Role of Dopamine in the Neurotoxicity Induced by Amphetamines and Related Designer Drugs

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INTRODUCTION

In 1971, extensive excitement about the increasing abuse of amphetamines piqued the authors' interest in the effects of amphetamine and its analogs on biogenic amine metabolism; specifically, whether the biosynthesis of biogenic amines may be altered. In the prior year, Mandell and Morgan (1970) reported that methamphetamine (METH) produced an increase in adrenal tyrosine hydroxylase (TH) activity. Fibiger and McGeer (1971) also observed that chronic treatment with METH caused an increase in TH activity in the adrenal gland and a decrease in enzyme activity in the neostriatum.

METHAMPHETAMINE STUDIES

METH Effects on the Dopaminergic System

In an attempt to simulate in rats the dosage regimen commonly employed by abusers of amphetamines, METH was administered (10 or 15 mg/kg every 6 hours; four to six doses), after which the animals were killed (Koda and Gibb 1971: Koda and Gibb 1973). TH activity and catecholamine concentrations were measured in various brain regions and in the adrenal. Neostriatal TH activity was depressed in a dose-dependent manner and reached its nadir at 36 hours. Dopamine (DA) and norepinephrine concentrations were initially elevated, but then decreased in parallel with TH activity. Adrenal TH activity was elevated. presumably because of stress associated with the toxic doses of METH.

It was later determined whether this was a generalized response to METH of all transmitter systems or whether it was characteristic of specific systems. In the dosage used, METH did not affect striatal choline

acetyltransferase or glutamic acid decarboxylase; however, tryptophan hydroxylase (TPH) activity was dramatically decreased (Hotchkiss et al. 1979). These observations suggested that METH selectively altered the dopaminergic and serotonergic systems, but did not change the striatal cholinergic or GABAergic systems.

METH Effects on the Serotonergic System

While there are significant similarities in the response of the dopaminergic and serotonergic systems to METH, there are also qualitative and quantitative differences. Decreases that occur in the serotonergic parameters are much larger than the changes in parameters of the dopaminergic system; moreover, the doses required to obtain the response in the serotonergic system are lower. Furthermore, the decrease in striatal TH activity is not observed until approximately 12 hours after METH administration, while there is a pronounced effect in the serotonergic system within 15 to 30 minutes. (figure 1). TPH activity and serotonin (5-HT) concentrations declined rapidly, while concentrations of 5-hydroxyindoleacetic acid (5-HIAA) were transiently elevated after a single dose of METH; tryptophan content was also elevated after a single dose of METH. Similar responses occurred with *p*-chloroamphetamine and amphetamine (Peat et al. 1985). Since dopaminergic fibers are confined to fewer regions of the brain, while the serotonergic system is present in many brain areas, the effect of METH on the brain serotonergic system is more widespread than is the dopaminergic response (Hotchkiss and Gibb 1980).

When only a single dose of METH (10 mg/kg) was administered, TPH activity returned to normal in all areas within 2 weeks after administering the drug (Bakhit and Gibb 1981). However, with repeated administration of METH (five doses, given every 6 hours), TPH activity in the neostriatum, cerebral cortex, nucleus accumbens, and hippocampus recovered to some extent but remained significantly depressed 110 days after the last dose of the drug had been administered; neostriatal TH activity was also depressed after 110 days.

These findings suggest that, although a single exposure to METH does not result in permanent alteration of the serotonergic system, repeated administrations of large doses of METH result in sustained damage. These observations, together with the METH-induced morphological alterations (Ricaurte et al. 1982) and the compromised uptake of DA (Wagner et al. 1980), suggest that METH, given in repeated, large doses, is neurotoxic to brain serotonergic and dopaminergic neurons.

Role of DA and Its Reactive Metabolites

After the response to METH had been relatively well characterized, the mechanism responsible for the effect was still unidentified. Since DA

