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Effects of the Experimental Diabetes on Dopamine D_1 Receptor-Mediated Locomotor-Enhancing Activity in Mice

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SAITOH, A., K. MORITA, M. SODEYAMA AND J. KAMEI. *Effects of the experimental diabetes on dopamine D_1 receptor-mediated locomotor-enhancing activity in mice.* PHARMACOL BIOCHEM BEHAV **60**(1) 161–166, 1998.—The effects of diabetes on the dopamine-related locomotor-enhancing activities were studied in mice. Although spontaneous locomotor activity in diabetic mice was significantly greater than that in nondiabetic mice, the locomotor-enhancing effects of methamphetamine (4 mg/kg, SC), cocaine (20 mg/kg, SC) and SKF82958 (1 mg/kg, SC), a selective dopamine D_1-receptor agonist, in diabetic mice were significantly lower than those in nondiabetic mice. When dopamine level in the whole brain was reduced by pretreatment with 6-hydroxydopamine (6-OHDA), spontaneous locomotor activity was significantly reduced in both nondiabetic and diabetic mice. There was no significant difference in the total spontaneous locomotor activity counts within 3 h between 6-OHDA–treated nondiabetic and 6-OHDA–treated diabetic mice. Furthermore, the locomotor-enhancing effect of SKF82958 in 6-OHDA–treated diabetic mice was also significantly lower than that in 6-OHDA–treated nondiabetic mice. In a binding assay, the B_{max} values of [^{3}H]SCH23390 binding to whole-brain membranes of diabetic mice were significantly lower than those in nondiabetic mice. However, there was no significant difference in the K_d values between nondiabetic and diabetic mice. These results suggest that the decreased density of dopamine D_1 receptors in diabetic mice may result in hyporesponsiveness to dopamine-related locomotor enhancement. © 1998 Elsevier Science Inc.

Methamphetamine Cocaine SKF82958 Locomotor activity Diabetic mice Dopamine D_1 receptor

DIABETIC mellitus is a widespread illness that often results in a triad of pathology; neuropathy, retinopathy, and peripheral neuropathy. Although deficits of central nervous system function are more rare, major depression, phobic disorders, and antisocial personality disorder have been shown to occur in diabetes at higher rates than in the general population (24), and it has been suggested that these psychiatric disorders can be corrected with glucose control (22). Moreover, it has been reported that cognitive deficits are sometimes associated with the diabetic state (26). The mechanisms through which diabetes may contribute to the development of, or be a risk factor for, psychiatric disorders are not clear. It has been suggested that psychiatric disorders associated with dopaminergic dysfunction in the central nervous systems [e.g., (11)]. The study of the effects of diabetes on the dopaminergic functions may find a clue to clarify the mechanisms of the development of psychiatric disorders in diabetic state.

Dopamine is one of the principal neurotransmitters in major neural systems of the brain (5,20). The mesolimbic pathway originates from dopamine-synthesizing neurons in the midbrain ventral tegmental area and innervates to the ventral striatum, nucleus accumbens, and olfactory tubercle. This system is thought to influence motivated behaviors, including activity related to reward or discrimination (17–19). Furthermore, many behavioral studies have shown evidence that the mesolimbic dopamine system plays an important role in regulating of exploratory and locomotor behavior (6,7). On the other hand, some studies have demonstrated the existence of two dopamine receptor classes, which have been referred to as D_1-like (D_1A and D_5 or D_1B) and D_2-like (D_2, D_3, and D_4)

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receptors (1,8). Several studies have indicated that expression of hyperlocomotion related to dopamine transmission. Both the D_1 and D_2 receptor subfamilies have been suggested to mediated behavior responses. Antagonists of D_1 and D_2 receptors have been shown to block several well-characterized behaviors, including locomotor hyperactivity (17,18). Interestingly, activation of dopamine D_1 receptors is required for the full expression of D_2 dopamine receptor-mediated behavioral responses in normal animals (3,21).

