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Methamphetamine decreases mouse striatal dopamine transporter activity: roles of hyperthermia and dopamine

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Abstract

Multiple methamphetamine administrations rapidly decrease rat striatal dopamine transporter activity. To determine the species specificity of this phenomenon, the present studies examined effects of this stimulant on the dopamine transporter in mice. As in rats, multiple methamphetamine injections rapidly reduced striatal dopamine transporter activity; a decrease that was partially reversed 24 h later. Moreover, methamphetamine decreased binding of the dopamine transporter ligand, WIN35428, but to a lesser degree than the change in dopamine transporter function. These decreases did not appear to result from residual methamphetamine introduced by the original drug treatment. As in rats, hyperthermia contributed to this phenomenon. Unlike in rats, a role for dopamine was not observed in mice as dopamine depletion, resulting from α-methyl-*p*-tyrosine pretreatment, did not prevent this decrease. In addition, unlike in rats, pretreatment with either a dopamine D_1 or D_2 receptor antagonist (SCH23390 or eticlopride, respectively) did not attenuate the methamphetamine-induced reduction in dopamine uptake. These findings demonstrate both similarities and differences in the acute effects of methamphetamine on dopamine transporter function in mice and rats, and suggest the mouse as an additional model for assessing the acute effects of methamphetamine on the dopamine transporter.

Keywords: SCH23390; Eticlopride; Species-specificity; Monoamine

1. Introduction

This laboratory has shown that multiple administrations of methamphetamine cause a rapid, partially reversible decrease in dopamine transporter activity in rat striatum, as assessed by measuring [^{3}H]dopamine uptake in synaptosomes prepared from methamphetamine-treated rats (Kokoshka et al., 1998). Differences between effects on dopamine transporter activity and ligand binding were also observed; that is, multiple administrations of methamphetamine cause a decrease in [^{3}H]WIN35428 binding that, unlike the dopamine transporter activity, does not recover by 24 h after treatment. This reduction in dopamine transporter function is not due to acute loss of transporter protein or residual METH introduced by the original subcutaneous injections (Kokoshka et al., 1998).

Two factors have been identified that contribute to the rapid reduction in rat striatal [^{3}H]dopamine uptake induced by multiple administrations of methamphetamine: hyperthermia and dopamine. It has been established that methamphetamine-induced hyperthermia contributes to the acute changes in dopamine transporter activity induced by multiple injections since blockade of hyperthermia attenuates this effect of the stimulant (Metzger et al., in press). Moreover, Metzger et al. (in press) observed that, like hyperthermia, dopamine contributes to the decrease in dopamine transporter function following multiple administrations of methamphetamine since dopamine depletion resulting from pretreatment with α-methyl-*p*-tyrosine attenuates this rapid methamphetamine-induced effect.

In order to elucidate the mechanism of this dopamine transporter response to methamphetamine and its potential clinical relevance, it is important to evaluate the existence and nature of this phenomenon in species other than rat. Thus, we determined the response of the dopamine transporter to methamphetamine in the CF-1 mouse and observed both similarities and differences to that found in the rat.

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2. Materials and methods

2.1. Animals

Male CF-1 mice (25–30 g; Charles River; Portage, MI) were maintained under conditions of controlled temperature and lighting, with food and water provided ad libitum. On the day of the experiment, mice were housed in groups of eight in plastic cages, and maintained in an ambient temperature of 24°C, unless otherwise specified in figure legends. Core (rectal) body temperatures were determined using a digital rectal thermometer (Physiotemp Instruments, Clifton, NJ). Mice were sacrificed by decapitation. All procedures were conducted in accordance with approved National Institutes of Health guidelines.

2.2. Drugs and chemicals

(±)-Methamphetamine hydrochloride and (−)-cocaine hydrochloride were supplied generously by the National Institute on Drug Abuse (Rockville, MD). Pargyline hydrochloride and α-methyl-*p*-tyrosine hydrochloride were purchased from Sigma (St. Louis, MO). [7,8-^{3}H]Dopamine (46 Ci/mmol) was purchased from Amersham Life Sciences (Arlington Heights, IL). [*N*-methyl-^{3}H]-WIN35428 (84.5 Ci/mmol) was purchased from New England Nuclear (Boston, MA). Drugs were administered as indicated in the legends of appropriate figures, and doses were calculated as the respective free bases. Drugs were dissolved in 0.9% saline.

