DISCRIMINATIVE STIMULUS PROPERTIES OF COCAINE:
TOLERANCE AND CROSS-TOLERANCE CHARACTERISTICS

THESIS

Presented to the Graduate Council of the
North Texas State University in Partial
Fulfillment of the Requirements

For the Degree of

Master of Science

By

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May, 1985

Master of Basic Health Sciences (Pharmacology), May, 1985, 58 pp., 2 tables, 7 figures, bibliography, 70 titles.

Rats were trained to discriminate an injection of cocaine, 5.0 mg/kg, from an injection of saline, using a two-lever choice paradigm: one lever was correct after cocaine injection, the other lever was correct after a saline injection. After training, cocaine and methamphetamine were generalized to the cocaine lever, but phenethylamine (PEA) was only partially generalized. Cocaine was injected every 8 hrs, 20.0 mg/kg, and the discriminability of 5.0 mg/kg was tested every other day. Redetermination of the cocaine generalization curve after 6 days of chronic administration showed a shift to the right, from an ED50 of 4.1 mg/kg in the pre-chronic condition to 10.0 mg/kg. Tolerance did not develop to the behavioral effects of cocaine, measured by time to the first reinforcement and response rate. There was cross-tolerance to methamphetamine; however, no evidence for cross-tolerance to PEA was obtained. Following the acquisition of tolerance, chronic administration of cocaine was terminated, and the discriminability of 5.0 mg/kg was tested every other day for loss of tolerance. After 8 days the ED50 returned to 5.0 mg/kg.
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INTRODUCTION

Cocaine is a naturally occurring alkaloid obtained from coca leaves of the shrub Erythroxylon coca. Its chemical nomenclature (in Chemical Abstracts) is 8-azo-bicyclo \( <3.2.1> \) octane-2-carboxylic acid, 3-benzoyloxy-8-methyl methyl ester \( <1-R-(exo-exo)> \). The coca shrub normally grows in western South America and is also cultivated in Java and Mexico. The use of cocaine in man extends over several centuries. According to Inca records, in South America some 3,000 years ago coca leaves were given as a reward for special services (Cohen, 1975). Coca leaves were also used to increase stamina, and when food was scarce, the leaves were used as a dietary supplement (Aldrich and Barker, 1976).

Cocaine was first chemically isolated from coca leaves in 1860, and shortly thereafter, one of the first scientific studies on cocaine was conducted by Sigmund Freud. Freud wrote several papers on cocaine's ability to cure morphine and alcohol addiction. Freud's colleague, Carl Koller, discovered the ability of cocaine to act as an anesthetic. Concurrently in America, William Halstead, a surgeon from Johns Hopkins University, discovered that cocaine could be used as a local anesthetic by blocking
Figure 1. Chemical structure of cocaine.
peripheral sensory nerves (Aldrich et al., 1976). For the next decade, cocaine was considered a "wonder" drug and was thought to cure ailments such as digestive disorders, cachexia, and asthma (Gay, Inaba, Sheppard and Newmeyer, 1975).

In the beginning of the 20th century, many medicines and foods contained cocaine. However, increased reports of psychological dependence to cocaine emerged. It was not until the "Harrison Narcotic Act" of 1914 which labeled cocaine as a "banned narcotic," that the use of cocaine in foods and medicines was discontinued. From 1914 to 1970, cocaine has been mainly used by various underground cults. However, in the last fifteen years, there has been an upsurge in the use of cocaine. It has re-emerged in "middle class America" as the illicit drug of status (Gay et al., 1975).

Effects of Cocaine Administration in Humans

Cocaine is an extensively abused drug possessing central nervous system (CNS) stimulant and anesthetic properties. It has been reported that cocaine has CNS stimulant properties similar to amphetamine, but possesses a shorter duration of action (Jasinski, Griffith, Car,
Gorodetzky and Kullberg, 1974). Furthermore, in a human study in which subjects were blind to treatment conditions of amphetamine or cocaine, the subjective effects produced by the two drugs were indistinguishable and could be classified as interchangeable (Fischman and Schuster, 1982).

However, in a study with 85 recreational users of drugs (Siegel, 1977), 69% of the males and 95% of the females ranked cocaine as the drug of choice over all other types of recreational drugs. The main reasons for cocaine popularity with subjects were as follows:

1. Cocaine was viewed by users as a social drug which facilitated social behavior.
2. Cocaine was viewed by users as the "ideal" drug in terms of convenience of use, minimal bulk, rapid onset of effects, minimal duration of action with few side effects, a high degree of safety and no after effects.
3. Cocaine was viewed by users as an exotic drug which had appeal because of its rarity, high price and historical associations with high-status people.

There have been only a limited number of controlled
experiments on the effects of cocaine administration in man. In one experiment, intranasal and intravenous routes of acute administration of single doses of cocaine (10.0 and 25.0 mg) were studied (Resnick, Kestenbaum and Schwartz, 1977). Results indicated that 10.0 mg cocaine administered intranasally produced little systemic changes and only minimal changes at 25.0 mg. However, cocaine administered intravenously produced substantial systemic effects. Both, systolic blood pressure and heart rate increased in a dose-related manner, and elevation of mood was also reported. Other systemic effects in controlled human experimentation have included elevation of mood (Byck, Jatow, Barash and Van Dyke, 1977), decreased sleep (Post, Gillin, Wyatt and Goodwin, 1974), decreased rapid-eye-movement sleep (Post et al., 1974), and decreased appetite (Resnick et al., 1977).

Recently, Fischman and Schuster (1982) investigated intravenous doses of cocaine in man. In their study, physiological measurements such as heart rate, blood pressure, respiration rate, and temperature were recorded during acute and chronic administration of cocaine. Behavioral measures to assess the drug's effects were also noted. Plasma levels of cocaine were monitored to correlate behavioral effects with physiological effects. The study confirmed reports of increased heart rate, blood
pressure, respiration rate, temperature, and mood elevation. These effects were dose-related to plasma levels of cocaine.