Our previous report indicated that spontaneous locomotor activity in diabetic mice was significantly greater than that in nondiabetic mice. Furthermore, haloperidol and SCH23390, a selective dopamine D_1 receptor antagonist, significantly reduced spontaneous locomotor activity in diabetic mice, but not in nondiabetic mice (13). Moreover, the rate of dopamine turnover in the limbic forebrain in diabetic mice was significantly higher than that in nondiabetic mice (13). These results support the idea that enhancement, rather than reduction, of neurotransmission in mesolimbic dopamine systems may occur in diabetic mice compared with that in nondiabetic mice. Many studies have now demonstrated that the mesolimbic dopamine system has an important role in the mediation of the locomotor-enhancing action of psychomotor stimulants, such as amphetamine, methamphetamine, and cocaine. In addition to the alteration in the dopamine turnover, receptor density alteration my occur concurrently in the limbic forebrain of then diabetic mice. Furthermore, functional abnormalities in mesolimbic dopamine systems of diabetic mice may alter the locomotor-enhancing action of psychomotor stimulants. To test this hypothesis, we examined the effect of diabetes on locomotor-enhancing effects of methamphetamine and cocaine in mice.

METHOD

Animals

Male ICR mice (Tokyo Animal Laboratory Inc., Tokyo, Japan), weighing about 20 g at the beginning of the experiments, were used. They had free access to food and water in an animal room that was maintained at 22 ± 1°C with a 12-L: 12-D cycle. Animals were rendered diabetic by an injection of streptozotocin (STZ; 200 mg/kg, IV) prepared in 0.1 N citrate buffer at pH 4.5. Age-matched naive mice were injected with the vehicle alone. The experiments were conducted 2 weeks after injection of STZ or vehicle. Mice with serum glucose levels above 400 mg/dl were considered diabetic. This study was carried out in accordance with the Declaration of Helsinki and/or 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.

Locomotor Activity

The locomotor activity of mice was measured by an ambulometer (ANB-M20, O'hara Co., Tokyo). The principle of the device and the measurement method have been described by Hirabayashi and Alam (9). Briefly, a mouse was placed in a tilting-type round activity cage 20 cm in diameter and 19 cm high. Any slight tilt of the activity cage, which was caused by horizontal movement of the animals, was detected by microswitches. Total activity counts during each 10-min period were automatically recorded for 30 min prior to the injection, and for 180 min following the administration of saline or drugs. Mice were placed in the tilting cages for a habituation period of 30 min, after which they were injected with SC saline or drugs. The locomotor activity of mice was measured between 1300–1700 h. After the end of behavioral test, the mice were decapitated under ether anesthesia and blood sample was rapidly corrected. Serum glucose levels was estimated by the *o*-toluidine methods (4).

Radioligand Binding Assay

The mice were decapitated under ether anesthesia and the brain was rapidly removed. The whole brain tissue was kept frozen at −80°C until use. Tissue were homogenized in 10 vol of ice-cold 0.32 M sucrose solution with a tissue homogenizer (Polyttron, PT-10, Kinematica) and centrifuged at 900 × *g* for 10 min. The supernatant was recentrifuged at 11,500 3 *g* for 20 min. The pellets were resuspended in buffer and centrifuged at 11,500 3 *g* twice for 20 min. The final pellets were resuspended in buffer (50 nM Tris-HCl, pH 7.4).

Tissue suspension 500 ml, with 380 ml buffer, 10 ml of 10 mM cis-flupentixol (displacer) or H_2O and 10 ml of various concentrations of [^{3}H]SCH23390 ranging from 15 to 2000 pM were incubated together at 25°C for 120 min. The incubation was terminated by a rapid vacuum filtration using a Whatman GF/C glass filters. The filters were washed three times with 4 ml of buffer. The radioactivity of the filters was measured in a liquid scintillation counter. The specific binding of [^{3}H]SCH23390 was about 90% of the total binding. The B_{max} and K_d value were calculated individually for each mouse by Scatchard analysis for six to eight concentrations of the ligands; the assays were performed in duplicate.

