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Mitochondrial permeability transition pore: a potential drug target for neurodegeneration

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Abstract

The mitochondrial permeability transition pore (mPTP) has been considered a key contributor to cell death, inducing the process in several major neurodegenerative diseases. To date, the molecular nature of the mPTP remains confounding but its significance is universally acknowledged. Several targets have been screened and inhibition of mPTP has emerged as an attractive field for researchers. Nowadays, *in silico*-directed studies help to explore new small molecules targeting the mPTP to improve their drug-like properties and bioactivity. Here, we briefly summarize the role of mPTP in neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson disease (PD), and Huntington's disease (HD), and discusses current and future potential therapeutic targets.

Introduction

Mitochondria, the power house of the cell, have an essential role in cell survival by providing energy in the form of ATP, regulating intracellular calcium homeostasis, and maintaining redox stress inside the cell. Mitochondria are also important in regulating ion channels, securing cellular signal transduction, and in causing pathophysiological events [1]. In the central nervous system (CNS), mitochondria are crucial for neuronal survival and death by regulating cellular survival and various apoptotic pathways [2,3]. Structurally, mitochondria are rod-shaped (0.75–3 mm), double membrane-bound organelles. The two membranes of mitochondria, outer and inner, comprise phospholipids and proteins. Compared with the outer membrane of mitochondria (OUM), which is smooth and permeable to a large number of nutrients, ions, and energy molecules (ATP and ADP), the inner membrane of mitochondria (IMM) is more complex, intensively folded, and relatively impermeable to large molecules. The impermeable nature of the IMM is crucial in maintaining the homeostasis of the inner mitochondrial environment as well as integrity of the mitochondria [4]. Different ion channels and transporters in IMM help in communications between mitochondria and the external environment. For instance, calcium (Ca^{2+}) is taken into mitochondria from cytoplasm by energy-driven uniporters, while the efflux of Ca^{2+} from the mitochondria to the cytoplasm is regulated by ion gradient-driven antiporters. Increased oxidative stress and impaired energy metabolism compromise Ca^{2+} homeostasis, causing further calcium overload and mishandling by the mitochondria. This

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abnormal condition result in the quick efflux of calcium through a nonselective pathway that eventually leads to the formation of the mPTP [4,5].

Mitochondrial permeability transition pore

After the discovery of the permeability transition pore by Hunter *et al.* [6], the permeability transition (PT) was later explained as an increase in the permeability of IMM to ions and solutes with molecular masses up to 1.5 kDa, leading to mitochondrial matrix swelling and cellular death through apoptosis (programmed cell death) and necrosis (nonprogrammed, autolysis) [7]. Furthermore, Hunter and Haworth characterized mPTP as a nonselective channel with a peak conductance of ~1.3 nS [8]. Although the concept of mPTP was considered as *in vitro* artefact of uncertain pathophysiological significance, investigators later supported the essence of mPTP formation in disease manifestation [9]. Until recently, the structure of mPTP was controversial, but research by Szabó and Zoratti [10], Halestrap [11], and others suggested that the mPTP comprised a voltage-dependent anion channel (VDAC) in the OMM [12], adenine nucleotide translocator (ANT) in the IMM [13], and cyclophilin D (CypD) in the mitochondrial matrix [4,14,15]. VDACs contribute to outer membrane permeability and are associated with the mitochondrial benzodiazepine receptor; thus, they regulate extramitochondrial cholesterol transfer to the intermembrane space [16]. ANT allows the influx of phosphorylated and nonphosphorylated derivatives of adenine nucleotides through the IMM, and CypD helps in protein folding because it exhibits peptidyl propyl isomerase activity [5]. CypD is also a key component of mitochondrial permeability transition and is involved in neurodegenerative diseases.

Under normal physiological conditions, all components of mPTP are disaggregated and, upon apoptotic or stressing stimuli, unite to form pores of 1.0–1.3 nm that trigger the nonselective flux of molecules [17]. Given the mechanistic basis of mPTP formation, researchers proposed that mPTP formation is initiated by the binding of ANT with CypD in IMM, where CypD translocates from the mitochondrial matrix to the IMM. This binding facilitates the formation of a tunnel-like structure comprising ANT and VDAC and connects the mitochondrial matrix to the cytosol by crossing both mitochondrial membranes [4,12,13,17]. The formation of mPTP is not only a key event in cell death, but is also suggested to be important for mitochondrial function and cell survival [18,19]. Using a calcium-overload model, assembly of the C-subunit of ATPase (C-subunit), inorganic polyphosphate (polyP), and polyhydroxybutyrate (PHB) were found to be required for mPTP opening [20].