**Effects of Cocaine Administration in Animals**

Often human experimentation poses severe restrictions on experimental designs; there are obvious difficulties in testing cocaine use in humans, even in the experimental laboratory, because of the abuse potential of the drug. For this reason, there have been relatively few studies that have examined chronic administration of cocaine in man. Most of the literature on acute and chronic administration of cocaine has dealt with animal subjects and has correlated the behavioral and pharmacological effects of the drug in animals to man.

The behavioral effects of cocaine administration in animals are contingent on a number of variables such as dose, environment, route of administration, and species. Some of the gross unconditioned behavioral measures altered by cocaine administration have included locomotor activity, stereotypic behavior, aggression, heart rate, and convulsant actions.

Locomotor activity is typically measured by the rate
at which an animal crosses a beam of light in an enclosed space. Increased locomotor activity has been observed in dogs (Tatum and Seevers, 1929), rats (Post and Rose, 1976; Ho, Taylor, Estevez, Englert and McKenna, 1977), rhesus monkeys (Tatum and Seevers, 1929), and mice (van Rossum and Simons, 1969). Stereotypic behavior consists of the spontaneous occurrence of a repeated sequence of motor responses such as head bobbing, or continual bitting or licking. In several species including man (Gay et al., 1975), cocaine has been reported to increase stereotypic behavior.

Cocaine has also been reported to alter convulsant effects (Eidelberg, Lesse and Gault, 1975; Stripling and Ellinwood, 1976). Stripling and Ellinwood (1976) have reported that cocaine increases the convulsant effects in rats. Rats were administered high doses of cocaine and the effects on convulsant actions were monitored. The effects on convulsions were dose-dependent; as the cocaine dose increased, the incidence and intensity of convulsions increased. Other systemic effects produced by cocaine administration in animals have included increased heart rate, respiratory rate, and blood pressure (Matsuzaki, Spingler, Misra and Mule', 1976), which parallel the corresponding increases in the systemic effects observed in man.
Effects of Chronic Cocaine Administration

There has been much controversy concerning the effects of chronic administration of cocaine. For most drugs of abuse, tolerance is frequently cited as a reason for increasing the dose, and often, increased dosage leads to serious medical and social problems. Tolerance is usually described as a decreased drug-effect related to a prior history of drug administration (Goldstein, Aronow and Kalman, 1974). Typically, when a particular dose is administered repeatedly, tolerance is assessed as a decreased effect of that dose and/or a shift to the right of the entire dose-effect curve. However, with respect to cocaine, it is apparent that repeated administration per se does not guarantee tolerance. For example, tolerance to cocaine in man has been reported only rarely. There have been several anecdotal reports of cocaine tolerance in man (Caldwell and Seever, 1974; Jaffe, 1975). In these studies, it was observed that substantial amounts of cocaine, up to 10 gm per day, could be administered by chronic cocaine users. Since 1.2 gm of cocaine in a normal individual is considered toxic, this phenomenon was described as metabolic tolerance. Recently, Fischman and Schuster (1982) determined that acute tolerance to cocaine developed if patients self-administered 32 mg cocaine.
within a one-hour period. The discriminability of cocaine was tested every 15 minutes by using a subjective mood questionnaire. As chronic administration of cocaine continued, patients indicated that there was a decreased subjective effect of cocaine. Byck and Van Dyke (1977) also reported tolerance to cocaine in a self-administration study. However, generally, tolerance to cocaine in humans has been reported only rarely, and the role of this factor in cocaine dependence is generally considered to be nonexistent (Byck and Van Dyke, 1977).

Most of the literature suggests that tolerance does not develop to chronic cocaine administration in man (Cohen, 1975; Tatum and Seevers, 1932). Indeed, there have even been reports suggesting that sensitivity develops to cocaine for various behavioral measures following chronic administration (Gay et al., 1975). Sensitivity, in contrast to tolerance, is defined as increased responsiveness to a drug which is acquired after prior exposure to that drug, and has been described as a shift to the left of a dose-effect curve after prior administration of a drug.

The controversy as to whether tolerance or sensitivity develops after chronic administration of cocaine also exists in animal studies. Most animal studies have examined behavioral effects of chronic administration of
cocaine. For example, tolerance has been reported in animals with respect to open field motor activity (Roy, Bhattacharyya, Pradhan and Pradhan, 1978), sweetened-milk intake (Woolverton, Kandel and Schuster, 1978b), convulsant effects (Castellani, Ellinwood and Kilbey, 1978), stereotyped behavior (Roy et al., 1978), operant responding (Woolverton, Kandel and Schuster, 1978a), and discriminative stimulus paradigm (McKenna and Ho, 1977). However, many other studies using similar procedures have failed to find tolerance. Thus, little or no tolerance, and sometimes enhanced sensitivity, has been reported in animals for convulsant actions (Stripling and Ellinwood, 1977), stereotypic behavior (Downs and Eddy, 1932; Collins, Lesse and Dagan, 1979; Kilbey and Ellinwood, 1977), and locomotor activity (Stripling and Ellinwood, 1977; Bhattacharyya and Pradhan, 1979; Ho et al., 1977).

The effects of cocaine administration in animals have paralleled the effects of cocaine administration in man (Glennon and Rosecrans, 1981). For example, in one animal study, monkeys were trained to self-administer two doses of cocaine (0.25 and 0.50 mg/kg) through indwelling intravenous catheters (Deneau, Yanagita and Seevers, 1969). Similar to the Fischman and Schuster study (1982), monkeys also self-administered cocaine. Cocaine, a powerful reinforcer, was self-administered cocaine until behavioral
toxicity occurred. Behavioral observations of chronic cocaine administration included convulsions, hyperactivity, stereotypy, tremors, pilo-erection, and ataxia.

