Methamphetamine and Related Drugs: Toxicity and Resulting Behavioral Changes in Response to Pharmacological Probes

Lewis S. Seiden and Mark S. Kleven

INTRODUCTION

Some substituted phenethylamines are toxic to certain neurons in the brain. In view of this neurotoxicity, we will review some data relevant to this process. First, we will review data showing that methamphetamine (METH), a prototypic psychomotor stimulant, which has been widely used for nonmedical purposes at doses often a good deal higher than therapeutic doses, is neurotoxic to dopamine (DA) and serotonin (5-hydroxytryptamine (5-HT)) systems. Second, we will examine the evidence that other substituted phenethylamines are also neurotoxic to certain transmitter systems. Last, we will examine the behavioral and pharmacological consequences of neurotoxicity that result from exposure to some of these amphetamine-related drugs.

Phenethylamines can be ring- and/or side chain-substituted, and many of these derivatives show potent pharmacological effects (Weiner 1985). Of phenethylamines without ring substitutions, pharmacologically active compounds tend to be mainly psychomotor stimulants, possessing sympathomimetic, antifatigue, and reinforcing effects in humans using the drugs. The antifatigue and reinforcing properties are likely to be responsible for their abuse potential. In very high doses, such as those used by human amphetamine abusers, the amphetamine-type drugs can lead to a psychotic state, which has paranoid delusional symptoms that are very often indistinguishable from an acute psychotic episode seen in patients with schizophrenia (Jonsson and Gunne 1970). Outbreaks of METH epidemics have occurred in several countries including the USA, Sweden. and Japan (Kramer et al. 1967; Inghe 1969; Brill and Hirose 1969).

The prototype amphetamine enhances release and blocks reuptake of DA, norepinephrine (NE), and 5-HT and is also a monoamine oxidase inhibitor. As a result of these effects, drugs in this class are potent indirect agonists at monoaminergic receptors. In experimental animals, amphetamine

stimulates locomotor activity at low doses and causes stereotypic activity at higher doses; amphetamine also interferes with food and water consumption. These behavioral effects are related to amphetamine's actions on DA, NE, and 5-HT systems (Lewander 1977; Moore 1978).

Amphetamine-related drugs such as 3,4-methylenedioxyamphetamine (MDA) or 3,4-methylenedioxymethamphetamine (MDMA), with substitutions on the benzene ring, tend to show hallucinogenic activity at lower doses and psychomotor stimulation at higher doses (Climko et al. 1986). In contrast to the behavioral effects of ring-substituted amphetamines, side-chain analogs show psychomotor stimulation at low doses and hallucinogenic activity at higher doses. Their abuse potential raises the question of whether amphetamine-like drugs may have long-lasting and/or toxic effects on the central nervous system (CNS). The data show that some of these ring-substituted compounds have toxic effects on the DA and 5-HT systems, whereas others seem to be toxic mainly to the 5-HT system. Also of interest are some structure-activity relationships, the toxicity to DA and/or 5-HT fibers, and a possible mechanism by which these drugs are toxic. Data from behavioral tests using pharmacological probes show that these neurotransmitter systems are compromised.

NEUROTOXIC EFFECTS OF AMPHETAMINE-RELATED DRUGS

Although the symptoms produced in humans suggested that the amphetamine type of drugs may engender a neurotoxic response in the CNS, there were no signs of brain pathology until the early 1970s. Koda and Gibb (1973) reported that 18 hours after a dosing regimen in which METH was injected every 5 hours, the V_{max} for tyrosine hydroxylase was reduced. Seiden et al. (1975-76) reported that, in monkeys administered amphetamine for several months and sacrificed 3 to 6 months after the last injection, the levels of DA in the brain were reduced. This long-term reduction in brain DA suggested but did not prove that METH was toxic to DA cells.