Drugs

The drugs used in this study were methamphetamine hydrochloride (Dainippon Pharmaceutical Co., Osaka, Japan), cocaine hydrochloride (Takeda Pharmaceutical Industries, Inc., Osaka, Japan), 6-hydroxydopamine (6-OHDA, Sigma Chemical Co., St. Louis, MO), desipramine hydrochloride (Sigma Chemical Co.), SKF82958 hydrobromide (Sigma Chemical Co.), and [^{3}H]SCH23390 (Amersham Laboratories, Buckinghamshire, UK., 3.7 MBq). 6-OHDA was dissolved in 0.9% NaCl containing 10 mM ascorbic acid. Other drugs were dissolved in 0.9% NaCl. All doses refer to the salt forms of the drugs.

To distract the presynaptic dopaminergic neurons, 6-OHDA was pretreated according to the method of Narita et al. (23). Mice were treated with 6-OHDA (25 mg, ICV) 72 h prior to the experiment. Additionally, desipramine (25 mg/kg, SC) was given to mice 10 min prior to the 6-OHDA to block the uptake of 6-OHDA into noradrenergic terminals (23).

Statistics

Behavioral data (total activity counts) and binding data (B_{max} and K_d value) were statistically evaluated with a one-way repeated measures analysis of variance (ANOVA) followed by a Dunnett's test for multiple comparisons.

RESULTS

The body weights of diabetic mice (24.8 ± 0.3 g, n = 124) were significantly reduced when compared with those of nondiabetic mice (33.7 ± 0.6 g, n = 128). Serum glucose levels in diabetic mice (562.8 ± 9.6 mg/dl, n = 124) were significantly elevated when compared with those in nondiabetic mice (185.3 ± 3.7 mg/dl, n = 128).

Effects of Methamphetamine, Cocaine, and SKF82958 on Locomotor Activity

The mean total activity counts of SC saline-treated diabetic mice was significantly greater than that of nondiabetic mice [diabetic mice, 706.8 ± 145.9 counts/3 h, $n = 10$; nondiabetic mice, 177.1 ± 50.8 counts/3 h, $n = 10$, $F(1, 19) = 11.76$, $p < 0.01$]. Methamphetamine, at doses of 1–4 mg/kg, SC, dose dependently increased the total activity counts over 3 h in both nondiabetic and diabetic mice (Fig. 1). As shown in Fig. 1, however, the mean total locomotor activity after SC administration of the highest dose of methamphetamine (4 mg/kg) in nondiabetic mice (3006.8 ± 394.4 counts/3 h, $n = 9$) was significantly greater than that in diabetic mice [1684.3 ± 309.2 counts/3 h, $n = 9$, $F(1, 17) = 6.96$, $p < 0.05$] (Fig. 1).

Cocaine-treated nondiabetic mice also showed a dose-dependent increase in locomotor activity. However, diabetic mice failed to exhibit locomotor hyperactivity following treatment with cocaine over a wide range of doses (Fig. 2). Furthermore, the mean total locomotor activity counts after SC administration of the highest dose of cocaine (20 mg/kg) in diabetic mice (776.8 ± 102.9 counts/3 h, $n = 9$) was significantly less than that in nondiabetic mice [1305.3 ± 152.7 counts/3 h, $n = 9$, $F(1, 23) = 8.86$, $p < 0.01$] (Fig. 2).

As shown in Fig. 3, SKF82958, a selective dopamine D_1-receptor agonist, increased the total locomotor activity counts over 3 h in a dose-dependent manner in nondiabetic mice. However, SKF82958 had no significant effect on the total locomotor activity counts in diabetic mice (Fig. 3). The mean total locomotor activity counts after SC administration of SKF82958 (1 mg/kg) in nondiabetic mice (1720.4 ± 152.6 counts/3 h, $n = 10$) was significantly greater than that in diabetic mice [1008.9 ± 131.6 counts/3 h, $n = 9$, $F(1, 19) = 9.63$, $p < 0.01$] (Fig. 3).

In the present study, there was no significant differences in the onset times of the locomotor-enhancing effect of methamphetamine, cocaine, and SKF82958 between nondiabetic and diabetic mice (data not shown).

