Neurotoxicity of Amphetamines and Their Metabolites

James W. Gibb, Michel Johnson, Ikram Elayan, Heng Keang Lim, Lisa Matsuda, and Glen R. Hanson

When amphetamine or an analog is administered in repeated high doses, neurochemical deficits in both the dopaminergic and serotonergic systems of selected areas of the brain are observed. Methamphetamine (10 to 15 milligrams per kilogram (mg/kg)), administered every 6 hours for 5 doses, decreases rat tyrosine hydroxylase (TH) activity and dopamine (DA) content in the neostriatum within 18 hours after the first dose (Koda and Gibb 1973). Interestingly, these neurochemical deficits persist in rats and nonhuman primates for extended periods of time after the drug is discontinued (Ellison et al. 1978; Bakhit et al. 1981; Woolverton et al. 1989).

Buening and Gibb (1974) demonstrated that DA plays a critical role in the neurochemical deficits observed after methamphetamine administration. The DA antagonists chlorpromazine and haloperidol, when administered concurrently with methamphetamine, completely blocked the metham-phetamine-induced alterations in neostriatal TH activity and DA content. Subsequent studies (Gibb and Kogan 1979) demonstrated that when the rate-limiting enzyme TH was inhibited by administering -methyltyrosine (MT), the neurochemical deficits normally observed with methamphet- amine were prevented. Consistent with the concept that DA is necessary for the methamphetamine-induced neurochemical deficits, the neuro-chemical deficits were again observed when DA synthesis was restored by administering L-dopa.

Not only is methamphetamine administration toxic to the dopaminergic system, but the serotonergic system in the various brain areas is also altered. Hotchkiss and Gibb (1980) reported that methamphetamine, administered as described above, decreased tryptophan hydroxylase (TPH) activity in the serotonergic nerve terminal of rat brain and spinal cord. Similarly, the content of 5-hydroxytryptamine (5-HT) and its metabolite 5-hydroxyindole acetic acid (5-HIAA) were also severely depressed. In contrast to the effects in the dopaminergic system, these serotonergic parameters were decreased by methamphetamine within 15 minutes after a single dose

(Bakhit and Gibb 1981) and were more pronounced than the dopaminergic deficits. Like the dopaminergic changes, these serotonergic alterations persisted for extended periods of time (Bakhit et al. 1981).

Interestingly, the serotonergic changes resulting from toxic doses of meth- amphetamine are also dependent on DA. When MT was administered concurrently with methamphetamine, the decreases in TPH activity and 5-HT and 5-HIAA content were prevented (Hotchkiss and Gibb 1980; Schmidt et al. 1985). When DA synthesis was reinstated by adding L-dopa to the dosing regimen, the neurochemical deficits were again observed. Further evidence for DA dependence was reported by Johnson and colleagues (1987), who destroyed the dopaminergic nerve terminals in the neostriatum by injecting 6-hydroxydopamine (6-OHDA) into the substantia nigra. Eleven days later the usual neurotoxic dosage regimen of metham- phetamine was administered and TPH activity in the neostriatum, cerebral cortex, and the hippocampus was determined. The usual decrease in TPH activity was observed in the cerebral cortex and hippocampus; however, in the neostriatum, which was deprived of dopaminergic input by prior administration of 6-OHDA, the deficit of TPH usually observed with methamphetamine was significantly attenuated.

The pronounced neurochemical deficits in the dopaminergic and serotonergic systems posed the question of whether methamphetamine, administered in these large, repeated doses, was a general neurotoxin affecting all neurotransmitter systems. Hotchkiss and colleagues (1979) found no effects on the cholinergic system or on the glutaminergic system as defined by an absence of any alteration of the respective synthesizing enzymes of these neurotransmitter systems.

Ricaurte and colleagues (1985) demonstrated that an analog of amphetamine, 3,4-methylenedioxyamphetamine (MDA), is neurotoxic to monoamine systems. They observed that neostriatal and hippocampal 5-HT and 5-HIAA contents were depressed after MDA administration and that hippocampal norepinephrine (NE) content was also compromised. In comparing the effects of methylenedioxymethamphetamine (MDMA) and methamphetamine, it was observed (Stone et al. 1986, 1987) that while methamphetamine decreased both TH and TPH activity, MDMA depressed only TPH activity without altering the DA-synthesizing enzyme. Although MDMA releases DA (Yamamoto and Spanos

1988), this analog is selectively neurotoxic to the serotonergic system at doses that do not cause any persisting effect on the dopaminergic system.

Further studies (Stone et al. 1988) provided extensive evidence that the neurochemical deficits induced by MDMA are DA dependent. The deficits in TPH activity and content of 5-HT and 5-HIAA normally seen in MDMA-treated rats were attenuated by concurrent administration of MT; these deficits returned when L-dopa was administered concurrently with MT and MDMA. Prior treatment with 6-OHDA (described above) selectively attenuated the serotonergic deficits in the neostriatum while no protection by 6-OHDA occurred in the hippocampus or cerebral cortex. Prior depletion of DA with reserpine attenuated the neurotoxicity of MDMA. From these experiments the authors concluded that DA and/or its metabolites play a key role not only in the neurotoxicity observed with methamphetamine, but also with its methylenedioxy analogs.

Because of the apparent role for DA in the toxicity caused by methamphetamine and its analogs, the authors reasoned that DA and/or a reactive DA metabolite may be oxidizing components of the dopaminergic and serotonergic nerve terminals to cause the persisting deficits in these two neuronal systems. To test this hypothesis, TPH activity was measured in cerebral cortex from rats treated with toxic doses of methamphetamine, MDMA, or p-chloroamphetamine (Stone et al. 1989). Three hours after receiving one of the amphetamines, the rats were killed and the supernatant fraction of the cerebral cortex containing TPH was obtained. An aliquot of the supertanant was then exposed to various reducing agents in a nitrogen atmosphere for a 24-hour period. As previously observed, enzyme activity from rats treated with the amphetamine analog was markedly impaired compared to that from untreated rats. TPH activity from rats treated with the amphetamine analog was essentially normal in those samples incubated with dithiothreitol, a reducing agent, in a nitrogen atmosphere; other reducing agents were not as effective. A time-response relationship revealed that the enzyme activity could be restored only during the first 6-hour period. After 6 hours, oxidation of the enzyme had apparently progressed to a point where it was irreversible.

