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Modulation of Passive Avoidance in Mice by the 5-HT_{1A} Receptor Agonist Flesinoxan: Comparison with the Benzodiazepine Receptor Agonist Diazepam

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The effects of the 5-HT_{1A} receptor agonist flesinoxan on passive avoidance in mice were compared with those of the benzodiazepine receptor agonist diazepam. In preliminary experiments, the retention latency to enter a dark compartment in mice subjected to single-training sessions with 0.6-mA electric foot shocks for 4, 8, or 16 s slightly increased in all of the test sessions (immediately, 24 h, and 1 week after the training sessions), but none of these changes were significant. In contrast, mice subjected to double-training sessions with 0.6-mA electric foot shocks for 16 s showed a significant increase in retention latency in all of the test sessions. Pretreatment with either flesinoxan or diazepam 30 min before the double-training sessions with 0.6-mA electric foot shocks for 16 s significantly decreased the retention latency in test sessions 24 h and 1 week later. In contrast, mice pretreated with flesinoxan 24 h before the single-training sessions with 0.6-mA electric foot shocks for 4, 8, or 16 s showed a significant increase in retention latency in the test sessions 24 h and/or 1 week later. Similar enhancements of retention latency in the test sessions 24 h and/or 1 week later were observed also in mice pretreated with flesinoxan 24 h before the double-training sessions. However, in this time interval following injection, pretreatment with diazepam did not affect the retention latency of mice in any of the test sessions. Neither flesinoxan nor diazepam, at the same doses and time intervals used in the passive avoidance study, modified the thresholds for flinching and jumping elicited by electrical stimuli. These results suggest that the activation of 5-HT_{1A} receptors, but not benzodiazepine receptors, has a dual effect on the formation of learning and memory for an aversive event that depends on the time interval following receptor activation.
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INTRODUCTION

The brain serotonin (5-hydroxytryptamine; 5-HT) system has been implicated in the pathophysiology and treatment of a wide variety of neuropsychiatric disorders (Murphy, 1990; Graeff *et al*, 1996; Murphy *et al*, 1999). A heterogeneous family of at least 14 distinct receptor subtypes has been shown to mediate the effect of 5-HT in the central nervous system (Hoyer and Martin, 1997). Among these, 5-HT_{1A} receptors have received particular attention as a possible target for the treatment of affective disorders such as anxiety and depression. In clinical studies, various 5-HT_{1A} receptor agonists have shown promising results with regard to anxiety disorder and depression (Olivier *et al*, 1999). However, there is also some clinical evidence that 5-HT_{1A} receptor agonists might have a different therapeutic spectrum to that of benzodiazepines for the treatment of various types of affective disorders. For example, 5-HT_{1A} receptor agonists have improved generalized anxiety disorder but not panic disorder, although benzodiazepins have been effective in both types of anxiety disorder (Balon *et al*, 1990; Dubovsky, 1990; Sheehan *et al*, 1993). It is thus possible that the emotional effects produced by 5-HT_{1A} receptor agonists might differ qualitatively from those produced by benzodiazepins.

Previously, we obtained data to support the above hypothesis in studies that compared the effects of benzodiazepines with those of 5-HT_{1A} receptor agonists on various emotional states of naive and stressed mice using our automatic hole-board apparatus (Takeda *et al*, 1998; Tsuji *et al*, 2000, 2001). In these experiments, we found that benzodiazepines and 5-HT_{1A} receptor agonists produced quite different effects. The most interesting findings were that pretreatment with the 5-HT_{1A} receptor agonists

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flesinoxan and *R*(+)-2-dipropylamino-8-hydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide (8-OH-DPAT) but not with the benzodiazepines diazepam and chlordiazepoxide 24 h before exposure to stress suppressed the decrease in various emotional behaviors produced by acute restraint stress. Several previous behavioral experiments have inspired the interpretation that disappearance of the behavioral response to stress stimuli reflects the development of stress adaptation (Kennett *et al*, 1985a, b; Ohi *et al*, 1989). Thus, our findings suggest that 5-HT$_{1A}$ receptor agonists but not benzodiazepines may facilitate some adaptive mechanisms involved in the recognition of and/or ability to cope with stress stimuli.

Apart from their emotional effects, both 5-HT$_{1A}$ receptor agonists and benzodiazepines affect the learning and memory system. The passive avoidance paradigm has been used to study learning and memory for a stress stimuli. The procedure is based on the innate preference of rodents for the dark compartment of the apparatus, and the suppression of this innate preference following exposure to inescapable shock; that is, passive avoidance performance is an adaptive response to a stressful experience that serves as a measure of learning and memory. Previous studies have demonstrated that various types of 5-HT$_{1A}$ receptor agonists as well as benzodiazepines impair passive avoidance performance (Nabeshima *et al*, 1990; Rowan *et al*, 1990; Mendelson *et al*, 1993; Anglade *et al*, 1994; Misane *et al*, 1998; Misane and Ögren, 2000). However, considering the differential effects of 5-HT$_{1A}$ receptor agonists and benzodiazepines on the stress response of mice that have been found in our previous studies (Takeda *et al*, 1998; Tsuji *et al*, 2000, 2001), additional detailed investigation should be necessary. Therefore, the present study was designed to further examine the effects of the 5-HT$_{1A}$ receptor agonist flesinoxan and the benzodiazepine receptor agonist diazepam in the formation of learning and memory for stress stimuli using the passive avoidance paradigm.

METHODS

The present studies were conducted in accordance with the Guide for Care and Use of Laboratory Animals adopted by the Committee on Care and Use of Laboratory Animals of the Tokyo Medical University and the Japanese Pharmacological Society.

Animals

Male ICR mice (Charles River, Japan) weighing 25–30 g were housed at a room temperature of 22 $\pm$ 1°C with a light–dark cycle (light on 6:00 am to 6:00 pm). Food and water were available *ad libitum*.

