLE 2

Apomorphine-Induced Stereotyped Behavior in Mice

Apomorphine Dose (mg/kg sc)	n	Stereotypy Score $\bar{x} \pm SE$	% of Stereotypy[a]	ED_{50} (95% confidence limits)
0	8	0.00 ± 0.00	-	
0.3	8	1.38 ± 0.26	23	0.80 (0.76-0.84)
1.0	8	3.25 ± 0.16	54	
3.0	8	5.38 ± 0.18	90	

[a] % of stereotypy based on maximum score = 6

$$\% \text{ stereotypy} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

TABLE 3

Apomorphine-Induced Climbing Behavior in Mice

Apomorphine Dose (mg/kg sc)	n	Climbing Score $\bar{x} \pm SE$	% of Climbing[a]	ED_{50} (95% confidence limits)
0	8	0.13 ± 0.13	-	
0.3	8	0.75 ± 0.41	11	0.58 (0.55-0.61)
1.0	8	5.25 ± 0.37	87	
3.0	8	5.75 ± 0.16	96	

[a] % of climbing based on maximum score = 6

$$\% \text{ climbing} = \frac{(\bar{x} \text{ of Dose Group}) - (\bar{x} \text{ of Control})}{(\text{Max. score}) - (\bar{x} \text{ of Control})} \times 100$$

TABLE 4

Effects of Morphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	48.1 ± 10.4	39.0 ± 15.8	33.6 ± 9.6	25.7 ± 7.1	14.9 ± 7.3	30.2 ± 13.9	24.6 ± 4.0	24.3 ± 2.8
2.5	41.5 ± 4.8	46.0 ± 17.9	48.2 ± 4.6	48.6 ± 4.9*	45.6 ± 5.7*	48.8 ± 4.0	43.6 ± 1.9*	40.1 ± 4.8*
5	48.7 ± 1.8	52.6 ± 0.4	53.7 ± 1.3	52.8 ± 0.4*	51.8 ± 0.8*	49.4 ± 2.0	47.2 ± 5.5*	47.4 ± 5.0*
10	48.7 ± 3.8	54.2 ± 3.6	55.9 ± 0.6*	53.5 ± 0.7*	51.1 ± 0.1*	49.8 ± 0.3	50.6 ± 0.1*	50.0 ± 0.7*

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	75.3 ± 21.5	50.0 ± 9.9	58.9 ± 26.7	60.4 ± 9.7	47.6 ± 1.8	49.7 ± 21.4
2.5	92.3 ± 9.5	89.5 ± 6.3*	48.1 ± 1.9	66.5 ± 8.5	31.2 ± 6.8	73.9 ± 4.5
5	104.0 ± 2.0	98.1 ± 6.5*	64.7 ± 6.3	49.0 ± 14.2	34.4 ± 21.7	44.3 ± 7.2
10	106.3 ± 4.2	100.7 ± 0.5*	92.6 ± 7.1	55.8 ± 9.1	37.2 ± 5.8	28.2 ± 0.8

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 4a

Effects of Morphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2426 ± 1002	1772 ± 1229	1223 ± 648	708 ± 362	275 ± 216	1105 ± 838	622 ± 198	599 ± 136
2.5	1746 ± 401	2139 ± 427	2347 ± 442	2385 ± 478	2112 ± 523	2401 ± 386	1900 ± 168	1634 ± 388
5	2379 ± 176	2772 ± 45	2889 ± 140	2790 ± 44	2689 ± 83	2440 ± 199	2260 ± 519	2270 ± 476
10	2386 ± 369	2954 ± 384	3121 ± 61	2865 ± 79	2615 ± 4	2477 ± 30	2558 ± 2	2501 ± 68

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	6128 ± 3242	2601 ± 992	4186 ± 3146	3744 ± 1175	2265 ± 167	2923 ± 2122
2.5	8616 ± 1748	8047 ± 1129	2318 ± 178	4487 ± 1124	1022 ± 426	5481 ± 668
5	10829 ± 406	9658 ± 1278	4225 ± 819	2605 ± 1395	1653 ± 1491	2018 ± 634
10	11324 ± 895	10150 ± 96	8629 ± 1308	3197 ± 1020	1414 ± 430	796 ± 46

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 5

Effects of Morphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	45.1 ± 1.0	33.4 ± 5.1	32.9 ± 7.7	8.0 ± 2.0	10.2 ± 7.1	10.5 ± 0.3	20.4 ± 13.7	23.4 ± 13.0
10	52.7 ± 0.2*	52.6 ± 0.4*	52.3 ± 1.7*	51.6 ± 1.5*	51.7 ± 1.3*	50.4 ± 1.8*	55.0 ± 4.3*	50.5 ± 1.4*
20	58.0 ± 1.7*	64.6 ± 1.6*	58.8 ± 0.5*	54.3 ± 1.8*	54.2 ± 1.0*	54.2 ± 0.9*	52.0 ± 0.4*	51.5 ± 0.4*
40	51.8 ± 2.4*	57.2 ± 1.2*	53.0 ± 0.5*	50.5 ± 1.9*	50.9 ± 3.1*	49.4 ± 3.8*	49.1 ± 4.0	49.8 ± 3.8

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	66.2 ± 0.4	39.7 ± 2.4	46.2 ± 10.8	41.5 ± 12.5	35.0 ± 2.1	49.4 ± 17.3
10	1094.7 ± 1.6*	104.0 ± 1.5*	99.1 ± 5.0*	70.3 ± 6.5	47.7 ± 5.2	40.2 ± 9.8
20	118.1 ± 0.6*	106.0 ± 1.3*	98.0 ± 2.0*	84.6 ± 5.0*	58.1 ± 0.3	42.1 ± 6.1
40	106.4 ± 1.7*	99.7 ± 7.3*	98.4 ± 2.4*	95.5 ± 2.1*	49.8 ± 14.2	39.4 ± 1.2

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 5a

Effects of Morphine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2030 ± 87	1139 ± 337	1142 ± 506	67 ± 31	154 ± 144	110 ± 5.5	603 ± 558	717 ± 610
10	2778 ± 18	2769 ± 38	2742 ± 173	2673 ± 150	2679 ± 129	2551 ± 177	3039 ± 473	2551 ± 142
20	3362 ± 195	4177 ± 206	3456 ± 60	2948 ± 191	2935 ± 104	2947 ± 93	2701 ± 43	2657 ± 38
40	2690 ± 246	3273 ± 138	2809 ± 55	2553 ± 187	2600 ± 312	2456 ± 371	2430 ± 391	2499 ± 377

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	4378 ± 51	1583 ± 190	2248 ± 1000	1879 ± 1038	1230 ± 149	2742 ± 1710
10	10960 ± 343	10820 ± 309	9845 ± 987	4985 ± 907	2299 ± 493	1712 ± 791
20	13943 ± 150	11240 ± 278	9613 ± 396	7189 ± 843	3379 ± 39	1808 ± 511
40	11324 ± 350	9984 ± 1452	9704 ± 475	9131 ± 547	2677 ± 1413	1552 ± 96

