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Neurotoxicity of Methamphetamine and 3,4-methylenedioxymethamphetamine

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Abstract

Amphetamines are a class of psychostimulant drugs that are widely abused for their stimulant, euphoric, empathogenic and hallucinogenic properties. Many of these effects result from acute increases in dopamine and serotonin neurotransmission. Subsequent to these acute effects, methamphetamine and 3,4 methylenedioxymethamphetamine (MDMA) produce persistent damage to dopamine and serotonin nerve terminals. This review summarizes the numerous interdependent mechanisms including excitotoxicity, mitochondrial damage and oxidative stress that have been demonstrated to contribute to this damage. Emerging non-neuronal mechanisms by which the drugs may contribute to monoaminergic terminal damage, as well as the neuropsychiatric consequences of this terminal damage are also presented. Methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) have similar chemical structures and pharmacologic properties compared to other abused substances including cathinone (khat), as well as a relatively new class of novel synthetic amphetamines known as ‘bath salts’ that have gained popularity amongst drug abusers.

Keywords

Methamphetamine; 3-4-methylenedioxymethamphetamine; neurotoxicity; excitotoxicity; oxidative stress; psychosis

Introduction

Amphetamines represent a class of widely abused psychostimulant drugs which include methamphetamine (Meth) and its derivative, 3,4-methylenedioxymethamphetamine (MDMA). Amphetamine abuse is a growing concern around the world due primarily to its ability to produce significant short term feelings of euphoria. An intense research focus has been directed towards understanding these acute effects as they promote the abuse liability of the amphetamines; however, the long term consequences of their abuse are rapidly emerging and include evidence of brain injury and neurotoxicity. This review will highlight

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All authors declare no conflicts of interest

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the underlying mechanisms associated with the neurotoxicity of amphetamines and discuss the neuropsychological consequences associated with the neuronal damage produced by the amphetamines. In addition, the review will introduce relatively new potential modulators that may contribute to the long-term effects of Meth and MDMA.

Neurotoxicity of Methamphetamine and MDMA

Acute Effects on Neurotransmitter Release

Methamphetamine treatment causes acute increases in both dopamine (DA) and serotonin (5HT) release. These increases result from the direct and indirect action of the drug on the DA transporter (DAT) and 5HT transporter (SERT). Meth is known to be a substrate for both transporters and is transported into the axon terminal (Rothman and Baumann, 2003, Fleckenstein et al., 2007). Following intracellular transport or diffusion, amphetamines can disrupt the vesicle proton gradient to cause an increase in cytoplasmic DA and 5HT from vesicular compartments (Sulzer and Rayport, 1990). Meth also affects cytoplasmic monoamine concentrations and DA release via altering the function of the vesicular monoamine transporter (VMAT-2) (Brown et al., 2002, Hansen et al., 2002, Riddle et al., 2002). Subsequent to increases in cytoplasmic DA and 5HT, reversal of the directionality of the DA and 5HT transporters causes significant, action potential-independent neurotransmitter efflux (Sulzer et al., 1995). Short-term decreases in neurotransmitter reuptake also contribute to increases in extracellular DA (Fleckenstein et al., 1997, Haughey et al., 2000). Secondary to increases in extracellular DA, Meth also causes acute increases in striatal glutamate as a result of D₁ DA receptor-mediated disinhibition of corticostriatal glutamate release (Mark et al., 2004). Unlike Meth, MDMA does not produce significant acute increases in striatal glutamate (Nash and Yamamoto, 1992a) but does appear to increase the extracellular concentration of glutamate in the hippocampus that may be mediated in part, through non-neuronal mechanisms (Nash and Yamamoto, 1992b, Anneken and Gudelsky, 2012). Both Meth and MDMA also increase 5HT release through similar transporter mediated mechanisms, though MDMA has a preferential affinity for SERT over DAT and consequently more pronounced effects on 5HT efflux (Rudnick and Wall, 1992, Rothman and Baumann, 2003).

