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Review Article

Review: Mechanisms of Methamphetamine Neurotoxicity

Emily Hensleigh*

Department of Psychology, University of Nevada Las Vegas, USA

*Corresponding author

Emily Hensleigh, Department of Psychology, University of Nevada Las Vegas, 4505 Maryland Parkway, Las Vegas, NV 89154, USA, Email: Emily.Hensleigh@unlv.edu

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Abstract

Methamphetamine administration results in various behavioral, physical, and neurological effects in both humans and animal species. The outcome and consequences of methamphetamine (METH) administration on neuronal damage depends on the dosage and duration of METH as well as additional exogenous and endogenous factors. Prolonged METH administration or high doses of METH result in long term neuronal deficits, mainly in dopamine systems. Several factors contribute to these long term effects of METH on neuronal pathways.

This review covers the mechanisms involved in METH neurotoxicity, focusing on hyperthermia, oxidative stress, excitotoxicity, and emerging mechanisms. These effects are discussed in reference to dopamine and, to a lesser extent, serotonin systems chiefly in preclinical models of neurotoxicity. This review begins with a brief summary of the mechanisms of action of METH, the clinical findings in long term METH abusers, and the neuronal markers of METH toxicity. The main sections focus on factors contributing to METH induced neuronal damage including: hyperthermia, oxidative stress, excitotoxicity, and recently identified mechanisms of microglia activation, blood brain barrier dysfunction, and apoptotic pathways.

INTRODUCTION

METH exerts several effects on monoamine systems after acute and long term administration. Acute administration of METH leads to rapid entry into the brain. METH's chemical resemblance to the monoamines allows METH to enter the presynaptic terminal through the monoamine transport proteins: dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET). METH readily enters into the presynaptic terminal and reverses transport of the vesicular monoamine transporter (VMAT2). Reversing the VMAT2 transporter results in reverse transport of neurotransmitters out of the synaptic vesicles into the intracellular space [1]. After this occurs, the membrane bound transport proteins reverse their ion gradient and pump the newly expelled neurotransmitters into the synaptic cleft [2]. This results in elevated levels of dopamine, norepinephrine, and serotonin in the intracellular space and synaptic cleft.

Two main mechanisms remove neurotransmitters from the synaptic cleft, enzymatic breakdown and reuptake. Monoamine oxidase (MAO) and to a lesser extent catechol-O-methyl-transferase (COMT) break down the monoamines in the synaptic cleft and cytosol [3]. Too much dopamine caused by reverse transport and inhibition of these enzymes lead to elevated monoamine levels which cause detrimental effects to cell membranes and dopamine terminals. The importance of elevated dopamine levels will be discussed in more detail in subsequent sections.

MARKERS OF METHAMPHETAMINE TOXICITY

In the clinical population, long term METH use leads to deficits in cognitive functioning. After prolonged use of METH, individuals can develop psychosis characterized by disorganized thought and speech patterns and hallucinations similar to those reported in schizophrenia [4]. Individuals who abuse METH also show problems with attention and distractibility [5]. Additionally, recovering METH abusers exhibit decreased performance in laboratory tests of executive function and working memory [6,7]. Decreased cognitive performance in METH users also correlates with decreased markers of dopamine systems and brain metabolism [8,9]. These combined findings implicate long term METH use leads to persistent cognitive deficits. These deficits are likely due to alterations in neurochemical systems as a result of prolonged METH use.

Prolonged administration of METH leads to several neurochemical alterations observable in humans and animals. Clinical studies indicate alterations in neurotransmitter systems of long term methamphetamine abusers. Wilson [10], looked at dopamine terminals and protein levels in the brains of deceased methamphetamine addicts who died from unrelated drug causes. Results indicated decreased tyrosine hydroxylase and dopamine transporters in the caudate of long term METH abusers, indicating

long term alterations within the dopamine system. Utilizing positron emission tomography imaging, several other deficits in dopamine systems have been illustrated. Decreased dopamine transporters and D2 receptors were observed in the prefrontal cortex in individuals with years of prolonged METH use [7,8]. Partial recovery of dopamine transporters was observed in METH addicts who were abstinent for twelve months, suggesting partial recovery with prolonged abstinence. However, dopamine transporter levels only returned to normal for some, but not all, subjects. Recovery of dopamine transporter levels additionally correlate with reported years of METH use [9]. Decreased D2 receptor binding occurs in the striatum of long term poly drug users who reported METH as their drug of choice. Increased D3 receptor binding occurs in the midbrain of these same users. Increased D3 receptors likely act as a compensatory mechanism for deficits of decreased dopamine throughout the brain. These receptors also control drug 'craving' rather than drug 'liking' suggesting these systems are altered in long term METH users [11]. However, the role of the D3 receptor in relation to long term METH use needs further characterization before any conclusions can be made.