In addition to the components discussed above, F1F0 ATP synthase is also involved in mPTP opening [21,22]. Using genetic approaches, Bonora *et al.* suggested that the dissociation of F1F0 ATP synthase dimers and involvement of the C-ring are crucial in mPTP induction [23]. Importantly, blocking the interaction of F1F0 ATP synapse with CypD alleviated mitochondrial and synaptic defects and improved cognitive function in diabetes milieu [24]. Under the influence of oxidative stress, the translocation of the tumor suppressor p53 was also reported in mitochondria, which elicits mPTP formation after interacting with CypD [25]. Using light scattering, fluorescence, and electron microscopy techniques, the induction of calcium-induced PTP was found to be significantly inhibited in

low osmotic-strength solutions [26]. Thus, the effect is linked to changes in the curvature of the IMM. Leung *et al.* proposed the participation of the phosphate carrier (PiC) in pore formation [27]. PiC is present in IMM and forms mPTP either by itself or by binding to ANT [27]. In rat brain cortex mitochondria, the calcium uniporter has a role in regulating mitochondrial permeability [28]. Additionally, using genetic silencing approaches, the involvement of soluble matrix peptidyl prolyl isomerase F cyclophilin D (PPIF) was confirmed in Ca^{2+}-induced mPTP opening [15,29,30]. Likewise, using an RNAi-based screening approach, Shanmughapriya *et al.* identified the necessary and conserved role of spastic paraplegia 7 (SPG7) in Ca^{2+} and ROS-induced PTP opening [31]. The authors proposed that SPG7 is a conserved core component that constitutes the PTP complex and regulates its function [31]. A mouse model of experimental autoimmune encephalomyelitis (EAE) lacking CyPD was found to be partially rescued from EAE by Forte *et al.*, suggesting CypD and mPTP as a potential target for neuroprotective therapy [32]. These studies suggest additional and important molecular components that can facilitate mPTP formation given the contrasting reports for the involvement of VDAC and ANT in mPTP formation [33,34]. Although there is disagreement over the involvement of VDAC and ANT as core components for mPTP configuration, CypD has been considered to be crucial in mPTP formation, at least in Ca^{2+}-dependent mechanisms [9] (Fig. 1).

mPTP opening is implicated in various neurodegenerative diseases, including AD, PD, prion disease, motor neuron disease (MND), HD, spinal muscular atrophy (SMA), and amyotrophic lateral sclerosis (ALS) [35–37]. The opening of mPTP is characterized by decoupling of electrochemical potential across the IMM and alterations of mitochondrial osmotic disturbances that accompanies Ca^{2+} mishandling and reduced ATP generation in the mitochondria [38]. Cellular death via the apoptotic pathway occurs when mPTP opening occurs, resulting in reduced mechanisms of oxidative phosphorylation and ATP hydrolysis [39]. In the process, the presence of sufficient ATP levels and transient opening of the mPTP results in cytochrome c release through the mitochondria, which activates caspase cascades and mitochondria-driven apoptosis [40]. In contrast to apoptosis, sustained and extensive mPTP opening limits ATP synthesis by mediating the uncoupling of oxidative phosphorylation [33]. With the onset of a high energy demand and compromised ATP production, the cell mass loses its structural and functional integrity, resulting in irreversible damage and narcotic cell death [40,41] (Fig. 2).

Role of mPTP in different neurodegenerative diseases

Alzheimer's disease and mPTP

AD is a progressive neurodegenerative disease that impairs memory and other important mental functions. The AD brain is characterized pathologically by the accumulation of toxic protein amyloid beta (Aβ) and neurofibrillary tangles (NFTs), formed by pathological forms of tau protein [42]. The deposition of neurotoxic aggregates is mediated by overproduction of toxic peptides and failure of clearance mechanisms. Studies have shown that these aggregates induce neuronal dysfunction, leading to cognitive and memory impairment [42,43]. The neurotoxicity effects of aggregates have been reported to be facilitated through free radical generation and calcium dysregulation [36,44]. The presence of Aβ has also been

