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Effects of selective serotonin reuptake inhibitors on immobility time in the tail suspension test in streptozotocin-induced diabetic mice

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Abstract

We examined the effects of fluoxetine and fluvoxamine, selective serotonin reuptake inhibitors (SSRIs), and desipramine, a selective noradrenaline (NA) reuptake inhibitor, given alone or in combination with diazepam on immobility time in the tail suspension test in diabetic mice. Immobility time was significantly longer in diabetic than in nondiabetic mice. Diazepam (0.1 and 0.3 mg/kg sc) dose-dependently decreased immobility time in diabetic mice to the level observed in saline-treated nondiabetic mice. However, diazepam had no significant effect on immobility time in nondiabetic mice. Fluoxetine (3–56 mg/kg ip) and desipramine (1–30 mg/kg ip) produced marked, dose-dependent suppression of immobility time in both nondiabetic and diabetic mice. However, anti-immobility effects of fluoxetine and desipramine in diabetic mice were less than those in nondiabetic mice. Fluvoxamine (3–30 mg/kg ip) produced a dose-dependent suppression of immobility time in nondiabetic mice but not in diabetic mice. The anti-immobility effects of fluoxetine, fluvoxamine and desipramine in nondiabetic mice were antagonized by pretreatment with diazepam (0.3 mg/kg sc). Furthermore, fluoxetine, fluvoxamine and desipramine had no effect on the immobility time in diazepam (0.3 mg/kg sc)-treated diabetic mice. These results indicate that the anti-immobility effects of SSRIs and desipramine are less in diabetic mice than in nondiabetic mice in the tail suspension test. Furthermore, in diabetic mice, SSRIs and selective NA reuptake inhibitors did not affect immobility time even though the prolonged duration of immobility was suppressed by pretreatment with diazepam.

Keywords: Antidepressant; Tail suspension test; Diabetes; Benzodiazepine anxiolytic; SSRI; Diazepam; Fluoxetine; Fluvoxamine; Desipramine

1. Introduction

Benzodiazepines and antidepressants are commonly administered together in the clinical treatment of affective disorders such as major depression, neurotic depression and anxious–depressive disorders. One reason for using this drug combination may be the frequent comorbidity of depression and anxiety. Benzodiazepines usually are coadministered with antidepressants to reduce symptoms associated with depression, which do not respond sufficiently well to antidepressants alone. Moreover, benzodiazepines are given to control the release of psychomotor inhibition, which may occur at the onset of action of antidepressants. Previous studies have demonstrated that benzodiazepines counteract the reduction in immobility induced by tricyclic antidepressants or monoamine oxidase inhibitors in the forced swimming test in mice (Van Der Meersch-Mougeot et al., 1993), an experimental procedure that is widely accepted for its value in predicting the antidepressive activity of antidepressants in humans (Porsolt et al., 1978). Similarly, it recently has been reported that the anti-immobility effects of selective serotonin reuptake inhibitors (SSRIs) in the forced swimming test are suppressed by benzodiazepines (Da-Rocha et al., 1997). These reports indicate that benzodiazepines may be able to alter the therapeutic efficacy of antidepressants in depression.

Diabetes has been reported to be associated with behavioral changes in animals (Mooradian, 1988; Tomlinson et al., 1992). Enhanced retention of passive avoidance training

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in mice (Leedom et al., 1987; Bellush and Rowland, 1989), increased grooming activity in a novel environment in rats (Ahmad and Merali, 1988) and poor retention of a previously learned avoidance response in a T-maze in mice (Flood et al., 1990) have also been reported. Furthermore, diabetic rats showed significantly more anxiogenic activity than nondiabetic rats in open-field, elevated plus maze, zero maze and social interaction tests (Ramanathan et al., 1998). Recently, we reported that the anxiolytic effect of diazepam in an unfamiliar environment was less in diabetic mice than in nondiabetic mice (Kamei et al., 2001). In addition, it has been reported that diabetic rats were resistant to the effects of several tricyclic antidepressants in the learned helplessness paradigm, an accepted animal model of depression (Massol et al., 1989a,b). It is well established that depression and anxiety are common among patients with diabetes (Lustman, 1988; Lustman and Clouse, 1990; Gavard et al., 1993). Furthermore, the prevalence of depression was unrelated to the type (IDDM or NIDDM) of diabetes (Anderson et al., 2001). Thus, preclinical studies in diabetic animals may be useful to investigate possible interactions between anxiolytic and antidepressant drugs. However, there are no reports in the literature about the effects of anxiolytics on the antidepressive effects of antidepressants in diabetic animals.

