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Effects of diabetes on methamphetamine-induced place preference in mice

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Abstract

The effects of diabetes on methamphetamine-induced place preference in mice were examined. Methamphetamine caused a dose-dependent place preference in both diabetic and non-diabetic mice. Methamphetamine preferentially induced place preference in diabetic mice as compared to those in non-diabetic mice. Indeed, methamphetamine-induced place preference at a dose of 0.3 mg/kg in diabetic mice was similar to that at 3 mg/kg in non-diabetic mice. Furthermore, methamphetamine-induced place preference in both diabetic and non-diabetic mice was significantly antagonized by pretreatment with quinpirole, a dopamine D_2/D_3 receptor agonist. Methamphetamine-induced place preference was also antagonized by pretreatment with 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT), a selective dopamine D_3 receptor agonist. On the other hand, 7-OH-DPAT produced significant place aversion in non-diabetic mice. 7-OH-DPAT produced neither place preference nor place aversion in diabetic mice. These results suggest that methamphetamine-induced place preference may be modulated by dopamine D_3 receptors. Furthermore, increased dopamine neurotransmission associated with the down-regulation of presynaptic dopamine D_3 receptor-mediated functions may account for the enhancement of methamphetamine's reinforcing effect in diabetic mice.

Keywords: Diabetes; Methamphetamine; Place preference; Dopamine D_3 receptor; Mesolimbic dopamine system; 7-OH-DPAT (7-hydroxy-2-(di-*n*-propylamino)tetralin)

1. Introduction

The conditioned place preference paradigm is a reliable technique for measuring the reinforcing properties of drugs, and is particularly useful for evaluating the reinforcing effects of psychostimulants such as methamphetamine and amphetamine. The conditioned place preference paradigm was recently used to demonstrate that morphine has a strong conditioning effect in mice as well as rats (Suzuki et al., 1993). Moreover, an additional important feature of the conditioned place preference paradigm is that both agonist and antagonists can be evaluated without any complicating behavioral motor effects (Hoffman, 1989).

It has been reported that the psychostimulant-induced place preference is abolished by pretreatment with dopamine receptor antagonists. Indeed, amphetamine-induced place preference was antagonized by pretreatment with haloperidol, a dopamine receptor antagonist (Spyraki et al., 1982), or 7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SCH23390), a selective dopamine D_1 receptor antagonist (Leone and Di Chiara, 1987). Furthermore, microinjection of (+)-amphetamine into the nucleus accumbens resulted in a place preference (Carr and White, 1986). Moreover, amphetamine increases extracellular dopamine in various terminal dopamine areas, as estimated by brain microdialysis studies in freely moving rats (Di Chiara and Imperato, 1988). Based on these results, Di Chiara (1995) proposed that enhanced dopamine release from the nucleus accumbens may play a critical role in the acquisition and expression of psychic dependence on drugs of abuse.

Dopamine D_3 receptors are part of the dopamine D_2-like receptor family (Sokoloff et al., 1990; Seeman and Van Tol, 1994). Dopamine D_3 receptors are found mainly in limbic regions of the brain, and are involved in cognition, emotion and endocrine functions (Lévesque et al., 1992).

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The dopamine receptor agonist 7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin (7-OH-DPAT) reportedly has a 50- to 100-fold higher affinity for dopamine D_3 receptors than dopamine D_2 receptors in genetically transfected cells (Lévesque et al., 1992). Thus, 7-OH-DPAT has been used to investigate possible dopamine D_3 receptor-mediated functions. Recent evidence has suggested that dopamine D_3 receptors may modulate the reinforcing effects of cocaine and morphine. Since the self-administration of cocaine in rats was decreased by co-administration of 7-OH-DPAT, Caine and Koob (1993) suggested that preferential stimulation of dopamine D_3 receptors by a low dose of 7-OH-DPAT may modulate the reinforcing properties of cocaine. Furthermore, Suzuki et al. (1995) reported that morphine-induced hyperlocomotion was attenuated by pretreatment with 7-OH-DPAT. They also indicated that the morphine-induced increase in the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in the limbic forebrain (nucleus accumbens and olfactory tubercle) was attenuated by 7-OH-DPAT. These results suggest that the activation of the presynaptic dopamine D_3 receptors in the mesolimbic dopamine system may attenuate the expression of morphine-induced hyperlocomotion. Moreover, it has been reported that the acquisition and expression of the morphine-induced place preference are antagonized by pretreatment with 7-OH-DPAT (Fonseca et al., 1995). These results suggest that the activation of dopamine D_3 receptors attenuates the rewarding properties of opioids.

