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PJBS

ISSN 1028-8880

Pakistan Journal of Biological Sciences

ANSInet
Asian Network for Scientific Information
308 Lasani Town, Sargodha Road, Faisalabad - Pakistan

OPEN ACCESS Pakistan Journal of Biological Sciences

ISSN 1028-8880
DOI: 10.3923/pjbs.2024.613.625

Review Article
Methamphetamine Neurotoxicity: Neurotoxic Effects, Mechanism of Toxicity, Molecular Mechanisms and Treatment Strategies

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Abstract

Methamphetamine (METH) is a highly addictive and dangerous drug that mainly affects neurotransmitters in the brain and leads to feelings of alertness and euphoria. The METH use can lead to addiction, which has become a worldwide problem, resulting in a slew of public health and safety issues. Recent studies showed that chronic METH use can lead to neurotoxicity, neuro-inflammation and oxidative stress which can lead to neuronal injury. This review discussed the history of METH use, the link between METH use and neurotoxicity, the molecular mechanism and the different treatment strategies. This study attempted to discuss some of the drug's principal impacts and gave proof in favor of a few of the cellular and molecular causes of METH neurotoxicity. In addition, it demonstrates the most recent treatment strategies involving mitigating METH-induced neurotoxicity. However, future studies are needed to better understand the mechanism by which METH use induced neurotoxicity.

Key words: Methamphetamine, neurotoxicity, neuroinflammation, excitotoxicity, treatment, oxidative stress

Citation: Al-Awthan, Y.S., M.K. AL-Homidi, A.R. Albalawi and K.I. Almousi, 2024. Methamphetamine neurotoxicity: Neurotoxic effects, mechanism of toxicity, molecular mechanisms and treatment strategies. Pak. J. Biol. Sci., 27: 613-625.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Methamphetamine (METH) is a highly addictive and dangerous drug that mainly affects neurotransmitters in the brain and leads to feelings of alertness and euphoria[1]. The METH is classified as a Schedule II drug under the Controlled Substances Act due to its high potential for abuse and addiction[2]. The METH was first synthesized in Japan in 1919 and was used during World War II to keep soldiers awake and alert. The METH has both short- and long-term impacts on the body. In the short term, users report an intense rush of euphoria, decreased appetite and increased energy, blood pressure and heart rate. However, these effects are short-lived and are followed by a crash that can last for days[3,4]. The long-term use of METH can lead to severe physical and mental health problems. Chronic use can cause damage to the brain's dopamine (DA) system, which can result in symptoms similar to Parkinson's disease. Recently, Vandenbark *et al.*[5] showed that chronic METH exposure can lead to long-lasting neuro-inflammation and neuronal injury but the exact mechanism is still unclear. It can also cause tooth decay, skin sores, weight loss, insomnia, paranoia, aggression, hallucinations and delusions. High-dose or chronic METH exposure causes excessive dopaminergic activity that can lead to the development of psychotic features[6]. Methamphetamine stimulates the release of monoamine neurotransmitters, including norepinephrine, DA and serotonin, which has an impact on the Central Nervous System (CNS). Users often require professional treatment to overcome their addiction. Treatment options include behavioral therapy, medication-assisted treatment, support groups such as Narcotics Anonymous or a combination of these approaches. However, a drug called levo-tetrahydropalmatine has recently been approved to be an important therapeutic drug for METH addiction and neurotoxicity[7]. In addition, there are new trends to develop anti-METH vaccines[8]. The addictive nature of METH and its effects on humans need a way forward to overcome it. To include articles in this review, a broad literature search was conducted in January, 2024 and repeated in March and April of the same year within the PubMed databases. The search terms "methamphetamine", "METH" and field-specific terms such as "pharmacokinetics, excitotoxicity, oxidative stress and treatment" were used. Finally, the research articles for the last 10 years ago have been narrowly distilled to provide an up-to-date summary of the current knowledge.

Chemical structure and names: The METH belongs to the amphetamine class because the amino group of (S)-amphetamine has a methyl substituent (Fig. 1). The full systematic name, according to IUPAC, is (2S)-N-methyl-1-phenylpropan-2-amine, which had the molecular formula $C_{10}H_{15}N$ and a molecular mass of 149.233 g/mol. The asymmetric carbon atom produces two enantiomers. Previously known as the [-]- or l-stereoisomer and the [+]- or d-stereoisomer, these two forms are now known as the R- and S-stereoisomers. The other names of METH include "crank", "snappy", "crystal", "glass" (Philippines), "tik" (South Africa), "yaa baa" (Thailand) and "shabu" (Arabia)[9].