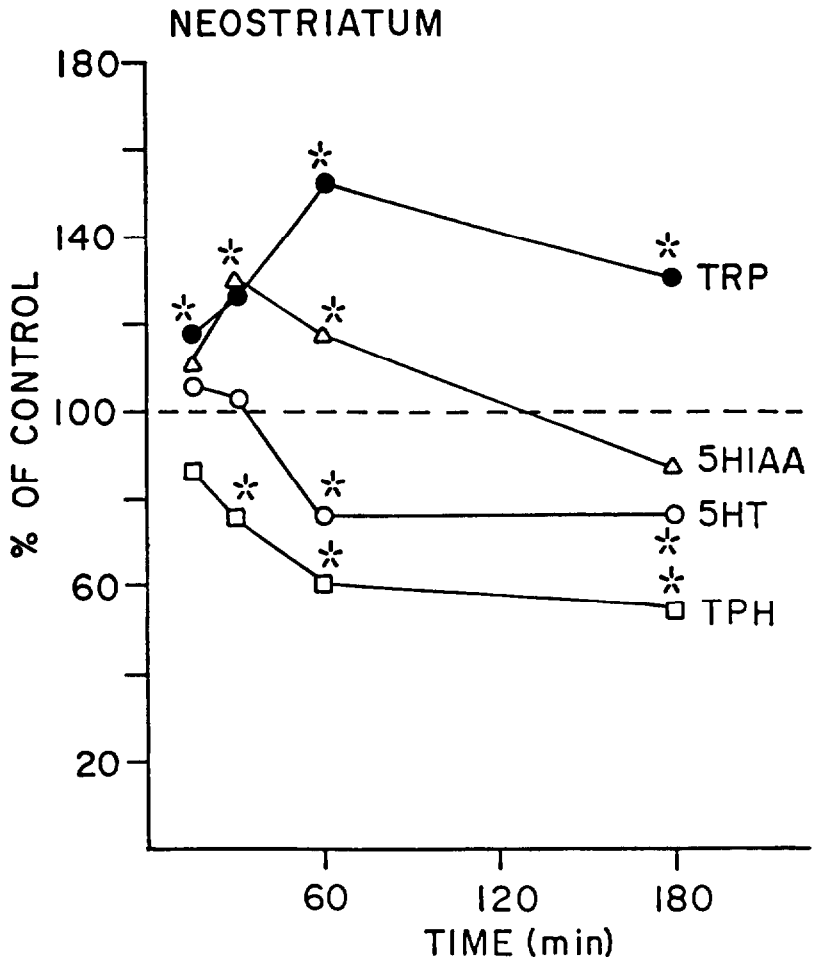

FIGURE 1. *Effect of acute METH on serotonergic parameters*

*Significantly different from control, $p<0.05$ by Student's *t*-test.

NOTE: A single dose of METH (10 mg/kg. SC) was administered and rats were killed 3 hours later. TPH activity and concentration of tryptophan (TRP), 5-HT. and 5-HIAA in the neostriatum were determined; saline control values (means ± SEM): 5-HT. 0.75±0.l; 5-HIAA, 0.72± 0.06, TRP, 5.68± 0.17 ng/mg; TPH activity, 24.5± 1.4 nmol/g tissue/hr (n=6 or more).

antagonists had previously been reported to attenuate other effects of amphetamines (Lasagna and McCann 1957; Randrup et al. 1963; Espelin and Done 1968), the influence of chlorpromazine or haloperidol on the METH-induced decreases in TH activity (Buening and Gibb 1974) was

investigated. Either drug prevented the response of TH to METH in the neostriatum; moreover, at the dosage used, haloperidol prevented and chlorpromazine attenuated the elevation of adrenal TH activity. More recently, it was found that the decrease in striatal TH activity is both a D_1- and D_2-mediated event (Sonsalla et al. 1986).

Whether the serotonergic responses to METH could be attenuated by DA antagonists was next examined (Hotchkiss and Gibb 1980). Surprisingly, haloperidol, administered concurrently, prevented the METH-induced decrease in neostriatal TPH activity (figure 2). Similar responses were observed in the cerebral cortex.

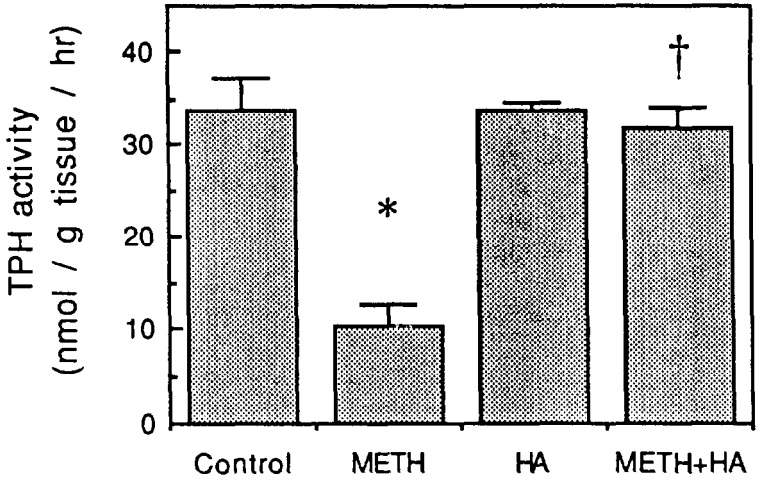

FIGURE 2. *Effect of HA on METH-induced decrease in neostriatal TPH activity*

*p<0.05 compared to control.

†p<0.05 vS. METH done by Student's *t*-test

NOTE: METH (15 mg/kg, SC) was administered four times at 6-hour intervals and rats were killed 5 days after the first administration. HA (3 mg/kg. IP) was administered on the same schedule (n=4 to 10).

Subsequent experiments revealed that DA is necessary for METH to cause neurotoxicity; when DA synthesis was inhibited with α-methyl-*p*-tyrosine (MT), the usual decrease in striatal TH activity observed after METH was prevented (figure 3A) (Kogan and Gibb 1979). Reinstatement of DA synthesis by administering, *l*-dopa. which circumvents the inhibited TH step, returned the METH-induced decreased in TH activity.