A major factor limiting pre-clinical measurement of subjective aspects of drug dependence has been lack of a suitable methodology for testing such questions. By definition, subjective events are not directly verifiable by experimenter observation, and because of the dangers of anthropomorphism, animal investigations of subjective events are particularly difficult. However, Lal and Emmett-Oglesby (1983) have argued that subjective events can be tested experimentally in animals if behavioral responses can be made specifically contingent upon detection of the subjective occurrence by the test subject. For example, subjects can be trained to use the internal discriminative stimuli (IDS) arising from drug injections as the basis for choosing which of several potential responses is correct. When only two responses are available, the response emitted, be it human-verbal or animal-choice behavior, resolves to "yes, the stimulus is present," or "no, it is not." The qualitative nature of such a binary decision can then be quantified through the method of population analysis; that is, the percent of subjects reporting the presence of the subjective event is a function of the stimulus intensity (Swanson and
Kinsbourne, 1978). In the past decade, many investigations have shown that subjective events arising from drug administration can be detected using discriminative stimulus methodology, and where direct comparisons have been made, drug effects thus measured are classified in parallel (e.g., LSD-like, narcotic-like) by humans and animals (Glennon and Rosecrans, 1981; Schuster and Balster, 1977).

**Cocaine as a Discriminative Stimulus**

In the drug discrimination procedure, one set of behaviors is reinforced under one set of conditions (e.g., presence of a drug) and a second set of behaviors is reinforced under another set of conditions (e.g., absence of a drug). For example, rats can be trained to discriminate an injection of cocaine from saline using an operant procedure where responses on one lever are reinforced only in the presence of cocaine, and responses on the second lever are reinforced only in the presence of saline. In this fashion, drugs such as cocaine (McKenna and Ho, 1977; McKenna and Ho, 1980; Colpaert, Neimegeers and Janssen, 1978; Colpaert, Neimegeers and Janssen, 1980; Emmett-Oglesby, Wurst and Lal, 1983; D'Mello and Stolerman,
1977), d-amphetamine (D'Mello and Stolerman, 1977; Huang and Ho, 1974, Stolerman and D'Mello (1978); Barrett and Leith, 1981), clonidine (Bennett and Lal, 1982), and morphine (Holtzman, 1982) have been used as discriminative stimuli.

Various scheduling contingencies of reinforcement can be employed which provide sensitive behavioral baselines against which the drug's effects can be measured. For example, a frequently used reinforcement contingency is the fixed ratio schedule (FR). The FR schedule requires that a behavior is reinforced after a specified number of responses, regardless of time. For example, a FR 10 schedule of bar pressing would require a rat to press the bar 10 times before a food reward would be given. Typically, the food reward is a 45 mg pellet. Other scheduling contingencies include variable ratio (VR), where a behavior is reinforced after a random number of responses; fixed interval (FI), where a behavior is reinforced after a designated time period; and variable interval (VI), where a behavior is reinforced after a random time interval. Cocaine's effect on operant responding depends on the rate of ongoing responding. For example, cocaine tends to increase low rates of responding such as occur with a fixed interval schedule. However, cocaine tends to decrease or leave unchanged high rates of
responding such as the fixed ratio schedule.

Barry (1974) has proposed that the discriminative stimulus properties of drugs may be used to classify them since closely related substances typically produce similar discriminative cues. Following this rationale, once the discriminative cue of cocaine has been established, other drugs can be substituted, and the test subjects will substitute to drugs with CNS stimulant properties similar to cocaine. For example, in one study (Colpaert, Neimegeers and Janssen, 1978a), rats were trained to discriminate 10.0 mg/kg cocaine from saline and a variety of drugs were tested for substitution for the cocaine discriminative stimulus. Results indicated that amphetamine drugs such as methylphenidate, nomifensine, d-amphetamine, and methamphetamine would substitute for the cocaine stimulus. Conversely, drugs such as LSD, morphine, phencyclidine, mescaline and imipramine would not substitute for the cocaine stimulus. Other studies which have confirmed these results include generalization of amphetamine (Colpaert, Neimegeers and Janssen, 1978b; Colpaert et al., 1978a; D'Mello and Stolerman, 1977), and methylphenidate (Ho and Silverman, 1978; Emmett-Oglesby, Wurst and Lal, 1983) to the cocaine stimulus. Thus, cocaine and amphetamine seem to possess similar discriminative stimulus properties, and supports Barry's (1974)
hypothesis that the discrimination paradigm could quantitatively assess a drug's pharmacological effects and classify them according to similar discriminative stimulus properties.

Mechanisms of Tolerance

With respect to tolerance, the increasing role of behavioral variables in tolerance are being defined consistently so that the term "behavioral tolerance" has emerged, which differs from pharmacokinetic or pharmaco-dynamic tolerance. Various other terms describing tolerance have included metabolic tolerance, physiological tolerance, and learned tolerance which all describe different mechanisms of tolerance or different experimental procedures (Kalant, LeBlanc and Gibbins, 1971; Corfield-Sumner and Stolerman, 1978).

Behavioral tolerance describes those aspects of drug tolerance that predominately depend upon behavioral factors for their expression. Typically, tolerance is observed only if the behavior is repeatedly performed while under the influence of the drug. For example, behavioral tolerance has been demonstrated involving pre-session vs. post-session cocaine administration (Woolverton et al.,
In that experiment, rats were trained to drink sweetened milk and then were subjected to a regimen of chronic cocaine administration. In a group receiving the drug pre-access to milk on a daily basis, milk consumption initially was disrupted, but over several administrations milk consumption increased which suggested tolerance developed to this effect. In a group receiving the drug immediately post-session, milk consumption during the next session was not affected; however, at the end of chronic administration, when this group was injected pre-session, no tolerance was observed. Because the two groups received equal quantities of drug, the paradigm focused attention on the role of ongoing behavior in the production of tolerance.

Pharmacokinetic tolerance describes those aspects of drug tolerance that predominantly depend upon metabolic factors for their expression. For example, tolerance may be due to A) decreased rate of absorption across biological membranes, B) decreased distribution due to altered homeostatic mechanisms, C) increased drug elimination, or D) increased metabolism. There is little evidence demonstrating that any of these mechanisms account for tolerance to the behavioral effects of the cocaine. For example, increased rate of drug metabolism has a negligible effect on drug responses that are effective
within minutes of drug administration (Goldstein et al., 1974). Furthermore, chronic cocaine administration does not result in an increased rate of drug elimination, nor does it increase the rate of metabolism of cocaine or its active metabolites (Miscra, 1975). Finally, no studies have demonstrated a decreased distribution of cocaine in the brain, or increased concentrations of drug elsewhere in the body during chronic cocaine administration (Miscra, 1975; Javaid, Fischman, Schuster and Dekirmenjian, 1978).

