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Antagonism of the discriminative stimulus properties of cocaine with the combination of a dopamine D_1 and D_2 antagonist

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Abstract. Antagonism of the discriminative stimulus properties of 10 mg/kg cocaine was studied in rats by use of the dopamine D_1 antagonist SCH 23390 and the D_2 antagonist haloperidol. Whereas SCH 23390 and haloperidol were by themselves unable to antagonize the cueing properties of cocaine, the combination of both dopamine antagonists resulted in a complete blockade of the cocaine cue. In the presence of a fixed dose of 0.01 and 0.04 mg/kg haloperidol, the ED_{50}'s (it is the effective dose in 50% of the animals) of SCH 23390 for cocaine antagonism were 0.043 and 0.012 mg/kg, respectively. Similarly, the ED_{50}'s of haloperidol in combination with 0.01 and 0.04 mg/kg SCH 23390 were 0.021 and 0.024 mg/kg. The combined treatment of haloperidol and SCH 23390 resulted in strong response-rate reductions. At all combination regimens resulting in a complete blockade of the cocaine cue, response rate was reduced to less than 20% of the control values. These results indicate that the cueing properties of cocaine are both dopamine D_1- and D_2-mediated and that a combined antagonism of both receptor subtypes can lead to a complete antagonism of the cueing properties of cocaine which is associated with severe attenuation of response rate.

Key words: cocaine, drug discrimination, dopamine D_1 antagonism, dopamine D_2 antagonism

INTRODUCTION

It is already well established that cocaine can serve as a discriminative stimulus under various experimental conditions in different animal species. Although cocaine blocks the neural uptake of various monoamine neurotransmitters including dopamine (DA), norepinephrine (NE) and serotonin (5-HT) (Koe 1976, Taylor and Ho 1978, Reith et al. 1986), it appears that its dopaminergic effects play an important role in the discriminative stimulus properties of cocaine. DA uptake inhibitors (e.g. GBR 12909, mazindol, nomifensine, bupropion) have been reported to substitute for the cuing properties of cocaine (Kleven et al. 1990, Cunningham and Callahan 1991, Broadbent et al. 1991, Woolverton 1991) whereas NE - (e.g. desipramine, tomoxetine, nisoxetine) or 5-HT uptake inhibitors (fluoxetine) (Kleven et al. 1990, Cunningham and Callahan 1991) fail to produce a partial or complete generalization. Furthermore, dopaminomimetic agents such as apomorphine and (d)-amphetamine have been shown to substitute for cocaine in various species and under a range of experimental conditions (Colpaert et al. 1976, D'Mello and Stolerman 1977, Mc Kenna and Ho 1980, De La Garza and Johanson 1983, 1985, 1986, Huang and Wilson 1986, Harland et al. 1989, Silverman and Schultz 1989, Callahan et al. 1991, Woolverton 1991). Partial generalization is also reported with the DA precursor L-DOPA given in combination with carbidopa (Spealman et al. 1991). Because selective DA_1 (e.g. SKF 38393) and DA_2 agonists (e.g. quinpirole) became available, various groups studied the role of these receptor subtypes in the discriminative stimulus properties of cocaine. Within rats, a complete generalization was mainly observed with the DA_2 agonist quinpirole whereas for SKF 38393 there was only a partial effect (Barrett and Appel 1989, Callahan et al. 1991, Witkin et al. 1991). In monkeys, quinpirole resulted either in a partial (Spealman et al. 1991, Katz and Witkin 1992) or no substitution (Kleven et al. 1990). Also for the DA_1 agonist SKF 38393 no generalization to the cocaine cue was reported (Kleven et al. 1990, Katz and Witkin 1992). For other DA_1 agonists (SKF 81297 and SKF 82958) a partial substitution for cocaine was measured (Spealman et al. 1991). Adding a selective DA_1 agonist to a DA_2 agonist did not improve the substitution for cocaine as compared to the DA_2 agonist alone (Spealman et al. 1991, Katz and Witkin 1992). These generalization or substitution experiments led to the conclusion that blockade of the dopamine reuptake is sufficient to mimic the cocaine cueing properties (Kleven et al. 1990). The data further suggest that although both DA_1 and DA_2 receptors contribute to the stimulus properties of cocaine, stimulation of either receptor subtype alone, or the combined stimulation of both receptor subtypes, as for instance demonstrated in monkeys, is not sufficient for the full expression of the discriminative stimulus properties of cocaine (Katz and Witkin 1992).