Additional neurotransmitter system deficits are observed through PET imaging studies. METH users exhibit lower serotonin levels and decreased glucose metabolism in the prefrontal cortex [12,13]. Six week abstinent METH users exhibit decreased VMAT2 binding in the striatum [14]. These deficits additionally correlate with cognitive functioning deficits, suggesting long-term METH use causes neuronal alterations which likely contribute to cognitive deficits.

Similar markers of long term METH administration occur in animal models. Wagner [15] observed decreased dopamine transporters in the striatum of rats after given two 25.0mg/kg doses of METH. Rodents given two 15.0mg/kg of METH also exhibited decreased dopamine metabolite levels in the striatum [16]. More recent studies trained rats to self administer METH, an arguably better way of modeling human drug use. After given free access to METH, rats exhibited decreased expression of tyrosine hydroxylase and dopamine transporters in the striatum and prefrontal cortex [17]. Overall, the effects of METH on serotonin systems are less characterized but, after two 15.0mg/kg doses of METH, rats exhibited decreased serotonin and 5-HIAA (a serotonin metabolite) in the striatum, indicating METH toxicity also affects serotonin systems [18].

The above studies suggest long term METH administration leads to specific neurotoxic damage in both humans and animals. Long term METH users exhibited decreased dopamine transporter levels and decreased D2 receptor binding in the striatum and decreased VMAT2 and glucose metabolism in the prefrontal cortex [7,10]. Animal studies indicate similar effects with decreased dopamine transporters, tyrosine hydroxylase levels, and serotonin levels in the rat striatum after a neurotoxic dose of METH [15-18]. The above results also suggest METH is more neurotoxic to dopamine systems, specifically in the striatum. However, more clinical and preclinical research is required to determine the extent to which METH affects dopamine and serotonin systems. These results further suggest rodents exhibit similar patterns of neural damage after given elevated doses of METH. This makes rodents a beneficial model for determining the mechanisms leading to METH neurotoxicity.

HYPERTHERMIA

Body temperature mediates the severity of damage to dopamine systems caused by METH in rats and mice. Decreasing an animal's core body temperature results in less METH induced fatalities. Additionally, rodents which became hyperthermic exhibit more neurotoxic effects compared to those which never became hyperthermic. Several studies suggest body temperature mediates METH neurotoxicity, but, METH's neurotoxic effects do not require a hyperthermic response. The following discusses evidence for the above claims that hyperthermia mediates neurotoxicity but is not required for neurotoxicity.

Elevated core body temperature results in increased dopamine loss in the rat striatum after neurotoxic dosing of METH. Bowyer [19], administered neurotoxic doses of METH to rats and monitored core body temperature finding decreased dopamine transporters in the striatum three days after the neurotoxic dose of METH with the severity of damage correlating with body temperatures. Additionally, elevated core body temperatures alone did not cause dopamine depletions in the striatum, suggesting hyperthermia does not cause neurotoxicity without METH. Pharmacological interventions (haloperidol, diazepam, MK-801) given before a neurotoxic regimen of METH decreased the severity of damage in the striatum. The neuroprotective effects of these pharmacologic interventions correlated with the ability of these compounds to lower core body temperature. However, during elevated environmental temperatures these drugs did not protect against METH-induced dopamine depletions, suggesting, the neuroprotective effects of these substances is likely due to their ability to lower core body temperature [19]. Ali [20], found similar effects in mice. Mice received a neurotoxic dosage of METH (4 injections of 10mg/kg every 2 hours) and were kept at normal room temperature or a cooler ambient temperature. Those kept at normal room temperature exhibited decreased markers of dopamine and serotonin in the striatum whereas cooler ambient temperatures attenuated these deficits. Additionally, pretreatment with phenobarbital attenuated dopamine and serotonin depletions in the striatum which correlated with the ability of this compound to regulate hyperthermic responses [21]. These studies suggest the severity of METH induced dopamine and serotonin depletion in the striatum depends on core body temperatures.

