Effect of OM-853, a Cerebral Metabolic Ameliorator, on Ambulatory Activity and Passive and Active Avoidance Responses in Mice and Mongolian Gerbils

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ABSTRACT Behavioral effects of OM-853 were investigated in both mice and Mongolian gerbils. In mice, OM-853 alone produced no marked change in the ambulatory activity, although it tended to lower it at 100 mg/kg, and this drug (5-100 mg/kg, p.o.) reduced the ambulation-increasing effect of scopolamine (0.5 mg/kg, s.c.) in a dose-dependent manner. Moreover, OM-853 (50 and 100 mg/kg, p.o.) prolonged the latency times shortened by scopolamine under the passive avoidance. On the other hand, in the discrete avoidance situation, OM-853 facilitated the acquisition of shuttle avoidance at 10 and 25 mg/kg, p.o. and lever-press avoidance at 25 and 50 mg/kg, p.o. in the pre-training administration schedule, and the former at 25-100 mg/kg, p.o. and the latter at 10 and 25 mg/kg, p.o. in the post-training administration schedule. In gerbils, OM-853 (50 mg/kg, i.p.) ameliorated the learning deficit of the lever-press avoidance response induced by forebrain ischemia. The present results suggest that OM-853 has beneficial actions on some types of learning and memory in normal, scopolamine-treated and ischemic animals. The possible mechanisms involved are discussed.

Keywords: OM-853, Ambulatory activity, Passive avoidance, Active avoidance, Forebrain ischemia

Several pharmacological agents, with widely different structures and profiles of action, are used in the treatment of cerebrovascular diseases. OM-853, (±)-methyl 3-ethyl-2,3,3a,4-tetrahydro-1*H*-indolo[3,2,1-de][1,5]naphthyridine-6-carboxylate monohydrochloride, has been developed as a cerebral metabolic ameliorator. In previous studies, OM-853 prevented delayed neuronal death in the hippocampus after a brief cerebral ischemia in rats and gerbils (1, 2), and significantly extended consciousness and delayed the onset time of EEG disturbances under a hypoxic condition (3). Furthermore, OM-853 has been reported to improve psychomotor activity, cognitive function, attention and concentration in elderly subjects (4). In these respects, it is expected that OM-853 may have beneficial effects on the cerebral disorders induced by hypoxic or anoxic conditions such as ischemia. However, there is yet little information about the behavioral pharmacological effects of OM-853. The aims of this study, therefore, were to assess the behavioral effects of OM-853 in normal and scopolamine-treated mice and ischemic gerbils.

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MATERIALS AND METHODS

Animals

The experimental animals were male mice of the ddY strain (Japan SLC, Inc., Hamamatsu) and male Mongolian gerbils (Seiwa Experimental Animal Laboratory, Fukuoka). The mice were housed in groups of 10 in aluminum cages of 30(W)×20(D)×10(H) cm with a wooden-flake floor mat (White Flake: Charles River Japan, Inc., Atsugi). The gerbils were housed in groups of 5 in Plexiglas cages of 35(W)×25(D)×15(H) cm with the floor mat. Solid diet (MF: Oriental Yeast Co., Tokyo) and tap water were freely given to the animals except during the times of the experiment. The breeding room was controlled so that the light-dark schedule (light period: 6:00-18:00) and room temperature (23±2℃) were

almost constant throughout the experimental period.

Drugs

The drugs used were OM-853 (Tokyo Tanabe Co., Tokyo), scopolamine hydrobromide (Sigma Chemical Co., St. Louis, MO, USA) and pentobarbital sodium (Tokyo Kasei Kogyo Co., Tokyo). OM-853 was dissolved in distilled water. Scopolamine and pentobarbital were dissolved in physiological saline. The volume administered was fixed at 0.1 ml/10 g and 0.5 ml/100 g body weight to the mice and the gerbils, respectively.

Apparatus and procedures

Ambulatory activity in mice: For measurement of the ambulatory activity of mice, a tilting-type ambulometer with an activity cage of 20 cm in diameter and 18 cm in height (AM-10; O'hara & Co., Ltd., Tokyo) was used. A mouse was put into the activity cage, and after an adaptation period of 30 min, drug administration was carried out. Then the ambulatory activity was measured for 60 min and 120 min in the cases of single administration of OM-853 (p.o.) and combined administration of OM-853 (p.o.) with scopolamine (s.c.), respectively.

