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Inability of Antipsychotics to Antagonize the Cueing Properties of Cocaine in Rats

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VAN CAMPENHOUT, N. P. DE HAES AND T. F. MEERT. *Inability of antipsychotics to antagonize the cueing properties of cocaine in rats.* PHARMACOL BIOCHEM BEHAV **64**(2) 435–438, 1999.—In this study the possible antagonistic effects of five different antipsychotics on the discriminative stimulus properties of 10 mg/kg cocaine were evaluated by use of a two-lever food-reinforced drug discrimination procedure in rats. To do so, rats were treated with several doses of haloperidol, risperidone, seroquel, sertindole, and olanzapine, either at 60 or 120 min prior to testing. With all compounds tested, no substantial antagonism of the cocaine cue was observed. Only with haloperidol (maximum 60%), risperidone (maximal 20%), and olanzapine (maximal 20%) a partial antagonism without clearcut dose–response was observed. Clozapine, seroquel, and sertindole did not influence the discriminative stimulus properties of cocaine. These results indicate that antipsychotics with different pharmacological profiles are unable to antagonize more than partially the cueing properties of 10 mg/kg cocaine in rats, pointing to the unique underlying stimulus properties of this stimulant. © 1999 Elsevier Science Inc.

Anti psychotics Cocaine Drug discrimination

THE fact that cocaine can exert an internal stimulus control of behavior is supported by data that indicate that cocaine can serve as a discriminative stimulus and reinforcer (8,12,23). Chronic administration of cocaine, however, has been associated with the development of a paranoid psychosis, similar to acute paranoid schizophrenia (2).

Although cocaine blocks the neural uptake of different monoamine neurotransmitters including dopamine (DA), norepinephrine (NE), and serotonin (5HT) (15,21,25), generalization and antagonism experiments indicate that the dopaminergic system, especially D_1 and D_2 dopamine receptors, plays an important, but not exclusive, role in the discriminative stimulus properties of cocaine (4,5). In generalization studies with rats, complete generalization was mainly observed with the D_2-agonist quinpirole, whereas for the D_1-agonist SKF38393 there was only a partial effect (1,3,28). In monkeys, quinpirole resulted either in partial (13,24) or no substitution at all (14). Also for SKF 38393, no generalization to the cocaine cue was reported (13,14). For other D_1-agonists (SKF 81297 and SKF 82958), partial substitution for cocaine was observed (24). Adding a selective D_1-agonist to a D_2-agonist did not improve the substitution for cocaine compared to the D_2-agonist alone (13,24). With regard to the antagonism of the discriminative stimulus properties of cocaine, similar conclusions were drawn. Various reports dealt with partial antagonism of the cocaine cue with selective and nonselective D_2-antagonists (such as haloperidol, spiperone, pimozide, and pipamperone), mixed D_2/monoamine antagonists (risperidone, ocaperidone), and D_1-antagonists (SCH 23390, SCH 39166, and A 66359) (1,3,7,8,10,13,18,26). In addition, rightward shifts in the cocaine dose–response functions, indicative of some competitive antagonism, have been reported with both D_1- and D_2-antagonists (6,14,16,24).

Within the last decade, several new antipsychotics have been developed, such as clozapine, olanzapine, ripseridone, seroquel, and sertindole. These antipsychotics bind to several receptors including dopaminergic receptor subtypes, histaminergic, serotonergic, alpha-adrenergic, and/or muscarinic receptors (19). To study the role of these newer antipsychotics on the antagonism of the discriminative stimulus properties of cocaine, these compounds were compared with haloperidol for antagonistic properties of 10 mg/kg cocaine in a cocaine–saline drug discrimination procedure in rats.

METHODS

Animals

Sixty male Hannover rats were used. The animals were housed individually in standard living cages. All housing and testing took place in a continuously illuminated and air-conditioned room (temperature: 21 ± 1°C; relative humidity: 65 ± 5%). Tap water was freely available. Access to dry powdered standard laboratory food was limited to 2 h a day at 1800 h.

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Apparatus

Six test cages (Coulbourn Instruments®) fitted with a house light and two levers were programmed by solid-state logic modules. Between the two levers, a food pellet receptacle was mounted 2 cm above the floor of the cages. The cages were placed in a light- and sound-attenuating outer box.