Circumstances which enhance hyperthermia also lead to greater neurotoxic effects. Tata [22], administered ten days of chronic unpredictable stress to rats followed by a neurotoxic dosage of METH. Alone, stress did not alter dopamine or serotonin content in the striatum. Chronic unpredictable stress however, elevated core body temperature after a METH injection resulting in decreased dopamine and serotonin content in the striatum. This indicates interactions between environmental stressors and hyperthermia's contribution to METH toxicity.

Lowering core body temperature, pharmacologically or environmentally, attenuates METH induced dopamine loss in the striatum. Miller and O'Callaghan [23], administered four injections of 10mg/kg METH every two hours to C57BL/6J mice

and monitored body temperature and dopamine depletion. METH increased core body temperature and resulted in diminished dopamine levels in the striatum whereas lowered core body temperature resulted in diminished dopamine depletions in the striatum. Additionally, MK-801 given to C57BL/6J mice before a neurotoxic regimen of METH significantly decreased elevated core body temperature, which, resulted in an attenuation of dopamine depletion in the striatum. Elevated ambient temperatures, however, resulted in the disappearance of the neuroprotective effects of MK-801 [23]. This finding suggests pharmacological intervention can attenuate striatal dopamine loss; however, these pharmacological manipulations do not have the same effect in elevated ambient temperatures.

Other pharmacological interventions exhibit neuroprotective properties independent of hyperthermia. Albers and Sonsalla [24], looked at core body temperature, METH toxicity in the striatum, and several pharmacological interventions, including: fenfluramine, dizocilpine, phenytoin, propranol, and dopamine receptor antagonists. Mice received a pharmacological intervention followed by a neurotoxic dose regimen of METH and monitored for core body temperature. Pharmacological interventions which decreased core body temperature resulted in partial or full protection against METH induced neurotoxic damage [24]. Reserpine, however, decreased core body temperature but did not protect against METH induced dopamine depletions in the striatum. Callahan, Cord, Yuan, McCann, and Ricaurte [25], found similar effects. Mice given a neurotoxic dosage of METH and WIN-35,428 (a dopamine transporter inhibitor) exhibited diminished damage to striatal dopamine neurons regardless of core body temperature. These studies suggest body temperature plays a role in neurotoxicity but not required for neurotoxicity to occur.

As the previous studies demonstrate, body temperature plays a role in neurotoxicity in the striatum; however, METH neurotoxicity occurs independent of hyperthermia. Notably, pharmacological and genetic interventions attenuate dopamine depletions in the striatum without respect to body temperature. Mice received a neurotoxic regimen of METH (3 injections of 3, 6, or 9mg/kg every 3 hours) and received a nNOS inhibitor while controlling for changes in body temperature. All three doses of METH caused dopamine depletion in the striatum with the two higher doses causing decreased neurofilament protein NF68 depletions. Mice pretreated with the nNOS inhibitor, however, exhibited neuroprotective effects in striatal dopamine neurons and an attenuated loss of NF68 in the striatum. The neuroprotective effects of the nNOS inhibitor occurred in both low and elevated ambient temperatures [26]. Itzhak, Martin, and Ali [27], found similar effects in nNOS knockout mice. After given a neurotoxic dosage of METH (3 injections of 5mg/kg every 3 hours), nNOS knockout mice did not exhibit decreased dopamine markers in the striatum regardless of elevated body temperature. Likewise, interleukin-6 knockout mice and c-Jun knockout mice exhibited elevated body temperatures in response to a neurotoxic dosage of METH, but, these mice did not show signs of striatal dopamine damage [28,29]. These pharmacological and genetic manipulations suggest hyperthermia is not required for METH neurotoxicity.

The accumulated evidence indicates hyperthermia mediates METH induced neurotoxicity but, neurotoxicity occurs independent of hyperthermia. Suggesting, hyperthermia mediates METH neurotoxicity but is not necessary for METH-induced neurotoxic damage. As suggested in the evidence outlined above, hyperthermia mediates METH neurotoxicity. Several studies indicate lowering core body temperature protects against serotonin and dopamine depletions in the striatum and factors which potentiate hyperthermia result in increased markers of neurotoxicity [19,22,24]. Other factors also attenuate neurotoxic damage independent of thermal responses [17,26,30]. These findings suggest hyperthermia potentiates, but is not necessary for, METH-induced neurotoxicity, suggesting additional factors likely contribute to neurotoxic events. Hyperthermia likely mediates other factors involved in METH induced neurotoxicity, such as excitotoxicity, reactive oxygen formation, microglia activation, and activation of apoptotic pathways.

