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Effects of Chronic SCH 23390 or Acute EEDQ on the Discriminative Stimulus Effects of SKF 38393

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GUI-HUA, C., B. D. PERRY AND W. L. WOOLVERTON. *Effects of chronic SCH 23390 or acute EEDQ on the discriminative stimulus effects of SKF 38393.* PHARMACOL BIOCHEM BEHAV **41**(2) 321-327, 1992.—Three groups of rats (n = 8/group) were trained in a two-lever, food-reinforced drug discrimination paradigm to discriminate the D_1 agonist SKF 38393 (SKF; 8.0 mg/kg, IP) from saline. After acquisition of the discrimination, the dose-response function for SKF (2.0-16 mg/kg, IP) was determined using a cumulative dosing procedure. In one group, the SKF dose-response function was redetermined 1 week after a regimen of 0.25 mg/kg of the D_1 antagonist SCH 23390 (SCH), IP, once/day for 10 days, again 1 week after a second regimen of 0.5 mg/kg SCH, IP, twice/day for 10 days, and a third time after a regimen of 1.0 mg/kg SCH, IP, twice/day for 21 days. SKF dose-response functions were redetermined in a group of control rats after identical injection regimens of saline. In the third group of rats, SKF dose-response functions were redetermined 24 h after an injection of *N*-ethoxycarboxyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) (irreversible antagonist) vehicle; again 24 h after an injection of 3.0 mg/kg; again 48 h after 6.0 mg/kg EEDQ; and finally 48 h after two consecutive daily injections of 6.0 mg/kg EEDQ (12 mg/kg total). The dose-response function for the percentage of responses that occurred on the SKF lever (%DL) shifted significantly to the left following the second regimen of SCH; there was no further shift after the third regimen. The effects of SKF on response rate were unchanged by SCH administration. Repeated administration of saline did not alter the SKF dose-response function for %DL or response rate. Administration of EEDQ vehicle or EEDQ also failed to alter the SKF dose-response functions for %DL. However, EEDQ itself decreased response rate and enhanced the rate-decreasing effects of SKF. Binding studies conducted 14 days after SCH exposure indicated a significant increase in B_{max} for D_1 binding sites in the corpus striatum in SCH-treated rats. B_{max} tended to increase in the nucleus accumbens, but did not achieve statistical significance. EEDQ treatment decreased B_{max} in corpus striatum 48 h after administration, but had no effect in nucleus accumbens. K_d was unchanged in either region by either treatment. The results demonstrate that repeated administration of the D_1 antagonist SCH can sensitize rats to the DS effects of the D_1 agonist SKF, perhaps via an up-regulation of D_1 receptors in the brain. Further, the results suggest that drug discrimination is a useful in vivo bioassay for measuring changes in CNS receptors.

Drug discrimination SCH 23390 SKF 38393 EEDQ D_1 receptors Behavior

DRUG discrimination has proven to be a sensitive and selective technique for studying the actions of drugs in the CNS. Perhaps the best example of this is the use of the technique to study opioid receptors (1,3,12,13). Sensitivity and selectivity have been observed with dopamine (DA) agonists and antagonists as well. Although the available data is less extensive than with opioids (5,15,27,30), it suggests that the discriminative stimulus (DS) effects of DA agonists is based upon actions at specific receptors in the CNS. If this is the case, then alteration of DA receptors should modify the DS effects of DA agonists. Repeated administration of SCH 23390 (Schering-Plough Corp., Bloomfield, NJ; SCH), a D_1 antagonist, has been shown to selectively increase the density of D_1 (DA) binding sites in corpus striatum (4,23). On the other hand, acute administration of *N*-ethoxycarboxyl-2-ethoxy-1,2-dihydroquinoline (Aldrich Chemical Co., Milwaukee, WI; EEDQ), a peptide coupling agent, has been shown to decrease the density of several different binding sites in the CNS, including D_1 sites (10,19). It has been shown previously that presynaptic changes in CNS DA systems can alter sensitivity to the DS effects of indirect DA agonists (6,29). The purpose of the present experiment was to determine whether postsynaptic receptor changes induced by repeated administration of SCH or acute administration of EEDQ could alter the DS effects of the D_1

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agonist SKF 38393 (7,8-dihydroxy-1-phenol-2,3,4,5-tetrahydro-1 *H*-2-benzazepine hydrochloride, Research Biochemicals, Inc., Natick, MA; SKF) and to relate those changes to changes in the number and affinity of D_1 binding sites in the CNS.

