Selective Vulnerability in Striosomes and in the Nigrostriatal Dopaminergic Pathway After Methamphetamine Administration

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Abstract Methamphetamine (METH), a commonly abused psychostimulant, causes dopamine neurotoxicity in humans, rodents, and nonhuman primates. This study examined the selective neuroanatomical pattern of dopaminergic neurotoxicity induced by METH in the mouse striatum. We examined the effect of METH on tyrosine hydroxylase (TH) and dopamine transporter (DAT) immunoreactivity in the different compartments of the striatum and in the nucleus accumbens. The levels of dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid and homovanillic acid, as well as serotonin (5-HT) and its metabolite, 5-hydroxyindolacetic acid, were also quantified in the striatum. Mice were given three injections of METH (4 mg/kg, i.p.) at 3 h intervals and sacrificed 7 days later. This repeated METH injection induced a hyperthermic response and a decrease in striatal concentrations of dopamine and its metabolites without affecting 5-HT concentrations. In addition, the drug caused a reduction in TH- and DAT-immunoreactivity when compared to saline-treated animals. Interestingly, there was a significantly greater loss of TH- and DAT-immunoreactivity in striosomes than in the matrix. The predominant loss of dopaminergic terminals in the striosomes occurred along the rostrocaudal axis of the striatum. In contrast, METH did not decrease TH- or DAT-immunoreactivity in the nucleus accumbens. These results provide the first evidence that compartments of the mouse striatum, striosomes and matrix, and mesolimbic and nigrostriatal pathways have different vulnerability to METH. This pattern is similar to that observed with other neurotoxins such as MPTP, the most widely used model of Parkinson’s disease, in early Huntington’s disease and hypoxic/ischemic injury, suggesting that these conditions might share mechanisms of neurotoxicity.

Keywords TH · DAT · Striosomes · Matrix · Striatum · Neurotoxicity · Dopamine · Parkinson’s disease

Abbreviations

METH Methamphetamine
PB Phosphate buffer
PBST Phosphate sodium buffer with Triton X-100
DA Dopamine
TH Tyrosine hydroxylase
DAT Dopamine transporter
MOR-I Opioid μ receptor
DOPAC 3,4-Dihydroxyphenylacetic acid
HVA Homovanillic acid
5-HT Serotonin
5-HIAA 5-Hydroxyindolacetic acid
MDMA 3,4-Methylenedioxyamphetamine
MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

In memoriam to Dr. J.A. Burzaco for his dedication to Parkinson’s patients.
Introduction

Methamphetamine (METH) is an illicit psychostimulant that is widely abused. The United Nations Office on Drugs and Crime (UNODC) conservatively estimates that there are between 15 and 16 million METH users worldwide, a figure similar to those for heroin and cocaine (UNODC 2008). The immediate effects of METH are associated with an increase in serotonin (5-HT) and dopamine (DA) concentrations in the synaptic cleft. METH exposure causes long-term neurotoxicity in rodents, nonhuman primates, and humans, and although some serotonergic loss is reported, mainly in rats (Wagner et al. 1980; Green et al. 1992; Nowak et al. 2007; Bortolato et al. 2009; Cadet et al. 2009), it predominantly affects the dopaminergic system (Seiden et al. 1976; Wagner et al. 1980; McCann et al. 1998; Melega et al. 2000; Cadet et al. 2007; Daberkow et al. 2008; Krasnova and Cadet 2009). In mice, repeated administration of METH produces neurodegeneration of dopamine axon terminals in the striatum and cell body loss in the substantia nigra (Sonsalla et al. 1996; Hirata and Cadet 1997). Damage has been demonstrated both histologically (O’Callaghan and Miller 1994) and biochemically (Sonsalla et al. 1989; Mann et al. 1997; Itzhak et al. 2000; Hogan et al. 2000; Staal et al. 2000; Nowak et al. 2007) and is reflected as a substantial decrease in the concentration of dopamine and its metabolites, a loss in the density of plasmalemmal and vesicular dopamine transporters, and a decrease in tyrosine hydroxylase (TH) activity. The mechanisms underlying this neurodegeneration are not fully understood currently, but a considerable body of data indicates that reactive oxygen and nitrogen species play an essential role (Itzhak et al. 1998, 2000; Deng and Cadet 1999; Imam et al. 2001; Krasnova and Cadet 2009).

