# Effects of Methamphetamine Use

# 6

HAROLD V. HALL
SANDRA B. McPHERSON
STUART W. TREMLOW
ERROL YUDKO

## Cerebral Injury and Death from Methamphetamine Use

The cerebral damage caused by methamphetamine intoxication can be formidable. Prolonged use is associated with injury to the dopamine system. Essentially, continued methamphetamine use likely leads to axonic degeneration of the dopamine axon terminals in the striatum, frontal cortex, nucleus accumbens, and amygdala. Hypersensitization of neurons occurs, for example, in increasing sensitivity of D-1 receptors. It is important to note that changes in catecholamines alone cannot explain behavior in humans when they are methamphetamine intoxicated.

Animal studies across several species demonstrate that high dosages of methamphetamine damage nerve cells (Swan, 1997). In rats, one high dose is enough to cause damage to neurons; prolonged administration increases the number of neurons that are killed off (Swan, 1997). In squirrels, a single dose of MDMA (which is structurally similar to methamphetamine and mescaline) in only slight doses significantly damages brain neurons that produce serotonin. Twelve to 18 months after exposure, serotonin-producing nerves grow abnormally or not at all. MDMA selectively damages serotonin neurons in virtually all species (Fischer et al., 1995). Buffenstein et al. (1997) showed through SPECT scanning of methamphetamine abusers in Hawaii that brain deterioration continues for months after abstinence, a finding that, if consistently cross-validated, suggests another unique and pathological feature of methamphetamine.

Not surprisingly, high doses of methamphetamine can cause death. A male under arrest died with a blood content greater than 60 mg per liter after swallowing a "baggie" of methamphetamine (Logan et al., 1996). A toxic reaction in humans can occur at levels as low as 50 mg of pure methamphetamine for nontolerant users. Ischemic stroke is associated with methamphetamine

inhalation (Rothrock et al., 1998). Massive strokes are fairly common. The second author conducted a neuropsychological evaluation of a 30-year-old, previously normal, federal employee who suffered multiple strokes and a vascularizing dementia after a single methamphetamine intoxication. Although a family history of strokes for members in their 60s and 70s was revealed, representing a possible vulnerability for the client, methamphetamine appeared to cause the client's strokes long before they would normally be expected, given his family history. Methamphetamine taken intranasally has caused caudal thalamic infarctions in an abuser (Sachdeva and Woodward, 1989). Ischemic stroke is associated with methamphetamine inhalation (Rothrock et al., 1997). More ominously, and as discussed above, preliminary data show continued destruction of brain tissue in humans several months after abstinence from methamphetamine (Buffenstein et al., 1997).

In sum, much of the data suggest there is no way of establishing a "safe" or "unsafe" level of methamphetamine for a particular person, or even for the same person with repeated doses. With other drugs, and certainly with alcohol, use of the particular substance must continue for a given time period (e.g., 12 months) and be accompanied by maladaptive behavior to qualify for a DSM-IV diagnosis of substance abuse. Preliminary data suggest that this is in marked contrast to methamphetamine abuse where a small number of intoxications can create catastrophic changes in physical and mental functioning.

## The Unpredictable Effects of Methamphetamine

There are multiple factors, in addition to its untoward effects on nontolerant users, that cause the effects of methamphetamine to be unpredictable. The properties of methamphetamine itself can create unpredictable reactions. Further, there may be impurities in the drug. Methamphetamine manufactured in clandestine labs is frequently impure (Kram et al., 1977; Sinnema and Verweij, 1981). Methamphetamine can be used to "cut" other drugs, which means that interactive effects must be considered. Also, a variety of toxic chemicals can be used as the precursors from which methamphetamine can be formed (e.g., ephedrine and pseudoephedrine, benzyl chloride, benzyl cyanide, methylamine); or as reagents, substances that react with precursors (e.g., hydriodic acid, iodine, mercuric chloride, sodium cyanohydridoborate); or as solvents (e.g., ethanol, ethyl chloroform, acetone). Residues of these substances may contaminate the final product.

