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Effect of the Dopamine $D_{1/5}$ Antagonist SCH 23390 on the Acquisition of Conditioned Fear

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INOUE, T., T. IZUMI, Y. MAKI, I. MURAKI AND T. KOYAMA. *Effect of the dopamine $D_{1/5}$ antagonist SCH23390 on the acquisition of conditioned fear.* PHARMACOL BIOCHEM BEHAV **66**(3) 573–578, 2000.—The authors previously reported that typical and atypical antipsychotic drugs inhibited the acquisition but not expression of conditioned fear. The present study examined the effects of the selective dopamine $D_{1/5}$ agonist (SKF 38393) and antagonist (SCH 23390) on the acquisition and expression of conditioned fear. Drugs were administered subcutaneously to male Sprague–Dawley rats 30 min before foot shock (2.5 mA for 5 min). Twenty-four hours after foot shock, rats were again placed and observed in the shock chamber without shocks (conditioned fear). Freezing behavior induced by conditioned fear, an index of anxiety or fear, was recorded using a time-sampling procedure. SCH 23390 (0.1–1 mg/kg) inhibited the acquisition of conditioned freezing. The administration of SCH 23390 at a dose of 0.1 mg/kg 30 min after foot shock did not affect conditioned freezing. Taken together, it is concluded that $D_{1/5}$ antagonism inhibits the acquisition of conditioned fear. SKF 38393 (3–20 mg/kg) failed to change the acquisition of conditioned fear. SCH 23390 or SKF 38393 administered prior to testing did not reduce the expression of conditioned fear. These results suggest that $D_{1/5}$ receptors may play a role in the development of fear or anxiety. © 2000 Elsevier Science Inc.

Dopamine $D_{1/5}$ receptor Anxiety Conditioned fear

SEVERAL lines of evidence indicate that various stressors activate the central dopaminergic system (7,26). Physical stress (foot shock, restraint, cold restraint, etc.) activate the mesolimbic, mesocortical, and nigrostriatal dopaminergic systems (7,8,13,26). To exclude the possibility that direct physical stimuli, such as pain, but not emotional changes induced by aversive stimuli activate dopaminergic systems, the authors examined the effects of two intensities of psychological stress (conditioned fear stress; CFS) on the dopamine (DA) metabolism in discrete seven brain regions, which reflects DA neurotransmission (13). Mild CFS increased DA metabolism in the medial prefrontal cortex (mPFC), hypothalamus, and amygdala, and severe CFS increased DA metabolism in the most of brain regions examined except for the striatum (13). Furthermore, an in vivo microdialysis study directly showed that increased DA metabolism induced by CFS reflected increased extracellular DA concentrations (28). These results suggest that emotional changes (fear or anxiety) increased DA activity because CFS per se does not induce physical stimuli.

The functional role of DA in fear or anxiety remained to be elucidated. D'Angio et al. (5) suggested that the mPFC DA activation induced by stress is not connected to the emotional reaction caused by the aversive nature of the stressor, but may rather reflect the heightened attention of the animal or the activation of cognitive processes in an attempt to cope with the stressor. This finding is consistent with our previous experimental data that mPFC lesions did not reduce conditioned freezing (14). However, DA systems in other brain regions might be related to fear or anxiety. Infusion of SCH 23390, a D_1 receptor antagonist, into the amygdala blocks the expression of potentiated startle response (18). In addition, amygdala lesions inhibits the acquisition of conditioned freezing (24).

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The authors previously reported that typical and atypical antipsychotic drugs (APDs) inhibited the acquisition but not expression of conditioned fear (17). Most of APDs examined in our previous study inhibited the acquisition of freezing induced by conditioned fear (17). Atypical APDs (clozapine, etc.) dose dependently inhibited the acquisition of conditioned freezing, although typical APDs showed bell-shaped dose–response curves for the effect on the acquisition of conditioned freezing. Because these APDs have antidopaminergic activity, it is assumed that antidopaminergic activity is relevant to the mechanism of action of APDs for the inhibitory effect on the acquisition of conditioned fear. The inhibitory effects of selective D_2-like antagonists on the acquisition of conditioned fear suggest that D_2-like receptors is attributable to these APDs' effects. On the other hand, the functional significance of D_1-like receptors (D_1 and D_5) for the acquisition of conditioned fear is not clear.

