Review Article

Mitochondrial dynamics in neurological diseases: a narrative review

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Background and Objective: The mitochondrion is a crucial organelle for aerobic respiration and energy metabolism. It undergoes dynamic changes, including changes in its shape, function, and distribution through fission, fusion, and movement. Under normal conditions, mitochondrial dynamics are in homeostasis. However, once the balance is upset, the nervous system, which has high metabolic demands, will most likely be affected. Recent studies have shown that the imbalance of mitochondrial dynamics is involved in the occurrence and development of various neurological diseases. However, whether the regulation of mitochondrial dynamics can be used to treat neurological diseases is still unclear. We aimed to comprehensively analyze mitochondrial dynamics regulation and its potential role in the treatment of neurological diseases.

Methods: A comprehensive literature review was carried out to understand the mechanisms and applications of mitochondrial dynamics in neurological diseases based on the literature available in PubMed, Web of Science, and Google Scholar.

Key Content and Findings: This review discusses the molecular mechanisms related to mitochondrial dynamics and expounds upon the role of mitochondrial dynamics in the occurrence and development of neurodegenerative diseases, epilepsy, cerebrovascular disease, and brain tumors. Several clinically tested drugs with fewer side effects have been shown to improve the mitochondrial dynamics and nervous system function in neurological diseases.

Conclusions: Disorders of mitochondrial dynamics can cause various neurological diseases. Elucidation of mechanisms and applications involved in mitochondrial dynamics will inform the development of new therapeutic targets and strategies for neurological diseases. Dynamin-related protein 1 (Drp1), as a highly relevant molecular for mitochondrial dynamics, might be a potential target for treating neurological diseases in the future.

Keywords: Drp1; mitochondrial dynamics; mitochondrial fusion protein; Alzeimer's disease; Parkinson's disease

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Introduction

Mitochondria are double membrane-bound organelles that contain DNA. The ancestor of mitochondria is believed to have invaded primitive single-celled organisms 1.5 billion years ago; most of the genetic material entered the nucleus, while a small part remained in the mitochondria (1). Mitochondria, the "energy factory" of the cells, produce adenosine triphosphate (ATP) with aerobic respiration. A study has also shown that mitochondria are the hub of material metabolism, reactive oxygen species (ROS) regulation, immune response, programmed cell death, and other processes (2).

Mitochondria are highly dynamic structures that change their shape, form, and number through fission and fusion. These dynamic changes can make mitochondria differ in shapes, appearing in the cytoplasm as dots, fragments, strips, lines, etc. It is believed that factors such as dynamin-related protein 1 (Drp1), mitochondrial fission 1 protein (Fis1), Dynamin 2 (Dnm2), mitochondrial fission factor (MFF), mitochondrial dynamics protein (Mid), mitochondrial fusion protein (MFN), and optic atrophy 1 protein (OPA1) are involved in mitochondrial fission and fusion (3). The mitochondrial dynamics, regulated by various chemical enzymes and proteins, are closely related to the multiple functions of mitochondria, such as cell proliferation, metabolism, and migration. In neuronal cells, mitochondria are coupled to the dynein or kinesin-1 family motor proteins, enabling transport through the axoplasm to meet the neuron's energy demands (4). Abnormal mitochondrial dynamics can affect the function of organ systems with high energy requirements, such as the nervous system.

With the aging of society, neurological diseases have become one of the leading causes of human death or disability, and it is difficult to fully restore the original neurological functions with existing treatments (5). An increasing amount of evidence shows that mitochondrial dynamics are involved in the occurrence and development of various neurological diseases (2). Our review reveals the different molecular mechanisms of mitochondrial dynamics and highlights their role in the emergence and development of various neurological disorders. Furthermore, our review summarizes the mitochondrial dynamics-related therapeutic drugs that can potentially shape to provide new therapeutic directions for neurological diseases. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2401/rc).

Methods

We searched articles in PubMed, Web of Science, and Google Scholar published until March 20, 2022. The key search terms included "the mechanisms of mitochondrial fission and fusion", "mitochondrial dynamics and neurological diseases", and "mitochondrial dynamics and treatment strategy". Sources are listed in *Table 1* and Table S1.