2.3. Synaptosomal [^{3}H]dopamine uptake and [^{3}H]WIN-35428 binding

[^{3}H]Dopamine uptake and [^{3}H]WIN35428 binding were determined in synaptosomal preparations as described previously by Kokoshka et al. (1998). Synaptosomes were prepared by homogenizing fresh striatal tissue in ice-cold 0.32 M phosphate-buffered sucrose (pH 7.4) followed by centrifugation ($800 \times g$ for 12 min; 4°C). Supernatants were then centrifuged ($22{,}000 \times g$ for 15 min; 4°C) and the resulting pellets (P2) resuspended in ice-cold 0.32 M phosphate-buffered sucrose (pH 7.4) for assessment of [^{3}H]dopamine uptake or [^{3}H]WIN35428 binding. Transport of [^{3}H]dopamine was determined in synaptosomes obtained from 5 mg of striatal tissue (original wet weight; or approximately 100 μg protein) per reaction tube. [^{3}H]Dopamine uptake assays were conducted in assay buffer (in mM: 126 NaCl, 4.8 KCl, 1.3 $CaCl_2$, 16 sodium phosphate, 1.4 $MgSO_4$, 11 dextrose, 1 ascorbic acid; pH 7.4) and initiated by addition of [^{3}H]dopamine (0.5 nM final concentration). Samples (incubation volume of 1 ml) were incubated for 3 min at 30°C. [^{3}H]WIN35428 binding (0.5 nM final concentration) was conducted in phosphate-buffered 0.32 M sucrose (pH 7.4) with synaptosomes obtained from 9 mg of striatal tissue per reaction tube. Samples (total incubation volume of 0.5 ml) were incubated on ice for 2 h. The remaining synaptosomal tissue (i.e., resuspended P2 not used for the uptake and binding assays) was retained and protein was determined according to the method of Lowry et al. (1951).

2.4. Dopamine content

On the day of the assay, frozen tissue samples were thawed, sonicated for 3–5 s in tissue buffer (0.05 M sodium phosphate/0.03 M citric acid buffer with 15% methanol (v/v); pH 2.78), and centrifuged for 15 min at $22{,}000 \times g$. Tissue pellets were retained and protein determined according to the method of Lowry et al. (1951). The supernatant was centrifuged a second time for 15 min at $22{,}000 \times g$. Twenty microliters of supernatant were injected onto a high performance liquid chromatograph system coupled to an electrochemical detector (+0.73 V) for separation and quantitation of dopamine levels using the method of Chapin et al. (1986).

2.5. Data analysis

The data represent means ± standard error of the mean (S.E.M.). Statistical analyses were conducted using analysis of variance followed by a Fisher-protected least significant difference multiple comparisons test. Differences among groups were considered significant if the probability of error was less than 5%. To calculate the correlation coefficient, the average core body temperature of methamphetamine-treated mice from all experiments conducted were compared to the respective decrease in [^{3}H]dopamine uptake seen in each methamphetamine-treated mouse using the Statview statistical program. The correlation was considered significant if the probability of error was less than 5%.

3. Results

Results presented in Fig. 1 demonstrate that multiple administrations of methamphetamine (four injections, 2–10 mg/kg, s.c., 2-h intervals) caused a dose-dependent decrease in [^{3}H]dopamine uptake in striatal synaptosomes prepared from mice decapitated 1 h after the last methamphetamine administration. Multiple administrations of a higher methamphetamine dose (20 mg/kg, s.c.) did not yield a greater decline in dopamine transporter activity than 10 mg/kg, s.c. (data not shown). The methamphetamine treatment also rapidly reduced the binding of a dopamine transporter ligand ([^{3}H]WIN35428), but to a lesser extent than the decrease in dopamine transporter function (Fig. 2). By 24 h after the last methamphetamine administration, the dopamine transporter activity partially recovered, whereas ligand binding to the dopamine transporter was reduced similarly at 1 and 24 h.

