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Review

Methamphetamine induced neurotoxic diseases, molecular mechanism, and current treatment strategies

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ABSTRACT

Methamphetamine (MA) is a extremely addictive psychostimulant drug with a significant abuse potential. Long-term MA exposure can induce neurotoxic effects through oxidative stress, mitochondrial functional impairment, endoplasmic reticulum stress, the activation of astrocytes and microglial cells, axonal transport barriers, autophagy, and apoptosis. However, the molecular and cellular mechanisms underlying MA-induced neurotoxicity remain unclear. MA abuse increases the chances of developing neurotoxic conditions such as Parkinson's disease (PD), Alzheimer's disease (AD) and other neurotoxic diseases. MA increases the risk of PD by increasing the expression of alpha-synuclein (ASYN). Furthermore, MA abuse is linked to high chances of developing AD and subsequent neurodegeneration due to biological variations in the brain region or genetic and epigenetic variations. To date, there is no Food and Drug Administration (FDA)-approved therapy for MA-induced neurotoxicity, although many studies are being conducted to develop effective therapeutic strategies. Most current studies are now focused on developing therapies to diminish the neurotoxic effects of MA, based on the underlying mechanism of neurotoxicity. This review article highlights current research on several therapeutic techniques targeting multiple pathways to reduce the neurotoxic effects of MA in the brain, as well as the putative mechanism of MA-induced neurotoxicity.

1. Introduction

MA is a highly addictive psychostimulant drug with substantial abuse potential that exhibits neurotoxic effects [1]. It is the second most common illegal drug worldwide and is most prevalent in North America, Asia, and Oceania [2,3]. MA-dependence causes long-term neuronal damage and has harmful effects on cognition, memory, and attention [4]. MA is a lipophilic drug that can pass the blood-brain barrier (BBB) easily [5] and penetrate into the brain, where it primarily augments the release of central and peripheral neurotransmitters, such as dopamine (DA), serotonin (also known as 5-HT, 5-hydroxytryptamine), norepinephrine, and glutamate. It does so by interacting with various receptors, such as the dopamine transporter (DAT), serotonin transporter (SERT), noradrenaline transporter (NET), and N-methyl-D-aspartate (NMDA) receptors, which are cell surface integral proteins, and vesicular monoamine transporter-2 (VMAT-2) embedded in vesicular

Abbreviations: 5-HT, 5-hydroxytryptamine; AD, Alzheimer's disease; ADAM10, a disintegrin and metalloproteinase domain-containing protein 10; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; ASYN, alpha-synuclein; ATF2, activating transcription factor 2; BBB, blood-brain barrier; CMA, chaperone-mediated autophagy; DA, dopamine; DAT, dopamine transporter; DAQ, dopaquinone; ER, endoplasmic reticulum; GDNF, glial cell line-derived neurotrophic factor; GSK3β, Glycogen synthase kinase 3β; IL, interleukin; KLH, keyhole limpet hemocyanin; MA, methamphetamine; mGluRs, metabotropic glutamate receptors; MAPs, microtubule-associated proteins; MAPT, microtubule-associated protein tau; MDMA, methylenedioxymethamphetamine; NET, noradrenaline transporter; NMDA, N-methyl-D-aspartate; PARP, poly ADP-ribose polymerase; PD, Parkinson's disease; PDI, protein disulfide isomerase; PKC, protein kinase C; ROCK2, Rho-associated kinase II; ROS, reactive oxygen species; SERT, serotonin transporter; SUMO-1, small ubiquitin-related modifier 1; TNF-α, tumor necrosis factor-alpha; UPS, ubiquitin-proteasomal system; VMAT-2, vesicular monoamine transporter-2.

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membranes [2,4]. Moreover, it also decreases monoamine metabolism by inhibiting monoamine oxidase [2]. Repeated administration of the drug to rodents or non-human primates decreases striatal concentrations of DA and DA metabolites in several brain regions [4].

MA causes arousal, euphoria, reduced fatigue, accelerated heart rate, positive mood, pupil dilation, elevated blood pressure, increased temperature, behavioral disinhibition, reduced appetite, and heightened alertness, attentiveness, and energy at low or moderate doses (5–30 mg/kg). Higher doses or elevated blood MA plasma levels result in euphoria, hypertension, violent behavior, paranoia, rapid or confused speech, rapid pulse, nervousness, sweating, and motor restlessness [2]. An overdose of MA is associated with non-fatal (tachycardia, hypertension, and altered mental state) and fatal cases. Fatalities arise mostly due to multiple congestion, cerebrovascular hemorrhage (attributed to hypertension), pulmonary edema and congestion, ventricular fibrillation, hyperpyrexia, or acute cardiac failure [2]. Sudden interruption of long-term use can lead to withdrawal, lasting for days, which is accompanied by anhedonia, dysphoria, irritability, severe cravings, and agitation [4,5]. Withdrawal symptoms are treated by both pharmacological (opioid receptor antagonists and antidepressants) and non-pharmacological (psychosocial behavioral therapy and contingency reward therapy) interventions [5].

Acute and chronic use of this drug can lead to serious neurotoxic effect due to oxidative stress and changes in the energy metabolism. MA-induced acute effects are mainly due to its action on DAT and VMAT-2, which are responsible for controlling the release of dopamine [1]. MA can also affect noradrenergic, serotonergic and glutaminergic system by interacting with monoamine transporter and NMDA receptors [4]. Significant behavioral and cognitive changes are the end outcomes of these intricate neurochemical modulation resulting from MA.

In this review, we discuss briefly on the principal mechanism of MA-induced neurotoxicity pertaining to different neurotoxic diseases and highlight the current research on several therapeutic approaches targeting multiple pathways to reduce the neurotoxic effects of MA in the brain. Till date there no FDA approved therapy for the treatment of MA-induced neurotoxicity. We anticipate this study provides research ideas and theoretical groundwork for developing more effective and efficacious therapeutic approach to protect against the MA-induced neurotoxicity in the future.

2. Molecular mechanisms of MA-induced neurotoxicity

Many factors are known to be involved in the neurotoxic effects of MA. Some of them are dopamine depletion, oxidative stress, endoplasmic reticulum stress, mitochondrial functional impairment, activation of astrocytes and microglial cells, axonal transport barriers, autophagy, and apoptosis (Fig. 1) [5]. However, the complete cellular and molecular mechanisms of MA-induced neuronal toxicity have not yet been described [6–8].

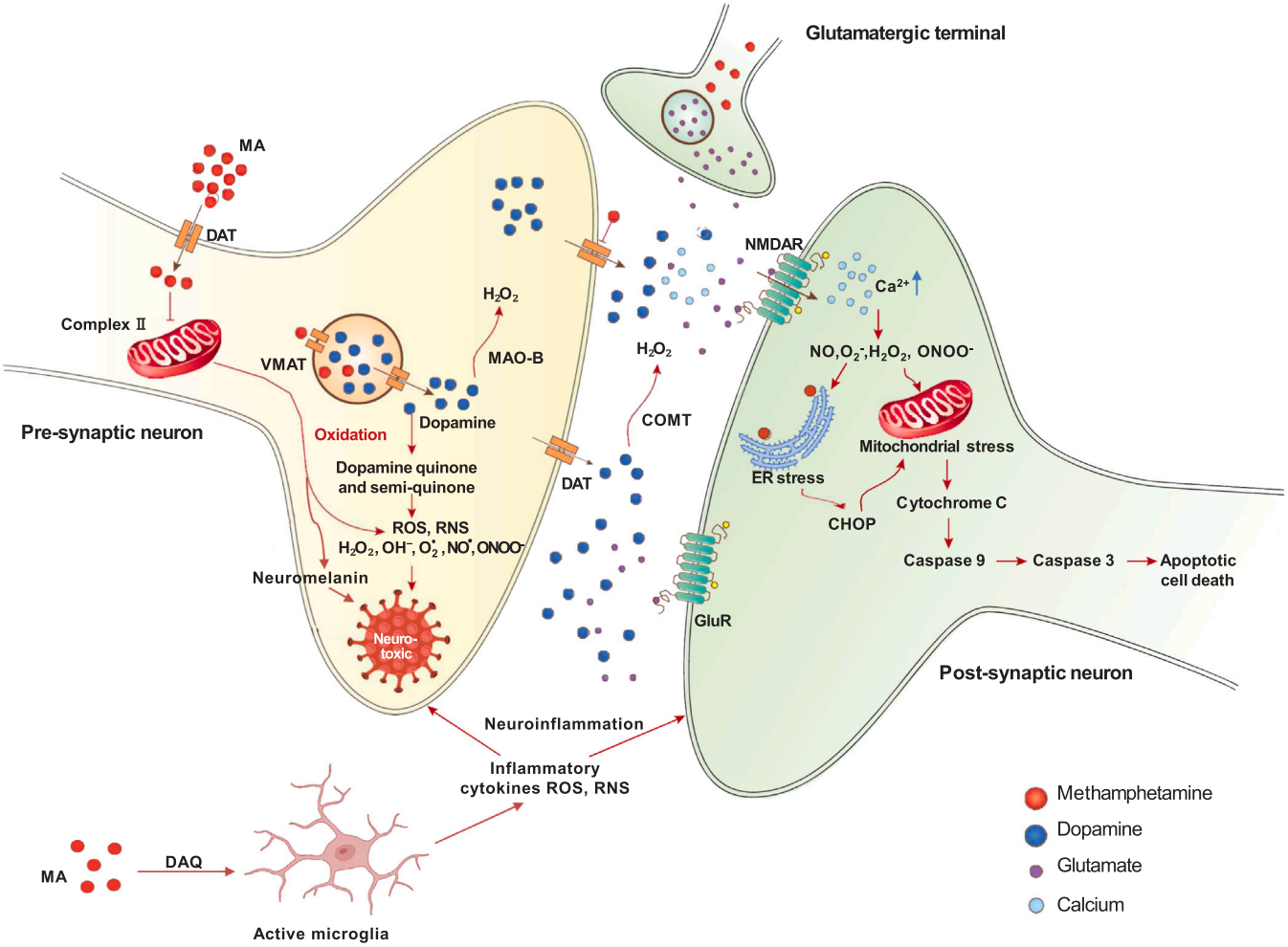

Fig. 1. A summary diagram illustrating the molecular mechanism of MA-induced neurotoxicity. MA shows the neurotoxic effects through dopamine depletion, oxidative stress, ER stress, mitochondrial functional impairment, and activation of microglia.

