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The anxiolytic-like effect of MCI-225, a selective NA reuptake inhibitor with 5-HT_3 receptor antagonism

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Abstract

We have previously reported that MCI-225, a selective noradrenaline (NA) reuptake inhibitor with serotonin (5-$HT)_3$ receptor antagonism, shows antidepressant-like properties in experiments using rodents. In this study, we investigated the effect of MCI-225 in anxiety models in comparison with diazepam, ondansetron, maprotiline, imipramine, and trazodone. In social interaction (SI) test in rats, MCI-225 (10 and 30 mg/kg, po), diazepam (1–10 mg/kg, po), and a selective 5-HT_3 receptor antagonist ondansetron (1 mg/kg, po) significantly increased SI to an unfamiliar partner under high light conditions without changes in ambulation. The increase in SI induced by MCI-225 and ondansetron was blocked by a 5-HT_3 agonist, 1-(*m*-Chlorophenyl)-biguanide (mCPBG, 1 mg/kg, ip), which did not change SI when administered alone. MCI-225 (10 mg/kg, po) showed comparable anxiolytic-like effect between single and 5-day repeated administration. On the other hand, maprotiline, trazodone, and imipramine did not affect SI at doses of 3–30 mg/kg, po. In the elevated plus-maze test in rats, MCI-225 (10–100 mg/kg, po) increased the number of entries into the open arms only, while diazepam increased not only the number of open-arms entries (30 mg/kg, po), but also the total number of entries (10 mg/kg, po). Ondansetron (0.001–1 mg/kg, po) was less effective. Maprotiline, imipramine, and trazodone did not affect the number of open-arm entries, while trazodone and imipramine (100 mg/kg, po) decreased the total number of entries. These results show that MCI-225 has an anxiolytic-like effect without causing sedation and suggest that the 5-HT_3 receptor antagonism of MCI-225 probably contributes to its anxiolytic-like property.

Keywords: MCI-225; Anxiolytic-like effect; NA reuptake inhibitor; 5-HT_3 antagonist

1. Introduction

The most widely accepted basis for depression is dysfunction of either the noradrenergic or serotonergic neurotransmitter systems (Burrows et al., 1998). Of these monoaminergic systems, the serotonergic system has been the focus of much research during the past decade, leading to the introduction of selective serotonin reuptake inhibitors (SSRIs), which show improved tolerability with less severe side effects and safety in overdose in comparison with tricyclic antidepressants (Burrows et al., 1998; Nutt, 1997). In addition to their antidepressant effects, SSRIs show anxiolytic effects and their clinical efficacy of these compounds in the treatment of obsessive–compulsive disorder (OCD) and panic disorder has been demonstrated (Feighner, 1999). However, SSRIs appear to be less efficacious than reference antidepressants in certain patient subgroups (Clerc et al., 1996) and they are not totally free of unwanted action. Nausea and sexual dysfunction, which are related to the nonselective serotonergic activation, can be enduring problems (Van Den Berg, 1995).

Another approach to the treatment of depression is the activation of another neurotransmitter, noradrenaline (NA), and new classes of selective noradrenaline reuptake inhibitors (NRIs) and serotonin and noradrenaline reuptake inhibitors (SNRIs) are under development. MCI-225 [4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-*d*]pyrimidine monohydrate hydrochloride, Fig. 1] is a potent NRI with serotonin (5-$HT)_3$ receptor antagonism (Eguchi et al.,

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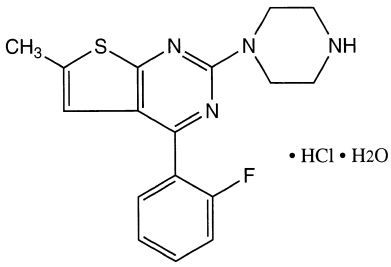

Fig. 1. Chemical structure of MCI-225.

