CHAPTER FIFTEEN

Effects of MDMA on the Human Nervous System

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1. INTRODUCTION

(±)3,4-Methylenedioxymethamphetamine (MDMA) is a ring-substituted amphetamine analog that was originally synthesized by Merck in Darmstadt, Germany. It was included as one of the several structurally related chemical compounds in a patent application that was filed in 1912, and approved in 1914 (Merck, 2012). MDMA received little attention for the next several decades. In 1953, the US Army Chemical Center funded a series of preclinical studies of MDMA, conducted at the University of Michigan, in mice, rats, monkeys, dogs, and guinea pigs (Hardman et al., 1973). Although it is sometimes stated that these studies were an effort to identify a potential "brainwashing" agent (Holland, 2001), these studies actually appear to have been general toxicity studies identifying lethal dosages (LD50s) of a variety of chemical agents (Hardman et al., 1973).

There are reports that MDMA was used by "New Age" thinkers in the 1960s, who appreciated its ability to produce feelings of well-being and "connectedness" (McDowell and Kleber, 1994; Watson and Beck, 1991). MDMA was introduced to psychologists in Northern California in 1976, with therapists on the East Coast following suit, shortly thereafter. In brief, therapists began employing MDMA as a psychotherapeutic adjunct or "catalyst" to enhance and improve results of insight-oriented psychotherapy (Shulgin, 1980). Although the number of patients who were treated with MDMA-induced psychotherapy is not known, its continued use in psychotherapeutic sessions took place until such practice became illegal in 1985 (Beck, 1978).

Contemporaneous with MDMA's use in psychotherapeutic circles was its use in recreational settings. Despite its popularity as a recreational drug, MDMA did not receive much attention from the federal government as a potential drug of abuse until 1985. In particular, an aggressive marketing campaign by a particular MDMA distributor in Texas made MDMA widely available, not only at dance venues, but at bars and convenience stores (McDowell and Kleber, 2004). This practice came to the attention of Senator Lloyd Bentson, who petitioned the Drug Enforcement Administration (DEA). As a

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result of Senator Bentson's efforts, MDMA was placed on Schedule I, and has remained there, since July 1, 1985 (Lawn, 1985).

In its decision to place MDMA on Schedule I, the DEA raised concerns over increasing recreational MDMA use, and that use of MDMA may pose a threat to public health, since a close structural relative, 3,4-methylenedioxyamphetamine (MDA), had recently been found to produce toxic effects on brain serotonin (5-HT)-containing neurons in rodents (Ricaurte et al., 1985). In addition to concerns about substance abuse and neurotoxicity, the DEA maintained that MDMA had no medical utility. This claim was challenged by a number of mental health specialists who believed that MDMA facilitated psychotherapy (Greer, 1985; Greer and Tolbert, 1986).

Despite its newly illegal status, MDMA became popular on college campuses and in large organized dance parties known as "raves", in spite of emerging evidence that MDMA, like MDA, was toxic toward brain 5-HT neurons in animals (Schmidt et al., 1985; Stone et al., 1986; Commins et al., 1987).

Since the discovery of the 5-HT neurotoxic potential of MDMA in animals, there has been significant research interest in its mechanisms of neurotoxicity, the parameters necessary to produce neurotoxicity, and whether such neurotoxicity extends to humans who use MDMA in recreational (or therapeutic) settings. Over 2001–2010, the Food and Drug Administration in the United States has approved a limited number of human MDMA studies to go forward. Government-sanctioned clinical research of MDMA in Switzerland and other European countries has also been conducted.

This chapter, as suggested by its title, will focus on the effects of MDMA on the human nervous system. To this end, we will begin by reviewing MDMA's mechanisms of action and its effects on the sympathetic nervous system (SNS). The bulk of our discussion will focus on MDMA's effects on the central nervous system (CNS), including its pharmacological and neurotoxic effects. Because a full understanding of MDMA pharmacology and neurotoxicology in humans requires understanding of its effects in preclinical models, these will be discussed as appropriate. Studies that have attempted to identify functional consequences of MDMA in humans, as well as potential neuropsychiatric sequelae of MDMA consumption, will be discussed. We will conclude with a summary of the research directed at determining the effects of MDMA on the human nervous system, limitations of this research, and potential future directions for MDMA studies in clinical populations.