With regard to the antagonism of the discriminative stimulus properties of cocaine, similar conclusions were drawn. Various reports dealt with a partial antagonism of the cocaine cue with different selective and non-selective DA_2 antagonists (such as haloperidol, spiperone, pimozide and pipamperone), mixed DA_2/monoamine antagonists (risperidone, ocaperidone) and DA_1 antagonists (SCH 23390; SCH 39166; A 66359) (Colpaert et al. 1976, Colpaert et al. 1978, Jarbe 1984, Huang and Wilson 1986, Barrett and Appel 1989, Silverman and Schultz 1989, Meert et al. 1990, Callahan et al. 1991, Meert 1991, Vanover et al. 1991). In addition, rightwards shifts in the cocaine dose-response functions, indicative of some competitive antagonism, have been reported with both DA_1 and DA2 antagonists (McKenna and Ho 1980, Colpaert 1986, Kleven et al. 1990, Spealman et al. 1991). Because both DA_1 and DA_2 antagonists result in only a partial antagonism of the cocaine cue and because the cueing properties of cocaine are thought to be DA_1- and DA_2-mediated, we decided to test whether a combined blockade of the dopamine DA_1 and DA_2 receptor subtypes could antagonize the cocaine cue. To do so, rats were trained to discriminate 10 mg/kg cocaine from saline in a two-lever food reinforced test procedure. After training, antagonism studies

were performed with haloperidol, SCH 23390, and the combination of fixed doses of haloperidol with variable doses of SCH 23390 as well as the reversal.

METHODS

Animals

Seventeen male Wistar rats weighing 240 ± 20 g at the beginning of the experiment 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 (see below).

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 (Meert et al. 1989). Daily discrimination training started after habituation and initial shaping to lever press for food on a fixed ratio 10 (FR-10) schedule. At 15 min before being placed in the test cage, the rats were injected IP with either 10.0 mg/kg cocaine or physiological saline. Depending on whether they were injected with cocaine or saline, they obtained food by pressing either the cocaine lever (DL) or the saline lever (SL), respectively. After every 10^{th} press (FR-10) on the correct lever, a 45 mg food pellet was delivered by a food dispenser. Responses on the incorrect lever (i.e. the SL after cocaine or the DL after saline) had no consequences. The lever assignments were DL: left, SL: right in about half of the animals and SL: left, DL: right in the other half. These assignments remained unchanged throughout the study. At the beginning of each session, the FRF--value was noted. The FRF-value is the sum of the total number of responses on both levers until ten responses are made on the appropriate lever and the first reinforcement is obtained. Fifteen min after the rat was placed in the test chamber, the session was terminated and all responses on both levers were recorded. The response rate (i.e., the total sum of the responses on both the DL and SL during the 15 min session) and the percentage responding on the selected lever (i.e. the ratio of the number of responses on the appropriate lever to the response rate) were calculated. After the session, the animal was returned to its living cage. Two hours later, it was allowed to feed freely for 1 hour. At weekends, no sessions were run and the animals were given free access to food between 10 a.m. and 12 noon.

Every week, each rat was run once daily on 5 consecutive days. Daily cocaine (D) or saline (S) injections were given according to two monthly alternating sequences, i.e., 1) D-S-S-D-S, S-D-D-S-S, S-D-S-D-D, D-S-D-S-D and 2)-S-D-D-S-S, D-S-D-S-D, D-S-S-D-D, S-D-S-D-S. Rats whose sequential numbers were odd were run according to one sequence, whereas even-numbered animals were run according to the alternative sequence. Discrimination training proceeded individually for each rat until ten consecutive sessions occurred in which an FRF-value ≤14 was obtained. Animals reaching this criterion were used for testing.

Test sessions were run on Fridays only and the training procedure was continued on the remaining days. On test days, the animal was given the treatment being studied and was put in the operant chamber at a specified time after the treatment. It was then noted on which of the two levers the animal first made a total of ten responses. This lever is referred to as the selected lever. Once this lever selection was established, the rat obtained a 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 FRF-value exceeded 14 on any of the 3 most recent training days.

