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Assessment of the Discriminative Properties of a Selective D3 Antagonist

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ASSESSMENT OF THE DISCRIMINATIVE PROPERTIES OF A SELECTIVE D_3 ANTAGONIST

by

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Two groups of male Sprague-Dawley rats (n=16) were used in a drug discrimination assay to assess the stimulus properties of PNU-99194A, currently the most selective D_3 dopamine antagonist. Eight rats were trained to discriminate cocaine-HCL (10 mg/kg) from saline and remaining eight rats were trained to discriminate PNU-99194A-HCL (10 mg/kg) from saline. PNU-99194A was tested for substitution (0-40 mg/kg, i.p and s.c.), antagonism (5-20 mg/kg), and potentiation (5-20 mg/kg) in the animals trained with cocaine. PNU-99194A did not substitute for cocaine at any dose tested. PNU-99194A did not alter cocaine discrimination when administered in combination with the training dose or with a lower dose of cocaine. d-Amphetamine (0-2.0 mg/kg, i.p.), cocaine (0-10 mg/kg, i.p. and s.c.), and caffeine (8.0-64.0 mg/kg, i.p.) were tested for substitution in the rats trained to discriminate PNU-99194A. Cocaine, d-amphetamine, and caffeine produced virtually no responding on the PNU-99194A-lever, although caffeine (64 mg/kg) produced a mean of 32% drug appropriate responding. The present results suggest that PNU-99194A produces discriminative stimulus effects that are uniquely different from known psychomotor stimulants.

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CHAPTER I

INTRODUCTION

Cocaine use and abuse are a major public health concern. Although recreational use has decreased by as much as 75% since 1985, heavy cocaine use has continued to increase (Kleber, 1995). The treatment of cocaine addiction has presented a challenge to both researchers and clinicians and there has been a concerted effort to develop social and pharmacological therapies. The social focus of addiction treatment has been on achieving abstinence and preventing relapse. A major barrier to achieving long term abstinence in cocaine addicts is the intense drug craving experienced by these individuals. If drug craving were diminished, addicts would be more receptive to behavioral interventions. Recent attempts to reduce drug craving in cocaine addicts have examined antidepressants such as desipramine, and more selective dopamine agents mazindol, amantadine, and bromocriptine (Callahan & Cunningham, 1993; Kleber, 1995; Wise, R., 1995). Extensive research has documented a critical role for dopamine in the reinforcing effects of cocaine. Therefore, dopaminergic compounds have been targeted as possible routes for pharmacotherapy treatments of cocaine addiction (Smith, Piercey, Roberts, 1995; Callahan, Appel, & Cunningham, 1991; Ritz, Lamb, Goldberg, & Kuhar, 1987). Pharmacotherapy research has been based on the premise that chronic cocaine use leads to alteration of the neurochemical environment, and that improvement of this drug-induced state would diminish cocaine craving and use (Kleber, 1995). Despite the volume of research on cocaine addiction, no drugs have been discovered for the clinical treatment of cocaine addiction that are analogous to the use of methadone in the treatment of heroin addiction (Kleber, 1995).

Cocaine blocks the re-uptake of dopamine, norepinephrine, and serotonin, although its reinforcing effects appear to be related to the blockade of dopamine re-uptake, which produces an increased extracellular dopamine concentration in the mesolimbic and mesocortical pathways in the brain (Kleber, 1995; Caine & Koob, 1993). The initial discovery of dopamine receptors resulted from research on the mechanism of antipsychotic drugs. Current research is focusing toward targeting specific dopamine receptors in an attempt to improve the likelihood of developing pharmacotherapies for drug addiction treatment.

Five dopamine-receptor subtypes have been identified but their roles in abuse and dependence are yet to be determined. Dopamine receptors are classified into two main groups D_1-like and D_2-like. D_1 and D_5 are classified as D_1-like, while D_2, D_3, and D_4 are under the D_2-like classification (Seeman & Van Tol, 1994).

The major difference between D_1 and D_5 receptors is that dopamine itself is ten times more potent at the D_5 receptor than at the D_1 receptor (Seeman & Van Tol, 1994). Although the D_3 receptor shows a close structural resemblance to the D_2 receptor, it has a much more discrete localization than do D_2 receptors, which are found in the majority of dopaminoceptive areas throughout the brian (Alam & Starr, 1994). D_3 receptors have been described as differing from D_1 and D_2 receptors with respect to their in vitro binding pharmacology, anatomic distribution and abundance (Sokoloff, Giros, Martres, Bouthenet, Schwartz, 1990). According to autoradiographic data, D_3 receptors are found mainly in the limbic areas of the brain, including the nucleus accumbens (Alam & Starr, 1994). Dopamine D_3 mRNA has also been found in the substantia nigra and the ventral tegmental area (Waters, Svensson, Haadsma-Svensson, Smith, & Carlsson, 1993). Localization of D_3 receptors in the mesolimbic area has led

to the speculation of their possible role in human psychosis, and the abuse liability of psychostimulants.

