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Differential Blockade of Chronic Versus Acute Effects of Intravenous Cocaine by Dopamine Receptor Antagonists

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TELLA, S. R. *Differential blockade of chronic versus acute effects of intravenous cocaine by dopamine receptor antagonists.* PHARMACOL BIOCHEM BEHAV 48(1) 151–159, 1994.—The objectives of this study were to investigate behavioral sensitization to repeated once daily IV injections of cocaine, and to determine whether dopamine receptor antagonists differentially block chronic versus acute cocaine effects. Acute cocaine (0.3–3.0 mg/kg) produced a dose-dependent increase in both horizontal and stereotypic movements in male Sprague-Dawley rats. Repeated once daily injections of 1 or 3 mg/kg of cocaine augmented these effects. Pretreatment with either the D_2 dopamine receptor antagonist haloperidol (0.03–0.3 mg/kg) or the D_1 dopamine receptor antagonist R(+)-SCH-23390 (0.003–0.1 mg/kg) dose dependently attenuated cocaine's behavioral effects in both sensitized and cocaine-naive animals. There was a rightward shift in the dose–effect relationship of these antagonists in blocking the expression of behavioral sensitization as compared to their ability to block the acute behavioral effects of cocaine. These results indicate that repeated once daily IV injections of cocaine produced behavioral sensitization and both D_1 and D_2 dopamine receptor antagonists attenuated the expression of this sensitization. The data also suggest that dopamine receptor antagonists were more potent in blocking cocaine's effects in cocaine-naive animals than in cocaine-sensitized animals.

Cocaine Behavioral sensitization Dopamine receptor subtypes Haloperidol R(+)-SCH-23390

REPEATED administration of psychomotor stimulants such as cocaine and amphetamine can produce a long-lasting and progressive enhancement in their behavioral effects (4,6,18, 30,33,35,37). Based on neurophysiological and molecular evidence obtained from sensitized animals, various hypotheses implicating dopamine have been put forward to explain this behavioral sensitization. These hypotheses include enhanced release of dopamine from dopaminergic nerve terminals as demonstrated both in vivo (2,17,28,34) and in vitro (3,22, 25,26,32), reduction in dopamine transporter function (16, 36), coupled with greater inhibitory potency of cocaine on this reduced function (16), subsensitivity of dopamine autoreceptors regulating impulse flow, and transmitter release (1,11, 19,42), and upregulation of postsynaptic dopamine receptor number (7,9,20,23,27,38,39) or function (12,13). Consistent with these observations of enhanced dopaminergic function is the recent behavioral evidence obtained using receptor subtype-selective agonists suggesting that sensitization induced by cocaine may involve long-lasting supersensitivity in postsynaptic dopamine receptors (8,40).

It has been reported that the dopamine receptor blocker haloperidol, although preventing the development of behavioral sensitization to cocaine, does not block its expression once sensitization has occurred (41). The reasons for the disagreement between the growing neurophysiological and molecular evidence favoring dopamine mechanisms and the pharmacological experiments not supporting such mechanisms in the expression of behavioral sensitization are not clear. One goal of this study was to examine the time course of development of behavioral sensitization to repeated once daily IV

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injections of various doses of cocaine. A second goal of the study was to elucidate the involvement of both D_1 and D_2 dopamine receptor subtypes in the expression of this sensitization by using the dopamine receptor subtype selective antagonists R(+)-SCH-23390 and haloperidol. Finally, the effects of these dopamine receptor subtype selective antagonists in blocking cocaine's acute behavioral effects were compared with their effects in attenuating the expression of behavioral sensitization to cocaine in sensitized animals.

METHOD

Subjects and Surgical Procedure

Male Sprague-Dawley rats weighing 300–400 g (Charles River Laboratories, Inc., Wilmington, DE) were used. Polyvinyl chloride catheters were inserted into the left femoral vein under halothane (2–3% in medical grade oxygen) anesthesia (for the infusion of drugs). The free ends of the catheters were passed SC to the dorsal portion of the neck region and externalized through a small incision in the skin. Catheters were protected by passing them through a metal spring connected to a rodent jacket (Alice King Chatham Medical Arts, Hawthorne, CA). The free ends of the springs were taken out through the space between the bars of the lid to the animal's home cage. To prevent the free end of the spring falling back into the cage, tape was placed around the spring 2–3 cm from the free end. This tape allowed the spring to move freely in the space between the metal bars of the cage lid while preventing the spring from falling back into the cage. There was a postoperative recovery period of 5 to 7 days prior to the commencement of experiments. All rats were housed individually with free access to water and food in a temperature- and humidity-controlled room on a 12 L : 12 D cycle.

