*Pharmacology Biochemistry and Behavior*, Vol. 44, pp. 907–911, 1993
Printed in the U.S.A. 

0091-3057/93 $6.00 + .00


# Discriminative Stimulus Properties of Cocaine in the Rat Using a Two-Choice Discrete-Trial Avoidance Paradigm

MAKOTO UKAI,[1] EIJI MORI AND TSUTOMU KAMEYAMA

*Department of Chemical Pharmacology, Faculty of Pharmaceutical Sciences, Meijo University, Nagoya 468, Japan*

Received 15 June 1992

UKAI, M., E. MORI AND T. KAMEYAMA. *Discriminative stimulus properties of cocaine in the rat using a two-choice discrete-trial avoidance paradigm.* PHARMACOL BIOCHEM BEHAV 44(4) 907–911, 1993.—The discriminative stimulus effects of cocaine were studied in rats trained to discriminate 10.0 mg/kg cocaine from vehicle in a shock avoidance paradigm. Rats used could discriminate 10.0 mg/kg cocaine from vehicle within an average of 20 sessions after the start of discrimination training. Cocaine produced dose-dependent stimulus effects at 1.0- to 10.0-mg/kg doses. Cocaine (10.0 mg/kg) generalized to the dopamine reuptake inhibitor 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine 2HCl (GBR 12909) (30.0 mg/kg), methamphetamine (0.3 mg/kg), apomorphine (0.3 mg/kg), and the $D_2$ dopamine agonist quinpirole (0.1 mg/kg), but not to the $D_1$ dopamine agonist SK&F38393 (3.0–30.0 mg/kg). 1-Phenyl-2,3,4,5-tetrahydro-[$^1$H]-3-benzazepine-7,8-diol HCl (SK&F38393) (10.0 mg/kg) combined with several doses (1.0–10.0 mg/kg) of cocaine shifted the stimulus generalization curve for cocaine to the left. Haloperidol (0.1 and 0.3 mg/kg), the $D_1$ dopamine antagonist 7-chloro-2,3,4,5-tetrahydro-3-methyl-phenyl-1-*H*-benzazepine-7-*ol* maleate (SCH23390) (0.01–0.3mg/kg), and the $D_2$ dopamine antagonist *S*(-)-sulpiride (20.0 and 40.0 mg/kg) only partially blocked the stimulus effects of cocaine. Haloperidol (0.3 mg/kg) combined with SCH23390 (0.03 mg/kg) completely blocked the stimulus effects of cocaine. In addition, haloperidol (0.3 mg/kg) blocked the stimulus effects of quinpirole (0.1 mg/kg), in common with cocaine. These data suggest that both $D_1$ and $D_2$ dopamine receptors contribute to the discriminative stimulus effects of cocaine.

Cocaine Dopamine receptors Discriminative stimulus effects Rat

COCAINE is a psychomotor stimulant that has prominent amphetamine-like subjective effects, resulting in its abuse (8). Although cocaine blocks the neuronal uptake of monoamine neurotransmitters including dopamine, norepinephrine, and serotonin (12,20), most of the behavioral effects of cocaine as well as other psychomotor stimulants have been attributed to enhanced activity of dopamine neurons in the CNS (2,17,21).

Drug discrimination procedure has been well established to clarify subjective effects of drugs (7). Cocaine reportedly produces stimulus effects in common with the dopamine releaser amphetamine and the dopamine reuptake inhibitor 1-[2-[bis(4-fluorophenyl)methoxy]ethyl]-4-(3-phenylpropyl)piperazine 2HCl (GBR 12909) (3,4,6,11,14,25). Further, it is evident that tolerance to the stimulus effects of cocaine develops after repeated administration of apomorphine in rats (26). Although dopaminergic mechanisms are thought to underlie the discriminative stimulus effects of cocaine, the involvement of receptor subtypes (e.g., $D_1$, $D_2$, and $D_3$) in the effects seems to be inconclusive. For instance, the $D_1$ dopamine agonist 1-phenyl-2,3,4,5-tetrahydro-[$^1$H]-3-benzazepine-7,8-diol HCl (SK&F38393) sometimes has been found to partially substitute for cocaine in rats (1,3,25), whereas the $D_1$ dopamine antagonist 7-chloro-2,3,4,5-tetrahydro-3-methyl-phenyl-1-*H*-benzazepine-7-*ol* maleate (SCH23390) blocks the cue (1,11). The $D_2$ dopamine agonist quinpirole has little cocaine-like activity in rhesus monkeys (11) and only partially substitutes for cocaine in squirrel monkeys (21), although it often has been found to fully substitute for cocaine in rats (1,3). Quinpirole is often used as the $D_2$ dopamine agonist, but it is reportedly more selective for $D_3$ than $D_2$ dopamine receptors (16). Because neither haloperidol nor spiperone fully inhibits the stimulus effects of cocaine (1,13), the stimulus effects of cocaine may be mediated through $D_3$ dopamine receptors.

