Effects of OM-853, a Novel Indolonaphthyridine Derivative, on Behavioral Responses in the Forced Swim Test in Rats

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ABSTRACT—Effects of OM-853 on behavioral responses in the forced swim test were studied. OM-853 significantly reduced the duration of immobility without any change in the exploratory activity. Imipramine also reduced the duration of immobility, but idebenone did not. On the other hand, vinpocetine enhanced the duration with a suppressive effect on ambulation. The anti-immobility effect of OM-853 was reversed by pretreatment with haloperidol. These results demonstrate that the effect of OM-853 on the swim test is different from that of idebenone and vinpocetine. Furthermore, the present results suggest that OM-853 may exert its anti-immobility activity through facilitated transmission of the dopaminergic and/or adrenergic systems.

Keywords: OM-853, Immobility, Amygdala

OM-853 ((±)-methyl 3-ethyl-2,3,3a,4-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine-6-carboxylate monohydrochloride, vinconate hydrochloride) is a novel indolonaphthyridine derivative, which is structurally related to vincamine, but possesses 4 rings instead of the 5 rings of vincamine. It is now under development as a cerebral metabolism ameliorator. Biochemical and histological investigation has shown that OM-853 ameliorates the glucose utilization under middle cerebral artery occlusion in rats (1), protects against delayed neuronal death in both rats and gerbils (2, 3), and facilitates metabolic turnover of dopamine, serotonin and norepinephrine in rat brain (4). Behavioral investigation has also shown that OM-853 improves spatial learning in Morris's water maze task of forebrain-lesioned rats (5), improves decreased latency by scopolamine in the one trial passive avoidance test in mice (6), and facilitates acquisition of shuttle- and lever-press avoidance responses in mice (6). A previous report suggested that activation of dopaminergic and/or adrenergic systems was involved in the anti-immobility effect of antidepressants in the swim test (7). Therefore, in the present study, we investigated the effects of OM-853 on behavioral responses of rats in the forced swim test and compared them with those of idebenone, a cerebral metabolism ameliorator, and vinpocetine, an ameliorator of cerebral circulation and a derivative of vincamine.

Male Wistar rats weighing 100–200 g were purchased from Nippon SLC (Hamamatsu) and housed in an air-conditioned room at 22 ± 1°C with a 12-hr light-dark cycle (lights on at 7:00). Immobility was measured by the method of Porsolt et al. (8) without pretraining. A rat was placed in a glass cylinder (height: 30 cm, diameter: 18 cm) containing 18-cm-deep water at 25°C. A rat was judged to be immobile whenever it remained floating in the water, in an upright position, making only very small movements necessary to keep its head above water. The total duration of immobility during 5 min was recorded. In separate experiments, ambulatory activity was measured. A rat was placed in an open field box (size: 90 x 90 x 45 cm), and the distance traveled during 5 min was recorded by a monitor system equipped with a computer (Chaser BTA-2 system, Muromachi Kikai, Tokyo). Each animal was tested only once and did not have any prior exposure to the experimental apparatus.

OM-853 and vinpocetine (Omnichem, Louvain-la-Neuve, Belgium) were orally administered 30 min before the experiments. Idebenone (Avan®, Takeda Chemical Industries, Osaka) was orally administered, whereas imipramine (hydrochloride salt, Sigma, St. Louis, MO, USA) and haloperidol (Katsura Chemicals, Tokyo) were intraperitoneally administered 60 min before the experiments. The volume of administration was fixed at 5 ml/kg. Data were expressed as the mean ± S.E.M., and statistical analyses were made by Duncan's multiple com-
comparison test.

OM-853, at a dose range of 12.5–200 mg/kg, significantly reduced the duration of immobility, but not dose-dependently (Table 1). Imipramine, a typical tricyclic antidepressant, decreased the duration of immobility in a dose-dependent fashion at doses of 20 and 30 mg/kg. However, idebenone (50–200 mg/kg) did not change the duration of immobility. In contrast, vinpocetine (100, 200 mg/kg) significantly enhanced the duration of immobility (Table 1).