METHOD

Animals and Apparatus

Twenty-four male Sprague-Dawley rats (Holtzman Co., Madison, WI) were maintained at 200–260 g (80 ± 5% of their initial free-feeding body weights) by restricting food intake. They were individually housed in stainless steel cages in a room maintained at 24°C and on a 12 L:12 D cycle (7 a.m.–7 p.m. light). In addition to the 45-mg food pellets (P. J. Noyes Co., Lancaster, NH) delivered during the experimental sessions, diet was supplemented with Teklad 4% Mouse and Rat Diet (Winfield, IA) to maintain stable body weights. Water was continuously available except during experimental sessions.

Four identical operant chambers for rats (R. Gerbrands Co., Arlington, MA) were used. In each chamber, two response levers were mounted on one wall and a food receptacle was located between them. Each chamber was illuminated at the onset of an experimental session by a single 6-w light located on the wall opposite the levers. Extraneous noise was diminished by enclosing each chamber in an insulated chest and by operating a ventilation fan mounted on the outside of each chest. An AIM-65 microcomputer (Dynatem Corp., Irvine, CA), connected to a custom-designed input/output interface (ERH Electronics, Delton, MI), located in an adjacent room, controlled external stimulus events and recorded lever presses.

Behavioral Procedure

Rats were randomly assigned to one of the four experimental chambers. In two chambers, the right lever was designated the drug-appropriate lever and the left lever the saline-appropriate lever. In the other two chambers, the reverse assignments were made. Half of the rats were shaped initially by successive approximation to press the drug-appropriate lever after injections of 8.0 mg/kg SKF and the remaining rats were shaped initially to press the saline-appropriate lever after saline (2.0 ml/kg) injections. Injections were given IP 30 min before the session and the rats were returned to their home cage. Twenty minutes after the injection (i.e., 10 min before the session), they were placed in the experimental chambers. Ten minutes later, the houselight was illuminated and food was available for every response on the injection-appropriate lever.

Ten-minute training sessions were conducted once a day, 7 days a week, following a double alternation sequence in which two sessions of drug pretreatments alternated with two sessions of saline pretreatments. Although this sequence was used in each rat, the daily order in which sessions were conducted was randomized so that the type of session in effect for one rat on a given day was not predictive of the type of session for subsequent rats. These manipulations controlled for the possibility of odor cues exerting discriminative control of behavior (8). During this training period, the response requirement on either lever was increased gradually so that under terminal conditions every tenth response (fixed-ratio 10: FR 10) on the lever appropriate to the injection resulted in the delivery of a food pellet. In addition, the contingency that incorrect responses reset the response requirement on the injection-appropriate lever was added. The double alternation training sequence continued until a rat met the following criteria for stimulus control over responding. First, in seven of eight consecutive sessions at least 80% of the responses before the delivery of the first food pellet had to occur on the injection-appropriate lever. Second, 90% of the responses that occurred throughout the 10-min session had to be on the injection-appropriate lever.

Once a rat met the criteria for stimulus control, test sessions were conducted using a pretreatment sequence of drug, saline, test, saline, drug, test as long as performance in the training sessions between test sessions remained at or above the criteria for stimulus control. If a rat's performance fell below criterion levels during the intervening training sessions, it was returned to the double alternation training sequence until discrimination again was at or above criterion levels. The SKF dose–response function was determined using a cumulative dosing procedure in which all points were obtained on a single test day. A test session consisted of five consecutive epochs, each of which consisted of a 30-min time-out period (TO), during which the chamber was dark and responses had no consequence, followed by a 5-min period during which the houselight was illuminated and responding on either lever resulted in food delivery. Injections were given at the beginning of each TO period in such a way as to achieve a cumulative dose of 16 mg/kg SKF before the final epoch. Specifically, saline was administered before the first TO and SKF doses of 2.0, 2.0, 4.0, and 8.0 mg/kg were administered before succeeding epochs. To control for the novelty of the test situation, multiperiod training sessions were conducted once/week. In these sessions, the training dose of SKF was administered before a randomly selected epoch, after which the session ended. Injections before any preceding epochs were saline. In addition, test sessions in which saline was administered before all epochs were occasionally conducted.