Procedure

The drug discrimination procedure has been described in detail elsewhere (17). Daily discrimination training started after habituation and initial shaping to lever press for food on a fixed ratio 10 (FR = 10) schedule during a 15-min session. At a fixed time (see below) before being placed in the test cage, the rats were injected with either the training drug or physiological saline. Depending on whether the animals were injected with drug or saline, they obtained food by pressing either the drug lever or the saline lever, respectively. Responses on the incorrect lever had no consequences. After training, the animals were tested on Fridays, while the training procedure was continued on the remaining days. On the test days, the animals were given the treatment being studied and put in the operant chamber at 60 or 120 min after the treatment. It was then noted on which of the two levers the animals first made a total of 10 responses. This lever was referred to as the selected lever. Once this lever selection was established, the rat obtained the first food pellet, and subsequent reinforcement was contingent upon pressing (FR-10) the selected lever. Testing was postponed to the next test day if the animal did not meet the training conditions of FRF-values of less than 14 during the 3 days preceding testing.

For generalization experiments, several doses of cocaine were either injected SC at 60 min or IP at 15 min before testing. For the antagonism studies, animals were pretreated SC with various doses of the antipsychotics at either 60 or 120 min prior to testing. Afterwards, an injection of 10 mg/kg cocaine was given 15 min before the experiment. For each compound, a complete dose–response curve was established in five animals.

Drugs

Cocaine hydrochloride and seroquel were dissolved in water; haloperidol and clozapine in water containing 1 eq H_2T, and risperidone, olanzapine, and sertindole in water with 2 eq H_2T. The doses of the test compounds were selected on the basis of the activity of these compounds in tests used to screen antipsychotic activity [such as the ATN-test; (19)]; and selected from the geometrical series: 0.01, 0.04, ..., 10, 40 mg/kg. All doses of drugs, saline, or vehicle were administered in a volume of 1 ml/100 g body weight. This was done to keep the injected volume constant over all experimental days.

Statistics

The Wilcoxon matched-pairs signed-ranks test [(22) two-tailed] was used throughout to evaluate differences between drug and vehicle treatments. ED_{50}s and 95% confidence limits were calculated according to Finney's iterative method (9).

RESULTS

For rats to learn to discriminate between 10 mg/kg cocaine and saline, as defined by 10 successive sessions with an FRF value ≤14, on average (±SEM) 28 sessions (±1.3) (min. 17—max. 38) were needed. At the end of training, the animals made 1602 (±76) responses during saline sessions with 99.2 (±0.3)% correct responding on the saline lever. In the corresponding drug sessions, the mean response rate and percentage responding on the cocaine lever were respectively 947 (±142) responses and 98 (±1.3%).

The ED_{50}s (±95% confidence limits) for generalization of cocaine in 10 mg/kg cocaine trained rats were 2.33 (1.72 –3.16) and 2.34 (1.56 – 3.51) mg/kg after SC and IP administration, respectively.

