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Comparison of the Behavioral Pharmacology of Phencyclidine to Related Compounds

Kathleen T. Brady

COMPARISON OF THE BEHAVIORAL PHARMACOLOGY OF PHENCYCLIDINE TO RELATED COMPOUNDS

BY

Kathleen T. Brady

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[redacted]

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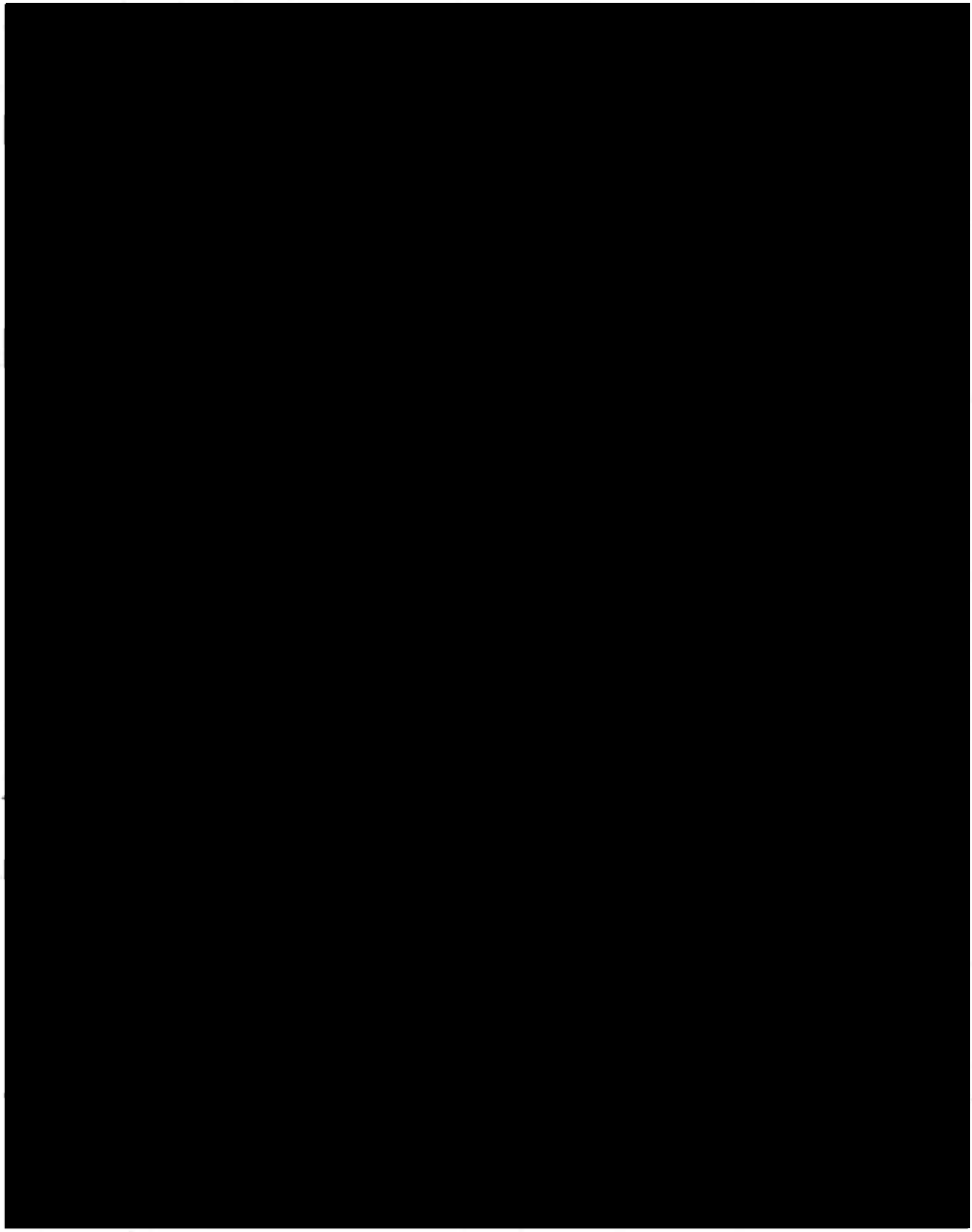

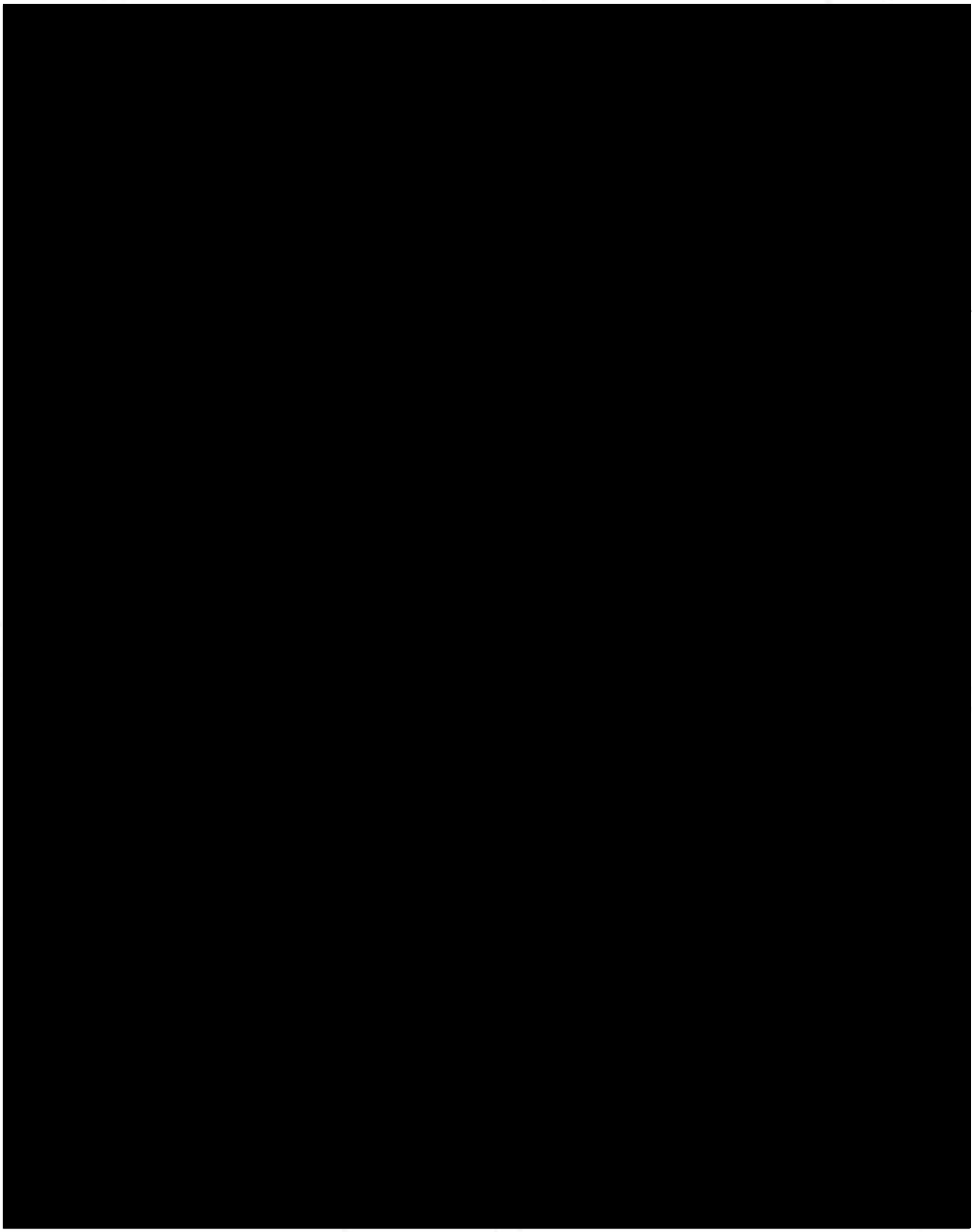

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To my family,

for their constant encouragement and support

and

To John,

for believing in me when I didn't believe in myself

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ABSTRACT

COMPARISON OF THE BEHAVIORAL PHARMACOLOGY OF PHENCYCLIDINE TO RELATED COMPOUNDS

Kathleen T. Brady, Ph.D.

Medical College of Virginia - Virginia Commonwealth University, 1981.

Major Professor: Dr. R.L. Balster

Phencyclidine (PCP) belongs to a class of drugs with a unique and characteristic spectra of pharmacological activity. PCP has recently become a major drug of abuse. Structural analogues of PCP have also been reported in street use. The following experiments explore the behavioral pharmacology of PCP and several compounds with PCP-like activity.

In Experiment I the effects of PCP were compared to three structural analogues in rhesus monkeys trained to lever press on a fixed-interval 5-min schedule of food presentation. Dose-response curves and potency estimates were determined for PCP, N-ethyl-1-phenylcyclohexylamine (PCE), 1-(1-(2-thienyl) cyclohexyl) piperidine (TCP) and ketamine. The effects of all four drugs on response rates were dependent on the baseline rate of responding. High doses of all four drugs decreased overall response rates. Onset and duration of drug effects were also determined and compared.

In Experiments II through VI the drug discrimination paradigm was used. Animals were trained to discriminate PCP (rats, 3.0 mg/kg i.p.; monkeys, 0.16 mg/kg i.m.) from saline in a two-lever drug discrimination task on a fixed-ratio 32 (FR 32) schedule of food presentation. After reliable discriminative control of lever choice was established, generalization tests were conducted every third day. Test periods consisted of

a 2-min period during which responding on either lever was reinforced (rats) or responding was recorded but not reinforced (monkeys). The PCP dose-response determination preceded generalization testing with other compounds. Dose-effect curves for each drug for percent drug-lever appropriate responding and for suppression of operant responding during test sessions were analyzed by linear regression.

In Experiment II the discriminative stimulus properties of PCP and five other arylcycloalkylamines were investigated in squirrel monkeys. Generalization testing was conducted with PCP, PCE, TCP, 1-(1-phenylcyclohexyl) morpholine (PCM), 1-(1-phenylcyclohexyl) pyrrolidine (PHP), and ketamine. All drugs produced dose-dependent PCP-appropriate responding. The dose necessary to suppress operant responding to fifty percent of vehicle rates was 3 to 8 times larger than the ED_{50} for drug-lever appropriate responding.

Experiments III, IV and VI were designed to explore similarities between the discriminative stimulus properties of PCP and a series of structurally dissimilar compounds. In Experiment III the discriminative stimulus properties of dexoxadrol and etoxadrol, both 2-(2,2-substituted 1,3 dioxolan-4-yl) piperidines, were studied in squirrel monkeys. Both compounds generalized to PCP in a dose-dependent manner. The dose necessary to suppress operant responding to fifty percent of vehicle rates was 3 to 7 times larger than the ED_{50} dose for drug-lever appropriate responding.

In Experiment IV the discriminative stimulus properties of stereoisomers of N-allylnormetazocine, a benzomorphan opioid with psychotomimetic properties, were investigated in squirrel monkeys and rats.

In both species, the (+) isomer and the racemic mixture produced dose-dependent PCP-appropriate responding. The (-) isomer did not produce PCP-appropriate responding, however it was more potent than the (+) isomer in overall response rate suppression. High doses of naloxone (rats, 30 mg/kg; monkeys, 1.0 and 3.0 mg/kg) did not block the drug-lever appropriate responding or response rate suppression produced by either isomer of N-allynormetazocine.

In Experiment V the discriminative stimulus properties of ketamine stereoisomers were investigated in rats. Both isomers and the racemic form of ketamine produced drug-lever appropriate responding and decreased response rate in a dose-dependent manner. There was no significant potency difference between (±)-ketamine and either of the isomers for either of these measures.

The stereoselectivity of the discriminative stimulus properties of cyclazocine, another opioid of the benzomorphan series, in squirrel monkeys was explored in Experiment VI. The (+) isomer produced dose-dependent PCP-appropriate responding. The (-) isomer and the racemic mixture did not produce PCP-appropriate responding at any of the doses tested. The (-) isomer was 300 times more potent than the (+) isomer in overall response rate suppression.

The work presented in this thesis suggests that PCP belongs to a unique class of drugs which can have a wide variety of chemical structures. The overalp in the behavioral pharmacology of PCP and the psychotomimetic opioids of the benzomorphan series is probably due to the activity of the (+) isomers of these compounds.

I. GENERAL INTRODUCTION

The current escalation in the abuse of 1-(1-phenylcyclohexyl) piperidine (phencyclidine; PCP) has brought an increasing amount of attention to the class of drugs to which it belongs, the dissociative anesthetics. Recent research has revealed this group of compounds to have a very unique and characteristic spectra of pharmacological activity. The research presented in this dissertation represents an attempt to further characterize the behavioral pharmacology of this group of compounds and to make some contribution to the body of literature concerned with the relationship of structure to behavioral activity. All compounds referred to in this thesis are racemic mixtures unless otherwise indicated.

A. History of Phencyclidine

Phencyclidine (PCP) was synthesized by Victor Maddox and associates of Parke-Davis and Co. General pharmacological testing (Chen et al., 1959) indicated that PCP produced surgical anesthesia in monkeys without cardiac or respiratory depression. As a result, PCP was developed by Parke-Davis and Co. as an anesthetic agent. In 1957, clinical trials revealed that doses of 0.25 mg/kg i.v. produced anesthesia sufficient for minor and some major surgery (Greifenstein et al., 1958). Phencyclidine was developed for use in humans under the trade name Sernyl (Munch, 1974). Because of post-operative thought disturbances and agitation produced by phencyclidine, in 1965 clinical investigations were discontinued. In 1967, the drug patent was changed to permit the manufacture of PCP for veterinary use as an animal immobilizing agent (Martin et al., 1972; Seal and Erikson, 1969) under the trade name Serynlan (Bio-Ceutic Laboratories, Inc.). At the present time, PCP is not commercially available. Ketamine (Ketalar), a ketone analogue of

PCP, is presently marketed by Parke-Davis and Co. as a dissociative anesthetic for veterinary and human use. It has a very similar pharmacological profile to that of PCP (McCarthy et al., 1965; Chen et al., 1966) but has a shorter duration of action and a lower incidence of emergence reactions (Corssen and Domino, 1966; Corssen et al., 1968).

Reports of illicit use of PCP began in 1967 on the West Coast (Meyers et al., 1967/1968). At this time, it was marketed as a mild psychedelic and sold in tablet and capsule forms. Because the effects were often unexpected and the dosage could not be titrated, there was a high incidence of adverse reactions and PCP lost popularity as a street drug (Burns et al., 1975).

In the next few years, PCP was still found on the street, but it was usually misrepresented as another drug, most commonly as Δ9-tetrahydrocannabinol (THC). A survey in Los Angeles (Lundberg et al., 1976) revealed that out of 94 street samples of drugs sold as THC, 74 contained only PCP, and only 8.7 percent of the total samples containing PCP were represented correctly as PCP.

In the early 1970's, there was a marked change in PCP street use (Lerner and Burns, 1978). This was probably due to a trend towards smoking PCP on leaf material rather than oral ingestion of a tablet or capsule. This allowed the user to more effectively control the dosage. Between 1972 and the present time, there has been a steady increase in the number of emergency room mentions involving PCP in the Drug Abuse Warning Network (DAWN) system. The sharpest increase in PCP-related emergency room mentions has been in the three year period between 1976 and 1979. The Drug Enforcement Administration (DEA) has ranked PCP second only to heroin in its 1979 priority ranking of efforts against

illicit drug traffic (Newmeyer, 1980).

The slang name of street phencyclidine and its physical form have continuously changed since its emergence as a drug of abuse. It has appeared as a powder, a tablet, a leaf mixture and a liquid (Lundberg et al., 1976). It can be taken orally, bu insufflation, or sprinkled on a combustible material. At the present time, it is most commonly sold as PCP, Angel Dust, Hog or Crystal. To date, at least five structural analogues of PCP have been discovered in illicit street use (Shulgin and MacLean, 1976).

B. Chemistry

Phencyclidine hydrochloride (1-(1-phenylcyclohexyl) piperidine hydrochloride) is a white, stable solid with a melting point of 234-236^{o}C (Domino, 1964). It is a weak base that is readily soluble in water (Domino, 1964) and highly lipophilic at physiological pH (James and Schnoll, 1976). A recent report (Maayani and Gross, 1980) indicate that PCP has a relatively high pKa value (pKa = 9.42 at 25^{o}C, pKa = 9.20 at 37^{o}C), a low water solubility (2.2×10^{-4}M at 23^{o}C) and a high oil-water partition coefficient. PCP is prepared by the reaction of 1-piperidonocyclohexanecarbonitrile (PCC) with Grignard reagent (Shulgin and MacLean, 1976). The synthesis is fairly easy which, no doubt, partially explains the widespread availability and use of the drug.

In addition to phencyclidine, over thirty chemically similar analogues have been synthesized (Maddox et al., 1965; Kalir et al., 1969; Weinstein, et al., Maayani et al., 1974; Geneste et al., 1976; Shulgin and MacLean, 1976). Although several of these analogues have been discovered in illicit street use, there is a paucity of biological data on these compounds. Ketamine is the only PCP analogue

which has been subjected to extensive pharmacological examination (McCarthy et al., 1965) and spectra of activity is very similar to that of PCP.

Most active PCP analogues involve substitutions for the piperidine ring (i.e., PHP, PCE) and less frequently the phenyl ring (i.e TCP). In addition to structural analogues, it appears that there may be some structurally unrelated chemicals, namely etoxadrol and dexoxadrol (Chen, 1965) which share many pharmacological properties with PCP.

A number of studies have indicated pharmacological similarities between PCP and several of its analogues. PCP, PCE, and TCP have been shown in a series of studies by Maayani and his group to have both anticholinergic and anticholinesterase activity using receptor binding and bioassay procedures (Kloog et al., 1977; Maayani et al., 1974; 1973; Paster et al., 1974; Pinchasi et al., 1977, 1978a, 1978b; Weinstein et al., 1973). Gehrmann and Killam (1979) found PCP, PCE and ketamine produced similar EEG effects in rhesus monkeys. Drug discrimination studies (Jarbe et al., 1975; Overton, 1975; Shannon, 1979) have shown that PCP-trained animals generalize to PCE, ketamine and several other structural analogues of PCP.

Pharmacological and behavioral characterization of PCP analogues and representatives of other chemical classes which may have PCP-like effects has rapidly developed during the years that the research described in this dissertation has been carried out. These more recent studies will be discussed in the context of the research in suceeding chapters.

C. Pharmacology

General Pharmacology

The most prominent effects of PCP and other arylcycloalkylamines

are on the central nervous system. Because the major focus of my research is on the central nervous system effects of the arylcycloalkylamines, the general pharmacology of these compounds will be dealt with only briefly. Domino (1964) has published a comprehensive review of the general pharmacological activity of PCP.

Anesthetic doses of PCP act as a mild pressor agent in man (Greifenstein et al., 1958; Johnstone et al., 1959) and several species of animals (Chen et al., 1959). This appears to be due to a cocaine-like effect in blocking reuptake of the catecholamines (Chen et al., 1965; O'Donnell and Wanstall, 1968) and to some direct action on α-adrenergic receptors (Ilett et al., 1966). Hypertensive crises have been reported in PCP overdose patients (Eastman and Cohen, 1975).

In humans, anesthetic doses of PCP produce small increases in the minute volume, rate and depth of respiration (Greifenstein et al., 1958). Anesthetic doses of PCP have no marked effect on respiration in several species of laboratory animals (Chen et al., 1959), but higher doses cause suppression of respiration, hypotension and bradycardia.

No evidence of acute cellular toxicity was reported in the first clinical studies of PCP (Greifenstein et al., 1958). Lerner and Burns (1978) have reported no evidence of hematologic, hepatic or renal toxicity in a study of chronic PCP use by humans for periods of time varying from 6 months to 5¼ years.

There have been a number of recent studies of the biodisposition of PCP. PCP is well absorbed after all routes of administration. It is rapidly metabolized via oxidative hydroxylation of the rings and excreted in the urine as conjugates (Ober et al., 1963; Lin et al., 1975; Wong and Bieman, 1976). Different species produce the same urinary

metabolites in differing amounts. While the biological activity of the metabolites is largely unexplored, there have been some reports of activity of several hydroxylated metabolites in rats, dogs and mice (Maddox et al., 1965; Domino, 1978; Cone et al., 1980).

PCP is highly lipophilic and distributes rapidly to the brain and other tissues. Studies with several species have found high concentrations in lung, liver and fat (Martin et al., 1980;Bailey et al., 1979; Law et al., 1979). Although PCP is rapidly metabolized, overdose patients frequently show signs of PCP intoxication for several days (Burns et al., 1975; James and Schnoll, 1976). James and Schnoll (1976) reported low levels of PCP persisted in both brain and adipose tissue of rats 48 hours after a single i.p. injection. Misra et al. (1979) reported that PCP and metabolites persisted for prolonged periods in rat brain and adipose tissue after a single injection and showed accumulation after multiple dosing. They also reported a high degree of melanin binding of PCP and its metabolites which implies a possible localization in the neuromelanin-rich substantia nigra and locus coeruleus. Some investigators (Misra et al., 1976; James and Schnoll, 1976) suggest that this sequestered PCP is a possible explanation for the prolonged and persistent cognitive dysfunction several days after PCP administration. Leighty and Fentiman (1980) recently reported several common fatty acids were conjugated to two metabolites of phencyclidine in an in vitro rat liver microsomal system. They suggested this as a mechanism by which PCP is retained in lipid containing tissues.

Another explanation for the occasional prolonged intoxications with PCP has been offered by several investigators (Done et al., 1977, 1978). PCP is a weak base with a pKa of approximately 9.20 (Maayani and Gross,

1980). Because of this, it should become ionized in the acid media of the stomach and become trapped there. The current treatment for PCP overdose is acidification of the urine coupled with gastric suctioning (Aronow and Done, 1978).

Central Nervous System Pharmacology

Neurotransmitter Systems

Catecholamine Systems. While there have been many recent studies of the effects of PCP on central neurotransmitter systems, no clear picture has emerged to explain its neurochemical mechanism of action. Leonard and Tonge (1969) reported that PCP produced a decrease in rat brain norepinephrine (NE) and a slight increase in dopamine (DA). They found that PCP potentiated reserpine-induced NE depletion, but had no effect on NE turnover. Another study by Leonard and Tonge (1970) reported an increase in rat brain tyrosine levels after PCP administration. Hitzeman et al. (1973) reported that PCP decreased the synthesis of DA and NE and increased the accumulation of the O-methylated metabolites of DA and NE. This implies that PCP either increases the release or decreases the reuptake of catecholamines from the extraneuronal space.

Consistent with this, several investigators have found that PCP inhibits the uptake of NE and/or DA in both cortical slices (Taube et al., 1975) and synaptosomes (Garey and Heath, 1976; Smith et al., 1977; Ary and Komiskey, 1980). Recently, Vickroy and Johnson (1980) reported that PCP stimulated tyrosine hydroxylase activity in rat synaptosomes without increasing the uptake of ^{3}H-tyrosine. They postulated that this stimulation might be an indirect action via the release of DA. This is in agreement with the findings of Ary and Komiskey (1980) that PCP decreased ^{3}H-DA accumulation into synaptosomes by decreasing uptake and

by releasing previously accumulated DA. Bagchi (1980) also reported that PCP increased the release of DA and stimulated DA synthesis in rat caudate synaptosomes. Doherty et al. (1980) found that PCP decreased the rate of striatal DOPA accumulation after the inhibition of L-aromatic amino decarboxylase in the rat striatum, but did not antagonize the increase in DOPA caused by haloperidol. PCP also decreased striatal levels of DA metabolites while potentiating the haloperidol-induced rise in DA metabolites. This work also supports the idea that PCP potentiates the synaptic effects of endogenous DA. In contrast, Leelavathi and Smith (1979) found that PCP given i.p. to rats had no effect on DA uptake in the striatum.

Raja and Guyenet (1980) reported that intravenous PCP increased the firing rate of dopaminergic neurons in the substantia nigra of rats and inhibited the firing of noradrenergic neurons in the locus coeruleus. Marwaha et al. (1980) reported that locally administered PCP depressed firing of noradrenergic rat cerebellar Purkinje cells. This effect was antagonized by antipsychotic drugs. These studies indicate that PCP has different effects on dopaminergic and noradrenergic systems. This is consistent with the results of Ary and Komiskey (1980) discussed previously which indicate that PCP decreased the accumulation of ^{3}H-NE into synaptosomes by blocking reuptake whereas the effect of PCP on ^{3}H-DA accumulation is caused by releasing previously accumulated ^{3}H-DA as well as as by blocking reuptake of ^{3}H-DA.

Several investigators have shown that PCP produces a dose-related increase in ipsilateral rotation in rats with electrolytic (Kanner et al., 1975; Finnegan et al., 1976) and 6-OH DA induced (Fessler et al., 1979) lesions of the substantia nigra. This is thought to indicate some

indirect DA agonistic and/or anticholinergic activity. The effect was antagonized by alpha-methyl-para-tyrosine (AMPT), haloperidol and arecoline and potentiated by trihexyphenidyl. A recent study by Glick et al. (1980) reported that PCP elicited dose-related rotation in naive rats which was dissimilar to the rotatory effects of dopaminergic or anticholinergic drugs. Studies of regional brain uptake of labeled 2-deoxy-D-glucose and hippocampal lesions indicate that PCP activates a hippocampal mechanism of rotation whereas dopaminergic drugs did not (Glick et al., 1980).

Balster and Chait (1978a) found that PCP enhanced amphetamine stereotypy in rats. Murray and Horita (1979) reported that PCP produced a very characteristic stereotyped behavioral syndrome in rats which was antagonized by DA receptor blockade. In addition, Schlemmer et al. (1978) reported that the DA receptor blocking agent pimozide antagonizes stereotyped behavior produced by PCP chronically administered to stump-tailed monkeys. Several investigators (Garey et al., 1980; Castellani and Adams, 1980) reported that haloperidol antagonized PCP-induced motor dysfunctions in rats. Both these investigations also found that PCP motor dysfunction was antagonized by low doses of the DA agonist apomorphine but potentiated by high doses of the drug. They suggest a presynaptic mechanism for this effect.

Generally, the literature suggests that PCP acts a a catecholaminergic agonist. In the noradrenergic system, it is likely that PCP acts by blocking reuptake of NE. The effect of PCP on the dopaminergic system is probably the result of blocking reuptake and causing release of DA.

Sertonergic systems. The effects of PCP on 5-hydroxytryptamine

(5HT) function are even more confusing. Tonge and Leonard (1969) found that in rat brain, PCP elevated 5HT levels and initially depressed but later elevated the levels of the major metabolite of 5HT, 5-hydroxyindoleacetic acid (5-HIAA). They found that PCP had no effect on the two enzymes involved in the synthesis and metabolism of 5HT, but that tryptophan concentration was increased. In later studies by these same investigators (Tonge and Leonard, 1971, 1972) opposite results on 5-HT and 5-HIAA levels were obtained in different sets of rats of the same strain. It is possible that this is due to the fact that the different groups had different control levels of 5-HIAA.

Several investigations (Smith et al., 1977; Leelavathi and Smith, 1979) have indicated that PCP blocks the uptake of ^{3}H-5HT in synaptosomal preparations from rat brains. Martin et al. (1979) reported a serotonergic syndrome of behavioral effects produced by phencyclidine in the rat which was antagonized by sertonergic antagonists. Jarbe et al. (1975) found that depletion of brain 5-HT did not block the discriminative stimulus properties of PCP, but it is unclear how complete the 5-HT depletion was.

Cholinergic systems. Leonard and Tonge (1970) found no change in acetylcholine (ACh) or cholinesterase (AChE) activity in rat brain after PCP administration. Domino and Wilson (1972), using hemicholinium, obtained evidence that PCP may increase ACh turnover and utilization without affecting whole brain levels. Hsu et al. (1980) reported that an acute dose of PCP increased choline acetyltransferase (CAT) in the hippocampus, decreased CAT in the cerebellum and increased AChE in all parts of the rat brain.