Neurotoxicity of METH was shown to occur in rats by virtue of the facts that: (1) levels of DA and activity of the enzyme that is rate limiting for DA synthesis were decreased for a long period after cessation of drug treatment (Ricaurte et al. 1980; Ricaurte et al. 1982; Hotchkiss et al. 1979); (2) the number of reuptake sites for DA were reduced (Ricaurte et al. 1980; Ricaurte et al. 1982); and (3) there was shown to be neuronal degeneration in DA-rich areas of the brain (Ricaurte et al. 1982; Ricaurte et al, 1984). It is important to stress that these three criteria must be met before neurotoxicity can be established. Similar effects upon 5-HT levels, reuptake sites, and morphology must also be observed before it can be concluded that 5-HT neurotoxicity has occurred. In this regard, multiple doses of METH have been shown to produce long-lasting reductions in tryptophan hydroxylase activity (Hotchkiss et al. 1979) as well as 5-HT content and uptake sites (Ricaurte et al. 1980) in the rat brain.

The criteria for neurotoxicity have been met for the hallucinogenic amphetamines MDA and MDMA (table 1). Levels of 5-HT were depleted as long as 8 weeks following a repeated administration of either MDA or MDMA (Ricaurte et al. 1985; Schmidt et al. 1986; Schmidt 1987a; Stone et al. 1987a; Stone et al. 1987b). Additionally, both MDA and MDMA reduced numbers of 5-HT uptake sites (Ricaurte et al. 1985; Commins et al. 1987; Schmidt 1987a), depressed tryptophan hydroxylase activity (Stone et al. 1986; Schmidt and Taylor 1987) and produced signs of neuronal degeneration (Ricaurte et al. 1985; Commins et al. 1987). It is clear from these data that neurotoxicity is directed primarily toward the 5-HT system. Much higher doses are required to produce significant reductions in the levels of DA or its metabolites.

TABLE 1. *Effects of amphetamine-related compounds on monoaminergic neurons*

Drug	Levels DA	Levels NE	Levels 5-HT	Uptake Sites DA	Uptake Sites 5-HT	Fink-Heimer
Amphetamine	⇓	⇔	⇓	⇓	⇓	+
Cathinone	⇓	⇔	⇔	⇓	⇔	-
METH	⇓	⇔	⇓	⇓	⇓	+
MDA	⇔	⇔	⇓	⇔	⇓	+
MDMA	⇔	⇔	⇓	⇔	⇓	+
Fenfluramine	⇔	⇔	⇓	⇔	⇓	-
Dethylpropion	⇔	⇔	⇓			
Mazindol	⇔	⇓	⇔			
PPA	⇔	⇔	⇔			
Cocaine	⇔	⇔	⇔			
MPH	⇔	⇔	⇔	⇔		

KEY: METH=methamphetamine PPA=phenylpropanolamine; MPH=methylphenidate.

More recently, the N-ethyl analog of MDA (MDE) was examined for possible neurotoxic effects (Stone et al. 1987a; Schmidt 1987b). In comparison to MDA and MDMA, MDE was much less potent in causing depletions of 5-HT 2 weeks after a multiple dose regimen (10 mg/kg every 6 hours for five consecutive intervals). This regimen also failed to reduce tryptophan hydroxylase activity; additionally, 5-HT uptake sites were not reduced 1 week after a single 20 mg/kg injection, unlike the reduction found with similar doses of MDA and MDMA (Schmidt 1987b). However,

as observed with MDA and MDMA, no effects of MDE on DA neurons were reported in these studies.

Fenfluramine, like MDMA and MDA, is a ring-substituted amphetamine derivative that has been found to meet all the criteria for neurotoxicity. When administered in doses higher than 12 mg/kg/day, depletions of 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) last up to 6 months after cessation of drug treatment (Harvey and McMaster 1975; Harvey et al. 1977; Clineschmidt et al. 1978; Steranka and Sanders-Bush 1979; Schuster et al. 1986; Kleven et al. 1988). Other long-lasting effects of fenfluramine include a decrease in 5-HT uptake sites (Schuster et al. 1986) and tryptophan hydroxylase activity (Steranka and Sanders-Bush 1979). Previous studies have also indicated that fenfluramine produces signs of neuronal degeneration (Harvey and McMaster 1975; Harvey and McMaster 1977; Harvey et al. 1977). Recent immunohistochemical studies also indicated that fenfluramine produced morphological damage to 5-HT terminal fields (Appel and De Souza 1988). Collectively, the neurochemical and histological data support the idea that fenfluramine is neurotoxic to 5-HT.

