Methamphetamine and MDMA Neurotoxicity: Biochemical and Molecular Mechanisms

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Contents

Abstract

Methamphetamine (METH) and methylenedioxymethamphetamine (MDMA) are psychostimulant drugs that are widely abused. The two drugs can also cause neurotoxic damage and neurodegeneration in several regions of the brains of humans, nonhuman primates, and rodents. METH-induced behavioral and neurotoxic abnormalities occur consequent to alterations of dopamine terminal

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physiology, which leads to massive release of dopamine (DA) in the synaptic clefts of several brain regions. Increased DA levels in synaptic clefts are further enhanced by METH-induced blockade of DA re-uptake into DA terminals through the DA transporter (DAT). METH toxicity is not only accompanied by terminal dysfunctions/degeneration but also by impairments in complex networks that subserve cognitive and emotional processes. MDMA, a ring-substituted derivative of phenyl-isopropylamine, is structurally similar to METH. MDMA is a substrate of the serotonin transporter (SERT) through which it enters monoaminergic terminals where it triggers release of serotonin (5-HT) from storage vesicles into synaptic clefts of brain regions that receive serotoninergic terminals from the ventral and dorsal midbrain raphe nuclei. In addition, MDMA has been shown to cause selectively neurotoxic damage to serotonergic nerve terminals in rats, guinea pigs, and nonhuman primates even though toxic damage to the human brain has been debatable. There is also evidence that some MDMA users exhibit cognitive deficits. Nevertheless, there is, at present, no firm evidence that links drug-induced DA and/or 5-HT depletion to cognitive impairments. More studies are necessary to clarify the importance of these changes in the development of beneficial therapeutics to the treatment of patients who suffer from METH and MDMA use disorders.

Keywords

Methamphetamine · MDMA · Psychostimulants · Dopamine · Neurotoxicity · Oxidative stress · Apoptosis · Hyperthermia

Abbreviations

ADHD	Attention Deficit Hyperactivity Disorder
ATG	Autophagy-related genes
DA	Dopamine
DAT	Dopamine transporter
ER	Endoplasmic Reticulum
5-HIAA	5-hydroxyindoleacetic acid
α-MT	α-methyl-*p*-tyrosine
COMT	catechol-*O*-methyltransferase
CNS	Central Nervous System
CuZnSOD	copper-zinc superoxide dismutase
HHA	3,4-dihydroxyamphetamine
HHMA	3,4-dihydroxymethamphetamine
HMA	4-hydroxy-3-methoxy-amphetamine
5-HT	serotonin
L-DOPA	L-3,4-dihydroxyphenylalanine
MDA	methylenedioxyamphetamine
MDMA	methylenedioxymethamphetamine
METH	methamphetamine
MK-801	dizocilpine

MTF-1	metal responsive transcription factor 1
MTs	metallothioneins
NET	norepinephrine transporter
Nrf2	NF-E2-related factor 2
PARP	poly (ADP-ribose) polymerase
SERT	serotonin transporter
ROS	Reactive Oxygen species
TPH	tryptophan hydroxylase
TH	tyrosine hydroxylase
ULK1	autophagy activating kinase
VMAT2	vesicular monoamine transporter 2

1 Introduction

Methamphetamine (METH) is presently prescribed under the name, desoxyn, for the treatment of attention deficit hyperactivity disorder (ADHD) (Castells et al., 2018; Punja et al., 2016) and narcolepsy (Thorpy & Bogan, 2020). It has very limited use in the treatment of obesity. Methylenedioxymethamphetamine (MDMA) is sometimes used as an adjunctive approach to psychotherapy and has been reported to be effective in reducing symptoms of post-traumatic stress disorder (PTSD) in the context of controlled settings (Mithoefer et al., 2018; Krediet et al., 2020). The most popular use of these drugs is by adolescents and adults who are seeking the psychological and emotional effects associated with their intake (Chomchai & Chomchai, 2015). A significant number of the recreational users then progress to meet criteria for METH use disorders (MUD) based on diagnostic criteria listed in the Fifth Edition of the Diagnostic and Statistical Manual (DSM-V) of the American Psychiatric Association (APA) or the International Classification of Diseases (ICD10) (Saunders, 2017). METH use is only second to that of marijuana when comparing all illicit drugs, with the use of alcohol and nicotine being more prevalent in comparison to other drugs with rewarding properties or abuse liability.

