Pharmacological Actions of SM-9018, a New Neuroleptic Drug with Both Potent 5-Hydroxytryptamine₂ and Dopamine₂ Antagonistic Actions

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Abstract—Pharmacological studies were undertaken to clarify the profile of cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl) hexahydro-1H-isoindole-1,3-(2H)-dione hydrochloride (SM-9018), a new neuroleptic drug. SM-9018 had very high binding affinities for both 5-hydroxytryptamine₂ (5-HT₂) and dopamine₂ (D₂) receptors, unlike many other neuroleptics. SM-9018 also strongly inhibited 5-HT₂ receptor-mediated behavior such as tryptamine-induced clonic seizure and D₂ receptor-mediated behavior such as methamphetamine-induced hyperactivity, apomorphine-induced stereotypy and climbing behavior. SM-9018 possessed only a weak cataleptogenic activity, which may be clinically related to extrapyramidal side effects, despite its potent D₂ antagonistic activity. Moreover, SM-9018 induced weak central depressant effects such as inhibition of spontaneous locomotor activity and motor coordination, as compared with classical neuroleptics (haloperidol and chlorpromazine). These results suggest that SM-9018 is a new neuroleptic drug with both potent 5-HT₂ and D₂ antagonistic activities and with low cataleptogenic and central depressant activities.

Although neuroleptic drugs continue to represent the best form of treatment for schizophrenia, they still possess two major disadvantages. First of all, schizophrenic patients with a preponderance of negative symptoms such as apathy and social withdrawal do not respond to neuroleptic treatment (1). Secondly, many neuroleptics produce extrapyramidal side effects (1).

The pharmacological blockade of central dopamine-2 (D₂) receptors in limbic areas and the frontal cortex, sites of action of known neuroleptics, is held responsible for the marked control of positive symptoms (2, 3). However, this action in the striatum produces extrapyramidal side effects (4). On the other hand, the mechanism of the negative symptoms is still unclear. It has nevertheless been reported that the selective 5-hydroxytryptamine₂ (5-HT₂) receptor antagonists ritanserlin and setoperone ameliorate negative

symptoms and reduce the incidence of extrapyramidal side effects caused by neuroleptic maintenance therapy (5–7).

Cis-2-(4-(4-(1,2-benzisothiazol-3-yl)-1-piperazinyl) butyl) hexahydro-1H-isoindole-1,3(2H)-dione hydrochloride (SM-9018) is a new neuroleptic drug with both potent 5-HT₂ and D₂ antagonistic action. The chemical structure of SM-9018 differs from analogs of known antipsychotic agents such as butyrophenone, phenothiazine and benzamide derivatives (Fig. 1). Present in vitro and in vivo experiments were undertaken to clarify the pharmacological profile of SM-9018 and to

Fig. 1. Structural formula of SM-9018.

compare it with those of other neuroleptics.

Materials and Methods

Male Sprague-Dawley rats (170–290 g) and male ddY mice (20–30 g) were used. All in vivo experiments were carried out in air conditioned laboratory rooms (temperature $24 \pm 1^\circ\text{C}$, relative humidity $55 \pm 5\%$).

1. Biochemical studies

Rats were decapitated, the brains were immediately removed, and the cortex and striatum were dissected on ice. Protein content of synaptic membrane preparations was determined by the method of Lowry et al. (8). K_i values were derived from IC50 values of binding assays according to the relationship $K_i = \text{IC}_{50}/(1 + S/K_d)$, where S is the concentration of the radioligand and K_d is the dissociation constant. IC50 values, which produce 50% inhibition of specific binding of radioligand, were constructed from Hill plots by least squares linear regression with computer assistance. K_d values were 1.5 nM and 0.11 nM in the present binding assays using ^3H -ketanserin and ^3H -spiperone, respectively.

