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Methamphetamine-Induced Neurodegeneration: Role of Oxidative Stress, Neuroinflammation, Excitotoxicity and Mitochondrial Toxicity

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ABSTRACT

Background: Methamphetamine (METH) is a potent psychostimulant associated with substantial neurotoxicity and progressive neuronal damage. Its neurodegenerative effects involve multiple interconnected cellular and molecular mechanisms, including oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction.

This study aimed to examine the major mechanisms underlying METH-induced neurodegeneration and summarize potential therapeutic approaches targeting these pathways

Methods: Experimental evidence concerning METH-induced alterations in dopaminergic and glutamatergic neurotransmission, reactive oxygen species (ROS) generation, microglial activation, inflammatory signaling, mitochondrial dysfunction, excitotoxicity, and apoptosis was evaluated. Evidence regarding antioxidant, anti-inflammatory, mitochondrial-protective, and glutamate-modulating interventions was also considered.

Results: METH markedly increases dopamine and glutamate release, promoting ROS generation and excitotoxic neuronal injury. Oxidative stress contributes to lipid, protein, and DNA damage, whereas microglial activation increases inflammatory cytokines, including TNF-α, IL-1β, and IL-6. METH-associated mitochondrial dysfunction further increases ROS production, decreases ATP availability, and promotes apoptotic signaling. These mechanisms interact through reinforcing feedback pathways that accelerate neuronal degeneration. Several experimental compounds, including antioxidants and glutamate-modulating agents, demonstrate neuroprotective potential.

Conclusion: METH-induced neurodegeneration results from interconnected oxidative, inflammatory, excitotoxic, and mitochondrial mechanisms. Multi-target therapeutic strategies may provide greater neuroprotection than approaches directed toward a single pathway

Keywords: Methamphetamine; Neurodegeneration; Oxidative Stress; Neuroinflammation; Mitochondrial Dysfunction

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INTRODUCTION

Methamphetamine (METH) is a potent psychostimulant that produces profound effects on the central nervous system (CNS) [1,2]. Its high lipid solubility enables rapid passage across the blood–brain barrier, where it interacts with monoaminergic and glutamatergic neurotransmitter systems [3]. METH markedly increases the extracellular concentrations of dopamine (DA), norepinephrine, serotonin, and glutamate (Glu), producing intense stimulation, increased alertness, euphoria, and behavioral changes. However, repeated or high-dose exposure can produce persistent neuronal alterations and neurodegeneration, particularly within dopaminergic pathways of the striatum and related brain regions [4]. METH-associated neurotoxicity has therefore become an important experimental model for understanding mechanisms involved in neuronal injury and neurodegenerative disorders [5,6].

A major feature of METH toxicity is excessive dopaminergic neurotransmission [7,8]. METH disrupts vesicular dopamine storage and dopamine transporter function, resulting in increased cytoplasmic and extracellular DA concentrations [9,10]. Excessive intracellular DA can undergo auto-oxidation and enzymatic metabolism, producing reactive oxygen species (ROS), dopamine quinones, and other reactive metabolites [11]. These products can damage cellular proteins, membrane lipids, and nucleic acids. In addition, increased DA metabolism may interfere with normal neuronal homeostasis and contribute to degeneration of dopaminergic terminals. The severity of these effects depends on the dose, duration, and frequency of METH exposure, with repeated exposure generally producing more pronounced neurochemical and structural alterations [12,13].

Oxidative stress represents one of the central mechanisms through which METH causes neuronal damage [14]. Oxidative stress occurs when ROS production exceeds the capacity of endogenous antioxidant systems to neutralize reactive molecules [15]. METH exposure increases the generation of

superoxide, hydrogen peroxide, hydroxyl radicals, and reactive nitrogen species, while simultaneously impairing antioxidant defenses [16,17,18]. Excessive ROS can initiate lipid peroxidation, protein oxidation, DNA damage, and mitochondrial dysfunction [19,20]. Increased lipid peroxidation products, including malondialdehyde, have been reported following METH exposure and are associated with damage to neuronal membranes. Oxidative damage may also promote apoptosis and amplify other pathological processes involved in neurodegeneration [21].

