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Effects of Perospirone (SM-9018), a Potential Atypical Neuroleptic, on Dopamine D_1 Receptor-Mediated Vacuous Chewing Movement in Rats: A Role of 5-HT_2 Receptor Blocking Activity

YUKIHIRO OHNO,[1] KUMIKO ISHIDA-TOKUDA, TADASHI ISHIBASHI AND MITSUTAKA NAKAMURA

Research Center, Sumitomo Pharmaceuticals Co., Ltd., 3-1-98 Kasugade-naka, Konohana-ku, Osaka 554, Japan

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OHNO, Y., K. ISHIDA-TOKUDA, T. ISHIBASHI AND M. NAKAMURA. *Effects of perospirone (SM-9018), a potential atypical neuroleptic, on dopamine D_1 receptor-mediated vacuous chewing movement in rats: A role of 5-HT_2 receptor blocking activity.* PHARMACOL BIOCHEM BEHAV **57**(4) 889–895, 1997.—We compared the acute and subacute effects of perospirone (SM-9018), a novel neuroleptic with potent 5-HT_2 and D_2 blocking actions, and of haloperidol (HAL) on dopamine D_1 receptor-mediated vacuous chewing movement (VCM) in rats. A selective D_1 agonist, SKF 38393 (SKF), markedly increased the incidence of VCM, which was blocked by SCH 23390 (a D_1 antagonist) but not by sulpiride (a D_2 antagonist). Perospirone and HAL inhibited the SKF-induced VCM in a dose-dependent manner. The potency of the inhibitory actions of perospirone was considerably weaker (about 30 times) than that of HAL despite their similar affinities for D_1 receptors. Subacute treatment with perospirone for 2 weeks failed to affect the behavioral sensitivity of rats to SKF. However, the HAL treatment markedly enhanced the incidence of the SKF-induced VCM. On the other hand, the selective 5-HT_2 antagonists ritanserin and ketanserin significantly reduced the inhibitory actions of HAL and SCH 23390 on the SKF-induced VCM. In addition, combined treatment of ritanserin with HAL for 2 weeks abolished the enhancement of SKF-induced VCM by HAL treatment. These findings suggest that perospirone is weaker than HAL in altering the behavioral sensitivity of D_1 receptor-mediated VCM under repeated administration, which may be related to the 5-HT_2 blocking activity of perospirone. © 1997 Elsevier Science Inc.

Perospirone (SM-9018) Haloperidol Neuroleptics Vacuous chewing movement D_1 receptors 5-HT_2 receptors Tardive dyskinesia

TARDIVE dyskinesia (TD) is an extrapyramidal motor disorder characterized by stereotypical movement of the orofacial regions and sometimes of limbs and trunk, which often occurs upon reduction or cessation of drug dosing after long-term neuroleptic treatments (4,12). Although the pathophysiological mechanisms of TD are still uncertain, the supersensitivity of striatal dopamine receptors and/or the imbalance of D_1 and D_2 receptor functions after repeated neuroleptic treatments have been implicated in its incidence (12,15,20,28). Previous studies have shown that selective D_1 agonists [e.g., SKF 38393 (SKF)] produce vacuous chewing movement (VCM) in animals, which resembles the clinical symptoms of TD (13,20, 28). Characteristic features of D_1 receptor-mediated VCM in the rat include bursts of purposeless opening and closing of the jaw and tongue protrusion. The D_1 receptor-mediated VCM is known to be induced without agonist administration

[1] To whom requests for reprints should be addressed. E-mail: ohno@sumitomopharm.co.jp

by long-term neuroleptic treatment, markedly enhanced by neuroleptic withdrawal, and, like TD in humans, can be suppressed by neuroleptic supplementation (8,20,27,31,34,36). In addition, several atypical neuroleptics (e.g., clozapine) with low liability for TD in humans are reported to be weaker than the typical neuroleptics [e.g., haloperidol (HAL)] for induction of the VCM (30,31). Thus, D_1 agonist-induced VCM seems to be a model useful for evaluation of the propensity of neuroleptics to cause TD in humans.

