12-1999

Discriminative Stimulus Effects of (+)-7-OH-DPAT in Rats: Importance of D_3 Receptors

April J. Christian

DISCRIMINATIVE STIMULUS EFFECTS OF (+)-7-OH-DPAT IN RATS: IMPORTANCE OF D_3 RECEPTORS

by

April J. Christian

A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Master of Arts
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
December 1999

ACKNOWLEDGMENTS

I would like to begin by acknowledging my advisor, Dr. Lisa Baker for her enthusiasm and support of the research contained in this thesis.

Secondly, I would like to thank the members of my graduate committee, Dr. Al Poling and Dr. Scott Kollins, for taking the time to review my work. Julie Scrivener at The Graduate College also deserves an acknowledgment.

I would also like to thank two undergraduate students, Kristen Beuving and Adam Prus for their time assisting me with the implementation of the research contained in this thesis. A special thanks is extended to Kelly Garner, Amy Goodwin, other colleagues in the Behavioral Neuropharmacology Lab, and Lynn Plew, Animal Facility Manager.

Lastly, I would like to thank my boyfriend, and best friend, Jon, for giving me the strength to complete this manuscript in due time. I thank you for the unselfish love you have given me.

April J. Christian

DISCRIMINATIVE STIMULUS EFFECTS OF (+)-7-OH-DPAT IN RATS: IMPORTANCE OF D_3 RECEPTORS

April J. Christian, M.A.

Western Michigan University, 1999

Despite the reported relatively high binding affinity of 7-OH-DPAT to dopamine D_3 receptors, results of recent investigations with the highly selective D_3 receptor antagonist, PNU-99194A have questioned the importance of D_3 receptors in the discriminative stimulus effects of 7-OH-DPAT. In the present study, sixteen male Sprague-Dawley rats (N=8/group) were trained to discriminate (+)-7-OH-DPAT (0.03 mg/kg, sc) from saline in a two-lever operant procedure using a fixed-ratio 20 schedule of water reinforcement. After stable performance was established, substitution tests were conducted with the D_3-prefering agonist, (+)-PD-128907 and the psychostimulant cocaine. Additionally, antagonism were conducted with the selective D_2 antagonist, remoxipride. Cocaine failed to produce generalization, but (+)-PD-128907 did substitute for the (+)-7-OH-DPAT cue. Remoxipride appeared to partially block (+)-7-OH-DAPT discrimination. Future investigations with highly selective D_3 antagonists are discussed.

TABLE OF CONTENTS

LIST OF FIGURES

INTRODUCTION

Recent investigations of the behavioral pharmacology of addictive psychostimulant drugs have focused on the dopamine (DA) D_3 receptor subtype, (Bevins, Klebaur, & Bardo, 1997; Caine & Koob, 1995; Lamas, Negus, Nader, & Mello, 1996; Spealman, 1996) a subdivision of the D_2 family of dopamine receptors (Civelli et al., 1991; Sibley & Monsma, 1992). This receptor subtype is localized in limbic regions of the brain (Levesque et al., 1992), areas well known to be involved in the reinforcing and discriminative stimulus properties of the psychostimulant drugs. Increased understanding of the role of D_3 receptors in mediating the behavioral effects of psychostimulants may benefit the development of pharmacological treatment interventions for psychostimulant abuse, as well as central nervous system (CNS) diseases. However, investigations on the importance of D_3 receptor mediation of psychostimulant drug actions are limited due to the lack of highly selective D_3 receptor ligands.

Despite the fact that compounds with clear selectivity for D_3 receptors have not become generally available, it has been shown that several dopamine agonists, some of

which had previously been considered highly selective for D_2 receptors, have a relatively high affinity for D_3 receptors (Burris et al., 1995; DeMattos et al., 1993; Levesque et al., 1992; Pugsley et al., 1995). Compounds such as 7-OH-DPAT (7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin) and (+)-PD-128907 have been reported to have as much as a 100-fold greater affinity for D_3 over D_2 receptors based on in vitro binding assays (Burris et al., 1995; DeMattos et al., 1993; Levesque et al., 1992; Pugsley et al., 1995). Therefore, these compounds along with other compounds with moderate selectivity for D_3 receptors, are currently used to analyze D_3 receptor function (Levesque et al., 1992; Pugsley et al., 1995). 7-OH-DPAT and PNU-99194A, a highly selective D_3 receptor antagonist, have been used to investigate the role of D_3 receptors in the reinforcing and discriminative stimulus properties of psychomotor stimulants.

Several investigations have shown either complete or partial generalization to 7-OH-DPAT and other putative D_3 agonists in animals trained to discriminate cocaine (Acri et al., 1995; Lamas et al., 1996; Spealman, 1996) or *d*-amphetamine (Baker, Svensson, Garner, & Goodwin, 1998; Bevins et al., 1996). However, results of recent investigations by Baker et al. (1998) and Garner and Baker

(1999), question the importance of the D_3 receptor mediation of the discriminative stimulus effects of (+)-7-OH-DPAT. Results from these studies revealed that PNU-99194A failed to block the stimulus generalization produced by (+)-7-OH-DPAT in rats trained to discriminate *d*-amphetamine or cocaine.