2.1. Oxidative stress

MA is a common drug of abuse which promotes the release of various neurotransmitters and induces euphoria and hallucinations. It has been established that the MA-induced oxidative stress plays a crucial role in causing cellular toxicity. Many studies have shown that MA causes neurotoxic effects which are mediated in part by the reactive oxygen species (ROS). These ROS can damage cellular macromolecules such as proteins, lipids and DNA which leads to the loss of cellular functions [9, 10] MA results in the production of various oxidative species, leading to lipid peroxidation, protein misfolding, and nuclear damage [11]. MA enters the neurons, displaces dopamine from its vesicles, and releases it into the synaptic cleft, resulting in high intracellular and synaptic dopamine levels. This leads to the auto-oxidation and increased metabolism of dopamine resulting the formation of various ROS, like hydrogen peroxide (H_2O_2), as by-products [5]·H_2O_2 produces hydroxyl radicals that are highly reactive and are responsible for the increase in oxidative damage [5]. Moreover, dopamine can also be oxidized into quinones and semiquinones, which are further converted to superoxide and nitrogen radicals that can cause further oxidative damage [5]. Oxidative stress is a principal factor involved in the destruction of dopaminergic neurons. These dying neurons release neuromelanin, which exacerbates neuroinflammation and the neurodegenerative process [12]. Disturbance in the redox balance by MA is detrimental to the axon terminals and cell bodies as it causes the oxidation of proteins, lipids, and nucleic acids. MA also inhibits mitochondrial complex II, further elevating oxidative stress and increasing the number of damaged mitochondria [11]. MA-induced overexpression of alpha-synuclein (ASYN) is known to enhance cellular oxidative stress, which can be attenuated by the reduction of ASYN expression using inhibitors of ASYN gene (*SNCA*) [13,14]. Conversely, MA induces the activation of nitric oxide synthase (NOS) and increases the production of nitric oxide, which leads to the increased expression of ASYN in vitro [15] as well as in the mouse striatum and hippocampus [16].

Protein oxidation causes the binding of cysteinyl residues, thereby forming disulfuric bridges, altering the protein conformation, and leading to the formation of misfolded proteins, such as ASYN, ubiquitin, prion protein, and parkin. MA also causes lipid oxidation to produce highly reactive 4-hydroxynonenal [11].

2.2. Neuroinflammation

MA has been shown to trigger inflammatory responses in areas where the DA and 5-HT terminals are damaged. These damaging effects are caused by the activation of microglia [17,18]. MA causes the activation of microglia in the striatum, cortex, and hippocampus. The mechanism through which these activations occur is still unknown; however, dopaquinones (DAQs), a metabolite of dopamine, are thought to be the major activators of microglia. DAQ causes the activation of microglia through changes in microglial gene expression [19]. During MA exposure, elevated cytosolic DA and oxidative stress can stimulate the synthesis of DAQs, which could lead to microglial activation. Microglial activation results in the elevated level of a different potentially neurotoxic molecules such as pro-inflammatory cytokines, proteinases, and ROS which causes the neuroinflammation [20]. Activated microglia are also responsible for the secretion of high amount of excitotoxic glutamate which mediates the excitotoxicity and neuroinflammation leading to the neurodegenerations [21].

Glutamate, a principle excitatory neurotransmitter, is also thought to be a major contributor for causing neuroinflammation. Repeated administration of MA induces glutamate receptor activation and glutamate release. This causes the phosphorylation of PI3/Akt molecules leading to the activation of transcription factor NF-κB and ultimately activate the neuroinflammation via production of inflammatory mediators, such as interleukin-1β (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) [22]. These cytokines can upregulate extracellular glutamate levels by inhibiting the uptake and enhancing the release of glutamate from microglial cells, initiating a feed-forward loop that promotes neurotoxicity [23]. Many research have shown the elevation of these pro-inflammatory cytokines following MA administration which plays a major role in mediating brain injury [24].

2.3. Excitotoxicity

Glutamate is the most prevalent excitotoxic neurotransmitter in the human brain. Increase in extracellular glutamate concentration leads to the excitotoxicity [25]. When L-glutamate, an abundant ionic form of glutamate, is released excessively into the extracellular space from neuron and glial cells, it causes neuronal injury or death via excitotoxicity [26]. It involves activation of glutamate receptors, increase in intracellular calcium levels, activation of a variety of calcium-dependent enzymes, generation of free radicals and nitric oxide (NO), and activation of apoptotic pathways [27]. All these events lead to the failure of cellular organelles, such as mitochondria and endoplasmic reticulum (ER), breakdown of cytoskeletal proteins, and DNA damage. Excessive release and accumulation of glutamate activates a number of downstream signaling pathways, including an increase in Ca^{2+} inflow, which results in an increase in intracellular Ca^{2+} concentration [25]. Excessive glutamate accumulation activates NMDA receptors and metabotropic glutamate receptors (mGluRs) [26]. Activation of mGluRs results in phosphorylation of protein kinase C (PKC), which regulates the function of NMDARs, leading to increased influx of Ca^{2+} Increased levels of intracellular Ca^{2+} initiates a series of cellular processes that can activate protein kinases, phosphatases, and NOS, enhancing the NO production and ultimately results in ER stress [26,27]. ER stress is mainly caused due to different toxic stimuli and accumulated misfolded proteins. The resulting ER stress activates ER-resident transmembrane proteins such as activating transcription factor-6 (ATF6), inositol requiring protein-1 (IRE1), and protein kinase RNA-like ER kinase (PERK). These are responsible for decrease production of proteins and specific genes expression that protects from proteotoxic stress [28,29]. These proteins activates C/EBP homologous protein (CHOP) which leads to the initiation of ER-stress induced apoptotic process [30]. ER stress induces apoptosis through death receptors activation and involvement of mitochondrial dependent cell death pathways [31]. It was observed that high dose of MA stimulate the expression of ER stress genes like CHOP, ATF4 and caspase-12 [32]. MA-induced ER stress are also linked with dopaminergic toxicity through the dopamine receptor (D1) activation [33]. Studies also demonstrated that the AMPK/FOXO3A signaling pathways is responsible for the D1-receptor mediated activation of autophagy following MA treatment [34].

2.4. Mitochondrial toxicity

MA is lipophilic and easily enters the cell membranes of intracellular organelles, including mitochondria [35]. It induces neuropathological effects in the brain by developing mitochondrial impairment, caspase activation, and apoptotic neuronal death [6,17]. It reduces mitochondrial respiratory chain complex activity, and increases the production of reactive oxygen species (ROS) and levels of proteins involved in mitochondrial fission, leading to mitochondrial fragmentation and apoptotic cell death [17]. Escalating doses of MA destroyed mitochondrial biogenesis, but immediately after its discontinuation, it induced compensatory and protective mechanisms, such as increased gene expression involved in mitochondrial biogenesis and glial cell line-derived neurotrophic factor (GDNF), which is a trophic factor involved in neuronal survival [35]. MA administration also disturbs mitochondrial biogenesis by reducing the levels of mitochondrial biogenesis-related factors such as peroxisome proliferator activated receptor gamma coactivator-1α (PGC1α), nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (TFAM) in rat hippocampus [36]. MA exposure increased the expression of pro-apoptotic

proteins Bax and Bad and reduced the expression of the anti-apoptotic protein Bcl-2, resulting in the release of cytochrome c from the mitochondria into the cytosol. This release causes sequential activation of caspase-3, − 6, and − 7, which induce cellular apoptosis [6].

MA produces toxic effects in various regions of the brain, including the cortex, striatum, and hippocampus [37]. Proteomic profiling of proteins in different parts of the brain showed that 14 proteins in the striatum, 12 proteins in the hippocampus, and 4 proteins in the frontal cortex were differentially expressed after MA administration. The pathophysiology of MA neurotoxicity is linked to these proteins, including oxidative stress, apoptosis, and mitochondrial/energy metabolism. The content of CuZnSOD was reduced in the striatum and hippocampus after MA administration, whereas the content of ASYN was increased in the striatum, hippocampus, and cortex. Similarly, mitochondrial enzymes related to ATP synthesis were also reduced in these brain regions, which may contribute to the neurotoxic effects of MA.

There are two main pathways involved in the clearance of proteins: the non-lysosomal ubiquitin-proteasomal pathway and the lysosome-mediated autophagy pathway, in which autophagy is the principal degradation pathway in many cases. Mammalian target of rapamycin (mTOR) is a major negative regulator of autophagy [11]. MA impairs the ubiquitin proteasomal system (UPS) and markedly enhances autophagy and alters the amount and structure of proteins that are crucial for dopaminergic neurons [11]. Following MA injection, the ubiquitin-conjugating enzyme E2N might be a compensatory mechanism in the cells to protect them against MA-induced increase in abnormal protein levels [37]. MA treatment disturbs protein homeostasis by affecting the autophagy-lysosomal system and increasing ASYN accumulation and aggregation [13]. Similarly, MA produces changes in the parkin protein, which is a ubiquitous ubiquitin-protein ligase with neuroprotective properties [38]. Both proteins were found to be aggregated in the Parkinson's disease (PD) brains.

MA increases the number of autophagic vacuoles within catecholaminergic neurons, and inhibition of autophagy is detrimental to MA-treated catecholamine-containing cells. mTOR inhibition by rapamycin was found to be protective against MA-toxicity [11]. Ferrucci et. al. also showed that the pre-treatment with the asparagine or glutamine, which are known to inhibit autophagic pathway, enhanced the MA toxicity even in the moderate doses of MA [39]. These results show the apoptotic nature of MA-induced cellular death, when autophagy is impaired.

MA also induces neuronal programmed necrosis by activating the receptor-interacting protein kinase 3-related signaling pathways [40]. The receptor-interacting serine threonine kinase (RIP3) is considered a crucial molecule for causing neurodegeneration via the programmed necrosis by generating a necrotic protein complex [40–42]. This complex leads to phosphorylation of RIP3 and ultimately phosphorylate mixed linkage domain like-protein (MLKL) which destroys the membrane bilayer by generating pores and leads to necrotic death [42]. MA exposure stimulate formation of complex of RIP3 and RIP1 which leads to phosphorylation of RIP3. This activated RIP3 will the activates MLKL to form oligomers that disrupts cell membrane promoting mitochondrial damage resulting in neuronal necrosis [40].

3. MA-toxicity: relevance to neurotoxic diseases

3.1. Parkinson's disease (PD)

PD is a common neurodegenerative disorder characterized by the prominent loss of midbrain dopaminergic neurons and the presence of characteristic cytoplasmic inclusions in dying neurons that mostly contain the aggregated forms of a presynaptic protein, ASYN. ASYN is a soluble protein that has critical functions in synaptic plasticity, neurotransmitter release, and synaptic vesicle pool maintenance [17]. It is encoded by the *Snca* gene, which was the first to be identified as being associated with the familial form of PD. Abnormal accumulation of ASYN is closely related to central neuroinflammation and neurodegeneration in the substantia nigra in a rodent model of PD [43]. ASYN undergoes post-translational modifications, such as phosphorylation, nitration, acetylation, ubiquitylation, and methylation at various sites [44] and these modifications alter the normal functioning of the protein [45]. The phosphorylation at serine129 residue of ASYN is most abundantly found in aggregates and considered the most toxic form involved in the pathogenesis of PD.