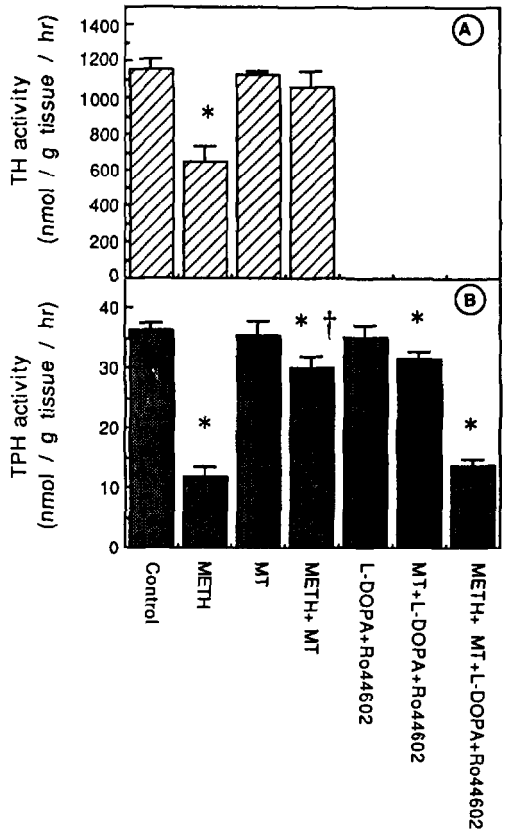

FIGURE 3. *A. Inhibition of DA synthesis on the METH-induced decrease in neostriatal TH activity. B. Inhibition of DA synthesis on the METH-induced &crease in neostriatal TPH activity*

*p<0.05 vs. Control

†p<0.001 vs. METH alone, by Student's *t*-test

NOTE: A. METH (15 mg/kg, SC) was administered four times at 6-hour intervals, and rats were killed 5 days after the first administration. MT (60 mg/kg, lP) was administered on the same schedule. B. METH (IS mg/kg. SC) was administered five times at 6-hour intervals, and rats were killed 18 hours after the first administration. MT (60 mg/kg. IP), *l*-dopa (50 mg/kg. IP), and RO 44602 (25 mg/kg, IP) were administered concurrently (n=4 to 10).

More fascinating was the response of the serotonergic system to MT and METH. When DA synthesis was interrupted by concurrent administration of MT, TPH activity remained normal after METH; however, when DA synthesis was reinstated by administering concurrently *l*-dopa, a peripheral

dopa decarboxylase inhibitor (RO 44602). MT, and METH, the METH-induced depression of TPH activity was again observed (figure 3B).

It was thought that additional evidence for involvement of DA in the serotonergic response to METH could be obtained by selectively destroying the dopaminergic input to the neostriatum with bilateral injections of the neurotoxin 6-hydroxydopamine (6-OHDA) into the substantia nigra. METH was then administered to determine whether the decrease of TPH activity caused by METH would be absent in the neostriatum but present in the other regions. 6-OHDA was injected bilaterally into the substantia nigra 11 days prior to METH administration. In the neostriatum, deprived of dopaminergic input, there was no decrease in TPH activity. In the frontal cortex and hippocampus, however, the METH-induced decrease in TPH activity still occurred (Johnson et al. 1987).

In summary, three different approaches were used to examine the role of DA in the METH response: first, blockade of DA receptors by haloperidol or more specific DA antagonists prevented the METH-induced alteration of the dopaminergic and serotonergic systems, suggesting that DA may be involved in these alterations; second, when DA synthesis was inhibited, the METH-induced changes were prevented in both monoaminergic systems; finally, when dopaminergic input to a specific brain region was interrupted, the METH-induced decrease in TPH activity in that brain region was selectively abolished.

OTHER DRUG STUDIES

Effect of MDMA on Serotonergic and Dopaminergic Systems

In 1985, Seiden and his coworkers reported that 3,4-methylenedioxyamphetamine (MDA) caused a decrease in brain 5-HT and 5-HIAA concentrations; 5-HT uptake was also compromised (Ricaurte et al. 1985). We compared the effects of the methylenedioxy derivatives of METH and amphetamine on the serotonergic and dopaminergic parameters previously demonstrated as altered by METH administration (Stone et al. 1986).

When 3,4-methylenedioxymethamphetamine (MDMA) or MDA was administered to rats in a single dose, TPH activity was markedly depressed. Multiple doses of MDMA or MDA resulted in a further decline in TPH activity (figure 4). In contrast to METH, however, neither MDA nor MDMA altered neostriatal TH activity. The decrease in TPH activity was accompanied by a dramatic decrease in 5-HT and 5-HIAA concentrations; these changes in TPH activity and in 5-hydroxyindole content also occurred in other serotonergic terminal areas such as the hippocampus and cerebral cortex. Both neostriatal DA and homovanillic acid (HVA) were initially elevated 3 hours after a single dose of MDMA, but had returned to normal

by 24 hours. Dihydroxyphenylacetic acid (DOPAC) concentrations were initially decreased (15 minutes) and had recovered by 24 hours.

