REVIEW

Acta Neurobiol Exp 2023, 83: 414–431
DOI: 10.55782/ane-2023-2488

Molecular mechanisms and treatment strategies for methamphetamine-induced neurodegeneration, inflammation and neurotoxicity

Samareh Omidvari[1#], Zahra Azimzadeh[2#], Fariborz Rashnoo[3], Foozhan Tahmasebinia[2], Aliasghar Keramatinia[2], Navid Ahmady Roozbahany[4,5], Hojjat Allah Abbaszadeh[1,2,4]*, Shahram Darabi[6]*

[1] Hearing Disorders Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran,
[2] Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran,
[3] Department of General Surgery, School of Medicine, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran,
[4] Department of Biology and Anatomical Sciences, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran,
[5] Private Practice, Bradford ON, Canada,
[6] Cellular and Molecular Research Center, Research Institute for Non-Communicable Diseases, Qazvin University of Medical Sciences, Qazvin, Iran,
[#] Co-first author
** Email: Dr.Abbaszadeh@sbmu.ac.ir*

Methamphetamine (METH) is a highly addictive psychostimulant known for its profound impact on the nervous system. Chronic METH use leads to neurotoxicity characterized by various molecular and structural alterations in the brain. This review article primarily aims to elucidate the mechanisms underlying METH-induced neurotoxicity. METH's mechanism of action involves the inhibition of dopamine, serotonin, and norepinephrine reuptake, resulting in altered synaptic function. Prolonged METH exposure triggers oxidative stress, endoplasmic reticulum stress, mitochondrial dysfunction, impaired axonal transport, autophagy, and programmed cell death, ultimately contributing to neurotoxicity. These neurotoxic effects manifest as increased neuronal firing rate, disruptions in intracellular ion balance (Ca^{2+} and Na+), energy production imbalances, and excessive reactive oxygen species production. The blood-brain barrier is compromised, leading to structural, functional, and neurochemical alterations, particularly in the fronto-striatal circuit. While our comprehensive review addresses these intricate molecular and structural changes induced by METH, we also examined the latest therapeutic strategies designed to mitigate neurotoxicity. Our investigation sheds light on the critical need to comprehend the complex pathways underlying METH-induced neurotoxicity and develop effective treatment approaches.

Key words: methamphetamine, neurotoxicity, inflammation, brain diseases, substance-related disorders

INTRODUCTION

Methamphetamine (METH) is a widely abused psychostimulant known for its high potential for addiction and neurotoxic effects (Azimzadeh et al., 2023; Yan et al., 2023). METH ranks as the second most commonly utilized illicit substance globally and exhibits the highest incidence rates in Asia, North America, and Oceania (Sulzer and Zecca, 1999; Kalivas and Volkow, 2005; Cruickshank and Dyer, 2009; Seo et al., 2020). Long-term dependence on METH has severe repercussions on the nervous system, leading to neuronal damage and impairments in attention, cognitive functions, learning, and memory (Moaveni et al., 2022; Salas-González et al., 2022). Due to its lipophilic nature (Davidson et al., 2022), METH efficiently crosses the blood-brain barrier (BBB) and significantly influences neurotransmitter

Received 17 July 2023, accepted 26 October 2023

release, including dopamine (DA), serotonin, norepinephrine, and glutamate by binding to various receptors such as dopamine transporter (DAT), serotonin transporter (SERT), norepinephrine transporter (NET), N-methyl-D-aspartate (NMDA) receptors, and vesicular monoamine transporter-2 (VMAT-2). These receptors are embedded in vesicular membranes and are integral proteins situated on the cell surface (Faraone, 2018; Su et al., 2022). METH is comprised of various derivatives, with MDMA (3,4-methylenedioxymethamphetamine) and MDE (3,4-methylenedioxyethylamphetamine) being prominent among them. While axonal loss and neurodegeneration are well-documented, the exact mechanistic processes remain a subject of ongoing research. Current hypotheses include the synthesis of harmful MDMA metabolites, free radical production, oxidative stress, excitotoxicity, apoptosis, and mitochondrial dysfunction (Büttner, 2011). The biochemical effects of METH rely on its ability to enter monoaminergic terminals, interact with vesicular monoamine transporters, displace monoamines into the terminals' cytoplasm, and subsequently release them into the synaptic clefts (Cadet et al., 2007). Additionally, METH reduces monoamine metabolism by inhibiting monoamine oxidase (Tatsuta et al., 2005). Research indicates that repeated METH administration to animals leads to reduced DA concentrations and its metabolites in various brain regions, including the striatum (Ricaurte et al., 1992; Krasnova et al., 2010; Granado et al., 2011). METH produces various effects at low to moderate doses, including increased increase in heart rate and blood pressure, increase in body temperature, arousal, behavioral disinhibition, increase in alertness, euphoria, reduced fatigue, positive mood, decreased appetite, and pupil dilation (Martin et al., 1971; Perez-Reyes et al., 1991; Anglin et al., 2000; Harris et al., 2003; Mendelson et al., 2006; Cruickshank and Dyer, 2009). Nonetheless, increased plasma levels or higher doses of METH can lead to symptoms such as nervousness, violent behavior, paranoia, rapid or incoherent speech, euphoria, as well as hypertension, rapid pulse, sweating, and motor agitation. These signs and symptoms are indicative of an overdose, which could be either fatal or non-fatal (Logan, 1996). Fatalities associated with METH often result from conditions such as hyperpyrexia, cerebrovascular hemorrhage (caused by hypertension), ventricular fibrillation, pulmonary congestion and edema, multiple organ failure, or acute cardiac failure (Jordan and Hampson, 1960; Zalis and Parmley, 1963; Kojima et al., 1984; Martin et al., 1971; Hong et al., 1991; Katsumata et al., 1993; Perez Jr et al., 1999; Waksman et al., 2001; Wijetunga et al., 2003; Ago et al., 2006). Withdrawal symptoms may occur when METH use is abruptly discontinued, lasting for several days and characterized by anhedonia, intense cravings, irritability and agitation (Oswald and Thacore, 1963; Watson et al., 1972; Gossop et al., 1982; Srisurapanont et al., 1999; Kalechstein et al., 2003; London et al., 2005; McGregor et al., 2005). Pharmacological approaches, including opioid receptor antagonists and antidepressants, as well as non-pharmacological methods like psychosocial behavioral therapy and contingency reward therapy, are employed to manage withdrawal symptoms (Thrash et al., 2009). METH exerts severe damage on the nervous system, both in the short-term and long-term, primarily through oxidative stress and alterations in energy metabolism (Granado et al., 2013) (Fig. 1).

One of the notable changes induced by METH in the nervous system is its profound impact on the DA system which are accompanied by significant alterations in behavior and cognition (Nordahl et al., 2003; Shrestha et al., 2022). METH's high lipid solubility allows it to readily traverse the BBB (Nordahl et al., 2003; Schep et al., 2010) and its structural similarity to DA enables it to be taken up by dopaminergic cells through binding to DAT (Iversen, 2006). Normally, DAT functions to remove DA from the synaptic cleft, terminating its neurotransmitter effects (Wang et al., 2015). However, METH's binding to DAT disrupts the reuptake of extracellular DA and leads to the reverse transport of DA out of the cell, resulting in an increase in DA concentration within the synaptic cleft (Panenka et al., 2013) (Fig. 2). At high concentrations, METH can even diffuse through axons due to its lipophilic properties, exacerbating the accumulation of extracellular DA (Shin et al., 2018). Another critical factor in METH-induced DA release is the VMAT-2, an integral membrane protein responsible for shuttling DA from the cytosol into synaptic vesicles (Sulzer et al., 2005; Fleckenstein et al., 2009). This transport process is closely associated with a proton pump ATPase. Research indicates that METH, acting as a "weak base," disrupts the proton gradient on both sides of the vesicle, which is essential for DA sequestration, causing DA to leak from the vesicle into the cytosol (Schwartz et al., 2006; Panenka et al., 2013). Furthermore, METH may decrease the functionality and density of VMAT-2 on the cellular membrane (Eyerman and Yamamoto, 2005; McFadden et al., 2012) (Fig. 2). In tandem, these interactions between METH, DAT, and VMAT-2 lead to a surplus of DA in both intracellular and extracellular environments. This review article examines the main molecular mechanisms and brain structural changes associated with METH-induced neurotoxicity. It also summarizes recent findings on potential therapeutic methods that target various pathways to mitigate the negative impacts of METH in the central nervous system. Despite the lack of an FDA-approved treatment for METH-induced neurotoxicity, this paper provides valu-

able insight for future research and the development of more therapeutic interventions that are efficient in safeguarding against the deleterious impacts of METH.

Molecular mechanisms underlying neurotoxicity induced by METH exposure

The mechanisms of neurotoxicity induced by METH consumption are complex and involve DA reduction, oxidative stress, stress on the endoplasmic reticulum, impairment of mitochondrial function, barriers of axonal transport, activation of microglial cells, activation of astrocytes, autophagy, and programmed cell death (Fig. 1) (Hwang et al., 2020; Khoshsirat et al., 2020; Meng et al., 2020; Mirakabad et al., 2021). Notwithstanding extensive research, there is still an incomplete understanding of the molecular and cellular mechanisms responsible for neuronal toxicity induced by METH exposure. Studies suggest that oxidative stress induced by METH exposure have a critical role in promoting cytotoxicity by producing ROS that destruct macromolecules inside the cells (Wells et al., 2009; Ramkissoon and Wells, 2015; Khoshsirat et al., 2019).

Oxidative stress

METH causes the production of various oxidative species which results in lipid peroxidation, nuclear damage, and protein misfolding (Ferrucci et al., 2017; Jang et al., 2017). METH exposure induces oxidative stress, a critical factor in neuronal damage. This oxidative stress is a consequence of various mechanisms: When METH enters the neurons, it releases DA into the synaptic cleft, leading to high levels of DA that cause auto oxidation and increased DA metabolism, producing hydrogen peroxide (H_2O_2) as a by-product. H_2O_2 then produces hydroxyl radicals that cause oxidative damage

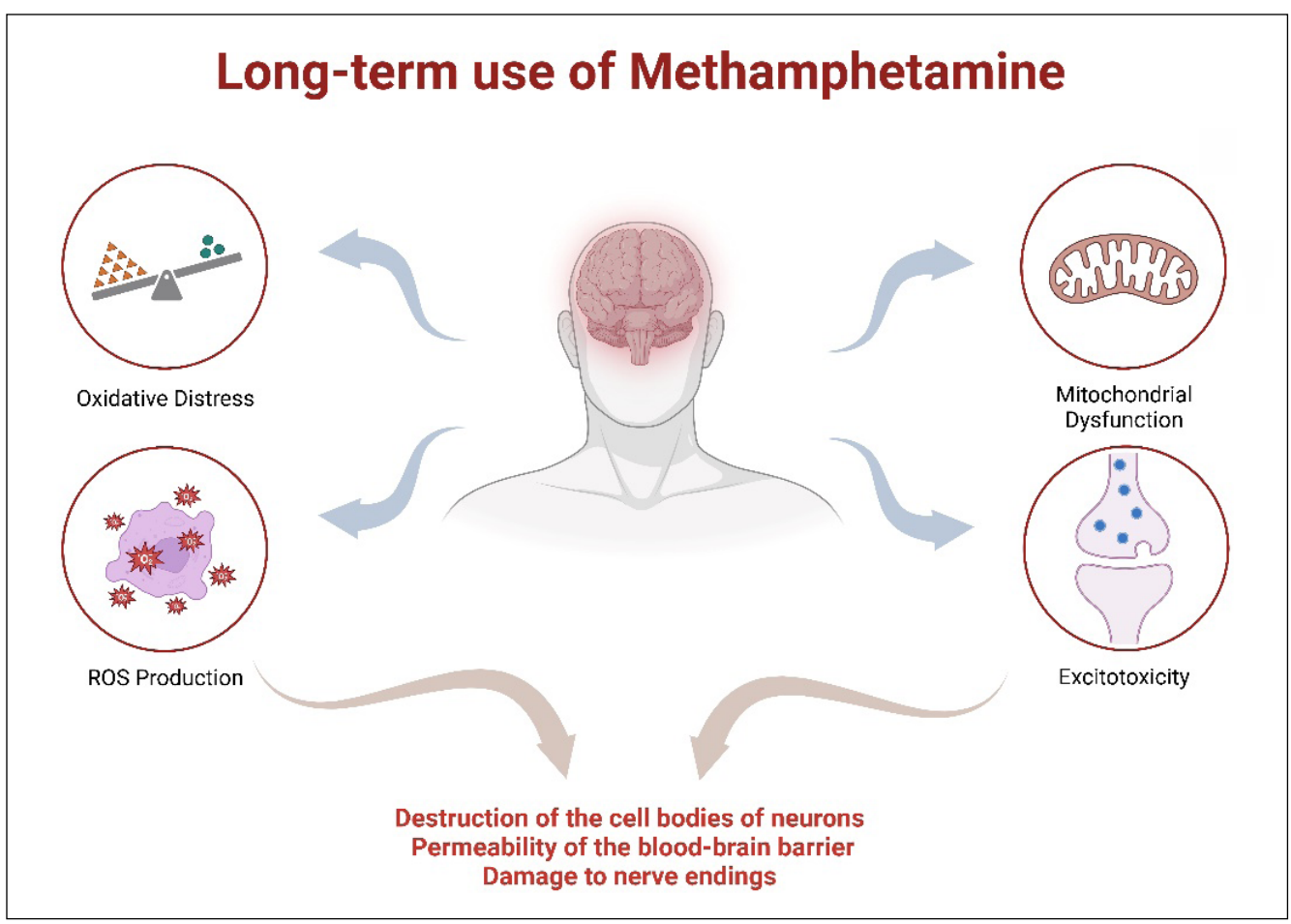

Fig. 1. Long-term use of methamphetamine causes an increase in oxidative stress, dysfunction of brain mitochondria and excitotoxicity, which causes a lot of damage to the brain structure and causes the destruction of the cell bodies of neurons, permeability of the BBB, and damage to nerve endings, which eventually It causes severe problems in the brain and causes death. The figures included in this study were created using the BioRender website (https://www.biorender.com/).