The present study examined the effects of the selective dopamine $D_{1/5}$ agonist SKF 38393 hydrochloride [(±)-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine-7,8-diol hydrochloride] and antagonist SCH 23390 [R-(+)-7-chloro-8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1-phenyl-1H-3-benzazepine] (25) on the acquisition and expression of conditioned fear, using freezing behavior as an index of fear or anxiety.

METHOD

Animals

Male Sprague–Dawley rats obtained from Shizuoka Laboratory Animal Center (Shizuoka, Japan), weighing 250–300 g, were housed in groups of four and maintained in a 12 L:12 D (light phase; 0630–1830 h), temperature-controlled environment (22 ± 1°C) with free access to food and water. Experiments began after a 2-week period of acclimatization. Rats were tested between 0800 and 1300 h.

Drugs

SCH 23390 maleate (Schering-Plough, Bloomfield, NJ) and (±)SKF 38393 hydrochloride (RBI, Natick, MA) were dissolved in saline and injected subcutaneously (SC) in a volume of 1 ml/kg.

General Procedure

As described previously (16), rats were individually subjected to inescapable electric foot shock for a total of 2.5 min [five foot shocks (2.5-mA scrambled shock, 30-s duration) were delivered at intershock intervals of 35–85 s (mean 60 s)] in a chamber with a grid floor (19 × 22 × 20 cm, Medical Agent Co., Japan). Electric shock was provided by a Model SGS-02D Shock Generator (Medical Agent Co., Japan). This provides a high-voltage, high-resistance circuit with resistance controlled by dial settings calibrated by the manufacturer in a short-circuit current. At the setting of 2.5 mA, this generator actually gives the shock intensity of 0.2 mA to rats. Twenty-four hours after foot shock, the rats were again placed in the shock chamber and observed for 5 min without shocks. Conditioned fear, as measured by freezing, develops to the contextual stimuli of the conditioned chamber with these procedures (9). During the observation period, the duration of freezing behavior was recorded using a modification of a time-sampling procedure (9) as previously described (16). Freezing was defined as the absence of all observable movement of the skeleton and the vibrissae, except those related to respiration. All other behavior was scored as activity. The animal was classified as either freezing or activity according to its behavior throughout the entire 10-s period. The percentage score (%freezing) represented the number of 10-s periods during which the animal froze for the entire 10 s. These procedures were approved by the Hokkaido University School of Medicine Animal Care and Use Committee, and in compliance with the Guide for the Care and Use of Laboratory Animals, Hokkaido University School of Medicine.

Experiment on Acquisition of Conditioned Fear

Thirty minutes after receiving a single subcutaneous injection of drugs or saline, rats were individually subjected to a single foot shock session for 5 min in the shock chambers (the same parameters as above), and then returned to home cages. Twenty-four hours after foot shock, the rats were individually placed in the same shock chambers without shocks and observed for 5 min.

To obviate the possibility that the drug remained 24 h after the injection and had a direct effect on the expression of conditioned freezing, in a separate experiment, SCH 23390 (0.1 mg/kg) was administered 30 min after foot shock. Twenty-four hours after foot shock, the rats were individually placed in the same shock chambers without shocks and observed for 5 min.