Passive avoidance response in mice: The apparatus for the passive avoidance (PA-M5; O'hara & Co., Ltd.) consisted of two chambers, a bright one and a dark one, which were separated by a guillotine door. Each chamber had a floor made of stainless steel grid. On the first day, an acquisition trial was begun by placing a mouse into the bright chamber, and after 3 sec, the guillotine door was opened. When the mouse moved completely into the dark chamber, the door was closed, and an electric foot shock of 75 V (AC), which might be sufficiently aversive, was applied through the grid floor for 2 sec. Immediately after presenting the electric shock, the mouse was returned to its home cage. A retention trial was held 24 hr later. The trial was carried out in the same manner as in the acquisition trial, except that the guillotine door was opened while the mouse entered the dark chamber, and no shock was applied. A cut-off time of 300 sec was taken in the retention trial as an establishment of the passive avoidance response. OM-853 (0: distilled water, 10, 25, 50 and 100 mg/kg, p.o.) and scopolamine (0.5 mg/kg, s.c.) were administered 10 min before the acquisition trial.

Discrete avoidance responses in mice: The experimental chamber for the shuttle avoidance response was 30(W) × 9(D) × 15(H) cm with 2 photo-beams arranged 18 cm apart. The experimental chamber for the lever-press avoidance response was 18(W) × 9(D) × 10(H) cm, with a stainless steel lever, which could be pressed with a force of more than 1.5 g. The floor of the chambers for both shuttle and lever-press avoidance responses consisted of a stainless steel grid, and it was wired to pass an electric current. A speaker for presenting a warning stimulus was set in the ceiling of each experimental chamber. A behavior-controlling and data-recording apparatus (GT-7705 and GT-7715, respectively; O'hara & Co., Ltd.) were used in this experiment. The temporal parameters of the discrete avoidance schedule were an intertrial interval of 25 sec and a warning duration of 5 sec. A shock of an electric current of 100 V, 0.3 mA, 50 Hz AC was given to a mouse through the grid of the experimental chamber. The maximum duration of the shock presentation was 3 sec, and an escape contingency was inserted in the schedule. The indices of the discrete avoidance response were a response rate (number of shuttles or lever-presses/min) and an avoidance rate (number of avoidance responses/number of avoidance trials).

In both the shuttle and lever-press avoidance responses, effects of OM-853 (0, 10, 25, 50 and 100 mg/kg, p.o.) on the acquisition process were evaluated. OM-853 was administered 10 min before the start of a training session (pre-training OM-853) or immediately after the end of a training session (post-training OM-853). The session consisted of 5 min (10 avoidance trials) and 20 min (40 avoidance trials) training in the shuttle and lever-press situations, respectively.

Ischemic operation and avoidance training in gerbils: The gerbils were anesthetized by GOF mixed gas [3(N_2O):1(O_2) with 2% halothane]. The common carotid arteries were occluded for 15 min with Sugita aneurysm clips. Then these clips were released to recirculate the blood flow. OM-853 (50 and 100 mg/kg, i.p.) and pentobarbital (40 mg/kg, i.p.) were administered 4 times: 10 min before the ischemia, 3 hr, 24 hr and 48 hr after the ischemia. Eight days after the ischemic operation, the training of the discrete lever-press avoidance response was started. The apparatus and procedure were the same as those used in the mouse experiment. Each training session consisted of 40 trials at intervals of 30 sec.

Histopathology

The gerbils were anesthetized with pentobarbital at 50 mg/kg, i.p. at 14 days of survival. They were briefly perfused with heparinized saline by transcardiac perfusion, followed by perfusion-fixation with 10% formalin solution. Coronal sections of 5 μm in thickness were cut and stained with Cresyl violet.

Statistical analysis

Statistical comparisons of the mean ambulatory activity counts and the acquisition processes of the discrete avoidance responses were conducted using Dunnett's multiple range test. The results of the passive avoidance experiment were analyzed by one-way ANOVA followed by the Mann-Whitney *U*-test.