Apparatus

Activity was recorded using an Autotrack system (Columbus Instruments, Columbus, OH) composed of photocell equipped activity monitors (Model, Opto-Varimex, Columbus Instruments). Activity monitors were placed in ventilated, illuminated, and sound-attenuated individual chambers. The activity monitor had a maximal observation area of 43.2 × 44.4 cm with 15 beams on each axis. Horizontal counts were the total number of beams, on both the X and the Y axis, which were interrupted by the animal. A time interval was judged to be stereotypic if the animal repeatedly breaks and makes the same beam for that time interval.

Behavioral Sensitization to Repeated Daily IV Injections of Cocaine

Four groups of six rats each were tested with 0.3, 1, or 3 mg/kg IV bolus doses of cocaine or 0.3 ml/kg IV saline. Rats were transported in their home cages to the testing room, weighed, and placed along with the home cage lid within the observational area of activity monitors. The venous catheter was flushed with 0.2 ml saline and connected to a long polyethylene tube that exited the sound-attenuated chamber and was connected to a saline syringe. The chambers were then closed and a 30 min period was allowed for the animals to acclimate to the testing environment prior to the injection of cocaine or saline. Cocaine or saline was injected once daily for 2 weeks followed by an immediate flush with 0.4 ml saline from outside the chamber through the polyethylene tubing. No injections were given on weekends. Starting from the first day of the third week (day 15), the effect of pretreatment with 0.1, 0.03, 0.3 mg/kg IV doses of haloperidol in that order on the behavioral response to cocaine or saline was tested. Haloperidol was administered using a separate syringe every other day 30 min prior to the cocaine or saline injections (i.e., just before closing the doors of the testing chambers). Each day of haloperidol testing was followed by a day of testing where the haloperidol vehicle (0.85% lactic acid, 0.3 ml/kg) was injected IV 30 min prior to cocaine or saline. To determine the involvement of conditioning, saline was substituted for cocaine on the second day of the fourth week (day 23) in the 3 mg/kg cocaine treated group of rats.

Two additional groups of six rats each were prepared with IV catheters as described above and then given once daily IV injections of 1 mg/kg cocaine (one group) or 0.3 ml/kg saline (one group) for 2 weeks with no injections on weekends. Similar to the procedure used for haloperidol testing, the effect of pretreatment with 0.03, 0.01, 0.003, or 0.1 mg/kg IV doses of R(+)-SCH-23390 in that order on the behavioral response to cocaine or saline in these groups was tested starting from the first day of the third week (day 15).

Effect of Dopamine Receptor Antagonists on the Acute Behavioral Effects of IV Cocaine

Three groups of six rats each (one control group and one group each for haloperidol and R(+)-SCH-23390 testing) were prepared with chronic IV catheters. These rats were handled as was done with chronic cocaine groups, except that saline was substituted for cocaine during the first 2 weeks and during those days that followed the antagonists testing days. Similar to chronic cocaine groups, starting from the first day of third week, IV doses of 0.1, 0.03, or 0.01 mg/kg haloperidol or 0.03, 0.01, or 0.003 mg/kg R(+)-SCH-23390 were administered in that order to their respective groups 30 min prior to an IV injection of 1 mg/kg cocaine. The response to cocaine in the presence of the dopamine antagonists in these acute groups was compared with the corresponding response to cocaine obtained in the acute control group where saline was administered prior to cocaine.

The mean responses to cocaine or saline injections in the presence of the dopamine receptor antagonists in the chronic groups were expressed as a percentage of the preceding days mean control response to cocaine or saline. The mean responses to 1 mg/kg cocaine in the presence of haloperidol or R(+)-SCH-23390 in the acute groups were expressed as a percentage of the mean of the corresponding responses to cocaine in the acute control group. This method of presentation was used to take into account the different baseline levels of activities present between the chronic and acute groups.

Drugs

The following drugs were used: (−)-cocaine hydrochloride (Mallinkrodt, St. Louis, MO), R(+)-SCH-23390 hydrochloride, (Research Biochemicals Inc., Natick, MA) and haloperidol (Sigma Chemical Co., St. Louis, MO). Cocaine and R(+)-SCH-23390 were dissolved in sterile physiological saline, while haloperidol was dissolved in 0.85% lactic acid. All doses are expressed as the salt (cocaine and R(+)-SCH-23390) or the base (haloperidol). Drugs were injected IV in a volume of 0.3 ml/kg.

Data Analysis

The raw data (horizontal counts and stereotypic time) were subjected to either analysis of variance for repeated measures

followed by post hoc tests (contrasts) for determining individual effects, or one-way analysis of variance followed by Tukey tests as appropriate. The data obtained with saline substitution was analyzed by an unpaired t-test. Data are expressed as mean ± 1 SE.

