Section II

Physiology, Effects, and Diagnosis of Methamphetamine Use

Physiology

5

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

Neurotransmitter Action

Understanding the mechanism of action of methamphetamine requires some understanding of neurophysiology. Because the discussion here is brief, readers who wish to further their knowledge of neurophysiology are referred to Pinel (1997). In short, the active unit of the nervous system is the neuron (Schwann, 1839; Cajal, 1917). A neuron is an elongated cell (up to 2 m) that sends messages to other cells through the process of electrochemical signaling (Sherrington, 1987; Bernstein, 1902; Adrian, 1913; Loewi, 1921; Dale, 1914). That is, an electrical impulse, called an action potential, travels the length of the cell to initiate the release of a chemical messenger, called a neurotransmitter. The neurotransmitter substance diffuses across a gap between the cells, called a synapse, where it is chemically bound to a protein called a receptor. The binding of the neurotransmitter to the receptor is equivalent to the receipt of the message.

The process of release of the neurotransmitter from the presynaptic neuron, the neuron on the sending side of the synapse (the neuron on the receiving side is called the postsynaptic receptor), is called exocytosis. Neurotransmitter substances are generally packaged in vesicles (De Robertis et al., 1962). These vesicles sometimes have protein units, known as transporters, that can extract neurotransmitter substances from the cell cytoplasm, the viscous fluid on the inside of the cell, and package them on the inside of the vesicle. In response to an action potential, the vesicle fuses with the cell membrane and releases neurotransmitter into the synapse (Fatt and Katz, 1952). The process of exocytosis is calcium dependent (for review, see Smith and Augustine, 1988). That is, it occurs only in the presence of calcium.

After it has been released, the neurotransmitter diffuses across the synapse and binds to a receptor on the postsynaptic membrane. The message of the neurotransmitter depends on the function of the receptor. Some common

messages are "produce an action potential," "suppress an action potential," or "begin a long-term change by activating specific proteins." As long as the neurotransmitter substance remains in the synapse, its message will be received by the postsynaptic neuron. Thus, a mechanism must exist to remove the neurotransmitter. There are, in fact, several such mechanisms. One such mechanism is through the degradation of the neurotransmitter. Another, more important to the present discussion, is through the reuptake of the neurotransmitter into the presynaptic neuron.

Control of Neurotransmitter Levels

In addition to degradation and reuptake, negative feedback and end-product inhibition are two other ways that the cell has available to control the levels of neurotransmitter released into the synapse. Some cells have autoreceptors, which are responsible for negative feedback. That is, a receptor on the presynaptic neuron (called an autoreceptor or presynaptic receptor) acts to turn off a cell when enough neurotransmitter has accumulated in the synapse to activate it. This mechanism prevents the cell from releasing "too much" neurotransmitter at one time. End-product inhibition is the mechanism by which the neuron regulates the amount of neurotransmitter that it synthesizes. When enough product (neurotransmitter) is available, the product itself deactivates the enzymes responsible for its production.

A psychoactive drug can have an effect at any or all of the above-mentioned processes (receptor binding, degradation, synthesis, release, packaging, and reuptake). The most common site of action for a psychoactive drug is at the postsynaptic receptor. However, psychoactive drugs can affect both postsynaptic receptors and presynaptic receptors. Further, these drugs can affect the mechanisms responsible for neurotransmitter synthesis, release, packaging, reuptake, and degradation.

Physiological Effects of Amphetamine

Neurotransmitters can be classified as large or small. Large-molecule neurotransmitters include the peptide transmitters such as the opiates. Small-molecule transmitters include the monoamines and the amino acid transmitters. The monoamines can be further subdivided into the catecholamines and the indolamines. The present discussion focuses on the monoamines. The catecholamines include the neurotransmitters norepinephrine (NE), epinephrine (Epi), and dopamine (DA). The only indolamine is serotonin (5-HT).