Table 1. Effects of OM-853 and various drugs on the duration of immobility and ambulatory activity in rats

| Drug       | Dose (mg/kg) | Duration of immobility (sec) | Ambulatory activity (moved distance, cm) |
|------------|--------------|------------------------------|-----------------------------------------|
| Vehicle    | —            | 100.1 ± 5.4                  | 1580±165                                |
| OM-853     | 12.5         | 83.4 ± 8.1*                  | N.D.                                    |
|            | 25           | 63.4 ± 3.7**                 | 1350±210                                |
|            | 50           | 67.3 ± 3.0**                 | N.D.                                    |
|            | 100          | 76.0 ± 5.2**                 | 1270±201                                |
|            | 200          | 72.2 ± 5.1**                 | N.D.                                    |
| Vehicle    | —            | 84.7 ± 7.3                   | 2030±167                                |
| Idebenone  | 50           | 93.4 ± 4.2                   | N.D.                                    |
|            | 100          | 91.1 ± 5.0                   | N.D.                                    |
|            | 200          | 95.4 ± 7.4                   | 1600±249                                |
| Vehicle    | —            | 89.8 ± 5.8                   | 1610±249                                |
| Vinpocetine| 50           | 97.9 ± 5.3                   | N.D.                                    |
|            | 100          | 121.0 ± 7.0**                | N.D.                                    |
|            | 200          | 132.9 ± 4.9**                | 900±161*                                |
| Vehicle    | —            | 93.8 ± 3.3                   | 1760±287                                |
| Imipramine | 20           | 62.8 ± 7.2**                 | N.D.                                    |
|            | 30           | 57.2 ± 6.4**                 | 1780±207                                |

OM-853 and vinpocetine (p.o.) were given 30 min before the experiments, and idebenone (p.o.) and imipramine (i.p.) were given 60 min before the experiments. Each value represents the mean ± S.E.M. of 8–10 rats. N.D.: not determined. *P < 0.05, **P < 0.01, compared with the corresponding vehicle.

In separate experiments, OM-853 did not increase the exploratory activity in normal rats (Table 1). Idebenone and imipramine also did not change the ambulation of normal rats, whereas vinpocetine significantly suppressed the activity (Table 1).

In the next experiments, we examined the participation of the dopaminergic and/or adrenergic systems in the reduction in the duration of immobility by OM-853.

The anti-immobility effect of OM-853 was reversed by pretreatment with haloperidol at doses that did not affect the duration of immobility (Table 2). OM-853 combined with haloperidol tended to enhance the duration of immobility, compared with that of the control group, although there was no significant difference between the two groups.

It has been pointed out that anticholinergic agents and psychomotor stimulants, called false positives, reduce the duration of immobility in the forced swim test and increase locomotor activity (9). In this study, we confirmed that OM-853 did not significantly change the ambulatory activity (Table 1). Therefore, we do not think the effect of OM-853 on the duration of immobility is like that of false positives. On the other hand, vinpocetine enhanced the duration of immobility. The effect may be due to the sup-

Table 2. Inhibitory effects of haloperidol on OM-853-induced reduction of the duration of immobility in rats

| Group               | Duration of immobility (sec) |
|---------------------|-----------------------------|
| 1. Control          | 82.6 ± 3.6                  |
| 2. OM-853           | 63.6 ± 6.4*                 |
| 3. OM-853 + Haloperidol (A) | 99.3 ± 5.0*** |
| 4. Haloperidol (A)  | 83.0 ± 6.5                  |
| 5. OM-853 + Haloperidol (B) | 90.8 ± 6.3*** |
| 6. Haloperidol (B)  | 74.8 ± 8.6                  |

Each value represents the mean ± S.E.M. of 7–8 rats. OM-853 (200 mg/kg, p.o.) or haloperidol (i.p.) was given 30 min or 60 min before water immersion, respectively. Haloperidol (A): 0.025 mg/kg, Haloperidol (B): 0.01 mg/kg. *P < 0.05, compared with group 1; **P < 0.01, compared with group 2.
pressive effect of vinpocetine, as shown in Table 1.