Several animal models have been developed to evaluate putative antidepressants (Porsolt et al., 1978; Willner, 1990). Among these, the tail suspension test proposed by Steru et al. (1985; 1987) is a convenient model in which many antidepressants reduce immobility time, indicating that this is an index of antidepressant activity (Teste et al., 1993; Fujishiro et al., 2001).

The primary aim of this study was to investigate the effects of fluoxetine and fluvoxamine, SSRIs and desipramine, a selective noradrenaline (NA) reuptake inhibitor, in the tail suspension test in streptozotocin-induced diabetic mice. We also studied whether diazepam, a typical benzodiazepine anxiolytic, could modify the effects of fluoxetine, fluvoxamine and desipramine in the tail suspension test in diabetic mice.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science, Tokyo), 4 weeks of age and weighing approximately 20 g at the beginning of the experiments, were used. They were housed 10 per cage and had free access to food and water. The animal room was maintained at 24 ± 1 °C and 55 ± 5% humidity with a 12-h light–dark cycle (light on at 0800, light off at 2000). Animals were rendered diabetic by an injection of streptozotocin (200 mg/kg iv) dissolved in 0.1 N citrate buffer at pH 4.5. Age-matched control mice were injected with vehicle alone. The experiments were conducted 2 weeks after injection of vehicle or streptozotocin. To compare immobility time and plasma glucose levels to diabetic mice, male ICR mice (6-week-old) treated with streptozotocin (200 mg/kg iv) 5 days before the test were used (Section 3.2). Mice with plasma glucose levels of about 4000 mg/l were considered to be diabetic. Blood was collected from the tail vein of a mouse, and plasma glucose levels were determined using a glucose analyzer (ANTSENSE II, Sankyo, Tokyo, Japan). This study was carried out in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the Committee on the Care and Use of Laboratory Animals of Hoshi University, which is accredited by the Ministry of Education, Science, Sports and Culture.

2.2. Drugs

The drugs used in this study were streptozotocin (Sigma, St. Louis, MO), D(+)-glucose (Kanto Chemical), diazepam (Cercine, Takeda Chemical Industries, Osaka, Japan), fluoxetine hydrochloride (Tocris Cookson, UK), fluvoxamine maleate (Meiji Seika Kaisha, Tokyo, Japan) and desipramine hydrochloride (Sigma). Glucose was dissolved in purified water and administered in a volume of 0.1 ml/10 g of body weight. Diazepam, which was a solution dissolved in 40% benzyl alcohol, 10% ethanol, 1.5% propylene glycol and 42.8 mg/ml benzoic acid, was diluted in saline and administered in a volume of 0.1 ml/10 g of body weight. Fluoxetine was dissolved in saline and administered in a volume of 0.19 ml/10 g of body weight. Fluvoxamine and desipramine were dissolved in saline and administered in a volume of 0.1 ml/10 g of body weight. Glucose (30 mmol/kg), fluoxetine (3–56 mg/kg), fluvoxamine (3–56 mg/kg) and desipramine (1–30 mg/kg) were injected intraperitoneally 30 min before the test. Diazepam (0.1 and 0.3 mg/kg) was injected subcutaneously 35 min before the test. In Section 3.2, 6-week-old mice were treated with streptozotocin (200 mg/kg iv) 5 days before the test.

2.3. Tail suspension test

The tail suspension apparatus was made of a white translucent plastic box (30 × 30 × 30 cm) with a hook in the middle of ceiling from which to suspend the mouse. Mice were suspended by the tail using adhesive Scotch tape affixed to the hook which was connected to a strain gauge (TAIL SUSPENSION AMP, Neuroscience, Tokyo, Japan) that picked up all movements of the mouse and transmitted them to a central processing unit which calculated the total duration of immobility and the power of movements during the 10 min of the test. Each mouse was suspended individually. The movements of the mice were measured for 10 min and digitized and processed by Super Scope II (GWI; Somerville, MA, USA). The threshold level was set so as to exclude respiration movement. Immobility time was defined as the total duration that the animal showed no movement.