RESULTS

Behavioral Sensitization to Repeated Daily IV Injections of Cocaine

The IV administration of cocaine (0.3–3 mg/kg) on day 1 produced a dose-dependent increase in total horizontal counts recorded during the 60 min postinjection period. Horizontal counts in the groups treated with 1 and 3 mg/kg cocaine were significantly ($p < 0.05$) higher than in the saline-treated control group. Once daily injections of 1 and 3 mg/kg cocaine resulted in progressive enhancements in horizontal counts across days (Fig. 1). Statistically significant enhancement in horizontal counts first occurred on the second or fourth day in the groups treated with 3 or 1 mg/kg cocaine, respectively.

Cocaine also produced a dose-dependent increase in stereotypic behavior. Stereotypic times in the groups treated with 1 and 3 mg/kg cocaine were significantly ($p < 0.05$) higher than in saline-treated controls. Once daily injections of 1 mg/kg cocaine resulted in a progressive enhancement in stereotypic time compared to that observed on day 1 (Fig. 1). The enhancement in the stereotypic response to daily injections of 1 mg/kg cocaine was maximal by day 4. The stereotypic time responses to the subsequent six injections of 1 mg/kg cocaine given on days 4–12 were similar in magnitude to that after 3 mg/kg cocaine ($p = 0.86$).

Interaction of Haloperidol With Chronic IV Cocaine

Pretreatment with 0.1, 0.03, or 0.3 mg/kg haloperidol on days 15, 17, and 19, respectively, produced a dose-dependent attenuation of horizontal counts following cocaine (0.3–3 mg/kg) as compared to the preceding day's cocaine control response (Figs. 2 and 4). Total horizontal counts in the saline-treated control group were significantly attenuated by 0.1 and 0.3 mg/kg, but not by 0.03 mg/kg haloperidol. However, 0.03 mg/kg haloperidol significantly attenuated the increase in horizontal counts produced by cocaine (0.3–3 mg/kg). Horizontal counts (4660 ± 798) to 1 mg/kg cocaine on the vehicle control day (on day 16) after testing 0.1 mg/kg haloperidol (on day 15) was significantly ($p < 0.05$) greater than the corresponding horizontal counts (3682 ± 524) on the day before (day 12) testing haloperidol. This enhanced response to 1 mg/kg cocaine also occurred on the other vehicle control days 18 (4563 ± 860) and 22 (4628 ± 806). Because the control response to 1 mg/kg cocaine was significantly enhanced on the day after 0.1 mg/kg haloperidol treatment, this resulted in a higher control value when the 0.03 mg/kg dose of haloperidol was tested. In view of this, the 0.03 mg/kg dose of haloperidol was tested in another group of six rats that were initially sensitized with 10 daily injections of 1 mg/kg cocaine. Results in this group of rats were similar to those described above (data not shown).

Pretreatment with haloperidol also produced a dose-dependent attenuation of stereotypic time to cocaine (0.3–3 mg/kg) as compared to preceding day's cocaine control response (Figs. 3 and 4). Total stereotypic time in the saline-treated control group was significantly attenuated by 0.1 and 0.3 mg/kg haloperidol. However, 0.03 mg/kg haloperidol did significantly attenuate the increases in stereotypic time produced by cocaine. Unlike horizontal counts, there was no enhancement in stereotypic time to the control cocaine injection on the day after 0.1 mg/kg haloperidol.

