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Phencyclidine-induced potentiation of brain stimulation reward: acute effects are not altered by repeated administration

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ABSTRACT

Phencyclidine-induced potentiation of brain stimulation reward: acute effects are not altered by repeated administration

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The effects of phencyclidine (PCP; 2.5 or 5.0 mg/kg) on brain stimulation reward (BSR) were evaluated in rats implanted with lateral hypothalamic stimulating electrodes using the curve-shift paradigm. Acute systemic administration of either dose of PCP caused a parallel leftward shift in the function that related stimulation frequency to response rate, lowering self-stimulation thresholds: thus, like most other drugs of abuse, PCP lowered the "dose" of stimulation required to maintain normal levels of responding, presumably by potentiating the rewarding impact of the stimulation. The threshold-lowering effects of 2.5 mg/kg were similar to those of 5.0 mg/kg, although a slight transient decrease in response asymptotes was observed at the 5.0 mg/kg dose. No progressive changes in the reward-potentiating effects of PCP were evident when rats were repeatedly tested under the influence of the drug once per week for eight weeks. After the eight weeks of brain stimulation testing was completed, the rats were tested in activity chambers following administration of 5.0 mg/kg of PCP once every third day; the rats appeared to be maximally sensitized to the locomotor-stimulating properties of the drug during the first session. Thus, the failure to observe progressive changes in the threshold-lowering effects of PCP might be due to maximal sensitization of the reward system during brain stimulation testing, prior to the first administration of the drug.

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Phencyclidine, commonly known as PCP, is a synthetic drug that has been of interest to pharmacologists for more than three decades. Although it is an often abused and dangerous drug that is sold on the street as "angel dust", recent work has established that PCP is a valuable pharmacological tool that has a place in scientific research. For example, the observation that PCP-induced psychosis and schizophrenia share similar clinical features has provided a useful model for the study of the neurological dysfunction underlying the disease (Snyder, 1980). Furthermore, while pursuing the mechanisms by which PCP exerts its wide variety of behavioral effects, scientists discovered an important interaction between the drug and a novel membrane protein, the N-methyl-D-aspartate (NMDA) receptor (Anis et al., 1983). Binding studies with PCP and related ligands have helped to identify the anatomical distribution of the NMDA receptor (Vincent et al., 1979; Zukin and Zukin, 1979), a protein that is now thought to play an essential role in learning and memory phenomena such as long-term potentiation and synaptic plasticity (Harris et al., 1984). More recently, the advent of potentially lifesaving drugs (such as MK-801) that can protect against cerebral damage in victims of stroke or ischemia, but share at least one neuronal mechanism of action with PCP (Piercey et al., 1988; Martin et al., 1976), has renewed interest in legitimate utilization of phencyclidine-related ligands. In light of regulations which govern the approval of new drugs, further characterization of the neurobiological effects and abuse liability of phencyclidine is warranted before similar chemicals are introduced for wide-spread medical use.

I. History of phencyclidine

First synthesized in 1957 by chemists at Parke, Davis & Company, 1-(1-phenylcyclohexyl) piperadine was soon introduced to the medical community as the experimental drug phencyclidine (Chen et al., 1959; Domino, 1978; Sioris and Krenzelok,

1978). On the basis of preclinical evaluation, phencyclidine was originally believed to be an anesthetic that possessed analgesic properties, while being devoid of depressant actions on respiration or the heart. Consequently, the drug was marketed for human applications as Sernyl. However, physicians reported that Sernyl elicited a dissociative state of anesthesia, in which patients remained semi-conscious, but were unable to move or experience pain. Furthermore, patients were often agitated, hostile and delirious upon emerging from anesthesia. At times, these side effects resembled the characteristics of acute schizophrenia, leading scientists to classify the drug as a psychotomimetic. Phencyclidine was consequently withdrawn from human use in 1965, and its utilization was restricted to non-humans.

Phencyclidine has become a public health concern in countries such as the United States, where it is classified as a Schedule II drug under the 1970 Controlled Substance Act (Crider, 1986). Presently, PCP has no legitimate applications in humans and possesses significant abuse potential, making any use of the drug in humans tantamount to abuse. Phencyclidine is easily synthesized, and is less expensive than other illegally used drugs such as heroin and cocaine (Wish, 1986). It is used by a relatively small but stable number of people: experience with the drug was increasing in young adults (over age 20) living in metropolitan areas during the late 1970's to the early 1980's, while the percentage of high school seniors in the United States who had tried PCP reached a low of 1% over the same period of time (Crider, 1986). Phencyclidine can be self-administered in a number of ways by humans, although it is most commonly added to tobacco or marijuana and smoked. Alternatively, it can be snorted, ingested in tablet form or mixed with beverages, or injected intravenously (McCarron, 1986). The typical "high" from a single dose of PCP lasts from 4 to 6 hours, while the dysphoric effects can linger for days (Sioris and Krenzelok, 1978). The hallmark of this drug, however, seems to be its unpredictability and wide spectrum of effects on the user.

A. Central effects of phencyclidine

Phencyclidine has been characterized as a sympathomimetic anesthetic, because it possesses both central nervous system (CNS)-stimulant and CNS-depressant properties (Chen et al., 1959; Domino, 1978). While some of the CNS effects of PCP have been compared to those of the stimulant amphetamine, others have been compared to those of the barbiturate pentobarbital (Balster, 1986). There are many indications, however, that the sympathomimetic effects are more evident in rodents, while the depressant effects are predominant in primates (Chen et al., 1959; Domino, 1978; Balster and Chait, 1978b).

In humans, low doses of PCP (5-10 mg) produce various neurological effects, such as ataxia, nystagmus (rapid involuntary oscillation of the eyeballs), and slurred speech. The psychological effects elicited by PCP within this dose range vary from euphoria to agitation, and are often combined with a dissociative state associated with distortions in body image, numbness, and feelings of warmth. At medium doses (10-20 mg), the symptoms of intoxication are more pronounced: the user is often stuporous, manifesting psychological effects such as confusion, disorientation, agitation, and frank psychotic symptoms including hallucinations, paranoia, and delusions (Sioris and Krenzelok, 1978; McCarron, 1986). It is the symptoms within this dose range that contribute to the propensity of PCP to be associated with personal injury and violent crime (Wish, 1986; Lerner and Burns, 1986). Higher doses (greater than 20 mg) produce catatonic muscular rigidity, drowsiness, hypersalivation, an increase in heart rate and blood pressure, analgesia, amnesia and anesthesia or coma (Sioris and Krenzelok, 1978; McCarron, 1986). Massive doses of the drug (greater than 100 mg) can cause convulsions or coma (Sioris and Krenzelok, 1978). A particularly interesting characteristic of PCP is that not only can it exacerbate symptoms in chronic schizophrenics, but it can also initiate the expression of latent schizophrenia (Luisada and Brown, 1976; Allen and Young, 1978). In humans, phencyclidine-induced psychosis is virtually indistinguishable from schizophrenia because it produces both the positive (hallucinations, delusions) and negative

(lack of affect, decreased social interaction) symptomatology that is characteristic of the disease; on the other hand, amphetamine-induced psychosis produces only positive symptoms (Javitt, 1987; Steinpreis et al., 1991).

B. Rationale for the illegal use of phencyclidine by humans

While the effects of PCP have been described as too frightening and unpredictable by some users (Fram and Stone, 1986), others self-administer it for a variety of reasons (Siegel, 1978; Gorelick et al., 1986). Initially, PCP use is maintained because it is euphorigenic, and elicits feelings of strength, power, and invulnerability. It is also thought that the drug is sought because it causes a psychic numbing that allows the user to temporarily escape from troubling life-issues. Some individuals appear to enjoy the unpredictability of the drug, and the hallucinations that may accompany the euphoric state. The ability of PCP to elicit bizarre behavior and a feeling of lack of control might allow some users to express violent behavior that is inhibited in a non-intoxicated state (Fram and Stone, 1986); consistent with this suggestion, PCP has been shown to possess anxiolytic properties in lower animals (Chait et al., 1981).

Despite the serious health and social consequences of chronic intake, long-time users experience great difficulties in discontinuing PCP use and are reported to "crave" the drug when it is unavailable (Gorelick et al., 1986). Distress has also been observed in primates by Balster and Woolverton (1980), who found evidence of a robust withdrawal syndrome in monkeys whose PCP had been withdrawn after a month of availability.

C. Conclusions

Thus, the ability of PCP to cause both a euphoric "rush" and various hallucinogenic effects makes it a drug of choice for a small but stable number of individuals. This broad spectrum of effects in the user suggests that PCP has a mechanism of action that is unique when compared to other illicit drugs.

II. Pharmacology of phencyclidine

Since its legal use was restricted to non-humans in the mid-1960's, most of the empirical data that are available on the pharmacology and mechanism of action of phencyclidine have been obtained through the use of laboratory animals (Balster, 1986). This approach has enabled scientists to circumvent a problem prevalent in humans, that of co-administration of PCP and other psychoactive chemicals, either intentionally (marijuana, ethanol) or in association with contaminants in illicitly purchased drug (Lewis and Hordan, 1986). Despite these efforts, PCP's mechanisms of action in the brain remain obscure. Analogous to the wide variety of behavioral effects that are observed in humans who are intoxicated with the drug, PCP has profound effects upon a number of neurotransmitter systems in the brain. Since each of these effects alone can cause drastic alterations in interactions between systems, the study of phencyclidine is a formidable task. Certain of the pharmacological effects of PCP are shared by a number of drugs that are habitually self-administered by humans, while others appear to be unique and may account for the fundamentally different subjective effects of the drug.

A. *Phencyclidine binds to at least two distinct sites in the brain*

It was originally believed that PCP and the synthetic "sigma" opiates (*N*-allylnormetazocine, pentazocine, cyclazocine) exerted their pharmacological effects at a single receptor, based on similarities among the dysphoric effects that these drugs elicit in animals (Martin et al., 1976). Drug discrimination studies (Shannon, 1981) demonstrating that rats and monkeys generalize from PCP to *N*-allylnormetazocine (also known as NANM, or SKF 10,047) served to reinforce this belief. Moreover, competitive interactions between PCP and SKF 10,047 in receptor binding assays (Zukin and Zukin, 1979; Sircar et al., 1986) prompted the designation of this site as the "PCP/sigma" receptor. However, recent studies employing novel, more selective pharmacological agents have provided evidence for the existence of at least two distinct binding sites for

phencyclidine (Vignon et al., 1986). These two sites are now designated the "NMDA-associated PCP site", with selective ligands 1-[1-(2-thienyl)cyclohexyl] piperadine (TCP) and MK-801 (dizocilpine), and the "sigma/haloperidol" receptor, with selective ligands (+)3-(3-hydroxyphenyl)-N-(1-propyl) piperadine ([+]3-PPP) and 3-ditolylguanidine (DTG; Sonders et al., 1988). It is important to note that the NMDA-associated PCP site is designated as a "site" because it is not associated with any known signal transduction system (Johnson and Jones, 1990), while the sigma/haloperidol receptor is thought to be coupled to "G" proteins and phosphoinositide turnover (Walker et al., 1990). However, it has been exceedingly difficult to attribute the behavioral properties of phencyclidine exclusively to actions at either the NMDA-associated PCP site or the sigma/haloperidol receptor, since there are substantial redundancies in the pharmacological profiles of PCP- and sigma-related ligands.

1. PCP binding to NMDA-associated sites

a. Biochemistry

Receptors for the excitatory amino acids (EAAs) glutamate and aspartate are ubiquitous in the brain. Utilization of new, selective agents enabled Watkins and Evans (1981) to postulate the existence of at least three EAA receptor subtypes, named for the exogenous agonists that selectively stimulate them: kainate, quisqualate, and N-methyl-D-aspartate (NMDA). Of these original three subtypes, the NMDA receptor has received the greatest attention. The effects of glutamate and NMDA can be blocked by two classes of agents, known as competitive and non-competitive antagonists. It is currently accepted that competitive antagonists such as AP5 (2-amino-5-phosphovaleric acid) and (+/-)CPP (cis-[+/-]-3-[2-carboxypiperazine-4yl] propyl-1-phosphonic acid) exert their effects by blocking access to the NMDA receptor itself (Kemp et al., 1987). On the other hand, non-competitive agents such as PCP, MK-801, and ketamine are thought to act by blocking an ionophore (Anis et al., 1983; Honey et al., 1985) that is intimately associated with the

NMDA receptor (Jarvis et al., 1987). Although they have the same net pharmacological effect, these two classes of compounds do not have a common mechanism of action at the NMDA receptor complex and therefore do not compete with each other for binding sites (Martin and Lodge, 1985). The NMDA-associated ionophore is a voltage-dependent ligand-gated channel that is normally blocked by Mg^{2+} (Nowak et al., 1984). When an NMDA agonist is in place and the membrane containing the NMDA receptor is depolarized, the Mg^{2+} ion is ejected from the mouth of the ionophore, simultaneously opening the channel to ion flux (especially calcium) and exposing the putative PCP site (Kemp et al., 1987). When PCP is bound to this site, it attenuates activity at the NMDA receptor complex by blocking the ion channel (Honey et al., 1985). Because of this unusual mechanism of action, there has been some debate as to whether PCP interacts with an actual receptor (generally thought to consist of both a recognition site and a signal transduction system), or merely with a binding site which blocks ion flux when occupied (Johnson and Jones, 1990).

b. Distribution of the NMDA-associated PCP site

Selective radioligands ligands have helped to distinguish the NMDA-associated PCP site from the sigma/haloperidol receptor (Vignon et al., 1986), and have facilitated the anatomical localization of NMDA receptors. Autoradiographic studies using [^{3}H]TCP (Contreras et al., 1986) indicate that the highest densities of NMDA-associated PCP sites were in areas such as cortex, hippocampus, and dentate gyrus; moderate densities were observed in the caudate nucleus, nucleus accumbens, and periaqueductal gray, while the lowest densities were found in the brainstem, hypothalamus, and substantia nigra. While [^{3}H]TCP is selective for NMDA-associated PCP sites, the sigma/haloperidol ligand SKF 10,047 also displayed a small degree (32-fold less than TCP and 9-fold less than PCP) of binding to these same sites.

c. Behavioral effects of NMDA antagonists

Disruption of NMDA receptor function has a number of behavioral manifestations. For example, administration of AP5 (Morris et al.,1986) or MK-801 (Whishaw and Auer, 1989) interferes with memory-associated performance in the Morris water maze, probably by blocking long-term potentiation (Harris et al., 1984). Both competitive and non-competitive NMDA antagonists are potent inhibitors of neuronal death after ischemia or stroke (McDonald et al., 1989). Phencyclidine produces stereotypy in rodents characterized by locomotion, ataxia, and headweaving (Greenberg and Segal, 1985) that is largely mimicked by both MK-801 (Hiramatsu et al., 1989) and (+/-)CPP (Koek and Colpaert, 1990). However, there is some evidence that the locomotor activity elicited by MK-801 can be qualitatively distinguished from that of PCP (Lehmann-Masten and Geyer, 1991), possibly due to less affinity for the sigma/haloperidol receptor (Wong et al., 1988). Drug discrimination studies reveal that while the behavioral effects of competitive and non-competitive NMDA antagonists are similar, the two classes of agents can be distinguished from each other by both rats (Jackson and Singer, 1988; Koek et al., 1990) and primates (France et al., 1989); these data imply that blockade of NMDA receptor function alone is not sufficient to produce the full spectrum of subjective effects that are experienced after administration of PCP. Although primates (Balster and Woolverton, 1980) and dogs (Risner, 1982) self-administer PCP, rats tend to avoid environments associated with administration of the drug in conditioned place preference studies (Barr et al., 1985; Iwatomo, 1986). Finally, PCP, ketamine and MK-801 increase self-stimulation in rats (Kornetsky and Esposito, 1979; Schaefer and Michael, 1990; Herberg and Rose, 1989; Corbett, 1989).