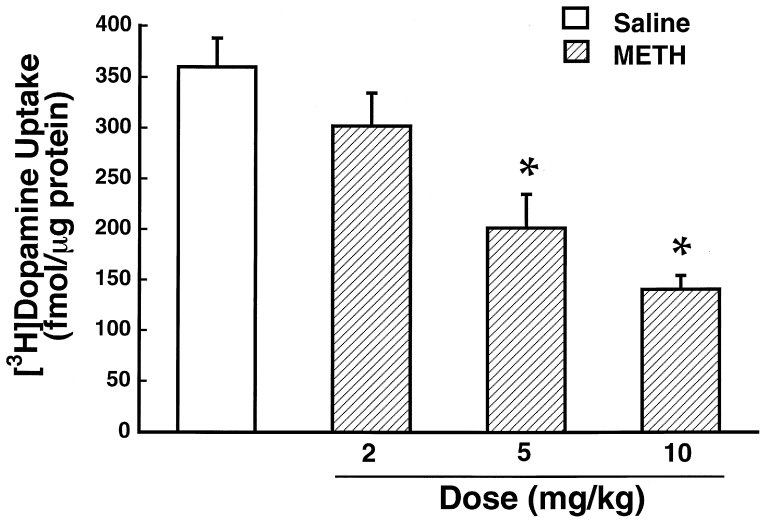

Fig. 1. Multiple administrations of methamphetamine decreased [^{3}H]dopamine uptake in mouse striatum in a dose-dependent manner. Mice received methamphetamine (four injections; 2–10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.), and were sacrificed 1 h after the final methamphetamine or saline administration. Columns represent means and vertical lines 1 S.E.M. of determinations in six to eight mice. * [^{3}H]Dopamine uptake values different from saline-treated controls ($P \leq 0.05$).

Since it is known that methamphetamine can directly decrease striatal [^{3}H]dopamine uptake, a "washout" experiment was conducted using a protocol that demonstrated previously to remove virtually all methamphetamine from tissues (Fleckenstein et al., 1997; Kokoshka et al., 1998). Results presented in Fig. 3 show that repeated washing of synaptosomes from methamphetamine-treated mice did not abolish the decrease in dopamine transporter function, suggesting that this phenomenon was not a result of residual methamphetamine introduced by the original in vivo subcutaneous injection.

The role of body temperature in mediating the methamphetamine-induced decrease in dopamine transporter activity was tested by assessing the correlation between the degree of hyperthermia and the loss of dopamine transporter activity induced by the stimulant. A significant correlation between the magnitude of the methamphetamine-induced hyperthermia and the degree of methamphetamine-induced acute (1 h after the last methamphetamine treatment) deficits in [^{3}H]dopamine uptake was observed ($P \leq 0.01$; $n = 67$), suggesting that hyperthermia contributes to the decrease in dopamine up-

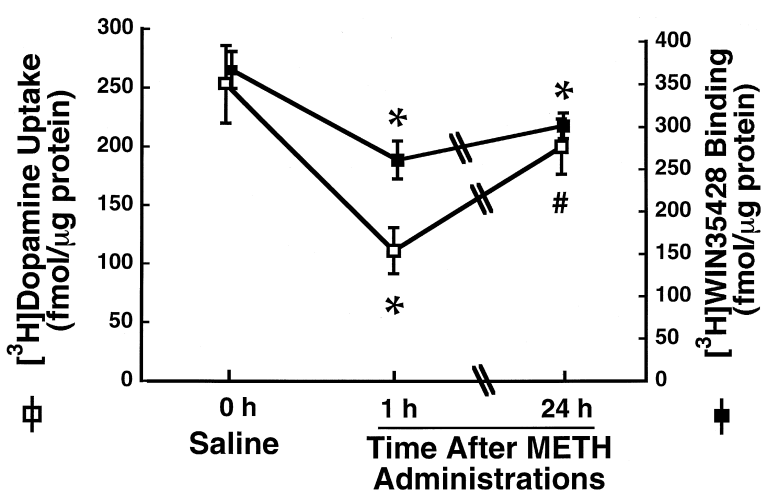

Fig. 2. Multiple administrations of methamphetamine decreased [^{3}H]dopamine uptake and [^{3}H]WIN35428 binding in mouse striatum. Mice received methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.). Mice were sacrificed 1 or 24 h after the final methamphetamine or saline administration. Symbols represent means and vertical lines 1 S.E.M. of determinations in six to eight mice. * [^{3}H]Dopamine uptake or [^{3}H]WIN35428 binding values different from saline treatment groups; #[^{3}H]dopamine uptake values different from methamphetamine 1 h treatment group ($P \leq 0.05$).