2.1. MECHANISM OF ACTION

Like most amphetamine analogs, MDMA stimulates the CNS and the SNS, primarily by releasing 5-HT, dopamine (DA), and norepinephrine (NE), and blocking their inactivation via reuptake (Steele et al., 1994; Green et al., 2003). Key to these actions is the interaction between MDMA and monoamine transporters. This is known from

results of in vitro studies using nerve ending suspensions (synaptosomes) (Nichols et al., 1982; Steele et al., 1987), transfected cells (Rudnick and Wall, 1992; Verrico et al., 2007) and in vivo studies using microdialysis (Gudelsky and Yamamoto, 2008) and transgenic animals (Fox et al., 2007). Of note, results from receptor binding studies suggest that MDMA, in addition to its indirect monoamine-mediated actions, may also produce direct effects on monoamine receptors, particularly 5-HT_2 receptors (Battaglia et al., 1989a,b; Teitler et al., 1990; but see Sadzot et al., 1989). In this regard, it is important to recall that MDMA, as typically used on the street and in most experimental and clinical studies, consists of an equal mixture of S(+) and R(−) enantiomers, with the R(−) enantiomer appearing to have the most prominent direct action on $5HT_2$ receptors (Lyon et al., 1986). Both MDMA enantiomers also appear to have the potential to inhibit monoamine oxidase activity (Leonardi and Azmitia, 1994).

A major, as yet unanswered, question is whether the above mentioned effects of MDMA on monoamine-containing neurons fully account for its spectrum of behavioral effects. While it may well be that the subjective effects of MDMA are the end-product of a mix and blend of effects of MDMA on pre- and postsynaptic elements of 5-HT, DA, and NE neurons, a unique site or mechanism of action of MDMA has not been excluded. Early binding studies identified a novel binding site for MDMA (Gehlert et al., 1985). Although subsequent studies revealed that the binding site in question was located on the glass-fiber filters used to carry out the binding assays, rather than in the brain tissue under study (Wang et al., 1987; but see Zaczek et al., 1989).

That release of 5-HT and other monoamines may not be the sole mechanism by which MDMA produces its behavioral effects is suggested by the observation that fluoxetine, which blocks MDMA-induced 5-HT release (Schmidt et al, 1987), does not block MDMA's reinforcing subjective effects in humans (McCann and Ricaurte, 1993; but see Lietchi et al., 2000). Similar observations have been reported in animals (Piper et al., 2008). Of course, this leaves open the possibility that DA and NE, acting alone or in concert with 5-HT, may mediate MDMA's behavioral effects (Liechti and Vollenweider, 2000, 2001). These considerations notwithstanding a novel mechanism of action for MDMA are conceivable. Indeed, several investigators have postulated that MDMA may be the prototype of a new drug class (Nichols et al., 1986; Vollenweider et al., 1998).

2.2. PHARMACOLOGY

2.2.1. Absorption and Metabolism

MDMA is typically taken orally in the form of tablets, capsules, or pills. The dose generally ranges from 75 to 150 mg, although experienced users often take more (Parrott, 2005). MDMA is well absorbed from the gastrointestinal tract and its onset of action is typically within 30 min of ingestion even though the time to peak plasma concentrations is approximately 2–3 h (Kolbrich et al., 2008a,b; Mueller et al., 2009). The plasma half-life of

MDMA in humans ranges from 6 to 9 h (Chu et al., 1996; de la Torre et al., 2000; Kolbrich et al., 2008a,b). Notably, MDMA has nonlinear pharmacokinetics (Chu et al., 1996; de la Torre et al., 2000; Kolbrich et al., 2008a,b), with increases in plasma MDMA concentrations exceeding those predicted by the increase in dose. Also of note is the fact that nonlinear MDMA pharmacokinetics begins at plasma MDMA concentrations of approximately 125–150 ng/ml (Mueller et al., 2009). This effectively renders every consumer who takes a typical dose of MDMA a "poor metabolizer", because the hepatic cytochrome P_{450} isoenzyme that metabolizes MDMA (CYP2D6) is inhibited and/or saturated at this relatively low plasma MDMA concentration (125–150 ng/ml) (Mueller et al., 2009).

In humans, the major route of degradative metabolism of MDMA involves ring *O*-demethylenation, with formation of the catechol dihydroxymethamphetamine (HHMA) (Meyer et al., 2008). HHMA is then *O*-methylated to form HMMA, and/or *N*-demethylated to form HHA. In contrast to what is seen in rodents, only a small fraction of MDMA is *N*-demethylated to MDA in humans. In particular, in rodents, approximately 50% of MDMA is metabolized to MDA (Chu et al., 1996), whereas in humans, <5% of MDMA is converted to MDA (de la Torre et al., 2004; Kolbrich et al., 2008a,b). Unlike other MDMA metabolites, MDA is known to be pharmacologically active in humans (Naranjo et al., 1967). In addition to *O*-demethylenation and *N*-demethylation, other identified metabolic pathways of MDMA in vivo include deamination and conjugation (*O*-glucuronidation and *O*-sulfation) (Meyer et al., 2008).