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 6

Effects of Naloxone on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	51.2 ± 5.2	35.3 ± 1.8	17.3 ± 7.2	35.0 ± 17.2	24.4 ± 20.4	24.5 ± 4.4	21.9 ± 4.1	16.0 ± 9.3
10	45.9 ± 0.6	32.9 ± 1.7	18.7 ± 4.4	15.4 ± 3.2	30.8 ± 5.3	36.4 ± 1.8	21.4 ± 1.9	24.6 ± 14.9
20	47.9 ± 2.9	30.1 ± 8.4	17.4 ± 3.3	24.5 ± 6.9	23.1 ± 9.5	31.8 ± 4.5	28.3 ± 16.4	15.0 ± 0.4
40	40.9 ± 3.2	32.0 ± 5.1	28.6 ± 2.7	26.5 ± 0.7	20.7 ± 5.7	23.4 ± 11.7	24.4 ± 12.6	25.1 ± 11.8

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	74.6 ± 14.1	47.9 ± 13.1	47.0 ± 18.7	66.7 ± 27.8	44.6 ± 3.9	56.2 ± 25.1
10	61.7 ± 0.1	59.2 ± 9.4	45.5 ± 1.1	59.4 ± 5.7	53.5 ± 8.5	63.1 ± 8.7
20	64.4 ± 9.6	51.9 ± 8.4	28.6 ± 7.0	55.7 ± 12.7	47.3 ± 12.3	47.6 ± 14.3
40	65.2 ± 3.1	51.5 ± 4.1	64.5 ± 10.0	42.7 ± 4.3	39.0 ± 12.1	55.8 ± 2.4

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 6a

Effects of Naloxone on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2653 ± 533	1249 ± 127	350 ± 248	1518 ± 1199	1008 ± 992	620 ± 215	496 ± 178	341 ± 297
10	2105 ± 53	1088 ± 114	368 ± 163	247 ± 99	975 ± 323	1330 ± 133	460 ± 79	825 ± 731
20	2303 ± 274	976 ± 506	315 ± 115	647 ± 337	624 ± 438	1034 ± 285	1066 ± 925	226 ± 11
40	1682 ± 259	1051 ± 329	824 ± 153	703 ± 36	460 ± 237	685 ± 547	756 ± 615	770 ± 591

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	5769 ± 2107	2465 ± 1251	2553 ± 1754	5218 ± 3704	2004 ± 345	3785 ± 2816
10	3807 ± 4	3589 ± 1108	2070 ± 103	3564 ± 678	2930 ± 910	4060 ± 1099
20	4243 ± 1234	2950 ± 1659	864 ± 398	3261 ± 1418	2394 ± 1167	2473 ± 1362
40	4259 ± 400	2670 ± 423	4264 ± 1287	1846 ± 367	1663 ± 942	3115 ± 268

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 7

Effects of Naltrexone on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	51.1 ± 7.7	44.2 ± 5.8	34.8 ± 6.0	19.9 ± 1.0	23.9 ± 1.9	25.1 ± 19.6	38.3 ± 7.8	27.0 ± 5.3
10	49.6 ± 4.2	43.2 ± 6.7	26.2 ± 4.3	29.1 ± 0.2	22.0 ± 10.1	27.8 ± 5.1	37.5 ± 5.9	37.7 ± 4.9
20	51.2 ± 3.1	29.6 ± 8.5	22.8 ± 0.6	26.3 ± 11.0	14.7 ± 1.4	22.0 ± 8.4	15.2 ± 6.0*	19.0 ± 9.8
40	47.9 ± 0.7	47.4 ± 0.7	38.4 ± 2.8	35.2 ± 0.7	36.3 ± 1.7	38.4 ± 0.5	39.2 ± 1.5	39.1 ± 0.3

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	78.7 ± 10.7	60.0 ± 16.3	63.1 ± 7.7	40.7 ± 13.3	58.5 ± 2.1	42.6 ± 1.7
10	76.6 ± 8.0	65.4 ± 0.7	56.3 ± 0.9	53.5 ± 7.6	70.9 ± 2.4	48.4 ± 3.8
20	69.3 ± 10.3	36.3 ± 13.2	44.1 ± 26.8	60.9 ± 7.6	35.3 ± 7.7	60.5 ± 14.4
40	85.2 ± 1.6	76.5 ± 1.4	66.4 ± 3.7	48.0 ± 1.8	62.8 ± 21.0	61.4 ± 5.0

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 7a

Effects of Naltrexone on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2669 ± 786	1988 ± 514	1247 ± 414	398 ± 39	573 ± 92	1011 ± 980	1526 ± 595	755 ± 286
10	2480 ± 419	1908 ± 576	703 ± 223	845 ± 10	587 ± 444	798 ± 283	1441 ± 439	1447 ± 371
20	2634 ± 318	950 ± 505	519 ± 27	812 ± 576	217 ± 39	553 ± 367	267 ± 181	455 ± 370
40	2297 ± 70	2245 ± 69	1481 ± 216	1238 ± 50	1320 ± 119	1472 ± 42	1537 ± 115	1525 ± 24

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	6302 ± 1674	3863 ± 1955	4041 ± 973	1831 ± 1080	3422 ± 243	1815 ± 143
10	5936 ± 1228	4272 ± 93	3171 ± 101	2915 ± 811	5036 ± 338	2353 ± 369
20	4914 ± 1426	1491 ± 958	2660 ± 2360	3761 ± 924	1302 ± 542	3865 ± 1746
40	7260 ± 266	5853 ± 217	4429 ± 489	2304 ± 173	4386 ± 2644	3791 ± 609

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 8

Effects of Ethylketocyclazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	52.1 ± 4.4	40.2 ± 0.6	24.0 ± 1.5	21.6 ± 4.8	34.9 ± 9.6	27.9 ± 8.1	20.6 ± 14.3	9.0 ± 0.3
5	1.7 ± 1.7*	0.7 ± 0.7*	6.4 ± 1.0*	19.1 ± 11.0	18.2 ± 2.3	27.8 ± 6.2	28.2 ± 4.4	17.8 ± 0.4
10	2.2 ± 2.2*	1.8 ± 1.8*	2.2 ± 2.2*	2.3 ± 2.3	7.8 ± 0.1*	2.3 ± 0.9*	8.8 ± 3.1	14.6 ± 7.6
20	4.7 ± 1.5*	1.8 ± 1.8*	2.2 ± 2.2*	2.3 ± 2.2	2.1 ± 2.1*	1.5 ± 1.5*	2.7 ± 2.7	3.8 ± 1.0

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	73.4 ± 5.3	53.4 ± 3.6	54.3 ± 10.4	44.6 ± 10.9	38.3 ± 0.8	40.5 ± 2.0
5	20.5 ± 10.7*	47.2 ± 7.0	79.3 ± 14.5	82.6 ± 1.7	79.6 ± 1.8*	73.6 ± 3.8
10	4.2 ± 4.2*	20.2 ± 4.3*	36.1 ± 5.8	64.5 ± 8.3	72.4 ± 18.5	73.6 ± 13.9
20	7.0 ± 0.8*	5.8 ± 3.0*	17.0 ± 7.1	37.6 ± 18.2	49.0 ± 7.0	58.7 ± 10.2