Studies conducted during the past three decades have supported the thesis that brain dopamine (DA) is an essential ingredient in the generation of behavioral changes associated with the self-administration of drugs with rewarding properties. DA contributes to incentive salience and is necessary for identifying wanted elements from the environment (Berridge & Robinson, 2016). Drugs of abuse that increase dopaminergic signals alter and sensitize dynamic mesolimbic mechanisms that evolved to attribute incentive salience to rewards (Le Moal & Koob, 2007). Such drugs interact with incentive salience integrating Pavlovian associative information with physiological state signals (Berridge & Robinson, 2016). Specific proteins, called DA transporters (Mulvihill, 2019), which are located in the presynaptic membrane of dopaminergic terminals, serve to remove DA from the synaptic cleft to end its action (Sulzer & Rayport, 1990; Sulzer, 2011). After entering DA terminals, METH accumulates into vesicles in a pH gradient-dependent fashion (Sulzer & Rayport, 1990; Sulzer et al., 1992). Psychostimulants like METH are thought to

reduce intracellular gradients of synaptic vesicles thereby promoting release and blockade of re-uptake of monoamines into the vesicles. These chemical events lead to massive DA release in the synaptic cleft in brain regions that receive dopaminergic projections from the midbrain (Krasnova & Cadet, 2009; Xi et al., 2009). Accumulation of DA within DA terminals and reverse transport-mediated release into the synaptic cleft work in tandem to cause degeneration of monoaminergic terminals in the striatum (O'Callaghan & Miller, 1994; Krasnova & Cadet, 2009) and evidence of neuronal death in several regions of the rodent brain (Cadet et al., 2003, 2005). This chapter describes the mechanisms by which METH and its analogs, methylenedioxymethamphetamine (MDMA), can cause neurotoxic damage to monoaminergic terminals and non-aminergic cell bodies in the brain.

2 Methamphetamine Toxicity and Underlying Mechanisms

2.1 Dopamine and Oxidative Stress

Methamphetamine enters DA neurons through the DAT and via passive diffusion. In monoaminergic neurons, DA accumulates in vesicles, disrupts the pH gradient required for vesicular DA sequestration, and displaces DA into the cytoplasm (Sulzer & Rayport, 1990). METH causes release of monoamines from monoaminergic terminals via plasmalemmal uptake transporters including the DA transporter (DAT), the norepinephrine transporter (NET), and the serotonin (5-HT) transporter (SERT) via a mechanism called reverse transport (Sulzer 2011). Thus, METH acts through the vesicular monoamine transporter 2 (VMAT-2) to cause excessive release of dopamine into DA terminals followed by excessive DA release into the synaptic cleft through the DAT (Sulzer 2011). DA accumulates in the cytoplasm where it alters the concentration gradient and likely helps to favor the reverse transport of DA via the DAT. DA is an important component of the mechanisms that underlie METH neurotoxicity (Cubells et al., 1994). DA is known to autoxidize to generate reactive oxygen species (ROS) such as hydrogen peroxide, superoxide radicals, and hydroxy radicals (Cadet & Brannock, 1998), a process that is pH-dependent (Umek et al., 2018).

The involvement of DA in its toxic effects is possibly one of the reasons why METH can cause toxicity in monoaminergic terminals of several mammalian species including rats, mice, guinea pigs, cats, and monkeys (see Cadet et al., 2003; McCann & Ricaurte, 2004; Krasnova & Cadet, 2009 for more detailed discussions). Specifically, animals given repeated doses of METH have consistently been shown to suffer significant decreases in DA and 5-HT levels in the striatum, cortex, in the olfactory bulb (Deng et al., 2007; Cadet et al., 1994b), decreases in striatal DAT binding, DAT immunoreactivity, and tyrosine hydroxylase (TH) immunoreactivity (Bowyer et al., 2008; Deng et al., 1999) and TH protein levels (O'Callaghan & Miller, 1994). Animals that self-administer METH also show deficits in dopaminergic systems (Krasnova et al., 2010) characterized by deficits similar to those observed after experiment-injected drugs. Morphological studies have provided evidence that reduced markers related to the integrity of DA and 5-HT systems are

secondary to degeneration of DA and 5-HT axonal terminals (Ricaurte et al., 1982). Evidence for DA involvement in METH toxicity is provided by observations that neurotoxicity can be prevented or attenuated by agents such as α-methyl-p-tyrosine, which block DA synthesis and decrease DA levels in the striatum (Kuhn et al., 2008). Importantly, treatment with immediate DA precursor, L-3,4-dihydroxyphenylalanine (L-DOPA), which restores cytoplasmic DA levels, enhances METH toxicity (Kuhn et al., 2008).

As mentioned above, DA autooxidation generates reactive oxygen species (ROS) such as hydrogen peroxide and superoxide radicals, quinones, and semiquinones (Cadet, 1988a, b; Cadet & Brannock, 1998). The Cadet laboratory has tested the involvement of reactive species including superoxide radicals in METH toxicity by using transgenic mice that overexpress the human copper-zinc superoxide dismutase (CuZnSOD), a cytosolic enzyme that catalyzes the breakdown of superoxide radicals (Cadet et al., 1994a, b; Jayanthi et al., 1998). These mice that have much higher CuZnSOD enzyme activity in the cytosol than control wild-type animals (Jayanthi et al., 1998) are protected against METH toxicity (Cadet et al., 1994a, b). These studies were the first ones to test the mechanisms of psychostimulant toxicity using transgenic animals.