Before being used in tests, the animals were given 1 week of habituation to a double treatment condition. That is, before every administration of saline or cocaine, the animals were always given an additional subcutaneous injection of saline 60 min prior to the test. The double treatment on training days was continued for the duration of the experiments.

Drugs

Cocaine hydrochloride was dissolved in water and 1 eq H_2T and 3 eq H_2T was used for dissolving haloperidol and SCH 23390 respectively. The doses of haloperidol and SCH 23390 were selected from the geometrical series 0.0025, 0.01, ..., 0.63, 2.50 mg/kg. Occasionally, additional doses from the geometrical series 0.00125, 0.0050, ..., 1.25, 5.00 mg/kg were used. All doses of drugs, saline or vehicle were administered in a volume of 1 ml/100 g body weight, except for the combination treatments where a volume of 0.5 ml/100 g was used for all substances. This was done in order to keep the injected volume constant over all experimental days.

Statistics

The Wilcoxon matched-pairs signed-ranks test (Siegel 1956; two-tailed) was used throughout in order to evaluate differences between drug and vehicle treatments. ED_{50}'s (ED_{50}: the effective dose in 50% of the animals tested) and 95% confidence limits were calculated according to Finney's iterative method (Finney 1971).

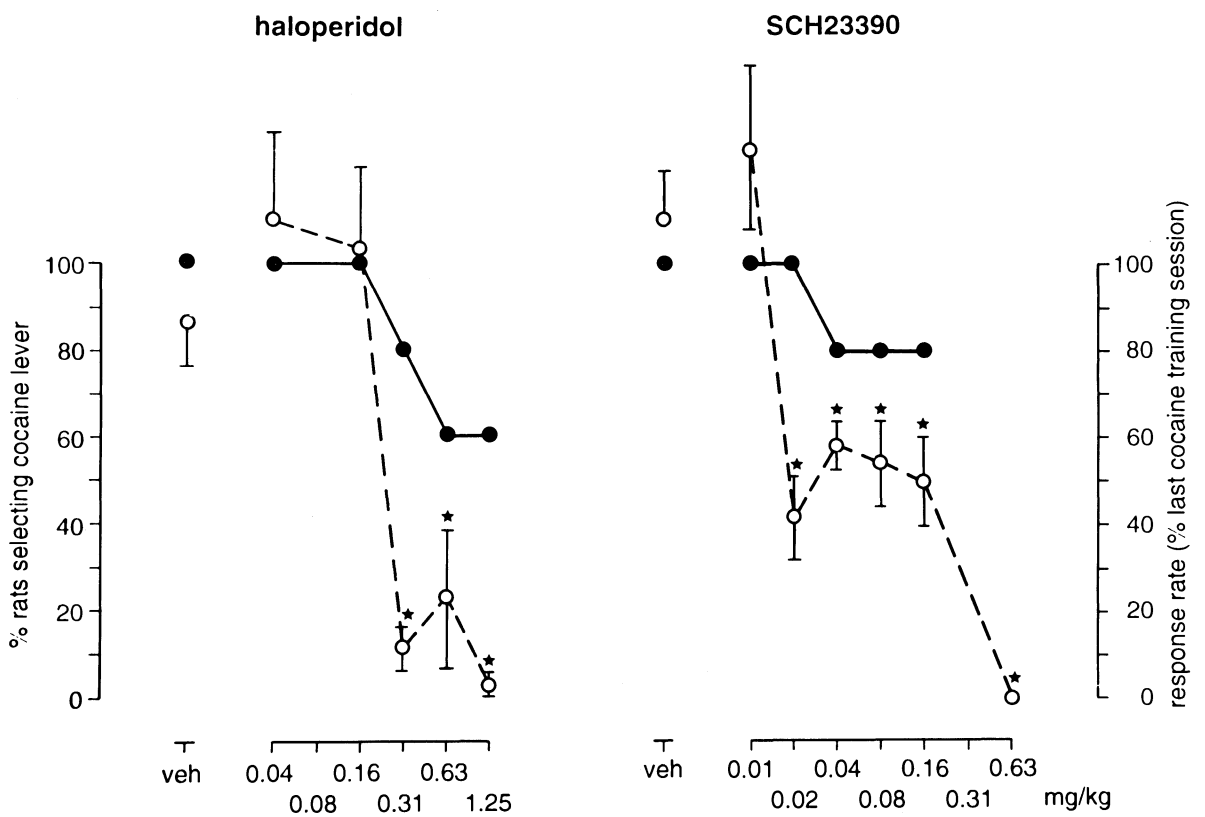

Fig. 1. Antagonism of the cueing properties of 10 mg/kg cocaine with haloperidol and SCH 23390. The drugs were injected SC at 60 min before test and at 45 min before the IP injection of cocaine. The left ordinate expresses the percentage of rats selecting the cocaine lever (bold line). The right ordinate gives the response rate, expressed as a percentage of responses on the most recently preceding cocaine training session (o---o). Each data point is based on the results of 5 rats. Differences in response rate with the vehicle control condition were evaluated with the Wilcoxon test (Two-tailed, $*P < 0.05$; Siegel 1956).