After the SKF dose–response function had been determined, the rats were randomly divided into three groups of eight. One group (SCH) was exposed to three consecutive regimens of daily injections of SCH 23390: 1) 0.25 mg/kg IP, once/day for 10 days; 2) 0.5 mg/kg IP, twice/day for 10 days; 3) 1.0 mg/kg IP, twice/day for 21 days. In each case, training sessions were suspended during chronic treatment and began again 24 h after the last injection of SCH. Post-SCH dose–response functions for SKF were redetermined after four consecutive training sessions, including one multiperiod session, at criterion performance. The day post-SCH on which the SKF dose–response function was redetermined varied between rats. The control group (SAL) was given an identical sequence of daily saline injections (1.0 ml/kg). A third group (EEDQ) was first treated with EEDQ vehicle (1.0 ml/kg) and the SKF dose–response function was redetermined 24 h later. Next, the rats were exposed to three consecutive EEDQ regimens, each followed by a redetermination of the SKF dose–response function: 1) 3.0 mg/kg IP, 24 h pre-SKF; 2) 6.0 mg/kg, IP, 48 h pre-SKF; 3) 6.0 mg/kg 96 h pre-SKF and 6.0 mg/kg 48 h pre-SKF. Thus, because of the brief injection regimen, the initial vehicle treatment served as a within-subject control in the EEDQ group.

D_1 Receptor Binding

Rats in the SCH and SAL groups were sacrificed by decapitation 14 days after the last injection of final injection regimen. For the EEDQ rats, the third injection regimen (6.0 +

6.0 mg/kg, IP, 96 and 48 h) was repeated at least a week after the final SKF dose-response redetermination. The rats were sacrificed 48 h after the second dose of EEDQ. Brains were removed and dissected over ice according to the method of Heffner et al. (11). Corpus striatum and nucleus accumbens were wrapped individually in aluminum foil, flash frozen in liquid nitrogen, and stored at −70°C until assayed.

Radioligand binding methods for D_1 receptor binding sites were adapted from Sidhu and Kebabian (25). D_1 binding sites were labeled with [^{125}I] SCH 23982 (NEN Dupont, 2200 Ci/mmol). For the binding studies, immediately prior to each assay tissue from individual animals was slowly thawed and disrupted by sonification using intermittent 5-s bursts with a Branson Sonifier in 20 vol (w/v) 50 mM Tris-HCl buffer (pH 7.5, 25°C, with 5 mM NaEDTA and 50 nM NaCl). This homogenate was centrifuged at 45,000 × *g* for 15 min at 4°C. The resulting pellet was resuspended in 20 vol 50 mM Tris-HCl (pH 7.5, 25°C with 50 nM NaCl) and centrifuged as above. The final pellet was suspended in assay buffer. D_1 binding sites were quantified using saturation studies (six concentrations ranging from 0.01–1.5 nM). Aliquots of tissue (final concentration of 50–120 μg protein/ml) in 50 nM Tris-HCl buffer (pH 7.5, 25°C, with 100 nM NaCl) were incubated with increasing concentrations of radioligand for 60 min at 37°C. Parallel incubations in the presence of flupenthixol defined specific binding. Ketanserin (10^{-6} M) was included in all tubes to eliminate binding to 5-HT2 sites. Final assay volume was 200 μl. Incubation was terminated by filtration under reduced pressure over Whatman GF/B filters using a Branndel Cell Harvester modified for radioligand binding assays. Filters were rinsed three times with 5.0 ml ice-cold 50 mM Tris-HCl buffer (pH 7.7, 25°C). The filters were placed in vials and radioactivity was counted using a Micromedic gamma counter with efficiency of 90%. Raw counts from all assays were transformed using RADLIG (18), a radioligand binding analysis software package that contains EBDA and a version of LIGAND derived from the original (18,20). Protein content was determined using the commercially available Bio-Rad assay.