1997b). MCI-225 has been shown to possess a potent antidepressant-like effect in experiments using rodents (Eguchi et al., 1997b). Furthermore, MCI-225 showed an anti-amnesic effect in basal forebrain-lesioned rats (Eguchi et al., 1995) or scopolamine-treated rats (Eguchi et al., 1994), and enhanced attentional eye tracking in midpontine pretrigeminal preparations (Eguchi et al., 1997a). These effects of MCI-225 on learning, memory, and attention may be related at least in part to its 5-HT_3 receptor antagonism. The anxiolytic effects of selective 5-HT_3 receptor antagonists are controversial in both animal anxiety models and clinical studies (Olivier et al., 2000). Menard and Treit (1999) described that 5-HT_3 antagonists are reasonably consistent across a variety of behavioral tests, although there is some suggestion that 5-HT_3 receptors in different regions of the brain might mediate different fear behaviors. In clinical trials, some investigators have reported positive effects in generalized anxiety disorder and panic disorder, but others did not (Kunovac and Stahl, 1995; Olivier et al., 2000).

In this study, we investigated the effect of MCI-225 in two nonconditioned behavior anxiety models, i.e., the social interaction (SI) test and elevated plus-maze. These models can create an anxiety state in normal rats in a reproducible and relatively simple paradigm while minimizing or eliminating some of the confounding factors of other conditioned assays (Dunn et al., 1989). For the comparison, the effects of diazepam, ondansetron, and three antidepressants (maprotiline, imipramine, and trazodone) were also evaluated. Furthermore, in order to clarify the mechanism of action of MCI-225, the effect of the co-administration of MCI-225 and a selective 5-HT_3 agonist (Kilpatrick et al., 1990; Morain et al., 1994) was examined.

2. Methods

2.1. Animals

Male Wistar rats (Japan Laboratory Animals) weighing 200–350 g were used. All rats were housed in air-conditioned rooms which were maintained at 22 ± 3°C at a humidity of 55 ± 20% with a 12-h light–dark cycle (light period: 0700–1900). All animals were allowed to take food and water ad libitum.

2.2. Drugs

MCI-225 and ondansetron were synthesized in our laboratory, and maprotiline was extracted from a commercial preparation. Other compounds were purchased commercially. MCI-225 and diazepam (Profarmaco Nobel) were suspended in 0.5% Tween 80, and maprotiline was suspended in distilled water. Ondansetron, imipramine (Sigma), and trazodone (Sigma) were dissolved in distilled water. 1-(*m*-Chlorophenyl)-biguanide (mCPBG, Sigma) was dissolved in saline. All drugs were prepared immediately before use and administered in a volume of 1 ml/kg. mCPBG was administered intraperitoneally 15 min before testing. Other compounds were administered orally 1 h before testing.

2.3. Social interaction test

The method of Dunn et al. (1989) was used with modification. Rats used in this test were housed in pairs for more than 1 week prior to testing. The test consisted of familiarizing each pair (cage mates) of rats to the test arena (32 × 45 × 25 cm), the floor of which was divided into six squares and brightly lit (700 lx), for 8 min on 2 consecutive days. On the third day, each rat was randomly assigned according to weight to an unfamiliar partner. Each pair of unfamiliar rats were placed in the test arena and observed for SI behavior and ambulation for 10 min. SI time per pair of rats was measured as time spent sniffing the partner, climbing over and crawling under the partner, mutual grooming, genital investigation and, following and walking around the partner. Aggressive behavior was not considered as SI behavior and the number of squares crossed was scored. In an experiment to evaluate the effect of repeatedly administered MCI-225, MCI-225 and vehicle were preadministered for 4 days. On the next day, rats were challenged by MCI-225 or vehicle 1 h prior to the SI test.

2.4. Elevated plus-maze

The procedures of Pellow et al. (1985) were used with modification. Rats used for this test were housed in groups of five or six. The elevated plus-maze was made of wood and consisted of two open arms (50 × 10 cm) and two enclosed arms (50 × 10 × 40 cm) with an open roof, arranged so that the two open arms were opposite each other. The maze was elevated at a height of 60 cm. The light level on the enclosed arms was increased by two desk lamps so that the light level in all arms was approximately equivalent (360–400 lx). In the plus-maze, each rat was placed individually in the center of the maze, facing one of the open arms. An observer in the same room sat 2 m away and scored for 5 min the number of entries into each type of arm and the total time spent in each type of arm. All experimental procedures in the present study were approved by the Internal Animal Care and Use Committee and were in compliance with the Guide for the Care and Use of Laboratory Animals.

