Methamphetamine-Induced Neuronal Damage: Neurotoxicity and Neuroinflammation

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Abstract
Methamphetamine (METH) is a highly addictive psychostimulant and one of the most widely abused drugs worldwide. The continuous use of METH eventually leads to drug addiction and causes serious health complications, including attention deficit, memory loss and cognitive decline. These neurological complications are strongly associated with METH-induced neurotoxicity and neuroinflammation, which leads to neuronal cell death. The current review investigates the molecular mechanisms underlying METH-mediated neuronal damages. Our analysis demonstrates that the process of neuronal impairment by METH is closely related to oxidative stress, transcription factor activation, DNA damage, excitatory toxicity and various apoptosis pathways. Thus, we reach the conclusion here that METH-induced neuronal damages are attributed to the neurotoxic and neuroinflammatory effect of the drug. This review provides an insight into the mechanisms of METH addiction and contributes to the discovery of therapeutic targets on neurological impairment by METH abuse.

Key Words: Methamphetamine, Neurotoxicity, Neuroinflammation, Excitotoxicity, Apoptosis

INTRODUCTION
Methamphetamine (METH) is a well-known psychostimulant that can cause neurotoxicity and is one of the most widely abused drugs worldwide (Elkashef et al., 2008). The continuous use of METH promotes neurodegeneration and cognitive decline (Rusyniak, 2011; Dean et al., 2013). In addition, chronic METH abuse is reported to cause selective patterns of brain deterioration leading to memory impairment (Meredith et al., 2005).

The abuse of METH is closely related to the release of neurotransmitters such as dopamine (DA) (Saha et al., 2014; Lin et al., 2016). During the development of drug addiction, drug-seeking behavior proceeds from seeking the reward effect of drugs to being triggered by drug-associated cues (Robbins et al., 2008). Therefore, greater decrease in dorsal striatal DA in METH abusers might promote habitual drug use (Wang et al., 2012). METH increases DA neurotransmission via regulation of dopamine transporters (DATs) activity (Lin et al., 2016; Sambo et al., 2017). A recent study shows that a decrease of DATs in METH abusers increases the risk of developing Parkinson’s disease (Chen et al., 2013; Granado et al., 2013). Parkinson’s disease (PD) is caused by degeneration of DA neurons in the midbrain. Biochemical and neuroimaging studies of human METH users revealed that the levels of DA and DATs were decreased, and microglia activation in striatum and other areas of the brain was also detected, which appears to be similar to that observed in PD patients (Granado et al., 2013). METH is also known to cause neuronal inflammation, which eventually leads to neural degeneration (Cadet and Krasnova, 2009). Directly or indirectly, METH-induced neuroinflammation makes the brain more susceptible to neuropathology (Cadet and Krasnova, 2009).

Neuronal cells are highly susceptible to pro-inflammatory cytokine-induced damage, and exposure to pro-inflammatory cytokines has been shown to cause neuronal cell apoptosis (Castino et al., 2007). Moreover, neuroinflammation can increase the oxidative stress by excessive release of harmful reactive oxygen species (ROS), which further promote neuronal damage and subsequent inflammation resulting in a feed-forward loop of neurodegeneration (Fischer and Maier, 2015). There are a number of excellent reviews outlining the health and societal concerns stemming from METH abuse and overdose, yet there remains a paucity of information related to neuroinflammation and neurotoxicity in METH abusers (Matsumoto et al., 2014). Therefore, to provide a guide for future
research, we want to review neuronal cell apoptosis through neurotoxic and neuroinflammatory mechanisms caused by METH.