Data Analysis

The percentage of total responses that occurred on the drug-appropriate lever and the rate of responding on both levers during test sessions were calculated for each rat and the mean and SEM were calculated for the group. Dose-response functions were compared using analysis of variance (ANOVA). One rat in the SAL group died during the experiment and data from that rat were discarded. In addition, after exposure to the second regimen of SCH two rats in the SCH group responded exclusively on the saline lever in test sessions. Their data were excluded from the analysis. D_1 binding data were analyzed using ANOVA with posthoc comparisons using Bonferroni *t*-test (9). Effects were considered significant for *p* values less than or equal to 0.05.

Drugs

SKF was dissolved in sterile water. Injections were generally administered in a volume of 1.0 ml/kg and the concentration was varied appropriately. However, because of solubility limitations, SKF was prepared in a maximum concentration of 4.0 mg/ml. For doses higher than 4.0 mg/kg, injection volume was increased accordingly. SCH was dissolved in propylene glycol : water (1 : 3). EEDQ was dissolved in ethanol diluted sequentially with propylene glycol and water (final v/v/v/ ratio of 1 : 1 : 2). All injections were given IP.

RESULTS

The SAL rats met the criteria for stimulus control after a mean of 47 training sessions (range 36–54 sessions) and the SCH rats met the criteria after a mean of 51 training sessions (range 29–91 sessions). SKF (2.0–16 mg/kg) produced a dose-dependent increase in the percentage of responses that occurred on SKF-appropriate lever in both the SCH (Fig. 1) and the SAL (Fig. 2) rats with little effect on the response rate of either group. Note that a cumulative dose of 8.0 mg/kg engendered less than the minimum 80% SKF-appropriate responding seen with that dose under training conditions, probably because some elimination of drug administered in early doses had taken place. Rats met criteria for stimulus control after a mean of 8 sessions (range 6–14 sessions) after all regimens and there was no systematic difference between the SAL

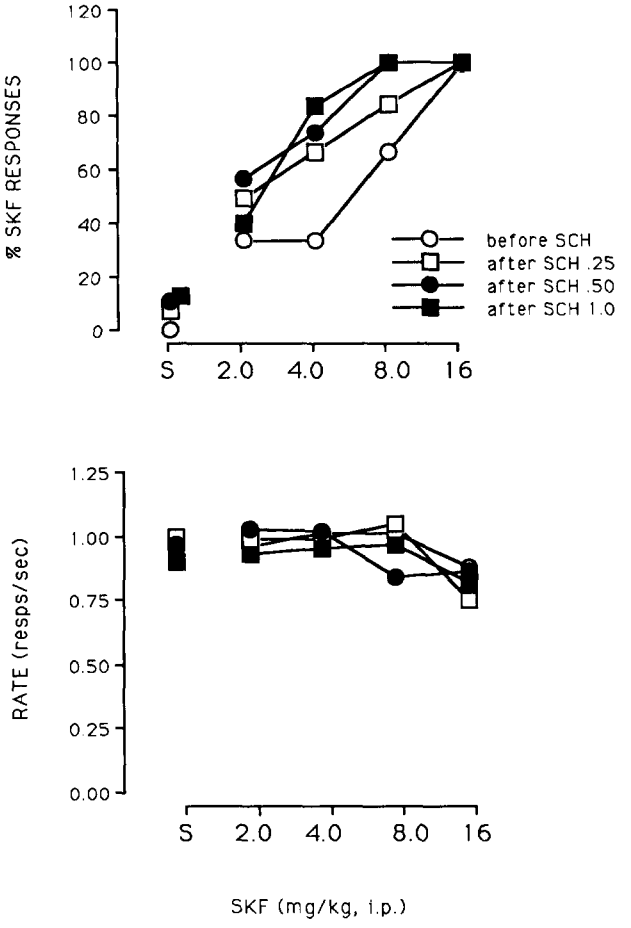

FIG. 1. Effects of SKF 38393 in rats given repeated injections of SCH (10–21 days). Rats were trained to discriminate SKF (8.0 mg/kg, IP) from saline. Upper graph, percentage of responses during test sessions that occurred on the SKF-appropriate lever as a function of cumulative dose of SKF; lower graph, response rate during test sessions as a function of dose. Each point represents the mean of six rats. Measures of variability are omitted for clarity. For % SKF responses, SEM was generally less than 20%. For response rate, SEM was approximately 0.2 resp/s.