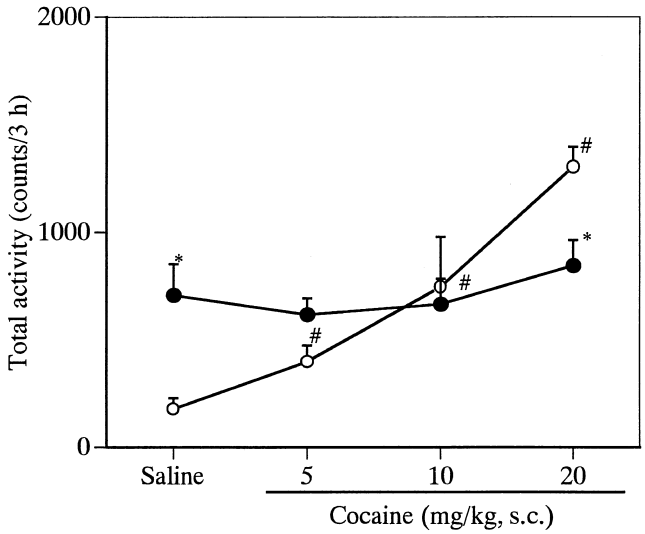

FIG. 2. Effects of cocaine (5, 10, and 20 mg/kg) on spontaneous locomotor activity in nondiabetic (open circle) and diabetic (closed circle) mice. Each point represents the mean total locomotor activity counts ± SE of 8–10 animals for 3 h after SC administration of cocaine. #$p < 0.05$ compared with the respective saline-treated group. *$p < 0.05$ compared with the value of nondiabetic mice.

Effect of 6-OHDA Treatment on the Spontaneous Locomotor Activity and SKF82958-Induced Hyperlocomotion

Figure 4 shows the effects of pretreatment with 6-OHDA on the spontaneous locomotor activity and SKF82958-

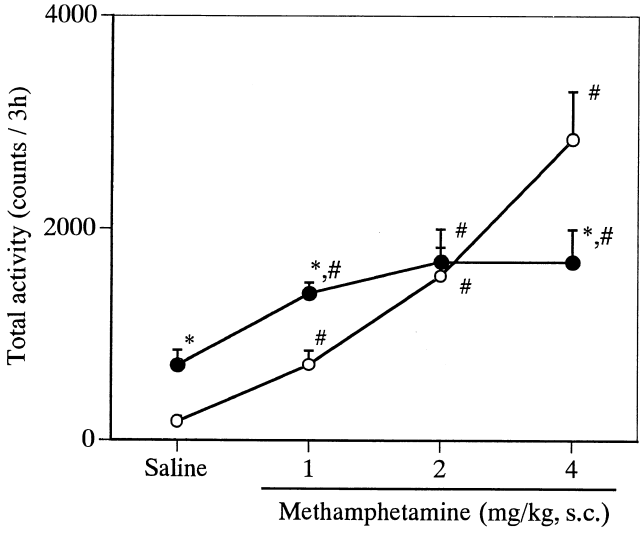

FIG. 1. Effects of methamphetamine (1, 2, and 4 mg/kg) on spontaneous locomotor activity in nondiabetic (open circle) and diabetic (closed circle) mice. Each point represents the mean total locomotor activity counts ± SE of 8–10 animals for 3 h after SC administration of methamphetamine. #$p < 0.05$ compared with the respective saline-treated group. *$p < 0.05$ compared with the value of nondiabetic mice.