Perospirone [*cis-N*-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl)cyclohexane-1,2-dicarboximide] is a potential atypical neuroleptic that has potent 5-HT_2 and D_2 antagonistic activities (9,21,24). Perospirone showed a high affinity for D_2 receptors and blocked various behaviors induced by dopamine agonists (9). However, unlike the typical neuroleptics, perospirone potently blocked the 5-HT_2 receptor-mediated behaviors and showed weak activities in inducing acute extrapyramidal side effects (e.g., catalepsy and bradykinesia) (9,24). In addition, we have recently shown that perospirone was weaker than HAL in causing supersensitivity and upregulation of striatal D_2 receptors after subacute treatment (25,26). However, the action of perospirone on D_1 receptor-mediated VCM still remains to be determined. In the present study, we compared the acute and subacute effects of perospirone with those of HAL on SKF-induced VCM in rats to further evaluate the propensity of perospirone to cause TD in humans. Because perospirone, unlike HAL, shows high affinity for 5-HT_2 and 5-HT_{1A} receptors (14), the effects of 5-HT_2 and 5-HT_{1A} receptor antagonists were also studied to clarify the mechanisms underlying differences between the actions of perospirone and HAL in the expression of VCM.

METHODS

Animals

Male Sprague–Dawley rats (Nihon SLC, Shizuoka, Japan) each weighing 150–250 g were used for all studies. Animals were kept in an air-conditioned room at 23 ± 2°C and 55 ± 10% relative humidity under a 12 L:12 D cycle (dark period 2000–0800 h) with free access to commercial food pellets and tap water.

Measurement of VCM

The rats were placed in individual clear plastic cages (25 × 41 × 19 cm, width × length × height) in a quiet, well-lighted, and air-conditioned room and allowed to accommodate for at least 1 h. The animals were then given an intraperitoneal (IP) injection of SKF (1–10 mg/kg); episodes of VCM were counted by an experienced observer during 20–40 min (5-min intervals) after the injection. The VCM was defined as repetitive chewing movements with tongue protrusion that are not directed onto any evident physical material (36). The observation period was set based on the finding that the control animals (which received saline alone) occasionally exhibited spontaneous VCM during the first 20 min after the injection (see Fig. 1). Perospirone (1–10 mg/kg), HAL (0.03–0.3 mg/kg), SCH 23390 (1 mg/kg), and sulpiride (300 mg/kg) were orally administered 1 h before the SKF injection. In the experiments with 5-HT_2 or 5-HT_{1A} antagonists, ritanserin (0.01–0.3 mg/kg IP), ketanserin (0.01–0.3 mg/kg IP), propranolol (3 and 10 mg/kg IP), or NAN-190 [1-(2-methoxyphenyl)-4-(4-(2-phthalimido)butyl)piperazine HBr; 3 and 10 mg/kg IP] was injected simultaneously with an oral administration of HAL

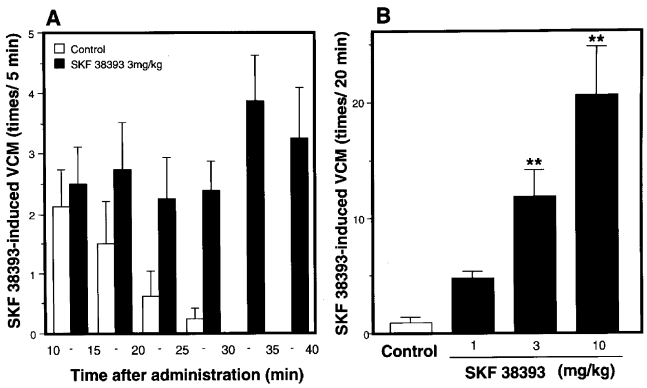

FIG. 1. Time-course (A) and dose–response (B) of SKF 38393-induced vacuous chewing movement (VCM) in rats. Each column shows the mean ± SEM of 8 animals. $^{**}p < 0.01$, significantly different from the control value (one-way ANOVA and Duncan's test).

(0.3 mg/kg) or SCH 23390 (1 mg/kg). Eight rats per dose group were used.

In the subacute experiments, rats were treated once a day with an oral (PO) dose of HAL (3 mg/kg/day), perospirone (10 mg/kg/day), or vehicle for 2 weeks. The daily dosage of perospirone and HAL was adjusted to be about three times the ED_{50} value in the rat conditioned avoidance response test, which can predict the clinical dosage of neuroleptics for schizophrenia treatment (18). In some experiments, ritanserin (3 mg/kg/day IP) was given simultaneously with HAL (3 mg/kg/day PO) to the rats for 2 weeks. After a 3-day withdrawal of the treatments, the animals received an injection of SKF (3 mg/kg IP), and the incidence of VCM was counted in the same manner as described previously. Six to 14 rats per group were used.

