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Role of Mitochondria in Methamphetamine-Induced Dopaminergic Neurotoxicity: Involvement in Oxidative Stress, Neuroinflammation, and Pro-apoptosis—A Review

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Abstract Methamphetamine (MA), an amphetamine-type psychostimulant, is associated with dopaminergic toxicity and has a high abuse potential. Numerous in vivo and in vitro studies have suggested that impaired mitochondria are critical in dopaminergic toxicity induced by MA. Mitochondria are important energy-producing organelles with dynamic nature. Evidence indicated that exposure to MA can disturb mitochondrial energetic metabolism by inhibiting the Krebs cycle and electron transport chain. Alterations in mitochondrial dynamic processes, including mitochondrial biogenesis, mitophagy, and fusion/fission, have recently been shown to contribute to dopaminergic toxicity induced by MA. Furthermore, it was demonstrated that MA-induced mitochondrial impairment enhances susceptibility to oxidative stress, pro-apoptosis, and neuroinflammation in a positive feedback loop. Protein kinase Cδ has emerged as a potential mediator between mitochondrial impairment and oxidative stress, pro-apoptosis, or neuroinflammation in MA neurotoxicity. Understanding the role

and underlying mechanism of mitochondrial impairment could provide a molecular target to prevent or alleviate dopaminergic toxicity induced by MA.

Introduction

Methamphetamine (MA) abuse has been a global health issue for the past several decades [1]. MA is an amphetamine-type psychostimulant with high lipid solubility, thus it can easily pass through the blood–brain barrier [2]. In the brain, dopaminergic cells take up MA through the dopamine transporter (DAT) as a substrate due to its similarity to dopamine (DA). Additionally, MA can enter dopaminergic axons slowly by lipophilic diffusion at high concentrations. MA induces abnormal DA release into the synaptic cleft, which might mediate its abuse potential and dopaminergic neurotoxicity [3]. Moreover, an increase in extravesicular cytosolic DA may largely account for MA-induced neurotoxicity [4–6]. MA-induced vesicular or synaptic DA release primarily results from DA displacement from synaptic vesicles through the vesicular monoamine transporter-2 (VMAT-2) or the reverse transport of DA into synaptic cleft through the DAT [7, 8]. The nigrostriatal DA projection has been reported to be more susceptible to MA-induced dopaminergic neurotoxicity than the mesocorticolimbic DA projection [9–11], as shown in patients with Parkinson's disease (PD). Serotonergic toxicity has also been well-recognized after MA administration, although to a lesser extent and to a more diffuse pattern than dopaminergic toxicity [12–14].

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Mitochondrial impairment has long been suggested to play a pivotal role in MA-induced dopaminergic neurotoxicity. Earlier studies demonstrated that energetic metabolism in mitochondria is deregulated following MA administration [15–19]. In recent years, evidence has suggested that disrupted mitochondrial dynamics, including biogenesis, mitophagy, and fusion/fission, are involved in MA neurotoxicity [20–26]. In this review, we introduce the functional and structural changes in mitochondria induced by MA. In particular, we highlight the role of mitochondrial changes on the oxidative stress, pro-apoptosis, and neuroinflammation induced by MA.

Overview of MA Neurotoxicity

Accumulating evidence indicates that dopaminergic toxicity can result from long-term MA abuse. Initially, Wilson et al. [27] showed reduced striatal DA levels in chronic MA abusers. This finding has been supported by positron emission tomographic (PET) studies reporting decreased DAT levels in the striatum of MA abusers [28–30]. These changes in dopaminergic markers in the striatum might last for months to years after MA abstinence. Although the striatum, especially the caudate nucleus, is the most vulnerable to DA loss after chronic MA abuse [31], prolonged decreases in DAT levels have been observed in other brain regions, including the nucleus accumbens and prefrontal cortex [32].

Dopaminergic damage shown in MA abusers has been reproduced in animal models. A single, high-dose of MA or binge administration of moderate-to-high doses of MA induced significant and sustained decreases in levels of DA, tyrosine hydroxylase (TH), and DAT in the striatum [12, 33–42]. Dosing schedules that more closely resemble human MA abuse pattern, including self-administration and escalating dosing regimen, have also been reported to induce dopaminergic damage [43–46]. However, the self-administration and escalating dosing regimen of MA appeared to be less effective than binge doses of MA in inducing dopaminergic neurotoxicity [43, 45–47]. In addition, prior injection with escalating MA doses (0.1–4.0 mg/kg over 14 days) attenuated dopaminergic toxicity induced by binge doses of MA (6 mg/kg×4) [48]. Furthermore, the extent of DA loss in the striatum of individuals with MA abuse [31] was comparable to the degree of DA loss induced by MA binge exposure in rodents [49, 50]. Thus, MA binge exposure in rodents has mainly been used as an animal model to study the neurotoxic mechanism of MA.