1) ^3H -Ketanserin binding assay

^3H -Ketanserin binding was assayed in the rat cortex membrane using a previously described method (9) with a slight modification. Briefly, rat cortex was homogenized in 9 volumes of ice-cold 0.32 M sucrose using a teflon-glass homogenizer and then centrifuged ($700 \times g$, 10 min, 4°C). The supernatant was suspended in 10 volumes of ice-cold 50 mM Tris-HCl buffer (pH 7.4) and centrifuged for 10 min at $43,500 \times g$ and 4°C . The pellet was resuspended in 10 volumes of the same buffer. This suspension was incubated at 37°C for 10 min and centrifuged at $43,500 \times g$ at 4°C for 10 min. The pellet was washed twice more with 10 volumes of buffer. The resulting pellet was resuspended in buffer, and the final concentration of the suspension was adjusted to 0.5 mg protein/ml. This suspension was stored at -80°C . A 0.8-ml portion of this membrane suspension was placed in a tube, and 0.1 ml of either test compound or vehicle was added, followed by 0.1 ml of ^3H -ketanserin (77.0 Ci/mM, Amersham) at a final concentration of 1 nM. The tubes were incubated at 37°C for 30 min. Assays were carried out in triplicate. One

milliliter of sample was added to 5 ml ice-cold buffer and then filtered through Whatman CF/B glass fiber filters, which were then washed twice with 5 ml of buffer. Radioactivity trapped on the filters was measured by liquid scintillation spectrometry. Specific binding was defined as the excess over the non-specific binding in the presence of 0.01 mM ketanserin and 20 nM prazosin required to mask ^3H -ketanserin binding to α -1 receptors (10).

2) ^3H -Spiperone binding assay

^3H -Spiperone binding was assayed in the rat striatum membrane using a previously described method (2) with a slight modification. Briefly, rat striatum was homogenized in 20 volumes of ice-cold TEAN buffer (15 mM Tris-HCl, pH 7.5, 5 mM Na_2EDTA , 0.02% (1.1 mM) ascorbate and 0.0125 mM nialamide). This homogenate was incubated at 37°C for 60 min and centrifuged at $43,500 \times g$ for 10 min, and the pellet was washed twice more with 20 volumes of the buffer. The pellet was resuspended in the buffer, and the final concentration of the suspension was adjusted to 0.5 mg protein/ml. A 0.8-ml portion of this membrane suspension was placed in a tube, and 0.1 ml of either test compound or vehicle was added, followed by 0.1 ml of ^3H -spiperone (70.5 Ci/mM, Amersham) at a final concentration of 0.5 nM. Tubes were incubated at 37°C for 10 min. Assays were carried out in triplicate. One milliliter of sample was added to 5 ml of ice-cold buffer, filtered through Whatman CF/B glass fiber filters, and washed twice with 5 ml of buffer. Radioactivity trapped on the filters was measured by liquid scintillation spectrometry. Specific binding was defined as the excess over the non-specific binding in the presence of 0.01 mM spiperone.

2. Behavioral studies

1) Behavioral tests related to 5-HT₂ antagonism

The method of Niemegeers et al. (11) was utilized with a slight modification. Clonic seizures in rats were observed in individual clear plastic cages ($25 \times 41 \times 19$ cm). Tryptamine (40 mg/kg) was injected intravenously into the rats 1 hr after oral administration of the test drugs. Inhibition of tryptamine-

induced behavior was judged to be positive unless bilateral clonic seizures of the forepaws was observed for a period of 5 min after tryptamine injection. Six rats at each dose level were used to determine the ED₅₀ value which decreased the incidence of clonic seizures by 50%. ED₅₀ values were obtained from three or more doses of test drugs using the method of Litchfield and Wilcoxon (12). The same method was used to calculate the ED₅₀ values in the following *in vivo* studies.

2) Behavioral tests related to D₂ antagonism

Methamphetamine-induced hyperactivity:

The locomotor activity of rats was measured in individual clear plastic cages (25×41×19 cm) using an Automex (Columbus Instruments). Rats were injected intraperitoneally with methamphetamine (2 mg/kg) 1 hr after oral administration of test drugs. Locomotor activity was measured for 90 min after methamphetamine injection. Six rats at each dose level were used to determine the ED₅₀ value which produces 50% depression of methamphetamine-induced hyperactivity.