Fig. 3. Washing of synaptosomes did not eliminate the methamphetamine effect on dopamine transporter function. Mice received methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.). Mice were sacrificed 1 h after the final methamphetamine or saline administration. Columns represent means and vertical lines 1 S.E.M. of determinations in six to eight mice. *[^{3}H]Dopamine uptake values different from saline treatment groups ($P \leq 0.05$).

take caused by methamphetamine treatment (Fig. 4). As shown in Fig. 4, core body temperatures in mice varied considerably after methamphetamine treatment (i.e., 36°C to 40°C). However, body temperatures varied substantially less if methamphetamine-treated mice were maintained in a warmer ambient temperature. Hence, to eliminate the confound of varying core body temperatures, data presented in Figs. 5 and 6 were obtained using methamphetamine-treated mice that were maintained similarly hyperthermic by exposing them to a warmer ambient temperature (28.5°C).

The role of dopamine in causing the decrease of dopamine transporter function after multiple injections of methamphetamine was assessed by depleting dopamine content via the administration of α-methyl-*p*-tyrosine, a tyrosine hydroxylase inhibitor. A dose of 200 mg/kg (i.p.) of α-methyl-*p*-tyrosine was chosen based on the time– and dose–response studies conducted by Corrodi and Hanson (1966) and Dominic and Moore (1969). It was administered 5 and 1 h prior to, and 3 h after the first injection of the multiple methamphetamine administration treatment regimen. This α-methyl-*p*-tyrosine regimen depleted striatal dopamine content levels by 86% as assessed 12 h after the first α-methyl-*p*-tyrosine injection (i.e., the time corresponding to that of decapitation; $n = 7$ for each group; saline-treated mice = 138.8 ± 9.0 pg/μg protein versus α-methyl-*p*-tyrosine-treated mice = 19.9 ± 1.3 pg/μg protein). Similar reductions following a single 200 mg/kg (i.p.) injection of α-methyl-*p*-tyrosine or a 250 mg/kg (i.p.) injection of its methylester salt cause comparable dopamine deficits (approximately 75%) 4 to 8 h after treatment (i.e., the time corresponding to the first administration of methamphetamine). Despite this reduction in dopamine concentration, α-methyl-*p*-tyrosine treatment did not alter the methamphetamine-induced decline in [^{3}H]dopamine uptake (Fig. 5A). Corresponding mice core body temperatures are shown in Fig. 5B. Since the α-methyl-*p*-tyrosine treatment did not block methamphetamine-induced hyperthermia in the presence of an