Step-Through Passive Avoidance Task

A two-compartment step-through passive avoidance apparatus (Muromachi Kikai, Japan) was used. The apparatus is divided into bright ($10 \times 12 \times 15\,cm^3$) and dark compartments ($14 \times 18 \times 15\,cm^3$) by a wall with a guillotine door. The bright compartment was illuminated by a fluorescent light (8 W). The animals were injected with the test compounds as described below. After a specified time interval following injection, passive avoidance training was performed. Mice were placed in the bright compartment and allowed to explore for 30 s, at which point the guillotine door was raised to allow the mice to enter the dark compartment. When the mice entered the dark compartment, the guillotine door was closed and an electrical foot shock (0.6 mA) was delivered for 4, 8, or 16 s (nonshocked control mice were not subjected to electric foot shocks when entering the dark compartment). Training sessions were conducted once (single-training) or twice (double-trainings) during the light phase (1:00–4:00 pm) of the 12-h day/night cycle. The second double-training session was carried out immediately after first the session. Test sessions were performed immediately, 24 h, or 1 week after training sessions. The mice were placed in the bright compartment and allowed to explore for 30 s, and then the guillotine door was raised. The latency to enter the dark compartment was recorded for up to 300 s. Flesinoxan (0.25–1 mg/kg, i.p.), diazepam (0.25–1 mg/kg, i.p.), or their respective vehicle was administered 30 min or 24 h before the start of training sessions. The doses of flesinoxan and diazepam were determined based on our previous findings (Tsuji *et al,* 2000, 2001).

Pain Threshold

The dark compartment of the passive avoidance apparatus (Muromachi Kikai, Japan) was used to determine the pain threshold to electrical stimuli. Mice were allowed 15 min to habituate to the environment of the apparatus before a series of inescapable shocks was delivered. Each series consisted of 10 shocks at the following intensities (mA): 0.01, 0.02, 0.04, 0.06, 0.08, 0.1, 0.2, 0.4, 0.6, and 0.8. The shock duration was 2 s and the shocks were delivered at 30-s intervals. Thresholds for flinching (forepaws off the grid floor) and jumping (all four paws off the grid floor) were measured.

Drugs

The drugs used in the present study were flesinoxan hydrochloride (provided by Solvay, The Netherlands) and diazepam (Wako, Japan). Flesinoxan was dissolved in saline. Diazepam was dissolved in Tween 20 until it produced a clear solution, and then diluted with saline to reach the proper concentrations. The final concentration of Tween 20 in the solution was 1%.

Statistical Analysis

The data are presented as the mean $\pm$ SEM. Student's *t*-test was used to analyze the data from experiments that examined the effects of pretreatment with flesinoxan and diazepam 30 min before double-training sessions on passive avoidance performance (Figure 2) and the effects of pretreatment with flesinoxan and diazepam on the pain threshold (Figure 7). Other data (Figures 1, 3–6) were analyzed by one-way repeated measures analysis of variance (ANOVA) followed by Dunnett's test.

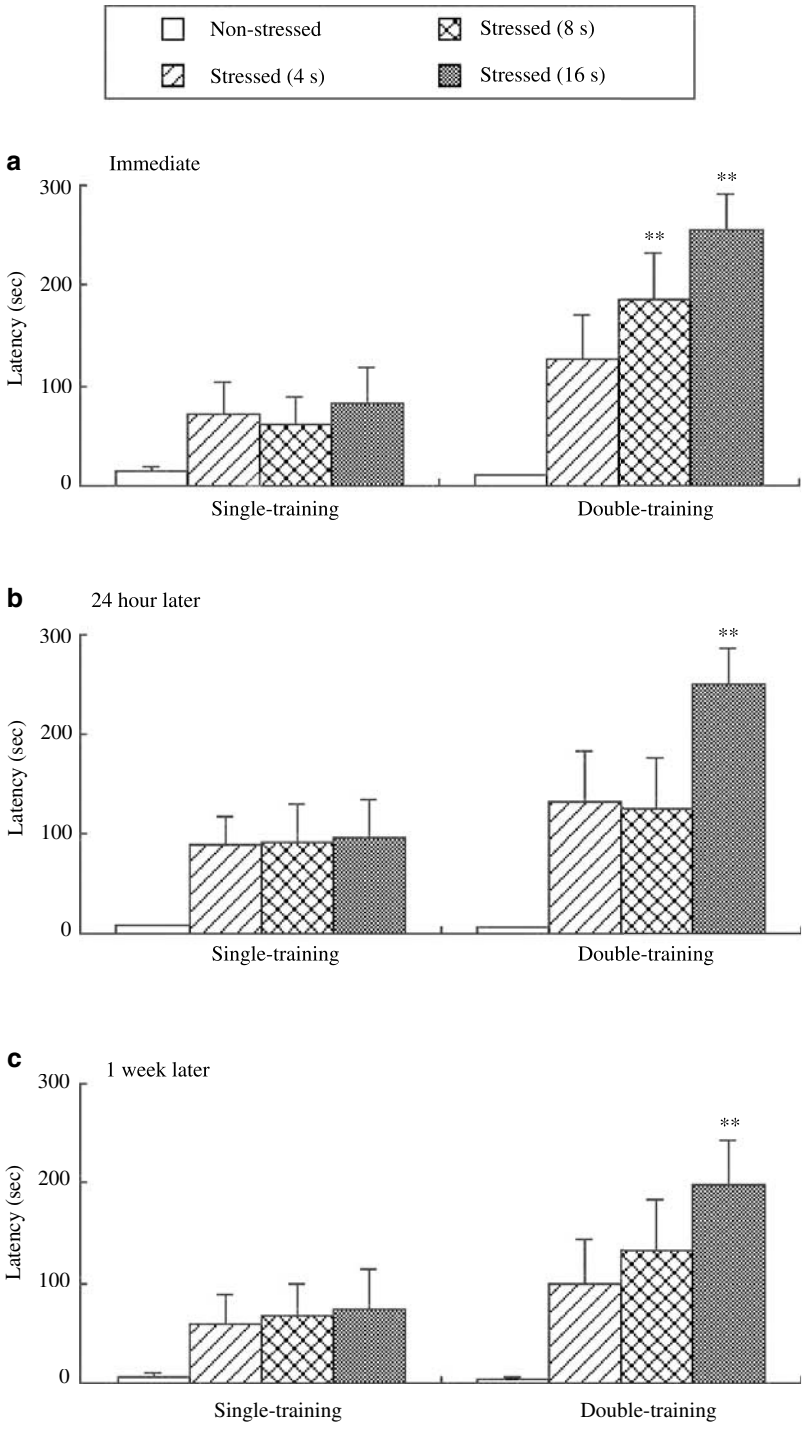

Figure 1 Passive avoidance performance in mice subjected to the single- or double-training sessions with electrical foot shocks of various durations. Mice were subjected to the single- or double-training session 0.6-mA electrical foot shocks of various durations (4–16 s). Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Each column represents the mean with SEM of 10 mice. $^{**}P<0.01$ *vs* nonstressed group (open column).