Glucose, fluoxetine, fluvoxamine and desipramine were injected intraperitoneally 30 min before the test. Diazepam was injected subcutaneously 35 min before the test.

2.4. Locomotor activity

Spontaneous locomotor activity of the mice was measured by a digital counter with an infrared sensor (NS-AS01, Neuroscience). A mouse was placed in a transparent plastic cage ($27 \times 17 \times 13$ cm), and put on a transparent plastic ceiling setting the infrared sensor at the center. The infrared light from a mouse accompanied by the movement was detected. Mice were placed in the measurement cage for a habituation period of 60 min, and then each drug was injected. Total activity counts were automatically recorded for 10 min. Glucose, fluoxetine, fluvoxamine and desipramine were injected intraperitoneally 30 min before the measurement of locomotor activity. Diazepam was injected subcutaneously 35 min before the test.

2.5. Statistics

The data are expressed as means with S.E.M. Significant differences were determined by one-way or two-way analysis of variance (ANOVA) followed by the Bonferroni/Dunn test for multiple comparisons. Student's t test was used to evaluate differences between two groups. Factorial significance of the interaction between diabetes and body weights in each behavioral parameter was assessed using an analysis of covariance (ANCOVA) with body weights as the covariate. P values less than .05 were considered significant.

3. Results

3.1. Effect of diabetes on body weights and immobility time in the tail suspension test in mice

Effect of diabetes on body weights and immobility time in the tail suspension test in mice is shown in Table 1. Body weights in diabetic mice were significantly less than in nondiabetic mice. Furthermore, immobility time was significantly increased in diabetic mice compared to nondiabetic mice. An ANCOVA revealed that immobility time was not significantly affected by an interaction effect [$F(1,96) = 0.075$, $P = .7841$]. Therefore, the variance of the interaction effect was modified to the residual. Then, an ANCOVA revealed that immobility time was significantly affected by diabetes [$F(1,97) = 5.500$, $P < .05$], but not by body weights [$F(1, 97) = 0.004$, $P = .9499$].

Table 1
Effect of diabetes on body weights and immobility time in the tail suspension test in mice

	Body weights (g)	Immobility time (s)
Nondiabetic mice ($n = 50$)	35.6 ± 0.4	229.3 ± 13.9
Diabetic mice ($n = 50$)	24.8 ± 0.4 *	319.1 ± 12.6 *

Nondiabetic and diabetic mice were injected intraperitoneally with saline 30 min before the tail suspension test. Values represent the mean ± S.E.M. ($n = 50$).

* $P < .05$ vs. nondiabetic mice.

Table 2
Modification of immobility time in the tail suspension test by plasma glucose levels in mice

	Immobility time (s)	Plasma glucose levels (mg/l)
Nondiabetic mice	244.6 ± 21.5	1859 ± 7.7
Glucose (30 mmol/kg ip)	263.1 ± 22.2	5564 ± 24.6 *
Streptozotocin (200 mg/kg iv, on Day 5)	281.5 ± 28.2	4514 ± 53.4 *
Streptozotocin (200 mg/kg iv, on Day 15) (diabetic mice)	339.4 ± 18.3 *	5853 ± 14.4 *

Streptozotocin (200 mg/kg) was injected intravenously 5 or 15 days before the test. The glucose-treated group was treated intraperitoneally with glucose (30 mmol/kg ip) 30 min before the tail suspension test. The other group was treated intraperitoneally with vehicle 30 min before the tail suspension test. Plasma glucose levels were measured immediately after the tail suspension test. Values represent the mean ± S.E.M. of 8–10 mice.

* $P < .05$ vs. vehicle-treated nondiabetic mice.

3.2. Modification of immobility time in the tail suspension test by plasma glucose levels in mice

Modification of immobility time by plasma glucose levels in mice is shown in Table 2. Plasma glucose levels and immobility time in the tail suspension test in diabetic mice were significantly greater than in nondiabetic mice.