RESULTS

In order 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) 34.24 (± 2.64) sessions were needed. At the end of training, and based on the first two subsequent saline sessions, the animals made 1535 (± 73.92) responses during saline sessions with a mean FRF value of 10.47 (± 0.14) and with 99.62 (± 0.13)% correct responding on the saline lever. In the corresponding drug sessions, the mean response rate, FRF value and percentage responding on the cocaine lever were respectively 664.15 (± 52.79) responses, 10.18 (± 0.12) and 99.08 (± 0.22)%.

In these cocaine-trained rats, antagonism studies were performed with both haloperidol and SCH 23390. Haloperidol at doses up to 1.25 mg/kg produced a partial antagonism (Fig. 1, left panel). At both 0.63 and 1.25 mg/kg haloperidol, the two highest doses tested, 2 out of 5 rats (i.e. 40%) selected the saline lever. In terms of FRF-values, no differences between haloperidol and vehicle treated rats were observed, with means ranging between 10.2 (± 0.2) and 12.0 (±1.0). The percentage responding of the vehicle-treated rats on the selected (cocaine) lever was 99.78 (±0.19)%. At 0.16 mg/kg haloperidol, the percentage responding on the selected lever reduced significantly ($P<0.05$) to 67.60 (± 8.72)%. This reduction remained present at all higher doses of haloperidol tested. In terms of response rate, expressed as a percentage of the last cocaine training session, differences from vehicle ($P < 0.05$) were present from 0.31 mg/kg haloperidol onwards. At 1.25 mg/kg haloperidol, drug responding was reduced to 3.5 (± 2.8)% of the last