METH can also cause neuronal apoptosis in several brain regions, including the striatum, cortex, hippocampus, and olfactory bulb (Cadet et al., 2005; Deng & Cadet, 2000; Deng et al., 2001, 2007; Ladenheim et al., 2000). Because METH administration is associated with the production of reactive oxygen species (ROS) (Jayanthi et al., 2004) and because ROS can cause apoptosis and DNA damage (Li & Trush, 1993; Radi et al., 2014), it is likely that METH might induce neuronal apoptosis through ROS-mediated DNA damage, mitochondrial and ER (endoplasmic reticulum) stress. This idea was initially supported by the observations that METH-induced poly (ADP-ribose) polymerase (PARP) cleavage, increase in caspase-3 activity, and neuronal death were all attenuated in the striata of CuZnSOD transgenic mice (Deng & Cadet, 2000), documenting the participation of superoxide radicals not only in METH-induced terminal degeneration (Cadet et al., 1994b) but also in METH-induced cell death. A role for oxidative stress in METH toxicity is also supported by data obtained from microarray analyses that have identified changes in an early wave of changes in the expression of several genes that participate in transcriptional regulation including immediate early genes of the fos and jun families (Cadet et al., 2001). More delayed changes in mRNA levels were detected in changes that are involved in DNA repair, including APEX, PolB, LIG1, and DNA mismatch repair proteins MSH3 and PMS1 after toxic doses of the drug (Cadet et al., 2001, 2002). These observations are important in terms of suggesting that repeated exposures to METH might impair the functions of several families of genes involved in proper cellular functions.

It is also of interest to note that, in addition to depleting DAT at the DA terminals, injections of METH can also alter its functionality via the formation of DAT-associated complexes of higher molecular weight (Hadlock et al., 2009). This phenomenon is attenuated by either prevention of METH-induced hyperthermia or pretreatment with the DA synthesis inhibitor, α-methyl-p-tyrosine (α-MT),

implicating DA itself in causing these changes (Baucum 2nd et al., 2004). Reactive species also are implicated in DAT complex formation because in vitro exposure to the reducing agent, β-mercaptoethanol, reverses this process (Baucum 2nd et al., 2004). Concurrent with METH-induced DAT complex formation, METH treatment causes a loss of DAT monomer immunoreactivity and a decrease in DAT function (Baucum 2nd et al., 2004).

More evidence for a role of oxidative mechanisms in causing METH toxicity is the report that METH induces the transit of transcription factor NF-E2-related factor 2 (Nrf2) transit from cytosolic into nuclear fractions where the protein exerts its regulatory functions (Jayanthi et al., 2009). Nrf2 and metal responsive transcription factor 1 (MTF-1) participate in transcriptional activation of MT-1/2 genes in response to oxidative stress caused by exposure to heavy metals (Miyazaki et al., 2010). Astrocytes can act to protect surrounding neurons against excess DA and DA-quinone formation by increasing the production of quinones-quenching molecules such as metallothioneins (MTs) (Miyazaki et al., 2010). Increases in DA might promote nuclear translocation of Nrf2, upregulating MT1/2 expression in astrocytes with secondary protection against METH toxicity via Nrf2 functions. This idea is supported by the report of Granado et al. (2011b) who showed that Nrf2 deficiency could exacerbate METH-induced damage to dopamine neurons and potentiate glial activation.

2.2 Role of DAT and VMAT-2 in METH Toxicity

The role of DAT and VMAT-2 in METH toxicity has been investigated using both pharmacological and genetic means. Specifically, administration of the DAT inhibitor, methylphenidate, 1 h after METH treatment, can reverse METH-induced decreases in vesicular DA uptake, reductions in VMAT-2 ligand binding, and decreases in VMAT-2 immunoreactivity in vesicular subcellular fractions 6 h after injections of the drugs (Sandoval et al., 2003). Modafinil, an anti-narcoleptic drug that has been used off-label to treat psychostimulant addiction, acts as a DAT blocker (Zolkowska et al., 2009), and is neuroprotective against METH toxicity, as documented by attenuation of METH-induced decreases in TH immunoreactivity and DA striatal content (Raineri et al., 2011). Importantly, mice with genetic deletion of DAT are also protected against drug-induced DA depletion, reactive astrocytosis, and ROS production in the striatum (Fumagalli et al., 1999).

A role for VMAT-2 in METH-induced damage to striatal DA terminals is also supported by studies showing that pretreatment with the irreversible inhibitor of vesicular transport, reserpine, exacerbates toxicity of the psychostimulant (Kuhn et al., 2008). These observations suggest that DA accumulation into monoaminergic terminals might have led to increased ROS production and subsequent damage to those terminals. Additionally, the post-METH injections of labeline, an alkaloid constituent of Indian tobacco (Lobelia inflata) that negatively impacts VMAT-2 functions (Teng et al., 1998; Dwoskin & Crooks, 2002), also reversed METH-induced depletion of striatal DA levels, decreases in synaptosomal,

membrane-associated, and vesicular VMAT-2 immunoreactivity measured at 24 h after drug treatment (Eyerman & Yamamoto, 2005). Importantly, Fumagalli et al. (1999) also reported that METH toxicity was exacerbated in heterozygous mice that had decreased VMAT-2 expression. When taken together, these studies confirm a role for both DAT and VMAT-2 in METH toxicity.