There are two basic methods for producing methamphetamine, each of which requires 2 to 4 days to produce a batch. One method involves the reaction of phenyl-2-propanone (P-2-P), phenylacetine, and methylamine. The other method uses ephedrine as a precursor chemical, which does not

necessitate use of a controlled precursor. This method, referred to as the ephedrine/red phosphorus method, requires the use of hydrogenator. Red phosphorus is on the list of less restricted chemicals in many states, and information that this chemical can be obtained from the fireworks and matchmaking industries has been widely disseminated on the Internet since 1996 (e.g., see deadlock@paranoia.com). The striking pad on match covers is about 40% red phosphorus and 30% antimony sulfide, with lesser amounts of glue, iron oxide, manganese dioxide, and glass powder. Some of these chemicals, alone or in combination, can cause toxic reactions in the methamphetamine user. In addition, the ephedrine/red phosphorus method often produces "garbage" methamphetamine. Unless simple precautions are followed, which are typically not followed by makers who are often chronic methamphetamine users themselves, high amounts of iodoephedrine and azirine are produced as contaminants.

Most methamphetamine is not the clear, pure hydrochloride salt we typically associate with the drug, but contains impurities that can be identified by their color as follows:

- Red: Methamphetamine from pseudoephedrine; the red coloring of the tablet was not washed away.
- Orange: Ephedrine sulfate was used; the sulfate was reduced to sulfur.
- Purple: The iodine from the phosphorus-iodine reaction was not chemically washed.
- Green: Copper somehow made its way into the mixture, possibly because of the mixing vessel.
- Brown: A tablating agent or oxidized red coloring was present in the reduction.

Use of drugs other than methamphetamine affects the user's response to methamphetamine. Cocaine intoxication causes cross-tolerance to discriminative and reinforcing effects of methamphetamine in animal studies (Peltier et al., 1996). It is important to understand that although the terms to describe cross-reverse tolerance (i.e., sensitivity) vary as shown in Table 6.1, they refer to the same concept; the terms can be gleaned from the animal and human literature, DSM-IV (1994) and DSM-IV-TR (2000), and other sources.

Polydrug abuse is the rule rather than the exception in adult offenders (Kassebaum and Chandler, 1994). Repeated use of methamphetamine alone can decrease sensitivity and increase tolerance to more methamphetamine (Ando et al., 1996). Even innocuous foods can cause cross-reverse tolerance (i.e., sensitivity) to methamphetamine. In many users, caffeine increases sensitivity to the effects of methamphetamine (Ando et al., 1986). Cocaine, L-dopa, and a variety of other substances have been associated with cross-reverse

**Table 6.1 Terms Used to Describe Methamphetamine-Like Effects by Another Substance Following Termination of Methamphetamine[a]**

| | Term | Source |
|---|---|---|
| 1. | Supersensitivity, Recurrence | Ando, Hironaka, and Yanagita (1986), *Psychopharmacology Bulletin* |
| 2. | Sensitivity | Asami, Kuribara, and Tadokoro (1986), *Yakubutsu Seishin Kodo* |
| 3. | Transferable Effects | Kuribara and Tadokoro (1989), *Japanese Journal of Pharmacology* |
| 4. | Cross-Reverse Tolerance | Fujii, Kuribara, and Tadokoro (1990), *Japanese Journal of Pharmacology* |
| 5. | Cross-Reverse Tolerance | Fujii, Kuribara, and Tadokoro (1990), *Japanese Journal of Pharmacology* |
| 6. | Response Generalization | Oliveto, Bickel, Hughes, Terry, Higgins and Badger (1993), *Behavioral Pharmacology* |
| 7. | Unlabeled, refers to methamphetamine-like action (e.g., diet pills, khat) | American Psychiatric Association (2000), like action (e.g., diet pills, khat), *Diagnostic and Statistical Manual of Mental Disorders* (4th edition, text revision) |

*Note:* Substances producing methamphetamine-like effects reported in the literature include caffeine, phenobarbitol (an antiseizure medication), theophylline (a stimulant found in tea), methylphenidate (a compound commonly found in diet pills which is structurally different from methamphetamine but with methamphetamine-like stimulant properties), L-dopa (used in treatment of Parkinson's Disease), bromocriptine (a compound with antidepressant properties), morphine, benzphetamine (a mixture of benzadrine and other methamphetamine compounds), ephedrine (a component of methamphetamine), and cocaine.