RESULTS

Passive Avoidance Performance in Mice Subjected to Single- or Double-Training Sessions with Electrical Foot Shocks of Various Durations

Passive avoidance in mice subjected to single- or double-training sessions with electrical foot shocks of various durations is shown in Figure 1. The retention latency to enter the dark compartment in mice subjected to single-training sessions slightly increased in all of the test sessions (immediately, 24 h, and 1 week after the training sessions) as compared with that of nonshocked control mice, but none of these changes were significant. In contrast, the retention latency to enter the dark compartment in mice

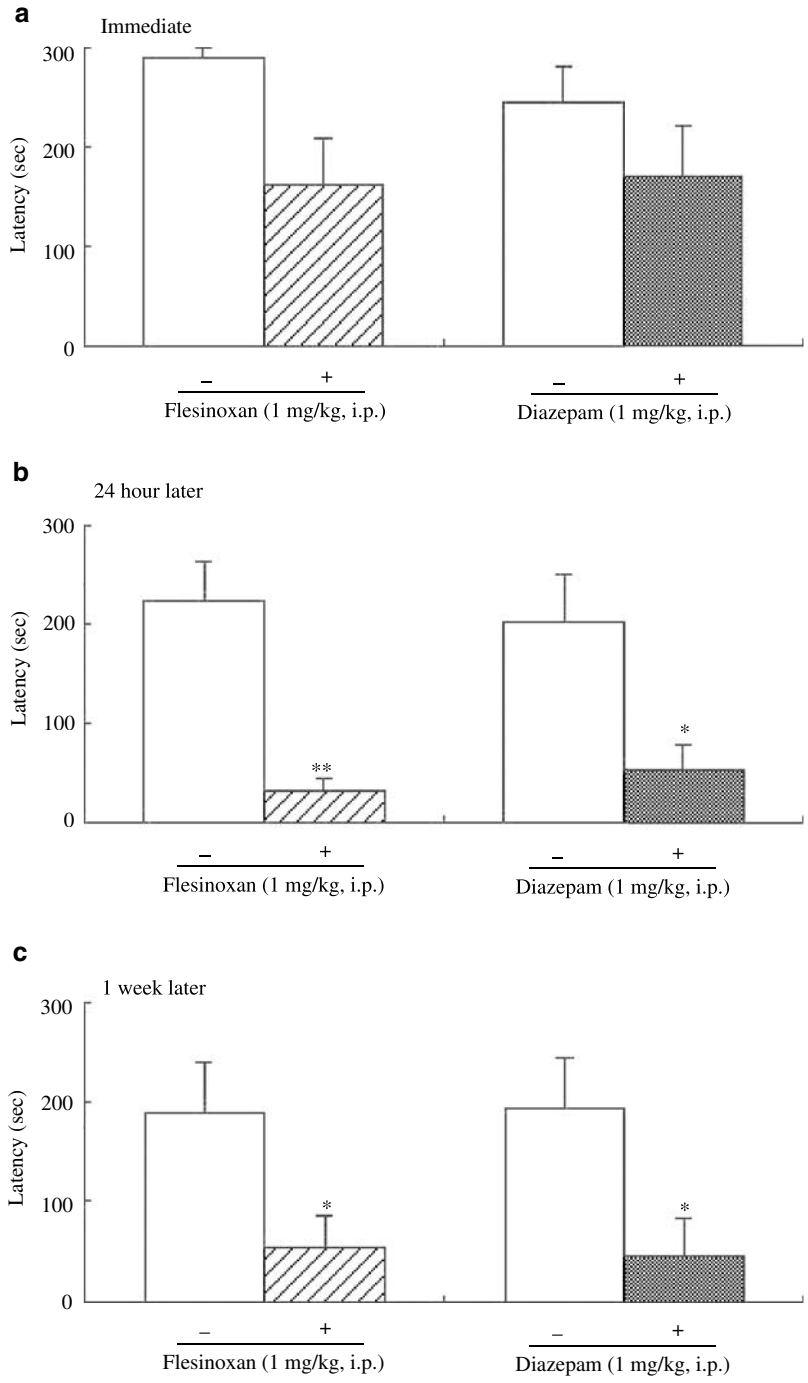

Figure 2 Effects of pretreatment with flesinoxan and diazepam 30 min before the training session on passive avoidance performance in mice. Mice were subjected to the double-training session with a 0.6-mA electrical foot shock of 16 s duration. Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Flesinoxan (1 mg/kg, i.p.) and diazepam (1 mg/kg, s.c.) were administered 30 min before the training session. Each column represents the mean with SEM of eight mice. $^{*}P<0.05$, $^{**}P<0.01$ *vs* vehicle-pretreated group (open column).

subjected to double-training sessions was much higher than that in mice subjected to single-training sessions. The retention latency in mice subjected to 0.6-mA electrical foot shock for 16 s significantly increased in all of the test sessions as compared with that in nonshocked control mice ($F(3,36)=8.070$, $P<0.01$ immediately; $F(3,36)=6.135$, $P<0.01$ at 24 h; $F(3,36)=3.998$, $P<0.05$ at 1 week after the training sessions).