2.2.2. Sympathomimetic Effects

Sympathomimetic effects of MDMA include mydriasis, tachycardia, increased diastolic and systolic blood pressure, and decreased appetite (Downing, 1986; Vollenweider et al., 1998; Mas et al., 1999; Cami et al., 2000; Kolbich et al., 2008a,b). Effects on blood pressure and heart rhythm are not always predictable or dose-related (see Vollenweider et al., 1998; Hua et al., 2009). Interestingly, the beta-blocker, pindolol, prevents MDMA-induced increases in heart rate but not increases in blood pressure (Hysek et al., 2010). Cardiovascular complications occasionally include cardiac arrhythmias, hypertensive crises, and stroke (hemorrhagic or ischemic) but these are relatively rare (Ricaurte and McCann, 2005). Body temperature is also typically mildly elevated (see Parrot et al., 2012) but significant, sometimes fatal, malignant hyperthermia can occur (Henry et al., 1992), resulting in rhabdomyolysis and multiorgan failure. In these instances, uncoupling or disruption of the balance between heat production and dissipation is suspected (Mills et al., 2004). Recent findings in animals suggest that neuronal activity in the dorsomedial hypothalamus, a brain region known to be involved in stress responses and thermoregulation, is necessary for some of the sympathomimetic effects of MDMA to occur (Rusyniak et al., 2008). MDMA-elicited increases in peripheral sympathetic discharge to the cutaneous vascular bed undoubtedly also contribute to hyperthermia, by reducing heat dissipation through the skin (Blessing et al., 2003).

2.2.3. Subjective Behavioral Effects

Shulgin and Nichols (1978) were the first to report on the subjective effects of MDMA. They indicated that MDMA produced an alteration in consciousness with sensual and emotional overtones. Other commonly reported behavioral effects of MDMA include increased physical energy, subjective sense of closeness to others, heightened sensual awareness, euphoria, loquaciousness, and empathy toward others (Downing, 1986; Kolbrich et al., 2008a). These effects typically last several hours, and it is not uncommon for MDMA consumers to use a "booster" dose to recoup or prolong the above mentioned effects. The days after MDMA ingestion, users typically experience lack of energy, dysphoria, and difficulty concentrating.

2.3. NEUROTOXICOLOGY

2.3.1. Animals

2.3.1.1. Serotonin Neurotoxicity

Over 1975–2000, an extensive body of data has accrued demonstrating that MDMA has neurotoxic potential toward brain 5-HT neurons. Animals treated with MDMA develop lasting depletions of brain of 5-HT, 5-hydroxyindoleacetic acid (5-HIAA), tryptophan hydroxylase (TPH), the serotonin transporter (SERT), and the vesicular monoamine transporter-type 2 (see Steele et al., 1994; Gibb et al., 1994; Lew et al., 1997; Green et al., 2003; Gudelsky and Yamamoto, 2003). Notably, these lasting neurochemical deficits in MDMA-treated animals are accompanied by morphologic/structural signs of damage to 5-HT axons and axon terminals. For example, Commins et al. (1987) found evidence of axon terminal degeneration using the silver degeneration method of Fink and Heimer. Using more specific immunocytochemical methods, Molliver and colleagues demonstrated loss of 5-HT-immunoreactive (IR) axons and axon terminals (O'Hearn et al., 1988; Wilson et al., 1989; Axt et al., 1994). Importantly, at short survival times after MDMA administration (1–3 days), the same investigators found numerous, markedly swollen 5-HT-IR axons, many of which appeared fragmented (Axt et al., 1994; Molliver et al., 1990). These data, coupled with tract-tracing results based on anterograde transport of tritiated proline from the raphe to the forebrain (Callahan, 2001) and evidence of the "pruning" phenomenon after MDMA exposure (Fischer et al, 1995), provide strong evidence that lasting serotonergic neurochemical deficits produced by MDMA are the result of destruction of 5-HT axons and axon terminals. Indeed, virtually identical effects are produced by 5,7-dihydroxytryptamine (5,7-DHT), a well-documented 5-HT neurotoxin (Jonsson, 1980; Baumgarten and Lachenmay, 2004).

Thus, as used in this chapter, the term *serotonin neurotoxicity* refers to a lasting loss of various chemical markers that are unique to 5-HT neurons (5-HT, 5-HIAA, TPH, and

SERT) and are accompanied by anatomic evidence of structural damage to 5-HT axons. The term makes no assumptions about reversibility of the neuronal injury or potential functional consequences.

Serotonin neurotoxicity after MDMA has been shown to have broad species generality. In particular, MDMA-induced 5-HT neurotoxicity has been documented in rats, guinea pigs, squirrel monkeys, cynomolgus monkeys, rhesus monkeys, and baboons (see Steele et al., 1994; Gibb et al., 1994). In all these species, MDMA neurotoxicity is selective for 5-HT neurons. Noradrenergic neurons are invariably spared. DA neurons are also typically unaffected except after unusually high dosages or when MDMA treatment is carried out at a high ambient temperature (Commins et al., 1987; Yuan et al., 2002; but see Sanchez et al., 2004). However, even under these conditions, the toxic effect of MDMA on brain DA neurons is modest, except in the mouse. For reasons that have yet to be elucidated, mice differ from all other animal species in which MDMA has been tested in that the mouse incurs selective DA neural injury, with 5-HT neurons only developing toxicity when the dosage of MDMA is inordinately high (Stone et al., 1987; Logan et al., 1988).