2. Phencyclidine binding to sigma/haloperidol receptors

a. Biochemistry

A flurry of recent activity aimed at further characterizing the so-called sigma/haloperidol receptor has produced a complex picture. Consequently, the definition of the "sigma receptor" has undergone numerous revisions. Initially, the existence of this binding site was postulated on the basis of pharmacological experiments in dogs using the synthetic opiates N-allynormetazocine (SKF 10,047) and cyclazocine: these ligands elicited a dysphoric state in animals that was radically different from that of more classical (μ, κ, δ) opiates (Martin et al., 1976). Su (1982) found that the binding characteristics of [^{3}H]SKF 10,047 did not resemble those of traditional opiate receptors. Therefore, this new subtype was initially designated the "σ opiate" receptor. Subsequent research demonstrated that the term "σ opiate" was somewhat of a misnomer, since the effects of ligands such as SKF 10,047 were not attenuated by the opiate antagonist naloxone (Shannon, 1982). On the other hand, the antipsychotic haloperidol was demonstrated to exert potent biochemical effects at this receptor (Su, 1982; Tam and Cook, 1984). Furthermore, the development of more selective σ- ([+]3-PPP and DTG) and PCP- (MK-801, TCP) ligands has confirmed that the σ opiate receptor is distinct from the PCP site that is associated with the NMDA receptor complex (Largent et al., 1986). Consequently, what was once called the σ opiate receptor is now commonly referred to as the "sigma/haloperidol" receptor.

Since phencyclidine possesses moderate affinity for the sigma/haloperidol receptors, and sigma/haloperidol receptors have been associated with schizophrenia (Weissman et al., 1988), it is possible that these receptors play a role in the expression of the psychotomimetic properties of PCP-like drugs. However, because non-selective sigma/haloperidol ligands have also been shown to possess some activity as NMDA antagonists at concentrations that elicit behavioral effects (Lacey and Henderson, 1986; Church et al., 1986), the psychotomimetic properties of PCP-like drugs can not be

attributed exclusively to their interaction at either the NMDA-associated PCP sites or sigma/haloperidol receptors.

b. Distribution of the sigma/haloperidol receptors

The sigma/haloperidol receptor does not appear to be a subtype of the dopamine receptor: although the dopamine (D_2) antagonists haloperidol, chlorpromazine and pimozide potently displace [^{3}H]SKF 10,047, the dopamine agonist apomorphine does not bind to the sigma/haloperidol receptor (Su, 1982). Furthermore, receptor autoradiography indicates that binding sites labeled with the highly selective sigma/haloperidol ligand [^{3}H](+)3-PPP only sparsely populate dopamine-rich areas; labeled sigma/haloperidol receptors were found primarily in limbic regions (hippocampus), and in cerebellar, brainstem and midbrain (dorsal raphe, periaqueductal grey) regions, but not in the caudate putamen or the nucleus accumbens (Largent et al., 1984; Tam, 1985; Gundlach et al., 1986).

c. Behavioral effects of sigma/haloperidol ligands

The behavioral effects of sigma/haloperidol ligands in rodents are similar to those seen after administration of phencyclidine. Greenberg and Segal (1986) demonstrated that SFK 10,047 elicited locomotion, sniffing, head weaving, and repetitive mouth movements to the same extent as did PCP. Drug discrimination studies also reveal that PCP generalizes to SKF 10,047 (Shannon, 1981; Koek et al., 1990). However, it is again noted that all of these behavioral effects could be due to interactions of sigma/haloperidol ligands with the NMDA receptor complex. Future comparisons between the behavioral effects of PCP and those of sigma/haloperidol ligands agents which do not attenuate NMDA receptor function ([+]3-PPP and DTG) might demonstrate that some behaviors can be attributed primarily to actions at sigma/haloperidol receptors, while others to non-competitive antagonism of the NMDA receptor complex.

B. *Phencyclidine interacts with several neurotransmitter systems*

Phencyclidine has been shown to interact with virtually all of the classical neurotransmitters in the brain, including the monoamines (dopamine, norepinephrine, serotonin) and acetylcholine. However, due to the prevailing theories concerning the roles of dopamine and glutamate in the etiology of schizophrenia (Kim et al., 1980; Kornhuber and Kornhuber, 1986; Javitt, 1987; Carlsson, 1988), the interaction of PCP with dopamine-containing neurons has received the most attention. The fact that PCP appears to enhance dopaminergic function by a variety of mechanisms corroborates the claims of Snyder (1980) that the state elicited by this drug is an exceptional model for schizophrenia.

1. Dopamine

Phencyclidine causes a number of dose-dependent effects on the dopaminergic system, and more than one action is implicated in these effects. Phencyclidine does not bind directly to dopamine receptors (Vincent et al., 1978); rather, it affects dopamine function by increasing extracellular dopamine (DA) levels. Although it was once thought that PCP increases extracellular DA by acting as releasing agent (Vickroy and Johnson, 1982), it now appears that the predominant action of the drug is the inhibition of monoamine reuptake. After local application into the caudate nucleus, both PCP and the prototypical catecholamine reuptake inhibitor nomifensine increase extracellular DA levels, and decrease the spontaneous firing rates of striatal cells (Gerhardt et al., 1987). There is substantial evidence to suggest that inhibition of dopaminergic cell firing rates after PCP is a compensatory response to increases in extracellular dopamine. Inhibition of the firing rates of caudate neurons by local application of PCP is reduced by pretreatment with either reserpine or 6-hydroxydopamine (6-OHDA), suggesting that the actions of PCP require dopamine and functional DA terminals (Johnson et al., 1984). Furthermore, Ceci and French (1989) found that the inhibition of VTA firing rates induced by intravenous administration of high doses of PCP is attenuated by destruction of the nucleus accumbens.

Phencyclidine-induced depressions in the firing rates of DA cells located in the medial prefrontal cortex are mimicked by dopamine and are blocked by the DA antagonist fluphenazine, which also suggests that decreases in cell firing were caused by blockade of DA reuptake (Gratton et al., 1987). Recent evidence suggests that the PCP-induced inhibition of DA reuptake might be associated with a third binding site for PCP: the drug binds to the cocaine-binding site on a putative DA carrier protein (Kuhar et al., 1988) that has been found in both animals (Rothman et al., 1989) and humans (Akunne et al., 1991). Microdialysis studies in freely moving rats reveal increases in extracellular DA levels after perfusion of PCP into the striatum or the nucleus accumbens (Hernandez et al., 1988); likewise, increases in baseline DA levels are found after systemic administration of PCP (Carboni et al., 1989). Finally, dopamine (D_2) receptors throughout the rat brain are down-regulated after chronic treatment with PCP (Quirion et al., 1982), which is an additional indication of PCP-induced increases in synaptic DA levels.

While PCP's actions as a DA uptake inhibitor are relatively clear, electrophysiological studies suggest that its action on the activity of dopaminergic cells is complex. It appears that low doses of PCP may cause impulse-dependent release of DA through actions at the level of the DA cell body. Single cell recordings indicate that low doses of intravenous PCP increase the firing rate of nigrostriatal dopamine neurons (Raja and Guyenet, 1980). Systemic administration of PCP causes marked increases in the levels of DA metabolites in both the mesolimbic and striatal systems in *ex vivo* studies (Deutch et al., 1987). In a more recent electrophysiological study, Freeman and Bunney (1984) have demonstrated that intravenous phencyclidine has a biphasic effect on firing rates of dopaminergic neurons: low doses of PCP increase the firing rate of dopaminergic neurons located in the substantia nigra pars compacta (SNC) and ventral tegmental area (VTA), while higher doses decrease the firing rates in both areas. The inhibitory but not the excitatory effects of PCP on firing rate are attenuated by systemic administration of the DA antagonist haloperidol: this confirms that the inhibitory effects involve impulse-

regulating feedback mechanisms and suggests that the excitatory effect involves activation of dopaminergic neurons by one of PCP's other actions. This is most likely an action involving NMDA-associated PCP sites, since MK-801 also activates dopaminergic neurons in the VTA, while the selective sigma/haloperidol selective ligand DTG fails to produce any stimulation of firing rates (French and Ceci, 1990).

The behavioral effects of PCP also involve dopamine. Balster and Chait (1978a) and Greenberg and Segal (1985) found that administration of PCP exacerbates amphetamine-elicited sterotyped behaviors. Similarly, apomorphine potentiates PCP-induced stereotypy (Castellani and Adams, 1981). Augmented locomotor activity elicited by PCP is lost after 6-OHDA lesions of the mesolimbic dopamine system (French and Vantini, 1984); in rats with unilateral 6-OHDA lesions of the substantia nigra, PCP elicits ipsiversive circling (Fessler et al., 1979).

The relationship of PCP's action at the NMDA receptor complex with its effects on DA systems remains obscure. The non-competitive NMDA antagonist MK-801 has been shown to possess biochemical and behavioral effects on the dopamine system that are qualitatively similar to those of PCP, despite having little affinity for either the sigma/haloperidol receptor (Wong et al., 1988) or the putative DA uptake carrier protein (Reid et al., 1990). Dopaminergic cells in the VTA are activated by intravenous MK-801 (French and Ceci, 1990), and the drug increases DA metabolism in the striatum (Rao et al., 1990). In microdialysis studies, increased levels of synaptic DA were observed in both the nucleus accumbens and caudate nucleus after local administration of MK-801 (Imperato et al., 1990), although no effect was observed when the drug was administered systemically (Kashihara et al., 1990). Systemic MK-801 elicits ipsiversive circling in animals with 6-OHDA lesions of the striatum, suggesting that the locomotor effects of NMDA antagonists are dependent upon intact dopamine terminals (Clineschmidt et al., 1982). In addition, the locomotion and stereotypy that are elicited by MK-801 in rats can be attenuated by haloperidol and clozapine (Tiedtke et al., 1990).

There also appears to be a complex interaction of sigma/haloperidol receptors with the dopaminergic system. Early work (Martin et al., 1976) indicated that the sigma/haloperidol agonist SKF 10,047 and apomorphine produced similar effects in the dog. The fact that the prototypical dopamine antagonist haloperidol binds to the sigma/haloperidol receptor also suggests a functional interaction (Tam and Cook, 1984). The sigma/haloperidol ligands pentazocine and SKF 10,047 increase dopamine metabolism, despite a complete lack of affinity for dopamine receptors (Iyengar et al., 1990). Locomotor hyperactivity can be elicited by SKF 10,047, but is lost after 6-OHDA lesions of the nucleus accumbens. Dopamine neurons in the VTA can be activated by SKF 10,047 (Freeman and Bunney, 1984); rimcazole (BW 234U), a putative antipsychotic drug that is a sigma/haloperidol receptor antagonist with no affinity for DA receptors, blocks SKF 10,047-induced increases in VTA cell firing and locomotor activity, but has no effect on amphetamine-induced hyperactiviy (Ceci et al., 1988). Moreover, rimcazole (Ferris et al., 1986) and another sigma/haloperidol antagonist, BMY 14802 (Matthews et al., 1986; Taylor and Dekleva, 1987) appear to block brain dopamine function through a non-dopaminergic mechanism. These results strongly suggest that PCP and other sigma/haloperidol ligands can indirectly modulate the dopaminergic system without interacting with the dopamine receptor itself. However, it is also possible that SKF 10,047 modulates DA cells by virtue of its weak non-competitive antagonism of NMDA receptors. Since the most selective sigma/haloperidol agonist available (DTG) is devoid of direct actions on dopaminergic neurons of the VTA (French and Ceci, 1990), it appears that the effects of PCP on the dopamine system could result from simple blockade of the NMDA-associated ionophore.

2. Norepinephrine

The pharmacologists from Parke, Davis & Company who were the first to characterize PCP believed that its effects were mediated by norepinephrine (Chen et al.,

1959). Indeed, PCP is a potent competitive inhibitor of NE uptake *in vitro* (Smith et al., 1977). In electrophysiology studies using single cell recording techniques, Raja and Guyenet (1980) found that low doses of intravenous PCP consistently inhibit the firing rate of noradrenergic neurons in the locus coeruleus. The effects of PCP on the noradrenergic system require functional NE-containing terminals, since blockade of PCP-elicited depressions in the firing rate of cerebellar Purkinje neurons can be achieved by 6-OHDA lesions of NE terminals (Marwaha et al., 1980). Thus, it appears that the effects of PCP on noradrenergic neurons are at least qualitatively similar to its presynaptic actions on the dopaminergic system.