Experiment on Expression of Conditioned Fear

Twenty-four hours after a single foot shock session for 5 min, rats were treated with drugs or saline. Thirty minutes af-

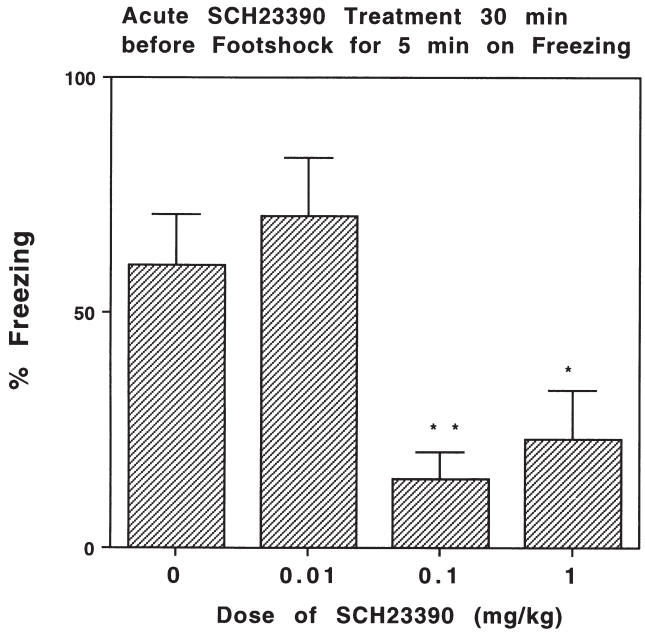

FIG. 1. Effects of the $D_{1/5}$ antagonist SCH23390 administered prior to foot shock on conditioned freezing in the test observed 24 h after foot shock. Thirty minutes after a single SC injection of SCH23390, rats were individually subjected to 2.5-mA foot shock stress for 5 min. Twenty-four hours after footshock, rats were placed in the shock chamber without shocks and observed for 5 min. Represented are the mean percentages ± SEM of freezing scored for a 5 min observation period. The number of rats/group was 8; $F(3,28) = 7.581$, $p < 0.001$, $^*p < 0.05$; $^{**}p < 0.01$ vs. saline controls.

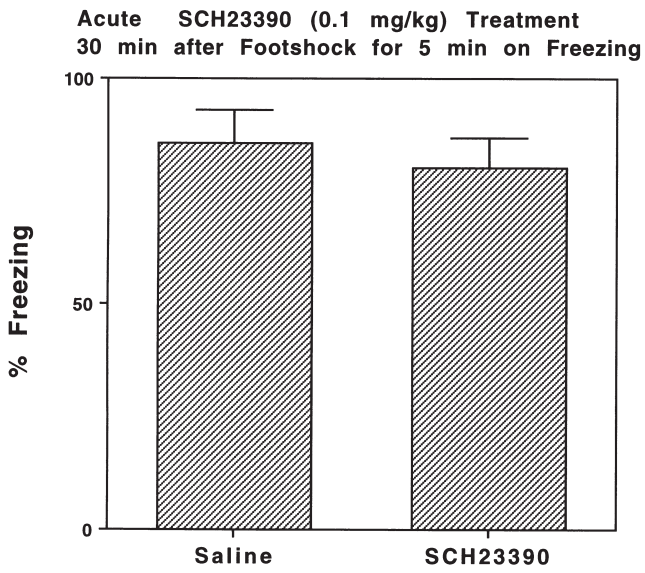

FIG. 2. Effects of the $D_{1/5}$ antagonist SCH23390 administered 30 min after foot shock (conditioning) on conditioned freezing. Thirty minutes before a single SC injection of SCH23390, rats were individually subjected to 2.5-mA foot shock stress for 5 min. Twenty-four hours after foot shock, rats were placed in the shock chamber without shocks and observed for 5 min. Represented are the mean percentages ± SEM of freezing scored for a 5-min observation period. The number of rats/group was 8; $t = 0.559$, $df = 14$, $p = 0.585$.