The nigrostriatal pathway is more likely to be susceptible to MA-induced dopaminergic toxicity than the mesocorticolimbic pathway [10, 11]. Unlike clinical findings, nigral neuronal death has been observed in rodents after

MA binge exposure. Earlier studies showed fewer TH- and Nissl-positive cells after MA binge exposure (10 mg/kg, i.p.×4) [51], which was confirmed with more rigorous stereological measures [38, 39, 41, 52, 53]. Notably, recent research reported that TH-immunostaining co-localized with amino-cupric-silver staining in the substantia nigra after single (30 mg/kg, i.p.) or multiple (5 or 10 mg/kg, i.p.×3) MA administration, revealed degenerative changes in dopaminergic cell bodies in that region [53]. In addition, TUNEL- or Fluoro-Jade-positive cells have been observed in the striatum following MA administration [39, 42, 54–56]. Zhu et al. [56] reported that GABA-parvalbumin-positive neurons are most vulnerable to MA (30 or 40 mg/kg, i.p.×1)-induced apoptosis in the striatum, while somatostatin-positive interneurons were resistant to this change. MA administration has also been reported to induce significant dopaminergic terminal damage in the amygdala and frontal cortex [12, 13]. Interestingly, cytoplasmic inclusion bodies with α-synuclein-immunoreactivity, which are analogous to Lewy bodies in Parkinson's disease (PD), have been found in the dopaminergic cells in the substantia nigra after MA binge exposure (5 mg/kg, i.p.×3) [57] or exposure to MA (1 µM for 12 h or 3 mM for 24 h) in PC12 cells [58, 59]. In addition, MA abuse has been suggested to contribute to the increased risk of PD users [60–62]. Therefore, in vivo and in vitro models of MA use might be valuable in studying the cellular and molecular mechanisms of PD.

Mitochondrial Dysfunction in MA-Induced Dopaminergic Toxicity

Changes in Energetic Metabolism

Mitochondria are important bioenergetic organelles for maintaining normal cell function. The Krebs cycle [tricarboxylic acid (TCA) cycle] and electron transport chain (ETC) are the essential metabolic pathways for producing ATP. Electron flow through complexes I, II, III, and IV of the ETC is accompanied by proton pumping into the mitochondrial intramembranous space, and establishes the mitochondrial transmembrane potential ($\Delta\Psi m$) and pH gradient. This proton-motive force produces ATP through complex V (H^+-ATP synthase) of the ETC [63–65].

In this context, MA administration has been shown to inhibit several important Krebs cycle and ETC enzymes. Earlier study by Burrow and Meshul [15] showed that mitochondria were significantly less immunoreactive for Krebs cycle intermediates in the basal ganglia of rats at 1 week after the final MA administration (15 mg/kg, s.c.×4). Similarly, a single MA administration at doses as low as 0.5 and 1.0 mg/kg significantly decreased citrate synthase and succinate dehydrogenase activities in tissue

homogenates [18]. In addition, a number of studies have examined the expression and activity of ETC enzymes after MA administration; however, the results were inconsistent depending on the species, dosing regimen, and time point [16–19, 66–74]. Brown et al. [16] showed that the activity of complexes II–III, specifically complex II, decreased, but complex I activity remained unchanged at 1 h after the final administration with MA (10 mg/kg, s.c.×4) in the striatum of rats. In line with this finding, an intrastriatal infusion of malonate, a complex II inhibitor, potentiated dopaminergic toxicity induced by intrastriatal infusion of MA [66]. On the other hand, complex I activity decreased significantly in the striatum at 5 h after the MA administration (10 or 20 mg/kg, s.c.×2) in mice [17] or 5 days after the MA administration (10 mg/kg, s.c.×2) in rats [19]. In addition, Feier et al. [18] showed that striatal complex IV activity decreased significantly at 2 h after a single dose of MA (0.5–2.0 mg/kg, i.p.) in rats. In this regard, intrastriatal infusion of ETC enhancers, decylubiquinone or nicotinamide, significantly attenuated the MA-induced dopaminergic toxicity [67, 68]. The main findings on changes in ETC enzymes following the MA administration are summarized in Table 1.