3. Serotonin

There is a great deal of evidence to support the notion that drugs which modulate the activity of serotonergic neurons in the brain elicit hallucinations in humans (Rasmussen and Aghajanian, 1990); one such example is lysergic acid diethylamide (LSD). Therefore, it is tempting to speculate that the hallucinogenic properties of PCP are mediated by interactions with serotonin-containing neurons. Although the role of serotonin (5-HT) in PCP-induced behaviors is far from clear, there is certainly evidence for an interaction. For example, studies using *ex vivo* synaptosomal preparations from rat cortex indicate that PCP is a potent inhibitor of 5-HT uptake (Smith et al., 1977). Likewise, acute administration of PCP increases levels of 5-HT in cortical preparations from mouse brain (Nabeshima et al., 1985). In electrophysiology studies using single cell recording techniques, Raja and Guyenet (1980) found that low doses of intravenous PCP had essentially no effect on serotonergic neurons of the raphe nucleus. Taken together, these data suggest that PCP interacts with postsynaptic (5-HT$_2$) receptors, while having less of an effect on autoreceptors (5-HT$_1$) found predominantly on cell bodies of the raphe nucleus (Rasmussen and Aghajanian, 1990).

4. Acetylcholine

In addition its to actions on monoamine systems, PCP and related ligands are also anticholinergic agents. Since anticholinergic agents can elicit locomotion in rodents (Sanberg et al., 1987; Mueller and Peel, 1990; Carlezon et al., 1991) and hallucinations in humans (Wilkinson, 1987; Ziskind, 1988), disruption of cholinergic function may further contribute to the behavioral effects of PCP. Phencyclidine inhibits acetylcholinesterase (Kloog et al., 1977) and is a weak blocker of muscarinic acetylcholine receptors (Vincent et al., 1978). At behaviorally relevant doses, PCP is a potent antagonist at the nicotinic ionophore (Eldefrawi et al., 1980), and causes a dose-related inhibition of stimulated acetylcholine (ACh) from rat striatal slices (Leventer and Johnson, 1983). There is some evidence that the anticholinergic properties of PCP in the brain are indirectly mediated by effects at the NMDA receptor complex (Snell and Johnson, 1986), although agents that increase levels of synaptic dopamine can also inhibit ACh release through indirect mechanisms (Stoof et al., 1982). Supporting of the role of dopamine in this anticholinergic effect, Leventer and Johnson (1983) found that haloperidol blocked the inhibitory effect of PCP on ACh release. In rats with nigrostriatal lesions, PCP elicits ipsiversive turning; the anticholinergic agent trihexyphenadyl potentiated this effect, but the cholinomimetic arecoline attenuated rotation (Finnegan et al., 1976). Thus, it is possible that the action of PCP on ACh-containing neurons is synergistic with its effects on dopamine-containing neurons.

C. Conclusions

Phencyclidine exerts pharmacological effects at a number of sites in the brain. Its actions at each of these sites are reminiscent of other drugs which are used illicitly by humans. However, a predominant effect of PCP is to enhance levels of synaptic dopamine by means of a variety of mechanisms. It is presumably the interaction with dopaminergic

neurons which underlies the abuse liability of PCP, and mediates its propensity to facilitate behavior in various animal models of addiction (Wise and Bozarth, 1987).

III. Phencyclidine and animal models of addiction

The challenge in the study of addiction is to identify the pharmacological characteristics and physiological effects of a drug which contribute to its ability to control behavior. The actions of a drug that reinforce habitual behavior cannot be directly observed; consequently, the concept of drug reward is inferred by psychologists on the basis of observations of behavior. The attributes of a drug that are relevant to addiction can be gleaned using animal models by manipulating environmental contingencies, or by altering the anatomy or neurochemistry of the brain. Thus, full characterization of the reinforcing properties of a drug is best accomplished by the study of its effects on behavior in several paradigms.

A. *Properties of rewarding drugs*

1. Rewarding drugs serve as operant reinforcers

Drugs that are abused by humans serve to establish lever-pressing habits in lower animals as well, and such habits are discussed in psychological theory in relation to the notion of instrumental (Thorndike, 1898) or operant (Skinner, 1938) reinforcement. Skinner (1938) observed that if the occurrence of an operant (a discrete response) is followed by presentation of a rewarding stimulus, the strength of the operant is increased. In the self-administration paradigm, a laboratory animal is given the opportunity to perform an arbitrary task, such as lever-pressing, that results in delivery of an injection of a drug. If the frequency of lever-pressing increases as a result of the drug injections, that drug is termed an instrumental or operant reinforcer. Thorndike (1898) suggested that the process of instrumental conditioning involves the "stamping-in" of stimulus-response associations; Thorndike (1933) and Skinner (1933) were the first to apply the term "reinforcement" to

the instrumental paradigm. Thus, the rewarding properties of a drug in the self-administration paradigm are inferred by the extent to which a drug can serve as an operant reinforcer, and act to "stamp-in" habitual responding.

Several routes of administration have been employed in the self-administration, including intravenous injection or direct infusion into discrete areas of the brain. Intravenous injections of drugs such as cocaine, amphetamine, and opiates serve as powerful operant reinforcers in primates (Griffiths and Balster, 1979). Furthermore, both intravenous (Weeks, 1962; van Ree et al., 1978; Collins et al., 1984) and intracranial (Phillips and LePaine, 1980; Bozarth and Wise, 1981b; Britt and Wise, 1983) opiates can act as reinforcers in rodents. However, the conditions under which an injection of phencyclidine consistently serves as an operant reinforcer are not clear. Although it is self-administered by primates (Balster and Woolverton, 1980) and dogs (Risner, 1982), rodents do not work for injections of PCP as reliably as they do for other drugs of abuse such as morphine or cocaine (Collins et al., 1984).

2. Animals approach environments paired with rewarding drugs

Addicts not only develop attachments to rewarding drugs, they also develop attachments to environmental stimuli which have come to be repeatedly associated with ingestion of those drugs. Thus, it can be said that habit-forming drugs not only have the ability to modify stimulus-response associations, but they also have the ability to modify stimulus-stimulus associations. Such associations are discussed in psychological theory in relation to the notion of Pavlovian or "respondent" reinforcement (Skinner, 1938). A second animal model of drug addiction, the conditioned place preference paradigm (CPP), employs respondent conditioning in order to characterize the rewarding properties of drugs. In the CPP paradigm, a neutral environmental stimulus is paired with a reinforcing drug stimulus; after such pairing, the previously neutral environment acquires reinforcing properties via Pavlovian conditioning (Wise, 1989). Whereas the contingency between the

response and drug administration is critical in the self-administration paradigm, the animal never receives drug as a result of any behavior in the CPP. Merely by virtue of contiguous pairing of environment with drug, the environment develops the capacity to elicit approach; the stimulus-stimulus association of the reinforcing properties of the drug with the environment presumably causes rats to develop a conditioned preference for the environment itself. A conditioned place preference is manifested by a tendency to approach, enter, and remain within the drug-associated environment. According to Schneirla (1959), approach and continued contact with a stimulus is an index of its rewarding value; thus, time spent in the drug-associated environment can be thought of as an indicator of the rewarding properties that the environment has acquired. The ability of a drug to establish the rewarding properties of the environment implies that the drug itself is rewarding (Wise, 1989).

Most rewarding drugs have been shown to elicit conditioned place preferences. Beach (1957) found that rats developed a tendency to approach an environment in which they had been administered morphine. Robust conditioned place preference for morphine-associated environments was also found by Rossi and Reid (1976), and demonstrated for a number of other drugs used illicitly by humans including d-amphetamine (Reicher and Holman, 1977), heroin (Bozarth and Wise, 1981a), and cocaine (Spyraki et al., 1982).

Interestingly, some drugs often abused by humans do not reliably produce conditioned place preferences: these include nicotine (Iwamoto, 1990; Fudala et al., 1985; Clarke and Fibinger, 1987; Jorenby et al., 1990), ethanol (Black et al., 1973; Asin et al., 1985), and phencyclidine (Barr et al., 1985; Iwamoto, 1986). This suggests that either the rewarding properties are masked by other effects of these drugs, or that these drugs can be reinforcing to humans for fundamentally different reasons.

3. Rewarding drugs potentiate or amplify the impact of other rewards

Another characteristic of habit-forming drugs is that they can potentiate the impact other types of rewards. A drug is said to be rewarding if it adds to the ability of natural rewards, such as feeding or sexual activity, to control the behavior of an animal. At appropriate doses, feeding can be facilitated by d-amphetamine (Blundell and Latham, 1976; Colle and Wise, 1988b), opiates (Jenck et al., 1986), and Δ^9-tetrahyrocannabinol (THC), the psychoactive substance in marijuana (Hollister, 1971; Trojniar and Wise, 1991). Likewise, it has been demonstrated that opiates facilitate sexual behavior in the male rat (Mitchell and Stewart, 1990). Most abused drugs, including phencyclidine, also facilitate responding in a heuristic model of reward in which animals self-administer reinforcing electrical stimulation to discrete areas of their brain; as will be discussed below, brain stimulation reward (BSR) has a number of practical advantages over natural rewards for laboratory studies of the reward-potentiating effects of drugs.

4. Rewarding drugs reinstate extinguished self-administration habits

Finally, rewarding drugs can reinitiate extinguished behaviors (Stewart and de Wit, 1987). For example, in animals that have had drug self-administration habits extinguished, non-contingent or "priming" injections drug can quickly reinstate responding. This phenomenon has been observed in rodents with both natural and heuristic rewards: "free" or priming administration of food (Eiserer, 1978), cocaine (de Wit and Stewart, 1981), heroin (de Wit and Stewart, 1983) or rewarding brain stimulation (Gallistel, 1973) all facilitate the initiation of responses previously associated with delivery of the stimulus. To date, the ability of PCP to reinstate extinguished responding in animals has not been evaluated.

B. Intracranial Self-Stimulation and animal models of reward facilitation

Olds and Milner (1954) found that direct electrical stimulation of several brain regions is rewarding; the medial forebrain bundle (MFB) is a common site for stimulating electrode placement, because stimulation in this region sustains high rates of responding and has a low incidence of aversive side effects. Brain stimulation reward (BSR) can be very powerful reinforcer: it can be preferred to a number of natural rewards, including food, water, sex, or maternal behavior (Wise, 1980). A striking example of its reinforcing power was reported by Routtenberg and Lindy (1965), who demonstrated that when placed under conditions in which food and BSR were available for only one hour per day, animals spent the entire hour self-stimulating and failed to eat. Over a period of days, these animals continued to choose BSR despite the resulting starvation, until death.

Brain stimulation reward offers an optimal system within which to test the reward-potentiating actions of drugs of abuse. Unlike the rewards associated with food or sex, BSR is relatively impervious to satiety. Since there is little change in the strength of BSR during testing, it does not require short testing sessions, nor does it require that animals be in a state of deprivation. Furthermore, as opposed to natural rewards, the parameters of stimulation can be electronically controlled by the experimenter; the "dose" of electrical stimulation received by an animal can be more accurately measured than the amount of food actually ingested during a feeding study.

A number of habit-forming drugs--most notably opiates and amphetamine-- have been reported to facilitate ICSS. In early studies, increases in the rate of ICSS were taken to reflect increases in the rewarding impact of stimulation. Unfortunately, response rates are sensitive to the motor capacity of an animal as well as the rewarding impact of the stimulation, and can be altered by a variety of treatments that have no effect on the impact of the stimulation. For example, administration of a paralytic drug, such as curare (Edmonds and Gallistel, 1974), or increasing the pressure required to depress the lever (Miliaressis et al., 1986) each have profound effects upon ICSS. Inferences based upon

simple rate measures might lead to the erroneous conclusion that curare or increased lever resistance attenuate the r·inforcing properties of the stimulation, when in truth the treatments simply incapacitate the animal, or make the requisite task more difficult. Another concern raised against early ICSS studies is that animals were traditionally tested at a single set of stimulation parameters, and that these parameters frequently produced maximal rates of responding. Drawing inferences about the rewarding effects of stimulation from examination of a single intensity and frequency is as questionable as drawing inferences about a drug based upon the study of a single dose (Stellar and Rice, 1989). When levels of stimulation that sustain maximal levels of responding are tested, simple rate measures are not sensitive to changes in the rewarding impact of the stimulation. Experiments employing a "choice measure" suggest that maximal response rates reflect performance constraints: if animals are given a "choice" between low and high frequencies, both of which produce maximal rates of responding, they reliably select the higher stimulation parameters (Waraczynski et al., 1987; Miliaressis and Malette, 1987). Thus, inferring that a drug modulates the impact of BSR on the basis of changes in response rates alone has been strongly criticized (Valenstein, 1964; Gallistel, 1983; Stellar and Rice, 1989; Wise, 1989; Wise and Rompré, 1989).

One way to avoid the major limitations of simple rate studies is to focus on minimal rather than maximal responding. The minimum stimulation required to sustain reliable responding is termed the "threshold" level of stimulation, and it sustains responding at levels well below the demonstrated capacity of the animal. There are several ways to measure thresholds; each is designed to determine the minimal level of stimulation that is clearly rewarding. One commonly used method to estimate the rewarding threshold is the "detection threshold" paradigm (Esposito and Kornetsky, 1977; Esposito and Kornetsky, 1978; Kornetsky and Esposito, 1979; Kornetsky and Esposito, 1981). In this method, the threshold for detection of rewarding electrical stimulation is estimated by successive approximation. Non-contingent brain stimulation is given at the beginning of each trial; if

the animal lever-presses, an identical level of stimulation is delivered following the lever-press. If the animal does not respond, a new trial is given at a higher level of current. Testing continues in this fashion over a descending series of stimulation intensities until the animal does not lever-press, at which time an ascending series of intensities is tested. Reward threshold is operationally defined as the midpoint between the intensities where lever-pressing is initiated on ascending series, and discontinued on descending series. Alterations in the rewarding threshold after drug treatment are manifested by changes in the intensity that sustains contingent responding. Another approach is termed the "autotitration" method (Schaefer and Holtzman, 1979; Nazzaro and Gardner, 1980; Gardner et al., 1988). This method measures the minimal stimulation required to maintain responding rather than the minimal stimulation required to elicit responding. The animal is tested under conditions where two operant levers are available; when the animal presses the "primary" lever, rewarding stimulation is delivered. However, after a predetermined amount of responding the stimulation intensity is decreased by a small amount. A response on the "secondary" lever does not itself deliver stimulation, but instead resets the stimulation level to its original intensity. Threshold is operationally defined as the average current at which the animal makes a "reset response", and any alteration of this threshold by psychoactive drugs is thought to reflect an interaction with the rewarding qualities of the stimulation.

