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Involvement of Central Cholinergic Mechanism in RU-24969-Induced Behavioral Deficits

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NODA, Y., Y OCHI, E SHIMADA AND M OKA *Involvement of central cholinergic mechanism in RU-24969-induced behavioral deficits* PHARMACOL BIOCHEM BEHAV **38**(2) 441–446, 1991 —The present study was undertaken to investigate the role of cholinergic mechanisms in the behavioral effects of RU-24969, a compound with serotonin$_{1B}$ (5-HT$_{1B}$) receptor agonist properties RU-24969 caused an increase in locomotion (2–5 mg/kg IP) and an impairment of spontaneous alternation (SA) behavior in a T-maze (0 5–2 0 mg/kg IP) in mice, effects that were also induced by the cholinergic hypofunction with scopolamine treatment (0 5–5 0 mg/kg IP), an acetylcholine (ACh) receptor antagonist The impairment of the SA behavior by RU-24969 was enhanced by scopolamine Both the hyperlocomotion and the SA impairment by RU-24969 were markedly reduced by propranolol (20 mg/kg IP) which has 5-HT$_{1A}$/5-HT$_{1B}$ receptor antagonist properties, as well as by physostigmine (0 05–0 2 mg/kg IP), an ACh esterase inhibitor, and oxotremorine (0.005–0 01 mg/kg IP), an ACh receptor agonist Moreover, these behavioral deficits of RU-24969 were diminished in mice pretreated intracerebroventricularly with AF64A (30 nmol/body), a presynaptic cholinergic neurotoxin, whereas scopolamine induced the deficits even in animals with the same treatment These results suggest that the serotonergic behavioral deficits observed after RU-24969 treatment may be caused by an inhibition of ACh release through its action on the presynaptic receptor (particularly RU-24969-sensitive sites) localized on the cholinergic terminals

5-HT$_1$ receptor agonist Spontaneous alternation Locomotion Behavioral deficit Presynaptic receptor ACh release

RECENT advances in the study of serotonin (5-HT) binding sites have yielded various new agonists and antagonists for these receptors. Some of them have proved valuable for investigating roles of serotonergic neurons in the modulation of animal behaviors. 5-HT or 5-methoxy-3-(1,2,3,6-tetrahydropyridine-4-yl)-1H indole (RU-24969), a compound with serotonin$_{1B}$ (5-HT$_{1B}$) receptor agonist properties, are known to induce prominent hyperlocomotion in rodents (5, 10, 12, 17, 20). The hyperlocomotion is antagonized by propranolol and pindolol, β-blockers with a substantial affinity for 5-HT$_{1A}$/5-HT$_{1B}$ receptors (4, 6, 14–16, 24, 25, 35, 37), but not by metoprolol (β_1-blocker) and butoxamine (β_2-blocker) with no affinity for the 5-HT$_1$ receptors (4). Further, it is not influenced by clenbuterol, a β-agonist (17). Thus 5-HT$_1$ receptors have been considered to be involved in the RU-24969-induced locomotor response (12,14). During the behavioral study of some 5-HT agonists, we found that RU-24969, in addition to the increase in locomotor activity, disrupted spontaneous alternation (SA) behavior, a learning task with no strong source of motivation in mice. Such behavioral changes have also been reported to be induced commonly by anticholinergic drugs, and suggested as a result of hypofunction of the cholinergic neuronal system (2, 7, 9, 21, 23, 30, 32).

Some biochemical studies have indicated an influence of serotonergic afferents from the raphe nuclei on the activity of cholinergic neurons. Butcher et al. (3) reported that acetylcholine (ACh) synthesis in the rat striatum increased after electrolytic lesions of the raphe B_7 area, and decreased after lesions of the B_8 area. On the other hand, ACh turnover in the rat hippocampus and cortex was shown to increase after destroying the raphe serotonergic neurons with 5,7-dihydroxytryptamine in rats (29). Moreover, Gillet et al. (13) demonstrated that 5-HT inhibited the K^+-evoked release of ACh from rat striatal slices.