A number of studies have indicated that D_3 receptors may modulate the reinforcing properties of cocaine in rats (Kleber, 1995; Caine & Koob, 1993; Sokoloff, et al., 1990). Cocaine self-administration is modulated by dopamine D_3 receptor ligands, which suggests that these receptors may be an important target for the discovery of a possible treatment of cocaine abuse (Caine & Koob, 1993). Acri et al. (1995) found that high affinity dopamine D_3 receptor ligands (+)-PD 128907 (4aR10bR-(+)-trans-3,4,4a, 10b-tetrahydor-4-n-propyl-2H5H (4,3-b)-1,4-oxazin-9-ol), and 7-OH-DPAT (±)-7-hydroxy-2-(N,N-di-n-proylino) tetralin) produce discriminative stimulus effects similar to those of cocaine. However, D_3 agonists produce behavioral depression and response rate reduction, which are unlike the effects of cocaine and other dopamine agonists (Acri, et al., 1995). Based on these findings, Acri et al. (1995) suggest the D_3 receptor may be involved in the subjective effects of cocaine and may also mediate behavioral effects that are different from those of cocaine.

Various researchers are actively seeking an effective pharmacotherapy for the possible treatment of cocaine addiction. Although it has been suggested that D_3 receptors may contribute to the reinforcing properties of cocaine, there may be some species differences with respect to the distribution and possible interaction of neurons with these dopamine receptor subtypes (Kleber, 1995). There is increasing evidence that a D_3 antagonist might provide effective therapy for many dopamine related problems without many of the extrapyramidal side effects which have been associated with antagonism of the nigrostraital dopamine pathway or the sedative effects that are associated with antagonism of the mesocortical pathways (Carlsson & Piercey, 1995). Therefore, researchers are focusing on D_3 receptors and new classes of drugs that bind

with varying degrees of selectivity to these receptors. For example, the D_3-preferring antagonists, (+)-AJ76 (cis-(+)-1S,2R-5-methoxy-1-methyl-2-(n-propylamino)-tetralin), (+)-UH232 (cis-(+)-1S,2R-5-methoxy-1-methyl-2-(di-n-propylamino)-tetralin), and DS-121 (S-(-)-3-(3-cyanophenyl)-N,n-propylpiperidine) reduce the breaking point on progressive ratio schedules of cocaine self-administration in rats, which indicates these drugs block the reinforcing effects of cocaine (Richardson, et al., 1993; Roberts & Ranaldi, 1995; Smith, et al., 1995).

One of the most promising new D_3 selective antagonists is PNU-99194A (cis-(+)-1S,2R-5-methoxy-1-methyl-2-(di-n-propylamino)-tetralin) (Pharmacia & Upjohn Inc., Kalamazoo, MI). PNU-99194A has been shown to be the most selective D_3 antagonist at this time, having a 20 fold preference for D_3 receptors over D_2 receptors (Waters, et al., 1993).

It is well known that the psychomotor stimulants, cocaine and amphetamine, establish a conditioned place preference in rats (Phillips, Broekkamp, & Fibiger, 1983). Similarly PNU-99194A establishes a conditioned place preference in rats over a wide range of doses (Kling-Petersen, Ljung, Wollter, & Svensson, 1995). Other behaviors associated with psychostimulants, such as hyperactivity and grooming behaviors have also been observed in animals injected with PNU-99194A at levels that do not significantly increase dopamine release in the striatum or nucleus accumbens (Waters, et al., 1993). This may be an indication that PNU-99194A may be acting on post-synaptic D_3 receptors, which is also supported by the fact that rats will not self-administer these new D_3 selective antagonists, either (Roberts & Ranaldi, 1995; Waters, et al., 1993).

Drug discrimination assays are useful tools in the characterization of the neuronal mechanisms underlying the in vivo effects of drugs (Callahan & Cunningham,

1993). It is believed that drug induced internal states can become biologically meaningful because they function as interoceptive stimuli which signal the availability of reinforcement (Appel, White, & Holohean, 1982).

It is established that pharmacological agents that increase dopaminergic transmission generally substitute for cocaine in this procedure (Baker, Riddle, Saunders, & Appel, 1993). The D_3 preferring antagonists, (+)-UH232, (+)-AJ76, and (-)-DS121 have also been examined in drug discrimination procedures. (+)-UH232 and (+)-AJ76 do not appear to produce discriminative stimulus effects like those of cocaine (Callahan, Piercey, & Cunningham, 1992). Although (-)-DS121 produces a significant amount of drug-appropriate responding in rats trained to discriminate either cocaine or amphetamine from saline, it does not substitute completely for either drug. However, unlike the aminotetraline derivatives, (-)-DS121 partially attenuated the discriminative stimulus effects of both amphetamine and cocaine (Clark, et al., 1995). In contrast, selective D_3 agonists 7-OH-DPAT and (+)-PD 128907 were recently shown to produce stimulus generalization in rats trained to discriminate cocaine from saline, although at doses that markedly decreased response rate (Acri, et al., 1995).