A few investigators have questioned the 5-HT neurotoxic potential of MDMA based on the observation that treatment with MDMA and structurally related drugs (e.g. p-chloroamphetamine (PCA)) does not generally lead to a glial reaction (Rowland et al., 1993; O'Callaghan and Miller, 1994; Pubill et al., 2003; Wang et al., 2004, 2005; Rothman et al., 2004; Thomas et al., 2004; *but see* Wilson et al., 1993; Aguirre et al., 1999; Orio et al., 2004). However, when considering this line of reasoning, it is important to recognize that established 5-HT neurotoxins (e.g. 5, 7-DHT) also fail to consistently induce a glial reaction in brain regions distant from the site of intracerebral toxin injection (see Hardin et al., 1994; Frankfurt and Azmitia, 1984; Rowland et al., 1993; Bendotti et al., 1994; Straiko et al., 2007). Thus, in our view, rather than casting doubt on the neurotoxic potential of MDMA and other substituted amphetamines (e.g. PCA), these findings indicate that additional research is needed to more fully characterize the determinants, timing, nature, and role of astroglial and microglial responses to neuron-selective lesions involving fine, relatively sparse, axonal projections (e.g. 5-HT projections). Indeed, when much denser axonal projections are damaged by MDMA (e.g. dopaminergic axonal projections to mouse striatum), both a glial reaction and positive silver staining response are consistently observed (O'Callaghan and Miller, 1994; Thomas et al., 2004), and the neurotoxic potential of MDMA toward DA neurons in the mouse goes unquestioned.

More recently, Rothman and colleagues questioned the 5-HT neurotoxic potential of MDMA based on results obtained in Western blot studies revealing no reduction in the abundance of a 70 kDa band that was thought to correspond to the SERT protein (Rothman et al., 2003, 2004; see also Wang et al., 2004, 2005). These investigators postulated that lasting serotonergic effects of MDMA represented neuroadapative changes

(involving SERT trafficking), rather than damage to brain 5-HT neurons. To examine this issue further, we studied the in vivo expression of the SERT protein and other 5-HT neuronal markers (5-HT, 5-HIAA, and TPH) after MDMA and related drugs, using the established 5-HT neurotoxin, 5,7-DHT, as a positive control. Results indicated that the 70 kD band in question did not correspond to the SERT protein, as it did not exhibit the known relative regional distribution of brain SERT was resistant to 5,7-DHT treatment, and was present in SERT-KO animals (Xie et al., 2006). In contrast, a more diffuse band at approximately 63–68 kD (which has the expected regional brain distribution of the SERT, was markedly reduced after 5,7-DHT treatment and absent in SERT-KO animals) was decreased after MDMA administration (Xie et al., 2006), indicating that the SERT protein (like other 5-HT neuronal markers) is decreased after MDMA exposure. Recently, these results have been confirmed by others (Bhide et al., 2009; Cunningham et al., 2009; Biezonski and Meyer, 2010).

Still others have questioned the 5-HT neurotoxic potential of MDMA because recovery of axonal 5-HT markers has been shown to occur over time (Battaglia et al., 1991; Scanzello et al., 1993; Hatzidimitriou et al., 1999). However, with regard to recovery, it is important to recall that MDMA neurotoxicity is limited to 5-HT axons and axon terminals and that cell bodies in the brainstem raphe nuclei are invariably spared. Sparing of 5-HT nerve cell bodies leaves open the possibility that, with time, regenerative sprouting can occur. Indeed, after 5, 7-DHT lesions that spare nerve cell bodies, regenerative sprouting of 5-HT axons has been demonstrated (Zhou and Azmitia, 1986; Frankfurt and Beaudet, 1987). Thus, the recovery observed after MDMA exposure should not be taken to indicate that MDMA lacks neurotoxic potential toward 5-HT axons and axon terminals. Rather, the recovery observed reflects a fundamental feature of the MDMA lesion: namely, that it is restricted to axons and axon terminals and that, by sparing 5-HT nerve cell bodies, leaves open the potential for future regenerative sprouting. A key question in this regard is whether the regenerative sprouting that takes place leads to the reestablishment of the original 5-HT innervations patterns. In nonhuman primates that have sustained severe 5-HT lesions, this does not appear to be the case (Fischer et al, 1995; Hatzidimitriou et al., 1999).