METABOLITES OF AMPHETAMINE

Methamphetamine administered directly into the brain is not neurotoxic (Matsuda 1987; Molliver et al. 1986; Berger et al. 1990; Paris and

Cunningham 1990). Furthermore, when methamphetamine or its analogs are incubated with brain slices or homogenates, no impairment of TH or TPH activity is observed. This finding led to an investigation of whether an amphetamine metabolite is responsible for neurotoxicity (Matsuda et al. 1989). Ketamine-anesthetized rats received bilateral injections of either p-hydroxyamphetamine (pOHA) or p-hydroxynorephedrine (pOHN) at doses of 0.5, 5, or 50 micrograms (g) administered directly into the neostriatum. Three hours later, striatal DA and 5-HT contents were determined. The 50 g dose of pOHA or pOHN decreased the concentration of striatal DA to 27 percent and 18 percent of control, respectively. The 5-HT content was also decreased by both metabolites, but not to the same extent as DA. The DA metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) declined in parallel with DA, but 5-HIAA content was not changed by pOHA and was actually elevated after injection of pOHN. The decline in DA and its metabolites reached its nadir at 6 hours and returned to control levels by 48 hours. Surprisingly, TH activity was not altered when either pOHA or pOHN was administered intrastriatally. TPH activity was actually elevated when either of the higher doses of the two amphetamine metabolites was administered.

The effect of systemic administration of these amphetamine metabolites on the content of DA and its metabolites and on 5-HT was then examined. When pOHA was administered systemically (5, 15, or 30 mg/kg), the concentration of DA and its metabolites in the neostriatum was depressed. The effect on the neostriatal serotonergic system was not as pronounced as that on the dopaminergic system; hippocampal serotonin content was altered only at the higher dose of pOHA and hypothalamic 5-HT concentrations were decreased at both the 15 mg and 30 mg doses. The authors then determined the effect of the monoaminergic uptake inhibitors amfonelic acid and cocaine on the response to systemically administered pOHA. The decrease in DA and its metabolites was attenuated by amfonelic acid (1 mg/kg, administered 30 minutes before pOHA), but cocaine failed to alter the effects of systemic pOHA administration.

The metabolites of amphetamine, in the doses administered, decrease the concentrations of DA and its metabolites as well as 5-HT. The pronounced decrease in DA and its metabolites returned to normal within 48 hours. No decrease in either TH or TPH activity was observed concurrent with the decrease in DA. From these observations it appears that these amphetamine metabolites transiently decrease the neurotransmitter concentrations, but are not neurotoxic since the activity of the synthesizing enzymes TH and TPH are not altered.

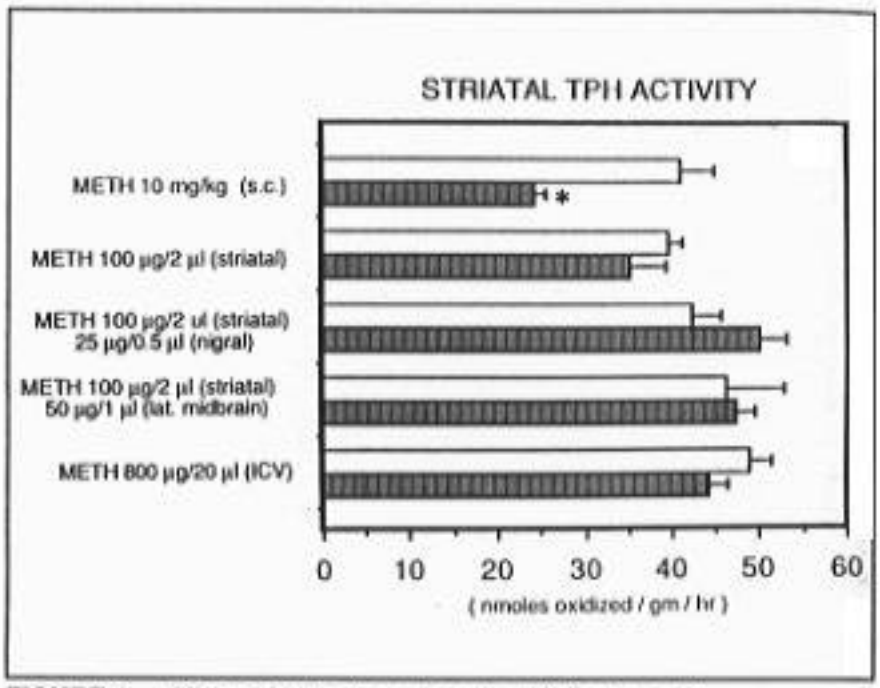

FIGURE 1. *Effects of systemic and cerebral injections of methamphetamine (METH) on neostriatal TPH activity. Rats were anesthetized with ketamine (175-225 mg/kg, IP) 30 min prior to METH treatments (both systemic and cerebral injections) and were killed 3 hr later. Regional cerebral and ICV injections were performed as described. Columns represent average striatal TPH activities (nanomoles (nmoles)/gm/hr) ± SEM (n = 3 to 8).*

KEY: □ = saline (SC)- or mannitol (cerebral injections)-treated controls; ▣ = METH-treated. * = $p < 0.05$ compared to respective controls.