Persistent DA and 5HT Terminal Damage

Subsequent to the acute effects of exposure, Meth produces long-term damage to dopaminergic and serotonergic axon terminals in the striatum, hippocampus, and prefrontal cortex (Ricaurte et al., 1980, Wagner et al., 1980, Seiden et al., 1988). In contrast, MDMA produces damage to serotonergic, but not dopaminergic axon terminals in the striatum, hippocampus, and prefrontal cortex (Battaglia et al., 1987, O'Hearn et al., 1988). The damage associated with Meth and MDMA has been shown to persist for at least 2 years in rodents, non-human primates and humans (Seiden et al., 1988, Woolverton et al., 1989, McCann et al., 1998, Volkow et al., 2001a, McCann et al., 2005). Neurochemical markers of this toxicity include decreases in the expression of tyrosine and tryptophan hydroxylase, the rate limiting enzymes for DA and 5HT, respectively as well as decreases in DA and 5HT tissue content, and decreases in DAT and SERT expression coupled with decreases in neurotransmitter uptake V_{max} without changes in K_m (Hotchkiss and Gibb, 1980, Wagner et al., 1980, Ricaurte et al., 1982, Ricaurte et al., 1985, Commins et al., 1987). Beyond changes in tissue content and neurotransmitter specific proteins, morphological changes indicative of axon terminal damage have been reported including the presence of swollen, distorted nerve terminals and positive Fink-Heimer staining, as well as edematous and degenerative changes seen using electron microscopy (Lorez, 1981, Ricaurte et al., 1982, Sharma and Kiyatkin, 2009). Further confirmation of the damage to terminals produced by substituted amphetamine exposure, recent Meth and MDMA self-administration studies with longer

access/exposure paradigms show decreases in DAT and SERT and tyrosine hydroxylase, as well as decreases in tissue content, all indicative of drug-induced monoaminergic terminal damage (Krasnova et al., 2010, Do and Schenk, 2011, McFadden et al., 2012a, McFadden et al., 2012b).

Neuronal Damage

Though not as extensively studied, there is also supporting evidence that Meth may produce cell death, in addition to damaging DA and 5HT terminals. Increases in terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL), a marker for apoptotic cell death, has been reported after exposure to Meth in the prefrontal cortex and striatum (Kadota and Kadota, 2004, Cadet et al., 2005, Zhu et al., 2006b). This cell death has been identified in different subpopulations of GABA-interneurons. Within the hippocampus, cell death of calbindin-containing GABA interneurons has been demonstrated after Meth and Meth-contributes to the death of parvalbumin containing striatal GABA interneurons (Zhu et al., 2006a, Kuczenski et al., 2007). Mitochondrial damage and endoplasmic reticulum stress have been associated with this Meth-induced apoptosis (Cadet et al., 2005). Specifically, Meth has been shown to produce apoptosis through increases in caspase-3 activity and the Fas/FasL cell death pathways (Jayanthi et al., 2005). Meth also produces DNA damage and alterations in the expression of Bcl-2 related genes, which may contribute to GABA interneuron cell death (Jayanthi et al., 2001, Jeng et al., 2006).

Fewer studies have shown cell death after MDMA but there is evidence that MDMA causes apoptosis in primary hippocampal cultures (Stumm et al., 1999). MDMA has also been reported to cause cell death in cultured cortical neurons in a 5-HT_{2A} receptor-dependent manner. In these studies, drug exposure produces increases in reactive nitrogen species as well as increases in caspase-3, indicative of apoptotic cell death (Capela et al., 2007). In vivo studies have demonstrated that MDMA exposure increases protein levels of apoptosis associated proteins such as BAX, cytochrome c and caspase-3 levels in the hippocampus (Tamburini et al., 2006, Wang et al., 2009, Soleimani Asl et al., 2012, Anneken et al., 2013). Furthermore, Wang et al. 2009 showed an increase in TUNEL staining in the hippocampus of MDMA treated rats that may be associated with the loss of parvalbumin interneurons (Anneken et al., 2013).