Results from studies by McElroy (1994), Sanger et al. (1997), and Varty and Higgins (1997) have demonstrated that the racemic form of this compound acquires stimulus control in rats. An investigation by Sautel et al. (1995) gives indirect evidence for the D_3 receptor mediation of the discriminative stimulus effects of 7-OH-DPAT. The potencies of cue substitution by several dopamine agonists were more strongly correlated with D_3 than D_2 in vitro potencies (Sanger, & Depoortere, 1997). A study by Varty and Higgins (1997) supports results of Sanger and Depoortere (1997) with evidence for D_3 receptor mediation of the discriminative stimulus effects of 7-OH-DPAT. Data suggest that the pharmacological profile of the various dopaminergic drugs to generalize to the 7-OH-DPAT cue was most consistent with D_3, rather than D_2 receptor interaction. However, these conclusions are based on the use of D_2 and D_3 agonists, and the racemic form of 7-OH-DPAT. Reports have suggested that the (+)-

enantiomer is the more active (Wikstrom et al., 1985) and exhibits a higher D_3 affinity (Baldessarini et al., 1993; Damsma et al., 1993). Therefore, investigations with the (+)-enantiomer, and D_3 and D_2 antagonists, it may be possible to determine whether D_3 or D_2 receptors modulate (+)-7-OH-DPAT's discriminative stimulus effects.

The establishment of (+)-7-OH-DPAT as the discriminative cue has helped to accelerate assessment of D_3 receptor involvement in the discriminative stimulus properties of psychostimulants (Baker et al., in press). Results from this investigation showed that the discriminative stimulus effects of (+)-7-OH-DPAT were not blocked by the highly selective D_3 antagonist, PNU-99194A. These findings are consistent with Baker et al. (1998) and Garner and Baker (1998). Results from Garner and Baker (1999) indicate that remoxipride, a selective D_2 antagonist, blocks (+)-7-OH-DPAT substitution for cocaine at doses that appear to reverse the response rate suppression. Antagonism tests with highly selective D_3 antagonists, such as PNU-99194A, and D_2 antagonists, such as remoxipride could determine the contribution of D_3 versus D_2 receptor mediation of 7-OH-DPAT's discriminative stimulus effects.

The primary goal of the present study was to assess the antagonism of (+)-7-OH-DPAT by the D_2 antagonist, remoxipride. Baker et al. (in press) investigated the (+)-enantiomer of 7-OH-DPAT as a training cue in drug discrimination. To extend previous findings, the present study assessed D_3 receptor mediation of (+)-7-OH-DPAT discrimination by training animals to discriminate this compound from saline and testing for antagonism with remoxipride. Additionally, stimulus generalization was assessed with a highly selective D_3 agonist, (+)-PD-128907, and with cocaine, a nonselective dopamine agonist.

METHOD

Subjects

Sixteen male Sprague-Dawley rats (Harlan Breeding Laboratories, Indianapolis, IN) aged approximately two months and weighing approximately 225-250g at the beginning of the study served as subjects. The animals had no previous operant training and were drug naïve at the beginning of the present experiment. The rats were housed individually in plastic cages, in a colony maintained on a 12hr light:dark cycle (07:00-19:00hr) and at a relatively constant temperature (19-23°C) and humidity (62-77%). Commercial rat feed was freely available and water was restricted to amounts received during 20 min training sessions and an additional 30 minutes per day. Free access to water was given for 24 hours approximately every seven days. The animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health, and the experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of Western Michigan University (Appendix A).

Apparatus

Training and testing sessions were conducted in eight standard operant chambers (ENV-001; MED Associates Inc., St. Albans, VT), housed in sound and light attenuating shells equipped with fans to provide ventilation and masking noise. Each chamber contained an overhead 28V house light and a liquid reinforcer delivery mechanism (0.1 ml) that was mounted equidistant between two removable levers on the front panel of the chamber. A center removable lever was located between those two levers and used only during the initial auto-shaping sessions. A Zenith 320-SX microcomputer programmed with MED Associates Inc., St. Albans, VT; version 2.0) was used to control experimental events and data collection.

Drugs

(+)Pharmacia & Upjohn generously provided (+)-7-OH-DPAT-hydrobromide, and remoxipride-hydrochloride. (+)-PD-128907-hydrochloride was purchased from Research Biochemicals International (Natick, MA). National Institute on Drug Abuse (Bethesda, MD) provided cocaine-hydrochloride. All drugs were dissolved in bacteriostatic 0.9% saline. All drugs were administered by subcutaneous (sc) injection, except cocaine hydrochloride,

which was administered by intraperitoneal (ip) injection. All doses of each drug were calculated based on the salt.

Errorless Training Procedure

Prior to discrimination training, rats (N = 8/group) were auto-shaped to lever press on the center lever under a schedule of continuous water reinforcement. No injections were given prior to these sessions. Once lever pressing was established, injections of either (+)-7-OH-DPAT (0.03 mg/kg) or saline (0.9% NaCl) were given. Drug or saline was administered subcutaneously 15 minutes prior to daily (Monday-Saturday) sessions. Training began under a fixed-ratio 1 (FR1) schedule of water reinforcement with only the stimulus-appropriate (drug or saline) lever present. Half of the animals were reinforced with water (0.1 ml) for left-lever responses following saline; conditions were reversed for remaining animals. Three sessions were conducted under each condition. During training, neither condition (drug or saline) prevailed for more than two consecutive (20 min) sessions. Levers were wiped with isopropyl alcohol before each session to reduce the influence of olfactory stimuli on lever pressing (Extance & Goudie, 1981).

