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Antidepressant-like effect of leptin in streptozotocin-induced diabetic mice

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Abstract

We previously reported that streptozotocin (STZ)-induced diabetic mice showed the depressive-like behavior in the tail suspension test. It has also been reported that leptin-deficient obese mice demonstrate the depressive-like behavior. Since STZ-induced diabetes causes a marked decrease in plasma leptin levels, it is possible that decrease in leptin levels and the depressive-like behavior may somehow be related. Therefore, we examined the effect of leptin on the depressive-like behavior of STZ-induced diabetic mice in the tail suspension test. The prolonged duration of immobility in diabetic mice was dose-dependently and significantly suppressed by single treatment with leptin (0.1–1 mg/kg, i.p.) without affecting on the locomotor activity. Leptin did not affect either the duration of immobility or the locomotor activity in non-diabetic mice. The anti-immobility effect of leptin (1 mg/kg, i.p.) in diabetic mice was significantly antagonized by the selective serotonin$_2$ (5-HT$_2$) receptor antagonist LY53,857 (0.03 mg/kg, s.c.), but not by the selective 5-HT$_{1A}$ receptor antagonist WAY-100635 (0.03 mg/kg, s.c.). Antagonists administered alone did not affect either the duration of immobility or the locomotor activity in diabetic mice. In conclusion, we suggest that leptin exerts the antidepressant-like effect in diabetic mice mediated by, at least in part, 5-HT$_2$ receptors.

Keywords: Depressive-like behavior; Diabetes; Leptin; Serotonin; Tail suspension test

1. Introduction

Leptin, a product of obese gene, is secreted by white adipose tissues into the blood (Zhang et al., 1994). Circulating leptin informs the brain about adipocyte mass, thereby controlling appetite and body weight homeostasis mediated by the activation of its receptors in the hypothalamus (Halaas et al., 1995; Pelleymounter et al., 1995). Interestingly, leptin receptor mRNA and protein are also expressed in several areas of the brain including cerebral cortex, medial habenular nucleus, hippocampus and dorsal raphe nucleus (Huang et al., 1996; Shioda et al., 1998). In addition, leptin crosses the blood–brain barrier via a saturable transport mechanism (Banks et al., 1996). Therefore, it has been suggested that leptin may have the variety of regulatory functions in the central nervous system such as mood regulation. Recently, Lu et al. (2006) reported that circulating leptin level was decreased by exposure to chronic stress in rats, which is used as an experimental model of depression. In addition, they also revealed that acute treatment with leptin suppressed the depressive-like and anhedonic-like behaviors observed in chronic-stressed rats. Since several subjects with depression, but not all, exhibit hypoleptinemia (Kraus et al., 2001; Westling et al., 2004, but not Deuschle et al., 1996) and successful treatment of antidepressant improves the hypoleptinemic state in depressive subjects (Esel et al., 2005), Lu et al. (2006) suggest that leptin treatment might be effective in the treatment of depression, particularly for those patients with low leptin levels.

Leptin has the interaction with the central serotonergic systems (Hay-Schmidt et al., 2001; Fernandez-Galaz et al., 2002). Finn et al. (2001) revealed that leptin receptor mRNA was detected on approximately 40% of the serotonin (5-HT) neurons in the caudal portions of the dorsal raphe and median raphe where the serotonergic cell bodies are abundantly located. In addition, they also revealed that Ob-Rb splice variant, which can induce STAT3 activation, is expressed in the raphe (Finn et al., 2001). Calapai et al. (1999) reported that repeated leptin treatment increased the 5-HT turnover rate in the brain mediated by inhibition of nitric oxide synthesis. Furthermore, anorectic effect and antidepressant-like effect of leptin are mediated by serotonergic systems (Yamada et al., 2003; Lu et al, 2006).

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Therefore, it is well accepted that a part of leptin's action is mediated via central serotonergic system.