Another method of measuring treatment-induced changes in the impact of BSR is the "curve-shift" paradigm (Edmonds and Gallistel, 1974). The curve-shift paradigm determines the reward threshold by measuring response rates across a range of stimulation frequencies. In the curve-shift paradigm, the intensity, duration, and train (cycles per pulse) of the electrical brain stimulation traditionally remain constant, while the stimulation frequency (pulses of stimulation per second) is varied systematically within a test session. Each animal is tested with stimulation frequencies high enough to sustain responding at what appears to be the response maximum (asymptote), at low frequencies that fail to

sustain responding, and at moderate intensities that sustain intermediate levels of responding. When response rates are plotted across the range of frequencies, the shape of rate-frequency curve takes the form of an ogive (see Fig. 1).

The curve-shift paradigm is so-designated because the question of interest is how a given treatment shifts the rate-frequency curve. Two types of shifts in the curve are of interest: lateral (right or left), and vertical (up and down). Drug-induced lateral displacements of the rate-frequency function imply that the rewarding impact of the stimulation has been altered. For example, parallel lateral shifts to the left (toward lower frequencies) signify that lower levels of stimulation sustain pre-treatment levels of responding, and imply that the rewarding impact of the stimulation is increased. Parallel rightward shifts imply that pre-treatment levels of stimulation are no longer reinforcing, and that higher levels are required to sustain normal response rates. Vertical shifts, however, reflect changes in the capacity to respond, but imply nothing about the rewarding impact of the stimulation. A treatment that raises the performance requirements of an animal, such as an increase in the force required to depress the lever, causes downward vertical shifts in the rate-frequency function without causing a major lateral shift in the curve (Miliaressis et al., 1986).

It is essential to measure the response rate of the animal over a sufficient range of stimulation "doses" in the curve-shift paradigm so that both the reward threshold and maximal response rate can be determined. In fact, the curve-shift paradigm for measuring changes in the impact of BSR is analogous to a dose response curve (Liebman, 1983; Wise, 1989), which characterizes the pharmacological effects of a drug on a biological response. At appropriate doses, drugs such as amphetamine (Gallistel and Karras, 1984) and nicotine (Bauco and Wise, 1991) cause parallel leftward shifts in the rate-frequency function, reducing the "dose" of stimulation that is required to sustain normal responding; such an effect suggests that their rewarding effects summate with the rewarding effects of brain stimulation, and implies that these drugs are rewarding in their own right.

A distinct advantage of the curve-shift paradigm involves the scaling of treatment effects. Shifts in stimulation threshold are measured in logarithmic units, which makes it possible to quantify differences in the reinforcing properties of drugs on a ratio scale (Gallistel and Freyd, 1987; Wise and Rompré, 1989). This technique allows direct quantitative comparisons of threshold shifts not only between several doses of a particular drug, but also between optimal doses of two or more different drugs. Treatments that produce changes of the same magnitude on a logarithmic scale are assumed to produce equal changes in the rewarding impact of brain stimulation.

C. *Effects of drugs of abuse on ICSS*

Many drugs that are abused by humans tend to facilitate ICSS in rodents. For example, amphetamine increases the rate of ICSS (Stein, 1964; Domino and Olds, 1972), lowers BSR thresholds (Esposito et al., 1980), and produces a parallel leftward shift of the rate-frequency funci⁻ on at low and moderate doses in the curve-shift paradigm (Gallistel and Karras, 1984; Gallistel and Freyd, 1987; Colle and Wise, 1988a). Acute administration of morphine causes an initial suppression of response rates, followed several hours later by an acceleration of bar pressing (Adams et al., 1972; Bush et al., 1977). Low to moderate doses of morphine also decrease the rewarding threshold for rewarding brain stimulation (Kornetsky and Esposito, 1977; Kelley and Reid, 1977), causing leftward shifts in the rate-frequency function (Glick et al., 1982; West and Wise, 1988). Like morphine, nicotine has a biphasic effect on lever-pressing, with initial periods of suppression followed by increases in response rates (Pradhan and Bowling, 1971); nicotine also causes parallel leftward shifts of the rate-frequency function in the curve-shift paradigm (Bauco and Wise, 1991). The parallel leftward shifts observed in the rate-frequency functions using the curve-shift paradigm imply that amphetamine, nicotine and morphine increase the rewarding impact of BSR, and do not merely increase the ability of an animal to respond at high rates. On the other hand, ethanol has been more difficult to

characterize using ICSS: systemic doses of ethanol have been reported to increase response rates in some cases (Lorens and Sainati, 1978; De Witte and Bada, 1983), and decrease it in others (Carlson and Lydic, 1976; Schaefer and Michael, 1987). It has been reported that systemic ethanol has no effect on self-stimulation thresholds (Unterwald and Kornetsky, 1985); likewise, administration of ethanol by intravenous drip has no consistent effect on the impact of BSR (Wise et al., in press).

Although not tested in the curve-shift paradigm, there is evidence which sugges'. that other classes of habit-forming drugs can potentiate BSR. Like morphine and nicotine, Δ^9-tetrahydrocannabinol (THC, the psychoactive substance in marijuana) has biphasic effects on ICSS rates (Becker and Reid, 1977), and decreases self-stimulation thresholds (Gardner et al., 1988). Reward-enhancing effects of benzodiazepines and barbiturates, however, have been more difficult to demonstrate using ICSS. The benzodiazepine diazepam increases response rates at low doses, and decreases responding at higher, sedative doses (Olds, 1976; Caudarella et al., 1982); chlordiazepoxide increases response rates (Olds, 1976) and decreases reward thresholds (Ichimaru et al., 1985). Although the range of doses that stimulate behavior is especially narrow with the barbiturate pentobarbital (Wise, 1980), rate-stimulating effects can be found at doses lower than those that cause sedation (Olds, 1976). Finally, caffeine increases lever-pressing both when each response is rewarded (FR-1 schedule) and in a paradigm where only low levels of responding are rewarded (differential reinforcement for low levels of responding, or DRL), suggesting that the drug causes a non-specific stimulation of behavior (Valdes et al., 1982). Interestingly, it has been reported that this increase in activity can be accompanied by increases in reward thresholds, implying that the rewarding impact of the stimulation is diminished after caffeine (Mumford et al., 1988; Mumford and Holtzman, 1991). Whether caffeine, benzodiazepines or barbiturates alter the rewarding effects of BSR or simply change the response capacity of animals might become clearer if these drugs were tested in the curve-shift paradigm.

It has been reported that administration of PCP stimulates fixed-interval responding for brain stimulation (Schaefer and Michael, 1990), and decreases the threshold for rewarding brain stimulation (Kornetsky and Esposito, 1979). To date, however, no studies employing the curve-shift paradigm have been reported.

IV. The present investigation

The purpose of the present investigation was to assess the effects of phencyclidine on brain stimulation reward. In order to dissociate the reward-relevant effects of PCP from potential effects on response capacity, the curve shift paradigm was employed. The two doses selected for this study were based upon biochemical and behavioral indices of the pharmacological activity of PCP in rodents. Doses of PCP in the range of 2.5 to 5 mg/kg have been demonstrated to possess physiological actions consistent with increases in synaptic dopamine using *in vivo* microdialysis techniques (Carboni et al., 1989). Furthermore, acute systemic administration of PCP has been shown to elicit dose-dependent increases in spontaneous locomotion; high levels of activity, with minimal ataxia, have been constantly observed at a dose of 5.0 mg/kg (Greenberg and Segal, 1985; Hiramatsu et al., 1989; Lehmann-Masten and Geyer, 1991). Therefore, since Wise and Bozarth (1987) have suggested that drug-induced locomotion and drug-induced reward are mediated by a common neural substrate, a dose of 5.0 mg/kg was selected. Furthermore, because excessive locomotor activation could potentially interfere with the requisite response in the BSR paradigm, a dose with less propensity to stimulate locomotion (2.5 mg/kg) was also selected. Several rate-frequency functions were taken after acute administration of PCP to determine the extent and duration of the behavioral effects of the drug.

Animals were tested once per week for eight weeks in the BSR paradigm to determine if any systematic changes in the effectiveness of PCP would develop after repeated administration. The classic view of addiction has been that the effects of drugs of

abuse are characterized by tolerance after repeated administration: that is, that increasing doses are needed to have the same effectiveness, or conversely, that a constant dose yields progressively weaker effects (Himmelbach, 1943; Goldstein and Goldstein, 1961; Collier, 1968; Jaffe and Sharpless, 1968; Kalant, 1977; Edwards et al., 1981; Koob and Bloom, 1988). In recent years, however, this belief has become increasingly questioned. Recently, it has been suggested that the rewarding effects of abuse drugs undergo reverse-tolerance, or sensitization. Evidence suggesting sensitization to the rewarding effects of opiates and psychomotor stimulants has come from studies involving the drug self-administration paradigm (Piazza et al., 1990; Horger et al., 1990) and conditioned place preference paradigm (Lett, 1989). In order to determine whether any rewarding effects of PCP undergo tolerance or sensitization, animals were tested eight times in the BSR paradigm with the same dose of PCP. Since sensiti g effects are greatest after repeated intermittent administration of a drug (Robinson and Becker, 1986), testing was performed at one week intervals to maximize the potential for sensitization.

After repeated testing was completed in the BSR paradigm, the locomotor-stimulating effects of phencyclidine were evaluated: animals received repeated intermittent PCP at 5.0 mg/kg in an activity chamber to quantify the extent of locomotor sensitization in naive animals, and to determine if prior experience with either stimulation or the combination of stimulation and PCP altered the course of any sensitization.

METHODS

I. Subjects

Forty male Long-Evans rats, weighing 275-300g at the time of purchase (Charles River, Boston, MA), were used. Twenty-four of the animals were implanted with stimulating electrodes and tested in the BSR paradigm, while the remaining 16 were used

as naive control animals when locomotor activity was evaluated. All animals were individually housed in hanging wire mesh cages, and maintained on a 12 hr light (0800-2000)-12 hr dark cycle. Food and water were freely available except during testing.

II. Surgery

Each of the 24 animals tested in the BSR paradigm was anesthetized with an intraperitoneal injection of 65 mg/kg sodium pentobarbital (Somnotol), and administered 0.6 mg/kg atropine sulfate to minimize bronchial secretions. It was then placed in a Kopf stereotaxic instrument, with the incisor bar set at 5 mm above the intra-aural line. Each animal was implanted with bilateral, monopolar, 254 μm stainless steel electrodes that were insulated with varnish except at their cross section. The electrodes were aimed at the lateral hypothalamic level of the medial forebrain bundle, 0.8 mm posterior to bregma, 1.8 mm lateral to the midline, and 8.0 mm below dura (Pelligrino, Pelligrino, and Cushman,1979). The anode was an uninsulated stainless steel wire wrapped around two of the four stainless steel screws that were threaded into the skull. The entire assembly was then permanently affixed to the skull with acrylic dental cement.

III. Materials and Apparatus
A. Stimulator

A constant current generator delivered the brain stimulation, and was computer controlled using a microprocessor-based system (Campbell et al., 1985). The stimulation was administered in 0.5 sec trains of 0.1 ms rectangular cathodal pulses. Each animal was connected to the stimulator by a flexible wire lead and a mercury commutator (Mercotac, San Diego, CA.).

B. BSR Test Cages

Animals were tested in 26 X 26 cm cages with a floor of stainless steel rods spaced 1 cm apart. The cage had a single operant lever which protruded 2.5 cm from the rear wall at a height of 7.5 cm from the floor. Depression of the operant lever closed a microswitch, and caused delivery of the stimulation. Each test cage was enclosed within a sound-attenuating box.

C. Locomotor test cages

Locomotor activity boxes (20.5 X 40.5 X 24.5 cm) were constructed of wood (rear and two side walls), a wire screen ceiling, a floor with stainless steel rods spaced 1 cm apart, and a horizontally hinged plexiglas front door. Horizontal locomotion was estimated by recording the number of beam interruptions using two photocells, which were positioned 3.5 cm above the floor and spaced evenly across the longitudinal axis of each box. Each box was connected via an interface to computer situated in an adjacent room. White noise (75 dB) was present during testing.

IV. Procedure
A. Screening for self-stimulation

The animals were first given brain stimulation a minimum of 10 days after surgery. Stimulation frequency was set at 106 Hz, and the current intensity was initially set at a low value of 200 μa. Animals were shaped to lever-press, and received a 0.5 sec train of stimulation for each response (FR-1). If the animal did not lever-press despite shaping, the current was increased in 10 μa steps until either the animal began to responding at a rate of 40 lever presses per minute, or the intensity had reached 700 μa. If the animal lever-pressed at a rate of greater than 40 lever-presses per minute at 200 μa, the current was lowered in 10 μa steps until responding ceased. The current was then re-adjusted until the animal again responded at a rate of 40 lever-presses per minute. The screening procedure

continued until the animal lever-pressed consistently for one hour per day on three consecutive days. If the animal did not learn to lever-press at current intensities below 700 µa, or if the stimulation produced aversive side effects (gross head or body movements) at the lowest current intensity that would sustain responding, the screening procedure was reinitiated using the second (right) electrode. If stable responding was not established using stimulation at either electrode, the animal was discarded.

B. Stabilization of self-stimulation

Following the initial screening phase, the response rates of each animal were stabilized over a descending series of frequencies. Stabilization began using a pulse frequency of 106 Hz at the stimulation current deemed appropriate for each animal during ICSS screening. The pulse frequency was then decreased in "steps" of approximately 10% (0.05 log units) at one minute intervals during each rate-frequency determination. In the first 5 seconds of each one-minute determination the animal was given 5 programmed stimulation trains at the frequency that would next be available; the animal was then allowed to lever-press for 50 seconds during which the total number of lever presses was collected. Stimulation was unavailable during the final 5 seconds of each minute. The animal then received the next 5 sec priming phase at a stimulation frequency 0.05 log units lower than the previous one. After responding had been evaluated over a series of 18 frequencies (which comprised a rate-frequency function, or curve), the procedure was repeated using the same series of frequencies. During this stabilization procedure, the current intensity for each animal was further adjusted in 5 µa steps so that the threshold frequency (theta-zero), which represents an estimate of the lowest stimulation frequency that is rewarding for the animal, was approximately in the center of the 18 min curve. Threshold for each rate-frequency function (curve) was estimated according to the following method (Rompré and Wise, 1989): a least-squares line of best fit was plotted using the pulse frequencies that sustained responding at 20, 30, 40, 50 and 60% of the maximal rate (asymptote). Theta-

zero was then defined by extrapolation as the frequency at which the line of best fit intersected the ab ᵛ ᵛ ᵎ ꞏ ꞏus, if the maximum frequency tested was 106 Hz, the stimulation intensity for each animal was adjusted so that the threshold frequency was between 40 and 66 Hz. Stabilization lasted for a total of 90 minutes per day (five 18 min curves); once the threshold of each animal was consistently within the middle of the ꞏꞏcquency curve for two consecutive days, stimulation intensity was held constant for the remainder of the study. Each animal was ready for acute drug testing when the average daily self-stimulation thresholds varied by less than 10% across 3 consecutive days of testing.