Mechanisms of Neurotoxicity

Excitotoxicity describes a series of events initiated by excessive glutamate release, which promotes increases in intracellular calcium levels leading to the activation of calcium-dependent proteolytic enzymes, free radical and nitric oxide (NO) production, and activation of apoptotic pathways, ultimately culminating in cellular damage (Bruno et al., 1993, Nicholls, 2004). Excessive glutamate release has been proposed to play a role in the neurotoxicity caused by both Meth and MDMA. Binge doses of Meth, but not MDMA, cause increases in extracellular glutamate in the rat striatum through activation of the striatonigral pathway (Nash and Yamamoto, 1992a, Stephans and Yamamoto, 1994, Mark et al., 2004) and inhibition of these increases in glutamate is protective against Meth neurotoxicity to DA terminals within the region (Mark et al., 2004). The evidence of excitotoxic damage within the striatum is marked by increases in calpain-specific spectrin proteolysis, mediated by glutamate in an AMPA receptor-dependent manner (Staszewski and Yamamoto, 2006).

There is limited evidence for the role of excitotoxicity in nerve terminal damage caused by MDMA. Early studies suggesting that NMDA receptors were involved in 5HT terminal damage after MDMA exposure were confounded by the fact that an NMDA antagonist also prevented hyperthermia (Finnegan et al., 1989). When hyperthermia was maintained in the

presence of NMDA antagonism, NMDA antagonists no longer prevented MDMA induced 5HT terminal damage (Colado et al., 1998).

Excitotoxicity has also been proposed as a mechanism leading to the decreases in cell bodies after Meth and MDMA. Increases in glutamate in the striatum and hippocampus are known to correlate with increases in glutamate levels during Meth exposure. Recently, it was shown that somatostatin, which is a known inhibitor of glutamate neurotransmission, has the ability to reduce Meth-induced cell death in the striatum (Afanador et al., 2013). The decrease in the number of parvalbumin in the hippocampus of MDMA treated rats has been linked to the increases in extracellular glutamate and cyclooxygenase activity observed during MDMA exposure (Anneken et al., 2013).

Oxidative Stress

Oxidative stress represents another mechanism by which both Meth and MDMA cause neuronal damage. Reactive oxygen species are formed subsequent to substituted amphetamine exposure through numerous mechanisms. Acute increases in cytoplasmic and extracellular DA contribute to oxidatively damaged axon terminals after both Meth and MDMA exposure (Schmidt et al., 1985, Stone et al., 1988, Sprague et al., 1998). Direct oxidation of DA leading to quinone formation, iron-catalyzed DA metabolism via the Fenton Reaction, and metabolism of DA by monoamine oxidase-A contribute to superoxide and hydrogen peroxide production (Graham, 1978, Yamamoto and Zhu, 1998, LaVoie and Hastings, 1999). In addition, Meth or MDMA treatment leads to oxidative stress via increases in reactive nitrogen species resulting from increased nitric oxide synthase activity (Imam et al., 2000, Darvesh et al., 2005), the latter most likely derived from increases in glutamate activated NMDA or AMPA receptors (Eyerman and Yamamoto, 2007). Oxidative stress is further enhanced by depletions in antioxidant enzymes after drug exposure (Jayanthi et al., 1998, Jayanthi et al., 1999). Subsequent to Meth exposure, oxidative damage is manifested as lipid peroxidation and protein carbonyl formation (Yamamoto and Zhu, 1998, Gluck et al., 2001). Specific nitration and nitrosylation of proteins important for monoamine synthesis and release including VMAT-2 and tyrosine and tryptophan hydroxylase have also been reported (Kuhn et al., 1999, Kuhn and Geddes, 1999, Eyerman and Yamamoto, 2007). The oxidative modification of these proteins is particularly significant as it restricts their activity and contributes to their degradation, thus playing a major role in the neurotoxicity profile of the amphetamines. Antioxidant treatments have also been shown to be neuroprotective against the damage produced by Meth or MDMA and substantiates the significant contribution of oxidative stress to the neurotoxicity of substituted amphetamines (Gudelsky, 1996, Sanchez et al., 2003, Fukami et al., 2004).

