Mechanisms of Methamphetamine-induced Dopaminergic Neurotoxicity

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Abstract

Methamphetamine (METH) is a powerful stimulant of abuse with potent addictive and neurotoxic properties. More than 2.5 decades ago, METH-induced damage to dopaminergic neurons was described. Since then, numerous advancements have been made in the search for the underlying mechanisms whereby METH causes these persistent dopaminergic deficits. Although our understanding of these mechanisms remains incomplete, combinations of various complex processes have been described around a central theme involving reactive species, such as reactive oxygen and/or nitrogen species (ROS and RNS, respectively). For example, METH-induced hyperthermia, aberrant dopamine (DA), or glutamate transmission; or mitochondrial disruption leads to the generation of reactive species with neurotoxic consequences. This review will describe the current understanding of how high-dose METH administration leads to the production of these toxic reactive species and consequent permanent dopaminergic deficits.

Keywords: basal ganglia, dopamine, dopamine transporter, methamphetamine, neurotoxicity, vesicular monoamine transporter-2

Introduction

Abnormal dopaminergic (DAergic) signaling is characteristic of disease states such as Parkinson's disease and schizophrenia. Dopaminergic signaling involves a delicate balance between dopamine (DA) release and re-uptake by the presynaptic nerve terminal. Under normal circumstances, neuronal activation promotes the vesicular release of DA into the synapse. The DA transporter (DAT) removes DA from the synapse, and the vesicular monoamine transporter-2 (VMAT-2) transports cytoplasmic DA into vesicles for storage, release, and protection from oxidation and reactive consequences. Accordingly, dysfunction in DAT and/or VMAT-2 function may have neurotoxic consequences that result in damage to DA neurons.

Psychostimulants potently alter central DA signaling with high-dose administration of some of these agents leading to persistent DAergic deficits. For example, multiple high-dose administrations of the DA-releasing agent, METH, causes persistent DAergic deficits in humans[1] and various other mammalian models.[2-4] In contrast, cocaine-like analogs act as DAT inhibitors and produce little, if any, persistent DAergic deficits. Several phenomena contribute to the METH-induced DAergic deficits including hyperthermia, generation of reactive species, alterations in

DAT and VMAT-2 activity, and changes in glutamate signaling. This article will review each of these phenomena and discuss critical components of METH-induced DAergic neurotoxicity.

Vesicular Monoamine Transporter-2

VMAT-2 is responsible for packaging DA into synaptic vesicles in preparation for synaptic release. It has been suggested that one component of the neurotoxic METH insult is its ability to prevent DA uptake into vesicles or promote the efflux of vesicular DA into the cytoplasm; an effect that leads to DA auto-oxidation, ROS formation, and nerve terminal damage.[5-7] Consistent with this hypothesis, Riddle et al[8] demonstrated that multiple high-dose administrations of METH rapidly (within 1 hour) redistribute VMAT-2 protein within the nerve terminal such that fewer VMAT-2, and presumably associated cytoplasmic vesicles, are available to sequester DA and prevent its oxidation. Several subsequent studies demonstrate that METH alters the subcellular distribution of VMAT-2.[9-11] This trafficking effect and the neurotoxic consequences of METH administration are disrupted by posttreatment with methylphenidate.[11]

Surprisingly, the D2 receptor is a critical component of both the effect of METH and the protective effect of methylphenidate. Thus, pretreatment with DA D2 receptor antagonists prevents METH-induced decreases in vesicular DA uptake,[12] while D2 receptor agonists traffic VMAT-2 in a similar manner to methylphenidate.[13] It appears as though changes in the subcellular localization of VMAT-2 are important for METH-induced neurotoxicity since this effect is attenuated by treatments that prevent the METH-induced redistribution of VMAT-2.[11]

Dopamine Transporter

In addition to the VMAT-2, the DAT is a principal regulator of cytoplasmic DA concentrations. Under normal physiological conditions, the DAT transports extracellular DA back into the nerve terminal. However, within minutes after amphetamine administration,[14] nonvesicular DA efflux occurs through reversal of the DAT[15] creating high extracellular DA concentrations and stimulation of DA receptors.

When assessing DAT activity in synaptosomes prepared from treated rats, single or multiple high-dose administrations of METH decrease DA uptake within 1 hour.[16] Administration of a single high dose of METH reversibly decreases DAT function, which is likely to be the result of a phosphorylation and internalization of the DAT.[17,18] Kokoshka et al[19] reported that in contrast to a single high dose, multiple high-dose injections lead to a decrease in DAT activity, which is not fully reversible and is associated with a persistent decrease in striatal DAT activity and protein levels observed days after METH administration (also E.L. Riddle, unpublished data, 2006). METH-induced reduction in DAT activity and/or cell surface localization may decrease DAT-mediated DA efflux, which could lead to the buildup of cytosolic DA and the promotion of DA-mediated reactive species formation.