Neuroinflammation is another important component of METH-induced neuronal injury. METH exposure can activate microglia, the principal immune cells of the CNS, leading to the production of inflammatory cytokines, chemokines, ROS, and other neurotoxic mediators [22]. Activated microglia can release tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), and interleukin-6 (IL-6), which can further increase neuronal stress and promote tissue injury [23]. Toll-like receptor signaling and downstream NF-κB and MAPK pathways have also been implicated in METH-associated inflammatory responses. Importantly, oxidative stress and neuroinflammation may form a positive feedback loop in which ROS stimulate inflammatory signaling, while inflammatory cells generate additional ROS, thereby intensifying neuronal damage.

Glutamate-mediated excitotoxicity further contributes to METH-induced neurodegeneration. Glutamate is the major excitatory neurotransmitter in the CNS, and excessive extracellular Glu can produce prolonged activation of NMDA and other glutamate receptors [24]. This results in excessive Ca^{2+} influx and activation of intracellular enzymes capable of damaging proteins, membrane structures, and DNA. METH-induced increases in glutamate release can therefore promote neuronal excitotoxicity [25]. Moreover, inflammatory activation of glial cells may further disturb glutamate uptake and increase extracellular glutamate concentrations, linking excitotoxicity with neuroinflammation and oxidative stress.

Mitochondrial toxicity provides an additional pathway through which METH compromises neuronal survival. Mitochondria are essential for ATP production, calcium regulation, and cellular redox balance, but they are also highly susceptible to oxidative damage. METH can impair mitochondrial respiratory-chain activity, reduce ATP production, increase mitochondrial ROS generation, and alter mitochondrial dynamics [26,27]. Damage to mitochondria can promote membrane depolarization and release of cytochrome c, ultimately activating apoptotic pathways. Alterations in mitochondrial fission, mitophagy, and biogenesis may further reduce the ability of neurons to maintain functional mitochondria.

The interaction among these mechanisms is particularly important. Dopamine dysregulation can initiate oxidative stress, while mitochondrial impairment can further increase ROS production. ROS and damaged neuronal components can activate microglia, leading to neuroinflammation, whereas inflammatory mediators can enhance glutamate excitotoxicity. Excitotoxic calcium overload can subsequently increase mitochondrial dysfunction and apoptotic signaling [28,29]. Thus, METH-induced neurodegeneration should be considered a complex and interconnected process rather than the consequence of a single molecular pathway.

Despite extensive evidence concerning individual mechanisms, a comprehensive understanding of how oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial toxicity interact remains important for identifying effective therapeutic strategies. Antioxidants, anti-inflammatory compounds, mitochondrial protective agents, and modulators of glutamatergic signaling have therefore been investigated as potential interventions. A clearer understanding of these interconnected pathways may facilitate the development of multi-target approaches for reducing METH-associated neuronal injury. Accordingly, the present study focuses on the major molecular and cellular mechanisms underlying METH-induced neurodegeneration, with particular emphasis on oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction.

METHODOLOGY

The present study was designed as a comprehensive experimental investigation of methamphetamine (METH)-induced neurodegeneration, with particular emphasis on oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction. Evidence from in vivo animal models and in vitro neuronal and glial cell models was considered to characterize the major molecular mechanisms associated with METH-induced neuronal injury and to evaluate potential neuroprotective interventions.

Experimental studies involving METH exposure were evaluated according to the biological model, treatment conditions, and investigated mechanism. Relevant experimental models included rodents, neuronal cell lines such as PC12 and SH-SY5Y cells, primary neuronal cultures, and other established neural models. METH exposure was assessed in relation to dopaminergic and glutamatergic neurotransmission, reactive oxygen species (ROS) generation, inflammatory signaling, mitochondrial dysfunction, excitotoxicity, and neuronal apoptosis or necrosis.

For evaluation of oxidative stress, studies measuring ROS generation, lipid peroxidation, antioxidant status, mitochondrial oxidative damage, and related molecular markers were considered. Particular attention was given to markers such as malondialdehyde (MDA), nitric oxide, superoxide, hydrogen peroxide, glutathione, and antioxidant enzymes. Changes in oxidative damage to proteins, lipids, and DNA were also considered as indicators of METH-associated cellular injury.

For assessment of neuroinflammation, experimental evidence concerning microglial activation and inflammatory signaling was evaluated. Major inflammatory mediators, including TNF-α, IL-1β, and IL-6, together with NF-κB, MAPK, TLR4/MyD88, PI3K/Akt, and related signaling pathways, were considered. Studies examining the interaction between activated microglia, ROS production, glutamate release, and neuronal damage were included.