Discrimination Training Procedure

Discrimination training began on the seventh training session, with both levers present. Injections of either (+)-7-OH-DPAT (0.03 mg/kg) or saline (0.9% NaCl) were given. Drug or saline was administered subcutaneously 15 minutes prior to daily sessions. Half of the animals were reinforced with water (0.1 ml) for left-lever responses following saline; conditions were reversed for remaining animals. Levers were wiped with isopropyl alcohol before each session to reduce the influence of olfactory stimuli on lever pressing (Extance & Goudie, 1981). During training, injections were given in a pseudo-random order and neither condition (drug or saline) prevailed for more than two consecutive (20 min) sessions. The schedule of reinforcement was increased until all animals were responding reliably under a fixed-ratio 20 schedule of water reinforcement (FR 20) for each experimental condition. In addition, the two groups of animals were frequently run in different orders. The criterion for discrimination was a minimum of 80% condition-appropriate lever selection prior to the delivery of the first reinforcer for nine out of ten consecutive training sessions.

Testing Procedure

Tests for antagonism and stimulus generalization tests were given after the aforementioned criteria were met. Test sessions were conducted in a similar manner to training sessions with the exception that no reinforcers were delivered and the animal was removed from the chamber upon completion of 20 consecutive responses on either lever, or when 20 minutes elapsed, whichever occurred first. For tests of antagonism, remoxipride was given 30 minutes prior to the testing session, followed with the respective (+)-7-OH-DPAT dose 15 minutes prior to testing. For each drug tested the order of doses was counterbalanced among subjects, and approximately half the animals received tests after drug maintenance sessions while the other half received tests after saline maintenance sessions. Subjects were administered at least two training sessions between test sessions and were required to maintain the 80% criterion under both training conditions before each test. A dose-response curve was determined with all 16 subjects (0.0, 0.003, 0.01, 0.03, and 0.10 mg/kg). A subgroup of these animals were administered stimulus generalization tests with several doses of (+)-PD-128907 (0.0, 0.01, 0.03, 0.10, and 0.30 mg/kg; n=8) and cocaine (0.0, 1.5, 2.5, 5.0, and 10 mg/kg; n=8).

Another subgroup was administered antagonism tests with remoxipride (3.0 and 10.0 mg/kg; n=8) in combination with each of several doses of (+)-7-OH-DPAT (0.0, 0.01, 0.03, and 0.10 mg/kg).

Data Analysis

Dose response data were presented as the percent of total responses made on the drug-appropriate lever during test sessions. Response rate was presented as the number of responses made (on either lever) per second during test sessions. For each dose tested, the mean and standard error of the mean were calculated for each of these dependent measures. In the event that an animal did not complete at least 15 total responses during a test session, the percentage of drug-lever appropriate responses for that test was not included in the statistical analyses. Drug-lever selection that was 80% or greater was considered evidence for stimulus generalization. Complete antagonism was defined as drug-appropriate responding less than 20%. Drug appropriate responding between 20% and 80% was considered evidence for partial substitution or partial antagonism. Dose response curves were also analyzed using a nonlinear regression, and ED_{50}'s and confidence intervals were calculated. A one-way analysis

of variance (ANOVA) was also conducted on the effects of (+)-7-OH-DPAT (0.0, 0.003, 0.01 and 0.03 mg/kg), (+)-PD-128907 (0.0, 0.01, 0.03,0.10, and 0.30 mg/kg), and cocaine hydrochloride (0.0, 1.5, 2.5, 5.0, and 10.0 mg/kg) on percent and rates of lever pressing. In the event that the dependent variables were significant, a Tukey's post hoc test was employed to determine were the significant differences were. Statistical analyses were conducted using the software GraphPad Prism (Version 2.0; GraphPad, Inc., San Diego, CA).

RESULTS

Acquisition and (+)-7-OH-DPAT Discrimination

All rats acquired the (+)-7-OH-DPAT discrimination. Eight of the 16 rats met the discrimination criterion of at least 80% correct responding prior to the first reinforcer for 10 consecutive sessions, and the remaining eight rats met the criterion in nine out of 10 consecutive sessions. The mean number of sessions to criterion for the sixteen rats was 34 (S.E.M. = 11.75; Range: 22-63; Median = 28).

Figure 1 illustrates the (+)-7-OH-DPAT dose-response curve (n = 16). This compound dose-dependently increased percentage of drug-appropriate responding, with full substitution following 0.03 and 0.10 mg/kg, and partial substitution following 0.01 mg/kg. The ED_{50} was 0.01 mg/kg (95% confidence intervals: 0.008-0.012 mg/kg). The percent drug-appropriate responding following doses of 0.03 and 0.10 mg/kg was significantly different from saline ($F_{3,63} = 61.27$, $p < 0.0001$). This compound also significantly decreased response rate in a dose-dependent manner ($F_{3,63} = 6.27$, $p = 0.0012$). Response rate was signifi-

cantly different from saline following the 0.10 mg/kg dose($p < 0.01$).