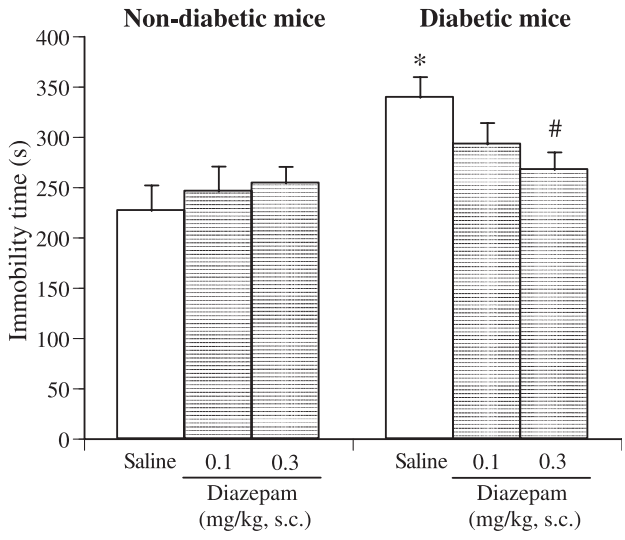

Fig. 1. Effect of diazepam on immobility time in the tail suspension test in nondiabetic and diabetic mice. Diazepam was injected subcutaneously 35 min before the test. Each column represents the mean ± S.E.M. of 8–10 mice. * $P < .05$ vs. nondiabetic mice. $^{\#}P < .05$ vs. respective saline-treated group.

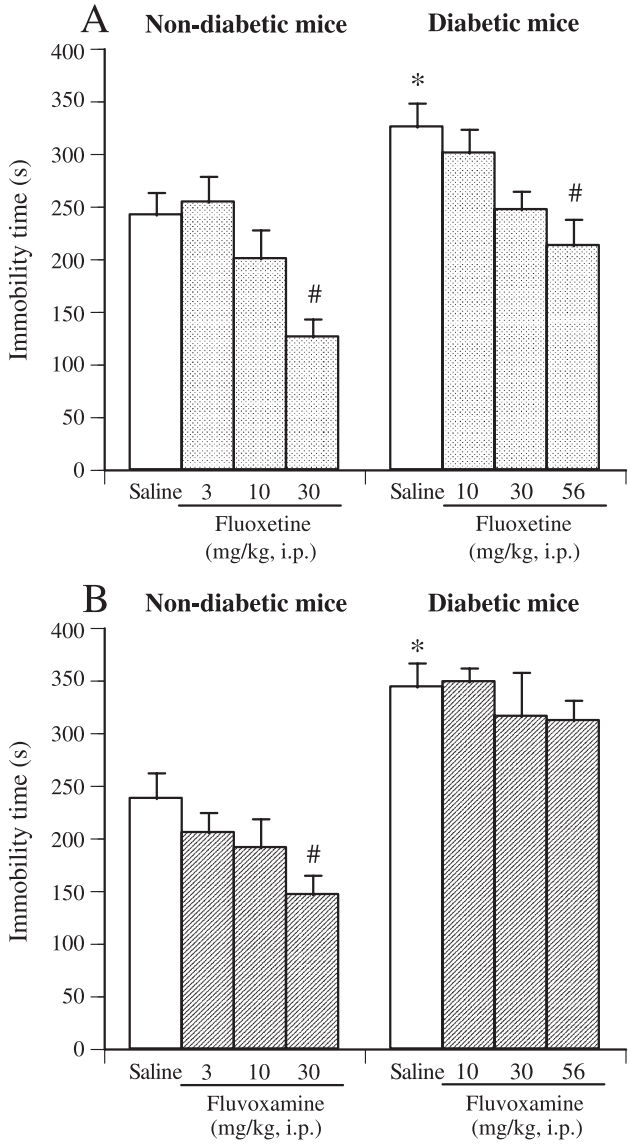

Fig. 2. Effect of SSRIs on immobility time in the tail suspension test in nondiabetic and diabetic mice. Fluoxetine (3–56 mg/kg ip) and fluvoxamine (3–56 mg/kg ip) were injected 30 min before the test. Each column represents the mean ± S.E.M. of 8–10 mice. * $P < .05$ vs. nondiabetic mice. # $P < .05$ vs. respective saline-treated group.