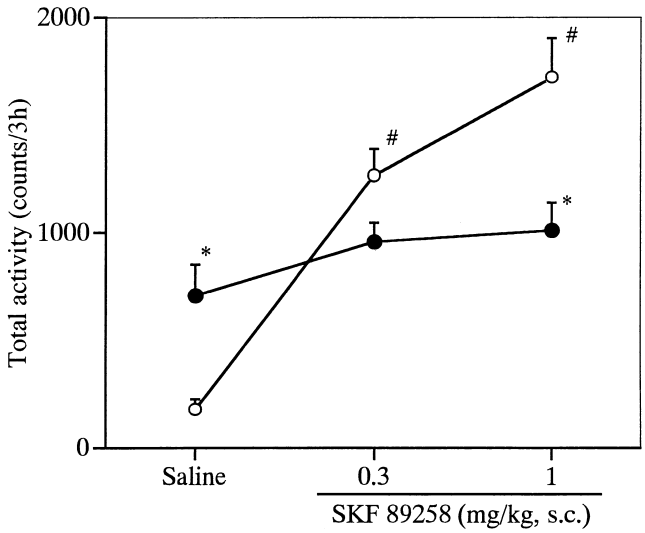

FIG. 3. Effects of SKF82958 on spontaneous locomotor activity in nondiabetic (open circle) and diabetic (closed circle) mice. Each point represents the mean total locomotor activity counts ± SE of 8–10 animals for 3 h after SKF82958 treatment. #$p < 0.05$ compared with the respective saline-treated group. *$p < 0.05$ compared with the value of nondiabetic mice.

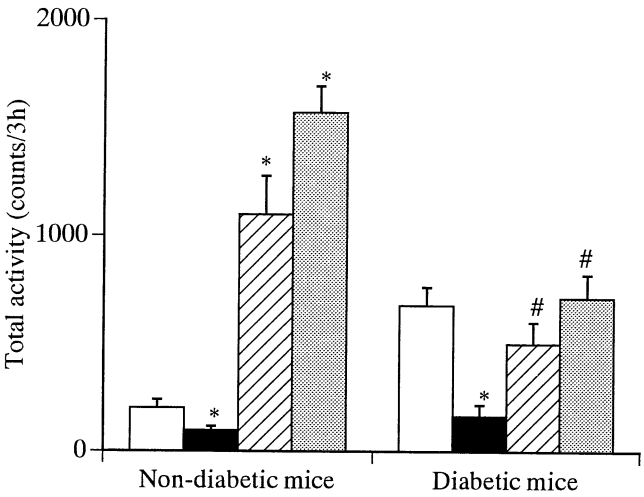

FIG. 4. Effects of SKF82958 (0.3 mg/kg, SC, hatched column; 1 mg/kg, SC, dotted column) on spontaneous locomotor activity in 6-OHDA (25 μg, ICV)-treated nondiabetic and 6-OHDA–treated diabetic mice. Each column represents the mean total locomotor activity counts ± SE of 9–10 animals for 3 h after SKF82958 treatment. *$p <$ 0.05 compared with the respective saline-treated group (open column). #$p < 0.05$ compared with the respective value of SKF82958-induced locomotor activity in 6-OHDA–treated animals (closed column).

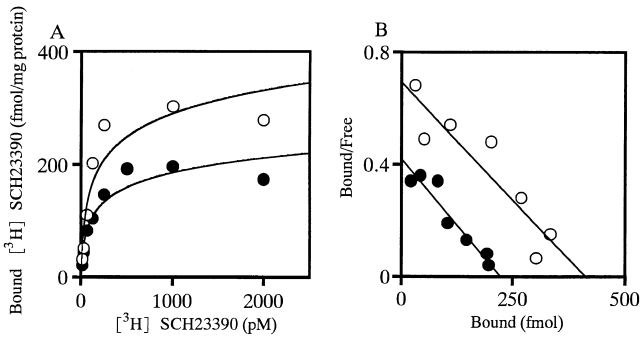

FIG. 5. Typical saturation curves (A) and Scatchard plot (B) for the specific binding of [3H]SCH23390 to whole brain membranes in nondiabetic (open circle) and diabetic (closed circle) mice.