2.3 Role of Dopamine Receptors in METH Toxicity

After its release into the synaptic cleft, DA exerts its functions by interacting with five DA receptors that fall into two classes, D1-like and D2-like receptors (Beaulieu et al., 2015). It was therefore possible that these receptors might have been involved in METH toxicity. Several studies have now documented a significant role for DA receptors in the mediation of METH toxicity (Angulo et al., 2004; Beauvais et al., 2011; Jayanthi et al., 2005; Xu et al., 2005). For example, administration of the DA D_1 -like receptor antagonist, SCH23390 [R-(+)-7-chloro-8-hydroxy-3-methyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine], given before each of 5 METH injections attenuated drug-induced decreases in TH activity and DA levels in the rat striatum. SCH23390 also blocked METH-induced decreases in tryptophan hydroxylase (TPH) activity and 5-HT levels in the striatum and cortex measured 18–20 h after METH treatment (Sonsalla et al., 1986). The DA D_2 -like receptor antagonist, sulpiride, also blocked METH-induced toxic effects on DA systems without affording any protection against its deleterious effects on striatal and cortical 5-HT terminals (Sonsalla et al., 1986). In addition, a single injection of SCH23390 prior to a single high METH dose also attenuated long-term decreases in DA levels (Jayanthi et al., 2005), decreased DAT binding and TH protein levels (Xu et al., 2005). SCH23390 also inhibited METH-induced reactive astrocytosis (Xu et al., 2005). SCH23390 also protected against cell death caused by a single large injection of METH (Jayanthi et al., 2005; Xu et al., 2005). The protection afforded by SCH23390 against METH-mediated cell death depends, in part, on the activation of the Fas/FasL death pathway because pretreatment with SCH23390 caused suppression of METH-induced increased expression of FasL and caspase-3 in neurons (Jayanthi et al., 2005). Jayanthi et al. (2009) also measured the expression of several genes that are regulated during endoplasmic reticulum (ER) stress. These included ATF3, HSP27, Hmox1, HSP40, CHOP/Gadd153and of ATF4, ATF6, BiP/GRP78, and of GADD34. SCH23390 also attenuated or blocked METH-induced increases in the expression of the majority of these genes. Repeated METH injections can also cause substantial increases in the expression of proteins that participate in ER- and mitochondrial-dependent stress responses, with these changes being also blocked by SCH23390 (Beauvais et al., 2011). However, the D_2-like receptor antagonist, raclopride, was found to have only small to moderate effects on ER stress proteins and only small effects on mitochondrial-dependent cellular stress proteins (Beauvais et al., 2011). Both DA D_1 and D_2 receptors appear to be required for METH toxicity since both D_1R (Ares-Santos et al., 2012) and D_2R (Granado et al., 2011a) knockout mice are protected, to different degrees, against METH neurotoxicity.

2.4 Role of Microglia on METH-Induced Toxicity

METH toxicity is accompanied by reactive astrocytosis (Bowyer et al., 1994) and microglial activation (Pubill et al., 2002; Krasnova et al., 2016; Yang et al., 2020) in various brain regions. In the normal brain, microglial cells exist in a resting state but, in response to inflammation or brain damage, these cells increase in size, migrate to the site of the injury, and phagocytize dying and dead cells (Quarta et al., 2020). Although microglial activation is important for immune responses, their overactivation can result in neurotoxic consequences via the production of reactive oxygen species and other neurotoxic products including caspases that can lead to neuronal death (Rodríguez-Gómez et al., 2020; Simpson & Oliver, 2020). As noted above, injections of toxic doses of METH also increase reactive microglial responses in several brain regions. For example, METH induces microgliosis in brain areas that suffer from neuronal degeneration (Thomas & Kuhn, 2005a; Thomas et al., 2004a, b). Reserpine and clorgyline that exacerbate METH toxicity also potentiate METH-induced microglial activation in the mouse striatum (Thomas et al., 2008). In contrast, attenuation of METH neurotoxicity by dizocilpine (MK-801), dextromethorphan, α-methyl-p-tyrosine, or modafinil inhibits METH-induced microglial activation (Kuhn et al., 2008; Thomas & Kuhn, 2005b; Raineri et al., 2012, 2015). Anti-inflammatory drugs, ketoprofen and indomethacin, and the second-generation tetracycline and minocycline, afford protection against METH-induced toxicity and microgliosis (Asanuma et al., 2003, 2004; Zhang et al., 2006). Another study analyzed METH-induced structural changes and microglial activation in the brain (Thanos et al., 2016). These authors found that METH administration was accompanied with increased striatal volume and microglial activation in the striatum (Thanos et al., 2016). Most studies had assessed microgliosis after noncontingent injections of the drug. It was therefore important to measure neuroinflammation in animals that self-administer the drug. Gonçalves et al. (2017) undertook a self-administration study and reported upregulation of vascular cell and intercellular adhesion molecule, concomitant with the presence of T cell antigen CD4 and tissue macrophage marker CD169 in the brain parenchyma. METH self-administering also exhibited microglial activation, astrogliosis, and increased production of tumor necrosis factor-alpha, interleukine-1 beta, and matrix metalloproteinase-9 (Gonçalves et al., 2017).