RESULTS

Effects on the ambulatory activity in mice

Figure 1 shows the ambulatory activity after administration of OM-853 (10, 30 and 100 mg/kg, p.o.). OM-853 alone produced no marked change in the ambulatory activity, but tended to lower it at 100 mg/kg. Figure 2 shows the combined effects of OM-853 (1, 2.5, 5, 10, 25, 50 and 100 mg/kg, p.o.) with scopolamine (0.5 mg/kg, s.c.) on the ambulatory activity. The mean overall ambulatory activity counts after the combined administration of OM-853 (5–100 mg/kg, p.o.) with scopolamine were significantly less than the scopolamine-saline treated control value.

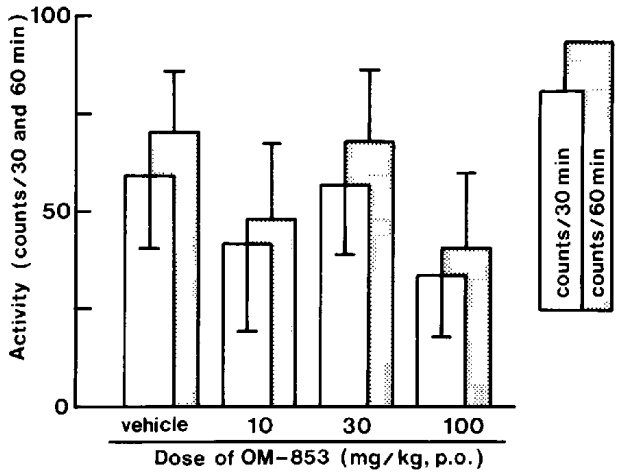

Fig. 1. Effect of OM-853 on the ambulatory activity in mice. Mean overall ambulatory activity counts for 30 and 60 min are presented. Each column indicates the mean ± S.E. of 20 mice.

Effects on the passive avoidance response in mice

Figure 3 shows the intermediate and quartile latency times of each group of mice in the retention trials. Scopolamine (0.5 mg/kg, s.c.) significantly shortened the latency time. OM-853 at 50 and 100 mg/kg, p.o. significantly ameliorated the scopolamine-induced shortening of the latency.

Effects on the acquisition of the discrete avoidance response

The shuttle avoidance response in mice: Figures 4 and 5 show effects of OM-853 (10, 25, 50 and 100 mg/kg, p.o.), administered before and after each training session, respectively, on the acquisition of the discrete shuttle avoidance response by means of the avoidance rate. The group of naive (no drug administration) mice highly avoided (47%) the electric shock in the 1st session. Although the avoidance rate declined in the 2nd session, the naive mice progressively acquired the avoidance response thereafter, attaining an avoidance rate of higher than 60% with a stable response rate in the 6th session. In