OXIDATIVE STRESS

Oxidative stress occurs when endogenous scavenger systems cannot adequately remove reactive oxygen species. This may occur for several reasons triggered from internal or external events. First, an over production of reactive oxygen species may over burden selective scavenger systems leading to oxidative damage. Second, damage to the scavenger system themselves may lead to decreased clearance of reactive oxygen species. Third, a deficit in the system's ability to repair oxidative damage may further potentiate injury to the cell. The following section focuses on METH's involvement in dopamine release and dopamine's role in the formation of reactive oxygen species.

Individuals who abuse METH take the drug in a dose-binge pattern. This pattern consists of repeated administrations of METH over the course of short time periods. Due to METH's half life of ten to twelve hours, this dosing pattern results in elevated blood plasma levels of METH. These elevated plasma levels can lead to large amounts of dopamine release [31].

Dopamine release is essential for neurotoxicity to occur. Blocking dopamine transporters results in neuroprotective effects to dopamine systems suggesting dopamine release is involved in neurotoxicity. Dopamine transporter knock-out mice exhibited less terminal degeneration after four doses of METH relative to wild type mice [32]. Two weeks following the neurotoxic regimen, mice which did not receive a tyrosine hydroxylase inhibitor exhibited decreased dopamine levels in the striatum, but no effect on serotonin, relative to mice which received the inhibitor [33]. Potentiating dopamine release by the administration of L-DOPA while mice were administered a neurotoxic regimen of METH resulted in decreased serotonin in the cortex relative to mice given a neurotoxic regimen alone [34]. These studies suggest excess dopamine release plays a role in the neurotoxic effects of METH on dopamine terminals, but, may not play as large a role on serotonin systems.

More specifically, dopamine damage relies on dopamine release in the synaptic cleft and intracellular space. Neurotoxicity depends in part on both excessive dopamine within in the cytoplasm and dopamine release in the synaptic cleft. Pargyline, an MAO inhibitor which causes increased cytoplasmic dopamine,

results in increased terminal damage in the striatum when given before a neurotoxic dose of METH [35]. Rats given clorgyline, another MAO inhibitor, exhibited similar effects on dopamine systems after given a neurotoxic regimen, suggesting increased intracellular dopamine exacerbates dopamine terminal damage. Thomas, Francescutti-Verbeem and Kuhn [36], gave mice four injections of 5.0 mg/kg METH and several pharmacological treatments. Mice given drugs which increased dopamine release, such as L-Dopa, clorgyline, or reserpine, exhibited decreased tyrosine hydroxylase and increased microglia activation. Reserpine decreased core body temperature but still resulted in deleterious effects whereas L-Dopa and clorgyline did not alter core body temperature. Agents which block dopamine release or synthesis, such as AMPT, resulted in decreased damage to dopamine systems and decreased microglia activation. AMPT did not alter core body temperature. The results of this study indicate dopamine release correlates with terminal damage and this damage results independent of thermoregulatory responses.

Excessive dopamine release leads to auto-oxidation and formation of reactive oxygen species. After neurotoxic dose of METH, increased reactive oxygen species form in the rat striatum. However, when pretreated with reserpine, which depletes dopamine, no reactive oxygen species occurred in the striatum, suggesting dopamine stores are necessary for formation of reactive oxygen species [37]. Further evidence for oxidation in neurotoxicity comes from studies which block oxidative stress. De Vito and Wagner [38], examined the effects of four antioxidants and superoxide dismutase (an inhibitor of endogenous scavenger systems) on METH damage. Rats were given one of four antioxidants (vitamin E, mannitol, ethanol, or absorbic acid) or superoxide dismutase followed by a neurotoxic dose of METH. Superoxide dismutase decreased dopamine and serotonin levels in the striatum relative to rats only given METH. In addition, all four antioxidants protected against decreased levels of dopamine and serotonin in the striatum. Similarly, rats given the antioxidant N-acetyl-L-cysteine prior to four injections of 7.5 mg/kg METH exhibited a dose-dependent protective effect against dopamine depletions in the striatum [39]. Bromocriptine, a hydroxyl radical scavenger, given before METH also protected against dopamine depletions within the striatum further suggesting a role of dopamine auto-oxidation and reactive oxygen species production in METH neurotoxicity [40]. The antioxidant sulforaphane when given before or after a 10.0 mg/kg dosing pattern of METH attenuated the deleterious effects on dopamine transporters in the striatum [41]. LaVoie and Hastings [42], also examined the role of dopamine oxidation in the striatum immediately after four injections of 15.0mg/kg METH. Results indicated increased dopamine oxidation in the striatum, similar to previous findings. However, when controlling for temperature, no difference in dopamine oxidation occurred in the striatum and dopamine levels did not differ between the temperature controlled and non temperature controlled rats. This suggests elevated temperatures likely plays a role in dopamine oxidation but dopamine can form reactive oxygen species regardless of temperature effects.