Many studies have shown that exposure to toxins, such as the synthetic heroin compound 1-methyl-4-phenyl-tetrahydropyridine (MPTP), herbicides and pesticides [46,47] and the highly abused drug MA [48,49] as a contributor to the development of Parkinson's disease. Such neurotoxins cause a significant depletion in striatal dopamine. So, these toxins are used in creating animal models mimicking Parkinson's disease. Neurotoxicity induced by MA in experimental animals and human abusers is similar to that in patients with PD [50]. Because of this similarity, MA treatment is widely used as a drug-induced model of PD [51]. Moreover, MA increases ASYN protein expression both in vitro and in vivo, which plays a major role in producing the neurotoxic effects of MA [50]. MA-induced progressive nigrostriatal loss was observed to occur in a retrograde fashion, which is similar to PD pathology [52].

3.1.1. Increased risk of pd in ma-abusers

MA abuse has been linked to an increased risk of developing PD. A dose-dependent association was observed between MA abuse in humans and structural alterations of SN neurons, suggesting an increased risk of PD [12]. Detoxified human MA-abusers have reduced striatal blood flow and DA transporter levels such that there is a sustained reduction in the DA transporters even after 2–3 years of abstinence, stretching the vulnerability of MA abusers towards a higher risk of PD. In an experiment, MA self-administering rats exhibited 50 % loss of striatal TH fibers at 56 d of forced abstinence, whereas 80 % of striatal TH fibers were already lost in the patients with PD that exhibited motor symptoms [52]. Thus, striatal toxicity produced by MA and its long-lasting effects might shift the slope of DA loss over time and enhance the vulnerability of developing PD later in life for MA-abusers [52]. A single high dose of MA resulted in noteworthy neuronal apoptotic death in the substantia nigra and striatum [43].

3.1.2. Molecular mechanism of MA triggered PD

MA use is considered as one of the risk factors for the development of PD. Many pre-clinical research have been performed investigating the effects of MA on brain tissue and its tendency to cause brain DA neuronal damage such as that observed in Parkinson's disease. MA and PD shares some common steps in causing neurotoxicity. Dopamine, ASYN and parkin are common pathogenic molecule involved in the pathogenesis of PD.

Overexpression or aggregation of ASYN is associated with intracellular inclusions of this disease known as the Lewy bodies which is the pathological hallmark of the PD. Altered expression of ASYN and abnormal functioning trigger the neurodegeneration of DA neurons. Many earlier studies have shown the effects of ASYN in causing neurodegenerative disorders including PD. In chronic MA users ASYN aggregation and accumulation were observed in the dopaminergic neuron in the substantia nigra suggesting a crosstalk between PD and MA-induced neurotoxicity. Many studies have shown that MA-induced the selective increase in the ASYN level [45,53,54]. Meng et al. showed that MA-induced the expression of ASYN and increased its phosphorylation at Ser129. These phosphorylated ASYN accumulates in Lewy bodies suggesting that the accumulation of ASYN phosphorylated at Ser129 have a significant role in pathogenesis of PD [55]. Many studies have also shown the effects of ASYN in the cytoskeletal dynamics leading to the microtubule depolymerization. Overexpression of ASYN leads to the tubulin depolymerization which results impaired maturation of fibrils leading to the neurodegeneration [56]. Although tau pathology is not a prominent feature of PD, recent studies have demonstrated increasing

evidence of tauopathy in PD. It was also observed that chronic exposure to MA also led to increased tau phosphorylation via GSK3β leading to microtubule instability and neurodegeneration [57]. GSK3β is a primary kinase for phosphorylation of tau at Ser396 and can also directly phosphorylate ASYN at Ser129 (Fig. 2) [13,58]. This phosphorylation of tau are considered important events for developing the tau aggregates that accumulate in PD brain.

Knocking out ASYN in vivo reduced the neurotoxic effects of MA, suggesting that ASYN plays an important role in mediating MA-toxicity [57]. MA was also shown to induce a conformational change in the N-terminal region in ASYN, thereby causing the release of dopamine, suggesting an association between MA abuse and increased incidence of PD [44,59]. It was observed that ASYN nitration was associated with ASYN aggregation in the Lewy bodies of diseased PD brains. Nitration of ASYN at the tyrosine 39 residue (nT39 ASYN) has been consistently found to be involved in the oligomerization and fibrilization of the protein and is accumulated abnormally in patients with PD (Fig. 2) and ASYN-transgenic mice. Qiao et al. demonstrated that MA increased nT39 ASYN, thereby promoting apoptosis, as evidenced by the enhancement of cleaved caspase-3 and cleaved poly ADP-ribose polymerase (PARP) both in vitro and in vivo. The same group showed that MA exposure caused a sharp increase in the generation of NOS, which can nitrate ASYN at T39. Moreover, inhibition of nT39 ASYN by inhibition of NOS significantly reduced MA-induced ASYN aggregation and neurotoxicity [44].

The increase in ASYN induced by MA was shown to result from the reduction in cytosine methylation of the Snca promoter region of the gene in the substantia nigra of male Wistar rats by reducing the occupancy of methyl CpG binding protein 2 and DNA methyltransferases 1 in the *Snca* gene [43]. MA-induced overproduction of NOS and nitric oxide results in the S-nitrosylation of protein disulfide isomerase (PDI) in PC12 cells, leading to its dysfunction and an inability of the cells to reduce ASYN aggregation. PDI is an ER chaperone that plays an important role in proper protein folding and misfolded protein rearrangement caused by nitrosative and oxidative stress. S-nitrosylation of PDI results in the loss of function of PDI. Thus, pharmacological inhibition of NOS significantly reduced the S-nitrosylation of PDI and ASYN aggregation in MA-treated cells [16].

Ubiquitin-proteasomal system (UPS) protein is a major protein clearing system that consists of many factors, including the 26 S proteasome, a large ATP-dependent proteolytic complex, and enzymes, such as the ubiquitin activating enzyme (E1), ubiquitin conjugates (E2), and ubiquitin-protein ligases (E3) (such as parkin and ubiquitin C-terminal hydroxylase L1, etc.) [60,61]. Cytoplasmic inclusions in PD brains are co-localized with parkin. Parkin acts as E3 ubiquitin ligase in degrading UPS protein and its function is impaired by external stimuli like MA. This impaired functioning results in the accumulation of substrate proteins like ASYN due to their incomplete degradation [62]. Many studies have revealed that parkin recognizes ASYN, promotes its degradation, and protects against neurotoxic effects [62,63]. However, repeated administration of MA results in the rapid reduction of parkin protein and 26 S proteasomal activity via lipid peroxidation-mediated damage [60]. MA rapidly reduced parkin levels and 26 S proteasome activity by conjugating parkin with 4-hydroxy-2-nonenal (4-HNE), while simultaneously raising 20 S proteasome levels and chymotrypsin-like activity [60]. MA-induced oxidative damage to parkin and the 26 S proteasome is interdependent. Degradation of parkin is due to decreased functioning of the 26 S proteasome, and alternatively, degradation of parkin leads to a deficit in 26 S proteasome function, suggesting the key role of parkin in protecting dopaminergic neurons from degeneration [63–65]. Flack et al. also demonstrated that self-administration of MA promoted deficits in parkin, TH, and dopamine-β-hydroxylase (a noradrenergic marker) in the rat myenteric plexus of the distal colon, concurrent with the upregulation of ASYN, which occurs before TH immunoreactivity deficits occur in the striatum. These results indicate the potential progression of MA-induced neurotoxicity from the enteric nervous system to the central nervous system (CNS) [38]. Upon exposure to MA, parkin levels initially increase and then decrease depending on the dosage and time of exposure [66]. Bazylianska et. al. also showed that high dose of MA leads to damage of parkin and decreases its cytoplasmic fraction [67]. This decrease in the cytoplasmic fraction and immunoreactivity is possibly due to the DA-mediated oxidative damage to the parkin [67].

The neurotoxic effects of MA on human brains are comparable to

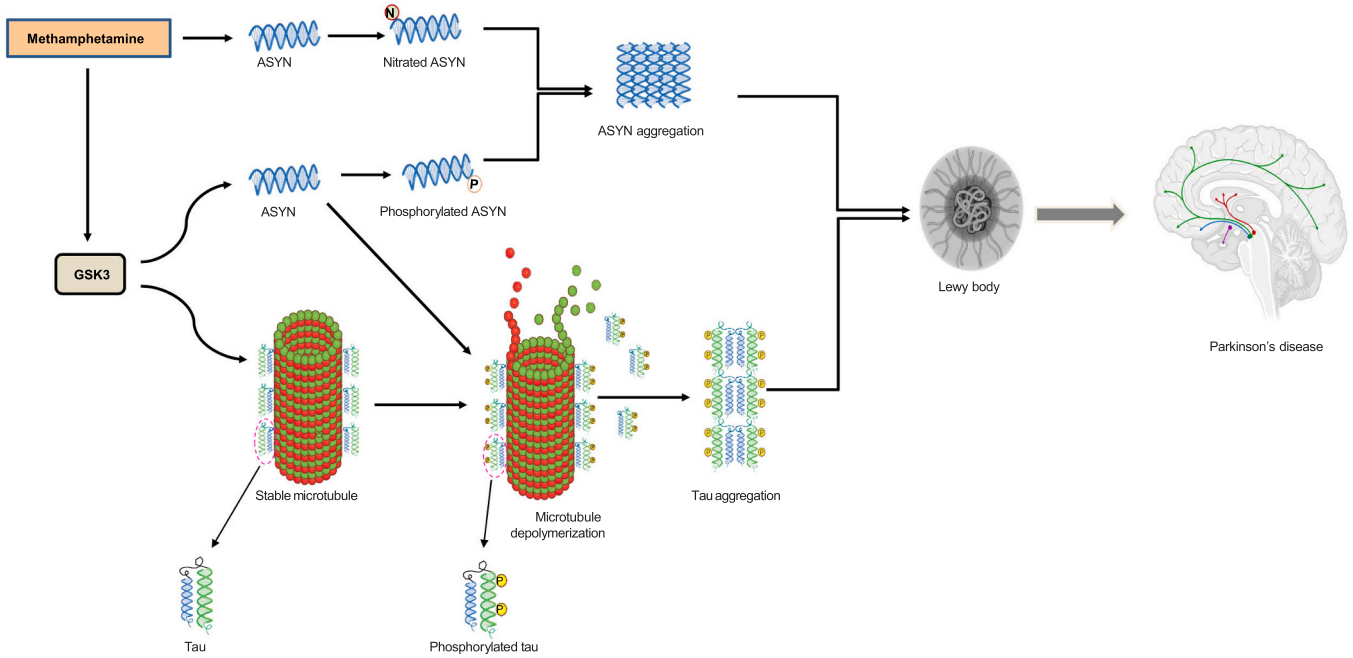

Fig. 2. MA-induced protein aggregation leading to formation of Lewy body. MA induces expression of ASYN and increase its phosphorylation and nitration leading to ASYN aggregation. Chronic MA exposure also causes increase phosphorylation of tau via GSK3β. This phosphorylation of tau causes the microtubule depolymerization and finally leads to aggregation of tau. These aggregated ASYN and tau leads to the formation of Lewy body in the brain causing the Parkinson's disease.