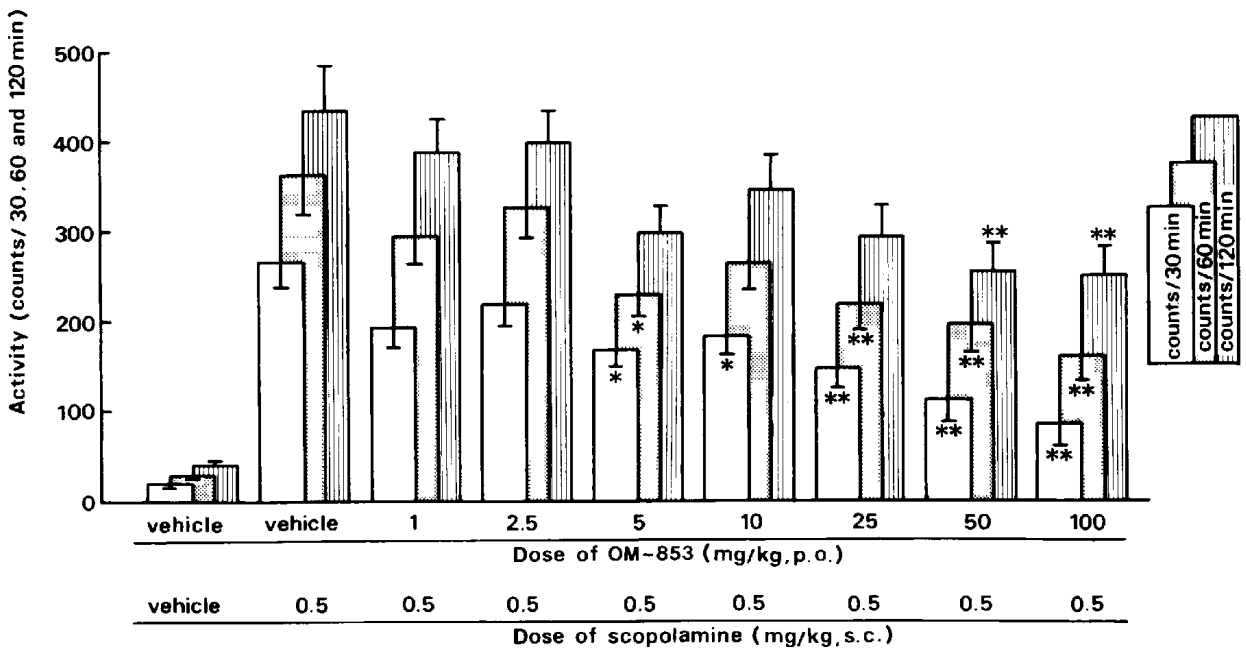

Fig. 2. Effect of combined administration of OM-853 with scopolamine on the ambulatory activity in mice. Mean overall ambulatory activity counts for 30, 60 and 120 min are presented. Each column indicates the mean ± S.E. of 27–31 mice. *$P<0.05$, **$P<0.01$, compared with the scopolamine-treated control (Dunnett's multiple range test).

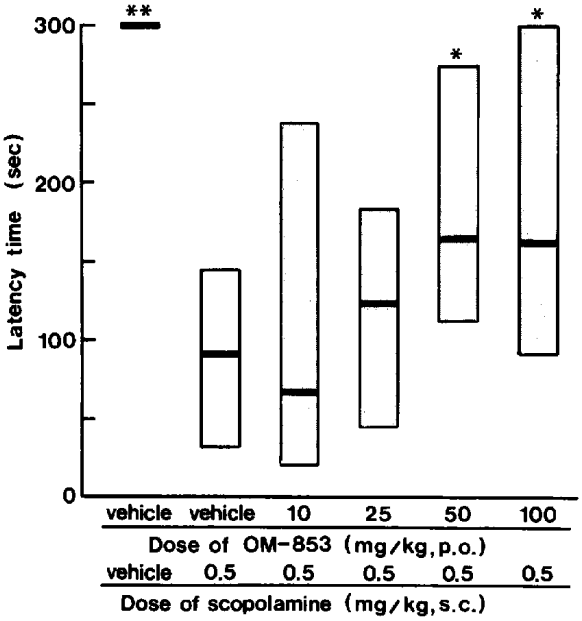

Fig. 3. Effect of OM-853 on the retention of the passive avoidance response in mice. Each column indicates the median and interquartile ranges of 19–20 mice. *P<0.05, **P<0.01, compared with the scopolamine-treated control (Mann-Whitney *U*-test).

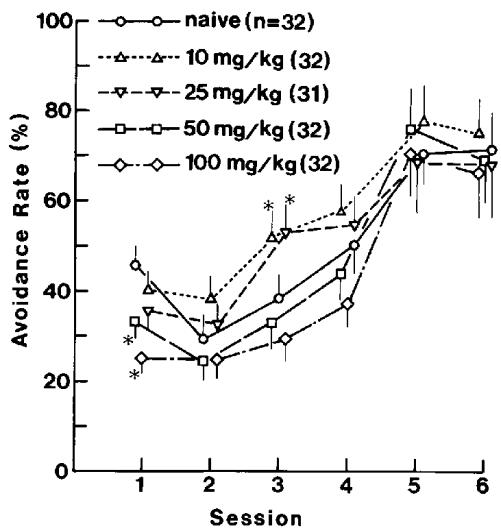

Fig. 4. Effect of OM-853 (10, 25, 50 and 100 mg/kg, p.o.) on acquisition of the discrete shuttle avoidance response in mice. The drug was administered 10 min before each training session of 10 avoidance trials. In this figure, only the changes in the avoidance rate are shown, because there was no difference in the response rate among the groups. *P<0.05, **P<0.01, compared with the naive (no drug administration) mice (Dunnett's multiple range test). Figure in each parenthesis is the number of animals used.

the 1st session, pre-training with OM-853, at doses of 50 and 100 mg/kg, p.o., significantly decreased the avoidance rate (81.5 and 61.5%, respectively), and the avoidance rate tended to be decreased (88.4 and 81.6%, respectively) in comparison with those in the naive mice. Pre- and post-training OM-853, at doses of 10 and 25, and at doses of 25–100 mg/kg, respectively, elicited a slight, but significant increase in the avoidance rate in the 2nd–4th sessions without producing a marked change in the response rate (data not shown).