Cathinone and phenylpropanolamine are side-chain-substituted amphetamines that have thus far met only some of the criteria for neurotoxicity. Like *d*-amphetamine, cathinone releases and, at very high concentrations, blocks uptake of DA (Wagner et al. 1982). Similarly, cathinone mimics *d*-amphetamines long-lasting toxic effects on DA levels and uptake sites (Wagner et al. 1982). The possibility that neuronal damage occurs following neurotoxic doses of cathinone has not been examined. Neurotoxic effects of phenylpropanolamine are unlike those reported for other substituted phenethylamines. When very high doses (200 mg/kg by injection) are administered, slight decreases in frontal cortex DA have been observed (Woolverton et al. 1986). with no effects on other monoamine systems.

Several substituted phenethylamines, such as methylphenidate (MPH) and mazindol, are notably lacking in toxic effects on DA or 5-HT (Wagner et al. 1980). However, mazindol does produce a slight decrease in NE, following repeated administration. None of the other neurotoxic amphetamine derivatives have been found to have long-lasting effects on the NE system. Both amphetamine and MPH are potent monoamine-releasing agents; however, MPH appears to act primarily on a pool that does not depend upon recent synthesis (Scheel-Kruger et al. 1977). The newly synthesized transmitter pool seems to be required for the neumtoxicity produced by METH, since inhibition of DA synthesis blocks the neurotoxicity of METH (Commins and Seiden 1986; Wagner et al. 1983).

The similarities in acute neurochemical effects of cocaine and amphetamine-like compounds raise the possibility that repeated exposure to cocaine might

produce long-term neurotoxic changes similar to those produced by METH. Most previous studies have examined effects of repeated doses of cocaine within 24 hours after the last injection (Roy et al. 1978; Taylor and Ho 1976; Taylor and Ho 1977). These studies reveal that exposure to cocaine for up to 45 days causes only small decreases in DA and/or 5-HT levels. Longer lasting consequences of repeated exposure to cocaine have only recently been examined (Trulson and Ulissey 1987; Trulson et al. 1986; Trulson et al. 1987). For example, it has been reported that repeated cocaine administration to rats reduced striatal and mesolimbic tyrosine hydroxylase activity 60 days after the last injection (Trulson et al. 1986; Trulson et al. 1987), a finding that suggests that prolonged exposure to cocaine might produce long-lasting damage to DA-containing neurons. A reduction in tyrosine hydroxylase activity for several days or weeks is consistent with toxicity to catecholamine neurons. However, using neurochemical methods, we have not found such evidence of neurotoxicity (Kleven et al., in press). Repeated injections of either moderate (20 mg/kg/day) or high doses (100 mg/kg/day) of cocaine for 10 days failed to produce long-term reductions in the concentration of monoamines or metabolites in any of the brain regions examined, including the striatum. Similarly, increasing exposure to 21 days of continuous infusion of a high dose of cocaine (100 mg/kg/day) failed to significantly deplete DA and 5-HT in the striatum or other regions examined. Higher doses of cocaine were lethal within 4 days of exposure. Therefore, long-lasting depletions of monoamines do not seem to occur following cocaine administration.

The data reviewed above indicate that amphetamines and a number of their analogs are neurotoxic to DA and/or 5-HT. Although both ring- (MDA, MDMA, MDE) and side-chain-substituted amphetamines (METH, cathinone, mazindol) have been found to produce neurotoxicity, some differences are apparent. First, side-chain-substituted phenethylamines are primarily toxic to DA neurons, with effects on 5-HT appearing at higher doses. On the other hand, ring-substituted phenythylamines are selectively toxic to 5-HT neurons, with effects on DA evident only at much higher doses. Second, these two classes of substituted phenethylamines may also differ in terms of potency, either absolute or relative to other behavioral effects.