Apomorphine-induced stereotypy: The method of Yamasaki et al. (13) was utilized with a slight modification. Rat stereotypy was observed in individual stainless-steel mesh cages (15×20×20 cm). Apomorphine (1.25 mg/kg) was injected intravenously 1 hr after oral administration of test drugs. Inhibition of apomorphine-induced stereotypy was judged to be positive unless stereotyped licking and biting were observed for 30 min after apomorphine injection. Six rats at each dose level were used to determine the ED₅₀ value required to inhibit stereotypy by 50%.

Apomorphine-induced climbing behavior:

The method of Protais et al. (14) was utilized with a slight modification. The climbing behavior of mice was observed in individual cylindrical stainless-steel wire cages (diam., 12 cm; height, 14 cm). Apomorphine (1 mg/kg) was injected subcutaneously 1 hr after oral administration of test drugs. Climbing was observed between 10 and 20 min after apomorphine injection and was scored as follows: 3: pronounced, 2: moderate, 1: slight and 0: absent. Five to ten mice at each dose level were used to determine the ED₅₀ value which reduced the climbing score by 50%.

3) Catalepsy test

The method of Yamasaki et al. (13) was utilized with a slight modification. Catalepsy in rats and mice was evaluated 1 hr after oral administration of test drugs using a horizontal bar positioned 9 cm (rats) or 5 cm (mice) above the bench. Cataleptogenic activity was judged to be positive when the forepaws of the rats and mice remained on the bar for more than 30 sec. Six rats and eight to ten mice at each dose level were used to determine the ED₅₀ value required to induce catalepsy in 50% of the animals.

4) Behavioral tests related to alpha-1 antagonism

Norepinephrine-induced lethality:

The method of Yamasaki et al. (13) was utilized with a slight modification. Rat death was observed in individual stainless-steel mesh cages (15×20×20 cm). Norepinephrine (1.25 mg/kg) was injected intravenously 1 hr after oral administration of test drugs. Inhibition of norepinephrine-induced lethality was judged to be positive unless death was observed 30 min after norepinephrine injection. Six rats at each dose level were used to determine the ED₅₀ value required to inhibit death by 50%.

Ptosis test: Ptosis in the mouse was observed 1 hr after oral administration of test drugs, and was scored as follows: 4: complete closure, 3: marked closure, 2: moderate closure, 1: slight closure and 0: absent. Ptosis was judged to be positive when the mean ptosis score of both eyes was more than 2. Ten mice at each dose level were used to determine the ED₅₀ value which induced ptosis in 50% of animals.

5) Behavioral tests related to anticholinergic action

The method of Lippmann and Pugsley (15) was utilized with a slight modification. Oxo-tremorine-induced muscular tremors of mice were observed in individual clear plastic cages (12×12×18 cm). Oxotremorine (0.5 mg/kg) was injected subcutaneously 1 hr after oral administration of test drugs. Tremors were observed for 10 min after oxotremorine injection and was scored as follows: 2: pronounced, 1: moderate and 0: absent. Ten mice at each dose level were used to determine the ED₅₀ value required to reduce the tremor score by 50%.

6) Gross behavioral tests

Spontaneous locomotor activity: The spontaneous locomotor activity of groups of 5 mice was measured in individual clear plastic cages (25×41×19 cm) using an Automex (Columbus Instruments). Locomotor activity of 10 min duration was measured 1 hr after oral administration of test drugs. Ten groups of mice at each dose level were used to determine the ED₅₀ value required to inhibit locomotor activity by 50%.