The effects of cerebral injections of methamphetamine on striatal TPH activity were also investigated (figure 1). In an anesthetized rat, systemically administered methamphetamine (10 mg/kg) decreased striatal TPH activity. However, bilateral injections of methamphetamine into the neostriatum (100 g) failed to decrease striatal TPH activity 3 hours after treatment. To determine whether multiple areas of the brain are involved in methamphetamine-induced changes in striatal TPH, microinjections of methamphetamine were administered into the substantia nigra or lateral midbrain and into the striatum. Three hours after treatment, injections of methamphetamine into the striatum (100 g) and the substantia nigra (25 g) or the lateral midbrain (area of B9 serotonergic cell bodies) (50 g) did not reduce TPH activity in the neostriatum.

Similarly, in rats treated with methamphetamine (800 g intracerebroventricularly (ICV)), TPH activity was unaffected in the cerebral cortex and hypothalamus (data not shown) as well as in the neostriatum. These results suggest that direct application of methamphetamine to neural tissues has no effect on TPH activity; however, the possibility cannot be ruled out that the duration of exposure of locally injected methamphetamine, in any region, was too brief to be effective.

METABOLITES OF MDMA

As indicated above, large doses of MDMA cause profound and persisting neurochemical deficits in the serotonergic nerve terminals without any lasting effects on the dopaminergic nerve terminals. Since the parent compound is not toxic when injected directly into the brain (Molliver et al. 1986; Paris and Cunningham 1990), the possibility that one or more MDMA metabolites cause the neurotoxicity observed after administration of large doses of the drug was considered.

2,4,5-Trihydroxyamphetamine

While investigating the metabolism of MDMA, two of the authors' colleagues identified eight metabolites formed in vivo (Lim and Foltz 1991*a*, 1991*b*). The authors injected synthesized metabolites into rats to determine their possible neurotoxicity (figure 2). Rats received a single injection of either 0.25 or 0.5 micromoles (mole) of 2,4,5-trihydroxy-amphetamine (THA) ICV and were killed 7 days later (figure 3).

TPH activity was dramatically decreased in the hippocampus to 5 or 1 percent of control, respectively, with 0.25 or 0.5 moles of the metabolite. The content of 5-HT and 5-HIAA in the hippocampus was also decreased. The striatal serotonergic system was more resistant to the effects of THA. In this structure, TPH activity was decreased to 74 percent and 81 percent of control 1 week after a single injection of 0.25 or 0.5 mol of THA, while the concentration of 5-HT and 5-HIAA remained unaltered. THA administration dramatically decreased all dopaminergic parameters in the striatum.

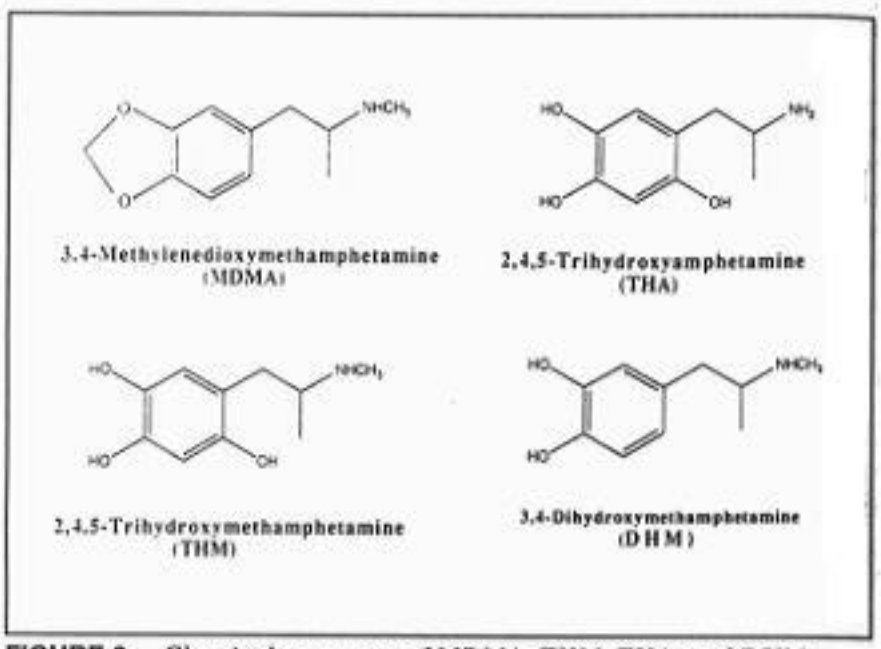

FIGURE 2. *Chemical structures of MDMA, THM, THA, and DHM.*

In response to the administration of 0.25 or 0.5 mol of THA, striatal TH was reduced to 67 and 10 percent of control, respectively (figure 4). A similar decrease in content of DA and its metabolites was observed in the striatum contralateral to the site of injection. When enzyme activity in the dopaminergic and serotonergic cell bodies from the THA-treated rats was examined, no change was observed in the medial or dorsal raphe TPH activity. However, TH activity in the substantia nigra was decreased to 59 and 20 percent of control in animals treated with 0.25 or 0.5 mol of THA, respectively. To assess the response of the noradrenergic system, hippocampal NE content was measured in the THA-treated animals. NE content was lowered to 10 and 18 percent of control after 0.25 and 0.5 mol of THA, respectively.

2,4,5-Trihydroxymethamphetamine

Corresponding experiments were conducted with another analog of MDMA, 2,4,5-trihydroxymethamphetamine (THM). A single dose of 50, 100, or 200 g was administered ICV 5 days before sacrificing the rats and TPH activity was determined in various areas of the brain (figure 5).