2.3.1.2. Relevance of Animal Data to Humans

As discussed in detail elsewhere (Ricaurte et al., 2000; McCann and Ricaurte, 2007) and as recently emphasized by Easton and Marsden (2006), determining the relevance of 5-HT neurotoxicity findings in animals to human MDMA users requires consideration of a number of important factors including possible species differences in drug metabolism, route and schedule of drug administration, and, perhaps most importantly, dosage. Each of these factors is discussed, in turn, below:

Species differences in drug metabolism: 5-HT neurotoxic effects of MDMA have been demonstrated in rats, guinea pigs, squirrel monkeys, cynomolgus monkeys, rhesus

monkeys, and baboons. The mouse is the only animal that is relatively resistant to MDMA-induced 5-HT neurotoxicity but, curiously, develops DA neurotoxicity. As there are marked differences in MDMA metabolism among these various species, it seems unlikely that species differences in drug metabolism will render humans insensitive to 5-HT neurotoxicity. Nevertheless, use of animal models in which the metabolism of MDMA resembles that observed in humans seems advisable for future studies. As yet, it is unclear if the neurotoxic effects of MDMA are produced by the parent compound or metabolites. Should the parent compound be the active toxic chemical species, the importance of species differences in MDMA metabolism for issues related to neurotoxicity would be diminished.

Route of drug administration: It have shown that regardless of whether MDMA is administered orally or subcutaneously, it produces comparable 5-HT neurotoxic effects in the rat. Similar results have been obtained in rhesus monkeys (Kleven et al., 1989; Slikker et al., 1988, 1989), although the oral route of administration may afford modest degree of protection in the squirrel monkey (Ricaurte et al., 1988c).

Dose: At first glance, doses of MDMA that produce 5-HT neurotoxicity in rats (10–20 mg/kg (Schmidt et al., 1985; Schmidt, 1987)) appear much higher than those typically used by humans (approximately 1–2 mg/kg). However, when comparing doses across species, it is important to take into account differences in body size, particularly when these are substantial (as is the case between a 0.20 kg rat or a 1 kg squirrel monkey and a 70 kg human). This is because fundamental physiological processes that govern drug responses are a function of body size, and these typically occur faster in smaller animals. Accordingly, interspecies scaling principles dictate that small animals generally require larger doses (on an mg/kg basis) than humans to sustain the same drug effect. Indeed, by taking into account known relationships between body size, physiological processes, and drug responses, allometric equations have been developed to allow for more accurate extrapolation of doses in small laboratory animals to humans. For example, a commonly used allometric equation is

$$D_{\text{human}} = D_{\text{animal}}\left(W_{\text{human}}/W_{\text{animal}}\right)^{0.67}$$

where D, is the dose of drug in milligrams (mg), W, the weight in kilograms (kg), and 0.67 is an empirically determined exponent. It is to be noted that the foregoing allometric equation incorporates various models for extrapolating animal data to humans, and is widely used experimentally as well as the pharmaceutical industry and the Food and Drug Administration (FDA). When applied to MDMA, this equation indicates that a 10–20 mg/kg dose, which is known to produce 5-HT neurotoxic effects in a 0.2 kg rat (Schmidt et al., 1985; Schmidt, 1987 also Preliminary results)

translates to a 1.45–2.89 mg/kg dose in a 70 kg human being. Notably, this is the same dosage range of MDMA required to produce the psychoactive effect of interest in human beings. Thus, the available animal data suggest that the margin of safety for MDMA (with regard to 5-HT neurotoxicity) may be narrow. In other words, there is reason to suspect that even single doses of MDMA may be associated with a significant risk of brain 5-HT neurotoxicity in humans. However, despite the strengths of the allometric approach, it is important to recognize that the method is not perfect, and that it may yield estimates of doses in animals that are not exactly equivalent to those in humans (or vice versa), for a variety of reasons including possible species differences in absorption, metabolism, or elimination.