Subsequent experiments were designed to characterize further the response of the serotonergic system to MDMA. When a single low dose (5 mg/kg) of MDMA was administered, there was an initial decrease in TPH activity and concentrations of 5-HT and 5-HIAA. These serotonergic parameters

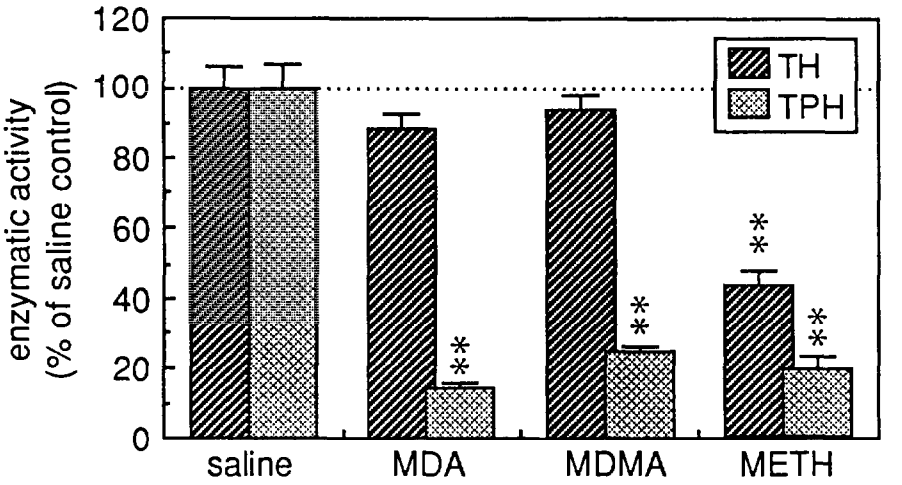

FIGURE 4. *Effect of multiple-dose drug treatment on neostriatal TH and TPH activity*

**p<0.01 vs. saline control, by Student's *t*-test.

NOTE: Rats were administered five SC doses of MDA (10 mg/kg). MDMA (10 mg/kg). or METH (15 mg/kg), one dose every 6 hours. and killed 18 hours after the last dose. Results are presented as the means ± SEM, expressed as a percent of saline control. Control values were: TH, 2645± 163 nmol tyrosine oxidized/g tissue/hr and TPH, 45.0± 3.5 nmol 14CO2 liberated/g tissue/hr

returned toward control and were essentially normal 2 weeks after the single dose. If, however, higher doses of MDMA (10 mg/kg, given every 6 hours) were administered and the serotonergic parameters were monitored for varying periods of time after discontinuing treatment, neostriatal TPH activity and concentrations of 5-HT and 5-HIAA remained significantly depressed for at least 110 days (figure 5) (Stone et al. 1987). The timecourse of recovery was similar in other serotonergic terminal regions examined.

Role of DA in MDMA-Induced Changes in the 5-HT System

The possible role of DA in the MDMA-induced alterations of the serotonergic system was then examined. Techniques previously used in studying the role of DA in the METH-induced neurochemical effects were employed. When DA synthesis was inhibited with MT, the effect of multiple doses of MDMA on TPH activity (figure 6) and concentrations of 5-HT and 5-HIAA was attenuated. The degree of protection with MT seemed to be a function of the size and number of doses of MDMA used as well as a function of the serotonergic parameter that was measured.

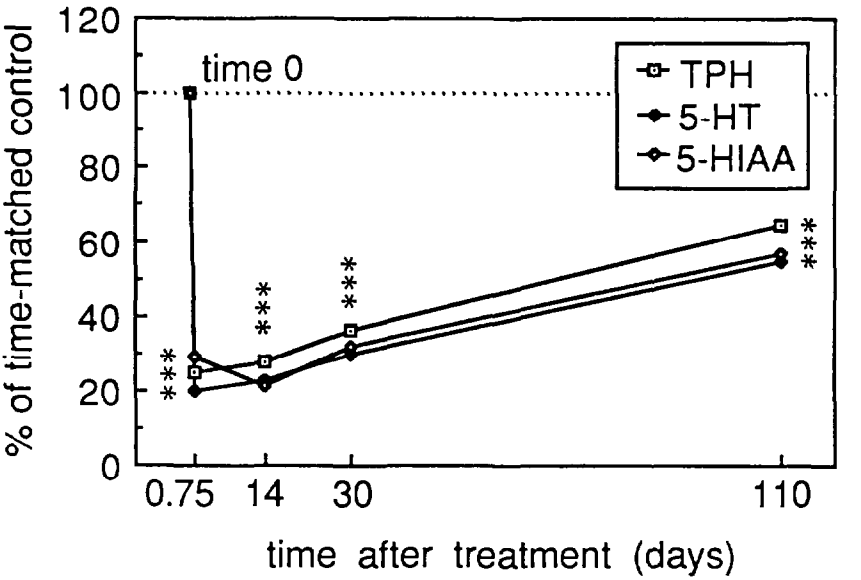

FIGURE *5. Long-term recovery of neostriatal serotonergic parameters after multiple doses of MDMA*

*p<0.01 vs. time-matched saline, by Student's *t*-test

NOTE: Rats were administered live doses of MDMA (10 mg/kg). one dose every 6 hours, and killed at specified times thereafter. Results are the means ± SEM (n=6 to 10). expressed as a percent of time-matched saline-treated control.