(Stokes et al., 1999; Zhu et al., 2006). Thus, METH-induced accumulation of DA in both the cytosol and synaptic regions leads to the formation of quinone and semi-quinone compounds through an autoxidation process, generating significant quantities of reactive oxygen species (ROS) (Fig. 2) (Stokes et al., 1999; Zhu et al., 2006). These ROS include substances such as hydrogen peroxide, hydroxyl radicals, and superoxide radicals. Additionally, a portion of DA is involved in the creation of hydrogen peroxide with the assistance of monoamine oxidase (MAO) (Hermida-Ameijeiras et al., 2004; McDonnell-Dowling and Kelly, 2017; Yang et al., 2018). METH also hinders the production of antioxidants, which encompass compounds like glutathione, superoxide dismutase (SOD), and catalase (Tata and Yamamoto, 2007; Huang et al., 2013). Consequently, the imbalance between ROS and the free radical scavengers leads to oxidative stress within dopaminergic terminals. This excess of ROS can disrupt lipid and protein metabolism, impair mitochondrial function, and cause damage to nuclear DNA, elevating the vulnerability to neuronal harm and cell death (Potashkin and Meredith, 2006).

The destruction of dopaminergic neurons resulting from METH use is predominantly due to oxidative stress (Rumpf et al., 2017). This leads to the release of neuromelanin, aggravating the process of neuroinflammation and neurodegeneration (Rumpf et al., 2017). METH also causes disturbances in the redox balance, leading to the oxidation of nucleic acids, lipids and proteins. Additionally, METH blocks mitochondrial complex II, which increases oxidative stress and mitochondrial dysfunction (Lazzeri et al., 2018). The increased expression of alpha-synuclein (α-SYN) caused by METH amplifies cellular oxidative stress. Inhibitors of the *synuclein alpha* gene (*SNCA*) can reduce this stress. Conversely, METH activates nitric oxide synthase (NOS), which results in elevated α-SYN expression *in vitro*, as well as in the mouse striatum and hippocampus (Wu et al., 2014; Wang et al., 2017b; Gandelman et al., 2021). Oxidation of proteins results in the formation of disulfuric bridges through the binding of cysteinyl residues. This process changes the shape of the protein and leads to the creation of misfolded proteins like α-SYN, parkin, prion, and ubiquitin. Moreover, METH leads to lip-

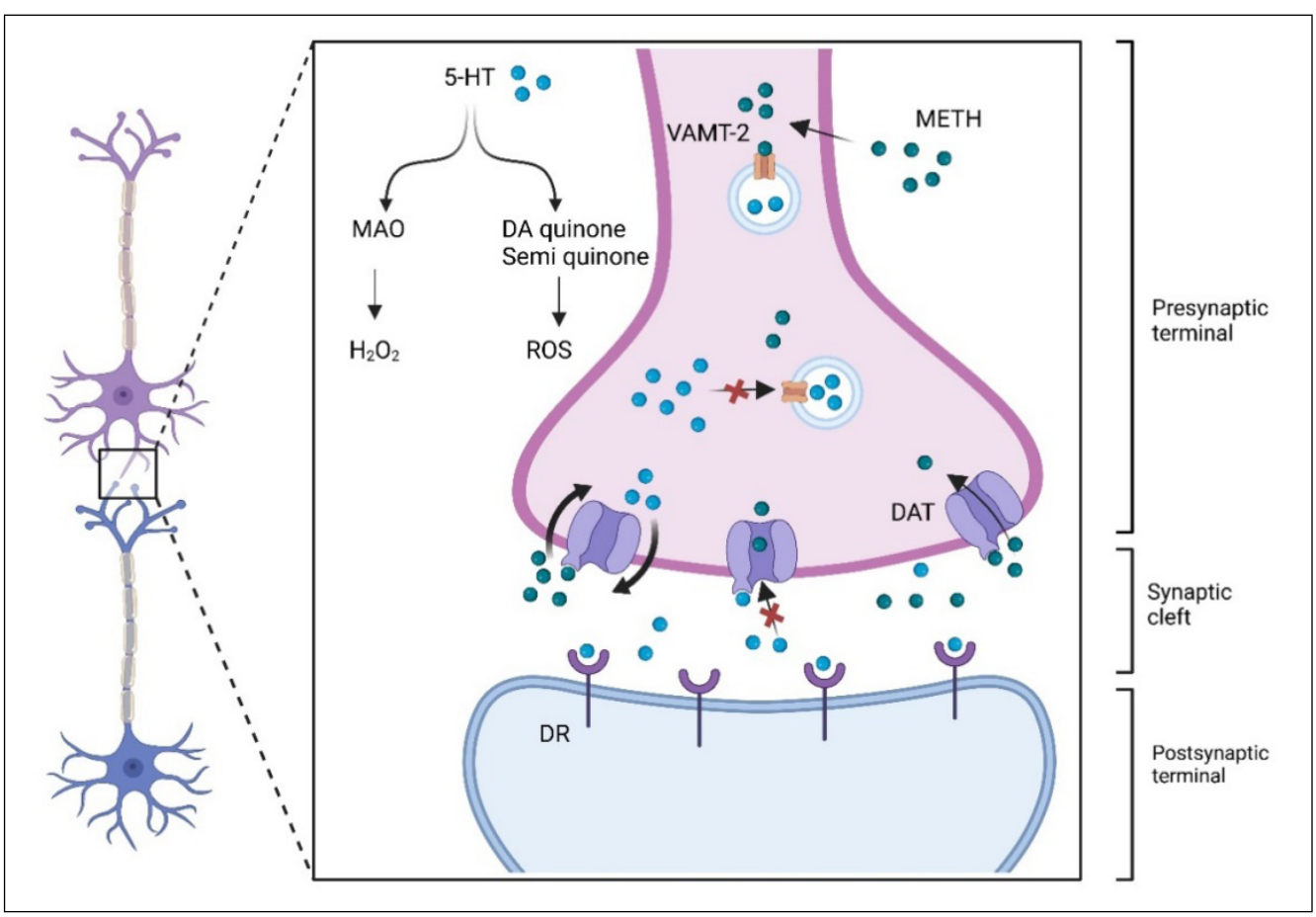

Fig. 2. METH modulates the DA system and impacts the release of DA and thereby induces oxidative stress. The figures included in this study were created using the BioRender website (https://www.biorender.com/).

id oxidation, which produces 4-hydroxynonenal that is highly reactive (Lazzeri et al., 2018).

Activation of microglial cells

METH is known to induce inflammation in regions where the 5-HT as well as DA and terminals are impaired, primarily by activating microglia (Halpin et al., 2014; Valian et al., 2019). The microglia activation in the hippocampus, cortex, and striatum is caused by an unknown mechanism, although it is believed that dopaquinones (DAQs), a DA metabolite, is the primary microglia activator *via* gene expression (Kuhn et al., 2006). METH exposure can increase cytosolic DA and oxidative stress, leading to the synthesis of DAQs, which results in microglial activation. This leads to the secretion of potentially neurotoxic agents such as ROS, proteinases, and pro-inflammatory cytokines, triggering neuroinflammatory processes (Smith et al., 2012).

Excitotoxicity

Excitotoxicity, a damaging process stemming from the overstimulation of neurons, is a significant consequence of METH. METH's impact on the neurotransmitter system, particularly in relation to glutamate, plays a crucial role in this phenomenon. Excitotoxicity is implicated in various neurological conditions and is a critical aspect of the neurotoxic effects associated with METH abuse, including cognitive deficits, neuroinflammation, and other neurological impairments. METH disrupts the balance of glutamate, a major excitatory neurotransmitter in the brain, leading to excessive release and impaired reuptake. METH administration results in the release of excessive glutamate into the extracellular space, leading to the activation of glutamate receptors and an increase in intracellular calcium levels, initiating excitotoxicity (Ambrogini et al., 2019). The resulting surge in glutamate over activates NMDA receptors, which are glutamate receptors, ultimately contributing to excitotoxicity. This harmful process can lead to neuronal damage and cell death. The activation of glutamate receptors, especially NMDA receptors, triggers pathways involving the phosphorylation of protein kinase C (PKC) and subsequent modulation of NMDA receptor activity, leading to calcium influx and the generation of nitric oxide (NO) and free radicals (Tseng et al. 2010; Moratalla et al. 2017). Elevated calcium levels activate enzymes such as NOS, phosphatases, and protein kinases, promoting NO production and ER stress. ER stress activates transmembrane proteins such as ATF6, IRE1, and PERK, which further downregulate specific genes involved in protecting against proteotoxic stress (Szegezdi et al., 2006; Hetz, 2012). The activation of CHOP, triggered by ER stress, initiates apoptosis through death receptors and mitochondrial-dependent pathways (Bahar et al., 2016; Sano and Reed, 2013). METH exposure has been shown to induce the expression of ER stress genes such as ATF4, caspase-12, and CHOP (Jayanthi et al., 2004; Sano and Reed 2013; Mirakabad et al. 2021). Activation of dopamine receptor (D1) is associated with dopaminergic toxicity and ER stress induced by METH (Beauvais et al., 2011). Autophagy activation through the D1-receptor is mediated by the AMPK/FOXO3A signaling pathway following METH administration (He et al., 2022).

Glutamate is a principal neurotransmitter excitation and is considered to have a significant role in promoting neuroinflammation. Following frequent METH administration, glutamate receptor is activated and glutamate is released, and subsequently of PI3/Akt molecules is phosphorylated, which activates the transcription factor NF-κB, finally activating neuroinflammation by producing pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and interleukin-1β (IL-1β) (Prakash et al., 2017). A feed-forward loop can occur where these cytokines stimulate the increase of extracellular glutamate levels, which can hinder the absorption and increase the release of glutamate from microglial cells, ultimately leading to neurotoxicity (Yamamoto et al., 2010).

The elevation of these inflammatory cytokines after METH administration has been shown to play a significant role in causing brain damage, as evidenced by several studies (Kobeissy et al., 2022). Excessive extracellular glutamate is the most common cause of excitotoxicity in the human brain (Chamorro et al., 2016). Excessive release of l-glutamate into the extracellular space by neuron and glial cells activates glutamate receptors, resulting in an increase in calcium levels inside the cells and subsequently calcium-dependent enzyme activation. This, in turn, produces nitric oxide (NO) and free radicals, causing neuronal damage or neural death through excitotoxicity (Tseng et al., 2010). Excessive glutamate accumulation results in the initiation of subsequent signaling pathways such as the elevation of intracellular calcium levels and metabotropic glutamate receptors (mGluRs) or NMDA receptors activation (Moratalla et al., 2017).

In addition to affecting the neurotransmitter glutamate, METH disrupts the normal regulation and release of catecholamines, including dopamine, adrenaline, and noradrenaline (Fig. 3). METH enters neurons either through uptake mechanisms or the DAT, displacing noradrenaline (NA) and DA from their vesicles and raising their levels in the cytosol. METH further inhibits

the breakdown of NA and DA by MAO, which would normally reduce their concentrations. As a result, NA and DA are released into the synaptic cleft through uptake and DAT, while METH takes their place inside the neuron (Fig. 3). This recurring process maintains elevated neurotransmitter levels, leading to the overstimulation of postsynaptic neurons. This overstimulation is closely linked to the behavioral and physiological effects of amphetamine use, and the excessive activation of these neurons contributes to the excitotoxicity associated with METH abuse.