Table 2 summarizes results of neurotoxicity studies that have utilized the same regimen of drug injections (twice daily for 4 days) and survival times (2 weeks). In addition, the ability of these drugs to suppress milk intake in rats is also presented. It is clear that ring-substituted amphetamines are more potent in terms of absolute dose required to reduce amine content than is the parent compound amphetamine. With regard to relative potency, METH is toxic to DA and 5-HT neurons at doses that are more than tenfold higher than doses that produce anorexia, whereas fenfluramine, MDA, and MDMA are toxic to 5-HT neurons at doses that are only three

TABLE 2. *Relationship between behavioral and neurotoxic potency*

Drug	Dose††	Neurotoxicity* DA-striatum	5-HT-hippo	Anorectic ED_{50}†
METH	100	65%	57%	1.6
Cathinone	100-200	50%	⇔	3.9
PPA	100-200	64%	⇔	>100
Dethylpropion	25	⇔	67%	10.0
MDA	10	⇔	41%	2.5
MDMA	20	⇔	30%	2.8
Fenfluramine	6.25	⇔	43%	5.0

*Levels of transmitter % of control.

†Reduction of intake of sweetened condensed milk during 15-minute sessions.

††mg/kg injected twice daily for 4 days, rats were sacrificed 2 weeks after the last injection.

KEY: PPA=phenylpropanolamine; ⇔=no effect.

to four times higher than those needed to suppress milk-drinking activity in rats. These data suggest that ring substitution increases neurotoxic potency to a greater extent than increasing behavioral potency.

BEHAVIORAL EFFECTS OF NEUROTOXIC AMPHETAMINES

The most robust behavioral change that has been observed after a brief regimen of amphetamine-related drugs is altered sensitivity to subsequent administration of the same or a related drug. The underlying effect is not apparent until it is unmasked by pharmacological challenge. Thus, long-lasting behavioral effects of neurotoxic amphetamines may be more subtle than those produced by monoamine neurotoxins such as 6-hydroxydopamine (6-OHDA) or 5,6-dihydroxytryptamine (5,6-DHT). Perhaps this is because, with the toxic amphetamines, levels of neurotransmitter are usually depleted to about 50 percent of normal. Studies in which monoamine neurons are lesioned using 6-OHDA or 5,6-DHT show behavioral deficits when levels are depleted to 80 or 90 percent of normal. Even in these studies, the most common finding is a change in sensitivity to pharmacological probes (Heffner and Seiden 1979; Levine et al. 1980).

The original observation of long-term depletions of DA in the rhesus monkey was made during a study of the development of tolerance to the effects of daily injections of METH (Fischman and Schuster 1977). In this study, it was found that behavioral tolerance to METH on a differential-reinforcement-of-low-rate (DRL) task persisted long after the repeated METH regimen. In a similar study conducted later, monkeys treated with repeated METH showed reduced sensitivity to apomorphine and increased

sensitivity to haloperidol (Finnegan et al. 1982). Increased sensitivity to haloperidol and tolerance to METH's effects on locomotor activity of rats (Lucot et al. 1980) and a force-lever task in rhesus monkeys (Ando et al. 1985) have also been reported following a regimen of METH. Since, in each of these studies, repeated administration of METH produced substantial decreases of DA, tolerance to subsequent METH injections is most likely related to selective destruction of DA terminals.

In contrast to studies in which tolerance to METH was observed, sensitivity to the effects of MDMA on DRL performance in rats has been found to increase as a consequence of a neurotoxic regimen of MDMA (Li et al., in press). Acute administration of MDMA at 2, 4, and 6 mg/kg increased the response rate and decreased the reinforcement rate of rats performing under a DRL 72-second schedule, similar to that observed with other psychomotor stimulants. Repeated administration of MDMA for 4 days (6 mg/kg, SC, twice daily), to rats performing on the DRL schedule produced a shift to the left of the MDMA dose response curve and also increased the maximal response to MDMA at all dosages. Since levels of 5-HT but not NE or DA were significantly depleted following the MDMA regimen, the behavioral results suggest that 5-HT neurons normally exert an inhibitory action upon the psychomotor stimulant effects of MDMA. Since the psychomotor stimulant effects of amphetamines appear to be mediated primarily by the DA system, these results provide evidence that 5-HT and DA may represent opposing systems insofar as they play a role in DRL schedule-controlled behavior.