Motor coordination: Motor coordination in mice was measured using a rota-rod treadmill (Muromachi Kikai). Performance of mice on the rota-rod for 1 min was measured 1 hr after oral administration of test drugs. Inhibition of motor coordination was judged to be positive when the mice dropped from the rota-rod in under 1 min. Ten mice at each dose level were used to determine the ED₅₀ value required to inhibit motor coordination by 50%.

Potentiation of hexobarbital-induced anesthesia: Hexobarbital-induced anesthesia of mice was estimated using the duration of righting reflex loss. Hexobarbital (70 mg/kg) was injected intraperitoneally 1 hr after oral administration of test drugs. Potentiation of hexobarbital-induced anesthesia was judged to be positive when the mice lost the righting reflex for twice the mean duration of the vehicle-treated group. Ten mice at each dose level were used to determine the ED₅₀ value which potentiated the duration of anesthesia by 50%.

3. Test compounds and reagents

SM-9018, ketanserin and prazosin was synthesized in our laboratory and chlorpromazine hydrochloride (Sigma) was obtained from a commercial source. Haloperidol (Keselan, Sumitomo), zotepine (Lodopin, Fujisawa), clocapramine (Clofekton, Yoshitomi), thioridazine (Melleril, Sankyo), sulpiride (Abilit, Sumitomo) and spiperone (Spiropitan, Eisai) were obtained by extraction. In the *in vivo* experiments, test compounds were suspended in 0.5% methylcellulose solution and administered orally. Tryptamine hydrochloride (Nacalai), methamphetamine hydrochloride (Dainippon), apomorphine hydrochloride (Sandoz), norepinephrine hydrochloride (Nacalai) and oxotremorine (Sigma) were dissolved in saline. Hexobarbital (Nagase) was dissolved in 0.04

N NaOH. In the *in vitro* experiments, test drugs were dissolved in 1% ethanol solution.

Results

Binding affinities for 5-HT₂ and D₂ receptors: SM-9018 concentration-dependently inhibited the specific binding of ³H-ketanserin to the 5-HT₂ receptors of the synaptic membrane of rat cerebral cortex at a concentration of 0.1 to 10 nM (Fig. 2), and the K_i value was 0.613 nM. SM-9018 demonstrated a very high binding affinity for 5-HT₂ receptors, with a potency 6, 190 and 150 times higher than that of ketanserin, haloperidol and chlorpromazine, respectively (Table 1). SM-9018 showed the highest affinity for 5-HT₂ receptors of all neuroleptics tested in the present study (Table 1).

SM-9018 also concentration-dependently inhibited specific binding of ³H-spiperone to the D₂ receptors of the synaptic membrane of rat striatum at a concentration of 1 to 100 nM (Fig. 2), with a K_i value of 1.41 nM. SM-9018 showed the highest affinity for D₂ receptors of all neuroleptics studied, being slightly higher than haloperidol and 19 times higher than chlorpromazine (Table 1).

SM-9018, unlike haloperidol, chlorpromazine and other neuroleptics, had high affinities to both 5-HT₂ and D₂ receptors. Of the other neuroleptics, only zotepine demonstrated a similar ratio of 5-HT₂ : D₂ binding affinity to that of SM-9018 (Table 1).

Antagonistic actions on 5-HT₂ and D₂ receptor-mediated behavior: SM-9018 dose-dependently antagonized tryptamine-induced clonic seizures, which are regarded as being induced through 5-HT₂ receptors (16) at doses of 1 to 10 mg/kg in rats; and the ED₅₀ value of the antagonism was 1.4 mg/kg, *p.o.* SM-9018 was 10 and 11 times more potent than haloperidol and chlorpromazine, respectively (Table 2).