Endoplasmic reticulum (ER) dysfunction: a key player in METH-induced neurotoxicity

Prolonged exposure to METH has profound consequences on neuronal health, with one of the central aspects being the disruption of the ER. The ER is a critical cellular organelle responsible for maintaining cellular homeostasis by regulating calcium signaling. METH-induced oxidative stress exacerbates this dysfunction, leading to detrimental effects on neurons. METH triggers a cascade of events that disturb intracellular calcium levels within the ER. The drug promotes excessive extracellular glutamate release, which activates glutamate receptors, ultimately resulting in increased intracellular calcium levels (Tseng et al., 2010; Moratalla et al., 2017). Elevated calcium levels within the cell activate enzymes like nitric oxide synthase (NOS), phosphatases, and protein kinases. This activation leads to the generation of nitric oxide (NO) and initiates ER stress (Tseng et al., 2010; Moratalla et al., 2017). ER-resident transmembrane proteins, such as ATF6, IRE1, and PERK, respond to this stress by downregulating specific gene expressions crucial for defending against proteotoxic stress (Szegezdi et al., 2006; Hetz, 2012). The ER, under stress, activates a programmed cell death process known as apoptosis, triggered through death receptors and mitochondrial-dependent pathways (Sano and Reed 2013; Bahar, Kim, and Yoon 2016). High METH doses stimulate the expression of ER stress-related genes, including ATF4, caspase-12, and CHOP (Jayanthi et al., 2004; Sano and Reed, 2013; Mirakabad et al., 2021). Moreover, the activation of dopamine receptor D1 is associated with dopaminergic toxicity, primarily driven by ER stress induced by METH exposure (Beauvais et al., 2011). Intriguingly, after METH administration, autophagy ac-

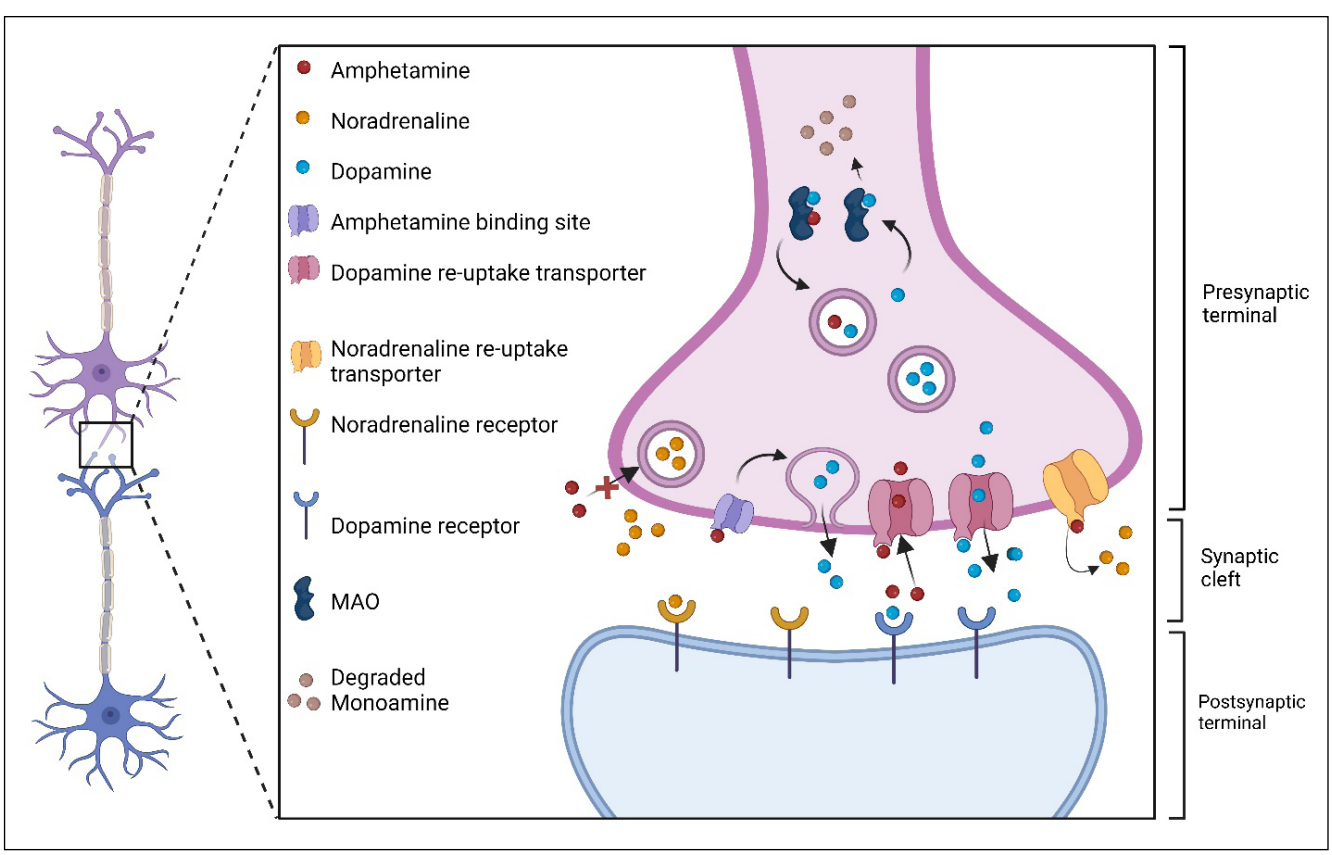

Fig. 3. METH-induced disruption of neurotransmitter release in the synaptic cleft. The figures included in this study were created using the BioRender website (https://www.biorender.com/).

tivation through the D1-receptor is mediated by the AMPK/FOXO3A signaling pathway (He et al., 2022). In response to METH doses leading to apoptosis, the calcium-responsive cytosolic cysteine protease known as calpain becomes activated. Calpain's involvement in ER-dependent cell death indicates a clear connection between ER stress and calcium dysregulation, both contributing to METH-induced neuronal cell death (Cadet et al., 2007). The intricate interplay between METH-induced ER stress and calcium dysregulation significantly contributes to neuronal damage. While the mechanisms are complex and multifaceted, these processes collectively underlie the neurotoxicity associated with METH exposure. The disruption of ER function, coupled with the induction of apoptosis within the ER, underscores the severity of neuronal damage caused by this psychostimulant. Understanding these molecular and cellular events is essential for comprehending the comprehensive impact of METH on the central nervous system. This knowledge provides critical insights into potential therapeutic interventions aimed at mitigating the detrimental effects of METH.

Mitochondrial dysfunction

METH is a lipophilic substance that easily penetrates the membranes of various organelles inside the cells, including the mitochondria (Valian et al., 2017). Its impact on the brain causes neurological damage by inducing mitochondrial dysfunction, caspase activation, and apoptosis (Valian, Ahmadiani, and Dargahi 2017; Huang et al., 2019; Valian et al., 2019). METH reduces the activity of mitochondrial respiratory chain complexes and elevates ROS production and proteins related to mitochondrial fission, which causes mitochondrial fragmentation and apoptosis (Valian et al., 2019). METH blocks mitochondrial complex II, which increases oxidative stress and mitochondrial dysfunction (Lazzeri et al., 2018). As the amount of METH administered increases, it causes a reduction in the production of new mitochondria, but when the administration is stopped, the body activates protective responses to compensate for the damage. These include increased expression of genes associated with mitochondrial biogenesis and the release of glial cell line-derived neurotrophic factor (GDNF), which helps to promote the survival of neurons (Beirami et al., 2018). Additionally, METH administration disrupts mitochondrial biogenesis by reducing the levels of mitochondrial biogenesis-related factors such as PGC1α, NRF1, and TFAM in the rat hippocampus (Beirami et al., 2018). Furthermore, METH exposure increases the expression of pro-apoptotic proteins Bax and Bad, while reducing the expression of the anti-apoptotic protein Bcl-2. This results in the release of cytochrome c from the mitochondria into the cytosol, causing the subsequent activation of caspase-3, -6, and -7, which ultimately trigger programmed cell death (Huang et al., 2019). METH is harmful to different brain regions, such as the hippocampus, cortex, and striatum (Li et al., 2008). Proteomic analysis revealed that the expression of specific proteins is altered in these regions after METH administration, with oxidative stress, programmed cell death, and mitochondrial metabolism implicated in the underlying pathophysiology. Notably, METH administration reduced Cu, Zn, SOD levels in the hippocampus and striatum, while α-SYN was elevated in the cortex hippocampus, and striatum. Additionally, the decline in ATP synthesis-related mitochondrial enzymes in these areas may play a role in the neurotoxic effects of METH.

Autophagy

Proteins undergo degradation primarily through two key pathways: the autophagy pathway and the ubiquitin-proteasomal pathway. Autophagy is a fundamental degradation process, and its regulation is chiefly under the sway of the mammalian target of rapamycin (mTOR), a pivotal autophagy suppressor (Lazzeri et al., 2018). In the context of METH exposure, it's noteworthy that this substance disrupts the ubiquitin-proteasomal system while significantly escalating autophagic activity. This has profound implications for proteins critical to the health of DA neurons (Lazzeri et al., 2018). Following METH exposure, an enzyme known as E2N, which participates in the ubiquitination process, appears to emerge as a cellular defense mechanism against the buildup of aberrant proteins induced by METH. This defensive response may be a compensatory effort aimed at thwarting protein aggregation and the resultant cellular damage caused by the drug (Li et al., 2008). METH also disrupts proteostasis by impacting the autophagy-lysosomal system, resulting in increased accumulation of α-SYN (Li et al., 2018). Additionally, METH induces alterations in the parkin protein, which is an E3 ubiquitin ligase and possesses neuroprotective characteristics (Flack et al., 2017). Both proteins are found to aggregate in Parkinson's disease (PD) brains (Tahmasebinia and Emadi, 2016; Tahmasebinia and Pourgholaminejad, 2017; Khoramgah et al., 2019; Mitoma and Manto, 2019; Pourgholaminejad and Tahmasebinia, 2019). In the realm of METH-induced effects, there is a noteworthy increase in autophagic vacuoles within neurons containing catecholamines. Intriguingly, inhibiting autophagy exacerbates the toxicity of METH in these cells (Lazzeri et al., 2018). Conversely, studies have shown that the administra-

tion of rapamycin, an mTOR inhibitor, can confer protection against METH-induced toxicity. Moreover, pre-exposure to asparagine or glutamine, compounds known to impede the autophagic process, has been observed to amplify METH's toxicity, even at moderate doses (Ferrucci et al., 2021). These findings collectively suggest that when autophagy is compromised, METH-induced cellular demise follows an apoptotic pathway.

Programmed cell death

METH exerts its neurotoxic effects through a mechanism involving neuronal programmed necrosis, triggered by the activation of signaling pathways associated with receptor-interacting protein kinase 3 (RIP3) (Zhao et al., 2021). Within this process, the formation of a necrotic protein complex orchestrated by RIP3 assumes a pivotal role in the initiation of neurodegeneration through programmed necrosis (Han et al., 2011; Sun et al., 2012; Zhao et al., 2021). This intricate cascade unfolds as RIP3 phosphorylation occurs, subsequently triggering the phosphorylation of mixed lineage kinase domain-like protein (MLKL). MLKL activation leads to the creation of pores in the cell membrane, culminating in necrotic cell death (Sun et al., 2012). Under METH exposure, there is an induction of a complex formation between RIP3 and RIP1, culminating in RIP3 phosphorylation. Activated RIP3 then proceeds to activate MLKL, resulting in the formation of oligomers that disrupt the cell membrane. This disruption, in turn, leads to mitochondrial damage and ultimately contributes to neuronal necrosis (Zhao et al., 2021). In summary, METH-induced neurotoxicity involves the initiation of neuronal programmed necrosis, driven by intricate signaling pathways centered on RIP3 activation and the subsequent downstream events that culminate in cell membrane disruption and neuronal demise.

Axonal transport barrier

Impairments in axonal transport in the context of METH use are influenced by several interconnected factors that collectively create barriers to the normal movement of cellular components along axons. METH disrupts the stability of microtubules, which serve as essential tracks for motor proteins responsible for cargo transport. This destabilization, coupled with METH-induced alterations in motor protein function, hinders the efficient movement of organelles and other essential components. Additionally, METH generates oxidative stress within neurons, leading to damage of critical axonal transport elements. Mitochondrial dysfunction induced by METH reduces the energy supply required for axonal transport, further compromising this process. Prolonged METH use can result in neuronal damage and degeneration, impacting the overall health and integrity of axons (Yu et al., 2015). The disruption of proteostasis by METH, which leads to the accumulation of abnormal proteins like alpha-synuclein, can physically obstruct axonal transport. Neuroinflammation, DA dysregulation, synaptic dysfunction, and compromised cellular homeostasis all contribute to the complex network of factors that collectively impede axonal transport in METH-induced neurotoxicity. These barriers to axonal transport represent significant challenges in understanding and mitigating the neurological consequences of METH use (Mavroeidi et al., 2021).

