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Physiological and behavioral effects of methamphetamine in a mouse model of endotoxemia: a preliminary study

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Abstract

We investigated the effects of methamphetamine (METH) on core body temperature (Tb) and motor activity (MA) with or without exposure to a peripheral immune challenge. Mice were exposed to an escalating METH treatment and then to a METH treatment known to cause neurotoxicity (binge METH treatment). This was followed by a challenge with lipopolysaccharide (LPS). Three days later, METH and saline-treated control groups were challenged with an acute test dose of METH (METH test). Animals exposed to the escalating METH treatment exhibited a significant increase in Tb only after the initial exposure to METH (Day 1) and following the METH test (Day 7). The hyperthermic effect produced by the METH test (Day 7) was reduced in mice previously exposed to combined exposure to binge METH and LPS treatments. The escalating METH treatment produced MA sensitization to the METH test. Animals treated with the binge METH, LPS injection or both treatments combined prevented MA sensitization to the METH test. These findings suggest that induction of peripheral endotoxemia in animals with a history of METH reduced the hyperthermic response to a subsequent challenge with METH.

Keywords: Methamphetamine; Lipopolysaccharide; Core body temperature; Motor activity; Telemetry; Hyperthermia; Mice

1. Introduction

Converging lines of evidence suggest that methamphetamine (METH) abuse and viral-induced events elicit synergistic cellular processes that lead to neuropathogenesis. For instance, a considerable number of studies suggest that METH and the HIV-1 Tat protein, a viral protein released during HIV-1 infection (Ensoli et al., 1993), exhibit similar toxicological properties. The neurotoxic consequences of both METH and Tat are mediated in part by the production of oxidative stress and activation of several redox-regulated transcription factors (Sheng et al., 1996; Asanuma and Cadet, 1998; Shi et al., 1998; Nicolini et al., 2001). METH treatments inducing hyperthermia have been shown to induce the expression of glial fibrillary acidic protein (GFAP), oxidative stress, free radical formation and the expression of genes known to regulate the expression of inflammatory genes (e.g., (Cadet et al., 1994; Fukumura et al., 1998; Yamamoto and Zhu, 1998; Fumagalli et al., 1999). Similarly, studies have shown that Tat-mediated potentiation of transcription factors including NF-κB, AP-1 and CREB may lead to the induction of apoptosis and inflammatory responses (Buonaguro et al., 1994; Kruman et al., 1998; Lee et al., 2001). Consistent with these findings, a recent study found that combined administration of METH and Tat produced a synergistic increase in the expression of inflammatory cytokines in the CNS, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (1L-1β) (Flora et al., 2003). Despite this progress, the functional consequences of the interaction of METH with AIDS and with HIV are not well understood.

Since prolonged expression of cytokines in the CNS that occurs in HIV encephalopathy (see Williams and Hickey, 2002) may represent a key pathogenic process in HIV-1-induced neuropathology, our initial approach was to determine the physiological and behavioral consequences of treatment with METH in a lipopolysaccharide (LPS) model

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for peripheral endotoxemia. Studies have shown that locomotor sensitization is observed in animals treated with METH and different amphetamine-like psychostimulants (for a review, see Pierce and Kalivas, 1997). Moreover, previous studies have shown that exposure to either METH or LPS produced marked changes in core body temperature (Tb) and motor activity (MA) (Kozak et al., 1994; O'Callaghan and Miller, 1994; Albers and Sonsalla, 1995; Segal and Kuczenski, 1997). The purpose of the present study was to characterize the synergistic effects of METH and LPS on Tb and MA in C57BL/6J mice. To this end, we tested whether METH-induced hyperthermia and MA sensitization were altered in a model of peripheral endotoxemia. Tb and MA were recorded in animals first exposed to an escalating METH treatment and then to a METH treatment known to produce neurotoxic effects in mice (binge METH) (O'Callaghan and Miller, 1994; Albers and Sonsalla, 1995). Animals were then injected with LPS 1 h following the binge METH treatment. Three days later, experimental and saline control groups were tested with a METH test. Our investigation sought to provide preliminary evidence whether induction of peripheral endotoxemia in animals with a history of binge METH alters the behavioral and physiological consequences of a subsequent METH exposure.