In animal studies, streptozotocin (STZ)-treated rodents are often used as an animal model of type 1 diabetes because STZ induces pancreatic β-cell death and hyperglycemia associated with decreased insulin secretion (Arison et al., 1967; Tarui et al., 1987). STZ-induced diabetic rodents show changes in the central nervous system as indicated by neurochemical, electrophysiological, morphological and behavioral studies (Hilakivi-Clarke et al., 1990; McCall, 1992; Biessels et al., 1994; Magarinos and McEwen, 2000). We previously reported that STZ-induced diabetic mice showed the depressive-like behavior in the tail suspension test (Kamei et al., 2003), which is often used to screen putative antidepressants (Steru et al., 1985). This behavioral change was not detected in mice in the early stage of STZ-induced diabetes or in hyperglycemic mice induced by glucose injection (Kamei et al., 2003). Since STZ does not cross the blood–brain barrier and has an early excretion rate (Schein, 1969; Karunanayake et al., 1974), we have suggested that the depressive-like behavior of STZ-induced diabetic mice is induced by the diabetic state rather than by STZ itself. It has been reported that circulating leptin level was significantly decreased by STZ-induced diabetes (Havel et al., 1998; Sindelar et al., 1999; Tsubone et al., 2005). In addition, leptin-deficient obese mice exhibit the depressive-like behavior (Collin et al., 2000) in the Porsolt's forced swimming test (Porsolt et al., 1977). Therefore, we hypothesized that the depressive-like behavior of STZ-induced diabetic mice was reversed by injection of leptin.

Therefore, we first examined the effect of leptin on the depressive-like behavior of STZ-induced diabetic mice in the tail suspension test. Second, we examined whether the anti-immobility effect of leptin in diabetic mice was mediated by 5-HT_{1A} and/or 5-HT_2 receptors because the activation of these 5-HT receptors was involved in the antidepressant-like effect of serotonergic antidepressants in the mouse tail suspension test (Mayorga et al. 2001; Miyata et al. 2004).

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science Co., Ltd., 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 8:00, light off at 20:00). Mice were rendered diabetic by an injection of STZ (200 mg/kg, i.v.) dissolved in citrate buffer at pH 4.5. Age-matched control mice were injected with the vehicle alone. Six-week-old mice (i.e. 14 days after the induction of diabetes) with hyperglycemia (plasma glucose levels >400 mg/dl) were defined as diabetic. Blood glucose levels were determined by a glucose analyzer (ANTSENSE II, Sankyo Co. Ltd., Tokyo, Japan). All behavioral observations were performed between 11:00 and 17:00 each day. The animals were used only once. 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 Chemical Co. St. Louis, MO), leptin (PeproTech EC Ltd., UK), *N*-[2-[4-(2-methoxyphenil)-1-piperazinyl]-ethyl]-*N*-2-pyridinylcyclohexanecarboxamide (WAY-100635; the selective 5-HT_{1A} receptor antagonist; Sigma Chemical Co.), 6-methyl-1-(1-methylethyl)-ergoline-8β-carboxylic acid 2-hydroxy-1-methylpropyl ester (LY53,857; the selective 5-HT_2 receptor antagonist; Sigma Chemical Co.). Leptin, WAY-100635 and LY53,857 were dissolved in saline. All drugs were administered in a volume of 0.1 ml/10 g of body weight. The dose range and time schedule of leptin treatment were referred to the previous reports (Yamada et al., 2003) and our pilot study. The doses of WAY-100635 and LY53,857 were according to our previous report (Miyata et al., 2004) showing these antagonists inhibited the antidepressant-like effect of fluoxetine, the selective 5-HT reuptake inhibitor, in the mouse tail suspension test. Unlike other potent 5-HT_2 receptor antagonist such as ketanserin, LY53,857 has low affinity at α_1-, α_2-adrenoceptors or 5-HT_{1A} receptors (Cohen et al., 1985). Therefore, LY53,857 offers the advantage of high selectivity with minimal effects on the cardiovascular system after in vivo administration.

2.3. Measurement of plasma leptin and insulin levels

The blood samples were collected by tail prick into the heparinized tubes, and then, blood glucose level was measured by the glucose analyzer. After the centrifugation at 10,000 ×*g* for 10 min at 4 °C, the plasma was removed and stored at −80 °C until analysis. Blood was collected between 14:00 and 15:00. Plasma leptin levels and plasma insulin levels were determined by the commercially available mouse leptin ELISA kit (Morinaga, Inc., Japan) and mouse insulin ELISA kit (Morinaga, Inc., Japan) following the manufacturer's directions.