The disruption of the Krebs cycle and ETC is further evidenced by altered $\Delta\Psi m$, oxygen consumption, and ATP production [64]. Exposure to MA reduced $\Delta\Psi m$ in striatal, mesencephalic cultures [24, 75, 76] or SH-SY5Y cell cultures [72, 74, 77]. These findings have been further supported by in vivo studies with mitochondria isolated from MA-administered mice [39, 41, 42]. $\Delta\Psi m$ started to decrease as early as 1 h after MA exposure (1.68 mM) in SH-SY5Y cells [72], which is consistent with our findings [42] that $\Delta\Psi m$ decreased 0.5 h after a single, high dose of MA (35 mg/kg, i.p.). In addition, numerous in vitro and in vivo studies have reported the decline of both mitochondrial oxygen consumption and ATP content in response to MA exposure [67, 75, 78–80].

Disruption of Mitochondrial Dynamics

Mitochondria were considered to be relatively static organelles for many decades; however, this concept has been

Table 1 Summary of preclinical studies on changes in ETC enzyme activity and expression after MA administration (exposure) in vivo or in vitro

Subjects	MA dosing regimen	Time-point after the last MA administration (exposure)	Findings			References
			Brain regions	Changes		
Rat	5 mg/kg/day, i.p. for 28 days	NS	Striatum, SN, NAc, FC, OC	Complex IV protein expression	↓	[69]
Rat	10 mg/kg, i.p.×4 at 2-h intervals	2 h	Striatum, NAC, SN	Complex IV protein expression	↓	[70]
		24 h and 7 days		Complex IV protein expression	–	
Rat	10 mg/kg, s.c.×4 at 2-h intervals	1 h	Striatum	Complex I–III activity	–	[16]
				Complex II activity	↓	
Mouse	30 mg/kg/day, i.p. for 7 days	1 days	Striatum	Complex I protein expression	↓	[71]
SH-SY5Y cells	At a concentration of 1.68 mM for 48 h	Immediately		Protein expression of complex I, II, and III	–	[72]
				Protein expression of complex IV and V	↓	
Mouse	10 mg/kg, i.p.×4 at 2-h intervals	7 days	Striatum	Protein expression of complex I and V	↓	[73]
Rat	5 mg/kg, i.p.×4 at 2-h intervals	12 h	FC	Complex I activity	↓	[74]
Mouse	10 or 20 mg/kg, i.p.×2 at 12-h interval	5 h	Striatum	Complex I activity	↓	[17]
				Complex IV activity	–	
Rat	0.5–2.0 mg/kg, i.p.×4	2 h	Striatum	The activity of complex I and II	–	[18]
				The activity of complex II–III and IV	↓	
Rat	10 or 20 mg/kg, i.p.×2 at 2-h interval	5 days	Striatum	Complex I activity	↓	[19]

NS not specified, *SN* substantia nigra, *NAc* nucleus accumbens, *FC* frontal cortex, *OC* occipital cortex

changed by recent progress in understanding the dynamic nature of mitochondria, including biogenesis, mitophagy, and fusion/fission [81]. Several important findings in mitochondrial dynamics after MA exposure (administration) have come in recent years.

Mitochondrial biogenesis can be roughly defined as an increase in the number and/or mass of mitochondria. Thus, mitochondrial biogenesis requires the transcription of nuclear and mitochondrial DNA, synthesis of proteins and lipids, and assembly of these components into fully functioning mitochondria. Altered mitochondrial biogenesis can be assessed by the level of related transcription factors and coactivators, or the mRNA expression of ETC components [81]. Elevated levels of cytochrome c oxidase subunit 1 (COX1) mRNA, a part of complex IV, has been reported in the substantia nigra of mice at 12 h following a toxic dose of MA (45 mg/kg, s.c.) [82, 83]. A more recent study showed that repeated escalating doses of MA (1–14 mg/kg, i.p. over 14 days) induced the mRNA expression of proliferator-activated receptor-γ coactivator-1α (PGC-1α) or mitochondrial transcription factor A (TFAM), both mitochondrial biogenesis-related factors, in the substantia nigra of rats [84]. Considering that most in vivo and in vitro studies have reported MA-induced decreases in ETC protein expression and activity, as summarized in Table 1, increases in the mRNA level of PGC-1α or TFAM may compensate for the disrupted mitochondrial bioenergetic metabolism against MA insult.