Maayani et al. (1974) have demonstrated theoretically and experi-

mentally that PCP and ACh have similar electrostatic charge distribution patterns and that PCP is a competitive inhibitor of both the muscarinic cholinergic receptor and the cholinesterases. While these effects would tend to offset each other, comparison of affinity constants indicate that PCP has a higher affinity for the cholinesterases than for the cholinergic receptor. However, the overall behavioral effect of PCP appears to be anticholinergic. Maayani et al. (1974) reported that PCP-induced anesthesia in the guinea pig and hyperactivity in mice were both antagonized by tacrine, an anticholinesterase agent. Other studies have confirmed that while PCP has both anticholinergic and anticholinesterase activity, the in vivo activity appears to be predominately anticholinergic (Weinstein et al., 1973; Paster et al., 1974; Kloog et al., 1977; Pinchasi et al, 1977; Glick et al., 1980).

A study by Adams (1980) supports this finding in reporting that PCP-induced increases in locomotor activity in the rat were potentiated by atropine and blocked by physostigmine. However, Chait and Balster (1979) reported no effect of atropine on PCP-induced suppression of operant responding in squirrel monkeys and only partial antagonism of the PCP effect by physostigmine.

GABA systems. Leonard and Tonge (1970) found no change in whole brain levels of histamine or glutamic acid in rats given PCP. They did find a significant depletion of gamma aminobutyric acid (GABA) which correlated in time course with the behavioral activity of the drug. Menon et al. (1980) reported that pretreatment with GABA-potentiating drugs blocked the locomotor stimulation by PCP in mice. Myslobodsky et al. (1979) reported that inhibition of the enzyme which metabolizes GABA (GABA-transaminase) inhibits the stereotypic behavior and vigorous

rotation produced by ketamine in rats. More recently, there have been reports that PCP increased the activity of the rate-limiting enzyme in GABA synthesis in the hippocampus of mice (Spoerlein et al., 1980) and rats (Hsu et al., 1980). Wood and Hertz (1980) reported that ketamine increased whole brain GABA content in mice and inhibited GABA uptake in an in vitro system. It appears that part of the actions of PCP and ketamine may be due to GABA antagonism in the brain, possibly through blockade of the receptor.

There are probably a variety of reasons for the apparent conflicts in the results of these neurochemical studies. These range from differences in assay methods, different drug doses, differences in time from drug administration until measurement as well as species, strain and sub-strain of subjects used. While it is likely that the pharmacological profile of PCP is due to its combined effect on all of the neurotransmitter systems, it is possible that certain discrete effects may be the result of an effect on a single neurotransmitter system.

Behavioral Pharmacology

Human behavior. During the time that PCP was undergoing investigation for use as an anesthetic in humans, there were several reports of its effects on human volunteers. In an early clinical trial, Greifenstein et al. (1958) found that 0.25 mg/kg i.v. produced complete anesthesia without depression of respiration or circulation. Muscle relaxation was poor and many of the patients' eyes remained open and vertical nystagmus was noted. In all patients there was profuse salivation. Higher doses (0.5 -1.0 mg/kg) produced agitation followed by rigidity, catatonia and, in some cases, convulsions. They also noted some instances of severe excitement and hallucinatory disturbances upon emergence. The

type of anesthesia produced by PCP and related compounds has subsequently been termed "dissociative anesthesia" (Corssen and Domino, 1966; Pender, 1971) because rather than losing consiousness, the patient seems to become dissociated from the environment.

The subjective effects of subanesthetic doses of PCP have been reported by several investigators (Davies and Beech, 1960; Luby et al., 1959; Cohen et al., 1960; Eakker and Amini, 1961). Most commonly, there was an alteration in body image with feelings of estrangment. The subjects felt drowsy or inebriated with a sense of apathy. Disorganization of thought and perceptual distortion were also reported.

Objective measurements reveal impairment of sensory and cognitive processes by subanesthetic doses of PCP. Rosenbaum et al. (1959) reported decreased reaction times and impairment of rotary pursuit and weight discrimination. Davies and Beech (1960) found PCP impaired the learning and recall of learned words and the ability to define proverbs. Cohen et al. (1962) reported impairment of symbolic reasoning and sequential thinking tasks. Morgenstern et al. (1962) found sensory impairments in all modalities. The most sensitive were two point discrimination and touch, but there was also impairment of visual fields, auditory acuity, position sense, taste and visual acuity.

Several investigations have compared the effects of PCP to psychotic processes. Both Rosenblum et al. (1959) and Cohen et al. (1962) concluded that the effects of PCP on thought processes more closely simulated the performance of schizophrenic patients than did the effects of other hallucinogens tested including LSD. Other investigators (Luby et al., 1959, 1962; Levy et al., 1960) found that PCP given to schizophrenics exacerbated many of the symptoms of schizophrenia. In light of

this, it is particularly interesting that one phenomenon associated with PCP use is the development of a schizophreniform state (Stein, 1973; Fauman et al. 1975, 1976; Rainey and Crowder, 1975) which often does not appear until days after ingestion of the drug. The duration of the episode may be from several days to several weeks even though there is no detectable drug in the blood or urine. While reports of this phenomenon are rare, it is possible that it is not recognized as PCP-induced when seen. The phenomenon does not appear to be dose-dependent and may be due to abnormal metabolism of PCP, contaminants of PCP (Shulgin and MacLean, 1976; Bailey et al., 1976) or precipitation of a latent psychopathology.

Animal behavior. There are dramatic species differences in the gross behavioral effects of PCP. Chen et al. (1959) found that PCP could produce CNS stimulation or depression depending on the species of animal and dose used. In rodents, hyperactivity was prominently observed. Ataxia and catalepsy were seen at the highest doses indicating some degree of central nervous system depression. In all other species tested, a quieting or calming effect was reported at low doses progressing to a cataleptoid response and general anesthesia at higher doses. Higher doses produced convulsions in many species.

Gross behavioral effects of PCP in subhuman primates resemble those reported in man. These include ataxia, nystagmus, excessive salivation and rhythmic movements (Balster and Chait, 1976). The marked difference between the effects of these compounds in rodents and in primates makes primate work in this area especially important.

Conditioned Behavior. One way to approach the study of the central nervous system effects of a compound is to study its effects on learned

behavior. Adey and Dunlop (1960) found that i.p. injections of both PCP and PCE (1.0 - 3.0 mg/kg) disrupted conditioned approach performance in cats for up to 24 hours after drug administration. Lower doses (0.3 - 1.0 mg/kg) disrupted the performance for shorter periods of time. Domino (1964) reported that PCP disrupted condition avoidance responding in rats in a non-specific manner. Increasing doses of PCP (1.0 - 8.0 mg/kg i.p.) blocked avoidance and escape to the same extent and caused gross disruption of behavior.

Brown and Bass (1967) conducted a study of the effects of i.m. injections of PCP on accuracy and response latency in a three-key avoidance paradigm with rhesus monkeys. The subjects were required to press the key with the smallest form to avoid electric shock. There was a dose-dependent increase in response latency (0.05 - 0.25 mg/kg) until a dose was reached at which the animals did not respond at all (0.5 mg/kg).

Studies of the effects of PCP on animals trained under a multiple or chained fixed-interval fixed-ratio schedule (FIFR) of food presentation have been conducted with pigeons (Wenger, 1976), mice (Wenger and Dews, 1976), rhesus monkeys (Balster and Chait, 1976) and squirrel monkeys (Chait and Balster, 1976). In both pigeons and mice, PCP was found to increase FI response rates at low doses while decreasing response rates at high doses. The response rate increases caused by PCP in the FI component were dependent on the control rate of responding in a manner consistent with the rate-dependency hypothesis of Dews (1958). Only dose-dependent decreases in response rates were seen in the FR component. In rhesus monkeys (Balster and Chait, 1976), PCP produced only dose-dependent decreases in responding over the doses tested (0.25 -

2.0 mg/kg, i.m.). Both schedule components were equally affected by the drug. While Chait and Balster (1978) also reported a dose-related decrease in responding in both components of the multiple schedule with i.m. injections of PCP (0.01 - 0.60 mg/kg) in squirrel monkeys, a small but consistent increase in FI responding was seen with low doses of PCP. The response rate decreases in the FI component were consistent with the rate-dependency hypothesis (Dews, 1958) in that high rates of responding were decreased more than low rates of responding.

A review by Balster and Chait (1978b) includes a table with estimates of the relative potency of PCP for disruption of FR performance taken from the data in the papers discussed so far (Table 1). One observation they made was that while the squirrel monkey is slightly more sensitive to the effects of PCP on observable behavior than the rhesus monkey, it is 3 times less sensitive to the effects of PCP on food reinforced operant responding.

Chait and Balster (1978) studied the effects of i.m. injections of PCP (0.20 - 0.64 mg/kg) in squirrel monkeys trained on a variable-interval (VI) schedule of food presentation. They saw small response-rate increases at low doses and a dose-dependent decrease in responding at higher doses. Murray (1978) found that i.p. injections of PCP had a similar effect on response rates in female rats trained to respond on a VI schedule of water presentation. Low doses (0.25 - 1.0 mg/kg) increased response rates and higher doses (2.0 and 4.0 mg/kg) decreased response rates in a dose-dependent manner. Glick et al. (1979) found that PCP, ketamine and PCE all had a biphasic effect on response rates in rats trained to perform a spatial alternation task in a two-lever chamber. While low doses increased response rates and higher doses decreased

TABLE 1

DOSES OF PHENCYCLIDINE PRODUCING 50% DECREASES IN FIXED-RATIO RESPONDING IN VARIOUS SPECIES OF LABORATORY ANIMALS

Species	ED 50
Mouse	10.00 mg/kg[a]
Pigeon	0.70 mg/kg[b]
Squirrel Monkey	0.27 mg/kg[c]
Rhesus Monkey	0.08 mg/kg[d]

a. by inspection of dose-response curve in Wenger and Dews (1976)

b. by inspection of dose-response curve in Wenger (1976)

c. reported in Chait and Balster (1978a)

d. by inspection of dose-response curve in Balster and Chait (1976)

response rates, all three drugs produced only dose-dependent decreases in the accuracy of performance in the spatial alternation task. Balster and Baird (1979) found that low doses of PCP (1 and 3 mg/kg i.p.) produced large response rate increases in mice trained to lever press on a differential reinforcement of low rate (DRL) schedule, whereas higher doses resulted in decreased response rates.

In an interesting study of the effects of ketamine on FI performance, Meliska and Trevor (1978) found that a low dose of ketamine (7.5 mg/kg, i.p.) increased response rates in drug-naive and drug-experienced rats, but a higher dose (15.0 mg/kg, i.p.) decreased responding in drug-naive rats and increased responding in drug-experienced rats. Because the response rate increase reported in this latter group did not occur until 30-40 min after drug injection, they postulated that is was due to the actions of a ketamine metabolite. Both doses of ketamine increased spontaneous locomotor activity in all groups tested. Moerschbaecher and Thompson (1980) found that PCP decreased response rates and increased error rates in a dose-dependent manner in rhesus monkeys trained on a complex multiple-schedule repeated-acquisition operant task.

There have been several studies making direct comparisons between the effects of PCP and other pharmacological agents on schedule-controlled behavior. Wenger and Dews (1976) reported that both PCP and ketamine produced effects similar to those of d-amphetamine and dissimilar to those of pentobarbital in mice trained on a multiple FIFR schedule of food presentation. Balster and Baird (1979) also found that the effects of PCP on DRL responding for food reinforcement in mice were more similar to the effects of d-amphetamine than they were to the effects of pentobarbital. In contrast, Brandao et al. (1980) found that

low doses of ketamine increased punished responding in pigeons, whereas all doses of d-amphetamine tested produced only decreases in punished responding. Pentobarbital produced large increases in punished responding in this paradigm. Chait and McMillan (1980) also found that PCP and pentobarbital both increased punished responding in pigeons. In summary, it appears that the effects of PCP on schedule-controlled behavior may have two components. On food-reinforced behavior, the effects are amphetamine-like, whereas the effects of PCP on punished behavior seem to closely resemble the effects of the barbiturates.

Reinforcing properties. With most drugs of abuse, animals can be trained to perform a task to self-administer the drug. There have been several reports that rhesus monkeys can be trained to lever press for i.v. infusions of PCP (Balster et al., 1973; Pickens et al., 1973; Balster and Woolverton, 1979). This is of special interest because PCP is often classified as a hallucinogen and while hallucinogens are abused by humans, they are not reliably self-administered by laboratory animals (Deneau et al., 1969). Moreton et al. (1977) have also demonstrated the ketamine is reliably self-administered by rhesus monkeys. This suggests that PCP and the dissociative anesthetics represent a unique class of hallucinogens.

Recently, Balster and Woolverton (1979) have shown that rhesus monkeys given unlimited access to PCP can self-administer sufficient amounts to produce physical dependence. This physical dependence was evidenced in a withdrawal syndrome consisting of priapism, tremors, irritability and preconvulsive activity. McCarthy and Harrigan (1976) using an unlimited access paradigm with ketamine in rhesus monkeys, found that ketamine produced physical dependence with withdrawal symptoms

similar to those described for PCP (Balster and Woolverton, 1979).

Carroll and Meisch (1980a) established that oral PCP could serve as a reinforcer in rhesus monkeys over a range of concentrations. They found that food deprivation increased PCP intake as it does other drug reinforcers (Carroll and Meisch 1979, 1980b; Meisch and Kliner, 1979; Carroll et al., 1979).

Tolerance. There have been several recent studies of tolerance development to PCP. Pinchasi et al. (1978a) studied the effects of chronic PCP and PCE on rotarod performance in mice. They found that reversible tolerance developed to both drugs. The extent of tolerance depended upon dose, frequency and route of administration. Woolverton et al. (1980) studied the effect of chronic PCP administration on milk intake by rats. A 2-fold shift to the right in the dose-response curve was seen after seventy consecutive days of PCP administration (4.0 - 8.0 mg/kg, i.p.).

Pryor et al. (1977) reported that i.p. injections of 2.5 mg/kg PCP for six days produced tolerance to the disruptive effect of 2.5 mg/kg PCP in rats responding on a FR10 schedule of food presentation. In contrast, the increase in locomotor activity caused by PCP was enhanced by this treatment. In a recent report, Ruffing and Domino (1980) provided evidence for first dose tolerance, demonstrated by a significantly shortened duration of suppression of bar pressing in rats trained on a FR schedule of food presentation after PCP administration (3.2 mg/kg, i.p.).

Balster and Chait (1976) found that daily injections of gradually increasing doses of PCP (0.2 - 1.0 mg/kg, i.m.) over a four-month period produced a significant shift to the right in the dose-response curve of

two out of three rhesus monkeys trained on a chain FIFR schedule of food presentation. Comparisons of the gross behavioral effects of an acute dose of PCP (1.0 mg/kg, i.m.) in these three subjects to the effect in three naive monkeys also indicated tolerance development.

Chait and Balster (1978) studied the effect of chronic i.m. PCP (82 - 126 days) given up to four times a day in increasing doses to squirrel monkeys. Although the regimens were individualized to maximize tolerance development, a comparison of pre- and post- chronic dose-effect curves for the effects of PCP on operant behavior revealed only a 2-fold tolerance development. In general using chronic regimens designed to maximize tolerance development, experimental evidence indicates only a 2- to 4-fold shift in the PCP dose-effect curve.

Several studies have explored the mechanism of the development of tolerance to PCP. Murray and Horita (1979) reported no difference in maximum brain levels of PCP between rats tolerant to the effects of PCP on schedule-controlled performance and non-tolerant rats. This argues against a dispositional mechanism of tolerance to PCP. However, in other studies behavioral effects of PCP have been shown to correlate well with brain levels of PCP (Martin et al., 1980; Woolverton et al., 1979). For example, Woolverton et al. (1979) found less ^{3}H-PCP in the brains of high-weight rats than in the brains of low-weight animals which correlated with diminished effects of PCP in the high-weight group.

Several studies implicate a learned component in the development of tolerance to PCP. Woolverton and Balster (1979) administered PCP (8 mg/kg, i.p.) to rats trained on a FI schedule of water delivery for 36 days either before or after the experimental session. In this experimental situation, the subjects receiving post-session PCP would not be

able to learn to respond under the influence of PCP. Redetermination of the dose-effect curve after chronic dosing revealed a 2-fold shift to the right in both groups. However, greater tolerance occurred to the effects of PCP on response patterning and tolerance was lost more slowly in the pre-session group demonstrating a slight contribution of behavioral variables to tolerance development. Ruffino and Domino (1980) also demonstrated a learned component in the first dose tolerance to PCP mentioned earlier in this section. Rats given the first dose of PCP in their home cages and the second dose in the operant situation showed tolerance only after the second dose. The tolerance demonstrated in this group after the second dose was equal to the tolerance demonstrated after the first dose in the group given the drug for the first time in the operant situation indicating a learned behavioral tolerance. It seems likely that both behavioral and pharmacological variables play a part in the development of tolerance to PCP.

The discriminative stimulus paradigm. Because so many of the experiments in this dissertation involve the use of the drug discrimination paradigm, I will discuss this procedure in some detail.
A discriminative stimulus is any feature of an animal's environment which specifically covaries with the availability of a reinforcing stimulus (Schuster and Balster, 1977). When an operant behavior is reinforced only in the presence of a specific stimulus, the frequency of the occurrence of that behavior in the presence of the stimulus increases. The behavior is then said to be under the control of the stimulus.

The first demonstration that a drug could serve as a discriminative stimulus for a choice task was carried out by Conger (1951). He trained rats to respond differentially in a T-maze for food reinforcement

based on the administration of ethanol or placebo. Since this discovery, many drugs have been found to serve as discriminative stimuli using a variety of experimental designs. Basically, in a drug discrimination study the animals are trained to respond differently under different drug conditions. One response (e.g. left lever press) is reinforced under one drug state, while a different response (e.g. right lever press) is reinforced under the second or the no drug state.

Behavior which has been brought under stimulus control may also occur in the presence of different but similar stimuli. For example, if an animal is trained to respond one way when a white light is on, and another way in the dark, lights of decreasing intensity will produce an increasingly larger percentage of dark-appropriate responding. This phenomenon is termed stimulus generalization or transfer. A generalization gradient is the function that relates responding to different values of a test stimuli. The amount of responding appropriate for the training stimulus which is produced by a novel stimulus is considered to be an indication of the similarity of the two stimuli. On the basis of this, it is possible to determine to what extent various pharmacological agents are similar or different using this paradigm.

With drug stimuli, generalization can be tested along the qualitiative as well as the quantitative dimensions. A dose-effect determination can be made which indicates that as drug doses lower than the training dose of a drug are given, the animal emits less and less drug-appropriate responding in a dose-dependent manner. This is a quantitative generalization gradient. Along the qualitative dimensions, generalizations have been shown to occur between drugs with a similar spectra of pharmacological properties, but not between drugs of different drug

classes and pharmacological properties. For example, d- amphetamine has been found to generalize to methamphetamine, but not to LSD or psilocybin. This finding has been consistently replicated by many investigators using a variety of drug classes (Barry, 1974; Schuster and Balster, 1977).

In testing drugs for generalization along the qualitative dimensions, it is very important to control for equality of the quantitative dimension. For this reason, it is necessary to test a complete dose range of the novel compound. Another major problem with interpreting drug generalization data has been called by Overton (1974) "transfer test overinclusiveness". Often in generalization testing the injection of a drug unlike the training drug will result in mostly nondrug choices in spite of the fact that this same compound is known to be discriminable from vehicle. This same phenomenon could be true of other novel compounds which produce predominately drug-appropriate responding.

The discriminative stimulus paradigm is a powerful tool in the sense that it is a method for measuring some very specific properties of psychoactive compounds. In addition, information about behavioral disruption produced by a drug can be obtained from this same task by measuring response rate suppression, runway latency or some other indication of non-specific impairment. This paradigm is also valuable in trying to determine the mechanisms of drug action, as well as for screening compounds. The present studies use this technique in order to explore some of the structural relationships between PCP and drugs which produce a PCP-like discriminative cue.

Specificity of the discriminative stimulus properites of PCP. Overton (1974) first established that PCP could serve as a discriminative

stimulus in rats trained in shock-escape T-maze task. Using the same experimental paradigm, Overton (1975) compared the discriminative stimulus effects of ketamine, PCP and pentobarbital in rats. Transfer tests showed no generalization between PCP or ketamine and pentobarbital. While transfer tests showed generalization between PCP and ketamine in animals trained to discriminate either drug from saline, rats could be trained to discriminate PCP from ketamine in a drug versus drug task.

Jarbe and Henriksson (1974) could not obtain stimulus control with i.p. injections of 2.0 mg/kg PCP vs. saline in rats with a T-shaped water maze task. In a later study (Jarbe et al., 1975) using rats trained in an electrified T-maze task, a dose-related acquisition of drug discrimination with PCP (1.0 - 4.0 mg/kg, i.p.) vs. saline was reported. Transfer tests conducted with various doses of morphine, chlorpromazine, ditran, pentobarbital, Δ9-THC and Δ8-THC indicated that none of these drugs generalized to PCP. Dose-related generalization was reported for ketamine and PCE. The order of potency of these compounds for stimulus control in this study was: PCE > PCP > ketamine. Poling et al., (1979) trained rats to discriminate PCP from saline in a two-lever food-reinforced drug discrimination task. He tested for generalization to agonists and antagonists of the dopaminergic, cholinergic, sertonergic and GABA neurotransmitter systems. The specificity of the PCP cue was again demonstrated in that only ketamine produced PCP-appropriate responding. They concluded that these results paralleled previous findings using other procedures which suggest that the effects of PCP probably reflect a wide variety of neurochemical actions produced by the drug.

In an abstract, Shannon (1979) reported generalization testing of a

number of drugs using rats trained in a two-choice discrete trial avoidance task to discriminate PCP from saline. Generalization testing was carried out with a series of structural analogues of PCP as well as with other psychoactive drugs including d-amphetamine, scopolamine, LSD and Δ9-THC. He found that only the PCP analogues and the psychotomimetic benzomorphan opioid N-allylnormetazocine (SKF 10,047), produced a PCP-like cue. This finding of similar stimulus properties between PCP and an opioid is very important in the context of this dissertation since it was at this point that studies of the stereoisomers of benzomorphans were begun.

Similarities in the Effects of PCP and Opioids

Concurrent with the studies described in this dissertation comparing the effects of PCP to its analogues as well as opioids and non-opioid analgesics, other investigators have been exploring these relationships. Studies from other laboratories will be reviewed in this background section although most of what follows was not known at the time the present studies were designed. Many of the studies to be described in this dissertation have been published and are a part of this developing research field. The relationship between this research and these other recent studies will be described in the various chapters in which the data are presented.

There have been a number of recent studies comparing the discriminative stimulus properties of phencyclidine with those of a variety of opioids. Holtzman (1980) trained rats to discriminate between PCP and saline in a two-choice discrete trial avoidance paradigm. Dose-dependent PCP-appropriate responding was produced by cyclazocine, a psychotomimetic benzomorphan opioid, N-allynormetazocine, ketamine and dextrorphan, the

d-isomer of levorphanol. A variety of other opioids (ethylketocyclazocine, ketocyclazocine, pentazocine and dextromethorphan) which were tested did not generalize to PCP.

Herling et al. (1980) trained different groups of pigeons to discriminate dextrorphan, ketamine or cyclazocine from saline in a two-lever FR20 operant task. All subjects showed dose-related drug-appropriate responding when administered any of the training compounds or PCP. Neither ethylketazocine nor nalorphine generalized to the training drugs. In the dextrorphan trained animals, the l-isomer, levorphanol, resulted in saline responding whereas both dextromethorphan and cyclorphan, another psychotomimetic opioid, produced dose-dependent drug-appropriate responding.

Teal and Holtzman (1980) trained rats to discriminate between saline and high or low doses of cyclazocine in a two-choice discrete trial avoidance paradigm. Generalization testing determined that ketocyclazocine and N-allylnormetazocine produced discriminative stimulus effects comparable to both training doses of cyclazocine. Ethylketocyclazocine, pentazocine and levallorphan produced generalization in animals trained with the low dose but not the high dose of cyclazocine. Morphine and nalorphine did not produce drug-appropriate responding in animals trained with either dose of cyclazocine. Both ketamine and PCP produced drug-lever appropriate responding in both groups of animals. Mescaline, d-amphetamine and LSD did not produce drug-lever appropriate responding in either group of animals. High doses of naltrexone failed to completely block stimulus control of behavior by either of the cyclazocine training doses. It was concluded that at least part of the discriminative stimulus properties of cyclazocine are attributable to a non-narcotic component of action of the drug. In this light, it is interesting that

Harris (1980) could not antagonize the rate-decreasing effects of N-allylnormetazocine or cyclazocine on fixed-interval performance in rats with high doses of naloxone or naltrexone.

Young et al. (1980) trained rhesus monkeys to discriminate ketamine from saline in a two-lever operant task. PCP, PCE and dextrorphan produced dose-dependent drug-appropriate responding whereas cyclazocine, N-allynormetazocine and codeine did not. They suggested that species differences may account for the disagreement between the results of this study and the body of literature supporting the similarities between the discriminative cue produced by dissociative anesthetics and that produced by the psychotomimetic opioids. In any case, the drug discrimination literature suggests an overlap in the pharmacologies of PCP and the psychotomimetic opiates which has been verified in other experimental systems.

Martin et al. (1976) have postulated three different types of opiate receptors based on three different syndromes produced by congeners of morphine in the nondependent chronic spinal dog. Mu receptor agonists, of which morphine is the prototype, produce miosis, bradycardia, hypothermia and depression of nociceptive responses. Kappa agonists, of which ketocyclazocine is the prototype, constrict pupils, depress flexor response and produce sedation without markedly affecting pulse rate. N-allylnormetozocine (SKF 10,047), the prototype sigma receptor agonist, produces mydriasis, tachypnea, tachycardia and mania in the chronic spinal dog. These three receptors show marked differences in sensitivity to naltrexone. Whereas the mu receptor agonists were very sensitive to antagonism by naltrexone, approximately ten times more naltrexone was required to antagonize the effects of kappa agonists and even higher doses were reported to be necessary to antagonize the effects

of the sigma agonist. In an abstract, Vaupel and Jasinski (1979) reported that the profile of activity of PCP in the chronic spinal dog was very similar to that of N-allylnormetazocine. Both drugs produced dose-dependent depression of the flexor reflex, tachycardia, increased skin twitch reflex latency and hyperthermia. This finding was undoubtedly the basis for Shannon's study (1979) which was discussed earlier in which the sigma agonist, N-allylnormetazocine, was shown to generalize in rats trained to discriminate PCP from saline.

Another line of evidence implicating similarities between the dissociative anesthetics and the psychotomimetic opioids is found in the receptor binding literature. Recently several groups of investigators (Vincent et al., 1978; Zukin and Zukin, 1979; Hampton et al., 1979) have reported specific binding sites for phencyclidine in the rodent central nervous system. While Maayani and Weinstein (1980) argued that this specific binding is actually an artifact of the rapid filtration method used in these binding studies, Vincent et al. (1980) reported in detail a binding technique which makes it possible to measure all of the PCP binding to the filters and subtract this from the total binding to obtain specific binding.

The PCP binding site described by Vincent et al. (1979) fulfills many of the requirements used in describing a specific pharmacological receptor. ^{3}H-PCP is bound specifically and with a high affinity (Kd = 0.25 μM) to a single, saturable and reversible site. Bound ^{3}H-PCP can be displaced by non-radioactive PCP and a series of PCP analogues. There is good correlation between the apparent affinities of a series of analogues for this binding site and the pharmacological activities of these analogues as measured by the mouse rotarod assay. The binding

activity is concentrated in the synaptosomal fractions with highest concentrations in the cerebral cortex and corpus striatum and no detectable binding in the spinal cord. Vincent et al. (1980) found that while PCP and its derivatives bind specifically and reversibly to rat peripheral organs as well as rat brain, only the affinities for the brain receptor correlate with the pharmacological activities in the rotarod test.