We have recently found that the dopaminergic terminal loss induced in the striatum by MDMA, another amphetamine derivative compound, occurs predominantly in the striosomes compared to the matrix (Granado et al. 2008a). Interestingly, this pattern of dopaminergic terminal neurotoxicity is similar to that shown in early stages of MPTP-induced neurotoxicity in monkeys (Irvani et al. 2006) and in the adult weaver mouse (Graybiel et al. 1990). A predominant loss of TH in the striosomes has also been shown in a transgenic mouse model of dopa-responsive dystonia (Sato et al. 2008). Remarkably, this pattern not only applies to dopaminergic terminals but also extends to medium spiny neurons within the striosomal compartment, as found in early stages of Huntington disease (Hedreen and Folstein 1995) and after forebrain hypoxic-ischemic injury (Burke and Baimbridge 1993). Interestingly, these neurons are dopaminergic: they are innervated by dopaminergic terminals and express D1 or D2 dopamine receptors.

The striosome/matrix cytoarchitectonic organization of the striatum plays a central role in the functional organization of the striatum. Because of their connections with the limbic system, striosomes are functionally associated with reward-related behaviors (White and Hiroi 1998) and stimulant-induced neuronal events (Moratalla et al. 1996). The matrix is connected to sensorimotor regions of the brain and is more closely associated with normal motor functions (Berretta et al. 1997; Brown et al. 2002). Given the functional importance of the striosomes/matrix organization, an imbalance in the physiological dopaminergic activity or in differential signaling efficacy between these two compartments has been associated with the pathogenesis of abnormal and persistent motor behaviors and pathological reinforcement induced by repetitive administration of dopaminergic drugs (Moratalla et al. 1996; Hiroi et al. 2002; Sato et al. 2008; Crittenden et al. 2009; Darmopil et al. 2009).

To investigate whether the differential vulnerability of these two compartments to METH toxicity underlies the pathological consequences of METH abuse, we studied the relative susceptibility of the striatal compartments to the neurotoxic effects of METH by evaluating changes in the expression of two dopaminergic nigrostriatal markers, TH and dopamine transporter (DAT), 7 days after repeated METH administration. Our results show that striosomes are more vulnerable to METH than matrix.

Experimental Procedures

Animals and Treatment

Adult female C57BL/6J mice (20–25 g, Harlan Iberica, Barcelona, Spain) were housed in groups of 4–6 per cage at the Instituto Cajal in conditions of constant temperature at 21 ± 2°C, in a 12 h light/dark cycle, with free access to food and water. All experimental procedures were approved by the Bioethics Committee of the Instituto Cajal (following DC86/609/EU).

Mice received three injections of METH (4 mg/kg, i.p.) with 3 h intervals between injections. Control mice were given saline. Doses are expressed as free base. METH was obtained from Sigma-Aldrich (Madrid, Spain).

Measurement of Rectal Temperature

Rectal temperature was measured using a digital readout thermocouple (BAT-12 thermometer, Physitemp Instruments, Clifton, NJ, USA) with a resolution of 0.1°C and accuracy of ±0.1°C attached to a RET-3 Rodent Sensor. The sensor was inserted 2 cm into the mouse rectum while the mouse was lightly restrained by holding in the hand. A steady
readout was obtained within 10 s of probe insertion. Temperature readings were taken every 30 min immediately before and after METH injections and hourly thereafter.