The lever-press avoidance response in mice: Figures 6 and 7 show acquisition processes of the discrete lever-press avoidance response in the pre- and post-training regimens, respectively, by means of the avoidance rate. The naive mice showed an average avoidance rate of below 20% throughout the 12 sessions of training. Pre-training (25 and 50 mg/kg, p.o.) and post-training (10 and 25 mg/kg, p.o.) with OM-853, respectively, significantly increased the avoidance rate in comparison with that of the naive mice. No marked change in the response rate was produced by OM-853 (data not shown).

The lever-press avoidance response in ischemic gerbils: Figure 8 shows acquisition processes of the discrete lever-press avoidance response in the sham-operated, ischemia-control (no drug administration), and ischemia-drug administered gerbils by means of the avoidance rate. The acquisition in the ischemia-control gerbils was significantly delayed in comparison with that in the sham-operated gerbils. The treatment with pentobarbital (40 mg/kg, i.p.) significantly ameliorated the impaired avoidance acquisition induced by the ischemic operation. OM-853

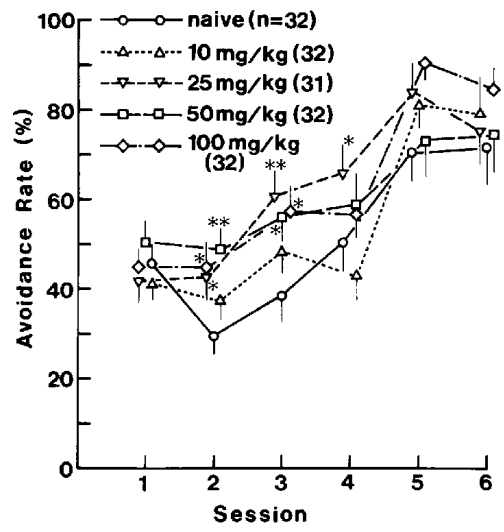

Fig. 5. Effect of OM-853 (10, 25, 50 and 100 mg/kg, p.o.) on acquisition of the discrete shuttle avoidance response in mice. The drug was administered immediately after each training session of 10 trials. The data are shown in the same way as in Fig. 4.

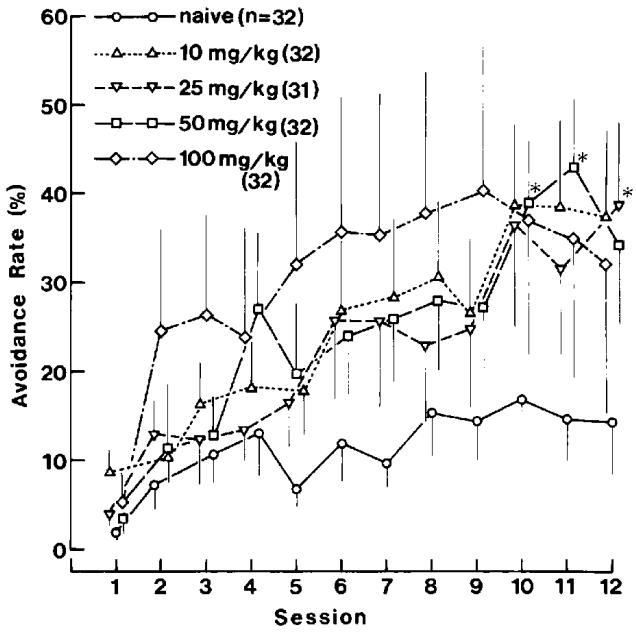

Fig. 6. Effect of OM-853 (10, 25, 50 and 100 mg/kg, p.o.) on acquisition of the discrete lever-press avoidance response in mice. The drug was administered 10 min before each training session of 40 avoidance trials. The data are shown in the same way as in Fig. 4.