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 8a

Effects of Ethylketocyclazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2734 ± 453	1615 ± 44	577 ± 69	487 ± 205	1308 ± 667	844 ± 453	630 ± 590	81 ± 5
5	6 ± 6	1 ± 1	42 ± 13	486 ± 419	335 ± 83	809 ± 345	814 ± 246	316 ± 13
10	10 ± 10	7 ± 7	10 ± 10	11 ± 11	62 ± 1	6 ± 4	87 ± 54	272 ± 222
20	25 ± 14	7 ± 7	10 ± 10	10 ± 10	9 ± 9	5 ± 5	14 ± 14	16 ± 7

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	5412 ± 722	2863 ± 381	3058 ± 1125	2105 ± 973	1548 ± 63	1642 ± 165
5	535 ± 439	2273 ± 660	6502 ± 2302	6830 ± 281	6344 ± 279	5434 ± 564
10	36 ± 36	426 ± 172	1340 ± 417	4227 ± 1066	5588 ± 2684	5605 ± 2043
20	50 ± 11	43 ± 34	339 ± 241	1747 ± 1366	2449 ± 683	3552 ± 1193

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 9

Effects of Pentazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	50.1 ± 7.1	42.1 ± 0.6	24.2 ± 5.9	18.6 ± 9.6	17.4 ± 3.9	14.6 ± 5.4	32.0 ± 16.0	31.2 ± 2.8
20	47.0 ± 2.1	46.7 ± 1.4	46.9 ± 0.0*	49.9 ± 9.3*	51.9 ± 6.0*	50.5 ± 9.9*	43.3 ± 2.2	24.1 ± 5.2
40	55.3 ± 2.7	50.3 ± 3.9	46.8 ± 2.2*	47.3 ± 4.1	48.5 ± 2.9*	46.6 ± 3.3*	47.7 ± 1.0	41.4 ± 1.5
80	49.6 ± 4.2	43.3 ± 7.0	45.3 ± 2.9*	46.0 ± 4.4	42.9 ± 4.7*	40.9 ± 7.3	36.7 ± 8.2	30.3 ± 7.2

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	73.2 ± 5.0	51.8 ± 11.8	54.4 ± 19.0	43.7 ± 15.6	53.1 ± 2.1	41.5 ± 16.7
20	95.6 ± 5.2*	88.2 ± 8.8	52.2 ± 1.7	65.4 ± 0.0	48.5 ± 3.1	89.5 ± 13.0*
40	100.1 ± 6.4*	92.3 ± 3.1*	76.8 ± 1.3	43.6 ± 10.3	35.5 ± 7.5*	46.6 ± 8.2
80	92.7 ± 1.9*	76.1 ± 13.4	64.5 ± 9.6	51.9 ± 7.9	26.6 ± 0.3*	48.1 ± 6.8

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 9a

Effects of Pentazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2558 ± 708	1770 ± 53	619 ± 284	440 ± 359	319 ± 137	242 ± 158	1284 ± 1027	980 ± 177
20	2214 ± 195	2182 ± 129	2200 ± 0	2577 ± 931	2732 ± 622	2646 ± 1001	1881 ± 186	607 ± 250
40	3060 ± 298	2550 ± 397	2196 ± 207	2257 ± 384	2357 ± 282	2180 ± 310	2297 ± 97	1718 ± 126
80	2476 ± 415	1922 ± 608	2057 ± 26	2133 ± 401	1860 ± 402	1727 ± 596	1415 ± 599	970 ± 438

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	5387 ± 729	2824 ± 1226	3321 ± 2070	2155 ± 1366	2831 ± 263	1998 ± 1386
20	9172 ± 996	7865 ± 1560	2723 ± 178	4278 ± 2	2366 ± 305	8178 ± 2322
40	10062 ± 1286	8533 ± 563	5896 ± 192	2004 ± 898	1314 ± 533	2243 ± 763
80	8587 ± 355	5971 ± 2036	4245 ± 1234	2754 ± 821	710 ± 18	2356 ± 655

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 10

Effects of Cyclazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	53.9 ± 9.5	51.3 ± 7.7	36.1 ± 10.0	29.9 ± 7.2	26.2 ± 16.3	11.7 ± 6.5	13.4 ± 6.1	31.7 ± 6.1
2.5	58.4 ± 2.6	59.8 ± 1.0	63.0 ± 4.2*	56.5 ± 3.9*	43.7 ± 9.2	38.9 ± 10.5	43.7 ± 5.2*	33.4 ± 12.6
5	57.7 ± 2.0	60.7 ± 2.2	61.8± 4.2*	60.2 ± 0.3*	46.2 ± 4.3	29.6 ± 5.2	28.6 ± 6.3	24.6 ± 2.5
10	55.4 ± 0.1	58.7 ± 3.8	57.2 ± 1.9	62.6 ± 1.1*	64.2 ± 0.3*	53.5 ± 3.6*	42.4 ± 3.1*	35.5 ± 5.4

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	88.1 ± 16.8	48.7 ± 4.7	36.3 ± 4.7	52.1 ± 11.2	37.5 ± 2.6	45.0 ± 6.4
2.5	119.0 ± 5.8	80.6 ± 18.1	77.1 ± 3.7*	40.0 ± 11.2	54.6 ± 8.8	36.5 ± 11.9
5	120.3 ± 4.3	67.2 ± 2.4	54.8 ± 0.6	43.0 ± 5.6	36.2 ± 18.8	48.7 ± 3.6
10	117.1 ± 3.3	100.3 ± 5.3*	54.9 ± 11.4	37.5 ± 6.0	32.1 ± 11.2	30.1 ± 2.1

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 10a

Effects of Cyclazocine on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2997 ± 1021	2694 ± 794	1402 ± 720	948 ± 430	954 ± 854	180 ± 153	216 ± 163	1042 ± 386
2.5	3416 ± 298	3576 ± 114	3989 ± 524	3203 ± 440	1989 ± 799	1624 ± 830	1936 ± 450	1277 ± 844
5	3333 ± 226	3690 ± 268	3830 ± 513	3626 ± 34	2154 ± 392	901 ± 307	860 ± 362	612 ± 122
10	3073 ± 16	3462 ± 449	3280 ± 211	3915 ± 136	4120 ± 42	2870 ± 385	1806 ± 262	1290 ± 382

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	8041 ± 2965	2392 ± 458	1342 ± 339	2839 ± 1161	1410 ± 195	2063 ± 576
2.5	14183 ± 1376	6825 ± 2914	5960 ± 564	1723 ± 894	3056 ± 958	1470 ± 865
5	14479 ± 1042	4526 ± 325	3005 ± 65	1878 ± 477	1666 ± 1361	2385 ± 349
10	13729 ± 781	10085 ± 1072	3142 ± 1252	1439 ± 449	1157 ± 720	910 ± 128