Further studies are necessary to identify the impact of METH on inflammatory markers in the human brain by using PET ligands that are used to measure neuroinflammation (Kreisl et al., 2020). Moreover, it is of interest to investigate the specific biochemical and molecular mechanisms that underlie METH-induced microgliosis and the manner by which these activated microglial cells might lead to degeneration of monoaminergic terminals and neuronal cells in the brain. These studies will have implications for both the clinical course and treatment of METH use disorders.

3 METH Preconditioning Protects aAgainst METH Toxicity

Pretreatment with multiple low-dose injections of METH or with gradually escalating doses of the drug provide partial protection against the deleterious effects of a high-dose METH challenge (Cadet et al., 2009, 2011; Danaceau et al., 2007; Graham et al., 2008).

METH doses were increased gradually in an attempt to mimic progressively larger doses of the drug used by some human METH addicts. This approach labeled *METH preconditioning* was associated with almost complete protection against dopamine depletion in the striatum and frontal cortex caused by subsequent challenges with toxic METH doses (Cadet et al., 2009). A subsequent study by Hodges et al. (2011) also reported that this regimen resulted in prolonged protection, with a second challenge of METH causing no further decreases in striatal DA or 5-HT levels in comparison to a single METH challenge. Another study has also reported that METH self-administration could also attenuate the persistent deficits in dopaminergic neuronal function and increases in GFAP immunoreactivity caused by a subsequent binge METH exposure (McFadden et al., 2012).

Neuroprotection induced by METH pre-conditioning might be related to reductions in METH hyperthermia (McFadden et al., 2012). Another possible explanation for the neuroprotective effects of METH is the fact that, by reducing striatal DAT and increasing high-molecular DAT complexes that are nonfunctional, the striatum might have become less susceptible to the toxic effects of a METH challenge (Krasnova et al., 2011). This line of reasoning is consistent with the recent report that a low, sub-toxic dose of METH was able to attenuate 6-OHDA-induced decreases in ATP levels and mitochondrial dehydrogenase activity (El Ayadi & Zigmond, 2011). In any case, the observations that repeated injections of low doses of METH can provide a certain degree of protection against acute METH toxic doses suggest a partial explanation as to why users of large METH doses do not show Parkinsonism at a young age

4 METH Self-Administration Animal Model with Extended Access

As reviewed above, noncontingent preclinical models are widespread used to study mechanisms underlying METH effects in the brain because they reliably reproduce the changes in DA markers found in the brains of human METH addicts. However, there are some limits to the relevance of noncontingent models to compulsive and chronic METH use in humans. Mainly, noncontingent METH models do not consider primary reinforcing effects of METH, do not reproduce craving, and do not allow investigators to test if METH-induced toxic changes correlate with vulnerability to relapse. Considering these challenges, the Cadet laboratory at NIDA had consistently studied METH self-administration on brain dopaminergic systems, transcriptional changes, and immune responses in the rat brain (Krasnova et al., 2016).

Extended METH self-administration can cause neurotoxicity and inflammation in the brain.

Extended access to METH self-administration was associated with a progressive escalation of drug intake by rats and significant decreases in their body weights. This pattern of METH intake resulted in persistent dose-dependent depletion of striatal and cortical DA levels measured at various times after cessation of drug treatment; METH intake also caused decreases in the expression of striatal and cortical TH and

DAT proteins (Krasnova et al., 2010). Also, METH induced dose-dependent increases in astrogliosis (measured by GFAP expression) in both striatum and cortex (Krasnova et al., 2010). As seen in human METH addicts, METH self-administration caused increases in D1 DA receptor protein levels at 2 h post-drug; D2 DA receptor protein levels were decreased after 1 month withdrawal (Krasnova et al., 2013).

Autophagy is a highly regulated process that cells use to degrade cytoplasmic contents, and flaws in this process is associated with protein aggregation present in neurodegenerative disorders (Nixon & Yang, 2011). Larsen et al. (2002) demonstrated that exposure to METH induced the formation of autophagic granules. The Cadet lab also used drug self-administration model to test the idea that compulsive METH takers might show evidence of drug-induced autophagic changes in the brain. Indeed, there were significant increases in mRNA levels of autophagy-related genes including Atg2a, Atg5, Atg14, and Atg16L1 in the dorsal striatum of compulsive METH-rats. Levels of two autophagy biomarkers, autophagy activating kinase (ULK1) and phospho-Beclin1, were also increased (Subu et al., 2020). These observations are consistent with the idea that autophagic changes might be important contributors to METH toxicity (Roohbakhsh et al., 2016).