Mitophagy is a process of defective mitochondria being degraded by mitochondria-specific autophagy in cells. Thus, reduced mitophagy has been suggested to lead to an accumulation of defective mitochondria [85]. In mitophagy, several specialized proteins, such as PTEN-induced putative kinase 1 (PINK1) and Parkin, target and modify mitochondrial proteins, and recruit autophagosomes [81]. Fornai et al. [86] reported Parkin-positive intracellular inclusion bodies in the substantia nigra of mice after MA binge exposure (5 mg/kg, i.p.×4). More specifically, Lenzi et al. [23] showed that the number of damaged mitochondria and proportion of Parkin-positive mitochondria increased, while the total number of mitochondria was unchanged in PC12 cells after exposure to a low concentration of MA (1 μM for 72 h). Consistently, autophagic vacuoles surrounded damaged mitochondria in MA-exposed cells. Moreover, PINK1 gene silencing decreased Parkin recruitment to damaged mitochondria and the number of mitophagic vacuoles, and increased the proportion of damaged mitochondria and apoptotic cells after MA, suggesting that PINK1 and Parkin inhibition contributes to the pathophysiology of MA toxicity. In line with this finding, it was shown that MA (10 mg/kg, i.p. or 10 mg/kg, i.p.×4)-induced decreases in Parkin protein and mRNA levels followed by reduced 26S proteasome activity in the striatum of rats [20, 22]. In addition,

Parkin overexpression in the nigrostriatal area with adeno-associated viral vectors attenuated dopaminergic terminal damage induced by MA (7.5 mg/kg, i.p.×4) in the striatum [87]. Importantly, Lin et al. [24] found that a high MA concentration (1 or 2 mM) induced mitochondrial dysfunction and ultrastructural changes related to mitophagy, accompanied by sustained elevation of cleaved protein kinase Cδ (PKCδ), a persistently active form of PKCδ, in a rat mesencephalic dopaminergic neuronal cell line. In this study, PKCδ gene knockdown or overexpression of a cleavage resistant PKCδ mutant restored normal regulation of autophagy and protected dopaminergic neuronal cells from MA-induced apoptosis. These results suggest that PKCδ plays a role in the MA-induced deregulation of mitophagy. Taken together, mitophagy enables dopaminergic neurons to maintain normal mitochondrial function and attenuate MA neurotoxicity.

The constant cycles of mitochondrial fusion/fission allow cells to reorganize mitochondrial networks and sequester damaged mitochondrial components into daughter mitochondria that are removed by mitophagy [88, 89]. Two large GTPases, mitofusin 1 and mitofusin 2 mediate the tethering of mitochondrial outer membranes [90], whereas optic atrophy 1 (OPA1) protein, a dynamin-like GTPase, promotes the fusion of mitochondrial inner membranes [91]. Another large GTPase, dynamin-related protein 1 (Drp1), along with fission protein 1 (Fis1) mediates mitochondrial fission by forming an oligomeric ring that constricts to divide mitochondria [81, 92]. The balance between fusion and fission is critical for maintaining normal mitochondrial morphology and function. Thus, altered fusion/fission plays a role in the pathophysiology of various neurodegenerative diseases, including PD [93]. Excessive fission events, and the consequent mitochondrial fragmentation, have been reported in a cybrid model of sporadic PD [94]. Similar findings have been reported in MA-exposed cells. Parameyong et al. [25] reported that exposure to MA (1.0 mM for 24 h) increased the levels of Fis1 protein and Drp1 oligomers in SH-SY5Y cells, however, neither OPA1 nor mitofusin 1 levels were changed. In a follow-up study [26], mitochondrial translocation of Fis1 and Drp1 preceded mitochondrial fragmentation in MA (1.0 mM for 24 h)-exposed SH-SY5Y cells, and these changes were dependent on the intracellular Ca^{2+} concentration. Consistently, Tian et al. [21] showed that exposure to MA (300 μM for 24 h) induced mitochondrial translocation and oligomerization of Drp1 and accompanying mitochondrial fragmentation in rat hippocampal neural progenitor cells. However, they suggested that MA-induced acceleration of mitochondrial fission is not related to intracellular Ca^{2+} concentration. Thus, the mechanism involved in accelerating fission events might depend on MA concentration, although further data are needed.

Mitochondria and MA-Induced Oxidative Stress

Oxidative stress plays an important role in MA-induced dopaminergic toxicity. An increase in reactive oxygen species (ROS) concentration due to increased ROS production and/or decreased antioxidant activity can cause oxidative stress [95]. Increased ROS concentration oxidizes biomolecules, including lipids, proteins, and nucleic acids, leading to damage and malfunction of cellular components. In this respect, several studies have reported increased oxidative stress markers in plasma or post-mortem brain tissue of MA users and abusers [96–98]. As discussed earlier, MA inhibits VMAT-2 and DAT, resulting in an excessive extravesicular cytosolic- or synaptic-DA in dopaminergic neurons. Excess DA can be autoxidized to quinone or semi-quinone, which can generate a superoxide radicals, hydroperoxide, and further hydroxyl radicals [99, 100]. In addition, DA metabolism, which is mediated by monoamine oxidase (MAO), produces hydrogen peroxide as a by-product.