2. Materials and methods

2.1. Subjects and surgical procedure

Female C57BL/6J mice (20–26 g/3 months old) were anesthetized with halothane (1.0–1.5%) and body temperature was maintained at 37.0 ± 0.5 °C by a heating pad. Radio transmitters (Data Sciences, St. Paul, MN) were implanted in the peritoneal body cavity to monitor Tb and MA signals. Following surgical implantation and appropriate wound closure, the animals were allowed 3 weeks to recover prior to the study. Animal maintenance and experimental procedures were in accordance with the "National Institutes of Health Guide for the Care and Use of Laboratory Animals" (Publication No. 85-23, revised 1985).

2.2. Drugs

LPS was purchased from Sigma (St. Louis, MO). (+) METH hydrochloride was kindly provided by the National Institute on Drug Abuse (Rockville, MD). LPS and METH were dissolved in 0.9% saline and injected intraperitoneally. LPS (10 μg) was administered in a volume of 0.5 ml. METH was administered in a volume of 1.0 mg/ml ip.

2.3. General experimental procedures

Mice were individually housed in Plexiglas cage (L 24 cm × W 22 cm × H 21 cm) in a room maintained at 20–22 °C on a 12:12-h light/dark cycle (on 06:00, off 18:00) with ad libitum access to standard food and water. Animals were allowed at least a week to habituate to this environment. The telemetry system for monitoring vital signs consisted of two parts, a surgically implanted radio transmitter (TA10ETA-F20, Data Sciences) and a receiver (RPC-1, Data Sciences). Tb and MA sensors were located in the transmitter body. The cages were positioned on the receiver plates. Radio signals from the animals' Tb and MA (number of horizontal movements) were continuously (24 h a day) monitored for a month with a fully automated data acquisition system (Dataquest A.R.T., Data Sciences).

2.4. Drug treatment schedule

Mice were initially exposed to an escalating dose cycle of METH (3.0, 5.0 and 10.0 mg/kg ip, single dose per day, consecutive days). Each injection was given at 5:00 p.m. The day after completion of the escalating dose cycle, METH-treated animals were randomly divided into four groups ($n = 5–6$ per group) and exposed to one of the following treatments (see Table 1): (1) saline (NO METH/NO LPS) control treatment (1 ml/kg 0.9% saline, every 2 h, for a total of four injections). Mice were also treated with a single injection of saline (0.5 ml) 1 h after the last saline injection; (2) LPS (NO METH/LPS) control treatment (1 ml/kg 0.9% saline, every 2 h, for a total of four injections). Mice were treated with a single injection of LPS (10 μg in 0.5 ml) 1 h after the last saline injection; (3) binge METH/NO LPS treatment (10 mg/kg METH, every 2 h, for a total of four injections). Mice were treated with a single injection of saline (0.5 ml) 1 h after the last METH injection; (4) binge METH/LPS treatment (10 mg/kg METH, every 2 h, for a total of four injections). Mice were treated with a single injection of LPS (10 μg in 0.5 ml) 1 h after the last METH injection. The time of the initial injection for all groups was at 10:00 am.

Table 1
Treatment schedules

Group size (n)	Days 1–3, escalating dose cycle (METH mg/kg or Sal mg/ml)			Day 4, treatment + immunological challenge (groups)	Days 5–6	Day 7, test single injection (METH mg/kg)
5	3	5	10	Saline control + saline (NO METH/NO LPS)	No drug	3
6	3	5	10	Saline control + LPS (NO METH/LPS)	No drug	3
6	3	5	10	Binge METH + saline (METH/NO LPS)	No drug	3
6	3	5	10	Binge METH + LPS (METH/LPS)	No drug	3

Table 2
Baseline levels of Tb and MA. Results reflect the mean ± S.E.M.

	NO METH/ NO LPS	NO METH/ LPS	METH/ NO LPS	METH/LPS
Tb (°C)	35.74 ± 0.14	35.36 ± 0.53	35.69 ± 0.19	35.94 ± 0.13
MA (counts/h)	50.8 ± 11.78	37.3 ± 8.4	26.67 ± 7.9	55.7 ± 14.9