those observed in animal models. Repeated administration of high-dose MA causes long-term reduction in dopamine levels and the number of DA uptake sites in the striatum [68]. MA primarily affects the nigrostriatal dopaminergic pathways but are more resistant to mesolimbic pathways. This was evidenced by the finding that there is no effect on TH level in the nucleus accumbens of rodent treated with MA which is similar to the situation in PD where striatum is more affected than nucleus accumbens [69,70]. DA depletion which is the major marker in PD is observed in the brains of MA abusers. MA treatment in mice resulted in a sharp reduction in the dopamine levels and the concentration of its major metabolite, dihydroxyphenylacetic acid (DOPAC), in the striatum [45]. MA alters vesicular storage of DA and decreases monoamine metabolism by inhibiting monoamine oxidase [2,11]. Moreover, MA reverts and/or inhibits the activity of DAT. All of these events (Fig. 3) result in a dramatic increase in the levels of free DA, which undergoes self-oxidation and spontaneous conversion to highly toxic quinones [11] leading to long lasting damage of striatal neurons which is similar to the condition observed in the neurodegenerative process in PD. MA shows its effects of dopamine dysregulation through the activities of dopamine receptor. Chronic treatment with MA induces the stimulation of dopamine receptors (D1 and D2). D1 receptors are thought to be primarily responsible for MA-induced alteration and possibly MA-induced neuronal apoptosis in the dorsal striatum [71]. He et al. confirmed the activation of autophagy mediated by D1 receptor through the AMPK/-FOXO3A signaling pathway. D2 receptor are also involved in the MA-induced neurotoxicity. Recent research demonstrated the loss of dopaminergic striatal marker and the death of dopaminergic neurons in the substantia nigra following MA administration were both prevented in genetically modified mice by inactivating D2 receptor demonstrating a major role of D2 receptor in MA toxicity [72]. Involvement of D2 receptor in MA-induced apoptosis is also confirmed through the inhibition of apoptotic effects by D2 receptor antagonist [73]. These MA-induced alteration in dopaminergic system is much correlated to the conditions observed in PD indicating increasing risk of inducing PD by chronic MA abuse.

3.2. Alzheimer's disease (AD)

MA-induced toxic effects are similar to those observed in AD [37]. AD, a neurodegenerative disease, can only be treated symptomatically, as curative therapy is not yet available for this disease [74]. AD is characterized by the reduced memory and learning activities, presence of extracellular amyloid-β (Aβ) plaques and neurofibrillary tangles in the neurons, neuronal death, and the synaptic loss contributing to the cognitive decline in a progressive manner [75,76]. Aβ protein accumulation in AD contributes to dendritic spine loss [77,78]. Different theories have been proposed to explain pathogenesis of AD; however, Aβ is one of the most extensively studied components in the pathogenesis of AD.

3.2.1. AD and glutaminergic neurotransmitter system

Glutamate is the most abundant excitatory neurotransmitter in the CNS. Neuroplasticity, neuronal transmission, processing of memory and learning activities are all mediated by glutamate [79]. Ionotropic glutamate receptors can permeate the monovalent cations, $Na+$ and K^+, as well as the divalent cation, Ca^{2+}, depending on the subtype of AD. AD

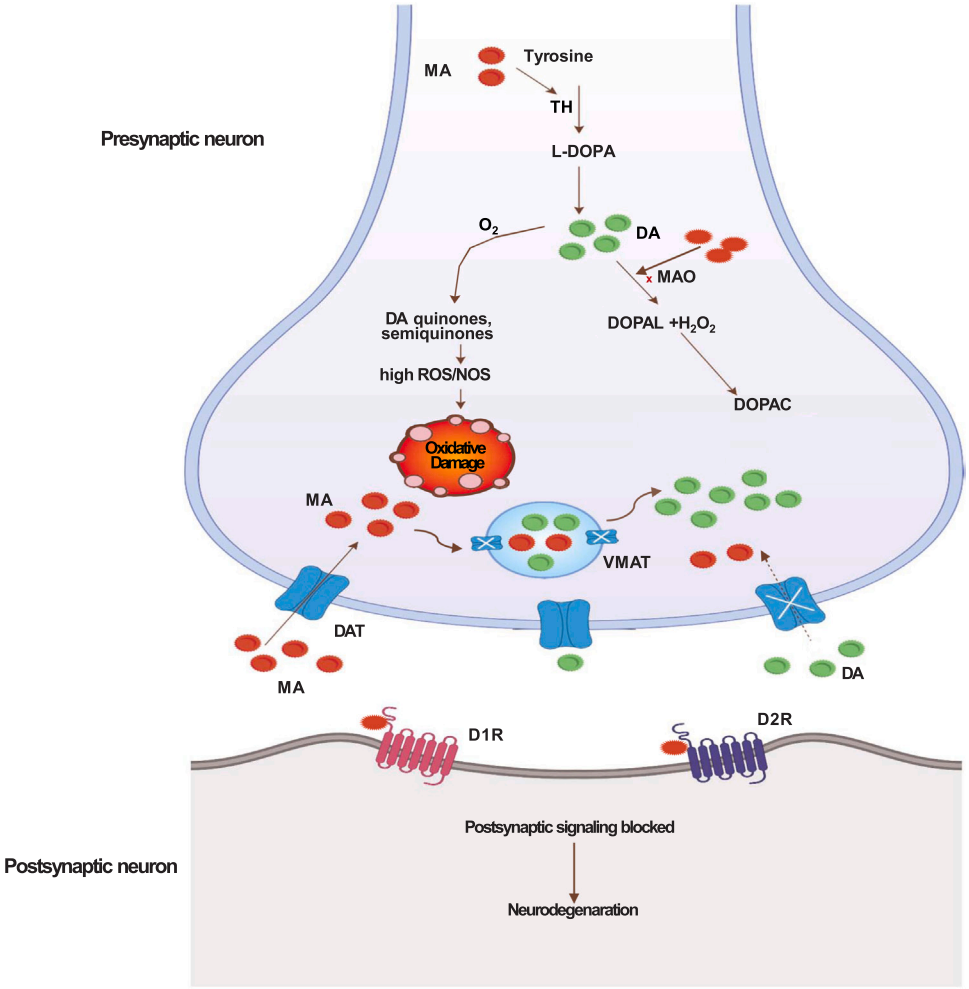

Fig. 3. MA and its effect on dopamine biology in dopaminergic synapse leading to neurodegenerative condition similar to PD. MA exposure leads to increased level of free DA accumulation which converts to highly toxic quinones causing increased ROS level. MA alters the vesicular storage of DA and decreases monoamine metabolism by inhibiting monoamine oxidase. MA also revert or inhibit the activity of DAT resulting in high accumulation of DA. Chronic treatment of MA also stimulate the activation of dopaminergic receptors. All of these events lead to neurodegenerative conditions.

is linked with changes in glutamate signaling, and high number of glutaminergic neurons are found in AD affected tissues [80–82]. NMDA receptors are only activated synoptically under certain physiological conditions, such as during the induction of synaptic plasticity, leading to excitotoxicity and neurodegeneration [76,80]. The hippocampus, which consists of high densities of glutamate receptors, particularly NMDA receptors, is of particular importance for memory and learning activity. Glutaminergic synapses with pronounced plasticity with regard to the strength and number of individual synapses show the ability to express long-term potentiation (LTP) [80]. NMDA receptor mediates plasticity though LTP [76,83]. As a result of open NMDA receptors and high levels of synaptic activity, permanent alterations in the expression of post-synaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors occur along with LTP of synaptic transmission [76]. However, mild and moderate stimulation of synapses promotes long-term depression in the NMDA receptor [80]. The relationship between NMDA receptors and Aβ has been examined in several studies [84]. It has been observed that Aβ-promoted spine loss is linked to a reduction in NMDA receptors [85–88]. Additionally, it was found that synaptic disruption and loss led to the cognitive abnormalities in AD patients.

3.2.2. *Molecular mechanism of MA-induced AD*

The chronic consumption of MA triggers premature aging and disruption of brain function. Symptoms of toxicity due to MA are similar to those seen in AD and cause impaired working memory and decision making condition [89,90]. One of the parts of the striatum and key elements for addiction, called nucleus accumbens, shows close interaction with both the limbic structure (amygdala and hippocampus) and prefrontal cortex, which are found to be altered in AD. Moreover, AD causes a decrease in the size of subparts of the basal ganglia, which is the region responsible for addiction [91,92]. MA addiction results in notable behavioral sensitization along with significant alterations in different parts of the brain [93,94]. In addition, it was observed that loss of cerebral gray matter is common in MA users, indicating a significant decline in mental function [95].

The neurobiological variation observed in the hippocampus results in reduced neurogenesis and synaptic plasticity. MA shows a strong affinity towards the hippocampus, which is considered the primary psychostimulant target because of its effect on serotonergic and dopaminergic neurons [18]. Due to this, chronic use of MA results in a reduced volume of the hippocampus, while a high dose of MA disrupts the BBB, resulting in higher hippocampal neuronal degeneration, which ultimately leads to memory loss and learning inabilities [89]. In addition, MA has a significant impact on glutamate signaling and can alter the hippocampal glutaminergic neurotransmission system [96–98].

MA disrupts the BBB structurally and functionally [99]. A derivative of MA, 3,4-methylenedioxymethamphetamine (MDMA), causes long-term alterations in the permeability of the BBB in the hippocampus and striatum [100]. Glucose transporters, GLUT1 and GLUT3, are impaired by MA [101]. MA-induced alterations in BBB permeability are related to alterations in hippocampal tight junction protein levels and increased activity and immunoreactivity of matrix meatalloproteinase-9 (MMP-9) [102].