Zukin and Zukin (1979) found that bound ^{3}H-PCP could be displaced by non-radioactive PCP, a series of PCP analogues and N-allylnormetazocine with relative potencies that closely paralleled the potency of these compounds in drug discrimination tests in rats. In more recent studies (Zukin and Zukin, 1980), it was reported that specific phencyclidine binding was displaced by cyclazocine and related benzomorphans, but not by morphine or naloxone.

Recently, Palmour et al. (1980) isolated specific PCP binding sites in the rat and African green monkey brain. They found that bound PCP was displaced by low concentrations of structural analogues of PCP and moderate concentrations of cyclazocine and N-allylnormetazocine. A possible sigma receptor was also isolated by these investigators. Cross-displacement experiments indicated that PCP did not bind this receptor.

Su et al. (1980) have reported that PCP and fifteen structural analogues displace ^{3}H-naloxone in the opiate receptor binding assay. The relative potencies for displacement correlated well with potencies on the mouse rotarod and the rat discriminative stimulus test. The IC50 for PCP was 25 μM, about 10-fold less than the IC50 for morphine. Smith et al. (1980) reported that ketamine displaced ^{3}H-naloxone in the opiate receptor binding assay. The potency of ketamine in this assay was

reduced by sodium, suggesting that ketamine interacts with the opiate receptor as an agonist. It was also found that the (+) isomer was a more potent agonist than the (-) isomer. In this study, ketamine was found to be approximately 3-fold less potent than morphine in displacing ^{3}H-naloxone. Vaught (1980) reported that both PCP and ketamine inhibited ^{3}H-dihydromorphine binding in mouse brain homogenate, but both were approximately 3000-fold less potent than morphine or naloxone.

In light of these findings, it is interesting that there has been relatively little exploration of the analgesic properties of PCP and ketamine. The literature on the subject up to this point present a rather unclear and inconsistent picture. Chen et al. (1959) reported no analgesic effect of PCP in mice using a tail pinch test for analgesia. In several other species in which analgesia was examined by pricking the skin with a knife, analgesia was only seen at doses of PCP which produced catalepsy or general anesthesia. Chen and Weston (1960) reported PCP-induced impairment of the response to nociceptive stimuli in rhesus monkeys, but only at doses which also impaired visual and auditory responses. There have been several reports of PCP-induced analgesia in humans, but only at doses with grossly observable effects on behavior (Johnstone et al., 1959; Collins et al., 1960; Muir et al., 1961). Many and King (1979) reported PCP-induced analgesia in the rat tail flick test at doses which led to no grossly observable behavioral changes (0.05 mg/kg, s.c.). This analgesia was antagonized by pretreatment with naloxone. In contrast, Markowitz and Kornetsky (1978) reported a hypersensitivity to foot shock in rats following low doses of PCP (1.25 - 5.0 mg/kg, i.p.). Because different routes of administration were used, it is difficult to make a direct comparison between these two studies.

Sadove et al., (1971) reported an analgesic effect of ketamine in humans at doses which did not produce catalepsy but did produce dizziness and sedation. Ryder et al (1978) reported that ketamine had analgesic activity in mice using the phenlyquinone writhing test. This analgesia was reversed by high doses of naloxone (10 mg/kg, i.p.).

In summary, there appear to be some interesting areas of overlap in the pharmacologies of PCP and the opiates, particularly the sigma agonists. The drug discrimination data indicates that PCP and some psychotomimetic opiates cross-generalize. The receptor binding literature indicates that certain psychotomimetic opiates displace PCP in the PCP binding assay and PCP and ketamine displace opiates in the opiate binding assay. While the similarities in analgesic activity of PCP and the opiates are less convincing, there are no doubt some interesting lines to pursue in further exploring pharmacological similarities between these groups of compounds.

Stereospecific Effects of Opioids and Ketamine

Another interesting area to be investigated in clarifying the overlap between the psychotomimetic opioids, many of which are from the benzomorphan series, and the dissociative anesthetics lies in the stereospecificity of the actions of the benzomorphans. The benzomorphans have an unusual seperation of activity between the optical isomers. In many cases, while greater analgesic activity lies in the (-) isomer, this isomer will precipitate withdrawal in the morphine-dependent rhesus monkey. The (+) isomer generally has less analgesic activity, but it has been found that this isomer will suppress withdrawal in the morphine-dependent rhesus monkey (Villarreal, 1970). In working with a

racemic mixture in the benzomorphan series, it is probable that one is working with a mixture of two active compounds which each have their own distinct spectra of pharmacological activity. All of the work described so far relating to the similarities between PCP and the psychotomimetic opioids has been done with racemic mixtures of the opioids. Initial studies of the stereoisomers of N-allylnormetazocine (Swain et al., 1973) revealed the (-) isomer to be a nalorphine-like antagonist capable of precipitating withdrawal in the morphine-dependent rhesus monkey. On the other hand, the (+) isomer was described as a non-narcotic CNS depressant which produced marked ataxia in rhesus monkeys, an effect we now know to be similar to that produced by PCP.

Studies investigating pure stereoisomers of other benzomorphans have also indicated a substantial difference in their pharmacological profiles. The (+) isomers of pentazocine and cyclazocine have been found to be inactive in inhibiting phenylquinone-induced writhing in mice (Pearl and Harris, 1966) and in inhibiting the contraction of the guinea pig ileum (Harris et al., 1969). In addition, the (-) isomer of cyclazocine is reported to be more than 400 times more potent than the (+) isomer as a meperidine antagonist (Pearl and Harris, 1966) and as an antagonist of morphine in the rat tail flick test (Pearl et al., 1968). In contrast to its substantially more prominent antagonist effects, the (-) isomer of cyclazocine was only 5 to 20 times more potent than the (+) isomer in the mouse rotarod test and in decreasing locomotion in mice (Pearl et al., 1968). McMillan and Harris (1972) found that the (-) isomers of both cyclazocine and pentazocine were 2 to 3 times more potent than the (+) isomers in decreasing rates of schedule-controlled responding in pigeons but 30 times more potent than the (+) isomers in

blocking the rate-decreasing effects of morphine on schedule-controlled responding. In a recent study (Cowan et al., 1979), (-)-cyclazocine was reported to be 1.6 times more potent than (+)-cyclazocine as an anti-convulsant, and (+)-pentazocine was reported to be 5.6 times more potent than its (-) isomer as a pro-convulsant. These studies indicate that while the (+) isomers of these benzomorphans do not have opiate-like properties, they are indeed active compounds. The (-) isomers appear to possess most of the opioid antagonist activity.

Clinical studies have reported that the (-) isomer of pentazocine is a more potent analgesic (Forrest et al., 1969) and respiratory depressant (Bellville and Forrest, 1968) in man than the (+) isomer. Results from this study also indicated that the (+) and (-) isomers have different subjective effects in man. The (+) isomer produced feelings of anxiety while the (-) isomer produced a morphine-like sedation.

The stereospecificity of the pharmacological properties of the dissociative anesthetics have also recently been the subject of investigation. While PCP is not optically active, ketamine does have a chiral center. Several studies have indicated differences in the pharmacological properties of the individual ketamine enantiomers in animals. Marietta et al. (1977), using rats, reported that the (+) isomer of ketamine would elicit periods of hypnosis lasting twice as long as the (-) isomer after equimolar doses. The (+) isomer also caused less post-hypnotic locomotor stimulation than the (-) isomer at equihypnotic doses. Ryder et al., (1978) found that in mice the (+) isomer of ketamine was 3 times more potent than the (-) isomer as an analgesic using the phenylquinone writhing test, 1.5 times more potent in hypnotic activity and 1.8 times more potent in causing locomotor stimulation. A recent clinical study by White et al. (1980) indicated that (+)-ketamine produced more effective

anesthesia than (-)-ketamine, with less incidence of psychic emergence reactions or agitated behavior. Meliska et al. (1979) examined the effects of ketamine enantiomers in rats trained on a FI schedule of food presentation. Low doses of (-)-ketamine increased response rates in a rate-dependent manner, the low control rates were increased more than the high control rates. The (+) isomer did not increase response rates at any dose. Higher doses of both drugs produce dose-dependent decreases in FI responding. Smith et al. (1980) have investigated the interaction of racemic ketamine and ketamine enantiomers with the opiate receptor. They found that (±)-ketamine displaced ^{3}H-naloxone. The (+) isomer was 3 to 4 times more potent than the (-) isomer in displacing naloxone. This stereoselectivity is consistent with the studies mentioned previously (Ryder et al., 1978; White et al., 1980) indicating that (+)-ketamine has a greater analgesic effect than the (-) salt. Thus, there is some evidence for qualitative differences in the effects of ketamine enantiomers.

Similarities in the Effects of PCP, Etoxadrol and Dexoxadrol

Another group of compounds which are structurally dissimilar to PCP, the 2-(2,2 substituted 1,3 dioxolan-4-yl) piperidines, also seem to share many pharmacological properties with the dissociative anesthetics. Chen (1973) reported that with increasing doses the sequence of observable effects of PCP and ketamine in laboratory animals is similar for etoxadrol and dexoxadrol. This is of particular interest in light of the recent findings just reviewed concerning the overlap between the psychotomimetic opiates and phencyclidine, because most of the early investigations of dexoxadrol focused on its analgesic properties. Clinical studies (Simopoulos et al., 1970; Lasagna and Pearson, 1965; Williams et al., 1969) have

shown dexoxadrol to be an analgesic of efficacy similar to aspirin in man, although psychotomimetic properties were consistently seen at higher doses.

Etoxadrol has been investigated for clinical use as an anesthetic. As with PCP and ketamine, humans anesthetized with etoxadrol maintain pharyngeal, laryngeal and lid reflexes. Tachycardia, tachypnea as well as nystagmus and emergence delirium have been observed (Wilson et al., 1970; 1973; Fredrickson et al., 1976). As a consequence of these findings, etoxadrol has been classified along with PCP and ketamine as a dissociative anesthetic (Cohen, 1965).

D. Specific Aims

The following studies were designed to investigate the behavioral pharmacology of the dissociative anesthetics and related compounds. In Experiment I, the effects of phencyclidine and three structural analogues on food reinforced fixed-interval performance in rhesus monkeys were compared. In Experiment II, five structural analogues of PCP were tested for generalization to PCP in squirrel monkeys trained to discriminate PCP from saline in a two-lever operant task.

Because of the many similarities between PCP, etoxadrol and dexoxadrol reported in the literature, Experiment III was designed to explore the discriminative stimulus properties of dexoxadrol and etoxadrol in squirrel monkeys trained to discriminate PCP from saline in a two-lever operant task. This should help to further define the link between the arylcyloalkylamines and these structurally dissimilar compounds.

Most of the studies discussed in the previous pages concerning generalization between PCP and psychotomimetic opiates used the racemic

mixture of the opiates. In the case of N-allylnormetazocine, the (+) and the (-) isomers have been shown to have different pharmacological profiles (Swain et al., 1973). In Experiment IV, the discriminative stimulus properties of the pure stereoisomers of N-allylnormetazocine were studied in rats and squirrel monkeys trained to discriminate PCP from saline. Because cyclazocine also demonstrates a seperation of pharmacological activity between its stereoisomers, Experiment VI was designed to further investigate the overlap in the discriminative stimulus properties of cyclazocine and PCP-like drugs in the light of any possible stereospecificity in the discriminative stimulus properties of cyclazocine. In Experiment V, the discriminative stimulus properties of the stereoisomers of ketamine were investigated in rats trained to discriminate PCP from saline.

The purpose of this work is to further define the behavioral pharmacology of PCP and compounds which are structurally and/or pharmacologically similar to PCP. A good deal of attention has been focused on the overlap in the pharmacologies of the dissociative anesthetics and the psychotomimetic opiates. Hopefully, investigations of the behavioral and pharmacological similarities of such structurally diverse compounds could provide insight in the general area of psychotomimetics and psychotic behavior.

II. COMPARISON OF PHENCYCLIDINE AND THREE ANALOGUES ON FIXED-INTERVAL PERFORMANCE IN RHESUS MONKEYS (EXPERIMENT I)

A. Introduction

The illicit synthesis of phencyclidine (PCP) and many of its derivatives is a relatively simple process and several analogues, most notably 1-1-(2-thienyl) cyclohexyl piperidine(TCP) and N-ethyl-1-phenyl-cyclohexylamine (PCE), are known to have appeared in street use (Shulgin and MacLean, 1976). For this reason, as well as to ascertain structure-activity relationships, there is a need to determine the pharmacological properties of different arylcycloalkylamines and how they compare to those of PCP (Chen et al., 1959).

McCarthy et al. (1965) found that ketamine, 2-(o-chlorophenyl)-2-methyl aminocyclohexanone, had much the same spectra of pharmacological activity as PCP, but was less potent. They reported that the duration of anesthesia produced by ketamine in monkeys was shorter than that of PCP, and the onset of the anticonvulsant activity of ketamine in mice was more rapid than with PCP. Chen (1965) found that PCP, TCP, PCE and ketamine all produced a similar, characteristic catalepsy in pigeons. TCP and PCE were found to be relatively equipotent to PCP and ketamine was approximately 1/10 as potent as PCP.

Pinchasi et al. (1978a) compared PCP, PCE and TCP on forced rotarod performance in mice. They found PCE to be slightly more potent than PCP or TCP. Furthermore, PCE was found to have a rapid onset and offset. Peak effects of PCE were observed 5 to 10 min after subcutaneous injection, with performance returning to normal within 60 min, even at the highest dose (20 mg/kg). Kalir et al. (1969, 1978) also found PCE to be slightly more potent than PCP in disrupting mouse rotarod activity.

Several investigators (Maayani et al., 1973, 1974; Paster et al., 1974; Pinchasi et al., 1977, 1978a, 1978b; Weinstein et al., 1973) have reported that PCP, PCE and TCP have both anticholinergic and anticholinesterase activity using both receptor binding and bioassay procedures. The purpose of this study was to compare the effects of PCP, TCP, PCE, and ketamine (Figure 1) on fixed-interval (FI) performance in rhesus monkeys.

B. Methods

Animals

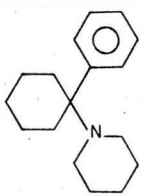
The subjects were four adult male rhesus monkeys which had previously been used in a study of the effects of cannabinoids on fixed-interval responding (Brady and Balster, 1980a). At least two months during which no drugs were administered intervened between these studies. The same behavioral performance was used in both studies. The animals were maintained at a constant weight (6-8 kg) by adjusted post-session feedings and had free access to water in their home cages.

Apparatus

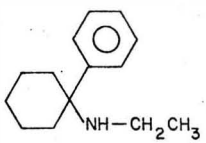
The experimental sessions were conducted in an upright refrigerator shell equipped with an exhaust fan and a house light on the ceiling. The monkeys were seated in a primate chair, which restricted movement by a waist stock and shoulder rings, for the duration of the experimental session. Immediately before initiation of the session, the chair was placed in the chamber facing the front door upon which a response lever, three colored stimulus lights and a food trough were mounted. Lever pressing was maintained by the presentation of two 1 gram banana flavored food pellets (Noyes, Formula L) by an automatic feeder (BRS/LVE PDC) located outside on the chamber door. The experimental contingencies were controlled by solid state programming equipment located in an

FIGURE 1

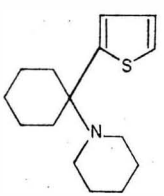
Chemical structures of PCP and analogues used in Experiment I.



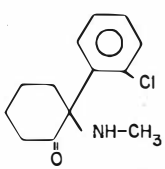
PHENCYCLIDINE
(PCP)



N-ETHYL PHENYLCYCLOHEXYLAMINE
(PCE)



THIENYLCYCLOHEXYL
PIPERIDINE
(TCP)



KETAMINE

adjacent room. Data were recorded automatically in the form of response totals and cumulative response recordings.

Procedure

The animals had been trained to respond on a multiple FI 5 min time out 1 min schedule of food presentation. At the beginning of the session, the house light and the lights over the lever were illuminated. The first response after 5 min resulted in food delivery. If the animal did not respond within 1 min (limited hold 1 min) after the 5-min interval had elapsed, the available food pellets were forfeited and the schedule advanced into a 1-min time out during which the lever lights were turned off and responding had no consequence. A reinforced response automatically advanced the schedule into the time out which occurred between each fixed-interval. The session was terminated after the fifteenth FI component, at which time the house light and lever lights were extinguished. Experimental sessions were conducted seven days a week.

When stable responding was achieved, drug injections were given i.m. on the day following three consecutive baseline days when response rates varied by less than 20 percent, usually every fourth day. The animals were injected while in the primate chair 5 min before the initiation of the session. The animals were then kept in a holding area until immediately before the initiation of the session when the chair was placed in the operant chamber. The different drugs were given in a random sequence which differed for each animal. Each drug was given to two subjects in an ascending dose order and to the remaining two subjects in a descending dose order.

Data Analysis

Non-injection response rates for the three days preceding each injection were used to calculate baseline response rates. For rate-dependency analysis (Kelleher and Morse, 1958), the FI was divided into five 1-min segments and drug effects on local response rates were graphed as a function of the average rates of responding in corresponding segments of the FI for the baseline days. The duration of the limited hold was not used in the calculation of response rates for the terminal bin. Only treatment days during which overall responding exceeded 0.1 response per sec were included in rate-dependency calculations. Responses per sec for each of the fifteen intervals in the session were calculated by measuring the height of the peak for each interval on the cumulative records and calculating the number of responses.

Drugs

Phencyclidine HCl was supplied by Bio Ceutic Laboratories (Sernylan). Ketamine HCl was supplied by Parke-Davis and Co. (Ketalar). They were diluted with 0.9 percent saline to a concentration that resulted in an injection volume of 0.2 ml/kg. PCE and TCP as the HCl salts were supplied by the National Institute on Drug Abuse. These drugs were dissolved in saline to a concentration that resulted in an injection volume of 0.2 ml/kg. Vehicle injections of 0.2 ml/kg saline were given once during the testing of each drug. All injections were given i.m. 5 min pre-session. Doses refer to the salts.

C. Results

The FI 5 min schedule of reinforcement generated positively accelerated patterns of responding characteristics of FI performance. The baseline rates ±1 S.E.M. throughout the experiment for each of the

four subjects were 1.36 ± .08, 1.1 ± .05, .23 ± .01, and 1.53 ± .05 responses per sec. Although response rates for each monkey were fairly stable, there were wide differences between monkeys. As a consequence the data is presented as percent change from baseline rates averaged across animals.

Figure 2 shows the group dose-response curves for each of the four compounds tested. Dose-related decreases in responding were seen for all four compounds. The slope of the dose-effect curve was also similar for each of the drugs. Although only decreases in average response rates are seen in this figure, each of the four compounds produced modest response rate increases at lower doses. These increases are not evident in the group averages because they were small increases and they occurred at different doses in the different subjects. At the higher doses of each compound, similar observable effects could be seen prior to or after the sessions while the subjects were seated in the restraining chair. Sedation, incoordination, excessive salivation and nystagmus were often noted. Animal B7784 showed an unusual insensitivity to TCP. Doses up to 6 times those which completely suppressed responding in the other animals were needed to suppress responding in this animal. The large standard error for the effect of 0.4 mg/kg TCP is largely due to the lack of effect of this dose of TCP on animal B7784.

Table 2 shows the ED_{50} values for suppression of operant responding for each of the four compounds tested as calculated by linear regression. A comparison of the potency of the three analogues to PCP shows that TCP is slightly more potent than PCP, PCE is slightly less potent than PCP, and ketamine is approximately 1/10 as potent as PCP in suppressing operant responding. The differences between PCP and TCP are small

FIGURE 2

Group dose-response curves for PCP and three analogues on suppression of operant responding. The effect as percent of baseline is plotted as a function of drug dose. Baseline rates were determined by averaging the non-injection response rates for the three days preceding each injection. The points above VEH represent the results of vehicle injections. Points represent means ± S.E.M. for four subjects except TCP where data is from three subjects. Only one animal was tested at 0.8 mg/kg PCP.

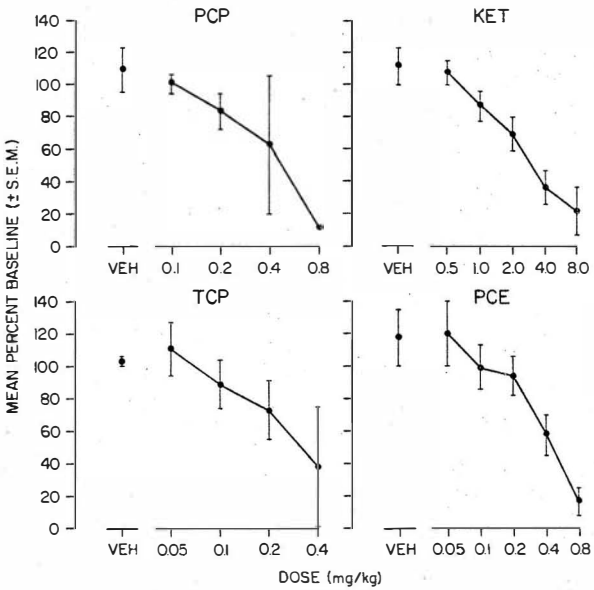

PCP
KET
TCP
PCE
MEAN PERCENT BASELINE (± S.E.M.)
DOSE (mg/kg)
VEH
0.1
0.2
0.4
0.8
0.5
1.0
2.0
4.0
8.0
0.05
0.1
0.2
0.4
0.8
0
20
40
60
80
100
120
140

TABLE 2

POTENCY OF PCP AND THREE ANALOGUES ON
FIXED-INTERVAL PERFORMANCE IN RHESUS MONKEYS

DRUG	ED50* DOSE (mg/kg)	RATIO TO PCP (mg/kg)	RATIO TO PCP (moles/kg)
PCP	.28	--	--
TCP	.25	1.12	1.14
PCE	.33	.84	.725
KET	2.89	.097	.095

*Dose resulting in a 50% decrease in response rates as determined by linear regression.

suggesting that these drugs are roughly equipotent.

Figure 3 shows the time course of the effects of two doses of each drug tested in all animals except TCP where the data is from only three animals. Each data point represents the mean percent of baseline responding for three consecutive 5-min intervals plus the time outs. PCP and 0.8 mg/kg PCE showed peak activity 24-41 min after drug injection. The lower dose of PCE (0.4 mg/kg) showed maximum activity 42-59 min after injection. The onset of activity for ketamine was apparent during the first 18 min of the session. Recovery from the low dose (4.0 mg/kg) of ketamine began within 30 min of drug administration. At both doses of PCE and the high dose of TCP, the animals did not recover during the 1½ hour session.

Figures 4-7 are rate-dependency plots for the two highest doses of all drugs tested in each subject. The rate-dependency plot for the drug doses which resulted in overall response rates less than 0.1 response per sec are not shown. Each point is the ratio of the drug rate of responding to control rate of responding plotted against the control rate of responding during each of the five 1-min portions of the FI. The heavy dashed horizontal line represents the no-effect line, where the drug rate is equal to the control rate during each portion of the interval. A typical rate-dependent effect is evidenced by a shift from the no-effect line towards a line with a negative slope. All four drugs produce this effect in all animals at least at one dose and generally at both high doses. In a number of cases this was a dose-dependent effect with a greater negative slope at the highest dose.

D. Discussion

Our findings show marked similarities between the actions of PCP,

FIGURE 3

Time course of the effects of PCP and three analogues on operant responding during a 1½ hour operant session. On the ordinate is percent baseline responding. The baseline rates were determined by averaging the non-injection response rates for the three days preceding the injection. The abscissa represents the 15 6-min intervals of the 1½ hour session graphed in groups of three, such that each point represents 18 min of responding.

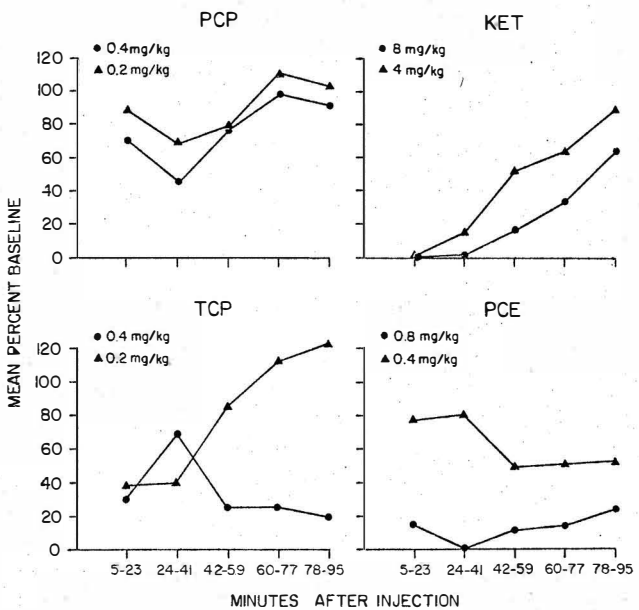

PCP
● 0.4mg/kg
▲ 0.2 mg/kg
KET
● 8 mg/kg
▲ 4 mg/kg
TCP
● 0.4 mg/kg
▲ 0.2 mg/kg
PCE
● 0.8 mg/kg
▲ 0.4 mg/kg
MEAN PERCENT BASELINE
0
20
40
60
80
100
120
5-23
24-41
42-59
60-77
78-95
MINUTES AFTER INJECTION

FIGURE 4

Rate-dependency plots for PCP and analogues in animal B002. The two highest doses not producing complete suppression were plotted, except in the case of TCP where the high dose (0.4 mg/kg) resulted in overall response rates less than 0.1 response per sec. On the ordinate is drug rate/control rate. On the abscissa is control rate in response per sec. Control rate was determined by averaging the non-injection response rates for the three days preceding the drug injection day.

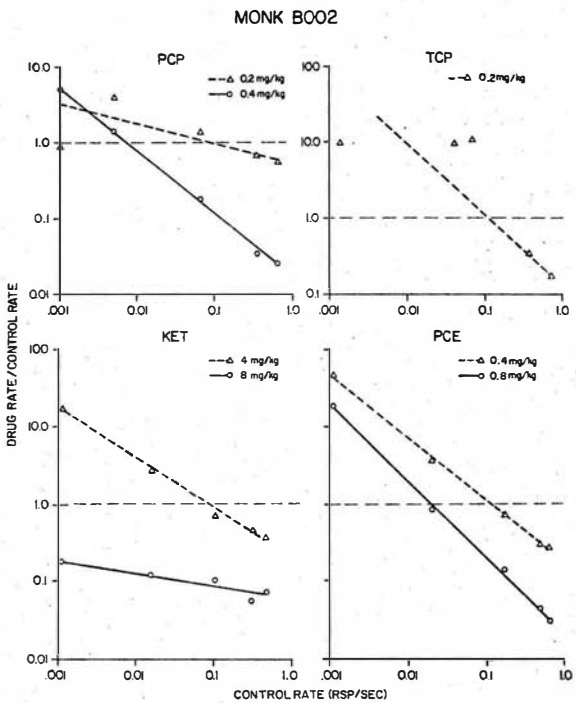

MONK B002
PCP
0.2 mg/kg
0.4 mg/kg
TCP
0.2mg/kg
KET
4 mg/kg
8 mg/kg
PCE
0.4 mg/kg
0.8 mg/kg
DRUG RATE/CONTROL RATE
CONTROL RATE (RSP/SEC)
10.0
1.0
0.1
0.01
100
.001
0.01
0.1
1.0

FIGURE 5

Rate-dependency plots for PCP and analogues in animal B4115. The two highest doses not producing complete suppression were plotted. On the ordinate is drug rate/control rate. On the abscissa is control rate in responses per sec. Control rate was determined by averaging the non-injection response rates for the three days preceding the drug injection day.