Conditioned Avoidance Response

The experiments were performed as described previously (32). Briefly, rats were trained to avoid a scrambled electrical shock delivered through the grid floor of an automatically controlled shuttle box (Tokai-Irika MU-1184, Tokyo, Japan). A daily session with 13 trials (6.5 min) was used, with each trial consisting of a 5-s warning tone and light [conditioned stimulus (CS)] followed by electrical shock [unconditioned stimulus (US); 5 s]. The conditioned avoidance response was a movement from one compartment to the other during the 5-s CS–US interval to avoid the shock. Unconditioned escape response was a similar movement after the onset of shock. Only rats that showed the conditioned avoidance response in at least 9 out of 10 trials after a 3-trial initiation period in a session (13 trials) were subjected to the experiments. The test session was carried out 1 h after oral administration of perospirone (1–30 mg/kg) or HAL (0.3–3 mg/kg), and the numbers of avoidance and escape responses were recorded. The control responses of each rat were also monitored in the pretest session, which was performed 24 h before the test session. Eight to 16 rats at each dose level were used to determine the ED_{50} value, which reduces control responses by 50%.

p-Chloroamphetamine (p-CAMP)-Induced Hyperthermia

Experiments were performed as described previously (26). The rats received a subcutaneous injection of the 5-HT re-

leaser *p*-CAMP (4 mg/kg), and the rectal temperature was measured before and 1 h after the *p*-CAMP injection. Perospirone (0.3–10 mg/kg), HAL (1–30 mg/kg), or vehicle was orally administered just before the *p*-CAMP injection. Ten rats at each dose level were used to determine the ED_{50} value, which inhibits the *p*-CAMP-induced hyperthermia by 50%.

[^{3}H]SCH 23390 Binding Assay

The [^{3}H]SCH 23390 binding assay was performed as described previously (6). Briefly, the striatum was dissected out of the brain, homogenized in ice-cold 50 mM Tris-HCl (pH 7.4), and centrifuged at 20,000 × *g* for 10 min. The resulting membrane fraction was incubated at 25°C for 45 min in 50 mM Tris-HCl containing 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.2 nM [^{3}H]SCH 23390, and different concentrations of unlabeled test drugs. After the incubation, samples were filtered through Whatman GF/B filters, and the radioactivity retained on the filters was measured by liquid scintillation counting. Nonspecific binding was determined in the presence of 300 μM SKF. The K_i values were calculated according to the following equation, $K_i = IC_{50}/(1 + S/K_d)$, where the K_d value of [^{3}H]SCH 23390 was 0.22 nM.

Drugs

Perospirone hydrochloride, HAL, and sulpiride were synthesized in our laboratory. These drugs and SCH 23390 hydrochloride (Res. Biochem. Inc., Natick, MA, USA), ketanserin (Res. Biochem. Inc.), ritanserin (Res. Biochem. Inc.), (−)propranolol (Sigma Chemical, St. Louis, MO, USA), and NAN-190 (Res. Biochem. Inc.) were suspended in 0.5% methylcellulose; (+)SKF hydrochloride (Res. Biochem. Inc.) and *p*-CAMP hydrochloride (Sigma) were dissolved in saline solution. In the subacute experiments, perospirone, HAL, and ritanserin were first dissolved in 1% lactic acid, then the pH of the drug solution was adjusted to 4.5–5.5 by the addition of NaOH. [*N*-methyl-^{3}H]SCH 23390 (83 Ci/mmol) was purchased from Amersham (Buckinghamshire, UK).

Statistics

Data were expressed as the mean ± SEM. The ED_{50} values were determined by the method of Litchfield and Wilcoxon (19). Differences among the multiple treatment groups were determined by one-way analysis of variance (ANOVA) followed by Duncan's test. Comparison of data between two groups was performed by Student's *t*-test. A *p*-value of less than 0.05 was considered to be statistically significant.

RESULTS

Pharmacological Characteristics of Perospirone and HAL

Table 1 summarizes the actions of perospirone and HAL on D_2, D_1, and 5-HT_2 receptors in rats. Perospirone showed a high affinity, similar to that of HAL, for the striatal D_2 receptors and inhibited the conditioned avoidance response and the methamphetamine-induced hyperactivity with about one-third to one-quarter the potency of HAL. These drugs also had similar affinities for the striatal D_1 receptors. However, perospirone was about 200 times more potent than HAL in binding to the cortical 5-HT_2 receptors. Perospirone potently inhibited *p*-CAMP-induced hyperthermia and tryptamine-induced forepaw seizure, whereas the actions of HAL were very weak (Table 1).