MA also causes genetic variation, which ultimately leads to degenerative brain diseases [103]. MA increases the risk of developing AD via a synuclein-mediated pathway. Polymorphism in some *SCNA* genes is associated with AD, and MA has been shown to enhance the hippocampal level of ASYN protein [104]. This enhancement in ASYN increases Aβ production from β-amyloid precursor protein (βAPP), and this connection between these two proteins has perceptible effects on AD progression [105]. MA also causes significant changes in the brain related to AD at an epigenetic level [106]. MA increases lipid peroxidation and total glutathione status, activates activator protein 1 (AP-1), and increases TNF-α, suggesting the possibility of triggering AD [107]. MA administration also enhances the expression of histone acetyltransferase proteins, which are considered key regulators of the expression of AD-related genes [108–110]. A single MA injection can cause a increase in the levels of acetylated H4K5 and H4K8 in a time dependent manner, as demonstrated by Martin et al., and this acetylation is associated with hippocampal LTP [110,111]. MA administration causes an increase in the level of activating transcription factor 2 (ATF2), which is responsible for histone acetylation. In addition, there is evidence that high and/or prolonged exposure to MA enhances the ASYN neuronal level by depressing methylation of the SNCA promoter region, suggesting a triggering effect of the drug on promoting AD [54].

MA can also trigger AD through microRNA (miRNA) dependent modifications [103]. MA causes AP-1 activation, a contributor to the pathogenesis of AD, via the miR-144 dependent downregulation of a disintegrin and metalloproteinase domain-containing protein 10 (ADAM10) [112]. Chronic use of MA causes a decrease in plasma expression of miR-181a [113] which is a key regulator of mammalian AMPA-type glutamate receptor [114] and is associated with AD pathogenesis. MA administration also downregulates the expression of both miR-212–3p and miR-138–5p, which are important regulators of neuronal plasticity and are associated with AD [115,116]. Besides these miRNAs other non-coding RNAs are also contributing to the MA-induced neurotoxicity and pathogenesis of AD. Many studies have demonstrated that MA-induced behavioral effects are influenced by changes in the expression of the non-coding RNA in the ventral tegmental region and nucleus accumbens [117]. Changes in the expression of long non-coding RNAs in the nucleus accumbens are of much important in regulating the MA-induced locomotor sensitization [118]. β secretase cleaving enzyme (BACE1) is considered as a crucial enzyme in AD pathophysiology. Overexpression of BACE1 leads to the accumulation of amyloid protein Aβ resulting in progression of AD. Expression of BACE1 is controlled by a long non-coding RNA BACE1 antisense transcript (BACE1-AS). MA treatment can positively modulate BACE1 transcription ultimately leading to Aβ production and AD pathology. Li, J., et al. confirmed a novel circular RNA, circHomer1 contributing to the MA-induced neuronal damages. They found that the knockdown of circHomer1 decreased the neuronal damage induced by MA treatment indicating the possibility of circHomer1 as a possible target for developing therapy on MA addiction [119]. Homer1 which is major gene related to synapses were found to have altered in neurological and psychiatric disorders. Recent studies also showed the alteration in expression of circHomer1 in some AD brain region [120]. These facts suggest that the MA-induced alteration in the expression of circHomer1 can leads to the possibility of AD. Another non-coding circular RNA circHIPK2 is found contributing to the activation of astrocytes following MA treatment via regulation of ER stress and autophagy [121]. Huang, R., et al. showed that MA treatment enhances the expression of these circHIPK2 and silencing their expression via circHIPK2 siRNA inhibited MA-induced astrocyte activation and autophagy. Also, this non-coding RNA, circHIPK2 is found to involved in Sigma-1 receptor (σ-1R) activation which is associated with the many neurological diseases including AD [122].

MA exposure significantly increases the expression of AD-associated pathological proteins, including amyloid precursor protein (APP) and phosphorylated tau protein [123]. Tau proteins are the major microtubule-associated proteins (MAPs) of normal mature neurons and are highly soluble protein isoforms produced by alternative splicing of the microtubule-associated protein tau (MAPT) gene. Higher accumulation of tau is considered one of the hallmarks of AD pathogenesis [124]. Tau is also considered as the building block for intraneuronal neurofibrillary tangles (NFT) seen in the brains of patients with AD. Tangles develop initially in the hippocampus and then extend to the entire brain, ultimately leading to shrinkage of the brain [125]. MAPs are responsible for regulating microtubule dynamics in the mammalian CNS by promoting their assembly and thus controlling the outgrowth of neurites and dendrite development, which is considered an essential step in neurogenesis [103] and Exposure to MA reduces MAP2 levels and decreases the density of dendritic spines in the hippocampus [126].

Cleaved tau (C-tau) levels in the hippocampus increase significantly with higher exposure to MA through caspase-dependent proteolysis of tau [127]. Aβ-dependent caspase activation promotes the formation of NFT by increasing the production of C-tau, which leads to neurodegeneration [128]. (Fig. 4).

3.3. Other MA-induced neurotoxic diseases

Activation of microglia in the brain due to excessive exposure to MA leads to reactive microgliosis [129], which is thought to be driving phenomenon for exacerbate neurotoxic diseases due to MA addiction [130]. The brains of MA addicts are characterized by significant microglial activation in dopaminergic and serotoninergic innervation areas, which could accelerate the development of neurodegenerative diseases such as Huntington disease (HD) [131]. HD is an inherited neurodegenerative disorder characterized by choreiform movements, psychiatric symptoms, and dementia. Byars et al. reported that substance abuse could be one of the potential factors for early age onset of HD [132]. Fleming et. al. in their study presented cases of persistent MA use responsible for potentially hastening the onset of motor symptoms in HD, leading to secondary neurodegenerative diseases [131]. However, they suggested the requirement of further research to better explain the relationship between substance abuse and the progression of HD.

Human immuno-deficiency virus-1 (HIV-1) patients who abuse MA have a higher incidence of HIV-1-associated dementia (HAD) [133]. HAD is one of the most frequent consequences of HIV-1 infection and is characterized by cognitive impairments as well as motor and behavioral dysfunctions. MA causes oxidative stress in the brain through ROS formed due to damaged dopaminergic neurons caused by an increase level of dopamine and glutamate in the brain [134,135]. In addition, HIV viral proteins (gp120 and Tat) causes oxidative stress in the brain, causing alterations in the BBB [136,137]. MA potentiated oxidative stress induced by the HIV-1 proteins gp120 and Tat at the BBB. In a study performed by Banerjee, Zhang et al. observed that animals treated with MA and HIV-1 viral proteins caused a decrease in the expression of submembranous peripheral zonula occludens-1 (ZO-1) protein and occludin. These proteins are the major components of the tight junction (Tj) protein in the BBB [138,139]. A decrease in the expression of ZO-1 and occludin causes alteration in the microenvironment of Tj protein, leading to impaired BBB and exacerbated oxidative stress in the brain.

Chronic use of MA can also leads to vascular events such as myocardial infraction and stroke which can occur in young age people [140]. Blood pressure elevation, vasculitis, or other vascular toxicity are proposed as significant mechanisms leading to stroke which can be either ischemic or hemorrhagic [141]. So, MA use appears to be one of the risk factor leading to stroke in user.

4. Current treatment strategies against MA-induced neurotoxicity

To treat MA-induced neurotoxicity, many strategies have been adapted to produce effective and efficient pharmaceutical effects. Most treatment strategies are currently under clinical and preclinical investigation (Summarized in Table 1). Treatment strategies are based on the mechanisms of neurotoxicity induction.

4.1 T. argeted therapy against oxidative stress

Many studies have shown that oxidative stress is one of the leading causes of MA-induced neurotoxicity. MA causes dopaminergic cell death by increasing the production of ROS and diminishing cellular ATP levels. MA interferes with dopamine reuptake, leading to its autooxidation and increased metabolism, which ultimately leads to the production of various ROS, superoxide, and nitrogen radicals, which are responsible

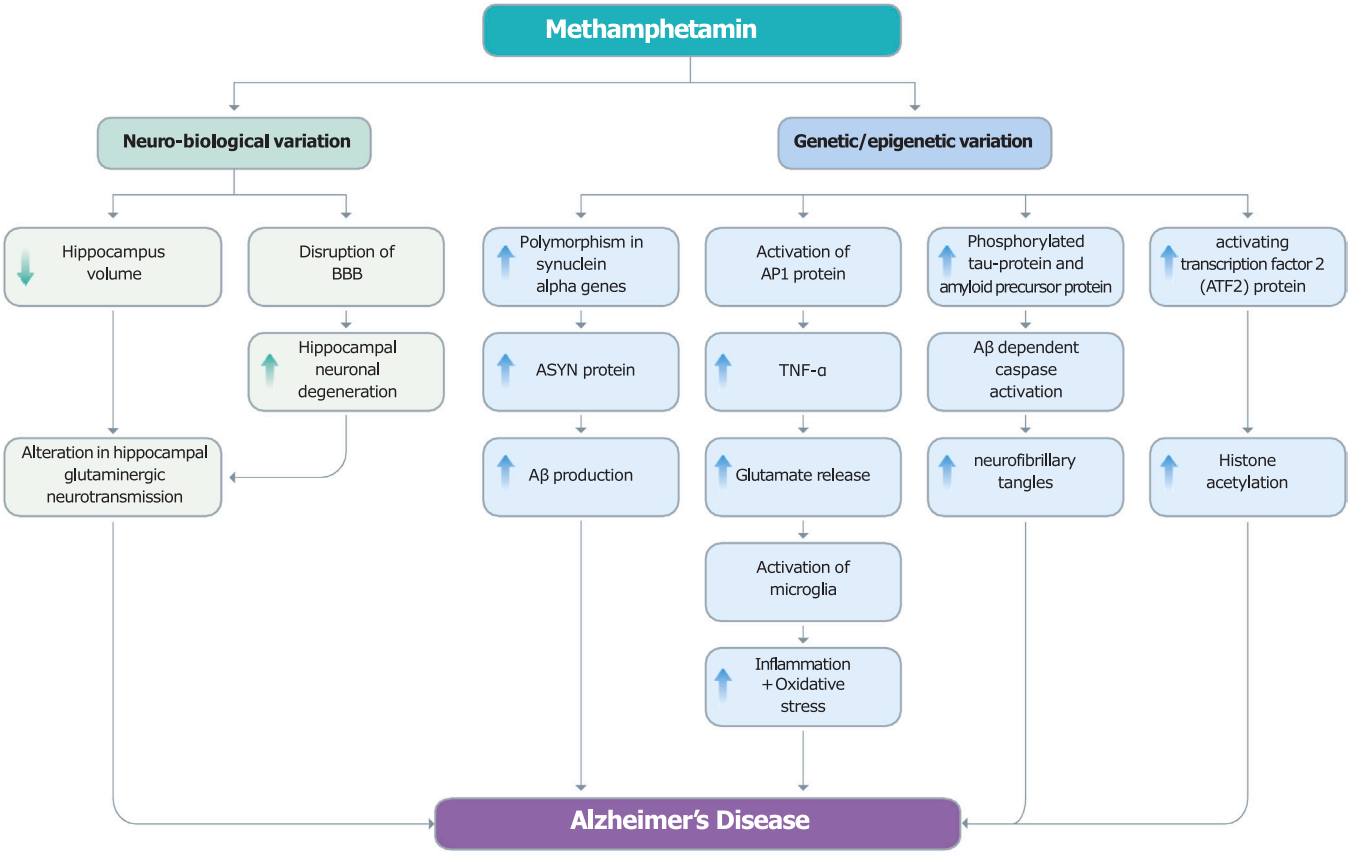

Fig. 4. Flowchart summarizing the molecular mechanism of MA-induced Alzheimer's disease (AD).