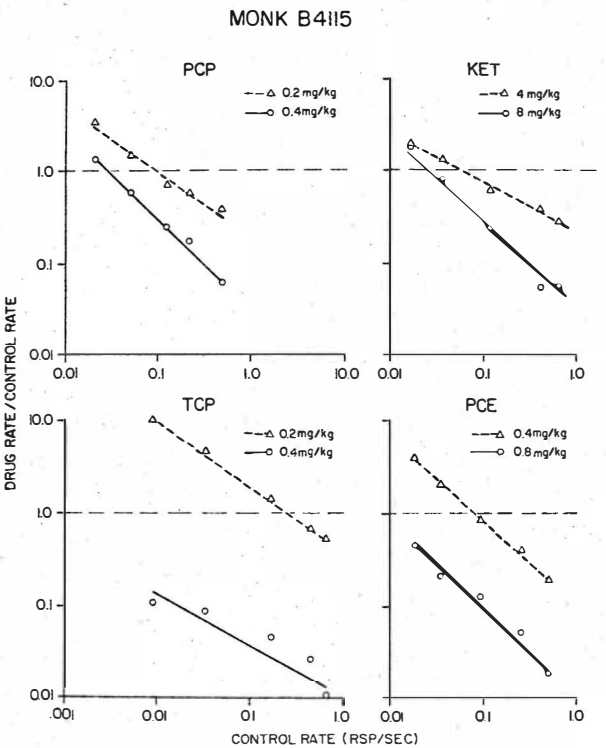

MONK B4115
PCP
0.2 mg/kg
0.4mg/kg
KET
4 mg/kg
8 mg/kg
TCP
0.2mg/kg
0.4mg/kg
PCE
0.4mg/kg
0.8mg/kg
DRUG RATE / CONTROL RATE
CONTROL RATE (RSP/SEC)
10.0
1.0
0.1
0.01
.001
0.01
0.1
1.0
10.0

FIGURE 6

Rate-dependency plots for PCP and analogues in animal B7784. The two highest doses not producing complete suppression were plotted. On the ordinate is drug rate/control rate. On the abscissa is control rate in responses per sec. Control rate was determined by averaging the non-injection response rates for the three days preceding the drug injection day.

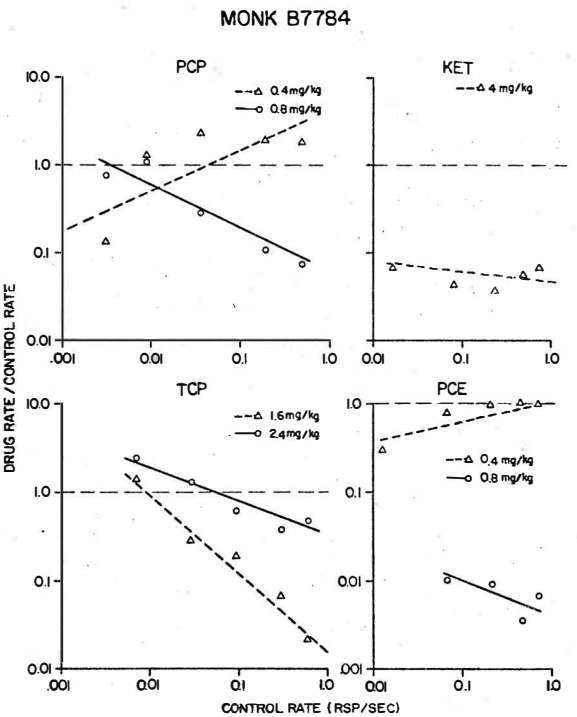
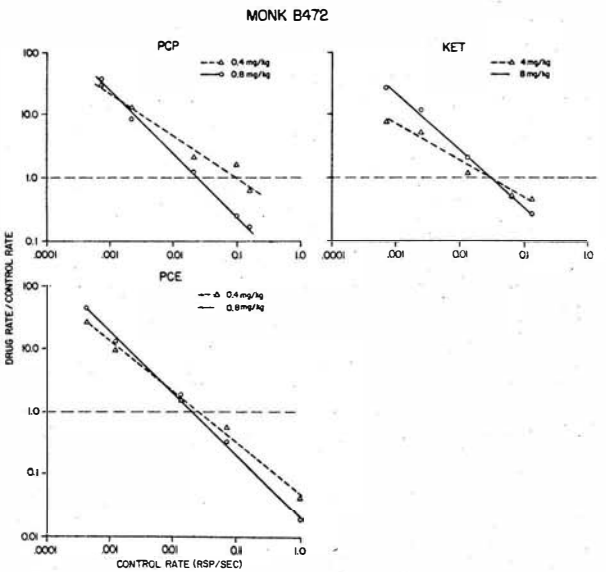

MONK B7784
PCP
0.4 mg/kg
0.8 mg/kg
KET
4 mg/kg
TCP
1.6 mg/kg
2.4 mg/kg
PCE
0.4 mg/kg
0.8 mg/kg
DRUG RATE / CONTROL RATE
CONTROL RATE (RSP/SEC)
10.0
1.0
0.1
0.01
.001
0.01
0.1
1.0

FIGURE 7

Rate-dependency plots for PCP and analogues in animal B472. The two highest doses not producing complete suppression were plotted, except in the case of TCP which was not tested in this animal. On the ordinate is drug rate/control rate. On the abscissa is control rate in responses per sec. Control rate was determined by averaging the non-injection response rates for the three days preceding the drug injection day.


MONK B472
PCP
0.4 mg/kg
0.8 mg/kg
KET
4 mg/kg
8 mg/kg
PCE
0.4 mg/kg
0.8mg/kg
DRUG RATE / CONTROL RATE
CONTROL RATE (RSP/SEC)

PCE, TCP and ketamine. Although not quantitated in this experiment, high doses of all four drugs produced a similar set of observable alterations in the animals which included incoordination, excessive salivation and nystagmus. These effects are similar to those reported by Balster and Chait (1978) for moderate doses of PCP in subhuman primates. Some evidence of response rate increases at low doses of each drug were seen, but these increases were not substantial enough to be evident in the group dose-effect curve. Response rate decreases were seen at the higher doses of all drugs. Chait and Balster (1977; 1978; 1979) have reported a similar effect in squirrel monkeys using schedule-controlled perfor ces. Low doses of PCP produced small increases in rates of responding, while higher doses produced a dose-dependent decrease in response rate.

In addition, all four drugs had a similar rate-dependent effect. The rate-dependency hypothesis states that the effect of a drug on a performance will depend on the baseline rate of that performance (Kelleher and Morse, 1968). The FI schedule is particularly well suited to study rate-dependent effects because it generates a typical positively accelerating pattern of responding characterized by low rates of responding at the beginning of the fixed-interval and high rates of responding near the end of the fixed-interval. A typical rate-dependent effect of drug is to increase the low rates of responding at the beginning of the fixed-interval, and decrease the high rates of responding in the later part of the interval (Kelleher and Morse, 1968). This would be represented graphically by a line with a negative slope, indicating an increase in responding in the initial bins, where the control rates were lower and a decrease in the later bins where the control rates were high. In the case of the higher doses of the drugs which decreased

responding in all bins, the negatively sloped line which falls below the no-effect line indicates a greater decrease in the later bins than in the initial bins. This type of rate-dependent effect is similar to that described for a variety of behaviorally active compounds (Kelleher and Morse, 1968). Several other investigators have reported similar effects of PCP on local rates of responding in operant performance in squirrel monkeys (Chait and Balster, 1978), mice (Wenger and Dews, 1976) and pigeons (Wenger, 1976). In the present study, this rate-dependent effect was dose-dependent. The negative slope of the regression line was generally more marked at higher doses than at the lower doses.

The potency differences between the four compounds were similar to those found by Chen (1965) where PCP was roughly equipotent to TCP, slightly more potent than PCE, and more than 10-fold more potent than ketamine in producing catalepsy in pigeons. This comparison of PCP and PCE is in disagreement with the findings of Kalir et al. (1978) and Pinchasi et al. (1978a) who found PCE to be slightly more potent than PCP in disrupting mouse rotarod performance.

The time course results indicate that the effects of ketamine on operant performance are evident 5-23 min after i.m. injection, and recovery begins within ½ hour of the injection. The onset of PCE and PCP were similar, requiring at least 24-41 min to peak effect. Kalir et al. (1978) measured brain levels of PCE and PCP and correlated these with activity in disrupting rotarod performance in mice. They found a maximum accumulation at 20 min after subcutaneous administration and a slow time course of elimination. They found that while peak behavioral activity correlated with peak brain levels, the offset of behavioral activity was faster than the elimination of the compound from mouse brain.

The marked insensitivity of animal B7784 to TCP warrants further comment. After the experiment was over, this animal and subject B4115 were injected with 1.0 mg/kg PCP. This dose produced dramatic observable behavioral effects in animal B4115, but had no observable effects on animal B7784. It is difficult to attribute the insensitivity of animal B7784 to his history of PCP dosing, since this degree of tolerance was not seen in the other subjects who had similar history of PCP injections. In addition, a study by Chait and Balster (1978) using squirrel monkeys given chronic PCP progressing to four daily injections found only a 2-fold shift in the dose-response curves. It is more likely that this is an idiosyncratic response.

In conclusion, these four drugs have been found to have qualitatively similar effects on operant responding in the rhesus monkey. This is consistent with other studies showing these compounds to have similar pharmacological effects (Chen, 1965; Kalir et al., 1969, 1978; McCarthy et al., 1965; Paster et al., 1974; Weinstein et al., 1973) and research demonstrating that the stimulus properties of the These analogues generalize to PCP in a drug discrimination paradigm (Overton, 1975; Shannon, 1979). It is clear that PCP is only representative of a class of arylcycloalkylamines with similar behavioral effects and possibly similar potential for abuse.

III. DISCRIMINATIVE STIMULUS PROPERTIES OF PHENCYCLIDINE AND FIVE ANALOGUES IN THE SQUIRREL MONKEY (EXPERIMENT II)

A. Introduction

In Experiment I, we found that PCP, PCE and TCP and ketamine had qualitatively similar effects on fixed-interval performance in rhesus monkeys (Brady et al., 1980). It is becoming apparent that a wide variety of structural modifications can be made in the PCP molecule without markedly altering its pharmacological profile.

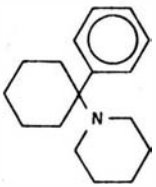
As discussed in the general introduction, drug discrimination studies indicate that PCP and some of its analogues have similar discriminative stimulus properties. Several investigations (Jarbe et al., 1975; Overton, 1975; Shannon, 1979; Poling et al., 1979) indicate that rats trained to discriminate PCP from saline generalize to structural analogues of PCP but not to a variety of structurally unrelated psychoactive drugs.

While most studies suggest pharmacological similarities between PCP and many of its structural analogues, Gehrmann and Killam (1979) found that 1-(1-phenylcyclohexyl) pyrrolidine (PHP) produced a qualitatively different EEG profile from other analogues. In addition, they reported that 1-(1-phencyclohexyl) morpholine (PCM) was inactive in the dose range they tested. PHP has been discovered in illicit street use (Shulgin and MacLean, 1976).

The present study was designed to compare the discriminative stimulus properties of PCP to those of PCE, TCP, PHP, PCM and ketamine (Figure 8) in the squirrel monkey. There have been relatively few reports using the squirrel monkey as a subject in drug discrimination studies. It seems especially important to explore the discriminative stimulus properties of PCP in primates because of the apparent species-

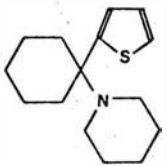
FIGURE 8

Chemical structures of PCP and analogues used in Experiment II.



PCP

1-(1-phenylcyclohexyl) piperidine

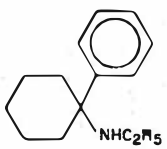


TCP

1-[1-(2-thienyl) cyclohexyl] piperidine

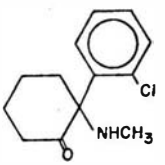
PHP

1-(1-phenylcyclohexyl) pyrrolidine



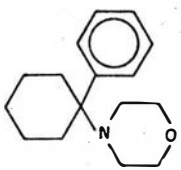
PCE

N-ethyl-1-phenylcyclohexylamine



KET

2-(o-chlorophenyl)-2-(methylamino)cyclohexanone



PCM

1-(1-phenylcyclohexyl) morpholine

specificity of some of the pharmacological activities of this compound. The gross behavioral effects of PCP in man include ataxia, nystagmus and rhythmic movements (Burns et al., 1975; Greifenstein et al., 1958). These effects more closely resemble the effects of PCP in subhuman primates than its effects in rodent species (Balster and Chait, 1976, 1978; Chen et al., 1959). In order to ascertain the specificity of the PCP cue in the squirrel monkeys, generalization testing was also conducted with mescaline, morphine and ketocyclazocine.

B. Methods

Subjects

The subjects were four experimentally naive adult male squirrel monkeys (Saimiri sciureus, Santa Cruz, Bolivia, Primate Imports, Port Washington, New York). The animals were maintained at 80% of free-feeding weights (0.8 to 1.0 kg) throughout the experiment by adjusted post-session feedings. They had unlimited access to water in their home cages.

Apparatus

The subjects were restrained about the waist in a plastic primate chair for the duration of the experimental session. In the lower center of the panel facing the subject seated in the chair was a brass food trough into which 97 mg Noyes banana-flavored food pellets could be delivered via a Gerbrands model D-1 automatic feeder. There were two response levers facing the subject equidistant to the right and left above the food trough. A clear Plexiglas divider with two arm holes was installed between the subject and the response levers. To reach a lever or the food trough the subject had to reach through the armhole. The placement of the Plexiglas divider was such that the animal could press

only one lever at a time. The purpose of this device was to prevent unwanted response topographies and to force the animal to make a choice between the levers. Above the response panel were four stimulus lights.

The animal was injected while in the primate chair and the chair immediately placed in a sound and light attenuating isolation cubicle for the pretreatment time and the duration of the experimental session. The only source of light was the four stimulus lights above the levers which were illuminated at the initiation of the session. Solid state programming equipment and recording devices were located in an adjacent room.

Procedure

The subjects were trained to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Initially, the subjects were trained to respond on either lever on an FR1 schedule. Once lever pressing was established, drug injections were begun. Each animal received either saline or 0.16 mg/kg PCP 5 min pre-session on a double alternation schedule, i.e. two days of PCP injections followed by two days of saline injections. From this point on, responding on only one lever was reinforced during the session. For two animals, responses on the left lever produced reinforcement on PCP days and responses on the right lever produced reinforcement on saline days. The lever conditions were reversed for the other subjects. Responses on the incorrect lever reset the FR contingency for reinforced responding on the correct lever. Response requirements were gradually increased until all animals reliably responded under a FR32 schedule.

When reliable FR32 responding was established, extinction probes

were initiated. Every third session was begun with a 2-min period during which responding was not reinforced, after which the session was continued as usual on the FR32 schedule. Discrimination training was continued until the subject had ten consecutive extinction probes with 80 percent or more responding on the appropriate lever.

Following discrimination training, the effects of substituting 0.02, 0.04, 0.08, 0.24, 0.32 and 0.4 mg/kg doses of PCP for the 0.16 mg/kg training dose were determined. Two animals received the doses in ascending order, and two animals received the doses in descending order. The four middle doses were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day. Test sessions were conducted only if the animal completed the first fixed-ratio on the appropriate lever on the control day preceding the test day. The test session consisted of a 2-min extinction period after which the animals were returned to their cages. The double alternation continued on control days with the test sessions interspersed such that one PCP and one saline training day preceded each successive test day.

Following the PCP dose-response determination, stimulus generalization testing was conducted in a similar manner with six doses of ketamine (0.2 - 4.0 mg/kg), PHP (0.02 - 0.4 mg/kg), PCE (0.02 - 0.4 mg/kg), TCP (0.02 - 0.4 mg/kg) and PCM (0.2 - 4.0 mg/kg). These doses were chosen to cover a range from no effect to marked suppression of response rates during the 2-min test sessions. For each animal, two determinations were made of the four middle doses of each drug. In one animal, a seventh dose of PCE (0.48 mg/kg) was tested in order to determine a dose which completely suppressed responding.

The order in which the different drugs were given to each animal was randomized. All doses of a given drug were administered to a given subject before testing the next drug. For PCE and ketamine, two animals received each drug in ascending dose order, and two animals received each drug in a descending dose order. Only three subjects were tested with TCP, PHP and PCM. For PCM and TCP, two animals received the drugs in a descending dose order and one animal received the drug in an ascending dose order. For PHP, two animals received the drug in an ascending dose order, and one animal received the drug in a descending dose order.

Following generalization testing with the structural analogues of PCP, stimulus generalization testing was conducted in these four subjects plus two additional monkeys,trained as described earlier,in a similar manner with three doses of morphine (0.64 - 2.56 mg/kg), ketocyclazocine (0.01 - 0.04 mg/kg) and mescaline (3.0 - 30.0 mg/kg). The order in which these three drugs were given to each animal was randomized. All doses of a given drug were administered to a given subject before testing the next drug. All animals received the drugs in ascending dose order. Each dose was tested twice in each subject.

Drugs

PCP was supplied by Bio Ceutic Laboratories (Sernylan). Ketamine HCl was supplied by Parke-Davis and Co. (Ketalar). PCE, TCP, PHP and PCM were supplied by the National Institute on Drug Abuse. The mescaline was supplied by Mann Research Laboratories. For these drugs, doses refer to the hydrochloride salts. Morphine sulfate was supplied by the National Institute on Drug Abuse. The drugs were diluted with or dissolved in sterile saline to a concentration that resulted in an

injection volume of 0.2 ml/kg. Ketocyclazocine sulfonate, a generous gift of Dr. J.H. Woods from the University of Michigan, was dissolved in 2-3 drops of lactic acid. The pH of the solution was then adjusted to 7.4 with 2-3 drops of NaOH. The solution was then diluted with sterile saline to a concentration that resulted in an injection volume of 0.2 ml/kg. All injections were given i.m. 5 min pre-session. For all drugs except ketocyclazocine, vehicle injections were 0.2 ml/kg of 0.9 percent saline. For ketocyclazocine, vehicle injections were 0.2 ml/kg of saline mixed with the amount of lactic acid and NaOH necessary to keep the highest dose of ketocyclazocine in solution. All doses refer to the salts.

Data Analysis

The overall response rates for total responses on both levers as well as the proportion of responses on the PCP-appropriate lever were calculated from responding on test days. For each drug, a saline test session conducted at the end of the drug dose-response determination was used to calculate vehicle response rates and percent PCP-lever responding after vehicle administration for that drug. Percent drug-lever responding was determined by dividing the number of PCP-lever appropriate responses made during the test period by the total number of responses made during that time and multiplying by 100. The effective dose 50 percent (ED_{50}) for each analogue was determined by least squares linear regression analysis using the linear portion of the dose-response data for percent drug-lever responding and the descending limb of the dose-response data for percent of vehicle response rates. For the doses which were tested twice, the average of the two values was used in the calculation of the ED_{50}.

One sample t-tests ($\alpha \leq 0.05$) were carried out comparing the percent of baseline response rate following the administration of the three lowest doses of each analogue tested with a hypothesized mean of 100 percent of baseline. Comparisons were made for each drug individually at all three doses in all animals as well as testing the effect of the lowest doses of all drugs in all animals grouped together. A two sample paired t-test ($\alpha \leq 0.05$) was carried out comparing the percent drug-lever appropriate responding following a saline training day to the percent drug-lever appropriate responding following a PCP training day for the doses of each drug which were tested twice in each animal.

C. Results

The number of sessions to reach the criteria for beginning the PCP dose-response curve ranged from 38 to 60 ($\bar{x} = 47.3 \pm 2.33$) in different subjects. The training dose of PCP (0.16 mg/kg) produced approximately 85 percent drug-lever appropriate responding (Figure 9, upper left panel). Higher doses of PCP produced an even higher percentage of drug-lever appropriate choices. At the 0.08 mg/kg dose of PCP, the animals made approximately 78 percent drug-lever appropriate choices without any significant decrease in response rate. All five analogues produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Figure 9). At some doses, each of the analogues produced stimulus control of responding comparable to or greater than that of the PCP training dose. For all six compounds, the slopes of the lines for percent drug-lever appropriate responding were similar (Table 3). For those drug doses that were tested twice, there was no significant difference ($p \geq .05$) between the percent drug-lever appropriate

FIGURE 9

Group dose-response curves for PCP and five analogues for suppression of operant responding and for percent drug-lever appropriate responding. The percent of vehicle response rate ± S.E.M. averaged across animals (dashed lines) and the percent drug lever responding ± S.E.M. averaged across animals (solid lines) are on the ordinate with the corresponding drug dose on the abcissa. Vehicle rates were averaged for the 2-min test session with saline pretreatment at the end of each drug dose-response determination for all animals tested with that day. The number of animals tested with each drug is indicated in each panel. Only one animal was tested with 0.48 mg/kg PCE.

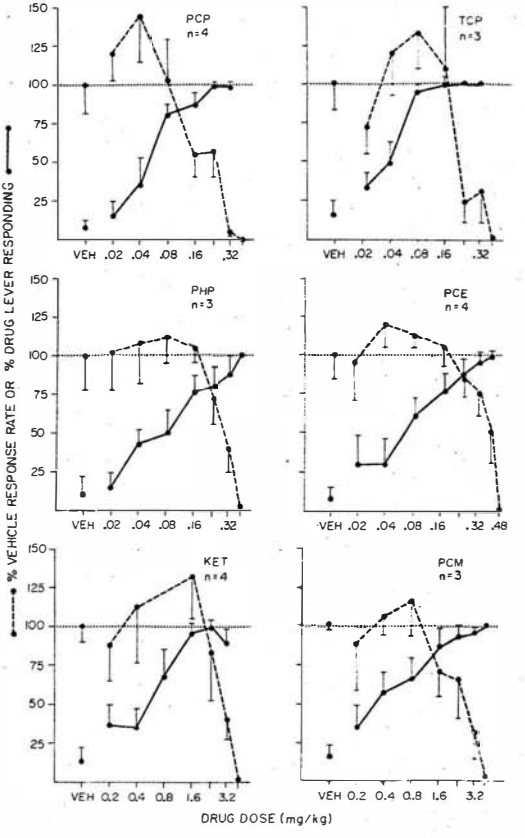

PCP
n=4
TCP
n=3
PHP
n=3
PCE
n=4
KET
n=4
PCM
n=3
% VEHICLE RESPONSE RATE OR % DRUG LEVER RESPONDING
DRUG DOSE (mg/kg)
VEH .02 .04 .08 .16 .32
VEH .02 .04 .08 .16 .32 .48
VEH 0.2 0.4 0.8 1.6 3.2

TABLE 3

POTENCY OF PCP AND FIVE ANALOGUES FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATE IN SQUIRREL MONKEYS

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression / Drug-Lever Responding
PCP	.05 (.04-.07)	1	78.4	.17 (.13-.25)	1.0	-115	3.4
TCP	.03 (.02-.05)	0.61	80.4	.24 (.16-.36)	1.4	-280	7.7
PHP	.06 (.05-.08)	1.2	59.7	.28 (.24-.34)	1.6	-254	3.7
PCE	.07 (.05-.1)	1.4	73	.33 (.28-.4)	1.9	-222	4.6
PCM	.35 (.24-.5)	6.8	55.1	2.3 (1.7-3.4)	13.3	-147	6.6
KET	.58 (.4-.76)	11.3	90.2	2.3 (1.9-2.7)	13.2	-246	3.9

* Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (µg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50% decrease in response rates as determined by linear regression and 95% confidence limits in parenthesis.

responding for the test days following saline training days and the test days following PCP training days.

Overall response rates for each animal remained fairly stable throughout the experiment. Average values ± S.E.M. in responses per sec for the response rates on vehicle test days for each animal were: .64 ± .03, 1.9 ± .22, 1.87 ± .13 and 2.1 ± .31. The effect of PCP and the analogues on overall response rate was often biphasic. Mean response rate increases over vehicle control rates were frequently seen with low doses of each drug (Figure 9). T-tests making individual comparisons between the percent of vehicle responding produced by the three lowest doses of each compound and a null hypothesis mean of 100 percent failed to indicate that these response rate increases were significant ($p \geq 0.05$). T-tests comparing the percent of vehicle responding for the lowest doses of all drugs tested grouped together to the 100 percent null hypothesis also showed no significant difference ($p \geq 0.05$). Higher doses of all six compounds produced a dose-dependent decrease in response rate. At the higher drug doses some animals did not respond at all. Test days for which the animals response rates were less than 0.05 response per sec were not included in the percent drug-lever appropriate responding tabulation. Table 3 shows the ED_{50} values for suppression of operant responding and for percent drug-lever responding for each of the six compounds tested. The relative potency for producing drug-lever appropriate responding was: TCP > PCP > PHP > PCE > PCM > ketamine. The relative potency for suppression of operant responding was: PCP > TCP > PHP > PCE > PCM = ketamine. In all cases, the dose necessary to suppress operant responding to 50 percent of vehicle rates was 3 to 8 times larger than ED_{50} dose for drug-lever appropriate responding.

For all six analogues, similar observable effects after administration of high doses were noted when the animals were removed from the experimental chamber at the end of the test session. These include excessive salivation, nystagmus and ataxia.

Figure 10, shows the dose-response determinations for morphine, ketocyclazocine and mescaline for percent PCP-appropriate responding and for percent of control response rates. None of these drugs produced dose-dependent drug-lever appropriate responding. Each drug was tested up to doses which produced marked suppression of response rates.

D. Discussion

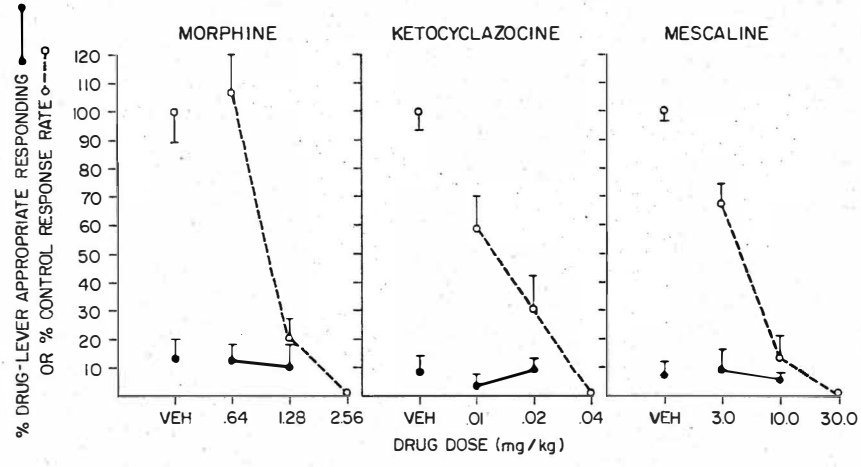
The results of this experiment indicate that all five analogues tested have discriminative stimulus properties similar to those of PCP. All five analogues produced PCP-appropriate responding in a dose-dependent fashion. At least one dose and usually two or three doses of each of these drugs produced stimulus control of responding comparable to the PCP training dose. Furthermore, for all six compounds, the highest doses given produced stimulus control of responding greater than PCP training dose.

The data for the generalization testing with morphine, ketocyclazocine and mescaline emphasize the specificity of the phencyclidine discriminative cue and validate the procedure used in this experiment. Ketocyclazocine is a benzomorphan opioid and mescaline is a hallucinogen. Like results reported by Shannon (1979) and Poling et al. (1979), our data indicate that the arylcycloalkylamines may represent a unique class of psychoactive drugs.

All of the analogues tested had comparable effects on rate of responding. For each compound, there was a relatively low dose which produced a

FIGURE 10

Group dose-response curves for morphine, ketocyclazocine and mescaline for suppression of operant responding for percent drug-lever appropriate responding in the squirrel monkey. The percent of vehicle response rate ± S.E.M. averaged for 6 animals (dashed lines) and the percent drug-lever appropriate responding ± S.E.M. averaged for 6 animals (solid lines) are on the ordinate with the corresponding drug dose on the abscissa. Two determinations were made for the effects each dose of each drug. Vehicle rates were calculated over the 2-min test session with vehicle pretreatment at the end of each drug dose-response determination.