The acute effects of METH on DAT function are not the result of a loss of transporter protein, as assessed by Western blotting with reducing reagents.[19] Of interest, Western blotting without reducing agents reveals that a neurotoxic METH regimen profoundly decreases DAT monomer immunoreactivity accompanied by the formation of higher weight DAT complexes 12 to 48 hours

after treatment.[20] A single high-dose (nonneurotoxic) administration of METH has little effect on DAT complex formation, suggesting that complex formation may be a result of, or a contributor to, METH-induced toxicity.

Reactive Species

An important element in METH toxicity is the formation of reactive species, such as reactive oxygen and nitrogen species (ROS and RNS, respectively). Various approaches, including quantifying the formation of reactive species,[21-24] administering antioxidants/radical scavengers,[25-27] and/or administering METH to superoxide dismutase (SOD) transgenic mice,[28,29] indicate that reactive species contribute to METH-induced persistent DAergic deficits. In addition, Kuhn and colleagues[30,31] recently provided evidence linking microglial activation and METH toxicity. METH treatment leads to microglial activation and activated microglia produce reactive species.[32] Of importance, mice treated chronically with METH develop tolerance and show blunted METH toxicity and microglial activation[33] further supporting the role of microglial activation in METH-induced DAergic toxicity.

Along with the reactive species generated by microglia, reactive species production is likely a result of multiple additional processes (discussed in more detail below), including (1) the auto-oxidation of cytosolic DA[34-36]; (2) METH-induced striatal glutamate release,[37,38] subsequent mitochondrial dysfunction,[39] and glutamate receptor-induced nitric oxide (NO) production[40]; (3) activation of D1 receptors within the striatum leading to increased neuronoal NO synthase (nNOS) mRNA expression[41] and presumably increased NO and reactive species levels; and (4) METH-induced inhibition of mitochondrial function that increases mitochondrial-mediated reactive species generation.[42]

Mitochondria and Energy Balance

As noted above in the Reactive Species section, METH-induced inhibition of mitochondrial function contributes to the persistent DA deficits caused by the stimulant. Mitochondria are responsible for cellular energy production in the form of adenosine triphosphate (ATP), which is used by the cell for numerous functions. Mitochondria use enzymatic reactions, including the citric acid cycle and electron transport chain (ETC), in the generation of ATP. METH inhibits the ETC[42] and many ETC inhibitors increase reactive species, resulting in DAergic neurotoxicity.[43] In contrast, administration of substrates for energy metabolism (to counteract ETC inhibition) attenuates METH-induced DAergic toxicity.[44] In addition to ETC inhibition, energetic stress caused by administration of the citric acid cycle inhibitor, malonate, worsens the persistent DAergic deficits caused by METH.[45,46] Together, these data strongly implicate mitochondrial dysfunction as a component of METH-induced neurotoxicity.

Glutamate

Glutamate signaling is another important component of METH-induced DAergic deficits. Parenteral administration of METH evokes striatal glutamate release[37,38] via the "direct" pathway.[47] Glutamate likely contributes to the persistent deficits caused by METH treatment, as evidenced by findings that administration of the N-methyl-D-aspartate (NMDA) antagonist,

MK801, prevents these deficits.[48-52] One confounding feature of these studies is that MK801 prevents METH-induced hyperthermia, and this may contribute to the neuroprotection. On the other hand, posttreatment with NMDA antagonists attenuates the persistent deficits caused by amphetamine analogs, suggesting a protective effect independent of body temperature.[53] Further evidence for a role of glutamate independent of temperature includes findings that mGluR5 antagonists prevent METH-induced deficits in a temperature-independent manner.[54] However, the mechanism by which mGluR5 antagonists prevent METH toxicity may simply be via the inhibition of glutamate release.[55]

Dopaminergic cells within the striatum possess α-amino-5-hydroxy-3-methyl-4-isoxazde propionic acid (AMPA) and NMDA receptors.[56] Glutamate-induced activation of these receptors promotes Ca^{2+} influx into the DAergic neuron, an effect, when excessive, that can result in mitochondrial damage and neuronal toxicity.[39] In addition, glutamate-induced activation of NMDA receptors increases NO production via nNOS.[40] Dopaminergic neurons can be regulated by NO generated from DAergic, non-DAergic neurons, or glia since NO is a diffusible gas. NO alters DAT function[57] and can lead to reactive species production (by reacting with superoxide to produce peroxynitrite),[32,58] each of which may contribute to persistent DA deficits.