induced hyperlocomotion in both diabetic and nondiabetic mice. 6-OHDA lesion significantly decreased the spontaneous locomotor activity counts in both nondiabetic mice [vehicle, 201.7 ± 37.3 counts/3 h, $n = 10$; 6-OHDA, 96.3 ± 20.6 counts/3 h, $n = 10$, $F(1, 18) = 6.46$, $p < 0.05$] and diabetic mice [vehicle, 679.0 ± 84.6 counts/3 h, $n = 10$; 6-OHDA, 162.3 ± 52.5 counts/3 h, $n = 10$, $F(1, 18) = 28.16$, $p < 0.01$]. There was no significant difference in spontaneous locomotor activity counts between 6-OHDA–treated nondiabetic mice and 6-OHDA–treated diabetic mice. SKF82958 increased the total locomotor activity counts over 3 h in a dose-dependent manner in both 6-OHDA–treated nondiabetic mice and 6-OHDA–treated diabetic mice. However, SKF82958-induced locomotor activity in 6-OHDA–treated diabetic mice (0.3 mg/kg, 502.1 ± 98.0 counts/3 h, $n = 9$; 1 mg/kg, 713.9 ± 106.9 counts/3 h, $n = 9$) was significantly less than that in 6-OHDA–treated nondiabetic mice [0.3 mg/kg, 1099.8 ± 179.2 counts/3 h, $n = 9$; 1 mg/kg, 1572.0 ± 121.9 counts/3 h, $n = 8$, $F(1, 18) = 28.25$, $p < 0.01$] (Fig. 4).

In Vitro [3H]SCH23390 Binding Assay

In binding assays, the saturable, specific binding of [3H]SCH 23390 was observed in all experiments performed in both nondiabetic and diabetic mice. Figure 5 shows a typical experiment. Nonspecific binding accounted for about 10% of the total binding. The K_d values of [3H]SCH23390 binding to the whole-brain membranes of nondiabetic and diabetic mice were not significantly different. In contrast, the B_{max} values of [3H]SCH23390 binding to whole-brain membranes of diabetic mice were significantly, $F(1, 9) = 6.46$, $p < 0.05$, lower than those of nondiabetic mice (Table 1).

DISCUSSION

Our previous reports (13–16) and the present study indicate that spontaneous locomotor activity in diabetic mice is significantly greater than that in nondiabetic mice. Previously, haloperidol and SCH23390, a selective dopamine D_1 receptor antagonist, significantly reduced the spontaneous locomotor activity in diabetic mice to the same level as that in nondiabetic mice (13). Furthermore, the rate of dopamine turnover in the limbic forebrain in diabetic mice was significantly higher than that in nondiabetic mice (13). Based on these results, we concluded that the enhanced spontaneous locomotor activity in diabetic mice may result from increased dopamine neurotransmission, which might be due to an increase in dopamine release from presynaptic dopamine neurons. In this study, pretreatment with 6-OHDA significantly decreased spontaneous locomotor activity in both nondiabetic mice and diabetic mice. There was no significant difference in spontaneous locomotor activity counts between 6-OHDA–treated nondiabetic mice and 6-OHDA–treated diabetic mice. It is well known that 6-OHDA lesions to the mesolimbic dopamine system can reduce the activation produced by a variety of environmental and intracerebral manipulations (6,10,12). The fact that spontaneous locomotor activity was reduced in both nondiabetic and diabetic mice following pretreatment with 6-OHDA may be closely associated with mesolimbic dopamine systems. Therefore, the results of this study strongly support our previous hypothesis that diabetic mice may exhibit enhanced dopamine neurotransmission, perhaps due to an increase in dopamine release from presynaptic nerve terminals, relative to that in nondiabetic mice.

It is well known that the activation of postsynaptic dopamine D_1 receptor subtypes in the mesolimbic dopamine system plays an important role in the expression of hyperlocomotion in mice (2,7). The present study demonstrated that

TABLE 1

EFFECTS OF DIABETES ON THE SPECIFIC BINDING OF [3H]SCH23390 TO MOUSE WHOLE-BRAIN MEMBRANES

	Bmax (fmol/mg Protein)	K_d (pM)	n*
Nondiabetic mice	292.8 ± 28.6	651.2 ± 77.2	5
Diabetic mice	191.9 ± 18.2†	486.7 ± 62.6	5

The number of binding sites, B_{max} (mean ± SE), and the binding affinity constant, K_d (mean ± SE), were calculated separately for each mice by Scatchard analysis.