We recently reported that spontaneous locomotor activity in diabetic mice was significantly greater than that in non-diabetic mice (Kamei et al., 1994). Furthermore, haloperidol and SCH23390, a selective dopamine D_1 receptor antagonist, significantly reduced spontaneous locomotor activity in diabetic mice, but not in non-diabetic mice (Kamei et al., 1994). Moreover, dopamine turnover (DOPAC + HVA/dopamine) in the limbic forebrain in diabetic mice was significantly higher than that in non-diabetic mice (Kamei et al., 1994). These results led us to propose the possibility that neurotransmission in mesolimbic dopamine systems may be enhanced, rather than reduced, in diabetic mice relative to that in non-diabetic mice (Kamei et al., 1994). Moreover, we recently reported that morphine-induced place preference in diabetic mice was stronger than that in non-diabetic mice (Kamei et al., 1995). Based on these results, we suggested that the enhanced morphine-induced place preference in diabetic mice may reflect the enhanced dopamine transmission in the mesolimbic dopamine system in diabetic mice (Kamei et al., 1995). Thus, it is possible that methamphetamine-induced place preference, like morphine-induced place preference, may be greater in diabetic mice than in non-diabetic mice.

Thus, the aim of the present study was to compare methamphetamine-induced place preference in diabetic and non-diabetic mice to clarify our hypothesis that functional abnormalities in mesolimbic dopamine systems, especially dopamine D_3 receptor function, in diabetic mice may alter the reinforcing effect of methamphetamine.

2. Materials and methods

2.1. Animals

Male ICR mice (Tokyo Laboratory Animals Science, 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 which was maintained at 22 ± 1°C with a 12-h light-dark cycle. Animals were rendered diabetic by an injection of streptozotocin (200 mg/kg, i.v.) prepared in 0.1 N citrate buffer at pH 4.5. Age-matched non-diabetic mice were injected with vehicle alone. The experiments were conducted 2 weeks after injection of streptozotocin 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.

2.2. Place conditioning

Place conditioning was conducted as previously described using a minor modification of an unbiased procedure (Suzuki et al., 1990). The apparatus used was a shuttle box (15 × 30 × 15 cm: w × l × h) which was divided into two compartments of equal size. One compartment was white with a textured floor and the other was black with a smooth floor. For conditioning, mice were confined to one compartment after drug injections and to the other compartment after saline injections. Conditioning session consisted of 6 alternate day injections of drug or vehicle (saline). Immediately following drug injection, mice were confined to one compartment. Following vehicle injections they were confined to the other compartment. Treatment compartment and the presentation order of drug and vehicle were counterbalanced for each drug dose. Conditioning sessions were 60 min in duration. On day 7, tests of conditioning were performed as follows: the partition separating the two compartments was raised to 7 cm above the floor, and a neutral platform was inserted along the seam separating the compartments. The time spent in each compartment during a 900-s session was then measured in a blinded fashion by an infrared beam sensor (KN-80, Natume, Tokyo, Japan). The position of the mouse was defined by the position of its body. All sessions were conducted under conditions of dim illumination and masking white noise.

2.3. Drugs

Streptozotocin was purchased from Sigma (St. Louis, MO, USA). Methamphetamine hydrochloride was purchased from Dainippon Seiyaku (Tokyo, Japan). 7-OH-DPAT {(±)-7-hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin} and quinpirole (trans-(−)-4a*R*-4a,5,6,7,8,8a,9-octahydro-5-propyl-1*H*-pyrazolo[3,4*g*]quinoline) were purchased from Research Biochemicals, Natick, MA, USA). Streptozotocin was dissolved in 0.1 N citrate buffer. Other drugs were dissolved in sterile 0.9% NaCl solution. 7-OH-DPAT was injected s.c. at 10 min before methamphetamine injection. Quinpirole was injected i.c.v. 10 min before methamphetamine administration. Intracerebroventricular (i.c.v.) administration (5 μl/mouse) was performed according to the method described by Haley and McCormick (1957) using a 50 μl Hamilton syringe. Each antagonist was injected before each conditioning session for methamphetamine. The dose, route and schedule for quinpirole and 7-OH-DPAT in this study were determined as described previously (Kamei and Saitoh, 1996a; Funada et al., 1995).

2.4. Data analysis

Conditioning scores represent the time spent in the drug-paired place minus the time spent in the vehicle-paired place and are expressed as means ± S.E. Dose-response curves were analyzed using a one-way random factorial analysis of variance and linear regression analysis. The Wilcoxon test was used to determine whether individual doses produced a significant conditioning ($^{*}P < 0.05$).