confirmed in mitochondria of human AD brain [37] and transgenic (Tg) animal models of AD [45]. It is unclear whether Aβ in mitochondria is generated *in situ* or imported. However, researchers have suggested that Aβ is derived from extracellular and intracellular pools and then internalized in the mitochondria [46]. For example, a study in isolated rat mitochondria by Hanson Petersen *et al.* showed the co-localization of extracellularly applied Aβ and mitochondrial markers in IMM, suggesting that Aβ is taken by the cells [47]. Similarly, studies using confocal microscopy confirmed the presence of $A\beta_{42}$ fragments co-localized with complex II of the respiratory chain in IMM and OMM, and with the chaperon matrix protein HSP60 [48,49]. Studies in patients with AD and Tg-AβPP mice suggested formation of the complex after the binding of Aβ with CypD in cortical mitochondria [37,45]. The interaction between Aβ and CypD causes the formation of mPTP, resulting in reduced mitochondrial potential, decreased mitochondrial respiratory function, and increased formation of free radicals, leading to oxidative stress and the release of pro-apoptotic proteins [4,5].

Potential drugs designed to interfere with the Aβ-CypD complex could help relieve the neurotoxic effect of Aβ. Given that the pathophysiological cascades of AD start with mPTP formation, therapeutic interventions against mPTP could be helpful in reversing disease pathology [4]. Hence, mPTP has been studied widely as a potential drug target for neurodegenerative diseases [4,35]. The specific binding of Aβ has also been shown with other mitochondrial proteins that cause cell physiology defects and efficient respiratory halts in AD [50,51]. Lustbader *et al.* elucidated the binding of Aβ with Aβ-binding alcohol dehydrogenase (ABAD), also called 17-β-dehydrogenase type-10 (HSD-10), an intracellular enzyme in the mitochondrial matrix, which resulted in increased cellular oxidative stress, DNA fragmentation, and reactive oxygen species (ROS) generation [45,46,51]. Increased expression of HSD-10 was associated with increased mitochondrial Aβ in the hippocampus region of the AD brain compared with healthy brain [52]. Studies in transgenic AD mice suggested that inhibition of the ABAD/HSD-10-Aβ interaction significantly diminished mitochondrial Aβ accumulation, thus protecting neuromitochondrial and learning and/or memory functions in AD mice [45]. Another study in Tg mAPP/ABAD mice showed that ABAD-Aβ interactions affected the expression levels of endophilin-1 (EP-1), a cytoplasmic SH3 domain-containing protein, and Prdx-2, an antioxidant protein [53], which mediate neuronal death by activating JNK (c-jun-N terminal kinase) signaling [53,54]. In addition, compromised oxidative phosphorylation during ADpathologyhasbeen widelystudiedand Aβ wasfoundtoaffect ATP synthase, cytochrome c oxidase, cytochrome c reductase (complex III), complex I, and complex IV activities [55,56]. Furthermore, Aβ has also been implicated in disease progression by inducing lipid peroxidation and superoxide radical production, and reducing cellular antioxidant levels [56]. Indeed, suppression of mitochondrial ROS by eliminating damaged mitochondria significantly protected against Aβ-mediated mitochondrial and synaptic dysfunction [57]. Recent studies demonstrated that enhancing the clearance of dysfunctional mitochondria by augmenting PTEN-induced putative kinase 1 (PINK1) function reduced cerebral and mitochondrial Aβ, and improved mitochondrial and synaptic function as well as cognition [57]. Furthermore, suppressing excessive mitochondrial fission or ROS generation significantly reversed AD-derived mitochondrial

defects and axonal mitochondrial transport in human transmitochondrial cybrid cells [58–61].