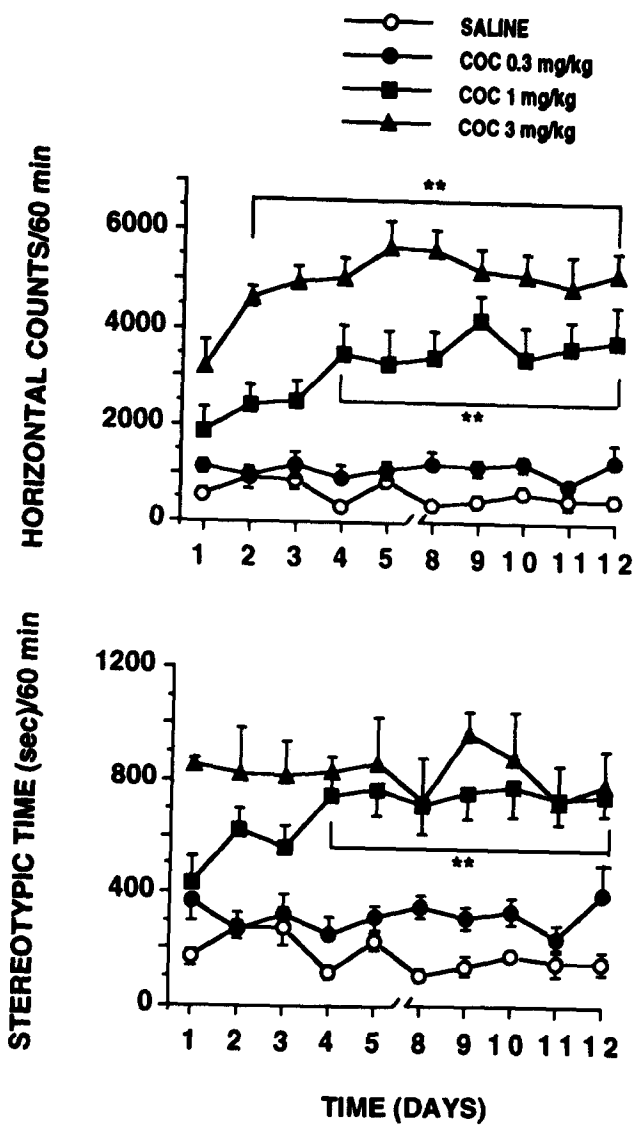

FIG. 1. Time course of development of behavioral sensitization to repeated once daily IV injections of cocaine (0.3–3 mg/kg) in rats. Both the horizontal counts (top panel) and stereotypic time (bottom panel) are the sum of data collected for 60 min immediately after the cocaine or saline injection. There were six animals in each group. $^{**}p < 0.01$ as compared to values on day 1.

Effect of Saline Substitution in Cocaine-Sensitized Animals

When saline was substituted for cocaine on day 23 in the group that had received daily injections of 3 mg/kg cocaine, both horizontal activity (3341 ± 460 counts) and stereotypic time (684 ± 204 s) remained significantly ($p < 0.01$) elevated compared to corresponding values on day 23 in the group that received daily injections of saline (horizontal activity, 822 ± 306 counts; stereotypic time, 202 ± 57 s).

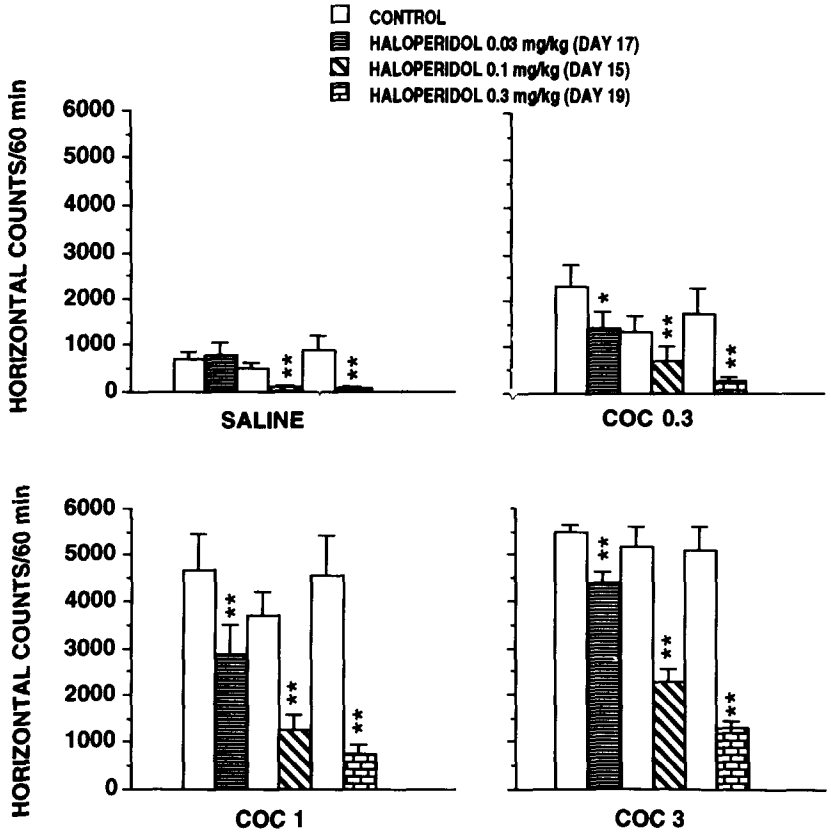

FIG. 2. Attenuation by haloperidol of horizontal counts following IV cocaine (0.3–3 mg/kg) or saline (0.3 ml/kg) injections in rats previously treated with once daily IV injections of cocaine or saline for 2 weeks with no injections on weekends. The open bar preceding each dose of haloperidol in all four groups represents control responses in the absence of haloperidol obtained on the day before haloperidol testing. There were six animals in each group. $*p < 0.05$, $**p < 0.01$ compared to the preceding day's control response.