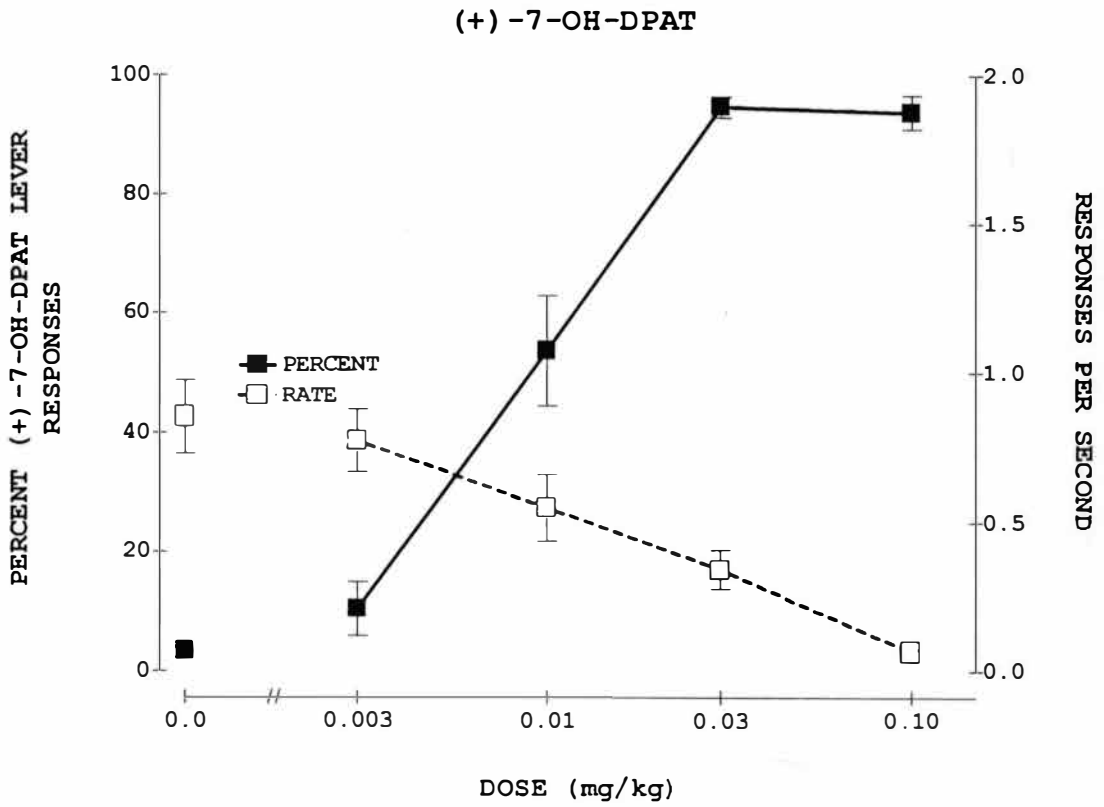

Figure 1. Results of Dose-response Tests With (+)-7-OH-DPAT.

Substitution Tests

(+)-PD-128907, a highly selective D_3 agonist, substituted fully for (+)-7-OH-DPAT at a dose of 0.30 mg/kg, with an ED_{50} of 0.08 mg/kg (95% confidence interval = 0.04-0.14; Figure 2, top; n = 8). Partial generalization of (+)-PD-128907 occurred at a dose of 0.10 mg/kg. There was no substitution at doses of 0.01 and 0.03 mg/kg (+)-PD-128907. A repeated-measures ANOVA showed a significant effect of (+)-PD-128907 on percent drug-lever responding ($F_{4,39} = 24.86$, $p < 0.0001$). Percent drug-lever responding following 0.0 mg/kg was significantly different from that following 0.10 mg/kg ($p < 0.001$) and 0.30 mg/kg ($p < 0.001$). Response rate was also significantly decreased by (+)-PD-128907 in a dose-dependent manner ($F_{4,39} = 6.022$, $p = 0.0013$). However, only the dose of 0.30 mg/kg produced a significant difference from saline ($p < 0.05$).

The bottom of Figure 2 illustrates the results of tests administered with cocaine (n=8). There was partial generalization at doses of 1.5 and 10.0 mg/kg. The effect of cocaine on percent drug-lever responding was not statistically significant. Response rate was decreased