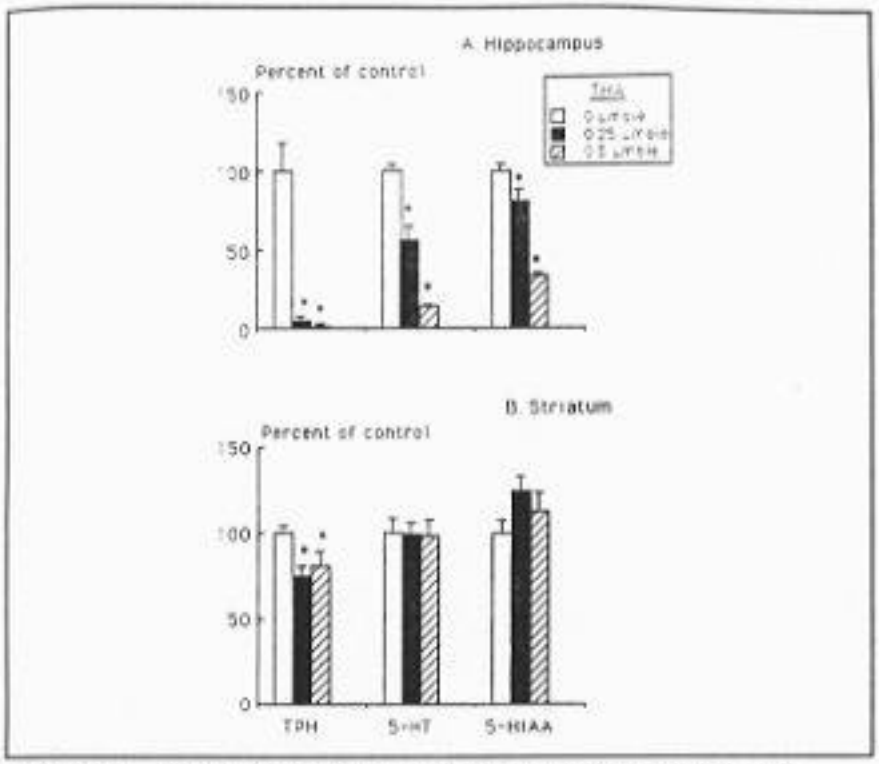

FIGURE 3. *Effect of THA on the hippocampal (A) and striatal (B) serotonergic systems. Rats received a single ICV injection of THA (0 µmol, open bar; 0.25 µmol, black bar; or 0.5 µmol, striped bar) in 20 µl of 0.1% ascorbate saline vehicle and were killed 7 days later. TPH activity was measured in the brain structure ipsilateral to the injection while 5-HT and 5-HIAA concentrations were measured in the brain structure contralateral to the injection. Means ± S.E. (n = 5-8) are expressed as a percentage of control (0 µmol). Control TPH activities, expressed in nmol of hydroxylated tryptophan per hr/g of tissue, were 49.9 ± 9.1 in the hippocampus and 120 ± 4.8 in the striatum. Control 5-HT concentrations (µg/g tissue) were 0.40 ± 0.02 in the hippocampus and 0.50 ± 0.04 in the striatum. Control 5-HIAA concentrations (µg/g tissue) were 0.30 ± 0.01 in the hippocampus and 0.40 ± 0.03 in the striatum. Statistical analysis was performed by ANOVA followed by a Fisher test.*

KEY: * = $p < 0.05$ versus control.

SOURCE: Reprinted with permission from Elayan et al. 1992.

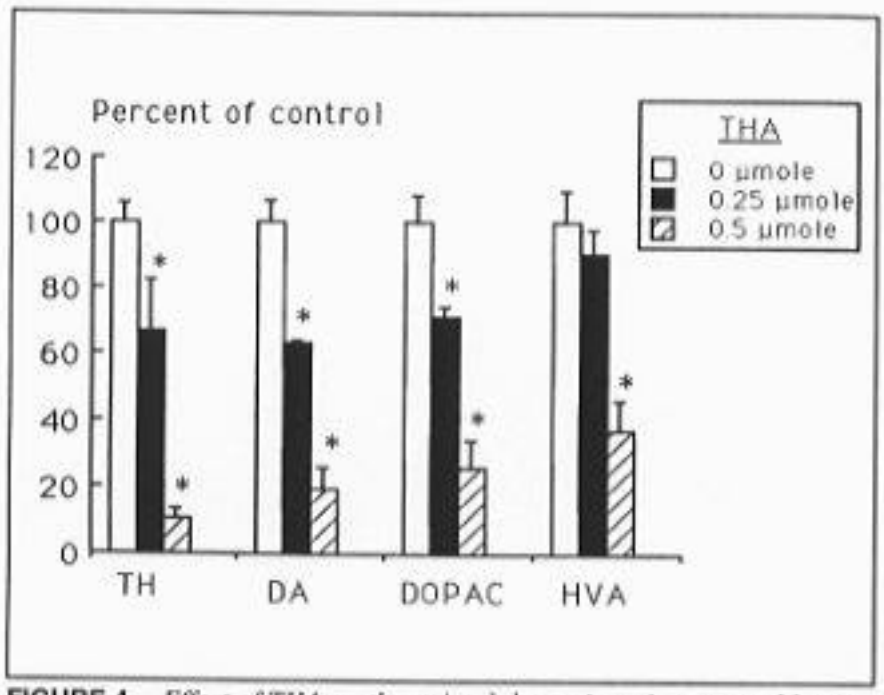

FIGURE 4. *Effect of THA on the striatal dopaminergic system. Means ± S.E. (n = 5-8) are expressed as a percentage of control (0 µmol, open bar). Control TH activity was 1.4 ± 0.1 µmol of hydroxylated tyrosine per h per g of tissue while control values were 8.0 ± 0.6 for DA, 0.60 ± 0.05 for DOPAC, and 0.50 ± 0.05 for HVA (µg/g tissue). Statistical analysis was performed by ANOVA followed by a Fisher test.*

KEY: * = $p < 0.05$ versus control.

SOURCE: Reprinted with permission from Elayan et al. 1992.