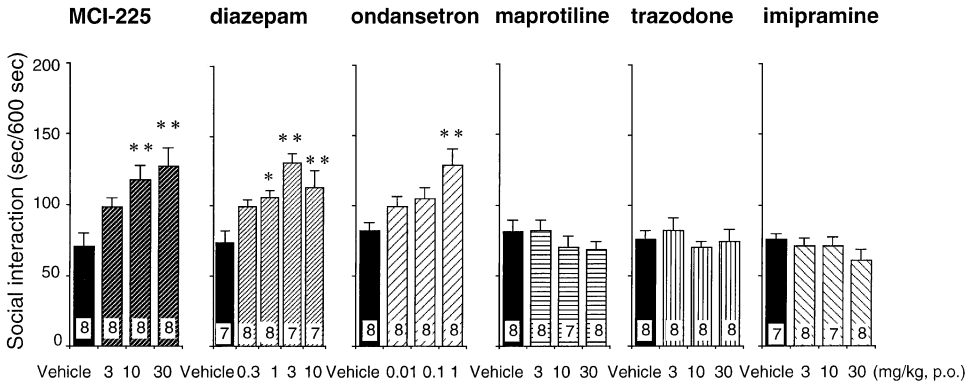

Fig. 2. Effects of MCI-225 and reference compounds on SI time in rats. All compounds, including vehicle, were administered orally 60 min prior to testing. Data are presented as the mean and S.E.M. The number of animals in each group is shown in each column. $*P<.05$, $**P<.01$ compared to the vehicle-treated group (two-tailed Dunnett's test following one-way ANOVA).

2.5. Statistical analysis

The results of all experiments are expressed as the mean and S.E.M. Data from the elevated plus-maze test and the SI test by single administration of MCI-225 were analyzed by one-way ANOVA followed by Dunnett's test. Data from the SI test by repeated administration of MCI-225 and by combined administration of MCI-225 with mCPBG were analyzed by one-way ANOVA followed by the Tukey–Kramer test.

3. Results

3.1. Social interaction test

3.1.1. Effects of single administration

When tested 1 h after a single dose of MCI-225, diazepam, and ondansetron, the compounds showed significant effects on SI, as revealed by one-way ANOVA [$F(3,28)=6.120$, $P<.01$; $F(4,32)=6.890$, $P<.01$; and $F(3,28)=5.177$, $P<.01$, respectively]. MCI-225 caused a dose-dependent increase in SI to an unfamiliar partner placed in a highly illuminated arena (Fig. 2). The increase of SI by MCI-225 at doses of 10 and 30 mg/kg, po was significant ($P<.01$). Diazepam also increased SI at 1 mg/kg, po ($P<.05$), and at 3 and 10 mg/kg, po ($P<.01$). Ondansetron also increased SI at a dose of 1 mg/kg, po. On the other hand, maprotiline, imipramine, and trazodone did not affect SI at any dose tested (Fig. 2). No compound except imipramine (100 mg/kg, po) decreased the number of the line crossings (Fig. 3).

3.1.2. Effect of repeated administrations of MCI-225

When tested 1 h after the challenged dosing of MCI-225 and vehicle, there was significant drug effect on SI, as revealed by one-way ANOVA [$F(2,21)=7.185$, $P<.01$]. SI time in MCI-225 (10 mg/kg, po) treated groups for both 1 day and 5 days were significantly longer than that in the vehicle-treated group ($P<.01$, and $P<.05$, respectively). The effect of the repeatedly administered MCI-225 was as potent as that of single administration (Fig. 4A). MCI-225 did not affect locomotion (Fig. 4B).