Discussion

Mechanisms of mitochondrial dynamics

Mitochondrial fission

Mitochondrial fission is a complex process in which mitochondria are fragmented through division and segregated into separate mitochondrial organelles. Drp1, a large GTPase protein belonging to the Dynamin family, plays a vital role during mitochondrial fission. It comprises 4 distinct domains: an N terminal GTPase domain, a middle domain, a variable domain, and a C-terminal GTPase

Table 1 The search strategy summary

Items	Specification
Date of search	March 20, 2022
Databases and other sources searched	PubMed, Web of Science, and Google Scholar
Search terms used	See Table S1 for details
Time frame	Articles published between January 1, 2008 and March 20, 2022
Inclusion criteria	English original publications (basic science and clinical), reviews and abstracts
Selection process	In this review, WLJ and XL collected and organized the literature. They discussed with JQ and jointly selected the literature related to the core content of the review. Finally, all authors reached an agreement on the manuscript

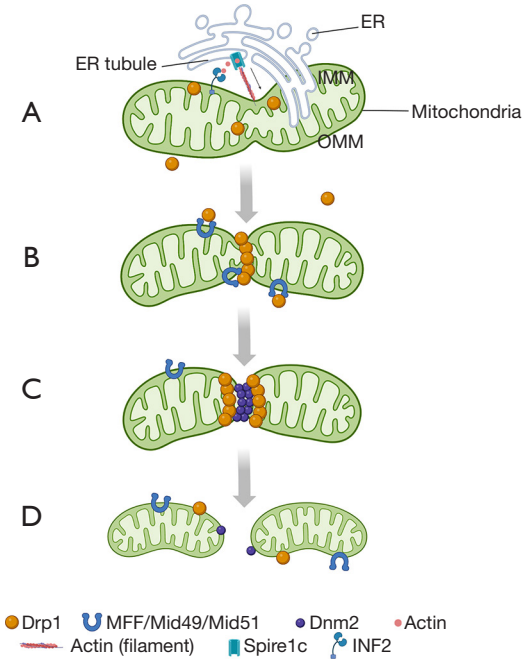

Figure 1 Mechanism of mitochondrial fission. (A) The ER tubules surround mitochondria, and then actin nucleation and polymerization are induced at mitochondria-ER interface points by the ER-bound INF2 and mitochondrial Spire1C. The mechanical force needed to propel mitochondrial preconstriction is provided by this mechanism. (B) MFF and Mid recruit Drp1 from the cytoplasm to the outer mitochondrial membrane. Multiple Drp1 molecules aggregate and are distributed around mitochondria to form oligomeric rings constricting the mitochondria. (C,D) Dnm2 is drawn to the Drp1-mediated mitochondrial constriction neck and breaks off the membrane. ER, endoplasmic reticulum; IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; INF2, inverted formin 2; MFF, mitochondrial fission factor; Drp1, dynamin-related protein 1; Dnm2, dynamin 2.

effector domain (GED). The force that triggers membrane constriction is thought to arise from the conformational changes caused by GTPase-induced hydrolysis (1). One study suggested that Drp1 in the cytoplasm is recruited to the outer mitochondrial membrane (OMM) before fission, which binds to receptors such as MFF and Mid (6). Multiple Drp1 molecules aggregate and are distributed around mitochondria to form oligomeric rings, leading to constriction. The Fis1 protein was previously thought to be a Drp1 adaptor in mitochondrial fission but was later confirmed not to contribute directly to mitochondrial fission in normal cell homeostasis (7). However, Fis1 has been found to promote fission by inhibiting the GTPase activity of fusion-related proteins OPA1 and MFN (8,9). Ji *et al.* (10) found that Drp1 constantly formed and disassembled from the oligomeric ring structure regardless of mitochondrial fission, which could signal to induce and maintain Drp1 oligomeric rings to constrict mitochondria. They also showed that actin filaments significantly activated Drp1 by recruiting them to mitochondria and helping them to form oligomeric rings. Phosphorylation of Drp1 at ser616 promotes mitochondrial fission (11), and phosphorylation of Drp1 at ser637 reduces the GTPase activity and inhibits Drp1 recruitment to mitochondria, thereby preventing mitochondrial fission (12).

Contact sites between mitochondria and the endoplasmic reticulum (ER) are essential for mitochondrial fission (13). The ER tubules surround mitochondria and induce actin nucleation and polymerization at mitochondrion-ER contact sites through ER-bound inverted formin 2 (INF2) and mitochondrial Spire1C. Polymerized actin, which might also recruit myosin II, then provides the mechanical force to drive the preconstriction of mitochondria (14). After the initial constriction by ER tubules, the mitochondrial diameter decreases from 300–500 to 150 nm, which allows Drp1 oligomeric rings to form (15). Finally, Dnm2 is recruited to the Drp1-mediated mitochondrial constriction neck and cuts off the membrane (*Figure 1*) (16).

One study has inferred that the contact between lysosomes and mitochondria also promotes mitochondrial fission, with RAB7 binding to GTP in lysosomes being one factor that initiates the coupling (17). Time-lapse confocal microscopy in Hela cells demonstrated that mitochondria fission occurs at the contact point between lysosomes and mitochondria, where both Drp1 and ER tubules aggregate. Furthermore, Fis1 was found to recruit TBC1D15, a RAB7 GTPase-activating protein that can hydrolyze RAB7 GTP to untether lysosomes from the mitochondrial network. This finding suggests that the contact and reseparation of lysosomes and mitochondria might play a pivotal role during mitochondrial fission (17).

