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Rapid communication

A rapid and reversible change in dopamine transporters induced by methamphetamine

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Received 20 February 1997; accepted 25 February 1997

Abstract

Because high doses of methamphetamine promote free radical formation, and striatal dopamine transporters are rapidly inactivated by oxidative events, we determined the effect of a single high dose of methamphetamine on dopamine transporter activity in striatal synaptosomes. One hour after methamphetamine administration, dopamine uptake decreased by 48%. This dramatic decline was totally reversed by 24 h after treatment. These findings suggest that methamphetamine reversibly decreases dopamine transporter activity by oxidative mechanisms.

Keywords: Methamphetamine; Dopamine transporter; Free radical

Methamphetamine abuse is a major health problem (U.S. Department of Justice, 1996). Of particular concern are reports that high doses of this phenylethylamine cause long-term deficits in monoamine systems in brain regions such as the striatum (Sonsalla et al., 1986; Ricaurte et al., 1982). There is evidence that dopamine released by methamphetamine is a causative factor due to the tendency of dopamine to form reactive oxygen species (Schmidt et al., 1985). This hypothesis is supported by a recent report from Giovanni et al. (1995). Of particular relevance to the present study is the report by Stone et al. (1989) that a single dose of methamphetamine causes a rapid, but reversible, decrease in the activity of tryptophan hydroxylase (the rate-limiting synthesizing enzyme of serotonin) consequent to the production of reactive oxygen species. This finding suggests that other monoamine functions might be similarly altered.

Dopamine transporters on striatal synaptosomes are rapidly inactivated by reactive oxygen species (Berman et al., 1996). The vulnerability of dopamine transporters to oxidative inactivation suggests that reactive oxygen species promoted by methamphetamine may rapidly reduce the function of this membrane carrier protein, much like its effects on tryptophan hydroxylase activity. To test this hypothesis, we administered a single dose (s.c.) of 15 mg/kg methamphetamine to male (200–250 g) Sprague-Dawley rats. Striatal synaptosomes were prepared from the brains of animals decapitated either 1 or 24 h after treatment and incubated in the presence of [^{3}H]dopamine (0.5 nM final concentration) according to the technique described by Fleckenstein et al. (1996).

One hour after a single high dose of methamphetamine, the apparent activity of the dopamine transporter was dramatically reduced by 48%. Transporter activity returned to 112% of control by 24 h after treatment (see Fig. 1). It was determined that the reduction in the dopamine transporter activity 1 h after drug treatment was not due to the direct effects of residual methamphetamine in the synaptosomal preparation. For example, the methamphetamine concentration in synaptosomes prepared from drug-treated animals was approximately 1 nM: this was less than 1% of the concentration of methamphetamine (291 ± 4 nM) required to decrease [^{3}H]dopamine accumulation in synaptosomes by 50%. Moreover, successive washing of synaptosomes prepared from methamphetamine-treated rats did not diminish the methamphetamine-induced decrease in [^{3}H]dopamine uptake, thereby supporting the conclusion that this methamphetamine effect was not due to residual levels of the drug.

Our findings revealed for the first time that a single high dose of methamphetamine can cause a rapid, but reversible, reduction in striatal dopamine transporter activity. This effect is distinct from the permanent deficits

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PII S0014-2999(97)00148-9

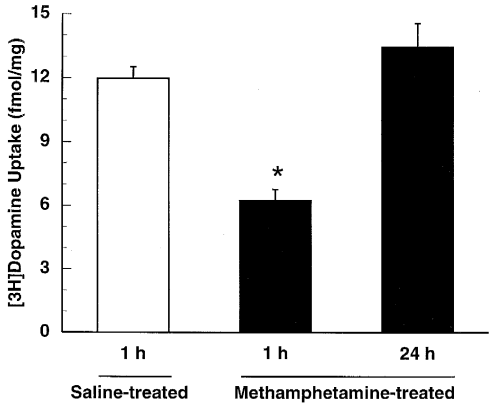

Fig. 1. Treated rats (solid columns) received methamphetamine (15 mg/kg, s.c.) 1 or 24 h prior to decapitation. Control rats (open column) received saline vehicle (1 ml/kg, s.c.) 1 h prior to decapitation. Columns represent the means ± S.E.M. ($n = 8$ rats). * Value for methamphetamine-treated rats that differs significantly from saline-treated controls ($P < 0.0001$ via ANOVA; Scheffe post-hoc comparison).

which occur in dopamine transporters after multiple administrations of high doses of methamphetamine. The long-term reductions are likely associated with degeneration of dopamine terminals due to the neurotoxicity caused by multiple exposures to this drug (Ricaurte et al., 1982). Although the involvement of oxygen radicals in this rapid effect after a single drug dose was not tested directly, the ability of methamphetamine to stimulate the formation of reactive oxygen species (Stone et al., 1989; Giovanni et al., 1995), and the vulnerability of the dopamine transporter to oxidative inactivation (Berman et al., 1996), suggest that reactive species may be an important mediator of this reduction in dopamine transporter activity. Particularly intriguing is the temporary nature of the methamphetamine-induced reduction in the transporter function. The restoration of transporter activity was not likely due to production of new replacement transporter protein since the 6.3 day turnover half-life for the dopamine transporter protein (Fleckenstein et al., 1996) is much too long to account for the rapid and complete restoration of function observed in the present study.

One possible explanation for the relatively rapid recovery of dopamine transporters is that a methamphetamine-initiated oxidative inactivation of the transporter was reversed by reducing events. This possibility is supported by the fact that an antioxidant environment restores tryptophan hydroxylase activity after decreasing to approximately 50% of control 1 h following a similar methamphetamine treatment (Stone et al., 1989). These novel findings concerning dopamine transporters may have very important mechanistic implications relative to behavioral and neurochemical consequences of high-dose methamphetamine treatment. In addition, if reactive oxygen species are the mediators of this deficit in transporter activity, it is possible that oxidation of this protein is an effective means for rapid and reversible regulation of dopamine reuptake into its respective neurons and may be an important form of physiological regulation for this function.

Acknowledgements

This research was supported by USPHS grants DA00869, DA04222 and DA10236 from the National Institute on Drug Abuse.

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