Effects of Pretreatment with Flesinoxan and Diazepam 30 min before the Double-Training Sessions on Passive Avoidance Performance in Mice

The effects of pretreatment with flesinoxan and diazepam 30 min before the double-training sessions on passive avoidance performance in mice are shown in Figure 2. In these experiments, mice were subjected to 0.6-mA electrical

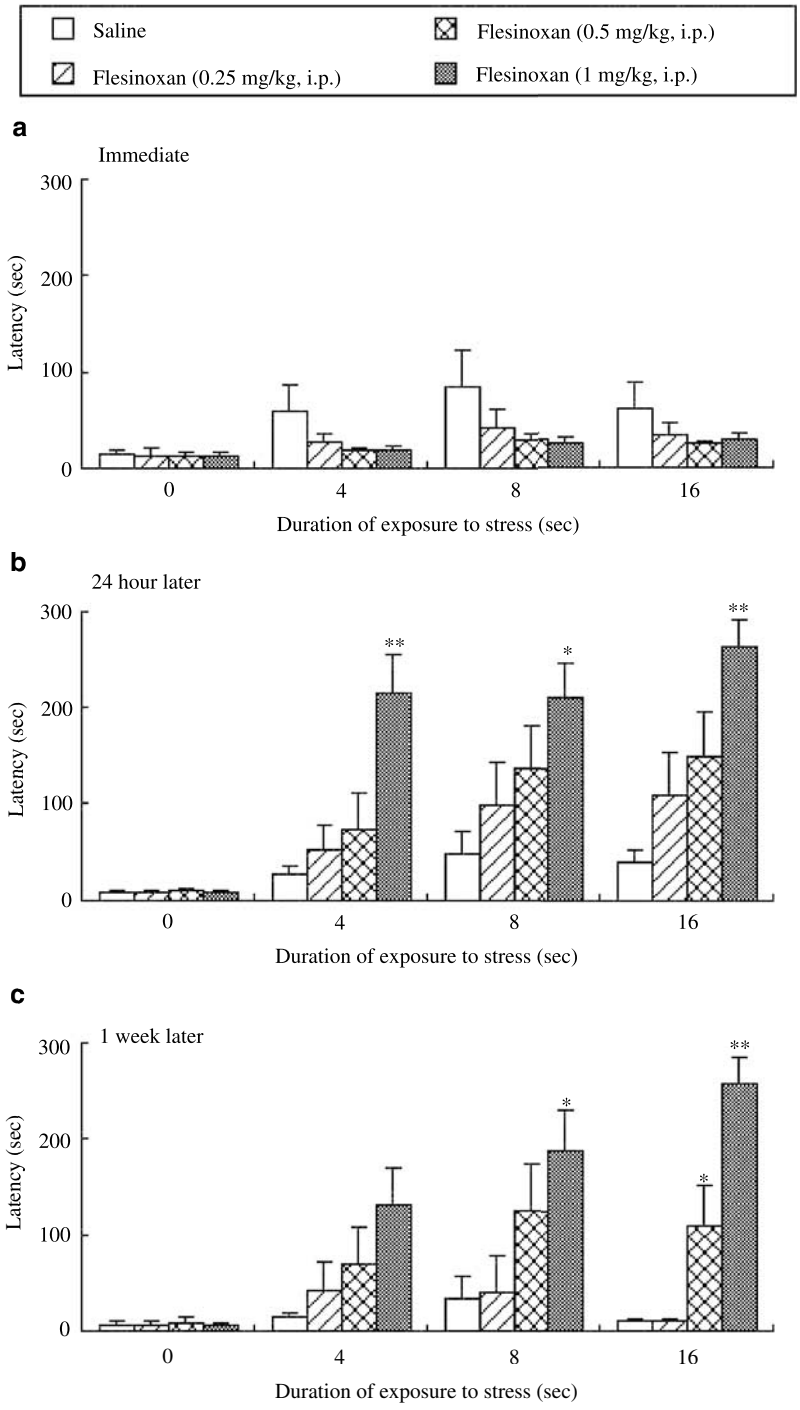

Figure 3 Effects of pretreatment with flesinoxan 24 h before the single-training session on passive avoidance performance in mice. Mice were subjected to the single-training session with 0.6-mA electrical foot shocks of various durations (4–16 s). Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Flesinoxan (0.25–1 mg/kg, i.p.) was administered 24 h before the training session. Each point represents the mean with SEM of 10 mice. $^{*}P<0.05$, $^{**}P<0.01$ *vs* saline-pretreated group (open column).

foot shocks for 16 s in the training sessions. As shown in Figure 2a, pretreatment with flesinoxan (1 mg/kg, i.p.) or diazepam (1 mg/kg, i.p.) 30 min before the training sessions slightly decreased the retention latency in the immediate test sessions, but this effect was not statistically significant. Significant decreases in retention latency were observed with flesinoxan at 24 h ($P<0.01$) and 1 week ($P<0.05$) after the training sessions (Figure 2b and c). Similarly, mice that had been pretreated with diazepam 30 min before the training sessions also showed a significant decrease in retention latency at 24 h and 1 week after the training sessions ($P<0.05$) (Figure 2b and c).