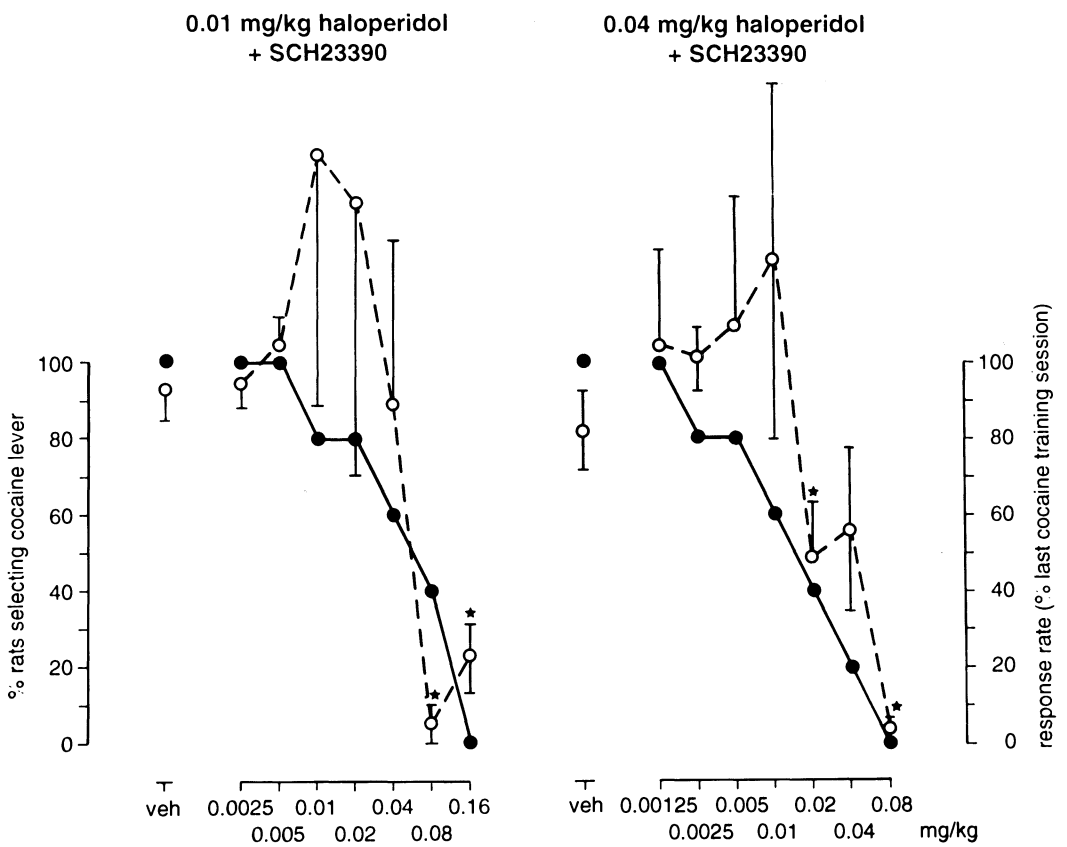

Fig. 2. Antagonism of the cuing properties of 10 mg/kg cocaine with SCH23390 in the presence of either 0.01 or 0.04 mg/kg haloperidol. See also the legend to Fig. 1.

drug session. With increasing doses of SCH 23390 up to 0.16 mg/kg, only 1 out of 5 rats selected the saline lever (Fig. 1, right panel). Higher doses could not be tested because at 0.63 mg/kg SCH 23390 all animals had a complete response inhibition. As compared to vehicle treatment, SCH 23390 reduced response rate from 0.02 mg/kg onwards while having no effects at all ($P > 0.05$) on the FRF values and on the percentage responding on the selected lever.

In order to test whether the combination of haloperidol plus SCH 23390 could antagonize the cocaine cue, various doses of SCH 23390 were tested in the presence of either 0.01 or 0.04 mg/kg haloperidol (Fig. 2). Both in the presence of 0.01 and 0.04 mg/kg haloperidol, SCH 23390 produced a dose-related antagonism of the cocaine cue with a complete antagonism at respectively 0.16 and 0.08mg/kg SCH 23390. The ED_{50} (± 95% confidence limits) of SCH 23390 for the antagonism of the cuing properties of 10 mg/kg cocaine was 0.043 (0.025-0.073) mg/kg in the presence of 0.01 mg/kg haloperidol and 0.012 (0.0067-0.022) mg/kg in the presence of 0.04 mg/kg haloperidol. Increasing the dose of haloperidol by a factor of 4 resulted in a decrease of the ED_{50} of SCH 23390 by a factor of 3.6. In both haloperidol conditions, rate reducing effects were present from a dose of 0.08 mg/kg SCH 23390 onwards. A rate reduction was also present with the combination of 0.04 mg/kg haloperidol and 0.02 mg/kg SCH 23390. With regard to the FRF values and the percentage responding on the selected lever, no differences with the vehicle control conditions were present ($P > 0.05$).

A third series of experiments tested whether similar results could be obtained with haloperidol in the presence of fixed doses of 0.01 or 0.04 mg/kg SCH 23390. In both cases, haloperidol produced a dose-related antagonism of the cuing properties of