Altered Metabolism and Mitochondrial Damage

Meth and MDMA also contribute to monoaminergic terminal damage through altered energy metabolism, including mitochondrial damage. During exposure to Meth or MDMA, there is a high demand for energy and acute increases in energy metabolism in brain regions that exhibit increased activity produced by the drugs (Pontieri et al., 1990, Quate et al., 2004). Soon after the excessive increase in energy metabolism reported during drug exposure, there is evidence of compromised energy metabolism and depleted energy stores (Chan et al., 1994, Huang et al., 1999, Darvesh et al., 2002). These decreases in energy metabolism are further exacerbated by damage to mitochondria and specific complexes of the electron transport chain including complex II–III and IV (Burrows et al., 2000). More specifically, decreases in complex II after Meth and MDMA (Burrows et al., 2000b; Nixdorf et al., 2001) were shown to be mediated by glutamate and nitric oxide (Brown et al., 2005) and when substrates for complex II–III are supplied after drug exposure or when increases in glutamate were blocked, mitochondria damage as well as DA and 5HT terminal damage

were prevented. Collectively, these results provide strong support for the role of glutamate in mediating compromised mitochondrial bioenergetics to produce axon terminal damage (Stephans et al., 1998, Darvesh and Gudelsky, 2005).

Emerging Mechanisms of Neurotoxicity

Numerous, complex interacting mechanisms have been identified as significant contributors to the neurotoxic effects of Meth and MDMA, yet many studies only consider how these mechanisms originate within neurons. Because both drugs are always administered systemically and may affect both brain and peripheral organ function, it is important to consider how the non-neuronal effects of substituted amphetamines contribute to the neuronal damage produced by the drugs. Identification and understanding of these non-neuronal contributors is important because they have the potential to significantly contribute to the excitotoxicity, oxidative stress and metabolic compromise that follows Meth and MDMA exposure. Furthermore, the elucidation of these non-neuronal mediators of toxicity could reveal novel targets for the treatment of the complex neurotoxicity produced by Meth and MDMA.

Peripheral Organ Damage

Meth and MDMA have been reported to cause significant peripheral organ damage (Smith and Fischer, 1970, Turillazzi et al., 2010). Clinical reports suggest that the cardiac, renal, muscular, and hepatic organ systems may be especially susceptible to damage by Meth and MDMA (Jones et al., 1994, Ellis et al., 1996, Milroy et al., 1996, Kamijo et al., 2002, Ben-Abraham et al., 2003, Wijetunga et al., 2003, Ago et al., 2006). Specifically, MDMA has been shown to oxidatively modify hepatocellular mitochondrial proteins (Moon et al., 2008). The mechanism by which amphetamines contribute to mitochondrial damage in peripheral organs is unknown, though it can be speculated that the drugs produce reactive oxygen species subsequent to the metabolism of the drugs in the liver by the cytochrome p450 system, or secondarily as a result of the hyperthermic or cardiac effects of the drugs (Skibba et al., 1989, Wang et al., 1990, Hong et al., 1991, Cherner et al., 2010, Pourahmad et al., 2010). The significance of drug-mediated peripheral organ damage is highlighted by the dependence of the brain on peripheral organ function and that alterations in peripheral physiology can contribute to neuronal pathology. For example, Meth has been shown to produce liver damage and concurrent increases in both peripheral and brain ammonia, a neurotoxic byproduct of protein and amino acid metabolism (Halpin and Yamamoto, 2012). Liver damage is associated with these increases in ammonia as the liver metabolizes ammonia to urea via the urea cycle so it can be efficiently excreted via the kidneys (Felipo and Butterworth, 2002b). When these increases in both plasma and brain ammonia were blocked, Meth induced damage to DA and 5HT terminals was also attenuated (Halpin and Yamamoto, 2012). In fact, ammonia per se has been shown to cause neurotoxicity via excitotoxicity, oxidative damage, and metabolic compromise similar to that produced by Meth and MDMA (Kosenko et al., 1995, Felipo and Butterworth, 2002a, Kosenko et al., 2003, Gorg et al., 2007). Accordingly, ammonia should now be considered as a peripherally derived mediator of Meth neurotoxicity that likely contributes synergistically to the neurotoxic mechanisms that were classically thought to result from the neuronal effects of the drug.