The purpose of the present study was to examine PNU-99194A in a drug discrimination procedure, since it is currently the most selective D_3 antagonist. In the first experiment rats were trained to discriminate cocaine from saline. Substitution tests with PNU-99194A were administered. In addition PNU-99194A was tested in combination with cocaine to determine whether it would block cocaine discrimination or potentiate the effects of a lower dose of cocaine. In experiment two a separate group of rats were trained to discriminate PNU-99194A, and substitution tests were conducted with cocaine, d-amphetamine, and caffeine.

CHAPTER II

METHOD

Subjects

Sixteen male Sprague-Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN) aged approximately six months at the beginning of the study served as subjects. These animals had previous operant training but were drug naive at the beginning of the experiment. The rats were housed individually in wire mesh cages, in a colony maintained on a 12 hour light/dark cycle (0700 to 1900) and at a relatively constant temperature (20-22°C). Commercial rat feed was provided ad libitum, and water was restricted to amounts received during 20 minute training sessions and an additional 15 minutes per day. Free access to water was given for 24 hours approximately every 14 days.

Apparatus

Training and testing sessions were conducted in eight standard operant chambers (MED Associates Inc., St Albans, VT. ENV-001), housed in sound and light attenuating shells, which provided ventilation and masking noise. A 28 volt house light and dipper (0.1 ml) mounted equidistant between two levers were also contained within the chambers. A Zenith 320-SX programmed with MED-PC instrumentation and software (MED Associates Inc., St Albans, VT, version 2.0) was used to control the experimental events and data collection.

Drugs

Cocaine-hydrochloride (National Institute on Drug Abuse, Rockville, MD), PNU-99194A-hydrochloride (Pharmacia & Upjohn, Kalamazoo, MI). d-amphetamine-sulfate (NIDA), and caffeine-hydrochloride (Pharmacia & Upjohn, Kalamazoo, MI) were used in the two experiments. All drugs were dissolved in sterile physiological saline (0.85%) and given intraperitoneally (i.p.), except PNU-99194A, which was dissolved in sterilized distilled water and administered subcutaneously (s.c.), unless otherwise noted. Cocaine was administered s.c. when used as a testing compound in the PNU-99194A trained animals Doses of each drug were calculated based on the salt.

Behavioral Procedures

Eight rats were trained to discriminate cocaine (10 mg/kg, i.p.) from saline using a two-lever operant task under a fixed ratio 20 (FR20) resetting schedule. The remaining eight rats were trained to discriminate PNU-99194A (10 mg/kg, s.c) from saline using a two-lever operant task under a FR20 resetting schedule. Each of these compounds were given 15 minutes prior to training. Four animals in each group were reinforced with water for responding on the right lever after drug injections and on the left lever after saline injections. Conditions were reversed for the remaining four animals in each group.

Training sessions lasted for 20 minutes and were conducted seven days a week, with approximately every 14th day off. Drug and saline injections were given in random order with the restriction no animal received more than two consecutive drug or two consecutive saline conditions. Training under each condition began on a FR1 schedule. Once responding was stable, the number of consecutive correct responses

required for reinforcement was increased until the final FR20 was reached. Responses on the inappropriate lever reset the response counter. Testing began when each animal obtained at least 85% correct responses before the first reinforcer for at least nine out of ten consecutive sessions.

Substitution Testing

When each subject reached the above criterion, substitution tests began. The animals trained to discriminate cocaine received substitution tests with cocaine (1.25-10 mg/kg), and PNU-99194A (1.25-40 mg/kg, i.p and s.c.). Animals trained to discriminate PNU-99194A received substitution tests with PNU-99194A (1.25-10 mg/kg), cocaine (1.25-10 mg/kg, i.p. and s.c.), d-amphetamine (0.25-2.0 mg/kg), and caffeine (8.0-64 mg/kg). Control tests were also administered with saline.

Antagonist Testing

Antagonist tests were also conducted with the animals trained to discriminate cocaine. For these tests PNU-99194A (5-20 mg/kg) was given in combination with the 10 mg/kg training dose of cocaine. Control tests were administered with saline injections given in combination with cocaine and also two saline injects one for each route of administration. Both injections were administered approximately 15 minutes prior to test sessions with the PNU-99194A (s.c.) injection administered first.

Potentiation Testing

Potentiation tests were conducted with the cocaine trained animals using PNU-99194A (5-20 mg/kg) in combination with 1.25 mg/kg of cocaine. Both drugs were administered approximately 15 minutes prior to test sessions with the PNU-99194A (s.c.) injection administered first.