In summary, evidence supports oxidative stress contributes to METH induced neuronal damage. METH administration leads to excess dopamine release in the intracellular and extracellular space. This excess dopamine release contributes to damage in dopaminergic systems. Increasing dopamine release with pharmacological agents increases this damage whereas depleting dopamine leads to neuroprotective effects [32-36]. These results are likely due to auto-oxidation of dopamine both intracellularly and extracellularly. Buffering against the effects of reactive oxygen species by administration of antioxidants leads to protective effects against METH induced dopaminergic damage, suggesting, reactive oxygen species significantly contribute to dopamine damage. Additionally, hyperthermia may potentiate formation of reactive oxygen species and dopamine damage but reactive oxygen species may also form independent of hyperthermia [37-42]. Reactive oxygen species play a role in terminal damage caused by elevated METH blood plasma levels but, the extent of which dopamine release and reactive oxygen species are responsible for neuronal damage remains unknown. Reactive oxygen species likely interact with several other endogenous effects of METH, such as hyperthermic responses and excitotoxcity, leading to the deleterious effects observed after long-term METH administration.

The extent in which reactive oxygen species lead to neuronal damage needs better characterization. Future studies should examine the roles of hyperthermia and excitoxicity in combination with reactive oxygen species formation. By understanding these interactions, we can better characterize ways to decrease neuronal damage. The effects of reactive oxygen species on serotonin systems are less characterized relative to dopamine systems. Future studies should also examine the effects of reactive oxygen species relative to METH's effects on serotonin systems. After better characterizing these events, we can better understand the role of oxidative stress in neurotoxicity.

EXCITOTOXICITY

Excitotoxicity remains a damaging cellular process and can lead to neuronal death. Neuronal excitotoxicity occurs due to frequent and extended firing of glumatatergic neurons or over activation of glutamate receptors, such as NMDA. The extensive activation of these receptors, either pharmacologically or by excessive glutamate release, leads to elevated calcium levels in the intracellular space. This intracellular calcium can lead to several damaging effects to the neuron. Elevated calcium levels activate several apoptotic pathways as well as several enzymes responsible for degradation of cellular support structures. Intracellular calcium levels also lead to DNA damage and mitochondrial dysfunction. Several of these effects are also observed after neurotoxic doses of METH. Many findings support a role of glutamate induced excitotoxicity contributing to METH damage.

Several studies indicated elevated glutamate release after METH administration. Abekawa, Ohmori, and Koyama [33], used in vivo microdialysis to quantify glutamate release in the striatum and nucleus accumbens while rats underwent four 4.0mg/kg METH injections every 4 hours. Over the course of the eight injections, glutamate release increased within the striatum but not in the nucleus accumbens. This release correlated with METH induced dopamine release and depletion of dopamine and dopamine metabolites three days after METH abstinence. Stephans [31], found similar effects in the striatum. Using *in*

vivo microdialysis, glutamate concentrations in the striatum continually escalated after three injections of 10.0mg/kg METH. Seven days after this dosing, dopamine tissue content within the striatum was significantly reduced. Additionally, glutamate release in the striatum tends to be specific to METH. Nash and Yamamoto [43], measured dopamine and glutamate release in the striatum after neurotoxic dosing of METH and MDMA. Both drugs increased dopamine release in the striatum but, only METH resulted in elevated glutamate release. This suggests METH selectively releases glutamate relative to MDMA. Combined, these studies illustrate glutamate release occurs in the striatum after neurotoxic dosing of METH and excessive glutamate release correlates with increased METH induced dopaminergic damage.