SM-9018 dose-dependently inhibited D₂ receptor-mediated behavior such as methamphetamine-induced hyperactivity in rats at doses of 1 to 6 mg/kg; and the ED₅₀ value of the inhibition was 2.2 mg/kg, *p.o.* SM-9018 was 26% as potent as haloperidol, but eight and forty times more potent than chlorpromazine and thioridazine, respectively (Table 2). SM-9018 and other neuroleptics

Fig. 2. Inhibition of ^3H -ketanserin binding to the 5-HT_2 receptors of the synaptic membrane of rat cerebral cortex and ^3H -spiperone binding to the D_2 receptors of the synaptic membrane of rat striatum by SM-9018, haloperidol, chlorpromazine and ketanserin. Symbols with vertical bars represent means $\pm$ S.E. of 3 to 4 separate experiments.

also inhibited other D_2 receptor-mediated behaviors such as apomorphine-induced rat stereotypy and mouse climbing behaviors. As the ED_{50} values of antagonism of these drugs show in Table 3, SM-9018 was less potent than haloperidol and more potent than chlorpromazine and thioridazine.

Unlike haloperidol and chlorpromazine, SM-9018 possessed potent antagonistic activities to both 5-HT_2 and D_2 receptor-mediated behaviors.

Cataleptogenic activity: SM-9018 induced catalepsy in rats and mice at larger doses than

those required for D_2 antagonism. ED_{50} values of the cataleptogenic activity were 150 and 57 mg/kg, p.o., in rats and mice, respectively (Table 4). SM-9018 in rats was 8% and 31% less potent than haloperidol and chlorpromazine, respectively (Table 4). The relative cataleptogenic activity of SM-9018 against D_2 antagonism was weaker than that of haloperidol and chlorpromazine in rats and mice and was similar to that of thioridazine in mice (Table 4).

Antagonistic actions on α -1 and acetylcholine receptor-mediated behavior: Ptosis

Table 1. Binding affinities of SM-9018 and other neuroleptics to 5-hydroxytryptamine₂ (5-HT₂) receptors and dopamine₂ (D₂) receptors

Drugs	K _i (nM)		5-HT ₂ /D ₂
	5-HT ₂	D ₂	
SM-9018	0.613±0.105	1.41±0.23	0.43
Haloperidol	116 ±10	1.76±0.46	66
Chlorpromazine	91.1 ±23.5	27.2±12.1	3.3
Ketanserin	3.89±0.52	—	—
Zotepine	15.6 ±5.1	32.8±9.1	0.48
Clozapamine	153 ±13	26.1±10.3	5.9
Thioridazine	262 ±51	46.1±10.6	5.7
Sulpiride	>3000	>3000	—

K_i values were obtained from the inhibition by neuroleptics of ³H-ketanserin binding to the synaptic membrane of rat cerebral cortex (5-HT₂) and ³H-spiperone binding to the synaptic membrane of rat striatum (D₂). Results are means±S.E. of 3 to 4 separate experiments. 5-HT₂/D₂: K_i value of 5-HT₂ binding/that of D₂ binding.

Table 2. Antagonism of tryptamine-induced clonic seizure and methamphetamine-induced hyperactivity in rats by SM-9018 and other neuroleptics

Drugs	ED50 (mg/kg, p.o.)	
	Clonic seizure	Hyperactivity
SM-9018	1.4 (0.59–3.3)	2.2 (1.0–4.9)
Haloperidol	14 (6.8–27)	0.56 (0.28–1.1)
Chlorpromazine	16 (8.2–30)	17 (9.7–31)
Thioridazine	26 (10–67)	87 (55–140)

ED50 values and 95% confidence limits in parenthesis were obtained 1 hr after neuroleptic administration.

Table 3. Antagonism of apomorphine-induced stereotypy in rats and climbing behavior in mice by SM-9018 and other neuroleptics

Drugs	ED50 (mg/kg, p.o.)	
	Stereotypy	Climbing
SM-9018	5.8 (3.6–9.5)	3.5 (1.1–11)
Haloperidol	2.0 (1.2–3.3)	0.67 (0.13–3.3)
Chlorpromazine	94 (68–130)	4.2 (2.9–6.0)
Thioridazine	>300	7.0 (3.1–16)

ED50 values and 95% confidence limits in parenthesis were obtained 1 hr after neuroleptic administration.

induced by neuroleptics and norepinephrine-induced lethality are regarded as being induced through α -1 receptors (17). SM-9018 dose-dependently antagonized norepinephrine-induced lethality at doses of 3 to 10 mg/kg in rats, with an ED50 value of 5.1 mg/kg, p.o. SM-9018 also induced ptosis in mice with an ED50 value 19 mg/kg, p.o. SM-9018, with regard to α -1 antagonism

against D₂ antagonism, was less potent than chlorpromazine and more potent than haloperidol in both behavioral tests (Table 5).