The present study was designed to further characterize the discriminative stimulus effects of cocaine with special reference to dopamine neurons using a two-choice discrete-trial avoidance paradigm, unlike food reinforcements reported previously (1,3,13,25). In addition, a shock-avoidance paradigm

[1] To whom requests for reprints should be addressed.

seems more appropriate for the discriminative stimulus effects of cocaine-like drugs than food reinforcements because cocaine and amphetamine reduce food intake, leading to the changes in motivation of animals (8).

## METHOD

### *Animals*

Subjects were male Fischer-derived rats (Nihon Charles River Co. Ltd., Atsugi, Kanagawa, Japan) weighing 210–230 g at the start of discrimination training. Rats were housed in a ventilated colony room where they had continuous access to food and water. The lights in the room were illuminated between 8:00 a.m. and 8:00 p.m.

### *Drugs*

The following drugs were used: cocaine HCl (Shionogi Co., Ltd., Osaka, Japan); methamphetamine HCl and haloperidol (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan); apomorphine HCl (Sigma Chemical Co., St. Louis, MO); *S*(-)-sulpiride, SK&F38393, and GBR 12909 (Research Biochemicals Inc., Natick, MA); quinpirole HCl (Eli Lilly and Co., Indianapolis, IN); and SCH23390 (Schering Corp., Bloomfield, NJ). Doses of cocaine, haloperidol, and *S*(-)-sulpiride were expressed in terms of the free base. The others were expressed in terms of the salt. SK&F38393, SCH23390, and *S*(-)-sulpiride were dissolved in 8.5% lactic acid and 1.0 N sodium hydroxide in 3 : 2 ratio. GBR 12909 was dissolved in sterile water and the others in 0.9% saline. Cocaine, GBR 12909, *S*(-)-sulpiride, SCH23390, and haloperidol were given IP and the others SC. The dopamine antagonists and the others were given 60 and 30 min before the session, respectively. All injections were made in a volume of 1.0 ml/kg body weight.

### *Apparatus*

The apparatus (25 × 35 × 32 cm) has been described in detail elsewhere (23,24). Briefly, it has one "starting" lever on one wall and two "choice" response levers on the wall opposite to the starting lever. The choice response levers were separated by a clear Plexiglas partition, 5.0 cm wide, that extended from the ceiling of the test chamber to 1.0 cm above the grid floor (Neuroscience Inc., Tokyo, Japan). A constant-current shock generator (SGC-001, Muromachi Kikai Co., Ltd., Tokyo, Japan) delivered a scrambled electric shock to the grid floor of the chamber, which was housed within a ventilated, lightproof, and sound-attenuating enclosure. Personal computers (PC-9801, UV2, NEC Corporation, Tokyo, Japan) were used to control the schedule contingencies.

### *Procedures*

*Discrimination training.* Rats were trained to discriminate 10.0 mg/kg cocaine from vehicle in a two-choice discrete-trial avoidance paradigm. The onset of a trial was signalled by the simultaneous illumination of the house light and the presentation of white noise. At this time, the rat was required to press the starting lever mounted on one wall of the test chamber and then to press one of the two choice levers mounted on the opposite wall. The first starting response of the trial terminated the white noise and the appropriate choice response extinguished the house light and ended the trial. Beginning 5.0 s after the onset of the trial, a 1.5- to 3.0-mA shock was delivered to the grid floor of the chamber every 3.0 s in a 0.5- to 1.0-s pulse until the two-response chain was completed. The intertrial interval was 50 s, during which time the chamber was dimly illuminated by a red light. Experimental sessions ended after 21 trials or 30 min, whichever came first. The first trial of each session was considered a "warm-up" and was excluded from the data analysis. Training sessions were conducted 6 days/week. Either cocaine (10.0 mg/kg) or its vehicle was injected IP 30 min before each training session. Training continued until rats could reliably complete at least 18 of 20 trials (i.e., 90% exclusive of the first trial) on the appropriate choice lever under both conditions.