Glucose (30 mmol/kg ip) significantly increased plasma glucose levels in nondiabetic mice to the same levels observed in diabetic mice, but did not modify immobility time (Table 2). In addition, mice treated with streptozotocin (200 mg/kg iv) 5 days before the test had increased plasma glucose levels to the same levels as those observed in diabetic mice (Table 2).

3.3. Effect of diazepam on immobility time in nondiabetic and diabetic mice

Treatment with diazepam (0.1 and 0.3 mg/kg sc) dose-dependently and significantly reduced immobility time in diabetic mice. Indeed, diazepam (0.3 mg/kg sc) reduced the immobility time in diabetic mice to the level observed in saline-treated nondiabetic mice. On the other hand, diazepam had no significant effect on immobility time in nondiabetic mice (Fig. 1).

3.4. Effects of SSRIs on immobility time in nondiabetic and diabetic mice

Fluoxetine (3–56 mg/kg ip) dose-dependently reduced immobility time in both nondiabetic and diabetic mice. The reduction of immobility time in nondiabetic mice was statistically significant at a dose of 30 mg/kg. However, the effect of fluoxetine was less in diabetic mice than in nondiabetic mice, since the reduction of the immobility time in diabetic mice was significant at a dose of 56 mg/kg.

Fluvoxamine (3–30 mg/kg ip) also dose-dependently and significantly decreased immobility time in nondiabetic mice. However, fluvoxamine, at a dose range of 10–56 mg/kg sc, did not affect immobility time in diabetic mice (Fig. 2A and B).

3.5. Effect of desipramine on immobility time in nondiabetic and diabetic mice

The selective NA reuptake inhibitor desipramine (1–30 mg/kg ip) dose-dependently and significantly decreased immobility time in both nondiabetic and diabetic mice. The reduction of immobility time in nondiabetic mice was statistically significant at 10 mg/kg. However, the effect of desipramine was less in diabetic mice than in nondiabetic mice because the reduction of immobility time in diabetic mice was significant at 30 mg/kg (Fig. 3).

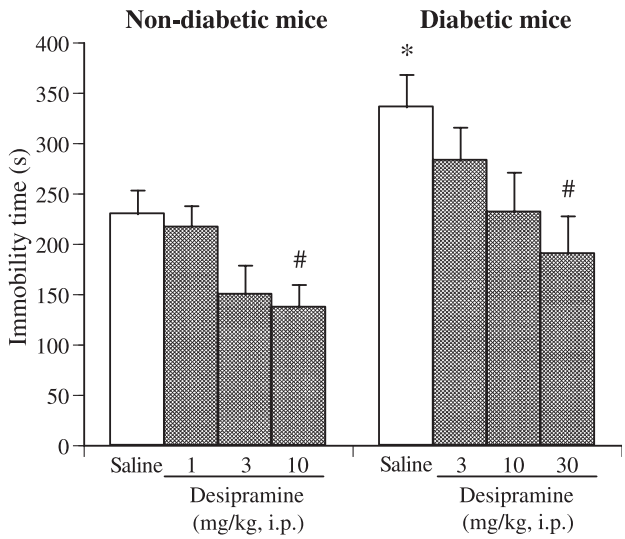

Fig. 3. Effect of desipramine on immobility time in the tail suspension test in nondiabetic and diabetic mice. Desipramine was injected intraperitoneally 30 min before the test. Each column represents the mean ± S.E.M. of 8–10 mice. * $P < .05$ vs. nondiabetic mice. # $P < .05$ vs. respective saline-treated group.

3.6. Effects of SSRIs and desipramine on immobility time in diazepam-treated nondiabetic and diabetic mice

The suppression of immobility time in nondiabetic mice induced by fluoxetine (3–30 mg/kg ip), fluvoxamine (3–30 mg/kg ip) and desipramine (1–10 mg/kg ip) was not observed when nondiabetic mice were pretreated with diazepam (0.3 mg/kg sc). Furthermore, fluoxetine (10–56 mg/kg ip), fluvoxamine (10–56 mg/kg ip) and desipramine (3–30 mg/kg ip) did not modify the reduction of immobility time by pretreatment with diazepam (0.3 mg/kg sc) in diabetic mice (Fig. 4).