It was believed that the fission site of the mitochondrion is in the center of its long axis. However, a recent study observed hundreds of spontaneous mitochondrial fissions and found a bimodal distribution with mitochondrial fission either in the midzone (within the central 50% of the long axis of the mitochondria) or periphery (less than 25% from a tip of the long axis of the mitochondria) (18). A further study found peripheral fission to be associated with increased ROS, decreased mitochondrial membrane potential (MMP), and high levels of calcium ions in the mitochondrial

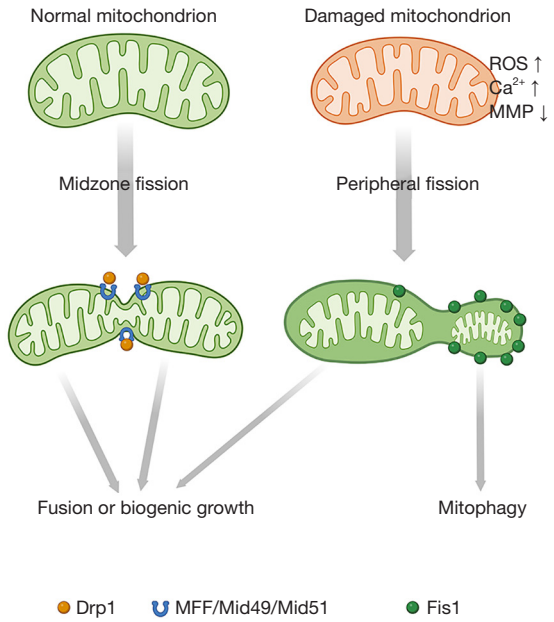

Figure 2 Different ways that mitochondrial fission leads to distinct outcomes. Damaged mitochondria are likely to undergo peripheral fission, whereas normal mitochondria are likely to undergo midzone fission. Drp1 and MFF participate in midzone fission, and Fis1 participates in peripheral fission. After peripheral mitochondrial fission, the smaller daughter enters mitophagy for degradation and reuse. ROS, reactive oxygen species; MMP, mitochondrial membrane potential; Drp1, dynamin-related protein 1; MFF, mitochondrial fission factor; Fis1, mitochondrial fission protein 1.

compartment (19). Compared to those in peripheral fission, mitochondria in midzone fission appear devoid of these changes. Mitochondrial-ER contacts lead to precontraction during midzone fission, where MFF proteins bind to Drp1 and are distributed at the mitochondrial fission sites. The Fis1 protein is mainly involved in peripheral mitochondrial fission, is distributed throughout the mitochondrial outer membrane, and is highly aggregated in the smaller daughter mitochondria but not at the fission site (18,19). After peripheral fission, the smaller daughter undergoes autophagy to be degraded, while the mitochondria after midzone fission are typically normal. Therefore, peripheral mitochondrial fission is asymmetric fission, in which the healthy daughter can continue to function, but the smaller daughter is degraded and reused. On the other hand, midzone fission is symmetrical fission, in which copies of the mitochondria are created. After midzone fission, the daughter can exist independently or function via fusion within the mitochondrial network (*Figure 2*) (20).

Mitochondrial fusion

Mitochondrial fusion is the process by which 2 small mitochondria fuse into 1 large mitochondrion, which is the basis for the network distribution of mitochondria. First, the 2 mitochondria interact in reverse, contraction and fusion of the outer membrane occur, and finally, the inner membranes are fused (21). MFN1 and MFN2, composed of 4 distinct domains [a GTPase domain, 2 transmembrane (TM) domains, HR1 (heptad repeat 1) domain, and HR2 (heptad repeat 2) domain], mediate the outer membrane fusion. During the fusion process, the 2 MFNs are dimerized by the HR2 domain and embedded into mitochondrial outer membranes by the TM domains. Subsequently, the MFNs' GTP hydrolysis induces the 2 mitochondria to come into closer contact, and fusion of the outer membranes occurs (22). MFN1-KO (knock out) can cause mitochondrial fission and spherical swelling, and the expression of either of the MFNs can rescue the phenotype (23). This may be related to the robust GTP-dependent membrane tethering activity of MFN1 (24). However, a recent study has found that the human MFN C-terminus is exposed to the mitochondrial intermembrane space (IMS), suggesting that MFNs carry a single TM domain with conserved redox-regulated cysteine residues and exposure of the HR2 domain to the IMS (25). Thus, further research is necessary to examine the topology of the TM domain in MFNs.