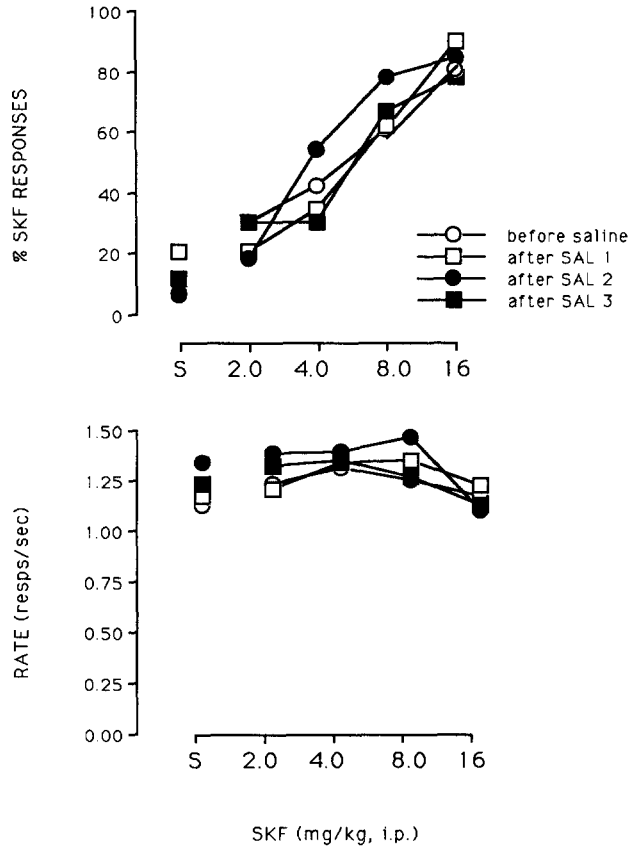

FIG. 2. Effects of SKF 38393 in rats given repeated injections of saline (10–21 days). Rats were trained to discriminate SKF (8.0 mg/kg,IP) from saline. Upper graph, percentage of responses during test sessions that occurred on the SKF-appropriate lever as a function of cumulative dose of SKF; lower graph, response rate during test sessions as a function of dose. Each point represents the mean of seven rats. Variability was as in Fig. 1.