Acute and Subacute Effects of Perospirone and HAL on SKF-Induced VCM

The animals that received saline alone often exhibited spontaneous VCM, which usually subsided within 20–25 min after the injection (Fig. 1A). Administration of the D_1 agonist SKF (3 mg/kg IP) markedly increased the incidence of VCM, which persisted for over 40 min (Fig. 1A). The SKF-induced increase of VCM occurred in a dose-dependent manner, and the total number of VCMs during 20–40 min after the SKF injection significantly increased from 0.88 ± 0.48 (saline control) to 20.6 ± 4.15 at 10 mg/kg (Fig. 1B). Oral administration of perospirone (1–10 mg/kg) and HAL (0.03–0.3 mg/kg) dose-dependently inhibited the VCM induced by 3 mg/kg of SKF (Fig. 2). The inhibitory actions of perospirone on VCM were considerably weaker (about 30 times) than those of HAL in that SKF-induced VCM was nearly suppressed by perospirone at 10 mg/kg and by HAL 0.3 mg/kg. The SKF-induced VCM was also blocked by the selective D_1 antagonist SCH 23390 (1 mg/kg PO) but not by the selective D_2 antagonist sulpiride (300 mg/kg PO) (Fig. 2).

In the subacute experiments, the rats were treated with perospirone (10 mg/kg/day), HAL (3 mg/kg/day), or vehicle for 2 weeks, and the changes in behavioral sensitivity of rats to 3 mg/kg (IP) of SKF were examined after 3-day withdrawal

TABLE 1

COMPARISON OF THE ACTIONS OF PEROSPIRONE AND HALOPERIDOL ON D_2, D_1, AND 5-HT_2 RECEPTORS IN RATS

Receptor Antagonism	Perospirone	Haloperidol
D_2 receptors		
Binding affinity* (K_i, nM)	1.4 ± 0.2	1.8 ± 0.5
Methamphetamine hyperactivity* (ED_{50}, mg/kg PO)	2.2 (1.0–4.9)	0.6 (0.3–1.1)
Conditioned avoidance response (ED_{50}, mg/kg PO)	3.6 (1.6–7.9)	0.9 (0.5–1.7)
D_1 receptors		
Binding affinity (K_i, nM)	210 ± 18	138 ± 7.6
5-HT_2 receptors		
Binding affinity* (K_i, nM)	0.6 ± 0.1	116 ± 10
Tryptamine clonic seizure* (ED_{50}, mg/kg PO)	1.4 (0.6–3.3)	14 (6.8–27)
p-CAMP-induced hyperthermia (ED_{50}, mg/kg PO)	1.8 (0.9–3.4)	>30

Values in parentheses indicate the 95% confidence limit.
*Data quoted from Hirose et al. (9).

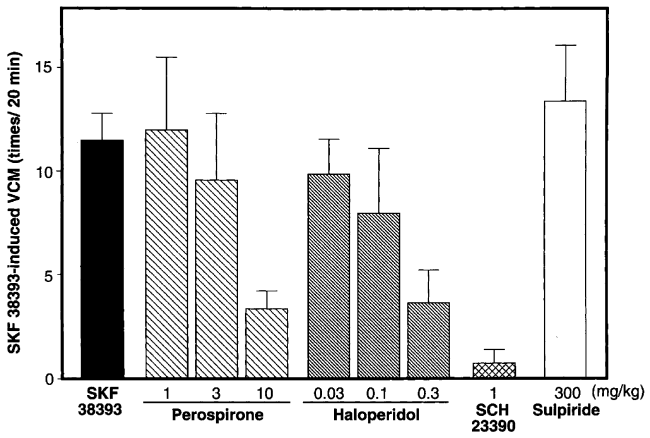

FIG. 2. Effects of perospirone, haloperidol, and other neuroleptics on SKF 38393-induced vacuous chewing movement (VCM) in rats. Perospirone, haloperidol, SCH 23390, and sulpiride were orally administered 1 h before an IP injection of SKF 38393 (3 mg/kg). Each column shows the mean ± SEM of 8 animals.