OPA1 (optic atrophy 1 protein) mediates the fusion of the inner mitochondrial membrane. Knockdown of OPA1 triggers mitochondrial fission, while its overexpression causes mitochondrial elongation (26). The structure of OPA1 is similar to that of MFNs, with both containing the TM and the GTPase domain. When the inner membrane is fused, the TM domain becomes embedded into the inner membrane, while the remaining OPA1 exists in the intermembrane space (27). The research conducted thus far does not indicate that the GTPase domain of OPA1 plays a role in inner membrane fusion. OPA1 has multiple proteolytic cutting points, forming longer L-OPA1 and shorter S-OPA1 after hydrolysis. It has been substantiated that L-OPA1 can participate in mitochondrial inner membrane fusion alone, while S-OPA1 cannot (28). Cardiolipin (CL) is a negatively charged, mitochondrion-specific lipid in the inner mitochondrial membrane (IMM) and is necessary to assemble the oxidative phosphorylation complexes (29). Experiments have shown that L-OPA1 interacts synergistically with CL to enable inner membrane fusion and that S-OPA1 plays a regulatory role in this

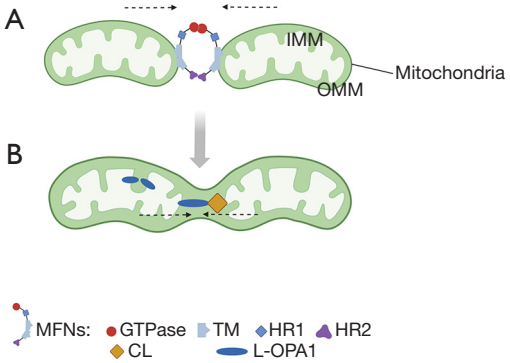

Figure 3 The structure of MFNs and the mechanism of mitochondrial fusion. (A) During the fusion process, the 2 MFNs are dimerized by HR2 and embedded into the mitochondrial outer membranes by the transmembrane domain, promoting the 2 mitochondria to come into closer contact by GTP hydrolysis and then fusing the outer membranes. (B) L-OPA1 interacts with CL to promote inner membrane fusion, and S-OPA1 plays a regulatory role in this process. However, the interaction between the 2 OPA1 only induces the formation of mitochondrial cristae but does not play a role in fusion. IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; MFNs, mitochondrial fusion protein; HR2, heptad repeat 2; TM, transmembrane; GTP, guanosine triphosphate; CL, cardiolipin; OPA1, optic atrophy 1 protein.

process. However, the interaction between the 2 OPA1 can only promote the formation of mitochondrial cristae but does not lead to fusion (30). One study has confirmed that the effect of OPA1 on IMM fusion is dependent on MFN1, revealing a close connection between the inner and outer membrane fusion process (31). Further experiments are required to understand the underlying mechanisms of mitochondrial fusion (*Figure 3*).

Mitochondrial transport

In mature neurons, mitochondria move bidirectionally over long distances during processes. The kinesin-1 family (KIF5A, B, and C) drive mitochondrial anterograde transport to distal axons, while the cytoplasmic dynein and the dynactin complex mediate retrograde transport from distal ends to the cell body. Syntaphilin (SNPH) holds axonal mitochondria stationary via its docking interaction with the microtubule (MT) network (4,32). Mitochondria redistribute in response to metabolic changes when neurons encounter physiological or pathological stress, thereby restoring energy homeostasis. The coordination of a group of MT-based transport and anchoring machinery composed of motors, adapters, and anchors is principally responsible for this highly dynamic redistribution of axonal mitochondria. The dynamic interaction of these motors, adaptors, and anchors enables long-distance bidirectional trafficking of axonal mitochondria and causes them to halt or become stationary, which leads to their re-mobilization and redistribution (33).

Mitophagy

Mitophagy is a crucial mitochondrial quality control system that keeps neurons healthy and functional by eliminating undesirable and damaged mitochondria. PTEN-induced kinase 1 (PINK1)/Parkin-dependent mitophagy is the most common and well-studied mitophagy pathway (34). The translocase of the outer membrane (TOM) imports PINK1 into the mitochondria under normal physiological circumstances (35). When the potential of the mitochondrial membrane decreases, PINK1 cannot be imported into the mitochondria and builds up on the OMM instead. PINK1 is an upstream protein of Parkin and mediates mitophagy by activating Parkin (36). It was also reported that PINK1 stabilized in depolarized mitochondria phosphorylates MFN2, which attracts and binds Parkin to promote mitophagy (37). Activated Parkin then polyubiquitinates multiple OMM protein substrates, including voltage-dependent anion channel 1 (VDAC1), MFN1, and MFN2, which could be recognized by autophagy adaptor proteins P62/SQSTM1, which mediates the interaction with LC3 (38,39). These adaptors promote the formation of autophagosomes to engulf damaged mitochondria. Subsequently, lysosomes fuse with autophagosomes to degrade these mitochondria (40). Mitophagy prevents accelerated cellular senescence and programmed cell death under physiological conditions, while excessive mitophagy is detrimental to cellular homeostasis.