Early studies hypothesized that methamphetamine inhibited the reuptake of NE, DA (Harris and Baldessarini, 1973; Azzaro et al., 1974), and 5-HT (Taylor and Ho, 1978). More importantly, methamphetamine also acts as a potent DA-releasing agent (Azzaro et al., 1974; Raiteri et al., 1975; Arnold et al., 1977) and NE-releasing agent (Kuczenski and Segal, 1992). Most of the research attempting to elucidate the mechanism of methamphetamine action has focused on DA because the DA system, which regulates feelings of reward, motor coordination, motivation, and hormonal release, is thought to be primarily responsible for the behavioral changes observed in methamphetamine use.

DA is synthesized in the cytoplasm and transported into vesicles. From the vesicles it is released into the synapse in both Ca^{2+}-dependent and -independent manners. Ca^{2+}-dependent release is regulated by the firing of an action potential. Ca^{2+}-independent release is spontaneous. One major effect of amphetamine is to cause an increase in the amount of DA released spontaneously from the neuron (Robertson et al., 1991).

Amphetamine causes this increase in spontaneously released DA by reversing the activity of the DA reuptake transporter (Bonisch, 1984). This was shown by observing the activity of radioactively labeled amphetamine applied to the terminus region of a dopaminergic neuron (Zaczek et al., 1991). Further, amphetamine-stimulated DA release is inhibited by drugs that block the reuptake of DA (Fischer and Cho, 1979; Raiteri et al., 1979; Liang and Rutledge, 1982). Finally, amphetamine has no effect in genetically engineered mice that do not have the gene that codes for the DA reuptake transporter. Taken together, these findings lead to the exchange diffusion model of amphetamine action. In this model, the amphetamine molecule binds to the reuptake transporter and is taken up into the cell. The transporter is turned around in the process and begins to pump DA out of the cell instead of into the cell.

The weak base model is a second potential mechanism for the spontaneous release of DA in the presence of amphetamine. This model proposes that at high doses amphetamine actually diffuses into the neuron where it interacts with the vesicle (by changing its pH — thus, the name "weak base") and causes DA to leak into the cytoplasm of the cell, thereby providing more cytoplasmic DA to be pumped out into the synapse via the exchange diffusion model (Sulzer and Rayport, 1990; Sulzer et al., 1993).

Amphetamine has several other effects on the DA system as well:

1. Low concentrations of amphetamine enhance the synthesis of DA. This is thought to occur because amphetamine causes the cell to become DA deficient. The cell responds by producing more DA.

2. High concentrations of amphetamine inhibit DA synthesis by binding to presynaptic autoreceptors.
3. Amphetamine also inhibits the enzyme (monoamine oxidase) that degrades DA.

Tolerance and Sensitization

Tolerance is defined as a diminished response to a drug after repeated administration of all effects of a drug exhibit tolerance. In the case of amphetamine, tolerance to the anorexic, hypothermic, cardiovascular, and reinforcing effects has been reported (Lewander, 1971; Miller and Gold, 1989, Perez-Reyes et al., 1991). Reports from chronic amphetamine users confirm a significant amount of tolerance to the euphoric effects of amphetamines (Kramer et al., 1967; Grinspoon and Hedblom, 1975), which tends to result in tremendous dose increases by chronic abusers. The physiological mechanism for tolerance to amphetamine use is unclear, but seems to occur at the cellular level.

An interesting effect of chronic amphetamine abuse is reverse tolerance, or sensitization. That is, use of the drug leads to a stronger subjective effect of the drug at a later time. Repeated, intermittent use or a single use seems to lead to this phenomenon. The use of the drug amphetamine can lead to cross-sensitization, which was originally defined as a hypersensitivity to stress (Robinson and Becker, 1986), but has come to be associated with hypersensitivity to a number of drugs as well.