The excitotoxic mechanism was evaluated by examining METH-associated alterations in glutamate release and glutamate receptor activity, particularly NMDA receptor signaling and intracellular Ca^{2+} accumulation. Evidence of endoplasmic reticulum stress, activation of apoptotic signaling, and cytoskeletal damage was also considered to

characterize downstream effects of excessive glutamatergic stimulation.

For mitochondrial toxicity, studies investigating mitochondrial respiratory-chain activity, ATP production, ROS generation, mitochondrial morphology, fission and fusion, mitophagy, and mitochondrial biogenesis were assessed. Molecular markers including DRP1, FIS1, PINK1, Parkin, PGC-1α, NRF1, and TFAM were considered where reported. Evidence of cytochrome-c release and mitochondrial-dependent apoptosis was also evaluated.

Finally, studies investigating potential therapeutic approaches against METH-induced neurotoxicity were assessed and grouped according to their principal protective mechanism. These included antioxidant, anti-inflammatory, anti-excitotoxic, mitochondrial-protective, and anti-apoptotic interventions. Treatment agents such as melatonin, curcumin, resveratrol, cinnamaldehyde, thymoquinone, gastrodin, erythropoietin, α-pinene, rosmarinic acid, and other experimentally investigated compounds were considered. The overall evidence was synthesized to identify how these interventions counteract oxidative stress, inflammation, excitotoxicity, and mitochondrial dysfunction associated with METH exposure.

RESULTS

The analysis demonstrated that methamphetamine (METH) exposure produces neurodegenerative changes through interconnected mechanisms involving oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction. Across the experimental models, METH exposure was consistently associated with increased dopaminergic and glutamatergic activity, elevated reactive oxygen species (ROS), inflammatory signaling, mitochondrial impairment, and neuronal cell death.

Methamphetamine-Induced Neurotoxicity

METH exposure produced marked alterations in central neurotransmitter systems, particularly dopamine (DA), serotonin, norepinephrine, and glutamate (Glu). Increased DA release and impaired neurotransmitter reuptake were associated with oxidative damage and degeneration of dopaminergic terminals. Excessive Glu release was also observed following METH exposure, indicating an interaction between dopaminergic stimulation and glutamatergic excitotoxicity. These changes were accompanied by neuronal damage and behavioral abnormalities in experimental models.

Oxidative Stress

A prominent finding was the elevation of oxidative stress following METH exposure. Increased ROS and lipid peroxidation were accompanied by elevated malondialdehyde (MDA) levels and depletion of cellular antioxidant capacity. Oxidative damage affected proteins, lipids, and DNA, while increased nitric oxide production further contributed to neuronal injury. METH-associated oxidative stress was particularly evident in dopaminergic brain regions and was linked with mitochondrial dysfunction and neuronal degeneration.

Table 1. Major oxidative and cellular changes associated with METH exposure

Parameter	Effect of METH exposure	Major consequence
ROS	Increased	Oxidative damage
MDA	Increased	Lipid peroxidation
Nitric oxide	Increased	Nitrosative stress
Antioxidant capacity	Decreased	Reduced cellular defense
Protein oxidation	Increased	Protein dysfunction
DNA damage	Increased	Nuclear injury
ATP production	Decreased	Energy failure

Neuroinflammation

METH exposure resulted in substantial activation of neuroinflammatory pathways. Increased microglial activation was associated with enhanced production of pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6. Activation of TLR4/MyD88 and NF-κB signaling was identified as an important component of the inflammatory response. MAPK and PI3K/Akt-associated signaling were also altered following METH exposure. The inflammatory response was accompanied by increased ROS production and extracellular Glu, suggesting a positive feedback interaction between inflammation, oxidative stress, and excitotoxicity.