Additional evidence supporting glutamate's role in METH-induced neurotoxic damage comes from pharmacological interventions. Administering neurotoxic doses of METH to mice along with NMDA agonists caused increased dopamine depletions in the striatum relative to a neurotoxic pattern of METH alone [44]. Sonsalla first demonstrated the administration of NMDA receptor antagonists (MK-801, phencyclidine, and ketamine) attenuated the deleterious effects of METH but not MPTP, a toxic agent similar to the amphetamines, suggesting the effects of glutamate release may be specific to METH induced damage. Additional studies using competitive and non-competitive NMDA antagonists, such as dizocilpine and memantine, resulted in attenuated dopamine and serotonin depletions in the striatum and prefrontal cortex [18,44]. These studies suggest pharmacologically blocking the effects of glutamate attenuate dopaminergic damage. However, as mentioned in the hyperthermia section, these agents also lower body temperature which makes it difficult to determine the extent of effects glutamate has on neurotoxic damage.

It remains unclear whether the neuroprotective effects of these drugs are due to blocking glutamatergic excitotoxicity or their effect on thermoregulation. One study gave mice four injections of 15.0mg/kg METH while controlling for elevated or low temperatures. Mice given the neurotoxic dosing pattern showed decreased dopamine and tyrosine hydroxylase levels in the striatum and mice in elevated temperatures showed a more potentiated effect. These depletions were blocked by the NMDA antagonist dizocilpine and this neuroprotective effect occurred in elevated and low temperatures [21]. These results suggest the effects of glutamate on neurotoxcity may partially be independent of hyperthermia. However, this is not enough to conclude glutamate excitotoxicity is completely independent of thermoregulatory responses. Future studies need to determine the effects of thermoregulation and glutamate excitotoxicity on METH induced dopamine and serotonin depletions.

As was described earlier, dopamine content also plays a role in neurotoxic damage. The effects of excitoxocity likely occur regardless of glutamate content. More recent research looked at various metabotropic glutamate receptors (mGlur) in relation in excitotoxicity. Rats received four 5.0mg/kg METH injections and either an antagonist or agonist for the mGlur5, mGlur1, or mGlur2/3 receptors followed by quantification of dopamine depletion and reactive oxygen species production. Neither mGlur1 or mGlur 2/3 receptor agonists or antagonists affected dopamine release, dopamine depletions, or formation of reactive oxygen species. Antagonists for mGlur5 decreased formation of reactive oxygen species and protected against dopamine depletion, however, dopamine release was not affected indicating the neuroprotective effects of mGlur5 antagonists are independent of the dopamine levels [45].

The above studies illustrate glutamate excitoxicity plays a role in METH induced neurotoxicity. Studies indicated METH administration increases glutamate release in the nucleus accumbens and striatum [31,33]. Blocking glutamate receptors also results in neuroprotective effects on dopamine systems [19,24,44,46]. However, the extent to which glutamate release contributes to METH neurotoxicity needs further characterization. The effects of glutamate release on other factors of neurotoxicity should also be further identified.

RECENTLY CHARACTERIZED MECHANISMS

Early research on the mechanisms of METH induced neurotoxicity looked at hyperthermia, oxidative damage, and exitotoxicity. However, more recent evidence suggests several other mechanisms contribute to METH induced neurotoxicity. This section will briefly cover evidence for the role of microglia activation, apoptotic pathway activation, and DNA damage. Microglia activation typically occurs after infections or neuronal injury, and, has recently been observed after neurotoxic doses of METH. Mice given a neurotoxic dose of METH followed by an anti-inflammatory drug exhibited decreased microglia activation relative to those given a neurotoxic regimen alone [47]. LaVoie, Card, and Hastings [48], examined microglia activation in the striatum 12 hours, one day, two days, four days, or six days after four injections of 15.0mg/kg METH. Results indicated microglia activation did not occur at 12 hours after METH but was present at one day, highest at two days after METH, and still present but to a lesser extent at five days. Results indicated minor degeneration of dopamine terminals starting at two days with the greatest deficits observed at four and six days post METH, suggesting microglia activation occurs prior to dopamine terminal degeneration. These studies illustrate increased microglia activation in conjunction with METH administration but, do not indicate whether microglia activation contributes to dopamine terminal depletion. Recent evidence suggests microglia activation may occur due to increased glutamate release or terminal damage. Animals given MK-801 or dextromethorphan, agents which inhibit glutamate, followed by a neurotoxic dose of METH show decreased microglia activation and neuroprotective effects on dopamine systems [36]. This indicates glutamate likely plays a role in neuroprotective effects observed in some microglia inhibiting agents. More recently, mice given a neurotoxic regimen of METH followed by minocycline (an agent which blocks the production of reactive oxygen species and activation of microglia activation) exhibited decrease microglia activation and reactive oxygen formation but did not exhibit neuroprotection of dopamine terminals in the striatum [49]. Little evidence exists on the effects of activated microglia on METH induced striatal damage. It remains unclear whether microglia activation contributes to neurotoxic events or is a product of already accumulating neuronal damage. If microglia activation does mediate neurotoxic events, this likely occurs through interactions with glutamate release, reactive oxygen species, and possibly hyperthermic responses.

