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Short communication

Effect of methamphetamine on tryptophan hydroxylase activity: Role of hyperthermia

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Abstract

A single administration of methamphetamine (15 mg/kg, s.c.) decreased activity of the 5-hydroxytryptamine (5-HT)-synthesizing enzyme, tryptophan hydroxylase, in rat striatum 1 h after administration. Methamphetamine also increased core body temperatures by greater than 3°C in these rats. Prevention of hyperthermia attenuated the methamphetamine-induced decrease in tryptophan hydroxylase activity. Core temperature at the time of injection (from 37.7°C to 40°C) did not influence the magnitude of this decrease. Moreover, augmenting methamphetamine-induced hyperthermia (from approximately 41 to 42°C) did not cause a further decrease in tryptophan hydroxylase activity. These data indicate that temperature contributes to, but is not solely responsible for, methamphetamine-induced 5-HT neuronal impairment. © 1997 Elsevier Science B.V.

Keywords: Hyperthermia; Methamphetamine; 5-HT (5-hydroxytryptamine); Serotonin

1. Introduction

Abuse of the amphetamine analog, methamphetamine, has become a major world-wide health problem. Hence, considerable attention is being directed towards elucidating mechanisms whereby methamphetamine impairs monoaminergic neurons. Administration of high doses of methamphetamine impairs central dopamine and 5-hydroxytryptamine (5-HT) neuronal function, as indicated by decreased concentrations of associated monoamines and activities of their respective synthesizing enzymes (for review, see Gibb et al., 1994). Although mechanisms underlying these deficits are unclear, an association between damage to dopamine neurons and the hyperthermia resulting from multiple administrations of methamphetamine has been described (Bowyer et al., 1992; Bowyer et al., 1994; Albers and Sonsalla, 1995). Distinct from these studies, the purpose of this study was to investigate whether the transient decrease in 5-HT neuronal function caused by a single methamphetamine injection is likewise influenced by variations in core body temperature. Results reveal that prevention of hyperthermia attenuates the decrease in 5-HT neuronal impairment caused by methamphetamine and thereby demonstrate further the role of temperature in the neuronal impairment caused by this stimulant. These data also reveal that other factors, in addition to temperature, contribute to methamphetamine-induced 5-HT neuronal impairment.

2. Materials and methods

Male Sprague–Dawley rats (200–230 g; Simonsen Laboratories, Gilroy, CA, USA) were provided food and water ad libitum. All procedures were conducted in accordance with approved National Institutes of Health guidelines. Core (rectal) body temperatures were determined using a digital thermometer (Physiotemp Instruments, Clifton, NJ, USA) and temperature manipulations performed as described in figure legends. Basal temperatures of the rats in the colony ranged from 37.2 to 37.8°C. Methamphetamine hydrochloride was supplied generously by the National Institute on Drug Abuse. One hour following methamphetamine treatment, rats were decapitated and striatal tissue was assayed for activity of the rate-limiting enzyme in 5-HT synthesis, tryptophan hydroxylase (Johnson et al., 1992). Tryptophan hydroxylase activity was used as an index of 5-HT neuronal function. Unlike the high lethality rate observed commonly during the ensuing hours after multiple methamphetamine administrations, there was less than 10% lethality among rats in this study, presumably

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owing to fact that these animals were decapitated 1 h after a single methamphetamine injection.

3. Results

Reversible, short-term decreases in tryptophan hydroxylase activity occur in rats after a single high-dose methamphetamine injection (Bakhit and Gibb, 1981). Consistent with this finding, results presented in Fig. 1 demonstrate that striatal tryptophan hydroxylase activity was decreased 1 h after methamphetamine (15 mg free base/kg) administration. Core body temperatures were increased concurrently after drug treatment.