For substitution tests with the training drugs, all doses were tested twice, once after a drug maintenance sessions and once after a saline maintenance session. For all other tests, each dose was tested once, either after a saline or drug maintenance session. The order of doses tested was counterbalanced among subjects and assigned in a pseudo-random order, so that four animals tested after drug and four tested after saline maintenance sessions in each group.

Data Analysis

Dose response date were presented as the mean percent of total responses made on the drug-appropriate lever during test sessions. Response rate was indicated as the mean number of responses made (on either lever) per second during test sessions. For persent drug-appropriate responding data, results from animals that did not complete at least 20 total responses during test sessions were not included in the statistical analyses. Response rate from these animals were included in the statistical analyses. Drug-appropriate responding above 80% ws considered evidence for sustitution. Antagonism was when drug-appropriate responding was below 20% when given in combination with another drug. Potentiation was defined as drug-appropriate responding over 80% when a lower dose of the training compound was combined with another drug. The results of dose response tests with cocaine and PNU-99194A, were analyzed by a two factor analysis of variance, with dose as one factor and injection route as the other factor. the statistical analyses were performed using the statistical software GraphPad Prism (GraphPad, Inc., San Diego, CA.).

CHAPTER III

RESULTS

All sixteen animals met the discrimination criterion (see Table 1) with a range of 28-105 sessions.

Table 1

Sessions to Criteria

Cocaine

Subject	Number of Sessions
9	47
10	42
11	33
12	38
13	65
14	28
15	71
16	51
Mean:	46.88

PNU-99194A

Subject	Number of Sessions
17	72
18	70
19	59
20	53
21	105
22	59
23	81
24	46
Mean:	68.13

Figure 1 illustrates the cocaine dose response curve and the substitution tests with PNU-99194A. Lower doses of cocaine produced drug-appropriate responding in a dose dependent manner.