C. Acute drug testing: BSR

Three rate-frequency curves (18 min each) were determined for each animal prior to drug injection; the first determination served to stabilize responding and the data were r.ot used in the analysis. If there was less than a 10% difference between the threshold frequencies of the second and third curves, the animal was removed from the test cage and given an intraperitoneal injection of drug (PCP; 2.5 or 5.0 mg/kg) or vehicle (physiological saline). The animal was then immediately returned to the test cage, and five more rate-frequency curves were determined.

D. Repeated Drug Testing: BSR

Animals were tested with PCP or vehicle eight times during the BSR phase of the experiment, approximately once per week, according to the following procedure: after each BSR drug-test, animals received a five day hiatus during which brain stimulation was not available. On the sixth day, three rate-frequency curves were determined for each animal in order to re-stabilize responding. On the following day, three rate-frequency curves were again determined: if there was less than a 10% difference between the threshold frequencies of the second and third pre-injection curves, the animal was considered ready for re-testing.

After each animal was administered the same treatment as in the first drug test, it was immediately returned to the test cage, and five more rate frequency curves were determined.

If there was more than a 10% difference between the second and third pre-injection threshold determinations, the animal was not tested further on that particular day. Pre-injection thresholds were then determined on consecutive days until the responding had again stabilized (less than a 10% difference between the threshold frequencies of the second and third curves), at which time the animal was re-tested. If an animal did not consistently lever-press for stimulation at all of the highest four frequencies in the threshold determination, the stimulation was delivered at higher frequencies: the next four stimulation frequency "steps" (0.05 log units each) were added on the high end of the rate-frequency function, and the lowest four stimulation frequencies were no longer used. The animal was deemed ready for re-testing when its performance on this new series of stimulation frequencies had stabilized.

Each animal received repeated intermittent drug-testing in this fashion until it had received drug or vehicle treatment on eight occasions.

E. Saline Test

On the ninth testing occasion, each animal was injected with saline under otherwise identical testing conditions.

F. Measurement of locomotor activity

Approximately one week after animals had completed the BSR phase of the experiment, the locomotor-stimulating properties of PCP were evaluated. Animals that had received stimulation and PCP (2.5 or 5.0 mg/kg) or stimulation and saline vehicle were administered 5.0 mg/kg PCP intraperitoneally, and immediately placed in the locomotor test boxes. In order to control for any effects of brain stimulation experience on locomotor activity, 8 naive (unstimulated) animals were injected with 5.0 mg/kg PCP, while 8 other

unstimulated animals were tested with vehicle alone; these animals were weight-matched and handled for the 10 days immediately prior to locomotor activity testing. Horizontal locomotor activity was estimated for 2 hours following injection in darkness during the light cycle. This procedure was repeated every third day until the animals had been tested in the locomotor apparatus a total of eight times.

V. Histology

The 24 rats used in the BSR phase were deeply anesthetized with an intraperitoneal injection of chloral hydrate (400 mg/kg) after they completed the locomotor phase of the experiment. A 1.5 mA anodal current was passed through the electrode that had delivered the stimulation during testing in order to deposit metallic particles at site of the electrode tip. Each rat was then perfused with 60 cc physiological saline, followed by 60 cc of a formalin-cyanide solution (10% formalin, 3% potassium ferricyanide, 3% potassium ferrocyanide, and 0.5% trichloroacetic acid) that reacts with the metallic particles at the site of the electrode tip to form a blue mark. After the brain was removed, it was stored in 10% formalin for a minimum of 5 days before sectioning. Each brain was then quickly frozen using dry ice, and sliced in 40 μm coronal sections. Sections that contained the electrode track were mounted on slides; a representative slice from the center of the lesion was traced under low magnification, and transposed to the closest matching map from the stereotaxic atlas of Pelligrino, Pelligrino, and Cushman (1979).

VI. Statistical Analysis

A two-way (Treatment x Time) analysis of variance (ANOVA) with repeated measures was used to evaluate the effects of acute PCP or vehicle on frequency thresholds; likewise, an identical two-way ANOVA with repeated measures was used to examine the acute effects of treatment on response asymptote across the 90 minute period. The effects of repeated administration of PCP or vehicle on both BSR threshold and response

asymptote were also individually analyzed using two-way (Treatment x Days) repeated measure ANOVAs. The effects of saline on threshold and response asymptote (the ninth test session) were individually analyzed using one-way (Treatment) ANOVAs. Acute locomotion was analyzed using a one-way (Prior Treatment) ANOVA; repeated locomotion, with a two-way (Prior Treatment x Session) repeated measures ANOVA.

In the event of significant main effects or interactions, *post hoc* comparisons were made using Tukey's Honestly Significant Difference (HSD) t-test.

VII. Drug

Phencyclidine hydrochloride (National Institute on Drug Abuse, Washington, DC) was dissolved in a sterile physiological (0.9%) saline, and was prepared daily immediately prior to administration.

RESULTS

Acute Treatment: BSR

Acute administration of phencyclidine at doses of 2.5 and 5.0 mg/kg caused parallel leftward shifts of the functions that relate response rates to stimulation frequency. Data from a representative animal in the 2.5 mg/kg group (Fig. 1) or the 5.0 mg/kg group (Fig. 2) indicate that a lower "dose" of stimulation sustains pre-injection levels of responding after administration of either dose of PCP, but not after saline vehicle alone (Fig. 3).

The threshold-lowering effects of PCP were strongest during the first hour after administration (Fig. 4): a Treatment x Time ANOVA (with repeated measures) revealed a significant effect of treatment ($F_{2,21}= 7.11$, $p<0.01$) and time after injection ($F_{4, 84}= 6.01$, $p<0.01$) on stimulation threshold. Stimulation thresholds for animals treated with either 2.5 or 5.0 mg/kg were significantly lower (Tukey's HSD) than saline vehicle-treated
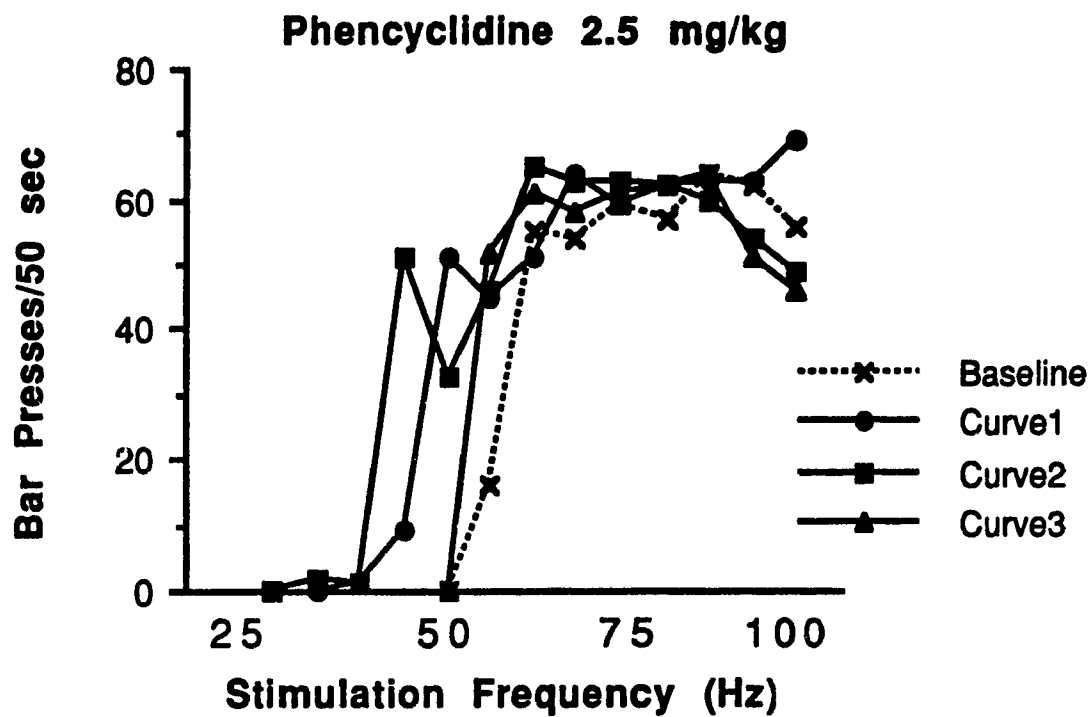
Figure 1.   Rate of bar pressing (per 50 seconds) as a function of stimulation frequency during pre-injection baseline, and after intraperitoneal PCP at 2.5 mg/kg. Data are from a single representative animal.
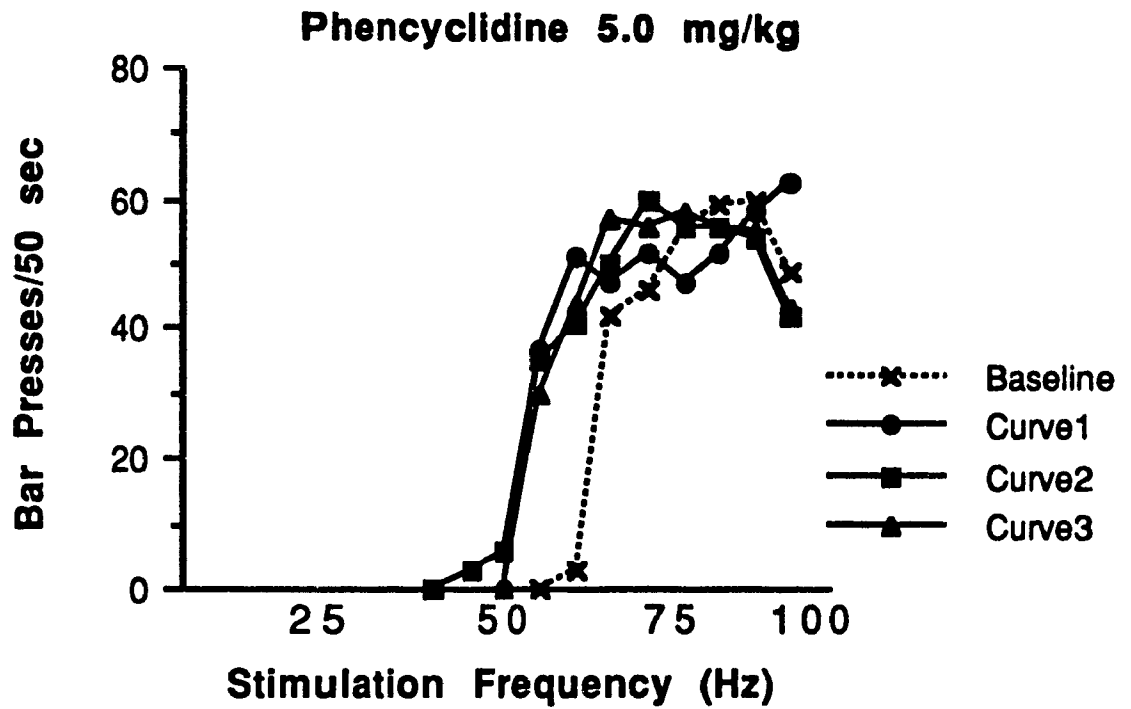
Figure 2.   Rate of bar pressing (per 50 seconds) as a function of stimulation frequency
during pre-injection baseline, and after intraperitoneal PCP at 5.0 mg/kg.
Data are from a single representative animal.
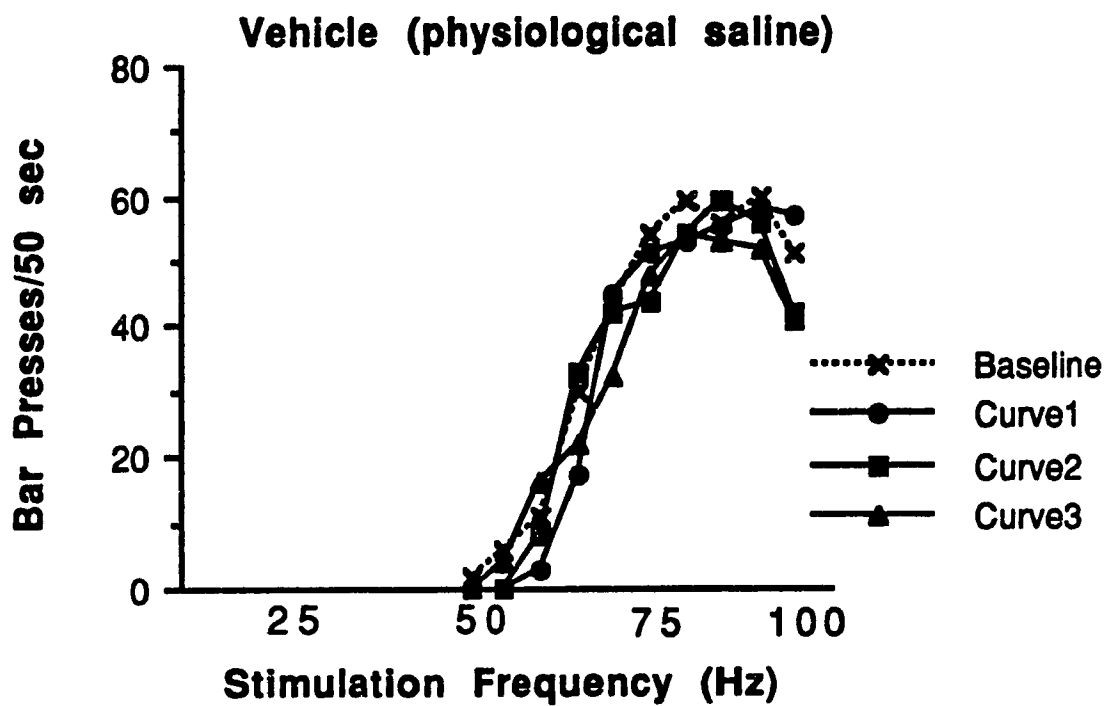
Figure 3.   Rate of bar pressing (per 50 seconds) as a function of stimulation frequency

during pre-injection baseline, and after intraperitoneal saline vehicle. Data

are from a single representative animal.