*n = number of Scatchard plots.

†$p < 0.05$ vs. nondiabetic mice.

methamphetamine, cocaine and SKF82958 increased locomotor activity in nondiabetic mice in a dose-dependent manner. The locomotor-enhancing effects of these drugs were significantly lower in diabetic mice than in nondiabetic mice. Indeed, cocaine and SKF82958 had no significant locomotor-enhancing effect in diabetic mice. It is possible that enhanced spontaneous locomotor activity in diabetic mice, i.e., an increase in dopamine release from presynaptic dopamine neurons overshadows the locomotor-enhancing effects of dopamine agonists, such as methamphetamine, cocaine and SKF82958. To test this possibility, we examined the effect of SKF82958 on the locomotor activity in 6-OHDA-treated mice, which would exclude the influence of dopamine release from presynaptic dopamine nerve terminals. SKF82958 increased total locomotor activity counts over 3 h in a dose-dependent manner in both nondiabetic and diabetic mice. However, SKF82958-induced locomotor activity in diabetic mice, at a dose of either 0.3 or 1.0 mg/kg, SC, was significantly less than that in nondiabetic mice. Based on these results, we conclude that diabetic mice are hyporesponsive to postsynaptic dopamine D_1 receptor-mediated locomotor-enhancing action. In addition, the binding of [^{3}H]SCH23390, a specific dopamine D_1 receptor ligand, to whole-brain membranes of diabetic mice was also examined. The affinity of [^{3}H]SCH23390 binding to dopamine D_1 receptors in whole brain did not change in diabetic mice during 2 weeks course of diabetes. Contrary to that, the B_{max} values showed a decreased whole-brain dopamine D_1-receptor density in diabetic mice, compared to that in nondiabetic mice. Thus, it is likely that the hyporesponsiveness to dopamine D_1 receptor-mediated locomotor-enhancing effects in diabetic mice may be due to impaired postsynaptic dopamine D_1-receptor function in the limbic forebrain.

We found that methamphetamine produced a significant locomotor-enhancing effect in diabetic mice. In contrast, cocaine had no significant effect on the locomotor activity in diabetic mice. It is well known that methamphetamine increases synaptic concentrations of dopamine by inhibiting its uptake into neurons and enhancing its release from interneuronal stores, whereas cocaine increases synaptic concentrations of dopamine simply by inhibiting its uptake. Thus, it is likely that the inhibition of dopamine uptake along with enhancement of the release of dopamine by methamphetamine may account for the discrepancy in the locomotor-enhancing effects in diabetic mice between methamphetamine and cocaine, because an increase in dopamine release from presynaptic nerve terminals occurred in diabetic mice. However, further studies are necessary before this issue can be resolved with greater certainty.

Xu et al. (30,31) reported that cocaine did not have a locomotor-enhancing effect in dopamine D_1-receptor mutant mice, whereas the spontaneous locomotor activity in dopamine D_1-receptor mutant mice was significantly greater than that in the wild type. Based on these results, they suggested that dopamine D_1-receptor mutant mice showed enhanced basal levels of locomotion because a reduction in dopamine D_1 receptor-mediated dopamine transmission in other limbic and cortical areas relieved the normal inhibitory influence of these structures on locomotor activity. Considerable evidence supports this suggestion that dopamine D_1 receptor neurotransmission within the prefrontal cortex and amygdala regulates dopamine neurotransmission within the nucleus accumbens (25,27–29) In this study, we found that dysfunction of dopamine D_1 receptor occurred at supraspinal levels in diabetes. These results led us to propose the possibility that heightened spontaneous locomotor activity in diabetic mice may be due to a coordinated lack of dopamine D_1 receptor-mediated neurotransmission throughout the mesocorticolimbic dopamine system, which may result from a decreased density of dopamine D_1 receptors in diabetic mice. Further studies are necessary before this possibility can be established with greater certainty.

In conclusion, the present results suggest that a decreased density of dopamine D_1 receptors in diabetic mice may result in hyporesponsiveness to dopamine-related locomotor enhancement.

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