Parkinson's disease and mPTP

PD currently affects around 6.3 million people worldwide, and is expected to affect 8 million–9 people by 2030 [62]. It mainly affects motor neurons through the loss of dopaminergic neurons in the substantia nigra pars compacta (SNPc) and the presence of excess α-synuclein protein in presynaptic neuronal cells. The presence of clumps of α-synuclein protein, also called Lewy bodies, is the hallmark of PD. Clinical symptoms associated with the disease are body stiffness, bradykinesia, frequent tremors, postural instability, and balance disorders. An impaired cellular redox state, defective metabolism, and dysfunctional mitochondria are also reported in PD [36,62]. The sporadic form of the PD is reflected through the loss of Ca^{2+} homeostasis and α-synuclein aggregates [62,63]. Defects in mitochondrial respiratory complex I and mitochondrial autophagy (mitophagy) are also associated with PD [62]. Similar to AD, mPTP formation in PD through mitochondrial dysfunction occurs in the same manner and includes a series of events, including IMM depolarization, impaired oxidative phosphorylation, increased ROS production, mitochondria matrix swelling, IMM cristae unfolding, loss of Ca^{2+} homeostasis, and the release of apoptogenic proteins through the OMM, which eventually leads to cell death. mPTP opening has been linked to neuronal death by various mechanisms, including excitotoxicity, neurotoxicity, apoptosis, and necrosis [64].

Huntington's disease and mPTP

HD, also known as Huntington's chorea, is an inherited disorder caused by mutations in the gene encoding Huntington (*Htt*), located on Chr 4 [65]. Abnormal elongation of cytosine-adenine-guanine (CAG) triplet repeats in *Htt* results in pathological elongation of polyglutamine in the Htt protein, which gradually damages brain cells. The disease mainly affects basal ganglia and causes uncontrolled movements, mood disorders, psychiatric problems, mental disabilities, and dementia. Metabolic deficiencies have been reported in patients with HD, suggesting the relevance of mitochondrial dysfunction in its pathogenesis. Additionally, mitochondrial abnormalities, such as mPTP formation, Ca^{2+} mishandling, and redox stress, have been implicated in *in vivo* and *in vitro* models of HD [66,67].

mPTP as a potential drug target

Irreversible mPTP formation has been linked to various neurodegenerative diseases, and pharmacological, genetic interventions have been identified and formulated to inhibit mPTP formation [33,68]. Of all the components thought to be involved in mPTP formation, CypD is the most important.

Mitochondrial dysfunction is an early pathological feature of AD. AD-derived mitochondria exhibit failure in respiratory function, energy metabolism, and mitochondrial morphological alterations [57–60,69–76]. Mitochondria isolated from cortical and hippocampal brain regions of patients with AD showed significant increased expression of CypD compared with non-AD brain mitochondria [37]. Increased CypD expression is also positively

associated with increased Aβ expression [4]. In addition, mouse models of AD that express mutant forms of APP also showed age-dependent increases in CypD in cortical and hippocampus regions of the brain compared with their littermate controls [4,45]. CypD ablation has also been studied for preventing mPTP formation, given that CypD is considered a crucial molecule for mPTP opening [4,5]. Research using a mAPP model has established various events that occur during mPTP formation [4,5], including increased expression of CypD in cortical mitochondria that translocate to the IMM, altered Ca^{2+} homeostasis, and mitochondrial swelling [4,5,77]. Interestingly, ablating CypD with cyclosporine A (CsA), a CypD inhibitor, mitigated these detrimental effects [37,45]. The binding affinity of CypD with Aβ has been proven experimentally, and was found to be sequence specific [37,45]. Mitochondria from a CypD-deficient mAPP mouse model (*mAPP*/*Ppif*$^{-/-}$) showed reduced mitochondrial swelling and permeability transition following Ca^{2+} induction compared with mAPP mice [4,37,45]. However, introduction of CsA in mAPP mitochondria relieved mitochondrial dysfunction in response to Ca^{2+} [4,37,45]. Given the role of CypD in ameliorating spatial learning and memory function, a radial arm water-maze test was performed and *mAPP*/*Ppif*$^{-/-}$ mice showed considerable improvements in the test compared with mAPP mice [4,37,45]. Different selective approaches have been designed and modified to target lipophilic cations to mitochondria. Smith *et al.* showed that mitochondria-targeted antioxidants comprising hydrophobic delocalized cations linked to antioxidant quinone moieties had beneficial impacts resulting from a reduction in oxidative effects [78]. Similarly, Warne *et al.* designed and synthesized JW47, a CypD inhibitor, using a quinolinium cation tethered to cyclosporine. In the EAE disease model, JW47 showed significant protection of axons and improved motor assessments with minimal immunosuppression [79]. The use of multiple pharmacological approaches will facilitate the development of new drugs by increasing the drug-like properties and bioactivities of candidate molecules, such as enhancing mitochondrial biogenesis, and suppressing excessive mitochondrial ROS production and mPTP opening.