Pharmacodynamic tolerance describes those aspects of drug tolerance that predominately depend upon alterations of receptor sites or neurotransmitter release. Thus, pharmacodynamic tolerance to cocaine may be due to decreased release of neurotransmitter due to catecholamine synthesis, increased presynaptic reuptake of catecholamines, decreased receptor sites, or decreased receptor sensitivity (Figure 2). Data from discrimination procedures have supported the proposal that pharmacodynamic tolerance mediates the interoceptive discriminative stimulus produced by cocaine. For example, McKenna and Ho (1977), using drug discrimination methodology, demonstrated that tolerance developed to cocaine based on repeated administration of cocaine, which occurred without practice on the behavioral task. In that study, they trained rats to discriminate 10.0 mg/kg cocaine from saline. Sub-
Figure 2. Pharmacodynamic mechanisms of tolerance.
sequently, training was halted and subgroup of rats were injected with cocaine three times per day at five hour intervals for seven days, while the second subgroup of rats were injected with saline three times per day at five hour intervals. After seven days, the animals were tested for tolerance by determining the percent cocaine-lever choice after administration of 2.5 and 5.0 mg/kg cocaine. Results indicated that there was no significant difference in animal's percent cocaine-lever choice before and after repeated injections of saline; however, there was a significant decrease in the animal's percent cocaine-lever selection before and after repeated injections of cocaine. Since tolerance developed without practice on a behavioral task, behavioral tolerance could not account for the tolerance observed in this experiment. Also, since there has been no evidence demonstrating decreased amounts of neurotransmitter levels during tolerance, it is unlikely that a pharmacokinetic mechanism is responsible for mediating tolerance to the discriminative stimulus properties of cocaine. Therefore, there has been increasing popularity with the proposal that a pharmacodynamic mechanism mediates tolerance to the discriminative stimulus properties of cocaine.
Neurochemical Mediators of Cocaine

Cocaine exhibits a wide range of pharmacological activity, and its profound effects on behavior are thought to be mediated by catecholamines, specifically dopamine, in the brain. In vitro studies of neurochemical effects of cocaine administration have demonstrated increases in concentrations of dopamine (Patrick and Barchas, 1976), and slight increases of norepinephrine (Pradhan, Roy and Pradhan, 1978). There is also evidence that concentrations of 5-hydroxytryptamine decrease when cocaine is given acutely, and increase as cocaine is given chronically (Friedman, Gershon and Rotrosen, 1975).

Several studies have used the discriminative stimulus procedure to examine the neuropharmacological characteristics of drugs inducing stimulus generalization with cocaine as a cue (Colpaert, et al., 1976; McKenna and Ho, 1980; Colpaert et al., 1978b). These experiments used the rationale that if amphetamine and cocaine produce interchangeable discriminative stimulus properties, and if these two drugs indirectly release brain dopamine, then direct dopaminergic receptor agonists should also mimic the cocaine stimulus. For example, in one experiment (Colpaert et al., 1978b) rats were trained to discriminate 10.0 mg/kg cocaine from saline. After training, various dopamine
agonists such as bromocryptine, amantadine, apomorphine, and piribedil were tested for selection of the cocaine lever. These drugs substituted for the cocaine lever, which suggests that dopamine is responsible for mediating the cocaine stimulus. In the same experiment, noradrenergic agonists and antagonists were tested and did not result in substitution to the cocaine stimulus. Similarly, cholinergic and anticholinergic drugs were tested and did not result in substitution to the cocaine lever. In similar studies, (Colpaert et al., 1978a; McKenna and Ho, 1980) apomorphine also substituted for the cocaine stimulus. However, when a selective dopamine receptor blocking drug, haloperidol, was administered, partial substitution of the cocaine stimulus could be detected. The inability of haloperidol to antagonize the cocaine cue completely suggests that there may be non-dopaminergic mechanisms involved in the production of the cocaine stimulus. These results are also consistent with reports that dopamine receptor blocking drugs are ineffective in blocking cocaine self-administration in animals (Woods, Herling and Winger, 1976).

Phenethylamine is an endogenous trace amine whose behavioral effects in animals has been reported to mimic amphetamine (Jackson, 1972; Reisner and Jones, 1977; Braestrup, 1977). It has been proposed that phenethylamine
is an endogenous amphetamine which mediates the actions of amphetamine related compounds (Borison, Mosnaim and Sabelli, 1975; Chuang, Karoum and Perlow, 1981). Colpaert et al. (1980) suggested that phenethylamine may be responsible for mediating the discriminative stimulus properties of cocaine. In that study, rats were trained to discriminate 5.0 mg/kg cocaine from saline. Drugs which inhibited the enzyme monoamine oxidase type B, induced generalization to the discriminative stimulus properties of cocaine. Since phenethylamine is a preferred substrate for this enzyme, Colpaert concluded that phenethylamine may be responsible for mediating discriminative stimulus properties of cocaine and possibly other central nervous system stimulants.

Huang and Ho (1974) reported that in rats trained to discriminate amphetamine, neither phenethylamine (1.0 mg/kg) nor iproniazid, a MAO inhibitor, substituted for amphetamine. In contrast, Goudie (1982) trained rats to discriminate 30 mg/kg phenethylamine from saline. Substitution tests with cocaine and amphetamine demonstrated that partial selection of the phenethylamine lever occurred for both drugs. Thus, higher doses of phenethylamine may be required for substitution to either the cocaine or amphetamine discriminative stimulus.
**Conclusion**

Cocaine can serve as a discriminative stimulus (Colpaert et al., 1976; McKenna and Ho, 1980; Emmett-Oglesby et al., 1983). That is, subjects can be trained to select one response in the presence of a particular dose of cocaine and an alternative response in the absence of cocaine. McKenna and Ho (1977) trained rats to discriminate 10.0 mg/kg cocaine from saline. Following chronic administration of cocaine, selection of the cocaine lever for two doses of cocaine was significantly decreased after chronic administration of cocaine compared to selection of the cocaine lever prior to chronic cocaine administration. However, this study did not report a time-course for the development or loss of tolerance.