Prevalence and epidemiology: The METH belongs to the amphetamine-type stimulant family, which also includes amphetamine, methylene deoxy methamphetamine and other amphetamines[10]. The METH was first manufactured in the early 1900s and was unregulated as a nasal decongestant, alertness enhancer and weight loss aid. It was widely utilized by several armed forces throughout World War II, the Korean War and the Vietnam War. In the 1950s, Japan had a high prevalence of abuse, followed by the United States in the 1960s. The term "crank" alludes to biker gangs' transportation of METH hidden in the crankcase of their motorcycles. From the 1970s through the 1990s, the Southwestern and West Coast States (including Hawaii) had the highest rate of abuse. Over the last decade, all regions of the United States have seen a considerable increase in the number of people taking drugs and visiting emergency rooms. According to a recent report, 27 million people used METH and related amphetamine-type stimulants in 2019, accounting for 0.5% of the global adult population. As per UNODC (2020), the rate of METH use in the population of North America, Australia and Asia was 2.3, 1.3 and 0.5%, respectively[11].

It is regarded as the second most prevalent drug after cannabis[12]. Adolescent abuse has recently been regarded as rampant. When reporting their drug past, METH addicts are often dishonest and distrustful of medical personnel[13]. According to a recent report of Al-Asmari[14], the number of METH-related deaths in Jeddah, Saudi Arabia, increased by more than 500%. Most of the cases were violent, unintentional and suicides.

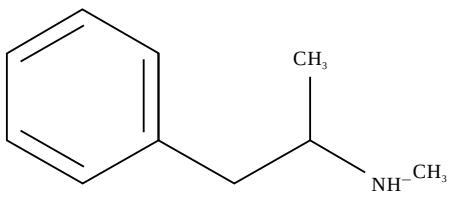

Fig. 1: Chemical structure of METH

Data from the National Survey on Drug Use and Health (NSDUH) for 2021 show that 6.0% of the population or about 16.8 million persons aged 12 or older, had used methamphetamine at least once in their lifetime (2021 DT 1.1). According to recent reports 36 million people are predicted to have used amphetamines in 2021[15].

Compared to non-users, young people who used methamphetamine had a higher likelihood of having conduct disorder. An estimated 95,000 children in Australia between the ages of 4 and 17 were reported to have a conduct disorder in 2022[16]. In addition, extreme methamphetamine use was linked to a sudden death in a recent case report by Chansaengpetch *et al.*[17].

A major problem in the Middle East and North Africa (MENA) region is methamphetamine usage. For example, methamphetamine was found to be the most commonly abused illicit drug in Kuwait, where amphetamines were found to be collected in greater amounts than other psychoactive substances[18].

There is no one clear explanation for the seemingly lower rates of METH abuse in the MENA region when compared to the rest of the world due to the complexity of the data. Here are a few potential motivators:

- Because of religious and cultural reasons, METH usage can be severely stigmatized in MENA nations. Because of this stigma, fewer people may ask for assistance or confess to using, which could result in underreported cases
- In the MENA region, strict drug prohibitions and severe punishments may discourage some people from using METH. But this can also drive the drug trade underground, which complicates the process of gathering statistics
- Some MENA nations may have less developed public health data collection and reporting systems than other regions. This may result in incomplete or erroneous data regarding drug use

Methamphetamine abuse is still a major issue in the world, having a terrible impact on both individuals and communities. It is a major cause of violent crime, the spread of infectious diseases and societal evils including child neglect and unemployment. Knowing its effects aids in the development of treatment and preventative plans.

MECHANISM OF TOXICITY

Methamphetamine-induced neurotoxicity: As a lipophilic substance, METH may easily cross the blood-brain barrier and enter the brain, where it predominantly increases the release of central and peripheral neurotransmitters such as DA, serotonin, norepinephrine and glutamate (Glu)[19]. The effects of METH on the Central Nervous System (CNS) have been extensively studied and it has long been known that METH promotes DA neurotransmission by regulating the activity of DA transporters[20]. Additionally, it inhibits monoamine oxidase, which lowers monoamine metabolism[21]. The METH causes blocking the transport of endogenous neurotransmitters, inhibiting synaptic reuptake and decreasing the expression of transporters at the cell surface[22]. Since Glu is a key excitatory neurotransmitter in the brain, it has been suggested that Glu contributes significantly to the excitotoxicity brought on by METH[23]. At low or moderate dosages, METH induces euphoria, faster heart rate, reduced weariness, increased temperature, higher blood pressure, pupil dilation, reduced appetite, behavioral disinhibition and increased alertness and energy. While higher doses result in hypertension, paranoia, confused speech, nervousness and sweating[20]. Acute or chronic consumption of METH can lead to several neurotoxic effects due to oxidative stress which happens mainly due to the release of DA[21]. According to Kohno *et al.*[24], METH is also known to cause excessive release of DA and Glu, which damages the presynaptic membrane by causing oxidative stress and the production of peroxide radicals which lead eventually to brain degeneration directly or indirectly. According to Chao *et al.*[25], Sig-1Rs can activate microglia in response to METH stimulation by generating reactive oxygen species (ROS) and activating the PI3K/Akt and mitogen-activated protein kinase pathways. A recent study looked at the ability of calcitriol to protect against METH-induced reductions in striatal serotonin (5-HT) release and content in male rats. These findings imply that calcitriol can give significant protection against the 5-HT depleting effects of neurotoxic METH dosages[26].