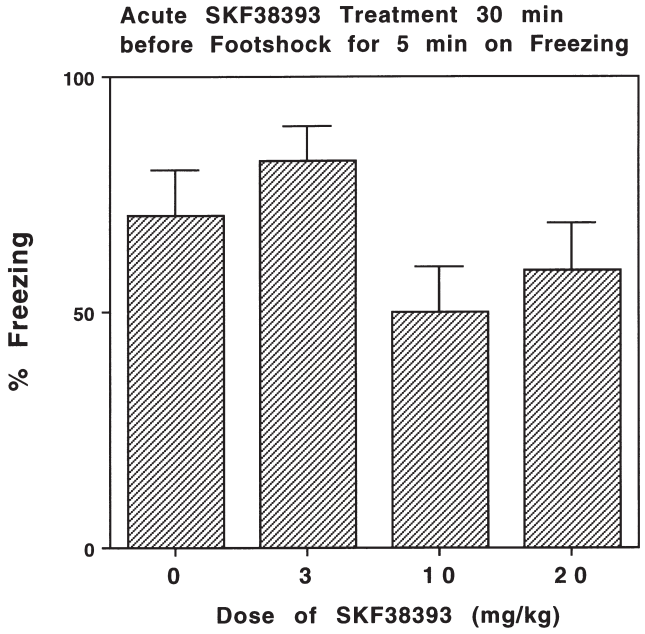

FIG. 3. Effects of the $D_{1/5}$ agonist SKF38393 administered prior to foot shock on conditioned freezing in the test observed 24 h after foot shock. Thirty minutes after a single SC injection of SKF38393, rats were individually subjected to 2.5-mA foot shock stress for 5 min. Twenty-four hours after footshock, rats were placed in the shock chamber without shocks and observed for 5 min. Represented are the mean percentages ± SEM of freezing scored for a 5-min observation period. The number of rats/group was 8; $F(3,28) = 2.324$, $p = 0.097$.

ter the injection, the rats were placed in the shock chamber without shocks and observed for 5 min.

Pain

Effects of SCH 23390 on foot shock-induced pain were examined as described previously (16). Vocalization was used as indicative of nociception. Thirty minutes after drug injection (SCH 23390 0.1 mg/kg, SC), rats were individually placed in a shock chamber with a grid floor. After a 5-min adaptation period, rats were subjected to 15 series of scrambled electric foot shocks. Each series was 10-s duration and spaced at 40-s intervals, ranging from 0.4 to 3.2 mA in 0.2-mA steps, presented in ascending order. The response of rats to each shock was recorded, and minimal intensities of electric foot shocks, at which vocalization first appeared, were determined.

Data Analysis

All the data are presented as the means ± SEM of the individual values of the rats from each group. The statistical analysis of the data was performed using unpaired *t*-test or a one-way analysis of variance followed by Duncan's test for multiple comparisons.

RESULTS

Effect on Acquisition of Conditioned Fear

The selective $D_{1/5}$ antagonist SCH 23390 administered prior to foot shock reduced conditioned freezing in the test observed 24 h after foot shock, $F(3, 28) = 7.581$, $p < 0.001$ (Fig. 1). SCH 23390 at the doses of 0.1 and 1 mg/kg reduced conditioned freezing significantly. Administration of SCH 23390 (0.1 mg/kg) 30 min after foot shock did not affect conditioned freezing in the test 24 h after foot shock, t(14) = 0.559,