The present study was designed to confirm the functional interaction between serotonergic and cholinergic neurons in the central nervous system using behavioral pharmacology techniques.

METHOD

Animals

Male mice of Std-ddY strain (Japan SLC Inc., Shizuoka, Japan) weighing 25 ± 5 g were used as subjects They were housed in plastic cages, given food (CE2, Clea Japan Inc.) and tap water ad lib and were kept in a regulated environment (24 ± 1°C, 60 ± 5% humidity), with a 12/12-h light-dark cycle (6 a m., 6 p.m.). No mice were ever used more than once.

Drugs

The following drugs were purchased from the commercial sources. scopolamine hydrobromide (scopolamine, Sigma), phy-

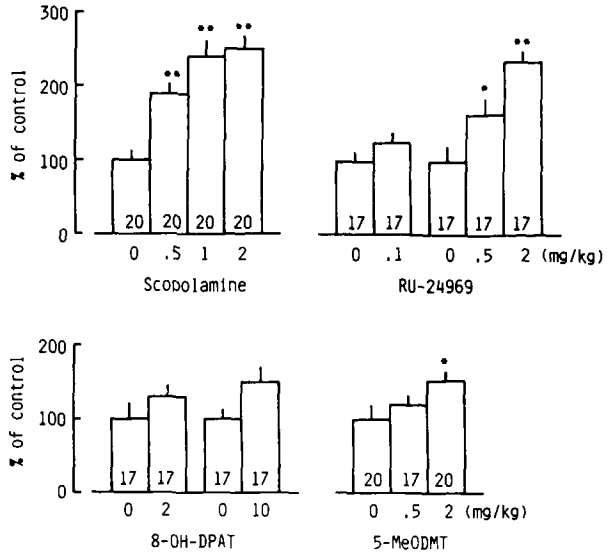

FIG 1 Effect of 5-HT-related agents and scopolamine on spontaneous alternation behavior in mice Drugs were administered IP 30 min before testing spontaneous alternation, except for 5-MeODMT study (where it was administered 15 min before the test) The SA test was carried out as described in the Method section The columns represent mean (±S E) number of SA failures expressed in percent of control (vehicle-treated group) The numbers of mice in each group are indicated inside the columns and doses below the columns. Significantly different from vehicle-treated group *$p<0$ 05, **$p<0$ 01

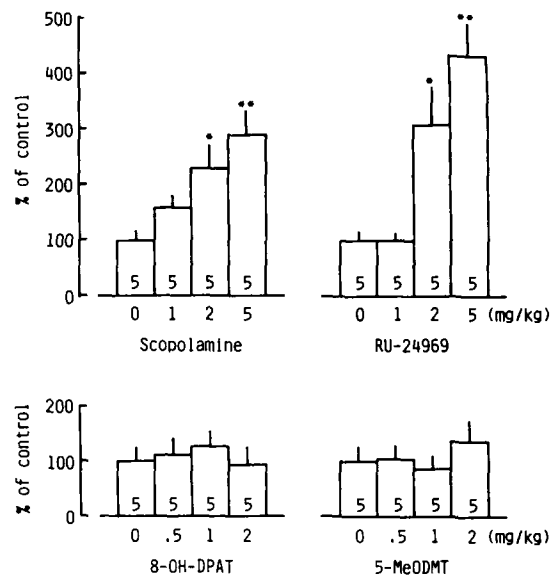

FIG 2 Effect of 5-HT-related agents and scopolamine on locomotor activity in mice Locomotor activity was measured for 45 min immediately after drug administration The columns represent mean (±S E) 45-min cumulated locomotor activity counts expressed in percent of control (vehicle-treated group) The numbers of mice in each group are indicated inside the columns and doses below the columns Significantly different from vehicle-treated group *$p<0$ 05, **$p<0$ 01