The anti-immobility effect of OM-853 was reversed by pretreatment with haloperidol, which has a dopamine- and α-blocking activity, at doses having no effect on the duration of immobility. The result suggests that OM-853 may exert its antiimmobility action through the facilitation of transmission of the dopaminergic and/or adrenergic systems. On the other hand, the prototype of the 5-HT₁A agonist 8-OH-DPAT has been reported to reduce the duration of immobility in mice (10). The finding suggests that a modified function of the serotonergic system may also affect the duration of immobility and that a 5-HT₁A antagonist may exert an enhanced tendency or an enhancement in the duration of immobility. Since 8-OH-DPAT inhibited an enhanced release of serotonin by OM-853 (11), OM-853 may possess the antagonistic action of 5-HT₁A. This leads to the idea that OM-853 may tend to enhance the duration of immobility. In practice, however, OM-853 alone reduced the duration of immobility. Therefore, OM-853 alone may have a stronger effect on the dopaminergic and/or adrenergic systems than the serotonergic system; but OM-853 may have unmasked the antagonistic action of 5-HT₁A, when haloperidol blocked the effect of OM-853 on the dopaminergic and/or adrenergic systems.

Pretreatment with scopolamine completely abolished OM-853-induced slight hypothermia, and OM-853 augmented reserpine-induced hypothermia (unpublished observation, K. Shuto). Furthermore, OM-853 antagonized tetrahydrocannabinol-induced catalepsy (personal communication from Prof. T. Nabeshima, Nagoya University). These results suggest that OM-853 may be different from typical tricyclic antidepressants and that the anti-immobility action of OM-853 may be independent of the probable effect on the hypothalamus which plays critical roles in the regulation of body temperature. Furthermore, OM-853 may exert its anti-cataleptogenic action through activation of the dopaminergic and/or adrenergic systems in the tetrahydrocannabinol model because the levels of dopamine and norepinephrine in the brain decrease in the model and because anticholinergic agents and dopaminergic agents are effective in the model. A serotonergic dysfunction is also present in the separation model, but it is uncertain whether OM-853 is effective in the model. Although OM-853 may have exerted its anti-immobility through activation of the dopaminergic and/or adrenergic systems, the effect of OM-853 was less potent than that of imipramine in the model. Therefore, OM-853 may not be promising for the treatment of depression such as endogenous depression. However, tricyclic antidepressants are effective in the forced swim test, and their usefulness for improving the depressive state following stroke has been indicated (12). Furthermore, an ameliorator of energy metabolism in the brain such as idebenone improves the depressive state following stroke, and OM-853 also improved energy metabolism in cerebral ischemic models. Therefore, OM-853 may be useful in the treatment of emotional disturbances such as the depressive state following stroke.

Local application of drugs has implied that the amygdala may be site of action for certain antidepressant drugs in the forced swim test. Araki et al. have shown that infusion of imipramine or desipramine into the amygdala reduced the duration of immobility, but these drugs were not effective when applied into the nucleus accumbens (13). Duncan et al. have reported that infusion of imipramine or pargyline into the amygdala shortened the duration of immobility (14). They also demonstrated that the anticholinergic agent atropine or the psychostimulant amphetamine produced no effect when applied on the same site. Furthermore, it has been reported that sulpiride, a D₂-antagonist, enhances the duration of immobility by its injection into the amygdala (15). These findings indicate that the amygdala may play an important role in the swim test. Therefore, OM-853 may act on the amygdala to produce its anti-immobility effect in the swim test.

The present results demonstrate that OM-853 reduced the duration of immobility, and OM-853 was different from idebenone and vinpocetine in the forced swim test. The results also suggest that OM-853 may exert its effect via facilitation of transmission of dopaminergic and/or adrenergic systems and may be different from idebenone and vinpocetine in its effect on neurotransmitters in the central nervous system. In addition, OM-853 may be useful in the treatment of emotional disturbances such as the depressive state following stroke. Further investigations would be needed to clarify the mechanism of action and the active site(s) of OM-853.

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