An acute model of PD prepared in *Ppif*$^{-/-}$ mice, using neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), showed cytoprotection compared with control mice [80]. CypD-deficient mice also displayed a considerable reduction in brain infarct size after acute middle cerebral artery occlusion and reperfusion. These results strongly supported a vital role of CypD in an ischemic injury model in which calcium overload and oxidative stress are affected [30]. Likewise, in an *ex vivo* study by Li *et al.*, the essential role of CypD in mitochondrial permeability transition (CyD-mPT) was elucidated in glutamate-triggered delayed calcium deregulation (DCD) and excitotoxic cell death [81]. The study results suggested that, compared with cortical neurons isolated from control mice, cortical neurons from *Ppif*$^{-/-}$ mice were more resistant to DCD and cell death when induced with moderate but pathologically relevant glutamate concentrations. These studies highlight CypD as a strong candidate to prevent progression of chronic neurodegenerative diseases.

However, to establish the role of mPTP formation in the progression of neurodegenerative diseases, clinical studies have mostly used cyclosporine, a CypD inhibitor. Unfortunately, cyclosporine has certain limitations that restrict its use as a tool to look at the clinical potential of CypD inhibition and mitochondrial dysfunction. The limitations include toxicity

and immunosuppressive effects [82]. Other limitations, such as reduced tissue penetration and reduced ability to cross the blood–brain barrier (BBB), are other examples of issues that restrict the role of cyclosporine as a future potential candidate [83]. Using a fragment-based drug discovery approach based on nucleic magnetic resonance (NMR) and X-ray crystallography, Ahmed-Belkacem *et al.* generated a new family of nonpeptidic, small-molecule cyclophilin inhibitors, unrelated to CsA, with potent *in vitro* PPIase inhibitory activity [84].

Using molecular docking and virtual screening methods, Valasani *et al.* described the design, synthesis, diastereomeric crystallization, docking 2D quantitative structure–activity relationship (QSAR) studies, and pharmacophore modelling for a series of acetylcholinesterase inhibitors [86] and CypD-selective inhibitors [85,87] for AD treatment. Guo *et al.* elucidated quinoxaline derivatives that also bind CypD and inhibit mitochondrial swelling in response to Ca^{2+} [36,88]. Elkamhawy *et al.* reported novel quinazoline urea analogs that bind selectively to CypD, and showed neuroprotective effects against Aβ-induced toxicity in neuronal cells [89]. Azzolin *et al.* reported the use of antamanide, a natural cyclic peptide, to inhibit mPTP formation in a manner similar to CsA [90].

Using pharmacokinetics data, authors have determined that pharmacological tools can be developed against neurodegenerative pathologies [90–97]. In addition, according to the published literature, ~122 natural compounds derived from traditional plant sources are in use in modern medicine, of which 80% are used in forms similar to the naturally occurring molecules [98]. Natural products with antioxidant and anti-inflammatory activities have been found to be beneficial against mPTP formation [99–102]. Russo *et al.* described the potential of compounds from *Galanthus* spp., *Crocus sativus, Ginkgo biloba, Salvia* spp., and *Huperzia serrata* in ameliorating dementia or AD [103]. Modifications of plant products are also under way to further improve their efficacy and bioavailability [103]. Since 1929, compounds isolated or expressed in microbial systems have been used as important regulators of disease. Bryostatins are a group of macrolide lactones isolated from the bryozoan, *Bugula neritina*. Using bryostatin-1, a Phase 2 clinical trial (NCT00606164) was approved for the treatment of AD [104]. Their main pharmacological mechanism of action is modulation of protein kinase C (PKC) activity [105]. In an APP/PS1 transgenic mouse model of AD, oral administration of bryostatin-1 showed improvements in learning and enhanced long-acting memory, thus, highlighting this as a future potential candidate for treating AD [106]. Furthermore, natural redox-active compounds, such as polyphenols, which act as antioxidants, were also shown to be valuable [107,108].