Rat self-administration studies also supported the idea of the involvement of apoptotic changes secondary to exposure to METH because increased p53, but decreased Bcl-2 protein levels, were found in the dorsal striatum of these rats (Subu et al., 2020). These changes were accompanied by increased expression of cleaved initiator caspase-9 and effector caspase-6 in compulsive METH takers in comparison to rats that had become almost abstinent in the presence of adverse consequences (Subu et al., 2020). These observations indicate that exposure to METH might be associated with the initiation of phagophore formation (increased protein expression of ULK1), elongation and completion of autophagosome (upregulation of Atg5–Atg12–Atg16L, as well as activation of pBECN1). It is therefore not far-fetched to suggest that intake of large amounts of METH during self-administration may be accompanied by increased oxidative stress and secondary mitochondrial dysfunctions and activation of death cascades in the brain.

5 Cognition in Human METH Subjects

Chronic abuse of METH contributes to depression, psychosis, mood disturbances, and psychomotor dysfunctions in humans (Darke et al., 2008; Homer et al., 2008; Cadet et al., 2014). METH addicts also suffer from deficits in attention, working memory, and decision-making (Gonzalez et al., 2004; Verdejo-García et al., 2006; Harro, 2015; Cadet & Bisagno, 2016) but see also discussions by Proebstl et al. (2018) for an excellent analysis of the published literature. Withdrawal from the drug is also associated with anhedonia, irritability, and intense craving for the drug (Darke et al., 2008; Homer et al., 2008). These neurocognitive deficits may be consequences of neuropathological changes observed in the brains of these patients (Cadet et al., 2014). Specifically, humans who suffer from METH use disorders have been

reported to exhibit persistent decreases in DAT levels in the orbitofrontal cortex, dorsolateral prefrontal cortex, and the caudate-putamen (McCann et al., 1998; Sekine et al., 2003; Volkow et al., 2001a, c). METH abusers also show abnormal glucose metabolism in cortical and subcortical brain areas (Volkow et al., 2001b; Wang et al., 2004). In addition, there is prominent microglial activation in the brains of these individuals (Sekine et al., 2008). Alterations in DA tone produced by METH toxicity on dopamine terminals might not only influence the physiology of the brain but might also alter the complex networks that subserve cognitive and emotional processes. Nevertheless, a recent study has failed to show any direct connection between DA depletion and cognitive dysfunctions in adult rats (Schweppe et al., 2020). When taken together, the accumulated evidence suggests a real need for more comprehensive multisite clinical studies to assess the impact of METH of diverse populations that include participants who have used different patterns and amounts of the drug during their lifetimes.

6 Summary: METH Toxicity and Risk of Parkinsonism

Convincing evidence now exists that compulsive METH taking over several weeks can be neurotoxic. Although this study needs to be replicated, Kousik et al. (2014) have provided some evidence that METH self-administration is accompanied by long-lasting degeneration of dopaminergic terminals. It is important to try to replicate these types of studies that provide partial support for the notion that METH use is a risk factor for Parkinsonism in humans. Specifically, Callaghan et al. (2012) had reported that patients who were admitted to hospitals while suffering from METH use disorder had a much higher risk of presenting with Parkinsonism during a 16-year follow-up when these patients were compared to others who were admitted for appendicitis. In another retrospective study, Curtin et al. (2015) reviewed Utah's statewide records from 1996 through 2011 in order to identify any connection between METH usage and Parkinsonism. They also compared the METH using populations to those who used cocaine and to a no-drug group. They reported an increased risk for Parkinsonism in METH users but not in cocaine users. It is thus likely that some of the clinical observations in METH abusers might be secondary to METH-induced toxic responses including the production of free radicals (Cadet, 1988b; Cadet & Brannock, 1998). These clinical observations suggest that it will be necessary to develop therapeutic agents that inhibit or interfere with the biochemical and cellular substrates of METH toxicity in order to provide better interventions against METH-induced neuropsychiatric manifestations including, possibly, METH-associated Parkinsonism.

7 MDMA Neurotoxicity

MDMA is a ring-substituted derivative of phenylisopropylamine, structurally similar to METH and the hallucinogen, mescaline (Dunlap et al., 2018; Lyles & Cadet, 2003). MDMA impacts peripheral and central nervous system (CNS) functions