3.7. Effects of SSRIs, desipramine and diazepam on spontaneous locomotor activity in nondiabetic and diabetic mice

Fluoxetine (30 mg/kg ip), fluvoxamine (30 mg/kg ip), desipramine (10 mg/kg ip) and diazepam (0.3 mg/kg sc) did not affect spontaneous locomotor activity in nondiabetic mice. Furthermore, fluoxetine (56 mg/kg ip), fluvoxamine (56 mg/kg ip), desipramine (30 mg/kg ip) and diazepam (0.3 mg/kg sc) did not affect spontaneous locomotor activity in diabetic mice (Table 3).

Table 3
Effects of SSRIs, desipramine and diazepam on spontaneous locomotor activity in nondiabetic and diabetic mice

Drugs	Total activity (counts/10 min)	
	Nondiabetic mice	Diabetic mice
Saline (ip)	70.5 ± 24.2	102.7 ± 38.3
Fluoxetine (ip)	11.7 ± 5.5	25.2 ± 19.8
Fluvoxamine (ip)	76.7 ± 25	44.1 ± 19.1
Desipramine (ip)	47.0 ± 30.9	79.8 ± 35.4
Saline (sc)	85.7 ± 30.5	136.1 ± 42.7
Diazepam (sc)	45.0 ± 28.5	187.2 ± 43.7

Data represent the mean locomotor activity counts ± S.E.M. of 9–10 mice for 10 min. Each drug was administered at the effective or the maximal dose in the tail suspension test. A two-way ANOVA revealed that immobility time was not affected by respective drugs in both nondiabetic and diabetic mice. There was no statistically significant difference in each group.