Interaction of R(+)-SCH-23390 With Chronic IV Cocaine

Pretreatment with the D_1 dopamine receptor antagonist R(+)-SCH-23390 (0.003–0.1 mg/kg) produced a dose-dependent attenuation of horizontal movement and stereotypic time to cocaine as compared to the preceding day's cocaine control response (Fig. 4 and Table 1). A dose of 0.01 mg/kg R(+)-SCH-23390 produced a marked ($p < 0.01$) inhibition of cocaine's effect. There was no enhancement of the control response to 1 mg/kg cocaine tested on the day after treatment with R(+)-SCH-23390. The doses of R(+)-SCH-23390 that attenuated the increases in horizontal activity and stereotypic time produced by cocaine in sensitized animals also produced an identical degree of reduction in the horizontal activity and stereotypic time produced by saline in animals that had received once daily injections of saline (Fig. 4).

Effect of Dopamine Receptor Antagonists on Acute Behavioral Effects of IV Cocaine

Pretreatment with haloperidol (0.01–0.1 mg/kg IV) or R(+)-SCH-23390 (0.003–0.03 mg/kg IV) dose dependently attenuated the acute locomotor effects of cocaine (Fig. 4 and Table 1). These antagonists were more potent in blocking the acute effects of cocaine as compared to the expression of cocaine's behavioral effects in sensitized animals. For example, 0.003 mg/kg R(+)-SCH-23390 was marginally effective in attenuating the expression of cocaine's behavioral effects in sensitized animals, while this dose markedly attenuated the acute behavioral effects of cocaine. Similarly, haloperidol at any given dose produced a much greater blockade of the acute effects of cocaine as compared to cocaine's effects in sensitized animals.

DISCUSSION

Behavioral Sensitization to IV Cocaine

The data presented provide evidence for the first time that cocaine given as repeated once daily IV injections produces behavioral sensitization in rats. The present sensitization to IV cocaine is consistent with previous studies reporting behavioral sensitization to daily IP cocaine injections in experimental animals (18,30,35,37). Cocaine elicited a progressive enhancement in both horizontal and stereotypic movements. The development of behavioral sensitization to cocaine was dependent on dose with sensitization to 3 mg/kg cocaine occurring

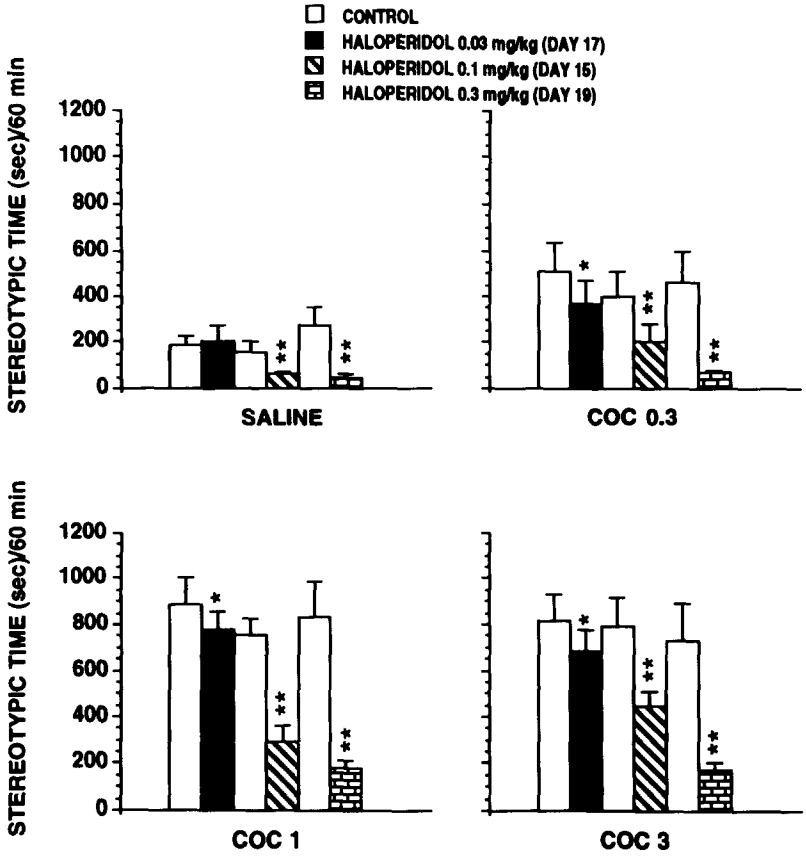

FIG. 3. Attenuation by haloperidol of stereotypic time following IV cocaine (0.3-3 mg/kg) or saline (0.3 ml/kg) injections in rats previously treated with once daily IV injections of cocaine or saline for 2 weeks with no injections on weeksends. The open bar preceding each dose of haloperidol in all four groups represents control responses in the absence of haloperidol obtained on the day before haloperidol testing. There were six animals in each group. $*p < 0.05$, $**p < 0.01$ compared to the preceding day's control response.

after a single dose. With a lower dose of 1 mg/kg, sensitization occurred after three daily doses, and after 0.3 mg/kg cocaine no sensitization was observed. These observations suggest that the rate of development of sensitization depends on the intensity of the stimulus used. Sensitization to horizontal activity occurred with both the 1 and 3 mg/kg doses of cocaine, while sensitization to stereotypic behavior occurred only with 1 mg/kg. It is likely that the stereotypic response to 3 mg/kg cocaine on day 1 was maximal and, thus, sensitization to subsequent injections did not occur due to this ceiling effect. However, doses greater than 3 mg/kg were not tested to determine the maximal stereotypic behavior to support this contention. But, it may be noted that the 1 mg/kg cocaine group exhibited on day 4 maximal stereotypic activity that was not significantly different in magnitude from the initial (day 1) or subsequent responses in the 3 mg/kg cocaine group.