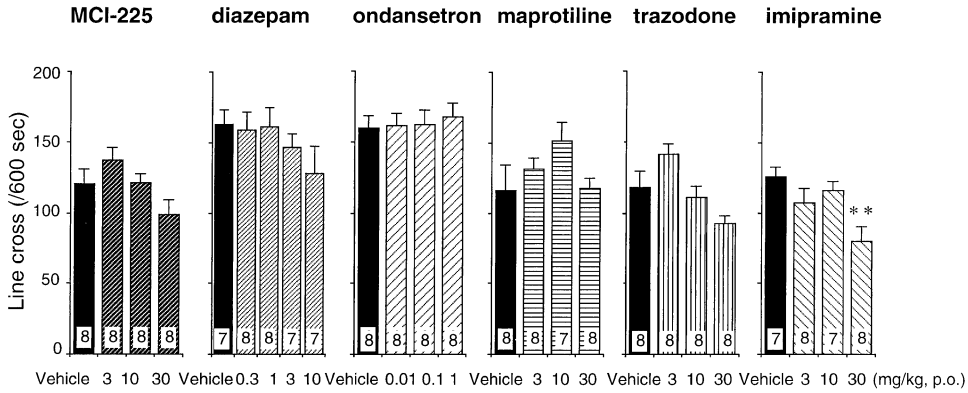

Fig. 3. Effects of MCI-225 and reference compounds on line crossing in the SI test. All compounds, including vehicle, were administered orally 60 min prior to testing. Data are presented as the mean and S.E.M. The number of animals in each group is shown in each column. $**P<.01$ compared to the vehicle-treated group (two-tailed Dunnett's test following one-way ANOVA).

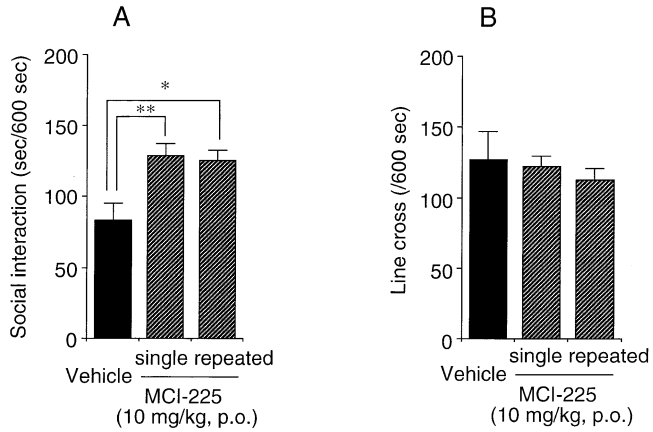

Fig. 4. Effects of single and 5-day repeated administration of MCI-225 in the SI test. Rats in single and repeated MCI-225 administration groups were pretreated with 0.5% Tween 80 and MCI-225 (10 mg/kg) for 4 days, respectively. On the fifth day, the rats in both groups were challenged by MCI-225 (10 mg/kg). Rats in the vehicle group were treated with 0.5% Tween 80 for 5 days. The SI test was carried out 1 h after the final administration. Data for SI (A) and line crossing (B) are presented as mean and S.E.M. ($N=8$). $*P<.05$, $**P<.01$, compared to vehicle-treated group (Tukey–Kramer test).

3.1.3. Effect of co-administration of mCPBG and MCI-225

mCPBG (1–10 mg/kg), when administered alone intraperitoneally, affects SI significantly [$F(3,28)=9.810$, $P<.01$] but not on line crossings. At doses of 3 and 10 mg/kg, ip, mCPBG reduced SI ($P<.01$, Fig. 5A). Dunnett's test revealed that mCPBG decreased line crossings at 10 mg/kg, ip. At a dose of 1 mg/kg, ip, mCPBG had no effect on SI nor line crossings. mCPBG (1 mg/kg, ip), when administered in combination with MCI-225 (30 mg/kg, po) or ondansetron (1 mg/kg, po), showed significant drug effects as revealed by one-way ANOVA [$F(3,27)=4.934$, $P<.01$; $F(3,27)=6.255$, $P<.01$, respectively]. mCPBG significantly attenuated the increase of SI induced by MCI-225 and ondansetron ($P<.01$, Fig. 5B and C).

3.2. Elevated plus-maze

Table 1 shows the effects of MCI-225 and reference compounds in the elevated plus-maze. After MCI-225 treatment, there were significant drug effects on the percent number of entries and percent time spent on the open arms [$F(5,42)=2.686$, $P<.05$; $F(5,42)=2.452$, $P<.05$, respectively] with no drug effect on the total number of arm entries. MCI-225 (10–100 mg/kg, po) increased open-arm exploration as indicated by a significant increase in the percentage entries into open arms. Percent time spent on the open arms was also increased by MCI-225 at doses of 30 and 100 mg/kg, po. After diazepam treatment, there were significant drug effects on the percent entries in the open arm, percent time in the open arms, and total entries [$F(3,28)=5.506$, $P<.01$; $F(3,28)=7.443$, $P<.01$; and $F(3,28)=3.769$, $P<.05$, respectively]. Diazepam increased percent entries in the open at 30 mg/kg, po ($P<.01$) and percent time in open arms at 10 and 30 mg/kg, po ($P<.01$), respectively. Total entries were also increased by diazepam at 10 mg/kg, po ($P<.05$) and ataxia was observed at 10 and 30 mg/kg, po (data not shown). After ondansetron treatment, one-way ANOVA revealed significant drug