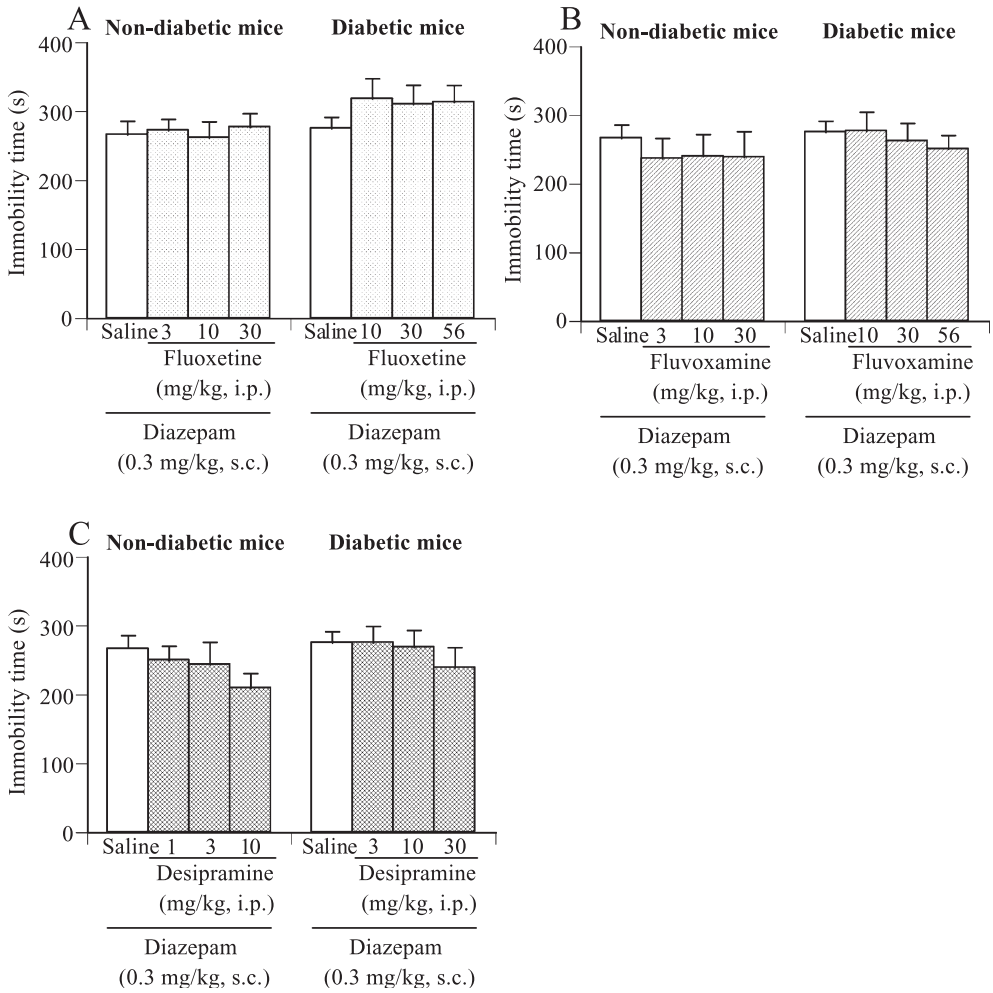

Fig. 4. Effects of fluoxetine, fluvoxamine and desipramine on immobility time in diazepam (DZP)-treated nondiabetic and diabetic mice. Fluoxetine (A), fluvoxamine (B) and desipramine (C) were injected intraperitoneally 30 min before the test. Diazepam was injected subcutaneously 5 min before the administration of SSRIs and desipramine. Data represent the mean ± S.E.M. of 8–10 mice.

4. Discussion

In the present study, immobility time in the tail suspension test in diabetic mice was significantly longer than in nondiabetic mice. The prolongation of immobility time in diabetic mice was not due to a reduction of body weights induced by diabetes. In addition, it seems unlikely that the prolonged duration of immobility in diabetic mice was due to a reduction of locomotor activity because spontaneous locomotor activity for 10 min was not significantly affected by diabetes. In the present study, we observed that treatment with glucose (30 mmol/kg ip) in nondiabetic mice significantly increased plasma glucose levels, but did not affect immobility time. In addition, we examined the influence of immobility time in mice in the early stages of diabetes (streptozotocin treatment fifth day). As the results show, although the increase in plasma glucose levels was observed, an influence of immobility time was not observed. On the other hand, Hilakivi-Clarke et al. (1990) reported that the duration of immobility in the forced swimming test was longer in diabetic mice than in nondiabetic mice, and this change was partially antagonized by a 1-week treatment with insulin (0.1 IU/g/day). The present results and previous reports suggest that hyperglycemia and/or insulin deficiency itself may be responsible for dysfunction of the CNS in diabetes.

Steru et al. (1985) reported that diazepam did not reduce immobility time in the tail suspension test. However, in the present study, administration of the benzodiazepine anxiolytic diazepam markedly reduced immobility time in diabetic mice to the level observed in saline-treated, nondiabetic mice. In contrast, diazepam did not affect immobility time in nondiabetic mice. In addition, we reported that diabetic mice showed enhanced anxiety-like behavior in an unfamiliar environment (Kamei et al., 2001). Interestingly, an enhanced anxiety-like state in diabetic mice was antagonized by flumazenil, a benzodiazepine receptor antagonist (Kamei et al., 2001). Based on these findings, it is possible that altered benzodiazepine receptor function in diabetic mice may affect immobility time. However, further studies are needed to address this problem.

In the present study, fluoxetine dose-dependently and significantly reduced the immobility time in nondiabetic mice. In addition, fluoxetine-treated diabetic mice exhibited a marked and dose-dependent reduction of immobility time when treated with higher doses of fluoxetine compared to nondiabetic mice. On the other hand, the significant suppressive effect of fluvoxamine was observed in nondiabetic, but not in diabetic mice. The present results demonstrate that the anti-immobility effects of SSRIs are less in diabetic than in nondiabetic mice. It has been reported that SSRIs such as fluoxetine and fluvoxamine facilitate serotonergic neurotransmission in both the cell body and nerve terminals (Artigas, 1995), and induce several pharmacological effects such as antidepressant, anxiolytic or hypophagic effects, by increasing serotonin (5-HT) availability. Interestingly, it has been shown that fluoxetine and fluvoxamine can produce different effects. Yamada et al. (1999) reported that *p*-chlorophenylalanine, a drug that depletes 5-HT levels, attenuated fluvoxamine-induced hyperglycemia but not fluoxetine-induced effects. In addition, systemic administration of fluoxetine, but not fluvoxamine, increases extracellular NA concentration in the rat prefrontal cortex as measured by microdialysis (Bymaster et al., 2002). These results led us to propose that activation of the noradrenergic system is related to the anti-immobility effects of fluoxetine in diabetic mice. In fact, the present study demonstrated that a selective NA reuptake inhibitor, desipramine, significantly decreased immobility time in both nondiabetic and diabetic mice, while the anti-immobility effect of desipramine was less pronounced in diabetic than in nondiabetic mice. These findings suggest that noradrenergic antidepressants may be useful for the treatment of depression in patients with diabetes. In contrast to the present study, it has been reported that SSRIs, but not tricyclic antidepressants, produced antidepressant effects in diabetic rats (Massol et al., 1989b). The discrepancy of the data may depend on the differences of species and/or the experimental procedures used.