It has recently been found that sensitivity to the analgesic effects of morphine is altered in rats previously treated with a neurotoxic regimen of MDMA (Nencini et al. 1988). Rats were injected twice a day for 4 days with 20 mg/kg MDMA or saline, and, after 14 days, nociception was determined by measuring reaction time to the tail immersion in heated water (55 °C). After determining baseline reaction times, rats were randomly assigned to four groups receiving saline or morphine (2.5, 3.55, or 5 mg/kg, SC), and the nociceptive test was repeated at various times after drug or saline administration. Morphine administration produced an analgesic effect that was more potent and prolonged in MDMA- than in saline-pretreated rats. These data indicate that morphine was more potent as a consequence of a neurotoxic regimen of MDMA.

During evaluation of neurotoxicity produced by fenfluramine, an apparent transitory depletion of 5-HT was observed, with recovery of levels occurring at 16 weeks for most regions except the hippocampus. It was of interest to examine this finding in greater detail because of previous work that had suggested irreversible effects of the drug. Tolerance to the anorectic effects of fenfluramine was observable 2 but not 8 weeks following a standard 4-day regimen of fenfluramine (6.25 mg/kg. twice daily). Because levels of 5-HT are apparently returning toward control values by 8 weeks in striatum

and hypothalamus, it is possible that tolerance to fenfluramine's anorectic effect is due to 5-HT depletion. Thus, sensitivity to the anorectic effect may be related to existing levels of 5-HT. Rats previously allowed to drink sweetened condensed milk during daily 15-minute sessions were treated with fenfluramine (6.25 mg/kg twice daily for 4 days) or saline. After 2 to 8 weeks, rats were administered fenfluramine acutely, tested for milk intake, and sacrificed 2 hours later. Acute adminitration of fenfluramine produced a dose-related decrease in milk intake and 5-HT levels in various brain regions. The milk intake data indicated that tolerance to the anorectic effect of fenfluramine occurred as a result of prior exposure to fenfluramine. However, levels of 5-HT were also depleted 2 and, to a lesser extent, 8 weeks after the fenfluramine regimen. There was apparent tolerance to the acute 5-HT-depleting effect of fenfluramine as a result of the 4-day fenfluramine regimen; partial recovery of this neurochemical tolerance was observed at 8 weeks. The results suggest that tolerance to the anorectic effects of fenfluramine may be due to a selective depletion of 5-HT.

CONCLUSION

The results of behavioral studies reviewed are summarized in table 3. It is clear that a neurotoxic regimen of METH produced tolerance to the effects of subsequent injections of METH on either conditioned or unconditioned behaviors. The regimen of METH produced long-lasting depletions of DA in each of these studies. Similarly, repeated administration of fenfluramine also produced decreases in 5-HT and tolerance to the anorectic effects of fenfluramine. Repeated administration of MDMA to rats performing a DRL schedule resulted in sensitization to the effects of MDMA. This latter finding is interpreted as being due to the effects, MDMA on DA release, in

TABLE 3. *Evidence of neurotoxin-induced behavioral changes in response to pharmacological probes*

Drug	Regimen	Test	Effect	Reference
METH	0.5-16 mg/kg/day	DRL	⇓ MA ⇑ Haloperidol	Fischman et al. 1977
METH	1-32 mg/kg/day	DRL	⇓ MA ⇑ Haloperidol	Finnegan et al. 1982
METH	100 mg/kg/day * 4	Locomotor	⇓ MA ⇑ Haloperidol	Lucot et al. 1980
METH	4-40 mg/kg/day * 4	Force Lever	⇓ MA	Ando et al. 1985
MDMA	6.0 mg/kg/inj * 8	DRL-40 sec	⇑ MDMA	Li et al., in press
MDMA	20 mg/kg/inj * 8	Tail Flick	⇑ Morphine	Nencini 1988
FEN	6.25 mg/kg/inj * 8	Milk Intake	⇓ FEN	Kleven et al. 1988a

Key: METH=methamphetamine; FEN=fenfluramine; ⇓=tolerance; ⇑=sensitization.

the absence of effects on 5-HT release, as a consequence of the prolonged depletions. Each of these studies has utilized pharmacological techniques to unmask the behavioral deficits produced by the neurotoxic regimen of drug. It should be noted that persisting behavioral effects of the chronic regimen of drug, in the absence of such pharmacological challenges appear not to have been reported. While pharmacological probes reveal an underlying change in DA and/or 5-HT function, the nature of behavioral deficits in the absence of drug challenge remains to be determined.