2.5. Data analysis

Data for Tb and MA were collected every 10 min over a 14-day period and averaged in 60 min time blocks. We grouped together and averaged the data for each condition from all groups tested and plotted the means ± standard error of the mean (S.E.M) for each group. Calculations were performed and results for drug/experimental treatment groups were averaged within groups and compared to their respective averaged controls. We calculated the basal Tb and MA at Day 1 (b_1), preceding the initiation of the escalating METH treatment regimens, and at Day 7 (b_2), preceding the METH test. The difference between both measures of basal Tb and MA were determined ($\Delta_b = b_2 - b_1$). The effects of repeated METH and LPS on b_1 and Δ_b were analyzed using a one-way analysis of variance (ANOVA) followed by Newman–Keuls post hoc test (STATISTICA, StatSoft, Tulsa, OK). To determine the effects of the METH test (3.0 mg/kg) on Tb and MA, mice were recorded for 120 min following METH administration. Radiotelemetry data were analyzed by comparing b_1 with mean values obtained 120 min following the initial METH exposure on Day 1 ($D1_{120}$) and on Day 7 ($D7_{120}$). These data were analyzed using a one-way ANOVA followed by Newman–Keuls post hoc test.

3. Results

3.1. Pharmacological interactions between METH and peripheral endotoxemia: effects on Tb

Baseline measurements of b_1 preceding experimental treatments were not different among groups [$F(4,27) = 1.19$, $P > .05$; Table 2]. Values for Δ_b were similar in all groups [$F(4,27) = 1.64$, $P > .05$; data not shown]. The consequences of drug treatments on the effects of the METH test on Tb are shown in Fig. 1. The effects of the METH test ($D7_{120}$) on Tb in mice exposed to the NO METH/NO LPS treatment were significantly different from b_1 (Fig. 1A). Post hoc analysis showed that $D1_{120}$ and $D7_{120}$ were significantly higher than b_1. Similar findings were obtained in mice exposed to the NO METH/LPS (Fig. 1B) and METH/NO LPS (Fig. 1C) treatments. Differences in Tb were also found in mice exposed to the METH/LPS treatment (Fig. 1D). However, post hoc analysis indicated that while $D1_{120}$ was significantly higher than b_1, $D7_{120}$ was not different from b_1 and significantly lower than $D1_{120}$.