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 11

Effects of SKF 10,047 on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	42.1 ± 17.0	47.3 ± 10.3	44.6 ± 5.9	46.9 ± 10.8	25.3 ± 14.8	13.8 ± 1.9	28.6 ± 0.7	33.3 ± 11.1
10	56.2 ± 0.9	59.0 ± 0.8	56.8 ± 1.6	54.9 ± 0.2	45.8 ± 4.9	46.7 ± 3.7*	41.7 ± 4.7*	41.8 ± 0.5
20	55.7 ± 0.7	59.8 ± 0.6	62.8 ± 0.9*	58.2 ± 1.8	49.6 ± 8.9	50.5 ± 6.3*	52.0 ± 4.0*	47.3 ± 6.6
40	53.7 ± 0.7	56.6 ± 1.7	58.4 ± 3.0*	58.8 ± 2.7	56.2 ± 3.9	51.1 ± 4.1*	45.3 ± 0.6*	46.8 ± 6.1

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	91.0 ± 21.6	54.1 ± 13.7	55.9 ± 19.3	35.1 ± 4.1	55.8 ± 13.3	50.0 ± 13.9
10	113.5 ± 0.9	88.5 ± 1.9	65.2 ± 1.1	47.9 ± 21.3	70.6 ± 4.1	54.6 ± 9.5
20	118.4 ± 1.1	99.8 ± 12.8*	77.9 ± 15.1	52.7 ± 12.9	38.1 ± 19.1	50.8 ± 1.5
40	113.9 ± 4.1	100.4 ± 1.1*	73.6 ± 12.2	47.5 ± 4.0	44.4 ± 1.8	25.2 ± 3.1

[a]Mean and standard error of the square root of the activity counts of 4 pairs of mice.

*P <0.05; One-way ANOVA, Dunnet's multiple comparison

TABLE 11a

Effects of SKF 10,047 on Locomotor Activity

Mean Activity Counts ± S.E.[a]

1. 15' Intervals over 2 Hours

Dose (mg/kg sc)	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Control	2059 ± 1432	2347 ± 972	2024 ± 525	2314 ± 1008	861 ± 750	194 ± 52	820 ± 41	1235 ± 738
10	3163 ± 97	3482 ± 99	3228 ± 180	3012 ± 17	2125 ± 444	2194 ± 343	1760 ± 390	1761 ± 41
20	3108 ± 78	3578 ± 73	3945 ± 109	3386 ± 209	2538 ± 880	2587 ± 637	2722 ± 419	2279 ± 626
40	2888± 74	3206 ± 188	3423 ± 353	3466 ± 321	3169 ± 433	2632 ± 421	2048 ± 55	2231 ± 571

2. 60' Intervals over 6 Hours

Dose (mg/kg sc)	60'	120'	180'	240'	300'	360'
Control	8743 ± 3938	3108 ± 1478	3495 ± 2160	1248 ± 285	3287 ± 1483	2678 ± 1381
10	12885 ± 199	7828 ± 331	4246 ± 147	2747 ± 2038	5007 ± 576	2981 ± 122
20	14015 ± 251	10125 ± 2563	6304 ± 2358	2941 ± 1356	1817 ± 1453	2579 ± 151
40	12983 ± 936	10080 ± 228	5572 ± 1796	2270 ± 378	1977 ± 157	644 ± 156

[a]Mean and standard error of the activity counts of 4 pairs of mice.

TABLE 12

The Effects of Acute Administration of Opiate Agonists, Antagonists, and Mixed Agonist-Antagonists on Apomorphine-Induced Climbing in Mice[a]

Treatment	Dose (mg/kg)	% Change Compared to Control	Sig.[b]
Vehicle[c]	-	-	-
Morphine	2.0	+7	-
	8.0	-6	-
Naloxone	5.0	+2	-
	20.0	+2	-
Naltrexone	5.0	-6	-
	20.0	-21	-
Ethylketocyclazocine[d]	5.0	-18	-
	20.0	-52	*
Pentazocine	20.0	-4	-
	80.0	-2	-
Cyclazocine	1.25	+7	-
	5.0	+4	-
SKF 10,047[d]	10.0	-9	-
	40.0	-25	*

[a]Drugs administered (n=8) ip 30 min. prior to apomorphine at 1.5 mg/kg sc.

[b]One-way ANOVA, Duncan's multiple-range test; *P <0.05

[c]Range of means over five experiments (5.5-6.0).

[d]General depressive effects including ataxia and flaccidity were observed at each dose.

TABLE 13

Effects of SKF 10,047 and EKC on

Apomorphine-Induced Stereotypy[a]

Treatment	Dose (mg/kg ip)	Stereotypy Score $\bar{x} \pm$ S.E.	% Change from Control	Sig.[b]
Vehicle	-	5.63 ± 0.26	-	-
SKF 10,047	40.0	5.00 ± 0.50	-11	-
EKC[c]	20.0	1.50 ± 0.98	-73	*

[a]Acute pretreatment 30 minutes prior to apomorphine at 1.5 mg/kg sc (n=8)

[b]One-way ANOVA, Duncan's multiple-range test; *P <0.05; significant difference compared to vehicle control.

[c]General depressive effects were observed.

TABLE 14

Effects of Acute Haloperidol Treatment on

Apomorphine (0.4 mg/kg) -Induced Locomotor Activity[a]

Mean Activity Counts ± S.E.[b]

1. 15' Intervals over 2 Hours

Treatment	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Vehicle	53.5 ± 1.1	49.3 ± 2.5	29.9 ± 6.6	25.6 ± 2.4	26.8 ± 5.9	32.8 ± 8.1	26.0 ± 7.3	34.6 ± 4.8
Haloperidol	48.6 ± 2.4	50.3 ± 1.9	38.7 ± 5.7	34.7 ± 4.5	20.2 ± 7.0	20.0 ± 5.8	27.0 ± 10.7	26.4 ± 3.1

2. 60' Intervals over 2 Hours

	60'		120'	
Treatment	$\bar{x}$ ± SE	% Change from Control	$\bar{x}$ ± SE	% Change from Control
Vehicle	83.3 ± 5.0	-	63.8 ± 6.4	-
Haloperidol	87.6 ± 6.0	+5	52.8 ± 5.0	-17

[a]Haloperidol administered at 1.25 mg/kg ip followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc.

[b]Mean and standard error of the square root of the activity counts of 8 pairs of mice.

*P <0.05; "t" test

TABLE 14a

Effects of Acute Haloperidol Treatment on

Apomorphine (0.4 mg/kg) -Induced Locomotor Activity[a]

Mean Activity Counts ± S.E.[b]

1. 15' Intervals over 2 Hours

Treatment	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Vehicle	2861 ± 115	2447 ± 232	1024 ± 458	675 ± 122	823 ± 352	1273 ± 467	835 ± 373	1266 ± 351
Haloperidol	2377 ± 236	2539 ± 185	1595 ± 471	1264 ± 351	558 ± 351	504 ± 234	1072 ± 582	726 ± 174

2. 60' Intervals over 2 Hours

	60'		120'	
Treatment	$\bar{x}$ ± SE	% Change from Control	$\bar{x}$ ± SE	% Change from Control
Vehicle	7007 ± 849	-	4196 ± 732	-
Haloperidol	7774 ± 1063	+11	2860 ± 511	-32

[a] Haloperidol administered at 1.25 mg/kg ip/day for five days followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc.

[b] Mean and standard error of the activity counts of 8 pairs of mice.