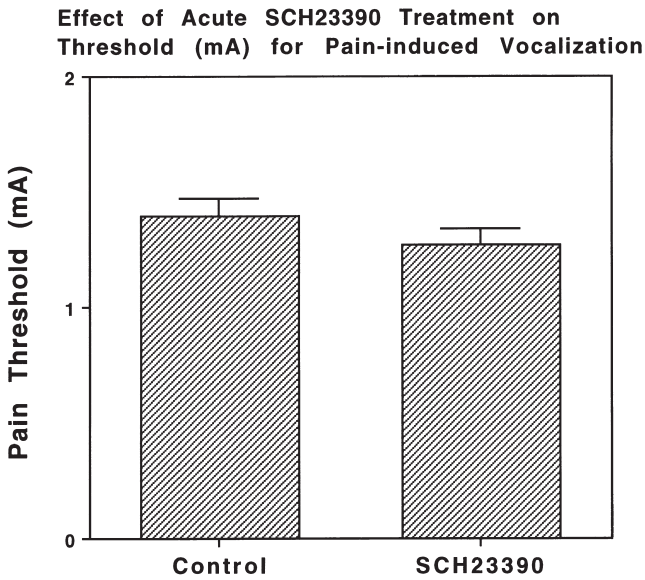

FIG 4. Effects of the $D_{1/5}$ antagonist SCH23390 (0.1 mg/kg SC) on pain-related behavior (vocalization). Thirty minutes after a single SC injection of SCH23390, rats were individually subjected to various intensities of foot shock in ascending order (0.4–3.2 mA). Data are represented as the means ± SEM of pain threshold (mA), at which vocalization first appeared. The number of rats/group was 8; $t = 1.256$, $df = 14$, $p = 0.23$.

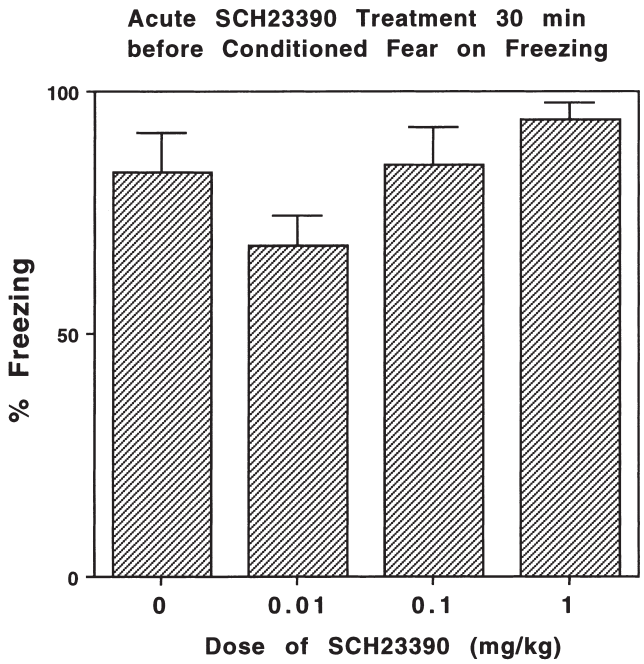

FIG. 5. Effects of the $D_{1/5}$ antagonist SCH23390 on the expression of conditioned freezing. Twenty-four hours after a single foot shock session (2.5 mA for 5 min), rats were treated with SCH23390 or saline. Thirty minutes after injection, the rats were placed in the shock chamber without shock and observed for 5 min. Represented are the mean percentages ± SEM of freezing scored for a 5 min observation period. The number of rats/group was 8; $F(3, 28) = 2.588$, $p = 0.073$.