SM-9018 dose-dependently antagonized the oxotremorine-induced tremors which are regarded as being induced through acetylcholine receptors (15) at doses of 30 to 300 mg/kg in rats, with an ED50 value of 150 mg/kg, p.o. SM-9018 was four to seven times less

Table 4. Cataleptogenic activities of SM-9018 and other neuroleptics in rats and mice

Drugs	Rats		Mice	
	ED50	Ca/Hy	ED50	Ca/Cl
SM-9018	150 (55–430)	68	57 (33–96)	16
Haloperidol	12 (6.2–23)	21	3.1 (1.6–6.0)	4.6
Chlorpromazine	46 (26–80)	2.7	18 (13–26)	4.3
Thioridazine	>300	—	79 (26–240)	11

ED50 values and 95% confidence limits (mg/kg, p.o.) in parenthesis were obtained 1 hr after neuroleptic administration. Ca/Hy: Cataleptogenic activities (ED50)/antagonism of methamphetamine-induced hyperactivity (ED50). Ca/Cl: Cataleptogenic activities (ED50)/antagonism of apomorphine-induced climbing (ED50).

Table 5. Antagonism of norepinephrine-induced lethality in rats and ptosis induction in mice by SM-9018 and other neuroleptics

Drugs	Lethality		Ptosis	
	ED50	L/H	ED50	P/C
SM-9018	5.1 (3.1–8.3)	2.3	8.7 (3.1–24)	2.5
Haloperidol	>30	—	4.1 (2.2–7.7)	6.1
Chlorpromazine	16 (9.5–25)	0.94	6.0 (4.0–9.0)	1.4

ED50 values and 95% confidence limits (mg/kg, p.o.) in parenthesis were obtained 1 hr after neuroleptic administration. L/H: Antagonism of lethality (ED50)/antagonism of hyperactivity (ED50). P/C: Ptosis inducing activity (ED50)/antagonism of climbing (ED50).

Table 6. Antagonism of oxotremorine-induced tremors in mice by SM-9018 and other neuroleptics

Drugs	ED50	T/C
SM-9018	150 (63–380)	43
Haloperidol	23 (10–52)	34
Chlorpromazine	36 (13–100)	8.6
Thioridazine	19 (8.6–43)	2.7

ED50 values and 95% confidence limits (mg/kg, p.o.) in parenthesis were obtained 1 hr after neuroleptic administration. T/C: Antagonism of tremor (ED50)/antagonism of climbing (ED50).

Table 7. Effects of SM-9018 and other neuroleptics on spontaneous locomotor activity, motor coordination and hexobarbital-induced anesthesia in mice

Drugs	ED50 (mg/kg, p.o.)		
	Inhibition		Potentiation
	Locomotor	Coordination	Anesthesia
SM-9018	15 (7.6–28)	34 (20–55)	37 (22–61)
Haloperidol	0.73 (0.34–1.6)	2.7 (1.4–5.2)	11 (5.8–20)
Chlorpromazine	5.8 (4.1–8.2)	4.5 (2.4–8.3)	11 (6.4–18)

ED50 values and 95% confidence limits in parenthesis were obtained 1 hr after neuroleptic administration.

potent than the other neuroleptics, with a weaker relative anticholinergic action against D_2 antagonism than those of chlorpromazine and thioridazine (Table 6).