sostigmine sulphate (physostigmine; Nakarai), oxotremorine (Sigma), 5-methoxy-N,N-dimethyltryptamine (5-MeODMT; Sigma) and (±)propranolol hydrochloride (propranolol; ICI). 8-Hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT), 5-methoxy-3(1,2,3,6-tetrahydropyridin-4-yl)-1H indole maleate (RU-24969) and ethylcholine mustard aziridinium ion hydrochloride (AF64A) were synthesized and checked for purity by SIMSs (Hitachi M-80B mass spectrometer) and ^{1}H-NMR spectra (Varian XL-300 spectrometer) in our laboratories.

Scopolamine, physostigmine, oxotremorine and propranolol were dissolved in 0.9% saline. 8-OH-DPAT and RU-24969 were dissolved in a minimal amount of HCl to expedite dissolution and diluted with water. 5-MeODMT was dissolved in 0.9% saline containing 0.5% ascorbic acid. AF64A solution was freshly prepared each day by allowing the precursor, acetylcholine mustard hydrochloride, to cyclise at pH 11.4–11.6 for 30 min at room temperature. The pH was then returned to 7.4 with concentrated HCl, and the solution diluted to 10 nmol/μl with water

Drugs were administered IP in a volume of 0.1 ml/10 g except for AF64A which was given intracerebroventricularly (ICV) in a 10 μl volume. All doses were expressed in terms of total salts.

Locomotor Activity

Five Animex activity meters (Farad Co., Sweden) were used to assess locomotor activity. Animals were placed individually into plastic cages (23×36×30 cm) on the activity meters just after drug administration, and then the activity was measured for 45 min. AF64A-treated mice were used 7 days after treatment

Spontaneous Alternation

The apparatus was a T-maze made of black plastic. Both the stem and each arm of the maze were 25 cm long, 5 cm wide and 10 cm high. The first 10 cm of the stem and the last 10 cm of each arm were separated by sliding doors into start and goal boxes, respectively.

The task was started by placing a mouse in the start box of the maze. After 10 s, three sliding doors were raised, allowing the animals to explore the maze. When a mouse entered the goal box in either of the arms, the sliding door was closed behind it. The animal was kept there for 10 s and then manually returned to the start box. Commonly, naive mice alternate between goal boxes (right and left), but scopolamine-treated animals tend to enter the same goal box repeatedly. The same trial was repeated 8 consecutive times and a choice of the same goal in any 2 consecutive trials was counted as a SA failure (0–7).

All drugs were administered IP 30 min before the test, except for 5-MeODMT which was administered 15 min before the test. AF64A-treated mice were used 7 days after treatment.

Statistics

Statistical differences among the values for individual groups were determined using Duncan's (locomotor activity counts) or Williams Wilcoxon's (number of SA failures) multiple-range tests.

RESULTS

Effect of 5-HT-Related Agents and Scopolamine on Spontaneous Alternation Behavior in Mice

Under the present experimental conditions, the mean number of SA failures was 1.2–1.8 in vehicle-treated mice. In the mice treated with RU-24969 (0.5 and 2 mg/kg IP) or scopolamine (0.5–2 mg/kg IP) the number of SA failures increased significantly, indicating that RU-24969, like scopolamine, induced an