Mechanisms: The mechanism by which MDMA damages brain 5-HT neurons has yet to be elucidated. An extensive series of pharmacological and toxicological studies has implicated endogenous brain DA and its oxidation products (see Gibb et al., 1994). However, much of the data implicating brain DA in MDMA neurotoxicity is confounded by drug effects on body temperature (Green et al., 2003), which can strongly influence MDMA neurotoxicity. Moreover, brain DA does not appear to be essential for the expression of MDMA neurotoxicity because even animals with near-total depletions of brain DA develop MDMA-induced 5-HT neurotoxic changes (Yuan et al., 2002). Recently, it was presented evidence that tyrosine, after nonenzymatic conversion to d(ihydr)o(xy)p(henyl)a(lanine) (DOPA) (then enzymatic conversion to DA), contributes to MDMA neurotoxicity, particularly in brain regions receiving little or no dopaminergic innervation. However, this finding is at seeming odds with the failure of reserpine to protect against MDMA neurotoxicity (Hekmatpanah and Peroutka, 1990; Yuan et al., 2002), and recent unpublished observations in our laboratory that the DOPA decarboxylase inhibitor, NSD1015, does not protect against MDMA-induced 5-HT neurotoxicity, if temperature changes are controlled. In addition to DA-derived free radicals, glutamate (GLU)-mediated reactive nitrogen species have been proposed to play a role in the neurotoxicity of amphetamine-type stimulants. However, the mechanism by which reactive species injure the 5-HT neuron is not entirely clear, nor is it certain that reactive species are the cause (rather than the consequence) of neurotoxicity. Energy dysregulation, possibly secondary to inhibition of mitochondrial function, may also be involved in the 5-HT neurotoxic action of MDMA. However, glucoprivation with 2-deoxy-D-glucose, a competitive inhibitor of glucose metabolism, fails to potentiate MDMA-induced toxicity to brain 5-HT neurons (Yuan et al., 2002). Based on the well-established neuroprotective effect of SERT inhibitors (Schmidt et al, 1987) and the finding that inhibitors of Na^+/H^+ and/or Na^+/Ca^{++} exchange potentiate METH-induced neurotoxicity, we proposed that ionic dysregulation, possibly secondary to prolonged transporter activation (known to be linked to ion flux), may play a role in substituted amphetamine neurotoxicity (Callahan et al., 2001).

However, more direct evidence in support of this hypothesis is needed. Finally, in recent years, there has been growing interest in the possibility that metabolites of MDMA play a role in the neurotoxic process.

2.3.2. Humans

Like animals, humans appear to be susceptible to MDMA-induced 5-HT neurotoxicity. In particular, there are two validated measures of MDMA-induced 5-HT damage in humans: (1) reductions in cerebrospinal fluid concentrations of 5-HIAA obtained at a time point when acute pharmacological effects have dissipated (i.e. weeks to months) after the last MDMA exposure and; (2) reductions in the SERT, as measured by PET, weeks to months after MDMA exposure. Abstinent MDMA users, like MDMA-treated animals, have been found to have reductions in both of these validated markers of MDMA-induced 5-HT neurotoxicity. In particular, squirrel monkeys treated with oral or systemic neurotoxic dosages of MDMA develop selective reductions in a variety of brain 5-HT neuronal markers including cerebrospinal fluid (CSF) 5-HIAA (Ricaurte et al., 1988a, 1988b; Insel et al., 1989; Ricaurte et al., 1992a; Fischer et al, 1995; Hatzidimitriou et al., 1999). Similar to MDMA-treated animals, abstinent MDMA users have been found to have selective reductions in CSF 5-HIAA (McCann et al., 1994, 1999a,b). While these findings are certainly consistent with the notion that MDMA leads to 5-HT neurotoxic injury, CSF measures are indirect. As such, reductions in CSF reductions in 5-HIAA are not conclusive evidence of MDMA-induced 5-HT damage.

The advent of positron emission tomography (PET) and single photon emission computed tomography (SPECT) methods has permitted direct visualization of neuron-specific markers in living humans, including markers of brain 5-HT axons and axon terminals (Huang et al., 2010). The first study validating molecular neuroimaging methods for detecting MDMA-induced 5-HT neurotoxicity strategies employed baboons treated with a known neurotoxic regimen of MDMA and PET scans with the first-generation PET SERT ligand, [^{11}C] McN5652. PET studies at 13, 19, and 40 days post-MDMA treatment revealed significant reductions in [^{11}C] McN 5652 binding ranging from 44% in the pons to 89% in the occipital cortex. Subsequent PET studies, 9 and 13 months later, revealed recovery in some regions, but persistent reductions in neocortical regions more than a year after MDMA treatment. This observation prompted parallel studies involving abstinent human MDMA users. These studies revealed significant reductions in SERT binding potential (McCann et al., 1998, 2005, 2008; Buchert et al., 2003, 2004, 2006, 2007; Thomasius et al., 2006). Subsequent studies using the second generation PET SERT ligand, [^{11}C] DASB, have revealed similar results in most (McCann et al., 2005, 2008; Kish et al., 2010b; Urban et al., 2012), but not all (Selvaraj et al., 2009) studies. In the one negative PET SERT study in MDMA users (Selvaraj et al., 2009), the absence of

significant differences between groups may, in part, have been related to lack of power in the study design.

SPECT methods with the SERT ligand [^{123}I] β-CIT have also been used to study abstinent recreational MDMA users. Although reductions of SERT density in the hypothalamus and midbrain of monkeys with documented 5-HT lesions is associated with reductions in [^{123}I]β-CIT measured by SPECT (Reneman et al., 2002), studies in abstinent MDMA users by the same group and others find persistent reductions of [^{123}I] β-CIT in cortical, but not midbrain regions (Semple et al., 1999; Reneman et al., 2001). These regional differences in [^{123}I]β-CIT changes in human MDMA users (as compared to the validated animal model), combined with the fact that [^{123}I]β-CIT binds to the DAT, in addition to the SERT, may limit the utility of SPECT for detecting MDMA-induced SERT reductions in humans.