Figure 4.   Mean frequency threshold (+/-S.E.M., n = 8 per group) of lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection threshold) as a function of time after intraperitoneal injection of

PCP (2.5 or 5.0 mg/kg) or saline vehicle.

animals at the end of the first (p<0.01), second (p<0.01), and third (p<0.05) 18-minute

rate-frequency determinations (0-54 minutes after administration of PCP). By the fourth

rate-frequency determination (55-72 min), no statistically significant differences were

evident: stimulation thresholds for animals treated with 2.5 mg/kg PCP had returned to pre-

injection levels, although thresholds for animals treated with 5.0 mg/kg PCP remained

slightly decreased. During the last curve (73-90 min), stimulation thresholds for animals in

the PCP 5.0 mg/kg group were again lower than saline vehicle-treated animals (p<0.01).

There were no significant differences between animals in the 2.5 or 5.0 mg/kg groups

across the 90 minute test period. The Treatment x Time interaction was non-significant

($F_{8,84}=1.35$, n.s.), indicating that the effects of time on stimulation threshold were similar

regardless of whether animals had received either dose of PCP or saline vehicle.

Acute administration of 5.0 mg/kg PCP caused a transient but significant decrease

in maximal response rates shortly after administration (Fig. 5). Although a Treatment x

Time ANOVA (with repeated measures) revealed no significant main effects, there was a

significant interaction ($F_{8,84}= 2.53$, p<0.05); during the second rate frequency

determination (19-36 min), the response asymptotes of animals administered 5.0 mg/kg

PCP were significantly lower (Tukey's HSD) than those of animals treated with 2.5 mg/kg

PCP (p<0.01) or saline vehicle (p<0.01).

Repeated Treatment: BSR

Repeated intermittent administration of PCP or saline vehicle led to no progressive

changes in threshold (Fig. 6). Since the effects of PCP were strongest within the first

hour, comparisons across days were made on the basis of the first three rate frequency

functions in each of the eight test sessions. Animals were tested with PCP or saline vehicle

once every seven to eight days (mean +/-S.E.M.= 7.51 +/- 0.04); a Treatment x Days

ANOVA (with repeated measures) revealed that the main effect of treatment ($F_{2,21}=20.35$,

p<0.0001) remained highly significant. However, there were no progressive changes in

Figure 5.   Maximal rates of responding (+/-S.E.M., n = 8 per group) for lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection asymptote) as a function of time after intraperitoneal injection of
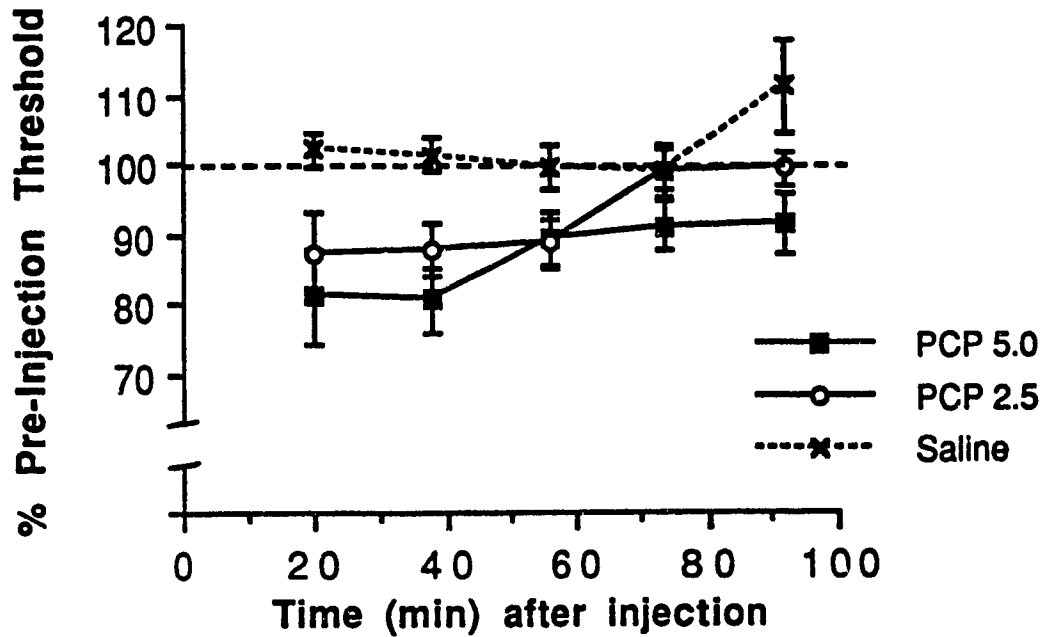
PCP (2.5 or 5.0 mg/kg) or saline vehicle.

Figure 6. Mean frequency threshold (+/-S.E.M., n = 8 per group) of lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection threshold) as a function of test session number. Animals received

an intraperitoneal injection of PCP (2.5 or 5.0 mg/kg) or saline vehicle

approximately once per week. Each point represents the mean threshold

averaged over the first three rate-frequency determinations of each test

session.

the threshold across stimulation days ($F_{7,147}$= 0.80, n.s.) nor was there a Treatment x Time interaction ($F_{14,147}$= 1.08, n.s.).

Response asymptote (Fig. 7) was significantly altered by repeated administration of PCP: a significant main effect of Treatment ($F_{2,21}$= 5.03, p<0.05) revealed that, over the course of the experiment, response asymptotes for animals treated with 2.5 mg/kg PCP were higher than those for animals treated with 5.0 mg/kg. However, the lack of a significant main effect of Days ($F_{7,147}$= 2.0, n.s.) or a Treatment x Days interaction ($F_{14,147}$= 0.93, n.s.) indicates that there were no progressive changes in asymptote due to repeated treatment.

Saline Testing: BSR

All animals responded at pre-injection levels after receiving saline injections during the ninth test session: saline alone had no effect on threshold ($F_{2,21}$=1.01, n.s.; Fig. 8) or asymptote ($F_{2,21}$=0.05, n.s.; Fig. 9), regardless of prior treatment.

Acute Treatment: Locomotion

After administration of 5.0 mg/kg PCP, animals that previously received the combination of stimulation and PCP had higher levels of locomotor activity than naive animals receiving either PCP or vehicle for the first time (Fig. 10). Animals formerly in the BSR phase of the study entered the locomotor phase 6.0 +/- 0.31 days after the saline test; a one-way ANOVA revealed a significant effect of prior treatment ($F_{4,35}$= 7.59, p<0.001). Administration of 5.0 mg/kg did not have any effect on locomotor activity in naive (unstimulated) animals receiving treatment for the first time; however, animals formerly treated with either 2.5 or 5.0 mg/kg PCP and stimulation were significantly more active than either group naive animals (p<0.01). Animals formerly treated with stimulation and saline vehicle were significantly less active than animals that had received stimulation
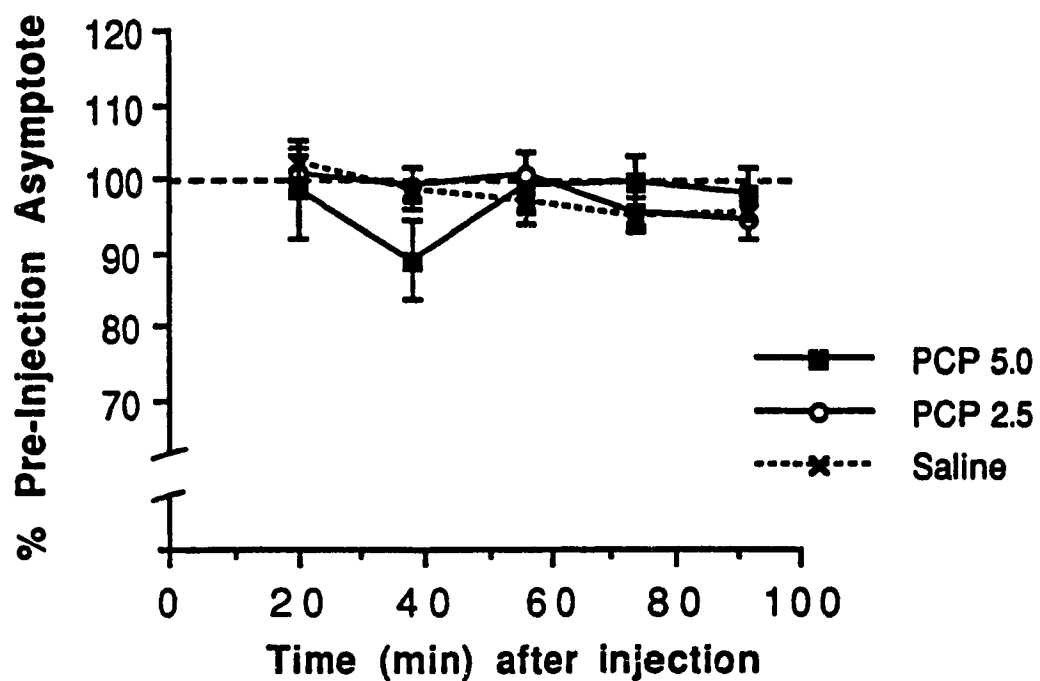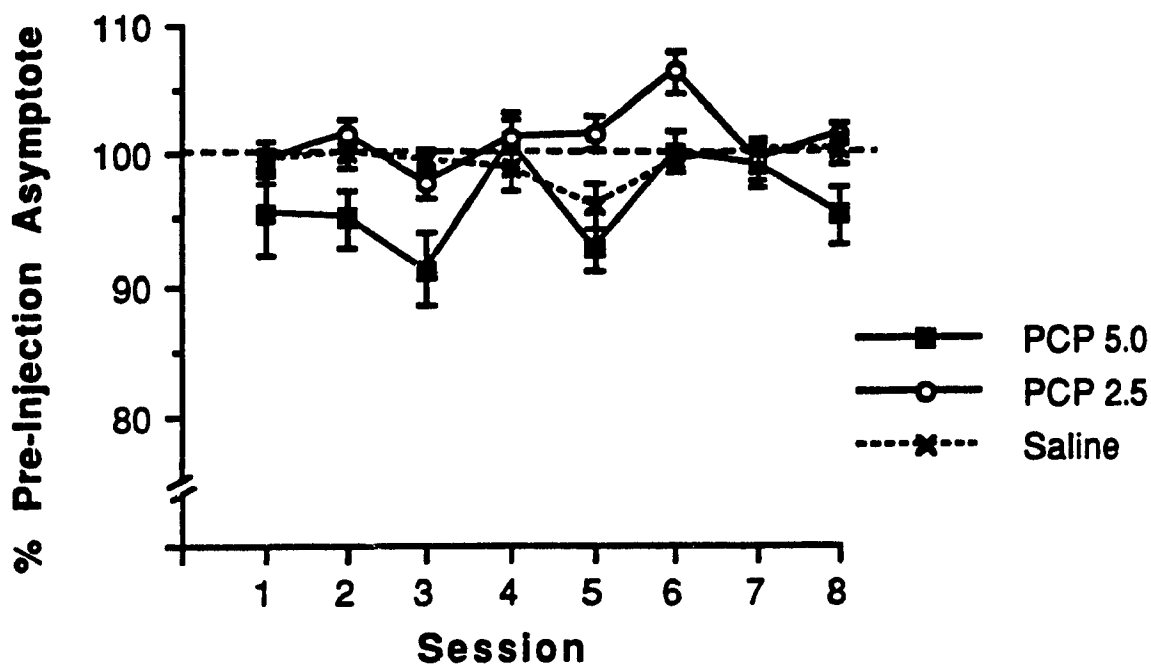
Figure 7.   Maximal rate of responding (+/-S.E.M., n = 8 per group) for lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection asymptote) as a function of test session number. Animals received

an intraperitoneal injection of PCP (2.5 or 5.0 mg/kg) or saline vehicle

approximately once per week. Each point represents the mean asymptote

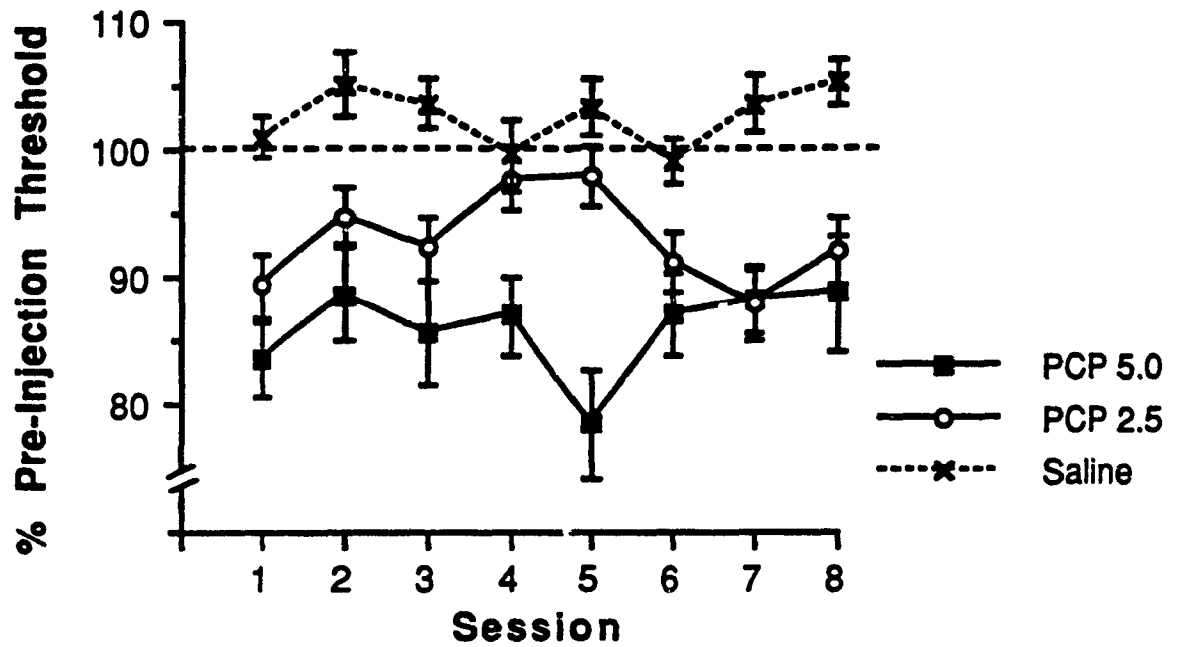averaged over the first three rate-frequency determinations of each test