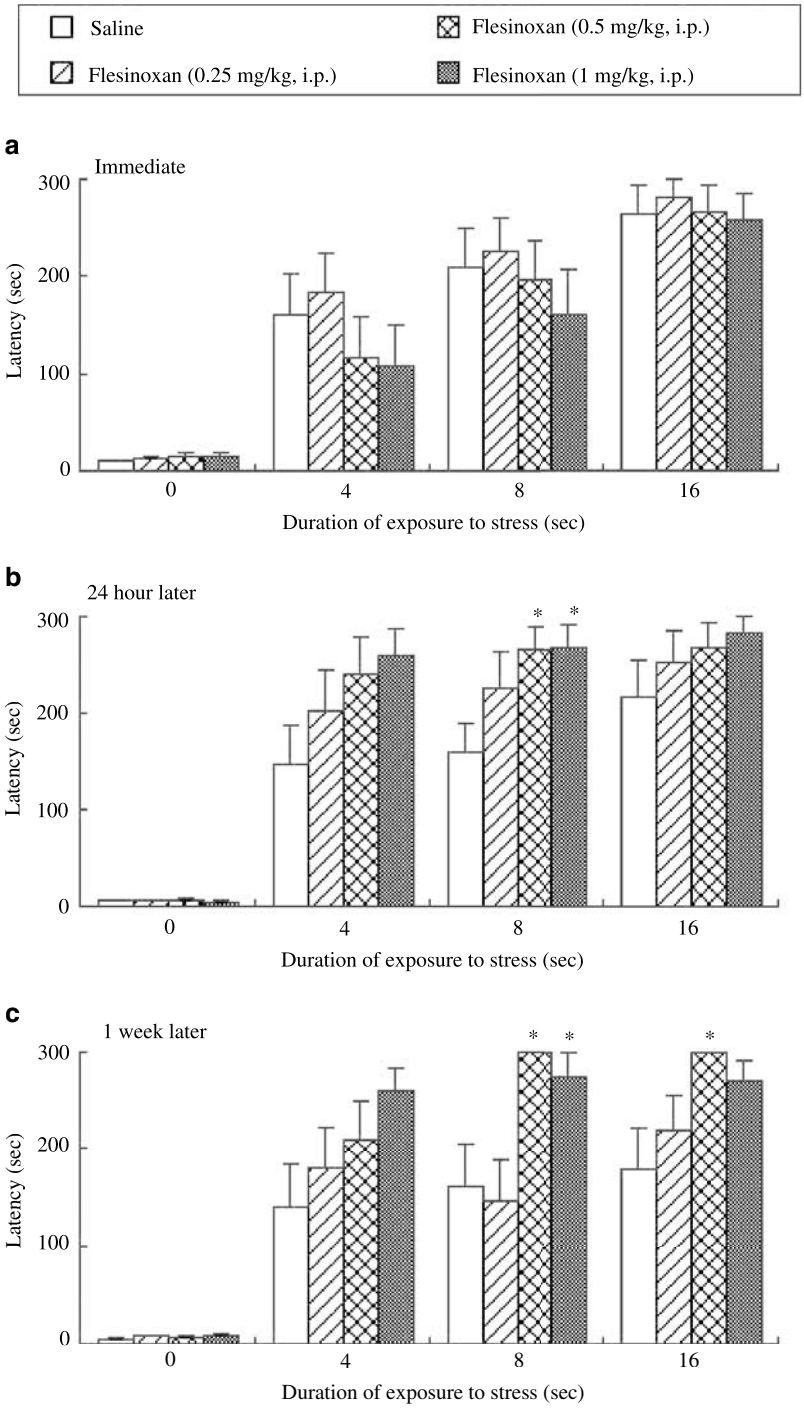

Figure 4 Effects of pretreatment with flesinoxan 24 h before the double-training session on passive avoidance performance in mice. Mice were subjected to the double-training session with 0.6-mA electrical foot shocks of various durations (4–16 s). Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Flesinoxan (0.25–1 mg/kg, i.p.) was administered 24 h before the training session. Each point represents the mean with SEM of 10 mice. *$P<0.05$ *vs* saline-pretreated group (open column).

Effects of Pretreatment with Flesinoxan 24 h before the Single- or Double-Training Sessions on Passive Avoidance Performance in Mice

The effects of pretreatment with flesinoxan 24 h before the single- or double-training sessions on passive avoidance performance in mice are shown in Figures 3 and 4. Pretreatment with flesinoxan (0.25–1 mg/kg, i.p.) 24 h before single- or double-training sessions did not change the retention latency in the immediate test sessions (Figures 3a and 4a). However, flesinoxan (1 mg/kg, i.p.)-pretreated mice showed a significant increase in retention latency at 24 h ($F(3,36)=7.478$, $P<0.01$ in the 4 s stressed group; $F(3,36)=3.253$, $P<0.05$ in the 8 s stressed