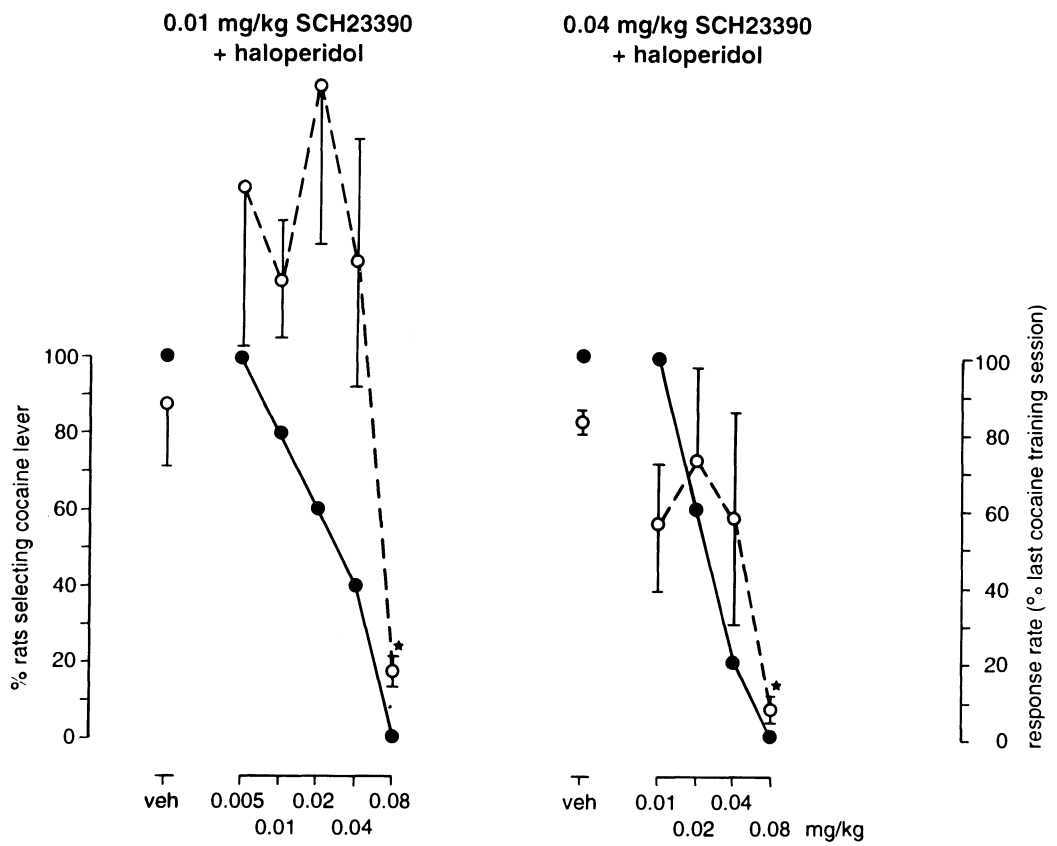

Fig. 3. Antagonism of the cueing properties of 10 mg/kg cocaine with haloperidol in the presence of either 0.01 or 0.04 mg/kg SCH 23390. See also the legend to Fig. 1.

cocaine with a complete antagonism at 0.08 mg/kg haloperidol. The ED_{50}'s of haloperidol in the presence of 0.01 and 0.04 mg/kg SCH 23390 were respectively 0.021 (0.013 - 0.034) and 0.024 (0.016 - 0.037) mg/kg. Increasing the dose of SCH 23390 from 0.01 to 0.04 mg/kg did thus not result in a decrease of the ED_{50} of haloperidol. For both combination treatments the complete antagonism of cocaine was accompanied by significant rate reducing effects. However, as with the other combination studies, there were no effects on the FRF values or on the percentage correct responding on the selected lever.