The present data also suggest possible differences in the motor effects to chronic cocaine as compared to chronic amphetamine. It has been shown that behavioral sensitization to chronic amphetamine, especially at high doses, consists of enhanced stereotypic behavior with a simultaneous reduction in locomotion (21,33). Such a pattern of response was not seen with chronic cocaine in the present study. This may possibly reflect some basic differences in the mechanisms involved in the motor activating effects of cocaine vs. amphetamine (10,31).

Effect of D_1 or D_2 Dopamine Receptor Antagonists on the Acute Effects of Cocaine and the Expression of Sensitization

The important finding of the present study is that the doses of the D_1 dopamine receptor antagonist R(+)-SCH-23390 and the D_2 dopamine receptor antagonist haloperidol required to attenuate the expression of the behavioral effects of cocaine in sensitized animals are considerably larger than the doses required to block cocaine's acute locomotor effects in cocaine-naive animals (Fig. 4). These antagonists in nonsedative doses clearly blocked the acute behavioral effects of cocaine. In contrast, with the exception of 0.03 mg/kg haloperidol, the doses of these antagonists needed to attenuate the expression of the behavioral effects of cocaine in sensitized animals are sedative as similar doses produced an identical reduction in locomotor activity in saline-treated animals. Although no attempt has been made in the present study to delineate the