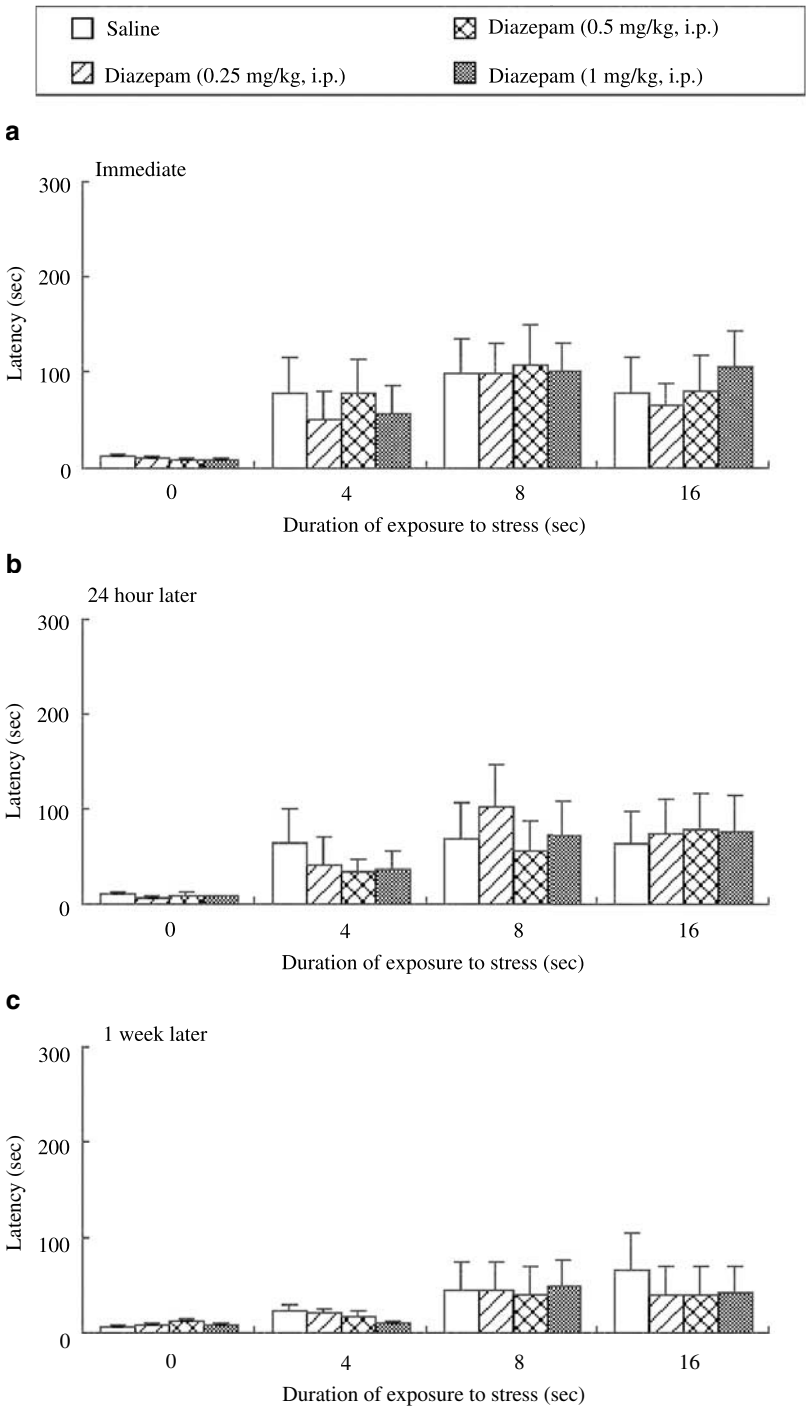

Figure 5 Effects of pretreatment with diazepam 24 h before the single-training session on passive avoidance performance in mice. Mice were subjected to the single-training session with 0.6-mA electrical foot shocks of various durations (4–16 s). Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Diazepam (0.25–1 mg/kg, i.p.) was administered 24 h before the training session. Each point represents the mean with SEM of 10 mice.

group; $F(3,36) = 7.037$, $P < 0.01$ in the 16 s stressed group) and/or 1 week ($F(3,36) = 3.964$, $P < 0.01$ in the 8 s stressed group; $F(3,36) = 20.417$, $P < 0.01$ in the 16 s stressed group) after the training sessions compared with saline-pretreated mice (Figure 3b and c). Similar enhancements of retention latency in the test sessions 24 h ($F(3,36) = 2.925$, $P < 0.05$ in the 8 s stressed group) and/or 1 week ($F(3,36) = 5.689$, $P < 0.01$ in 8 s stressed group; $F(3,36) = 3.100$, $P < 0.05$ in the 16 s stressed group) later were observed also in mice pretreated with flesinoxan 24 h before the double-training sessions (Figure 4b and c).

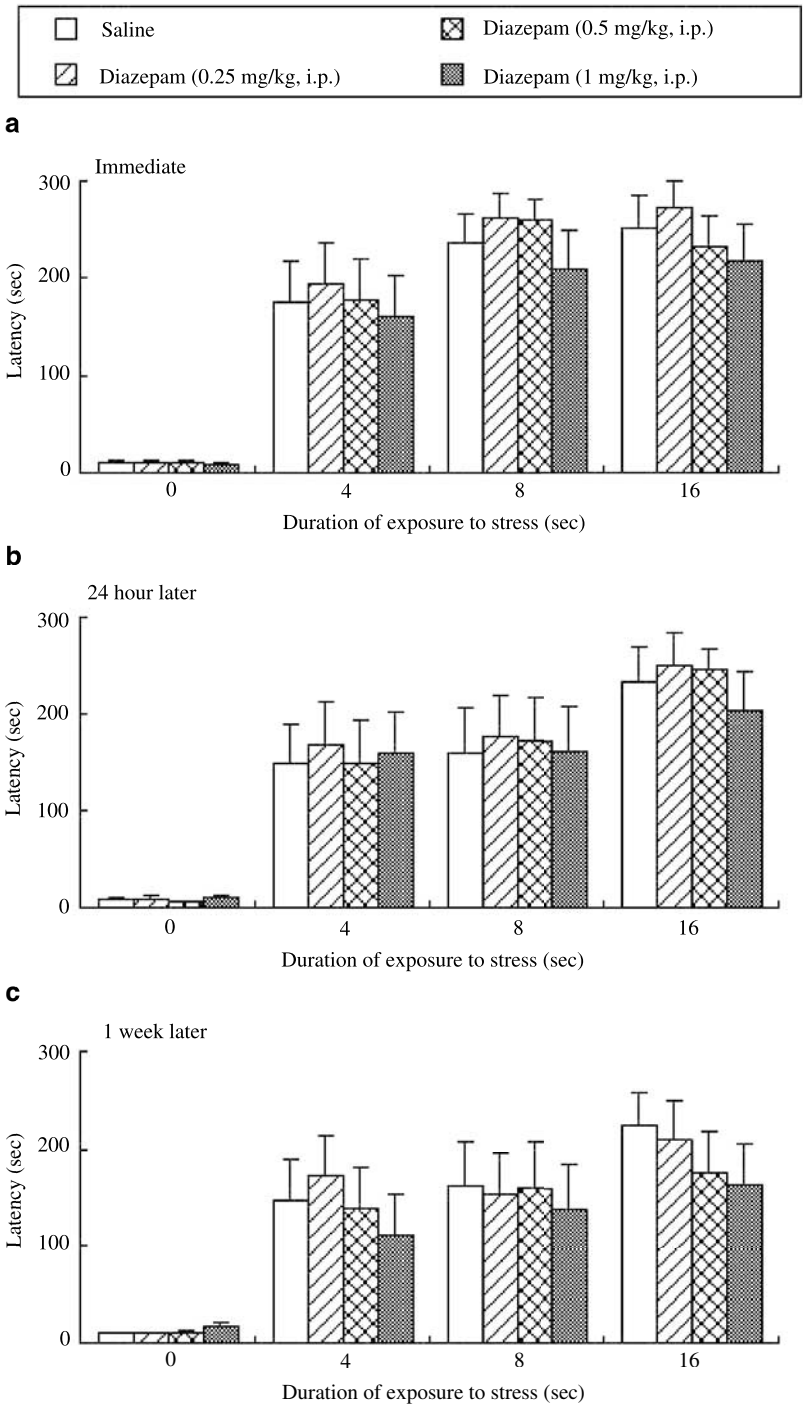

Figure 6 Effects of pretreatment with diazepam 24 h before the double-training session on passive avoidance performance in mice. Mice were subjected to the double-training session with 0.6-mA electrical foot shocks of various durations (4–16 s). Test sessions were performed immediately (a), 24 h (b), or 1 week (c) after the training session. Diazepam (0.25–1 mg/kg, i.p.) was administered 24 h before the training session. Each point represents the mean with SEM of 10 mice.