To target mitochondrial mPTP anomalies, candidate drug molecules can be selected by virtual screening of best-fi synthetic, semisynthetic, and/or microbial molecules and their chemical transformation into novel active analogs using *in silico* QSAR modeling, molecular docking, and absorption, distribution, metabolism, excretion and toxicity (ADME/T) studies. It will be necessary to design compounds with increased bioavailability, reduced toxicity and other properties that can overcome the BBB. This step will involve a large number of compounds and could be used to screen the most important novel formulations before wet lab testing. Figure 3 depicts ways in which to develop lead or drug-like molecules. Furthermore, virtually active compounds or series of compounds could be

synthesized by using suitable schemes followed by chromatographic purification and spectroscopic characterization. The lead molecules isolated would then be tested against neurodegenerative diseases *in vitro*, *ex vivo* and *in vivo*. Directing advanced studies using genomics and structural biology can create new frontiers for bioactive drugs with reduced or no adverse effects. Moreover, formulations with improved solubility and stability would also be useful for treating AD.

Concluding remarks

Here, we discussed the role of mitochondrial dysfunction and mPTP formation in mediating neurodegenerative diseases. Although the structural and mechanistic basis of mPTP formation associated with neurodegenerative diseases has not been clearly elucidated, the results obtained with mPTP inhibition suggest its promising role as a potential candidate in the treatment of various neurodegenerative diseases. Once the therapeutic aspects of mPTP inhibition through potential compounds have been elucidated further, more avenues for future research might become clear. Hence, exploring therapeutic interventions through potential therapeutic compounds can potentiate their use against different neurodegenerative diseases. The use of QSAR and molecular docking-guided lead optimization can help in screening virtual analogs and their drug-like potentials. Furthermore, wet lab preparations of selected candidate molecules and *in vivo* and *in vitro* testing can further translate the therapeutics for use in the clinic.

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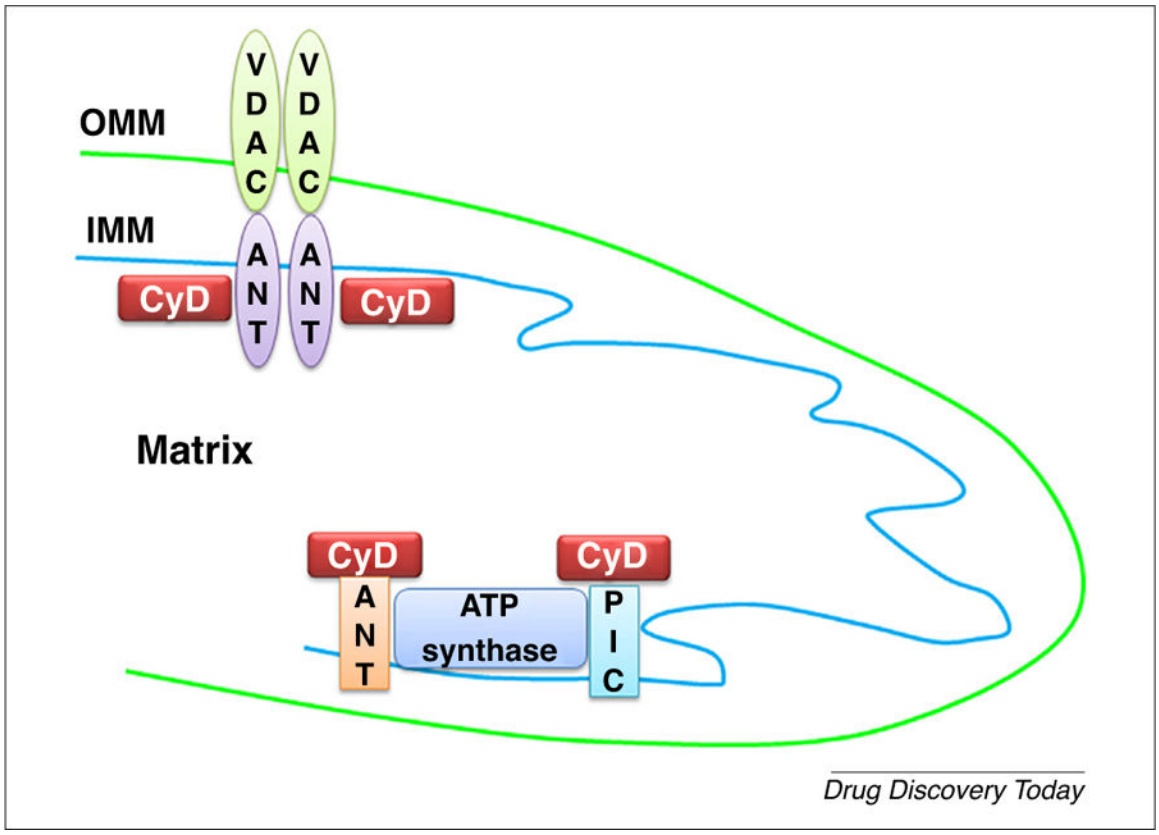

FIGURE 1.