Using a similar procedure to McKenna and Ho (1977), the present experiment will test the hypotheses that tolerance will develop to the discriminative stimulus properties of cocaine, and subsequently, tolerance will be lost once chronic administration of cocaine is terminated. Furthermore, this experiment will determine the rate of acquisition of tolerance and the loss of tolerance to the discriminative stimulus properties of cocaine.

In addition, because tolerance to drugs of abuse frequently confers cross-tolerance to other drugs of the
same class (Woolverton et al., 1978b), this experiment will also test the hypothesis that tolerance to cocaine will confer cross-tolerance to methamphetamine and phenethylamine. Methamphetamine was tested because it is a typical amphetamine-type drug, and other drugs of this class substitute to the stimulus for cocaine (Colpaert, et al., 1978). Phenethylamine was tested because it has been reported to generalize to the amphetamine stimulus, and phenethylamine in the brain has been proposed to mediate the stimulus properties of cocaine (Colpaert et al., 1980).
MATERIALS AND METHODS

Subjects

Sixteen rats of male Long-Evans hooded strain (Charles River Breeding Laboratories, Willmington, Mass.) were subjects. The rats, initially sixty-days old and weighing between 250-275 g, received ad libitum food (Purina Rat Chow) and water until their weights were stable at 320 g. Thereafter, weights were maintained at 320±5 g by limiting food availability. The rats were housed individually in a large colony room of constant temperature (21±1°C).

Apparatus

Discrimination training was carried out in sixteen standard operant behavioral chambers (Coulbourn Instruments). Each chamber was housed in a light and sound attenuated box and fan ventilated. A houselight was mounted centrally above a food cup, which was located between two response levers. Food reward (45 mg pellets Noyes Co.) was delivered by a pellet dispenser. Recording
of lever responses and scheduling of reinforcement contingencies was performed through TRS-80 Model III microcomputers (Radio Shack) and printers connected to the chambers through LVB interfaces (Med Tech Associates) using a modification of a program described by Emmett-Oglesby, Spencer, and Arnoult (1982).

Drugs

All drugs were dissolved in 0.9% saline solution and injected intraperitoneally 15 min. pre-session in a volume of 1 ml/kg body weight. All doses refer to the weight of the salt. Cocaine hydrochloride was obtained from Merck Chemical Company. Methamphetamine hydrochloride (sulfate) and phenethylamine hydrochloride were obtained from Sigma Chemical Company.

Preliminary Training

Rats were trained to press levers for food reinforcement. Initially, the rats were placed overnight in the operant chambers with each lever press reinforced (CRF; continuous reinforcement schedule). They remained on the
CRF schedule for 4 consecutive sessions. Subsequently, the session time in the operant chambers was reduced to 20 min. The number of lever presses required for food reinforcement gradually increased to a fixed ratio 2 (FR 2; every 2nd press on either lever produced a reinforcement), to a final FR 10 schedule (Table 1). The rats were then trained to press the levers alternately where only one of the levers resulted in the delivery of food (on the first session, only right lever responses produced reinforcement; on the second session, only left lever responses produced reinforcement, etc.).

**Discrimination Training**

After the subjects were trained to lever press, each rat randomly was assigned one lever for saline and one lever for cocaine. Following intraperitoneal (i.p.) cocaine (5.0 mg/kg) injection, only FR10 responses on one of the levers (the cocaine lever) were reinforced; responses on the saline lever were recorded but not reinforced. Similarly, following i.p. saline (1 ml/kg) injection, only FR10 responses on the saline lever were reinforced, and responses on the cocaine lever were recorded but not reinforced. For discrimination training a
TABLE 1

Training Schedule

<table>
<thead>
<tr>
<th>Number of sessions</th>
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<th>Session Time</th>
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<td>2</td>
<td>CRF</td>
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</tr>
<tr>
<td>7</td>
<td>FR 10 (alternating levers)</td>
<td>20 min</td>
</tr>
<tr>
<td>104</td>
<td>FR 10 Cor</td>
<td>10 min</td>
</tr>
</tbody>
</table>

KEY:

CRF = Continuous reinforcement schedule. Each lever press results in the delivery of food.

FR = Fixed ratio. Every designated lever press results in the delivery of food.

FR 10 Cor = Ten consecutive lever presses on the appropriate lever are required for food reinforcement.
fixed ratio 10 correction schedule (FR 10 Cor) was used (Table 1). This schedule required that ten consecutive responses occur on the appropriate lever before the subjects were reinforced with food. Any incorrect responses automatically required 10 additional responses be made on the correct lever before food was delivered. Responses on the incorrect lever were recorded but did not result in the delivery of food. An irregular sequence of cocaine and saline injections for each session (one session per day) was chosen in the following order: DSSDSDDSDS-SSFDDSSDSDD (D= 5.0 mg/kg cocaine, S = 1 ml/kg saline). In order for the rat to move up one step in the sequence (i.e. D to S) not more than four responses on the incorrect lever could occur prior to receiving reinforcement (i.e. prior to ten consecutive responses on the correct lever). If more than four incorrect responses occurred, the rat remained under the same condition until the criterion was met. Each session lasted either ten minutes, or until 50 reinforcers were obtained, which ever occurred first. For both training and testing, only responses emitted prior to obtaining the first reinforcement were used to record which lever was selected. To insure accurate discrimination, during training the correct lever (saline following saline injection or cocaine following cocaine injection) was recorded as being selected only if 10 responses were
emitted on the correct lever with 4 or fewer responses emitted on the incorrect lever. When this criterion was met for 10 consecutive sessions, testing was begun.