Immunohistochemistry

Seven days after the administration of METH (4 mg/kg, i.p. 3×), animals were deeply anesthetized (50 mg/kg, sodium pentobarbital) and transcardially perfused with 4% paraformaldehyde. Immunostaining was carried out in free-floating brain sections (30 μm) with standard avidin–biotin immunohistochemical protocols (Granado et al. 2008b, c; Martín et al. 2008; Rodrigues et al. 2007), with specific TH antisera (1:1,000; Chemicon International, Temecula, CA, USA), DAT monoclonal antibody (1:5,000; Chemicon International), and a μ opioid receptor (MOR-1) antisera (1:10,000; Chemicon International). After incubation with the primary (overnight) and secondary antisera (1 h; Vector Laboratories), peroxidase reactions were developed in diaminobenzidine. Quantification of TH and DAT striatal expression was performed with the aid of an image analysis system (AIS, Imaging Research Inc., Linton, England) using a 5× lens. The proportional TH- or DAT-stained area was determined in each visible striosome and in its surrounding matrix, through the rostrocaudal axis of the striatum (Granado et al. 2008a, b). The data are presented as the proportional stained area (total TH- or DAT-positive area/scan area) in the striatal compartments in control and METH-treated animals. Measurements were carried out in five animals per treatment (5–6 sections/animal). The proportional TH- or DAT-immunostained area in the whole striatum was also measured (Granado et al. 2008b).

Measurement of Monoamines and Metabolites in Striatum

Seven days after treatment, the mice were killed by cervical dislocation, the brains were rapidly removed, and the striatum dissected out on ice. Dopamine, serotonin, and the metabolites—3,4-dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindolacetic acid (5-HIAA)—were measured by high-performance liquid chromatography and electrochemical detection. The mobile phase consisted of KH₂PO₄ (0.05 M), octanesulfonic acid (0.4 mM), EDTA (0.1 mM), and methanol (16%) and was adjusted to pH 3 with phosphoric acid, filtered, and degassed. The flow rate was 1 ml/min. The high-performance liquid chromatography system consisted of a pump (Waters 510) linked to an automatic sample injector (Loop 200 μl, Waters 717 plus Autosampler) and a stainless steel reversed-phase column (Spherisorb ODS2, 5 μm, 150 × 4.6 mm²; Waters, Milford, MA, USA) with a pre-column and a coulometric detector (Coulochem II; Esa, Chelmsford, MA, USA). The working electrode potential was set at 400 mV with a gain of 1 μA (for dopamine) and 500 nA (for the remaining compounds). The current produced was monitored by means of integration software (Unipoint; Gilson, Villier Le Bel, France).

Statistics

Data are presented as mean ± standard error of the mean (S.E.M.). The results of rectal temperature measurements were analyzed using one-way analysis of variance (ANOVA) for repeated measures.

Data obtained from image analysis of striatal TH and DAT immunostaining were analyzed using one-way ANOVA. Relevant differences were analyzed pairwise by post hoc comparisons with Tukey’s test or Dunn’s test to determine specific group differences. P values less than 0.05 were considered statistically significant.

All statistical analyses were performed using SigmaStat 2.03 program, and graphical representations were obtained using SigmaPlot 9.0 software.

Results

METH Induces Hyperthermia

METH treatment (4 mg/kg, i.p., three injections given at 3 h intervals) resulted in significant changes in rectal temperatures (Fig. 1). The first injection of METH induced a marked hypothermic response (1.2°C below that of saline-treated

![Fig. 1 Effect of METH on mouse rectal temperature. Repeated METH administration (4 mg/kg, i.p., every 3 h, 3×) produced a decrease in rectal temperature of the animals after the first injection and an increase in the rectal temperature, peaking 30 min after the second and third injections. The arrows indicate the time of drug injection. Data represent mean ± S.E.M., n = 6 animals/group](image-url)
mice), peaking at 30 min and lasting at least 1 h. The second and third injections caused transient hyperthermia (1–1.5°C above saline) which reached a peak 30 min after each injection. The highest value was reached after the second injection of METH reaching 39.2°C. Statistical comparison revealed a significant difference between the response of mice to METH and to saline within the first 60 min following the first, second, and third injections (P < 0.001 as by one-way ANOVA RM) (Fig. 1).