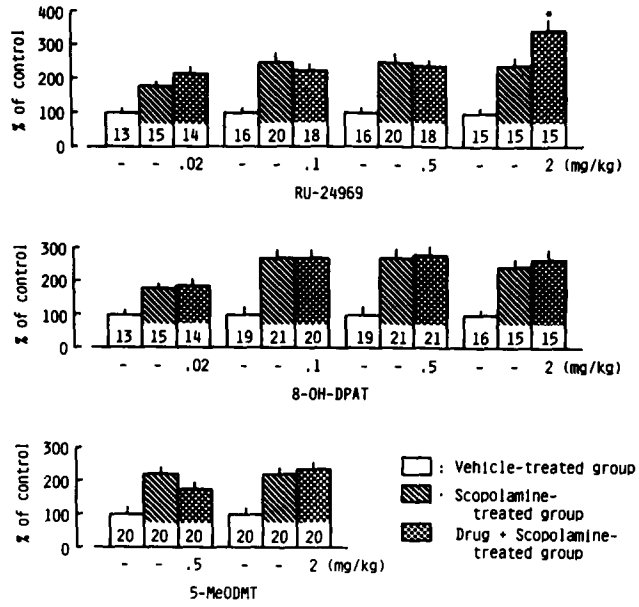

FIG 3 Effect of 5-HT-related agents on scopolamine-induced deficit of spontaneous alternation behavior in mice Scopolamine (1 mg/kg, IP) was administered simultaneously with 8-OH-DPAT or RU-24969, and 15 min before 5-MeODMT administration The columns represent mean (±S E) number of SA failures expressed in percent of control (vehicle-treated group) The numbers of mice in each group are indicated inside the columns and doses below the columns Significantly different from scopolamine-treated group *$p<0$ 05

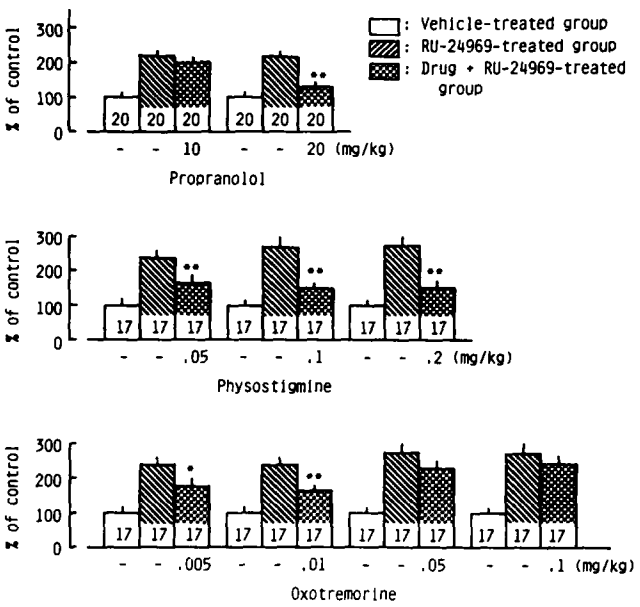

FIG. 4 Effect of physostigmine, oxotremorine and propranolol on RU-24969-induced deficit of spontaneous alternation in mice Drugs were administered IP simultaneously with RU-24969 (2 mg/kg, IP) 30 min before the testing spontaneous alternation The columns represent mean (±S E) number of SA failures expressed in percent of control (vehicle-treated group) The numbers of mice in each group are indicated inside the columns and doses below the columns Significantly different from RU-24969-treated group *$p<0$ 05, **$p<0$ 01

impairment of SA behavior. 5-MeODMT caused a slight increase in the SA failures at a large dose of 2 mg/kg IP, but 8-OH-DPAT (2–10 mg/kg IP) was without effect (Fig. 1).

Effect of 5-HT-Related Agents and Scopolamine on Locomotor Activity in Mice

The mean locomotor activity count for 45 min ranged from 775.0–1414.2 for the vehicle-treated groups. Treatment of the mice with RU-24969 (2–5 mg/kg IP) or scopolamine (2–5 mg/kg IP) produced a marked increase in the locomotor activity counts, in a dose-related manner. Such an effect was not caused by 5-MeODMT or 8-OH-DPAT (Fig 2).

Effect of 5-HT-Related Agents on Scopolamine-Induced Spontaneous Alternation Impairment in Mice

In the scopolamine (1 mg/kg IP)-treated mice, the mean number of SA failures was 3.2–4.0 and was significantly larger than that of the vehicle-treated mice (1.3–1 8). RU-24969, when injected simultaneously with scopolamine, caused a further increase in the number of SA failures. On the other hand, 5-MeODMT or 8-OH-DPAT did not alter the effect of scopolamine (Fig. 3).