Effects of Pretreatment with Diazepam 24 h before the Single- or Double-Training Sessions on Passive Avoidance Performance in Mice

The effects of pretreatment with diazepam 24 h before the single- or double-training sessions on passive avoidance performance in mice are shown in Figures 5 and 6. In contrast to flesinoxan, pretreatment with diazepam (0.25–1 mg/kg, i.p.) 24 h before the training sessions did not affect the retention latency in any of the test sessions.

Effects of Pretreatment with Flesinoxan and Diazepam on the Pain Threshold in Mice

The effects of pretreatment with flesinoxan and diazepam on the pain threshold are shown in Figure 7. Neither

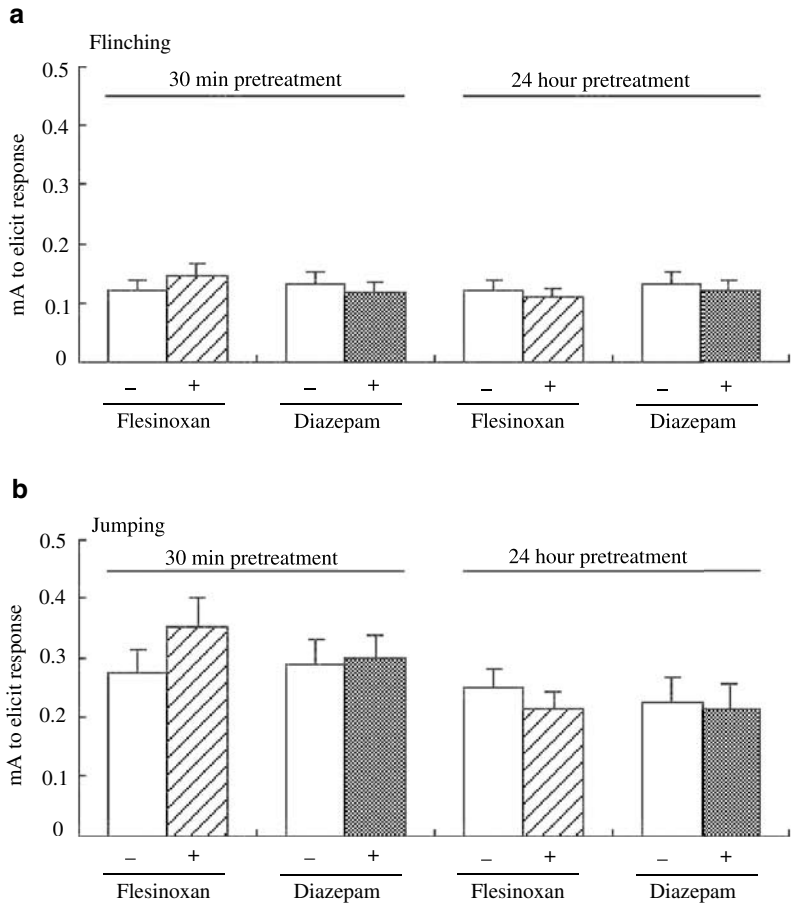

Figure 7 Effects of pretreatment with flesinoxan or diazepam on the pain threshold in mice. Flesinoxan (1 mg/kg, i.p.) and diazepam (1 mg/kg, i.p.) were administered 30 min or 24 h before the delivery of electrical foot shocks. Each column represents the mean with SEM of eight mice.

pretreatment with flesinoxan (1 mg/kg, i.p.) nor diazepam (1 mg/kg, i.p.), at the same time intervals used in the passive avoidance study, modified the thresholds for flinching (Figure 7a) and jumping (Figure 7b) elicited by electrical stimuli.

DISCUSSION

The first experiments in the present study demonstrated that the retention latency to enter the dark compartment in mice subjected to single-training sessions with 0.6-mA electric foot shocks for 4, 8, or 16 s slightly increased in all of the test sessions (immediate, 24 h, and 1 week after the training session) as compared with that of nonshocked control mice, but none of these changes were significant. These results suggest that mice had partially acquired the task under these conditions. In contrast, mice subjected to double-training sessions with 0.6-mA electric foot shocks for 16 s showed a significant increase in retention latency in all of the test sessions as compared with that of nonshocked control mice, indicating that mice had completely acquired the task under these conditions. Using these two different experimental conditions, the present study investigated the effects of the 5-HT$_{1A}$ receptor agonist flesinoxan on passive avoidance in mice compared with those of the benzodiazepine anxiolytic diazepam.

The present study demonstrated that pretreatment with either flesinoxan or diazepam 30 min prior to double-training sessions with 0.6-mA electric foot shocks for 16 s significantly decreased the retention of latency in test sessions 24 h and 1 week later. These results agree with previous findings by many investigators that various types of 5-HT$_{1A}$ receptor agonists as well as benzodiazepine anxiolytics impair passive avoidance performance (Nabeshima *et al*, 1990; Rowan *et al*, 1990; Mendelson *et al*, 1993; Anglade *et al*, 1994; Misane *et al*, 1998; Misane and Ögren, 2000). Therefore, the present findings confirm that the ability of mice to acquire a passive avoidance task is impaired at an early stage (30 min later) after the activation of 5-HT$_{1A}$ as well as benzodiazepine receptors.