Table 1
Summary of potential approaches for the treatment of MA-induced neurotoxicity.

Therapy	Agent	Mechanism	References
Oxidative stress targeted therapy	Zinc,VitC, Anthocyanine, baicalein, isoliquiritigenin, *trans*-cinnamaldehyde, alpha-tocoferol and deferoxamine, propofol, selenium, talipexole, 6,7,4'-Trihydroflavanone	Attenuates oxidative stress by decreasing ROS level in brain cell and protect from neuronal damage	[5,53,142, 146,147,149, 150,152–154, 156,158,162, 164,167]
Anti-excitotoxicity therapy	Melatonin, NAC, NMDA antagonists (izocilpine, clomethiazole, Topiramate, Neuropeptide Y)	Diminishes excitotoxicity of MA by reducing the release of glutamate activating NMDA receptors and other glutamate receptors	[174,175, 178–181,183, 185,186]
Targeted therapy against mitochondrial toxicity	Lithium, valproate, nicotinamide, Oxytocin	Attenuates the MA-induced alteration in gene expression of several proteins related to mitochondrial function and apoptotic pathways	[188–192]
Nanoparticle based therapy	Liposomal melatonin, cerebrolysin nanodelivery,	Enhanced neuroprotection due to higher penetration	[201–205]
Immunotherapy	MH6-KLH, SMA–KLH, anti-METH/AMP mAb4G9, mAb7F9	stimulate antibody production that binds with the drugs following the systemic absorption of MA thereby decreasing the amount of drug entering the CNS	[206–211]
Gene therapy	Lipo/siROCK2, PAG608 antisense cDNA or small interfering RNA, GPx-1 encoded adenovirus vector	Suppresses the expression of genes (ROCK2, PAG608) contributing to MA-induced apoptosis	[213,214, 216]
Other approaches	Parkin protein, cytokines like IFN-γ, Δ9-THC, CB2 agonist, CCK-8, 9cRA, 7,8-DHF, PFT-α, renin-angiotensin inhibitors, MMP-9 inhibitors, Prolactin, aromadendrin	Stimulation of respective targets	[157,195, 217–220,223, 225,226,228, 231–233, 241]

for neuronal apoptosis [5]. Different pharmacotherapies have been studied for efficacious and effective treatment strategies that will protect neuronal cells from oxidative stress generated by MA. Numerous antioxidants have been demonstrated to have anti-neurotoxic properties against MA.

Ajjimaporn et al. (2007) demonstrated that pre-treatment with zinc markedly decreased the loss of cell viability caused by MA. They found that zinc pretreatment with $ZnCl_2$ increased the expression of MT and prevented the generation of ROS and ATP depletion caused by MA [53, 142]. Many studies have shown that metallothionine, a cysteine-rich intracellular protein, can inhibit the activity of ROS such as hydrogen peroxides [143,144] and provides protection to the brain cells against DNA damage induced by chemicals or radiation [145]. In addition, MA-induced ASYN expression decreased significantly upon treatment with zinc chloride solution. The possible efficacy of zinc in retarding the neurotoxic effects of MA on ASYN requires further investigation.

Vitamin C protects the brain from MA-induced neurotoxicity. It decreases free radical generation, maintains glutathione homeostasis, and promotes the expression of heme oxygenase 1 (HO-1), which is important for preventing cellular damage in the brain by regulating redox homeostasis [146,147]. Vitamin C reduces intracellular ROS generation and protects neurons from MA toxicity by inducing HO-1 expression via the p38 mitogen-activated protein kinase (MAPK) pathway [148]. Huang et al. demonstrated that treatment of cells with vitamin C reduced the expression levels of Beclin-1, light chain 3-II (LC3-II), and cleaved caspase-3, suggesting the protecting effects of vitamin C against MA neurotoxicity via the attenuation of ROS generation, apoptosis, and autophagy [149].

Flavonoids, which are non-enzymatic antioxidants, have been shown to be effective in the treatment of MA-induced neurotoxicity. Anthocyananine, a flavonoid with potent antioxidant properties, exerts neuroprotective effects by preventing neuronal cell death [150]. A study performed in a whisker rat model showed that active anthocyanine administration in the brain depressed the brain's oxidative stress and alterations in dopamine. Anthocyananine, along with a significant neuroprotective effect, restored the cell's ability to buffer calcium, which is affected by the oxidative stress induced by dopamine and amyloid-β [151]. Another flavonoid, baicalein, also showed neuroprotective effects, inhibiting the loss of dopamine transporter in the striatum caused by MA-induced neurotoxicity. It acts by inhibiting lipid peroxidation and neutrophil ROS production [152]. Lee et al. showed that isoliquiritigenin, a flavonoid with a chalcone structure, significantly prevented MA-induced dopamine transport and tyrosine hydrolase reduction when administered intraperitoneally prior to MA exposure. It also suppressed the activation of glial cells and inhibited the expression of NOS and NF-κa, a transcription factor activated by blocking phosphorylation [153]. Another naturally occurring flavonoids, Cinnamaldehyde present in the plant *Cinnamomum cassia* also showed the neuroprotective effects on MA-induced cytotoxicity [154]. Rashidi et. al. in their recent study showed that *trans*-cinnamaldehyde (TCA) exerted the protective effect against MA-induced neurotoxicity by suppressing the cytotoxicity and oxidative stress. Thymoquinone (TQ), a major constituent of plant *Nigella sativa* was also shown to have protective effects against the MA toxicity [155]. Roohbakhsh et. al. demonstrated that TQ can exert neuroprotective effects against MA-induced neurotoxicity and hyper locomotor activity in mice due to its antioxidant properties. Lee et. al showed the therapeutic potential of 6,7,4'- Trihidroxyflavanone (THF) against the MA-induced neurotoxicity [156]. They observed that THF, a naturally occurring compound isolated from plant *Dalbergia odorifera* shows protective effects against MA-induced neurotoxicity by regulating MA-induced oxidative stress modulating the expression of apoptosis related proteins. They found that THF induced nuclear factor erythroid 2-related factor 2 (NrF2) nuclear translocation to enhance the generation of cytoprotective enzyme HO-1 via the PI3K/Akt/mTOR signaling pathway. In their another study Lee et. al. showed that Aromadendrin, isolated from *Chionanthus retusus* protected cells from MA-induced neurotoxicity by regulating ER stress and PI3K/AKT/mTOR pathways[157]. They observed that pre-treatment with aromadendrin restored the expression of anti-apoptotic proteins following MA treatment suggesting the protective role of aromadendrin against MA-induced neurotoxicity. These results suggested that small molecules from the flavonoid family have potential to develop into therapy against MA-induced neurotoxicity.

Park Lee et al. showed that α-tocopherol (α-TF) and deferoxamine (DFO) prevents the stress due to oxidant and lipid peroxidation which results in the decrease level of neuronal damage due to MA toxicity [158]. α-TF is a ROS scavenger with antioxidant activity which by donating its hydrogen atom protects cells from toxic effects of ROS [159]. Jimenez et al. demonstrated that MA administered along with α-TF partially inverted the neurotoxic action and apoptotic features in cerebellar granules [160]. DFO, a chelating agent, decreases the

concentration of oxidative radicals by inhibiting the iron-catalyzed production of radicals. DFO significantly reduces the edema and disruption of the BBB by reducing the level of free iron [161]. Park et al. in their study showed that a low dose of DFO (50 mg/kg) reduced the decrease in striatal DA and serotonin content caused by repeated administration of MA. The chelation of free iron with DFO prevents the production of hydroxyl radicals caused by MA, thereby reducing DA and serotonin depletion [158]. Propofol, an intravenous sedative-hypnotic agent, has a chemical structure similar to that of α-tocopherol and has antioxidant effects in various experimental models [162]. In a study performed by Shokrzadeh et al., propofol was used to attenuate MA-induced neurotoxicity in rats. They found that propofol significantly reduced lipid peroxidation and ROS production in brain tissue and mitochondria isolated from the brain. They also observed that propofol attenuated MA-induced glutathione oxidation, which can be correlated with the generation of antioxidant enzymes and were found to significantly reverse the MA-induced mitochondrial toxicity by inhibiting mitochondrial permeability transition pore opening, mitochondrial membrane potential collapse, and inhibition of the mitochondrial pathway of apoptosis signaling. They found that propofol administration could be a promising approach to protect against MA-induced neurotoxicity [163].

Selenium is a naturally occurring mineral obtained in soil, food, and water. It is frequently supplied as a dietary supplement and antioxidant [164]. Kim et al. investigated the potential effect of dietary selenium on the neurotoxicity of dopaminergic neurons. They found that the glutathione peroxidase (GPx) activity and the ratio of reduced glutathione GSH to oxidized glutathione GSSG in the cerebellum, hippocampus, striatum, and substratum nigra in MA-treated mice were dramatically increased after selenium repletion, indicating attenuation in MA neurotoxicity through GPx-mediated antioxidant mechanisms [165]. Imam et al. showed that selenium treatment prevented the depletion of DA and its metabolites, DOPAC and homovanillic acid (HVA), in the caudate nucleus resulting from MA treatment [166]. When SH-SY5Y neuronal cells are treated with selenium, the enhanced oxidative stress caused by MA is reversed, probably due to a decrease in GPx levels [167]. However, due to the narrow therapeutic range selenium supplementation should be performed with caution to minimize possible negative effects [168,169].

MA abusers are more likely to acquire Parkinson's disease. Talipexole, an antiparkinsonian agent, was found to react significantly with hydroxyl radicals through a reaction mechanism similar to MA-induced neurotoxicity, demonstrating the neuroprotective effect of talipexole [170,171]. Furthermore, Kish et al. stated that DA replacement might potentially restore striatal DA deficiency produced by MA [172]. These findings suggest that antiparkinsonian medicines and treatments targeting brain areas can alleviate MA effects in the brain.