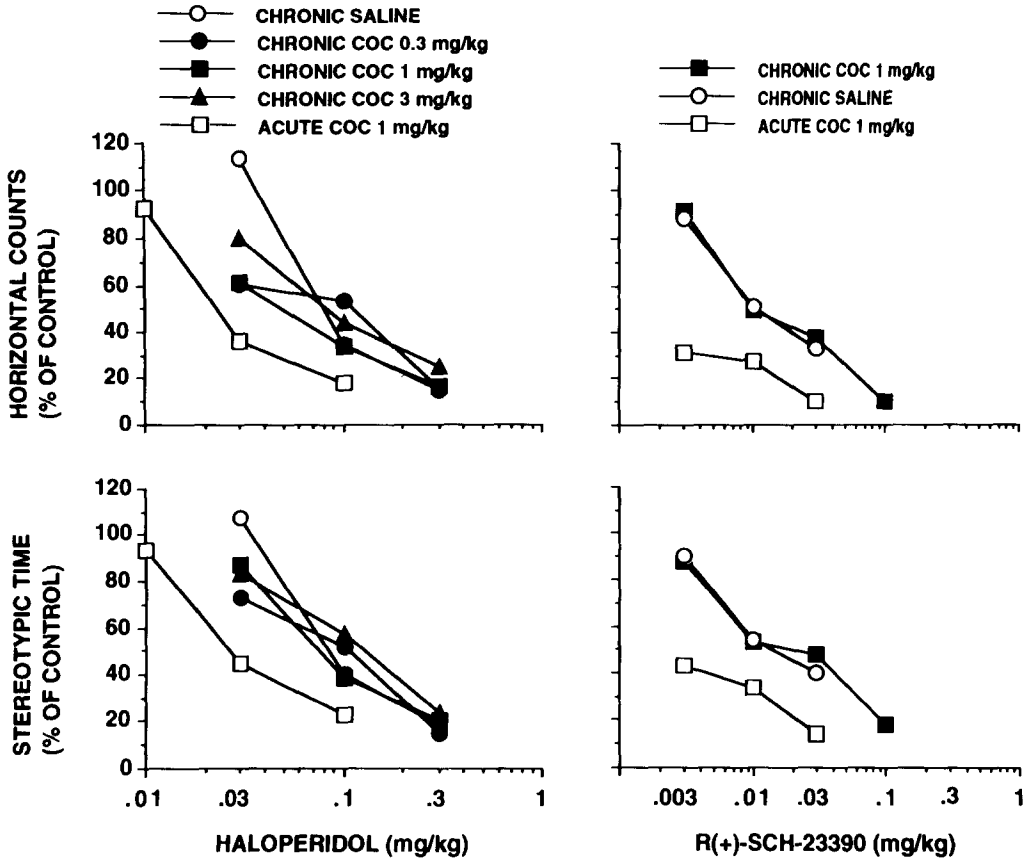

FIG. 4. Attenuation by haloperidol and R(+)-SCH-23390 of horizontal counts (top panels) and stereotypic time (bottom panels) following IV cocaine (0.3–3 mg/kg) or saline (0.3 ml/kg) in rats previously treated with repeated once daily IV injections of various doses (0.3–3 mg/kg) of cocaine or saline (chronic) and in cocaine-naive (acute) animals. The mean responses to cocaine or saline injection in the presence of haloperidol or R(+)-SCH-23390 in chronic groups (the data from Figs. 2 and 3 and Table 1) are expressed as a percent of their respective preceding day mean control responses to cocaine or saline in the corresponding groups. The mean responses to 1 mg/kg cocaine in the presence of haloperidol or R(+)-SCH-23390 in acute groups (the data from Table 1) are expressed as the percent of the mean of the corresponding responses to cocaine in the acute control group.

importance of the sedative action of dopamine antagonists per se in the attenuation of the expression of sensitization, a recent study suggests that this effect may be due to the specific blockade of dopamine receptors and not due to the resultant sedative actions per se (15). These authors reported that sodium pentobarbital, which reduced spontaneous locomotor activity in a manner similar to higher doses of the dopamine antagonists, had no effect on the expression of amphetamine conditioned place preference, while the dopamine antagonists did attenuate place preference. Although it is not known whether the conditioned place preference method is similar to the present method of behavioral sensitization, the present method of behavioral sensitization is similar to place preference with respect to the involvement of a conditioning component. However, the findings with the dopamine antagonists indicate that these two methods may have some critical differences. For example, in the present study the rightward shift in the doses required to attenuate the expression of behavioral sensitization as compared to that required to produce blockade of the acute effects of cocaine was seen with both D_1 and D_2 antagonists, whereas in the study by Hiroi and White (15) such a rightward shift was observed with D_2, but not with D_1 antagonists.

One previous report indicates that haloperidol, even at doses that produce marked sedation, is ineffective in antagonizing the behavioral sensitization produced by a single high dose (40 mg/kg) of IP cocaine (41). Based on this, it was hypothesized that locomotor effects of cocaine in sensitized animals may be mediated by dopamine-independent mechanisms. If this hypothesis were true for the present sensitization to IV cocaine, the antagonists curves for chronic cocaine groups would have showed a shift to the right of the chronic saline group. Contrary to this expectation, the curves for cocaine and saline in the presence of either R(+)-SCH-23390 or haloperidol are almost identical (Fig. 4). Because the saline substitution test revealed the involvement of a conditioning component similar to that reported using IP administration (14,29,41), the present discrepancy is unlikely to be related to the differences in the involvement of conditioning. One possibility may be the differences in the experimental procedures, such as single vs. repeated dosing. Another factor to be considered is the timing of the cocaine injection relative to

TABLE 1

ATTENUATION BY DOPAMINE RECEPTOR ANTAGONISTS OF LOCOMOTOR EFFECTS OF COCAINE IN CHRONIC (SENSITIZED WITH REPEATED COCAINE INJECTIONS) AND ACUTE (COCAINE-NAIVE) GROUPS OF RATS

	Horizontal Counts/60 Min		Stereotypic Time (s)/60 Min	
Treatment	Chronic*	Acute	Chronic*	Acute
R(+)-SCH-23390:				
Control	3784 ± 481	2551 ± 304	723 ± 56	527 ± 43
R(+)-SCH-23390 (0.003)	3470 ± 307	800 ± 129[a,d]	636 ± 33[b]	227 ± 34[c,f]
Control	3890 ± 528	2399 ± 292	761 ± 70	529 ± 45
R(+)-SCH-23390 (0.01)	1924 ± 385[b]	660 ± 104[c,d]	399 ± 44[b]	178 ± 29[c,f]
Control	3978 ± 301	2198 ± 329	761 ± 53	481 ± 35
R(+)-SCH-23390 (0.03)	1493 ± 259[b]	225 ± 51[c]	366 ± 37[b]	67 ± 15[c,f]
Control	3817 ± 397	–	715 ± 69	–
R(+)-SCH-23390 (0.1)	383 ± 80[c]	–	129 ± 31[c]	–
Haloperidol:				
Control	–	2551 ± 304	–	527 ± 43
Haloperidol (0.01)	–	2367 ± 362	–	494 ± 57
Control	4660 ± 798	2399 ± 292	884 ± 120	529 ± 45
Haloperidol (0.03)	2867 ± 639[b]	871 ± 143[c,d]	774 ± 83[b]	237 ± 31[c,f]
Control	3682 ± 525	2198 ± 329	754 ± 72	481 ± 35
Haloperidol (0.1)	1253 ± 333[b]	396 ± 52[c,d]	292 ± 71[b]	107 ± 11[c,d]
Control	4563 ± 861	–	830 ± 155	–
Haloperidol (0.3)	757 ± 168[b]	–	181 ± 32[b]	–

The control values preceding each dose of antagonist testing represent the responses to cocaine obtained in the absence of antagonists. There were six animals in each group. [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.001$ compared to the preceding control responses. [d]$p < 0.05$, [e]$p < 0.01$; [f]$p < 0.001$ compared to their corresponding effects in the chronic cocaine groups. Values in parentheses represent the dose (mg/kg) of antagonist. The dose of cocaine was 1 mg/kg.