[a] Based on a partial review of the literature. Other journals include *Life Sciences*, *Psychophamol*, *Pharmacol Biochem Behavior.*

tolerance. Most abusers are aware of this phenomenon and will deliberately attempt to recreate the effects of methamphetamine by using these substances when methamphetamine is unavailable. Alcohol, a central nervous system suppressant, is commonly used by addicts to decrease the effects of amphetamines, especially during withdrawal periods. In *State vs. Michael Lawrence* (2001), the defendant drank coffee to reexperience a methamphetamine-like "rush," including on the day he dismembered the murder victim, a Kirby vacuum cleaner salesman who came to his house. Table 6.2 lists some of the many studies from the empirical literature involving both humans and animals that show the association between caffeine and methamphetamine.

The common theme from the literature is that methamphetamine causes a lasting sensitivity to relapse. Various animal studies cited above (e.g., see Ando et al., 1986) suggest that relapse into states resembling methamphetamine intoxication can be triggered by environmental stress. These findings have not been generalized to humans. Replication of these findings for humans would suggest that the sudden onset of a state resembling a paranoid state could occur months or even years after an individual's last intoxication from methamphetamine.

**Table 6.2 Caffeine and Methamphetamine-Like Effects[a] (studies by date of publication)**

| | Subjects |
|---|---|
| 1. White and Keller (1984) | Rodents |
| 2. Ando, Hironaka, and Yanagita (1986) | Mice, rats |
| 3. Holtzman (1987) | Rats |
| 4. Chait and Johanson (1988) | Humans |
| 5. Kuribara and Tadokoro (1989) | Mice |
| 6. Fujii, Kuribara, and Tadokoro (1990) | Mice |
| 7. Stern, Chait, and Johanson (1989) | Humans |
| 8. Griffiths, Evans, Heishman, Preston, Sannerud, Wolf, and Woodson (1990) | Humans |
| 9. Oliveto, Bickel, Hughes, Shea, Higgins, and Fenwick (1992) | Humans |
| 10. Oliveto, Bickel, Hughes, Terry, Higgins, and Badger (1993) | Humans |
| 11. Mumford, Evans, Kaminski, Preston, Sannerud, Silverman, and Griffiths (1994) | Humans |
| 12. Kuribara (1994) | Mice |
| 13. Kuribara (1994) | Mice |

[a] Based on a partial review of the literature. Other sources of information include (a) the clinical-forensic evaluation/treatment of methamphetamine abusers by Harold V. Hall, Ph.D, ABPP (1988–2001); (b) consultation with Errol Yudko, Ph.D, Assistant Professor, Department of Psychology, University of Hawaii, Hilo, and consultant to Big Island Substance Abuse Center; (c) a special report of the Pacific Institute for the Study of Conflict and Aggression entitled "methamphetamine use and the mental health expert witness in criminal-forensic contexts," by H. V. Hall, S.B. Twemlow, and S.B. McPherson (January 1999); and (d) the defendant in State of Hawaii v. Michael Lawrence (September 1, 1999 evaluation).

## References


Ando, K., Hironaka, N., and Yanagita, T. (1986). Psychotic manifestations in amphetamine abuse — experimental study on the mechanism of psychotic recurrence. *Psychopharmacol. Bull.*, 22(3), 763–767.

Buffenstein, A., Coel, M., and Combs, B. (1997). Functional Neuroimaging of Chronic Crystal Methamphetamine Users. Unpublished grant application, University of Hawaii, John A. Burns School of Medicine.

Chait, L.D. and Johanson, C.E. (1988). Discriminative stimulus effects of caffeine and benzphetamine in amphetamine-trained volunteers. *Psychopharmacology*, 96(3), 302–308.

*Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV)*, published by the American Psychiatric Association, Washington, D.C., 1994.

*Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), Text Revision (DSM-IV-TR)*, published by the American Psychiatric Association, Washington, D.C., 2000.

Fischer, C., Hatzidimitriou, G., Wlos, J., Katz, J., and Ricaurte, G. (1995). Reorganization of ascending 5-HT axon projections in animals previously exposed to recreational drug 3,4-methylenedioxymethamphetamine (MDMA, "Ecstasy"). *J. Neuroscience*, 15, 5476–5485.

Fujii, T., Kuribara, H., and Tadokoro, S. (1990). Interaction between caffeine and methamphetamine by means of ambulatory activity in mice. *Yakubutsu Seishin Kodo*, 9(2), 225–231.