Effect of Cholinomimetics and 5-HT$_1$ Receptor Antagonist on RU-24969-Induced Behavioral Deficits in Mice

The RU-24969 (2 mg/kg IP)-induced behavioral deficits were attenuated by propranolol and methysergide that have substantial 5-HT$_1$ receptor antagonist properties, as well as by physostigmine, an ACh esterase inhibitor, and oxotremorine, an ACh receptor agonist (Figs. 4 and 5).

A significant attenuation of the SA impairment was obtained with 20 mg/kg IP of propranolol, 0.05–0 2 mg/kg IP of physostigmine or 0.005–0 01 mg/kg IP of oxotremorine (Fig. 4). These same drugs significantly attenuated the hyperlocomotion (20 mg/kg IP of propranolol, 0.05–0.1 mg/kg IP of physostigmine or 0.005–0.01 mg/kg IP of oxotremorine. Fig. 5). Methysergide at 5 mg/kg IP also reduced both behavioral deficits (data not shown). Neither spontaneous alternation nor locomotor activity was influ-

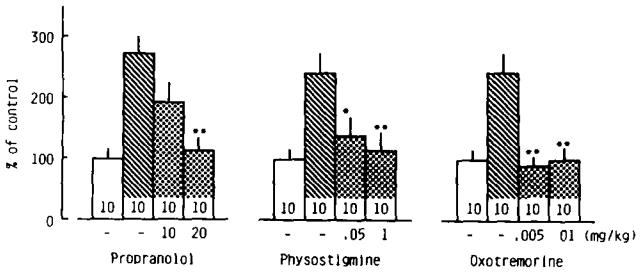

FIG 5 Effect of physostigmine, oxotremorine and propranolol on RU-24969-induced hyperlocomotion in mice Open bars vehicle-treated group, hatched bars RU-24969-treated group, dotted bars RU-24969 + Drug-treated group Drugs were administered IP simultaneously with RU-24969 (2 mg/kg, IP) Locomotor activity was measured for 45 min immediately after drugs administration The columns represent mean (±S E) 45-min cumulated locomotor activity counts expressed in percent of control (vehicle-treated group) The numbers of mice in each group are indicated inside the columns and doses below the columns. Significantly different from RU-24969-treated group *$p<0$ 05, **$p<0.01$

TABLE 1

EFFECT OF SCOPOLAMINE AND RU-24969 ON SPONTANEOUS ALTERNATION IN THE AF64A-PRETREATED MICE

Treatment	Dose (mg/kg, IP)	% of Sham Control (No of mice)
Sham control		100 0 ± 17 6 (18)
AF64A control		144 0 ± 15 9 (20)
AF64A + scopolamine	0 5	198 0 ± 13 1 (20)*
Sham control		100 0 ± 20 0 (15)
AF64A control		166 7 ± 13 3 (19)
AF64A + scopolamine	1 0	266 7 ± 20 0 (20)†
Sham control		100 0 ± 13 3 (20)
AF64A control		140 0 ± 20 0 (20)
AF64A + RU-24969	2 0	155 3 ± 13 3 (20)
Sham control		100 0 ± 20 0 (19)
AF64A control		166 7 ± 20 0 (19)
AF64A + RU-24969	5 0	193 3 ± 20 0 (19)

AF64A (30 nmol/body, ICV) was administered to mice 7 days prior to scopolamine or RU-24969 administration The SA test was carried out 30 min after the injection of scopolamine or RU-24969 The data represent mean (±S E) number of SA failures expressed in percent of control (sham control group) Significantly different from AF64A control group *$p<0$ 05, †$p<0$ 01