**Generalization Testing**

Generalization tests were conducted for cocaine (1.25, 2.5, 5.0, and 10.0 mg/kg), methamphetamine (0.32, 0.625, and 1.25 mg/kg) and phenethylamine (40.0 and 80.0 mg/kg). For all test sessions, drugs were injected 15 minutes pre-testing, and the lever on which 10 responses were first emitted was recorded as the selected lever. All generalization tests were separated by at least 4 training sessions in which the subjects selected the correct lever with 4 or fewer responses emitted on the incorrect lever. Rats which did not meet this criterion were not used for generalization testing.

**Tolerance Procedure**

Following training and testing, all rats were injected with cocaine, 20.0 mg/kg, every 8 hours for 10 days. On a once every 2 day basis, at a regularly scheduled cocaine
injection, 8 randomly selected subjects were injected with 5.0 mg/kg cocaine and tested for their discrimination of the cocaine stimulus. On test days the rats received a second cocaine injection to maintain the 20 mg/kg requirement of that dosing period. On days 6-10, generalization data were re-determined for cocaine, methamphetamine, and phenethylamine. During generalization testing, a dose of one of the drugs was substituted for a regularly scheduled injection of 20.0 mg/kg cocaine. Otherwise, rats continued to receive the 20.0 mg/kg cocaine dose every 8 hours during these tests. After generalization data were redetermined, chronic cocaine injections were halted, and again, on a once every 2 day basis, 8 randomly selected subjects were injected with 5.0 mg/kg cocaine and tested for their discrimination of the cocaine stimulus.

Data Collection

Data obtained from the cocaine discrimination are quantal (subjects are scored as "yes" or "no"). Direct statistical comparison of groups was done through Chi-Square analysis where the pretolerance results provide "expected" values, and the tolerance results provide "observed" values. The statistical tests determined the
effect on the selection of the cocaine lever of various drugs before and during tolerance.
RESULTS

The subjects took approximately 60 sessions of training to discriminate cocaine (5.0 mg/kg) from saline and meet the criterion of selecting the correct lever with four or fewer incorrect responses on ten consecutive sessions. The animals were trained for another 60 sessions and by the onset of the experiment, the discriminability of 5.0 mg/kg cocaine fluctuated between 80-90 percent (Figure 3).

Prior to chronic administration, the interoceptive stimuli produced by cocaine were dose-dependent with an approximate ED50 of 4.1 mg/kg (Figure 4). During chronic administration, the percentage of subjects selecting the cocaine-correct lever after 5.0 mg/kg cocaine progressively decreased (Figure 5). By the sixth day of chronic administration, only 13% of subjects selected the cocaine-correct lever following 5.0 mg/kg cocaine. A cocaine generalization curve determined at this time was shifted to the right with an approximate ED50 of 10.0 mg/kg (Figure 4). Chi-square analysis performed on the two overlapping doses (5.0 and 10.0 mg/kg) showed a significant effect of chronic cocaine treatment ($X^2=16.3; \text{df}=1; p<.01$).
Figure 3. Acquisition of discriminated responding. Abscissa: 112 training sessions shown as 56 sessions of cocaine and 56 sessions of saline. Ordinate: percentage of rats selecting the cocaine lever. The (X) indicates selection after 5 mg/kg cocaine injection; (O) indicates selection following saline injection. Each data point is the average of 4 sessions.
Figure 4. Generalization of cocaine to the cocaine stimulus before and during chronic administration of cocaine. Abscissa: dose of cocaine. Ordinate: percentage of rats completing the first 10 responses on the cocaine lever. Data show cocaine-lever selection before (O) and during (X) chronic treatment with 60 mg/kg/day cocaine.
After chronic administration of cocaine was terminated, the percentage of rats selecting the cocaine lever following a 5.0 mg/kg cocaine injection increased over time; after 8 days, 50% of the rats selected the cocaine lever (Figure 5). Following a 5.0 mg/kg cocaine injection, selection of the cocaine lever was significantly less during tolerance than 8 days after chronic cocaine injections were stopped ($X^2=6.45; \text{df}=1; p<.01$).

The time to obtain the first reinforcement in the session, both before and during tolerance, increased as a function of the dose of cocaine (Figure 6). The dose-effect curve obtained during tolerance was not significantly different from that obtained prior to chronic cocaine administration; thus, there was no evidence of sensitization or tolerance to the effects of cocaine on time to first reinforcement following chronic cocaine administration.

The responses per minute in the session, both before and during tolerance, decreased as a function of the dose of cocaine (Figure 7). The dose-effect curve obtained during tolerance was not significantly different from that obtained prior to chronic cocaine administration; thus, there was no evidence of sensitization or tolerance to the effects of cocaine on response rate due to chronic cocaine administration.
Figure 5. Generalization of 5.0 mg/kg cocaine to the cocaine stimulus before and during chronic administration of cocaine. Abscissa: left half: number of days of chronic administration of 20.0 mg/kg cocaine at 8 hr intervals. Right half: number of days after chronic administration. Ordinate: percentage of rats completing the first 10 responses on the cocaine lever following a 5.0 mg/kg dose of cocaine.
Figure 6. Effect of cocaine on the time to obtain reinforcement before and during chronic administration of cocaine. Abscissa: dose of cocaine or saline (SAL). Ordinate: time to complete 10 responses resulting in reinforcement. Response-rate data obtained for various doses of cocaine before (○) and during (▲) chronic treatment with 60 mg/kg/day cocaine.
Figure 7. Effect of response rate before and during chronic administration of cocaine. Abscissa: dose of cocaine or saline (SAL). Ordinate: number of responses per session time. Response rate data obtained for various doses of cocaine before (0) and during (▲) chronic treatment with 60 mg/kg/day cocaine.
Prior to chronic cocaine administration, methamphetamine was generalized to the cocaine stimulus, and phenylethylamine was partially generalized to the cocaine stimulus, with doses of phenylethylamine above 80.0 mg/kg producing behavioral toxicity (Table 2). Subjects were described as behaviorally toxic if no lever selection was made during the ten minute test session. Tolerance to cocaine conferred cross-tolerance to methamphetamine but not to phenylethylamine (Table 2). Chi-square analysis performed on overlapping doses of methamphetamine (0.32 and 0.625 mg/kg) before and during chronic administration of cocaine showed a significant effect of chronic cocaine treatment ($X^2=7.7; df=1; p<.01$).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/kg)</th>
<th>% Rats selecting cocaine lever</th>
<th>Number of rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontolerant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>0.32</td>
<td>43</td>
<td>7</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>0.625</td>
<td>71</td>
<td>7</td>
</tr>
<tr>
<td>Phenethylamine</td>
<td>40.0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Phenethylamine</td>
<td>80.0</td>
<td>60</td>
<td>5</td>
</tr>
<tr>
<td>Tolerant</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>0.32</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>0.625</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Phenethylamine</td>
<td>40.0</td>
<td>30</td>
<td>10</td>
</tr>
<tr>
<td>Phenethylamine</td>
<td>80.0</td>
<td>50</td>
<td>4</td>
</tr>
</tbody>
</table>
DISCUSSION