Table 2. Principal inflammatory responses following METH exposure

Marker/pathway	Observed response	Associated effect
Microglial activation	Increased	Neuroinflammation
TNF-α	Increased	Neuronal injury
IL-1β	Increased	Inflammatory signaling
IL-6	Increased	Neuroinflammatory response
TLR4/MyD88	Activated	NF-κB activation
NF-κB	Activated	Cytokine production
MAPK	Activated	Inflammatory signaling
ROS	Increased	Oxidative-inflammatory damage

Excitotoxicity and Neuronal Cell Death

The results indicated that excessive glutamatergic activity contributed substantially to METH-induced neuronal injury. Increased extracellular Glu promoted activation of NMDA receptors and excessive intracellular Ca^{2+} influx. This process was associated with activation of downstream enzymes and cellular pathways involved in membrane, protein, and DNA damage. METH exposure also increased markers associated with endoplasmic reticulum stress, including ATF4, CHOP, and caspase-12. These changes were accompanied by activation of apoptotic pathways and degradation of neuronal cytoskeletal components.

Mitochondrial Toxicity

METH exposure produced considerable mitochondrial dysfunction. Experimental findings indicated impaired mitochondrial respiratory-chain activity, reduced ATP production, increased mitochondrial ROS generation, and alterations in mitochondrial morphology. Changes in mitochondrial dynamics were accompanied by alterations in FIS1, DRP1, PINK1, and Parkin, suggesting disruption of

mitochondrial fission and mitophagy. Alterations in PGC-1α, NRF1, and TFAM further indicated impaired mitochondrial biogenesis. Mitochondrial fragmentation and cytochrome-c release were associated with activation of apoptotic pathways.

Table 3. Major mitochondrial alterations associated with METH neurotoxicity

Mitochondrial parameter	Effect of METH	Functional consequence
Respiratory-chain activity	Decreased	Energy dysfunction
ATP production	Decreased	Cellular energy failure
Mitochondrial ROS	Increased	Oxidative damage
Mitochondrial fragmentation	Increased	Structural dysfunction
PINK1/Parkin signaling	Altered	Abnormal mitophagy
PGC-1α/NRF1/TFAM	Altered	Impaired biogenesis
Cytochrome-c release	Increased	Apoptotic activation
RIP3/MLKL signaling	Activated	Necrotic cell death

Effects of Neuroprotective Treatments

The investigated therapeutic studies showed that several pharmacological and natural compounds reduced different aspects of METH-induced neurotoxicity. Antioxidant interventions such as resveratrol, curcumin, melatonin, thymoquinone, cinnamaldehyde, rosmarinic acid, tea polyphenols, and tertiary butylhydroquinone reduced oxidative damage and/or apoptotic responses. Other interventions, including erythropoietin, gastrodin, aromadendrin, α-pinene, thioperamide, and calcitriol, demonstrated protective effects through antioxidant, anti-inflammatory, anti-apoptotic, or signaling-related mechanisms.

Table 4. Representative neuroprotective interventions against METH-induced toxicity

Treatment	Experimental model	Principal protective effect
Calcitriol	Rat	Reduced serotonergic toxicity
Melatonin	Cells/rodents	Antioxidant and anti-excitotoxic effects
Resveratrol	Mice	Reduced oxidative damage and apoptosis
Curcumin	Rat/PC12 cells	Antioxidant protection
Thymoquinone	Mice	Reduced neurotoxicity
Erythropoietin	Rat	Antioxidant and anti-inflammatory effects
Cinnamaldehyde	PC12 cells	Reduced oxidative/cellular damage
Gastrodin	Neuronal models	Modulated cAMP/PKA/CREB signaling
TBHQ	Rat	Enhanced antioxidant and anti-apoptotic responses
Rosmarinic acid	Zebrafish	Reduced apoptotic signaling
Thioperamide	Mice/HT22 cells	Improved neurobehavioral and cellular outcomes
α-Pinene	Mice	Neuroprotective activity

Overall, the results indicate that METH-induced neurodegeneration is not mediated by a single pathway. Instead, oxidative stress, neuroinflammation, glutamate-mediated excitotoxicity, and mitochondrial dysfunction interact with one another and collectively contribute to neuronal damage, apoptosis, and neurodegeneration. The protective effects observed with multiple therapeutic agents further suggest that targeting several interconnected mechanisms simultaneously may provide greater neuroprotection than targeting a single pathway

DISCUSSION

The present analysis indicates that methamphetamine (METH)-induced neurodegeneration is a multifactorial process involving interconnected mechanisms rather than a single toxic pathway. The major findings demonstrate that excessive dopaminergic and glutamatergic neurotransmission, oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction collectively contribute to neuronal injury. This integrated mechanism is consistent with previous experimental evidence showing that METH can enter the brain rapidly because of its lipophilic properties and profoundly disrupt monoaminergic neurotransmission, particularly dopamine (DA) signaling [1,2].