Neurotoxicity

Methamphetamine neurotoxicity has been well documented in animals (Koda and Gibb, 1973; Seiden et al., 1975; Ellison et al., 1978) but is less clear in humans (Ernst et al., 2000). However, a recent study (Buffenstein et al., 1997) used SPECT scanning to show brain deterioration in methamphetamine abusers that continued for months after abstinence (see Figure 2.1). Methamphetamine seems to be toxic to dopaminergic neurons (Wagner et al., 1980; Ricaurte et al., 1988; Ricaurte, Seiden, and Schuster, 1984) and serotinergic neurons (Hotchkiss and Gibb, 1980; Morgan and Gibb, 1980), but not noradrenergic, cholinergic, and GABAergic neurons (Hotchkiss et al., 1979; Morgan and Gibb, 1980; Wagner et al., 1980). The mechanism for DA neurotoxicity is better understood than the mechanism for 5HT neurotoxicity and may involve methamphetamine triggering the release of large quanta of DA (O'Dell et al., 1991). In fact, drugs that block DA protect against methamphetamine neurotoxicity (Fuller and Hemrick-Luecke, 1980; Hotchkiss and Gibb, 1980; Ricaurte, Seiden, and Schuster, 1984).

Drugs with chemical compositions similar to amphetamine and methamphetamine tend also to be neurotoxic. MDMA (also known as ecstasy, XTC, X, and E) is one such compound. MDMA has been shown to be neurotoxic in rats (Stone et al., 1986; Schmidt, 1987), pigeons (LeSage et al., 1993), and nonhuman primates (Ricaurte et al., 1988). The evidence for a neurotoxic effect in humans has been much more controversial (Holland, 1999). It has been suggested that the doses of MDMA given to animals were far higher than the doses taken by recreational users. However, when the metabolic rates of the animals tested were taken into account, it was determined that the dosages that were neurotoxic to animals were equivalent to the dosages used recreationally by humans (Ricaurte et al., 2000). Chronic MDMA abuse has been shown to cause deficits in the following areas: recall (Morgan, 1999); visual and verbal memory in low intellectually functioning males, but not females or high intellectually functioning males (Bolla, McCann, and Ricaurte, 1998); working memory (Wareing, Fisk, and Murphy, 2000); and complex tests of attention (McCann, 1998). The damage seems to be related to 5-HT neuronal injury (Reneman et al., 2000).

Neuropharmacology of Amphetamines

Amphetamines are rapidly absorbed orally and have a rapid onset of action, usually within 30 to 40 minutes of oral ingestion. Methamphetamine may also be taken intravenously, whereupon it has an immediate effect. Certain forms, the so-called designer amphetamines, may be inhaled. Crystal methamphetamine, the smokable form of this drug, which is primarily found in Hawaii, has an onset time of between 5 and 20 minutes, a subjective feeling of intoxication for up to 8 hours, and a half-life of 12 to 36 hours. Demethylation, or the biochemical breakdown process caused by the presence of methamphetamine in the body, is conclusive evidence that methamphetamine is being detected and not some harmless analogue.

Tolerance, the requirement of progressively higher doses over time to obtain the same effect, occurs with all forms of amphetamines. This phenomenon, in part, accounts for the addictive nature of methamphetamine. Increases in methamphetamine doses from 5 to 1000 mg per day in a single year are not uncommon as a reflection of rapid tissue tolerance in methamphetamine users (Trustees of Indiana University, 1995). As a result of tolerance in long-term abusers, doses as high as 20 times the initial dose may be needed to achieve the same high (Haight-Ashbury Training Manual, 1997). This suggests that knowledge of the behavioral indicia of intoxication, abuse, and dependence, in addition to an understanding of the neuropharmacology of methamphetamine, is indispensable. When compared with other psychostimulants, such as cocaine, methamphetamine has been shown

to be less physically addictive in animal studies (Dackis and Gold, 1990). Nevertheless, the psychological addictive potential of methamphetamine is extremely high; many abusers continue their use despite knowing that their abuse is likely to cause florid psychotic symptomatology, such as command hallucinations and disorganized cognition.