*Discrimination testing.* Drug test sessions were conducted provided rats satisfied the performance criterion in two consecutive training sessions. During test sessions, both choice levers were activated so that a response on either choice lever after the starting response terminated the trial. Test sessions and training sessions were identical in all other aspects except for combination test with SK&F38393 plus cocaine. When SK&F38393 and cocaine were concomitantly administered, a cumulative dosing procedure was employed. On the test day, rats were injected with SK&F38393 (10.0 mg/kg) and cocaine (1.0 mg/kg) and placed in the chamber 10 min later to start the first test session. After completion of the 30-min test session, rats were removed to their home cage and injected with cocaine before the start of the next test session 10 min later. Test sessions were conducted in this manner with increasing doses of cocaine until rats completed at least 18 of 20 trials on the cocaine-appropriate lever.

### *Data Analysis*

The data were analyzed in terms of the number of trials completed on the cocaine-appropriate lever. Trials completed on the vehicle-appropriate lever were recorded but are not shown in the figures. All animals used completed all trials of every session. A dose of test drug was considered to produce discriminative stimulus effects comparable to those produced by the training dose (10.0 mg/kg) of cocaine if a rat completed at least 18 of 20 trials on the cocaine-appropriate lever. A dose of test drug was considered to antagonize stimulus effects comparable to those produced by the training dose (10.0 mg/kg) of cocaine if a rat completed at least 18 of 20 trials on the vehicle-appropriate lever. The dose-response curves for the effects of cocaine (1.0–10.0 mg/kg) alone and its combination

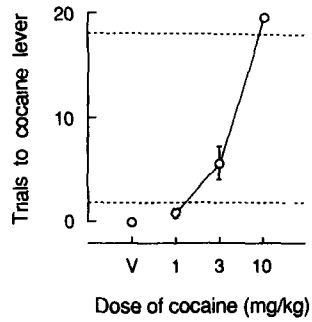


FIG. 1. Dose-response curves for discriminative stimulus effects of cocaine in the rat trained to discriminate 10 mg/kg cocaine from vehicle (V). Data are reported as the number of trials of a 20-trial session completed on the cocaine-appropriate lever. The remaining trials were completed on the vehicle-appropriate lever and are not shown. The broken horizontal lines at 18 and 2 responses represent the criteria for cocaine- and vehicle-appropriate responding, respectively, during training sessions. Symbols denote the mean ± SE of 10 rats.

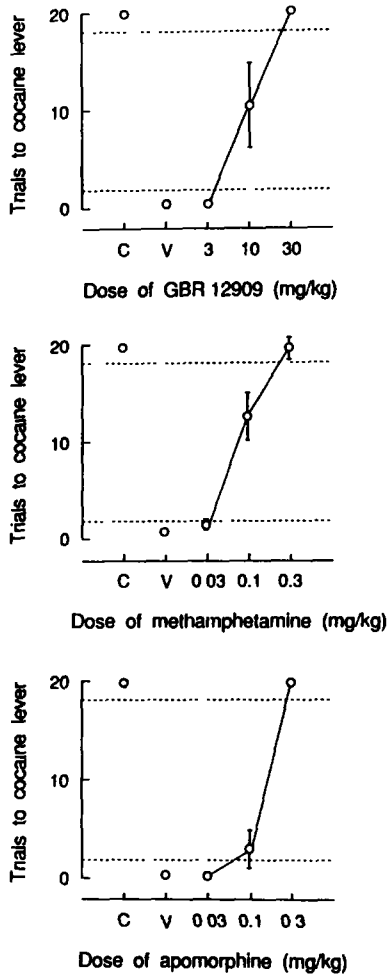


FIG. 2. Discriminative stimulus effects of graded doses of GBR 12909, methamphetamine, and apomorphine in rats trained to discriminate 10 mg/kg cocaine (C) from vehicle (V). Symbols denote the mean ± SE of 5 rats. Other details are the same as in Fig. 1.