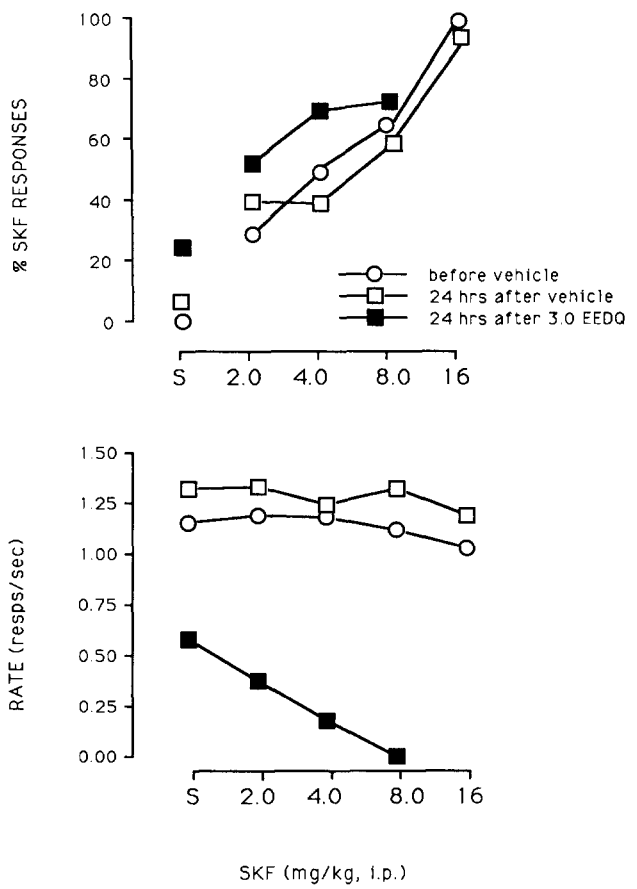

FIG. 3. Effects of SKF 38393 in rats given EEDQ vehicle or 3.0 mg/kg EEDQ 24 h before test sessions. Rats were trained to discriminate SKF (8.0 mg/kg, IP) from saline. Upper graph, percentage of responses during test sessions that occurred on the SKF-appropriate lever as a function of cumulative dose of SKF; lower graph, response rate during test sessions as a function of dose. Each point represents the mean of five rats. Variability was as in Fig. 1.

and SCH groups in this measure. There was no significant change in the percentage of responses that occurred on the SKF lever after the initial exposure to SCH ($p > 0.05$). However, the SKF dose-response function was shifted significantly to the left after repeated administration of 0.5 mg/kg/day SCH ($p < 0.025$) and 1.0 mg/kg/day SCH ($p < 0.025$). In contrast, the SKF dose-response function was unaffected after repeated injections of saline ($p > 0.05$, all comparisons). The effects of SKF on response rate were unaffected by the repeated injection regimen in either group of rats.

The EEDQ rats met the criteria for stimulus control after a mean of 43 training sessions (range 28–59 sessions). As in the other groups, SKF (2.0–16 mg/kg) produced a dose-dependent increase in the percentage of responses that occurred on SKF-appropriate lever but had little or no effect on response rate (Fig. 3). Pretreatment with the EEDQ vehicle did not alter the percentage of responses that occurred on the SKF lever. Pretreatment with 3.0 mg/kg EEDQ induced catalepsy beginning 5 min after injection. Although there was a tendency for responding on the SKF lever to increase at 2.0 and 4.0 mg/kg SKF 24 h after 3.0 mg/kg EEDQ, this effect did not achieve statistical significance. Moreover, the same tendency was noted following saline injections (points above S in Fig. 3, top panel). Response rate following saline injection was decreased to 0.62 resp/sec and the effect SKF on response rate was substantially enhanced. The higher dose of EEDQ, 6.0 mg/kg, also induced catalepsy and rats failed to lever press 24 h later (data not shown). When 6.0 mg/kg EEDQ was given 48 h presession, there was no effect on the percentage of responses that occurred on the SKF lever at any SKF dose or on response rate following saline injection in six of the rats (Fig. 4). The other two rats failed to reacquire the discrimination after this EEDQ regimen and could not be tested. Similarly, when 6.0 mg/kg EEDQ was given both 96 and 48 h presession, there was no change in the effect of SKF on SKF lever responding in five of the remaining rats while the effect of 16 mg/kg SKF on response rate was enhanced after this combination. The sixth rat failed to reacquire the discrimination after this regimen of EEDQ.

For rats in the SAL group, B_{max} was 248.1 (± 41.4, SEM) fmol/mg of protein in the corpus striatum and 291 (± 60.2, SEM) in the nucleus accumbens (Fig. 5). B_{max} was increased in the SCH group in the striatum to 430.8 (± 70.6 SEM; $p < 0.01$ vs. SAL group). B_{max} tended to increase in the SCH group in the nucleus accumbens as well, but failed to achieve statistical significance ($p = 0.057$) because of relatively high vari-