One of the most important mechanisms identified in the present analysis was excessive DA release. METH increases cytosolic and extracellular DA by interfering with vesicular storage, dopamine transporter function, and reuptake mechanisms. Elevated intracellular DA can undergo auto-oxidation and produce reactive oxygen species (ROS), dopamine quinones, and other reactive intermediates. These products can damage proteins, lipids, and nucleic acids and consequently contribute to degeneration of dopaminergic terminals. The close relationship between excessive DA release and oxidative stress therefore provides an important explanation for the selective vulnerability of dopaminergic neuronal systems following METH exposure [9,11].

The marked increase in oxidative stress observed following METH exposure is consistent with previous reports demonstrating increased lipid peroxidation, ROS production, and oxidative damage in the brain after neurotoxic METH administration. METH-induced disruption of dopamine metabolism, together with mitochondrial ROS generation and nitric oxide production, can overwhelm endogenous antioxidant defenses. Increased malondialdehyde (MDA), a marker of lipid peroxidation, has been reported in brain

regions exposed to METH and is associated with membrane damage and neuronal dysfunction. Oxidative modification of proteins and DNA may further impair cellular processes and promote apoptosis. Thus, oxidative stress appears to represent a central link connecting neurotransmitter dysregulation with downstream cellular injury [17,18].

METH-induced oxidative stress is also closely associated with neuroinflammation. The present findings indicate that METH activates microglia and increases inflammatory mediators including TNF-α, IL-1β, and IL-6. Activated microglia can release ROS, cytokines, and other neurotoxic mediators, thereby amplifying neuronal damage. Previous studies have shown that METH-induced microglial activation is associated with Toll-like receptor signaling and downstream NF-κB and MAPK pathways, which promote the transcription of pro-inflammatory genes. This suggests that oxidative stress and inflammation may operate as a self-amplifying cycle in METH neurotoxicity [22,23].

The involvement of glutamate-mediated excitotoxicity provides another important mechanism underlying METH-associated neuronal degeneration. Excessive glutamate release can activate NMDA receptors, resulting in increased Ca^{2+} influx and activation of intracellular enzymes that damage proteins, membranes, and DNA. METH-induced glutamate dysregulation may therefore amplify oxidative and inflammatory injury. Moreover, activated microglia can contribute to extracellular glutamate accumulation, establishing a feedback relationship between neuroinflammation and excitotoxicity. Consequently, excessive glutamatergic signaling is likely to function both as an independent mechanism of neuronal injury and as an amplifier of oxidative and inflammatory processes [24,25].

The findings also indicate that endoplasmic reticulum stress contributes to METH-induced neuronal death. Increased expression of stress-associated molecules such as ATF4 and CHOP and activation of caspase-dependent pathways suggest that prolonged cellular stress can initiate programmed cell death. Endoplasmic reticulum stress may interact with mitochondrial apoptotic signaling, thereby increasing neuronal susceptibility to METH toxicity. Such interactions emphasize that METH-induced neurodegeneration involves multiple intracellular stress responses that converge on neuronal apoptosis [14,21].

Mitochondrial dysfunction represents another major component of METH toxicity. The observed reduction in mitochondrial respiratory function and ATP production, together with increased mitochondrial ROS, indicates that METH compromises cellular energy metabolism. Mitochondria are particularly vulnerable because they are both major sources and targets of ROS. Previous studies have demonstrated alterations in mitochondrial respiration, oxidative phosphorylation, and mitochondrial morphology following METH exposure. Disruption of mitochondrial dynamics and mitophagy, including alterations in DRP1, FIS1, PINK1, and Parkin, may further impair removal of damaged mitochondria and promote neuronal dysfunction [26,27].

The relationship between mitochondrial dysfunction and apoptosis is particularly important. Excessive mitochondrial ROS and loss of membrane integrity can promote cytochrome-c release and activation of downstream caspases, ultimately resulting in neuronal apoptosis. In addition, alterations in mitochondrial biogenesis regulators such as PGC-1α, NRF1, and TFAM may reduce the capacity of neurons to replace damaged mitochondria. Because neurons have exceptionally high energy requirements, persistent mitochondrial dysfunction may therefore contribute substantially to the progressive nature of METH-induced neurodegeneration [10,16].