Mitochondrial dynamics and neurological diseases

The disruption of mitochondrial dynamics contributes to the pathogenesis of various neurological diseases (41). We describe the recent clinical and experimental observations on mitochondrial dynamics in various neurological diseases, focusing on the role of Drp1.

Mitochondrial dynamics and neurodegenerative diseases

Alzheimer disease (AD)

AD, one of the most common neurodegenerative diseases,

is characterized by progressive loss of neurons in the brain leading to cognitive impairment. Excessive production of β-amyloid peptide (Aβ) is one of the leading causes of this disease.

In one study, the size and number of neuronal mitochondria seen in biopsied brain tissue of those with AD appeared increased, with mitochondrial fragmentation and reduced aspect ratio (41). In related biochemical experiments, the expressions of fission and fusion-related proteins, such as Drp1, OPA1, and MFNs, appeared decreased, but the fission factor Fis1 was significantly increased (42).

The amyloid precursor can be cleaved to Aβ. Overexpression of the amyloid precursor leads to mitochondrial fission, which can be blocked by lyase inhibitors. Experimental results (41) indicate that Aβ can stimulate mitochondrial fission, and fission inhibitors can rescue mitochondrial fragmentation caused by amyloid precursors and neuronal dysfunction.

Aβ-induced S-nitrosylation of Drp1 has also been shown to trigger mitochondrial fission, synapse loss, and neuronal damage in AD (43). One study has also suggested that Aβ-induced calcium flux leads to increased phosphorylation of Drp1 at ser616 through CaMKII-dependent Akt activation, resulting in the recruitment of Drp1 to mitochondria and enhancement of mitochondrial fission (44). The Drp1 inhibitor, Mdivi-1, protects the mitochondrial structure and function in the cytoplasmic hybrid neurons of those with AD (45). According to Manczak *et al.* (46), aberrant mitochondrial dynamics, mitochondrial fragmentation, and synaptic damage are caused by increased Aβ production and its interaction with Drp1 in patients with AD. To lessen mitochondrial fragmentation, neuronal and synaptic damage, and cognitive impairment in patients with AD, it might be beneficial to block these aberrant interactions.

Drp1-regulated fission may be used to excise the damaged mitochondria for mitophagy. Moreover, a reduction in Drp1 recruits Parkin, which could increase mitochondrial fission or fusion (47). Tau is a member of the microtubule-associated protein (MAP) family and is involved in the occurrence of AD. Increased levels of Aβ, phosphorylation-Tau, and their abnormal interactions with Drp1 can induce increased mitochondrial fragmentation and reduce mitochondrial fusion in AD (48). In the neurons of those with AD, these aberrant interactions lead to the growth of dysfunctional mitochondria. An increased accumulation of Aβ and phosphorylation-Tau in the cytoplasm could deplete Parkin and PINK1 levels, reducing the effective number of autophagosomes targeted to the dysfunctional mitochondria. In AD, these occurrences ultimately result in a reduction in the clearance of dead and dying mitochondria (49).

In addition, oxidative stress, impaired energy metabolism, and impaired axonal mitochondrial transport are also closely related to AD (50-52). Considering the interaction of Drp1 with Aβ and Drp1 with Tau, the development of Drp1-based therapeutics for AD patients would be promising.

Parkinson disease

Parkinson disease (PD) is the second most common neurodegenerative disease globally. It is characterized by the loss of dopaminergic neurons and the formation of Lewy bodies with α-synuclein (α-syn).

Overexpression of α-syn in rats leads to its aggregation, abnormal mitochondrial dynamics, and oxidative stress, thereby inducing neurodegeneration. Furthermore, the Drp1 inhibitor, Mdivi-1, can rescue the above changes, suggesting that Mdivi-1 may have the potential to treat PD (53).

Mitochondrial dynamics and the development of PD are closely related. Patients with *OPA1* gene mutations show symptoms of PD, and the fibroblasts of these patients show a decrease in OPA1 protein level. Conversely, mitochondrial fission and mitophagy increase, suggesting that mutations in the mitochondrial fusion genes might be involved in the occurrence of PD (54).

Impaired mitophagy mediated by mutations in PINK1 may contribute to early-onset autosomal recessive PD (55). One study reported that PINK1-deficient mouse tissues showed significantly reduced phosphorylation of Drp1 at ser616, independent of Parkin inactivation. Similarly, PINK1-mutated PD patients and sporadic PD patients exhibited a decrease in the phosphorylation of Drp1 at ser616, suggesting that PINK1 may act independently on the phosphorylation of Drp1 at ser616 to affect the development of PD (56).

Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) leads to progressive and selective loss of motor neurons in the brain and spinal cord. One study reported that mitochondrial fission was highly enhanced in muscles and motor neurons of TDP-43-, FUS-, and TAF15-induced fly models of ALS and that overexpression of OPA1 or knockdown of Drp1 restored mitochondrial morphology (57). VPS54 gene mutation has also been shown to cause ALS. In mutant mice, the researchers observed an abnormal distribution of mitochondria, in which the mitochondria became smaller and the mitochondrial cristae disappeared; moreover, the expression of MFN2 and OPA1 was lower, and the

phosphorylation of Drp1 at ser616 was higher than that in the wild type mice (58). Tau is involved in the occurrence of ALS and has been shown to interact with Drp1, with a synchronous increase in phosphorylated tau and Drp1 leading to increased mitochondrial fission (59).

Huntington disease

Huntington disease (HD) is a fatal genetic disease characterized by a progressive loss of medium spiny neurons (MSN). HD is caused by expanded polyglutamine repeats in exon 1 of the HD gene (60).

Huntingtin protein (HTT), a product of the HD gene, is ubiquitously expressed in the brain and peripheral tissues. The mutant huntingtin protein (mHTT) has been shown to affect Drp1 GTPase activity, increasing mitochondrial fission (61). Song *et al.* (62) found that mHTT interacts with Drp1 *in vivo* and that mHTT binds Drp1 directly with greater affinity than does wild-type HTT. Compared to wild-type HTT, mHTT showed a significant increase in the enzymatic activity of Drp1. These results suggest that mHTT triggers mitochondrial fragmentation by interacting with Drp1.

Increased expression of Drp1 and Fis1 and decreased expression of Mfn1, Mfn2, and OPA1 were found in patients with HD relative to healthy controls (63). In BACHD (bacterial artificial chromosome Huntington disease)transgenic neurons that express the full-length human mHTT gene, it has been found that the number of mitochondria moving anterograde is significantly decreased (64). These changes might be responsible for abnormal mitochondrial dynamics in the cortex of patients with HD and may contribute to their neuronal damage.

Mitochondrial dynamics and epilepsy

Epilepsy is a disease in which abnormal discharge of neurons leads to brain dysfunction. Studies have shown that changes in mitochondrial dynamics are closely related to epilepsy. Transport kinesin 1 (TRAK1) is essential for the axonal transport of mitochondria in neurons. A related study in patients with epilepsy and animal models found that TRAK1 expression is decreased in the temporal lobe. Knockout of TRAK1 results in increased MFF and a greater number of seizures, while exogenous TRAK1 supplementation can rescue this dysfunction (65).

Mutations in the Drp1 gene can also cause neurological symptoms. In a case report, mutations in the Drp1 GTPase domain resulted in psychomotor retardation, muscle weakness, and paroxysmal myotonia (66). A thorough literature search illustrated that, among the different cases of Drp1 mutation, 77.8% had psychomotor retardation, 66.7% had limb paralysis, 82.8% had dystonia, and 59.4% had epilepsy (66). Status epilepticus (SE; a series of closely occurring seizures) induces apoptosis of dentate gyrus astrocytes and fragments and reduces mitochondrial length in male rats. The Drp1 inhibitor, Mdivi-1, can effectively mitigate astrocyte apoptosis. Further research found that the changes in mitochondrial dynamics are closely related to the phosphorylation of Drp1 but not of OPA1 (67). SE reduces the S-nitrosylation of Drp1in hippocampal CA1 neurons and reduces protein disulfide isomerase (PDI) expression and mitochondrial length. Knockdown of PDI, in turn, reduces S-nitrosylation of Drp1 and restores mitochondrial size. Therefore, Lee *et al.* (68) hypothesized that PDI-mediated S-nitrosylation of Drp1 is partly responsible for the altered mitochondrial dynamics in SE.

Mitochondrial dynamics and cerebrovascular diseases

Cerebrovascular diseases have become one of the leading causes of disability or death in adults. The timely and effective removal of hemodynamic barriers is the primary mode of treatment for the disease. A recent study has shown that mitochondrial dynamics can affect the pathogenesis and prognosis of cerebrovascular diseases (69). Blood flow in patients with ischemic stroke can be restored after thrombolysis or intravascular thrombectomy. During reperfusion, a large amount of oxygen is used by mitochondria to generate many oxygen radicals. However, oxidative stress occurs if the antioxidants present cannot neutralize the free radicals, and severe oxidative stress can lead to apoptosis (69). Baicalin treatment in oxygen-glucose deprivation/reperfusion (OGD/REP) PC12 cells inhibits Drp1 expression, decreases mitochondrial fission, promotes MFN2 generation, increases Drp1 Ser637 phosphorylation, and elevates MMP via the suppression of ROS production. These results suggest that baicalin protects against ischemia-reperfusion injury (70).