Components of the mitochondrial permeability transition pore (mPTP) according to the published literature. (a) Historical mPTP model that contains voltage-dependent anion channels (VDAC), adenine nucleotide translocators (ANT), and cyclophilin D (CypD). (b) Components of more recent models of mPTP formation. Abbreviations: IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; PiC, phosphate carrier.

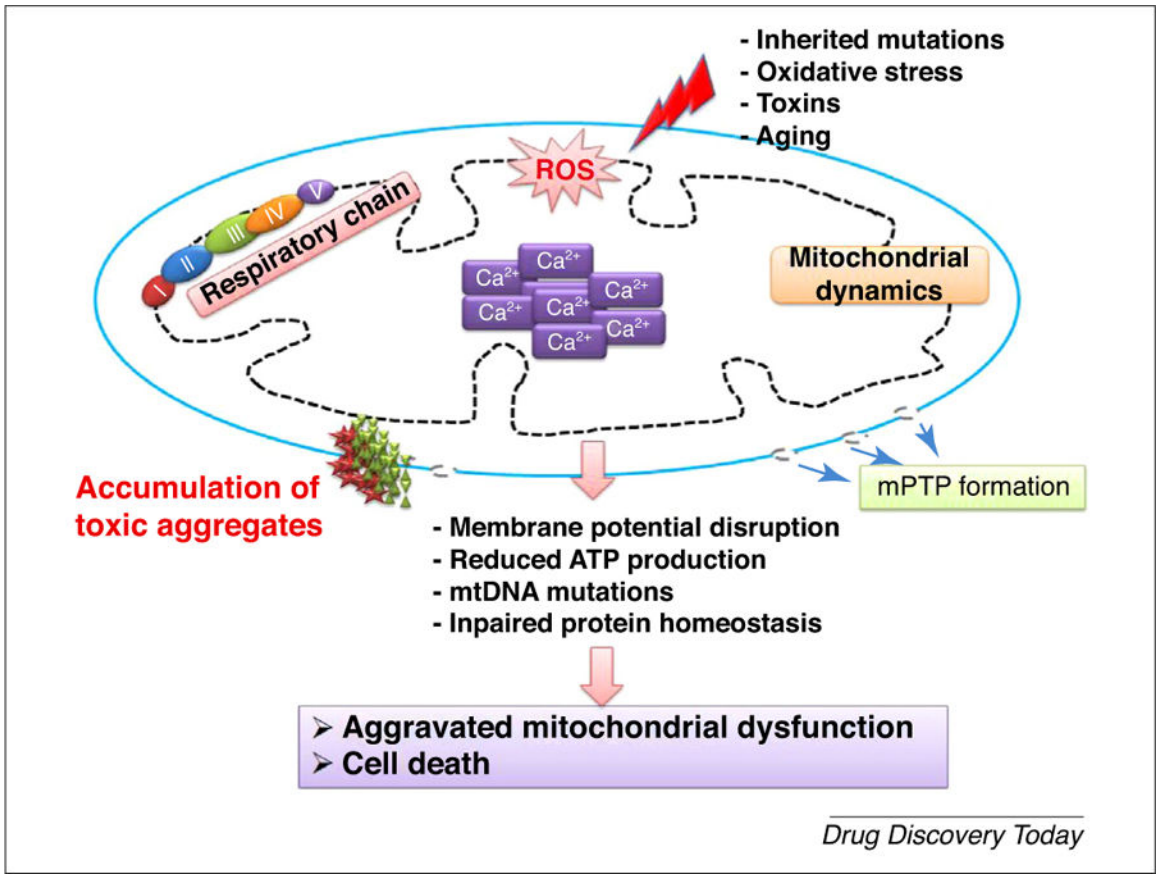

FIGURE 2.