On the other hand, the present study also showed that pretreatment of mice with flesinoxan but not diazepam 24 h before single-training sessions with a 0.6-mA electric foot shock for 4, 8, or 16 s produced a significant increase in the retention latency in test sessions 24 h and 1 week later. Furthermore, a similar enhancing effect of flesinoxan was observed in mice subjected to double-training sessions. The lack of an effect of pretreatment 24 h beforehand with flesinoxan on locomotor and/or exploratory behavior of mice has been confirmed in our previous studies (Tsuji *et al*, 2000, 2001), indicating that the effects of flesinoxan in the present passive avoidance are not likely nonspecific effects on general motor activity. The present findings

therefore suggest that the ability of mice to acquire a passive avoidance task is facilitated at a late stage (24 h later) after the activation of 5-HT$_{1A}$ receptors.

To assess whether the effects of drugs on passive avoidance performance are because of nonspecific actions on pain sensitivity, we performed a nociception assay using electric current as the nociceptive stimulus. It is unlikely that changes in pain sensitivity are involved in the effects of drugs on passive avoidance, since neither flesinoxan nor diazepam, at the same doses and time intervals used in the passive avoidance study, modified the thresholds for flinching and jumping elicited by the electrical stimuli.

An important point to explain the present findings may be whether changes in passive performance of mice produced by flesinoxan or diazepam reflect the changes in the emotional sensitivity or the learning and memory process for aversive stimuli. We have previously reported that both substances affected the emotional response of mice for stress stimuli in the hole-board test (Tsuji *et al*, 2000, 2001). However, the emotionality that is estimated by the hole-board test is abounding in generality. In contrast, emotionality that affects the passive avoidance task is apparently aversion. Therefore, our previous findings in the hole-board test should not be easily related to the present findings in the passive avoidance test. In the passive avoidance test, it is supposed that, if substances modify the emotional sensitivity of mice to electric foot shocks at the training sessions, the retention latency in the immediate test sessions may be changed as compared with that of vehicle-treated mice. However, we observed that neither flesinoxan nor diazepam affected the retention latency of mice in the immediate test sessions consistently throughout the present study. Based on these results, we suggest that changes in passive avoidance performance of mice produced by flesinoxan or diazepam may be based on changes in the learning and memory process rather than emotional sensitivity for an aversive event. Thus, the present findings suggest that the learning and memory process for an aversive event may be impaired at an early stage after the activation of benzodiazepine receptors. In contrast, the activation of 5-HT$_{1A}$ receptors has a dual effect on the learning and memory process for an aversive event that depends on the time interval following receptor activation.

Our present findings may also be helpful to pave the way for new psychotherapeutic strategies in the clinical realm. For example, exposure therapies are currently used to treat fear anxiety and other intense negative emotions by exposing the patient to the events that create the negative response. The key to the effectiveness of exposure therapies may be to correct the erroneous cognitions for the aversive events (Foa, 2000). The enhancement of acquisition of passive avoidance task observed at a late stage (24 h later) after the administration of 5-HT$_{1A}$ receptor agonist can be interpreted as the development of the ability to recognize exactly the aversive events. Thus, we here proposed the possibility that adequate activation of 5-HT$_{1A}$ receptors might be useful for some cognitive/behavioral therapies.

Although the distinct mechanisms of the facilitation of the ability of mice to acquire a passive avoidance task at a late stage (24 h later) after the administration of flesinoxan are unclear, preclinical studies of the pharmacokinetics of flesinoxan have indicated that these drugs disappear from the body within 24 h after administration (unpublished observation, Solvay Duphar BV, Weesp, The Netherlands). Therefore, under the present conditions, some secondary physiological changes resulting from 5-HT$_{1A}$ receptor activation rather than the effects of residual administered drug may be likely to account for the observed changes in passive avoidance performance. In particular, changes in postsynaptic 5-HT$_{1A}$ receptor function should be notable, since some investigators have suggested that postsynaptic rather than presynaptic 5-HT$_{1A}$ receptors may play a negative role in the modulation of passive avoidance performance (Mendelson *et al*, 1993; Misane *et al*, 1998). Functional changes in postsynaptic 5-HT$_{1A}$ receptors under the conditions in the present study have not been clearly defined, but several reports have indicated that postsynaptic 5-HT$_{1A}$ receptors are desensitized 24 h after a single administration of 5-HT$_{1A}$ receptor agonists (Forster *et al*, 1994; O'Connell and Curzon, 1996). Thus, it is possible that the desensitization of postsynaptic 5-HT$_{1A}$ receptors might be related to the facilitatory effects of flesinoxan observed in the present study. Otherwise, the involvement of changes in some physiological functions associated with 5-HT$_{1A}$ receptors should also be assumed. For example, brain-derived neurotrophic factor (BDNF) has been shown to be involved in the consolidation of passive avoidance task (Rose, 2000). Very recently, we found that pretreatment with flesinoxan significantly increased BDNF mRNA expression in hippocampus and amygdala 24 h later (unpublished observation). Additionally, it should also be noted that flesinoxan has antagonistic activity for α_1-adrenoceptors as well as agonistic activity for 5-HT$_{1A}$ receptors (Millan *et al*, 1994; Koek *et al*, 1998). There is growing evidence that the increase and decrease in the number and/or function of α_1-adrenoceptors may be closely related to the enhancement and impairment of passive avoidance performance, respectively (Knauber and Müller, 2000a, b). It is thus possible that the α_1-adrenoceptor system might be upregulated 24 h after the administration of flesinoxan by its antagonistic activity for α_1-adrenoceptors, and this might play a role in the enhancement of passive avoidance performance.

In conclusion, the present study clearly demonstrated that the activation of 5-HT$_{1A}$ receptors but not benzodiazepine receptors has a dual effect on the passive avoidance performance of mice that depends on the amount of time after receptor activation. In particular, enhancement of the ability of mice to acquire a passive avoidance task at a later stage (24 h later) after 5-HT$_{1A}$ receptor activation should be noted. These results suggest that the activation of 5-HT$_{1A}$ receptors may produce the delayed facilitation of some mechanisms regulating the learning and memory process for an aversive event.

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