session.
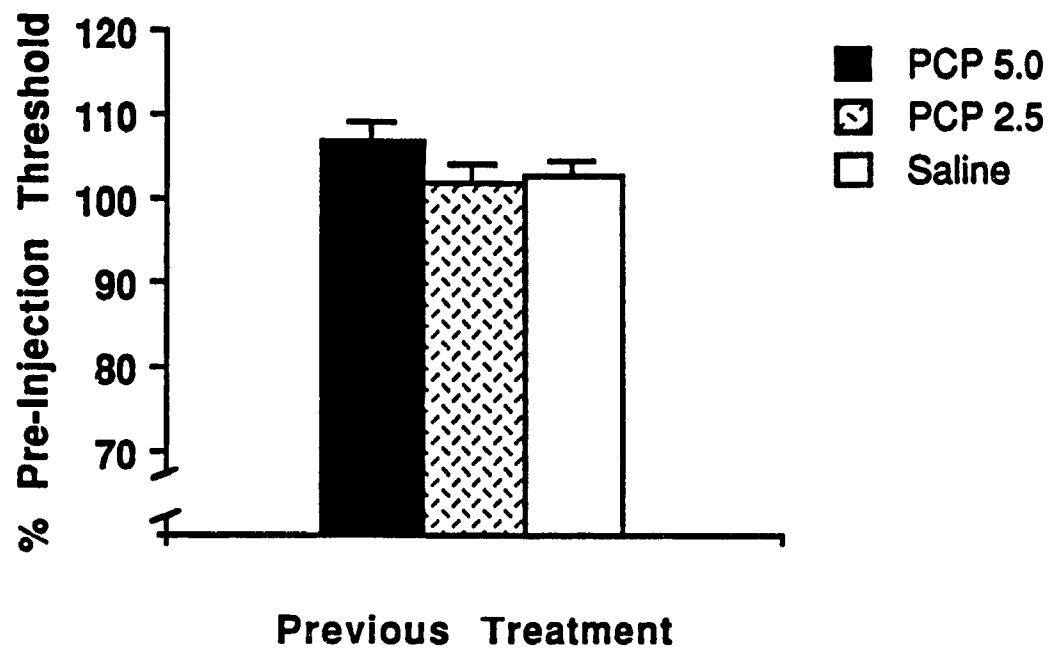
Figure 8.   Mean frequency threshold (+/-S.E.M., n = 8 per group) of lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection threshold) after all animals received an intraperitoneal injection of

saline vehicle during the ninth test session.
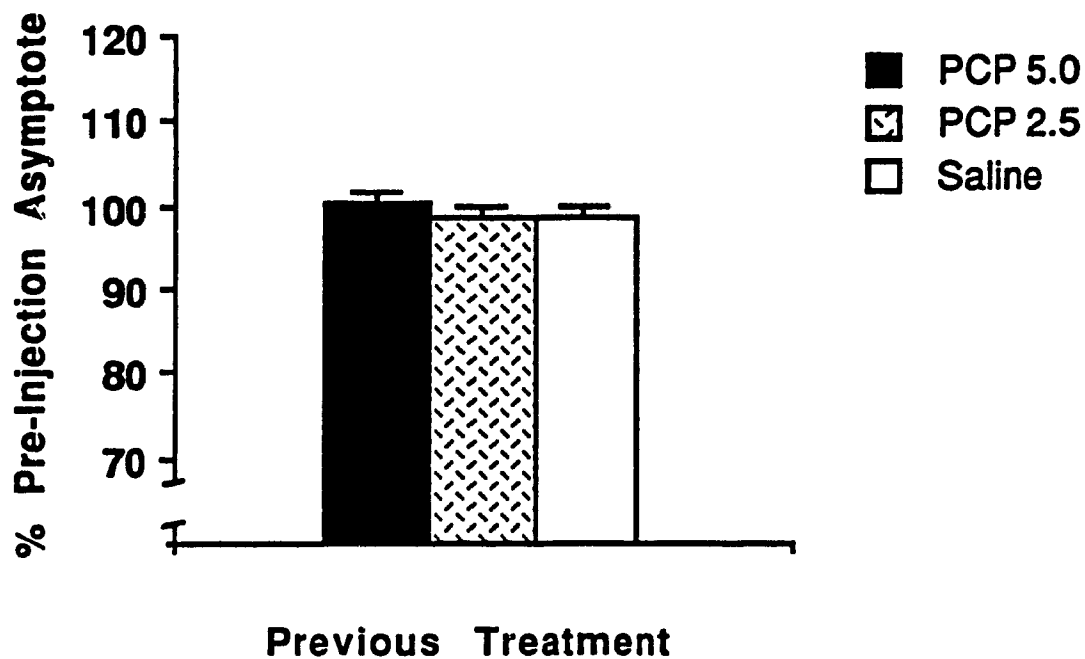
Figure 9.   Maximal rate of responding (+/-S.E.M., n = 8 per group) for lateral

hypothalamic brain stimulation reward (expressed as percentage of pre-

injection asymptote) after all animals received an intraperitoneal injection of

saline vehicle during the ninth test session.
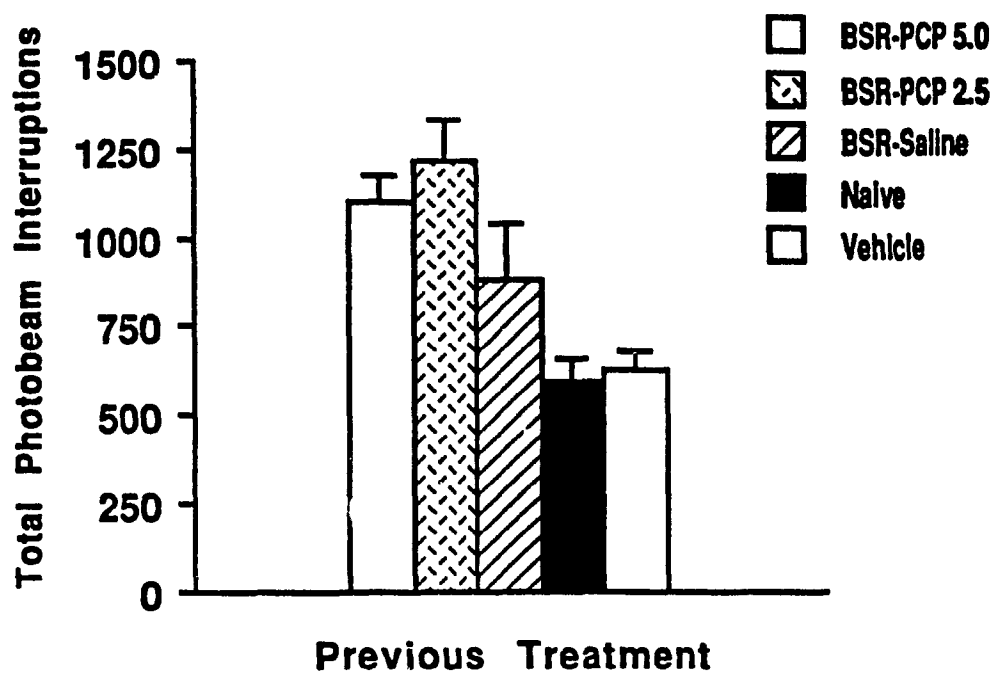
Figure 10. Mean (+/-S.E.M., n = 8 per group) locomotor activity counts (expressed as number of photobeam interruptions) after an acute intraperitoneal administration of 5.0 mg/kg PCP immediately before testing.

and 2.5 mg/kg PCP (p<0.05), although their locomotor scores were not statistically different from those of any other group of animals.

Repeated Treatment: Locomotion

Repeated treatment with 5.0 mg/kg PCP had different effects on locomotor activity depending on the animals' previous experience with the drug and stimulation (Fig. 11). A two-way ANOVA (with repeated measures) revealed a significant main effect of prior treatment ($F_{4,35}=11.68$, $p<0.0001$), and a significant Treatment x Session interaction ($F_{28,245}= 4.07$, $p<0.0001$). For naive animals treated with 5.0 mg/kg PCP, locomotor activity scores during the eighth session were significantly greater (Tukey's HSD) than during the first session ($p<0.01$). On the other hand, locomotor scores for animals that had been previously treated with stimulation and 2.5 or 5.0 mg/kg PCP were significantly lower during the last day of treatment than during the first activity session ($p<0.01$). Similarly, the locomotor scores of naive animals treated only with vehicle waned significantly during the course of the experiment ($p<0.05$). The locomotor activity scores of animals formerly tested with saline vehicle did not change after repeated treatment with 5.0 mg/kg PCP.

Histology

Tips of the stimulating electrodes were all localized within the medial forebrain bundle (Fig. 12).
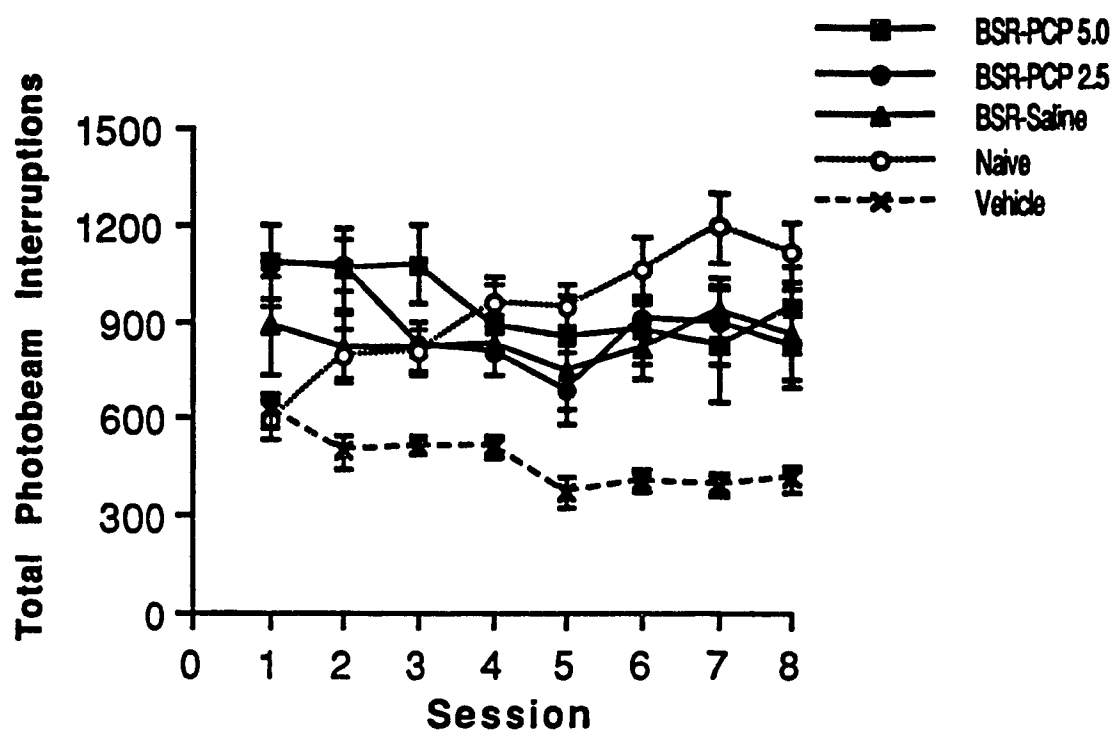
Figure 11.   Mean (+/-S.E.M., n = 8 per group) locomotor activity counts (expressed as number of photobeam interruptions) as a function of test session number. All animals received an intraperitoneal administration of 5.0 mg/kg PCP immediately before testing once every three days.

-0.06

-0.08

-1.0
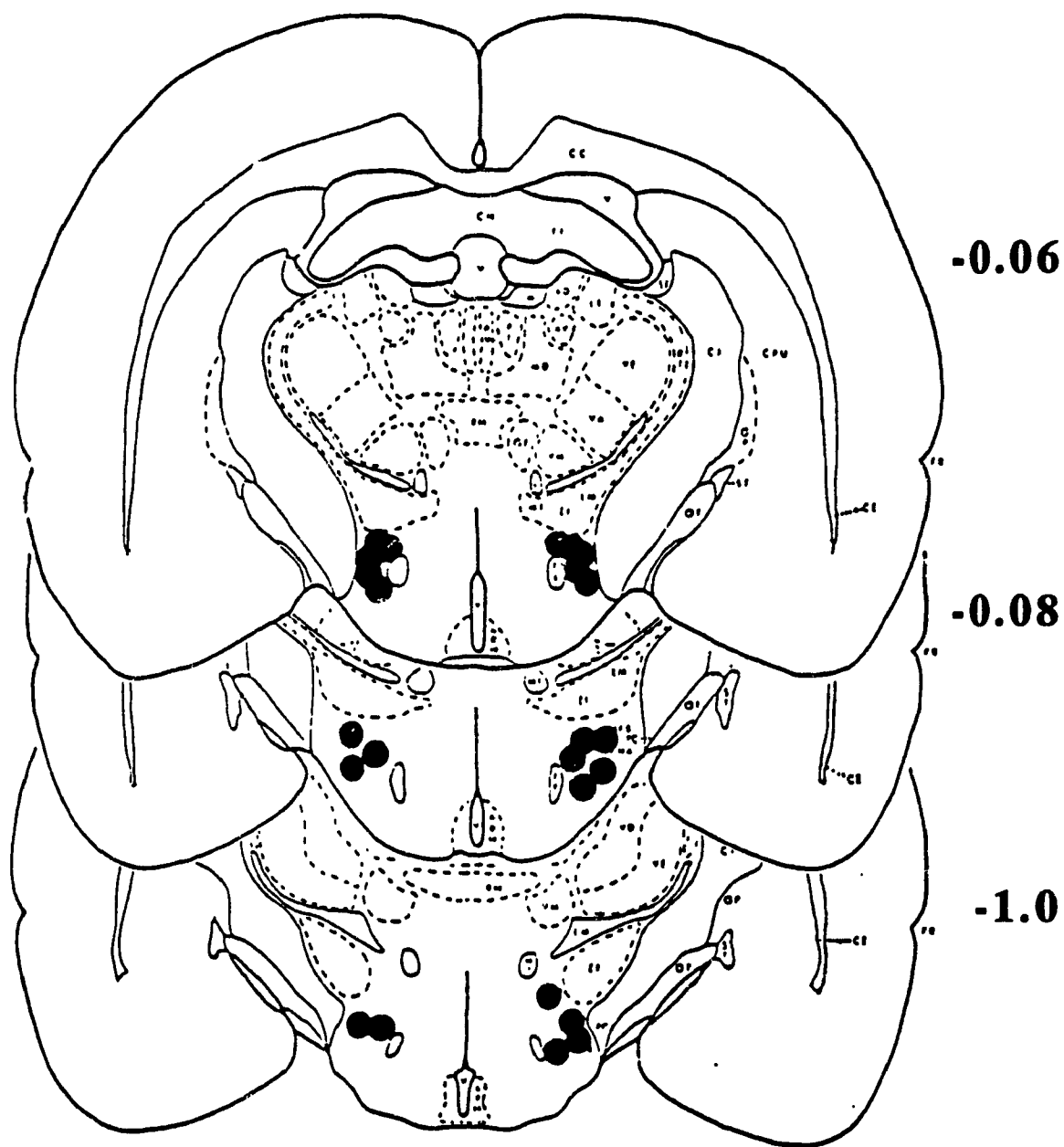
Figure 12.   Histological confirmation of stimulating electrode placement. Numbers

represent distance anterior to bregma, with skull elevated to 5 mm above the

intra-aural line.