3. Results

3.1. Effects of diabetes on methamphetamine-induced place preference

As shown in Fig. 1, none of the mice that received saline in conditioning sessions exhibited a significant preference for either compartment of the test box. The mean conditioning scores were −2.0 ± 33.8 s ($n = 8$) for non-diabetic mice and −1.3 ± 47.5 s ($n = 8$) for diabetic mice. The place conditioning produced by methamphetamine is also shown in Fig. 1. In non-diabetic mice, methamphetamine, at dose ranges from 0.3 to 3 mg/kg, s.c., caused a dose-related preference for the drug-associated place, and significant conditioning was observed at doses of 1 and 3 mg/kg. In diabetic mice, methamphetamine (0.1 mg/kg) produced a slight place preference, but this effect was not statistically significant. Significant conditioning was observed at doses of 0.3 mg/kg and 1 mg/kg in diabetic mice. At these doses, all of the diabetic mice exhibited preference for the drug-associated place.

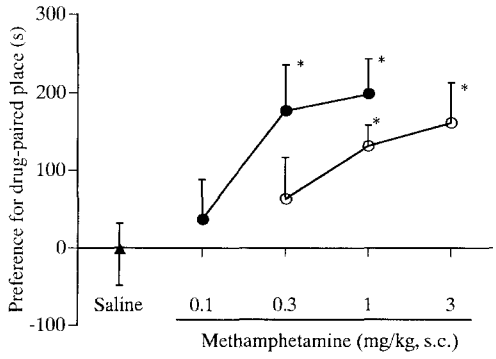

Fig. 1. Place conditioning produced by methamphetamine in diabetic (closed symbol) and non-diabetic (open symbol) mice. Each point represents the mean conditioning score ± S.E. of 8–12 mice. The asterisks denote significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$ vs. respective saline alone (triangle)).

3.2. Effect of quinpirole on methamphetamine-induced place preference

The effect of pretreatment with quinpirole, a dopamine D_2/D_3 receptor agonist, on the place preference produced by methamphetamine is shown in Fig. 2. Methamphetamine (3 mg/kg for non-diabetic mice and 0.3 mg/kg for diabetic mice) following i.c.v. pretreatment with saline produced a significant preference for the drug-paired place in both non-diabetic mice (163.6 ± 51.6 s, $n = 8$) and diabetic mice (166.1 ± 53.5 s, $n = 8$). However, methamphetamine-induced place preference was significantly antagonized by i.c.v. pretreatment with quinpirole (5 nmol) in both non-diabetic and diabetic mice. The mean conditioning score for methamphetamine following pretreatment with quinpirole in non-diabetic and diabetic mice was −12.9 ± 31.6 s ($n = 8$) and 17.8 ± 48.0 s ($n = 12$), respectively.

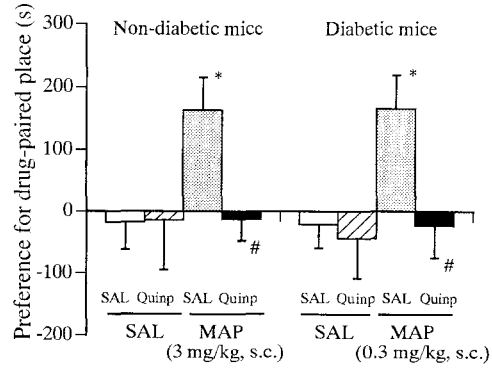

Fig. 2. Effect of quinpirole (Quinp; 5 nmol, i.c.v.) on methamphetamine (MAP)-induced place preference in diabetic and non-diabetic mice. Each column represents the mean conditioning score ± S.E. of 8–12 mice. The asterisks denote significant preference conditioning (Wilcoxon test: $^{*}P < 0.05$ vs. saline (SAL) alone). The sharp denotes a significant difference from methamphetamine alone (Wilcoxon test: $^{\#}P < 0.05$).

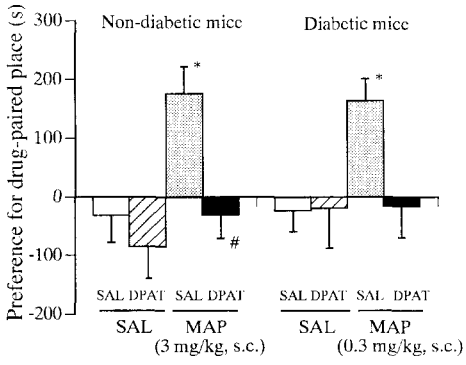

Fig. 3. Effect of 7-OH-DPAT (DPAT; 0.1 mg/kg, s.c.) on methamphetamine (MAP)-induced place preference in diabetic and non-diabetic mice. Each column represents the mean conditioning score ± S.E. of 8–12 mice. The asterisks denote significant preference conditioning (Wilcoxon test: * $P < 0.05$ vs. saline (SAL) alone). The sharp denotes a significant difference from methamphetamine alone (Wilcoxon test: # $P < 0.05$).