**METH-INDUCED NEUROTOXICITY**

**Dopaminergic pathway**

Methamphetamine is a psychostimulant that primarily induces the release of dopamine, serotonin and norepinephrine (Rothman et al., 2001). These neurotransmitters are involved in neuronal cell inflammation and necrosis in the mesolimbic region of the brain (Panenka et al., 2013). The process of intoxication of METH is closely related to the induction of DA release. Chronic METH intake regulates dopamine release by acting primarily on vesicle monoamine transporter-2 (VMAT-2) and plasma membrane DATs, two major molecules of the dopaminergic neuronal terminal (Fig. 1) (Kahlig and Galli, 2003). DATs are responsible for dopamine reuptake into the presynaptic dopaminergic neurons from the extracellular area, which is extremely important for regulating and maintaining dopamine homeostasis (Fleckenstein et al., 2007). Under normal circumstances, neuronal activation promotes the release of DA into the synapse (Nickell et al., 2014). The DATs removes DA from the synapse, and the VMAT-2 transports cytoplasmic DA into vesicles for storage, release, and protection from oxidation and reactive consequences (Riddle et al., 2006). However, METH causes abnormal trafficking of DATs, which means that METH increases extracellular dopamine levels by inhibiting dopamine reuptake, stimulating dopamine efflux, and internalizing DATs from the plasma membrane (Riddle et al., 2006). Moreover, METH increases the excitability of dopaminergic neurons in a DATs-dependent manner. The DAT is a member of Na+/Cl−-dependent co-transporters (Sonders et al., 1997), and bidirectional transport of dopamine through DATs is achieved by the movements of Na+/Cl− ions. METH enhances DATs-mediated inward current and promotes the excitability of dopamine neurons (Chu et al., 2008; Schmitt et al., 2014).

VMAT-2 is an integral membrane protein that transports monoamines from the intracellular cytosol into synaptic vesicles (Fleckenstein et al., 2009). However, METH causes synaptic vesicles to leak monoamines into the cytosol by disrupting the hydrogen pump-mediated proton gradient (Fleckenstein et al., 2007). Moreover, METH binds to VMAT-2 and competitively inhibits the uptake of monoamines leading to high concentrations of monoamines in the cytoplasm (Sülzer et al., 1992, 1993). Moreover, dysfunction of VMAT-2 due to METH interferes with physiological storage of DA, resulting in a significant increase in DA levels in endogenous cells (Lazzeri et al., 2007; German et al., 2012). Thus, high concentrations of DA, which can freely diffuse in cells, can easily cause large amounts of oxidative damage, which is associated with the neurotoxic effects of large amounts of METH (Hogan et al., 2000; Volkow et al., 2001; Eyerman and Yamamoto, 2007).

**METH-induced neurotoxicity**

Upon METH stimulation, large amounts of DA from cytosol and synaptic clefts are oxidized to quinone or semi-quinone. And, increasing of DA oxidation further leads to significant production of reactive oxygen species (ROS) such as hydroxyl radicals (OH−), hydrogen peroxide (H2O2) and superoxide anions (O2−) (Yang et al., 2018). These ROS can inhibit mitochondrial adenosine triphosphate (ATP) production, which in turn results in a depolarized mitochondrial membrane potential and mitochondrial dysfunction (Stokes et al., 1999; Zhu et al., 2006; Dawson and Dawson, 2017). Dysfunction of mitochondrial metabolism has been reported to play a very important role in METH-induced neurotoxicity, because it inhibits the Krebs cycle and electron transport chain (ETC) and potentiates oxidative stress (Ares-Santos et al., 2013). Therefore, defects in mitochondrial respiration can cause neuronal cell death and neurodegenerative diseases.

The hypothesis about the involvement of glutamate (Glu) in METH toxicity is supported by the discovery that METH causes Glu release in the brain (Baldwin et al., 1993; Abekawa et al., 1994). Glu is a major excitatory neurotransmitter in the brain and has been reported to play an important role in the excitotoxicity induced by METH (Moratalla et al., 2017). Specifically, large amounts of Glu by METH activate the N-methyl-D-aspartate receptor (NMDAR) and metabolic glutamate