Griffiths, R.R., Evans, S.M., Heishman, S.J., Preston, K.L., Sannerud, C.A., Wolf, B., and Woodson, P.P. (1990). Low-dose caffeine discrimination in humans. *J. Pharmacol. Exp. Ther.*, 252(3), 970–978.

Holtzman, S.G. (1987). Discriminative stimulus effects of caffeine: tolerance and cross-tolerance with methylphenidate. *Life Sci.*, 40(4), 381–389.

Kassebaum, G. and Chandler, S.M. (1994). Polydrug use and self control among men and women in prison. *J. Drug Educ.*, 24(4), 333–350.

Kram, T.C., Kruegel, B.S., and Kruegel, A.V. (1977). The identification of impurities in illicit methamphetamine exhibits by gas chromatography/mass spectrometry and nuclear magnetic resonance spectroscopy. *J. Forensic Sci.*, 22, 40–52.

Kuribara, H. (1994). Caffeine enhances the stimulant effect of methamphetamine, but may not affect induction of methamphetamine sensitization of ambulation in mice. *Psychopharmacology*, 116(2), 125–129.

Kuribara, H. (1994). Modification by caffeine of the sensitization to methamphetamine and cocaine in terms of ambulation in mice. *Life Sci.*, 55(12), 933–940.

Kuribara, H. and Tadokoro, S. (1989). Reverse tolerance to ambulation-increasing effects of methamphetamine and morphine in six mouse strains. *Jpn. J. Pharmacol.*, 49(2), 197–203.

*Lawrence Michael Borchardt v. State of Maryland*, No. 55, Sept. Term, 2000, *App v. New Jersey*, 530 US 566.

Logan, B.K., Weiss, E.L., and Harruff, R.C. (1996). Case report: distribution of methamphetamine in a massive fatal ingestion. *J. Forensic Sci.*, 41(2), 322–323.

Mumford, G.K., Evans, S.M., Kaminski, B.J., Preston, K.L., Sannerud, C.A., Silverman, K., and Griffiths, R.R. (1994). Discriminative stimulus and subjective effects of theobromine and caffeine in humans. *Psychopharmacology*, 115(1–2), 1–8.

Oliveto, A.H., Bickel, W.K., Hughes, J.R., Shea, S.Y., Higgins, S.T., and Fenwick, J.W., (1992). Caffeine drug discrimination in humans: acquisition, specificity and correlation with self-reports. *J. Pharmacol. Exp. Ther.*, 261(3), 885–894.

Oliveto, A.H., Bickel, W.K., Hughes, J.R., Terry, S.Y., Higgins, S.T., and Badger, G.J. (1993). Pharmacological specificity of the caffeine discriminative stimulus in humans: effects of theophylline, methylphenidate and buspirone. *Behav. Pharmacol.*, 4(3), 237–246.

Peltier, R.L., Li, D.H., Lytle, D., Taylor, C.M., and Emmett-Oglesby, M.W. (1996). Chronic d-amphetamine or methamphetamine produces cross-tolerance to the discriminative and reinforcing stimulus effects of cocaine. *J. Pharmacol. Exp. Ther.*, 277(1), 212–218.

Rothrock, J.F., Rubenstein, R., and Lyden, P.D. (1988). Ischemic stroke associated with methamphetamine inhalation. *Neurology*, 38(4), 589–592.

Sachdeva, K. and Woodward, K.G. (1989). Caudal thalamic infarction following intranasal methamphetamine use. *Neurology*, 39(2/1), 305–306.

Sinnema, A. and Verweij, A.M.A. (1981). Impurities in illicit amphetamine: a review. United Nations Office of Drug Use and Crime, 37–54.

Stern, K.N., Chait, L.D., and Johanson, C.E. (1989). Reinforcing and subjective effects of caffeine in normal human volunteers. *Psychopharmacology*, 98(1), 81–88.

Swan, N. (1997). Response to Escalating Methamphetamine Abuse Builds on NIDA-Funded Research. Available at http:\\www.drugabuse.gov/NIDA-Notes/NNVoI11N5/Escalating.html.

White, B.C. and Keller, G.E. (1984). Caffeine pretreatment: enhancement and attenuation of d-amphetamine-induced activity. *Pharmacol. Biochem. Behav.*, 20, 383–386.