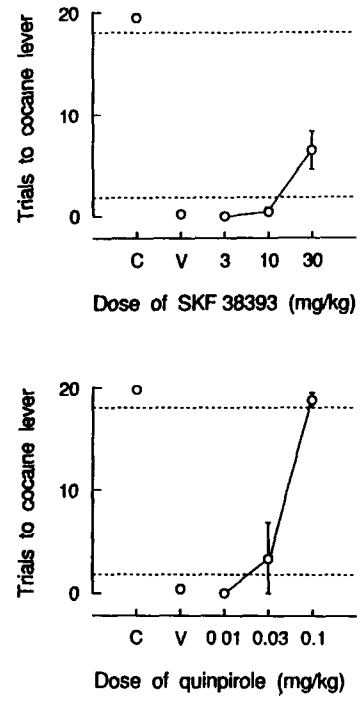


FIG. 3. Discriminative stimulus effects of graded doses of SK&F38393 and quinpirole in rats trained to discriminate 10 mg/kg cocaine (C) from vehicle (V). Symbols denote the mean ± SE of 5 rats. Other details are the same as in Fig. 1.

with SK&F38393 (10.0 mg/kg) were analyzed statistically by means of a two-factor analysis of variance (ANOVA), while the cumulative starting response latency by means of a one-factor ANOVA followed by the Newman-Keuls method for multiple comparisons (27).

## RESULTS

We at first trained 26 rats to discriminate 10.0 mg/kg cocaine from vehicle but discarded 7 rats from the study within 20 sessions because of their poor performance. Although several sessions for "shaping" with vehicle injections were not included, the stimulus effects of cocaine were established in an average of 20 sessions after the start of discrimination training and well maintained thereafter by the continuation of discrimination training between test sessions. A 1.0-mg/kg dose of cocaine did not engender responding appropriate for cocaine cue. Increasing the dose to 3.0 mg/kg produced partial stimulus effects. A training dose (10.0 mg/kg) of cocaine produced cocaine-appropriate responding (Fig. 1).

The dopamine reuptake inhibitor GBR 12909 (3.0 mg/kg) produced vehicle-appropriate responding, but increasing the dose to 30.0 mg/kg produced cocaine-appropriate responding (Fig. 2). Methamphetamine (0.3 mg/kg) and apomorphine (0.3 mg/kg) produced responding appropriate for the cocaine cue (Fig. 2).

The highest dose (30.0 mg/kg) of the $D_1$ dopamine agonist SK&F38393 that could be tested produced partial cocaine-appropriate responding, whereas the $D_2$ dopamine agonist

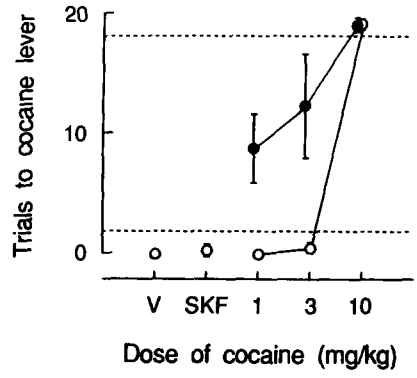


FIG. 4. Discriminative stimulus effects of cocaine and of its combination with 10 mg/kg SK&F38393 in rats trained to discriminate 10 mg/kg cocaine from vehicle (V). Symbols denote the mean ± SE ($n$ = 4) of cocaine-appropriate responding observed after cocaine alone (○) or SK&F38393 (10 mg/kg) plus cocaine (●). SK&F, 10 mg/kg SK&F38393 alone. ANOVA indicates a significant difference ($p < 0.05$) between cocaine alone and SK&F38393 plus cocaine. Other details are the same as in Fig. 1.

quinpirole (0.1 mg/kg) produced almost complete cocaine-appropriate responding (Fig. 3).

The dose-response curve for cocaine (1.0-10.0 mg/kg) shifted to the left by coadministration of a certain dose (10.0 mg/kg) of SK&F38393, although the shift was of a nonparallel nature (Fig. 4).

Haloperidol (0.3 mg/kg), the $D_1$ dopamine antagonist SCH23390 (0.3 mg/kg), and the $D_2$ dopamine antagonist *S*(-)-sulpiride (40.0 mg/kg) only partially reduced cocaine-appropriate responding (Fig. 5), while the higher doses of dopamine antagonists disrupted lever-pressing behavior. Haloperidol (0.3 mg/kg) combined with SCH23390 (0.03 mg/kg) completely blocked the stimulus effects of cocaine (Fig. 6). In addition, haloperidol (0.3 mg/kg) attenuated cocaine-like stimulus effects of quinpirole (0.1 mg/kg) by more than 90% (data not shown).