4.2. Anti-excitotoxicity therapy

As discussed earlier, the excitotoxicity of MA is caused by the higher release of glutamate activating NMDA receptors and other glutamate receptors, which leads to a hig Ca^{2+} influx and activates number of cellular activities. Thus, these receptors are considered potential sites for targeting MA-induced excitotoxicity and have gained much interest in the development of targeted therapies.

Melatonin, a pineal hormone, has potential protective action against oxidative stress and controls the intracellular movement of calcium ions in the CNS [173,174]. Ekthuwapranee et al. investigated the effect of melatonin on MA-induced alterations in cell proliferation. In this study, performed in hippocampal progenitor cells from adult Wistar rats, MA-induced alterations in the expression levels of NMDA receptor subunits, NR2A and NR2B, and Ca^{2+}-dependent protein kinase. They observed that pre-treatment with melatonin decreased the effects induced by MA, indicating a protective effect of melatonin against proliferation and neurogenesis resulting from MA exposure and prevents MA-induced memory and learning impairments [175]. Nopparat et al. investigated the fundamental action of melatonin on MA-induced neurotoxicity [176]. They found that melatonin has beneficial role in preventing Aβ generation in a cellular model of MA-induced AD. These observations suggest the potential role of melatonin in protection against mitochondrial dysfunction, dopaminergic degeneration, and apoptosis, which are considered potent contributors to MA-induced neurotoxicity.

Many researchers have also studied the effects of N-acetylcysteine (NAC), a precursor of the antioxidant glutathione, in models treated with MA because of its wide efficacy against different neurological disorders [177–179]. NAC has antioxidant activity and reduces the excitatory toxicity of glutamate, modulates DA release, improves mitochondrial dysfunction, and reduces the level of pro-inflammatory cytokines [180,181]. Hashimoto et al., from an in vitro study performed in monkeys, demonstrated that pre-treatment with IV bolus and subsequent continuous infusion of NAC in an MA-exposed model significantly reduced dopamine transport reduction [182]. Zhang et al. showed that NAC amine treatment in mice exposed to MA significantly reduced oxidative stress in the brain, liver, and kidneys by attenuating glutathione reduction and increasing the activity of glutathione, thereby suggesting the therapeutic potential of this drug in the treatment of MA-induced toxicity [183].

Several NMDA antagonists prevent MA-induced neurotoxicity. Baldwin et. al. showed that izocilpine, a potent non-competitive inhibitor of NMDA receptors, has an effective protective effect against MA-induced toxicity by preventing NMDA receptor overactivity downstream of DA release. Another drug, clomethiazole, a thiazole derivative with sedative and hypnotic effects, was found to be neuroprotective against MA-induced neurotoxicity by inhibiting dopamine release and, to some extent, by inhibiting NMDA mediated effects [184]. According to Ma et al. Topiramate, an anticonvulsant drug, has a higher potential to decrease MA-induced excitatory toxicity. They proposed that topiramate works by antagonizing multiple Glu receptors, blocking voltage-dependent Na+ channels, and inhibiting carbonic anhydrase [185]. Neuropeptide Y (NPY) is neuroprotective in several pathological conditions. Baptista et al. showed that MA-induced cell death is prevented by activating Y1 or Y2 receptors, and the Y1 subtype is responsible for preventing MA-induced neuronal differentiation [186].

Tetrahydropalmatine (THP) an active constituents of herbal plant species of genera Stephania and Corydalis has sedative, hypnotic and analgesic effects. THP is a dopamine receptor antagonist and reported to be used for the treatment of drug addiction. THP have shown to have neuroprotective effects against the MA-induced neurotoxicity [187]. Liu et. al. demonstrated that THP can alleviate the MA-induced neurotoxicity by regulating the brain-derived neurotrophic factor (BDNF) through the interaction between tyrosine kinase receptor B (TrkB)/calmodium (CAM). BDNF downregulation is related to the MA-induced neurotoxicity. THP decreases the influx of Ca^{2+} which will result in decrease CAM, increases TrkB and phosphorylate Akt. This leads to up-regulation the NF-κB and BDNF level thereby inhibiting apoptosis and MA-induced neurotoxicity [187].

4.3. Targeted therapy against mitochondrial toxicity

Enhancing mitochondrial activity may assist in alleviating neuronal plasticity and cellular resilience deficiencies associated with several neuropsychiatric diseases. *In vivo* studies performed by Bachmann et al. (2009) in SH-SY5Y cells showed that long-term therapy with lithium or valproate (VPA) protected against MA-induced damage at the mitochondrial level. MA-induced alterations in the gene expression of several proteins related to mitochondrial function and apoptotic pathways are attenuated by lithium or valproate, indicating the clinical utility of these drugs in MA-induced neurotoxicity [188]. MA can inhibit mitochondrial respiratory chain complexes by decreasing Krebs cycle enzyme activity Lithium and VPA reverses MA-induced energy metabolism dysfunction.

However, the effect of these drugs depends on the enzymes and brain parts involved, indicating the heterogeneity of oxidative stress parameters across the brain region [189].

Nicotinamide, a cofactor in the electron transport chain and a precursor of nicotinamide adenine dinucleotide (NAD), has been found to be effective in the treatment of mitochondrial encephalopathies [190]. In a study performed by Huang et al., nicotinamide treatment prior to MA administration decreased striatal DA and ATP content reduction, indicating the attenuation of the toxic effect of MA [191].

Oxytocin, a neuropeptide produced in the hypothalamus and released by the posterior pituitary, have also protective effects against the MA-induced toxicity [192]. Li et. al. has studied the neuroprotective effects of oxytocin against the MA-induced neuronal damage in rats. They found that the damage to the hippocampal neuron induced by the MA treatment is prevented by pre-incubation with the oxytocin. Pre-treatment with oxytocin attenuates the mitochondrial membrane potential and generation of ROS by regulating the MA-induced changes on apoptotic proteins in hippocampal neurons. Oxytocin treatment enhanced the expression of cleaved caspase-3 and reduced the expression of Bcl-2/Bax stimulated by MA treatment. Oxytocin attenuates MA-induced apoptosis via the activation of oxytocin receptor in hippocampal region. The involvement of oxytocin receptor activation in neuroprotective effects of oxytocin against MA-induced toxicity was confirmed by pre-incubating with a oxytocin receptor antagonist, atosiban. Pre-treatment with atosiban significantly prevented oxytocin mediated changes in hippocampal neuron which confirmed the association of neuroprotective effects of oxytocin with oxytocin receptor [192].

4.4. Anti-neuroinflammation therapy

Neuroinflammation plays a major role in causing neurotoxicity due to MA exposure and is also the most likely consequence of MA-induced damage. Since there are many mediators and pathways for neuroinflammation, there are also many endpoints that represent MA-induced damage [193]. The neurotoxicity of MA is mostly due to the inflammatory response generated by activated microglia. Sekine et. al. in their study suggested that chronic self-administration of MA can cause reactive microgliosis in the brains of human MA abusers [194]. Therefore, inhibiting microglial activation appears to be a viable strategy for reducing METH-induced neurotoxicity. Minocycline, a second-generation tetracycline, has both anti-inflammatory and neuroprotective effects and is a potent inhibitor of microglial activation and apoptotic pathways [195,196]. A study by Zhang et al. al. showed that minocycline significantly attenuated the increase in extracellular DA levels and DAT immunoreactivity following repeated administration of MA. They suggested that minocycline can possibly be used for inactivation of microglia and hence for the treatment of several symptoms related to MA exposure [197]. Ibudilast, a non-selective phosphodiesterase inhibitor, increases the glial derived neurotrophic factor (GFNF) level in the brain and attenuates the activation of microglia and cytokines responsible for pro-inflammation [198,199]. Modafinil, a cognitive-enhancing smart drug, also prevented MA-induced microglial activation in the brain, thus reducing the possibility of neuroinflammation [200].

4.5. Nanoparticles-based therapy

In the case of psychostimulant-induced neurotoxicity, treatment with a conventional drug at a standard dose did not induce satisfactory neuroprotection. Therefore, there is always a requirement for enhancing the drug dose or frequency of administration of these therapeutic drugs to achieve significant neuroprotection [201]. Nanoparticle-based therapy is considered more effective than parent drugs. Nanoparticles have better therapeutic effects because of their better penetration into the CNS at high concentrations. This will result in a slow and controlled release of therapeutic agents for an extended period of time [202]. Nguyen et al. performed an experiment to demonstrate the effectiveness of liposomal delivery of melatonin in MA-induced oxidative burden. Although melatonin can pass through the tissue and reach the cell compartment owing to its small molecular weight and amphiphilic nature, this therapy has certain disadvantages because of its short half-life and low solubility in water, which leads to variability in oral absorption. Thus, Nguyen et al. utilized liposomes to enhance drug solubility and absorption. They observed that liposomal melatonin was more efficacious than melatonin in MA-induced neurotoxicity in mice. Liposomal melatonin significantly attenuated hyperthermia, oxidative damage, mitochondrial dysfunction, proapoptotic changes, and dopaminergic loss by inactivating protein kinase C-δ [203]. The efficacy of nano-delivery of Cerebrolysin or H-290/51 in MA-induced neurotoxicity was studied in rat models at high and low ambient temperatures by Sharma et al. They showed that the standard dose of H-290/51 (50 mg/kg) or cerebrolysin (2.5 ml/kg) when delivered using TiO_2 nanowires, significant neuroprotection was observed [202,204]. These studies suggest that nanoparticle-based therapy could be a better option with enhanced efficacy for the treatment of MA-induced neurotoxicity. In addition, nanoparticles can also be utilized for imaging and MA detection in MA intoxication [205].

4.6. Immunotherapy

Immunotherapy in the form of passive immunization (monoclonal antibodies) can be utilized to decrease the quantity of drug entering the CNS by stimulating antibody production that binds with the drugs following the systemic absorption of MA [206]. Many studies have been performed on MA addiction and toxicity using passive immunization with monoclonal antibodies and have been studied with renewed interest, although inconsistent results were obtained with some previous studies [207]. A study performed by Miller et al. in rats showed that rats injected with a keyhole limpet hemocyanin (KLH) conjugated with methamphetamine-like hapten vaccine (MH6-KLH) and vaccine succinyl MA (SMA–KLH) had increased MA levels in serum and reduced levels in the brain after acute MA injection. They suggested that this anti-methamphetamine vaccine stimulates neuroprotection against MA-induced neurotoxicity [208]. Another study performed using anti-METH/AMP mAb4G9 was shown to protect rat brains from MA-induced damage [209,210]. Ballester et al. showed that the binding of a human monoclonal antibody to methylphenidate (mAb7F9) resulted in a significant reduction in the MA concentration entering the brain. A combinational method employing monoclonal and polyclonal antibodies was found to be more efficient in achieving a higher anti-MA antibody response and lowering MA levels in the brain [211]. Although vaccine immunotherapy is gaining interest in the treatment of MA, there are certain limitations, including the lack of complete blockade of the drug's effect, delay in adequate circulating antibody production, variation in antibody titers, and its inability to cross the BBB, making it more expensive [207,212].