Inflammation

Meth and MDMA have been shown to trigger inflammatory responses in areas where DA and 5HT terminals are damaged. Given the potential damaging effects of inflammation within the CNS, these processes have been suggested to play a role in the damage to monoamine nerve terminals. Of particular interest has been microglial activation, which

occurs during MDMA and Meth exposure. Meth causes activation of microglia in the striatum, cortex and hippocampus (Escubedo et al., 1998, Guilarte et al., 2003, Pubill et al., 2003, Thomas et al., 2004). The mechanism through which this activation occurs is not known; however dopaquinones are known to be strong activators of microglia (Kuhn et al., 2006). Thus, the increased cytosolic DA and oxidative stress during Meth can promote the production of dopaquinones and potentially promote microglial activation.

Glutamate may contribute to inflammation and microglial activation during Meth. For instance, glutamate receptor activation is known to stimulate microglial activation whereas antagonism suppresses the appearance of microglial activation (Neumann, 2001, Thomas and Kuhn, 2005). Furthermore, microglial activation correlates regionally with increases in extracellular glutamate observed during MDMA and Meth. During Meth exposure, microglial activation and increases in glutamate are seen in the striatum, prefrontal cortex and hippocampus; however the activation of microglia and increases in glutamate are not observed within the striatum and prefrontal cortex during MDMA exposure (Nash and Yamamoto, 1992a, Stephans and Yamamoto, 1994, Pubill et al., 2003, Mark et al., 2004).

The ability of activated microglia to promote neuronal damage during Meth and MDMA exposure has not been fully elucidated. Nevertheless, cytokines produced during microglial activation are known to enhance glutamate neurotransmission, and thus promote excitotoxicity (Zou and Crews, 2005). Increases in FasL, a member of the TNF α family of cytokines, can be seen in the rat striatum as early as 2–4 hour after a high Meth dose (Jayanthi et al., 2005). Similarly, other cytokines including IL5, TNF- α and IL-1 α have been reported to be increased in the mouse striatum following Meth (Sriram et al., 2006, Goncalves et al., 2008). Whether these cytokines contribute to Meth toxicity is unknown, but Sriram et al. 2006 showed that attenuation of microglial activation by minocycline did not reduce DA terminal damage. A caveat however, is that TNF α was still increased despite a reduction in microglial activation. The role of cytokines has also been implicated in mediating MDMA toxicity as several studies have shown that MDMA can increase IL1 β in the rat frontal cortex (Orio et al., 2004, O'Shea et al., 2005, Kuhn et al., 2006). It is not known if IL1 β mediates the MDMA-induced damage to 5HT neurons but when IL-1 β alone was administered intracerebroventricularly, toxicity to 5HT terminals was observed (Kuhn et al., 2006).

Cannabinoids

Cannabinoids are a class of molecules which are released during neuronal activation and have a role in modulating inflammation as well as neurotransmission. Two subtypes of receptors mediate most of the actions caused by cannabinoids with CB1 receptors being primarily located within the CNS and CB2 receptors in the periphery, mostly on immune related cells (Matsuda et al., 1990, Munro et al., 1993). The role of CB2 receptors within the CNS is not as clear due to the relatively sparse expression of CB2 receptors within the CNS. However, it has been shown more recently that microglia increase their expression of CB2 receptors during pathologic situations, mainly when inflammation occurs and when microglia become activated (Maresz et al., 2005, Yiangou et al., 2006) supporting the notion that CB2 receptors are known to have a regulatory role in inhibiting microglial activation and function (Puffenbarger et al., 2000, Ramirez et al., 2005). Interestingly, MDMA was shown to increase CB2 receptors on microglia (Torres et al., 2010). Given the suggested role of inflammatory processes and microglial activation with MDMA neurotoxicity, these changes in CB2 receptors may represent an attempt to suppress inflammatory processes and damage during MDMA exposure.