Methamphetamine-induced oxidative stress: The oxidative stress is caused by an imbalance between a biological system's ability to detoxify these reactive byproducts and the production and accumulation of ROS in cells and tissues disrupting oxidation-reduction (redox) reactions[27]. In normal and pathological situations, ROS are primarily created by mitochondria through the generation of free radicals, like superoxide radicals, hydrogen peroxide, hydroxyl radicals and singlet oxygen radicals inside endothelium and inflammatory cells[28]. The neurotoxic effects of METH are, in part, mediated by oxidative stress, which plays a crucial role in cellular toxicity. When METH enters neurons, it displaces DA from vesicles, resulting in elevated intracellular and synaptic DA levels which leads to the auto-oxidation and increased

metabolism of DA, producing ROS such as hydrogen peroxide as by-products which are responsible for oxidative damage[19]. Additionally, DA can be further oxidized into quinones and semiquinones, which generate nitrogen and superoxide radicals that contribute to oxidative stress[29]. Others have demonstrated that rats exposed to METH had higher levels of malondialdehyde, a byproduct of lipid peroxidation by ROS, in certain brain areas leading to the destruction of dopaminergic neurons[30]. In addition, oxidative stress caused by METH leads to the oxidation of cellular macromolecules including proteins, lipids and DNA[31]. Protein oxidation results in the formation of disulfuric bridges and misfolded proteins while lipid oxidation produces highly reactive 4-hydroxynonenal, which further contributes to cellular damage[31]. Also, epigenetic changes in DNA methylation levels were stimulated by METH indicating nuclear damage and neurological disorders[31,32]. The METH-induced oxidative stress also disturbs the redox balance and inhibits mitochondrial complex II, leading to elevated oxidative stress and increased mitochondrial damage. This process contributes to neurodegeneration and the release of neuro-melanin, which exacerbates neuro-inflammation and the neurodegenerative process[31,33]. Furthermore, METH increases nitric oxide production through nitric oxide synthase activation leading to the upregulation of alpha-synuclein expression which enhances cellular oxidative stress and contributes to neuronal damage[34].

Methamphetamine-induced neuro-inflammation: An inflammatory response in the brain or spinal cord is referred to as neuro-inflammation. The synthesis of cytokines, chemokines, ROS and secondary messengers mediates this inflammation[35]. The METH has been demonstrated to cause inflammatory reactions in regions that have damaged DA and Glu[24,36]. The molecular mechanism of METH-induced neuro-inflammation involves the activation of microglia. The exact mechanism of microglial activation is still unknown, but it is believed that dopaquinones (DAQs), metabolites of DA, play a significant role in gene expression of microglial cells[37]. Activated microglia release various neurotoxic molecules, including pro-inflammatory cytokines, proteinases and ROS, which contribute to neuro-inflammation[38]. The secretion of excite-toxic Glu by activated microglia also plays a role in mediating excite-toxicity and neuro-inflammation, ultimately leading to neurodegeneration[39]. Repeated administration of METH activates Glu receptors and promotes Glu release which leads to activation of transcription factor NF-B. The NF-B then triggers inflammatory mediators, such as Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-1β (IL-1β) and Interleukin-6 (IL-6). These cytokines can further enhance extracellular Glu levels by inhibiting uptake and increasing release from microglial cells, creating a feed-forward loop that amplifies neurotoxicity[40]. The effects of METH include the neuronal release of Damage-Associated Molecular Patterns (DAMPs), which can trigger neuro-inflammatory processes (Fig. 2). Moreover, the activation of microglia by METH is reported to be linked with Toll-Like Receptor 4 (TLR4), which is involved in the immune response to pathogens[41]. Billod *et al.*[42] reported that the TLR4 receptor can activate Myd88 pathways. As a result, Tumor Necrosis Factor Receptor-Related Factor 6 (TRAF6) and Interleukin-1 Receptor Related Kinase (IRAK) is activated, which results in the activation of Nuclear Factor-κB (NF-κB)[43]. According to White *et al.*[44], Sig-1Rs can activate microglia in response to METH stimulation by generating ROS and activating the PI3K/Akt and MAPK pathways. The NF-B signaling system and the MAPK signaling pathway share a strong relationship[45] and both are crucial for the activation of inflammatory cytokines by METH[46]. Kobeissy *et al.*[47] have demonstrated the increase of these cytokines following METH intoxication, highlighting their significant role in mediating brain injury associated with METH-induced neurotoxicity.