It has been demonstrated, at least for dopamine neurons in rats, that environmental temperature plays an important role in effecting methamphetamine toxicity (Bowyer et al., 1992). Environmental temperature can influence both basal body temperatures and the magnitude of methamphetamine-induced hyperthermia. Hence, as a first step towards evaluating the role of temperature in the effects of methamphetamine on 5-HT neurons, the effects of varying basal temperatures at the time of methamphetamine administration (i.e., initial core temperatures) and thereby the magnitude of methamphetamine-induced hyperthermia (i.e., final core temperatures) were investigated. Elevating initial core temperatures prior to methamphetamine injection (i.e., from 37.7 to 40.0°C) by increasing the environmental temperature to approx. 30°C (see figure legend for details) did not affect the magnitude of methamphetamine-induced decrease in tryptophan hydroxylase activity (Fig. 1). Moreover, augmenting methamphetamine-induced hyperthermia by increasing environmental temperature from 26 to approx. 30°C (final core temperatures of 40.9 and 42.1°C, respectively; see figure legend for details) also did not enhance the methamphetamine-induced decrease in tryptophan hydroxylase activity (Fig. 2).

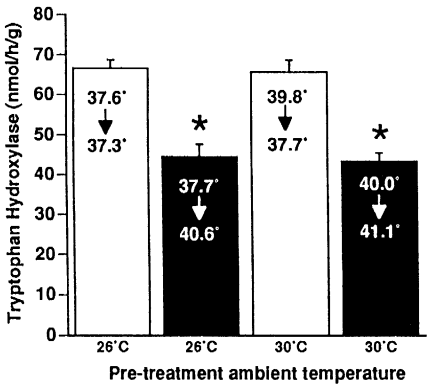

Fig. 1. Rats were maintained at 26°C or ~30°C for 1 h; after which, rectal temperatures were recorded ($t = 0$). Immediately thereafter, rats received saline vehicle (1 ml/kg, s.c.; open columns) or methamphetamine (15 mg free base/kg, s.c.; solid columns), and were removed to an ambient environment of 26°C. Body temperatures were recorded immediately prior to decapitation ($t = 60$ min). Mean temperatures recorded for each group at $t = 0$ min and 60 min, respectively, are indicated in each appropriate column: the SEM for each group was < 0.2°C. Columns represent mean tryptophan hydroxylase activities (nmol/h per g tissue) + 1 SEM of determinations in 7–8 rats. (*) Tryptophan hydroxylase values different from corresponding saline-treated controls; $P < 0.05$, ANOVA/Fisher's PLSD.

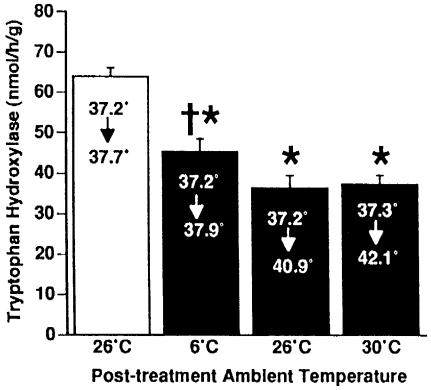

Fig. 2. Rats were maintained at 26°C and rectal temperatures were recorded ($t = 0$ min). Immediately thereafter, rats received saline vehicle (1 ml/kg, s.c.; open column) or methamphetamine (15 mg free base/kg, s.c.; solid columns), and were removed to an approx. 6°C, 26°C or approx. 30°C environment. Body temperatures were recorded immediately prior to decapitation ($t = 60$ min). Mean temperatures recorded for each group at $t = 0$ min and 60 min, respectively, are indicated in each appropriate column: the SEM for each group was < 0.2°C. Columns represent mean tryptophan hydroxylase activities (nmol/h per g tissue) + 1 SEM of determinations in 7–8 rats. * Tryptophan hydroxylase values different from corresponding saline-treated controls; † Tryptophan hydroxylase value different from methamphetamine-treated rats maintained at 26°C or 30°C; $P < 0.05$, ANOVA/Fisher's PLSD.