![Fig. 1. METH regulates dopamine release by acting on DAT and VMAT-2.](image-url)
receptor (mGluR) (Ohno et al., 1994; Battaglia et al., 2002; Tseng et al., 2010). Glu accumulation overstimulates various downstream signal transduction pathways associated with Ca\(^{2+}\) influx, which leads to increased intracellular Ca\(^{2+}\) concentrations (Chamorro et al., 2016). The excessive production of Ca\(^{2+}\) in cells activates protein kinases, phosphatase, and nitric oxide synthase (NOS) and promotes NO production (Moratalla et al., 2017). Excessive NO production leads to endoplasmic reticulum (ER) stress, activation of the apoptotic pathway, and eventually causes neurotoxicity by METH (Moratalla et al., 2017). Previous report supported that glutamate-mediated NO formation may also be involved in METH toxicity because knockout mice lacking neuronal nitric oxide synthase (nNOS or iNOS) are protected from METH-induced damage from monoaminergic axons (Itzhak et al., 1998). In addition, in many studies, various nNOS inhibitors are also known to protect against the depletion of monoaminergic axons caused by METH administration (Itzhak et al., 2000; Sanchez et al., 2003). These evidences indicate a glutamate/NO pathway plays a major role in METH-induced neurotoxicity (Fig. 2).

**METH-induced neuroinflammation**

METH is also known to contribute to neuronal inflammation through excessive release of DA and Glu (Kohno et al., 2019). The released DA is oxidized to form toxic quinones, leading to presynaptic membrane damage via oxidative stress, mitochondrial dysfunction and the subsequent production of peroxide radicals and hydrogen peroxide (Kohno et al., 2019). The impairment of mitochondrial energy metabolism as well as the release of inflammatory cytokines increases the response to synapses and neuroinflammation (Li et al., 2008; Tocharus et al., 2010; Panenka et al., 2013; Loftis and Janowsky, 2014). It has been reported that these METH-induced neuroinflammation is caused by targeting microglia, the innate immune cells of the central nervous system (Sekine et al., 2008).

Indeed, METH-mediated activation of microglia is associated with Toll-like receptor 4 (TLR4), which is involved in immune surveillance of pathogens and exogenous small molecules (Bachtell et al., 2015; Du et al., 2017). TLR4 is a receptor that can activate both the Myd88-dependent and Myd88-independent pathways (Billo et al., 2016). In the Myd88-dependent pathway, Myd88 activates tumor necrosis factor receptor-related kinase 6 (TRAF6), interleukin-1 receptor related kinase (IRAK) to induce nuclear factor-κB (NF-κB) activation (Shen et al., 2016). Consequently, the activation of TLR4 due to METH increases inflammatory mediators such as interleukin (IL)-1α, 1β, tumor necrosis factor (TNF)-α and IL-6 (Wan et al., 2017). In contrast, the MyD88-independent pathway leads to the induction of IFN-γ through the activation of TRIF-related adapter molecule (TRAM) and interferon regulatory factor 3 (IRF3) (Brempelis et al., 2017). The MyD88-independent pathway also induces NF-κB activation, but it occurs later than activation through the MyD88-dependent pathway (Liu et al., 2012). NF-κB is a well-known transcription factor involved in neurodegenerative progression, and it is considered to be a key target for prevention and treatment of neurodegenerative diseases (Majdi et al., 2019).

Sig-1R is an ER chaperone protein that is widely expressed throughout the brain and has a high affinity for METH (Hayashi et al., 2010). Sig-1R is closely related to toxicity and inflammation caused by METH (Hedges et al., 2018) via regulation of various mechanisms such as calcium homeostasis, glutamate activity, ROS formation, ER and mitochondrial function (Nguyen et al., 2015; Ruescher and Wieloch, 2015). Another study reported that activation of microglia due to METH stimulation can be mediated by Sig-1Rs via ROS generation and activation of mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways (Chao et al., 2017). The MAPK signaling pathway is also closely related to the NF-κB signaling pathway (Zanassi et al., 2001; Lee et al., 2006; Chen et al., 2009), with both playing key roles in the induction of inflammatory cytokines by METH (Liu et al., 2012).