To our knowledge, there are only two studies in which markers of brain 5-HT integrity have been directly assessed in human MDMA users (Kish et al., 2000, 2010a). These postmortem case studies found reductions in 5-HT, SERT, and TPH in deceased MDMA users that had recently used the drug. Acknowledging its limitations (study size and recency of drug use), these observations are consistent with the notion that MDMA is neurotoxic toward brain 5-HT neurons in humans.

2.4. LASTING CONSEQUENCES OF MDMA EXPOSURE

Given the known important role of brain 5-HT in a variety of behavioral functions (Jacobs and Fornal, 2000; Henninger, 1995), and the considerable preclinical and clinical data demonstrating that MDMA is neurotoxic toward brain 5-HT neurons reviewed above, numerous research laboratories have made efforts to identify potential functional consequences of MDMA-induced 5-HT damage. In 2009, the National Institute for Health Research in the United Kingdom funded a Health Technology Assessment to investigate the harmful health effects of recreational MDMA use (Rogers et al., 2009). This technology involved a systematic review of over 4000 publications that had been published prior to that date, and addressed potential consequences of recreational MDMA use. Although, since that time, more than 250 articles have been published on the acute and long-term effects of MDMA in humans, conclusions by Rogers and colleagues are still valid.

MDMA has both acute and subacute effects on a variety of behaviors (presumably related to its acute and downstream pharmacological effects). However, in the present context, "consequences" of MDMA refers to lasting (weeks to years) behavioral changes seen in MDMA users, unless otherwise stated. In addition, it is important to note that most recreational MDMA users have also been exposed to other illicit and licit recreational substances, and these are used in uncontrolled circumstances. As such, the strength and composition of MDMA is not generally verified and the role of exposure

to other substances in behavioral changes found in MDMA users cannot be excluded. Given these caveats, MDMA users, when compared to a variety of control groups, have been found to have lasting alterations in cognitive function, sleep, neuroendocrine function, and pain modulation. These differences will be reviewed, in turn.

2.4.1. Cognitive Function

Numerous researchers have explored the possibility that MDMA leads to altered cognitive processes, particularly in the area of memory function. A meta-analysis of findings from these studies (Rogers et al., 2009) indicates that, compared to controls, MDMA users have impaired memory on the six most commonly employed tests of immediate and delayed memory, including the ray auditory verbal learning test (immediate and delayed), the Rivermead behavioral test (prose recall, immediate, and delayed), and digit span (forward and backwards) (Bolla et al., 1998; Croft et al., 2001; Reneman et al., 2001; Reneman et al., 2006; Quednow et al., 2006; Lamers et al., 2006; de Win et al., 2008; Morgan, 1999; Morgan et al., 2002; Curran and Verheyden, 2003; Dafters et al., 2004; Gouzoulis-Mayfrank et al., 2000; Halpern et al., 2004; Wareing et al., 2004; McCardle et al., 2004). Subsequent studies questioning the validity of earlier results (e.g. Halpern et al., 2011), in fact, demonstrated significant effects despite a relative lack of power, as recently noted by Parrot (2011). Consistent with the notion that alterations in cognitive function in MDMA users are related to MDMA-induced neurotoxicity is the observation that deficits appear to be related to both lifetime exposure of MDMA and intensity of individual exposures (i.e. doses used) (Rogers et al., 2009; Parrott, 2011), both of which are known to influence the development of neurotoxicity in preclinical studies.

2.4.2. Sleep

Two studies (Allen et al., 1993; McCann et al., 2009) have used formal polysomnographic methods in abstinent MDMA users to assess the possibility that MDMA exposure leads to alterations in normal sleep neurophysiology. Both studies suggest that MDMA leads to chronic changes in sleep. In particular, MDMA users exhibit alterations in sleep architecture and circadian rhythms (Allen et al., 1993), and have an increased risk for obstructive sleep apnea (McCann et al., 2009). Given the importance of circadian rhythms and sleep quality in a variety of daytime functions (e.g. alertness, cognitive function, and endocrine function), these findings suggest that some of the behavioral differences that have been observed in MDMA users could be related, in part, to alterations in sleep timing, quality, or continuity.