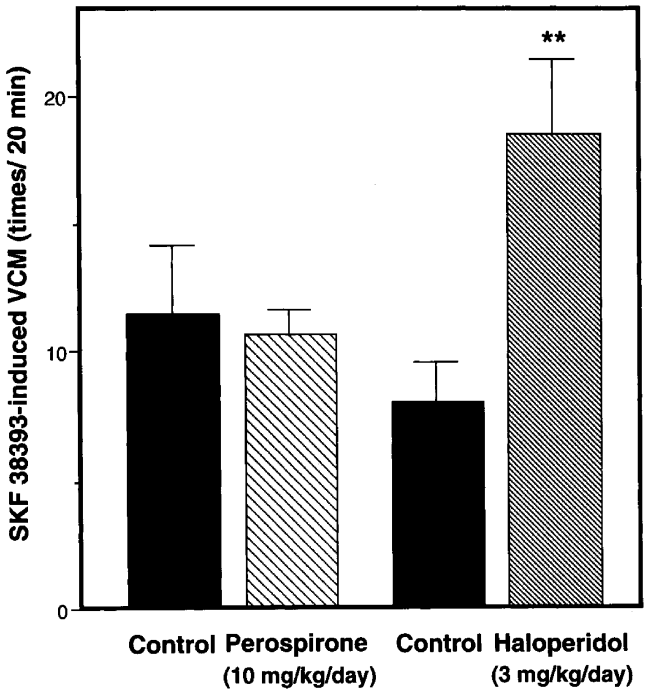

FIG. 3. Effects of subacute treatments with perospirone and haloperidol on SKF 38393-induced vacuous chewing movement (VCM) in rats. The animals were treated with perospirone (10 mg/kg/day PO), haloperidol (3 mg/kg/day PO), or vehicle for 2 weeks. The VCM induced by SKF 38393 (3 mg/kg IP) was measured after 3-day withdrawal of the treatments. Each column shows the mean ± SEM of 6 or 14 animals. $^{**}p < 0.01$, significantly different from the control value (Student's *t*-test).

of the treatment. The daily dosage of perospirone and HAL was the amount that blocked the conditioned avoidance response in rats (Table 1), which reflects their clinical potencies in schizophrenia treatment (18). As shown in Fig. 3, subacute treatment with perospirone did not significantly change the incidence of VCM induced by SKF. However, the HAL treatment markedly enhanced SKF-induced VCM, the incidence of the VCM being increased from 8.07 ± 1.51 (vehicle control) to 18.5 ± 2.91 times/20 min (Fig. 3).

Effects of 5-HT$_2$ and 5-HT$_{1A}$ Antagonists on the Actions of HAL and SCH 23390

We next examined the effects of selective 5-HT$_2$ antagonists, ritanserin and ketanserin, and 5-HT$_{1A}$ antagonists, propranolol and NAN-190, on the inhibitory actions of HAL and SCH 23390 in SKF-induced VCM. As shown in Fig. 4, treatment of rats with either ritanserin or ketanserin (0.01–0.3 mg/kg IP) dose-dependently attenuated the inhibitory effects of HAL on SKF (3 mg/kg IP)-induced VCM. The incidence of SKF-induced VCM was reduced to about 2.5 times/20 min by HAL alone, but the values were significantly increased to 9.13 ± 0.93 and to 7.63 ± 0.86 times/20 min by 0.3 mg/kg (IP) of ritanserin and ketanserin, respectively (Fig. 4). In addition, the inhibitory effects of SCH 23390 (1 mg/kg) on SKF-induced VCM was also significantly attenuated by pretreatment with ritanserin (0.03–0.3 mg/kg IP) (Fig. 5). In contrast, treatments of animals with propranolol and NAN-190 (3 and 10 mg/kg IP) did not significantly change the inhibitory action of HAL in the VCM model. None of the 5-HT$_2$ antagonists and 5-HT$_{1A}$ antagonists tested here affected SKF-induced VCM by itself (data not shown).

In the subacute experiments, the rats were treated with HAL (3 mg/kg/day), HAL (3 mg/kg/day) plus ritanserin (3 mg/kg/day IP), or vehicle for 2 weeks, and the VCM induced by SKF (3 mg/kg IP) was measured after 3-day withdrawal. Under these conditions, the enhancement of SKF-induced VCM by subacute haloperidol was almost abolished by simultaneous treatment with ritanserin (Fig. 6). The incidence of SKF-induced VCM in the rats treated with HAL plus ritanserin was similar in extent to that of the control group treated with vehicle alone.