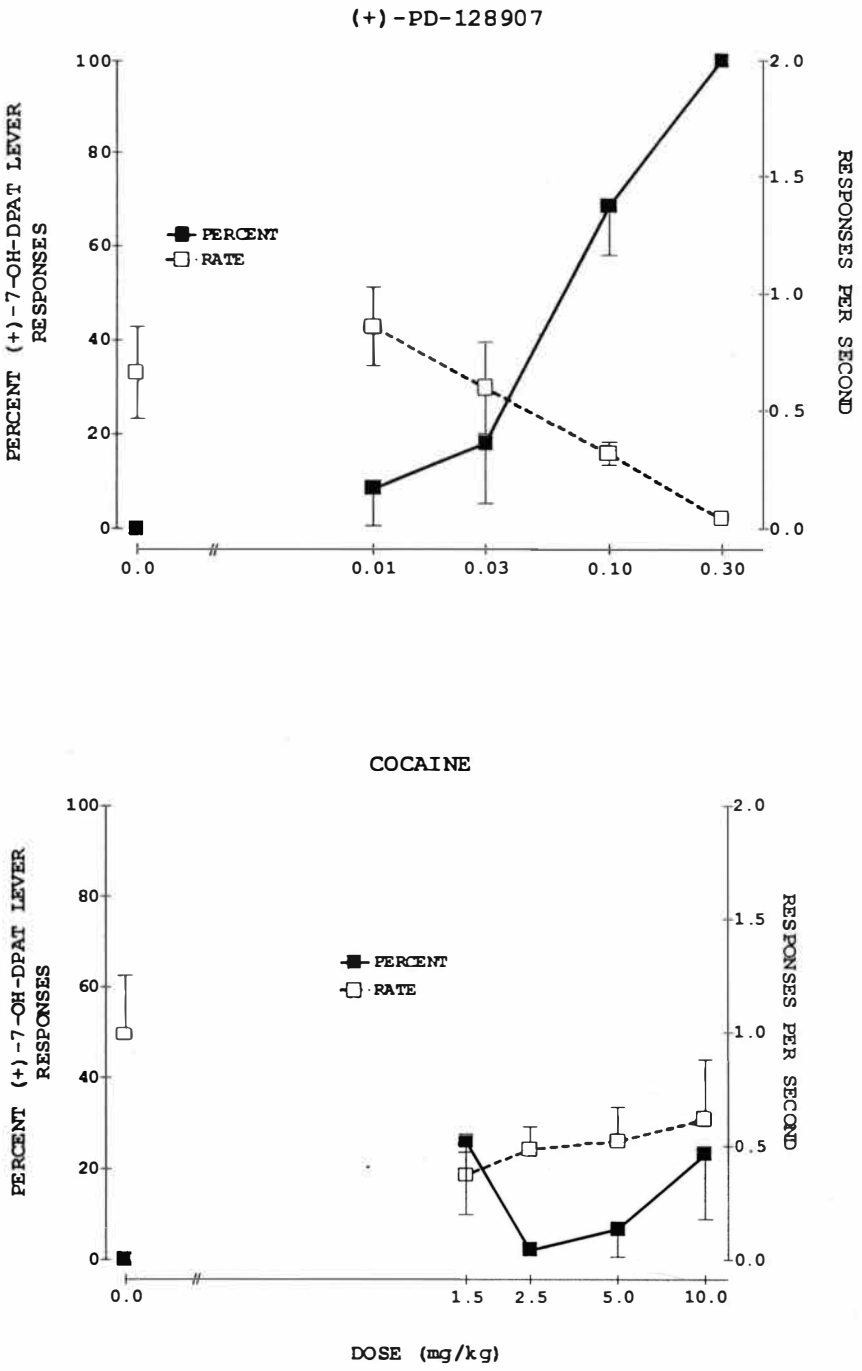

Figure 2. Results of Substitution Tests With (+)-PD-128907 and Cocaine Hydrochloride.

by cocaine, but this effect was not statistically significant.

Antagonism Tests

Figure 3 illustrates the results of tests administered with remoxipride (0.0, 3.0, and 10.0 mg/kg) in combination with (+)-7-OH-DPAT (0.0, 0.01, 0.03, and 0.10 mg/kg; n=8). Pretreatment with this selective D_2 antagonist shifted the (+)-7-OH-DPAT dose-response curve to the right, showing partial antagonism of (+)-7-OH-DPAT discrimination. The ED_{50} of (+)-7-OH-DPAT alone was 0.01 mg/kg (95% confidence intervals = 0.01-0.05 mg/kg). When administered in combination with 3.0 mg/kg remoxipride, the ED_{50} of (+)-7-OH-DPAT was 0.03 mg/kg (95% confidence intervals = 0.01-0.24 mg/kg). Following 10.0 mg/kg remoxipride, the ED_{50} of (+)-7-OH-DPAT was 0.06 (95% confidence intervals = 0.01-0.12 mg/kg). The training dose of (+)-7-OH-DPAT was not completely blocked by either dose of remoxipride. As stated above, (+)-7-OH-DPAT dose-dependently decreased response rate. Remoxipride appeared to attenuate the response rate reduction produced by 0.10 mg/kg (+)-7-OH-DPAT, but this effect was not statistically significant.