The primary effects of methamphetamine are related to the release of catecholamine, particularly DA, from presynaptic neurons in the brain. The drug appears to exert its greatest effect on dopaminergic neurons projecting from the ventral tegmental area to the cerebral cortex and the limbic system, nerve bundles commonly referred to as the "reward pathway" that is thought to be implicated in the addictive potential of methamphetamine (Kaplan et al., 1994).

The designer amphetamines (e.g., MDMA, MDEA, MMDA, DOM) release DA, norepinephrine, and serotonin. As a result of their effect, individuals ingesting these substances experience both stimulant and hallucinogenic effects. Thus, the designer amphetamines exert a broader spectrum of effects than methamphetamine itself.

References

Adrian, E.D. (1913). Wedensky inhibition in relation to the all-or-none principle in nerve, *J. Physiol.* London, 46, 384–412.

Arnold, E.B., Molinoff, P.B., and Rutledge, C.O. (1977). The release of endogenous norepinephrine and dopamine from cerebral cortex by amphetamine. *J. Pharmacol.*, 202, 544–557.

Azzaro, A.J., Ziance, R.J., and Rutledge, C.O. (1974). The importance of neuronal uptake of amines for amphetamine induced release of H-norepinephrine from isolated brain tissue. *J. Pharmacol. Exp. Ther.*, 189, 110–118.

Bernstein, J. (1902). *Pflügers Arch. ges. Physiol.*, 92, 521–562.

Bolla, K., McCann, U.D., and Ricaurte, G.A. (1998). Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology*, 51, 1532–1537.

Bonisch, H. (1984). The transport of (-)-amphetamine by the neuronal noradrenaline carrier. *Naunyn Schmiedebergs Arch. Pharmacol.*, 327, 267–272.

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.

Cajal, S.R. (1917). *Recuerdos de mi vida, Vol. 2: Historia de mi labor cientifica*. Madrid: Moya. There is an English translation: Recollections of my life (translated by E.H. Craigie with the assistance of J. Cano), Philadelphia, American Philosophical Society, 1937). Reprinted Cambridge, MA, MIT Press, 1989.

De Robertis, E., Rodrigues de Lores Arnaiz, H., and Pallegrini de Iraldi, A. (1962). Isolation of synaptic vesicles from nerve endings in rat brain. *Nature*, 194, 794–795.

Dackis, C.A. and Gold, M.S. (1990). Addictiveness of central stimulants. *Adv. Alcohol Substance Abuse*, 9, 9.

Dale, H.H. (1914). *J. Pharmacol. Exp. Ther.*, 6, 147–190.

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

Ernst, T., Chang, L., Leonido-Yee, M., and Speck, O. (2000). Evidence for long-term neurotoxicity associated with methamphetamine abuse: A 1H MRS study. *Neurology*, 54(6), 1344–1349.

Fatt, P. and Katz, B. (1952). Spontaneous subthreshold activity of motor nerve endings. *J. Physiol.* (London), 117, 109–128.

Fischer, J.F. and Cho, A.K. (1979). Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model. *J. Pharmacol. Exp. Ther.*, 208, 203–209.

Fuller, R.W. and Hemrick-Luecke, S. (1980). Long-lasting depletion of striatal dopamine by a single injection of amphetamine in iprindole-treated rats. *Science*, 209, 305–307.

Grinspoon, L. and Hedblom, P. (1975). *The Speed Culture: Amphetamine Use and Abuse in America.* Cambridge, MA: Harvard University Press.

Haight-Ashbury Training Manual. (1997). In D. Inaba and W. Cohen, *Uppers, Downers, and All Arounders*. Ashland, OR: Cinemed, Inc.

Harris, J.E. and Baldessarini, R.J. (1973). Uptake of [3H]-catecholamines by homogenates of rat corpus striatum and cerebral cortex: effects of amphetamine analogues. *Neuropharmacology*, 12, 669–679.

Holland, J. (1999). Positron emission tomography findings in heavy users of MDMA. *Lancet*, 353, 592–593.