Moreover, the early transient response to a single dose of MDMA was less attenuated by MT than was the persisting response that occurred after multiple doses of MDMA.

DA was then depleted by using a different drug to determine whether the response to MDMA would be attenuated. When a single high dose of MDMA (20 mg/kg) was administered after reserpine, MT, or MT plus reserpine pretreatment, the usual decrease in neostriatal TPH activity

remaining 3 days after MDMA treatment was completely prevented (figure 7). Additionally, when animals were injected with 6-OHDA bilaterally into the substantia nigra and a single dose of MDMA (10 mg/kg) was administered 11 days later, the acute (3 hours) MDMA-induced decline in neostriatal, but not hippocampal or cortical, TPH activity was significantly attenuated (figure 8).

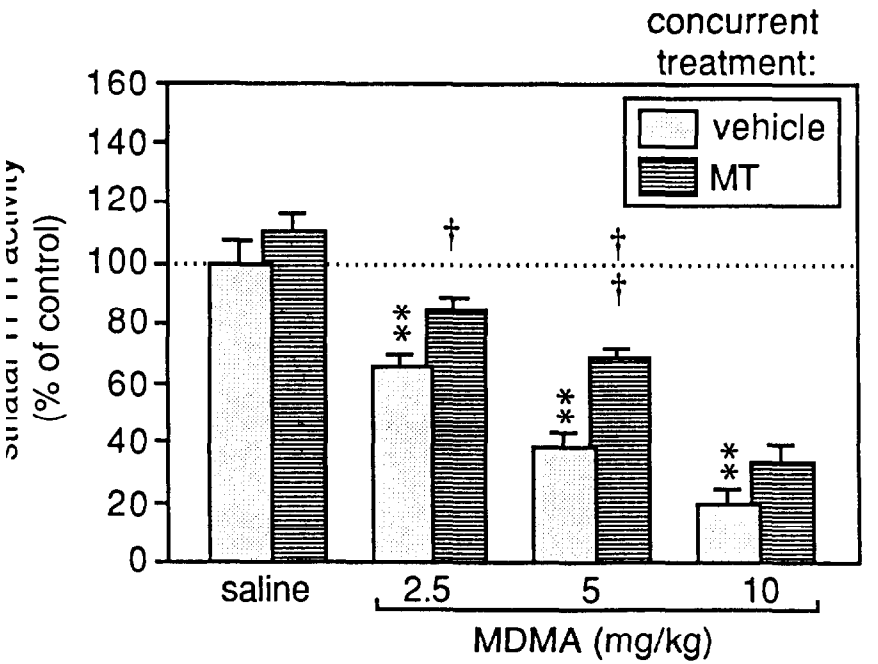

FIGURE 6. *Effect of concurrent MT on the neostriatal TPH deficit induced by multiple doses of MDMA*

**p<0.01 vs. vehicle-saline.

†p<0.05.

††p<0.01 vs. corresponding vehicle-MDMA group, by two-way ANOVA and Newman-Keuls multiple comparisons test.

NOTE: Rats were administered multiple doses of MDMA (2.5, 5, or 10 mg/kg, SC, five doses, one every 6 hr). Concurrent with each MDMA dose, MT (60 mg/kg) or saline vehicle was administered IP. Rats were killed 18 hours after the last dole. Results are the means of ± SEM (n=6 to 8). expressed as a percent of control (vehicle-saline).

It was previously demonstrated that amfonelic acid, a DA-uptake blocker, partially prevented the METH-induced decrease in TPH activity (Schmidt et al. 1985). Recently, effects were investigated of a specific DA-uptake blocker, GBR 12909, on the MDMA-induced response in the serotonergic

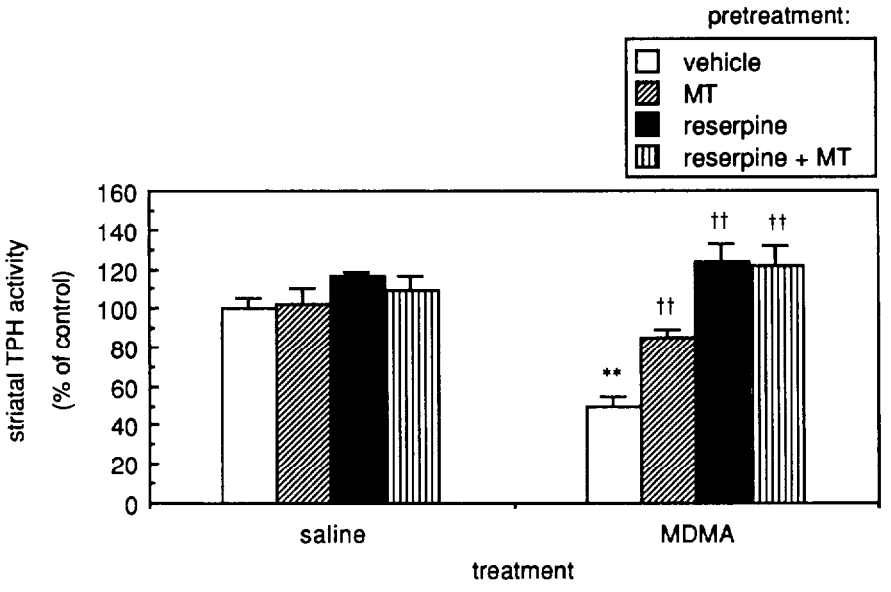

FIGURE 7. *Effect prior DA depletion on the neostriatal TPH deficit induced by a single high dose of MDMA*

**p<0.01 vs. vehicle-saline

†p<0.05.