TABLE 15

Apomorphine-Induced Stereotyped Behavior

Effects of Haloperidol (1.25 mg/kg) 72 Hours Pretreatment

Apomorphine Dose (mg/kg sc)	Treatment	n	Stereotypy Score $\bar{x} \pm SE$	% Stereotypy[a]	% Change Compared to Control	Sig.[b]
0.4	Vehicle	8	2.63 ± 0.38	44	-	-
	Haloperidol	8	2.88 ± 0.55	48	+10	-
0.8	Vehicle	8	3.38 ± 0.38	56	-	-
	Haloperidol	8	4.13 ± 0.30	69	+22	-

[a] % of stereotypy based on maximum score = 6.

$$\% \text{ stereotypy} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

[b] "t" test

TABLE 16

Haloperidol-Induced Supersensitivity

in the Climbing Mice Assay[a]

Treatment	Dose (mg/kg ip)	n	Climbing Score $\bar{x} \pm SE$	% Change	Sig.[b]
Vehicle	-	24	2.1 ± 0.3	-	-
Haloperidol	1.25	24	4.8 ± 0.3	+129	*

[a]Acute injection of haloperidol 72 hours prior to apomorphine at 0.4 mg/kg sc.

[b]"t" test, *P <0.001

TABLE 17

Climbing Mice Supersensitivity[a]

Simultaneous Administration of Vehicle and Opiate Agonists, Antagonists and Mixed Agonist-Antagonists

Treatment	Dose (mg/kg)	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle[c]	-	-	-
Vehicle-Morphine	2	+79	-
	8	-20	-
Vehicle-Naloxone	5	+27	-
	20	-32	-
Vehicle-Naltrexone	5	-20	-
	20	-4	-
Vehicle-EKC	5	+13	-
	20	+5	-
Vehicle-Pentazocine	20	+86	-
	80	0	-
Vehicle-Cyclazocine	1.25	-7	-
	5	0	-
Vehicle-SKF 10,047	10	-13	-
	40	-53	-

[a] Acute simultaneous administration, 72-hr. pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test.

[c] Range of means over four experiments (1.8-2.8).

TABLE 18

Climbing Mice Supersensitivity[a]

Simultaneous Administration of Haloperidol and Opiate Agonists, Antagonists and Mixed Agonist-Antagonists

Treatment	Dose (mg/kg)	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle[c]	1.25	-	-
Haloperidol-Morphine	2	+11	-
	8	-29	-
Haloperidol-Naloxone	5	-9	-
	20	-44	*
Haloperidol-Naltrexone	5	-50	-
	20	-51	*
Haloperidol-EKC	5	-3	-
	20	-56	*
Haloperidol-Pentazocine	20	+11	-
	80	-42	*
Haloperidol-Cyclazocine	1.25	-53	*
	5	-64	*
Haloperidol-SKF 10,047	10	-54	*
	40	-75	*

[a] Acute simultaneous administration, 72-hr. pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

[c] Range of means over four experiments (4.3-5.6)

TABLE 19

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and Naloxone[a]

Vehicle and Naloxone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.00 ± 0.42	-	-
Vehicle-Naloxone	5.0	2.13 ± 0.40	+7	-
	10.0	2.00 ± 0.71	0	-
	20.0	2.88 ± 0.64	+44	-
	40.0	1.38 ± 0.73	-31	-

Haloperidol and Naloxone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	4.00 ± 0.76	-	-
Haloperidol-Naloxone	5.0	2.50 ± 0.54	-37	-
	10.0	2.29 ± 0.78	-43	-
	20.0	1.63 ± 0.26	-59	*
	40.0	1.50 ± 0.42	-62	*

[a] Acute simultaneous administration, haloperidol ip - naloxone sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 20

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and Naltrexone[a]

Vehicle and Naltrexone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.38 ± 0.53	-	-
Vehicle-Naltrexone	2.5	1.75 ± 0.41	-26	-
	5.0	2.13 ± 0.40	-11	-
	10.0	1.75 ± 0.37	-26	-
	20.0	1.38 ± 0.50	-40	-

Haloperidol and Naltrexone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	4.00 ± 0.46	-	-
Haloperidol-Naltrexone	2.5	2.63 ± 0.53	-34	-
	5.0	2.63 ± 0.71	-34	-
	10.0	2.13 ± 0.42	-47	*
	20.0	1.63 ± 0.42	-59	*

[a] Acute simultaneous administration, haloperidol ip - naltrexone sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 21

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and EKC[a]

Vehicle and EKC

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	1.25 ± 0.49	-	-
Vehicle-EKC	2.5	1.38 ± 0.53	+10	-
	5.0	1.25 ± 0.45	0	-
	10.0	1.38 ± 0.53	+10	-
	20.0	1.75 ± 0.56	+50	-

Haloperidol and EKC

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	2.88 ± 0.52	-	-
Haloperidol-EKC	2.5	2.38 ± 0.38	-17	-
	5.0	1.88 ± 0.81	-35	*
	10.0	2.25 ± 0.68	-22	-
	20.0	1.25 ± 0.86	-57	*

[a] Acute simultaneous administration, haloperidol ip - EKC sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 22

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and Pentazocine[a]

Vehicle and Pentazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	1.63 ± 0.65	-	-
Vehicle-Pentazocine	10.0	1.63 ± 0.53	0	-
	20.0	2.13 ± 0.58	+31	-
	40.0	1.88 ± 0.58	+15	-
	80.0	1.88 ± 0.77	+15	-

Haloperidol and Pentazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	3.50 ± 0.80	-	-
Haloperidol-Pentazocine	10.0	4.50 ± 0.50	+29	-
	20.0	2.50 ± 0.89	-29	-
	40.0	2.25 ± 0.80	-56	*
	80.0	2.00 ± 0.57	-63	*

[a] Acute simultaneous administration, haloperidol ip - pentazocine sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 23

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and Cyclazocine[a]

Vehicle and Cyclazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	1.88 ± 0.74	-	-
Vehicle-Cyclazocine	0.625	2.25 ± 0.49	+20	-
	1.25	2.00 ± 0.50	+6	-
	2.5	1.88 ± 0.58	0	-
	5.0	2.00 ± 0.68	+6	-

Haloperidol and Cyclazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	3.88 ± 0.35	-	-
Haloperidol-Cyclazocine	0.625	4.00 +1.07	+3	-
	1.25	2.63 ± 0.60	-32	-
	2.5	2.00 ± 0.85	-48	*
	5.0	1.75 ± 0.59	-55	*

[a] Acute simultaneous administration, haloperidol ip - cyclazocine sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 24

Climbing Mice Supersensitivity

Simultaneous Administration of Haloperidol and SKF 10,047[a]

Vehicle and SKF 10,047

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	1.88 ± 0.48	-	-
Vehicle-SKF 10,047	5.0	2.00 ± 0.60	+6	-
	10.0	1.38 ± 0.38	-27	-
	20.0	1.63 ± 0.63	-13	-
	40.0	1.75 ± 1.00	-7	-

Haloperidol and SKF 10,047

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	3.50 ± 0.57	-	-
Haloperidol-SKF 10,047	5.0	2.13 ± 0.91	-39	-
	10.0	1.63 ± 0.57	-53	*
	20.0	1.75 ± 0.41	-50	-
	40.0	0.88 ± 0.48	-75	*