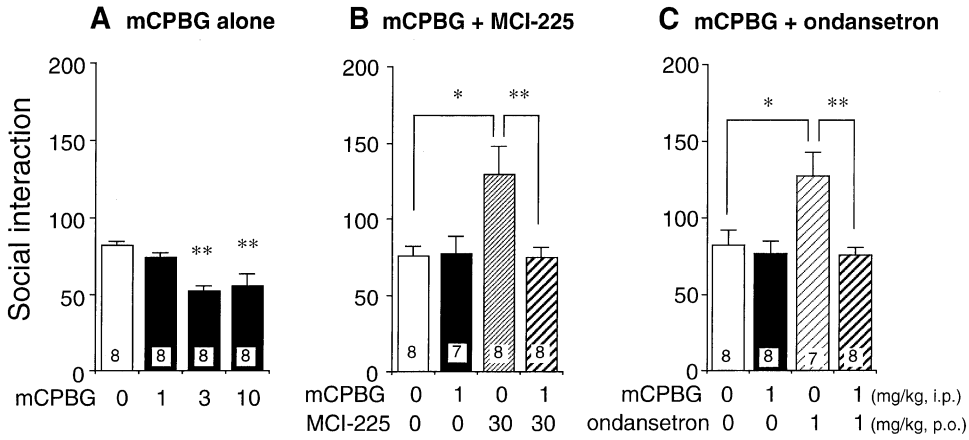

Fig. 5. Effect of mCPBG on SI time in naive rats (A), rats treated with MCI-225 (B), and rats treated with ondansetron (C). MCI-225 and ondansetron were administered orally 60 min prior to SI testing. mCPBG was administered intraperitoneally 15 min prior to testing. Data are presented as the mean and S.E.M. ($N=8$). $*P<.05$, $**P<.01$ compared to the vehicle-treated group (Tukey-Kramer test).

Table 1
Effects of MCI-225 and reference compounds in the elevated plus-maze in rats

Compound (mg/kg, po)	*N*	% Entries in open arms	% Time in open arms	Total entries
Vehicle	8	36.7 ± 4.4	26.2 ± 6.9	9.9 ± 1.0
MCI-225				
1	8	48.5 ± 3.2	31.9 ± 4.3	8.8 ± 1.0
3	8	47.5 ± 4.8	41.7 ± 5.7	10.1 ± 0.9
10	8	50.5 ± 2.8*	38.2 ± 5.3	10.3 ± 1.3
30	8	52.6 ± 2.4*	49.1 ± 4.5*	9.3 ± 1.1
100	8	50.7 ± 2.5*	47.7 ± 7.1*	7.8 ± 0.8
Vehicle	8	40.5 ± 2.5	25.4 ± 4.1	11.0 ± 1.9
Diazepam				
3	8	39.6 ± 2.9	27.6 ± 6.5	10.1 ± 1.3
10	8	49.1 ± 2.4	47.1 ± 3.9**	16.5 ± 0.7*
30	8	54.6 ± 4.1**	49.8 ± 3.6**	13.5 ± 1.7
Vehicle	8	43.0 ± 3.3	33.6 ± 3.5	8.3 ± 1.0
Ondansetron				
0.001	8	42.0 ± 2.8	24.4 ± 5.8	9.6 ± 1.7
0.01	8	35.0 ± 5.4	21.4 ± 4.8	9.8 ± 1.4
0.1	8	43.9 ± 2.0	41.1 ± 6.9	12.1 ± 1.3
1	8	48.6 ± 4.7	47.5 ± 8.2	11.5 ± 1.5
Vehicle	8	43.4 ± 2.9	27.5 ± 4.5	9.3 ± 1.1
Maprotoline				
10	8	35.0 ± 3.6	24.4 ± 4.8	9.8 ± 1.1
30	8	33.1 ± 6.1	18.0 ± 4.6	8.4 ± 0.7
100	7	29.9 ± 4.8	23.3 ± 4.7	7.4 ± 0.7
Vehicle	8	38.0 ± 4.3	26.3 ± 3.1	7.8 ± 0.9
Trazodone				
10	8	31.8 ± 2.6	21.5 ± 2.9	9.4 ± 0.8
30	8	38.3 ± 4.5	20.5 ± 3.0	4.9 ± 1.1
100	7	38.9 ± 5.3	23.0 ± 5.5	3.9 ± 0.9*
Vehicle	8	39.6 ± 2.7	28.6 ± 5.1	10.9 ± 1.4
Imipramine				
10	8	39.0 ± 3.9	24.5 ± 3.3	10.1 ± 1.0
30	8	34.6 ± 4.6	32.6 ± 6.3	7.3 ± 0.9
100	7	34.3 ± 3.7	18.9 ± 4.9	5.7 ± 1.1*