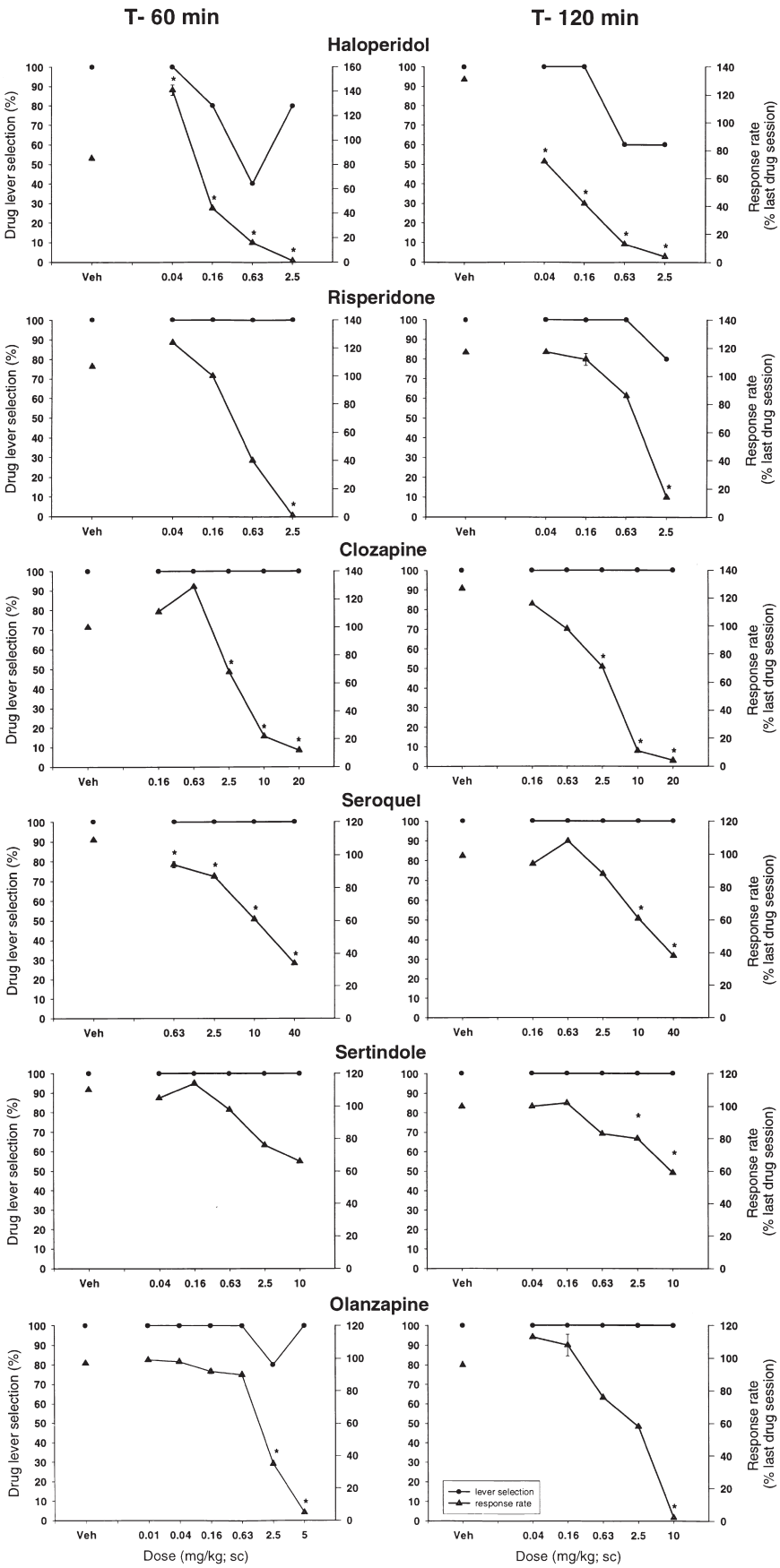
For the antagonism of the cueing properties of 10 mg/kg cocaine, the antipsychotics were tested after preinjection time periods of 60 and 120 min (Fig. 1). Haloperidol partially antagonized the discriminative stimulus properties of cocaine after both 1 h (20% antagonism with 0.16 and 2.50 mg/kg and 60% with 0.63 mg/kg) and 2 h (40% antagonism with 0.63 and 2.50 mg/kg) pretreatment. With risperidone, 20% antagonism was only present after 2 h pretreatment (with 2.50 mg/kg). Also, with olanzapine, 20% antagonism was seen at 2.50 mg/kg olanzapine at 1 h pretreatment. Clozapine, seroquel, and sertindole did not produce any antagonistic effects on the cueing properties of cocaine. With regard to the response rate, expressed as a percentage of the responses made during the last drug training session, all antipsychotics resulted in a decrease at the highest doses tested (Fig. 1). The lowest dose that significantly reduced response rate was 0.04, 2.5, 2.5, 0.63, >10.0, and 2.5 mg/kg for haloperidol, risperidone, clozapine, seroquel, sertindolem, and olanzapine, respectively, after 1 h pretreatment; the corresponding doses after 2 h were 0.04, 2.5, 2.5, 10, 2.5, and 10 mg/kg respectively.

DISCUSSION

It is well established that cocaine can be used as a discriminative stimulus in a two-lever reinforced drug discrimination procedure in rats (7,8,18). In the rats trained to discriminate 10 mg/kg cocaine from saline, the ED_{50}s for stimulus generalization of cocaine to its own training dose were 2.33 and 2.34 mg/kg at 60 min (SC) and 15 min (IP) pretreatment, respectively. Because no significant difference between these ED_{50}s was present, this indicates that the difference in time (60 vs. 15 min) or the difference in route of administration (IP or SC) has little influence on the discriminability of cocaine.