[a] Acute simultaneous administration, haloperidol ip - SKF 10,047 sc, 72-hr pretreat, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test, *P <0.05

TABLE 25

Effects of Chronic Haloperidol Treatment on

Apomorphine (0.4 mg/kg) -Induced Locomotor Activity[a]

Mean Activity Counts ± S.E.[b]

1. 15' Intervals over 2 Hours

Treatment	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Vehicle	53.3 ± 1.9	44.9 ± 2.3	28.6 ± 4.9	26.3 ± 2.5	35.7 ± 5.7	23.4 ± 7.7	31.6 ± 12.2	49.8 ± 4.5
Haloperidol	51.4 ± 1.8	52.7 ± 0.7*	41.4 ± 2.5	37.4 ± 5.2	44.1 ± 1.7	46.4 ± 2.7*	35.2 ± 7.9	24.9 ± 4.8*

2. 60' Intervals over 2 Hours

	60'		120'	
Treatment	$\bar{x}$ ± SE	% Change from Control	$\bar{x}$ ± SE	% Change from Control
Vehicle	80.3 ± 3.1	-	76.5 ± 8.7	-
Haloperidol	92.7 ± 4.2	+15	78.2 ± 6.6	+2

[a]Haloperidol administered at 1.25 mg/kg ip per day for five days followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc.

[b]Mean and standard error of the square root of the activity counts of 8 pairs of mice.

*$p < 0.05$, "t" test

TABLE 25a

Effects of Chronic Haloperidol Treatment on

Apomorphine (0.4 mg/kg) -Induced Locomotor Activity[a]

Mean Activity Counts ± S.E.[b]

1. 15' Intervals over 2 Hours

Treatment	0-15'	15'-30'	30'-45'	45'-60'	60'-75'	75'-90'	90'-105'	105'-120'
Vehicle	2852 ± 203	2036 ± 197	887 ± 321	708 ± 129	1372 ± 357	723 ± 426	1439 ± 752	2536 ± 416
Haloperidol	2654 ± 183	2782 ± 74	1729 ± 210	1479 ± 391	1955 ± 145	2175 ± 145	1428 ± 522	690 ± 281

2. 60' Intervals over 2 Hours

	60'		120'	
Treatment	$\bar{x}$ ± SE	% Change from Control	$\bar{x}$ ± SE	% Change from Control
Vehicle	6483 ± 485	-	6070 ± 1405	-
Haloperidol	8644 ± 786	+33	6248 ± 1060	+3

[a] Haloperidol administered at 1.25 mg/kg ip per day for five days followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc.

[b] Mean and standard error of the activity counts of 8 pairs of mice.

TABLE 26

Apomorphine-Induced Stereotyped Behavior

Effects of 5-Day Administration of

Morphine (10 mg/kg sc) and Haloperidol (1.25 mg/kg ip)[a]

Treatment	Stereotypy Score $\bar{x} \pm SE$	% Change from Control	Sig.[b]
Vehicle-Vehicle	2.25 ± 0.37	-	-
Vehicle-Haloperidol	5.50 ± 0.27	+144	*
Morphine-Vehicle	4.88 ± 0.44	+117	*
Morphine-Haloperidol	5.63 ± 0.26	+150	*

[a] Five days simultaneous administration, haloperidol ip - morphine sc followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 27

Apomorphine-Induced Stereotyped Behavior

Effects of 5-Day Administration of

Naltrexone (40 mg/kg sc) and Haloperidol (1.25 mg/kg ip)[a]

Treatment	Stereotypy Score $\bar{x} \pm SE$	% Change from Control	Sig.[b]
Vehicle-Vehicle	2.13 ± 0.44	-	-
Vehicle-Haloperidol	5.13 ± 0.40	+140	*
Naltrexone-Vehicle	2.63 ± 0.53	+23	-
Naltrexone-Haloperidol	5.25 ± 0.31	+146	*

[a] Five days simultaneous administration, haloperidol ip - naltrexone sc followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 28

Apomorphine-Induced Stereotyped Behavior

Effects of 5-Day Administration of
EKC (20 mg/kg sc) and Haloperidol (1.25 mg/kg ip)[a]

Treatment	Stereotypy Score $\bar{x} \pm SE$	% Change from Control	Sig.[b]
Vehicle-Vehicle	2.75 ± 0.53	-	-
Vehicle-Haloperidol	5.25 ± 0.37	+91	*
EKC-Vehicle	2.88 ± 0.13	+5	-
EKC-Haloperidol	5.13 ± 0.40	+87	*

[a] Five days simultaneous administration, haloperidol ip - EKC sc followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 29

Apomorphine-Induced Stereotyped Behavior

Effects of 5-Day Administration of
Cyclazocine (2.5 mg/kg sc) and Haloperidol (1.25 mg/kg ip)[a]

Treatment	Stereotypy Score $\bar{x} \pm SE$	% Change from Control	Sig.[b]
Vehicle-Vehicle	2.38 ± 0.26	-	-
Vehicle-Haloperidol	5.63 ± 0.18	+137	*
Cyclazocine-Vehicle	2.63 ± 0.38	+11	-
Cyclazocine-Haloperidol	3.75 ± 0.31	+58	*[c]

[a] Five days simultaneous administration, haloperidol ip - cyclazocine sc followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *$P < 0.05$

[c] Significantly different from vehicle-haloperidol group and vehicle-vehicle group.

TABLE 30

Apomorphine-Induced Stereotyped Behavior

Effects of 5-Day Administration of

SKF 10,047 (40 mg/kg sc) and Haloperidol (1.25 mg/kg ip)[a]

Treatment	Stereotypy Score $\bar{x} \pm SE$	% Change from Control	Sig.[b]
Vehicle-Vehicle	1.88 ± 0.35	-	-
Vehicle-Haloperidol	4.88 ± 0.48	+160	*
SKF 10,047-Vehicle	1.13 ± 0.40	-40	-
SKF 10,047-Haloperidol	1.88 ± 0.55	0	-

[a] Five days simultaneous administration, haloperidol ip - SKF 10,047 sc followed by a 72-hr. drug-free period, then apomorphine at 0.4 mg/kg sc (n=8 per group).