Mitochondria are a major site of ROS formation induced by MA [17, 70, 101]. Under physiological conditions, electron transport through the ETC is tightly coupled to ATP production, thus low levels of superoxide radicals are generated in normal cellular respiration. However, inhibiting ETC components can enhance the superoxide radical production due to leaking electrons. In this regard, Sipos et al. [102] showed that weak inhibition ($16 \pm 2\%$) of complex I significantly increased ROS formation, but strong inhibition (>70%) of complex III or IV was needed to induce a significant increase in ROS formation in isolated nerve terminals. These results suggest that synaptosomal mitochondria are more sensitive to complex I inhibition than complex III or IV inhibition in producing ROS [103]. As described above, MA inhibits the expression and activity of ETC components (Table 1). Interestingly, Thrash-Williams et al. [101] have shown that a free radical scavenger, salicylic acid significantly attenuated MA (10 mg/kg, i.p.×2)-induced complex I inhibition. Considering that the exposure to hydrogen peroxide or oxygen free radicals induces a robust inhibition of ETC components [104], MA-induced ETC inhibition produces ROS, which may further inhibit ETC components through positive feedback. Consistently, several studies have shown that an MA-induced decrease in $\Delta\Psi m$ was accompanied by increases in mitochondrial oxidative stress markers in vitro [24, 75, 77] and in vivo [39, 41, 42].

In normal conditions, superoxide radicals generated by ETC components are efficiently scavenged by superoxide dismutase (SOD) to form hydrogen peroxide. Hydrogen peroxide can be metabolized into water and oxygen by catalase or peroxidases, mainly glutathione peroxidase in brain. Thus, an imbalance in the mitochondrial antioxidant system induces mitochondrial oxidative stress in various neurotoxic and neurodegenerative conditions. Numerous studies have reported MA-induced increase in SOD activity in the nigrostriatal area [39, 105, 106]. Given the amount of evidence indicating a protective role of SOD overexpression in response to MA-induced neurotoxicity [107–110], an increase in SOD activity may be a compensatory response to superoxide radical production. Increased SOD activity should be followed by an anti-peroxide defense to remove hydrogen peroxide and block hydroxyl radical formation through Fenton's reaction. However, several studies have indicated that MA administration significantly reduced the activity of glutathione peroxidase (GPx) [34, 39, 106, 111], the main hydrogen peroxide scavenger in the brain. Especially, our previous in vivo [39] and in vitro [77] studies showed that MA-induced decrease in GPx activity was more pronounced in mitochondrial fraction than in cytosolic fraction. In line with findings, supplementing dietary selenium, a key element of GPx, mitigated dopaminergic neurotoxicity induced by MA [112], whereas selenium deficiency aggravated this neurotoxicity [34, 35]. Similar results have been reported in the postmortem brains of MA abusers [113], showing that Cu, Zn-SOD activity was increased, but GPx activity was unchanged in the caudate nucleus. Therefore, an increase in SOD activity that is not accompanied by increased GPx activity may contribute to MA-induced mitochondrial oxidative stress. In addition, reduced glutathione (GSH) levels decreased, and oxidized glutathione (GSSG) levels increased in the striatum after MA binge exposure (10 mg/kg, i.p.×4, at 2-h intervals) [34, 114]. These MA-induced changes in glutathione levels were also observed in the mitochondria of rat brain [115] and SH-SY5Y cells [77]. GSH is not only a GPx substrate, but it also maintains the protein thiol groups in a reduced form, allowing proteins to maintain normal function. In particular, considering that a decreased GSH/GSSG ratio can inhibit complex I activity by modifying thiol residues [116, 117], maintaining glutathione homeostasis in mitochondria may be critical to block mitochondrial dysfunction as well as mitochondrial oxidative stress in MA neurotoxicity. Interestingly, inhibiting PKCδ either pharmacologically or genetically restored glutathione homeostasis and GPx activity both in the mitochondrial and cytosolic fraction, and attenuated mitochondrial oxidative stress [39, 42, 77]. Although these results need to be examined in MA-induced neurotoxicity, PKCδ inhibition has been reported to increase Nrf2 DNA binding activity and up-regulate the expression of glutathione-synthesizing enzyme, γ-glutamylcysteine ligase in response to neurotoxic trimethyltin insult [118]. Thus, PKCδ might mediate oxidative damage and mitochondrial dysfunction by modulating the Nrf2-glutathione pathway in MA-induced neurotoxicity.