With regard to the antagonism of the cocaine cue with haloperidol, risperidone, clozapine, seroquel, sertindole, and olanzapine, no complete antagonism was observed. Of all tested antipsychotics, partial antagonism of the cueing effect of cocaine was measured after haloperidol, regardless of the difference in pretreatment time. With all antipsychotics at the highest doses tested, there was a clear decrease in response rate. These results indicate that antipsychotics with different pharmacological profiles are unable to antagonize the cueing properties of 10 mg/kg cocaine even at doses that strongly suppressed response rate. This is at variance with research data using the self-administration procedure (20). Here, olan-

FIG. 1. Effects of various antipsychotics in antagonism experiments in rats ($n = 5$ per drug) trained to discriminate 10 mg/kg cocaine from saline in a drug discrimination test. The compounds were injected subcutaneously at 60 or 120 min prior to testing. Abscissa: doses of the test compounds in mg/kg. The ordinates express the percentage of rats selecting the cocaine lever (circles) and the response rate of the rats (triangles), expressed as a percentage of the last drug session. Differences from vehicle were calculated using the Wilcoxon matched-pairs signed-ranks test [(22); two-tailed, * $p \leq 0.05$].


T- 60 min
T- 120 min
Haloperidol
Risperidone
Clozapine
Seroquel
Sertindole
Olanzapine
Drug lever selection (%)
Response rate (% last drug session)
Veh
0.01
0.04
0.16
0.63
2.5
5
10
20
40
lever selection
response rate
Dose (mg/kg; sc)

zapine produced a dose-dependent decrease of cocaine self-administration. These results suggest that pretreatment with olanzapine is capable of interfering with the reinforcing effects of cocaine, and illustrates the value of using multiple behavioral tests when evaluating the pharmacological effects of newer psychopharmacological agents. In rhesus monkeys, pretreatment with clozapine also attenuated the self-administration of cocaine without influencing the response pattern. This also suggests that clozapine can interfere with the reinforcing effects of cocaine (20,27). Comparing drug discrimination data with self-administration data, therefore, clearly indicate differences between the discriminative and reinforcing properties of cocaine as well as differences in compounds that interfere with both mechanisms of action of cocaine.

It is well accepted that the injection of cocaine produces, besides cueing and reinforcing properties, behavioral changes in animals due to dopamine overstimulation. Typical reactions in rats are cocaine-induced agitation and stereotypies (11). Classic neuroleptics such as haloperidol, can effectively antagonize these behavioral effects in a dose-related manner (11). In this study it became clear that this was also the case for the newer antipsychotics, because all treatments induced a decrease in responses most often accompanied with an increase of the latency to initiate responding. As such, a clear difference can be observed between the effects of the antipsychotics on response rate and on the cueing properties of cocaine in a same conditioning procedure.

Therefore, the results of these experiments indicate that the discriminative stimulus induced by cocaine is very specific and complex, because it cannot be antagonized by antipsychotics, including the newest generation. This is despite the fact that these newer compounds interact with multiple binding sites other than those of dopamine.