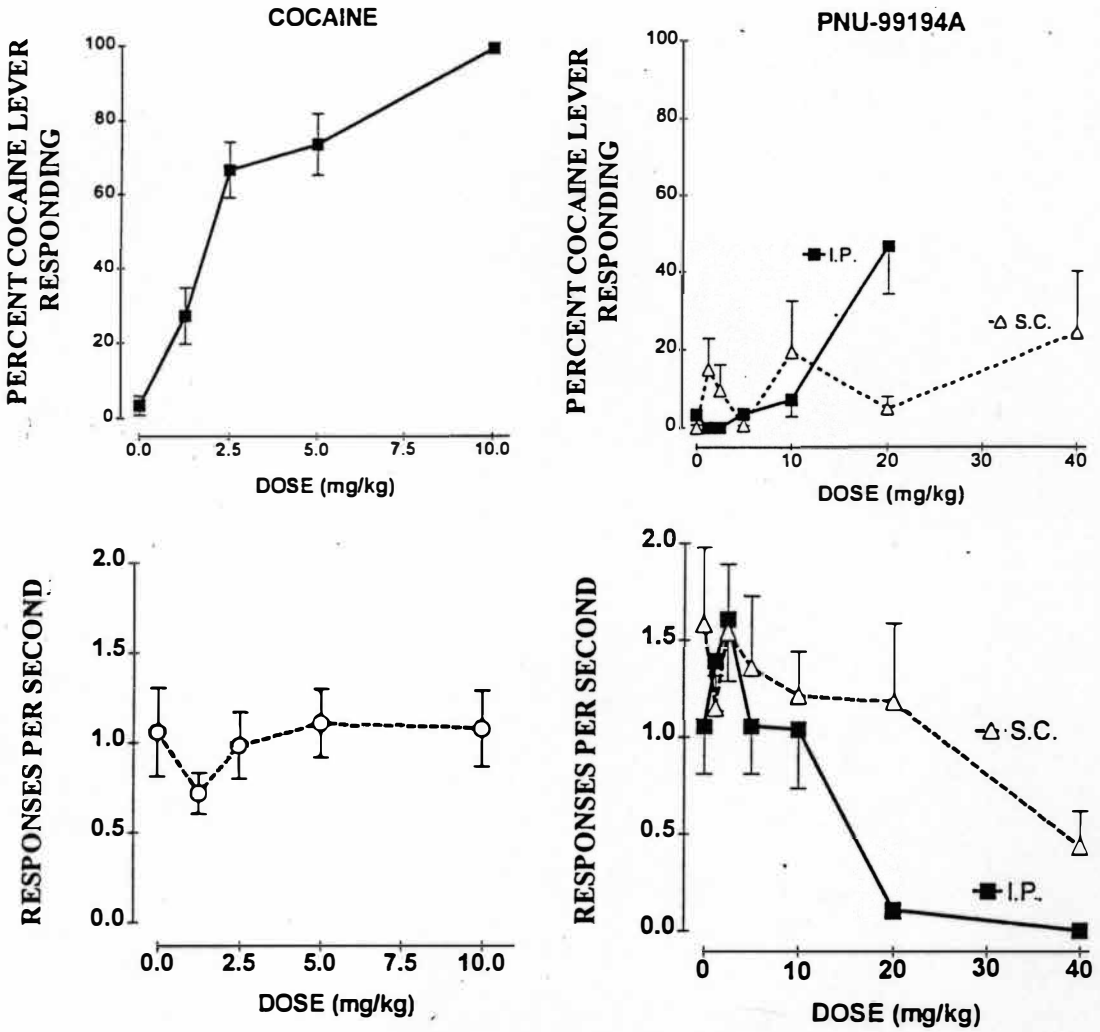


Figure 1. Cocaine Dose Response Curve (Left) and Results of Sustitution Tests With s.c. and i.p. Injections of PNU-99194A (Right) in Animals Trained to Discriminate Cocaine (10 mg/kg) From Saline.

PNU-99194A did not substitute for cocaine at any of the doses tested, even though more cocaine-appropriate responding was seen when the drug was administered i.p. versus s.c. At 40 mg/kg PNU-99194A severely disrupted responding when

administered i.p., and none of the eight animals completed 20 responses on either lever. A two factor (route, dose) ANOVA was conducted on the test results obtained with the doses up to 20 mg/kg. The dose effect on percent drug-lever responding was statistically significant ($F_{5,83}$=4.18 $p < 0.001$). Although the effect of route was not statistically significant, the route x dose interaction was statistically significant ($F_{5,83}$=5.57, $p < 0.0001$). The dose effect on response rate was statistically significant ($F_{6,97}$=5.74, $p<0.0001$). The effect of the route was statistically significant ($F_{1,97}$=4.64, $p<0.034$), however the route x dose interaction was not statistically significant.

The results of tests conducted with PNU-99194A (s.c.) in combination with 10 mg/kg cocaine (i.p.) and in combination with 1.25 mg/kg cocaine are shown in figure 2. The PNU-99194A doses tested (5-20 mg/kg) had virtually no effect on the discrimination of 10 mg/kg cocaine. Higher doses of PNU-99194A were not tested due to severe behavioral disruptions observed in the substitution tests. PNU-99194A also had little effect on drug-appropriate responding when administered in combination with 1.25 mg/kg cocaine.

Figure 3 shows the dose response curve for PNU-99194A. Lower doses of PNU-99194A produced drug-appropriate responding in a dose dependent manner. Figure 3 also illustrates the results of substitution tests with cocaine (0-10 mg/kg) administered both i.p. and s.c. in PNU-99194A trained animals. Slightly more responding occurred with i.p. than with s.c. injections of cocaine, although a two factor (route, dose) ANOVA was not statistically significant. Intraperitoneal injection of cocaine also suppressed response rates to a greater degree relative to control that did s.c. injections, but this also was not statistically significant. The dose effect was the closest to reaching significance ($F_{4,68}$=2.44,$p<0.055$).