TABLE 2

EFFECT OF SCOPOLAMINE AND RU-24969 ON LOCOMOTOR ACTIVITY IN THE AF64A-PRETREATED MICE

Treatment	Dose (mg/kg, IP)	% of Sham Control (No of mice)
Sham control		100 0 ± 14 3 (10)
AF64A control		172 9 ± 28 4 (10)
AF64A + scopolamine	2 0	321 2 ± 35 7 (10)*
Sham control		100 0 ± 24 1 (10)
AF64A control		176 3 ± 34 3 (10)
AF64A + RU-24969	2 0	209 5 ± 35 5 (10)
Sham control		100 0 ± 14 7 (10)
AF64A control		153 0 ± 32 4 (10)
AF64A + RU-24969	5 0	224 7 ± 50 7 (10)*

AF64A (30 nmol/body, ICV) was administered to mice 7 days prior to scopolamine or RU-24969 administration. Locomotor activity was recorded for 45 min after the injection of scopolamine or RU-24969 The data represent mean (±S E) 45-min cumulated locomotor activity expressed in percent of control (sham control group). Significantly different from AF64A control group *$p<0$ 05

enced by these drugs alone at the doses used for the antagonism study

Effect of Scopolamine and RU-24969 in AF64A-Pretreated Mice

Seven days after a single injection of 30 nmol/body AF64A ICV, a presynaptic cholinergic neurotoxin (11,28), the ACh content decreased by about 26% in the hippocampus, without any decrease in the striatum and frontal cortex (data not shown). Behaviorally, slight increases in the locomotor activity count (53–73%) and the number of SA failures (40–67%) were observed, although these effects were not statistically significant compared to untreated mice (Tables 1 and 2). The higher dose of AF64A (50 nmol/body ICV) markedly produced these behavioral deficits and reduced the ACh content (data not shown). In this experiment, the low dose of 30 nmol/body was employed to avoid the direct effects of AF64A on locomotor activity and SA behavior.

In the AF64A-pretreated mice, RU-24969 (2 and 5 mg/kg IP) did not further increase the number of SA failures. The higher dose (5 mg/kg IP) of RU-24969 was required to cause hyperlocomotion in AF64A-treated mice. By contrast, scopolamine increased the behavioral changes (0.5 and 1 mg/kg IP for SA impairment and 2 mg/kg IP for hyperlocomotion) to the same extent in the AF64A-treated mice as in the untreated mice (Tables 1 and 2)

DISCUSSION

The availability of RU-24969, a compound with 5-HT_{1B} receptor agonist properties, enabled us to study behavioral changes after activation of brain serotonergic systems. In earlier studies (12, 14, 17), RU-24969, like scopolamine (2,32), was shown to cause a marked increase in locomotor activity in animals. The present study showed that, besides the increase in locomotor activity, RU-24969 and scopolamine caused a significant impairment of SA behavior in mice. The impaired SA behavior was not likely to result from the hyperlocomotion, because the increase in SA failures by both drugs appeared at low doses that did not affect locomotor activity, and also because methamphetamine, which potently increases locomotor activity, did not deteriorate the SA behavior (data not shown). It is generally accepted that the scopolamine-induced hyperlocomotion and SA impairment result from a cholinergic hypofunction in the brain. This prompted us to investigate how the 5-HT_1 agonist, RU-24969, produced the behavioral deficits like those of scopolamine.