% DRUG-LEVER APPROPRIATE RESPONDING
OR % CONTROL RESPONSE RATE
MORPHINE
KETOCYCLAZOCINE
MESCALINE
120
110
100
90
80
70
60
50
40
30
20
10
VEH
.64
1.28
2.56
VEH
.01
.02
.04
VEH
3.0
10.0
30.0
DRUG DOSE (mg/kg)

consistent but statistically insignificant increase in overall response rates. These findings are consistent with other reports of increases in low rates of schedule-controlled responding with low doses of PCP in squirrel monkeys (Chait and Balster, 1977, 1978, 1979). For the most part, these response rate increasing doses produced less than 50 percent drug-lever appropriate responding. It is possible that this is due to some behavioral activity of these compounds at doses even lower than those producing the discriminative stimulus. It also possible that using a lower training dose of PCP, generalization would be seen at these response rate increasing doses. Higher doses of all compounds suppressed operant responding in a dose-dependent fashion. The slopes for the descending limb of the dose-response curves were similar for all six drugs.

For all of the PCP analogues, the ED_{50} value for response rate suppression was 3 to 8 times larger than the ED_{50} value for drug-lever appropriate responding. Doses could be found for all compounds which produced 70 to 100 percent drug-lever appropriate responding without decreasing response rates to below saline control levels. This indicates that the drug discrimination paradigm is a very sensitive method to assay the behavioral activity of PCP-like compounds.

The gross observable effects of high doses of all six drugs were also similar. Excessive salivation, nystagmus and an inability to maintain balance on a perch when returned to the home cage were the most notable features. Balster and Chait (1976, 1978) have reported comparable effects in primates after PCP administration.

Our data support most of the previous work in both *in vivo* and *in vitro* systems in showing pharmacological similarities between the

five analogues tested here and PCP. In agreement with Experiment I (Brady et al., 1980), we found that these analogues had similar observable effects on primates, as well as similar effects on schedule-controlled performance. The present study also supports the previous drug discrimination work done with PCP in a drug vs. saline task. In addition, PCP, PCE and TCE have been shown in several studies (Kloog et al., 1977; Maayani et al., 1974, 1973; Paster et al., 1974; Pinchasi et al., 1978a, 1978b, 1977; Weinstein et al., 1973) to have both anticholinergic and anticholinesterase activity using receptor binding and bioassay procedures.

One interesting descrepancy between our findings and those reported in the literature lies with the study by Gehrmann and Killam (1979) where they report a qualitative differences between the EEG changes produced by PHP and those produced by the rest of the analogues which they tested. Neither our study nor any in the literature indicates that the spectra of action of PHP differs from that of PCP in a variety of pharmacological assays.

There is some disagreement in the literature concerning the potency of the analogues relative to PCP. Most studies find PCM and ketamine to be approximately 1/5 to 1/10 as potent as PCP. There also seems to be general agreement that PCP, PHP and TCP are roughly equipotent. However, conflicting results have been obtained concerning the potency of PCE relative to PCP. Several investigators using motor effects of mice (Balster, 1980; Kalir et al., 1978; Pinchasi et al., 1978a) have reported that PCE is 2 to 3 times more potent than PCP. Jarbe et al. (1975) reported that PCE was somewhat more potent than PCP and Shannon (1979) found PCE to be nearly 6 times more potent than PCP in the discriminative

stimulus paradigm using rats. On the other hand, in the present study PCE and PCP were found to be roughly equipotent in producing drug-lever appropriate responding, and in Experiment I using rhesus monkeys (Brady et al., 1980) PCE was slightly less potent than PCP in suppressing response rates maintained under a fixed-interval schedule. Chen (1965) found PCE and PCP to be equipotent in producing catalepsy in pigeons. Thus, PCE appears in general to be more potent than PCP in rodents, but is either equipotent or somewhat less potent than PCP in monkeys and pigeons. While the reason for these discrepancies is not clear, it could reflect a difference in the biodisposition of PCE in rodents Kalir et al. (1978) found that a higher percentage of the injected amount of drug was found in the brains of mice after PCE administration than after PCP administration. Similar studies have not yet been done with primates.

One last point concerns the use of primates in drug discrimination procedures. There have been relatively few reports using squirrel monkeys in drug discrimination studies (Holtzman et al., 1976; Woolverton and Trost, 1978; Teal and Holtzman, 1980b). Woolverton and Trost (1978) found that squirrel monkeys could discriminate doses of cocaine 100-fold less than those used in many rat discrimination studies with cocaine. The training dose of PCP used in this study was 20 times less than that used in our rat studies and those reported by others (Jarbe et al., 1975; Overton, 1975; Shannon, 1979). This sensitivity coupled with the differences in the behavioral activity of the dissociative anesthetics between primates and rodents makes it especially important to assay the activity of PCP and its analogues in primates.

In conclusion, PCP was found to produce stimulus control over responding in squirrel monkeys in a dose-dependent manner. The drug discrimination paradigm provides a very sensitive measure of PCP's behavioral activity in so far as drug-lever appropriate responding was maintained at doses which produced no observable effects. The five structural analogues of PCP which were tested all produced dose-dependent PCP-appropriate responding and were similar to PCP in their observable effects as well as their effects on overall response rates. Several psychoactive compounds from different pharmacological classes did not produce PCP-appropriate responding.

IV. COMPARISON OF THE DISCRIMINATIVE STIMULUS PROPERTIES OF PHENCYCLIDINE DEXOXADROL AND ETOXADROL (EXPERIMENT III)

A. Introduction

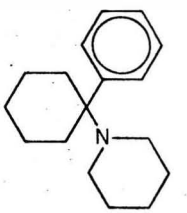
In spite of structural dissimilarities, evidence indicates that etoxadrol and dexoxadrol (Figure 11), both 2-(2,2-substituted 1,3 dioxolan-4-yl) piperidines, share many pharmacological properties with phencyclidine (PCP) and ketamine. With increasing doses, the sequence of observable effects in laboratory animals is similar for all four compounds (Chen, 1973). Generally, there is a progression from hyperactivity to ataxia, catalepsy, general anesthesia and convulsions. The prominence of these stages varies greatly among different species. For example, hyperactivity after low doses is quite prominent in rodents, but only occasionally reported in non-human primates and man (Chen et al., 1959; Hildago et al., 1971; Balster and Chait 1976, 1978).

As was the case with PCP and ketamine, etoxadrol has been investigated for use as an anesthetic. Initial studies with several laboratory species indicate striking similarities in the effects of ketamine and etoxadrol on the cardiovascular and respiratory systems (Hildago et al., 1971; Traber et al., 1970; Kelly et al., 1971) and in the electrophysiological effects of these two drugs (Tang and Schroeder, 1973; Julien and Kaven, 1975). Clinical trials indicated that humans anesthesized with etoxadrol maintain pharyngeal, laryngeal and lid reflexes. Tachycardia and tachypnea as well as nystagmus and emergence delirium have been observed (Wilson et al., 1970, 1973; Frederickson et al., 1976). As a consequence of these findings, etoxadrol has been classified along with PCP and ketamine as a dissociative anesthetic.

Most of the early investigations of dexoxadrol focused on its

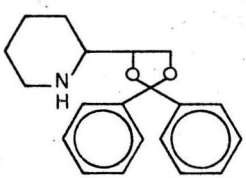
FIGURE 11

Chemical structures of PCP, dexoxadrol and etoxadrol.



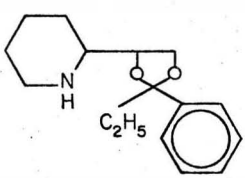
PCP

1-(1-phenylcyclohexyl) piperidine



DEXOXADROL

D-2-(2,2-diphenyl-1,3 dioxolan-4-yl) piperidine



ETOXADROL

D-2-(2,2-ethylphenyl-1,3 dioxolan-4-yl) piperidine

analgesic properties. Hildago and Thompson (1963) reported that dexoxadrol produced hyperalgesia and antagonized morphine-induced antinociception on the hot plate in mice. Collins and Weeks (1967) found that constant infusion of dexoxadrol in self-maintained morphine-dependent rats did not decrease the rate of morphine self-administration as most dependence-producing opiates do. On the basis of this finding, they concluded that dexoxadrol would probably not have opioid-like addiction liability in man. Clinical studies (Simopoulos et al., 1970; Lasagna and Pearson, 1965; Williams et al., 1969) have shown dexoxadrol to be an analgesic of efficacy similar to aspirin in man with psychotomimetic properties at higher doses.

The discriminative stimulus properties of PCP seem to be relatively specific in that only structural analogues of PCP and several psychotomimetic opioid derivatives N-allyl normetazocine , cyclazocine and dextrorphan generalize to PCP in rodents (Shannon, 1979; Holtzman, 1980), pigeons (Herling et al., 1980) and squirrel monkeys (Experiment II, Brady and Balster, 1981) trained to discriminate PCP from saline. This study was designed to determine if dexoxadrol and etoxadrol would generalize to PCP in squirrel monkeys trained to discriminate PCP from saline.

B. Methods

Subjects

The subjects were three adult male squirrel monkeys (Saimiri sciureus, Santa Cruz, Bolvia, Primate Imports, Port Washington, New York) which had previously been used in the study of the discriminative stimulus properties of structural analogues of PCP (Experiment II, Brady and Balster, 1981). The animals were maintained at 80% of

their free-feeding weights (0.8 to 1.0 kg) throughout the experiment by adjusted post-session feedings. They had unlimited access to water in their home cages where they were individually housed in standard primate caging.

Apparatus

The apparatus used in this study is identical to the one described in Experiment II.

Procedure

The procedure for training the subjects to discriminate PCP from saline has been described in Experiment II. The subjects had been trained to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Each animal received an injection of either physiological saline or 0.16 mg/kg PCP on a double alternation schedule, i.e. two days of PCP injection followed by two days of saline injections, etc. The animal was injected while in the primate chair, 20 min pre-session. The chair was immediately placed in a sound and light attenuating isolation cubicle (Coulbourn Model E10-20) for the pretreatment time and the duration of the experimental session. The only source of light in the cubicle was the four stimulus lights above the levers which were illuminated at the initiation of the session. For two animals, the left lever was reinforced on PCP training days and the right lever was reinforced on saline training days. The lever conditions were reversed for the other subject. Responses on the incorrect lever reset the FR contingency for reinforced responding on the correct lever.

Initially, every third session began with a 2-min period during which responding was not reinforced, after which the animal was continued

as usual on the FR32 schedule for the remaining 28 min. Test sessions were not initiated until an animal had performed 85 percent or more responses on the appropriate lever during four consecutive extinction probes. The effects of substituting various doses of PCP, etoxadrol and dexoxadrol for the 0.16 mg/kg dose of PCP were determined on test days. Test sessions were conducted every third day if the animal completed the first fixed-ratio on the appropriate lever on the training day preceding the test day. Test session consisted of a 2-min extinction period after which the animals were returned to their home cages. The double alternation continued on training days with the test sessions interspersed such that a PCP and a saline training day preceded each successive test day.

The three drugs were tested in a different order in each subject. For each drug, two animals received the doses in ascending order, and one animal received the doses in descending order. Tests were conducted with seven doses of PCP (0.02 - 0.4 mg/kg), and eight doses of dexoxadrol (0.06 - 1.92 mg/kg) and etoxadrol (0.04 - 0.8 mg/kg). The four middle doses of each compound were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day.

Data Analysis

Overall response rates on both levers and proportion of responses of the drug-appropriate lever were analyzed for test days. A vehicle test session conducted at the end of each individual drug dose-response determination was used to calculate vehicle response rates and percent drug-lever responding after vehicle administration for that drug. Drug-lever responding was determined by dividing the number of drug-lever

appropriate responses made during the test period by the total number of responses made during that time. Effects of test drug doses on overall response rates on both levers were calculated as the percent of the response rate on the vehicle test days conducted for each drug. The effective dose 50 percent (ED_{50}) for each drug was determined by least squares linear regression analysis using the dose-response data for percent drug-lever responding and for percent of vehicle response rates for the linear portions of the dose-response curves. For the doses which were tested twice, the average of the two values was used in the calculation of the ED_{50}.

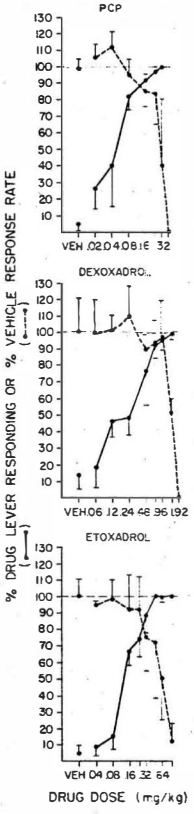
One sample t-tests ($\alpha \leq 0.05$) were carried out comparing the overall response rates following the administration of the rate-increasing doses of PCP and dexoxadrol with a hypothesized mean of 100 percent of baseline. A two sample paired t-test ($\alpha \leq 0.05$) was carried out comparing the percent drug-lever appropriate responding following a saline training day to the percent drug-lever appropriate responding following PCP training day for the doses of each drug which were tested twice in each animal.

C. Results

Figure 12 shows the dose-response relationship for mean percent vehicle response rate and mean percent drug-lever responding for PCP, dexoxadrol and etoxadrol. The training dose of PCP (0.16 mg/kg) produced 92 percent drug-lever appropriate responding on test sessions. Higher doses of PCP produced an even higher percentage of drug-lever appropriate choices. At the 0.08 mg/kg dose of PCP, the animals made approximately 82 percent drug-lever appropriate choices without any decrease in response rate. Both dexoxadrol and etoxadrol produced a dose-related increase in the percent of responses made on the PCP-

FIGURE 12

Group dose-response curves for PCP, dexoxadrol and etoxadrol for suppression of operant responding for percent drug-lever appropriate responding in the squirrel monkey. The percent of vehicle response rate ± S.E.M. average for 3 animals (dashed lines) and the percent drug-lever appropriate responding ± S.E.M. averaged for 3 animals (solid lines) are on the ordinate with the corresponding drug dose on the abscissa. Two determinations were made for the effects of the middle 4 doses of each drug. Vehicle rates were calculated over the 2 min test session with vehicle pretreatment at the end of each drug dose-response determination.


PCP
DEXOXADROL
ETOXADROL
% DRUG LEVER RESPONDING OR % VEHICLE RESPONSE RATE
(●——●)
(●- - -●)
VEH .02 0.4 0.8 1.6 3.2
VEH 0.6 1.2 2.4 4.8 9.6 19.2
VEH 0.4 0.8 1.6 3.2 6.4
DRUG DOSE (mg/kg)

appropriate lever. At least three doses of both compounds produced stimulus control of responding comparable to or greater than that of the PCP training dose. For all three compounds the slopes of the lines for percent drug-lever appropriate responding were similar (Table 4).

Response rates for the ½ hour session for each animal remained fairly stable throughout the experiment. Average values ± S.E.M. in responses per second for the response rates on the 4 vehicle test days for each animal were: 2.4 ± 0.32, 1.83 ± 0.20 and 1.21 ± 0.25. The effect of PCP and dexoxadrol on overall response rate was often biphasic. Response rate increases were frequently seen with at least one low dose of both drugs, however these were not statistically significant ($p \geq 0.05$). Higher doses of all three compounds produced a dose-dependent decrease in operant responding. Test days for which the animals response rates were less than 0.05 response per sec were not included in the percent drug-lever appropriate responding tabulation. For all three compounds, the slopes of the descending limb of the line for percent of vehicle responding were similar (Table 4).

Table 4 shows the ED_{50} values for suppression of operant responding and for percent drug-lever responding for each of the three compounds tested. For both suppression of overall response rate and for producing drug-lever appropriate responding, PCP was 4 to 5 times more potent than dexoxadrol and 2 to 3 times more potent than etoxadrol. For all three compounds, the dose necessary to suppress operant responding to 50 percent of vehicle rates was 4 to 7 times larger than the ED_{50} dose for drug-lever appropriate responding.

Similar gross behavioral effects were noted after administration of high doses of all three compounds. These included excessive salivation, nystagmus and ataxia. The nystagmus and salivation were seen less

TABLE 4

POTENCY OF PCP, ETOXADROL AND DEXOXADROL FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATES IN SQUIRREL MONKEYS

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression/ Drug-Lever Responding
PCP	.04 (0.3-.07)	1.0	67.9	.23 (.19-.39)	1.0	-121	5.3
Etoxadrol	.12 (.10-.15)	2.8	85.8	.46 (.32-.81)	2.0	-158	3.8
Dexoxadrol	.19 (.13-.26)	4.3	63.2	1.23 (.96-3.4)	5.3	-96	6.5

*Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (μg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50% decrease in response rates as determined by linear regression and 95% confidence limits in parenthesis.

consistently with etoxadrol and dexoxadrol than with PCP.

D. Discussion

Etoxadrol and dexoxadrol have PCP-like discriminative stimulus properties and all three suppress operant responding in a dose-dependent manner. In all cases, the ED_{50} dose for suppression of operant responding was 4 to 7 times larger than the ED_{50} dose for PCP-appropriate responding. This is consistent with Experiment II (Brady and Balster, 1981) in finding that in PCP-trained squirrel monkeys, a series of structural analogues of PCP produced PCP-appropriate responding in doses 3 to 8 times less than the doses necessary to suppress operant responding. In addition to suggesting a similar profile of behavioral activity, this is also an indication that the drug-discrimination paradigm is a very sensitive method for measuring the central nervous system activity of all of these compounds.

There have been a number of early reports (Zukin and Zukin, 1979; Vincent et al., 1979; Hampton et al., 1980) of a specific binding site for PCP in the rodent nervous system, suggesting the possibility of a receptor mediating the effects of PCP. The binding of the psychotomimetic opioids and dexoxadrol to these sites is of considerable interest (Zukin and Zukin, 1979; Hampton et al, 1980). The demonstration that etoxadrol and dexoxadrol possess discriminative stimulus properties similar to PCP provides a rationale for the use of these drugs which are chemically unrelated to PCP to characterize a putative PCP receptor.

In conclusion, the results of this experiment support the literature in finding many similarities in the pharmacological properties of PCP, dexoxadrol and etoxadrol (Chen, 1973). Both etoxadrol and dexoxadrol generalize to PCP in the drug discrimination task and all three

compounds have similar effects on grossly observable behavior. Further exploration of the link between these compounds will help to elucidate the nature of the overlap between the dissociative anesthetics and the psychotomimetic opioids.

V. DISCRIMINATIVE STIMULUS PROPERTIES OF STEREOISOMERS OF N-ALLYL-NORMETAZOCINE IN PHENCYCLIDINE-TRAINED SQUIRREL MONKEYS AND RATS AND THE EFFECTS OF NALOXONE (EXPERIMENT IV)

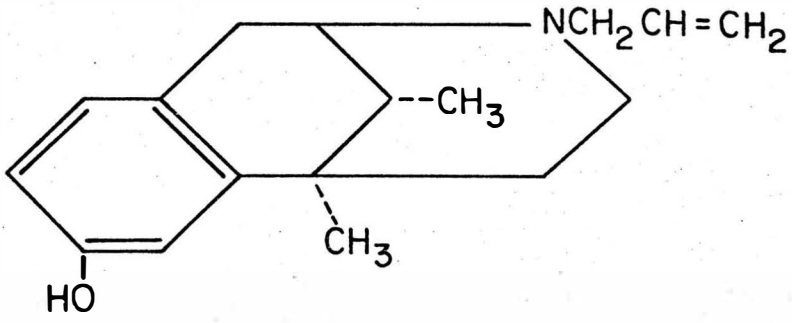
A. Introduction

On the basis of the spectra of effects produced by various opioids in the chronic spinal dog, Martin et al. (1976) have postulated three distinct opiate receptors: the mu receptor with morphine as the prototypic agonist, the kappa receptor with ketocyclazocine as the prototypic agonist, and the sigma receptor with N-allylnormetazocine (SKF 10, 047; Figure 13) as the prototypic agonist. N-allylnormetazocine is an opioid derivative of the benzomorphan series which produces hallucinations in man (Keats and Telford, 1964).

In a recent study exploring the discriminative stimulus properties of phencyclidine, Shannon (1979) found that N-allylnormetazocine produced PCP-appropriate responding in rats trained to discriminate PCP from saline in a two-lever drug discrimination task. The rats were also tested for generalization to a series of structural analogues of PCP as well as a variety of other psychoactive substances including ketocyclazocine, LSD, THC and morphine. Only N-allylnormetazocine and the structural analogues of PCP generalized to PCP. The specificity of the PCP cue was also demonstrated by Poling et al. (1979). In PCP trained rats tested for generalization to ketamine and to a series of classical agonists and antagonists of various neurotransmitter systems, only ketamine produced drug-lever appropriate responding. In Experiment II we found that only PCP analogues and not morphine, mescaline or ketocyclazocine generalize to PCP. Thus, the finding of generalization

FIGURE 13

Chemical structure of N-allylnormetazocine.



N-ALLYLNORMETAZOCINE

∝-2-Allyl-5,9-dimethyl-2'-hydroxy-6,7-benzomorphan

suggests similarities between the effects of PCP and sigma agonists.

It has also been demonstrated that rats and pigeons generalize between cyclazocine, another opioid derivative of the benzomorphan series and PCP, ketamine and dextrorphan, the (+) isomer of levorphanol (Teal and Holtzman, 1980a; Herling et al., 1980; Holtzman, 1980). In Martin's (Martin et al., 1976) classification of opioid receptors, cyclazocine also is considered to have a high affinity for the sigma receptor.

In the introduction, the unusual separation of activity between the optical isomers of benzomorphans was described. In working with a racemic mixture in the benzomorphan series it is probable that one is working with a mixture of two active compounds which each have their own distinct spectra of pharmacological activities. Studies with the stereoisomers of N-allylnormetazocine (Swain et al., 1973) revealed that the (-) isomer is a nalorphine-like antagonist which will precipitate withdrawal in the morphine-dependent rhesus monkey, whereas the (+) isomer is a non-narcotic CNS depressant which produces marked ataxia in rhesus monkeys, effects we now know to be similar to those produced by PCP. In all of the other studies described so far with N-allylnormetazocine, the racemic mixture was used.

Martin et al. (1976) reported that the effects of all three prototype agonists could be antagonized by naltrexone, but there were marked differences in sensitivity to antagonism. Ketocyclazocine antagonism required 10 times more naltrexone than morphine antagonism and even higher dose of naltrexone were required to antagonize the effects of N-allylnormetazocine. Iwamoto (1979) reported that the effects of N-allylnormetazocine on locomotor activity in mice were antagonized by large

doses of naloxone (> 20 mg/kg) whereas only 0.1 mg/kg naloxone antagonized the effects of morphine.

Other investigations have indicated that the effects of N-allylnormetazocine cannot be blocked by narcotic antagonists. Cowan et al. (1979) found that low doses of naloxone (0.01 to 10.0 mg/kg) could attenuate the anticonvulsant effects of three mu receptor agonists in mice, while the anticonvulsant activity of N-allylnormetazocine was not antagonized by moderate to large doses of naloxone. In a study of the effects of narcotics on schedule-controlled performance in rats, Harris (1980) found that naltrexone markedly antagonized the rate-decreasing effects of morphine but had no effect on the rate-decreasing effects of N-allynormetazocine. Teal and Holtzman (1980c) found that naltrexone did not completely block the cyclazocine-like stimulus effects of N-allylnormetazocine in rats trained to discriminate cyclazocine from saline.

The present study was designed to explore the discriminative stimulus properties of N-allylnormetazocine, both the racemic mixture and the pure stereoisomers, in rats and squirrel monkeys trained to discriminate PCP from saline. Rats were studied in addition to monkeys because of the extensive use of rat central nervous system tissues for receptor binding studies of opioids. The effect of naloxone pretreatment on the discriminative stimulus and response-rate disrupting activity of the stereoisomers was also examined.

B. Methods

Subjects

For the squirrel monkey study, the subjects were six adult male squirrel monkeys (Saimiri sciureus, Santa Cruz, Bolivia, Primate Imports, Port Washington, New York) which had previously been used in a study of

the discriminative stimulus properties of structural analogues of PCP (Experiment II; Brady and Balster, 1981) or dexoxadrol, etoxadrol and PCP (Experiment III; Brady and Balster, 1980b). The animals were maintained at constant weights (0.8 to 1.0 kg) throughout the experiment by adjusted post-session feedings. They were individually housed in standard primate caging where they had unlimited access to water.

For the rat study, the subjects were ten experimentally naive male Sprague-Dawley rats (Flow Laboratories, Dublin, VA). The animals were maintained at 80% of their free-feedings weights (280-340 grams) throughout the experiment by adjusted post-session feedings. They were individually housed in wire mesh cages where they had unlimited access to water.

Apparatus

For the squirrel monkey study, the apparatus is the same as described in the methods section of Experiment II.

For the rat study, a standard two-lever operant rat chamber (Model E10-10, Coulbourn Instruments, Inc., Lehigh Valley, Pennsylvania) housed inside a light and sound attenuating cubicle (Model E10-20, Coulbourn Instruments, Inc.) was used. The levers were 10 cm from the floor of the chamber and 13 cm from each other. A food cup into which 45 mg Noyes food pellets (Formula A) could be delivered via a Gerbrands model 01 automatic feeder was in the center of the wall equidistant from and 2 cm below the two response levers. A house light was located 20 cm directly above the food cup. Solid state programming equipment and recording devices were located in an adjacent room.

Procedure

The procedure for training the squirrel monkeys to discriminate PCP

from saline has been described in more detail in the methods section of Experiment II. The subjects were trained to respond on a fixed-ratio 32 (FR 32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Each animal received an injection of either physiological saline or 0.16 mg/kg PCP on a double alternation schedule, i.e. two days of PCP injections followed by two days of saline injections, etc. The animal was injected while in the primate chair, 5 min presession. The chair was immediately placed in the cubicle. The only source of light was the four stimulus lights above the levers which were illuminated at the initiation of the session. For three animals, the left lever was reinforced on PCP days and the right lever was reinforced on saline days. The lever conditions were reversed for the other three subjects. Responses on the incorrect lever reset the FR contingency for reinforced responding the correct lever.

The effects of substituting various doses of PCP, (±)-N-allylnormetazocine, (+)-N-allylnormetazocine and (-)-N-allylnormetazocine for the 0.16 mg/kg dose of PCP were determined on test days. Test sessions were conducted every third day if the animal completed the first FR on the appropriate lever on the control day preceding the test day. Test sessions consisted of a 2-min extinction period after which the animals were returned to their home cages. The double alternation continued on control days with the test sessions interspersed such that a PCP and a saline training day preceded each successive test day.

For each drug three animals received doses in ascending order and three animals received the doses in descending order. The PCP dose-response determination was conducted first in all subjects. The other drugs were administered in random order. Tests were conducted with five

doses of PCP (0.04-0.64 mg/kg), (±)-N-allylnormetazocine (0.04-.64 mg/kg), and (-)-N-allylnormetazocine (0.02-.32 mg/kg), and seven doses of (+)-N-allylnormetazocine (0.04-2.56 mg/kg). The doses were chosen to cover a range from no effect to nearly complete suppression of response rates during the 2-min test sessions. The three middle doses of each compound were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day.

Following the dose-response determination for all four compounds, the effect of naloxone on the response rate disrupting and discriminative stimulus properties of (+) and (-)-N-allylnormetazocine was determined in each animal. Test sessions were conducted in the manner described above with two doses of naloxone (1.0 and 3.0 mg/kg), 0.64 mg/kg (+)-N-allylnormetazocine alone and in combination with 1.0 and 3.0 mg/kg naloxone, and 0.32 mg/kg (-)N-allylnormetazocine alone and in combination with 1.0 and 3.0 mg/kg naloxone. All injections were given i.m. 5 min pre-session.

For the rat study, the subjects were shaped to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Initially, the subjects were trained to respond on either lever on a FR 1 schedule. Once lever pressing on both levers was established (two to ten sessions) drug injections were begun. Each animal received either saline or 3.0 mg/kg PCP 10 min pre-session on adouble alternation schedule. From this point on, responding on only one lever was reinforced during the session. The animal was placed in the chamber immediately after the injection and the house light was illuminated at the start of the session. For five animals,

responses on the left lever resulted in reinforcement on PCP days and responses on the right lever resulted in reinforcement on saline days. The lever conditions were reversed for the other five subjects. Responses on the incorrect lever reset the FR contingency for reinforced responding on the correct lever. Response requirements were gradually increased until all animals reliably responded under a FR 32 schedule (28 to 58 sessions).