DISCUSSION

QUESTION: Have you or anyone else had the opportunity to look at the changes in the neurochemical parameters in animals that self-administer some of the amphetamines?

ANSWER: No, not to my knowledge. What we have done is look at what the consequences are on self-administration from these chronic regimes.

In other words, we do not have them self-administering these toxic doses. We have done it with some rhesus monkeys that were self-administering methamphetamine. If you give them a regime that depletes the dopamine and serotonin, and then see what alterations there are in self-administration, it does go down, but we have not looked at that.

QUESTION: Do you get bigger effects on some of the behavioral parameters after the amphetamine treatments if you pretreat the animals with a low dose of alpha methyltyrosine during that period, during the post-amphetamine period? In the old days, when we had a partial lesion, we gave a low dose of AMFT, and it would reexpose the lesion. Have you tried that?

ANSWER: No. It is a good idea, though.

QUESTION: I find the technique of challenging the animals with various "typic" agents quite intriguing for assessment after prolonged exposure to MDMA or amphetamine. How long do those changes last? I saw in your slide something on the order of 2 weeks or a few days after the MDMA treatment. If you would come back a few months later, would that supersensitivity still exist?

ANSWER: We are not sure. We have not systematically looked at later times; we have done so accidentally, however. Sometimes we are not ready to do an experiment, and we have repeated the MDMA experiment, We have also, by chance, done tests 6 weeks later, and we have gotten essentially the same results.

QUESTION: Is that reasonably concordant then with the depleting effects of these treatments?

ANSWER: For MDMA, it is. It certainly would not be for fenfluramine. But we haven't looked functionally yet.

QUESTION: Because by 8 weeks you already see some sort of recovery?

COMMENT: I would like to show a slide because I believe the data are interesting. It has to do with the strategy of looking for a functional change after serotonin is lost following fenfluramine treatment.

There is a recent clinical report by Emil Coccaro and colleagues that I think might be relevant to the kind of thing you have done in rats. They have been looking at endocrine responses to fenfluramine in humans as a marker of central serotonergic function. And they have observed an increase in serum prolactin concentration, which is felt to be due to serotonin release. They reported that, in subjects who received a second dose of fenfluramine within 12 days after the first dose, that there was a blunted response to serum prolactin.

There are probably a multitude of explanations, but clearly one would be a possible persistent depletion of serotonin, the substrate whose release is required for the acute response to prolactin.

So I think the accumulation of the additional data as you have presented in rats and perhaps additional data like that in humans may help to clarify whether there are functional consequences of that loss of serotonin following fenfluramine.

RESPONSE: That is very interesting. I should mention that, for fenfluramine, the toxic dose as for MDMA is very close to the therapeutic dose.

I didn't go in much detail into what the effects of different doses were, but with fenfluramine we are getting toxicity in the range of 3, 6, and 10 mg/kg and to interfere with feeding behavior in the rat you arc dealing with an order of 2.0 mg/kg. So there isn't much of a window there. Similarly, for MDMA, the neurotoxic dose range is 10, 20 mg/kg and a human is taking approximately 2.0 mg/kg. Behaviorally effective doses are in the neighborhood of 4, 5, and 6 mg/kg.

In contrast to methamphetamine, where we are dealing with behaviorally effective doses that are in the range of 1 to 4 mg/kg, toxicity doses are in the range of 50 to 100.

So you see, according to our thinking, some of these drugs are more dangerous because the toxic doses are so very close to the behaviorally active therapeutic doses.

COMMENT: Just a very brief comment that originally followed up on the idea of pharmacologic challenge. It is a very powerful technique with which one can detect underlying or covert neurochemical deficits,

The beauty of it is not only can it uncover an otherwise unapparent deficit, but it is a technique that can be readily applied to humans.

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AUTHORS

Lewis S. Seiden, Ph.D., Professor
Department of Pharmacological and Physiological Sciences
and Department of Psychiatry

Mark S. Kleven, Ph.D., Research Associate (Assistant Professor)
Department of Pharmacological and Physiological Sciences

The University of Chicago
947 East 58th Street
Chicago, IL 60637