††p<0.01 vs. vehicle-MDMA by two-way ANOVA and Newman-Keuls multiple comparisons test.

NOTE: Rats were pretreated IP with MT (120 mg/kg. 90 min before), reserpine (5 mg/kg. 12 hr before) or a combination (60 mg/kg MT + 5 mg/kg reserpine, 90 min and 12 hr before, respectiely). A single dose of MDMA (20 mg/kg) was administered after the specified time following pretreatment, and rats killed 3 days later. Results are the means ± SEM (n=6 to 7), expressed as a percent of control (vehicle-saline).

system. GBR 12909 (20 mg/kg) was administered 15 minutes prior to MDMA (20 mg/kg), and rats were killed 3 days later. The DA-uptake blocker significantly attenuated the usual MDMA-induced decrease in striatal TPH activity (figure 9) as well as the decrease in neostriatal 5-HT and 5-HIAA content

These experiments provide evidence that DA and/or its reactive metabolites are likely involved in MDMA-induced changes in the serotonergic system. When DA synthesis was inhibited with MT, or when DA innervation was interrupted by 6-OHDA lesions, the effects of MDMA were prevented or attenuated. Depletion of DA with reserpine, or inhibition of DA uptake with GBR 12909, also attenuated the effects of MDMA on the serotonergic system.

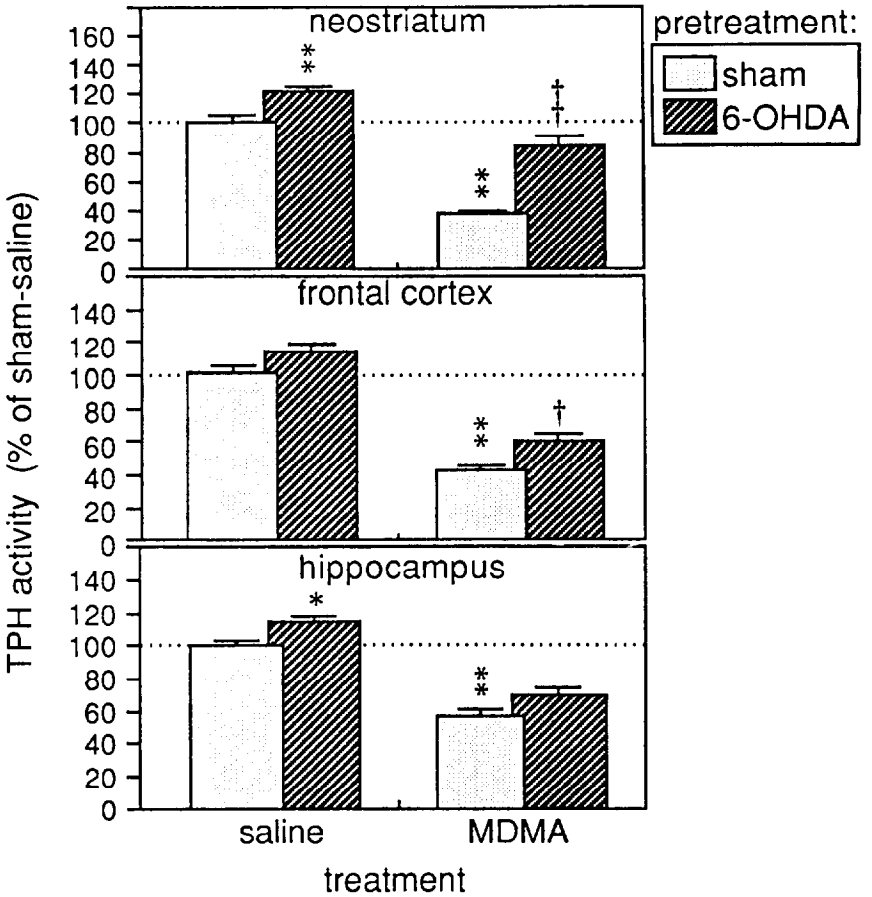

FIGURE 8. *Effect of prior substantia nigral lesions on the immediate MDMA-induced decreases in regional TPH activity*

**p<0.01 vs. sham-saline.

†p<0.05.

††p<0.01 vs. sham-MDMA by two-way ANOVA and Newman-Keuls multiple comparisons test.