DISCUSSION

I. Acute administration of phencyclidine

Acute administration of phencyclidine (2.5 and 5.0 mg/kg) elicited parallel leftward shifts of the functions that relate response rates to stimulation frequency, indicating that the drug increased the impact of BSR in animals implanted with MFB-stimulating electrodes. Like amphetamine (Gallistel and Karras, 1984) and nicotine (Bauco and Wise, 1991), phencyclidine caused significant decreases in the stimulation "dose" that was required to maintain normal levels of responding. The fact that the action of PCP summated with the rewarding effect of brain stimulation implies that the action of PCP was itself rewarding.

Although acute phencyclidine significantly potentiated the rewarding impact of lateral hypothalamic electrical stimulation, the magnitude of the threshold shift was relatively minor in comparison to shifts elicited by other drugs of abuse. A distinct advantage of the curve-shift paradigm is that it allows any shifts in stimulation threshold to be evaluated on a ratio scale (Gallistel and Freyd, 1987; Wise and Rompré, 1989). This technique allows direct quantitative comparisons of threshold shifts not only between several doses of a particular drug, but also between optimal doses of two or more different drugs. Averaged over the first 60 minutes after administration, 5.0 mg/kg phencyclidine decreased stimulation thresholds by approximately 0.1 log units. Nicotine can cause a leftward shift of 0.2 log units (Bauco and Wise, 1991), whereas d-amphetamine can cause parallel leftward shifts as large as 0.3 log units (Gallistel and Karras, 1984; Colle and Wise, 1988a), which represents a doubling of the rewarding impact of BSR (Gallistel and Freyd, 1987). While higher doses of phencyclidine may further potentiate BSR, behavioral observations from the present investigation suggest that testing animals in the curve-shift paradigm after administration of more than 5.0 mg/kg PCP might not yield meaningful results.

Phencyclidine caused a transient decrease in the capacity to lever-press at asymptotic rates for BSR at doses that decreased frequency thresholds. The response asymptotes of animals administered 5.0 mg/kg PCP were diminished by approximately 10% during the second rate-frequency determination, which was made during the period of 19 to 36 minutes after administration of drug. Side effects including ataxia, circling, and rearing were observed within this period. These effects became evident one or two minutes after injection, and peaked approximately 15 into the first rate-frequency determination. However, because the stimulation was always delivered in descending frequencies and testing began immediately following the injection of PCP, animals were able to lever press for the highest available frequencies at asymptotic rates during the first threshold determination, before the drug was fully absorbed and the side effects began to interfere with motor capacity. Consequently, the performance-debilitating effects of 5.0 mg/kg PCP were not evident until the second threshold determination. The side effects were most striking during the times that the animal was not self-stimulating, such as the 5 second inter-trial interval between frequency tests; they were less obvious during periods when stimulation was available, and the behavior of the animal was focused on the lever. Ataxia waned approximately 40 minutes after administration, as suggested by reinstatement of pre-injection levels of performance during the last three threshold determinations (37 to 90 min). Delivery of stimulation frequencies in random or ascending order might increase the time that 5.0 mg/kg PCP interferes with response capacity.

The side effects observed at 5.0 mg/kg PCP suggest that higher doses might cause more substantial disruptions in performance; indeed, in a pilot experiment, 10.0 mg/kg PCP lowered lever pressing rates to below 20% of pre-injection levels, making threshold determinations during the first hour of testing impossible (data not presented).

The dopamine-enhancing actions of PCP and other drugs of abuse have been evaluated by DiChiara and co-workers using *in vivo* microdialysis techniques (DiChiara and Imperato, 1988; Carboni et al., 1989). Since amphetamine, nicotine and phencyclidine

have been found to increase levels of synaptic dopamine, it is reasonable to suspect that the ability of PCP to enhance the impact of BSR is related to its action on the dopaminergic system. However, synaptic dopamine levels, as measured by microdialysis, appear to be of limited utility in predicting the magnitude of a drug's effects on BSR. For example, a 1.0 mg/kg dose of amphetamine caused an 1000-fold increase in nucleus accumbens dopamine (DiChiara and Imperato, 1988), and elicited a 0.3 log unit shift in the BSR threshold (Gallistel and Karras, 1984). At 5.0 mg/kg, PCP caused a 350% increase in nucleus accumbens dopamine (Carboni et al., 1989), and in the present investigation elicited a threshold shift of 0.1 log units. The maximal BSR threshold shift elicited by nicotine was twice as large as that of 5.0 mg/kg PCP (0.2 log units), and was found at 0.2 mg/kg (Bauco and Wise, 1991). However, the maximal increase in synaptic dopamine after treatment with nicotine was 220% (DiChiara and Imperato, 1988), and was observed at a dose 3 times larger (0.6 mg/kg) than that which maximally facilitated BSR. As more drugs of abuse are evaluated in the curve-shift paradigm, the nature of the relationship between facilitation of BSR and levels of synaptic dopamine can be further elucidated.

It has been suggested that the mechanism of PCP's elevation of synaptic dopamine involves blockade of the reuptake process (Gerhardt et al., 1987; Hernandez et al., 1988), perhaps by direct binding to the dopamine carrier protein (Rothman et al., 1989). It is tempting to speculate that this action contributes to the BSR-facilitating effects of PCP. However, it also appears that non-competitive blockade of the NMDA receptor is sufficient to facilitate BSR: MK-801 causes a leftward shift in the BSR rate-frequency function similar to that of PCP (approximately 0.1 log units: Corbett, 1989), despite having little affinity for the dopamine uptake protein (Reid et al., 1990). Although their mechanisms of action remain obscure, non-competitive NMDA antagonists have been shown to have facilitatory effects on the dopamine system, such as stimulation of the firing of VTA dopamine cells (French and Ceci, 1990). Yet, the recent data regarding the role of excitatory amino acids (EAAs) as modulators of dopaminergic neurons are controversial.

In one recent model, that of Carlsson (1988), it is proposed that glutamate and dopamine independently modulate the activity of GABAergic neurons which inhibit the excitatory pathway projecting from the thalamus to the cortex. According to this model, excitation of GABAergic cells in the striatum by glutamate inhibits thalamic input, thereby protecting cortical neurons from an overload of neuronal activity. On the other hand, inhibition of GABAergic cells by dopamine disinhibits the thalamocortical pathway, allowing increased levels of sensory input to reach the cortex. A shift in the balance between glutamate and dopamine via either DA agonists or NMDA antagonists could, in this model, open the "thalamic filter" and produce hyperarrousal in the organism. Dysfunctions or manipulations thought to "widen" the thalamic filter by disruption of glutamate function, independent of underlying dopaminergic tone, have been linked to the symptoms of schizophrenia (Carlsson, 1988). Since the association of PCP and schizophrenia has been well documented (Luisada and Brown, 1976; Allen and Young, 1978; Jackson and Singer, 1988; Javitt, 1987; Steinpreis et al., 1991), mere blockade of NMDA receptors might play a role in the central stimulant and psychotomimetic properties of PCP and related ligands. Regardless of the mechanism of action, the qualitative and quantitative similarities between the effects of PCP in the present study and MK-801 (Corbett, 1989) support the notion that blockade of NMDA receptor function might be sufficient to elicit small leftward shifts in the impact of BSR by interacting with complex subcortical feedback systems.

II. Repeated administration of phencyclidine

There was no evidence of sensitization or tolerance to the reward-facilitating effects of repeated phencyclidine. No progressive changes in either stimulation threshold or response asymptote were noted in any group of animals over the course of the eight weekly test sessions. Occasional slight increases in response asymptote were noted in animals receiving repeated administration of 2.5 mg/kg PCP, while 5.0 mg/kg caused decreases of a similar magnitude; however, there were no progressive changes in the effects of PCP on

response asymptotes. Although tolerance to ataxia has been observed in rodents after daily injections of a high dose of PCP (10.0 mg/kg) for two weeks (Nabeshima et al., 1987), tolerance to the performance-debilitating properties of 5.0 mg/kg PCP was not observed in the present experiment. Rather than progressive decreases in ataxia and circling, the magnitude of these side-effects was stable and occurred at unpredictable intervals over the eight weeks of testing. This finding suggests that a single weekly injection of 5.0 mg/kg PCP is not sufficient to cause tolerance to the ataxic effects of the drug. Finally, the response patterns observed after repeated phencyclidine do not appear to be permanent or due to conditioning, since administration of saline vehicle on the ninth testing occasion elicited pre-injection levels of responding.

Lack of sensitization of the reward-enhancing effects of PCP is consistent with earlier findings using repeated administration of opiates. Both Esposito and Kornetsky (1977) and Kelley and Reid (1977) found that administration of morphine decreased self-stimulation thresholds, but that the magnitude of this effect did not change after daily administration of morphine for up to 34 days. Similarly, it has been recently reported that the threshold-lowering effects of nicotine are not altered with repeated administration (Bauco and Wise, 1991). Lack of tolerance to the rewarding effects of these drugs in the self-stimulation paradigm implies that their reinforcing qualities are not altered despite chronic administration.

While morphine decreases self-stimulation thresholds, its effect on response rates is biphasic: following an initial period in which self-stimulation behavior was suppressed, an excitatory effect on response rate occurred several hours after injection (Adams et al., 1972). With repeated daily administration of morphine, tolerance to the suppressive effect was observed, while the excitatory effect appeared progressively sooner after injection (Bush et al., 1976). Interestingly, self-stimulation thresholds did not change as the excitatory effect became more evident, but instead only became "unmasked" at progressively earlier latencies (Kelley and Reid, 1977). As mentioned earlier, there were

no such progressive changes in response capacity after repeated intermittent administration of PCP, probably because a single administration per week is not sufficient to elicit tolerance to the ataxic effects of the drug. However, the results of the present investigation support earlier findings with morphine that response asymptotes and self-stimulation thresholds can be concurrently decreased. Although repeated amphetamine elicits progressive increases in self-stimulation response rates (Kokkinidis, 1980; Predy and Kokkinidis, 1984), without concurrent measurements of stimulation thresholds effects on reward cannot be distinguished from effects on performance capacity.

Although once-weekly injections of PCP were not sufficient to induce tolerance to the performance-debilitating effects of PCP, this schedule appears to have produced sensitization to the locomotor-stimulating effects of the drug. When animals were tested in a locomotor apparatus following the BSR phase of the experiment, a dose of 5.0 mg/kg PCP induced significantly more activity in animals that had been formerly treated with either 2.5 or 5.0 mg/kg PCP than in unstimulated animals that were receiving drug treatment and behavioral testing for the first time. However, it is difficult to attribute the increase in activity to the mere administration of PCP, since the locomotor scores of animals that had prior experience with stimulation and saline vehicle were not statistically different from the scores of animals that had received stimulation and 5.0 mg/kg PCP, or either group of unstimulated animals. Furthermore, with repeated testing unstimulated animals became progressively more sensitive to the locomotor-stimulating effects of PCP, while those animals previously treated with stimulation and PCP at 2.5 or 5.0 mg/kg were progressively less active.

Thus, repeated testing with PCP causes progressive sensitization to the locomotor-stimulating properties of the drug in unstimulated animals, but no systematic changes in the impact of BSR in animals implanted with MFB electrodes. Although it has been suggested that the neuronal substrates subserving locomotion and reward are homologous (Wise and Bozarth, 1987), the present data suggest an apparent dissociation. However, several

possible explanations for the observed pattern of results remain to be explored. Animals treated with stimulation and either dose of PCP were most active during their first exposure to the locomotor box, suggesting that they may have already maximally sensitized to the locomotor-stimulating effects of the drug. Since acute locomotor activity scores for the group of animals treated with stimulation and saline were not significantly different from scores of animals treated with stimulation and 5.0 mg/kg PCP, it remains possible that rewarding brain stimulation itself does cause some degree of sensitization of the putative neuronal pathway that subserves both drug reward and locomotor activity. Thus, the possibility that the putative reward system undergoes complete sensitization during self-stimulation screening or training cannot be discounted by the present study. Progressive sensitization to the locomotor-stimulating effects of PCP has been observed by others (Nabeshima et al., 1987), and was clearly observed in unstimulated animals in the present investigation; the fact that none of the animals that had been formerly treated with stimulation sensitized to the locomotion-enhancing effects of PCP suggests that there is a limit to the degree of sensitization that can occur. Experiments designed to vary the amount of rewarding electrical stimulation that is delivered to different groups of animals are needed to examine the reliability of this potential dissociation of reward and locomotion.

Thus, like most psychomotor stimulants, phencyclidine enhances the impact of brain stimulation reward. Neither the reward-facilitating nor the performance-debilitating effects of PCP undergo tolerance or sensitization with repeated intermittent testing. The fact that the reinforcing properties of PCP are not easily demonstrated in some animal models (intravenous self-administration, conditioned place preference), despite the potential to cause neurochemical effects analogous to those of other commonly abused drugs, implies that the rewarding effects of this complex drug may be masked in animals by dysphoric side effects that do not undergo tolerance with intermittent administration. Furthermore, lack of tolerance or sensitization to the reward-enhancing properties after

repeated intermittent administration suggests that the initially reinforcing properties of

phencyclidine can persevere despite chronic abuse by humans.

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