METH-induced brain structure changes

METH has a wide range of effects on the brain, ranging from acute to long-term and affecting both the CNS and PNS. METH has significant negative effects on the brain, including causing leakage BBB, activating glial cells, storing water in brain tissue (edema), and causing structural changes in brain cells (Kiyatkin and Sharma, 2009). These effects vary in severity in different regions of the brain (Kiyatkin and Sharma, 2009). Clinical studies using various imaging techniques show that moderate to high doses of METH cause sustained neurotoxicity, including structural and metabolic changes (Barr et al., 2006). METH directly affects BBB destruction and vascular toxicity (Chiang et al., 2019). Research utilizing neuroimaging techniques has shown that changes in the frontostriatal circuit and network dynamic systems are involved in the pathophysiology of METH (MAP) use. These changes can be attributed to structural, functional, and neurochemical factors. Chronic METH use has been found to damage DA function, especially in the striatum and prefrontal cortex, in both animal and human studies. Research has shown that individuals who misuse METH exhibit structural irregularities in the nuclear gray matter, cerebral cortex, and white matter, which can lead to tissue atrophy or hypertrophy due to toxic damage in these brain regions (Mahmoudiasl et al., 2019). When compared to healthy controls, chronic METH users showed higher white matter volume, abnormal tract morphology, lower N-acetyl-aspartate levels, higher levels of glial associated sugar myoinositol, lower glucose metabolism, and more white matter signal hyperintensities. The corpus callosum, frontal, temporal, and occipital lobes were found to be involved in these changes (Tobias et al., 2010). MRI studies have revealed ana-

tomical abnormalities in the brains of METH users, including lower amounts of gray matter and higher volumes of parietal cortex. Volumetric changes in the striatum have been linked to novelty seeking and improved cognitive function, suggesting that these changes may be compensatory adjustments made in response to METH-induced neurotoxicity (Thanos et al., 2016). METH users also had lower volumes of areas associated with emotional regulation and impulsivity, such as the anterior prefrontal/frontopolar, inferior frontal, and superior temporal cortices, as well as the amygdala and hippocampus. Gray matter changes in these areas may contribute to MAP traits, such as excessive emotional reactivity and dysregulated impulsivity (Chen et al., 2019). Research has repeatedly shown that the hippocampus and amygdala are involved in the pathophysiology of schizophrenia, affective psychosis, and drug addiction. Decreased gray matter volume in both the amygdala and hippocampus was observed in individuals with METH psychosis when compared to healthy controls (Orikabe et al., 2011). However, exogenous METH psychosis was associated with amygdala-dominant gray matter volume reduction. One study comparing the brain structures of current and former METH users found that users had larger putamens than controls. However, previous METH users had higher fractional anisotropy and lower mean diffusivity in the putamen and globus pallidus than current users and controls, possibly due to increased magnetic susceptibility linked to higher iron concentration (Andres et al., 2016). The toxic damage of METH on the brain can result in a range of anatomical anomalies, including smaller quantities of gray matter, higher volumes of parietal cortex, reduced volumes of the anterior prefrontal/frontopolar, inferior frontal, and superior temporal cortices, amygdala, and hippocampus. Additionally, inflammatory alterations, including microglial activation, are seen (Thanos et al., 2016). METH may also have a role in the pathophysiology of schizophrenia, affective psychosis, and drug addiction. In this disease, the magnitude of the reduction in gray matter is much larger in the amygdala than the hippocampus (Orikabe et al., 2011). Previous METH users had larger putamen, and the putamen and globus pallidus of previous users showed stronger fractional anisotropy and lower mean diffusivity, potentially resulting from greater magnetic susceptibility, which was linked to higher iron concentration (Andres et al., 2016). Chronic misuse of METH is specifically associated with DA function deficiencies and anatomical abnormalities in the cerebral cortex, white matter, and nuclear gray matter of humans (Table 1) (Tobias et al., 2010).

Therapeutic strategies

Various strategies have been developed to address the neurotoxicity caused by METH in order to achieve effective and efficient treatment. These strategies are currently being investigated in both clinical and preclinical studies. The approaches for treatment are rooted in the mechanisms that underlie the induction of neurotoxicity. The goal of this section is to examined therapeutic strategies for addressing METH-induced neurotoxicity. We will first cover strategies aimed at directly managing neurotoxicity, followed by approaches to prevent or reduce neurotoxicity.

Management of neurotoxicity

Oxidative stress is a prominent factor in METH-induced neurotoxicity. METH increases ROS production, depletes ATP levels, and interferes with DA reuptake, leading to the generation of ROS and nitrogen radicals, resulting in neuronal programmed cell death (Thrash et al., 2009). Researchers have investigated various pharmacotherapies for effective therapeutic strategies to protect brain cells against METH-induced oxidative stress.

Zinc: Zinc upregulates metallothionein expression, inhibiting ROS production and ATP depletion (Thornalley and Vašák, 1985; Hanada et al., 1991; Hart et al., 1995; Ajjimaporn et al., 2005; 2007). The administration of zinc prior to METH resulted in an upregulation of metallothionein expression and effectively inhibited the production of ROS and depletion of ATP (Thornalley and Vašák, 1985; Hanada et al., 1991; Hart et al., 1995; Ajjimaporn et al., 2005; 2007).

Vitamin C: Activates the p38 MAPK pathway, inducing HO-1 expression, reducing ROS generation (Rice, 2000; Hediger, 2002; Huang et al., 2012; Huang et al., 2017). The p38 MAPK pathway is activated by vitamin C, which induces HO-1 expression and reduces the generation of intracellular ROS, protecting neurons from METH toxicity (Rice, 2000; Hediger, 2002; Huang et al., 2012; 2017).

Flavonoids: Anthocyananine, baicalein, isoliquiritigenin, and cinnamaldehyde show neuroprotective effects (Wu et al., 2006; Ghosh et al., 2007; Lee and Jeong, 2021; Lee et al., 2021; Rashidi et al., 2021; Roohbakhsh et al., 2021).

Tocopherol: Prevents oxidative stress due to lipid peroxidation and ROS generation (Burton and Ingold, 1989; Peeters-Scholte et al., 2003; Park et al., 2006; Volti et al., 2006; Shokrzadeh et al., 2015). Since tocopherol and deferoxamine have been shown to prevent oxidative stress due to lipid peroxidation and ROS generation, it has been proposed that compounds with fla-

vonoid characteristics may have the possibility of being developed as treatment options for neurotoxicity caused by METH.

Selenium: Enhances glutathione peroxidase (GPx) activity, reducing neurotoxicity *via* antioxidant mechanisms (Kim et al., 1999). Selenium is a mineral and antioxidant that occurs naturally in water, soil, and food and is commonly used as a dietary supplement (Wang et al., 2017a). Scientists have investigated how consuming selenium-rich diets can affect the toxicity of dopaminergic neurons. So, based on their findings, by supplementing mice with selenium, the activity of glutathione peroxidase (GPx) was enhanced by selenium, along with an increase in the ratio of reduced glutathione GSH to oxidized glutathione GSSG in various brain regions in mice treated with a neurotoxic drug called METH (Kim et al., 1999). This suggests that selenium may reduce neurotoxicity induced by

Table 1. The results of some studies on the effects of METH on the brain structure.

Study	Main Result
Kiyatkin E et al.	CNS effects: Significant BBB leakage, acute glial activation, water storage in brain tissue (edema) and structural changes in brain cells.
Cho AK et al.	Synaptic effects: Enhancing releasing DA in CNS and norepinephrine in PNS and then block their reuptake in presynaptic nerve terminal.
Barr AM et al.	Acute effects: Euphoria, feelings of wellbeing, and alertness, increase in libido and a decrease in hunger. Immediate side effects in higher doses: Increased blood pressure, hyperthermia, stroke, cardiac arrhythmia, stomach cramps, and muscle tremor. Acutely harmful psychological side effects: Anxiety, insomnia, aggression, paranoia, and hallucinations.
Prakash MD et al.	Long-term use effects: Molecular abnormalities in the DA system result in reduced motor abilities, fast cognitive decline, increased anxiety, psychotic illnesses, aggressive conduct, hallucination, delusions, and depression.
Morley KC et al.	Prolonged use of moderate to high dosages effects: Sustained neurotoxicity, including structural and metabolic alterations.
Meredith CW et al.	Psychological withdrawal symptoms: Anhedonia, hypersomnia, anger, anxiety, violence, and extreme cravings for methamphetamine (Because methamphetamine abuse is associated with neurotoxicity, a decrease in receptor activity, and presynaptic monoamine depletion).
Shaerzadeh F et al.	Reasons of methamphetamine ability to cause neurotoxicity: Increased neuronal firing rate, increased intracellular Ca+2 and Na+ ions, dysregulation of mitochondrial activity, an imbalance in neuronal energy, and an excess production of reactive oxygen species.
Halpin LE et al.	Striatonigral pathway effects: Extracellular glutamate levels in the rat striatum increase after binge doses of meth, and reducing these levels shields the area's DA terminals from its neurotoxic effects.
Chiang M et al.	DA transmission effect: In CNS methamphetamine is inhibiting both the vesicular monoamine transporter (VMAT2) and the DA transporter and cause rise of DA concentration. Also, the polysynaptic contacts of many dopaminergic systems, including the mesolimbic, nigrostriatal, and mesocortical, are then influenced by elevated DA concentrations, which lead to elevated glutamate and DA signaling. Excessive DA signaling effect: Overpower GABAergic interneurons, DA systems dysregulated and perhaps manifesting signs of psychosis.
Buchanan JB, NL Sparkman,	Neurotoxicity effects: BBB damage, hyperthermia, seizures and vascular toxicity.
Berman S et al.	Brain effect of chronic misuse of methamphetamine: Specifically in the striatum and prefrontal cortex, DA function deficiencies are associated with anatomical abnormalities in the cerebral cortex, nuclear gray matter, and white matter of humans.
Tobias MC et al.	Toxic damage of brain: Brains of the chronic methamphetamine users (compared *in vivo* to those of healthy controls) had more white matter volume, abnormal tract morphology, lower levels of the amino acid N-acetyl-aspartate, higher levels of the glial-associated sugar myoinositol, lower glucose metabolism, and more white matter signal hyperintensities. These results were observed in the corpus callosum, frontal, temporal, and occipital lobes.
Thanos PK et al.	Changes of brain: Anatomical anomalies in the brains such as smaller quantities of gray matter (especially in frontal and temporal cortices) and higher volumes of parietal cortex. Reduced volumes of the anterior prefrontal/frontopolar, inferior frontal, and superior temporal cortices, amygdala and hippocampus, which are areas associated with emotional regulation and impulsivity. Also, inflammatory alterations including microglial activation is seen.
Orikabe L et al.	Psychological effect: Methamphetamine having a role in the pathophysiology of schizophrenia, affective psychosis, and drug addiction. It is also said that the magnitude of the reduction in grey matter was much larger in the amygdala than the hippocampus. The exogenous MA psychosis may be rather unique to the amygdala-dominant gray matter volume decrease.
Andres T et al.	Previous users in contrast to current users: Methamphetamine users had larger putamen. Also, the putamen and globus pallidus of previous MA users showed stronger fractional anisotropy (FA) and lower mean diffusivity (MD) compared to current users and controls. This presumably resulted from greater magnetic susceptibility, which was linked to higher iron concentration.

METH through antioxidant mechanisms mediating by GPx (Imam et al., 1999). According to Imam and colleagues (1999), administering selenium prevented the loss of DA in the caudate nucleus and decreased the DA relevant byproducts homovanillic acid and DOPAC caused by METH treatment. Additionally, in SH-SY5Y neuronal cells with selenium treatment, the increased oxidative stress resulting from METH exposure was reversed, which may be attributed to a reduction in GPx levels (Barayuga et al., 2013). Additionally, the administration of selenium prevented the reduction of DA and its metabolites induced by METH treatment in the brain. However, caution should be exercised when supplementing with selenium due to its narrow therapeutic range (Ghosh et al., 2015; Kiełczykowska et al., 2018).

Additionally, antiparkinsonian agents like talipexole and DA replacement therapy may help restore striatal DA levels affected by METH (Kondo et al. 1998; Kish et al. 2017).

Studies have found that METH abusers are at a greater risk of developing PD. Although the precise molecular mechanisms underlying PD remain to be completely elucidated (Mirakabad et al., 2020). The antiparkinsonian agent talipexole was found to have a neuroprotective effect similar to METH-induced neurotoxicity. Treatment with antiparkinsonian medications and therapies targeting the brain regions may have the potential to alleviate the effects of METH on the brain by restoring striatal DA deficiency caused by the drug. Furthermore, DA replacement therapy may also prove effective in this regard (Mizuno et al., 1993; Kondo et al., 1998; Kish et al., 2017).

Therapeutic approach to prevent or reduce excitotoxicity

Excitotoxicity in METH abuse is characterized by increased glutamate release which activates NMDA and other glutamate receptors, leading to calcium influx and activation of cellular activities. Therefore, the potential role of NMDA receptors in METH-induced excitotoxicity has led to the exploration of targeted therapies. Several therapeutic approaches target excitotoxicity:

Melatonin: Melatonin, a pineal hormone with antioxidant properties, has been studied for its ability to protect against oxidative stress and regulate intracellular calcium in the CNS (Suwanjang et al., 2016; Xu et al., 2016). Studies have shown that melatonin can reduce the effects of METH on cell proliferation, NMDA receptor subunits, Ca^{2}+-dependent protein kinase, and prevent memory and learning impairments resulting from METH exposure (Ekthuwapranee et al., 2015; Nopparat et al., 2022).

N-acetylcysteine (NAC): N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, has also shown efficacy in reducing glutamate excitotoxicity, improving mitochondrial dysfunction, and reducing inflammation in models treated with METH (Berk et al., 2008; 2014; Rapado-Castro et al., 2017).

Various NMDA antagonists (Baldwin et al., 1993) and other drugs such as topiramate (Ma et al., 2013), neuropeptide Y (Baptista et al., 2012), and tetrahydropalmatine (THP) (Liu et al., 2021) have demonstrated neuroprotective effects against METH-induced neurotoxicity. Additionally, lithium, valproate, and nicotinamide have been found to improve mitochondrial function and reverse METH-induced energy metabolism dysfunction.