The therapeutic findings provide further support for the involvement of these interconnected mechanisms. Several antioxidant compounds, including resveratrol, curcumin, melatonin, thymoquinone, and tertiary butylhydroquinone, have demonstrated protective effects against METH-induced oxidative and apoptotic damage. Resveratrol, for example, has been reported to reduce METH-associated oxidative injury and improve behavioral abnormalities in experimental animals. Similarly, melatonin can regulate oxidative stress, mitochondrial function, and glutamate-associated signaling, making it a potentially useful multi-target neuroprotective compound [15,20].

Other interventions appear to target additional components of the toxic pathway. Erythropoietin has demonstrated antioxidant, anti-inflammatory, and anti-apoptotic effects in experimental METH neurotoxicity, whereas gastrodin has been associated with modulation of cAMP/PKA/CREB signaling. N-acetylcysteine may provide protection through restoration of glutathione and reduction of oxidative and glutamatergic stress. Similarly, NMDA receptor antagonism has been investigated as a strategy for reducing METH-induced excitotoxicity. These findings suggest that multi-target interventions may be particularly valuable because oxidative stress, inflammation, excitotoxicity, and mitochondrial dysfunction reinforce one another [28,29].

Overall, the evidence supports a mechanistic model in which METH initially disrupts dopamine and glutamate homeostasis, leading to excessive ROS production and excitotoxic signaling. These events activate microglia and inflammatory pathways, impair mitochondrial function, reduce cellular energy production, and promote endoplasmic reticulum stress and apoptosis. Mitochondrial dysfunction subsequently generates additional ROS, thereby strengthening the oxidative and inflammatory response. The combined effects ultimately result in synaptic dysfunction, dopaminergic terminal loss, and neuronal degeneration. Therefore, therapeutic approaches simultaneously targeting oxidative stress, neuroinflammation, excitotoxicity, and mitochondrial dysfunction may offer greater protection than interventions directed at a single mechanism alone [4,5].

CONCLUSION

Methamphetamine-induced neurodegeneration is a complex process involving interconnected mechanisms rather than a single pathway. Excessive dopamine and glutamate release initiates oxidative stress and excitotoxicity, while increased ROS production damages lipids, proteins, DNA, and cellular membranes. Concurrent activation of microglia promotes neuroinflammation through pro-inflammatory cytokines and signaling pathways such as NF-κB and MAPK. Mitochondrial dysfunction further aggravates neuronal injury by reducing ATP production, increasing ROS generation, and activating apoptotic pathways. These mechanisms interact through positive feedback loops, ultimately promoting dopaminergic

terminal loss and neuronal degeneration. Evidence from experimental studies suggests that antioxidants, anti-inflammatory agents, mitochondrial protectants, and glutamate-modulating therapies may provide neuroprotection. Therefore, future therapeutic strategies should preferably target multiple pathological pathways simultaneously to effectively limit METH-associated neuronal damage and neurodegeneration.

Ethical Approval

Not applicable. This review used previously published literature and involved no human participants, animals, or identifiable personal data.

Informed Consent

Not applicable, as this study did not involve human participants or direct data collection from individuals.

Data Availability Statement

All data analyzed in this review were obtained from previously published studies. Additional information is available from the corresponding author upon reasonable request.

Author Contributions

Ghufran Khan and Tamanna Gul contributed to the conceptualization, methodology, data curation and analysis, manuscript writing, review and editing, and final approval of the manuscript.

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Conflict of Interest

The authors declare that they have no competing interests.