Results presented in Fig. 2 demonstrate that prevention of methamphetamine-induced hyperthermia by decreasing the ambient environmental temperature (i.e., by placing cages on ice) to approx. 6°C attenuated the decrease in tryptophan hydroxylase activity resulting from methamphetamine administration (Fig. 2). Rats were placed in a cool environment immediately after methamphetamine administration, and did not become hypothermic (final core temperatures of 37.9°C compared to 40.9°C for rats in warm and approx. 6°C environment, respectively). This protection does not result from a cool environment-induced decrease in central methamphetamine levels, since exposure to 6°C environment increases methamphetamine concentrations in rat brain (Fleckenstein et al., unpublished observation). Consistent with findings of Che et al. (1995), hyperthermia per se did not affect tryptophan hydroxylase activity in saline-treated rats (data not shown).

4. Discussion

Considerable attention has focused on the role of body temperature in effecting methamphetamine-induced neurotoxicity. The present findings demonstrate that, as has been observed for dopaminergic neurons after multiple drug

administrations, preventing methamphetamine-induced hyperthermia attenuates the decrease in 5-HT neuronal function, as reflected by reduced tryptophan hydroxylase activity. These data are consistent with previous findings that elevated body temperatures contribute to the acute 5-HT effects of another amphetamine analog, methylenedioxymethamphetamine (Che et al., 1995). These data are also consistent with the suggestion that the hypothermia induced by coadministration of the noncompetitive *N*-methyl-D-aspartate receptor antagonist dizocilpine with methamphetamine contributes to its ability to prevent 5-HT neurotoxicity associated with multiple high-dose methamphetamine administrations (Farfel and Seiden, 1996). However, the finding that blockade of hyperthermia did not prevent completely the effects of methamphetamine on tryptophan hydroxylase activity (Fig. 2) indicates that other factors, in addition to hyperthermia, contribute to 5-HT neuronal impairment caused by a single administration of methamphetamine. Further studies are required to elucidate these factors.

It is interesting to note that core body temperatures at the time of injection did not influence the magnitude of the methamphetamine-induced decrease. It has been suggested that the sudden change in body temperature rather than hyperthermia per se may be important in effecting methamphetamine-induced neurotoxicity. Data presented in Fig. 1 argue against this point: elevating initial core body temperature prior to methamphetamine injection and thereby limiting the magnitude of rise in core temperature resulting from methamphetamine administration (i.e., from 2.9 to 1.1°C) did not affect the magnitude of methamphetamine-induced decrease in activity of tryptophan hydroxylase.

Since neither the initial temperature nor the absolute rise necessarily correlates with the magnitude of methamphetamine-induced tryptophan hydroxylase impairment, the possibility that the degree of hyperthermia (i.e., the maximum core body temperature attained) might influence the extent of methamphetamine-induced impairment was assessed. Augmenting methamphetamine-induced hyperthermia (i.e., from 40.9 to 42.1°C) did not further decrease tryptophan hydroxylase activity (Fig. 2). Preventing methamphetamine-induced hyperthermia, however, attenuated the tryptophan hydroxylase activity loss suggesting that hyperthermia contributes to methamphetamine-induced 5-HT neuronal impairment. These data suggest that a threshold temperature exists above which methamphetamine-induced effects are comparably facilitated regardless of the extent of the rise in the hyperthermia. Although mechanisms whereby hyperthermia promotes toxicity are unknown, methamphetamine-induced decreases in tryptophan hydroxylase activity may be effected by reactive oxygen species (Stone et al., 1989) whose generation might be promoted by hyperthermia. Further experiments into mechanisms whereby hyperthermia contributes to methamphetamine-impaired aminergic neuronal function are required.

In summary, results from this study demonstrate that prevention of hyperthermia attenuates the methamphetamine-induced decrease in tryptophan hydroxylase activity. Neither core temperatures at the time of injection nor augmenting methamphetamine-induced hyperthermia affected the magnitude of this decrease. These data indicate that temperature contributes to, but is not solely responsible for, methamphetamine-induced 5-HT neuronal impairment.

Acknowledgements

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