Methamphetamine-induced excitotoxicity: The excitotoxicity is defined as cell death caused by excitatory amino acid toxicity. Neuronal excitotoxicity usually refers to the destruction and death of neurons caused by prolonged Glu exposure. It follows an excessive ion influx into the cell which activates enzymes that destroy proteins, membranes and nucleic acids[48]. In addition, Glu terminals repeatedly undergo depolarization-repolarization cycles. As a result, the degeneration of post-synaptic neurons occurs through the activation of NMDA (N-Methyl-D-Aspartate) ionotropic receptors which play a significant role in METH-induced excitotoxicity[49]. The molecular mechanisms underlying METH-induced excitotoxicity involve excessive release and accumulation of the neurotransmitter Glu, particularly the ionic form L-Glu, from both neuron and glial cells to the extracellular space[50] which contribute to excitotoxicity[10]. Another study has shown that high doses of METH stimulate the production of ER stress-related genes, including ATF4, CHOP and caspase-12 (Fig. 3). Furthermore, METH-induced ER stress has been linked to dopaminergic toxicity through the activation of DA receptor D. The apoptosis or programmed cell death, is induced by ER stress through the activation of death receptors and the involvement of mitochondrial-dependent apoptosis pathways[51]. Also, METH indirectly increases proteolysis of the cytoskeletal protein spectrin which contributes to DA terminal degradation in the striatum[52].

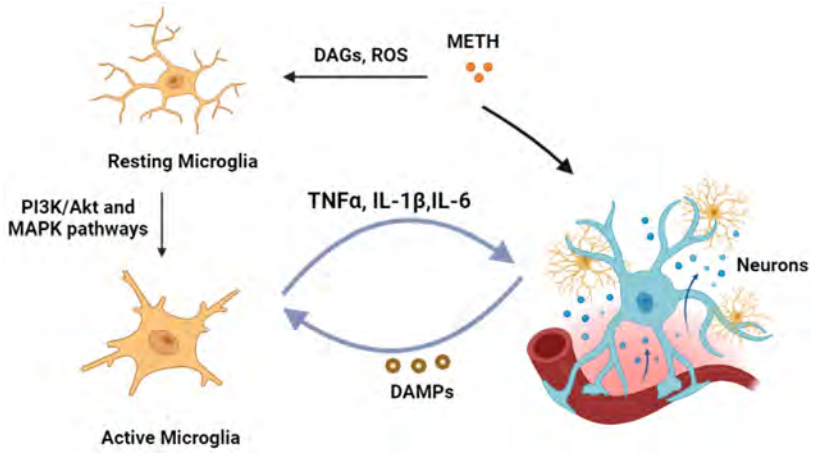

Fig. 2: Illustrating diagram of METH-induced neuro-inflammation
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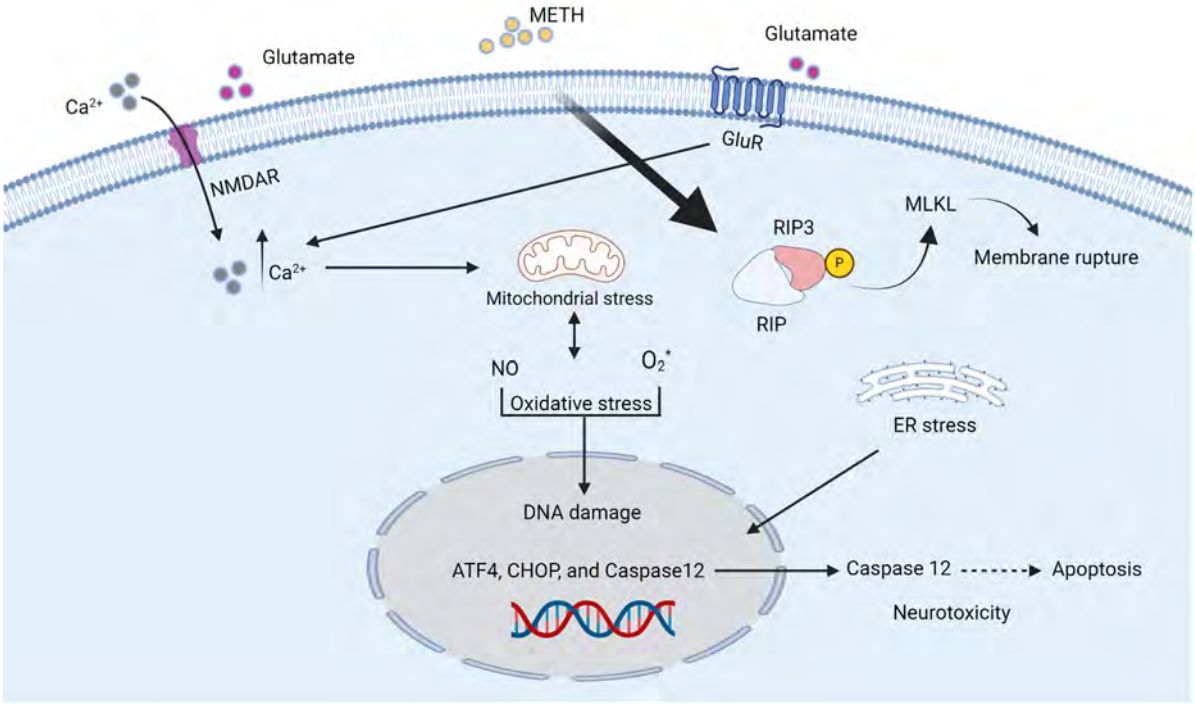