2.4. Tail suspension test

The tail suspension apparatus consisted of a white translucent plastic box (30×30×30 cm) with a hook in the middle of the 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 Inc., 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 strength of movements during the 10 min of the test. Each mouse was suspended individually. The movements of the mice were digitized and processed by a Super Scope II (GWI; Somerville, MA, USA). The threshold level was set so as to exclude respiration movement. The duration of immobility was defined as the total amount of time that the animal showed no movement. Leptin was injected i.p. 30 min before testing. WAY-100635 and LY53,857 were injected s.c. 30 min before the treatment with leptin.

Table 1
Effects of diabetes on body weights, blood glucose levels, plasma insulin levels and plasma leptin levels in mice

	Non-diabetic mice	Diabetic mice
Body weights (g)	38.3±0.5	26.1±1.3***
Blood glucose levels (mg/dl)	169.8±9.9	766.5±23.5***
Plasma insulin levels (pg/ml)	5554.75±410.91	64.63±17.18***
Plasma leptin levels (ng/ml)	2.04±0.50	0.23±0.15**

Each value represents the mean±SE of 8 mice. $^{**}p<0.01$ and $^{***}p<0.001$ statistically significant difference between non-diabetic and diabetic mice (Student's *t*-test or Aspin–Welch's *t*-test).

2.5. Spontaneous locomotor activity

Spontaneous locomotor activity of mouse was measured by a digital counter with an infrared sensor (NS-AS01, Neuroscience Inc., Tokyo, Japan). The apparatus detects the movement of animals on the basis of released infrared rays associated with their temperature, and records a digital count. Mice were placed individually in a transparent plastic cage (27×17×13 cm), a transparent plastic ceiling was installed, and an infrared sensor was placed at the center of the ceiling. Total activity counts were automatically recorded for 10 min according to the measurement period in the tail suspension test. Leptin was injected i.p. 30 min before testing. WAY-100635 and LY53,857 were injected s.c. 60 min before testing.

2.6. Statistics

Data were expressed as means with SE. The statistical significance of differences between groups was assessed by one-way and two-way analysis of variance (ANOVA) for factorial comparisons and by the Dunnett's test for multiple comparisons. Student's *t*-test or Aspin–Welch's *t*-test were used to evaluate differences between two groups. Significance was accepted at $p<0.05$.

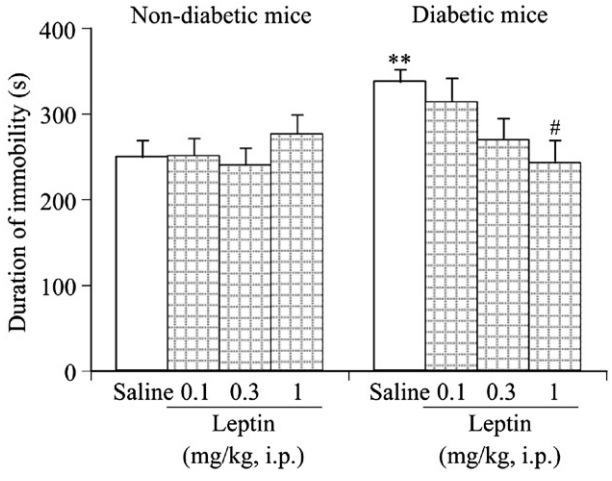

Fig. 1. Effect of leptin on the duration of immobility in the tail suspension test in non-diabetic and diabetic mice. Each column represents the mean±SE of 9–10 mice. $^{**}p<0.01$ vs. saline-treated non-diabetic mice (Student's *t*-test). $^{\#}p<0.05$ vs. respective saline-treated group (Dunnett's test). Two-way ANOVA values: diabetes [$F(1,68)=5.315$, $p<0.05$], leptin [$F(3,68)=1.397$, $p=0.25$], diabetes×leptin interaction [$F(3,68)=2.678$, $p=0.05$].