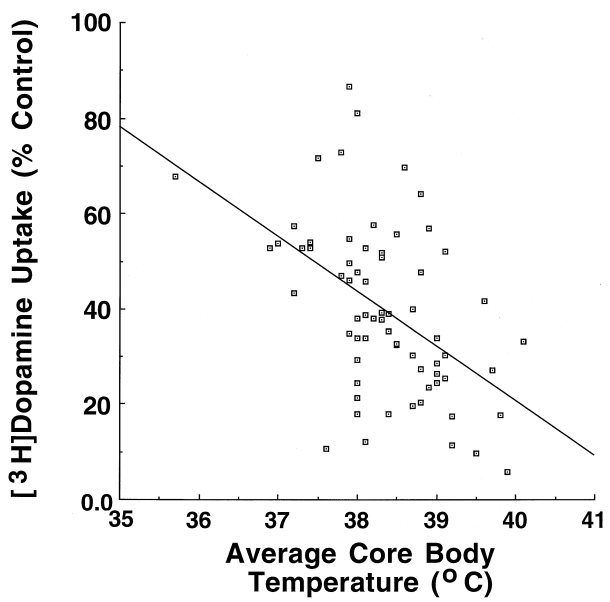

Fig. 4. Hyperthermia contributed to the methamphetamine-induced decrease in [^{3}H]dopamine uptake. These data are compiled from several experiments where mice received multiple administrations of methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) and were sacrificed 1 h after the final methamphetamine or saline administration. Symbols represent [^{3}H]dopamine uptake (expressed as percent control) and corresponding average core body temperature over the course of methamphetamine treatment (i.e., immediately prior to the first methamphetamine administration and thereafter each hour for 7 h; $n = 67$); the coefficient factor (r^2) was 0.248 with $P < 0.001$.

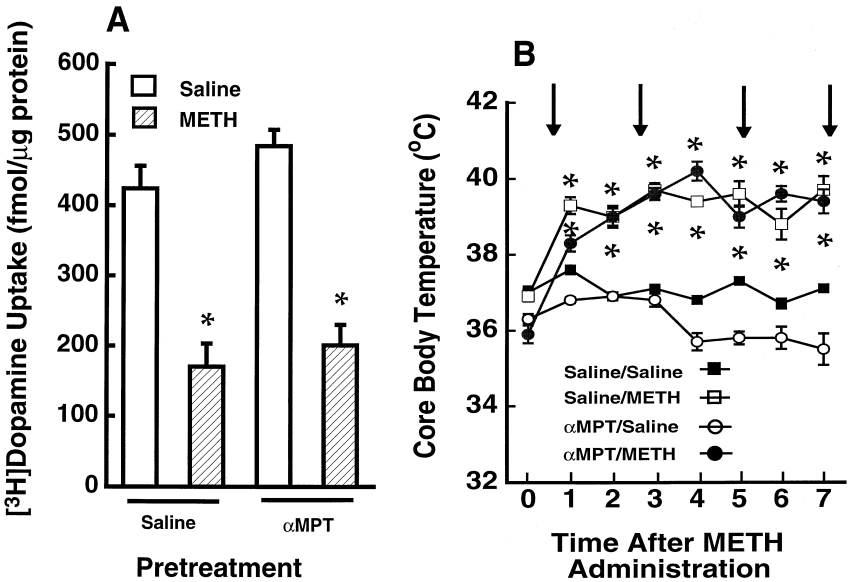

Fig. 5. Dopamine depletion did not alter the methamphetamine-induced rapid decrease in [^{3}H]dopamine uptake. (A) Mice received α-methyl-*p*-tyrosine (200 mg/kg, i.p.) or saline (5 ml/kg, i.p.) 5 and 1 h prior to, and 3 h after, the first administration of methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.) treatment. Upon saline or methamphetamine treatment, mice were exposed to an ambient temperature of 24°C or 28.5°C, respectively. Mice were sacrificed 1 h after the final methamphetamine or saline administration. Columns represent means and vertical lines 1 S.E.M. of determinations in seven to nine mice. * [^{3}H]Dopamine uptake values different from saline-treated controls ($P \leq 0.05$). (B) Core body temperatures immediately prior to the first methamphetamine administration and thereafter each hour for 7 h. Inverted arrows represent time-points of methamphetamine or saline administrations. Symbols represent means and vertical lines 1 S.E.M. of determinations in seven to nine mice. * Core body temperature values different from saline-treated groups ($P \leq 0.05$).

elevated ambient temperature, we investigated further whether dopamine contributes to the methamphetamine-induced decrease in dopamine transporter activity, by determining the role of dopaminergic receptors. This was achieved by pretreating mice with either a dopamine D_1 (SCH23390; 0.5 mg/kg, i.p.) or a dopamine D_2 (eticlo-