METH-Induced TH Loss in Mouse Striatum

Seven days after METH administration, immunohistochemistry revealed a marked overall decrease in density of TH-immunoreactive fibers in the striatum (Fig. 2) compared to the intense TH staining in saline-treated animals (Fig. 2a–f). Furthermore, in the caudoputamen of animals treated with METH, we saw patches or pockets with severe loss of TH-positive fibers compared with the rest of striatum. Although the TH fiber loss was similar along the rostrocaudal axis of the caudoputamen, we observed a significantly greater loss in the lateral part (Fig. 2d–f), suggesting that the motor areas are more vulnerable to METH than associative or limbic areas of the striatum. Quantitative image analysis revealed a significant decrease of 37.3% in TH-ir fibers within the caudoputamen of drug-treated animals 7 days after METH administration compared to saline-treated controls (P < 0.001) (Fig. 2g).

DAT Loss in the Striatum of METH-Treated Mice

To confirm that TH fiber loss reflected terminal damage and not just a reduction in TH synthesis, we used immunohistochemistry to evaluate the expression of dopamine transporter (DAT). DAT is located on dopaminergic terminals and is expressed independently of TH synthesis or accumulation. METH also produced a significant loss of striatal DAT-positive fibers 7 days after injection compared with saline-treated mice (Fig. 3). As expected, the pattern of DAT-ir loss paralleled the pattern of TH-ir loss, with a similar decrease in DAT-ir fibers along the rostrocaudal axis, and a greater loss of DAT-ir fibers in striosomes and in the lateral striatum (Fig. 3a–f). Quantification of DAT-ir by image analysis revealed a significant decrease of 67% in METH-treated mice compared to saline-treated animals (P < 0.001) (Fig. 3g).

Striosomes Are More Vulnerable to METH Neurotoxicity Than Matrix

Interestingly, in METH-treated animals, we also found that TH- and DAT-ir loss was greater in patches than in the rest

![Fig. 2](image_url)

**Fig. 2** Effect of METH on TH-immunoreactivity in the striatum. Photomicrographs of striatal sections from mice treated with saline (a–c) or METH (d–f) stained for TH. Animals were killed 7 days after treatment. Note the TH-ir loss in the METH-treated mice along the rostrocaudal axis of the striatum. (g) Histograms of the proportional stained area of TH-ir. METH (4 mg/kg, i.p., every 3 h, 3×) produced a reduction in TH-immunoreactivity levels. Data represent mean ± S.E.M., n = 6 animals/group. * P < 0.001 vs. saline, one-way ANOVA. Bar 500 μm.
of striatum (Fig. 4). To determine if these patches of highly damaged striatum corresponded to the location of striosomes, we performed immunostaining for MOR-1, a striosomal marker, in sections adjacent to those stained with TH or DAT. Areas immunostained with MOR-1 corresponded in number, size, and shape to the patches of greatest TH and DAT fiber loss (Fig. 4a–c).
matrix pattern in TH/DAT staining was no longer evident due to the greater TH and DAT loss in these areas.

To study the relative vulnerability of striosomes compared to the matrix, we quantified TH-ir in both striatal compartments: striosomes and matrix (Fig. 5). When we determined the proportional area stained by TH, we found significant differences between the METH- and saline-treated animals for both the striosomes and matrix in medial, central, and lateral areas of the striatum. We also found that the difference was greater for the striosomes (average 88%, $P < 0.001$) than for the matrix (average 53%, $P < 0.01$) in all areas; however, the difference in TH content between striosomes and matrix was greatest in the medial area and lowest in the lateral area. It should be noted that in METH-treated mice, there was greater overall damage in the lateral striatum compared to the medial and central matrix of striatum ($P < 0.05$, respectively) (Fig. 5).

Similar data were obtained when DAT-ir quantifications were performed (data not shown).