Global cerebral ischemia in rats transiently increases the phosphorylation of Drp1 at ser616 in the hippocampal CA1 region, suggesting that excessive mitochondrial fission is involved during the process of cerebral ischemia (71). After an ischemia-reperfusion injury, the mitochondrial fusion protein OPA1 is excessively cleaved, decreasing the level of active L-OPA1. Restoring the level of L-OPA1 by lentiviral transfection can alleviate neuronal death, restore mitochondrial morphology, and reduce infarct size (72).

Vascular smooth muscle cell (VSMC) activation and hyperproliferation are closely associated with

atherosclerotic stenosis. Moreover, platelet-derived growth factor (PDGF)-induced mitochondrial fission triggers VSMC proliferation during vascular remodeling. Knockdown of the exchange protein activated by cAMP1 (Epac1), localized in the mitochondria of VSMCs can attenuate PDGF-induced mitochondrial fission and alleviate VSMC hyperproliferation. These findings suggest that the inhibition of mitochondrial fission might reduce the possibility of arterial stenosis (73).

Mitochondrial dynamics and neural tumors

Mitochondrial dynamics play an essential role in the process of brain tumors. Mitochondria are involved in cellular processes such as proliferation, differentiation, metastasis, and apoptosis. Glioblastoma (GBM) is a highly aggressive, recurrent, and lethal brain tumor, involving the presence of brain tumor-initiating cells (BTICs) in its microenvironment. BTICs not only promote tumor growth and tumor recurrence after multimodal therapy but also contribute to the invasion of GBM (74). In contrast to those of non-BTICs cells, the mitochondria of the BTICs cells are more fragmented, and the phosphorylation of Drp1 at ser616 is greater than that at ser637, which increases Drp1 activity. One study showed that inhibiting AMP-activated protein kinase (AMPK) could rescue the slow growth of BTICs induced by Drp1 inhibition (75). It was suggested that AMPK might be a downstream regulatory molecule of Drp1. In BTIC tumor cells, roscovitine, a nonspecific inhibitor of cyclin-dependent kinase (CDK) 1/2/5, can inhibit the phosphorylation of Drp1 at ser616 and mitochondrial fragmentation, while the CDK1/2 inhibitor BMS265246 has no effect. This suggests that CDK5 may affect the phosphorylation of Drp1 at ser616. In non-BTIC tumor cells, inhibition of calcium/calmodulin-dependent protein kinase 2 (CAMK2) was shown to inhibit the phosphorylation of Drp1 at ser616, resulting in mitochondrial fragmentation. It has been further speculated that CDK5 activates the phosphorylation of Drp1 at ser616 to trigger mitochondrial fission in BTICs and that CAMK2 activates the phosphorylation of Drp1 ser637 to inhibit mitochondrial fission in non-BTIC tumor cells (75).

One study reported that nuclear factor κB (NF-κB)-inducible kinase (NIK) is associated with the formation of pseudopodia with extensive cell membrane bulges that promote the invasiveness of gliomas (76). Mitochondria are translocated to the pseudopodia front to meet the energy demands for the invasion, leading to a faster and more directional migration of cells (77). During this process, NIK recruits Drp1 to mitochondria, regulates the phosphorylation of Drp1, promotes mitochondrial fission, and increases tumor invasiveness (78). These findings highlight the importance of NIK in tumor pathogenesis and invite new therapeutic strategies that attenuate mitochondrial dysfunction through the inhibition of NIK and Drp1.

Potential therapeutic drugs

As discussed above, an imbalance in mitochondrial dynamics is involved in the occurrence and development of various neurological diseases. Consequently, improving mitochondrial dynamics might be an effective treatment for neurological disorders. Recently, several compounds have been demonstrated to enhance mitochondrial dynamics, but most are still in the preclinical stages. Here, we focus on those drugs that have been clinically tested and shown to have fewer side effects. Although these drugs were initially used to treat other diseases, they have also been shown to improve mitochondrial dynamics.

Leflunomide

Leflunomide is an anti-inflammatory drug that can treat autoimmune diseases such as rheumatoid arthritis and lupus nephritis by regulating T cell functions. Its primary mechanism involves inhibiting mitochondrial inner membrane dihydroorotate dehydrogenase (DHODH), limiting pyrimidine's *de novo* synthesis. A lack of pyrimidine, in turn, limits the expansion of antibody-producing cells by blocking cell cycle transition (79).