Another possible explanation is that 5-HT and NA levels in diabetic animal brain differed from those in nondiabetic animals. The concentrations of 5-HT and NA were markedly decreased in the dialysate collected from the ventromedial portion of the hypothalamus of diabetic rats (Shimizu, 1991). In addition, 5-HT turnover was reduced in the frontal cortex, striatum, hypothalamus and brainstem in chronically hyperglycemic diabetic rats (Bellush and Reid, 1991). Furthermore, streptozotocin-induced diabetes also decreases the rate of NA turnover (Trulson and Himmel, 1985; Kamei and Ohsawa, 1997). These reports supported the idea that the reduction of activity in serotonergic and noradrenergic systems may occur in diabetic mice compared to nondiabetic mice. These reports taken together with the results of the present study suggest that the decreased effects of antidepressants in diabetic mice may be due to the reduction of activity in serotonergic and noradrenergic systems. However, further studies are necessary before this issue can be resolved unequivocally.

In the present study, the anti-immobility effects of fluoxetine, fluvoxamine and desipramine in nondiabetic mice were not observed when the mice were pretreated with diazepam. A previous study demonstrated that the suppressive effects of fluvoxamine on conditioned fear-induced freezing behavior, an index of anxiety, were not observed in mice that had been pretreated with diazepam (Miyamoto et al., 2000). In addition, it has been reported that benzodiazepines counteract the reduction in immobility induced by tricyclic antidepressants, monoamine oxidase inhibitors or SSRIs in the forced swimming test in mice (Van Der Meersch-Mougeot et al., 1993; Da-Rocha et al., 1997). Our present data strongly support these previous reports because the anti-immobility effects of fluoxetine, fluvoxamine and

desipramine in nondiabetic mice were inhibited by pretreatment with diazepam. There are no clinical reports which indicate that the efficacy of antidepressants is inhibited by benzodiazepines. However, Amsterdam et al. (1994) reported that the adverse effect induced by SSRIs was reduced by benzodiazepine therapy. Therefore, it is likely that benzodiazepines might be able to disturb the therapeutic effectiveness of antidepressants in depression. The present study demonstrated that the prolongation of immobility time in diabetic mice was reduced to the same level as in nondiabetic mice by pretreatment with diazepam. In addition, the anti-immobility effects of SSRIs and desipramine were less in diabetic mice than in nondiabetic mice. Therefore, it is likely that the enhanced inverse agonistic function of benzodiazepine receptors in diabetic mice masked the anti-immobility effects of SSRIs and desipramine in the tail suspension test. However, fluoxetine, fluvoxamine and desipramine did not modify the suppressed duration of immobility by pretreatment with diazepam in diabetic mice. These results indicate that the anti-immobility effects of SSRIs and desipramine in diabetic mice are less than those induced in nondiabetic mice even though the prolonged duration of immobility in diabetic mice was suppressed by pretreatment with diazepam.

In conclusion, the present results indicate that the anti-immobility effects of SSRIs and selective NA reuptake inhibitors in the tail suspension test were less in diabetic mice than in nondiabetic mice. Furthermore, the anti-immobility effects of SSRIs and selective NA reuptake inhibitors in diabetic mice were less than in nondiabetic mice, even though the prolongation of immobility time in diabetic mice was suppressed by pretreatment with diazepam. The decreased antidepressant efficacy of SSRIs and selective NA reuptake inhibitors in diabetic mice may be due to a reduction of activity in serotonergic and noradrenergic systems and/or some other as yet unidentified mechanism(s).

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