All compounds were orally administered 60 min prior to test.
Mean values ± S.E.M. are shown.
* $P < .05$ compared to vehicle-treated group (two-tailed Dunnett's test following ANOVA).
** $P < .01$ compared to vehicle-treated group (two-tailed Dunnett's test following ANOVA).

effects on the percent time in the open arms [$F(4,35) = 3.304$, $P < .05$], while Dunnett's test did not show a significant change in the percent time at any doses tested. After trazodone and imipramine treatment, there were significant drug effects on total entries [$F(3,27) = 6.997$, $P < .01$; $F(3,27) = 4.336$, $P < .05$, respectively]. Both compounds decreased total entries at 100 mg/kg, po ($P < .05$). Maprotiline did not show a significant effect in the plus-maze test.

4. Discussion

In the present study, we examined the effect of MCI-225 in two nonconditioned behavior anxiety models in rats, i.e., SI test and elevated plus-maze, and compared it with the effects of reference compounds. As Dunn et al. (1989) pointed out, these models can create an anxiety state in normal rats without conditioning in a reproducible and relatively simple paradigm while minimizing or eliminating some of the confounding factors present in other conditioned assays. Furthermore, these methods have been validated both behaviorally and physiologically (File, 1980; Pellow et al., 1985). Griebel (1995) described that these anxiety animal models based on unconditioned responses are more sensitive to 5-HT_3 antagonists than animal models based on conditioned responses. In the SI test, MCI-225, diazepam, and ondansetron increased the amount of time spent in SI with an unfamiliar partner under high light conditions suggesting that these compounds possess anxiolytic-like activities. But maprotiline, imipramine and trazodone did not change SI. Although SI and the sensitivity of anxiolytics have been reported to depend on the experimental conditions and protocol (File, 1980; Gardner and Guy, 1984), the results obtained from reference compounds in the present study are largely consistent with those of the previous reports. For example, diazepam and ondansetron increased SI to an unfamiliar partner in a familiar cage (Dunn et al., 1991). Imipramine, maproti-

line, and trazodone have been reported to be negative in the SI test in rodents after single or repeated administration (Culter et al., 1997; Guy and Gardner, 1985; Popik and Vetulani, 1993).

Previous neurochemical studies have shown that MCI-225, maprotiline, and imipramine inhibit the reuptake of NA from rat synaptosomes (Eguchi et al., 1997b). The K_i values for NA reuptake inhibition in rat hypothalamic synaptosomes by MCI-225, maprotiline, and imipramine are 35.0, 19.7, and 22.2 nmol/l, respectively. These data suggest that NA reuptake inhibition by MCI-225 may not affect SI behavior.