Fig. 3: Illustrating diagram of oxidative stress, mitochondrial stress, ER stress, membrane rupture and apoptosis involved in METH-induced neurotoxicity
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Methamphetamine-induced mitochondrial toxicity: Mitochondrial toxicity is a phenomenon that arises as a side effect of some medications in which the mitochondria of a body's cells become damaged or decrease considerably in number[53]. In METH-induced mitochondrial toxicity, the lipophilic nature of METH makes it easy to enter cell membranes, including mitochondria. Inside the mitochondria, METH impairs their function and leads to neuropathological effects in the brain[50]. According to Lenzi *et al.*[54], METH-induced mitochondrial changes are associated with a decrease in fission/mitophagy proteins Fis1 and DRP1 and an increase in Pink1 and Parkin *in situ*, indicating that mitochondria are targets of METH-induced toxicity. Another study by Abdullah *et al.*[55] demonstrated that METH self-administration

has a significant impact on mitochondrial ultrastructure, OXPHOS SCs assembly and redox activity, as well as enhanced PDH activity, which could explain reported cellular dysfunction. One of the key effects of METH-induced mitochondrial toxicity is the reduction in mitochondrial respiratory chain complex activity. This reduction impairs the production of ATP, the cell's primary energy source. Additionally, METH exposure increases the production of ROS and promotes oxidative stress within the mitochondria[56]. The elevated ROS levels can cause damage to mitochondrial components and further impair mitochondrial function[57]. The METH exposure also affects mitochondrial dynamics, specifically leading to an increase in mitochondrial fission. This imbalance between fusion and fission processes disrupts the normal structure and function of mitochondria, contributing to their fragmentation. Mitochondrial fragmentation is associated with apoptotic cell death, as it releases pro-apoptotic proteins such as cytochrome c from the mitochondria into the cytosol[58]. Furthermore, METH exposure alters the expression of proteins involved in mitochondrial biogenesis, such as Nuclear Respiratory Factor 1 (NRF1), Peroxisome Proliferator-Activated Receptor Gamma Coactivator-1α (PGC1α) and Mitochondrial Transcription Factor A (TFAM). These changes negatively impact mitochondrial biogenesis and impair the overall health of mitochondria[59]. Moreover, METH can induce neuronal programmed necrosis through the activation of signaling pathways involving the activation of RIP3 leading to the phosphorylation of Mixed Linkage Domain-Like Protein (MLKL), which disrupts cell membranes and promotes necrotic cell death (Fig. 3). This process involves the formation of a complex between RIP3 and RIP1 and ultimately results in mitochondrial damage and neuronal necrosis[60]. Recently, Graves *et al.*[61] showed that METH therapy increased both axonal and somatic mitochondrial oxidative stress in substantia nigra pars compacta dopaminergic neurons, which is associated with a small but substantial increase in firing frequency and resulted in degeneration after drug withdrawal[61].

TREATMENT OF METH-INDUCED NEUROTOXICITY

Several techniques have been developed to achieve effective pharmacological output in the treatment of METH-induced neurotoxicity. The processes of neurotoxicity induction serve as the basis for treatment options. The most recent studies on strategies used in the treatment of METH-induced neurotoxicity were summarized as shown in Table 1.