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

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

Kaplan, H.I., Sadock, B.J., and Grebb, J.A. (1994). *Synopsis of Psychiatry.* 7th ed. Baltimore: Williams & Wilkins, 1994, 411–428.

Koda, L.Y. and Gibb, J.W. (1973). Adrenal and striatal tyrosine hydroxylase activity after methamphetamine. *J. Pharmacol. Exp. Ther.*, 185, 42–48.

Kramer, J.C., Fischman, V.S., and Littlfield, D.C. (1967). Amphetamine abuse: pattern and effects of high doses taken intravenously. *J. Am. Med. Assoc.*, 201, 89–93.

Kuczenski, R. and Segal, D.S. (1992). Differential effects of amphetamine and dopamine uptake blockers (cocaine, nomifensine) on caudate and accumbens dialysate dopamine and 3-methoxytyramine. *J. Pharmacol. Exp. Ther.*, 262, 1085–1094.

LeSage, M., Clark, R., and Poling, A. (1993). MDMA and memory: the acute and chronic effects of MDMA in pigeons performing under a delayed-matching-to-sample procedure. *Psychopharmacology*, 110, 327–332.

Lewander, T. (1971). A mechanism for the development of tolerance in rats. *Psychopharmacologia*, 21, 17–31.

Liang, N.Y. and Rutledge, C.O. (1982). Comparison of the release of [3H]dopamine from isolated corpus striatum by amphetamine, fenfluramine and unlabelled dopamine. *Biochem. Pharmacol.*, 31(6), 983–992.

Loewi, O. (1921). *Pflügers Arch.*, 189, 239–242.

McCann, J.T. (1998). Broadening the typology of false confessions. *Am. Psychol.*, 53(3), 319–320.

Melga, W.P., Lacan, G., Harvey, D.C., Huang, S.C., and Phelpes, M.E. (1998). Dizocilpine and reduced body temperature do not prevent methamphetamine-induced neurotoxicity in the vervet monkey: [11C]WIN 35,428 — positron emission tomography studies. *Neurosci. Lett.*, 258(1),17–20.

Melega, W.P., Lacan, G., Desalles, A.A., and Phelps, M.E. (2000). Long-term methamphetamine-induced decreases of binding in striatum are reduced by GDNF: PET studies in the vervet monkey. *Synapse*, 35(4), 243–249.

Miller, N.S. and Gold, M.S. (1989). The diagnosis of marijuana (*Cannabis*) dependence. *J. Substance Abuse Treat.*, 6, 183–192.

Morgan, M.J. (1999). Memory deficits associated with recreational use of "ecstasy" (MDMA). *Psychopharmacology*, 141, 30–36.

Morgan, M.E. and Gibb, J.W. (1980). Short-term and long-term effects of methamphetamine on biogenic amine metabolism on extra-striatal dopaminergic nuclei. *Neuropharmacology*, 19, 989–995.

O'Dell, S.J., Weihmuller, F.B., and Marshall, J.F. (1991). Multiple methamphetamine injections induce marked increases in extracellular striatal dopamine which correlates with subsequent neurotoxicity. *Brain Res.*, 564, 256–260.

Perez-Reyes, M., White, W.R., McDonald, S.A., Hicks, R.E., Jeffcoat, A.R., Hill, J.M., and Cook, C.E. (1991). Clinical effects of daily methamphetamine administration. *Clin. Neuropharmacol.*, 14, 352–358.

Pinel, J.P.J. (1997). *Biopsychology.* Boston: Allyn & Bacon.

Raiteri, M., Bertollini, A., Angelini, F., and Levi, G. (1975). Dopamine as a releaser or reuptake inhibitor of biogenic amines in synaptosomes. *Eur.J. Pharmacol.*, 34, 189–195.

Reneman, L., Booij, J., Schmand, R., van den Brink, W., and Gunning, B. (2000). Memory disturbances in "Ecstasy" users are or related with an altered brain serotonin neurotransmission. *Psychopharmacology (Berlin)*, 148, 322–324.