mCPBG, a selective 5-HT_3 agonist (Kilpatrick et al., 1990; Morain et al., 1994), decreased the SI time under the same conditions. Since mCPBG at 3 mg/kg, ip decreased SI without any change in locomotion, it is suggested that mCPBG has an anxiogenic-like effect at least at this dose. This is similar to the result reported by Mitchell et al. (1991), though they directly injected mCPBG to the lateral ventricles of rats and measured SI under low light condition. Andrews and File (1992) also have shown that mCPBG has an anxiogenic-like effect in rats tested in the elevated plus-maze. These results suggest that activation of 5-HT_3 receptors by mCPBG causes anxiogenic-like activity, although peripheral injection of mCPBG also has been reported to induce aversive-type behaviors in rats (Higgins et al., 1993). In the present study, mCPBG at a low dose (1 mg/kg, ip), did not affect SI and locomotion, but inhibited the increase in SI induced by MCI-225 and ondansetron. Therefore, the 5-HT_3 receptor antagonism of MCI-225 and ondansetron is considered to contribute to their anxiolytic-like effects. In vitro studies have shown that MCI-225 has a high affinity for 5-HT_3 receptors only (K_i = 81.0 nmol/l) among the receptors tested, including GABA-A, BZP, and 5-HT_{1A} receptors. An in vivo study showed that MCI-225 inhibited von Bezold–Jarisch reflex in rats, with the approximate ID_{50} of 22.2 mg/kg, po (Eguchi et al., 1997b). These results appear to support that anxiolytic-like effects of MCI-225 at the doses tested are due to its 5-HT_3 receptor antagonism.

In this study, MCI-225 showed no difference in potency between single and 5-day repeated oral administration. This result does not conflict with the result reported by Costall and Naylor (1991), which described that neither tolerance nor sensitization occurred in the anxiolytic-like effect of the repeatedly administered 5-HT_3 receptor antagonist, ondansetron. On the other hand, the antidepressant-like effect of MCI-225 has been reported to be potentiated by repeated administration (Eguchi et al., 1997b). Therefore, it is possible that different mechanisms of action may be involved in the anxiolytic-like and antidepressant-like actions of MCI-225. Another possibility is that certain neuronal changes may develop after repeated administration of MCI-225 and may contribute to the enhancement of the antidepressant-like activity, although Nakagawa et al. (1998) pointed out that the suppression of the 5-HT_3 receptor activity may also contribute to the action of antidepressants.

In the elevated plus-maze test, MCI-225 increased open-arm exploration without any change in the total number of entries. On the other hand, diazepam increased not only the open-arm exploration but also the total number of entries, and ataxia was observed in rats treated with high doses of diazepam. This result is consistent with an earlier observation by Moser (1989), which showed that diazepam increased the exploration of both arms. MCI-225 (10–100 mg/kg, po) has been shown not to change spontaneous locomotor activity in rats (Eguchi et al., 1997b). From these results, the change induced by MCI-225 is thought to be separate from the change in motor activity, at least at the doses tested.

In this test, ondansetron did not produce a significant effect. As described before, the anxiolytic-like effects of selective 5-HT_3 antagonists in animal models are controversial (Olivier et al., 2000). Some compounds have been reported to be effective while others to be inactive in the elevated plus-maze (Artaiz et al., 1995; Borsini et al., 1993; File and Johnston, 1989; Vasar et al., 1993). The differences in these results may be due to differences in the experimental conditions, since selective 5-HT_3 antagonists, for example, ondansetron, have been reported to be either positive or negative in the different reports (Artaiz et al., 1995; Borsini et al., 1993; Vasar et al., 1993). Other possibilities are that the discrepancies depend on the potency of the 5-HT_3 receptor antagonism of each compound in vivo, or on its selectivity for 5-HT_3 receptor subunits. There is strong evidence for the existence of multiple subunits of 5-HT_3 receptor (Fletcher and Barnes, 1998). In native tissue, both homomeric 5-HT_{3A} and heteromeric 5-$HT_{3A/3B}$ receptor complexes, which show the distinctive pharmacological properties, are likely to exist (Barnes and Sharp, 1999; Davies et al., 1999). Therefore, it is interesting to evaluate the effects of MCI-225 on the homomeric and heteromeric 5-HT_3 receptor complexes and to compare with those of selective 5-HT_3 receptor antagonists. Three antidepressants were negative not only in the SI test but also in the elevated plus-maze test. In this study, imipramine and trazodone decreased the total number of entries. The effect of imipramine is in accordance with an earlier observation by Pellow et al. (1985). Since both imipramine and trazodone markedly decreased the spontaneous motor activity in rats at 100 mg/kg, po (Eguchi et al., 1997b), the decreases in the total number of entries by these compounds appear to be related to their effects on gross behavior.

In conclusion, MCI-225 showed an anxiolytic-like effect in both the SI test and the elevated plus-maze test in rats. These results suggest that MCI-225 has anxiolytic action in addition to its antidepressant action. The 5-HT_3 receptor antagonism of MCI-225 may contribute to its anxiolytic-like effect.

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