2.4.3. Neuroendocrine Effects

Two studies have employed the neuroendocrine challenge method with 5-HT probes to assess the possibility that MDMA exposure leads to altered 5-HT-mediated endocrine function in abstinent MDMA users (McCann et al., 1999b; Gerra et al., 1998). In

the first study, the mixed 5-HT agonist and 5-HT releaser, m-chlorophenylpiperazine (m-CPP), was administered to abstinent MDMA users and non-MDMA using controls. MDMA users were found to have reduced cortisol and prolactin responses to m-CPP, in addition to diminished behavioral responses. It was concluded that differential responses to m-CPP in the two subject groups could be related to MDMA-induced neurotoxicity, and alterations in 5-HT input on neuroendocrine function (McCann et al., 1999b).

In the second study, Gerra and colleagues conducted a longitudinal study in abstinent MDMA users at baseline (time 0), as well as 3 and 12 months later. MDMA users and controls were challenged with the 5-HT releaser, fenfluramine, which is known to induce increases in both prolactin and cortisol. MDMA users were found to have persistent reductions in fenfluramine-induced prolactin, but reversible reductions in cortisol (i.e. reductions did not persist for the full 12-month period). Further, the extent of alterations in prolactin responses at the 12-month time point was directly related to MDMA exposure. Taken together, these observations were taken as evidence that MDMA can lead to persistent alterations in 5-HT-mediated prolactin responses.

2.4.4. Pain

Several studies (McCann et al., 1994; O'Regan and Clow, 2004; McCann et al., 2011) have explored the possibility that pain perception is altered in abstinent MDMA users, given the known role of 5-HT in the modulation of pain (Yoshimura and Furue, 2006; Lopez-Garcia, 2006). One study, conducted in MDMA users who had been abstinent, on average, for 5 months noted no differences in MDMA users' response to an ischemic pain task (McCann et al., 1994) when compared to control subjects. The second study found reduced cold-pain tolerance in MDMA users who had been abstinent from MDMA for only 3–4 days (O'Regan and Clow, 2004). Most recently, MDMA users who had been abstinent for weeks to months and matched non-MDMA-exposed controls were compared on a variety of standardized pain measurements. Further, given increasing data that MDMA users have alterations in sleep and the known influence of sleep disruption on pain (Edwards et al., 2008; Tiede et al., 2010), the potential relationship between polysomnographic sleep measures and pain outcomes were explored. Abstinent MDMA users were found to have reduced pressure pain thresholds, increased cold-pain ratings, and increased pain ratings during testing of diffuse noxious inhibitory control. Although numerous significant relationships between sleep and pain measures were identified, meditational modeling indicted that altered pain perception in MDMA users was not related to changes in sleep.

2.4.5. Neuropsychiatric Effects/Complications

In addition to acute and subacute neuropsychiatric effects of MDMA, which are presumably related to its pharmacological properties, there have also been numerous reports of chronic psychiatric problems in MDMA users. Although beyond the scope of this chapter, the most common psychiatric problems seen in MDMA users include depression, anxiety,

phobias, psychotic symptoms, and somatization disorders (Parrott et al., 2000, 2001, 2002; MacInness et al., 2001; Bobes et al., 2002; McCardle et al., 2004; Dafters et al., 2004; Lieb et al., 2002; Daumann et al., 2004; Sumnall and Cole, 2005; Karlsen et al., 2008). Although most of the authors of these reports draw attention to the fact that MDMA users tend to use "other drugs" in addition to MDMA, and that psychiatric problems may have drawn people to use MDMA (rather than having been caused by them), several studies have found a relationship between the extent of MDMA use and psychopathology (Parrott et al., 2000, 2002; de Win et al., 2004). While not conclusive, this observation is consistent with the notion that MDMA neurotoxicity could play a role in the psychiatric symptoms experienced by some MDMA users.

3. CONCLUSIONS

MDMA is a ring-substituted amphetamine analog with reinforcing psychoactive effects, in addition to neurotoxic potential toward central 5-HT neurons. Its major pharmacological effects appear to be secondary to actions at brain monoaminergic neurons, both as a potent monoamine releaser and as a reuptake inhibitor, although MDMA also binds directly to several brain 5-HT receptor subtypes. The mechanisms of MDMA-induced 5-HT neurotoxicity are not fully understood, but are known to be exacerbated by increased temperature, attenuated by hypothermia, and blocked by 5-HT reuptake inhibitors. A growing body of data indicates that humans, like animals treated with oral or systemic MDMA, are susceptible to MDMA-induced 5-HT neural injury. It is not clear whether 5-HT neural injury, which is best described as a distal axotomy of brain 5-HT neurons, is fully reversible in all brain regions. Studies in abstinent MDMA users have revealed deficits in a variety of behavioral functions known to be modulated by brain 5-HT, although it has not been definitively demonstrated that deficits are related to MDMA-induced 5-HT injury. Future research should be directed toward determining the mechanism of action of MDMA neurotoxicity, defining the parameters of MDMA use associated with neurotoxicity in humans, and determining the functional consequences (and reversibility) of MDMA neurotoxicity in both animals and humans.

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