NOTE: Lesions were induced bilaterally by local injection of 4 µg 6-OHDA/ 8 µL 0.1% ascorbate. vechile/side. Control rats received sham lesions of ascorbate vehicle alone. After an 11-day recovery period, acute MDMA (10 mg/kg) was adminstered SC and rats killed 3 hours later. Results are the means ± SEM, expressed as a percent of sham-saline (n=22 for sham-saline group, n=14 for 6-OHDA-saline group, n=6 to 8 for MDMA-treated groups). Because 6-OHDA itself significantly elevated TPH activity, values from MDMA-treated rats were expressed as a percentage ± SEM of their respective saline-treated control mean: in the neostriatum, TPH activity for the 6-OHDA-MDMA group was 67.6±5.1% vs. 37.5±2.3% for sham-MDMA, p<0.01 by Student's *t*-test. When similarly expressed, no significant differences were found between sham-MDMA and 6-OHDA-MDMA groups in the hippocampus or frontal cortex.

It is premature to define the exact mechanism by which DA is involved in the response to METH or MDMA. It is known- that these drugs release large quantities of DA and that DA can be readily oxidized to reactive metabolites, which could possibly cause destruction of nerve terminals (Graham 1978; Maker et al. 1986). Moreover, these effects could be enhanced by inhibition of monoamine oxidase, which is known to occur with these drugs (Susuki et al. 1980). The possibility that 6-DOHA is formed and subsequently destroys the nerve terminals, as suggested by Seiden and Vosmer (1984), also requires investigation.

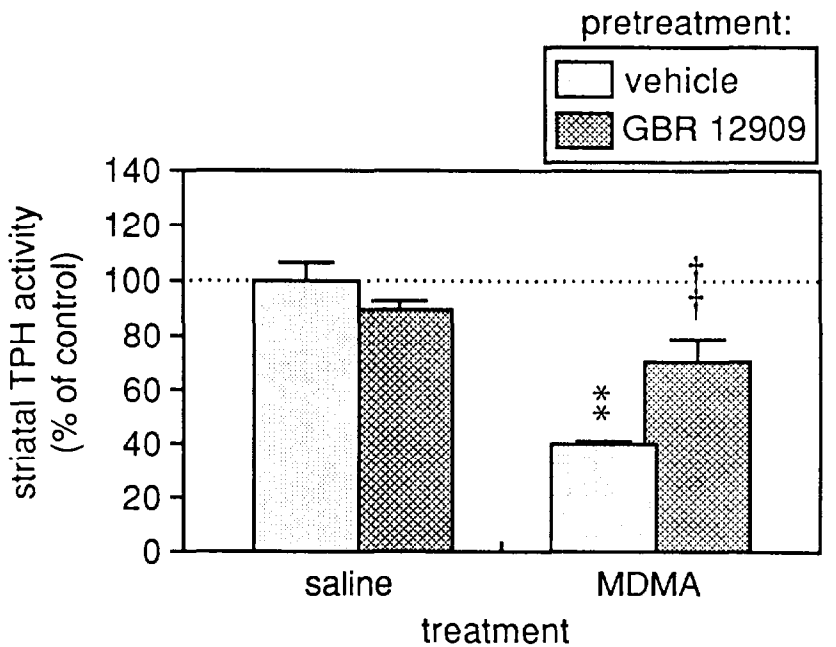

FIGURE 9. *Effect of DA-uptake inhibition on the neostriatal TPH deficit induced by a high single dose of MDMA*

**p<0.01 vs. vehicle-saline.

††p<0.01 vs. vehicle-MDMA by two-way ANOVA and Newman-Keuls multiple comparisons test.

NOTE: GBR 12909 (20 mg/kg, IP) or vehicle was administered 15 min prior to a single dose of MDMA (20 mg/kg. SC); rats were killed 3 days later. Results are the means ± SEM (n=5 to 6). expressed as a percent of control (vehicle-saline).

CONCLUSIONS

Observations made over the last 18 years concerning the effects of METH on the dopaminergic and serotonergic systems, comparisons of the monoaminergic responses to METH and MDMA, and the studies of the possible role of DA and/or its reactive metabolites as mediators in the alterations observed with these drugs provide evidence that DA is necessary for the effects to occur. Further studies are indicated to define more precisely the mechanism(s) responsible for the neurotoxic effects of these drugs. These studies may help to elucidate the potential neurotoxic effects of amphetamine and its related congeners in persons who ingest these agents, and may also have important implications in understanding the etiology of Parkinsonism and mental psychoses.

DISCUSSION

QUESTION: You have dopamine reuptake blockade, you have the SCH 23390 blocking, specifically blocking this tryptophan hydroxylase effect. Do you have a mechanism? How would you see that interaction taking place?

ANSWER: We have thought about that and I think one of the major challenges we have as a group is to determine the mechanism by which this occurs.

I think the results are compatible with the idea that Dr. Seiden has, that it is 6-hydroxydopamine. I think that it could be a 6-hydroxydopamine or some other reactive metabolite of dopamine that is causing the effect.

I think that probably dopamine is taken up and in some way oxidized and therefore may cause the destruction of the nerve terminals. But there are other possibilities as well that need to be explored to find out whether that indeed is the case. I think the jury is still out as to the mechanism that might occur.

COMMENT: That is the reason for mentioning the SCH 23390 being specific for blocking it and the sulpiride is not blocking it--

RESPONSE: In the serotonergic system.