When reliable FR 32 responding was established, test probes were initiated. Every third session began with a 2-min period during which responding on either lever was reinforced, after which the session was continued as usual on the FR 32 schedule. Discrimination training was continued until the subject had four consecutive test periods with 85 percent or more responding on the appropriate lever.

Following discrimination training, the effects of substituting 0.3, 1.0 and 10.0 mg/kg doses of PCP for the 3.0 mg/kg training dose were determined. Five animals received the doses in ascending order and five animals received the doses in descending order. All drug doses were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day. Test sessions were conducted only if the animal completed the first FR on the appropriate lever on the control day preceding the test day. Test sessions consisted of a 2-min period during which responding on either lever was reinforced, after which the animals were returned to their cages. The double alternation continued on control days with the test sessions interspersed such that one PCP and one saline training day preceded each successive test day.

Following the PCP dose-response determination, stimulus generalization

testing was conducted in a similar manner with five doses of (±)-N-allylnormetazocine (0.3-30.0 mg/kg), (+)-N-allylnormetazocine (0.3-30.0 mg/kg) and (-)N-allylnormetazocine (0.3-30.0 mg/kg). These doses were chosen to cover a range from no effect to nearly complete suppression of response rates during the 2-min test session. Each dose was tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day.

The order in which the different drugs were given to each animal was randomized. All doses of a given drug were administered to a given subject before testing the next drug. Five animals received each drug in ascending dose order and five animals received each drug in descending dose order.

Following the dose-response determination for all four compounds, the effect of naloxone on the response rate disrupting and discriminative stimulus properties of (+) and (-)-N-allylnormetazocine was determined in each animal. Test sessions were conducted in the manner described above with 30.0 mg/kg naloxone, 10.0 mg/kg (+)-N-allylnormetazocine alone and in combination with 30.0 mg/kg naloxone 10.0 mg/kg (-)-N-allylnormetazocine alone and in combination with 30 mg/kg naloxone. Naloxone was administered subcutaneously 20 min pre-session; N-allylnormetazocine was administered i.p. 10 min pre-session.

Data Analysis

Both overall response rates on both levers and proportion of responses on the drug-appropriate lever were analyzed for test days. A saline test session conducted at the end of each individual drug dose-response determination was used to calculate vehicle response rate and percent drug-lever responding after vehicle administration for that drug. Drug-lever responding was determined by dividing the number of

drug-lever appropriate responses made during the period by the total number of responses made during that time. Effects of test drug doses on overall response rates on both levers were calculated as the percent of the response rate on the vehicle test days conducted for each drug. For the doses that were tested twice, the average of the two values was used in the ED_{50} determination. The effective dose 50 percent (ED_{50}) for each drug was determined by least squares linear regression analysis using the dose-response data for percent drug-lever responding and for percent of vehicle response rates for the linear portions of the dose-response curves. These calculations were made after a log 10 transformation of the dose expressed as μg/kg of the base. A two sample paired *t*-test ($\alpha \leq 0.05$) was carried out comparing the percent drug-lever appropriate responding following a saline training day to the percent drug-lever appropriate responding following a PCP training day for each drug dose that was tested twice. A two sample paired *t*-test was carried out comparing the percent drug-lever appropriate responding and percent vehicle response rate following the administration of the N-allyl-normetazocine isomers alone to the percent vehicle response rate following the administration of N-allylnormetazocine in combination with naloxone.

Drugs

The pure stereoisomers of α-N-allylnormetazocine as well as the racemic mixture were synthesized by Dr. E.L. May for this study. The racemic mixture was in the form of the hydrochloride salt. The stereoisomers were in the form of the hydrobromide salts. The composition of all three was confirmed by C, H, N analysis and high-resolution mass spectrometry. Purity was assured by thin-layer chromatography on silica -gel.

PCP was obtained from Bio Ceutic Laboratories (Sernylan) in a sterile stock solution of 100 mg/ml. Naloxone HCl was supplied by Endo Laboratories. All drugs were diluted with or dissolved in sterile saline to a concentration that resulted in an injection volume of 0.2 ml/kg for the squirrel monkeys and 1.0 ml/kg for the rats. All squirrel monkey injections were i.m.; rat injections were i.p. except for the naloxone injections, which were s.c. Vehicle injections were 0.2 ml/kg (monkeys) or 1.0 ml/kg (rats) of 0.9 percent saline. For PCP and naloxone, doses refer to the hydrochloride salt. For the N-allylnormetazocine compounds, doses were administered based on the above described hydrochloride or hydrobromide hemihydrates salts, however potency estimates for all compounds were calculated on the base.

C. Results

Squirrel Monkey Study

The training dose of PCP (0.16 mg/kg) produced approximately 90 percent drug-lever appropriate responding (Figure 14, upper left panel). A higher test dose of PCP (0.32 mg/kg) produced an even higher percentage of drug-lever appropriate choices whereas 0.64 mg/kg almost completely eliminated responding on either lever. Both (±)-N-allylnormetazocine and (+)-N-allylnormetazocine produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Figure 14). At some dose, both compounds produced stimulus control of responding comparable to or greater than that of the PCP training dose. For these three compounds, the slopes of the lines for percent drug-lever appropriate responding were similar (Table 5). Unlike the racemic mixture and the (+) isomer of N-allylnormetazocine the (-) isomer did not result in over 40 percent PCP-appropriate responding at any of the

FIGURE 14

Group dose-response curves for PCP, (±)-N-allynormetazocine, (+)-N-allylnormetazocine and (-)-N-allylnormetazocine for the suppression of operant responding and for percent drug-lever appropriate responding in the squirrel monkey. The mean percent drug-lever appropriate responding ± S.E.M. averaged across animals (dashed lines) and the mean percent control response rate ± S.E.M. averaged across animals (solid lines) are on the ordinate with the corresponding drug dose on the abscissa. Vehicle rates were calculated over the 2-min test session with vehicle pretreatment at the end of each drug dose-response determination.

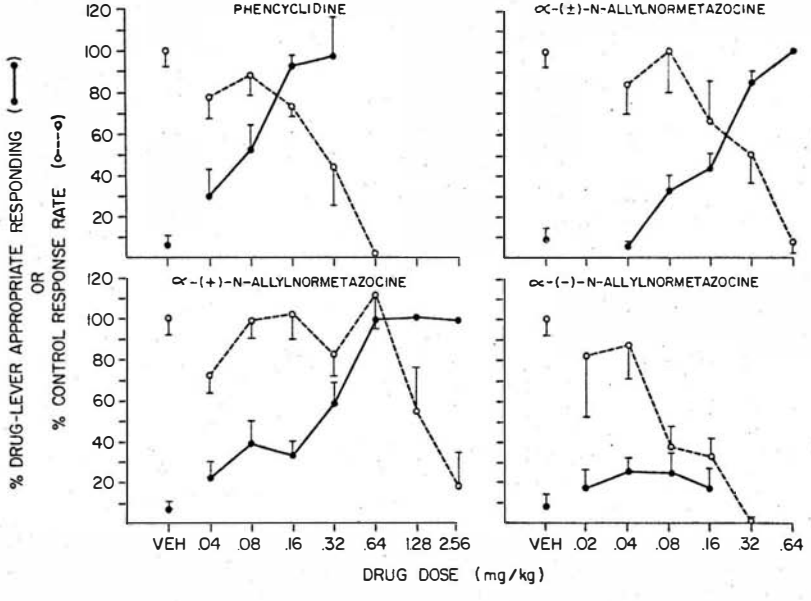

PHENCYCLIDINE
α-(±)-N-ALLYLNORMETAZOCINE
α-(+)-N-ALLYLNORMETAZOCINE
α-(-)-N-ALLYLNORMETAZOCINE
% DRUG-LEVER APPROPRIATE RESPONDING (●—●)
OR
% CONTROL RESPONSE RATE (○---○)
120
100
80
60
40
20
VEH .04 .08 .16 .32 .64 1.28 2.56
VEH .02 .04 .08 .16 .32 .64
DRUG DOSE (mg/kg)

TABLE 5

POTENCY OF PCP AND N-ALLYLNORMETAZOCINE FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATES IN SQUIRREL MONKEYS

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression Drug-Lever Responding
PCP	.07 (.01-.09)	1.0	83	.19 (.15-.28)	1.0	-105	2.9
(±)-N-Allyl-normetazocine	.14 (.12-.17)	2.1	80	.23 (.97-.36)	1.2	-101	1.7
(+)-N-Allyl-normetazocine	.19 (.16-.25)	2.9	106	1.1 (.97-1.3)	5.7	-143	5.7
(-)-N-Allyl-	-	-	-	.07 (.04-.1)	.34	-86	-

*Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (µg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50 decrease in response rates as determined by linear regression and 95% confidence limtis in parenthesis.

doses tested (Figure 14, lower right panel). For the drug doses that were tested twice, there was no significant difference ($P \geq .05$) between the percent drug-lever appropriate responding for test days following saline training days and test days following PCP training days for PCP, racemic and (+)-N-Allylnormetazocine.

Overall response rates for each animal remained fairly stable throughout the experiment. Average values ± S.E.M. for response rates on the four vehicles test days for each animal were: 1.8 ± .16, 1.03 ± .25, 1.2 ± .25, .93 ± .07, 2.25 ± .22, 1.2 ± .24 responses per sec. All four compounds produced a dose-dependent decrease in response rates. At the higher drug doses, some animals did not respond at all. Test days for which the animals' response rates were less than 0.05 response per sec for the 2-min extinction period were not included in the percent drug-lever appropriate responding tabulation. The slopes of the lines for response rate suppression are similar for all four compounds (Table 5).

A dose of 0.16 mg/kg PCP and 0.64 mg/kg (+)-N-allylnormetazocine resulted in greater than 90 percent PCP-lever approrpriate responses with only minimal effects on response rates, whereas for (±)-N-allyl-normetazocine, a high percentage of PCP lever responses only occurred at 0.32 mg/kg or greater; doses which decreased response rates over 50 percent. For (-)-N-allylnormetazocine, doses of 0.08 mg/kg or greater decreased response rates during the test sessions with no evidence of generalization to the PCP cue.

Table 5 shows the ED_{50} values for percent drug-lever responding and for suppression of operant responding for all four compounds. PCP was approximately 3 times more potent than the (+) isomer and twice as

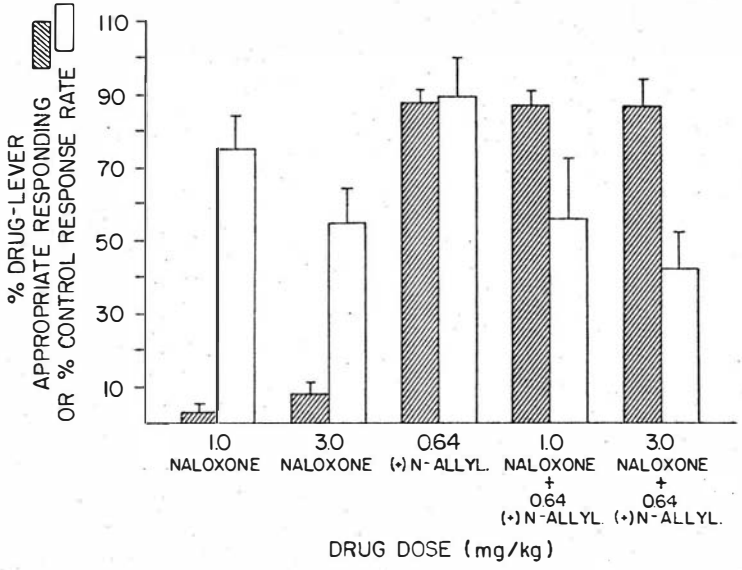
potent as the racemic mixture of N-allylnormetazocine in producing drug-lever appropriate responding. In so far as the (+) isomer is not more potent than the racemic mixture in producing PCP-appropriate responding and the (-) isomer does not produce PCP-appropriate responding, the data are inconsistent with the idea of an additive effect of the isomers in the racemic mixture for the production of the phencyclidine cue. The relative potency for suppression of operant responding was: (-) isomer > PCP > racemic mixture > (+) isomer. For response rate suppression, the relative potencies of the optical isomers of N-allylnormetazocine compared to the racemic mixture are consistent with an additive effect of the isomers. For PCP and (+)-N-allylnormetazocine, the dose necessary to suppress operant responding to 50 percent of vehicle rates was 3 to 6 times larger than the ED_{50} dose for drug-lever appropriate responding. In the case of (±)-N-allylnormetazocine, the ED_{50} dose for suppression of operant responding was only 1.7 times larger than the ED_{50} dose for drug-lever appropriate responding.

Although no systematic measure of observable effects was made, similar observable effects after administration of high doses of all four compounds were noted. These included excessive salivation, nystagmus and ataxia.

The effects of 1.0 and 3.0 mg/kg naloxone alone and in combination with 0.64 mg/kg (+)-N-allylnormetazocine on drug-lever appropriate responding and overall rate of responding are presented in Figure 15. The doses of naloxone tested did not produce over 10 percent PCP-appropriate responding and did not antagonize the PCP-appropriate responding produced by 0.64 mg/kg (+)-N-allylnormetazocine. Doses of 1.0 mg/kg and 3.0 mg/kg naloxone suppressed overall response rates to approximately 75 and 55 percent of control level respectively. There was no significant

FIGURE 15

Group dose-response data for percent drug-lever appropriate responding and percent control response rate for naloxone and (+)-N-allyl-normetazocine alone and in combination in squirrel monkeys. The percent of vehicle response rate ± S.E.M. (open bars) averaged for 6 subjects and the percent drug-lever appropriate responding ± S.E.M. (shaded bars) averaged for 6 subjects are on the ordinate with the corresponding dose on the abscissa.


% DRUG-LEVER APPROPRIATE RESPONDING OR % CONTROL RESPONSE RATE
110
90
70
50
30
10
1.0 NALOXONE
3.0 NALOXONE
0.64 (+) N-ALLYL.
1.0 NALOXONE + 0.64 (+) N-ALLYL.
3.0 NALOXONE + 0.64 (+) N-ALLYL.
DRUG DOSE (mg/kg)

difference ($p \geq 0.05$) the percent of control responding after either dose of naloxone when given alone and the percent of baseline responding for the naloxone -(+)-N-allylnormetazocine combination. Figure 16 shows the effects of 1.0 and 3.0 mg/kg naloxone alone and in combination with 0.32 mg/kg (-)-N-allynormetazocine on drug-lever appropriate responding and overall rate of responding. The data for naloxone alone are the same as those presented in Figure 15. This dose of (-)-N-allylnormetazocine suppressed overall response rates to approximately 5 percent of control and did not produce over 5 percent drug-lever appropriate responding. The (-)-N-allylnormetazocine combination with both doses of naloxone still produced less than 15 percent drug-lever appropriate responding. While neither dose of naloxone reversed the response-rate disruption produced by 0.32 mg/kg (-)-N-allylnormetazocine, the effect of the combination of the two drugs on overall response rates in both cases is less than one might expect by adding the effect of each drug given alone. However, there is no significant difference ($p \geq 0.05$) between the effect of 0.32 mg/kg (-)-N-allylnormetazocine alone and in combination with either dose of naloxone on percent of control response rate.

Rat Study

The average sessions to criteria (± S.E.M.) for acquisition of the PCP cue was 49.2 ± 10.7. Figure 17 shows percent of correct choices on saline and PCP test probes which started as soon as the subjects were responding consistently on a FR32 schedule. By the tenth test probe (5 saline, 5 PCP) the average percent of correct responses was approximately 70 percent for each lever. By the twelfth test probe (36 sessions), one animal had reached criteria. After 28 test probes (84 sessions) all subjects has reached the criteria for acquisition of the PCP discrimination cue. PCP dose-response determinations were started in each subject

FIGURE 16

Group dose-response data for percent drug-lever appropriate responding and percent control response rate for naloxone and (-)-N-allylnormetazocine alone and in combination in squirrel monkeys. The percent of vehicle response rate ± S.E.M. (open bars) averaged for 6 subjects and the percent drug-lever appropriate responding ± S.E.M. (shaded bars) averaged for 6 subjects are on the ordinate with the corresponding drug dose on the abscissa.

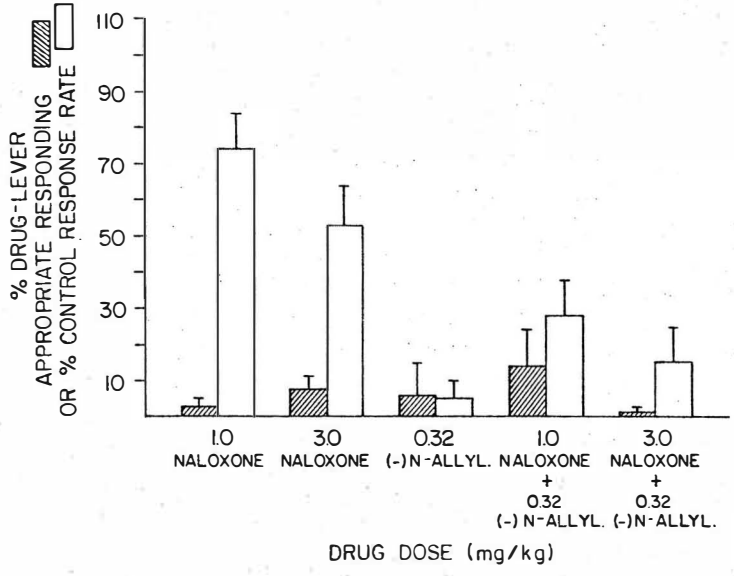
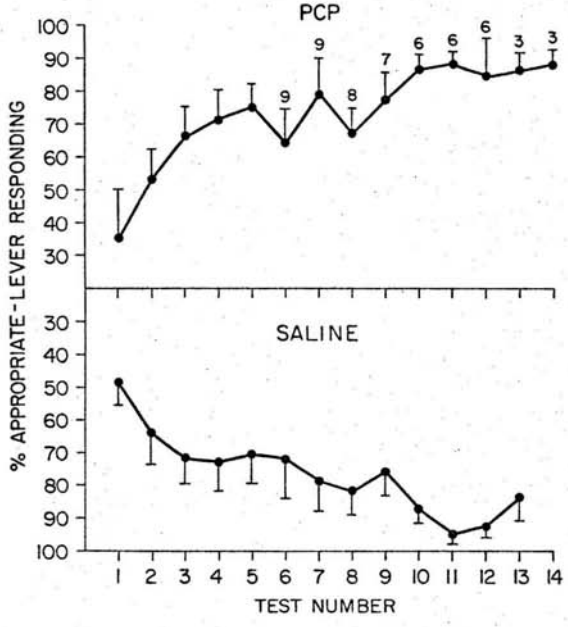

% DRUG-LEVER APPROPRIATE RESPONDING OR % CONTROL RESPONSE RATE
110
90
70
50
30
10
1.0 NALOXONE
3.0 NALOXONE
0.32 (-)N-ALLYL.
1.0 NALOXONE + 0.32 (-) N-ALLYL.
3.0 NALOXONE + 0.32 (-)N-ALLYL.
DRUG DOSE (mg/kg)

FIGURE 17

Group dose-response data for acquisition of PCP discrimination in rats. The percent saline or drug-lever responding ± S.E.M. averaged for all subjects tested is on the ordinate and the number of the test is on the abscissa. Six daily sessions comprise each test number, two training days followed by a saline test day and two training days followed by a PCP test day. Training began with 10 subjects. The numbers above the points of the PCP graph represent the number of animals tested at the point and the saline point below it. Animals were no longer tested after reaching criteria.


PCP
SALINE
% APPROPRIATE-LEVER RESPONDING
TEST NUMBER
100
90
80
70
60
50
40
30
1 2 3 4 5 6 7 8 9 10 11 12 13 14
9
9
8
7
6
6
6
3
3

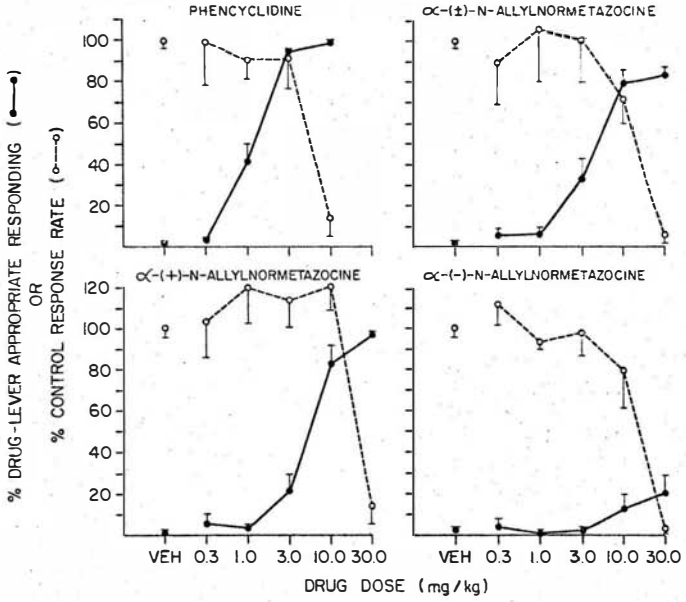
as soon as the acquisition criteria was reached.

The training dose of PCP (3.0 mg/kg) produced approximately 95 percent drug-lever appropriate responding (Figure 18, upper left panel). A higher dose of PCP (10 mg/kg) produced an even higher percentage of drug-lever appropriate choices, although rates of responding were markedly decreased and some animals did not respond at all. Both (±)-N-allylnormetazocine and (+)-N-allylnormetazocine produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Figure 18). The highest percentage of responses on the PCP lever was less than 85 percent for the racemate, whereas the (+) isomer reached levels greater than 95 percent, comparable to the PCP training dose. For these three compounds, the slopes of the lines for percent drug-lever appropriate responding were similar (Table 6). Unlike the racemic mixture and the (+) isomer of N-allynormetazocine, the (-) isomer did not produce greater than 20 percent PCP-appropriate responding at any of the doses tested (Figure 18, lower right panel), although doses were tested which markedly decreased response rates. For the compounds which generalized to PCP, there was no significant difference ($p \geq 0.05$) between the percent drug-lever appropriate responding for test days following saline training days and test days following PCP training days.

Overall response rates for each animal remained fairly stable throughout the experiment. Average values ± S.E.M for response rates on the four vehicle test days for each animal were: .8 ± .09, 1.8 ± .11, .97 ± .09, 1.5 ± .19, 2.53 ± .57, 1.2 ± .12 , 1.4 ± .24, .71 ± .02, .68 ± .08 and 1.12 ± .27 responses per sec. All four compounds produced a dose-dependent decrease in response rates. At the higher drug doses, some animals did not respond at all. Test days for which animals' response

FIGURE 18

Group dose-response curves for PCP, (±)-N-allylnormetazocine, (+)-N-allylnormetazocine and (-)-N-allylnormetazocine for suppression of operant responding and for percent drug-lever appropriate responding in the rat. The mean percent drug-lever appropriate responding ± S.E.M averaged across animals (solid lines) and the mean percent control response rate ± S.E.M. averaged across animals (dashed lines) are on the ordinate with the corresponding drug dose on the abscissa. Vehicle rates were calculated over the 2-min test session with vehicle pre-treatment at the end of each drug dose-response determination.


PHENCYCLIDINE
α-(±)-N-ALLYLNORMETAZOCINE
α-(+)-N-ALLYLNORMETAZOCINE
α-(-)-N-ALLYLNORMETAZOCINE
% DRUG-LEVER APPROPRIATE RESPONDING (●—●)
OR
% CONTROL RESPONSE RATE (○—○)
VEH 0.3 1.0 3.0 10.0 30.0
DRUG DOSE (mg/kg)

rates were less than 0.05 response per sec for the 2-min test period were not included in the percent drug-lever appropriate responding tabulation.

The training dose of PCP (3.0 mg/kg) and the 10.0 mg/kg test dose of (+)-N-allylnormetazocine resulted in greater than 80 percent PCP-lever appropriate responding with no effect on overall response rates. On the other hand, 80 percent or greater PCP-lever appropriate responses were only seen at doses (±)-N-allylnormetazocine that reduced response rates by 25 percent or more.

Table 6 shows the ED_{50} values for percent drug-lever responding and for suppression of operant responding for all four compounds. PCP was approximately 4 times more potent than the (+) isomer or the racemic mixture of N-allylnormetazocine in producing PCP-lever appropriate responding. The fact that the (+) isomer and racemic mixture are equi-potent in producing PCP-appropriate responding whereas the (-) isomer does not produce PCP-appropriate responding is inconsistent with the idea of an additive effect of the isomers in the racemic mixture for the production of the PCP-cue.

The relative potency for suppression of operant responding was: PCP > (-) isomer > racemic mixture > (+) isomer. For response rate suppression, the relative potencies of the optical isomers of N-allyl-normetazocine compared to the racemic mixture is roughly consistent with an additive effect of the isomers. For PCP, (+)-N-allylnormetazocine and (±)-N-allylnormetazocine, the dose necessary to suppress operant responding to 50 percent of vehicle rates was 2.8 times larger than the ED_{50} dose for PCP-lever appropriate responding.

TABLE 6

POTENCY OF PCP AND N-ALLYLNORMETAZOCINE FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATES IN RATS

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression / Drug-Lever Responding
PCP	.98 (.8-1.2)	1.0	74	2.7 (2.0-3.9)	1.0	-64	2.8
(±)-N-Allyl-normetazocine	3.95 (3.0-6.2)	4.0	62	11.1 (7.8-17.4)	4.1	-97	2.8
(+)-N-Allyl-normetazocine	4.45 (3.0-7.6)	4.5	71	12.6 (9.7-19.1)	4.7	-96	2.8
(-)-N-Allyl-normetazocine	-	-	-	6.7 (4.6-12.9)	2.5	-61	-

*Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (μg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50% decrease in response rates as determined by linear regression and 95% confidence limits in parenthesis.

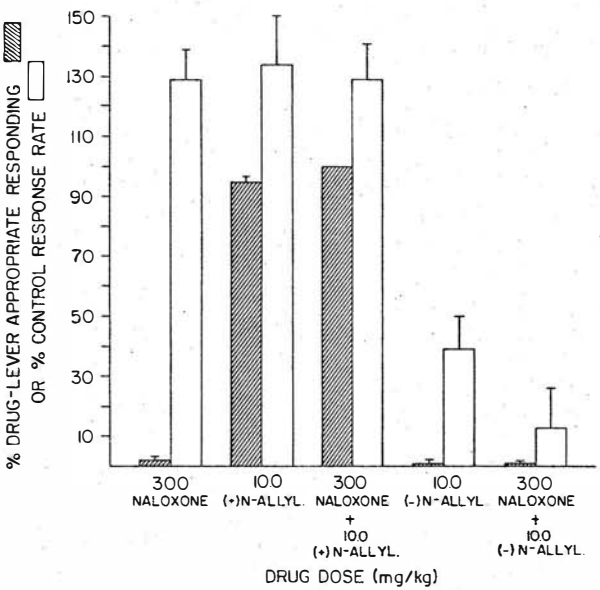
The effects of 30.0 mg/kg naloxone alone and in combination with 10.0 mg/kg of (+) and (-)-N-allylnormetazocine on drug-lever appropriate responding and overall response rates is presented in Figure 19. The dose of naloxone tested did not produce PCP-appropriate responding above saline levels and did not decrease overall response rates. Naloxone pretreatment did not antagonize the PCP-lever appropriate responding produced by 10 mg/kg (+)-N-allylnormetazocine and the combination had no greater effect on overall response rates. (-)-N-allylnormetazocine did not produce PCP-appropriate responding alone or in combination with naloxone. A dose of 10.0 mg/kg (-)-N-allylnormetazocine suppressed overall response rates to approximately 40 percent of control. There was no significant difference ($p \geq 0.05$) between the percent of control response rate after 10.0 mg/kg (-)-N-allylnormetazocine alone and the percent of control response rate after the administration of (-)-N-allylnormetazocine in combination with 30.0 mg/kg naloxone.