through its actions on the serotonergic system (Baumann & Rothman, 2009). MDMA is a substrate of the serotonin transporter via which it enters monoaminergic neurons and causes release of 5-HT from storage vesicles, followed by 5-HT release into the synaptic cleft by reversal of normal SERT function (Baumann & Rothman, 2009). Injections of large doses of MDMA cause massive release of 5-HT from presynaptic vesicles, followed by a rapid decrease in 5-HT and 5-hydroxyindoleacetic acid (5-HIAA) levels and decreased TPH activity (Górska et al., 2018; Lyles & Cadet, 2003). There do not appear to be losses of 5-HT uptake sites at early time points after MDMA administration (Lyles & Cadet, 2003). MDMA can also cause dose-dependent DA and NE release in the striatum and hippocampus in rats (Lyles & Cadet, 2003). Adverse effects of acute MDMA administration, including cardiovascular stimulation and elevated body temperature, are thought to involve monoamine release from sympathetic nerves in the periphery or nerve terminals in the CNS (Baumann & Rothman, 2009). MDMA is selectively neurotoxic to serotonergic nerve terminals in rats, guinea pigs, and nonhuman primates (Green et al., 1995). In mice, however, MDMA appears to affect mainly the nigrostriatal dopaminergic system (Cadet et al., 1995). MDMA users consistently show reduced SERT radionuclide ligand binding across multiple brain regions (Reneman et al., 2006). Some evidence has suggested that these levels began to recover with increased periods of MDMA abstinence. Recently, Erritzoe et al. (2011) reported significantly lower SERT binding potential in the neocortex (−56%), pallidostriatum (−19%), and amygdala (−32%), with the extent of binding correlated with lifetime MDMA usage. Kish et al. (2010) compared moderate Ecstasy/MDMA users with nonuser controls and reported that SERT binding was significantly reduced in all the cerebral cortices and hippocampus. The degree of these reductions was significantly associated with the extent of past MDMA usage. An additional molecular structural component of the serotonergic signaling pathway is the 5-HT_{2A} receptor. 5-HT_{2A} receptors are densely distributed in human cortex, 5-HT_{2A} receptor levels were reduced in multiple brain regions in the ongoing/acute MDMA user group, possibly because of ongoing MDMA-mediated increases in 5-HT release (Reneman et al., 2002).

Neurochemical and anatomical studies have reported long-term reductions in markers of 5-HT systems in rats. These include decreased levels of 5-HT and of its major metabolite, 5-HIAA, decreased number of 5-HT transporters, and decreased activity of the rate-limiting enzyme of 5-HT synthesis, TPH (Commins et al., 1987; De Souza et al., 1990). Severe reductions in 5-HT and 5-HIAA levels occurred in the rat neocortex, striatum, and hippocampus (De Souza et al., 1990). These abnormalities are reported to last for months or even years after drug administration (Lyles & Cadet, 2003). MDMA also perturbs the function of SERT (Green et al., 2003), a marker of the integrity of serotonin neurons (Blakely et al., 1994). By virtue of its moderating synaptic 5-HT levels, SERT is crucial for the process of 5-HT neurotransmission (Green et al., 2003). MDMA downregulates SERT function without altering SERT mRNA or protein expression, and this rapid downregulation is sustained for at least 90 min and is dose-dependent (Kivell et al., 2010).

Histologic studies in animals have shown that large doses of MDMA are associated with neurodegeneration particularly affecting the terminal portions of axons and

fibers; raphe cell bodies are spared (reviewed by Lyles & Cadet, 2003). In rats, histological studies using the Fink–Heimer staining method have also provided evidence for the degeneration of nerve terminals in the striatum and somatosensory cortex after chronic exposure to MDMA (Commins et al., 1987). Ricaurte et al. (2000) and Callahan et al. (2001) have also provided evidence that MDMA can cause reduction of the anterograde transport of [^{3}H]proline in ascending axons originating in the dorsal raphe nuclei, a subset of which comprise ascending 5-HT axons that project to various forebrain regions. A recent study found microtubular injury in frontal cortex after MDMA treatment. The most apparent alteration in the ultrastructure of the labeled cortical axons of MDMA-treated animals was the widespread disorganization of the microtubular system, suggesting a collapse of axonal microtubular system (with intact mitochondria) that leads to axonal swelling (Adori et al., 2011). These authors also found no signs of damage on dorsal raphe cell bodies. In nonhuman primates, reorganization of 5-HT projections has been reported to occur in the brains of nonhuman primates treated with MDMA (Ricaurte et al., 2000). Interestingly, it has been reported that MDMA toxic effects are stereospecific and involve the S(+) enantiomer. Repeated S(+)-MDMA injections induce striatal gliosis, whereas chronic R(−)-MDMA did not show any of these effects (Frau et al., 2013). Subsequently, mice injected with R(−)-MDMA did not show any indication of hyperthermia or neurotoxicity (Curry et al., 2018).