Within the CNS, CB1 receptors are localized predominantly on the terminals of neurons, where they function to regulate release of neurotransmitters (Ishac et al., 1996, Katona et al.,

1999). Most notably, these receptors are present on glutamate and GABA terminals, where they regulate the release of their respective neurotransmitters. CB1 receptors have been shown to inhibit release of glutamate in hippocampal and striatal neurons (Shen et al., 1996, Gerdeman and Lovinger, 2001, Huang et al., 2001). Additionally, CB1 receptor activation leads to increases in extracellular DA release within the nucleus accumbens, striatum and prefrontal cortex (Ng Cheong Ton et al., 1988, Chen et al., 1990, Malone and Taylor, 1999). This is interesting in light of the fact that CB1 receptors are not found on DA terminals, but rather colocalize with glutamatergic and GABAergic terminals (Herkenham et al., 1991, Tsou et al., 1998). Thus, it has been proposed that within the striatum, cannabinoids cause DA release indirectly, through its effects on glutamate (Fernandez-Ruiz et al., 2010). Recently, it was shown that a CB1 antagonist attenuates Meth-induced deficits in evoked dopamine release in the nucleus accumbens (Loewinger et al., 2012). Furthermore, a CB1 antagonist were shown to prevent the increases in DA caused by (+)-amphetamine within the nucleus accumbens shell region (Kleijn et al., 2012). In light of this evidence, there exists the possibility that CB1 receptors are involved in DA release caused by substituted-amphetamines and thus neurotoxicity.

Consequences of Neurotoxicity

Neuropsychological Effects

Given the numerous reports of cellular and terminal damage caused by Meth and MDMA to the CNS, neuropsychological impairments are likely consequences. Exposure to amphetamines also is correlated with numerous long-term neuropsychological impairments which are associated with the persistent and significant DA and 5HT terminal damage seen in the striatum, prefrontal cortex, and hippocampus after drug exposure. Long term use of Meth is associated with impaired impulse control, working memory, decision making, attention, and motor coordination (Rogers et al., 1999, Volkow et al., 2001b, Simon et al., 2002, Clark et al., 2006, Johanson et al., 2006). Withdrawal from Meth is associated with disturbed sleep, anxiety, depressed mood, reduced energy and agitation (McGregor et al., 2005). It is often believed that these long term impairments contribute to the high relapse potential observed with past Meth use. Abstinent patients who were previously dependent on the drug also have a high potential for relapse, exhibit deficits in cortex-mediated decision making, and have decreases in cortical dopaminergic activity known to be predictive of relapse (Paulus et al., 2005, Wang et al., 2012). In addition to the neuropsychiatric consequences associated with drug use, Meth use has also been associated with an increased risk of developing Parkinson's disease (Callaghan et al., 2010, Granado et al., 2013)

The use of MDMA has been associated with a number of neuropsychological impairments, consistent with the serotonergic damage in the prefrontal cortex, hippocampus and striatum produced by the drug. Several researchers have reported memory impairments in abstinent MDMA abusers (Krystal et al., 1992, Curran and Travill, 1997, Parrott et al., 1998). In addition to these memory impairments, there are significant reductions in executive functioning and attention, as well as enhanced impulsivity amongst MDMA abusers (Morgan, 1998, McCann et al., 1999). As with Meth these cognitive impairments have been suggested to underlie drug addiction processes observed with MDMA. While each of these impairments have been shown in numerous Meth- and MDMA-dependent subjects, it is also worth noting that the presence of these symptoms before substituted amphetamine use is unknown and may precede and contribute to their use and addiction.

Protracted Psychosis

The long-term damage produced by Meth or MDMA may also represent a vulnerability factor contributing to protracted psychosis and psychotic disorders, in addition to the acute

psychotic effects of the drugs (Flaum and Schultz, 1996). Abuse of amphetamines is associated with a significant increase in the prevalence of psychosis and this association is especially strong in the context of Meth use and amphetamine abuse in the mid-late teen years (Harris and Batki, 2000, McKetin et al., 2006). Psychosis presenting subsequent to amphetamine-type stimulant use or in the context of schizophrenia share many common features and have been suggested to share a common neural substrate (Hermens et al., 2009). Of these, substituted-amphetamine induced alterations to DA, GABA and glutamate neurotransmitter systems are likely the most significant contributors to protracted psychosis and vulnerability to psychotic disorders.