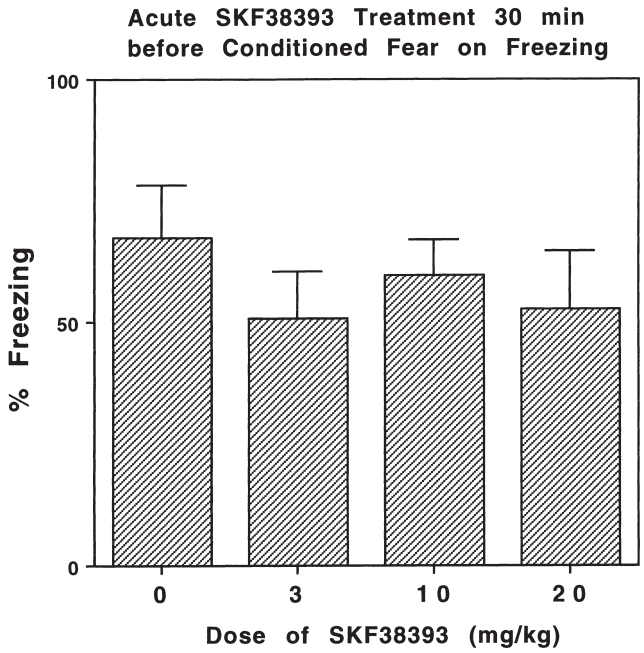

FIG. 6. Effects of the $D_{1/5}$ agonist SKF38393 on the expression of conditioned freezing. Twenty-four hours after a single foot shock session (2.5 mA for 5 min), rats were treated with SKF38393 or saline. Thirty minutes after injection, the rats were placed in the shock chamber without shock and observed for 5 min. Represented are the mean percentages ± SEM of freezing scored for a 5-min observation period. The number of rats/group was 8; $F(3, 28) = 0.56$, $p = 0.646$.

$p = 0.585$ (Fig. 2), excluding the direct effect of SCH 23390 on the expression of conditioned freezing. Accordingly, the inhibitory effect of SCH 23390 prior to foot shock on conditioned freezing indicates that SCH 23390 inhibited the acquisition of conditioned freezing. The $D_{1/5}$ agonist SKF 38393 did not affect the acquisition of conditioned freezing, $F(3, 28) = 2.324$, $p = 0.097$ (Fig. 3).

Effect of SCH 23390 on Pain

SCH 23390 (0.1 mg/kg), which blocked the acquisition of conditioned freezing significantly, did not change minimal intensities of electric foot shocks, at which a pain-related behavior (vocalization) first appeared, i.e., pain thresholds, $t(14) = 1.256$, $p = 0.23$ (Fig. 4).

Effect on Expression of Conditioned Fear

SCH 23390 or SKF 38393 did not affect the expression of conditioned freezing [SCH 23390, $F(3, 28) = 2.588$, $p = 0.073$; SKF 38393, $F(3, 28) = 0.56$, $p = 0.646$] (Figs. 5 and 6).

DISCUSSION

The present study showed that the selective $D_{1/5}$ antagonist SCH 23390 reduced the acquisition of conditioned freezing while the selective $D_{1/5}$ agonist SKF 38393 failed. SCH 23390 or SKF 38393 did not affect the expression of conditioned freezing. In a conditioned fear paradigm, classical anxiolytics benzodiazepines, and new anxiolytics serotonin1A (5-HT_{1A}) agonists and selective serotonin reuptake inhibitors (SSRIs) have been reported to inhibit both the acquisition and expression of conditioned freezing (10,11,15–17). Thus, the effects of a $D_{1/5}$ antagonist on CFS were different from those of the standard anxiolytics benzodiazepines, 5-HT_{1A} agonists and SSRIs with respect to the effects on the expression of conditioned freezing. The effect of a $D_{1/5}$ antagonist on the acquisition of conditioned freezing is likely to be an effect on the perception of the noxious foot shock (unconditioned stimulus), rather than anxiolytic effect, which should inhibit the expression of conditioned freezing.

There are a few animal studies and no clinical study examining the effects of $D_{1/5}$ receptor ligands on fear or anxiety. Davis et al. (6) studied the effect of SCH 23390 on the expression of conditioned fear in fear-potentiated startle, which is another conditioned fear paradigm and measures conditioned fear by an increase in the amplitude of a simple reflex (the acoustic startle reflex) in the presence of a cue previously paired with a shock. In their study, SCH 23390 dose dependently attenuated fear-potentiated startle (specific effect of fear), but also reduced baseline startle (nonspecific effect), indicating that the anxiolytic effect of SCH 23390 cannot be concluded (6). In the present study, SCH 23390 did not affect the expression of conditioned fear. Differences between their and our paradigms in behavioral indicators (startle vs. freezing) may explain the discrepancy between studies in the effect of SCH 23390 on the expression of conditioned fear. High doses of SCH 23390, which is reported to induce catalepsy (27), may inhibit general activity levels (21). This motor effect of SCH 23390 may interfere with finding the reduction in fear, which might have been caused by SCH 23390. In the ex-