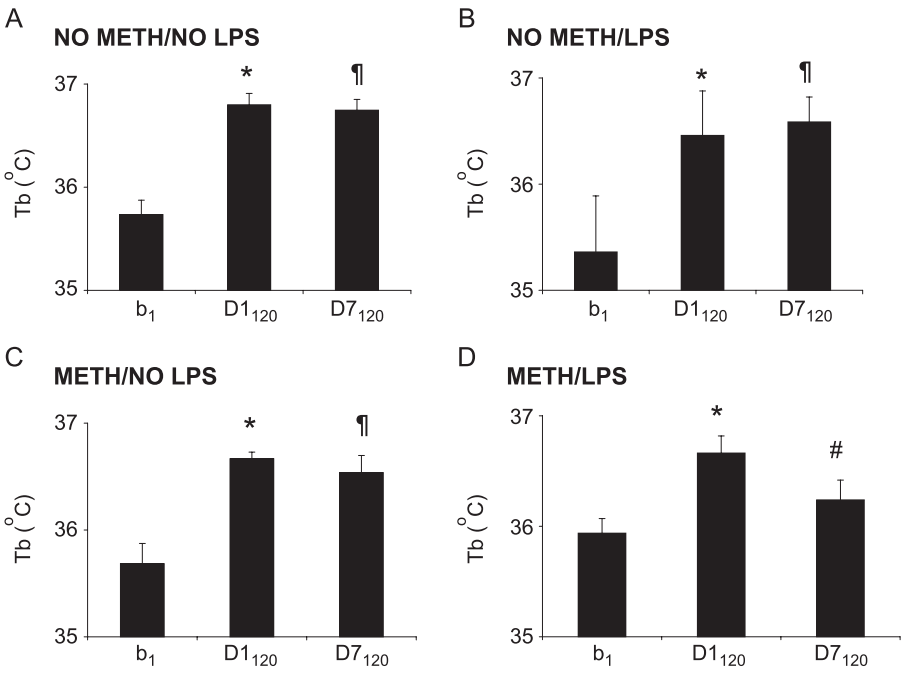

Fig. 1. Pharmacological interactions between METH and peripheral endotoxemia: effects of the METH test on Tb. Differences in Tb were found in animals exposed to the NO METH/NO LPS (A) [$F(2,8) = 23.73$, $P < .0005$], NO METH/LPS (B) [$F(2,10) = 10.74$, $P < .005$] and METH/NO LPS (C) [$F(2,10) = 11.4$, $P < .005$]. Treatments and post hoc analysis showed that $D1_{120}$ and $D7_{120}$ were significantly higher than b_1. Differences in Tb were also found animals exposed to the METH/LPS treatment (D) [$F(2,10) = 8.91$, $P < .01$], and post hoc analysis showed $D1_{120}$ was significantly higher than b_1. However, $D7_{120}$ was not different from b_1 and significantly lower than $D1_{120}$. Symbols (*, # and ¶) represent significance at $P < .05$. *=($b_1 \neq D1_{120}$); #=($D7_{120} \neq D1_{120}$); ¶=($D7_{120} \neq b_1$).

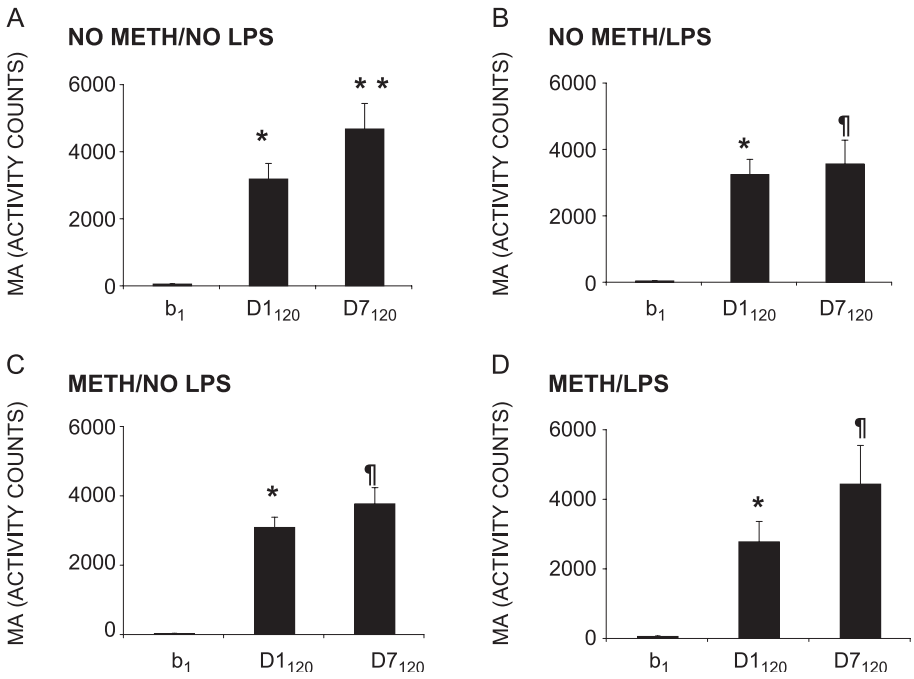

Fig. 2. Pharmacological interactions between METH and peripheral endotoxemia: effects of the METH test on MA. Differences in MA were found in animals exposed to the NO METH/NO LPS treatment (A) [$F(2,8)=28.0$, $P<.0005$], and post hoc analysis showed that $D7_{120}$ was significantly higher than b_1 and $D1_{120}$. In addition, $D1_{120}$ was significantly higher than b_1. Differences in MA as a result of the METH test were also found in animals exposed to the NO METH/LPS (B) [$F(2,10)=19.72$, $P<.005$], METH/NO LPS (C) [$F(2,10)=29.9$, $P<.0001$] and METH/LPS (D) [$F(2,10)=12.2$, $P<.005$] treatments. Post hoc analyses showed that $D1_{120}$ and $D7_{120}$ were significantly higher than b_1. However, $D7_{120}$ was not different from $D1_{120}$. Symbols (*, ** and ¶) represent significance at $P<.05$. *=($b_1 \neq D1_{120}$); **=($D7_{120} \neq b_1, D1_{120}$); ¶=($D7_{120} \neq b_1$).

3.2. Pharmacological interactions between METH and peripheral endotoxemia: effects on MA

Baseline measurements of b_1 preceding experimental treatments were not different among groups [$F(4,27)=1.24$, $P>.05$; Table 2]. We found no differences between baseline values preceding the test with the 3.0 mg/kg METH dose and baseline values preceding exposure to the drug treatments (Δ_b) [$F(4,27)=2.27$, $P>.05$; data now shown].