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 31

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of

Morphine and Haloperidol[a]

Vehicle and Morphine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.13 ± 0.52	-	-
Vehicle-Morphine	2.5	3.75 ± 0.88	+76	-
	5.0	3.63 ± 0.50	+70	-
	10.0	3.25 ± 0.37	+53	-

Haloperidol and Morphine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	5.38 ± 0.80	-	-
Haloperidol-Morphine	2.5	5.50 ± 0.38	+2	-
	5.0	5.38 ± 0.50	0	-
	10.0	5.25 ± 0.49	-4	-

[a] Five days simultaneous administration, haloperidol ip - morphine sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test

TABLE 32

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
Naloxone and Haloperidol[a]

Vehicle and Naloxone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.63 ± 0.60	-	-
Vehicle-Naloxone	5.0	2.50 ± 0.42	-5	-
	10.0	2.75 ± 0.80	+5	-
	20.0	2.88 ± 0.69	+10	-
	40.0	2.25 ± 0.67	+14	-

Haloperidol and Naloxone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	6.13 ± 0.35	-	-
Haloperidol-Naloxone	5.0	5.50 ± 0.57	-10	-
	10.0	5.88 ± 0.40	-4	-
	20.0	6.13 ± 0.48	0	-
	40.0	5.13 ± 0.52	-16	-

[a] Five days simultaneous administration, haloperidol ip - naloxone sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test

TABLE 33

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
Naltrexone and Haloperidol[a]

Vehicle and Naltrexone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	1.50 ± 0.38	-	-
Vehicle-Naltrexone	2.5	1.63 ± 0.32	+9	-
	5.0	1.38 ± 0.53	-8	-
	10.0	2.13 ± 0.58	+42	-
	20.0	1.63 ± 0.91	+9	-
	40.0	2.00 ± 0.76	+33	-

Haloperidol and Naltrexone

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	4.63 ± 0.75	-	-
Haloperidol-Naltrexone	2.5	4.13 ± 0.48	-11	-
	5.0	3.38 ± 0.60	-27	-
	10.0	2.50 ± 0.63	-46	-
	20.0	3.00 ± 0.78	-35	-
	40.0	3.50 ± 0.57	-24	-

[a] Five days simultaneous administration, haloperidol ip - naltrexone sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test

TABLE 34

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
EKC and Haloperidol[a]

Vehicle and EKC

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.00 ± 0.76	-	-
Vehicle-EKC	2.5	1.13 ± 0.40	-43	-
	5.0	1.88 ± 0.74	-6	-
	10.0	4.00 ± 0.82	+100	-
	20.0	2.13 ± 0.58	+7	-

Haloperidol and EKC

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	4.38 ± 0.57	-	-
Haloperidol-EKC	2.5	4.50 ± 0.60	+3	-
	5.0	2.63 ± 0.94	-40	-
	10.0	2.25 ± 0.45	-49	-
	20.0	2.50 ± 0.71	-43	-

[a] Five days simultaneous administration, haloperidol ip - EKC sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test

TABLE 35

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
Pentazocine and Haloperidol[a]

Vehicle and Pentazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.13 ± 0.40	-	-
Vehicle-Pentazocine	10.0	2.13 ± 0.79	0	-
	20.0	1.25 ± 0.37	-41	-
	40.0	1.87 ± 0.64	-12	-
	80.0	1.75 ± 0.45	-18	-

Haloperidol and Pentazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	5.25 ± 0.62	-	-
Haloperidol-Pentazocine	10.0	5.62 ± 0.50	+7	-
	20.0	6.00 ± 0.38	+14	-
	40.0	5.50 ± 0.65	+5	-
	80.0	4.75 ± 0.70	-10	-

[a] Five days simultaneous administration, haloperidol ip - pentazocine sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test

TABLE 36

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
Cyclazocine and Haloperidol[a]

Vehicle and Cyclazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	3.12 ± 0.67	-	-
Vehicle-Cyclazocine	0.38	3.12 ± 0.64	0	-
	0.75	3.12 ± 0.69	0	-
	1.5	3.38 ± 0.73	+8	-
	3.0	2.63 ± 0.53	-16	-

Haloperidol and Cyclazocine

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	5.88 ± 0.48	-	-
Haloperidol-Cyclazocine	0.38	3.63 ± 0.37	-38	-
	0.75	3.38 ± 0.80	-43	-
	1.5	3.00 ± 0.71	-49	*
	3.0	3.12 ± 1.09	-47	*

[a] Five days simultaneous administration, haloperidol ip - cyclazocine sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 37

Climbing Mice Supersensitivity

Chronic Simultaneous Administration of
SKF 10,047 and Haloperidol[a]

Vehicle and SKF 10,047

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Vehicle-Vehicle	-	2.38 ± 0.60	-	-
Vehicle-SKF 10,047	5.0	2.50 ± 0.38	+5	-
	10.0	1.75 ± 0.62	-26	-
	20.0	2.75 ± 0.67	+16	-
	40.0	2.14 ± 0.80	-10	-

Haloperidol and SKF 10,047

Treatment	Dose (mg/kg)	Climbing Score $\bar{x} \pm SE$	% Change Compared to Control	Sig.[b]
Haloperidol-Vehicle	1.25	5.25 ± 0.70	-	-
Haloperidol-SKF 10,047	5.0	3.50 ± 0.57	-33	-
	10.0	3.12 ± 0.69	-40	-
	20.0	2.38 ± 0.91	-55	*
	40.0	1.25 ± 0.37	-76	*

[a] Five days simultaneous administration, haloperidol ip - SKF 10,047 sc, followed by a 72-hour drug-free period, then apomorphine at 0.4 mg/kg sc, n=8 per group.

[b] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 38

The Effects of Naloxone on

Apomorphine-Induced Climbing Behavior

Treatment[a]	Dose (mg/kg ip)	n	Climbing Score $\bar{x} \pm SE$	% of Total Climbing[b]	% Change Potentiation of Climbing[c]
Vehicle + Naloxone	0	8	0.00 ± 0.00	0	-
	1	8	0.00 ± 0.00	0	-
	3	8	0.00 ± 0.00	0	-
	10	8	0.13 ± 0.13	2	-
Apomorphine + Naloxone	0	8	1.50 ± 0.42	25	-
	1	8	1.75 ± 0.37	29	+17
	3	8	2.75 ± 0.41	46	+83
	10	8	2.75 ± 0.25	46	+75

[a] Apomorphine (0.4 mg/kg sc) and naloxone administered simultaneously 0' prior to testing.

[b] % Climbing based on maximum score = 6

$$\% \text{ Climbing} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

[c] $$\% \text{ Change Potentiation of Climbing} = \frac{(\text{Apo.} + \text{Nal.}) - (\text{Veh.} + \text{Nal.})}{(\text{Apo.} + \text{Veh.})} \times 100$$

TABLE 39

The Effects of Ethylketocyclazocine on

Apomorphine-Induced Climbing Behavior

Treatment[a]	Dose (mg/kg ip)	n	Climbing Score $\bar{x} \pm SE$	% of Total Climbing[b]	% Change Potentiation of Climbing[c]
Vehicle + EKC	0	8	0.00 ± 0.00	0	-
	1	8	0.00 ± 0.00	0	-
	3	8	2.38 ± 0.92	40[d]	-
	10	8	1.63 ± 0.73	27[d]	-
Apomorphine + EKC	0	8	1.63 ± 0.63	27	-
	1	8	2.50 ± 0.68	42	+17
	3	8	2.38 ± 0.26	40	0
	10	8	2.00 ± 0.50	33	+23

[a] EKC administered 180' prior to testing; Apomorphine (0.4 mg/kg sc) administered 0' prior to testing.

[b] % Climbing based on maximum score = 6

$$\% \text{ Climbing} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

[c] $$\% \text{ Change Potentiation of Climbing} = \frac{(\text{Apo.} + \text{EKC}) - (\text{Veh.} + \text{EKC})}{(\text{Apo.} + \text{Veh.})} \times 100$$

[d] Hyperactivity rather than characteristic prolonged climbing seen after apomorphine.