ERK is a representative kinase that plays an important role in regulating neuronal and behavioral processes mediated by DA and Glu (Shiflett and Balleine, 2011). ERK is activated by neurotrophin or growth factor (Sun et al., 2016), and phosphorylated ERK is translocated to the nucleus and subsequently phosphorylates Elk-1 (Besnard et al., 2011). Activated Elk-1 promotes immediate early gene (IEG) transcription associated with neural adaptation (Davis et al., 2000). Another study
demonstrated that the ERK signaling pathway is linked to the regulation of dopamine D1 receptor involved in rewarding effects induced by METH (Mizoguchi et al., 2004). It has also been reported that METH can increase the activation of ERK phosphorylation in certain brain regions (Son et al., 2015). Once activated, ERK causes cAMP response element binding protein (CREB) phosphorylation and enhances the expression of c-Fos (Valjent et al., 2005). CREB is a transcription factor that is phosphorylated by different kinases, including protein kinase A (PKA) and protein kinase C (PKC) (Johannessen and Moens, 2007; Shin et al., 2012). CREB phosphorylation sequentially promotes the recruitment of co-activators such as CREB-binding protein (CBP)/p300 to the basal transcriptional machinery, which is followed by increased expression of target genes such as Arc, c-Fos, Egr1, Fos-b, and brain-derived neurotrophic factor (BDNF) (Barco et al., 2005; Beaumont et al., 2012). CREB phosphorylation increases CREB recruitment to the promoter of c-Fos (Krasnova et al., 2016). These are important processes that promote neuroinflammation by releasing various pro-inflammatory factors such as IL-6, IL-1β, TNF-α, monocyte chemotactic protein 1 (MCP-1), and cell adhesion molecule (ICAM-1) (Fig. 3) (Snider et al., 2013; Yang et al., 2018).

APOPTOSIS DUE TO METH-INDUCED NEUROTOXICITY AND INFLAMMATION

Mitochondria-mediated death pathway

As mentioned above, cytotoxicity and inflammation caused by METH leads to neuronal cell death. Besides ROS and NO, B-cell lymphoma 2 (Bcl-2) family proteins are also involved in METH-induced neurotoxicity and inflammation (Jayanthi et al., 2001). Previous studies have reported that METH exposure increases the expression of pro-apoptotic proteins such as Bax, Bad, Bid and decreases the expression of anti-apoptotic proteins such as Bcl-2 and Bcl-xl (Jayanthi et al., 2001, 2004; Beauvais et al., 2011). The increase of pro-apoptotic proteins by METH is due to the release of mitochondrial intermembrane space (IMS) proteins, including apoptosis inducing factor (AIF) and cytochrome c (Galluzzi et al., 2009). AIF and second mitochondria-derived activator of caspases/direct IAP-binding protein with low isoelectric point, PI (SMAC/DIABLO), which are released from mitochondria, activate the caspase-9 and -3 to induce neuronal cell death (Cadet et al., 2005). The release of cytochrome c is another key step in the caspase-dependent mitochondrial apoptotic pathway (Shin et al., 2018). Cytochrome c forms apoptosome, which is composed of Apaf-1, dATP and procaspase-9, and then induces sequential activation of the executioner caspases-3, -6 and -7 (Shin et al., 2018). Many studies regarding METH-mediated apoptosis show increased cytochrome c release from mitochondria and subsequent caspase activation after METH exposure in vitro (Nam et al., 2015; Park et al., 2017) and in vivo (Deng et al., 2002; Jayanthi et al., 2004; Beauvais et al., 2011; Dang et al., 2016). Another study suggested that activation of caspase-3 and PARP in the brain was also associated with METH toxicity (Deng et al., 2002). Therefore, these findings suggest that METH also affects neuronal cell death via regulation of mitochondrial pathway in the brain (Fig. 4).

ER-Dependent Death Pathway

In addition to the mitochondria-mediated apoptosis path-

Fig. 3. METH contributes to neuroinflammation. METH activates TLR4 and Sig-1R, triggering downstream signal pathways including NF-κB, MAPK and PI3K/Akt. Activation of CREB, c-Fos and BDNF promotes nerve inflammation through expression of various inflammatory cytokines.