Of the three serotonergic terminal areas examined, TPH activity in the hippocampus was most impaired to 58 and 10 percent of control in rats treated with 50 or 200 g of THM. Enzyme activity in the frontal cortex was decreased less than that observed in the hippocampus, while the striatum was least affected. TPH activity in the cell bodies did not decrease; in fact, enzyme activity was elevated in both the medial and dorsal raphe, depending on the dose of THM. The effect of THM on 5-HT content followed a pattern similar to TPH activity in the corres-ponding brain areas, while 5-HIAA concentrations were not altered by THM in these structures.

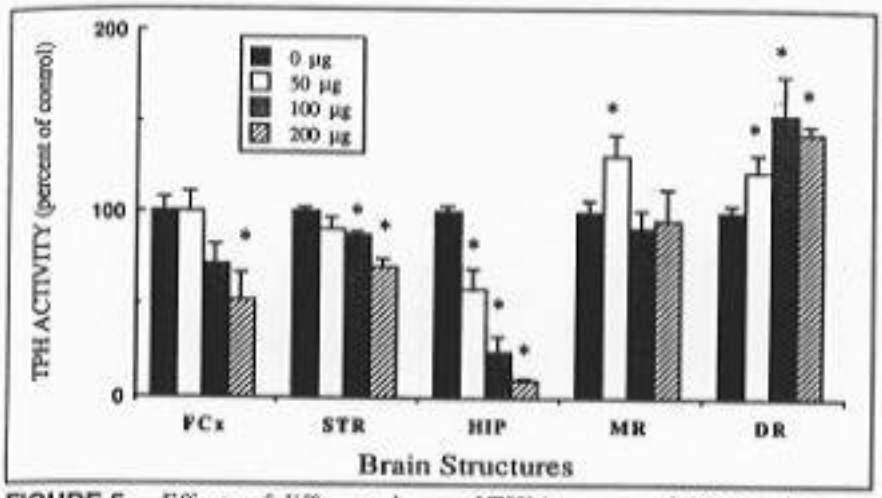

FIGURE 5. *Effects of different doses of THM on central TPH activity. The rats received one ICV injection of THM (50, 100, or 200 µg per 20 µl) or vehicle and were allowed to recover for 5 days. The results are expressed as a percentage of their respective control (means ± S.E.). The control values for TPH activity, expressed as nmol of hydroxylated tryptophan/h/g tissue, were: Fcx, 69.8 ± 5.4; STR, 109.6 ± 4.7; HIP, 143.8 ± 5.2. TPH activity in the MR and in the DR were 6 ± 0.4 and 17.3 ± 0.8 nmol of hydroxylated tryptophan/h/mg protein, respectively (n = 3-11).*

KEY: FCx = frontal cortex; STR = striatum; HIP = hippocampus; MR = median raphe; DR = dorsal raphe. * = $p < 0.05$ versus 0 µg.

SOURCE: Reprinted with permission from Johnson et al. 1992.

The effects of THM on the central dopaminergic system were then examined (figure 6). TH activity was markedly depressed to 76, 56, and 21 percent of control in the striatum of rats administered a single ICV injection of 50, 100, or 200 g, respectively, of THM 5 days previously. A decrease in the content of DA and its metabolites in these structures was also observed. TH activity was not altered in the substantia nigra. Another metabolite of MDMA, 3,4-dihydroxyamphetamine (DHM), was administered ICV (135 g) and the enzymatic response was examined.

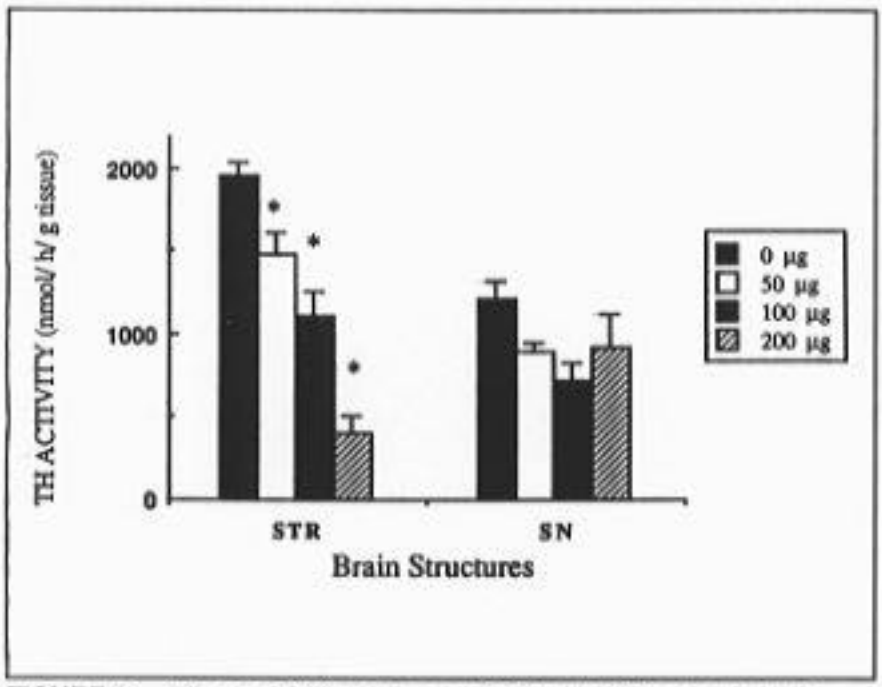

FIGURE 6. *Effects of different doses of THM on STR and substantia nigra (SN) TH activity. The animals were treated as described in figure 3. The results are expressed in nmol of hydroxylated tyrosine/h/g tissue (means ± S.E.) (n = 3-11).*

KEY: * = $p < 0.05$ versus 0 µg.

SOURCE: Reprinted with permission from Johnson et al. 1992.

The activity of TPH was unaltered by DHM, but TH activity was significantly elevated by this metabolite of MDMA.