The cell death cascade resulting from mitochondrial permeability transition pore (mPTP) formation and mitochondrial dysfunction in neurodegenerative diseases. In neurodegenerative diseases, oxidative stress resulting from toxins induces reactive oxygen species (ROS) generation, which promotes mitochondrial calcium mishandling and abrupt mitochondrial dynamics. Altered redox dynamics aggravate mitochondrial dysfunction by promoting mPTP formation, which promotes cell death.

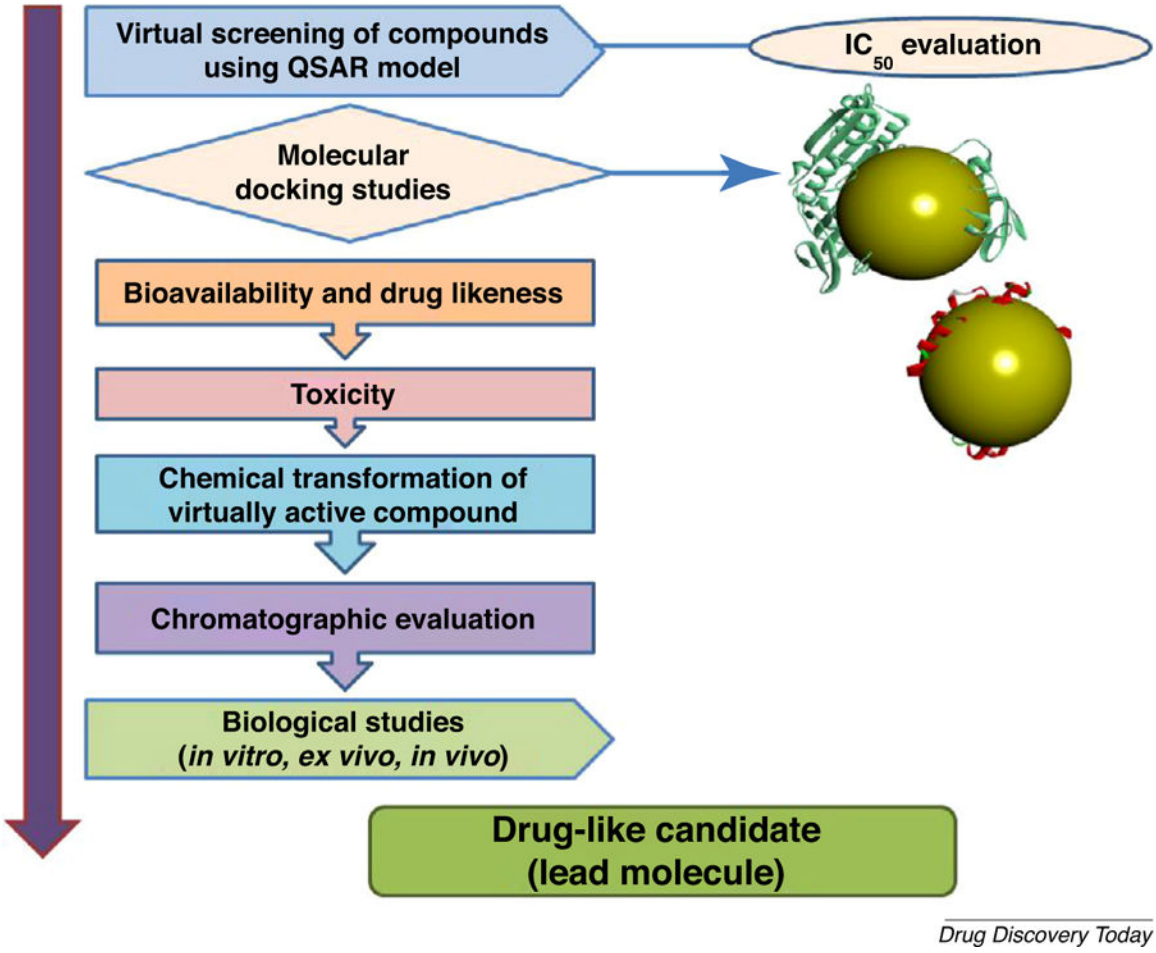

FIGURE 3.

Lead optimization using *in silico* quantitative structure–activity relationship (QSAR) modeling, molecular docking, bioavailability, drug likeness, and toxicity parameters followed by wet lab synthesis and biological validation.