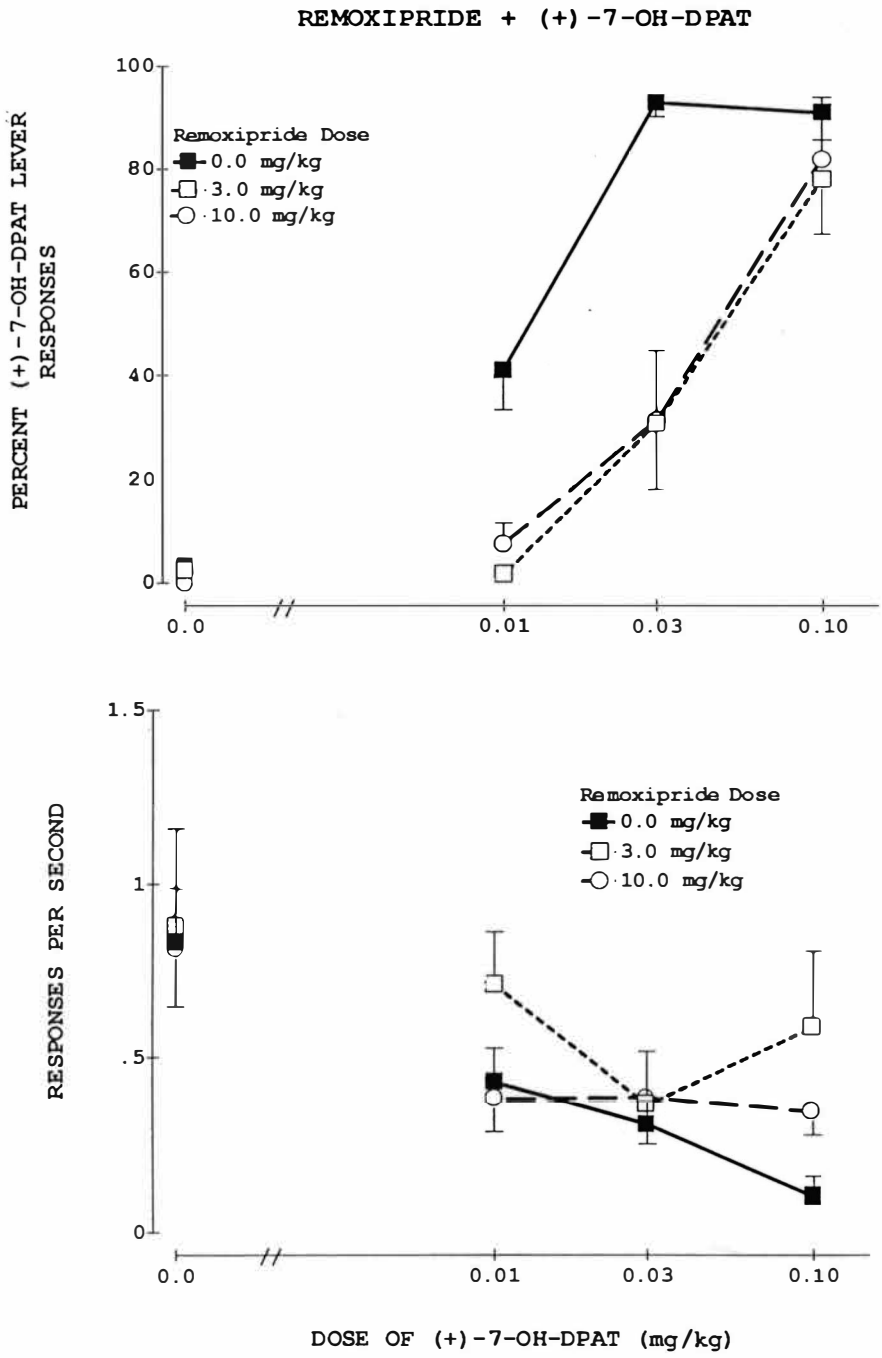

Figure 3. Results of Combination (Antagonism) Tests With DA D_2 Receptor Antagonist Remoxipride Co-administered With (+)-7-OH-DPAT.

DISCUSSION

The results of the present study support previous findings that 7-OH-DPAT or the (+)-isomer of this compound readily establishes stimulus control in rats (Baker et al., in press; McElroy, 1994; Sanger & Depoortere, 1997; Varty & Higgins, 1997). Previous studies have indicated a potential modulatory role of the D_3 receptor subtype in the stimulus effects of 7-OH-DPAT (Bevins et al., 1997; Sanger & Depoortere, 1997; Varty & Higgins, 1997). Bevins et al. (1997) reported a rightward shift in the 7-OH-DPAT dose-response curve with eticlopride pre-treatment (0.01, 0.05 mg/kg). However, because eticlopride is a D_2/D_3 antagonist, these results did not clearly distinguish the relative importance of D_3 versus D_2 receptors in the substitution of 7-OH-DPAT for *d*-amphetamine. Moreover, recent results from our laboratory have indicated that the discriminative stimulus effects of (+)-7-OH-DPAT may be mediated by D_2 receptors. For example, the highly selective D_2 agonist, PNU-91356A, produces complete generalization in animals trained to discriminate (+)-7-OH-DPAT (Baker et al., in press). Results of the present study demonstrated complete stimulus

generalization with a D_3-preferring agonist, (+)-PD-128907. Given these results, the question still remains regarding the importance of D_2 versus D_3 receptor mediation of the discriminative stimulus effects of (+)-7-OH-DPAT.