*The data for the haloperidol tested chronic cocaine (1 mg/kg) group was from Figs. 2 and 3.

the time of placement of the animals into the test environment, as pairing of these two variables has been reported to produce results that are different from that seen when injection and placement in the chamber are not paired (5). Further, because there was a rightward shift in the effects of the dopamine antagonists from the acute to the chronic cocaine condition (Fig. 4), testing with a single selected dose of these antagonists may not necessarily reveal the antagonistic ability of these agents on the expression of sensitization.

Relationship of the Present Behavioral Evidence to the Neurophysiological and Molecular Studies Supporting Dopaminergic Mechanisms in the Behavioral Sensitization

Although, the precise neurophysiological and molecular alterations underlying behavioral sensitization to repeated administration of cocaine or other psychomotor stimulants are not clearly established, there have been several studies reporting upregulation of dopamine receptor number and function especially in the nucleus accumbens, reduced ability of neurotransmitter inactivating mechanisms, increased inhibitory efficacy of cocaine on dopamine transporter in nucleus accumbens, and enhanced release of dopamine from dopaminergic nerve terminals in chronic cocaine-treated animals and in vitro striatal slice preparations (see introduction). In view of the above, it is possible that greater levels of dopamine receptor antagonists are required to antagonize this enhanced dopaminergic neurotransmission to cocaine challenge in sensitized animals vs. cocaine-naive animals. Consistent with this hypothesis is the present finding that there was a clear rightward shift in the dose-effect relationship of these antagonists in blocking the expression of behavioral sensitization as compared to their ability to block the acute behavioral effects of cocaine (Fig. 4). Thus, this rightward shift provides behavioral evidence supporting the hypothesis of enhanced endogenous dopaminergic activity in response to cocaine injection in sensitized animals, as compared to that in cocaine-naive animals. Further, the fact that the rightward shift occurred with both D_1 and D_2 dopamine receptor subtype selective antagonists indirectly suggests that the enhanced endogenous dopaminergic activity involves the mediation by both D_1 and D_2 dopamine receptors. Such an enhancement in dopaminergic transmission, at least theoretically, could result from an enhanced synaptic dopamine concentration (see introduction).

Recently, it has been hypothesized that the relatively long-lasting increased sensitivity of D_1 dopamine receptors in nucleus accumbens after repeated cocaine administration may be involved in behavioral sensitization (12,13). This enhancement in the electrophysiological response to D_1 dopamine receptor stimulation has been reported to persist for at least a month following cocaine administration and, thus, favor the possible importance of this change to the enduring behavioral sensitization. Because similar treatment regimens with cocaine do not increase D_1 receptor density (20,27), it has been suggested that this enhanced electrophysiological response to D_1 receptor stimulation in sensitized animals may be related to alterations in D_1 receptor-coupled transduction mechanisms (12, 24). Not consistent with this hypothesis is the recent behav-

ioral evidence that long-lasting enhanced responses to D_2 receptor agonists, but not to D_1 receptor agonists, may develop during sensitization to the chronic administration of methamphetamine or cocaine (40). Contrary to both these views, the present study using receptor subtype selective antagonists indicates that blockade of either one of these receptor subtypes is capable of independently attenuating the expression of locomotor sensitization. In view of the present finding that the rightward shift in attenuating the expression of sensitization as compared to their ability to block the acute effects of cocaine occurred with both D_1 and D_2 dopamine receptor subtype selective antagonists, it appears unlikely that the alteration in one subtype of dopamine receptor alone is involved in the expression of behavioral sensitization. The reasons for these diverse conclusions using subtype selective agonists (12, 13,40) vs. antagonists (present study), and electrophysiological (12,13) vs. behavioral approaches (40) are not clear from the present study. Future studies directed toward understanding the nature of the possible complex interaction between these receptor subtypes may help resolve these issues.

In summary, the present study reveals that repeated once daily IV injections of cocaine produces behavioral sensitization, and that both D_1 and D_2 dopamine receptor antagonists attenuate the expression of this sensitization. However, the doses of both D_1 and D_2 dopamine receptor antagonists required to attenuate the expression of behavioral sensitization are much larger than those required to block the acute behavioral effects of cocaine.

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