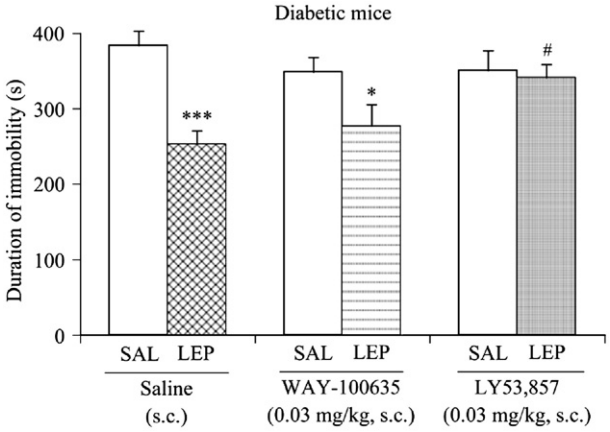

Fig. 2. Effects of LY53,857 and WAY-100635 on the anti-immobility effect of leptin (LEP; 1 mg/kg, i.p.) in diabetic mice. Each column represents the mean±SE of 8–10 mice. $^{*}p<0.05$ and $^{***}p<0.001$ vs. respective saline (SAL)-treated group (Student's *t*-test). $^{\#}p<0.05$ vs. SAL plus LEP-treated group (Dunnett's test). Two-way ANOVA values: leptin treatment [$F(1,46)=15.462$, $p<0.001$], antagonist treatment [$F(2,46)=1.351$, $p=0.27$], leptin×antagonist interaction [$F(2,46)=3.776$, $p<0.05$].

3. Results

3.1. Effects of STZ-induced diabetes on body weight, blood glucose level, plasma insulin level and plasma leptin level in mice

As shown in Table 1, body weight was significantly decreased by diabetes. Blood glucose level was significantly increased in diabetic mice. Plasma insulin level and plasma leptin level were significantly decreased in diabetic mice.

3.2. Effect of leptin on the duration of immobility in the tail suspension test in non-diabetic and diabetic mice

Treatment with leptin (0.1–1 mg/kg, i.p.) dose-dependently and significantly suppressed the duration of immobility in diabetic mice to the same levels observed in non-diabetic mice. On the other hand, leptin (0.1–1 mg/kg, i.p.) had no significant effect on the duration of immobility in non-diabetic mice (Fig. 1).

3.3. Effects of WAY-100635 and LY53,857 on the anti-immobility effect of leptin in diabetic mice

WAY-100635 (0.03 mg/kg, s.c.) or LY53,857 (0.03 mg/kg, s.c.) administered alone did not affect the duration of immobility in

Table 2
Effect of leptin on spontaneous locomotor activity in non-diabetic and diabetic mice

Drugs	Locomotor activity (counts)	
	Non-diabetic mice	Diabetic mice
Saline (i.p.)	342.2±22.6	342.3±23.8
Leptin (1 mg/kg, i.p.)	344.8±24.0	309.1±33.0

Data represent the mean±SE of 10 mice. There was no significant difference in each group (Student's *t*-test).

Table 3
Effects of WAY-100635 and LY53,857 on spontaneous locomotor activity in diabetic mice

Drugs	Locomotor activity (counts)
	Diabetic mice
Saline (s.c.)	316.6±21.8
WAY-100635 (0.03 mg/kg, s.c.)	307.0±28.1
LY53,857 (0.03 mg/kg, s.c.)	335.4±12.4

Data represent the mean±SE of 5 mice. There was no significant difference in each group (Dunnett's test).

diabetic mice. Pretreatment with LY53,857 (0.03 mg/kg, s.c.) significantly antagonized the anti-immobility effect of leptin. In contrast, pretreatment with WAY-100635 (0.03 mg/kg, s.c.) had no effect on the anti-immobility effect of leptin (Fig. 2).

3.4. Effects of leptin, WAY-100635 and LY53,857 on the spontaneous locomotor activity in non-diabetic and diabetic mice

Leptin (1 mg/kg, i.p.) had no significant effect on the spontaneous locomotor activity in either non-diabetic or diabetic mice (Table 2). In addition, WAY-100635 (0.03 mg/kg, s.c.) and LY53,857 (0.03 mg/kg, s.c.) had no effect on the spontaneous locomotor activity in diabetic mice (Table 3).