Therapeutic approaches to reduce neuroinflammation

Neuroinflammation plays a significant role in METH-induced neurotoxicity, and strategies to reduce it are vital. So, anti-neuroinflammation therapy is a potential approach to reduce the neurotoxicity caused by METH exposure (Northrop and Yamamoto, 2014).

Minocycline: METH-induced damage is mainly caused by the proinflammatory response initiated by activated microglia. To reduce this response, preventing microglial activation can be a promising strategy (Sekine et al., 2008). Minocycline is a type of tetracycline antibiotic that is highly effective in suppressing microglial activation and the pathways leading to programmed cell death (Yong et al., 2004; Yu et al., 2015). It has both anti-inflammatory and neuroprotective effects and can be used to treat symptoms related to METH exposure (Yong et al., 2004; Yu et al., 2015). According to Zhang and colleagues (2006), their research demonstrated that minocycline considerably reduced the rise of DA outside of cells and DAT immunoreactivity after frequent METH exposure. As a result, they proposed that minocycline could potentially be utilized to deactivate microglia and treat various symptoms linked to METH exposure (Zhang et al., 2006).

Ibudilast, is another compound that can inhibits microglial activation and cytokines responsible for inflammation. Ibudilast is a phosphodiesterase inhibitor that is not selective, so it can increase the level of glial-derived neurotrophic factor in the brain and decrease the activation of microglia and cytokines that cause inflammation (Beardsley et al., 2010; Charntikov et al., 2015).

Modafinil is a cognitive-enhancing medication that may reduce the chance of neuroinflammation by pre-

venting METH-induced microglial activation. Chronic self-administration of METH can cause reactive microgliosis in human METH abusers' brains, and inhibiting microglial activation could be a possible approach to decrease METH-induced neurotoxicity (Raineri et al., 2012).

Innovative approaches targeting METH-induced neurotoxicity

Nanoparticles

When it comes to treating psychostimulant-induced neurotoxicity, standard doses of conventional drugs are not enough to provide adequate neuroprotection. As a result, increasing the dosage or frequency of these drugs is often necessary to obtain significant neuroprotection (Sharma et al., 2009). However, nanoparticle-based therapy is proposed as a more promising than traditional drugs because nanoparticles can easily penetrate the CNS and release therapeutic agents over an longer period of time (Sharma et al., 2014). For example, liposomal delivery of melatonin was found to be more effective than regular melatonin in reducing oxidative burden in METH-induced neurotoxicity in mice (Nguyen et al., 2015). Similarly, delivering standard doses of H-290/51 or cerebrolysin using TiO2 nanowires resulted in significant neuroprotection in rat models (Sharma et al., 2009; 2014). These findings suggest that nanoparticle-based therapy could be a more efficient approach for treating MA-induced neurotoxicity and may also have applications in imaging and detecting METH intoxication (Mao et al., 2017).

Immunotherapy

Passive immunization through the use of monoclonal antibodies is a form of immunotherapy that can be employed to reduce the amount of drugs entering the central nervous system (Ballester et al., 2017). This therapy works by stimulating the production of antibodies that bind with the drugs following systemic absorption. Several studies have been carried out to investigate the efficacy of monoclonal antibodies in treating METH addiction and toxicity, but results have been inconsistent (Baracz and Cornish, 2016). One study performed on rats demonstrated that an anti-METH vaccine led to increased levels of METH in the serum and decreased METH level in the brain, suggesting that the vaccine may offer neuroprotection against neurotoxicity induced by METH. Based on another study, an anti-METH/AMP monoclonal antibody administration showed that it protected rat brains from METH-induced damage (Miller et al., 2013). A human monoclonal antibody to methylphenidate was also shown to significantly reduce the concentration of METH entering the brain (Gentry et al., 2006; White et al., 2014; Hambuchen et al., 2015). Combining monoclonal and polyclonal antibodies were more promising in producing a higher anti-METH antibody response and lowering METH levels inside the brain (Hambuchen et al., 2015). However, there are limitations to this form of therapy, including partial inhibition of the drug's impact, fluctuations in antibody levels, delay in antibody production, and the incapacity to cross the BBB, making it more costly. Despite these limitations, vaccine immunotherapy is gaining attention as a promising approach to address METH addiction. (Chen et al., 2013; Baracz and Cornish, 2016).

Gene therapy

The protein Rho-associated kinase II (ROCK2) has shown promise as a gene therapy target because inhibition of ROCK2 can protect cells in various pathophysiological conditions. In the case of neurotoxicity induced by METH, studies have demonstrated that ROCK2 plays a significant role and could be a potential therapeutic target for treating this condition. For example, a study by Yang et al. (2013) found that inhibiting the expression of ROCK2 in P12 cells with the help of Lipofectamine 2000 and a single interfering ROCK2 molecule inhibited apoptosis caused by METH, improved cell viability, and reversed the morphological alterations induced by METH exposure. Another potential therapeutic target for neurotoxicity induced by METH is the pro-apoptotic gene PAG608, which has been shown to be activated by p53 expression. Based on recent findings, suppressing PAG608 expression could decrease METH-induced toxicity (Yu et al., 1999). The antioxidant enzyme glutathione peroxidase (GPx) is considered a main factor in catalyzing H2O2 into water and alcohol (Sharma et al., 2021a). The protective role of selenium-dependent GPx-1 against METH-induced neurotoxicity has been established, and an adenoviral vector (Ad-GPx-1) containing the *GPx-1* gene was constructed to demonstrate its protective function. (Sharma et al., 2021b). According to the study, GPx-1 plays a protective role against METH-induced neurotoxicity, and an adenoviral vector containing the *GPx-1* gene (Ad-GPx-1) was created to demonstrate this. Overexpression of GPx-1 through Ad-GPx-1 therapy considerably decreased dopaminergic loss caused by METH in mice, and the interaction between NF-κB and GPx-1 is critical for its neuroprotective effects. These findings suggest that Ad-GPx-1 therapy might

be a potential treatment approach for preventing dopaminergic toxicity resulting from METH abuse (Sharma et al., 2021b).

CONCLUSIONS

METH is a highly addictive recreational drug that acts as a potent central nervous system stimulant. Long-term use of METH leads to neuronal damage, along with negative effects on learning, memory, attention, and cognitive function. This drug's ability to readily traverse the blood-brain barrier and interact with various cell surface receptors underscores its potential to induce neurotoxicity through mechanisms such as DA depletion, oxidative stress, astrocyte and microglial activation, axonal transport disruption, autophagy, and apoptosis. Despite significant advancements in understanding the intricacies of METH-induced neurotoxicity, a comprehensive understanding of the complete molecular and cellular pathways remains elusive.

Although the complete molecular/cellular pathways underlying neurotoxicity induced by METH exposure are still unknown, several studies have indicated a correlation between METH abuse and an increased risk of neurotoxic diseases, such as Parkinson's disease and Alzheimer's disease. The likelihood of PD is heightened by METH due to its ability to enhance the expression of a-Syn protein, leading to an increase in oxidative stress. Additionally, METH abuse has been associated with an increased probability of developing neurodegenerative diseases such as AD. According to research, METH may trigger the pathogenesis of AD by altering the neurobiology of the hippocampal region, disrupting the BBB, and inducing genetic and epigenetic modifications. METH addiction creates long-term structural damage to the brain, leading to neuropsychiatric deficits that make addiction difficult to overcome. The chances of relapse after current treatments for METH addiction are high, which is associated with long-term damage to the brain and resulting neurotoxicity. Despite significant progress in understanding the molecular mechanisms of neurotoxicity induced by METH, effective therapeutic strategies have not yet been developed and there is currently no FDA-approved treatment for this condition. Nevertheless, a multitude of ongoing research endeavors are dedicated to the development of innovative therapeutic strategies. While the majority of research has centered on the use of natural compounds to mitigate METH-induced neurotoxicity, researchers are actively exploring targeted therapies such as immunotherapy, nanoparticle-based therapy, and gene therapy. These emerging approaches offer promising avenues for intervention, instilling hope for individuals grappling with METH addiction and the resultant neurological consequences. In the pursuit of effective treatments for METH-induced neurotoxicity, fostering interdisciplinary collaboration, sustaining research efforts, and deepening our understanding of the intricate mechanisms involved are paramount. By harnessing the power of scientific innovation, we can aspire to alleviate the suffering associated with METH abuse and extend a brighter future to those affected by this devastating addiction.

ACKNOWLEDGMENT

We express our gratitude for the funding support provided by the Hearing Disorders Research Center at Loghman Hakim Hospital, affiliated with the Shahid Beheshti University of Medical Sciences in Tehran, Iran.

REFERENCES

Ago M, Ago K, Hara K, Kashimura S, Ogata M (2006) Toxicological and histopathological analysis of a patient who died nine days after a single intravenous dose of methamphetamine: a case report. Legal Med 8: 235–239.

Ajjimaporn A, Phansuwan-Pujito P, Ebadi M, Govitrapong P (2007) Zinc protects SK-N-SH cells from methamphetamine-induced α-synuclein expression. Neurosci Lett 419: 59–63.

Ajjimaporn A, Swinscoe J, Shavali S, Govitrapong P, Ebadi M (2005) Metallothionein provides zinc-mediated protective effects against methamphetamine toxicity in SK-N-SH cells. Brain Res Bull 67: 466–475.

Ambrogini P, Torquato P, Bartolini D, Albertini MC, Lattanzi D, Di Palma M, Marinelli R, Betti M, Minelli A, Cuppini R (2019) Excitotoxicity, neuroinflammation and oxidant stress as molecular bases of epileptogenesis and epilepsy-derived neurodegeneration: The role of vitamin E. Biochim Biophys Acta 1865: 1098–1112.

Andres T, Ernst T, Oishi K, Greenstein D, Nakama H, Chang L (2016) Brain microstructure and impulsivity differ between current and past methamphetamine users. J Neuroimmune Pharmacol 11: 531–541.

Anglin MD, Burke C, Perrochet B, Stamper E, Dawud-Noursi S (2000) History of the methamphetamine problem. J Psychoactive Drugs 32: 137–141.

Azimzadeh Z, Omidvari S, Niknazar S, Vafaei-Nezhad S, Abdollahifar M, Tahmasebinia F, Mahmoudiasl G, Abbaszadeh H, Darabi S (2023) Exploring amygdala structural changes and signaling pathways in postmortem brains: consequences of long-term methamphetamine addiction. Anat Cell Biol. 2023 Nov 22. doi: 10.5115/acb.23.193.

Baldwin H, Colado M, Murray T, De Souza R, Green A (1993) Striatal dopamine release in vivo following neurotoxic doses of methamphetamine and effect of the neuroprotective drugs, chlormethiazole and dizocilpine. Brit J Pharmacol 108: 590.

Ballester J, Valentine G, Sofuoglu M (2017) Pharmacological treatments for methamphetamine addiction: current status and future directions. Expert review clinical Pharmacol 10: 305–314.

Baptista S, Bento AR, Gonçalves J, Bernardino L, Summavielle T, Lobo A, Fontes-Ribeiro C, Malva JO, Agasse F, Silva AP (2012) Neuropeptide Y promotes neurogenesis and protection against methamphetamine-induced toxicity in mouse dentate gyrus-derived neurosphere cultures. Neuropharmacology 62: 2413–2423.

Baracz SJ, Cornish JL (2016) The neurocircuitry involved in oxytocin modulation of methamphetamine addiction. Front Neuroendocrinol 43: 1–18.

Barayuga SM, Pang X, Andres MA, Panee J, Bellinger FP (2013) Methamphetamine decreases levels of glutathione peroxidases 1 and 4 in SH-SY5Y neuronal cells: protective effects of selenium. Neurotoxicology 37, 240–246.

Barr AM, Panenka WJ, MacEwan GW, Thornton AE, Lang DJ, Honer WG, Lecomte T (2006) The need for speed: an update on methamphetamine addiction. J Psychiatry Neurosci 31: 301–313.

Beardsley PM, Shelton KL, Hendrick E, Johnson, KW (2010) The glial cell modulator and phosphodiesterase inhibitor, AV411 (ibudilast), attenuates prime-and stress-induced methamphetamine relapse. Eur J Pharmacol 637: 102–108.

Beauvais G, Atwell K, Jayanthi S, Ladenheim B, Cadet JL (2011) Involvement of dopamine receptors in binge methamphetamine-induced activation of endoplasmic reticulum and mitochondrial stress pathways. PLoS One 6: e28946.

Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, Anderson-Hunt M, Bush AI (2008) N-acetyl cysteine for depressive symptoms in bipolar disorder – a double-blind randomized placebo-controlled trial. Biol Psychiatry 64: 468–475.

Berk M, Dean OM, Cotton SM, Jeavons S, Tanious M, Kohlmann K, Hewitt K, Moss K, Allwang C, Schapkaitz I (2014) The efficacy of adjunctive N-acetylcysteine in major depressive disorder: a double-blind, randomized, placebo-controlled trial. J Clin Psychiatry 75: 5936.