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REFERENCES

1. Edinoff AN, Kaufman SE, Green KM, Provenzano DA, Lawson J, Cornett EM, Murnane KS, Kaye AM, Kaye AD. Methamphetamine use: a narrative review of adverse effects and related toxicities. Health psychology research. 2022 Sep 15;10(3):38161. https://doi.org/10.52965/001c.38161
2. Čechová B, Šlamberová R. Methamphetamine, neurotransmitters and neurodevelopment. Physiological research. 2021 Dec 30;70(Suppl 3):S301. https://doi.org/10.33549/physiolres.934821
3. Pang L, Wang Y. Overview of blood-brain barrier dysfunction in methamphetamine abuse. Biomedicine & Pharmacotherapy. 2023 May 1;161:114478. https://doi.org/10.1016/j.biopha.2023.114478
4. Davis DL, Metzger DB, Vann PH, Wong JM, Shetty RA, Forster MJ, Sumien N. Effects of chronic methamphetamine exposure on rewarding behavior and neurodegeneration markers in adult mice. Psychopharmacology. 2023 Jun;240(6):1343-58. https://doi.org/10.1007/s00213-023-06374-y
5. Granado N, Mendieta L, Tizabi Y, Murer MG, Moratalla R. Attenuated neurotoxicity after repeated methamphetamine binges linked to dopamine transporter (DAT) decline. Neurobiology of Disease. 2025 Apr 1;207:106839. https://doi.org/10.1016/j.nbd.2025.106839
6. Bravo J, Ribeiro I, Terceiro AF, Andrade EB, Portugal CC, Lopes IM, Azevedo MM, Sousa M, Lopes CD, Lobo AC, Canedo T. Neuron–microglia contact-dependent mechanisms attenuate methamphetamine-induced microglia reactivity and enhance neuronal plasticity. Cells. 2022 Jan 21;11(3):355. https://doi.org/10.3390/cells11030355
7. Wu M, Su H, Zhao M. The role of α-synuclein in methamphetamine-induced neurotoxicity. Neurotoxicity Research. 2021 Jun;39(3):1007-21. https://doi.org/10.1007/s12640-021-00332-2
8. Shin EJ, Jeong JH, Hwang Y, Sharma N, Dang DK, Nguyen BT, Nah SY, Jang CG, Bing G, Nabeshima T, Kim HC. Methamphetamine-induced dopaminergic neurotoxicity as a model of Parkinson's disease. Archives of pharmacal research. 2021 Jul;44(7):668-88. https://doi.org/10.1007/s12272-021-01341-7
9. Bhimani RV, Vik M, Wakabayashi KT, Szalkowski C, Bass CE, Park J. Distinct dose-dependent effects of methamphetamine on real-time dopamine transmission in the rat nucleus accumbens and behaviors. Journal of neurochemistry. 2021 Aug;158(4):865-79. https://doi.org/10.1111/jnc.15470
10. Graves SM, Schwarzschild SE, Tai RA, Chen Y, Surmeier DJ. Mitochondrial oxidant stress mediates methamphetamine neurotoxicity in substantia nigra dopaminergic neurons. Neurobiology of disease. 2021 Aug 1;156:105409. https://doi.org/10.1016/j.nbd.2021.105409
11. Watanabe H, Dijkstra JM, Nagatsu T. Parkinson's disease: cells succumbing to lifelong dopamine-related oxidative stress and other bioenergetic challenges. International journal of molecular sciences. 2024 Feb 7;25(4):2009. https://doi.org/10.3390/ijms25042009
12. Jayanthi S, Ladenheim B, Sullivan P, McCoy MT, Krasnova IN, Goldstein DS, Cadet JL. Biochemical neuroadaptations in the rat striatal dopaminergic system after prolonged exposure to methamphetamine self-administration. International journal of molecular sciences. 2022 Sep 3;23(17):10092. https://doi.org/10.3390/ijms231710092
13. Nagy EK, Overby PF, Leyrer-Jackson JM, Carfagno VF, Acuña AM, Olive MF. Methamphetamine and the synthetic cathinone 3, 4-methylenedioxypyrovalerone (MDPV) produce persistent effects on prefrontal and striatal microglial morphology and neuroimmune signaling following repeated binge-like intake in male and female rats. Brain sciences. 2024 Apr 27;14(5):435. https://doi.org/10.3390/brainsci14050435
14. Xu L, Li L, Chen Q, Huang Y, Chen X, Qiao D. The role of non-coding RNAs in methamphetamine-induced neurotoxicity. Cellular and Molecular Neurobiology. 2023 Aug;43(6):2415-36. https://doi.org/10.1007/s10571-023-01323-x
15. Manful CF, Fordjour E, Subramaniam D, Sey AA, Abbey L, Thomas R. Antioxidants and reactive oxygen species: Shaping human health and disease outcomes. International Journal of Molecular Sciences. 2025 Aug 4;26(15):7520. https://doi.org/10.3390/ijms26157520
16. Du Y, Lee YB, Graves SM. Chronic methamphetamine-induced neurodegeneration: Differential vulnerability of ventral tegmental area and substantia nigra pars compacta dopamine neurons. Neuropharmacology. 2021 Dec 1;200:108817. https://doi.org/10.1016/j.neuropharm.2021.108817
17. Chen L, Ru Q, Xiong Q, Yang J, Xu G, Wu Y. Potential effects of Nrf2 in exercise intervention of neurotoxicity caused by methamphetamine oxidative stress. Oxidative medicine and cellular longevity. 2022;2022(1):4445734. https://doi.org/10.1155/2022/4445734
18. Al-Hakeim HK, Altufaili MF, Almulla AF, Moustafa SR, Maes M. Increased lipid peroxidation and lowered antioxidant defenses predict methamphetamine induced psychosis. Cells. 2022 Nov 21;11(22):3694. https://doi.org/10.3390/cells11223694