Central depressant action: SM-9018 dose-dependently inhibited spontaneous locomotor activity and motor coordination and also potentiated hexobarbital-induced anesthesia in mice. The ED₅₀ values were 15, 34 and 37 mg/kg, p.o., in the inhibition of locomotion, coordination and the potentiation of anesthesia, respectively (Table 7). However, SM-9018 was 5% and 39% as potent as haloperidol and chlorpromazine, respectively, in the spontaneous locomotor activity test of mice (Table 7). SM-9018 showed only a weak depressant action on the central nervous system, as compared with haloperidol and chlorpromazine (Table 7).

Discussion

Unlike haloperidol, chlorpromazine and other neuroleptics, SM-9018 showed high binding affinities to both 5-HT₂ and D_2 receptors. In the 5-HT₂ binding assay, SM-9018 was 6 times more potent than the representative 5-HT₂ antagonist ketanserin (16), and it strongly blocked clonic seizures caused by tryptamine in rats. SM-9018 also produced potent antagonism against D_2 receptor-mediated behaviors. The potency of SM-9018 for blockade of methamphetamine-induced hyperactivity and apomorphine-induced stereotypy in rats was about 8 to 16 times greater than that of chlorpromazine. Since the clinical potency of neuroleptics correlates to their D_2 antagonistic activities (2), our findings suggest that SM-9018 would be effective for improving the positive symptoms of schizophrenia. While we cannot rule out a potential interaction of SM-9018 with D_1 receptors, our preliminary study revealed that SM-9018 only had about 1/30 the potency in binding to D_1 receptors as compared with binding to D_2 receptors (A. Hirose et al., unpublished data). On the other hand, 5-HT₂ antagonism of drugs has been recently reported to relate to the amelioration of negative symptoms of schizophrenia (5, 7). These findings suggest that SM-9018 may improve not only positive but also negative symptoms. The cataleptogenic activity of SM-9018

was weaker than those of haloperidol and chlorpromazine, and the relative cataleptogenic action of SM-9018 against D_2 antagonism was similar to that of thioridazine in mice. Thioridazine is known to possess a low incidence of extrapyramidal side effects. The lack of extrapyramidal side effects with this drug has generally been regarded as responsible for their anticholinergic properties (18). In the present experiment, the relative anticholinergic action of thioridazine was stronger than that of SM-9018. This result indicates that anticholinergic action is not involved in the low cataleptogenic action of SM-9018.

On the other hand, degeneration of 5-HT containing neurons has been shown to decrease the cataleptogenic activity of neuroleptics (19). Moreover, it has been reported that methysergide and cyproheptadine, which possess potent 5-HT₂ antagonistic activity, inhibit haloperidol induced-catalepsy in rats (20, 21) and Parkinsonism in monkeys (22). These findings suggest that 5-HT₂ antagonism may be related to the weak cataleptogenic activity of SM-9018. This hypothesis is supported by the clinical results that ritanserin with potent 5-HT₂ antagonistic activity ameliorates neuroleptic-induced extrapyramidal side effects (6, 7).

Ptosis induced by neuroleptics and nor-epinephrine induced-lethality are regarded as being mediated by α -1 receptors (17). Although the α -1 antagonistic action of SM-9018 was relatively weak as compared with its D_2 and 5-HT₂ antagonism, the potency of SM-9018 was between the values of chlorpromazine and haloperidol. As α -1 antagonism of drugs is thought to relate to sedative and hypotensive actions (17), these actions of SM-9018 were predicted to be weaker than those of chlorpromazine. On the other hand, the inhibitory action of SM-9018 on locomotor and motor coordination was weaker than that of haloperidol and chlorpromazine. This result is regarded as being held responsible for the relative low cataleptogenic activity of SM-9018 as opposed to the other neuroleptics.

SM-9018 had strong 5-HT₂ antagonism as well as D_2 antagonism, but only weak cataleptogenic and central depressant actions

in animals. These observations suggest that SM-9018 may improve both negative and positive symptoms without strong extrapyramidal side effects and central depressant actions in schizophrenic patients.

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