The determination of the relative importance of D_3 receptors in mediating the discriminative stimulus effects of (+)-7-OH-DPAT requires tests with highly selective D_3 and D_2 antagonists in combination with the training stimulus. Recently such compounds have become available. The present study documents that the discriminative cue associated with (+)-7-OH-DPAT (0.03 mg/kg) is only partially blocked by the highly selective D_2 antagonist, remoxipride. The rightward shift in the dose-response curve (Figure 3) suggests partial attenuation of the (+)-7-OH-DPAT discriminative stimulus cue. Specifically, the ED_{50} of (+)-7-OH-DPAT shifted from 0.01 mg/kg to 0.03 mg/kg when administered in combination with remoxipride. However, the 95% confidence intervals of each ED_{50} value overlapped. Moreover, discrimination of the training dose was only partially attenuated by either dose of remoxipride. These data support preliminary results of Baker et al. (in press) that reported partial

blockade of the (+)-7-OH-DPAT cue by remoxipride 3.0 mg/kg.

Preliminary data from our laboratory also indicate only partial antagonism of the (+)-7-OH-DPAT (0.03 mg/kg) cue by PNU-99194A (10.0 mg/kg). These data are consistent with previous results from Baker et al. (in press) that PNU-99194A does not block the discriminative stimulus effects of (+)-7-OH-DPAT. These results are also consistent with results that PNU-99194A does not block stimulus generalization produced by (+)-7-OH-DPAT in rats trained to discriminate *d*-amphetamine or cocaine (Baker et al., 1998; Garner & Baker, 1999). Thus, it appears that D_3 receptors are not selectively involved in the discriminative stimulus effects of (+)-7-OH-DPAT.

While the importance of D3 versus D2 receptor mediation of the (+)-7-OH-DPAT cue remains unclear, it is at least clear that the discrimination of this compound is not based on a general dopamine cue, because cocaine, a dopamine re-uptake inhibitor, failed to produce generalization. None of the doses tested (1.5 - 10.0 mg/kg) produced more than 30% drug-appropriate responding.

In summary, recent research using moderately selective D_3 receptor ligands have led to tentative conclusions regarding the involvement of this receptor subtype

in the behavioral actions of psychostimulant drugs. Clinical implications of this research are considerably important. Pharmacological and behavioral research of the D_3 receptor subtype may strongly impact the development of more effective treatments for CNS diseases, such as Parkinson's Disease, schizophrenia, and psychostimulant addiction. Results of recent studies, using 7-OH-DPAT and similar compounds should be considered diligently until more selective ligands become readily available for investigation. The drug discrimination assay is a usual tool for determining involvement of receptor subtypes underlying the discriminative stimulus effects of various compounds. Using this procedure, the present study demonstrated that the (+)-7-OH-DPAT cue appears to be specific, and may or may not be mediated selectively by a D_2 or D_3-mediated cue. Further investigations are needed to determine the relative importance of D_3 receptor mediation of (+)-7-OH-DPAT's discriminative stimulus effects. Experiments involving pre-treatment with the combination of D_2 and D_3 selective antagonists are planned. The results of these experiments could accelerate our knowledge of the importance of D_2 and D_3 receptor mediation of (+)-7-OH-DPAT discrimination.

Appendix A

Protocol Clearance From the Institutional Animal Care and Use Committee (IACUC)

WESTERN MICHIGAN UNIVERSITY
INVESTIGATOR IACUC CERTIFICATE

Title of Project D3 dopamine receptors in psychostimulant discrimination

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
See attached e-mail amendments

IACUC Chairperson

12-4-96
Date

Acceptance of Provisions

Signature: Principal Investigator/Instructor

12-1-96
Date

IACUC Chairperson Final Approval

12-5-96
Date

BIBLIOGRAPHY

Acri, J. B., Carter, S., Geter-Douglass, B., Dijkstra, D., Wikstrom, H., Katz, J. & Witkin, J. (1995). Assessment of cocaine-like discriminative stimulus effects of dopamine D3 receptor ligands. European Journal of Pharmacology, 281, R7-R9.

Baker, L. E., Hood, C. A., & Heidema, A. M. (in press). Assessment of D3 versus D2 receptor mediation of the discriminative stimulus effects of (+)-7-OH-DPAT in rats. Behavioural Pharmacology.

Baker, L. E., Miller, M. E., & Svensson, K. A. (1997). Assessment of discriminative stimulus effects of the D3 dopamine antagonist PNU-99194A in rats: Comparison with psychomotor stimulants. Behavioural Pharmacology, 8, 243-252.

Baker, L. E., Svensson, K. A., Garner, K. J., & Goodwin, A. K. (1998). The dopamine D3 receptor antagonist PNU-99194A fails to block (+)-7-OH-DPAT substitution for d-amphetamine or cocaine. European Journal of Pharmacology, 358, 101-109.

Baldessarini, R. J., Kula, N. S., McGrath, C. R., Bakthavachalam, J. W., Kebabian, J. W. & Neumeyer, J. L. (1993). Isomeric selectivity at dopamine D3 receptors. European Journal of Pharmacology, 239, 269.

Bevins, R. A., Klebaur, J. E., & Bardo, M. T. (1997). 7-OH-DPAT has d-amphetamine-like discriminative stimulus properties. Pharmacology, Biochemistry & Behavior, 38(2), 485-490.

Burris, K. D., Pacheco, M. A., Filtz, T. M., Kung, M-P, Kung, H. F., & Molinoff P. B. (1995). Lack of discrimination by agonists for D2 and D3 receptors. Neuropsychopharmacology, 12, 335-345.