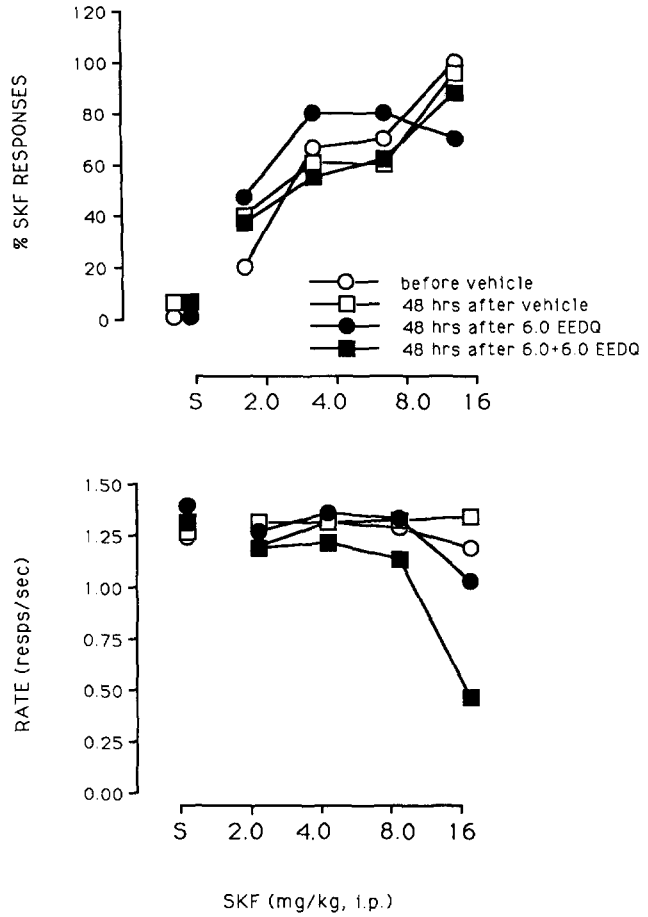

FIG. 4. Effects of SKF 38393 in rats given EEDQ vehicle or 6.0 mg/kg EEDQ 48 h before test sessions or 6.0 mg/kg EEDQ 96 and 48 h before test sessions. Rats were trained to discriminate SKF (8.0 mg/kg, IP) from saline. Upper graph, percentage of responses during test sessions that occured on the SKF-appropriate lever as a function of cumulative dose of SKF; lower graph, response rate during test sessions as a function of dose. Each point represents the mean of five rats. Variability was as in Fig. 1.

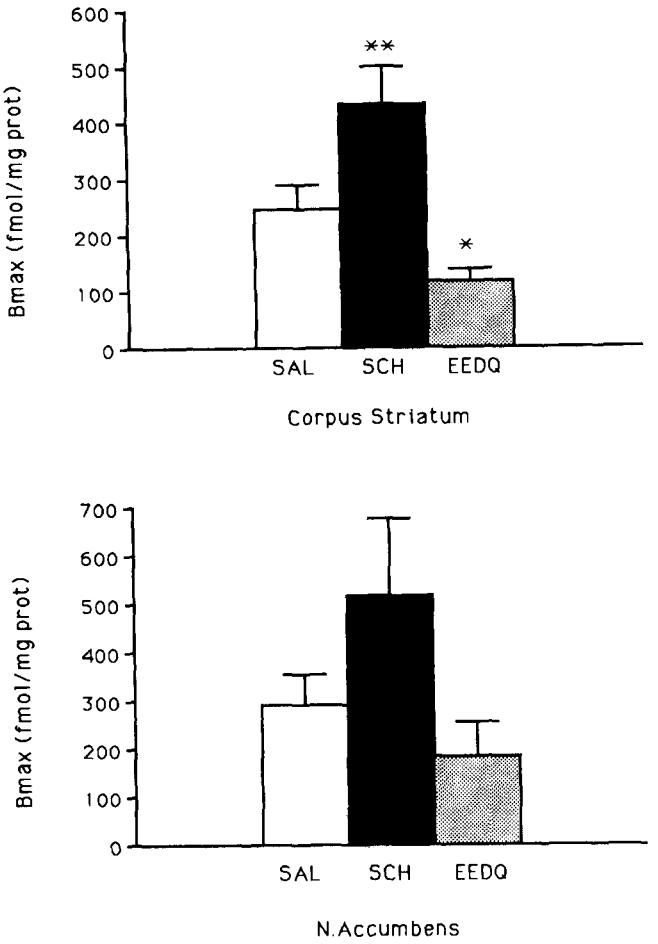

FIG. 5. Effects of saline, SCH, or EEDQ on the density of D_1 binding sites in corpus striatum (top graph) and nucleus accumbens (bottom graph). The bars represent the mean of five rats and the vertical lines represent the SEM. $*p < 0.05$; $**p < 0.01$.

ability in the SCH group. EEDQ significantly decreased B_{max} in the corpus striatum ($p < 0.05$), while differences in the nucleus accumbens were not statistically significant. Neither treatment altered the affinity (K_d) of the ligand for D_1 binding sites in either brain region (data not shown).