Table 1: Summary of recent studies (the last five years) on METH-induced neurotoxicity and treatment strategies in different experimental models

Treatment agent	Type of study	Experimental model	References
Calcitriol	*In vivo*	Rat	Cass and Peters[26]
Mesenchymal stem cells with antioxidant compound H-290/51	*In vivo*	Rat	Lafuente *et al.*[62]
α-Pinene	*In vivo*	Mice	Lee *et al.*[63]
Thioperamide	*In vivo*	Mice	Luo *et al.*[64]
Thyroid hormones	*In vivo*	Primary hippocampal neurons	Tamijani *et al.*[65]
Erythropoietin	*In vivo*	Rat	Garmabi *et al.*[66]
Melatonin	*In vivo*	Human neuroblastoma cells	Nopparat *et al.*[67]
	In vivo	Rat	Kraiwattanapirom *et al.*[68], Hein *et al.*[69] and Namyen *et al.*[70]
	In vivo	Mouse hippocampus	Lwin *et al.*[71]
Icariside II	*In vivo*	Mice	Huang *et al.*[72]
Cinnamaldehyde	*In vivo*	PC12 Cells	Saeed *et al.*[73] and Rashidi *et al.*[74]
Curcumin	*In vivo*	Rat	Hadizadeh-Bazaz *et al.*[75],
	In vivo	PC12 cell line	Ottonelli *et al.*[76] and Ryskalin *et al.*[77]
6,7,4'-trihydroxyflavanone	*In vivo*	SH-SY5y Cells	Lee and Jeong[78]
Aromadendrin	*In vivo*	SH-SY5y cells	Lee *et al.*[79]
Resveratrol	*In vivo*	Mice	Zeng *et al.*[80]
Rosmarinic acid	*In vivo*	Zebrafish	Shahrestani *et al.*[81]
Thymoquinone	*In vivo*	Mice	Roohbakhsh *et al.*[82]
Tertiary butylhydroquinone	*In vivo*	Rat	Meng *et al.*[83]
α-Synuclein	*In vivo*	Mice	Ding *et al.*[84]
Gastrodin	*In vitro*	Primary cortex neuronal culture	Ma *et al.*[85]
	In vivo	SH-SY5Y cells	Yang *et al.*[86]
Lupenone	*In vivo*	SH-SY5y Cells	Lee *et al.*[87]
Tea polyphenols	*In vivo*	PC12 Cells	Ru *et al.*[88]
Obestatin	*In vivo*	PC12 cells	Foroughi *et al.*[89]
Apelin-13	*In vivo*	PC12 Cells	Foroughi *et al.*[90]

Anti-oxidative stress therapy: A lot of investigations have found that oxidative stress is a major source of METH-induced neurotoxicity. The METH-induced dopaminergic cell death occurs through boosting ROS generation and decreasing cellular ATP levels. The METH inhibits DA reuptake, causing auto-oxidation, which results in the generation of different ROS, superoxide and nitrogen radicals, causing cell death[35]. Various pharmacotherapies have been investigated in a search for successful therapeutic techniques that will protect cells from the oxidative stress caused by METH. A variety of antioxidants have been shown to have anti-neurotoxic actions against METH.

According to Huang *et al*.[91] vitamin C protects cortical cells from the neurotoxicity caused by METH through the attenuation of the expression of cleaved caspase-3 and the reduction in the number of METH-induced apoptotic cells. The rosmarinic acid combined with ZnO nanoparticles showed high potential in counteracting the METH-mediated elevation in caspase-3 mRNA level in zebrafish[81]. Furthermore, Kish *et al*.[92] suggested that DA replenishment could potentially reverse the METH induced neurotoxicity.