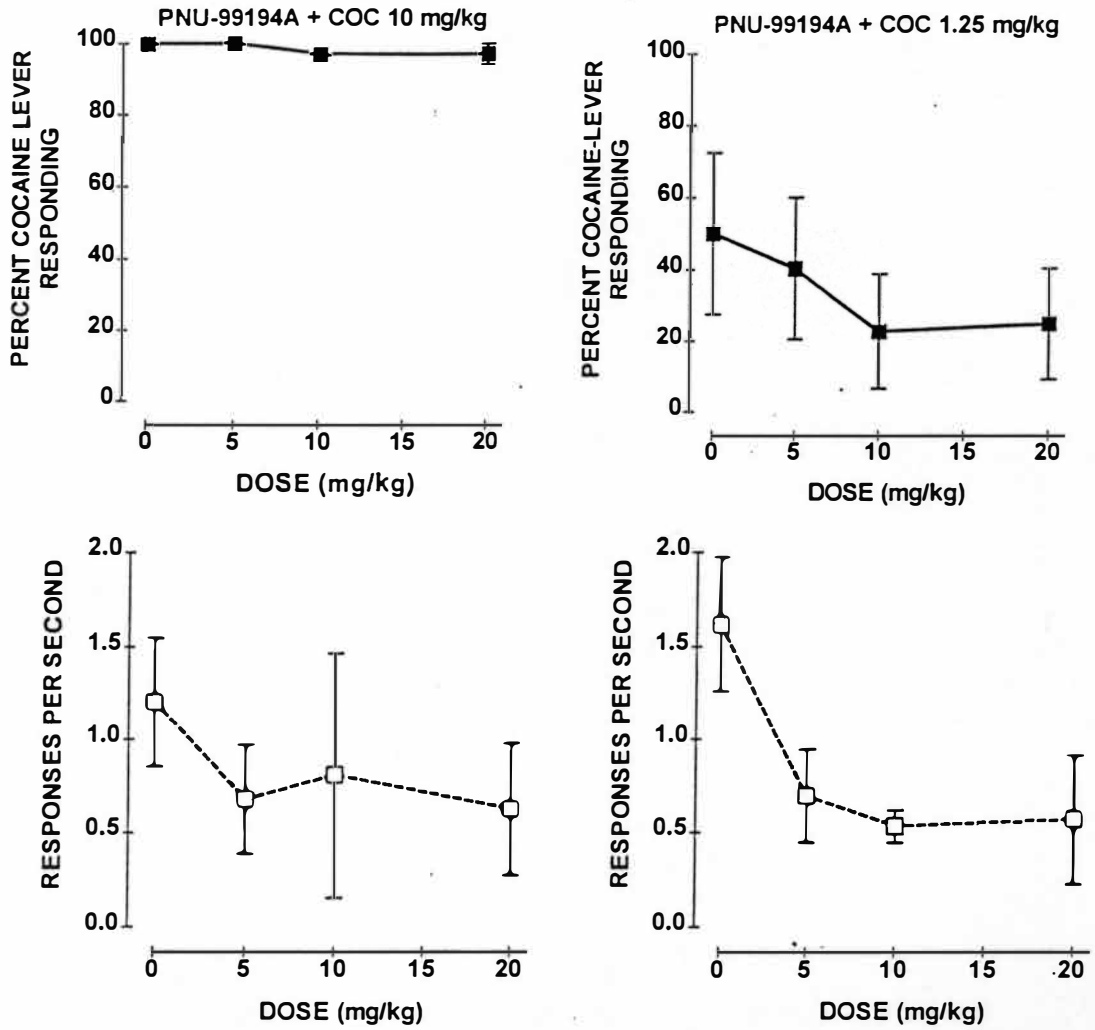


Figure 2. Results of Antagonist Tests (Left) With PNU-99194A (5-20 mg/kg) Given in Combination With Cocaine 10 mg/kg and Potentiation Tests (Left) With PNU-99194A Given in Combination With Cocaine 1.25 mg/kg. Each Data Point Represents a Mean From Eight Animals.

Dose response functions of the substitution tests with d-amphetamine and caffeine for PNU-99194A are illustrated in figure 4. Neither of these drugs produced a significant amount of responding on the PNU-99194A-lever. Response rate was substantially reduced with higher doses of these psychostimulants. A dose of 2 mg/kg