4.7. Gene therapy

Rho-associated kinase II (ROCK2) is a promising target for gene therapy. Inhibition of ROCK2 protects cell in a variety of pathophysiological conditions. MA abusers have been linked to PD development and silencing of ROCK2 protect neurons from MA toxicity. ROCKs are considered to play a significant role in the pathogenesis of PD and are also identified as a potential therapeutic target in MA-induced neurotoxicity in in vitro studies, which laid the groundwork for future in vivo studies. In a study performed by Yang et al., MA exposure increased the expression of ROCK2 protein in P12 cells. They showed that MA exposure leads to disorientation of dendritic arbors and shortening of neurite length, and the recovery of morphology was achieved in P12 cells treated with Lipofectamine 2000 (Lipo)/single interfering ROCK2. Lipo/

siROCK2 significantly reduced MA-induced apoptosis, increased cell viability, and reversed the morphological changes caused by MA exposure at P12. These results suggest that ROCK2 is a potential target for the treatment of MA-induced neurotoxicity [213]. In oxidative stress-induced apoptosis of neuronal cells, the pro-apoptotic gene PAG608 is activated and controlled by p53 expression. Studies have shown that suppression of PAG608 with PAG608 antisense cDNA or small interfering RNA decreases MA-induced toxicity. This suggests that MA-induced neurotoxicity is related to the induction of PAG608 expression to some extent in monoaminergic cells, making it a possible target for the therapeutic approach [214].

GPx is considered as the main an antioxidant enzyme that catalyzes H_2O_2 into water and alcohol [215]. Sharma et. al. in one of their findings suggested that selenium dependent glutathione peroxidase (GPx-1) is shows protective role against MA-induced neurotoxicity [216]. They constructed a GPx-1 gene encoded adenoviral vector (Ad-GPx-1) to prove the protective role of GPx-1 in MA-induced neurotoxicity. They observed the enhanced GPx activity and GPx-1 protein level in GPx-1 knockout mice and also found that interaction between NF-κB and GPx-1 is essential for the neuroprotective effects. Treatment with Ad-GPx-1 significantly reduced MA-induced dopaminergic loss via overexpression of *GPx-1* gene. They successfully demonstrated that Ad-GPx-1 therapy can prevent the dopaminergic toxicity following MA abuse [216].

4.8. Other approaches for protection against MA-induced neurotoxicity

Parkin, a ubiquitin-protein E3 ligase, is a part of the ubiquitin proteasome system that mediates the targeting of proteins for degradation. A decrease in parkin function results in degeneration of DA neurons, and overexpression of parkin protects DA from various cellular insults, including those involved in mediating MA neurotoxicity [195,217–219]. Parkin protects DA neurons in the substantia nigra from several assaults such as hydroxydopamine [220], overexpression proteins such as ASYN [221], and tau [222]. Lo Bianco et al. showed that in an ASYN rat model mimicking conditions of Parkinson's disease, lentiviral vector delivery of parkin minimized dopaminergic degradation [223]. In rats treated with MA, an increase in parkin levels reduced MA-induced reduction in striatal tyrosine hydroxylase immunoreactivity, suggesting a protective effect of parkin on dopaminergic terminals against MA-induced neurotoxicity [224].

Cytokines, such as interferon (IFN)-γ, can exert a variety of effects on the CNS. IFN-γ is an inflammatory cytokine that is critical for both innate and adaptive immunity. Yu et al. demonstrated that MA treatment significantly decreased the production of IFN-γ [225]. Hozumi et al. studied the neuroprotective effects of IFN-γ on MA-induced striatal neurotoxicity in mice. They showed that the intraperitoneal and intracerebroventricular injection of IFN-γ before MA exposure significantly prevented MA-induced reduction of DAT, suggesting a protective effect of IFN-γ against MA-induced neurotoxicity [226].

Many in vitro and in vivo studies have shown that natural cannabinoids such as Δ9-tetrahydrocannabinol (Δ9-THC), cannabinol, and synthetic CB receptor agonist, can attenuate experimentally induced neurotoxicity in pathological conditions such as glutamate excitotoxicity, hypoxia, ischemic stroke, brain trauma, and oxidative stress [227–230]. Castelli et al. investigated the neuroprotective effect of Δ9-THC on MA-induced neurotoxicity. They observed that the pre-and post-treatment of Δ9-THC significantly reduced MA-induced nNOS overexpression in the caudate putamen (CPu) and GFAP immunoreactivity in the prefrontal cortex. They showed that Δ9-THC reduced MA-induced brain damage by inhibiting nNOS overexpression and astrocyte activation, indicating the potential role of Δ9-THC in attenuating MA-induced neurotoxicity [231]. Another study performed by Torres et al. showed the potential neuroprotective effect of cannabinoid CB2 agonist against MDMA, a derivative of MA, induced neurotoxicity and the ability of this compound to inhibit IL-1β release and microglial activation in the frontal cortex and hypothalamus of MDMA-treated rats, suggesting that CB2 receptor is a potential target for drug-induced neurotoxicity [232].

The gut-brain peptide cholecystokinin (CCK) has a wide variety of biological actions in the gastrointestinal tract and CNS. CCK-8 plays an important role in learning and memory and in the pathogenesis of several brain diseases [233]. It acts as a modulator/neurotransmitter and modulates the release of neurotransmitters such as DA and gamma-aminobutyric acid (GABA) [234]. CCK-8 has been proven to have antioxidative and anti-inflammatory properties in previous research [235,236]. Furthermore, it exhibits neuroprotective properties in neural damage models. Gau et al. showed that pretreatment with CCK-8 reduced hyperlocomotion, behavioral sensitization, stereotypic behavior, and dopaminergic neurotoxicity induced by MA exposure, suggesting that CCK-8 is a prominent therapeutic agent for treating MA-induced neurotoxicity [237].

Other drugs under study for the treatment of MA-induced neurotoxicity include 9-*cis*-retinoic acid (9cRA), 7,8-dihydroxyflavone, and (PFT-α) etc. [238–240]. Reiner et. al. demonstrated that the derivatives of vitamin-A, 9cRA which is biologically functioning restored MA-induced decrease in immunoreactivity and mortality of T-helper cells in primary cultured dopaminergic neurons. Ren et al. discovered that 7,8-DHF dramatically reduced DAT and activation of microglia in the mouse striatum following MA exposure, suggesting a protective role of 7,8-DHF in reducing MA-induced neurotoxicity. Similarly, Chen et. al. demonstrated that treatment with the p53 inhibitor, PFT-α, antagonized MA-mediated behavioral deficits in mice. MA exposure reduced tyrosine hydroxylase immunoreactivity and increased terminal deoxynucleotidyl transferase-mediated dNTP nick end labeling, and PFT-α antagonizes these responses. These data suggest that PFT-α is neuroprotective against MA-induced neurodegeneration via transcription-dependent and -independent pathways.

MA-induced neurotoxicity is mainly due to the DA level imbalance and the degeneration of BBB. Damage to the BBB can lead to the release of the toxic and harmful substances to the CNS causing neurotoxic effects. The renin angiotensin system, MMP-9 inhibitors, and prolactin showed the protective effects in MA-induced neurotoxicity [241]. Zhao et. al. summarized the therapeutic benefits of renin angiotensin system, MMP-9 inhibitors, and prolactin. The renin angiotensin system regulates the DA level, MMP-9 inhibitors diminishes the behavioral sensitization by reducing DA level and prolactin regulates the tight junction and maintains the integrity of the BBB [241].

5. Conclusion and future perspectives

MA, a recreational drug with very high abuse potential, is a potent stimulant of the central nervous system. MA-dependence causes long-term neuronal damage, along with harmful effects on cognition, memory, and attention [3]. Due to its lipophilic nature, it can easily cross the BBB and enter the brain, where it releases various neurotransmitters by interacting with different cell surface receptors, which have the potential to trigger neurotoxic effects in the brain. Dopamine depletion, oxidative stress, activation of astrocytes and microglial cells, axonal transport barrier, autophagy, and apoptosis are considered major factors that play a crucial role in the neurotoxicity caused by MA. However, the complete molecular and cellular mechanisms underlying MA-induced neurotoxicity are still unknown. MA abuse has been linked to an increased risk of developing neurotoxic diseases, such as PD and AD. MA increases the risk of PD by increasing the expression of ASYN protein, thereby increasing oxidative stress. Furthermore, MA abuse is associated with an increased risk of developing AD and subsequent neurodegeneration. Previous studies suggest that MA triggers the pathogenicity of AD by causing neurobiological variations in the hippocampal region, disrupting the BBB, and causing genetic and epigenetic variations.

The long-term use of MA creates neuropsychiatric deficits, making

addiction to this substance exceedingly difficult to overcome. Relapse rates following current MA abuse treatments are high [242]. MA addiction is linked to long-term structural damage to the brain, which causes neurotoxic effects. Although considerable progress has been made in determining the mechanism of the neurotoxic effect of MA in the human brain, these findings have not yet led to the development of an effective therapeutic approach for the treatment of MA-induced neurotoxicity. To date, there is no Food and Drug Administration (FDA)-approved therapy for MA-induced neurotoxicity, although many studies are being conducted to develop effective therapeutic strategies. Most studies have focused on diminishing the effects of MA-induced neurotoxicity based on the underlying mechanism. This review article provides information about the potential mechanism of MA-induced neurotoxicity and discusses current research on various treatment strategies targeting different pathways to diminish the neurotoxic effects of MA in the brain. Although the majority of research so far has focused on utilizing natural compounds, researchers are currently trying to develop effective targeted therapies, such as immunotherapy, nanoparticle-based therapy, and gene therapy, for the treatment of MA-induced neurotoxicity.

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CRediT authorship contribution statement

Prabhat Shrestha: Conceptualization; Investigation; data curation; Visualization; Writing – original draft preparation; Writing – review & editing. **Nikita Katila**: Conceptualization; Writing – original draft preparation; Writing – review & editing. **Sooyeun Lee**: Conceptualization; Writing – review & editing. **Ji Hae Seo**: Conceptualization; Writing – review & editing. **Jee-Heon Jeong**: Conceptualization; Visualization; Supervision; Writing – original draft preparation; Writing – review & editing. **Simmyung Yook:** Conceptualization; Data curation; Visualization; Supervision; Writing – original draft preparation; Writing – review & editing; Funding acquisition.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

Author contributions

Conceptualization, writing—original draft preparation, P.S, N.K, S.L, J.S, J.J and. S. Y. All authors have read and agreed to the published version of the manuscript.

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