Moreover, several reports have suggested that oxidative stress could directly mediate the alteration in mitochondrial dynamics in MA neurotoxicity. A previous in vitro study by LaVoie et al. [119] reported that exposure to MA (10 μM) increased the levels of insoluble Parkin monomer and aggregates, which resulted in reduced Parkin E3 ligase activity. In this study, formation of DA quinone was critical for inhibiting Parkin activity. More specifically, DA quinones covalently bound to the cysteine thiol groups of Parkin and decreased its solubility and activity. Consistently, increased Parkin conjugation to 4-hydroxy-2-nonenal (4-HNE) has been reported to accompany inhibited ubiquitin-dependent 26S proteasome activity in the rat striatum as early as 1 h after the final MA injection (10 mg/kg, i.p.×4, at 2-h intervals) [22]. In addition, a thiol-containing compound, *N*-acetylcysteine (NAC) has been reported to attenuate the mitochondrial translocation and oligomerization of Drp1 induced by MA (300 μM for 24 h) in rat hippocampal neural progenitor cells [21]. Thus, mitochondrial oxidative stress could be both a cause and a consequence of disrupted mitochondrial function and dynamics.

Mitochondria and MA-Induced Apoptosis

As mentioned above, MA exposure (administration) could induce apoptotic cell death in vitro and in vivo. It has been reported that MA administration increases the expression of pro-apoptotic proteins, such as Bax, Bad, and Bid [41, 74, 120–122] and decreases the expression of anti-apoptotic proteins, such as Bcl-2 and Bcl-xL [41, 120–122], in the brain. The increase in pro-apoptotic proteins can permeabilize the mitochondrial outer membrane by forming a multimeric channel complex [123]. Bax has also been suggested to bind to components of the permeability transition pore complex (PTPC) and promote the mitochondrial permeability transition. In addition, Bax could alter the mitochondrial membrane curvature and promote mitochondrial fission and consequent mitochondrial fragmentation [124]. The resulting mitochondrial membrane permeabilization (MMP) could dissipate $\Delta\Psi$m and release mitochondrial IMS proteins, including cytochrome c and apoptosis-inducing factor (AIF) [123, 125]. Cytosolic release of cytochrome c is a key step in the caspase-dependent mitochondrial apoptotic pathway. Cytochrome c can be assembled into the apoptosome with apoptotic peptidase activating factor-1 (Apaf-1), deoxyadenosine triphosphate (dATP), and procaspase-9 and induce sequential activation of executioner caspases-3, -6, and -7. Regarding this topic, a number of studies have shown increase in cytochrome c release from mitochondria and consequent caspase activation following MA exposure in vitro [77, 126] and *in vivo* [39, 42, 74, 121, 127, 128]. In addition, it was reported that

caspase-independent pathway is also been involved in the mitochondria-associated apoptosis after a toxic dose of MA (40 mg/kg, i.p.) in the striatum of mice [127].

PKCδ is one of the proteins cleaved by caspase-3. Caspase-3-mediated proteolytic cleavage between the catalytic and regulatory domains can permanently activate PKCδ [129, 130]. In addition, PKCδ has been reported to translocate into various cell organelles, including the mitochondria, in the presence of apoptotic stimuli and mediate apoptotic processes [131]. We recently reported that increased PKCδ cleavage and mitochondrial translocation of cleaved PKCδ were followed by mitochondrial dysfunction (i.e., reduced $\Delta\Psi$m), mitochondrial oxidative stress, and apoptotic changes in the striatum of mice following MA binge exposure [39, 41, 42, 132] or in SH-SY5Y cells following MA exposure (1.5 mM for 12 h) [77]. Interestingly, a PKCδ gene knockout inhibited ultrastructural mitochondrial damage and pro-apoptotic changes induced by MA through activation of the PI3K/Akt signaling pathway [41]. These results were consistent with reports suggesting that PKCδ cleavage is a key event amplifying apoptotic cascades in dopaminergic neurotoxicity produced by 6-hydroxydopamine [130] or dieldrin [133]. Therefore, PKCδ cleavage and mitochondrial translocation of cleaved PKCδ may reinforce mitochondria-dependent apoptosis induced by MA.