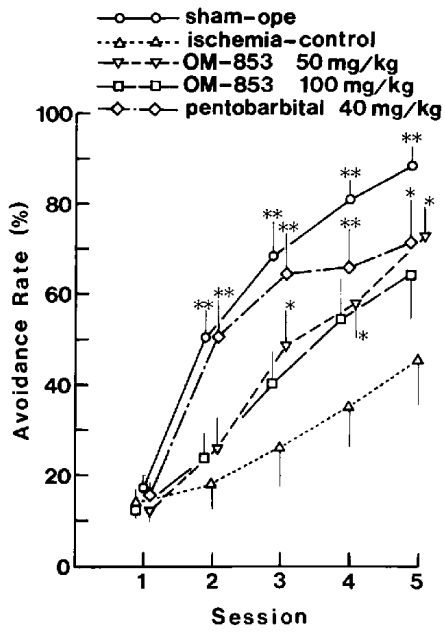

Fig. 8. Effect of OM-853 (50 and 100 mg/kg, i.p.) and pentobarbital (40 mg/kg, i.p.) on the acquisition of the discrete lever-press avoidance response in Mongolian gerbils subjected to 15-min ischemia. These drugs were administered 4 times: 10 min before and 3, 24, and 48 hr after the operation, and the training of 40 trials per session was started from the 8th post-operative day. Each value indicates the mean ± S.E. of 16 gerbils. * $P<0.05$, ** $P<0.01$, compared with the ischemia-control (Dunnett's multiple range test).

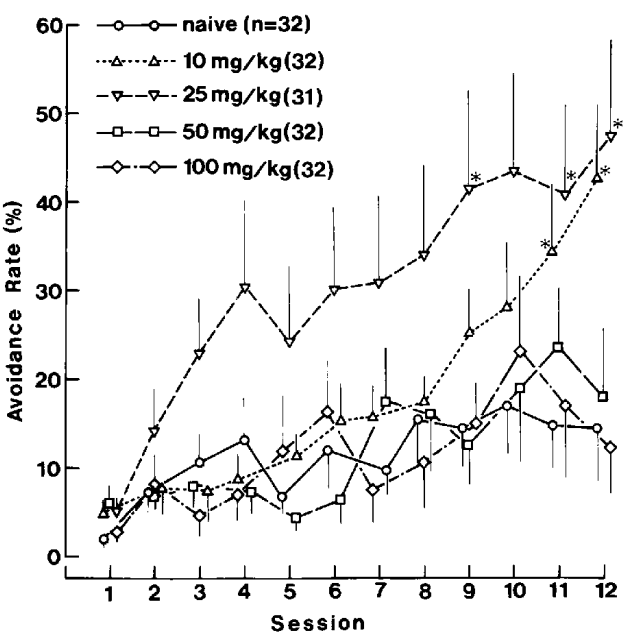

Fig. 7. Effect of OM-853 (10, 25, 50 and 100 mg/kg, p.o.) on acquisition of the discrete lever-press avoidance response in mice. The drug was administered immediately after each training session of 40 avoidance trials. The data are shown in the same way as in Fig. 4.

ameliorated the impaired avoidance acquisition equally at doses of 50 mg/kg and 100 mg/kg, although the effect of the latter dose did not attain a statistically significant level ($0.05<P<0.1$).

Histopathology in ischemic gerbils: Representative photographs of the gerbil brain are shown in Fig. 9. The gerbils subjected to 15-min ischemic insults revealed severe neuronal damage in the brain. The most damaged areas were the hippocampal CA1 sector and dorsolateral part of the striatum, followed by the hippocampal CA3 sector and the neocortex. OM-853 (50 and 100 mg/kg, i.p.) and pentobarbital (40 mg/kg, i.p.) showed a protective effect against the dorsolateral part of the striatum and hippocampal CA3 sector. The protective effect of 50 mg/kg of OM-853 (i.p.) was approximately equal to that of 100 mg/kg (i.p.), and was weaker than that of pentobarbital. However, protection against the hippocampal CA1 sector was not observed in any drug-treated animals.