The data demonstrate that cocaine can produce interoceptive stimuli that rats can discriminate reliably from saline. The acquisition of cocaine discrimination is similar to previous studies that have used cocaine as a discriminative stimulus. The majority of studies have arbitrarily used 10.0 mg/kg cocaine as the training dose (McKenna and Ho, 1977; McKenna and Ho, 1980; Colpaert, et al. 1976; Colpaert et al., 1978a; Hutchings, Gonzalez and Altshuler, 1978). However, lower training doses have been used as a discriminative stimulus in rats. For example, Colpaert et al. (1980), trained subjects to discriminate 5.0 mg/kg cocaine. Similarly, Emmett-Oglesby, Wurst and Lal (1983) trained rats to discriminate 1.25 mg/kg cocaine; thus, these experiments establish that cocaine can produce a powerful discriminative stimulus for a range of doses. The present experiment used 5.0 mg/kg cocaine as the training dose because tolerance has not been reported using this dose as a discriminative stimulus, and to support the hypothesis that tolerance can be produced in a discrimination procedure independent of the training dose of cocaine.
There has been controversy regarding the development of tolerance in a discrimination procedure. For example, Gonzalez et al., (1978) trained rats to detect 10.0 mg/kg cocaine, and administered 10.0 mg/kg 4 times per day, and tolerance was not observed. However, McKenna and Ho (1977) trained rats to discriminate 10.0 mg/kg cocaine and administered 20.0 mg/kg, 3 times per day, for 7 days and tolerance was produced. The present study found that tolerance developed to the discriminative stimulus properties of cocaine after 6 days of cocaine injection, 20.0 mg/kg, 3 times per day. These data agree with those of McKenna and Ho (1977), and extend the previous findings to show the time course for the development and loss of tolerance.

The failure to obtain tolerance in previous experiments may have been due to variables such as different strains of rats used in the two studies. Also, Gonzalez et al. (1978), did not report the duration of cocaine administration during chronic dosing and administered lower doses during chronic administration in attempting to induce tolerance than in the present experiment. Therefore, the previous failure to obtain tolerance may have been either due to limited duration of administration or to limited amount of drug necessary to produce tolerance since the present experiment demonstrates that tolerance develops
slowly over the course of approximately 6 days with large
doses of cocaine.

Chronic administration of cocaine produced a 2-3 fold
shift to the right of the cocaine generalization curve
(Figure 4). This magnitude of tolerance is similar to that
seen in studies of cocaine and amphetamine tolerance where
behavioral measures such as milk drinking or operant
responding were employed (Woolverton et al., 1978b;
Woolverton et al., 1978a); however, in contrast to those
studies, tolerance in this study was not contingent on
performing a task in the presence of the drug. Comparable
to previous reports (McKenna and Ho, 1977; Barrett and
Leith, 1981), this demonstration of tolerance in a drug
discrimination procedure occurred when subjects were
withheld from testing and injected chronically. Therefore,
the development of tolerance to the discriminative stimulus
properties of cocaine occurred as a result of chronic
administration, and no interaction with a reinforced
response was required.

Tolerance in a drug discrimination paradigm has also
been reported for rats trained to discriminate morphine and
then injected daily, using a procedure similar to the one
in the present study (Miksic and Lal, 1977). However,
these results were interpreted as artifactual (Colpaert,
1976). That is, what appears to be tolerance may actually
be the result of exposing subjects to larger doses which retrains them to attend to a higher magnitude of the stimulus. The present results are incompatible with this hypothesis because when chronic injection of cocaine was terminated, baseline sensitivity was spontaneously recovered without retraining subjects to attend to the lower stimulus value. Therefore, the present results indicate that tolerance does occur to the discriminative stimulus properties of cocaine.

The data on recovery of baseline sensitivity demonstrate the stability of the cocaine discrimination. In the present experiment subjects were not trained for 21 days, and they were injected with 20.0 mg/kg, three times per day, for 10 days. In spite of these experimental manipulations, stimulus control was maintained. These results were obtained from tests in which lever selection was reinforced; thus, selection of the saline lever following 10.0 mg/kg cocaine occurred for a majority of subjects during the first 6 days of recovery. The finding that cocaine was increasingly generalized to the cocaine lever suggests that reinforcement of the saline lever choice during the initial recovery tests did not bias the results to continue selecting the saline lever. These results suggest that the rats were under stimulus control throughout the experiment; therefore, lever selection
during testing accurately reflects the extent to which the
test stimulus resembles the stimulus that was trained prior
to chronic drug administration.

Tolerance to the discriminative stimulus properties of
cocaine did not confer tolerance or sensitization to the
behaviorally disruptive effect of cocaine as measured by
the time required to obtain the first reinforcement in the
session (Figure 6) and responses per minute (Figure 7). In
previous studies of tolerance to the disruptive behavioral
effects of cocaine, tolerance was only observed if the
behavior was repeatedly performed during cocaine intox-
ication (Woolverton et al., 1978b). In fact, previous
studies have typically shown enhancement of the behavior-
ally disruptive effects of cocaine when chronic adminis-
tration was not contingent on the performance of behavior
(Roy et al., 1978; Ho et al., 1978; Stripling and Ellin-
wood, 1977). In the present study, the lever-press
response was not practiced during chronic cocaine adminis-
tration, and therefore, these results are consistent with
previous findings on lack of tolerance to the behavioral
effects of cocaine. The lack of sensitization in the
present study may be due to the relatively shorter time
course of chronic administration than in previous studies.