DISCUSSION

The discriminative stimulus properties of cocaine have been argued to be dopamine D_1- and D_2-mediated. However, it has been repeatedly demonstrated (see introduction) that selective D_1 and D_2 agonists only partially substitute for cocaine and selective D_1 and D_2 antagonists could not completely antagonize the cuing properties of cocaine. In order to evaluate further the efficacy of D_1 and D_2 antagonists against cocaine, antagonism studies were conducted with the D_2 antagonist haloperidol, the D_1 antagonist SCH 23390 and the combination of fixed doses of haloperidol with increasing doses of SCH 23390 and *vice versa*. Whereas both haloperidol and SCH 23390 had only very limited cocaine antagonistic effects, the combined treatment of both dopamine antagonists resulted in a complete blockade of the cuing properties of 10 mg/kg cocaine (Figs. 2 and 3). Complete antagonism of 10 mg/kg cocaine was obtained with 0.01 mg/kg haloperidol plus 0.16 mg/kg SCH 23390, 0.04 mg/kg haloperidol plus 0.08 mg/kg SCH 23390, 0.01 mg/kg SCH 23390 plus 0.08 mg/kg haloperidol and 0.04 mg/kg SCH 23390 plus 0.08 mg/kg haloperidol. The ED_{50}'s of SCH 23390 for cocaine antagonism in the presence of 0.01 and 0.04 mg/kg haloperidol were respectively 0.043 and 0.012 mg/kg. Similarly, the ED_{50}'s of haloperidol co-administered with 0.01 and 0.04 mg/kg SCH 23390 were 0.021 and 0.024 mg/kg. Because doses up to 0.08 mg/kg haloperidol and 0.16 mg/kg SCH 23390 were almost inactive when given on their own, these results indicate that the combination of inactive doses of haloperidol with SCH 23390 are able to antagonize the cueing properties of 10 mg/kg cocaine fully. The combined antagonism studies thus clearly confirm the conclusions from previous studies indicating that both the dopamine D_1 and the dopamine D_2 neurotransmitter system are involved in the cuing properties of cocaine (Barrett and Appel 1989, Callahan et al. 1991, Woolverton 1991, Katz and Witkin 1992). However, as opposed to some generalization studies in monkeys with selective D_1 and D_2 agonists (Spealman et al. 1991), it was demonstrated here that the combination of a D_1 and a D_2 antagonist had a greater efficacy than each antagonist alone. The differences in conclusion with regard to the efficacy of the combination of D_1 and D_2 compounds on the cocaine cue might be due to differences in experimental conditions (generalization *versus* antagonism studies), animal species (monkeys *versus* rats) and doses and routes of cocaine used (0.3 to 0.5 mg/kg IV in the monkeys *versus* 10 mg/kg IP in rats).

The present study did not allow estimation of the exact contribution of both dopaminergic receptor subtypes in the cueing properties of cocaine. The antagonism studies with the fixed doses of haloperidol indicated that increasing the doses of haloperidol by a factor of 4 from 0.01 to 0.04 mg/kg resulted in an almost 4-fold decrease in the ED_{50} of SCH 23390 from 0.043 to 0.012 mg/kg. The apparent additive activity of the two dopaminergic subsystems was not reflected in the second group of combination studies with fixed doses of SCH 23390. Increasing the dose of SCH 23390 from 0.01 to 0.04 mg/kg did not result in a 4-fold decrease in the ED_{50} for haloperidol. Further studies, with isobolographic analysis, are needed to clarify the exact contribution of the two dopamine subtypes in the cueing properties of cocaine.

Whenever antagonism occurred, a strong reduction in response rate was seen. A complete antagonism was always obtained in animals performing less than 20% of their normal response rate. Also in

terms of response rate reductions there were some additive effects between haloperidol and SCH 23390. Whereas response rate reductions started with 0.31 mg/kg haloperidol or 0.02 mg/kg SCH 23390 alone, a combination of 0.01 mg/kg SCH 23390 plus 0.08 mg/kg haloperidol already diminished responding by more than 60 %. The combinations of SCH 23390 plus haloperidol did not affect the accuracy of lever selection. Neither in terms of FRF-values nor in terms of the percentage responding on the selected lever was a deterioration present. With haloperidol alone, animals will show a reduction in the percentage reponding on the selected lever probably due to an interference of the drug with the response-reinforcement contingency (Colpaert et al. 1978, Meert et al. 1990).

In conclusion, the results presented here indicate that the cueing properties of 10 mg/kg cocaine can be completely blocked by the combined treatment of the dopamine D_1 antagonist SCH 23390 and the dopamine D_2 antagonist haloperidol. Because a complete antagonism can be observed with doses of both dopamine antagonists having a very limited intrinsic activity, a clear synergism is present. The mutual interaction between the dopamine D_1 and D_2 system was also present in terms of response rate reduction. All combination treatments that blocked the cocaine cue clearly diminished response rate. The data globally confirm the role of both the dopamine D_1 and D_2 receptor subtypes in the discriminative stimulus properties of cocaine in the rat. Further studies are needed to clarify the exact mutual contribution of both dopamine receptor subtypes in the cueing properties of cocaine.

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