DISCUSSION

The present experiment is consistent with previous experiments demonstrating that the D_1 agonist SKF 38393 can function as a DS in rats, probably as a result of D_1 receptor stimulation (5,15,16). Further, the present results demonstrate that repeated administration of a D_1 antagonist in a regimen that increases the number of D_1 binding sites in the brain can increase the sensitivity to the DS effects of a D_1 agonist. The increase in the concentration of D_1 binding sites as a consequence of repeated administration of SCH is consistent with previous findings (4,24). The present experiment extends the duration of that effect from 2 (4) or 3 (23) days to 2 weeks. Moreover, it has been reported that repeated administration of SCH can increase sensitivity to the grooming response induced by SKF (22) and to the DS (7) and reinforcing (17) effects of cocaine. Taken together, these experiments suggest that the upregulation of a population of D_1 receptors in the brain as a consequence of repeated exposure to a D_1 antagonist can have behavioral consequences.

In contrast, EEDQ had no effect on the DS effect of SKF under conditions that decreased the number of D_1 binding sites in striatum. The decrease in D_1 binding sites in the present experiment was consistent with previous reports (10,19). The reason for the lack of change in the DS effects of SKF is unclear, although it is consistent with the lack of change in D_1 agonist-induced repetitive jaw movements after EEDQ pretreatment previously reported (24). Moreover, others have failed to observe altered physiological and behavioral responses to D_1 and D_2 agonists after long-term administration of D_2 antagonists (14). It is possible that there is a sufficient functional reserve of D_1 receptors so that significant receptor changes may not be followed by significant behavioral changes. It should be noted that stimulus control by SKF was lost over the course of EEDQ treatments in three rats, evidence, perhaps, for a functional consequence of EEDQ administration. However, D_1 binding sites were not systematically lower in these rats relative to the rest of the group. In

addition, EEDQ induced catalepsy and decreased response rate, further evidence for a functional consequence of EEDQ administration. The interaction with SKF for this effect was one of enhancement rather than the attenuation that would have been predicted by D_1 receptor inactivation. Because of the nonspecific nature of response rate decreases, it is difficult to make firm conclusions about the mechanism(s) of these effects. That is, other actions of either SKF or EEDQ may have mediated the response rate decreases that were seen.

Although the CNS site(s) that mediate SKF discrimination are not known, one might predict that the nucleus accumbens is involved. Studies utilizing local CNS injections with indirect DA agonists have consistently found substitution when the agonist was injected into the accumbens but not into the striatum (21,28). In this context, the apparent relationship between CNS changes and behavioral changes in the present experiment is somewhat surprising. That is, sensitization to the DS effects of SKF was associated with an increase in D_1 binding sites in the striatum but not in the accumbens. It may, of course, be the case that the SKF discrimination is based upon an action initiated in the striatum. However, the decrease in striatal D_1 binding following EEDQ without a concomitant change in the DS effects of SKF argues against this account. Alternatively, it is possible that the increase in D_1 binding seen in the accumbens, although not statistically significant, was biologically significant. These are issues that can only be addressed by further research.

It is unclear what the full extent of the behavioral consequences of D_1 receptor upregulation might be. The present research implies that increased sensitivity to the behavioral effects of drugs whose mechanism of action involves D_1 receptors is a likely result. In addition to the direct D_1 agonist SKF, sensitivity has been reported to increase the reinforcing (17) and DS (7) effects of cocaine in animals given repeated exposure to SCH 23390. If, as has been postulated (2,26), D_1 receptors play a permissive role in the expression of DA-mediated behaviors, upregulation of those receptors may have broad behavioral implications.

ACKNOWLEDGEMENTS

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