Miret-Casals *et al.* (80) used high-throughput screening to prove that leflunomide is an activator of MFN2. Further research found that leflunomide can deplete pyrimidine stocks through DHODH inhibition, triggering cell cycle arrest and upregulating MFN2 expression. This also promotes mitochondrial elongation and fusion, conferring antiapoptotic activity to cells (80). The ability of leflunomide to improve mitochondrial dynamics has been used to treat pancreatic cancer and mitral aortic valve disease. Enhanced mitochondrial fission inhibits metastasis in triple-negative breast cancer, and leflunomide has been shown to counteract this inhibitory effect (81-83).

Currently, no direct evidence suggests that leflunomide improves mitochondrial dynamics in neurological disorders; however, given its favorable effect on neuroinflammation, leflunomide might be a direction of future research (84).

Pioglitazone

Pioglitazone is an agonist of peroxisome proliferator-activated receptor γ (PPAR-γ) and is commonly used to treat diabetes. Mitochondrial disorders play a significant role in neuropathy in patients with Down syndrome, in which PPAR-γ coactivator-1α (PGC-1α) is the primary mediator that coordinates mitochondrial biogenesis, cellular respiration, and energy metabolism. Pioglitazone can upregulate PGC-1α as well as mitochondrial fusion factors such as OPA1 and MFN1. Moreover, it can improve mitochondrial dynamics, reduce ROS production, and increase ATP production (85). Using a diabetic rabbit model, researchers found that pioglitazone enhanced cardiomyocyte mitochondrial biogenesis, increased kinetics-related protein expression, improved mitochondrial structure and function, and reduced atrial remodeling (86). Paraoxonase 2 (PON2) enhances mitochondrial function against oxidative stress and has therapeutic potential for those with PD. Pioglitazone increases PON2 expression, inhibits neuroinflammation in patients with PD, prevents neurodegeneration and loss of dopaminergic cells in the substantia nigra region, and improves mitochondrial dynamics and function (87,88). Pioglitazone also reduces Aβ-induced neurotoxicity and modulates blood-brain barrier function in AD models (89,90). However, a controlled trial showed that pioglitazone did not delay the onset of cognitive disorder in patients with AD (91). Therefore, more detailed studies are required to understand the effectiveness of pioglitazone in AD treatment.

Tolfenamic acid

Tolfenamic acid, a nonsteroidal anti-inflammatory drug (NSAID), attenuates learning and memory impairments in AD and reduces specificity protein 1 (SP1)-mediated cyclin-dependent kinase 5 (CDK5) expression (92). It has been confirmed that CDK5 can regulate the phosphorylation of Drp1 at ser537 and affect mitochondrial fission, which may be one of the mechanisms by which tolfenamic acid regulates mitochondrial dynamics (93). In a mouse model, tolfenamic acid pretreatment attenuated the toxicity induced by intraperitoneal injection of 3-Nitropropionic acid, restored mitochondrial dynamics and function, and improved neurological symptoms (94). However, a different study reported that tolfenamic acid can localize to the mitochondria of yeast cells, causing mitochondrial damage and ROS generation, thus inhibiting cell growth (95). Further research is needed to understand tolfenamic acid's possible usages in improving mitochondrial dynamics in the treatment of neurological diseases.

Summary

Mitochondrial dynamics is one mechanism by which mitochondrial function adapts to different environments and energy demands. Nervous systems with high metabolic demands are highly dependent on mitochondrial function; therefore, neuronal activity is strongly influenced by mitochondrial dynamics. Disorders in mitochondrial dynamics, especially alterations in Drp1, can cause various neurological diseases. In preclinical experiments, several compounds restored proper mitochondrial dynamics and nerve function. Our review focuses on a few drugs with fewer side effects than these compounds and those that have passed clinical trials. Restoration of proper mitochondrial dynamics using these drugs might be a promising therapeutic strategy for neurological diseases in the future.

As discussed above, alterations in Drp1 are necessary for mitochondrial dynamics and are involved in the occurrence and development of various neurological diseases. We speculate that Drp1 might be highly correlated with neurological diseases, even though the alterations of Drp1 are distinct in each disease type. Based on these considerations, the main questions that remain to be elucidated in future studies are as follows: (I) are the alterations of Drp1 common causes of neurological diseases? (II) Are changes in Drp1 secondary or primary? (III) Would the treatments targeting Drp1 affect other mitochondrial dynamics molecules and dampen efficacy? Further studies exploring these questions will help to identify more ideal therapeutic targets.

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Footnote

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Supplementary

Table S1 Example of the detailed search strategy (PubMed)

Items	Specification
Selection process	215 references were found. After our carefully discussion and selection, 88 references were included in this study
Search terms	Drp1; mitochondria; MFN; Alzeimer's disease; Parkinson's disease; FIS1; epilepsy; leflunomide; tolfenamic acid; autophagy
Filters	Studies did not focus on autophagy

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