TABLE 40

The Effects of SKF 10,047 on

Apomorphine-Induced Climbing Behavior

Treatment[a]	Dose (mg/kg ip)	n	Climbing Score $\bar{x} \pm SE$	% of Total Climbing[b]	% Change Potentiation of Climbing[c]
Vehicle + SKF 10,047	0	8	0.13 ± 0.13	2	-
	1	8	0.25 ± 0.25	4	-
	3	8	0.50 ± 0.27	8	-
	10	8	2.00 ± 0.76	33[d]	-
Apomorphine + SKF 10,047	0	8	1.50 ± 0.42	25	-
	1	8	2.25 ± 0.45	38	+33
	3	8	2.50 ± 0.38	42	+33
	10	8	3.00 ± 0.19	50	+67

[a] SKF 10,047 administered 90' prior to testing; Apomorphine (0.4 mg/kg sc) administered 0' prior to testing.

[b] % Climbing based on maximum score = 6

$$\% \text{ Climbing} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

[c] $$\% \text{ Change Potentiation of Climbing} = \frac{(\text{Apo. + SKF 10,047}) - (\text{Veh. + SKF 10,047})}{(\text{Apo. + Veh.})} \times 100$$

[d] Prolonged climbing similar to apomorphine-induced climbing.

TABLE 41

Induction of Hyperactivity in Mice

by Ethylketocyclazocine at 5 mg/kg sc

Pretreat (min.)	Hyperactivity Score[a] $\bar{x} \pm SE$	% of Hyperactivity[b]
30	0.00 ± 0.00	0
60	0.00 ± 0.00	0
90	0.00 ± 0.00	0
120	0.38 ± 0.26	10
150	1.13 ± 0.64	28
180	1.88 ± 0.58	47
210	1.88 ± 0.48	47
240	0.75 ± 0.53	19
270	1.00 ± 0.65	25
300	0.88 ± 0.40	22
330	0.75 ± 0.53	19
360	0.38 ± 0.38	10

[a] Hyperactivity measured in stick cages; n=8.

[b] % of hyperactivity based on maximum score = 4

$$\% \text{ hyperactivity} = \frac{\bar{x} \text{ of Pretreat Group}}{\text{Max. score}} \times 100$$

TABLE 42

Ethylketocyclazocine-Induced Hyperactivity in Mice

Dose[a] (mg/kg sc)	Hyperactivity Score[b] $\bar{x} \pm SE$	% of Hyperactivity[c]	ED_{50} 95% Confidence Limits
0	0.25 ± 0.16	-	
1.25	1.88 ± 0.93	28	
2.5	1.00 ± 0.50	13	7.1 (6.0-8.7) mg/kg sc
5.0	2.50 ± 0.75	44	
10.0	3.25 ± 0.85	57	

[a] 180' pretreat; n=8.

[b] Hyperactivity measured in stick cages.

[c] % of hyperactivity based on maximum score = 6.

$$\% \text{ hyperactivity} = \frac{(\bar{x} \text{ of Dose Group}) - (\bar{x} \text{ of Vehicle Group})}{(\text{Max. score}) - (\bar{x} \text{ of Vehicle Group})} \times 100$$

TABLE 43

Ethylketocyclazocine-Induced Hyperactivity in Mice[a]

Effects of Various Blocking Agents

Compound	Dose (mg/kg ip)	Pretreat	% Change Compared to Control[b]	Sig.[c]
Naloxone	10.0	10'	-8	-
	100.0	10'	-17	-
Haloperidol	1.0	180'	-54	*
Apomorphine	0.1	5'	-65	*
Muscimol	1.0	30'	-63	*
Bicuclline	1.0	30'	0	-
α-MPT	300.0	4 hrs.	-81	*
Phentolamine	10.0	60'	-47	*
Prazosin	2.5	30'	-97	*
Yohimbine	5.0	30'	0	-
Clonidine	0.025	30'	-35	-
Propranolol	2.5	30'	+20	-
PCPA	300.0	72 hrs.	-46	-
Methysergide	10.0	30'	+7	-
Atropine	5.0	30'	-5	-
Reserpine	5.0	17 hrs.	-74	*
TBZ	5.0	60'	-81	*
	40.0	60'	-90	*

[a] EKC at 5 mg/kg sc; 180' pretreat; Hyperactivity measured in stick cages.

[b] Control = EKC + vehicle; range of control means for 4 separate experiments--3.0-3.9; maximum score = 6; n=8.
% Change from corresponding control score.

[c] One-way ANOVA, Duncan's multiple-range test; *P <0.05

TABLE 44

Induction of Climbing Behavior in Mice

by SKF 10,047 at 40 mg/kg sc

Pretreat (min.)	Climbing Score[a] $\bar{x} \pm SE$	% of Climbing[b]
30	1.38 ± 0.42	35
60	2.75 ± 0.31	69
90	2.88 ± 0.48	72
120	2.50 ± 0.57	63
150	2.38 ± 0.46	60
180	1.75 ± 0.53	44

[a] n=8

[b] % of climbing based on maximum score = 4.

$$\% \text{ climbing} = \frac{\bar{x} \text{ of Pretreat Group}}{\text{Max. score}} \times 100$$

TABLE 45

SKF 10,047 -Induced Climbing in Mice

Dose[a] (mg/kg sc)	Climbing Score $\bar{x} \pm SE$	% of Climbing[b]	ED_{50} 95% Confidence Limits
0	0.00 ± 0.00	-	
3	0.50 ± 0.38	+8	
10	1.88 ± 0.58	+31	14.6 (12.8-16.8) mg/kg sc
30	4.50 ± 0.71	+75	

[a] 90' pretreat; n=8.

[b] % of climbing based on maximum score = 6.

$$\% \text{ climbing} = \frac{\bar{x} \text{ of Dose Group}}{\text{Max. score}} \times 100$$

TABLE 46

SKF 10,047-Induced Cage Climbing in Mice[a]

Effects of Various Blocking Agents

Compound	Dose (mg/kg ip)	Pretreat	% Change Compared to Control[b]	Sig.[c]
Naloxone	10.0	10'	-8	-
	100.0	10'	-12	-
Haloperidol	1.0	180'	-73	*
Apomorphine	0.1	5'	-64	*
Muscimol	1.0	30'	-89	*
Bicuclline	1.0	30'	-9	-
α-MPT	300.0	4 hrs.	-97	*
Phentolamine	10.0	60'	-37	*
Prazosin	2.5	30'	-90	*
Yohimbine	5.0	30'	-12	-
Clonidine	0.025	30'	-8	-
Propranolol	2.5	30'	+9	-
PCPA	300.0	72 hrs.	+25	-
Methysergide	10.0	30'	-66	*
Atropine	5.0	30'	+48	-
Reserpine	5.0	17 hrs.	-11	-
TBZ	5.0	60'	-75	*
	40.0	60'	-97	*

[a] SKF 10,047 at 40 mg/kg sc; 90' pretreat.

[b] Control = SKF 10,047 + vehicle; range of control means for 4 separate experiments--3.9-5.0; maximum score = 6; n=8.
% Change from corresponding control score.

[c] One-way ANOVA, Duncan's multiple-range test; *P <0.05

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