The consequences of drug treatments on the effects of the METH test on MA are shown in Fig. 2. Differences in MA were found in mice exposed to the NO METH/NO LPS treatment (Fig. 2A). Post hoc analysis showed that $D7_{120}$ was significantly higher than b_1 and $D1_{120}$. $D1_{120}$ was also significantly higher than b_1. The effects of the METH test in mice exposed to the NO METH/LPS (Fig. 2B), the METH/NO LPS (Fig. 2C) and METH/LPS (Fig. 2D) treatments were similar. Post hoc analysis showed that $D1_{120}$ and $D7_{120}$ were significantly higher than b_1. However, $D7_{120}$ was not different from $D1_{120}$.

4. Discussion

This initial investigation demonstrated that administration of the binge METH treatment together with a major immune response altered the animal's hyperthermic response to subsequent exposures to METH. Multiple factors are likely responsible for the pharmacological effects of METH in the LPS model of endotoxemia. Evidence suggests that both treatments, binge METH and LPS, share similar pharmacological and neurotoxicological properties. The binge METH or the LPS treatments could have damaged temperature regulation. However, these results were not observed in animals treated with either binge METH or LPS treatments alone. Alternatively, findings from the present study may indicate that combined exposure to binge METH and LPS produced tolerance to the hyperthermic effects of a METH test dose. Since studies have shown that preexposure to an escalating dose cycle of METH protects against the neurotoxic effects of binge METH (e.g., (Schmidt et al., 1985; Abekawa et al., 1997)), it is likely that the neurotoxic effects of binge METH were attenuated in the present study. A recent study by Segal et al. (2003) showed that an escalating dose cycle of METH attenuated the behavioral and neurochemical responses to a single binge with a high dose of METH. The binge METH regimen used in this study has been known to produce neurotoxic effects in mice, which includes a long-lasting reduction in striatal dopamine (DA) and serotonin (5-HT) concentrations and uptake sites, changes in glutamatergic transmission and an increased hydroxyl radical formation (for a review, see Davidson et al., 2001). However, the neurotoxicological consequences of METH were not determined in the present study. Moreover, the mechanisms mediating the pharmacological interactions between METH and LPS remain unknown. Further studies

are needed to characterize the consequences of combined administration of METH and LPS (or interactions with specific cytokines) on the animal's physiological (e.g., body and brain temperature and cardiovascular responses) and behavioral responses (e.g., MA and craving to the reinforcing properties of METH) to future METH exposure.

Several pharmacological and neurotoxicological effects of systemic administration of LPS are similar to those observed after administration of binge METH. The systemic effects of LPS on CNS function are well documented and include effects on behavior, temperature, sleep and increased cytokine gene expression (Dantzer and Kelley, 1989; Kent et al., 1992; Laye et al., 1994). Many of the effects produced by systemic LPS are also similar to those observed in many infection states, including HIV-1. Administration of LPS activates microglia, which consequently increases the expression of several proinflammatory factors, including TNFα IL1α and IL1β (see Zetterstrom et al., 1998; Dantzer, 2001). In addition to inducing the production of these proinflammatory factors, LPS-mediated activation of microglia produces several cytotoxic factors that induce neurodegeneration, including nitric oxide (NO), eicosanoids and reactive oxygen species (ROS) (Minghetti and Levi, 1998; Liu et al., 2002). These proinflammatory and cytotoxic factors have been implicated in the degeneration of DA neurons observed in LPS-treated animals (e.g., (Liu et al., 2000; Gayle et al., 2002)). In fact, studies have shown that intranigral injection of LPS produces degeneration of nigral DA neurons and depletion of striatal DA levels (Castano et al., 1998; Lu et al., 2000; Gao et al., 2002). Consistent with these findings, acute or binge administration of METH have been shown to induce glial proliferation, microgliosis and expression of genes known to regulate the expression of inflammatory genes in the CNS, including TNF-α and 1L-1β (Pu et al., 1996; Escubedo et al., 1998; Fukumura et al., 1998; Flora et al., 2003). Based on the role of TNF-α and other inflammatory cytokines regulating hyperthermia (for a review, see Saper, 1998), the potential synergistic activation of TNF-α and other cytokines in animals exposed to the binge METH treatment together with a major immune response may serve as an important mediator of the attenuated hyperthermic response.

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