Mitochondria and MA-Induced Neuroinflammation

It has been widely recognized that mitochondrial impairment and neuroinflammation are synergistically involved in the pathology of neurodegenerative diseases [134]. In addition, accumulating evidence has found crosstalk between mitochondrial dysfunction and neuroinflammation in dopaminergic neurotoxicity models. For instance, a mitochondrial complex I inhibitor, rotenone or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was reported to induce microglial activation and pro-inflammatory cytokines in the nigrostriatal area [135–139]. In the opposite direction, intrastriatal microinfusion of lipopolysaccharide (LPS), a powerful inflammogen, has been shown to inhibit mitochondrial complex I activity in the substantia nigra as well as striatum of rats [140, 141]. In these models, oxidative stress and pro-inflammatory cytokines have been suggested as important mediators of the crosstalk between mitochondrial impairment and neuroinflammation [138, 140–143].

Neuroinflammation may play an important pathophysiologic role in MA-induced neurotoxicity. Neurotoxic doses of MA have been reported to induce microglial activation, as indicated by elevated expression of microglia-specific marker proteins and morphological changes in the nigrostriatal area [38, 39, 41, 42, 122, 144, 145]. These findings
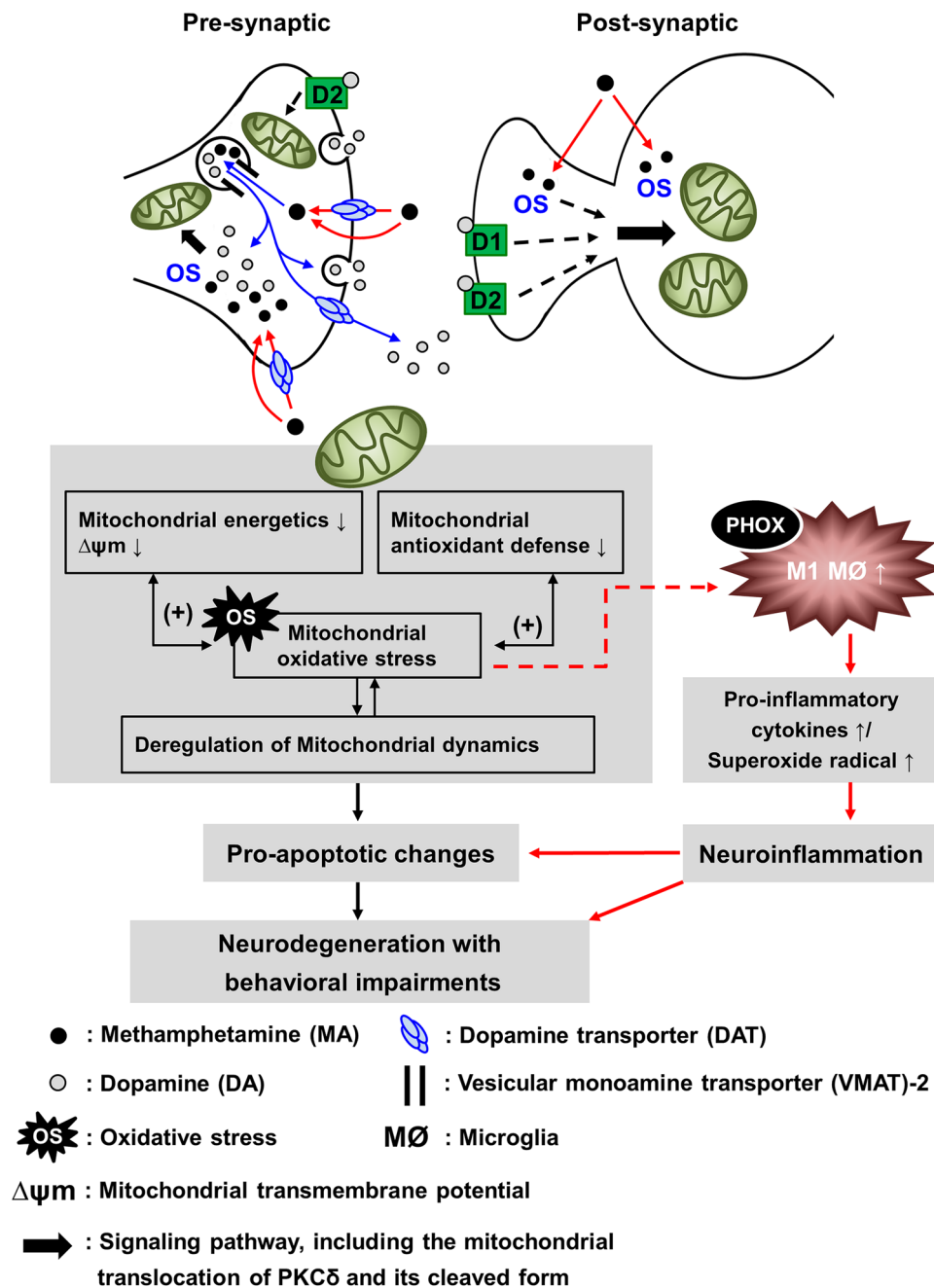
Fig. 1 The role of mitochondria in the neurotoxicity induced by MA. MA can be taken up into dopaminergic cells by DAT as a substrate. Additionally, MA can diffuse into cells due to its lipophilicity [154]. In dopaminergic neurons, MA displaces the DA in the vesicles through VMAT-2, and then leads to an excess cytosolic DA, which can be released into synaptic cleft by reverse transport via DAT. Intracellular MA and excess cytosolic DA induce the reduction of $\Delta\Psi m$ by impairing mitochondrial energetics. Mitochondrial dysfunction together with reduced mitochondrial antioxidant defense can produce mitochondrial oxidative stress (OS), which, in turn, leads to further inhibition of mitochondrial function in a positive loop (+), and possibly alters mitochondrial dynamics. In addition, synaptic DA binds to pre- or post-synaptic DA receptors and can affect the mitochondrial function. MA-induced mitochondrial dysfunction can also trigger pro-apoptosis. Moreover, mitochondrial oxidative stress could induce neuroinflammation by stimulating microglial (MØ) transformation into pro-inflammatory M1 phenotype and by facilitating the membranous translocation of p47phox and assembly of NADPH oxidase (PHOX). Mitochondrial translocation of PKCδ and its cleaved form might mediate the interplay between mitochondrial dysfunction, mitochondrial oxidative stress, neuroinflammation and pro-apoptotic changes. Finally, these signaling processes contribute to the neurodegeneration and behavioral impairments induced by MA