**Striatal Dopamine and 5-HT Concentrations in METH-Treated Mice**

Seven days after METH administration (4 mg/kg, three times at 3 h intervals), there was a reduction (76%) in the striatal dopamine content (ng/g tissue) of METH-treated mice compared to saline ($P < 0.001$). The metabolites of dopamine, DOPAC and HVA, were also affected by treatment with METH. DOPAC was reduced by 64% ($P < 0.001$) and HVA levels by 59% ($P < 0.001$) in the METH-treated mice (Fig. 6). There were no differences between METH- and saline-treated animals in striatal 5-HT concentration or 5-HIAA concentration ($P = 0.67$ and $P = 0.63$, respectively) (Fig. 6).

**METH Administration Does Not Affect TH-ir in the Nucleus Accumbens**

In contrast to our finding that administration of METH produces a marked loss of TH and DAT fibers in the striatum, we found no change in TH- or DAT-ir in the nucleus accumbens (NAc) (Fig. 7). Quantitative image analysis revealed no significant difference in TH-ir in the NAc between METH- and saline-treated mice 7 days after METH administration ($P = 0.12$) (Fig. 7c). These studies demonstrate that METH selectively reduces dopaminergic terminals in the striatum, but not in the NAc.

**Discussion**

Previous studies have shown that acute administration of repeated doses of METH to mice induces a long-term neurotoxic effect reflected by selective loss of nigrostriatal dopamine markers. The overall aim of this study was to investigate whether the striosome and matrix compartments of the mouse striatum show differential vulnerability to METH as evidenced by differences in TH- and DAT-immunostaining. This study provides the first evidence that METH produces a greater loss of TH/DAT positive terminals in the striosomes than in the matrix, suggesting that the striosomes are differentially affected by METH. Furthermore, under our experimental conditions, METH produces no toxicity in the mesolimbic dopaminergic pathway.

Levels of TH- and DAT-immunoreactivity are commonly used indexes of dopaminergic terminal damage (Iravani et al. 2005; Pavón et al. 2006; Granado et al. 2008a, b; Darmopil et al. 2008, 2009), and decreased TH levels have been reported after treatment with dopaminergic neurotoxins including METH, MDMA, 6-OHDA, and MPTP (Moratalla et al. 1992; Fornai et al. 2004; Broening et al. 2005; Iravani et al. 2005; Pavón et al. 2006; Thomas et al. 2009). In this study, we have demonstrated a marked loss of TH expression in the striosomes of mice treated with METH. In addition, this decrease in TH expression is accompanied by a reduction in DAT, an important marker of functional dopaminergic nerve terminals. The decrease in DAT expression indicates that the decreased TH-ir is not due to a decrease in TH synthesis but rather due to neuronal damage of dopaminergic terminals. This is further supported by the reduction in the concentration of dopamine and its principle metabolites in the striatum of METH-treated mice.
Although the mechanism underlying the neurodegeneration of dopaminergic nerve terminals is not known, a substantial body of evidence indicates that oxygen and nitrogen reactive species play an essential role. A single injection of METH induces a rapid increase in 2,3-DHBA in the striatal dialysate lasting for at least 2 h, a clear indication that hydroxyl radicals are being formed (Battaglia et al. 2002). Oxygen reactive species could come from auto-oxidation of extravesicular dopamine producing hydrogen peroxide (H$_2$O$_2$) which forms hydroxyl radicals and superoxide anion (O$_2^-$) (Simola et al. 2007). These species could, in turn, react with NO to generate the potent oxidant peroxynitrite (ONOO$^-$) and other reactive oxygen radicals (Beckman 1991; Radi et al. 1991). METH increases 3-nitrotyrosine levels in mouse striatum, an index for ONOO$^-$ production, and this effect is absent in nNOS knockout mice or mice overexpressing Cu/Zn superoxide dismutase (SOD) (Imam et al. 2001). In addition, nNOS inhibitors completely prevent the loss of dopamine induced by METH (Itzhak et al. 2000; Sanchez et al. 2003), and the neurotoxic effects of METH in the striatum are attenuated in transgenic mice overexpressing Cu/Zn-SOD (Cadet et al. 1994; Hirata et al. 1996). The latter results are particularly relevant since SOD is more abundant in the matrix than in the striosomes (Medina et al. 1996; Zhang et al. 1994) and this distribution
pattern tightly corresponds with the relative preservation of TH- and DAT-ir in the matrix following METH. Therefore, it seems reasonable to propose that the increased susceptibility of the striosomal compartment to the damaging effects of METH may be related to a lower antioxidant capacity in striosomes than in matrix. It is likely that at higher doses of METH, the differential vulnerability between striosomes and matrix that we report here might be lost since the higher METH dose would overwhelm the protective capacities of both compartments.