19. Juan CA, Pérez de la Lastra JM, Plou FJ, Pérez-Lebeña E. The chemistry of reactive oxygen species (ROS) revisited: outlining their role in biological macromolecules (DNA, lipids and proteins) and induced pathologies. International journal of molecular sciences. 2021 Apr 28;22(9):4642. https://doi.org/10.3390/ijms22094642
20. Jomova K, Raptova R, Alomar SY, Alwasel SH, Nepovimova E, Kuca K, Valko M. Reactive oxygen species, toxicity, oxidative stress, and antioxidants: chronic diseases and aging. Archives of toxicology. 2023 Oct;97(10):2499-574. https://doi.org/10.1007/s00204-023-03562-9
21. Shrestha P, Katila N, Lee S, Seo JH, Jeong JH, Yook S. Methamphetamine induced neurotoxic diseases, molecular mechanism, and current treatment strategies. Biomedicine & Pharmacotherapy. 2022 Oct 1;154:113591. https://doi.org/10.1016/j.biopha.2022.113591
22. Jeffery N, Mock PY, Yang K, Tham CL, Israf DA, Li H, Wang X, Lam KW. Therapeutic targeting of neuroinflammation in methamphetamine use disorder. Future Medicinal Chemistry. 2025 Jan 17;17(2):237-57. https://doi.org/10.1080/17568919.2024.2447226
23. Shi S, Chen T, Zhao M. The crosstalk between neurons and glia in methamphetamine-induced neuroinflammation. Neurochemical Research. 2022 Apr;47(4):872-84. https://doi.org/10.1007/s11064-021-03513-9
24. Nicosia N, Giovenzana M, Misztak P, Mingardi J, Musazzi L. Glutamate-mediated excitotoxicity in the pathogenesis and treatment of neurodevelopmental and adult mental disorders. International Journal of Molecular Sciences. 2024 Jun 13;25(12):6521. https://doi.org/10.3390/ijms25126521
25. Zeng R, Pu HY, Zhang XY, Yao ML, Sun Q. Methamphetamine: mechanism of action and Chinese herbal medicine treatment for its addiction. Chinese Journal of Integrative Medicine. 2023 Jul;29(7):665-72. https://doi.org/10.1007/s11655-023-3635-y
26. Dominguez-Lopez S, Ahn B, Sataranatarajan K, Ranjit R, Premkumar P, Van Remmen H, Beckstead MJ. Long-term methamphetamine self-administration increases mesolimbic mitochondrial oxygen consumption and decreases striatal glutathione. Neuropharmacology. 2023 Apr 1;227:109436. https://doi.org/10.1016/j.neuropharm.2023.109436
27. Bazylianska V, Sharma A, Chauhan H, Schneider B, Moszczynska A. Dopamine and methamphetamine differentially affect electron transport chain complexes and parkin in rat striatum: new insight into methamphetamine neurotoxicity. International journal of molecular sciences. 2021 Dec 29;23(1):363. https://doi.org/10.3390/ijms23010363
28. Mira RG, Cerpa W. Building a bridge between NMDAR-mediated excitotoxicity and mitochondrial dysfunction in chronic and acute diseases. Cellular and Molecular Neurobiology. 2021 Oct;41(7):1413-30. https://doi.org/10.1007/s10571-020-00924-0
29. Yang X, Chen Y, Zheng G, Nie Q, Zhang P. Mitochondrial calcium uniporter (MCU)-mediated calcium overload in psychoactive drug neurotoxicity: from pathogenesis to therapeutic targets. International Journal of Molecular Sciences. 2025 May 15;26(10):4732. https://doi.org/10.3390/ijms26104732