Hyperactivity of mesolimbic DA pathways is strongly associated with the positive symptoms of schizophrenia and a target of many antipsychotic drugs. At first glance, the hyperactive mesolimbic DA activity postulated to contribute to psychosis appears to be paradoxically associated with the dopaminergic depletions produced by Meth; however mesolimbic dopaminergic projections are relatively spared from Meth-induced dopamine terminal damage (Granado et al., 2010). Resiliency of mesolimbic dopaminergic projections to the terminal damage produced by Meth may be the result of increased antioxidant capacity, neuropeptide production, or a differential expression of glutamate receptors and monoamine transporters, and blunted glutamate release (Hung and Lee, 1996, Chung et al., 2005, Fitzpatrick et al., 2005, Sava et al., 2006). Although beyond the scope of the discussion of amphetamine-induced psychosis, it is worth noting that the mesocortical DA depletions produced by Meth may contribute to the negative, cognitive and affective symptoms associated with schizophrenia. Beyond changes in DA function, the alteration of glutamate and GABA neurotransmission produced by Meth represent mechanisms by which the drug contributes to psychosis. Sensory gating is important for modulating the perceptual distortions contributing to psychosis and has been shown to be affected by Meth (Hadamitzky et al., 2011). Meth-induced decreases in sensorimotor gating have been attributed to alterations in both glutamate and downstream GABA neurotransmission in cortico-striatal-thalamic-cortical sensory filtering circuits (Arai et al., 2008, Mizoguchi et al., 2009). Prolonged psychosis has also been reported after MDMA use, and although this has not been studied as in-depth as Meth-associated psychosis, alterations in hippocampal activity could potentially contribute to the psychotomimetic effects of MDMA (Nifosi et al., 2009, Potash et al., 2009, Patel et al., 2011).

Conclusion

In conclusion, numerous interacting mechanisms have been established to contribute to the damage produced by Meth and MDMA. These mechanisms include excitotoxicity, oxidative stress and metabolic compromise. More recently, novel contributors to Meth and MDMA neurotoxicity have been identified and include inflammation, peripheral organ damage and the endocannabinoid system (Figure 1). Further understanding of the monoaminergic terminal damage produced by substituted amphetamines is important because this damage is associated with numerous neuropsychological effects as well as increased vulnerability to developing psychosis. Beyond these effects, understanding the neurotoxic consequences of Meth and MDMA is important when more broadly considering the effects of other synthetic amphetamines and cannabis-related compounds. For instance, Meth and MDMA have similar chemical structures and pharmacologic targets to other commonly abused substances including cathinone (khat), as well as a relatively new series of synthetic amphetamines which have gained popularity amongst drug abusers, known as 'bath salts'. These compounds consist of cathinone derivatives, including mephedrone, methylone, methedrone and buthylone. These ingredients of bath salts have been reported to have similar pharmacologic profiles as methamphetamine and MDMA (Hadlock et al., 2011, Baumann et al., 2012, Cameron et al., 2013). Reports also note that acute intoxication resulting from

exposure to these novel compounds share characteristics with those seen after substituted amphetamine exposure (James et al., 2011, Kasick et al., 2012). Accordingly, understanding of the neuronal damage and neuropsychiatric consequences produced by the substituted amphetamines methamphetamine and MDMA may afford valuable insight to our understanding of the acute and long term consequences of exposure to cathinones and bath salts.

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Figure 1. Mechanisms of Meth and MDMA Neurotoxicity

Meth and MDMA produce persistent monoaminergic terminal damage that is associated with neuropsychiatric symptoms as well as increased vulnerability to psychosis. Acutely, drug exposure contributes to increases in DA and/or 5HT, and glutamate. These substituted amphetamines also produce acute hyperthermia and can contribute to liver damage. Downstream of these short-term effects, numerous interacting and feed-forward mechanisms have been identified as contributors to the neurotoxicity of these drugs of abuse. These mechanisms include excitotoxicity, metabolic compromise, oxidative stress, and more recently, inflammation and altered endocannabinoid system function.