Formation of toxic MDMA metabolites, which generate free radicals and associated oxidative stress and membrane damage, have been proposed as causal agents for the long-term MDMA-induced neurodegeneration (reviewed in Lyles & Cadet, 2003). Metabolism of MDMA results in the formation of methylenedioxyamphetamine (MDA) by *N*-demethylation; and 3,4-dihydroxymethamphetamine (HHMA), the major metabolite, by *O*-demethylation. *O*-demethylation of MDA subsequently results in 3,4-dihydroxyamphetamine (HHA). HHMA and HHA are metabolized by catechol-*O*-methyltransferase (COMT) to HMMA and to 4-hydroxy-3-methoxy-amphetamine (HMA) (reviewed by Green et al., 2003). The metabolites of MDMA might induce reactive species through redox cycling. Also, DA-induced oxidative stress in 5-HT terminals, and 5-HT_{2A} and dopamine D_1 receptor–mediated hyperthermia (Shioda et al., 2008) are all factors associated with MDMA neurotoxicity. In addition, it has been reported that acute MDMA can induce brain edema in rats due to blood–brain barrier disruption (Pérez-Hernández et al., 2017). A relatively recent study has also documented reactive microgliosis after injections of MDMA or its metabolite, MDA (Herndon et al., 2014).

8 Protective Mechanisms aAgainst MDMA-Induced Toxicity

Preconditioning with repeated MDMA dosing appears to exert some neuroprotective effects against larger MDMA doses. For example, Bhide et al. (2009) reported that repeated exposure of adult rats to MDMA provides neuroprotection against a challenge with large doses of MDMA that were shown to deplete 5-HT and decrease in SERT immunoreactivity. Alterations in MDMA pharmacokinetics or

MDMA-induced hyperthermia do not appear to contribute to the neuroprotection provided by preconditioning.

There are other agents that also provide protective effects against MDMA toxicity. Chipana et al. (2008) reported that memantine, an alpha-7 nAChR antagonist used for treatment of Alzheimer's disease, was able to provide complete protection against MDMA-induced reduction in cortical [^{3}H]paroxetine-binding sites. Fluoxetine, a SERT blocker, also provided long-lasting protection against MDMA-induced loss of SERT detected in vivo using micro-PET (Li et al., 2010).

9 Cognition in Human MDMA Subjects

The accumulated evidence suggests that heavy MDMA use is associated with cognitive impairments and mood disturbances, in some cases lasting for months after cessation of drug intake (Baumann & Rothman, 2009). Several studies have reported long-term deficits in memory and higher cognition, and other psychobiological functions in these substance abusers (Reneman et al. (2006). It is important to note that not all cognitive skills are affected and that there are also MDMA users who show normal neuropsychological functions (Parrott, 2006). The role of other psychiatric disorders needs to be considered when evaluating cognitive functions in MDMA abusers. MDMA can also disrupt neuroendocrine regulation that is influenced by 5-HT levels. For example, MDMA users showed significantly reduced prolactin and cortisol responses to the serotonergic agonist d-fenfluramine in comparison with control subjects (Gerra et al., 2000). It was suggested that MDMA might produce distinct prosocial and empathogenic effects that are very different from other stimulants (Bershad et al., 2016). MDMA oral administration produced acute subjective, emotional, sensual/sexual, and endocrine effects that were clearly distinct from those of the stimulant drugs methylphenidate and modafinil at comparable doses that produced similar sympathomimetic stimulant effects (Dolder et al., 2018). MDMA unique effects included drug liking, happiness, trust, well-being, sexual arousal, and decreased anxiety (Dolder et al., 2018).

In conclusion, MDMA users have been reported to suffer from cognitive and biochemical abnormalities. There is a need to correlate the changes of the serotonergic markers and other structural neuroimaging data to neuropsychological performance as well as responses to therapeutic interventions. Therapeutic interventions involving MDMA should be cautiously considered because of potential side effects linked to toxicity. Therefore, these should be done under strict medical supervision.

10 Conclusion

Toxicity of amphetamines is alarming because since it may result in either fatalities or functional impairments in the brain and/or peripheral organs of some individuals (Cadet et al., 2014). Nevertheless, there are many factors that can impact resulting cognitive and neurotoxicity associated with the use amphetamine analogs.

These factors include individual- and drug-related factors, with environmental insults playing substantial roles in modifying or exacerbating the deleterious effects of drugs on individuals (Mohammad Ahmadi Soleimani et al., 2016). For example, individual factors included protective mechanisms such as the levels of antioxidant enzymes based on individual genetic make-ups or dietary intake. Drug-related factors include patterns of drug dosing and length of drug exposure. Clearly, somebody who takes low doses over a very long time is at a much lower risk than another who repeatedly binges with large doses of the drugs. These issues need to be better addressed in basic science and in clinical settings. Here, the concept of preconditioning comes into play. Finally, preventive and therapeutic strategies against amphetamine use disorders should include discussions about ways to address potential long-term effects of these drugs in specific subsets of individuals instead of approaching patients as homogeneous groups. This work was supported by funds of the Intramural Research Program of the DHHS/NIH/NIDA.

11 Cross-References

- ▶ Cocaine as a Neurotoxin
- ▶ Mechanisms of Dopamine Oxidation and Parkinson's Disease
- ▶ Neurotoxicity in Psychostimulant and Opiate Addiction
- ▶ Neurotoxicity of Methamphetamine
- ▶ Neurotoxicity: A Complex Multistage Process Involving Different Mechanisms

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