DISCUSSION

The excess of D_1 receptor activity and/or the imbalance between D_1 and D_2 receptor functions have been suggested to be involved in the induction of TD (13,20,28), and D_1 receptor-mediated VCM has been widely studied as one of the models for TD in humans. Previous studies showed that neuroleptics including HAL suppressed D_1 receptor-mediated VCM upon acute administration but markedly enhanced it after repeated administration (8,20,27,34). The present study demonstrated that a newly developed neuroleptic, perospirone, when administered acutely, inhibited the VCM induced by SKF, suggesting that perospirone acts as an antagonist at D_1 receptors. However, the potency of perospirone for the antagonism of SKF-induced VCM was considerably weaker as compared with the action of HAL. In addition, subacute treatment with perospirone did not significantly change the behavioral sensitivity of rats to SKF after its withdrawal. Under the same conditions, however, subacute HAL treatment markedly enhanced the incidence of SKF-induced VCM. The daily dosage of perospirone and HAL in the subacute experiments was sufficient to inhibit the conditioning avoidance response and methamphetamine-induced hyperactivity, which are predicted models of the antipsychotic effects of neuroleptics (18). These findings suggest that perospirone is weaker than HAL in inducing the behavioral supersensitiv-

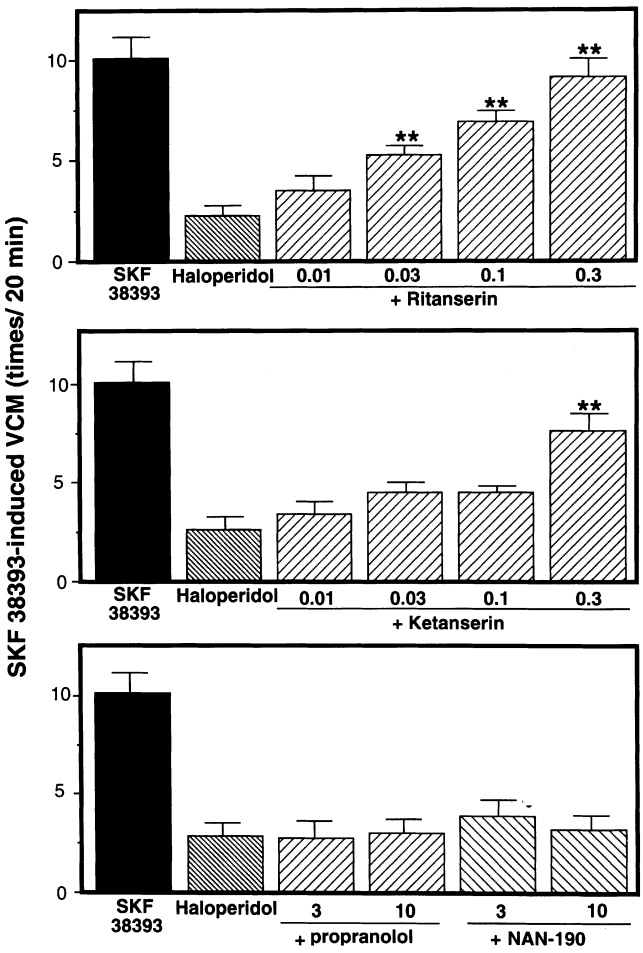

FIG. 4. Effects of 5-HT_2 and 5-HT_{1A} antagonists on the inhibitory action of haloperidol in SKF 38393-induced vacuous chewing movement (VCM) in rats. The animals received an IP injection of ritanserin, ketanserin, propranolol, or NAN-190 simultaneously with an oral dose of haloperidol (0.3 mg/kg) 1 h before the SKF 38393 injection. Each column shows the mean ± SEM of 8 animals. $^{**}p < 0.01$, significantly different from the value with SKF 38393 alone (one-way ANOVA and Duncan's test).