3.3. Effect of 7-OH-DPAT on methamphetamine-induced place preference

The effect of 7-OH-DPAT, a selective dopamine D_3 receptor agonist, on methamphetamine-induced place preference is shown in Fig. 3. Methamphetamine (3 mg/kg for non-diabetic mice and 0.3 mg/kg for diabetic mice) following s.c. pretreatment with saline produced a significant preference for the drug-paired place in both non-diabetic mice (176.5 ± 45.0 s, $n = 8$) and diabetic mice (163.6 ± 37.5 s, $n = 8$). This methamphetamine-induced place preference was significantly antagonized by pretreatment with 7-OH-DPAT (0.1 mg/kg) in non-diabetic mice. The mean conditioning score for methamphetamine following pretreatment with 7-OH-DPAT (−31.1 ± 40.0 s, $n = 8$) was significantly ($P < 0.05$) lower than that in saline-pretreated non-diabetic mice. On the other hand, a significant methamphetamine-induced place preference was not observed in 7-OH-DPAT (0.1 mg/kg)-pretreated diabetic mice. However, a statistically significant difference in methamphetamine-induced place preference was not observed between saline-pretreated diabetic mice and 7-OH-DPAT-pretreated diabetic mice.

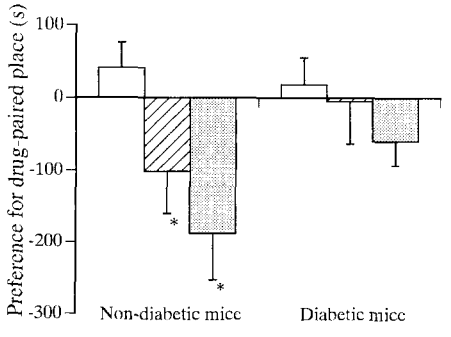

Fig. 4. Place conditioning produced by 7-OH-DPAT(1 mg/kg, s.c., hatched column; 3 mg/kg, s.c., dotted column) in diabetic and non-diabetic mice. Each column represents the mean conditioning score ± S.E. of 8–12 mice. The asterisks denote significant aversion conditioning (Wilcoxon test: * $P < 0.05$ vs. saline alone (open column).

3.4. 7-OH-DPAT-induced place conditioning in diabetic mice

The place conditioning produced by 7-OH-DPAT, a dopamine D_3 receptor agonist, is shown in Fig. 4. In non-diabetic mice, 7-OH-DPAT produced a significant aversion for the drug-associated place. 7-OH-DPAT, at doses of 1 and 3 mg/kg, induced a significant place aversion (mean conditioning scores of −101.4 ± 58.9 s, $n = 8$ for 1.0 mg/kg, s.c. and −188.3 ± 64.7 s, $n = 8$ for 3.0 mg/kg, s.c.). However, in diabetic mice, 7-OH-DPAT produced neither a preference nor aversion for the drug-associated place (mean conditioning scores of −5.0 ± 58.2 s, $n = 8$ for 1.0 mg/kg, s.c. and −59.8 ± 33.0 s, $n = 8$ for 3.0 mg/kg, s.c.).

4. Discussion

In the present study, methamphetamine produced a dose-dependent and significant place preference in both diabetic and non-diabetic mice. This methamphetamine-induced place preference was attenuated by pretreatment with quinpirole in both diabetic or non-diabetic mice. White and Wang (1984) reported that somatodendritic dopamine autoreceptors, which regulate the impulse flow of most mesolimbic dopamine neurons in the ventral tegmental area, exhibit the pharmacological characteristics of dopamine D_2 receptors. On the other hand, quinpirole possesses a high affinity for the recently described dopamine D_3 receptors. Sokoloff et al. (1990) reported that quinpirole has an approximately 100-fold higher affinity for the dopamine D_3 receptor than for the dopamine D_2 receptor. Tang et al. (1994) reported that quinpirole inhibits dopamine release through the activation of dopamine D_2 and dopamine D_3 receptors. Therefore, the present results suggest that the attenuation of methamphetamine-induced place preference by quinpirole may be mediated by a reduction in dopamine transmission through the activation of dopamine autoreceptors. In this regard, we also demonstrated that methamphetamine-induced place preference was attenuated by pretreatment with 7-OH-DPAT in both diabetic and non-diabetic mice. Lévesque et al. (1992) reported that the selectivity of 7-OH-DPAT for dopamine D_3 receptors is > 100-, > 1000- and > 10 000-fold greater than that for doapmine D_2, D_4 and D_1 receptors, respectively, suggesting that 7-OH-DPAT is a highly selective agonist for dopamine D_3 receptors. Furthermore, several microdialysis and brain-slice studies have indicated that 7-OH-DPAT reduces dopamine release in the nucleus accumbens and striatum (Damsma et al., 1993; Timmerman et al., 1991; Yamada et al., 1994). Therefore, dopamine D_3