Tolerance to the discriminative stimulus properties of
cocaine conferred cross-tolerance to the discriminative
stimulus properties of methamphetamine (Table 1). These results agree with several studies which have demonstrated that amphetamine-type drugs will substitute for the discriminative stimulus properties produced by cocaine (D'Mello and Stolerman, 1977; Emmett-Oglesby et al., 1983; Huang and Ho, 1974; McKenna and Ho, 1980). This finding supports the hypothesis that a common mechanism mediates tolerance to these two drugs, and this effect could be expected for other drugs with CNS stimulant properties of the amphetamine-type. Furthermore, following this rationale, drugs sharing the same neurochemical action and substitutes for the discriminative properties produced by cocaine will also show similar tolerance and cross-tolerance characteristics. Thus, the neurochemical mechanism mediating the subjective effects of cocaine and amphetamine-type drugs may be determined using the discrimination procedure.

Phenylethylamine (PEA) has been proposed as an endogenous neurotransmitter that may be responsible for mediating the cocaine cue (Colpaert et al., 1980). In this experiment, however, there was little generalization of PEA to the cocaine stimulus. This finding suggests that the discriminative stimulus properties of cocaine and PEA are different. This hypothesis is further supported by lack of cross-tolerance between cocaine and PEA.
The technique of using drugs in a discrimination paradigm has been successful in characterizing the subjective drug effects in animals (Schuster, Fischman and Johnson, 1981; Lal, 1977). However, in humans there is virtually little information concerning tolerance to the subjective effects of cocaine or amphetamine-type drugs. Although there are several reports of little tolerance to the subjective effects of cocaine (Jaffe, 1975), most of these reports are anecdotal and do not involve prolonged administration of multiple daily doses of cocaine. However, recently numerous studies have reported similarities in the comparison of the subjective effects produced in humans with those produced in animal models. Moreover, results of the drug discrimination procedure have closely paralleled human reports of the subjective effects of drugs (Glennon and Rosecrans, 1981). Recently, Fischman and Schuster (1982) in a controlled clinical experiment investigated tolerance to cocaine and reported that the euphoric effects of a 32 mg dose of cocaine were diminished if the dose was given within one-hour following a previous dose. This observation suggests that tolerance to the subjective effects of cocaine may be more prevalent and easily obtained than commonly believed. In this regard, drug discrimination learning in animals has been proposed as an assay for in vivo assessment of "subjectively"
experienced effects of drugs in subhuman subjects (Lal and Emmett-Oglesby, 1983; Jarbe, 1984); therefore, the drug discrimination paradigm offers a powerful methodology for investigating pharmacodynamic tolerance and may be a valuable methodology for determining the neurochemical mechanisms producing the subjective effects of cocaine.
SUMMARY

Rats were trained to discriminate an injection of cocaine, 5.0 mg/kg, from an injection of saline, using a two-lever choice paradigm: one lever was correct after cocaine injection, the other lever was correct after a saline injection. After training, cocaine and methamphetamine were generalized to the cocaine lever, but phenethylamine (PEA) was only partially generalized. Cocaine was injected every 8 hrs, 20.0 mg/kg, and the discriminability of 5.0 mg/kg was tested every other day. Redetermination of the cocaine generalization curve after 6 days of chronic administration showed a shift to the right, from an ED50 of 4.1 mg/kg in the prechronic condition to 10.0 mg/kg. Tolerance did not develop to the behavioral effects of cocaine, measured by time to the first reinforcement and response rate. There was cross-tolerance to methamphetamine; however, no evidence for cross-tolerance to PEA was obtained. Following tolerance, chronic administration of cocaine was terminated, and the discriminability of 5.0 mg/kg was tested every other day for loss of tolerance. After 8 days the ED50 returned to 5.0 mg/kg.

The results of this experiment demonstrated that
tolerance develops to the discriminative stimulus properties of cocaine when cocaine is injected for periods as short as 6 days. Secondly, results indicated that tolerance to the discriminative stimulus properties of cocaine was lost in approximately the same period of time that it was acquired. Thirdly, results indicated that PEA was only weakly generalized to cocaine, and no evidence was found that tolerance to cocaine confers cross-tolerance to PEA. Fourthly, results indicated that tolerance to the discriminative stimulus properties of cocaine confers cross-tolerance to the discriminative stimulus properties of methamphetamine. These data suggest a common mechanism may mediate tolerance to both drugs. Lastly, results indicated that tolerance to the discriminative stimulus properties of cocaine did not confer tolerance to the behaviorally disruptive effects of cocaine as measured by time to the first reinforcement or response rate. These data suggest that as compared to measures that rely on disruption of behavior, the drug discrimination paradigm may have significant advantages for studying tolerance in animals.
BIBLIOGRAPHY


conditions in discrimination of central nervous 
system stimulants in rats. Psychopharmacology. 

Potentiation of the behavioral and convulsant effects 
of cocaine by chronic administration in the rat. 

Sensitization to cocaine following chronic 
administration in the rat. In: Cocaine and Other 
Stimulants (Ellinwood, E.H., Jr. and Kilbey, M.M., 

reconsidered: limitations imposed by the statistical 
model. In: Stimulus Properties of 
Drugs: Ten Years of Progress (Colpaert, F.C. and 
Rosecrans, J.A., Eds.), pp.467-482. Elsevier/North 
Holland, Amsterdam.

Tatum, A.L. and Seevers, M.H. (1929). Experimental 
36: 401-410.

promazine and haloperidol-induced changes in some 
behavioral effects of cocaine and amphetamine. 
Communication at the 10th C.I.N.P. Congress.

and anorexigenic action. Psychopharmacologia 
14: 248-254.

Effects of repeated administration of cocaine on 
schedule-controlled behavior of rats. Pharmac. 
Biochem. Behav. 9: 327-337.

Tolerance and cross tolerance to cocaine and d-