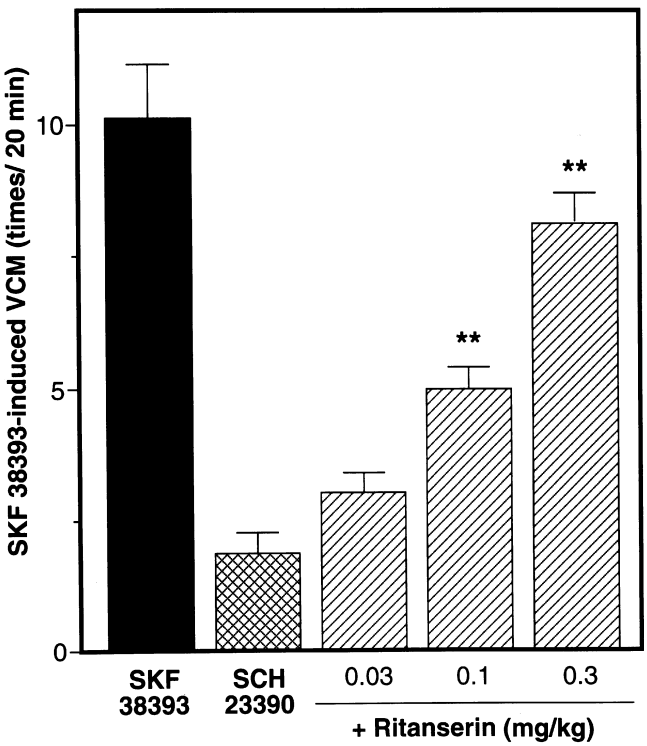

FIG. 5. Effects of ritanserin on the inhibitory action of SCH 23390 in SKF 38393-induced vacuous chewing movement (VCM) in rats. The animals received an IP injection of ritanserin simultaneously with an oral dose of SCH 23390 (1 mg/kg) 1 h before the SKF 38393 injection. Each column shows the mean ± SEM of 8 animals. $^{**}p < 0.01$, significantly different from the value with SKF 38393 alone (one-way ANOVA and Duncan's test).

ity of the D_1 receptor-mediated oral dyskinesia under repeated administration at clinical doses and that perospirone has a lower propensity for causing TD in humans.

It is of interest that the potency of perospirone in blocking SKF-induced VCM was about 30 times weaker than that of HAL despite the fact that its affinity for D_1 receptors was similar to that of HAL. Although D_2 receptor blockade has been shown to affect the inhibitory effects of D_1 antagonists on VCM in an oppositional (13,23,28) or cooperative (17,34) manner, the D_2 receptor affinity of perospirone was also similar to that of HAL. However, perospirone, unlike HAL, showed high affinity and potent blocking activity at 5-HT_2 receptors (Table 1). In addition, perospirone also has a relatively high affinity for 5-HT_{1A} receptors, where it may act as an antagonist, as described previously (14,21). We therefore examined the effects of 5-HT_2 antagonists (i.e., ritanserin and ketanserin) and 5-HT_{1A} antagonists (i.e., propranolol and NAN-190) on the HAL-induced inhibition of VCM to determine whether the 5-HT_2 and/or 5-HT_{1A} blocking actions of perospirone play a role in differentiating its action from that of HAL in the VCM model. In the present study, the selective 5-HT_2 antagonists ritanserin and ketanserin dose-dependently reduced the inhibitory actions of HAL and SCH 23390 in SKF-induced VCM. In addition, the enhancement of SKF-induced VCM by the withdrawal of subacute HAL treatment was abolished by simultaneous treatment with ritanserin. However, the 5-HT_{1A} antagonists propranolol and NAN-190 did not affect the action of HAL on VCM. Our findings suggest that the blockade of 5-HT_2 receptors, but not of 5-HT_{1A} receptors, can reduce the D_1 blocking actions of neuroleptics and prevent the increase in the behavioral sensitivity of D_1 receptor-mediated VCM after repeated treatment with neuroleptics. Thus, the 5-HT_2 blocking activity of perospirone seems to contribute to its reduced actions in the D_1 receptor-mediated VCM model as compared with HAL.

According to the current nomenclature, 5-HT_2 receptors in the brain may be subclassified into at least two subtypes: 5-HT_{2A} and 5-HT_{2C} receptors (3). Perospirone seems to bind to both 5-HT_{2A} and 5-HT_{2C} receptors in the rat brain, because our autoradiography study using ^{3}H-perospirone revealed a significant amount of its specific binding in the choroid plexus, which contains a high density of 5-HT_{2C} receptors, as well as in the cerebral cortex (unpublished observations). Although we did not employ a selective antagonist for 5-HT_{2A} and 5-HT_{2C} receptors in this study, the finding that the mixed