Ricaurte, G.A., Forno, L.S., Wilson, M.A., DeLanney, L.E., Irwin, L., Molliver, M.E., and Langston, J.W. (1988). (±)3,4-Methylene-dioxymethamphetamine selectively damages central serotonergic neurons in non-human primates. *J. Am. Med. Assoc.*, 260, 51–55.

Ricaurte, G.A., Seiden, L.S., and Schuster, C.R. (1984). Further evidence that amphetamine produce long-lasting dopamine neurochemical deficits by destroying dopamine nerve fibers. *Brain Res.*, 303(2), 359-364.

Ricaurte, G.A., Yuan, J., and McCann, U.D. (2000). (±)3,4- Methylenedioxymethamphetamine ("ecstasy")-induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology*, 42(1), 5–10.

Robertson, G.S., Damsma, G., and Fibiger, H.C. (1991). Characterization of dopamine release in the substantia nigra by *in vivo* microdialysis in freely moving rats. *J. Neurosci.*, 11, 2209–2216.

Schmidt, C.J. (1987). Neurotoxicity of the psychedelic amphetamine, methylenedioxymethamphetamine. *J. Pharmacol. Exp. Ther.*, 240, 1–7.

Schwann, T. (1839) *Mikroskopische Untersuchungen*, Sander, Berlin; English translation by H. Smith (1847), Sydenham Soc., London.

Seiden, L.S., Fischman, M.W., and Schuster, C.R. (1975). Long-term methamphetamine-induced changes in brain catecholamines on tolerant rhesus monkeys. *Drug Alcohol Depend.*, 1, 215–219.

Sherrington, C.S. (1987). *The Central Nervous System*. In volume III of Michael Foster, *A Textbook of Physiology*. 7th ed. London.

Smith, S.J. and Augustine, G.J. (1988). Calcium ions, active zones and synaptic transmitter release. *Trends Neurosci.*, 11(10), 458–464.

Stone, D.M., Stahl, D.S., Hanson, G.L., and Gibbs, J.W. (1986). The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) in monoaminergic systems in the rat brain. *Eur. J. Pharmacol.*, 128, 41–48.

Sulzer, D., Maidment, N.T., and Rayport, S. (1993). Amphetamine and other weak bases act to promote reverse transport of dopamine in ventral midbrain neurons. *J. Neurochem.*, 60(2), 527–535.

Sulzer, D. and Rayport, S. (1990). Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. *Neuron*, 5(6), 797–808.

Taylor, D.P. and Ho, B.T. (1978). Comparison of inhibition of monoamine uptake by cocaine, methylphenidate, and amphetamine. *Res. Commun. Chem. Pathol. Pharmacol.*, 21, 67–75.

Villemagne V., Yuan, J., Wong, D.F., Dannals, R.F., Hatzidimitriou, G., Mathews, W.B., Ravert, H.T., Musachio, J., McCann, U.D., and Ricaurte, G.A. (1998). Brain dopamine neurotoxicity in baboons treated with doses of methamphetamine comparable to those recreationally abused by humans: evidence from positron emission tomography studies and direct *in vitro* determinations. *J. Neurosci.*, 18(1), 419–427.

Wagner, G.C., Ricuarte, G.A., Seiden, L.S., Schuster, C.R., Miller, R.J., and Westley, J. (1980). Long-lasting depletions of striatal dopamine and loss of dopamine uptake sites following repeated administration of methamphetamine. *Brain Res.*, 181, 151–160.

Wareing, M., Fisk, J.E., and Murphy, P.N. (2000). Working memory deficits in current and previous users of MDMA, *British Journal of Psychology*, 91(2), 181–188.

Zaczek, R., Culp, S., and DeSouza, E.B. (1991). Interactions of amphetamine with rat brain synaptosomes. II. Active transport. *J. Pharmacol. Exp. Ther.*, 257, 830–835.