SHORT-TERM EFFECTS OF MDMA METABOLITES

In the studies cited above, the authors determined the effects of MDMA metabolites 5 to 7 days after administering the drug. In other experiments (described below), rats were administered 1 mol of THA, THM, or DHM ICV and the response was determined 3 hours later. THA decreased TPH activity to 79 percent of control in the neostriatum, but in the hippocampus enzyme activity was markedly decreased to 8 percent of control. THM decreased striatal TPH activity to 87 and 54 percent of control in the striatum and hippocampus, respectively. The only effect of DHM was an elevation of enzyme activity in the striatum.

When the response of the dopaminergic system was investigated, TH activity had decreased to 75 percent of control in the striatum following THA administration, but was unaffected by THM. THA elevated neostriatal content of DA (135 percent), DOPAC (287 percent), HVA (237 percent), and 5-HT (115 percent). THM elevated DOPAC (512 percent), HVA (366 percent), and 5-HIAA (149 percent), but decreased 5-HT (74 percent) striatal content.

The authors had previously demonstrated that the decrease in enzyme activity observed in rats treated for 3 hours with MDMA was reversed by exposing the supernatant fraction containing TPH to reducing conditions (dithiothreitol in a nitrogen atmosphere) for 24 hours. Incubating hippo- campal TPH from animals treated with THM failed to prevent the decrease in enzyme activity caused by the metabolite; this finding suggests that the enzyme changes produced by the metabolite occur by a different mechanism than those caused by the parent compound.

Because THA and THM are structurally similar to 6-OHDA, it was important to ascertain whether 6-OHDA administered in a similar fashion would produce the same response. Since TPH activity from the striatum and the hippocampus was not altered by 6-OHDA after 3 hours, the DA analog is not likely to be responsible for the toxicity associated with administering THA or THM.

It is well established that 5,7-dihydroxytryptamine (DHT) is toxic to serotonergic neurons. Lim and Foltz (1991*b*) reported that THA and THM cyclize, thus forming an indole molecule that is similar in structure to DHT. The effect of DHT on hippocampal TPH activity was therefore examined (figure 7). This serotonergic neurotoxin decreased enzyme activity to 18 percent of control. When TPH was incubated under the reducing conditions described above, there was no reversal of the enzyme activity. This observation would argue against the possibility that DHT is the neurotoxin responsible for MDMA-induced neurotoxicity.

The authors then investigated the effect on hippocampal TPH activity when incubated in vitro with THA (figure 8). The hippocampus or striatum of rats was excised and prepared slices were incubated for 1 hour in buffer containing 0.001, 0.01, 0.1, 0.5, or 5.0 millimoles (mM) THA.

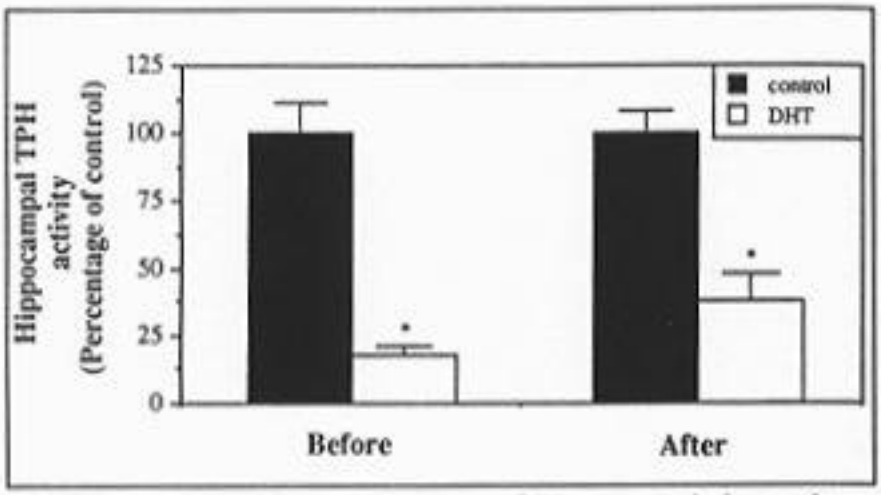

FIGURE 7. *Effect of DHT on hippocampal TPH activity before and after reducing conditions. Rats were administered 1 nmol of DHT by ICV injection and animals were sacrificed 3 hours later. Results are expressed as percentage of control. Control values, expressed as nanomoles of hydroxylated tryptophan/h/g tissue were 133.5 ± 14.5 before reducing conditions and 271.5 ± 20.4 after reducing conditions (means S.E.) (n = 5-8). TPH activity after reducing conditions was not significantly different from that before reducing conditions.*

KEY: * = $p < 0.05$

SOURCE: Reprinted with permission from Elayan et al. 1993.

As depicted in figure 8, TPH activity was markedly inhibited when the enzyme was incubated in vitro with THA. When the enzyme was incubated under reducing conditions, the enzyme activity was not restored to normal. As was observed in vivo, hippocampal TPH was more sensitive than striatal TPH since it was inhibited at a lower concentration of THA. The mechanism responsible for this interesting response is under investigation.