COMMENT: Right, and it wouldn't explain a 6-hydroxydopamine mechanism. It is fascinating that there is that D_1, D_2 relationship.

RESPONSE: Yes, those data are a bit confusing.

I think the fact that haloperidol and all the dopamine antagonists work doesn't bring much clarity to the situation. I think it muddies the water.

But it is there, and I think it is important that we show it here so that the total picture is presented.

COMMENT: I totally agree with the AMT. We have also found that AMT blocks the serotonergic depletion, so we are in agreement.

Furthermore, and we haven't reported it yet, PCPA would also be expected to block the serotonergic depletion. It does nothing to the serotonin toxicity. So you are right, it is somewhat of a mystery as to what is going on.

COMMENT: You have presented some evidence that dopamine may be involved in the neurotoxic action of methamphetamine in terms of dopaminergic neurons, and you presented evidence suggesting that it may be involved in not only the dopamine system but also the serotonin system.

I think one has to be very careful, and it goes back to something that Dr. Seiden raised earlier, that if you are going to speak of the ncurotoxicity, I really think you have to look at a wide array of neurochemical changes, not only at 1 or 2 days but at 2, 3, or 4 weeks. Then the changes should be correlated with morphological changes.

I have no doubt that the bearing on these data is that you have shown the pharmacological effects on tyrosine and tryptophan hydroxylase activity. I am not sure that I can equate those with effects on actual neurotoxicity.

The main reason for my suspicion is that in the experiment with AMT where the effect of methamphetamine on tyrosine hydroxylase activity can be blocked and then reinstituted by coadministering *l*-dopa, one would predict that if one is really talking about neurotoxic effects, then one ought to be able to observe the same changes 2 weeks later.

We have attempted that experiment, And while it is true that on an acute basis we can indeed restore an effect on neurochemical parameters at a day, that is not the case at 2 weeks. This leads me to suspect that one is really dealing with pharmacological effects of methamphetamine, reinstitution of these pharmacological effects with *l*-dopa. But that may not equate with a neurotoxic action of the drug. I think it is important because it opens up the issue of whether dopamine does in fact mediate a neurotoxic action of MDMA and these other compounds rather than some acute pharmacological effects of these drugs.

RESPONSE/QUESTION: I think that your point is well taken, but I would ask: Have you and Dr. Seiden demonstrated your uptake blockade after 2 weeks or so as well? And then I would address the question to you or him--have you done the Fink-Heimer work at longer periods of time?

ANSWER: No, we haven't done the Fink-Heimer work at the longer periods with the blocking agents. We have done the AMT protection experiment 2 weeks later. That seems to work on the 5-HT neurons.

QUESTION: What we really need is to do some morphological studies with something that is very selective for those particular neurons, and I agree with you that that is something we need to strive for. Are you doing that at the Addiction Research Center?

ANSWER: We are trying to look at it using some of the neuroanatomical techniques that you described in terms of localizing uptake sites.

COMMENT: Let me make something clear. We don't need any new techniques. The experiments are very simple; they just have to be done at 2 weeks rather than at 18 hours. And it may be that you are entirely correct, But until those experiments are performed at longer timcpoints, I don't think we know if we are dealing with pharmacology or toxicology.

QUESTION: In your experiments, have you ever looked at the hippocampus? It is interesting to note that there is very little dopamine in the hippocampus. And if the theory of the necessity for dopamine is correct, then you should not see the depletion of serotonin in the hippocampus.

ANSWER: Good point. We have looked at the hippocampus and have found that it is protected. We think that not only dopamine is involved, but probably other catecholamines as well.

QUESTION: How do you imagine that both a receptor antagonist and an uptake inhibitor would block the effects? It would seem that if dopamine is involved, it would either be acting on a membrane receptor or inside, but not both. I would also like to ask a more specific question. You showed that the alpha MT protected effect could be reversed by dopa. And I think you imagined that that was because of dopamine formation. But have you tried dopamine agonists to see if they would antagonize either the protective effect of alpha methyltyrosine or, particularly, the protective effect of the dopamine antagonists to try to verify that those protective effects really have to do with blockade of a dopamine receptor as opposed to some other possibility?

ANSWER: That is a good question. I haven't.

COMMENT: I think that one thing that we are not dealing with effectively is the degeneration in the cortex, which, in our hands, is quite extensive.

Somatosensory cortical, pyramidal cells die at a very high rate with chronic administration. It seems to me that the involvement of dopaminc in that is

less likely, and the postulation that a 6-hydroxydopamine mechanism that doesn't account for the sparing that one sees in certain regions.

RESPONSE: We do have experiments in progress that will address that cortex issue because it is one that needs to be resolved.

COMMENT: We feel that it is due to the formation of 5,6-DHT in the cortex. These cells are indeed innervated by serotonin cells and, as a matter of fact, we have an experiment that is being published in *Brain Research* where we show that if we inject 5,6-DHT into the ventricles, we can produce exactly the same type of degeneration in the pyramidal cells, due to the formation of the 5,6 from the 5-hydroxytryptamine. We are exploring the possibility of it being another catecholamine in addition to dopamine, so I think both of those may be helpful in answering your question.

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