receptors may play a role in controlling dopamine release or synthesis as an autoreceptor in dopamine neuronal terminals in the limbic area (Gobert et al., 1995). Thus, our data strongly suggest that the reduction of the mesolimbic dopamine system activity can reduce the rewarding effect of methamphetamine.

The nucleus accumbens is an important site for the mediation of the reinforcing properties of drugs of abuse. Furthermore, it has been reported that the dopamine-containing neurons of the ventral tegmentum and their tracts that innervate the limbic and frontal cortex are required for the acute reinforcing actions of cocaine and *d*-amphetamine (Roberts and Koob, 1982; Yokel and Wise, 1975, 1976). Although Spyraki et al. (1982) failed to observe an overall significant attenuation of amphetamine-induced place preference in rats with 6-hydroxydopamine lesions of the nucleus accumbens, there was a significant correlation between dopamine levels in the nucleus accumbens and the magnitude of the place preference. Furthermore, dopamine depletion in the nucleus accumbens varied between 60 and 90% of that in the controls, and the importance of a severe depletion of dopamine in attenuating a place-preference effect has been demonstrated. Moreover, it has been reported that the microinjection of (+)-amphetamine into the nucleus accumbens resulted in a place preference (Carr and White, 1986). These reports suggest that the nucleus accumbens is an important substrate in the psychostimulant-induced place preference. Locomotor activity in the experimental animals has been shown to be closely related to the activity of the mesolimbic dopaminergic system. We recently demonstrated that spontaneous locomotor activity in diabetic mice was significantly greater than that in non-diabetic mice. Furthermore, we also demonstrated that dopamine turnover (DOPAC + HVA/dopamine) in the limbic forebrain is significantly greater in diabetic mice than that in non-diabetic mice (Kamei et al., 1994). Moreover, we reported that increased spontaneous locomotor activity in diabetic mice was attenuated by pretreatment with 7-OH-DPAT (Kamei and Saitoh, 1996a). Based on these results, we suggested that the enhanced spontaneous locomotor activity in diabetic mice may result from increased dopamine release in mesolimbic dopamine systems, which might be due to the down-regulation of presynaptic dopamine D_3 receptor-mediated functions (Kamei and Saitoh, 1996a). In the present study, we also demonstrated that 7-OH-DPAT, at doses of 1 and 3 mg/kg, produced dose-dependent place aversion in non-diabetic mice. However, 7-OH-DPAT produced neither place preference nor place aversion in diabetic mice. It has been reported that CGS10746B (5-(4-methyl-1-piperazinyl)imidazo[2,1-*b*][1,3,5]-benzothiadiazepine), an inhibitor of dopamine release, produced a place aversion (Schechter and Meehan, 1994). Furthermore, as mentioned above, 7-OH-DPAT inhibits dopamine release from the nucleus accumbens, a major terminal area of the mesolimbic dopaminergic system, through the activation of dopamine D_3 receptors (Damsma et al., 1993; Timmerman et al., 1991; Yamada et al., 1994; Gobert et al., 1995). These results suggest that the activation of dopamine D_3 receptors in the mesolimbic dopamine system may produce place aversion. Thus, it is possible that the reduction in place aversion caused by 7-OH-DPAT in diabetic mice may be related to the dysfunction of dopamine D_3 receptors. Furthermore, the present findings also support our previous hypothesis (Kamei and Saitoh, 1996a) that diabetic mice are hyporesponsive to dopamine D_3 receptor-mediated modulation of dopamine release in the limbic area. Therefore, the increased dopamine neurotransmission which associated with the down-regulation of presynaptic dopamine D_3 receptor-mediated functions may be account for the enhancement of methamphetamine's reinforcing effect in diabetic mice. The mechanisms which lead to this dysfunction of dopamine D_3 receptors in diabetic mice is unclear. We previously suggested that some factor(s) derived from spleen cells may play an important direct or indirect role in the alternation of dopamine receptor functions (Kamei and Saitoh, 1996b). It is possible that these factor(s) in diabetic mice and the dysfunction of dopamine D_3 receptors may somehow be related.

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