Neither the hyperlocomotion nor the SA impairment appears to be common to all kinds of 5-HT_1 receptor agonists, because little or no deficits in either behavior were observed in animals treated with the 5-HT_1 receptor agonists, 5-MeODMT and 8-OH-DPAT (1, 8, 18, 36). Nevertheless, the RU-24969-induced hyperlocomotion has been considered to be mediated via 5-HT_1 receptors (12,14). Although no evidence is available at present to explain the difference in the effects of RU-24969 and 5-MeODMT or 8-OH-DPAT, it is tempting to speculate that the difference results from the different affinities for 5-HT_1 receptor subtypes (14, 19, 27, 33, 34). RU-24969 has been shown to have a higher affinity for the 5-HT_{1B} subtype than 5-MeODMT (nonselective 5-HT_1 receptor agonist) and 8-OH-DPAT (5-HT_{1A} receptor agonist). In the present study, the RU-24969-induced impairment of SA behavior as well as the hyperlocomotion was antagonized by propranolol and methysergide that have 5-HT_1 receptor antagonist properties. Further, it is suggested that propranolol has a high affinity for 5-HT_{1A}/5-HT_{1B} receptors, but not for 5-HT_{1C}/5-HT_{1D} receptors (19). Thus RU-24969-induced impairment of SA behavior, as well as the hyperlocomotion, may also be mediated via 5-HT_1 (particularly 5-HT_{1B} subtype, but not 5-HT_{1A}/5-HT_{1C}/5-HT_{1D} subtypes) receptors.

Oberlander (26) suggested that RU-24969-induced hyperlocomotion resulted from a 5-HT stimulus mediated by a dopaminergic system, and this assumption was confirmed by the subsequent experiments by Green et al (17). The present study has shown that cholinergic mechanisms may also be involved in RU-24969-induced behavioral changes. Namely, physostigmine and oxotremorine (cholinomimetics) attenuated the hyperlocomotion and SA impairment, and further, scopolamine added to the SA impairment by RU-24969

There are several lines of biochemical evidence suggesting that serotonergic afferents from the raphe nucleus tonically inhibit cholinergic neurons in the rat striatum, hippocampus and cerebral

cortex (31). For example, Gillet et al. (13) reported that 5-HT and serotonergic agonists inhibited K^+-evoked [^{3}H]ACh release from rat striatal slices. If RU-24969 has a similar action, the behavioral deficits would be lessened in mice with lesioned ACh terminals than in intact mice. To determine whether this was the case, we lesioned ACh nerve terminals by ICV injection of AF64A Pope et al. (28) reported that the same ICV dose of AF64A (30 nmol) reduced choline acetyltransferase activity in the hippocampus and the cerebellum in mice The higher dose (65 nmol/body) of AF64A was reported to reduce ACh content still further in various brain regions and also to inhibit passive avoidance response in mice (11). We confirmed that AF64A at 30 nmol/body reduced ACh content in the hippocampus of mice by about 26% (data not shown), indicating moderate lesions of the ACh terminals These mice showed only a slight, nonsignificant increase in locomotor activity and SA failures. In such mice, RU-24969 did not cause SA impairment, nor did it cause hyperlocomotion except at the higher dose (5 mg/kg IP) Besides, the hyperlocomotion at 5 mg/kg IP was much less in AF64A-treated mice (124% increase) than intact mice (333% increase). In contrast, scopolamine induced the behavioral deficits to the same extent as inducing the deficits in intact animals Therefore, it is reasonable to assume that 5-HT_1 receptors (5-HT_{1B} subtype) are located on the presynaptic terminals of cholinergic neurons, regulating the release of ACh and that RU-24969 induces the behavioral deficits by inhibiting ACh release via its possible interaction with 5-HT_1 receptors. In fact, a previous biochemical study has demonstrated that there are 5-HT_1 receptors of the 5-HT_{1B} type that are inhibitory to the release of ACh in the hippocampus (22)

In summary, we have shown that RU-24969, a compound with 5-HT_{1B} receptor agonist properties, induced hyperlocomotion and SA impairment in mice, behavioral changes commonly observed in the animals treated with anticholinergic drugs. Such behavioral deficits are likely due to an inhibition of ACh release through 5-HT_1 presynaptic receptors (particularly RU-24969-sensitive 5-HT_{1B} sites) localized on cholinergic terminals. This behavioral study supports the previous biochemical reports indicating that there are functional relationships between brain serotonergic and cholinergic neuronal systems.

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