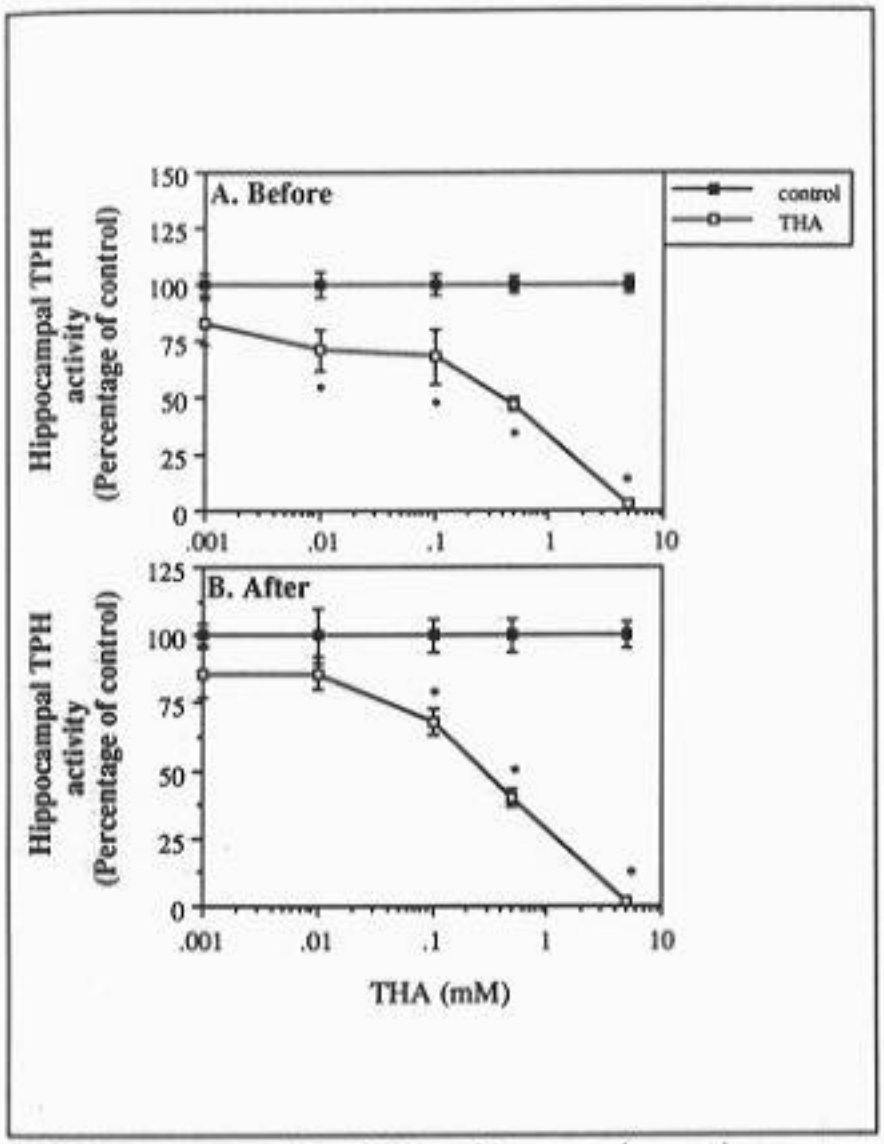

FIGURE 8. *In vitro effect of THA on hippocampal tryptophan hydroxylase activity before (A) and after (B) reducing conditions (a 20-24-h anaerobic incubation in the presence of diothiothreitol). Hippocampus was excised and incubated with 0.001, 0.01, 0.1, 0.5, or 5.0 mM THA for 1 hour under a flow of 95% O_2 and 5% CO_2. Results are expressed as percentage of control (n = 5-8).*

KEY: –■– = control; –□– = THA. * = $p < 0.05$ versus control

CONCLUSIONS

Methamphetamine, when administered in large doses, causes neurochemical deficits in both the dopaminergic and serotonergic nerve terminals of the brain that persist for extended periods of time. When the methamphetamine analog MDMA is administered, selective and persistent neurochemical deficits are observed in the serotonergic terminal regions. DA is essential for these neurochemical deficits. Reducing conditions reverse these amphetamine-induced changes, providing evidence that oxidative stress is an important component in causing the neurochemical deficits.

The role of metabolites of amphetamine or MDMA has been extensively explored. Although some of the responses to these metabolites are similar to those of the parent compounds, the neurochemical profile observed with the metabolites is distinctly different from the deficits induced by parent compounds. From these observations it appears that there are additional factors responsible for the neurochemical deficits caused by amphetamine and its congeners.

REFERENCES

Bakhit, C., and Gibb, J.W. Methamphetamine-induced depression of tryptophan hydroxylase: Recovery following acute treatment. *Eur J Pharmacol* 76:229-233, 1981.

Bakhit, C.; Morgan, M.E.; Peat, M.A.; and Gibb, J.W. Long-term effects of methamphetamine on synthesis and metabolism of 5-hydroxy-tryptamine in various regions of the rat brain. *Neuropharmacology* 20:1135-1140, 1981.

Berger, U.V.; Molliver, M.E.; and Grzanna, R. Unlike systemic administration of p-chloroamphetamine, direct intracerebral injection does not produce degeneration of 5-HT axons. *Exp Neurol* 109(3):257-268, 1990.

Buening, M.K., and Gibb, J.W. Influence of methamphetamine and neuroleptic drugs on tyrosine hydroxylase activity. *Eur J Pharmacol* 26:30-34, 1974.

Ellison, G.; Eison, M.S.; Huberman, H.S.; and Daniel, F. Long-term changes in dopaminergic innervation of caudate nucleus after continuous amphetamine administration. *Science* 201:276-278, 1978.

Elayan, I.; Gibb, J.W.; Hanson, G.R.; Foltz, R.L.; Lim, H.K.; and Johnson, M. Long-term alteration in the central monoaminergic systems of the rat by 2,4,5-trihydroxyamphetamine but not by 2-hydroxy-4,5-methyl-enedioxymethamphetamine or 2-hydroxy-4,5-methylenedio-xyamphetamine. *Eur J Pharmacol* 221:281-288, 1992.

Elayan, I.; Gibb, J.W.; Hanson, G.R.; Lim, H.K.; Foltz, R.L.; and Johnson, M. Short-term effects of 2,4,5-trihydroxyamphetamine, 2,4,5- tri-hydroxymethamphetamine and 3,4-dihydroxymethamphetamine on central tryptophan hydroxylase activity. *J Pharmacol Exp Ther* 265:813-818, 1993.

Gibb, J.W., and Kogan, F.J. Influence of dopamine synthesis on methamphetamine-induced changes in striatal and adrenal tyrosine hydroxylase activity. *Naunyn-Schmiedeberg Arch Pharmacol* 310:185-187, 1979.