Caine, S. B., & Koob, G. F. (1995). Pretreatment with the dopamine agonist 7-OH-DPAT shifts the cocaine self-administration dose-effect function to the left under different schedules in the rat. Behavioural Pharmacology, 6, 333-347.

Callahan, P. M., & Cunningham, K. A. (1993). Discriminative stimulus properties of cocaine in relation to dopamine D2 receptor function in rats. The Journal of Pharmacology and Experimental Therapeutics, 266(2), 585-592.

Civelli, O., Bunzow, J. R., Grandy, D. K., Zhou, Q-Y, Van Tol, H. M. (1991). Molecular biology of the dopamine receptor. European Journal of Pharmacology, 207, 277-286.

Damsma, G., Bottema, T., Westerink, B. C., Tepper, P. G., Dijkstra, D., Pugsley, T. A., MacKenzie, R. G., Heffner, T. G., & Wilkstrom, H. (1993). Pharmacological aspects of R-(+)-7-OH-DPAT, a putative dopamine D3 ligand. European Journal of Pharmacology, 249, R9.

DeMattos, S. B., Pugsley, T. A., Shih Y. S., Whetzel, S. Z., Georgie, L. M., VanLeeuwen, D. H., MacKenzie, R. G., Smith, S. J., Glase, S. A., Wise, L. D., & Heffner, T. G. (1993). Identification and characterization of a dopamine D3 selective compound, PD 128907. Society for Neuroscience Abstracts,19, 77.

Extance, K., & Goudie, A. J. (1981). Inter-animal olfactory cues in operant drug discrimination procedures in rats. Psychopharmacology, 91, 67-73.

Garner, K. J. & Baker, L.E. (1999). Analysis of D2 and D3 receptor-selective ligands in rats trained to discriminate cocaine from saline. Pharmacology, Biochemistry & Behavior, 64(2), 373-378.

Lamas, X., Negus, S. S., Nader, M. A., & Mello, N. K. (1996). Effects of the putative dopamine D3 receptor agonist 7-OH-DPAT in rhesus monkeys trained to discriminate cocaine from saline. Psychopharmacology, 124, 306-314.

Levant, B. (1997). The D3 dopamine receptor: Neurobiology and potential clinical relevance, Pharmacological Reviews, 49 (3), 231-252.

Levesque, D., Diaz, J., Pilon, C., Martres, M., Giros, B., Souil, E., Schott, D., Morgat, J., Schwartz, J. & Sokoloff, P. (1992). Identification, characterization and localization of the dopamine D3 receptor in the rat brain using 7-[3H]-hydroxy-N,N-di-n-propyl-2-

aminotetralin. Proceedings of national academy of science, 89, 8155-8159.

McElroy, J. F. (1994). Discriminative stimulus properties of 7-OH-DPAT, a dopamine D3-selective receptor ligand. Pharmacology Biochemistry and Behavior, 48, 531-533.

Pugsley, T. A., Davis, M. D., Akunne, H. C., MacKenzie, R. G., Shih Y. H., Damsma, G., Wikstrom, H., Whetzel, S. Z., Georgie, L. M., Cooke, L. W., DeMattos, S. B., Corbin, A. E., Glase, S. A., Wise, L. D., Dijkstra, D., & Heffner, T. G. (1995). Neurochemical and functional characterization of the preferentially selective D3 agonist PD 128907. The Journal of Pharmacology and Experimental Therapeutics, 275, 1355-1366.

Sanger, D. J., & Depoortere, R. (1997). Discriminative stimulus effects of apormorphine and 7-OH-DPAT: A potential role for dopamine D3 receptors. Psychopharmacology, 130, 387-395.

Sautel, F., Griffon, N., Levesque, D., Pilon, C., Schwartz, J/ C., & Sokoloff, P. (1995). A functional test identifies dopamine agonist selective for D3 versus D2 receptors. Neuroreport, 6, 329-332.

Sibley, D. R. & Monsma, J. R. (1992). Molecular biology of dopamine receptors. Trends in Pharmacological Sciences, 13, 61-69.

Sokoloff, P., Giros, B., Martres, M.P., Bouthenet, M.L., & Schwartz, J. C. (1990). Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature, 347, 146-151.

Spealman, R. D. (1996). Dopamine D3 receptor agonists partially reproduce the discriminative effects of cocaine in squirrel monkeys. The Journal of Pharmacology and Experimental Therapeutics, 278, 1128-1137.

Varty, G. B., & Higgins, G. A. (1997). Investigation into the nature of a 7-OH-DPAT discriminative cue: Comparison with d-amphetamine. European Journal of Pharmacology, 339, 101-107.

Wilkstrom, H., Andersson, B., Sanchez, D., Lindberg, P., Arvidssonl, L. E., Johansson, A. M., Nilsson, J. G.,

Svensson, K., Hjorth, S., & Carlsson, A. (1985) Resolved monophenolic 2-aminotetralins and 1,2,3,4,4*a*,5,6,10*b*-octahydrobenzol[*f*]quinolines: Structural and stereochemical considerations for centrally acting pre- and post-synaptic dopamine-receptor agonists. Journal of Medicinal Chemistry, 28, 215.