ANOVA revealed significant ($p < 0.05$) changes in the cumulative starting response latency after administration of some drugs, although all of the rats used in generalization and antagonism tests completed every 30-min session. The response latency of rats was decreased after injection of cocaine (3.0 and 10.0 mg/kg), methamphetamine (0.1 and 0.3 mg/kg), apomorphine (0.1 and 0.3 mg/kg), and quinpirole (0.1 mg/kg), while it was elevated after haloperidol (0.3 mg/kg) and haloperidol (0.3 mg/kg) plus SCH23390 (0.03 mg/kg) plus cocaine (10.0 mg/kg).

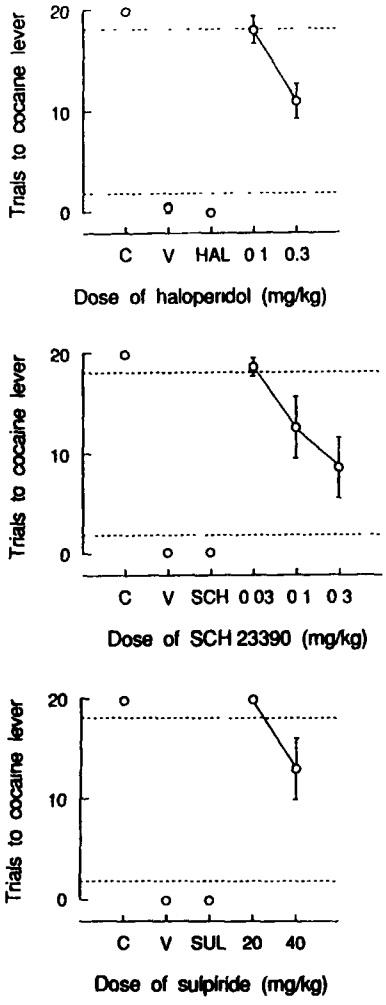


FIG. 5. Discriminative stimulus effects of cocaine and of its combination with graded doses of haloperidol, SCH23390, and *S*(-)-sulpiride in rats trained to discriminate 10 mg/kg cocaine (C) from vehicle (V). HAL, 0.3 mg/kg haloperidol alone; SCH, 0.3 mg/kg SCH23390 alone; SUL, 40 mg/kg *S*(-)-sulpiride alone. Symbols denote the mean ± SE of 5-9 rats. Other details are the same as in Fig. 1.

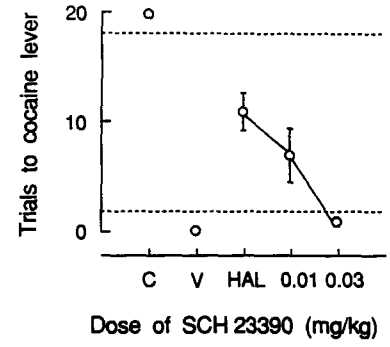


FIG. 6. Discriminative stimulus effects of cocaine and its combination with haloperidol plus graded doses of SCH23390 in rats trained to discriminate 10 mg/kg cocaine (C) from vehicle (V). Symbols denote the mean ± SE of 5 rats. Other details are the same as in Fig. 1.

## DISCUSSION

Average training sessions to reach criterion for discrimination were about 20 and the discrimination was stable thereafter, although the rats employed in this study may not be representative of the population because 7 of 26 were discarded during training sessions. The training sessions by using a shock avoidance paradigm were shorter than those by using food reinforcements (3,4). Moreover, the stimulus effects of cocaine were dose dependent, in common with food reinforcement.

The present result showing that the dopamine reuptake inhibitor GBR 12909 generalized to the cocaine cue in rats is consistent with that reported previously using food reinforcements in rats and rhesus monkeys (11,25). Because methamphetamine, a dopamine releaser, and apomorphine, a nonselective dopamine agonist, also generalized to the cocaine cue, it is likely that the discriminative stimulus effects of a 10.0-mg/kg dose of cocaine are mediated through the activation of dopaminergic neuronal systems. The above results correspond with the dopaminergic involvement in tolerance to the discriminative stimulus properties of cocaine (10.0 mg/kg) in rats (26).