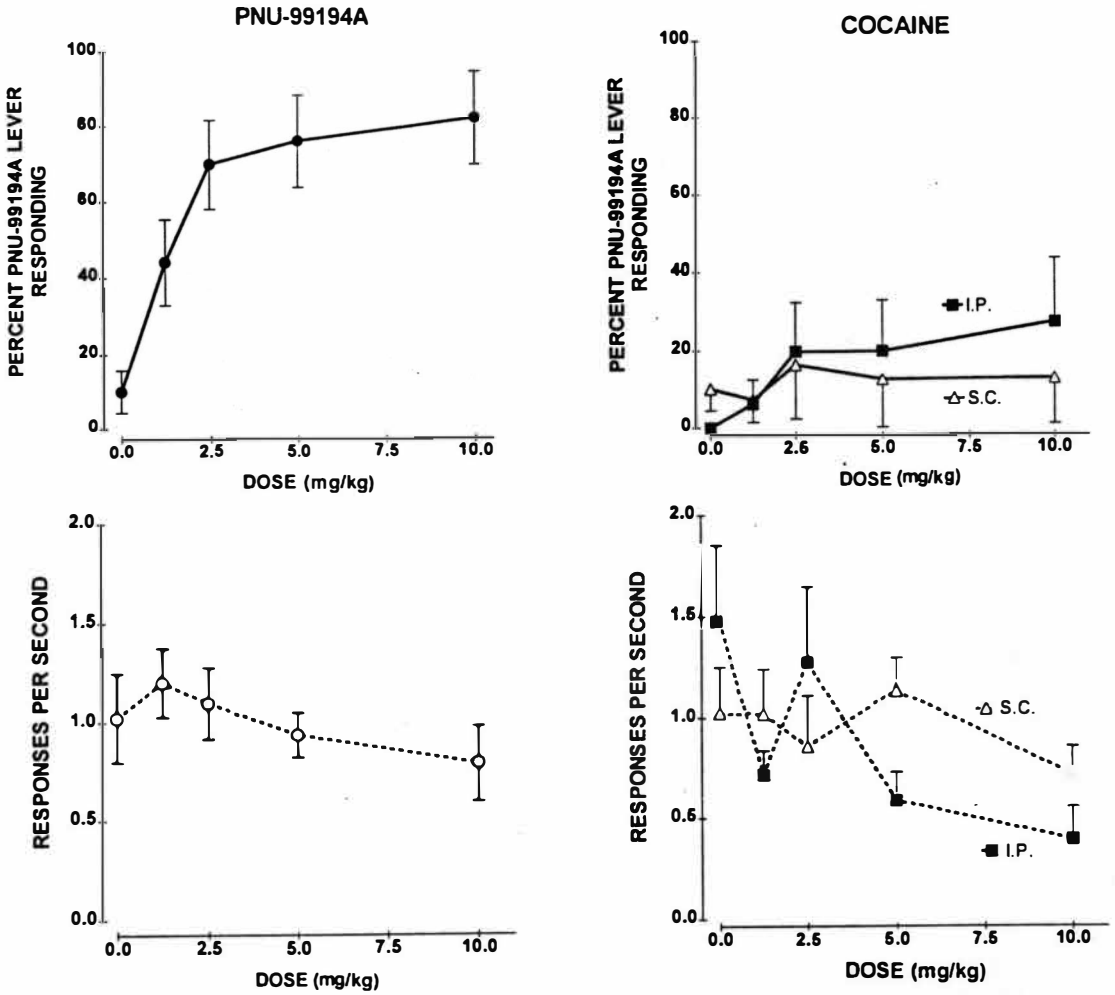


Figure 3. Dose Response Curve for PNU-99194A (Left) and Results of Substitution With s.c. and i.p. Cocaine (Right) in Animals Trained to Discriminate PNU-99194A (10 mg/kg, s.c.) From Saline. Percent Drug-Appropriate Responding is Shown in the Top Half of the Figure.

amphetamine completely suppressed responding in these animals. d-Amphetamine 1.0 mg/kg was tested in three animals trained to discriminate cocaine to confirm that these animals were discriminating a psychostimulant cue. Substitution occurred in all three animals tested (data not shown).

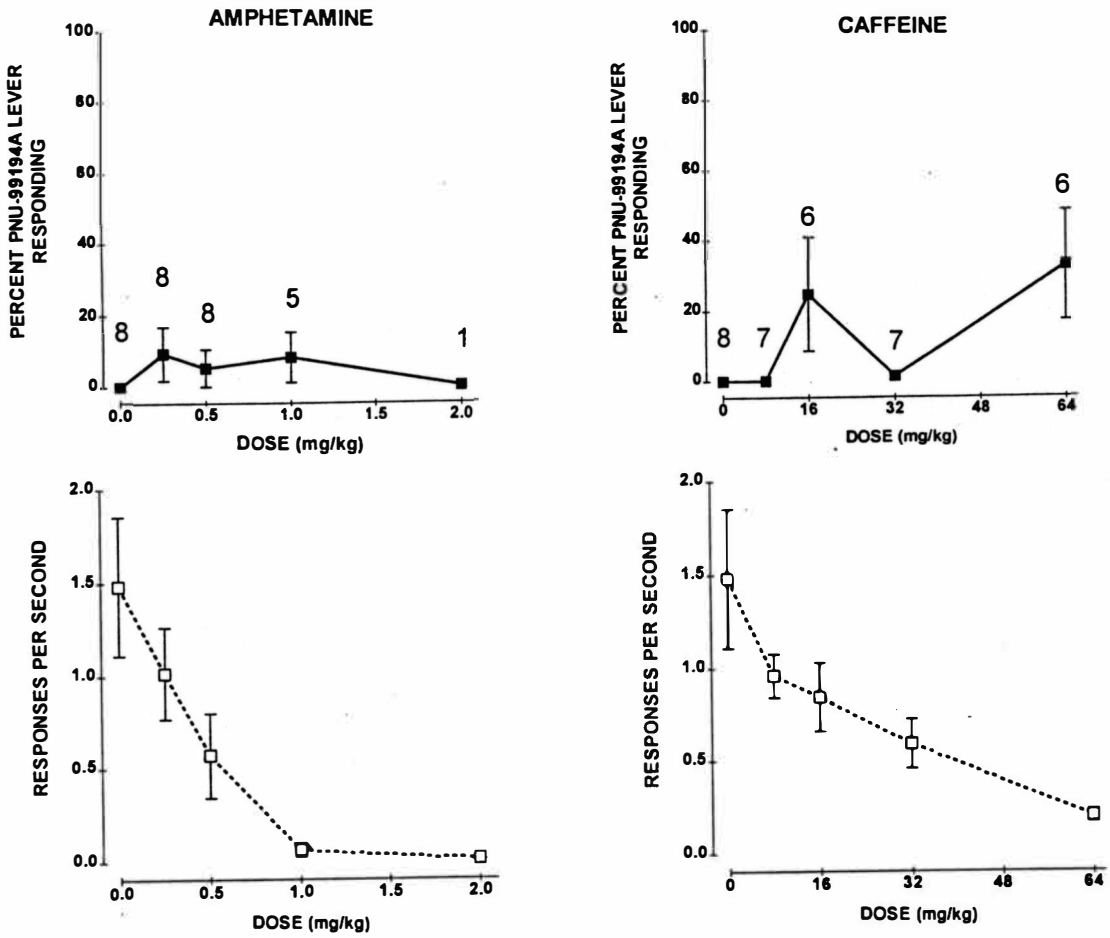


Figure 4. Results of Substitution Tests With d-Amphetamine (Left) and Caffeine (Right) in Animals Trained to Discriminate PNU-99194A From Saline (10 mg/kg, s.c). Percent Drug-Appropriate Responding is Shown in the Top Half and the Response Rate is Shown in the Bottom Half of Each Figure.