DISCUSSION

The present study demonstrated that OM-853 (5–100 mg/kg, p.o.) significantly reduced the ambulation-increasing effect of scopolamine and prolonged the scopolamine-induced shortening of the latency in the passive avoidance

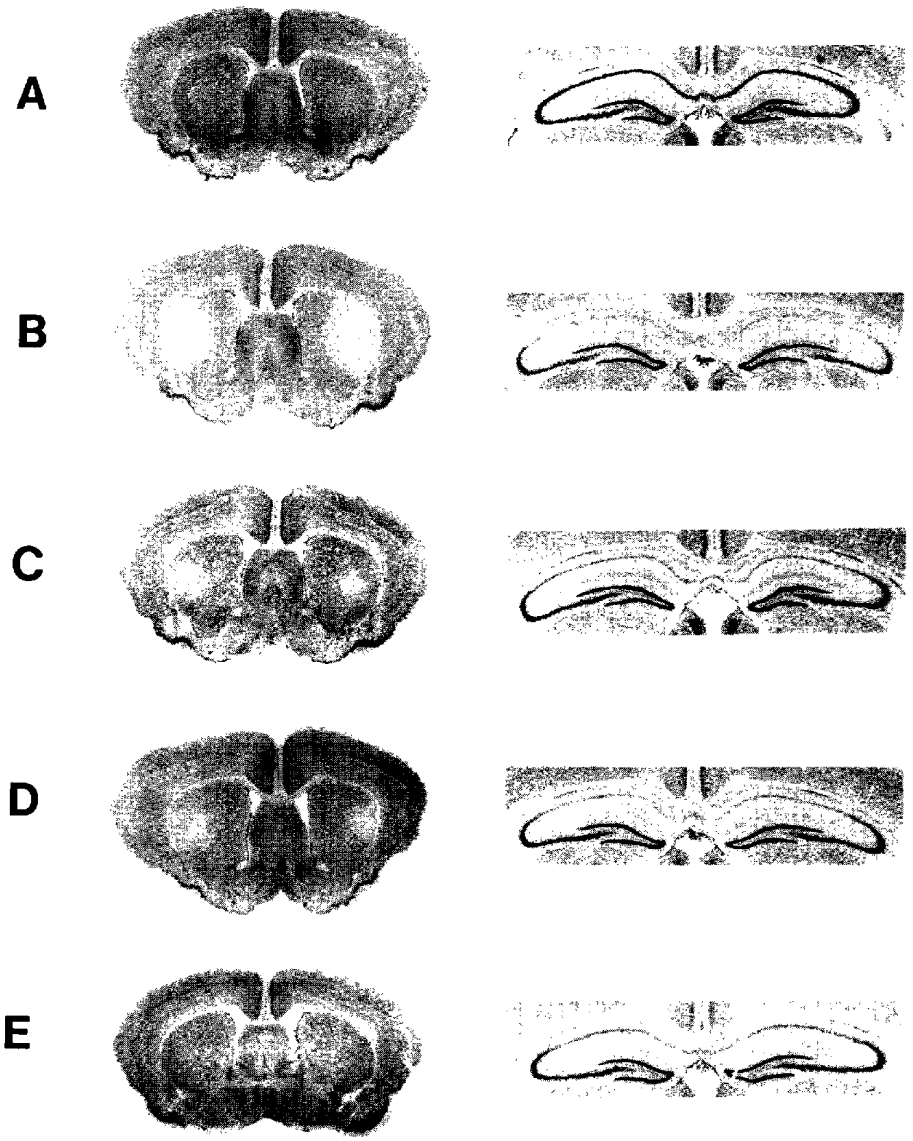

Fig. 9. Representative histological changes in the gerbil brain after 15 min of ischemia. A: sham-operated gerbil, B: ischemic control gerbil, C: OM-853 (50 mg/kg, i.p.)-treated gerbil, D: OM-853 (100 mg/kg, i.p.)-treated gerbil, E: pentobarbital (40 mg/kg, i.p.)-treated gerbil.

task at higher doses. Scopolamine is well known to cause hyperactivity in mice and rats (5, 6) through blockade of the muscarinic cholinergic system and the consequent stimulation of the dopaminergic system (7, 8). OM-853 augmented oxotremorine-induced tremor (unpublished data, K. Shuto et al.), and this drug has been demonstrated to have an affinity for muscarinic acetylcholine receptor (9). It is therefore thought that OM-853 has reversed the scopolamine-induced hyperactivity and shortening of the latency through activation of the cholinergic system. Furthermore, it seems that the tendency for the decrease in the ambulation by OM-853 at 100 mg/kg may be caused by an activation of the cholinergic system, because cholinomimetic agents lead to lowered locomotion at higher doses in normal animals (10). Moreover, the effective dose range for amelioration of scopolamine-induced passive avoidance deficit was different from that on the ambulatory activity. Lenegre et al. have shown that piracetam attenuated the memory deficits induced by scopolamine, although it did not affect scopolamine-induced hyperactivity (11). Perhaps the mechanisms of action of OM-853 against scopolamine-induced ambulatory activity and passive avoidance deficiency are different.