D. Discussion

The results in both squirrel monkeys and rats are consistent in showing that the PCP-like stimulus properites of racemic N-allylnormetazocine (SKF-10,047) in rats reported by Shannon (1979) and Holtzman (1980) reside in the (+) isomer. Our studies also show that the levo isomer is not without behavioral activity, but that this activity is not PCP-like. Therefore, (±)-N-allylnormetazocine, like many racemic benzomorphans (Villarreal, 1970), is a mixture of drugs with differing profiles of activity and is a poor candidate for a putative receptor agonist in the three receptor scheme proposed by Martin et al. (1976). Since PCP and (±)-N-allynormetazocine have similar profiles of activity in the spinal dog (Vaupel and Jasinsky, 1979), our finding that PCP and (+)-N-allylnormetazocine but not (-)-N-allylnormetazocine share stimulus properties

FIGURE 19

Group dose-response data for percent drug-lever appropriate responding and percent control response rate for naloxone, (-)-N-allyl-normetazocine and (+)-N-allylnormetazocine alone and in combination in rats. The percent of vehicle response rate ± S.E.M. (open bars) averaged for 10 subjects and the percent drug-lever appropriate responding ± S.E.M. (hatched bars) averaged for 10 subjects are on the ordinate with the corresponding drug dose on the abscissa.


% DRUG-LEVER APPROPRIATE RESPONDING
OR % CONTROL RESPONSE RATE
150
130
110
90
70
50
30
10
300 NALOXONE
100 (+)N-ALLYL.
300 NALOXONE + 10.0 (+)N-ALLYL.
100 (-)N-ALLYL
300 NALOXONE + 10.0 (-)N-ALLYL.
DRUG DOSE (mg/kg)

makes it likely that the (+) isomer is responsible for the sigma agonist profile of the racemate in the spinal dog. Indirectly, this also suggests that the (+) isomer would be the drug of choice to characterize putative sigma receptors in future research, and that stereospecific binding studies of the (+) and (-) isomers would be a fruitful approach.

The three receptor model of Martin et al. (1976) has proven to be very useful to characterize the discriminative stimulus properties of opioids in laboratory animals (Teal and Holzman, 1980; Woods et al., 1979). A number of studies have converged to suggest that a diversity of chemical classes may share stimulus properties which can be related to the sigma receptor. The discriminative stimulus effects of the benzomorphans N-allynormetazocine and cyclazocine have been shown to be similar to each other and PCP and/or ketamine (Shannon, 1979; Teal and Holtzman, 1979, 1980a; Herling et al., 1980; Holtzman, 1980). Dextrophan has also been reported to generalize to PCP and/or ketamine (Holtzman, 1980; Herling et al., 1980). The arylcycloalkylamine dissociative anesthetics have been consistently shown to share discriminative stimulus properties (Shannon, 1979; Experiment II, Brady and Balster, 1981). Finally, etoxadrol and dexoxadrol, two similar compounds which represent another distinct chemical class, also have been reported to generalize to PCP (Experiment III, Brady and Balster, 1980b). It has yet to be determined the exact extent of the overlap in the pharmacological properties in these diverse drugs, nor whether they may be acting through a common receptor mechanism. It is clear that a number of potentially useful tools are available to explore the pharmacology of PCP-like dissociative anesthetics as well as opioid sigma agonists.

Recently, there have been a number of reports (Zukin and Zukin, 1979; Vincent et al., 1979; Hampton et al., 1980) of a specific binding site for PCP in the rodent nervous system, suggesting the possibility of a receptor mediating the effects of PCP. A series of structural analogues of PCP and (±)-N-allylnormetazocine (Zukin and Zukin, 1979) have been found to bind this receptor and the relative affinities for binding correlate well with their relative potencies in cross-generalization to PCP in the drug-discrimination paradigm. Using the pure optical isomers of N-allylnormetazocine in this binding assay would be of considerable value in further characterizing this putative PCP receptor. In the light of our findings, it seems likely that the (+) isomer of N-allylnormetazocine may bind with a higher affinity than the (-) isomer. The data show a greater similarity between the effects of (+)-N-allylnormetazocine and PCP than between PCP and the racemic mixture.

For PCP and (+)-N-allylnormetazocine, the ED_{50} value for response rate suppression was approximately 3 or more times larger than the ED_{50} value for PCP-lever appropriate responding in the rat and the squirrel monkey. This is consistent with our other studies using squirrel monkeys trained to discriminate PCP from saline in which several structural analogues of PCP (Experiment II, Brady and Balster, 1981) as well as structurally dissimilar compounds (Experiment III, Brady and Balster, 1980b) produced drug-lever appropriate responding at doses 3 to 8 fold less than the doses which suppressed overall response rates. There was less difference between the ED_{50} value for PCP-appropriate responding and the ED_{50} value for response-rate suppression with (±)-N-allylnormetazocine in squirrel monkeys, but not in rats. However, in both rats and monkeys nearly complete generalization to PCP occurred with the (+) isomer at doses which did not disrupt responding, whereas response rate

decreasing doses of the racemate were needed to reach 80 percent or greater PCP-lever appropriate responding. The poor separation of the stimulus properties and response-rate disrupting properties in the racemate is probably due to the potent response rate disrupting effects of the (-) isomer contained in the mixture. In both the rat and monkey, the potency for disrupting responding by the racemate fell between the potencies of the (+) and (-) isomers indicating that the effects on operant behavior of the racemate may be explicable by adding the effects of the isomers.

A somewhat different picture emerges for predicting the potency of (±)-N-allylnormetazocine in generalizing to PCP based upon the potencies of the isomers. Since the (-) isomer was without PCP-like stimulus effects it might be expected that the potency of the racemate should be ½ that of the (+) isomer. In both the rat and the monkey, the (+) isomer and the racemic mixture were roughly equipotent. This raises the possibility that the (-) isomer may interact with (+) isomer to enhance its PCP-like stimulus properties. The general reliability of potency estimates from drug generalization gradients has not been well established. Nevertheless, the consistency of this finding in both rats and monkeys lends strength to the possibility that the (-) isomer may enhance the PCP-like stimulus properites of the (+) isomer, or conversely that the (+) isomer may allow the expression of PCP-like stimulus properties of the (-) isomer perhaps by antagonizing some non PCP-like activity.

Our data indicate that the discriminative stimulus and response rate disrupting effects of (+) and (-)-N-allylnormetazocine are not antagonized by naloxone in rats or squirrel monkeys. The doses of naloxone that we used were 30 to 100-fold higher than those necessary to antagonize the discriminative stimulus properties of morphine in rats

(Shannon and Holtzman, 1976) and squirrel monkeys (Schaefer and Holtzman, 1977; Teal and Holtzman, 1979). It has been reported (Martin et al., 1976) that naltrexone may antagonize (±)-N-allylnormetazocine-induced canine mania and that naloxone antagonizes the effects of (±)-N-allylnormetazocine on locomotor activity in mice (Iwamoto, 1979). Our data is more consistent with those studies reporting a failure of naloxone to block the effects of (±)-N-allylnormetazocine as an anticonvulsant in mice (Cowan et al., 1979), on schedule-controlled performance in rats (Harris, 1980) and its discriminative stimulus properties in cyclazocine-trained squirrel monkeys (Teal and Holtzman, 1980c). One possilbe explanation for this disagreement in the literature is that (±)-N-allylnormetazocine has some opiate and some nonopiate activity. Perhaps the effects of (±)-N-allylnormetazocine on schedule-controlled performance and its discriminative stimulus cueing properties are not mediated by opiate receptors and therefore are not antagonized by naloxone. A more complete study of naloxone interactions with N-allylnormetazocine would be necessary to explore this possibility.

In conclusion, both the racemic mixture of N-allylnormetazocine and the pure (+) isomer generalized to PCP in a dose-dependent fashion in squirrel monkeys and rats. None of the doses of the (-) isomer of N-allylnormetazocine generalized to PCP in either species. The potency of the racemic mixture for generalization to PCP relative to the potency of the (+) isomer is not consistent with additivity of the discriminative stimulus effects of the (+) and (-) isomer in the racemic mixture. All four compounds produced a dose-dependent decrease in overall response rates, and all four compounds produced similar observable effects in squirrel monkeys at high doses. The potency of racemic mixture for response rate suppression was consistent with addition of the effects

of the (-) and (+) isomers on overall response rate. In both species, neither the PCP-like discriminative stimulus effects of (+)-N-Allynormetazocine nor the response-rate disrupting effects of (-)-N-allylnormetazocine were antagonized by high doses of naloxone. This study suggests two very distinct pharmacological profiles for the stereoisomers of N-allylnormetazocine. Further work with pure optical isomers of this compound will be invaluable in further characterizing the sigma opiate receptor and the putative PCP receptor and in further exploring the similarities between the psychotomimetic opiates and the dissociative anesthetics.

VI. DISCRIMINATIVE STIMULUS PROPERTIES OF KETAMINE ENANTIOMERS IN PCP-TREATED RATS (EXPERIMENT V)

A. Introduction

Ketamine, 2-(o-chlorophenyl)-2-methyl aminocyclohexanone, is a dissociative anesthetic which is very similar to PCP in its spectra of pharmacological effects (McCarthy et al., 1965). It is a chiral compound which is used clinically as the racemic mixture of two optical isomers. While most studies of the pharmacological activity of ketamine have involved the use of the racemic mixture, several recent reports indicate differences in the activity of the enantiomers.

In rodents, the (+) isomer has been reported to be more potent than the (-) isomer in hypnotic activity (Marietta et al., 1977) and as an analgesic (Ryder et al., 1978). Meliska et al. (1979) reported that while high doses of both the (-) and the (+) isomer decreased rates of schedule-controlled responding in rats, low doses of the (-) isomer, but not the (+) isomer increased response rates. They concluded that there was a qualitative difference in the effects of the enantiomers on schedule-controlled behavior. In a recent clinical study, White et al. (1980) reported that (+)-ketamine produced more effective anesthesia with less incidence of emergence reactions than (-)-ketamine. Opiate binding studies (Smith et al., 1980) indicate that (+)-ketamine is 3 to 4 times more potent than (-)-ketamine in displacing ^{3}H-naloxone binding.

Studies of the discriminative stimulus properties of racemic ketamine and PCP have shown that these two drugs cross-generalize in rats (Overton, 1974; Jarbe et al., 1975; Shannon, 1979; Poling, et al., 1979; Holtzman, 1980), pigeons (Herling et al., 1980), squirrel

monkeys (Experiment II; Brady and Balster, 1981) and rhesus monkeys (Young et al., 1980). All of these studies have been done with a racemic mixture of ketamine. The present study was designed to investigate the discriminative stimulus properties of the stereoisomers of ketamine in rats trained to discriminate PCP from saline.

B. Methods

Subjects

The subjects were ten experimentally naive male Sprague-Dawley rats (Flow Laboratories, Dublin, VA). The animals were maintained at 80% of their free-feeding weights (280-340 grams) throughout the experiment by adjusted post-session feedings. They were individually housed in wire mesh cages where they had unlimited access to water.

Apparatus

The apparatus for this study is identical to the one described in detail in the methods section of Experiment IV. A standard two-lever operant rat chamber (Model E10-10, Coulbourn Instruments, Inc., Lehigh Valley, Pennsylvania) housed inside a light and sound attenuating cubicle (Model E10-20, Coulbourn Instruments, Inc.) was used.

Procedure

The procedure for training the rats to discriminate PCP from saline is described in detail in the methods section of Experiment IV. The subjects were trained to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Each animal received an injection of either physiological saline or 3.0 mg/kg PCP on a double alternation schedule, i.e., two days of PCP injections followed by two days of saline injections, etc. The animal was placed in the chamber immediately following the drug injection,

10 min pre-session. The house light was illuminated at the initiation of the session. For five animals, the left lever was reinforced on PCP days and the right lever was reinforced on saline days. The lever conditions were reversed for the other five subjects.

Initially, every third session began with a 2-min period during which responding on either lever was reinforced after which the animal was continued as usual on the FR32 schedule for the remaining 28 min. When an animal had performed 80 percent or more responses on the appropriate lever during four consecutive 2-min probes, test sessions were begun.

The effects of substituting various doses of PCP, (±)-ketamine, (+)-ketamine and (-)-ketamine for the 3.0 mg/kg dose of PCP were determined on test days. Test sessions were conducted every third day if the animal completed the first FR on the appropriate lever on the control day preceding the test day. Test sessions consisted of a 2-min period during which responding on either lever was reinforced after which the animals were returned to their home cages. The double alternation continued on control days with test sessions interspersed such that a PCP and a saline day preceded each successive test day.

For each drug, five animals received doses in ascending order and five animals received doses in descending order. The PCP dose-response determination was conducted first in all subjects. The other drugs were tested in random order. Tests were conducted with four doses of PCP (0.3-10.0 mg/kg), (±)-ketamine (1.0-30.0 mg/kg), (+)-ketamine (1.0-30.0 mg/kg) and (-)-ketamine (1.0-30.0 mg/kg). The doses were chosen to cover a range from no effect to nearly complete suppression of response rates during the 2-min test sessions. Each dose was tested twice in each animal; one determination was preceded by a PCP training day and

the second determination was preceded by a saline training day.

Data Analysis

The data was analyzed in an identical manner to that described in the methods section of Experiment II.

Drugs

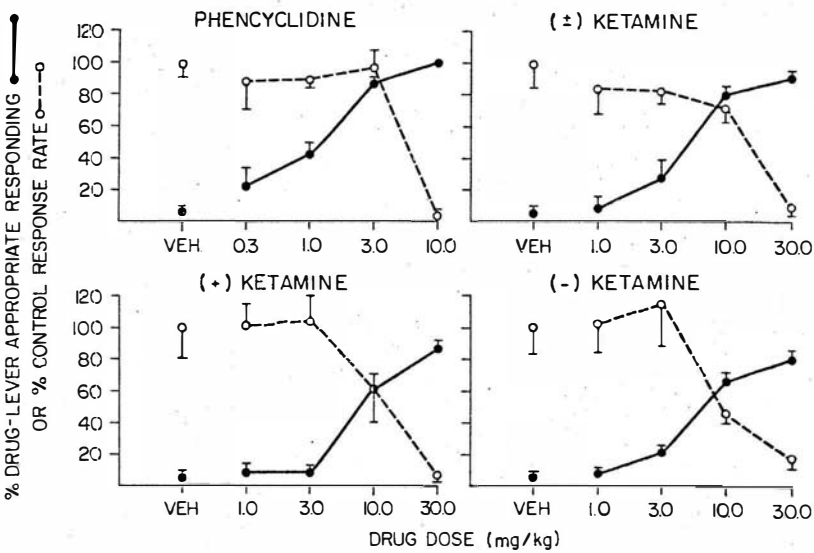
PCP was supplied by Bio-Ceutic Laboratories (Sernylan). Racemic ketamine HCl was supplied by Parke-Davis and Co. (Ketalar). The (-) and (+) isomers of ketamine were supplied by Bristol Laboratories. The drugs were diluted with or dissolved in sterile saline to a concentration that resulted in an injection volume of 1.0 ml/kg. All injections were given i.p. 10 min pre-session. Doses refer to the hydrochloride salts. Vehicle injections were 1.0 ml/kg of 0.9 percent saline.

C. Results

Overall response rates for each animal remained fairly stable throughout the experiment. Average values ± S.E.M. in responses per sec for the response rates on vehicle test days for each animal were: 1.91 ± 31, 1.03 ± .21, 1.45 ± .4, 1.1 ± .3, 1.01 ± .25, 1.56 ± .31, .98 ± .12, .86 ± .1, 1.33 ± .2, 1.28 ± .31. The training dose of PCP (3.0 mg/kg) produced approximately 85 percent drug-lever appropriate responding (Figure 20, upper left panel). This dose had no effect on response rate. All three forms of ketamine produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Figure 20). While each of the three compounds produced over 80 percent drug-lever appropriate responding at some dose, only the racemic mixture produced this level of drug-lever appropriate responding at doses which did not decrease response rates. For both stereoisomers, doses which produced greater than 50 percent drug-lever appropriate

FIGURE 20

Group dose-response curves for PCP, (±)-ketamine, (+)-ketamine and (-)-ketamine for suppression of operant responding and for percent drug-lever appropriate responding in rats. The mean percent drug-lever appropriate responding ± S.E.M. averaged across animals (solid lines) and the mean percent control response rate ± S.E.M. averaged across animals (dashed lines) are on the ordinate with the corresponding dose on the abscissa. Vehicle rates were calculated over the 2-min test session with vehicle pretreatment at the end of each drug dose-response determination.


% DRUG-LEVER APPROPRIATE RESPONDING
OR % CONTROL RESPONSE RATE
PHENCYCLIDINE
(±) KETAMINE
(+) KETAMINE
(-) KETAMINE
120
100
80
60
40
20
VEH
0.3
1.0
3.0
10.0
30.0
DRUG DOSE (mg/kg)

responding (10.0 mg/kg) also decreased response rates to approximately 50 percent of control. Test days for which the response rates were less than 0.05 response per sec were not included in the percent drug-lever appropriate responding tabulation.

Table 7 shows the ED_{50} values for suppression of operant responding and for percent drug-lever responding for each of the four compounds tested. The relative potency for producing drug-lever appropriate responding was: PCP > (±)-ketamine > (-)-ketamine > (+)-ketamine. The relative potency for response rate suppression was: PCP > (±)-ketamine = (+)-ketamine > (-)-ketamine. While the dose of PCP necessary to suppress operant responding to 50 percent of vehicle rates was 4 times larger than the ED_{50} dose for drug-lever appropriate responding, for the other three compounds there was approximately a 2-fold difference between the ED_{50} for response rate suppression and the ED_{50} for drug-lever appropriate responding. The slopes of the lines for drug-lever appropriate responding and for response rate suppression are similar for all four compounds (Table 7).

D. Discussion

The results of this experiment indicate that both stereoisomers of ketamine have discriminative stimulus properties similar to those of PCP. All three compounds produced PCP-appropriate responding in a dose-dependent fashion. The slopes of all of the dose-response curves were similar, also suggestive of qualitatively similar effects.

While the higher doses of all four compounds suppressed operant responding in a dose-dependent fashion, there was a greater difference between doses which produced drug-lever appropriate responding and doses which suppressed response rates for PCP than for any of the forms of

TABLE 7

POTENCY OF PCP AND KETAMINE ISOMERS FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATES IN RATS

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression/ Drug-Lever Responding
PCP	1.1 (.12-1.5)	1.0	58	4.1 (3.3-5.4)	1.0	-99	3.9
(±)KET	5.1 (4.0-7.1)	4.9	61	11.2 (8.6-15.5)	2.7	-86	2.2
(+)KET	7.1 (4.3-9.0)	6.8	71	11.3 (7.3-21.1)	2.8	-102	1.6
(-)KET	6.6 (4.8-8.3)	6.3	54	12.5 (7.9-25.1)	3.1	-95	2.0

*Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (µg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50% decrease in response rates as determined by linear regression and 95% confidence limits in parenthesis.

ketamine. In contrast, in Experiment II using squirrel monkeys trained to discriminate PCP from saline, for both PCP and (±)-ketamine the ED_{50} dose for response rate suppression was approximately 3 times larger than the ED_{50} dose for drug-lever appropriate responding. Perhaps species differences play a role in this discrepancy.

There is some inconsistency in the literature concerning the relative potencies of racemic ketamine and the (+) and (-) isomers. In both rats (Marietta et al., 1977) and mice (Ryder et al., 1978), (+)-ketamine is 3 times more potent than (-)-ketamine in producing analgesia and the racemic mixture falls approximately half-way between these two in potency. This is consistent with the finding by Smith et al. (1980) that (+)-ketamine is 3 to 4 times more potent than (-)ketamine in displacing ^{3}H-naloxone binding at the opiate receptor and the report of White et al. (1980) indicating that (+)-ketamine is approximately 3 times more potent than (-)-ketamine as an anesthetic in humans. In contrast, studies indicate that the stereoisomers and racemic mixture of ketamine are approximately equipotent in increasing non-specific locomotor activity in rodents (Marietta et al., 1977; Ryder et al., 1978; Meliska et al., 1978) and in causing loss of righting reflex and lethality in rats (Marietta et al., 1977). Our data indicate no large potency difference between racemic ketamine and the (+) and (-) isomers for production of PCP-appropriate responding or for suppression of operant responding. These data do not support the study of Meliska et al. (1980) reporting a qualitative difference in the effects of ketamine enantiomers on schedule-controlled performance in rats. They report that at doses up to 60 mg/kg i.p., (-)-ketamine produced only increases in response rates while at doses of 30 mg/kg and above, (+)-ketamine decreased response

rates in a dose-dependent fashion in rats trained on a FI schedule of food presentation.

Several investigations have indicated that low doses of racemic ketamine produce response rate increases in pigeons (Wenger, 1976), mice (Wenger and Dews, 1976) and rats (Meliska and Trevor, 1978) trained under FI schedule of food presentation. As mentioned earlier, Meliska et al. (1979) recently reported increases in response rates to as high as 3 times control rates after the administration of (-)-ketamine to rats trained under a FI schedule. In the same study, only response rate decreases were seen after (+)-ketamine administration. In the present study, low doses of all three compounds produced small response rate increases in individual animals, but when the data was averaged across animals no response rate increasing doses were found for any of the compounds. This possible discrepancy between this study and those reported in the literature could be due to a difference in baseline rates of perfromance between these studies. The effects of (±)-ketamine on operant performances have been shown to be dependent on the baseline rate of the performance (Wenger, 1976; Wenger and Dews, 1976) such that low rate performance is increased and high rate performance is decreased. Response rates after vehicle administration averaged 1.32 ± .16 responses per sec in this study. These relatively high rates may not be sensitive to rate-increasing effects.

The literature indicates that (±)-ketamine is approximately 1/5 to 1/10 as potent as PCP in a variety of pharmacological assays. In Experiment II (Brady and Balster, 1981) we found roughly a 9-fold difference in potency between PCP and ketamine as a discriminative stimulus and in response rate disruption in the squirrel monkey. This study in rats is in agreement with previous study in finding (±)-ketamine to

be consistently less potent than PCP as a discriminative stimulus and in disrupting operant performance, but we found a somewhat smaller (3 to 7-fold) potency difference between these compounds.

In conclusion, racemic ketamine, (+)-ketamine and (-)-ketamine produce dose-dependent drug-lever appropriate responding in rats trained to discriminate PCP from saline. The slopes of the dose-effect curves for all four drugs were similar. There was no significant potency difference between (±)-ketamine and either of the stereoisomers for producing drug-lever appropriate responding or for response rate suppression. Thus, there is no evidence for a qualitative difference in the PCP-like effects of stereoisomers of ketamine. This isomeric pair would be a poor candidate for studies of the stereospecificity of the effects of arylcycloalklamines.

VII. STEREOSELECTIVITY OF THE STIMULUS EFFECTS OF CYCLAZOCINE IN PCP-TRAINED SQUIRREL MONKEYS (EXPERIMENT VI)

A. Introduction

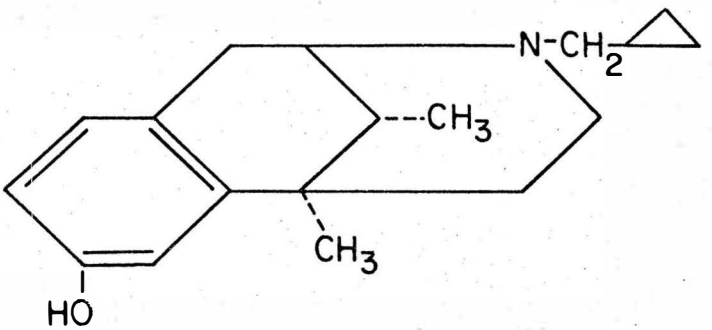
Several recent reports have indicated an overlap between the discriminative stimulus properties of phencyclidine (PCP) and those of cyclazocine, (±)-(2-cyclopropylmethyl-2'-hydroxy-5,9-dimethyl-6,7-benzomorphan, Figure 21). Teal and Holtzman (1980a) found that in rats trained to discriminate between saline and high or low doses of cyclazocine PCP produced dose-dependent drug-appropriate responding in both groups of animals. Herling et al. (1980) reported that PCP produced drug-appropriate responding in three groups of pigeons trained to discriminate dextrorphan, ketamine or cyclazocine from saline. In rats trained to discriminate PCP from saline, cyclazocine has been found to generalize to PCP (Holtzman, 1980).

Similar to other opioids, cyclazocine has a high degree of stereoselectivity in its pharmacological activity. The (-) isomer of cyclazocine and many other benzomorphans have been found to be more potent than the (+) isomers in tests for analgesic activity (Pearl and Harris, 1966; Harris et al., 1969), in effects on schedule-controlled behavior (McMillan and Harris, 1972) and in anticonvulsant activity (Cowan et al., 1979). The potency ratios for the pairs of isomers in these systems vary from reports that the isomers are nearly equipotent to reports that the (-) isomer is 400 times more potent than the (+) isomer.

In Experiment IV we found that the (+) isomer of N-allylnormetazocine, another opiate of the benzomorphan series, was responsible for the PCP-like discriminative stimulus properties of N-allylnormetazocine in both rats and squirrel monkeys. On the other hand, in both species the (-)

FIGURE 21

Chemical structure of cyclazocine.



CYCLAZOCINE

2-Cyclopropylmethyl-2'-hydroxy-
5,9-dimethyl-6,7-benzomorphan

isomer was more potent than the (+) isomer in overall response rate suppression.

Clinical studies have indicated that the (+) isomer of various opioids produce subjective effects which are qualitatively different form their complimentary (-) isomers. High doses of dextromethorphan and (+)-pentazocine produced nervousness, anxiety and psychotomimetic effects in man, whereas (-)-pentazocine and levomethorphan produced a morphine-like sedation (Jasinski, et al., 1971; Bellville and Forrest, 1968). Racemic cyclazocine has also been shown to produce anxiety, dysphoria and psychotomimetic symptomatology in man (Martin, 1967; Haertzen, 1970).

In addition, studies have suggested similarities in the discriminative stimulus effects of ketamine or PCP and dextrorphan in the pigeon (Herling et al., 1980), rhesus monkey (Young et al., 1980) and rat (Holtzman, 1980) whereas the l-isomer of dextrorphan, levorphanol, resulted in saline-appropriate responding in pigeons trained to discriminate dextrorphan from saline (Young et al., 1980). Rats trained to discriminate morphine from saline generalize completely to levorphanol but not even partially to dextrorphan (Winter, 1975; Shannon and Holtzman, 1976).

Experiment VI was designed to further investigate the overlap in the discriminative stimulus properties of cyclazocine and PCP. In the light of the stereospecificity of many of the pharmacological activities of cyclazocine, we tested both the (+) and (-) isomers and racemic cyclazocine for generalization to PCP in squirrel monkeys trained to discriminate PCP from saline.

B. Methods

Subjects

The subjects were the six adult male squirrel monkeys (Saimiri sciureus, Santa Cruz, Bolivia, Primate Imports, Port Washington, New York) which had previously been used in a study of the discriminative stimulus properties of N-allylnormetazocine (Experiment IV). The animals were maintained at constant weights (0.8 to 1.0 kg) throughout the experiment by adjusted post-session feedings. They were individually housed in standard primate caging where they had unlimited access to water.

Procedure

The procedure for training the squirrel monkeys to discriminate PCP from saline has been described in more detail in the methods section of Experiment II. The subjects were trained to respond on a fixed-ratio 32 (FR32) schedule of food presentation. Thirty-min sessions were conducted seven days a week. Each animal received an injection of either physiological saline or 0.16 mg/kg PCP on a double alternation schedule, i.e. two days of PCP injections followed by two days of saline injections, etc. The animal was injected while in the primate chair, 5 min pre-session. The chair was immediately placed in the cubicle. The only source of light was the four stimulus lights above the levers which were illuminated at the initiation of the session. For three animals, the left lever was reinforced on PCP days and the right lever was reinforced on saline days. The lever condition were reversed for the other three subjects. Responses on the incorrect lever reset the FR contingency for reinforced responding the correct lever.