The $D_2$ dopamine agonist quinpirole totally generalized to the cocaine cue, whereas the $D_1$ dopamine agonist SK&F38393 only partially generalized to the cue. These findings are consistent with those by using full $D_1$ agonists such as dihydrexidine and SK&F81297, as well as food reinforcements, in rats and monkeys (20,25). In the present study, SK&F38393 (10.0 mg/kg) shifted the dose-response curve for cocaine to the left, although the shift was of a nonparallel nature. The result is not in accordance with that reported lately, in which SK&F38393 (10.0 mg/kg) fails to influence the dose-response function of cocaine (3). The discrepancy between them may be due to the different experimental conditions. For example, there exist a) shock avoidance vs. food reinforcement, b) Fischer vs. Sprague-Dawley rats, and c) drug administration at 30 vs. 15 min prior to sessions. On the other hand, SK&F38393 (0.5-10.0 mg/kg) reportedly shifts the dose-response curve for the discriminative

stimulus effects of amphetamine to the left (19). Because amphetamine produces interoceptive cues similar to those of cocaine (5,9,13,18), it is highly possible that the discriminative stimulus effects of cocaine are enhanced by the $D_1$ dopamine agonist. In other words, the stimulation of $D_1$ dopamine receptors themselves might not be sufficient to mimic the stimulant cue but would be necessary for enabling the interoceptive state (3). It has been reported that the nonselective dopamine antagonists haloperidol and spiperone do not fully block the cocaine cue (1,3,13). The present results indicate that haloperidol, the $D_1$ dopamine antagonist SCH23390, and the $D_2$ dopamine antagonist *S*(-)-sulpiride only partially attenuated the effects of cocaine, while SCH23390 appears to have potent antagonistic properties against the stimulus effects of cocaine in different studies reported to date (1,3,10). Although haloperidol is considered a nonselective dopamine antagonist, it has relatively low affinity for $D_1$ dopamine receptors (15). In addition, haloperidol has reportedly more potent affinity for $D_2$ dopamine receptors than *S*(-)-sulpiride (16). To effectively block both $D_1$ and $D_2$ dopamine receptors, haloperidol should be combined with SCH23390. In fact, haloperidol (0.3 mg/kg) plus SCH23390 (0.03 mg/kg) completely blocked the stimulus effects of cocaine. These results indicate that both $D_1$ and $D_2$ dopamine receptors contribute to the discriminative stimulus effects of cocaine.

It has been reported that quinpirole is more selective for $D_3$ than $D_2$ dopamine receptors (16). Because quinpirole (0.1 mg/kg) produced responding appropriate for cocaine, it is possible that the stimulus properties of cocaine are mediated via $D_2$ dopamine receptors. Haloperidol (0.3 mg/kg), possessing approximately 20-fold selectivity for $D_2$ over $D_3$ dopamine receptors (16), inhibited the stimulus effects of quinpirole (0.1 mg/kg), in common with cocaine, thus suggesting that $D_3$ dopamine receptors do not play a major role in the stimulus effects of cocaine.

ACKNOWLEDGEMENT

The authors thank Eli Lilly and Co. and Schering Corp. for supplying the samples of quinpirole and SCH23390, respectively.