A similar pattern of greater striosomal damage in the striatum has been observed following the administration of other neurotoxins such as MDMA (Granado et al. 2008a, b) and MPTP (Iravani et al. 2005), or NMDA receptor agonists such as quinolinic acid (Figueroedo-Cardenas et al. 1998). It is also seen in early Huntington’s disease (Hedreen and Folstein 1995) and following ischemia/reperfusion injury (Burke and Baimbridge 1993; Medina et al. 1996). Given the role of free radicals in cell damage (Fiskum et al. 1999), the difference in SOD levels between the striatal compartments may offer at least a partial explanation for the differential vulnerability observed in all these conditions. It suggests that common mechanisms may underlie the cell damage caused by these different neurotoxins and neurodegenerative diseases.

On the other hand, METH increases the extracellular concentration of glutamate in striatum (Nash and Yamamoto 1992; Stephens and Yamamoto 1994), and glutamate is involved in mediating the neurotoxic effects of METH by overactivating N-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, causing excitotoxicity. In fact, NMDA receptor antagonists block the long-term dopamine loss induced by METH (Fuller et al. 1992; Layer et al. 1993; Ohmori et al. 1993; Thomas and Kuhn 2005; Ke et al. 2008). AMPA and NMDA glutamate receptors have differential distribution in the striatal compartments. AMPA receptors containing GluR1 may predominate in striosomes, while AMPA receptors with GluR4 are more abundant in the matrix (Martin et al. 1993). NMDA receptors also appear to predominate in striosomes as suggested by in vitro studies showing that NMDA had a greater stimulatory effect on the release of dopamine in the striosomes than in matrix compartment (Gauchy et al. 1996). Thus, striosomes and matrix appear to express different glutamate receptors or receptor subunit combinations which could have consequences relevant to the neuropathology induced by METH. The idea that differences in glutamate receptor activation play a role in the degree of neurotoxicity in different striatal compartments is supported by reports that calbindin expression is associated with relative resistance to MPTP damage since high intracellular levels of calcium binding protein may protect the cell against excessive calcium entry (Burke and Baimbridge 1993). Interestingly, the calbindin distribution pattern in the striatum corresponds with the pattern of relative protection against METH-induced dopaminergic loss in the matrix.

In conclusion, this study indicates that in mice METH produces greater damage to the dopaminergic nerve terminals in the striosomes than to those in the matrix, where the mesolimbic dopaminergic pathway is relatively preserved. The neurotoxicity which leads to this greater vulnerability of the striosomes and the nigrostriatal dopaminergic pathway may involve factors that are common to other types of neuronal injury such as those produced by ischemia, excitotoxicity, MPTP, or HD. Further studies are necessary to evaluate the precise mechanisms involved in this drug-induced cell damage and to determine why striosomes are uniquely sensitive to METH and to other neurodegenerative diseases.

Fig. 7 The NAc does not exhibit METH-induced neurotoxicity. Photomicrographs of TH-immunoreactivity in the NAc of mice treated with saline (a) or METH (b). Animals were killed 7 days after treatment. c Histograms of the proportional stained area of TH-immunoreactivity. METH (4 mg/kg, i.p., every 3 h, 3×) produced no reduction in TH-immunoreactivity. Data represent mean ± S.E.M., P = 0.12; n = 6 animals/group. Bar 500 μm.
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