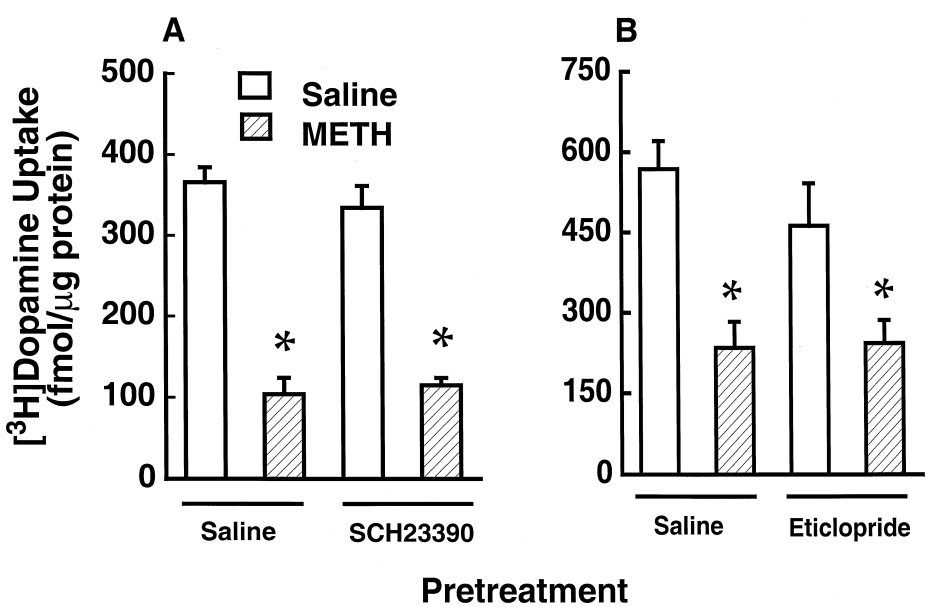

Fig. 6. Dopamine D_1 and D_2 receptor antagonists did not attenuate the methamphetamine-induced decrease in [^{3}H]dopamine uptake. (A) Mice received the dopamine D_1 receptor antagonist, SCH23390, (0.5 mg/kg, i.p.) or saline (5 ml/kg, i.p.) 15 min prior to either methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.). Upon saline or methamphetamine treatment, mice were exposed to an ambient temperature of 24°C or 28.5°C, respectively. Mice were sacrificed 1 h after the final methamphetamine or saline administration. Columns represent means and vertical lines 1 S.E.M. of determinations in seven to nine mice. * [^{3}H]Dopamine uptake values different from saline-treated groups ($P \leq 0.05$). (B) Mice received the dopamine D_2 receptor antagonist, eticlopride, (0.05 mg/kg, i.p.) or saline (5 ml/kg, i.p.) 25 min prior to each methamphetamine (four injections; 10 mg/kg, s.c.; 2-h intervals) or saline (5 ml/kg/injection, s.c.). Mice were sacrificed 1 h after the final methamphetamine or saline administration. Columns represent means and vertical lines 1 S.E.M. of determinations in seven to nine mice. * [^{3}H]Dopamine uptake values different from saline-treated groups ($P \leq 0.05$).

pride; 0.05 mg/kg, i.p.) receptor antagonist 15 or 25 min prior to each methamphetamine injection, respectively. Results presented in Fig. 6A and 6B demonstrate that neither SCH23390 nor eticlopride significantly attenuated the reduction in [^{3}H]dopamine uptake, substantiating the lack of a dopamine role for this methamphetamine effect on the dopamine transporter in mice.

4. Discussion

It was demonstrated previously that multiple high-dose administrations of methamphetamine transiently decrease striatal dopamine uptake into synaptosomes prepared from rats (Kokoshka et al., 1998). Therefore, an aim of this study was to determine the species-selectivity of methamphetamine-induced reduction in dopamine transporter activity. Since dopamine and hyperthermia mediate several short-term and persistent effects of methamphetamine (Bowyer et al., 1994; Farfel and Seiden, 1995; Metzger et al., in press; Schmidt et al., 1985; Wagner et al., 1980), an additional aim was to determine the roles of both hyperthermia and dopamine in this phenomenon. As shown by Kokoshka et al. (1998) in the rats, results presented herein demonstrate that striatal dopamine transporter activity rapidly decreased and partially recovered after multiple administrations of methamphetamine in mice (Fig. 2). Interestingly, the magnitude of the methamphetamine-induced decrease in uptake did not quantitatively correlate with the reduction in [^{3}H]WIN35428 binding. For instance, results presented in Fig. 2 demonstrate that the acute decline in [^{3}H]dopamine uptake was greater than the corresponding reduction in dopamine transporter-ligand binding 1 h after methamphetamine treatment. Moreover, [^{3}H]dopamine uptake partially recovered 24 h after the last injection of methamphetamine, whereas [^{3}H]WIN35428 binding did not recover (Fig. 2). These methamphetamine-induced decreases in uptake and binding were not due to residual drug introduced by the original subcutaneous injection, as the "washout" protocol eliminated any residual methamphetamine (Fleckenstein et al., 1997; Kokoshka et al., 1998); however, it did not eliminate the methamphetamine-induced reduction in dopamine transporter activity (Fig. 3).