Non-enzymatic antioxidants such as flavonoids have been proven to be beneficial in attenuation of METH-induced neurotoxicity. For example, anthocyananine protects neurons by avoiding cell death[93]. According to Ru *et al*.[88] findings, tea polyphenol supplementation may be a useful dietary preventive approach for METH-induced neurotoxicity and neurodegenerative diseases. Also, according to Foroughi *et al*.[90], apelin-13, an endogenous ligand, may be able to lessen the neurotoxicity caused by METH by reducing oxidative damage, apoptotic and autophagic cell death. A further investigation was planned to find out if the antioxidant Tertiary Butylhydroquinone (TBHQ) may lessen the neurotoxicity caused by METH in male Wistar rats. The findings show that TBHQ can improve the antioxidative stress and antiapoptotic actions of phosphatidylinositol 3-kinase and nuclear factor erythroid 2-related factor-2, which can reduce the ROS and apoptosis caused by METH[83]. Ma *et al*.[85] investigate gastrodin's neuroprotective effects against METH-induced neurotoxicity and show that it regulates the cAMP/PKA/CREB signaling pathway Cinnamaldehyde, a naturally occurring flavonoid found in the plant *Cinnamomum cassia*, similarly shown neuroprotective benefits against METH-induced cytotoxicity[73,74]. Thymoquinone, a significant component of the plant *Nigella sativa*, has also been demonstrated to protect against METH toxicity[82]. Also, Lee and Jeong[78] reported that 6,7,4'-trihydroxyflavanone, a compound isolated from the *Dalbergia odorifera* plant showed protective effects against METH-induced neurotoxicity. In addition, Lee *et al*.[79] found that aromadendrin, isolated from *Chionanthus retusus*, protected cells from METH-induced neurotoxicity via modulating ER stress and the PI3K/AKT/mTOR pathways. Also, Zeng *et al*.[80] demonstrated that pretreatment with natural polyphenol resveratrol (10 or 100 mg/kg) significantly improves memory impairments by preventing METH-induced oxidative damage and apoptosis in mice. Lafuente *et al*.[62] recently demonstrated that nano delivery of H-290/51 with mesenchymal stem cells significantly increased cerebral blood flow and decreased blood-brain barrier breakdown, edema development and brain pathology after METH exposure in a hot environment. Thioperamide, according to Luo *et al*.[64] has a neuroprotective effect against METH-induced cognitive impairment in rats and toxicity in HT22 cells via the raf-MEK-ERK signaling pathway.

According to Tamijani *et al*.[65], thyroid hormones activate the cell surface receptors for integrin αvβ3, which prevents METH-induced apoptosis in primary hippocampal neurons. To examine erythropoietin's (EPO) potential defense against METH neurotoxicity in male Wistar rats. Garmabi *et al*.[66] EPO showed significant neuroprotective effects on METH neurotoxicity due to its anti-inflammatory, antioxidant and antiapoptotic potential.

Anti-excitotoxicity therapy: The METH excitotoxicity is induced by increased Glu release, which activates NMDA receptors and other Glu receptors (Fig. 3), resulting in a high calcium ion influx and activation of a variety of cellular processes. As a result, these receptors are regarded as promising targets for METH-induced excitotoxicity and have sparked considerable interest in the development of targeted treatments. Neuropeptide Y is neuroprotective in a variety of disease situations. Baptista *et al*.[94] demonstrated that activating Y1 or Y2 receptors prevents METH-induced cell death and that the Y1 subtype is responsible for suppressing METH-induced neuronal differentiation. Melatonin, a pineal hormone, may protect against oxidative stress and regulate calcium ion intracellular transport in the CNS. Many recent studies reported the protective effect of melatonin on METH-induced changes in the expression levels of NMDA receptor subunits as well as Ca^{2+}-dependent protein kinase in human and experimental animals[67,68]. Nopparat *et al*.[67] found that melatonin can help reduce amyloid deposits inside the neuron in a cellular model of METH-induced toxicity. Many researchers have discovered that N-acetylcysteine, a precursor of the antioxidant glutathione, exhibits an

antioxidant effect and reduces Glu excitatory toxicity in animals treated with METH[95,96]. Also, dizocilpine, a powerful non-competitive NMDA receptor inhibitor, protects against METH-induced toxicity by inhibiting NMDA receptor overactivity downstream of DA release[10]. In addition, topiramate, an anticonvulsant, has a greater ability to reduce METH-induced excitatory toxicity by antagonizing numerous Glu receptors and inhibiting carbonic anhydrase[10]. It has been discovered that Levo-tetrahydropalmatine, an active component of herbal plant species from the genera *Corydalis* and *Stephania*, is neuroprotective against METH-induced neurotoxicity[7].

Anti-mitochondrial toxicity therapy: Increasing mitochondrial activity may be beneficial to alleviate cellular resilience and neuronal plasticity impairments which are linked to a number of neuropsychiatric illnesses. In a study by Bachmann *et al.*[97], demonstrated that SH-SY5Y cells protected against METH-induced mitochondrial damage when treated with lithium or valproate in a long-term therapy. Park *et al.*[98] showed that METH-induced translocation of NF-B/STAT3 and ERK phosphorylation and proteolytic cleavage of caspase-3 were significantly reduced by asiatic acid. According to the results of Lee *et al.*[87], lupenone, naturally occurring triterpenoids, can prevent METH-induced neuronal death in SH-SY5y cells by blocking the PI3K/Akt pathway. According to Ru *et al.*[88], peptide hormone obestatin may be able to lessen METH-induced neurotoxicity in PC12 cells by reducing apoptotic and autophagic responses. In addition, Li *et al.*[99] investigated oxytocin's neuroprotective properties against METH-induced neuronal injury in rats. They discovered that pre-incubation with oxytocin prevents the damage to hippocampus neurons caused by METH intoxication. In addition, Chen *et al.*[100] reported that quercetin exhibited antipsychotic efficacy by modulating mitochondrial function and neuro-inflammation, implying that it has the potential to be further developed as a treatment in METH-induced anxiety. Recently, METH-induced lipid peroxidation was substantially reduced by alpha-Pinene via activation of nuclear factor-erythroid 2-related factor, which up-regulated antioxidant enzymes[63].