Of interest, central administration of METH does not promote striatal glutamate release (or hyperthermia) and does not produce DAergic deficits[45] demonstrating that areas distant from the site of toxicity are an important component of METH toxicity.

D1 and D2 Receptors

D1 receptors have long been implicated in mediating the persistent DAergic deficits caused by METH. For example, pretreatment of rats with the D1 receptor antagonist, SCH23390, prevents the DAergic deficits caused by this stimulant.[59,60] D1 receptors affect acute METH-induced changes in DAT as well; for example, pretreatment with SCH23390 attenuates the acute decrease in plasmalemmal DA uptake caused by METH treatment.[61] Mechanisms underlying these effects have remained enigmatic because D1 receptors are localized to postsynaptic elements in the striatum (ie, spiny neurons of the "direct" pathway), as well as specific interneuron populations (ie, neuropeptide Y [NPY]/somatostatin/NOS positive interneurons).[62,63]

One mechanism whereby D1 receptors might affect METH-induced deficits is suggested by findings that administration of the D1 receptor agonist, SKF-82958, induces nNOS mRNA expression in mouse striata.[41] Neuronal NO synthase, in turn, may contribute to the persistent deficits caused by METH, as evidenced by findings that pretreatment of mice with nNOS inhibitors prevents these persistent DA deficits.[64,65] Further, METH does not cause persistent DA deficits in nNOS-deficient mice.[66] In addition, D1 receptors form oligomeric complexes with NMDA receptors[67] and D1 receptor activation potentiates NMDA transmission[68] providing interesting evidence of convergence of DA and glutamate signaling and possibly toxicity.

D2 receptors have also been implicated in contributing to the persistent DAergic deficits caused by METH, as evidenced by findings that pretreatment with D2 antagonists prevents the persistent damage caused by the stimulant[69]; an effect that at least, in part, is independent of its ability to

prevent hyperthermia.[70] Thus, D2 receptor activation plays a role in METH-induced DAergic deficits.

Hyperthermia

METH-induced hyperthermia is an important component of METH-induced DAergic neurotoxicity, as evidenced by studies demonstrating that prevention of hyperthermia significantly attenuates DAergic deficits.[50,71,72] Thus, over the last decade, it has become apparent that studies designed to elucidate the mechanisms of METH toxicity must consider body temperature responses. This importance is underscored by the fact that a variety of drugs that alter dopamine signaling prevent METH-induced hyperthermia. In particular, α-methyl-p-tyrosine (a DA synthesis inhibitor), SHC23390 (D1 antagonist), and eticlopride (D2 antagonist) prevent METH-induced hyperthermia.[50,61] In studies where hyperthermia is prevented, an elevated temperature must be reinstated before conclusions about neurotoxicity mechanisms can be made, and care must be taken while interpreting studies in which body temperature is not reported.

Summary

METH is a potent DA releaser from both vesicular and nerve terminal stores. Increased cytosolic DA levels provide oxidative stress specific for DAergic neurons. In addition, increased extracellular DA and subsequent DA receptor activation are likely involved in the majority of the effects leading to DAergic toxicity (ie, alterations in glutamate signaling). Since DAT and VMAT-2 are responsible for regulating intracellular and extracellular DA concentrations, they represent an important target in the treatment of DAergic neurodegeneration seen with abuse of amphetamines and perhaps Parkinson's disease as well. In particular, pharmacologic manipulation of DAT activity and/or cell surface expression can greatly influence extracellular DA levels and subsequent DA receptor signaling. In addition, alterations in the subcellular localization of VMAT-2, and associated vesicles, provide an avenue to prevent dangerous cytosolic accumulation of DA.

Although direct pharmacologic targeting of DAT and VMAT-2 may provide the means to combat DAergic neurodegeneration, indirectly targeting DAT and VMAT-2 via DA receptors should also be considered as a possible strategy. Most of the drugs used clinically, for the treatment of all diseases, act at G protein-coupled receptors (GPCRs),[73,74] demonstrating the efficacy and viability of GPCRs as pharmacologic targets. Accordingly, DA receptor agonists, such as pramipexole, have proven efficacious in the treatment of Parkinson's disease and may even provide some neuroprotection.[75] Of interest, pramipexole influences the subcellular localization of VMAT-2 in a manner that would be expected to attenuate METH toxicity,[76] thus underscoring the importance of increasing our understanding of DA signaling and DAergic neurodegeneration with a goal of being able to manipulate this system pharmacologically.