## REFERENCES

1. Barrett, R. L.; Appel, J. B. Effects of stimulation and blockade of dopamine receptor subtypes on the discriminative stimulus properties of cocaine. Psychopharmacology (Berl.) 99:13–16; 1989.
2. Bergman, J.; Madras, B. K.; Johnson, S. E.; Spealman, R. D. Effects of cocaine and related drugs in nonhuman primates. III. Self-administration by squirrel monkeys. J. Pharmacol. Exp. Ther. 251:150–155; 1989.
3. Callahan, P. M.; Appel, J. B.; Cunningham, K. A. Dopamine $D_1$ and $D_2$ mediation of the discriminative stimulus properties of d-amphetamine and cocaine. Psychopharmacology (Berl.) 103: 50–55; 1991.
4. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J. Discriminative stimulus properties of cocaine and d-amphetamine, and antagonism by haloperidol: A comparative study. Neuropharmacology 17:937–942; 1978.
5. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J. Discriminative stimulus properties of cocaine: Neuropharmacological characteristics as derived from stimulus generalization experiments. Pharmacol. Biochem. Behav. 10:535–546; 1979.
6. D'Mello, G. D.; Stolerman, I. P. Comparison of the discriminative stimulus properties of cocaine and amphetamine in rats. Br. J. Pharmacol. 61:415–422; 1977.
7. Holtzman, S. G. Drug discrimination studies. Drug Alcohol Depend. 14:263–282; 1985.
8. Jaffe, J. Drug addiction and drug abuse. In: Gilman, A.G.; Goodman, L.S.; Rall, T.W.; Murad, F., eds. The pharmacological basis of therapeutics. New York: Macmillan; 1985:532–581.
9. Jarbe, T. U. C. Discriminative stimulus properties of cocaine: Effects of apomorphine, haloperidol, procaine and other drugs. Neuropharmacology 23:899–907; 1984.
10. Kleven, M. S.; Anthony, E. W.; Goldberg, L.; Woolverton, W. L. Blockade of the discriminative stimulus effects of cocaine in rhesus monkeys with the $D_1$ dopamine antagonist SCH23390. Psychopharmacology (Berl.) 95:427–429; 1988.
11. Kleven, M. S.; Anthony, E. W.; Woolverton, W. L. Pharmacological characterization of the discriminative stimulus effects of cocaine in rhesus monkeys. J. Pharmacol. Exp. Ther. 254:312–317; 1990.
12. Koe, B. K. Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of rat brain. J. Pharmacol. Exp. Ther. 199:649–661; 1976.
13. McKenna, M. L.; Ho, B. T. The role of dopamine in the discriminative stimulus properties of cocaine. Neuropharmacology 19: 297–303; 1980.
14. Melia, K. F.; Spealman, R. D. Pharmacological characterization of the discriminative-stimulus effects of GBR 12909. J. Pharmacol. Exp. Ther. 258:626–632; 1991.
15. Meltzer, H. Y.; Matsubara, S.; Lee, J. Classification of typical and atypical antipsychotic drugs on the basis of dopamine D-1, D-2 and serotonin$_2$ pKi values. J. Pharmacol. Exp. Ther. 251: 238–246; 1989.
16. Sokoloff, P.; Giros, B.; Martres, M. P.; Bouthenet, M. L.; Schwartz, J. C. Molecular cloning and characterization of a novel dopamine receptor (D3) as a target for neuroleptics. Nature 347: 146–151; 1990.
17. Risner, M. E.; Jones, B. E. Role of noradrenergic and dopaminergic processes in amphetamine self-administration. Pharmacol. Biochem. Behav. 5:477–482; 1976.
18. Schechter, M. D. Amphetamine discrimination as a test for antiparkinsonism drugs. Eur. J. Pharmacol. 44:51–56; 1976.
19. Smith, F. L.; John, C. S.; Yang, T. F. T.; Lyness, W. H. Role of specific dopamine receptor subtypes in amphetamine discrimination. Psychopharmacology (Berl.) 97:501–506; 1989.
20. Spealman, R. D.; Bergman, J.; Madras, B. K.; Melia, K. F. Discriminative stimulus effects of cocaine in squirrel monkeys: Involvement of dopamine receptor subtypes. J. Pharmacol. Exp. Ther. 258:945–953; 1991.
21. Spealman, R. D.; Madras, B. K.; Bergman, J. Effect of cocaine and related drugs in nonhuman primates. II. Stimulant effects on schedule-controlled behavior. J. Pharmacol. Exp. Ther. 251:142–149; 1989.
22. Taylor, D.; Ho, B. T. Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. Res. Comm. Chem. Pathol. Pharmacol. 21:67–75; 1978.
23. Ukai, M.; Holtzman, S. G. Morphine-like discriminative stimulus effects of opioid peptides: Possible modulatory role of D-Ala$^2$-D-Leu$^5$-enkephalin (DADL) and dynorphin A(1-13). Psychopharmacology (Berl.) 94:32–37; 1988.
24. Ukai, M.; Nakayama, S.; Hamada, T.; Kameyama, T. Discriminative stimulus properties of the mixed agonist-antagonist pentazocine in the rat using two-choice discrete-trial avoidance paradigm. Pharmacol. Biochem. Behav. 33:355–359; 1989.
25. Witkin, J. M.; Nichols, D. E.; Terry, P.; Katz, J. L. Behavioral effects of selective dopaminergic compounds in rats discriminating cocaine injections. J. Pharmacol. Exp. Ther. 257:706–713; 1991.
26. Wood, D. M.; Emmett-Oglesby, M. W. Evidence for dopaminergic involvement in tolerance to the discriminative stimulus properties of cocaine. Eur. J. Pharmacol. 138:155–157; 1987.
27. Zar, J. H. Biostatistical analysis. Englewood Cliffs, NJ: Prentice Hall; 1984.