Having established that these methamphetamine-induced changes in dopamine transporter activity are not unique to rats, the contribution of hyperthermia and dopamine to this phenomenon was examined. Recent evidence suggests that hyperthermia contributes to the acute decrease in dopamine transporter function in rats following multiple administrations of methamphetamine, since this effect is attenuated by maintaining methamphetamine-treated rats normothermic (i.e., placing them in a cooler environment; Metzger et al., in press). To test whether hyperthermia similarly plays a role in the transient methamphetamine-induced reduction in dopamine transporter function in mice, the correlation between hyperthermia and [^{3}H]dopamine uptake was examined (Fig. 3). On average, the basal temperature of saline-treated mice was 37°C. After multiple administrations of methamphetamine, the core body temperature of mice substantially varied from 36°C to 40°C. A correlation analysis performed between [^{3}H]dopamine uptake activity and average core body temperature changes caused by methamphetamine showed that like in rats, temperature changes in mice also contributed to the drug-related [^{3}H]dopamine uptake decrease (Fig. 3).

To determine the dopamine role in the reduction of dopamine transporter activity, dopamine levels were depleted using an α-methyl-*p*-tyrosine pretreatment. Despite a reduction of approximately 86% in striatal dopamine levels, the decrease in dopamine transporter function induced by multiple injections of methamphetamine, regardless of body temperature, was not attenuated (Fig. 5A). These data fail to demonstrate a dopamine role in this methamphetamine-induced diminution in mice. However, a caveat with these data is that approximately 14% of dopamine was not depleted by α-methyl-*p*-tyrosine pretreatment, and may contribute to the effect observed in this experiment. Hence, methamphetamine may still cause the release of the remaining dopamine and activate dopaminergic receptor mechanisms that, in turn, alter dopamine transporter function. To test this possibility, the role of dopamine D_1 and D_2 receptors in the methamphetamine-induced reduction in dopamine transporter function was investigated. Results presented herein demonstrate that neither SCH23390 nor eticlopride pretreatment prevented the methamphetamine-induced decrease in dopamine uptake. These data, combined with the lack of effect of dopamine depletion, do not fully exclude a role for dopamine. For instance, cytoplasmic dopamine remaining after α-methyl-*p*-tyrosine treatment, could auto-oxidize and, thereby, decrease dopamine transporter function. Neither dopamine D_1 nor D_2 receptor antagonist administration would necessarily prevent such a dopamine-associated reactive oxygen species-induced decrease in dopamine transporter activity. Still, the α-methyl-*p*-tyrosine and dopamine antagonist data do not provide evidence for a dopamine role. Moreover, a role for oxygen radicals in mediating this effect remains to be determined. This is in contrast to rats where dopamine was clearly demonstrated to be a factor (i.e., since α-methyl-*p*-tyrosine pretreatment attenuated the methamphetamine-induced decrease in dopamine transporter function—even when rats were maintained hyperthermic (Metzger et al., in press)).

In summary, data presented in this paper reveal similarities and differences between the methamphetamine-induced decrease in dopamine transporter function in rats and mice. For instance, a hyperthermia-sensitive rapid reduction in striatal dopamine transporter activity occurs in both rat and mice after multiple administrations of methamphetamine. Although this response of the dopamine

transporter to methamphetamine appears to be at least partially dopamine-dependent in rats, a role for dopamine in the methamphetamine-induced decrease in dopamine transporter function in mice was not observed. Further studies are required to determine if other species similarities and differences for this methamphetamine-related phenomenon occur.

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