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 (Berlin) 99:13–16; 1989.
2. Brady, K. T.; Lydiard, R. B.; Malcolm, R.; Ballenger, J. C.: Cocaine-induced psychosis. J. Clin. Psychiatry 52:509–512; 1991.
3. Callahan, P. M.; Appel, J. B.; Cunningham, K. A.: Dopamine D1 and D2 mediation of the discriminative stimulus properties of *d*-amphetamine and cocaine. Psychopharmacology (Berlin) 103:50–55; 1991.
4. Callahan, P. M.; Cunningham, K. A.: Modulation of the discriminative stimulus properties of cocaine: Comparison of the effects of fluoxetine with 5-HT_{1A} and 5-HT_{1B} receptor agonists. Neuropharmacology 36:373–381; 1997.
5. Clark, D.; Exner, M.; Furmidge, L. J.; Svensson, K.; Sonesson, C.: Effects of the dopamine autoreceptor antagonist (−)−DS121 on the discriminative stimulus properties of *d*-amphetamine and cocaine. Eur. J. Pharmacol. 275:67–74; 1995.
6. Colpaert, F. C.: Interactions of haloperidol with discriminative responding controlled by 10 mg/kg cocaine in rats. Drug Dev. Res. 9:125–131; 1986.
7. Colpaert, F. C.; Niemegeers, C. J. E.; Janssen, P. A. J.: Cocaine cue in rats as it relates to subjective drug effects: A preliminary report. Eur. J. Pharmacol. 40:195–199; 1976.
8. 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.
9. Finney, D. J., ed.: Statistical methods in biological assay, 2nd ed. London: Griffin Press; 1971.
10. Huang, D.; Wilson, M. C.: Comparative discriminative stimulus properties of *dl*-cathinone, *d*-amphetamine, and cocaine in rats. Pharmacol. Biochem. Behav. 24:205–210; 1986.
11. Janssen, P. A. J.; Niemegeers, C. J. E.; Awouters, F.; Schellekens, K. A. H.; Megens, A. A. H. P.; Meert, T. F.: Risperidone (R64766), a new and highly effective antipsychotic with a novel mode of action. J. Pharmacol. Exp. Ther. 244:685–693; 1988.
12. Jarbe, T. U. C.: Discriminative stimulus properties of cocaine. Effects of apomorphine, haloperidol, procaine and other drugs. Neuropharmacology 23:899–907; 1984.
13. Katz, J. L.; Witkin, J. M.: Effect of quinpirole and SKF 38393 alone and in combination in squirrel monkeys trained to discriminate cocaine. Psychopharmacology (Berlin) 107:217–220; 1992.
14. 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.
15. Koe, B. K.: Molecular geometry of inhibitors of the uptake of catecholamines and serotonin in synaptosomal preparations of a rat brain. J. Pharmacol. Exp. Ther. 199:649–661; 1976.
16. McKenna, M. L.; Ho, B. T.; The role of dopamine in the discriminative stimulus properties of cocaine. Neuropharmacology 19:297–303; 1980.
17. Meert, T. F.; De Haes, P.; Janssen, P. A. J.: Risperidone (R64766), a potent and complete LSD antagonist in drug discrimination in rats. Psychopharmacology (Berlin) 97:206–212; 1989.
18. Meert, T. F.; De Haes, P. L. A. J.; Vermote, P. C. M.; Janssen, P. A. J.: Pharmacological validation of ritanserin and risperidone in the drug discrimination test procedure in the rat. Drug Dev. Res. 19:353–373; 1990.
19. Megens, A. A. H. P.; Kennis, L.; Vandenberk, J.; Awouters, F.: Chemistry and pharmacology of drugs acting on both 5-HT_2- and D_2-receptors. In: Kane, J. M.; Möller, H.-J.; Awouters, F., eds. Serotonin in antipsychotic treatment. Mechanisms and clinical practice. New York. Marcel Dekker, Inc.; 1996:153–179.
20. Meil, W. M.; Schechter, M. D.: Olanzapine attenuates the reinforcing effects of cocaine. Eur. J. Pharmacol. 340:17–26; 1997.
21. Reith, M. E. A.; Meisler, B. E.; Sershen, H.; Lajtha, A.: Structural requirements for cocaine congeners to interact with dopamine and serotonin uptake sites in mouse brain and to induce stereotyped behavior. Biochem. Pharmacol. 35:1123–1129; 1986.
22. Siegel, S., ed.: Nonparametric statistics for the behavioral sciences. New York: McGraw-Hill Book Co.; 1956.
23. Silverman, P. B.; Schultz, K. A.: Comparison of cocaine and procaine discriminative stimuli. Drug Dev. Res. 16:427–433; 1989.
24. 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.
25. Taylor, D.; Ho, B. T.: Comparison of inhibition of monoamine uptake by cocaine, methylphenidate and amphetamine. Res. Commun. Chem. Pathol. Pharmacol. 21:67–75; 1978.
26. Vanover, K. E.; Kleven, M. S.; Woolverton, W. L.: Blockade of the discriminative stimulus effects of cocaine in rhesus monkeys with the D1 dopamine antagonists SCH-39166 and A-66359. Behav. Pharmacol. 2:151–159; 1991.
27. Vanover, K. E.; Piercy, M. F.; Woolverton, W. L.: Evaluation of the reinforcing and discriminative stimulus effects of cocaine in combination with (+)−AJ 76 or clozapine. J. Pharmacol. Exp. Ther. 266:780–789; 1993.
28. 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.