agreed with a clinical study showing reactive microgliosis in the brains of MA abusers [146]. Specifically, expression of classical pro-inflammatory M1 microglial phenotype markers (CD16, CD32, CD68, and CD86) increased, whereas expression of alternative anti-inflammatory M2 microglial phenotype markers (arginase-1, CD163, and CD206) tended to decrease, though not statistically significantly in the striatum after MA binge exposure [38, 39, 42, 147]. Consistently, increased levels of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), have been reported after a single dose of MA (10 or 30 mg/kg, i.p.) in the striatum of mice [148, 149]. The involvement of neuroinflammation in MA neurotoxicity can be further supported by evidence that MA-induced dopaminergic toxicity was attenuated by the microglia inhibitor minocycline [150, 151] or by non-steroidal anti-inflammatory drugs, ketoprofen [152] and ibuprofen [153]. Although, little is understood about the direct link between mitochondrial impairment and neuroinflammation in MA neurotoxicity, PKCδ might be an important mediator. Our previous study [39] showed that restoring mitochondrial function and attenuating mitochondrial oxidative stress by PKCδ gene knockout blocked microglial activation and increased M1 phenotype markers in the striatum after repeated MA administration (8 mg/kg, i.p.×4, at 2-h intervals). In this study, mitochondrial oxidative stress and mitochondrial dysfunction preceded microglial activation, suggesting that mitochondrial dysfunction could promote neuroinflammatory changes through PKCδ-related signaling. A similar result was achieved in the striatum after a single MA injection (35 mg/kg, i.p.) showing that mitochondrial translocation of cleaved PKCδ and mitochondrial dysfunction are associated with microglial activation [42]. Further investigations are needed to determine the specific mediators between mitochondrial impairment and neuroinflammation in dopaminergic toxicity induced by MA.

Conclusion and Future Directions

Mitochondrial impairment is implicated in the pathophysiology of numerous neurodegenerative diseases. Mitochondrial changes have also been suggested to play a critical role in MA neurotoxicity. These changes include disrupted mitochondrial energetics (i.e., impaired Krebs' cycle and ETC, and the consequent decrease in $\Delta\Psi m$ and ATP production) and altered mitochondrial dynamics (i.e., imbalances between mitochondrial biogenesis and mitophagy, and between mitochondrial fusion and fission) in vivo and in vitro. In addition, mitochondrial impairment facilitates oxidative stress, pro-apoptotic processes, and neuroinflammatory events, which may further impair the mitochondrial function in a positive feedback manner after MA. Recent evidence has suggested that PKCδ might mediate this positive feedback interaction (Fig. 1). The results obtained so far in vivo and in vitro can help to elucidate the cellular and molecular mechanisms associated with mitochondria in MA-induced dopaminergic toxicity. Moreover, considering the importance of mitochondrial impairment in MA neurotoxicity, modulating mitochondrial function and dynamics may be useful targets for the pharmaco-therapeutic interventions that can prevent or attenuate acute or chronic dopaminergic toxicity induced by MA.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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