Hotchkiss, A.J., and Gibb, J.W. Long-term effects of multiple doses of methamphetamine on tryptophan hydroxylase and tyrosine hydroxylase in rat brain. *J Pharmacol Exp Ther* 214:257-262, 1980.

Hotchkiss, A.; Morgan, M.E.; and Gibb, J.W. The long-term effects of multiple doses of methamphetamine on neostriatal tryptophan hydroxylase, tyrosine hydroxylase activity, choline acetyltransferase and glutamate decarboxylase activities. *Life Sci* 25:1373-1378, 1979.

Johnson, M.; Elayan, I.; Hanson, G.R.; Foltz, R.L.; Gibb, J.W.; and Lim, H.K. Effects of 3,4-dihydroxymethamphetamine and 2,4,5-trihydroxy-methamphetamine, two metabolites of 3,4-methylene-dioxymethamphetamine, on central serotonergic and dopaminergic systems. *J Pharmacol Exp Ther* 261:447-453, 1992.

Johnson, M.; Stone, D.M.; Hanson, G.R.; and Gibb, J.W. Role of the dopaminergic nigrostriatal pathway in methamphetamine-induced depression of the neostriatal serotonergic system. *Eur J Pharmacol* 135:231-234, 1987.

Koda, L.Y., and Gibb, J.W. Adrenal and neostriatal tyrosine hydroxylase activity after methamphetamine. *J Pharmacol Exp Ther* 185:42-48, 1973.

Lim, H.K., and Foltz, R.L. In vivo formation of aromatic hydroxylated metabolites of 3,4-(methylenedioxy)methamphetamine in the rat: Identification by ion trap ms/ms and ms/ms/ms techniques. *Biol Mass Spectrom* 20:677-686, 1991*a*.

Lim, H.K., and Foltz, R.L. Ion trap tandem mass spectrometric evidence for the metabolism of 3,4-

(methylenedioxy)methamphetamine to the potent neurotoxins 2,4,5-trihydroxymethamphetamine and 2,4,5-trihydroxyamphetamine. *Chem Res Toxicol* 4:626-632, 1991*b*.

Matsuda, L.A. "Effects of Local Application of Methamphetamine and its Para-hydroxylated Metabolites on Central Monoaminergic Systems." Ph.D. dissertation, University of Utah, 1987.

Matsuda, L.A.; Hanson, G.R.; and Gibb, J.W. Neurochemical effects of amphetamine metabolites on central dopaminergic and serotonergic systems. *J Pharmacol Exp Ther* 251:901-908, 1989.

Molliver, M.E.; O'Hearn, E.; Battaglia, G.; and DeSouza, E.B. Direct intracerebral administration of MDA and MDMA does not produce serotonin neurotoxicity. *Soc Neurosci Abstr* 12:1234, 1986.

Paris, J.M., and Cunningham, K.A. Lack of neurotoxicity after intra-raphe microinjection of MDMA ("Ecstacy"). In: Harris, L., ed. *Problems of Drug Dependence, 1990.* National Institute on Drug Abuse Research Monograph 105. DHHS Pub. No. (ADM) 91-1754. Washington, DC: Supt. of Docs., U.S. Govt. Print. Off., 1990.

Ricaurte, G.; Bryan, G.; Strauss, L.; Seiden, L.; and Schuster, C. Hallucinogenic amphetamine selectively destroys brain serotonin nerve terminals. *Science* 229:486-488, 1985.

Schmidt, C.; Ritter, J.K.; Sonsalla, P.K.; Hanson, G.R.; and Gibb, J.W. Role of dopamine in the neurotoxic effects of methamphetamine. *J Pharmacol Exp Ther* 233:539-544, 1985.

Stone, D.M.; Stahl, D.C.; Hanson, G.R.; and Gibb, J.W. The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylene-dioxyamphetamine (MDA) on monoaminergic systems in the rat brain. *Eur J Pharmacol* 128:41-48, 1986.

Stone, D.M.; Johnson, M.; Hanson, G.R.; and Gibb, J.W. A comparison of the neurotoxic potential of methylenedioxyamphetamine (MDA) and its N-methylated and N-ethylated derivatives. *Eur J Pharmacol* 134:245-248, 1987.

Stone, D.M.; Johnson, M.; Hanson, G.R.; and Gibb, J.W. Role of endogenous dopamine in the central serotonergic deficits induced by 3,4-methylenedioxymethamphetamine. *J Pharmacol Exp Ther* 247:79-87, 1988.

Stone, D.M.; Hanson, G.R.; and Gibb, J.W. In vitro reactivation of rat cortical tryptophan hydroxylase following in vivo inactivation by methylenedioxymethamphetamine. *J Neurochem* 53:572-581, 1989.

Woolverton, W.L.; Ricaurte, G.A.; Forno, L.S.; and Seiden, L.S. Long-term effects of chronic methamphetamine administration in rhesus monkeys. *Brain Res* 486:73-78, 1989.

Yamamoto, B.K., and Spanos, L.J. The acute effects of methylenedioxy-methamphetamine on dopamine release in the awake behaving rat. *Eur J Pharmacol* 148:195-203, 1988.

ACKNOWLEDGMENTS

This work was supported by U.S. Public Health Service grants DA 00869 and DA 04222. The parent compounds were kindly supplied by the National Institute on Drug Abuse.

AUTHORS

James W. Gibb, Ph.D.
Professor and Chair

Michel Johnson, Ph.D.
Research Assistant Professor

Ikram Elayan, Ph.D.
Professor

Glen R. Hanson, Ph.D., DDS
Professor

Department of Pharmacology and Toxicology
University of Utah
Salt Lake City, UT 86112

Heng Keang Lim, Ph.D.
Research Scientist
Wyeth Ayerst Research
CN 8000
Princeton, NJ 08543-8000

Lisa Matsuda, Ph.D.
Assistant Professor
Department of Psychiatry
Medical University of South Carolina
Charleston, SC 29425

Click here to go to page 146