In summary, multiple factors contribute to the persistent DAergic deficits caused by METH. As summarized in Figure 1 these include (1) METH-induced inhibition mitochondrial function leading to decreased cellular energy and increased reactive species levels; (2) METH-induced decrease in DAT activity (including reverse transport) producing cytosolic DA buildup and reactive species formation; (3) METH-induced alterations in VMAT-2 activity and trafficking contributing to DA

buildup and reactive species formation via auto-oxidation of DA; (4) D1 receptor involvement in ROS formation, NMDA-receptor signaling, and DAT function; (5) D2 receptor involvement in VMAT-2 trafficking and glutamate receptor signaling; (6) METH-induced hyperthermia; (7) ionotropic glutamate receptor-induced Ca^{2+} influx and subsequent mitochondrial damage and reactive species formation, as well as NMDA receptor-mediated NO production; and (8) ROS production as a consequence of microglial activation. Systemic approaches will continue to be important for full elucidation of the interactions among these factors and will have broad correlations to human physiology and pathophysiology and more effective treatment development.
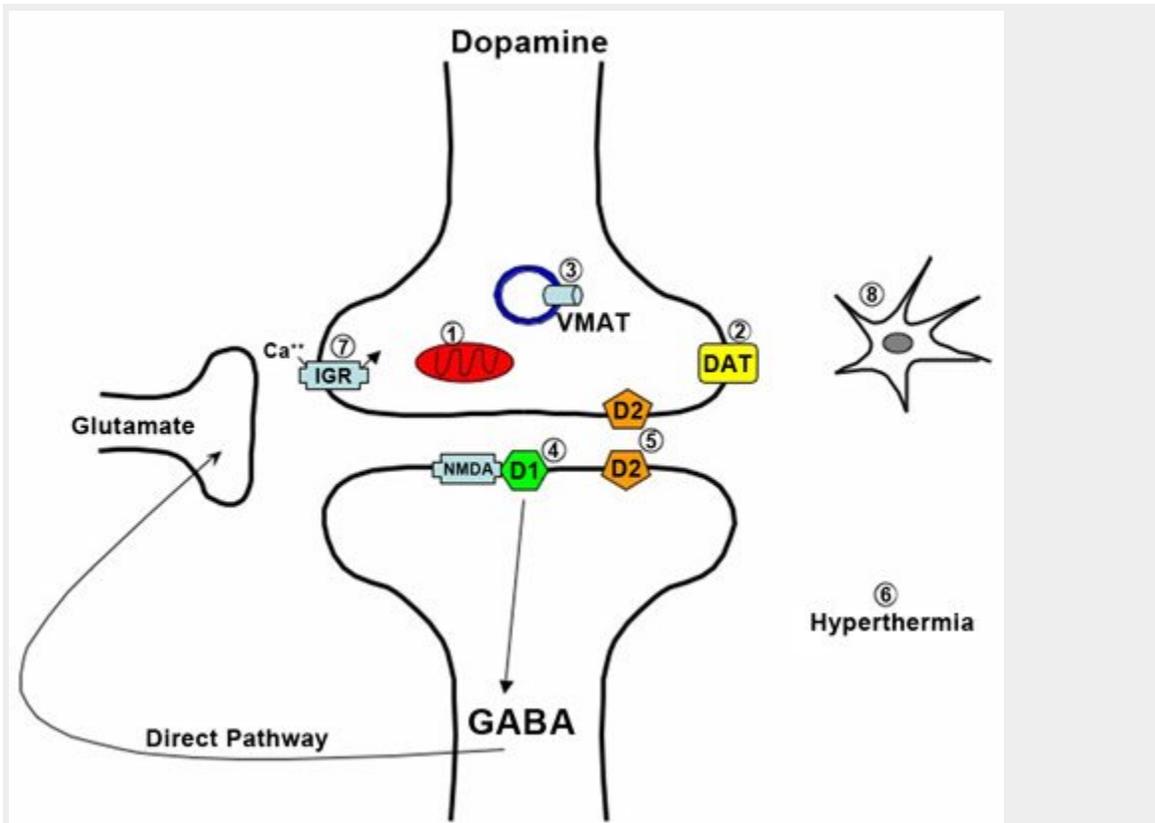
Figure 1. Schematic of the important components of METH-induced DAergic neurodegeneration. See Summary section for explanation. (1) mitochondria; (2) DAT, dopamine transporter; (3) VMAT, vesicular monoamine transporter-2; (4) D1, dopamine D1 receptor; (5) D2, dopamine D2 receptor; (6) hyperthermia; (7) ionotropic glutamate receptor (IGR); and (8) glial cells.

Acknowledgment

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