Burton GW, Ingold KU (1989) Vitamin E as an in vitro and in vivo antioxidant. Ann New York Acad Sci 570: 7–22.

Büttner A (2011) Review: The neuropathology of drug abuse. Neuropathol Appl Neurobiol 37: 118–134.

Cadet JL, Krasnova IN, Jayanthi S, Lyles J (2007) Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. Neurotox Res 11: 183–202.

Chamorro Á, Dirnagl U, Urra X, Planas AM (2016) Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation. Lancet Neurol 15: 869–881.

Charntikov S, Pittenger ST, Thapa I, Bastola DR, Bevins RA, Pendyala G (2015) Ibudilast reverses the decrease in the synaptic signaling protein phosphatidylethanolamine-binding protein 1 (PEBP1) produced by chronic methamphetamine intake in rats. Drug Alcohol Depend 152: 15–23.

Chen C, Hsu FC, Li CW, Huang MC (2019) Structural, functional, and neurochemical neuroimaging of methamphetamine-associated psychosis: A systematic review. Psychiatry Res Neuroimaging 292: 23–31.

Chen YH, Wu KL, Tsai HM, Chen CH (2013) Treatment of methamphetamine abuse: An antibody-based immunotherapy approach. J Food Drug Anal 21: S82-S86.

Chiang M, Lombardi D, Du J, Makrum U, Sitthichai R, Harrington A, Shukair N, Zhao M, Fan X (2019) Methamphetamine-associated psychosis: Clinical presentation, biological basis, and treatment options. Hum Psychopharmacol 34: e2710.

Cruickshank CC, Dyer KR (2009) A review of the clinical pharmacology of methamphetamine. Addiction 104: 1085–1099.

Davidson M, Mayer M, Habib A, Rashidi N, Filippone RT, Fraser S, Prakash MD, Sinnayah P, Tangalakis K, Mathai ML (2022) Methamphetamine induces systemic inflammation and anxiety: The role of the gut-immune-brain axis. Int J Mol Sci 23: 11224.

Ekthuwapranee K, Sotthibundhu A, Govitrapong P (2015) Melatonin attenuates methamphetamine-induced inhibition of proliferation of adult rat hippocampal progenitor cells in vitro. J Pineal Res 58: 418–428.

Eyerman DJ, Yamamoto BK (2005) Lobeline attenuates methamphetamine-induced changes in vesicular monoamine transporter 2 immunoreactivity and monoamine depletions in the striatum. J Pharmacol Exp Therapeut 312: 160–169.

Faraone SV (2018) The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehavioral Rev 87: 255–270.

Ferrucci M, Biagioni F, Busceti CL, Vidoni C, Castino R, Isidoro C, Ryskalin L, Frati A, Puglisi-Allegra S, Fornai F (2021) Inhibition of autophagy in vivo extends methamphetamine toxicity to mesencephalic cell bodies. Pharmaceuticals 14: 1003.

Ferrucci M, Ryskalin L, Biagioni F, Gambardella S, Busceti C, Falleni A, Lazzeri G, Fornai F (2017) Methamphetamine increases prion protein and induces dopamine-dependent expression of protease resistant PrPsc. Arch Ital Biol 155: 81–97.

Flack A, Persons AL, Kousik SM, Celeste Napier T, Moszczynska A (2017) Self-administration of methamphetamine alters gut biomarkers of toxicity. Eur J Neurosci 46: 1918–1932.

Fleckenstein AE, Volz TJ, Hanson GR (2009) Psychostimulant-induced alterations in vesicular monoamine transporter-2 function: neurotoxic and therapeutic implications. Neuropharmacology 56: 133–138.

Gandelman M, Dansithong W, Kales SC, Paul S, Maag G, Aoyama E, Zakharov A, Rai G, Dexheimer T, Whitehill BM (2021) The AKT modulator A-443654 reduces α-synuclein expression and normalizes ER stress and autophagy. J Biol Chem 297: 101191.

Gentry WB, Laurenzana EM, Williams DK, West JR, Berg RJ, Terlea T, Owens SM (2006) Safety and efficiency of an anti-(+)-methamphetamine monoclonal antibody in the protection against cardiovascular and central nervous system effects of (+)-methamphetamine in rats. Int Immunopharmacol 6: 968–977.

Ghosh D, McGhie, TK, Fisher D R, Joseph JA (2007) Cytoprotective effects of anthocyanins and other phenolic fractions of Boysenberry and blackcurrant on dopamine and amyloid β-induced oxidative stress in transfected COS-7 cells. J Sci Food Agriculture 87: 2061–2067.

Ghosh P, Bhattacharjee A, Basu A, Singha Roy S, Bhattacharya S (2015) Attenuation of cyclophosphamide-induced pulmonary toxicity in Swiss albino mice by naphthalimide-based organoselenium compound 2-(5-selenocyanatopentyl)-benzo [de] isoquinoline 1,3-dione. Pharmaceutical Biol 53: 524–532.

Gossop MR, Bradley BP, Brewis RK (1982) Amphetamine withdrawal and sleep disturbance. Drug Alcohol Dependence 10: 177–183.

Granado N, Ares-Santos S, Moratalla R (2013) Methamphetamine and Parkinson's disease. Parkinson's Dis 2013: 308052.

Granado N, Ares-Santos S, Oliva I, Martin ED, Colado MI, Moratalla R (2011) Dopamine D2-receptor knockout mice are protected against dopaminergic neurotoxicity induced by methamphetamine or MDMA. Neurobiol Dis 42: 391–403.

Halpin LE, Collins SA, Yamamoto BK (2014) Neurotoxicity of methamphetamine and 3,4-methylenedioxymethamphetamine. Life Sciences 97: 37–44.

Hambuchen MD, Carroll FI, Rüedi-Bettschen D, Hendrickson HP, Hennings LJ, Blough BE, Brieaddy LE, Pidaparthi RR, Owens SM (2015) Combining active immunization with monoclonal antibody therapy to facilitate early initiation of a long-acting anti-methamphetamine antibody response. J Medicinal Chem 58: 4665–4677.

Han J, Zhong CQ, Zhang DW (2011) Programmed necrosis: backup to and competitor with apoptosis in the immune system. Nature Immunol 12: 1143–1149.

Hanada K, Gange R, Siebert E, Hasan T (1991) Protective effects of cadmium chloride against UVB injury in mouse skin and in cultured human cells: a possible role of cadmium-induced metallothionein. Photodermatol Photoimmunol Photomed 8: 111–115.

Harris DS, Boxenbaum H, Everhart ET, Sequeira G, Mendelson JE, Jones RT (2003) The bioavailability of intranasal and smoked methamphetamine. Clin Pharmacol Therapeut 74: 475–486.

Hart B, Prabhu R, Eneman J, Durieux-Lu C, Janssen A (1995) Oxidant resistance of cadmium-adapted human lung fibroblasts. Toxicology 98: 1–13.

He T, Han C, Liu C, Chen J, Yang H, Zheng L, Waddington JL, Zhen X (2022) Dopamine D1 receptors mediate methamphetamine-induced dopa-

minergic damage: involvement of autophagy regulation via the AMPK/FOXO3A pathway. Psychopharmacology 239: 951–964.
Hediger MA (2002) New view at C. Nature Med 8: 445–446.
Hermida-Ameijeiras Á, Méndez-Álvarez E, Sánchez-Iglesias S, Sanmartín-Suárez C, Soto-Otero R (2004) Autoxidation and MAO-mediated metabolism of dopamine as a potential cause of oxidative stress: role of ferrous and ferric ions. Neurochem Int 45: 103–116.
Hetz C (2012) The unfolded protein response: controlling cell fate decisions under ER stress and beyond. Nat Rev Mol Cell Biol 13: 89–102.
Hong R, Matsuyama E, Nur K (1991) Cardiomyopathy associated with the smoking of crystal methamphetamine. JAMA 265: 1152–1154.
Huang E, Huang H, Guan T, Liu C, Qu D, Xu Y, Yang J, Yan L, Xiong Y, Liang T, Wang Q, Chen L (2019) Involvement of C/EBPβ-related signaling pathway in methamphetamine-induced neuronal autophagy and apoptosis. Toxicol Lett 312: 11–21.
Huang MC, Lin SK, Chen CH, Pan CH, Lee CH, Liu HC (2013) Oxidative stress status in recently abstinent methamphetamine abusers. Psychiatry Clin Neuroscis 67: 92–100.
Huang YN, Wang JY, Lee CT, Lin CH, Lai CC, Wang JY (2012) l-Ascorbate attenuates methamphetamine neurotoxicity through enhancing the induction of endogenous heme oxygenase-1. Toxicol Applied Pharmacol 265: 241–252.
Huang YN, Yang LY, Wang JY, Lai CC, Chiu CT, Wang JY (2017) L-Ascorbate protects against methamphetamine-induced neurotoxicity of cortical cells via inhibiting oxidative stress, autophagy, and apoptosis. Molecular Neurobiol 54: 125–136.
Hwang JS, Cha EH, Park B, Ha E, Seo JH (2020) PBN inhibits a detrimental effect of methamphetamine on brain endothelial cells by alleviating the generation of reactive oxygen species. Arch Pharmacal Res 43: 1347–1355.
Imam SZ, Newport GD, Islam F, Slikker Jr W, Ali SF (1999) Selenium, an antioxidant, protects against methamphetamine-induced dopaminergic neurotoxicity. Brain Res 818: 575–578.
Iversen L (2006) Neurotransmitter transporters and their impact on the development of psychopharmacology. Brit J Pharmacol 147: S82–S88.
Jang EY, Yang CH, Hedges DM, Kim SP, Lee JY, Ekins TG, Garcia BT, Kim HY, Nelson AC, Kim NJ (2017) The role of reactive oxygen species in methamphetamine self-administration and dopamine release in the nucleus accumbens. Addiction Biol 22: 1304–1315.
Jayanthi S, Deng X, Noailles PA, Ladenheim B, Cadet JL (2004) Methamphetamine induces neuronal apoptosis via cross-talks between endoplasmic reticulum and mitochondria-dependent death cascades. FASEB J 18: 238–251.
Jordan S, Hampson F (1960) Amphetamine poisoning associated with hyperpyrexia. Brit Med J 2: 844.
Kalechstein AD, Newton TF, Green M (2003) Methamphetamine dependence is associated with neurocognitive impairment in the initial phases of abstinence. J Neuropsychiatry Clin Neuroscis 15: 215–220.
Kalivas PW, Volkow ND (2005) The neural basis of addiction: a pathology of motivation and choice. American J Psychiatry 162: 1403–1413.
Katsumata S, Sato K, Kashiwade H, Yamanami S, Zhou H, Yonemura I, Nakajima H, Hasekura H (1993) Sudden death due presumably to internal use of methamphetamine. Forensic Sci Int 62: 209–215.
Khoramgah MS, Peyvandi AA, Niknazar S, Darabi S, Tahmasebinia F, Peyvandi H, Abbaszadeh HA (2019) Neuroprotective effects of curcumin on the proliferation and viability of neural stem cells against H 2 O 2. J Otorhinolaryngol Facial Plast Surg 5: 1–7.
Khoshsirat S, Abbaszadeh HA, Khoramgah MS, Darabi S, Mansouri V, Ahmady-Roozbahany N, Ahrabi B, Bahrami M, Vafaee S, Tahmasebinia F (2019) Protective effect of photobiomodulation therapy and bone marrow stromal stem cells conditioned media on pheochromocytoma cell line 12 against oxidative stress induced by hydrogen peroxide. J Lasers Med Sci 10: 163.
Khoshsirat S, Khoramgah MS, Mahmoudiasl GR, Rezaei-Tavirani M, Abdollahifar MA, Tahmasebinia F, Darabi S, Niknazar S, Abbaszadeh HA (2020) LC3 and ATG5 overexpression and neuronal cell death in the prefrontal cortex of postmortem chronic methamphetamine users. J Chem Neuroanat 107: 101802.
Kiełczykowska M, Kocot J, Paździor M, Musik I (2018) Selenium-a fascinating antioxidant of protective properties. Adv Clin Exp Med 27: 245–255.
Kim HC, Jhoo WK, Choi DY, Im DH, Shin EJ, Suh JH, Floyd RA, Bing G (1999) Protection of methamphetamine nigrostriatal toxicity by dietary selenium. Brain Res 851: 76–86.
Kish SJ, Boileau I, Callaghan RC, Tong J (2017) Brain dopamine neurone 'damage': methamphetamine users *vs.* Parkinson's disease–a critical assessment of the evidence. Eur J Neurosci 45: 58–66.
Kiyatkin EA, Sharma HS (2009) Acute methamphetamine intoxication: brain hyperthermia, blood–brain barrier, brain edema, and morphological cell abnormalities. Int Rev Neurobiol 88: 65–100.
Kobeissy FH, Shakkour Z, Hayek SE, Mohamed W, Gold MS, Wang KK (2022) Elevation of pro-inflammatory and anti-inflammatory cytokines in rat serum after acute methamphetamine treatment and traumatic brain injury. J Molecular Neurosci 1–11.
Kojima T, Une I, Yashiki M, Noda J, Sakai K, Yamamoto K (1984) A fatal methamphetamine poisoning associated with hyperpyrexia. Forensic Sci Int 24: 87–93.
Kondo T, Shimada H, Hatori K, Sugita Y, Mizuno Y (1998) Talipexole protects dopaminergic neurons from methamphetamine toxicity in C57BL/6N mouse. Neurosci Lett 247: 143–146.
Krasnova IN, Justinova Z, Ladenheim B, Jayanthi S, McCoy MT, Barnes C, Warner JE, Goldberg SR, Cadet JL (2010) Methamphetamine self-administration is associated with persistent biochemical alterations in striatal and cortical dopaminergic terminals in the rat. PloS One 5: e8790.
Kuhn DM, Francescutti-verbeem DM, Thomas DM (2006) Dopamine quinones activate microglia and induce a neurotoxic gene expression profile: relationship to methamphetamine-induced nerve ending damage. Ann New York Acad Sci 1074: 31–41.
Lazzeri G, Biagioni F, Fulceri F, Busceti CL, Scavuzzo MC, Ippolito C, Salvetti A, Lenzi P, Fornai F (2018) mTOR modulates methamphetamine-induced toxicity through cell clearing systems. Oxidative Med Cellular Longevity 2018.
Lee HS, Jeong GS (2021) 6,7,4'-Trihydroxyflavanone mitigates methamphetamine-induced neurotoxicity in SH-SY5y cells via Nrf2/heme oxyganase-1 and PI3K/Akt/mTOR signaling pathways. Molecules 26: 2442.
Lee HS, Kim EN, Jeong GS (2021) Aromadendrin protects neuronal cells from methamphetamine-induced neurotoxicity by regulating endoplasmic reticulum stress and PI3K/Akt/mTOR signaling pathway. Int J Mol Sci 22: 2274.
Li L, Chen S, Wang Y, Yue X, Xu J, Xie W, Qiu P, Liu C, Wang A, Wang H (2018) Role of GSK3β/α-synuclein axis in methamphetamine-induced neurotoxicity in PC12 cells. Toxicol Res 7: 221–234.
Li X, Wang H, Qiu P, Luo H (2008) Proteomic profiling of proteins associated with methamphetamine-induced neurotoxicity in different regions of rat brain. Neurochem Int 52: 256–264.
Liu L, Liu M, Zhao W, Zhao YL, Wang Y (2021) Tetrahydropalmatine regulates BDNF through TrkB/CAM interaction to alleviate the neurotoxicity induced by methamphetamine. ACS Chemical Neurosci 12: 3373–3386.
Logan BK (1996) Methamphetamine and driving impairment. J Forensic Sciences 41: 457–464.
London ED, Berman SM, Voytek B, Simon SL, Mandelkern MA, Monterosso J, Thompson PM, Brody AL, Geaga JA, Hong MS (2005) Cerebral metabolic dysfunction and impaired vigilance in recently abstinent methamphetamine abusers. Biol Psychiatry 58: 770–778.
Ma JZ, Johnson BA, Yu E, Weiss D, McSherry F, Saadvandi J, Iturriaga E, Ait-Daoud N, Rawson RA, Hrymoc M (2013) Fine-grain analysis of the treatment effect of topiramate on methamphetamine addiction with latent variable analysis. Drug Alcohol Dependence 130: 45–51.
Mahmoudiasl G, Abbaszadeh H, Rezaei-Tavirani M, Abdollahifar M, Khoramgah M, Niknazar S, Darabi S, Roozbahany N (2019) Nod-like