Anti-neuroinflammation therapy: Neuroinflammation is a primary cause of neurotoxicity caused by METH intoxication and is considered to be the most probable outcome of METH-induced damage. There are multiple endpoints that show METH-induced injury because there are many pathways and mediators for neuroinflammation[101]. The primary cause of METH's neurotoxicity is the inflammatory response brought on by activated microglia. According to Sekine *et al.*[102], METH users may experience reactive microgliosis in their brains as a result of continuous self-administration of the drug. Zhang *et al.*[103] reported that minocycline notably attenuated the rise in extracellular DA levels following multiple METH injections. They suggested that a number of symptoms linked to METH exposure could be treated by using minocycline to inactivate microglia.

The use of minocycline and modafinil after multiple METH injections attenuates the rise in extracellular DA and reduced METH-induced activation of microglial in brain cells, respectively. It results in the release of neuroinflammation[104].

Modafinil, a medication that improves cognition, also reduces METH-induced activation of microglial in brain cells, lowering the risk of neuroinflammation[104]. White *et al.*[44] found that anti-METH/AMP mAb4G9 protected rat brains from METH-induced neuroinflammation. In another study by Kraiwattanapirom *et al.*[68], tested the anti-neuroinflammation potential of melatonin by pretreating with 10 mg/kg of melatonin before administering METH. This treatment was able to decrease an increase in Neuron-Glial2 levels and activation in microglia and astrocytes. Furthermore, Namyen *et al.*[70] demonstrated the protective effects of melatonin against METH neurotoxic profiles, which include reactive gliosis, increased upregulation of primary pro-inflammatory cytokines, activation of neuroinflammatory signaling and suppression of anti-oxidative signaling. These characteristics may exacerbate structural impairment of the blood brain barrier. A recent study conducted by Hadizadeh-Bazaz *et al.*[75] reported that curcumin, the main component of *Curcuma longa*, could increase anti-oxidative enzymes and decrease malondialdehyde in mice neurons injected with METH. They also reported that curcumin could reduce the TNF-α levels to attenuate the neuroinflammation induced by METH. Furthermore, Lwin *et al.*[71] demonstrated that the administration of melatonin caused the METH-induced markers to return to control levels. Thus, they conclude that melatonin may be utilized as an anti-inflammatory medication to treat METH use disorder in people[69]. More recently, Huang *et al.*[72] administered Icariside II (ICS), the primary active component of the traditional Chinese medicine Epimedium. It results in the activation of Keap1-Nrf2 pathway thereby reducing glial cell activation and mitigating neurotoxicity. Also, Ottonelli *et al.*[76] found that cerebral edema, neuronal damage and blood brain barrier leakage in rat brains were dramatically reduced by curcumin alone (50 mg/kg, i.v.) and curcumin delivered via TiO_2 nanowired administration (25 mg/kg, i.v.).

CONCLUSION

Methamphetamine (METH) is a highly addictive drug that affects brain neurotransmitters, leading to severe physical and mental health issues. Short-term effects include euphoria, increased energy, decreased appetite and elevated heart rate and blood pressure, followed by a prolonged crash. Long-term use results in significant health problems, including neuro-inflammation and neuronal injury due to excessive dopaminergic activity. The METH's lipophilic nature allows it to cross the blood-brain barrier, causing neurotoxicity through interactions with cell surface receptors. Key factors in METH-induced neurotoxicity include dopamine depletion, oxidative stress and activation of microglia and astrocytes. While the exact chemical processes remain unclear, research focuses on mitigating these effects. Current studies explore targeted therapies like gene therapy, immunotherapy and nanoparticle-based treatments. This review highlights recent findings on METH-induced neurotoxicity and treatment strategies, emphasizing the need for further research to develop effective therapeutics.

SIGNIFICANCE STATEMENT

This review provides a comprehensive analysis of the neurotoxic effects of Methamphetamine (METH) use, highlighting the underlying molecular mechanisms and the different treatment strategies. By elucidating the pathways of METH-induced neurotoxicity and exploring innovative treatment strategies, this research aims to contribute to the development of more effective therapeutic interventions. Understanding these mechanisms is crucial for mitigating the public health crisis posed by METH addiction and improving outcomes for affected individuals.

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