Fig. 4. METH-induced neurotoxicity and neuroinflammation cause neuronal cell apoptosis. Neurotoxicity and neuroinflammation pathways are involved in METH-induced apoptosis. Increasing of DA and Glu by METH produce ROS and Ca^{2+} that act as secondary messengers for mitochondria- and ER-mediated apoptosis.
way, METH is related to the ER-dependent cell death pathway (Koumenis et al., 2002; Shah and Kumar, 2016). Oxidative stress due to METH exposure can cause cellular damage by causing dysfunction of cellular organelles such as the ER (Choi et al., 2010; Wang et al., 2016). Moreover, METH-mediated oxidative stress increases the expression of ER-resident chaperones such as BIP/GRP-78, P58IPK, and heat shock protein (HSP), which are important regulators of abnormal protein folding. ER stress can initiate an unfolded protein response (UPR) to restore proteolysis or to induce apoptosis (Shen et al., 2004). ER stress is also closely linked to three major signaling molecules: (1) activating transcription factor 6 (ATF6), (2) inositol requiring protein-1 (IRE-1), and (3) protein kinase RNA (PKR)-like ER kinase (PERK) (Shah and Kumar, 2016). The activity of these three molecules collectively constitutes an UPR (Tabas and Ron, 2011). ATF6 acts as a transcription factor for UPR induction, while phosphorylation of IRE-1 leads to the expression of ER-resident proteins such as BIP/GRP-78, GRP94 and C/EBP homologous proteins (CHOP)/growth arrest, and DNA damage-inducing gene 153 (Gadd153) (Tabas and Ron, 2011). In addition, PERK induces phosphorylation of eukaryotic initiation factor-2α (eIF2α), which results in the stimulation of activating transcription factor 4 (ATF-4), C/EBP homologous protein (CHOP), and caspase-12 (Gorlach et al., 2006). Since the ER contains the majority of intracellular Ca2+, the released Ca 2+ from the ER is absorbed by the mitochondria which then promotes ATP production (Gorlach et al., 2006).

As such, previous studies have shown that METH induces the expression of several ER stress genes, including 78kDa glucose regulated protein (GRP-78), CHOP, and ATF4, which leads to neurotoxicity in rat striatum (Bahar et al., 2016). Another study suggests that METH-induced apotosis is mediated by ER-dependent mechanisms including CHOP, spliced X-box binding protein 1 (XBP1), caspase-12, and caspase-3 (Xiong et al., 2017). In addition, a relatively high dose of METH promotes dopaminergic neuronal apoptosis via nuclear protein 1 (Nupr1)/CHOP pathway (Xu et al., 2017). ER stress and dysregulation of calcium homeostasis appear to be involved in neuronal cell death because METH can induce the activation of calpain (Suwanjang et al., 2010). The increased calpain in METH exposure is associated with the cytoskeleton protein spectra and microtubule tau activity in rat striatum and the hippocampus (Fig. 4) (Warren et al., 2005; Staszewski and Yamamoto, 2006).

CONCLUSIONS

METH is an addictive psychostimulant that acts on the central nervous system through various physiological pathways. Chronic use of METH can lead to memory deficit, and the deterioration of attention and executive functioning, which can be attributed to the direct neurotoxic and inflammatory effects of the drug. Cumulative studies have revealed the neurological effects of METH intake, however, specific mechanisms underlying METH-mediated neuronal damages remain unclear. In this review, we focused on the neurotoxicity and neuroinflammation caused by METH, which lead to neuronal cell death and impairment of brain function. We demonstrate that the process of neuronal damage by METH is closely related to oxidative stress, regulation of transcription factor, DNA damage, and various apoptosis pathways.

We hope that this review will help understanding the molecular mechanisms related to METH-induced brain damage and studies targeting the discovery of METH addiction therapy.

ACKNOWLEDGMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2016R1A6A1A03011325), and by the Keimyung University Research Grant of 2018 (BDP).

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