Disruption of the blood brain barrier plays a role in the detrimental effects of METH. Bowyer and Ali [18] gave mice four injections of METH followed by immediate infusion of Evans blue dye, used to trace and target deficits in blood brain barrier function. Immunohistochemistry and protein traces showed increased permeability of the blood brain barrier throughout areas of the striatum, amygdala, and hippocampus. Some studies indicate these disruptions occur due to increased hyperthermia. Kiyatkin, Brown, and Sharma [50], demonstrated increased permeability of the blood brain barrier in nucleus accumbens of rats directly after a neurotoxic dose of METH. Similarly, Bowyer showed disruption of the blood brain barrier in the caudate after a neurotoxic dose of METH. How increased METH administration leads to permeability in the blood brain barrier remains unclear. Increased hyperthermia likely plays a role in weakening areas of the blood brain barrier. Excitotoxicity and overproduction of reactive oxygen species also play a role in leakage of the blood brain barrier. However, future research should determine the contributing factors of blood brain barrier dysfunction. In addition, the consequence and long term effect of increased blood brain barrier permeability on the brain needs further characterization.

A final emerging mechanism identified in neurotoxicity is the activation of several apoptotic pathways. Neurotoxic doses of METH caused changes in the endoplasmic reticulum, damage to DNA, and dysfunction of the mitochondria which lead to activation of various apoptotic pathways. McCullough, Martindale, Klotz, Aw, and Holbrook [51], demonstrated METH and increased production of reactive oxygen species leads to disruption in the endoplasmic reticulum. Activation of endoplasmic reticulum apoptotic pathways was observed following one dose of 40.0mg/kg in the mouse striatum and increased DNA damage was also observed in these animals [52]. Disruption of the mitochondria occurs after high doses of METH and these disruptions activate several apoptotic pathways including caspase 9, caspase 3, and DFF40. Activation of theses pathways after METH administration have additionally been associated with DNA damage [53]. Evidence suggests formation of reactive oxygen species contributes to activation of these apoptotic pathways as well as the DNA damage observed after METH administration [54,55]. Since hyperthermia may potentiate formation of reactive oxygen species, it stands to reason elevated temperatures likely play a role in activation of apoptotic pathways. Future studies should examine the interactions between these events in relation to the extent of damage to dopamine and serotonin terminals. Additionally, future studies should examine the doses of METH required to cause mitochondrial and endoplasmic reticulum dysfunction and DNA damage.

Studies recently identified involvement of microglia activation, blood brain barrier dysfunction, and apoptotic activation in METH neurotoxicty. As the mechanisms of these factors become more apparent, research can focus on buffering against their deleterious effects on dopamine systems.

CONCLUSIONS

Prolonged administration of METH can lead to long-term damage to dopamine systems, mainly in the striatum, and serotonin systems to a lesser degree. Research has elucidated several mechanisms contributing to METH induced neurotoxic damage. METH releases monoamines by reversing transport of the VMAT2s and the monoamine transport proteins leading to increased monoamines in the intracellular and extracellular space. Increased intracellular monoamine levels, specifically dopamine, leads to formation of reactive oxygen species. Reactive oxygen species in turn activate apoptotic pathways and cause DNA damage. Reversing the monoamine transport proteins leads to increased monoamine release in the synaptic cleft. Elevated levels of monoamines increase core body temperature which potentiates several factors involved in METH neurotoxicity, including blood brain barrier dysfunction, microglia activation, and apoptotic pathway activation. Finally, increased monoamine levels leads to increased receptor binding which increases glutamate release. Elevated glutamate release leads to excitotoxicty, further potentiating formation of reactive oxygen species. These combined mechanisms interact and all contribute to neurotoxicity. In time, a better understanding of these mechanisms and the interaction among them will emerge.

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