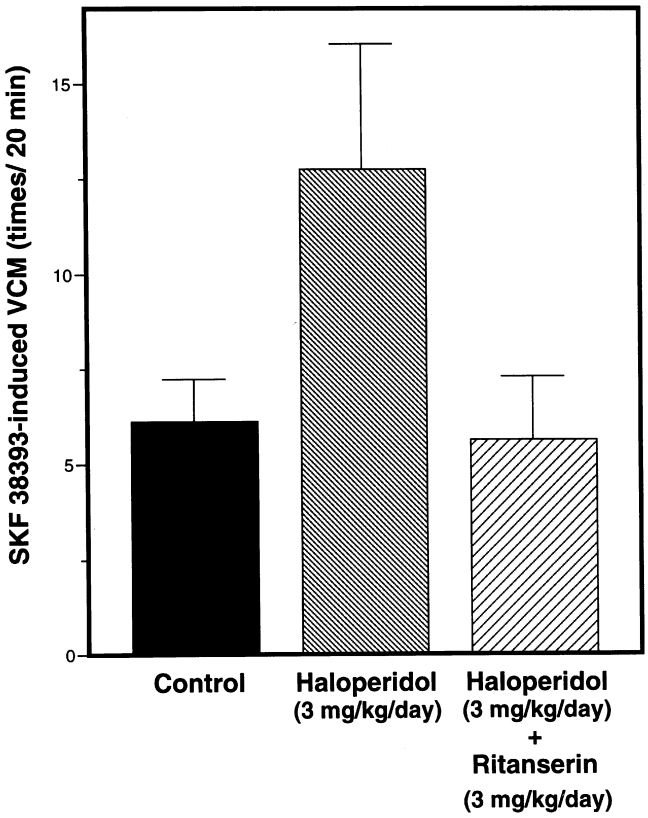

FIG. 6. Effects of ritanserin on the enhancement of SKF 38393-induced vacuous chewing movement (VCM) by subacute haloperidol in rats. The animals were treated with haloperidol (3 mg/kg/day PO), haloperidol (3 mg/kg PO) plus ritanserin (3 mg/kg IP), or vehicle for 2 weeks. The VCM induced by SKF 38393 (3 mg/kg IP) was measured after 3-day withdrawal of the treatments. Each column shows the mean ± SEM of 8 animals.

$5\text{-HT}_{2A/2C}$ antagonist ritanserin (minimal effective dose (MED) = 0.03 mg/kg) was more effective than the preferential 5-HT_{2A} antagonist ketanserin (MED = 0.3 mg/kg) (3) in reversing the inhibitory action of HAL implies that 5-HT_{2C} receptors might be involved in the serotonergic modulation of VCM. However, studies using selective ligands for 5-HT_{2A} and 5-HT_{2C} receptors are necessary to determine the subtype of 5-HT_2 receptors involved in D_1 receptor-mediated VCM.

Previous studies have demonstrated that blockade of 5-HT_2 receptors counteracts the D_2 blocking actions (e.g., increases in acetylcholine release and c-fos mRNA expression) of neuroleptics in the nigrostriatal dopaminergic system (10,11,22) and reduces D_2 antagonist-induced extrapyramidal side effects in rodents (1,24,29), monkeys (16), and humans (2,5). However, the actions of the 5-HT_2 antagonists on D_1 receptor-mediated responses have not been well documented. The present study, to our knowledge, is the first to demonstrate that 5-HT_2 antagonists can reduce the D_1 blocking action of SCH 23390 and HAL in the VCM model and can prevent the development of supersensitivity of D_1 receptor-mediated VCM by subacute HAL. However, the mechanism of action of 5-HT_2 antagonists in the nigrostriatal dopaminergic system is still uncertain. Because ritanserin and ketanserin failed to affect SKF-induced VCM by themselves, it seems unlikely that endogenous 5-HT tonically regulates VCM under our experimental conditions. On the other hand, previous studies have shown that blockade of 5-HT_2 receptors increases firing of the nigral dopamine neurons and enhances dopamine release and/or turnover in the striatum (7,22,35). In addition, Saller et al. (29) demonstrated that 5-HT_2 antagonists (e.g., ritanserin and ICI-169369) selectively potentiate the increase in dopamine turnover by neuroleptic administration (e.g., haloperidol) without affecting basal dopamine metabolism, suggesting that 5-HT_2 antagonists enhance the compensatory increase in the activity of the nigrostriatal dopaminergic neurons in response to dopamine receptor blockade. Such actions of 5-HT_2 antagonists may at least partly account for their counteraction to D_1 receptor antagonism by neuroleptics. However, our findings do not eliminate the possibility that neurotransmitter systems other than the dopaminergic system also have a role in the behavioral sensitivity of D_1 receptor-mediated oral dyskinesia, because abnormalities in GABA and glutamate systems have been observed in VCM-expressing animals treated with neuroleptics (30,33). Further studies are required to define the mechanisms underlying the interaction between D_1 and 5-HT_2 receptors in the expression of VCM.

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