receptor protein 3 and nod-like receptor protein 1 inflammasome activation in the hippocampal region of postmortem methamphetamine chronic user. Bratislavske lekarske listy 120: 769–776.
Mao K, Yang Z, Li J, Zhou X, Li X, Hu J (2017) A novel colorimetric biosensor based on non-aggregated Au@ Ag core–shell nanoparticles for methamphetamine and cocaine detection. Talanta 175: 338–346.
Martin WR, Sloan J, Sapira J, Jasinski DR (1971) Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. Clin Pharmacol Therapeut 12: 245–258.
McDonnell-Dowling K, Kelly J (2017) The role of oxidative stress in methamphetamine-induced toxicity and sources of variation in the design of animal studies. Curr Neuropharmacol 15: 300–314.
McFadden LM, Stout KA, Vieira-Brock PL, Allen SC, Nielsen SM, Wilkins DG, Hanson GR, Fleckenstein AE (2012) Methamphetamine self-administration acutely decreases monoaminergic transporter function. Synapse 66: 240–245.
McGregor C, Srisurapanont M, Jittiwutikarn J, Laobhripatr S, Wongtan T, White JM (2005) The nature, time course and severity of methamphetamine withdrawal. Addiction 100: 1320–1329.
McLellan AT, Lewis DC, O'brien CP, Kleber HD (2000) Drug dependence, a chronic medical illness: implications for treatment, insurance, and outcomes evaluation. JAMA 284: 1689–1695.
Mendelson J, Uemura N, Harris D, Nath RP, Fernandez E, Jacob III P, Everhart ET, Jones RT (2006) Human pharmacology of the methamphetamine stereoisomers. Clin Pharmacol Therapeutics 80: 403–420.
Meng Y, Ding J, Li C, Fan H, He Y, Qiu P (2020) Transfer of pathological α-synuclein from neurons to astrocytes via exosomes causes inflammatory responses after METH exposure. Toxicol Lett 331: 188–199.
Miller ML, Moreno AY, Aarde SM, Creehan KM, Vandewater SA, Vaillancourt BD, Wright Jr MJ, Janda KD, Taffe MA (2013) A methamphetamine vaccine attenuates methamphetamine-induced disruptions in thermoregulation and activity in rats. Biol Psychiatry 73: 721–728.
Mirakabad FST, Khoramgah MS, Abdollahifar MA, Tehrani AS, Rezaei-Tavirani, M, Niknazar S, Tahmasebinia F, Mahmoudiasl GR, Khoshsirat S, Abbaszadeh HA (2021) NUPR1-CHOP experssion, autophagosome formation and apoptosis in the postmortem striatum of chronic methamphetamine user. J Chem Neuroanatomy 114: 101942.
Mirakabad FST, Khoramgah MS, Tahmasebinia F, Darabi S, Abdi S, Abbaszadeh HA, Khoshsirat S (2020) The effect of low-level laser therapy and curcumin on the expression of LC3, ATG10 and BAX/BCL2 ratio in PC12 cells induced by 6-hydroxide dopamine. J Lasers Med Sci 11: 299.
Mitoma H, Manto M (2019) Neuroimmune diseases: from cells to the living brain. Springer.
Mizuno Y, Kowa H, Nakanishi T, Yanagisawa N (1993) Preliminary study of B-HT 920, a Novel dopamine agonist, for the treatment of Parkinson's Disease. Drug Investigat 5: 186–192.
Moaveni A, Feyzi YF, Rahideh ST, Arezoomandan R (2022) The relationship between serum brain-derived neurotrophic level and neurocognitive functions in chronic methamphetamine users. Neurosci Lett 772: 136478.
Moratalla R, Khairnar A, Simola N, Granado N, García-Montes JR, Porceddu PF, Tizabi Y, Costa G, Morelli M (2017) Amphetamine-related drugs neurotoxicity in humans and in experimental animals: Main mechanisms. Prog Neurobiol 155: 149–170.
Nguyen XKT, Lee J, Shin EJ, Dang DK, Jeong JH, Nguyen TTL, Nam Y, Cho HJ, Lee JC, Park DH (2015) Liposomal melatonin rescues methamphetamine-elicited mitochondrial burdens, pro-apoptosis, and dopaminergic degeneration through the inhibition PKCδ gene. J Pineal Res 58: 86–106.
Nopparat C, Boontor A, Panmanee J, Govitrapong P (2022) Melatonin attenuates methamphetamine-induced alteration of amyloid β precursor protein cleaving enzyme expressions via melatonin receptor in human neuroblastoma cells. Neurotoxic Res 40: 1086–1095.
Nordahl TE, Salo R, Leamon M (2003) Neuropsychological effects of chronic methamphetamine use on neurotransmitters and cognition: a review. J Neuropsychiatry Clin Neuroscis 15: 317–325.
Northrop NA, Yamamoto BK (2014) Methamphetamine neurotoxicity and neuroinflammatory processes. Neuroinflammat Neurodegenerat 443–462.
Northrop NA, Yamamoto BK (2015) Methamphetamine effects on blood-brain barrier structure and function. Front Neurosci 9: 69.
Orikabe L, Yamasue H, Inoue H, Takayanagi Y, Mozue Y, Sudo Y, Ishii T, Itokawa M, Suzuki M, Kurachi M (2011) Reduced amygdala and hippocampal volumes in patients with methamphetamine psychosis. Schizophrenia Res 132: 183–189.
Oswald I, Thacore VR (1963) Amphetamine and phenmetrazine addiction. Physiological abnormalities in the abstinence syndrome. British Medical J 2: 427–431.
Panenka WJ, Procyshyn RM, Lecomte T, MacEwan GW, Flynn SW, Honer WG, Barr AM (2013) Methamphetamine use: a comprehensive review of molecular, preclinical and clinical findings. Drug Alcohol Dependence 129: 167–179.
Park MJ, Lee SK, Lim MA, Chung HS, Cho SI, Jang CG, Le, SM (2006) Effect of α-tocopherol and deferoxamine on methamphetamine-induced neurotoxicity. Brain Res 1109: 176–182.
Peeters-Scholte C, Braun K, Koster J, Kops N, Blomgren K, Buonocore G, van Buul-Offers S, Hagberg H, Nicolay K, van Bel F (2003) Effects of allopurinol and deferoxamine on reperfusion injury of the brain in newborn piglets after neonatal hypoxia-ischemia. Pediatric Res 54: 516–522.
Perez-Reyes M, White WR, McDonald SA, Hicks RE, Jeffcoat AR, Hill JM, Cook CE (1991) Clinical effects of daily methamphetamine administration. Clin Neuropharmacol 14: 352–358.
Perez Jr JA, Arsura EL, Strategos S (1999) Methamphetamine-related stroke: four cases. J Emergency Med 17: 469–471.
Potashkin JA, Meredith GE (2006) The role of oxidative stress in the dysregulation of gene expression and protein metabolism in neurodegenerative disease. Antioxidants Redox Signal 8: 144–151.
Pourgholaminejad A, Tahmasebinia F (2019) The role of Th17 cells in immunopathogenesis of neuroinflammatory disorders. Neuroimmune Diseases: From Cells to the Living Brain, 83–107.
Prakash MD, Tangalakis K, Antonipillai J, Stojanovska L, Nurgali K, Apostolopoulos V (2017) Methamphetamine: effects on the brain, gut and immune system. Pharmacological Res 120: 60–67.
Raineri M, Gonzalez B, Goitia B, Garcia-Rill E, Krasnova IN, Cadet JL, Urbano FJ, Bisagno V (2012) Modafinil abrogates methamphetamine-induced neuroinflammation and apoptotic effects in the mouse striatum.
Ramkissoon A, Wells PG (2015) Methamphetamine oxidative stress, neurotoxicity, and functional deficits are modulated by nuclear factor-E2-related factor 2. Free Rad Biol Med 89: 358–368.
Rapado-Castro M, Dodd S, Bush A, Malhi G, Skvarc D, On Z, Berk M, Dean O (2017) Cognitive effects of adjunctive N-acetyl cysteine in psychosis. Psychol Med 47: 866–876.
Rashidi R, Moallem SA, Moshiri M, Hadizadeh F, Etemad L (2021) Protective effect of cinnamaldehyde on METH-induced neurotoxicity in PC12 cells via inhibition of apoptotic response and oxidative stress. Iranian J Pharmaceutical Res 20: 135.
Ricaurte GA, Martello AL, Katz JL, Martello MB (1992) Lasting effects of (+-)-3, 4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. J Pharmacol Exp Therapeutics 261: 616–622.
Rice ME (2000) Ascorbate regulation and its neuroprotective role in the brain. Trends Neuroscis 23: 209–216.
Roohbakhsh A, Moshiri M, Kakhki AS, Iranshahy M, Amin F, Etemad, L (2021) Thymoquinone abrogates methamphetamine-induced striatal neurotoxicity and hyperlocomotor activity in mice. Res Pharmaceutical Sciences 16: 391.

Rumpf JJ, Albers J, Fricke C, Mueller W, Classen J (2017) Structural abnormality of substantia nigra induced by methamphetamine abuse. Movement Disorders 32: 1784–1788.

Salas-González C, Gudayol-Ferre E, Villuendas-González ER, Padros--Blázquez F, González-Ramírez V, Murillo-Servín AK (2022) Memory and Executive function deficits in abstinent patients with methamphetamine use disorder. Int J Mental Health Addiction 1–14.

Schep LJ, Slaughter RJ, Beasley DMG (2010) The clinical toxicology of metamfetamine. Clinical Toxicol 48: 675–694.

Schwartz K, Weizman A, Rehavi M (2006) The effect of psychostimulants on [3 H] dopamine uptake and release in rat brain synaptic vesicles. J Neural Transmission 113: 1347–1352.