4. Discussion

In the present study, we observed the marked hyperglycemia, hypoinsulinemia and hypoleptinemia in STZ-induced diabetic mice. In addition, STZ-induced diabetic mice showed the depressive-like behavior in the tail suspension test. These alterations are consistent with the previous reports (Havel et al., 1998; Sindelar et al., 1999; Kamei et al., 2003; Tsubone et al., 2005). Interestingly, treatment with leptin dose-dependently and significantly suppressed the depressive-like behavior of diabetic mice without affecting on the spontaneous locomotor activity. On the other hand, leptin did not affect either the duration of immobility or the spontaneous locomotor activity in non-diabetic mice. These results indicate that leptin exerts the antidepressant-like effect in only diabetic mice. Recently, Lu et al. (2006) reported that single treatment with leptin exerted the antidepressant-like effect in chronic-stressed rats. These rats demonstrated low level of circulating leptin. They suggest that there is the relationship between hypoleptinemia and depressive-like state. Based on their findings, we suggest the possibility that the depressive-like behavior of STZ-induced diabetic mice is associated with their hypoleptinemic state.

We further investigated the role of 5-HT_{1A} and 5-HT_2 receptors on the antidepressant-like effect of leptin in diabetic mice. It is well accepted that 5-HT_{1A} receptors and 5-HT_{2C} receptors are involved in the antidepressant-like effect in the animal model of depression (Cryan and Lucki 2000; Mayorga et al. 2001). We previously reported that the antidepressant-like effect of fluoxetine in diabetic mice was mediated by the activation of 5-HT_2 receptors, but not 5-HT_{1A} receptors, in the tail suspension test (Miyata et al. 2004). In this study, we observed that the antidepressant-like effect of leptin in diabetic mice was significantly antagonized by inhibition of 5-HT_2 receptors, but not by inhibition of 5-HT_{1A} receptors. Therefore, we suggest that leptin exerts the antidepressant-like effect in diabetic mice mediated, at least in part, via 5-HT_2 receptors.

In the rat microdialysis studies, the extracellular 5-HT levels in the hypothalamus and the hippocampus are decreased by STZ-induced diabetes (Shimizu, 1991; Ohtani et al. 1997; Yamato et al. 2004). Therefore, leptin may activate 5-HT neurons in the central nervous system of diabetic mice, and this effect may exert the antidepressant-like effect. Because we previously reported that the antidepressant-like effect mediated by the activation of 5-HT_{1A} receptors was attenuated in STZ-induced diabetic mice in the tail suspension test (Miyata et al. 2004), this speculation is reasonable to explain our present findings. Several lines of evidence indicate that leptin regulates a wide range of neurotransmitters not only 5-HT. For example, leptin enhances glutamatergic responses in the central nervous system (Shanley et al., 2001; Irving et al., 2006). Administration of leptin decreases the serum corticosterone levels, hypothalamic noradrenaline, dopamine and 5-HT contents (Clark et al., 2006). Leptin increases expression of brain-derived neurotrophic factor mRNA and protein in the ventromedial hypothalamus (Komori et al., 2006). These neuronal networks may also underlie the antidepressant-like effect of leptin in diabetic mice. Therefore, further studies are necessary before this issue can be resolved unequivocally.

It has been recognized that patients with type 1 and type 2 diabetes have a higher prevalence of depression than the general population (Anderson et al., 2001). Diabetic patients with depression demonstrate poor glycemic control (Lin et al., 2004). In addition, psychiatric problems in diabetic patients are regarded as risk factors for the future development of diabetic complications (de Groot et al., 2001). However, little information is available to resolve this problem. Children with new-onset type 1 diabetes, who did not receive insulin therapy, demonstrate low circulating leptin levels (Hanaki et al., 1999). Subjects with obese and type 2 diabetes exhibit hyperleptinemia possibly associated with leptin resistance (Considine et al., 1996; Segal et al., 1996). Therefore, disruption of leptin signaling might relate to the higher incidence of depressive disorder in diabetes. In addition, improvement of leptin function might ameliorate the psychiatric problems in diabetes.

In conclusion, we suggest that leptin exerts the antidepressant-like effect in diabetic mice mediated, at least in part, via 5-HT_2 receptors.

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