In the acquisition of the shuttle avoidance response, the naive mice performed with a higher avoidance rate and response rate in the 1st session than in the 2nd session.

This phenomenon might be due to a non-specific exploratory activity reflecting an accelerated emotion induced by exposure to a new situation and electric shocks. Such a phenomenon was also observed by Kuribara and Tadokoro (12). OM-853 (10 and 25 mg/kg) improved the acquisition of the shuttle avoidance. A similar action has been reported in the mice treated with amilidine (13), piracetam and oxiracetam (14), suggesting that the cholinomimetic action of lower doses of OM-853 may accelerate the acquisition of shuttle avoidance in the normal mice. In contrast, pre-training with OM-853 (50 and 100 mg/kg, p.o.) significantly decreased the avoidance rate and tended to decrease the response rate in the 1st session. It is thought that these effects of OM-853 are caused by its inhibitory action on the exploratory activity. Moreover, pre-training with OM-853, at doses of 50 and 100 mg/kg, did not significantly improve the acquisition in the 2nd–6th sessions. This is probably because the decreased avoidance rate in the 1st session resulted in a lower starting point for the acquisition. It is also considered that such a dose-effect relationship demonstrated the bell-shape action of OM-853 on the learning and memory process. Furthermore, post-training with OM-853 at doses of 25–100 mg/kg on the shuttle avoidance and 10 and 25 mg/kg on the lever-press avoidance, accelerated the acquisition of avoidance responses, indicating that OM-853 improves memory consolidation. The effective doses of OM-853 in the shuttle avoidance were different from those in the lever-press avoidance. The characteristic behavioral differences between the shuttle and lever-press avoidance may have caused this difference. Kuribara et al. have reported that the shuttle and lever-press avoidance responses sometimes show different sensitivities to various kinds of psychoactive drugs (15).

The hippocampus, especially the CA1 sector, is thought to play a crucial role in learning and memory (16, 17). Several reports have demonstrated that transient forebrain ischemia produces damage in the hippocampal CA1 sector (delayed neuronal death) and sometimes disrupted learning and memory in experimental animals (18, 19). Several lines of evidence have also shown that the damage of the hippocampal CA3 sector (20), striatum (21), parietal cortex (22) or basal forebrain (23) caused an impairment of cognitive function. These findings suggest that not only the hippocampal CA1 sector but also other regions relate to cognitive function.

In the present study, ischemic insults induced severe neuronal damage in the various brain regions, and the acquisition of the lever-press avoidance response was impaired by the transient forebrain ischemia in gerbils. Pretreatment with pentobarbital and OM-853 prevented the neuronal damage in the striatum and hippocampal CA3 sector and ameliorated the impaired acquisition. The ameliorative effect of OM-853 on the avoidance acquisition was less potent than that of pentobarbital, because the protective effect of OM-853 was also less potent than that of pentobarbital against ischemic damage. Furthermore, 50 and 100 mg/kg of OM-853 showed almost the same effectiveness on the avoidance acquisition, although the effect of the latter dose did not attain a statistically significant level. The protective effect of pentobarbital is thought to be mediated by a powerful sedative action on the central nervous system through $GABA_A$ and benzodiazepine receptor stimulation (24). It should be considered that the protective effect of pentobarbital appears at an anesthetic dose. On the other hand, protection by OM-853 is thought to be exerted by amelioration of post-ischemic alterations of [^{3}H]PDBu, [^{3}H]IP_3 and [^{3}H]-forskolin binding (25). It is therefore expected that although OM-853 is less potent than pentobarbital, the former drug may be specific for prevention of ischemia-induced brain damage and behavioral disruption.

In conclusion, this study showed that OM-853 antagonizes the behavioral effects of scopolamine on ambulation and passive avoidance, accelerates acquisition processes of avoidance responses in normal mice and ameliorates the impaired acquisition induced by the ischemic insults in gerbils. It is therefore possible that OM-853 has beneficial actions on some types of learning and memory. However, further studies are also required to ascertain the mechanisms for the effect of OM-853.

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