CHAPTER IV

DISCUSSION

The purpose of these experiments was to attempt to characterize the discriminative stimulus effects of the D_3-preferring antagonist PNU-99194A. Results of other behavioral assays suggest that the D_3 preferring antagonists produce some similar behavioral effects to psychomotor stimulants, such as locomotor stimulation and establish a conditioned place preference in rats (Waters, et al., 1993; Kling-Petersen, et al., 1995). The present study is the first to demonstrate that PNU-99194A is capable of establishing and maintaining discriminative stimulus control in rats. PNU-99194A was observed to produce hyperlocomotion, and other behaviors associated with psychostimulants as noted by other researchers (Waters, et al., 1993; Kling-Petersen, et al., 1995). However, the data from the substitution tests indicates that the discriminative stimulus effects of this D_3 antagonist are not similar to those of drugs classified as psychomotor stimulants. All three psychostimulants tested failed to generalize and produce any significant PNU-99194A-lever responding.

Since PNU-99194A and cocaine were administered by different routes during training sessions, for the substitution tests both routes were tested with both drugs to eliminate route as a discriminative stimulus during testing procedures. The present results support previous reports that other D_3-preferring antagonists do not produce complete stimulus generalization in rats trained to discriminate cocaine or amphetamine (Callahan, et al., 1992; Clark, et al., 1995). Although less selective D_3 antagonists (+)-UH232 and (+)-AJ76, produce partial substitution for cocaine, PNU-99194A produces discriminative stimulus effects that are uniquely different from known

psychomotor stimulants. It appears that the mechanisms that mediate these psychomotor behaviors are distinct from the mechanisms responsible for the discriminative stimulus properties of D_3 antagonists.

Cocaine discrimination was not blocked by PNU-99194A when administered in combination with the training dose of cocaine. PNU-99194A seemed to have no effect on cocaine-lever responding when administered with a lower dose of cocaine on rats trained on a higher dose, either. This seems to suggest that D_3 receptors may not be critical for cocaine addiction.

Since animals can be trained to discriminate PNU-99194A, the drug discrimination procedure offers a valuable tool to investigate the functional significance of D_3 receptors in the modulation of psychomotor behavior.

Appendix A

IACUC Approval

WESTERN MICHIGAN UNIVERSITY
INVESTIGATOR IACUC CERTIFICATE

Title of Project: Analysis of a novel dopamine D3 antagonist in a drug discrimination procedure.

The information included in this IACUC application is accurate to the best of my knowledge. All personnel listed recognize their responsibility in complying with university policies governing the care and use of animals.

I declare that all experiments involving live animals will be performed under my supervision or that of another qualified scientist. Technicians or students involved have been trained in proper procedures in animal handling, administration of anesthetics, analgesics, and euthanasia to be used in this project.

If this project is funded by an extramural source, I certify that this application accurately reflects all procedures involving laboratory animal subjects described in the proposal to the funding agency noted above.

Any proposed revisions to or variations from the animal care and use data will be promptly forwarded to the IACUC for approval.

_____Disapproved _____✓Approved _____Approved with the provisions listed below

Provisions or Explanations:

Leonard Glennon
IACUC Chairperson

2-5-96
Date

Acceptance of Provisions

Signature: Principal Investigator/Instructor

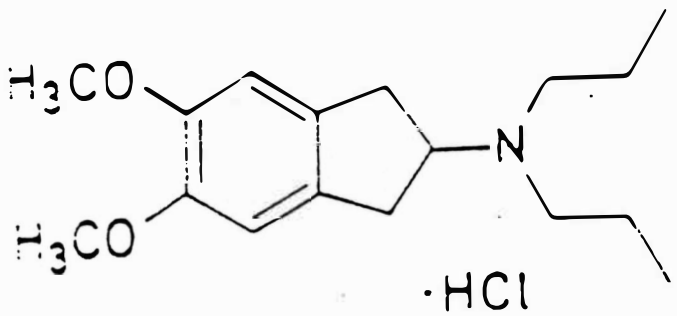
Date

IACUC Chairperson Final Approval

Date

Appendix B

Structure of PNU-99194A



(cis-(+)-1S,R-5-methosy-1-methyl-2-(di-n-propylamino)-tetralin

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