pression of conditioned fear, if the drug cause a marked motor effect, one could not conclude that the drug really has an anxiolytic or anxiogenic effect. Recently, bilateral intraamygdaloid administration of SCH 23390 was reported to reduce fear-potentiated startle (i.e., conditioned fear) without decreasing baseline startle (18). This result suggest the contribution of $D_{1/5}$ receptors in the amygdala to the expression of a fear-motivated behavior (potentiated startle). The effects of $D_{1/5}$ receptor ligands on the acquisition of conditioned fear have not been reported.

Like SCH 23390, typical and atypical APDs also inhibited the acquisition but not expression of conditioned freezing in our previous study (17). The potencies of eight APDs for inhibiting the acquisition of conditioned freezing were positively correlated with the K_i values for D_4 dopaminergic receptors that were reported by other investigators, but not with the K_i values for other monoamine and acetylcholine receptors including D_1 receptors. Several atypical and typical APDs have various degrees of affinities for D_1 receptors (20). Especially, some investigators suggested that anti-D_1 dopaminergic property may be relevant to the mechanism of action of the atypical APD clozapine (1,4). The present data suggests the possibility that D_1 receptors are partly relevant to the mechanism of action of APDs for inhibiting the acquisition of conditioned freezing.

One might account for the effects of SCH 23390 on the acquisition of conditioned freezing by a State-Dependent Learning (SDL) hypothesis (22). This SDL hypothesis postulates that acquisition of a task under a drug may require the same or similar drug state for recall. There has been few evidence that $D_{1/5}$ antagonists produce SDL. Nevertheless, additional experiments will be needed to further examine the role of SDL in the effects of $D_{1/5}$ antagonists on the acquisition of conditioned freezing.

In contrast to SCH 23390, SKF 38393 did not affect either the acquisition or expression of conditioned freezing. Consistent with our results, Kamei et al. (19) reported that SKF 38393 or SCH 23390 did not affect conditioned fear expression using stress-induced motor suppression as an index of fear. The reason why SKF 38393 did not aggravate the acquisition of conditioned freezing may be that $D_{1/5}$ receptors are fully activated by the intrinsic DA during conditioning by foot shock, and the addition of SKF 38393 does not result in more activation of $D_{1/5}$ receptors. In agreement with this idea, foot shock increases DA activity markedly in various brain regions including the amygdala (17). Because SKF 38393 is a $D_{1/5}$ partial agonist (2), $D_{1/5}$ agonists with full efficacy and high selectivity are necessary to be examined in the conditioned fear paradigm in future experiments.

The $D_{1/5}$ antagonist SCH 23390 is known to be a weak antagonist for 5-HT_2 receptors (K_i = 30 nM for 5-HT_2, 1.3 nM for D_1) (3,12). The authors, however, reported that 5-HT_2 antagonist ICI169,369 did not reduce the acquisition of conditioned freezing (16). Accordingly, the effect of SCH 23390 on the acquisition of conditioned freezing is not explained by its antagonistic activity for 5-HT_2 receptors.

If SCH 23390 has significant effects on pain, its administration may affect the acquisition of conditioned fear. In the present study, SCH 23390 did not affect the threshold of foot shock-induced pain. Other investigators reported similar findings that SCH 23390 had no effect on pain induced by electrical stimulation applied to the rat tail (23). Taken together, the inhibitory effect of SCH 23390 on the acquisition of conditioned freezing cannot be attributed to reduced sensitivity to electric foot shock.

In conclusion, the selective $D_{1/5}$ antagonist SCH 23390 inhibited the acquisition of conditioned freezing. These results suggest that $D_{1/5}$ receptors may play a role in the development of fear or anxiety.

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