Initially, every third session began with a 2-min period during which responding was not reinforced, after which the animal was continued

as usual on the FR 32 schedule for the remaining 28 min. When an animal had performed 85 percent or more responses on the appropriate lever during four consecutive extinction probes, test sessions were begun.

The effects of substituting various doses of PCP, (±)-cyclazocine (+)-cyclazocine, and (-)-cyclazocine for the 0.16 mg/kg dose of PCP were determined on test days. Test sessions were conducted every third day if the animal completed the first FR on the appropriate lever on the control day preceding the test day. Test sessions consisted of a 2-min extinction period after which the animals were returned to their home cages. The double alternation continued on control days with the test sessions interspersed such that a PCP and a saline training day preceded each successive test day.

For each drug, three animals received the doses in ascending order, and three animals received the doses in descending order. The PCP dose-response determination was conducted first in all subjects. The other drugs were administered in random order. Tests were conducted with five doses of PCP (0.04-0.64 mg/kg) and four doses (±)-cyclazocine (0.003-0.1 mg/kg), (-)-cyclazocine (0.001-0.03 mg/kg) and (+)-cyclazocine (0.1-3.0 mg/kg). The doses were chosen to cover a range from no effect to nearly complete suppression of response rates during the 2-min test sessions. All doses of each of the cyclazocine compounds were tested twice in each animal; one determination was preceded by a PCP training day and the second determination was preceded by a saline training day. All doses of a given drug were administered to a subject before testing the next drug. A vehicle test was conducted at the end of each dose-response determination.

Data-Analysis

The analysis of the data was performed in an identical manner to that described in the methods section of Experiment II.

Drugs

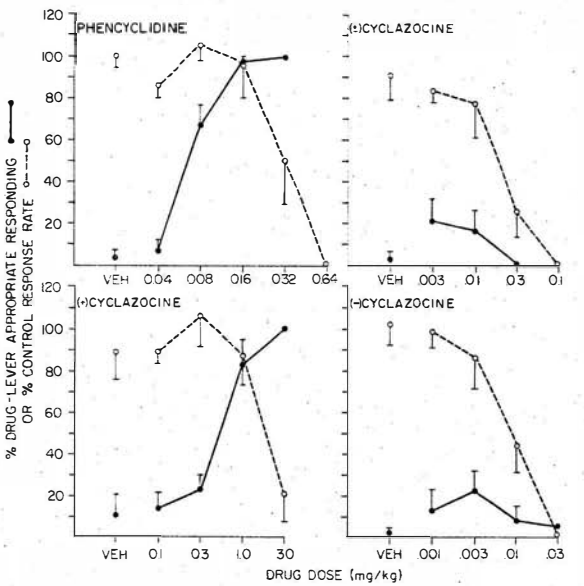
PCP was supplied by Bio Ceutic Laboratories (Sernylan). All three forms of cyclazocine were supplied by Sterling-Winthrop Research Institute. PCP was diluted with sterile saline to a concentration that resulted in an injection volume of 0.2 ml/kg. The cyclazocine compounds were dissolved in hydrochloric acid (1.35 mg HCl per 10 mg cyclazocine) and diluted with sterile saline to a concentration that resulted in an injection volume of 0.2 ml/kg. For PCP, vehicle injections were 0.2 ml/kg of 0.9 percent saline. For cyclazocine compounds, the vehicle injections were 0.2 ml/kg of the most concentrated hydrochloric acid-saline solution necessary to keep the highest dose of the drug tested in solution.

C. Results

The training dose of PCP (0.16 mg/kg) produced approximately 95 percent drug-lever appropriate responding (Figure 22, upper left panel). A higher test dose of PCP (0.32 mg/kg) produced an even higher percentage of drug-lever appropriate choices whereas 0.64 mg/kg completely eliminated responding on either lever. Of the cyclazocine compounds, only (+)-cyclazocine produced a dose-related increase in the percent of responses made on the PCP-appropriate lever (Figure 22, lower left panel). The 3.0 mg/kg dose produced 100 percent drug-lever appropriate responding in those subjects who responded. There was no significant difference ($p \geq 0.05$) between test days following saline training days and test days following PCP training days for the same dose of (+)-cyclazocine. For both PCP and (+)-cyclazocine, the slopes of the lines for percent drug-lever appropriate responding were relatively similar

FIGURE 22

Group dose-response curves for PCP, (±)-cyclazocine, (+)-cyclazocine and (-)-cyclazocine for suppression of operant responding and for percent drug-lever appropriate responding in the squirrel monkey. The mean percent drug-lever appropriate responding ± S.E.M. averaged across animals (solid lines) and the mean percent control response rate ± S.E.M averaged across animals (dashed lines) are on the ordinate with the corresponding drug dose on the abscissa. Vehicle rates were calculated over the 2-min test session with vehicle pretreatment at the end of each drug dose-response determination.


PHENCYCLIDINE
(+)CYCLAZOCINE
(+)CYCLAZOCINE
(-)CYCLAZOCINE
% DRUG-LEVER APPROPRIATE RESPONDING
OR % CONTROL RESPONSE RATE
120
100
80
60
40
20
VEH 0.04 0.08 0.16 0.32 0.64
VEH .003 .01 .03 0.1
VEH 0.1 0.3 1.0 3.0
VEH .001 .003 .01 .03
DRUG DOSE (mg/kg)

(Table 8). Neither racemic cyclazocine nor the (-) isomer produced over 25 percent PCP-appropriate responding at any of the doses tested (Figure 22, right panels).

Overall response rates for each animal remained fairly stable throughout the experiment. Response rates for the two saline test days before the PCP dose-response determination and the saline test day after the PCP dose-response determination were averaged and used as the PCP vehicle rate and as the control rate for all of the drugs and for the cyclazocine vehicle injection. These average values ± S.E.M. for each subject were 1.2 ± .20, .89 ± .05, 2.3 ± .22, 1.9 ± .31, 1.5 ± .16, 1.03 ± .11 responses per sec. Response rates after cyclazocine vehicle injections did not differ much from control response rates. All four compounds produced a dose-dependent decrease in response rates. At the higher drug doses, some animals did not respond at all. Test days for which an animal's response rates were less than 0.05 response per sec for the 2-min extinction period were not included in the percent drug-lever appropriate responding tabulation. The slopes of the lines for response rate suppression are similar for all four compounds (Table 8).

A dose of 0.16 mg/kg PCP and 1.0 mg/kg (+)-cyclazocine resulted in greater than 80 percent PCP-lever appropriate responses with only minimal effects on response rates. For (±)-cyclazocine and (-)-cyclazocine, doses of .003 mg/kg or larger decreased response rates during the test sessions with no evidence of generalization to the PCP cue.

Table 8 shows the ED_{50} values for percent drug-lever responding and for suppression of operant responding for all four compounds. PCP was approximately 8 times more potent than the (+) isomer of cyclazocine in producing drug-lever appropriate responding. The relative potency for

TABLE B

POTENCY OF PCP AND CYCLAZOCINE FOR STIMULUS GENERALIZATION AND SUPPRESSION OF OVERALL RESPONSE RATE

Drug	ED50* Drug-Lever Responding	Ratio to PCP	Slope**	ED50*** Response Rate Suppression	Ratio to PCP	Slope**	ED50s for Response Rate Suppression Drug-Lever Responding
PCP	.07 (.06-.08)	1.0	146	.31 (.03-.34)	1.0	-86	4.4
(±)-Cyclazocine	-	-	-	.012 (.001-.02)	0.04	-58	-
(+)-Cyclazocine	.57 (.34-.89)	8.1	84	1.9 (1.5-3.9)	6.1	-88	3.3
(-)-Cyclazocine	-	-	-	.008 (.004-.01)	0.03	-68	-

*Dose (mg/kg of base) resulting in 50% drug-lever appropriate responding as determined by linear regression and 95% confidence limits in parenthesis.

**In log dose (µg/kg) - percent effect units.

***Dose (mg/kg of base) resulting in a 50% decrease in response rates as determined by linear regression and 95% confidence limits in parenthesis.

suppression of operant responding was: (-) isomer > racemic mixture > PCP > (+) isomer. Since racemic cyclazocine was 3/4 as potent as the (-) isomer for response rate suppression, this is roughly consistent with an additive effect of the isomers on response rate suppression. For both PCP and (+)-cyclazocine, the dose necessary to suppress operant responding to 50 percent of vehicle rates was 3-4 times larger than the ED_{50} dose for drug-lever appropriate responding.

D. Discussion

Our results indicate that there is stereospecificity in the PCP-like stimulus properties of cyclazocine. In this study, the (+) isomer of cyclazocine produced PCP-appropriate responding in squirrel monkeys trained to discriminate PCP from saline, while the (-) isomer and the racemic mixture did not. However, the (-) isomer and the racemic mixture of cyclazocine were not behaviorally inactive. They were extremely potent in response rate disruption and in producing observable effects on behavior. In this sense, our study supports the literature in determining that the stereoisomers of cyclazocine have different spectra of pharmacological activity.

There is some discrepancy in the literature concerning the relative potency of the stereoisomers of cyclazocine for disruption of operant responding. McMillan and Harris (1977) found (-)-cyclazocine to be approximately 3 times more potent than (+)-cyclazocine in decreasing the rate of responding in pigeons trained under a multiple FR schedule of food presentation. Recently, Teal and Holtzman (1980b) reported that the (-) isomer of cyclazocine was 100 times more potent than the (+) isomer in disrupting operant responding in squirrel monkeys. In our study, (-)-cyclazocine was 200 times more potent than (+)-cyclazocine

in response rate suppression. While there have been no studies comparing the effects of stereoisomers of cyclazocine on operant performance in rodents, Pearl et al. (1968) reported that while (+)-cyclazocine was 150 times less active than the (-) isomer in the rat tail flick test, it was only 16 times less potent in disrupting rotarod performance in mice and 6.8 times less potent in decreasing motor activity in mice. This is consistent with the fact that rodent bioassays have been found to underestimate the potency of several benzomorphan opiates in primates (Taber et al., 1964; Pearl and Harris, 1966). It seems likely that the behavioral effects of cyclazocine isomers are not only stereoselective but also species-specific. This interesting area warrants further investigation.

An interesting discrepancy between this study and some earlier work lies in the failure of (±)-cyclazocine to generalize to PCP in our study. It has been reported that rats (Teal and Holtzman, 1980a) and pigeons (Herling, 1980) trained to discriminate (±)-cyclazocine from saline generalize to PCP. Futhermore, Holtzman (1980) found that rats trained to discriminate PCP from saline generalized to (±)-cyclazocine. It is possible that the species difference in the effects of cyclazocine isomers on operant responding could explain the disagreement between our study and the previous work. Because the (-) isomer of cyclazocine is much more potent relative to the (+) isomer in suppressing operant responding in squirrel monkeys, any dose of (±)-cyclazocine which contained enough of the (+) isomer to produce PCP-appropriate responding would also have enough of the (-) isomer to completely suppress responding. If the relative potency of the stereoisomers for disrupting operant behavior in rats is closer to that found by McMillan and Harris (1971) for pigeons, than it would be possible to find a dose of (±)-cyclazocine

which could produce a PCP-like discriminative cue without complete disruption of responding.

In a recent study, Teal and Holtzman (1980b) conducted generalization testing with (+) and (-)-cyclazocine in squirrel monkeys trained to discriminate between saline and either (-)-morphine or racemic cyclazocine. While both isomers substituted for the training dose of cyclazocine in the cyclazocine-trained group, the generalization of the (-) isomer and racemic mixture could be blocked by naltrexone whereas the generalization produced by the (+) isomer could not. In addition, the (+) isomers of levorphanol, methadone, and levomethorphan all produced cyclazocine-lever appropriate responding while the (-) isomers all generalized to morphine. They suggested that the effects of the (+) isomer of cyclazocine and other opiates are not mediated by opiate receptors. They also found that (-)-cyclazocine was 100 times more potent than (+)-cyclazocine in producing (±)-cyclazocine-appropriate responding. Because of this, they concluded that in the squirrel monkey, the (-) isomer is, for the most part, responsible for the discriminative stimulus properties of racemic cyclazocine. This is consistent with the failure of racemic cyclazocine and (-)-cyclazocine to generalize to PCP in the present study.

In Martin's (Martin et al., 1976) theory of three opiate receptor types based on the effects of various opiates in the chronic spinal dog, (±)-cyclazocine is reported to be an agonist of the sigma receptor as well as other opioid receptors. The effects of PCP in the chronic spinal dog are also very similar to those of the prototypic sigma agonist, (±)-N-allylnormetazocine (Vaupel and Jasinski, 1979). In Experiment IV, we showed that N-allynormetazocine has a very similar separation of activity in the behavioral pharmacology of its optical isomers as does

cyclazocine. In both rats and squirrel monkeys trained to discriminate PCP from saline, the (+) isomer generalized to PCP while the (-) isomer did not. The present study reemphasizes the need to further investigate the stereospecificity of the sigma receptor.

In conclusion, (+)-cyclazocine generalized to PCP in a dose-dependent fashion in squirrel monkeys trained to discriminate PCP from saline. Neither (±)-cyclazocine nor (-)-cyclazocine generalized to PCP at any of the doses tested. All four compounds produced a dose-dependent decrease in response rates. The (-) isomer was 300 times more potent than the (+) isomer for response rate suppression and the potency of the racemic mixture is consistent with addition of the (+) and (-) isomers. This study suggests two very distinct pharmacological profiles for the stereoisomers of cyclazocine.

VIII. FINAL DISCUSSION

Phencyclidine appears to belong to a unique class of drugs which have a variety of chemical structures. The studies presented in this dissertation indicate many similarities between the effects of PCP and several structurally similar and dissimilar compounds on a variety of behavioral measures.

In general, our findings are in agreement with the literature concerning the acute effects of PCP and PCP-like compounds on schedule-controlled behavior. In pigeons (Wenger, 1976), mice (Wenger and Dews, 1976), rats (Murray, 1978), rhesus monkeys (Balster and Chait, 1976) and squirrel monkeys (Chait and Balster, 1977, 1978, 1979) it has been reported that low doses of PCP cause response rate increases. When assessed, these response rate increases have been shown to be consistent with the rate-dependency hypothesis (Dews, 1958) in the sense that low baseline rates of responding are increased more than high baseline rates of responding after PCP administration.

In Experiment I we found that PCP and three structural analogues (PCE, TCP and ketamine) had qualitatively similar effects in rhesus monkeys trained to lever press on a fixed-interval (FI) schedule of food presentation. Low doses of all four compounds increased the low rate responding at the beginning of the FI and decreased the high rate responding at the end of the FI. High doses of all four compounds decreased responding in all parts of the FI.

Chait and Balster (1977, 1978, 1979) have reported that in squirrel monkeys, low doses of PCP produced small increases in response rates of schedule-controlled performances while higher doses produced dose-dependent decreases in response rates. In our squirrel monkey studies (Experiments II, III, IV and VI), we found a similar effect of PCP and

all of the PCP-like compounds. Every drug which generalized to PCP in the discriminative stimulus experiments produced small but consistent response rate increases at some low doses in almost every subject. In many cases, these response rate increases were not evident in the dose-response curves because they occurred at different doses for different animals, so when the data for different animals was averaged they were not visible. These response rate increases were not statistically significant.

In contrast, our rat studies (Experiments IV and V) show little indication of a trend towards response rate increases at low doses of PCP or any of the drugs tested. Although low doses of PCP and several other drugs occasionally produced response rate increases, these were not nearly as consistent as in the squirrel monkey studies. This is in contrast with much of the literature reporting response rate increases in schedule-controlled performance in rats after low doses of PCP and PCP analogues (Murray, 1978; Meliska and Trevor, 1978; Glick et al., 1979). This discrepancy could be due to different control rates of responding produced by schedules used in the experiments. The FR schedule used in our experiments generated fairly high response rates (> 1 responses per sec) None of the studies reporting response rate increases in rats used a FR schedule.

In Experiments II through VI, we demonstrated that a variety of compounds, some structurally similar to PCP and some structurally dissimilar to PCP, could produce drug-lever appropriate responding in squirrel monkeys and/or rats trained to discriminate PCP from saline. Generalizations in the drug discrimination paradigm have consistently been shown to occur between drugs with a similar spectra of pharmacological

properties, but generally not between drugs of different drug classes and pharmacological properties (Barry, 1974; Schuster and Balster, 1977).

In Experiment II, we demonstrated the specificity of the PCP cue by testing PCP-trained squirrel monkeys for generalization to morphine, ketocyclazocine and mescaline. None of these drugs produced PCP-appropriate responding. Other investigators (Jarbe et al., 1975; Poling et al. 1979; Shannon, 1979) have reported no generalization with a variety of other psychoactive compounds including Δ9-THC, LSD, morphine and mescaline in rats trained to discriminate PCP from saline. It seems clear, therefore, that the drug discrimination paradigm is a fairly specific assay for PCP-like behavioral activity. This makes it especially interesting when compounds which are structurally dissimilar to PCP, such as dexoxadrol, etoxadrol, (±) and (+)-N-allylnormetazocine, and (+)-cyclazocine generalize to PCP.

One interesting point which should be addressed concerns the lack of generalization of ketocyclazocine to PCP. We chose to test this drug because it is considered to be the prototypic agonist of the kappa receptor in Martin's (Martin et al., 1976) opiate receptor theory. Ketocyclazocine, like cyclazocine, is a benzomorphan opioid. In Experiment VI we found that (+)-cyclazocine but not (-)-cyclazocine or (±)-cyclazocine generalized to PCP in squirrel monkeys trained to discriminate PCP from saline. It is possible that (+)-ketocyclazocine would also generalize to PCP, but only the racemic mixture was tested in this study.

In all drug discrimination studies, animals are trained to perform different tasks under different drug conditions. In our experiments, a

left lever press was reinforced under the PCP or saline state and a right lever press was reinforced under the opposite state. Many drug discrimination experiments use the choice between two arms of a T-maze as the task to be performed differentially under different drug conditions. Regardless of the task involved, it is possible to obtain some measure of non-specific behavioral disruption from the same task by measuring response rate suppression, runway latency, or some other indication of non-specific impairment. Measures of response-rate disruption and drug generalization are independent of each other. For example, in our studies we saw response rate decreases at doses of (±)-cyclazocine, (-)-N-allynormetazocine and (-)-cyclazocine which did not produce drug-appropriate responding above saline levels.

In most of the drug discrimination literature, response rates are not reported. While drug discrimination is an invaluable tool in measuring some very specific properties of psychoactive compounds, it makes sense to gain whatever additional information is possible from this same task. For drugs which generalize to each other, it is interesting to compare potency for generalization to potency for behavioral disruption. In our experiments, we measured response rate suppression as well as drug-lever appropriate responding during the test periods. We then constructed dose-effect curves for both performances. By a linear regression on these dose-response curves, an ED_{50} dose (effective dose 50) for both measures was determined. This information enabled us to compare our test compounds to PCP with regard to the slopes of the dose-effect curves for generalization and drug-lever appropriate responding as well as the potency for response rate suppressionand the potency for drug-lever appropriate responding. We found that the slopes of the

dose-response curves for generalization and response rate suppression were similar for all of the drugs which generalized to PCP. In addition, in nearly every case these drugs were 3 to 8 times more potent in producing drug-lever appropriate responding than in response rate suppression. For most compounds, doses could be found which produced over 70 percent drug-lever appropriate responding without decreasing response rates below saline control levels.

For several drugs, however, the potency ratio for response rate suppression and generalization was consistently smaller than for the majority of the compounds which generalized PCP. One of these exceptions was (±)-N-allylnormetazocine. For this compound, the potency ratio for response rate suppression to drug generalization was 1.7 in the squirrel monkey and 2.8 in the rat. This is probably because only the (+) isomer produces PCP-lever appropriate responding while the (-) isomer is fairly potent in the response rate suppression. For (-) and (+)-ketamine in rats, there is also a relatively small difference between the ED_{50} for response rate suppression and the ED_{50} for drug-lever appropriate responding. The reason for this is not clear.

Considering the apparent sensitivity of the drug discrimination task for PCP-like compounds, it is of interest that most of the compounds which generalized to PCP produced small but consistent response rate increases at doses which did not produce drug-lever appropriate responding above saline levels. It would be interesting to determine if these response rate increases represent behavioral activity of PCP-like compounds at doses which are not discriminable from saline. It is possible that these doses are, in fact, discriminable from saline in animals trained to discriminate lower doses of PCP from saline. We plan

to investigate this possibility by progressively lowering the training dose of PCP in squirrel monkeys trained to discriminate 0.16 mg/kg PCP from saline then constructing PCP dose-response curves at these lower training doses.

It has been suggested that there may be some correlation between the ease with which a drug can serve as a discriminative stimulus ("discriminability") and the abuse liability of a drug (Overton, 1971). Overton and Batta (1977) investigated the relationship between the abuse liability and degree of discriminability of a variety of drugs. They used the number of training sessions required to establish discriminative responding in rats trained in a T-maze drug discrimination task as an index of discriminability. They did not find a usefully high correlation between abuse laibility and discriminability as measured by this procedure. Perhaps using an operant task and the ratio of potency for discrimination to response rate suppression as an index of discriminability, a different pattern would result. In any case, there is merit in measuring and reporting some measure of behavioral disruption in drug discrimination tasks for use in comparing drugs within a class and in comparing different classes of drugs.

Experiments III, IV, V and VI were designed to investigate the newly emerging overlap in the pharmacologies of PCP and the psychotomimetic opioids, particularly the sigma receptor agonists. In Experiment III, we demonstrated that dexoxadrol and etoxadrol, two compounds which are structurally dissimilar to PCP, generalized to PCP in the squirrel monkey trained to discriminate PCP from saline. Prior to our report of this finding (Brady and Balster, 1980b), the only compound other than the structural analogues of PCP which had been reported to

generalize to PCP was the psychotomimetic opioid, N-allylnormetazocine (Shannon, 1979). Dexoxadrol and etoxadrol are of particular interest because the former was investigated for use as an analgesic, but has psychotomimetic side-effects in man at doses which produced analgesia (Simopoulos et al., 1970; Lasagna and Pearson, 1965), while etoxadrol was investigated for use as an anesthetic (Fredrickson et al., 1976). These two compounds are very similar to each other in structure (Figure 11) but dissimilar from the arylcycloalkylamines (PCP, Figure 8) and the benzomorphan opioids (N-allylnormetazocine, Figure 13). Further investigation of the chemical and pharmacological commonalities among these three groups of compounds will be a useful approach to further research concerning the PCP-opioid overlap.

In Experiment IV, we found that in both squirrel monkeys and rats the PCP-like discriminative stimulus properties of N-allylnormetazocine were in the (+) isomer, while the (-) isomer was much more potent in overall response rate suppression. The racemic mixture is, therefore, actually a mixture of two active compounds with different behavioral pharmacologies. This is especially significant in view of the fact that N-allylnormetazocine is considered the prototypic sigma agonist in Martin's (Martin et al., 1976) theoretical proposal of three opiate receptors based on the pharmacological profile of various opiates in the chronic spinal dog. Considering the marked stereoselectivity of the actions of all opiates coupled with the peculiar seperation of pharmacological activity between the stereoisomers of opioids in the benzomorphan series (Villarreal, 1970), it seems particularly important to use pure stereoisomers in further investigation of the opioid sigma receptor.

Our study investigating the discriminative stimulus properties of

cyclazocine in PCP-trained squirrel monkeys (Experiment VI) demonstrates that for another benzomorphan opioid which has been found to generalize to PCP (Teal and Holtzman, 1980a; Herling et al, 1980; Holtzman, 1980) the PCP-like discriminative stimulus properties reside in the (+) isomer. In our study, the (-) isomer was approximately 200 times more potent then the (+) isomer in response rate suppression. This potency ratio is consistent with the large potency difference reported by Teal and Holtzman (1980) for the effect of cyclazocine stereoisomers on operant behavior in the squirrel monkey, but markedly different from the only 3 to 4-fold potency difference reported by McMillan and Harris (1971) for the effects of cyclazocine stereoisomers on operant behavior in the pigeon. The potency difference between the stereoisomers of cyclazocine for response rate suppression in the squirrel monkey probably explains the fact that racemic cyclazocine did not generalize to PCP in our study. It would be impossible to get a high enough dose of the (+) isomer in the racemic mixture to produce PCP-appropriate responding without a dose of the (-) isomer which would completely suppress responding.

The studies with enantiomers of N-allynormetazocine and cyclazocine (Experiments IV and VI) clearly support the idea that the (+) and (-) isomers in the benzomorphan series are often two different drugs with very different spectra of pharmacological activity. It also appears that the (+) isomers of cyclazocine and N-allynormetazocine are responsible for the PCP-like properties of these compounds. It would be interesting to investigate the stereoisomers of these compounds individually in the chronic spinal dog to see if the (+) isomer is in fact responsible for the sigma profile of activity in the chronic spinal dog. It would also be of interest to use pure stereoisomers of these compounds in which

investigations of specific binding sites for PCP and in exploring sigma opiate receptor binding. In this regard, I am currently training rats to discriminate (+)-N-allylnormetazocine from saline because we believe that this compound may prove to be a better prototype sigma receptor agonist than the racemic mixture. We have been successful in training the discrimination and plan to test various arylcycloalkylamines and benzomorphans for generalization. The (+)-N-allylnormetazocine cue may prove to be an excellent behavioral model for sigma agonist activity.

In Experiment IV, we demonstrated that high doses of naloxone did not antagonize the discrminative stimulus properties of the (+) isomer or the response rate suppression produced by the (-) isomer of N-allylnormetazocine in rats or squirrel monkeys. Although some investigators report antagonism of some of the effects of N-allylnormetazocine by high doses of opiate antagonists (Martin et al., 1976; Iwamato, 1979), investigations of the effects of N-allylnormetazocine on operant performance (Harris, 1980), as an anticonvulsant (Cowan et al., 1979), or as a discriminative stimulus (Teal and Holtzman, 1980c) indicate that these effects are not antagonized by naloxone. It is also of interest in this context that Teal and Holtzman (1980b) found that the drug-lever appropriate responding produced by (-) and (±)-cyclazocine in squirrel monkeys trained to discriminate (±)-cyclazocine from saline was blocked by high doses of naloxone while the drug-lever appropriate responding produced by the (+) isomer was not. In addition, Teal and Holtzman (1979) reported that in rats trained to discriminate cyclazocine was blocked by naloxone while the generalization of PCP and ketamine to cyclazocine was not. It is likely that the discriminative stimulus cue of cyclazocine reflects the different

pharmacological properties of both the (+) and (-) isomers. It also seems clear that some of the biological activities of racemic mixtures of cyclazocine and N-allylnormetazocine are not antagonized by naloxone and therefore probably not mediated by opiate receptors. It is possible that the (+) isomers are responsible for the non-opioid activity of these compounds. If this is the case, then the pharmacological overlap between the arylcycloalkylamines and the sigma agonists may lie in the non-opioid spectra of activity of these sigma agonists. This also suggests that the psychotomimetic side effects produced by some clinically used benzomorphans (e.g. pentazocine) may be eliminated by removing the (+) isomer without affecting the efficacy of the drug.

Experiment V was designed to determine if the stereoselectivity of the PCP-like discriminative stimulus properties of the opioids was also found in an arylcycloalkylamine with a chiral center. The results indicate that both stereoisomers of ketamine are approximately equipotent in producing drug-lever appropriate responding and in response rate suppression in rats trained to discriminate PCP from saline. This is consistent with much of the literature which indicates quantitative and qualitative similarities in the effects of stereoisomers of ketamine in a variety of procedures (Marietta et al., 1977; Ryder et al., 1978; Meliska et al., 1979). It is possible that other arylcyclalkylamines with chiral centers will be more useful in exploring the stereospecificity of the effects of this group of compounds.

In conclusion, PCP-like drugs have proved to be a very fascinating and unique class of compounds. The overlap between PCP and the psychotomimetic opioids is especially interesting. Further exploration in this direction could provide information of value in improving the

therapeutic usefulness of both classes of compounds and in adding to the body of knowledge concerning psychotomimetics and psychotic behavior. The research reported in this dissertation has contributed towards these aims.

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