Sekine Y, Ouchi Y, Sugihara G, Takei N, Yoshikawa E, Nakamura K, Iwata Y, Tsuchiya KJ, Suda S, Suzuki K (2008) Methamphetamine causes microglial activation in the brains of human abusers. J Neurosci 28: 5756–5761.

Seo MJ, Song SH, Kim S, Jang WJ, Jeong CH, Lee S (2020) Characteristics of Korean patients with methamphetamine use disorder based on the quantitative analysis of methamphetamine and amphetamine in hair. Arch Pharmacal Res 43: 798–807.

Sharma G, Shin EJ, Sharma N, Nah SY, Mai HN, Nguyen BT, Jeong JH, Lei XG, Kim HC (2021a) Glutathione peroxidase-1 and neuromodulation: Novel potentials of an old enzyme. Food Chem Toxicol 148: 111945.

Sharma HS, Ali S, Tian ZR, Patnaik R, Patnaik S, Lek P, Sharma A, Lundstedt T (2009) Nano-drug delivery and neuroprotection in spinal cord injury. J Nanosci Nanotechnol 9: 5014–5037.

Sharma HS, Ali SF, Tian ZR, Hussain SM, Schlager JJ, Sjöquist PO, Sharma A, Muresanu DF (2009) Chronic treatment with nanoparticles exacerbate hyperthermia induced blood-brain barrier breakdown, cognitive dysfunction and brain pathology in the rat. Neuroprotective effects of nanowired-antioxidant compound H-290/51. J Nanosci Nanotechnol 9: 5073–5090.

Sharma HS, Menon P, Lafuente JV, Muresanu DF, Tian ZR, Patnaik R, Sharma A (2014) Development of in vivo drug-induced neurotoxicity models. Expert Opin Drug Metab Toxicol 10: 1637–1661.

Sharma HS, Patnaik R, Sharma A, Sjöquist PO, Lafuente JV (2009) Silicon dioxide nanoparticles (SiO2, 40–50 nm) exacerbate pathophysiology of traumatic spinal cord injury and deteriorate functional outcome in the rat. An experimental study using pharmacological and morphological approaches. J Nanosci Nanotech 9: 4970–4980.

Sharma N, Shin EJ, Pham DT, Sharma G, Dang DK, Duong CX, Kang SW, Nah SY, Jang CG, Lei XG (2021b) GPx-1-encoded adenoviral vector attenuates dopaminergic impairments induced by methamphetamine in GPx-1 knockout mice through modulation of NF-κB transcription factor. Food Chem Toxicol 154: 112313.

Shin EJ, Tran HQ, Nguyen PT, Jeong JH, Nah SY, Jang CG, Nabeshima T, Kim HC (2018) Role of mitochondria in methamphetamine-induced dopaminergic neurotoxicity: involvement in oxidative stress, neuroinflammation, and pro-apoptosis—a review. Neurochem Res 43: 66–78.

Shokrzadeh M, Zamani E, Mehrzad M, Norian Y, Shaki F (2015) Protective effects of propofol against methamphetamine-induced neurotoxicity. Toxic Int 22: 92.

Shrestha P, Katila N, Lee S, Seo JH, Jeong JH, Yook S (2022) Methamphetamine induced neurotoxic diseases, molecular mechanism, and current treatment strategies. Biomed Pharmacotherapy 154: 113591.

Smith JA, Das A, Ray SK, Banik NL (2012) Role of pro-inflammatory cytokines released from microglia in neurodegenerative diseases. Brain Res Bull 87: 10–20.

Srisurapanont M, Jarusuraisin N, Jittiwutikan J (1999) Amphetamine withdrawal: I. Reliability, validity and factor structure of a measure. Australian New Zealand J Psychiatry 33: 89–93.

Stokes AH, Hastings TG, Vrana KE (1999) Cytotoxic and genotoxic potential of dopamine. J Neurosci Res 55: 659–665.

Su H, Bai J, Fan Y, Sun T, Du Y, Li Y, Wei Z, Chen T, Guo X, Yun K (2022) The distinct roles of various neurotransmitters in modulating methamphetamine-induced conditioned place preference in relevant brain regions in mice. Neuroreport 33: 101.

Sulzer D, Sonders MS, Poulsen NW, Galli A (2005) Mechanisms of neurotransmitter release by amphetamines: a review. Progress Neurobiol 75: 406–433.

Sulzer D, Zecca L (1999) Intraneuronal dopamine-quinone synthesis: a review. Neurotoxicity Res 1: 181–195.

Sun L, Wang H, Wang Z, He S, Chen S, Liao D, Wang L, Yan J, Liu W, Lei X (2012) Mixed lineage kinase domain-like protein mediates necrosis signaling downstream of RIP3 kinase. Cell 148: 213–227.

Suwanjang W, Abramov AY, Charngkaew K, Govitrapong P, Chetsawang B (2016) Melatonin prevents cytosolic calcium overload, mitochondrial damage and cell death due to toxically high doses of dexamethasone-induced oxidative stress in human neuroblastoma SH-SY5Y cells. Neurochem Int 97: 34–41.

Szegezdi E, Logue SE, Gorman AM, Samali A (2006) Mediators of endoplasmic reticulum stress-induced apoptosis. EMBO Rep 7: 880–885.

Tahmasebinia F, Emadi S (2016) Effects of clioquinol on the aggregation of beta-amyloid peptides in the presence and absence of metal ions and astrocyte-mediated inflammation. Eur J Immunol

Tahmasebinia F, Pourgholaminejad A (2017) The role of Th17 cells in auto-inflammatory neurological disorders. Progress Neuro-PsychoPharmacol Biol Psychiatry 79: 408–416.

Tata DA, Yamamoto BK (2007) Interactions between methamphetamine and environmental stress: role of oxidative stress, glutamate and mitochondrial dysfunction. Addiction 102: 49–60.

Tatsuta T, Kitanaka N, Kitanaka J, Morita Y, Takemura M (2005) Effects of monoamine oxidase inhibitors on methamphetamine-induced stereotypy in mice and rats. Neurochem Res 30: 1377–1385.

Thanos PK, Kim R, Delis F, Ananth M, Chachati G, Rocco MJ, Masad I, Muniz JA, Grant SC, Gold MS (2016) Chronic methamphetamine effects on brain structure and function in rats. PloS One 11: e0155457.

Thornalley PJ, Vašák M (1985) Possible role for metallothionein in protection against radiation-induced oxidative stress. Kinetics and mechanism of its reaction with superoxide and hydroxyl radicals. Biochim Biophys Acta 827: 36–44.

Thrash B, Thiruchelvan K, Ahuja M, Suppiramaniam V, Dhanasekaran M (2009) Methamphetamine-induced neurotoxicity: the road to Parkinson's disease. Pharmacological Reports 61: 966–977.

Tobias MC, O'Neill J, Hudkins M, Bartzokis G, Dean AC, London ED (2010) White-matter abnormalities in brain during early abstinence from methamphetamine abuse. Psychopharmacology 209: 13–24.

Tseng EE, Brock MV, Lange MS, Troncoso JC, Blue ME, Lowenstein CJ, Johnston MV, Baumgartner WA (2010) Glutamate excitotoxicity mediates neuronal apoptosis after hypothermic circulatory arrest. Ann Thorac Surg 89: 440–445.

Valian N, Abolhassan A, Dargahi L (2017) Escalating methamphetamine regimen induces compensatory mechanisms, mitochondrial biogenesis, and GDNF expression, in substantia nigra. J Cellular Biochem 118: 1369–1378.

Valian N, Heravi M, Ahmadiani A, Dargahi L (2019) Effect of methamphetamine on rat primary midbrain cells; mitochondrial biogenesis as a compensatory response. Neuroscience 406: 278–289.

Volti GL, Murabito P, Attaguile G, Rodella LF, Astuto M, Di Giacomo C, Gullo A (2006) Antioxidant properties of propofol when oxidative stress sleeps with patients. Excli J 5: 25–32.

Waksman J, Taylor Jr RN, Bodor GS, Daly FF, Jolliff HA, Dart RC (2001) Acute myocardial infarction associated with amphetamine use. Mayo clinic proceedings,

Wang KH, Penmatsa A, Gouaux E (2015) Neurotransmitter and psychostimulant recognition by the dopamine transporter. Nature 521: 322–327.

Wang N, Tan HY, Li S, Xu Y, Guo W, Feng Y (2017a) Supplementation of micronutrient selenium in metabolic diseases: its role as an antioxidant. Oxidative Med Cellular Longevity 2017.

Wang Y, Xu WN, Wu XF, Zhu LN, Qiao HH, Chen L, Liu C, Qiu PM (2017b) Snitrosylating protein disulphide isomerase mediates increased expression of α synuclein caused by methamphetamine in mouse brain. Nan Fang yi ke da xue xue bao J Southern Medical University 37: 1386–1390.

Watson R, Hartmann E, Schildkraut JJ (1972) Amphetamine withdrawal: affective state, sleep patterns, and MHPG excretion. Am J Psychiatry 129: 263–269.

Wells PG, McCallum GP, Chen CS, Henderson JT, Lee CJ, Perstin J, Preston TJ, Wiley MJ, Wong AW (2009) Oxidative stress in developmental origins of disease: teratogenesis, neurodevelopmental deficits, and cancer. Toxicological Sci 108: 4–18.

White SJ, Hendrickson HP, Atchley WT, Laurenzana EM, Gentry WB, Williams DK, Owens SM (2014) Treatment with a monoclonal antibody against methamphetamine and amphetamine reduces maternal and fetal rat brain concentrations in late pregnancy. Drug Metab Disposition 42: 1285–1291.

Wijetunga M, Seto T, Lindsay J, Schatz I (2003) Crystal methamphetamine-associated cardiomyopathy: tip of the iceberg? J Toxicol 41: 981–986.

Wu PH, Shen YC, Wang YH, Chi CW, Yen JC (2006) Baicalein attenuates methamphetamine-induced loss of dopamine transporter in mouse striatum. Toxicology 226: 238–245.

Wu XF, Wang AF, Chen L, Huang EP, Xie WB, Liu C, Huang WY, Chen CX, Qiu PM, Wang HJ (2014) S-nitrosylating protein disulphide isomerase mediates α-synuclein aggregation caused by methamphetamine exposure in PC12 cells. Toxicol Lett 230: 19–27.

Xu S, Pi H, Zhang L, Zhang N, Li Y, Zhang H, Tang J, Li H, Feng M, Deng P (2016) Melatonin prevents abnormal mitochondrial dynamics resulting from the neurotoxicity of cadmium by blocking calcium-dependent translocation of Drp1 to the mitochondria. J Pineal Res 60: 291–302.

Yamamoto BK, Moszczynska A, Gudelsky GA (2010) Amphetamine toxicities: classical and emerging mechanisms. Annals New York Academy Sciences 1187: 101–121.

Yan J, Liu J, Ren Q, Wang Q (2023) Molecular mechanisms of substance abuse and its neurotoxicity (Vol. 16648714) Frontiers Media SA.

Yang X, Liu Y, Liu C, Xie W, Huang E, Huang W, Wang J, Chen L, Wang H, Qiu P (2013) Inhibition of ROCK2 expression protects against methamphetamine-induced neurotoxicity in PC12 cells. Brain Res 1533: 16–25.

Yang X, Wang Y, Li Q, Zhong Y, Chen L, Du Y, He J, Liao L, Xiong K, Yi Cx (2018) The main molecular mechanisms underlying methamphetamine-induced neurotoxicity and implications for pharmacological treatment. Front Molecular Neurosci 11: 186.

Yong VW, Wells J, Giuliani F, Casha S, Power C, Metz LM (2004) The promise of minocycline in neurology. Lancet Neurol 3: 744–751.

Yu S, Zhu L, Shen Q, Bai X, Di X (2015) Recent advances in methamphetamine neurotoxicity mechanisms and its molecular pathophysiology. Behavioural Neurol 2015.

Yu Z, Luo H, Fu W, Mattson MP (1999) The endoplasmic reticulum stress-responsive protein GRP78 protects neurons against excitotoxicity and apoptosis: suppression of oxidative stress and stabilization of calcium homeostasis. Exp Neurol 155: 302–314.

Zalis EG, Parmley LF (1963) Fatal amphetamine poisoning. Arch Intern Med 112: 822–826.

Zeng R, Pu Hy, Zhang Xy, Yao Ml, Sun Q (2023) Methamphetamine: Mechanism of action and chinese herbal medicine treatment for its addiction. Chin J Integr Med 29: 665–672.

Zhang L, Kitaichi K, Fujimoto Y, Nakayama H, Shimizu E, Iyo M, Hashimoto K (2006) Protective effects of minocycline on behavioral changes and neurotoxicity in mice after administration of methamphetamine. Prog Neuropsychopharmacol Biol Psychiatry 30: 1381–1393.

Zhao X, Lu J, Chen X, Gao Z, Zhang C, Chen C, Qiao D, Wang H (2021) Methamphetamine exposure induces neuronal programmed necrosis by activating the receptor-interacting protein kinase 3-related signalling pathway. FASEB J 35: e21561.

Zhu J, Xu W, Angulo J (2006) Methamphetamine-induced cell death: selective vulnerability in neuronal subpopulations of the striatum in mice. Neuroscience 140: 607–622.