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Mutant Huntingtin, Abnormal Mitochondrial Dynamics, Defective Axonal Transport of Mitochondria, and Selective Synaptic Degeneration in Huntington's Disease

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Abstract

Huntington's disease (HD) is a progressive, fatal neurodegenerative disease caused by an expanded polyglutamine repeats in the HD gene. HD is characterized by chorea, seizures, involuntary movements, dystonia, cognitive decline, intellectual impairment and emotional disturbances. Research into mutant huntingtin (Htt) and mitochondria has found that mutant Htt interacts with the mitochondrial protein dynamin-related protein 1 (Drp1), enhances GTPase Drp1 enzymatic activity, and causes excessive mitochondrial fragmentation and abnormal distribution, leading to defective axonal transport of mitochondria and selective synaptic degeneration. This article summarizes latest developments in HD research and focuses on the role of abnormal mitochondrial dynamics and defective axonal transport in HD neurons. This article also discusses the therapeutic strategies that decrease mitochondrial fragmentation and neuronal damage in HD.

Keywords

Mutant huntingtin; Abnormal mitochondrial dynamics; Defective axonal transport; RNA silencing; BACHD mice; Mitochondrial trafficking

1. Introduction

Huntington's disease (HD) is characterized by chorea, seizures, involuntary movements, dystonia, cognitive decline, intellectual impairment and emotional disturbances [1–4]. HD has an autosomal dominant pattern of inheritance and an age-dependent penetrance. HD occurs in 4–10 per 100,000 persons, mainly of Caucasian origin, with mean age of onset at about 40 years. HD patients survive for about 15–20 years from disease onset and die mainly due to complications from the disease. It is caused by polyglutamine (polyQ) repeat expansion within the exon 1 of HD gene, that encodes an expanded polyQ stretch in the huntingtin (Htt) protein (Fig. 1). Wild-type (WT) and mutant Htt proteins are expressed

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ubiquitously in the peripheral and central nervous systems of patients with HD. In the postmortem brains of patients with HD, extensive medium spiny neuronal loss was observed in the striatum and also loss of pyramidal neurons was observed in the cerebral cortex and hippocampus. Neuronal loss has also been reported in the hypothalamus in postmortem brains from HD patients and from HD mouse models [1,5–8], and Htt protein aggregates have been found in pathological sites in the postmortem brains of patients with HD and of HD mouse models [9–18]. The causes of selective and premature death of medium spiny projection neurons are not completely understood. Currently, there are no drugs or agents available to treat or delay or prevent HD progression.

Over two decades of intense research using cell models, animal models, and postmortem HD brains have implicated multiple cellular changes in HD progression and pathogenesis. These changes include transcriptional dysregulation, caspase activation, expanded polyQ repeat protein interactions with other CNS proteins, NMDAR activation, calcium dyshomeostatis, defective axonal trafficking, and abnormal mitochondrial dynamics (e.g. increased fission and decreased fusion) [19–23]. In studies focusing on abnormal mitochondrial dynamics in HD, defective transport of mitochondria in axons and selective synaptic degeneration were found to play a central role in HD progression and pathogenesis.

The purpose of this article was to summarize the roles of mitochondrial dynamics and axonal transport in HD neurons. We will also highlight the relationship between mutant Htt and mitochondrial dynamics, and between mutant Htt and dynamin-related protein 1 (Drp1) – a mitochondrial protein that has been implicated in causing mitochondrial fragmentation and abnormal distribution, defective axonal transport of mitochondria and selective synaptic degeneration in a variety of neurodegenerative diseases. We also will discuss the therapeutic strategies that decrease mitochondrial fragmentation and neuronal damage in HD.

2. Mutant Huntingtin Aggregates and Oligomers in HD Pathogenesis

HD was the first among nine neurodegenerative diseases that had an expanded polyglutamine (polyQ) repeats as a dominant mutation in the coding part of the gene [19]. HD is caused by expanded polyQ repeats within exon 1 of HD gene. In HD patients, the number of polyQ repeats ranges from 36–120, whereas in healthy individuals, it ranges from 6–35 [4,24]. In HD, polyQ repeats are highly polymorphic in general, and the onset of disease is inversely correlates with polyQ repeat length.

Htt is a 350 kDa protein, ubiquitously expressed in the peripheral and central nervous systems (CNS) [25]. WT Htt is a cytosolic protein. However, increasing evidence from postmortem HD brains and HD mouse models revealed that a small part of mutant Htt is present in subcellular organelles, including the nucleus, plasma membrane, mitochondria, lysosomes, and endoplasmic reticulum [26–33]. Mutant Htt is reported to interacts with a large number of CNS proteins, and this abnormal interaction ultimately leads to the gain of function of mutant Htt in the progression of HD.

2.1. Mutant Htt aggregates

Mutant polyQ aggregates have been extensively reported in HD and other polyQ repeat-associated diseases and responsible for disease progression [4,34]. More recently, formations of oligomers, fibrils, and protofibrils have been found in HD cell cultures and HD animal models, including, flies, worms and mice [35–39]. Mutant oligomeric proteins are toxic and accumulate in neurons in age-dependent manner. These aggregates have been found to enter subcellular organelles, such as mitochondria in neurons from patients with Alzheimer’s disease [40–45] and Parkinson’s disease [46–52].

2.2. Mutant Htt oligomers

Recently, using cell culture systems, several investigators have focused on developing molecules that inhibit oligomer formation and apoptotic cell death [35,38,53–61]. Tremendous efforts are underway in several laboratories across the world to reduce the oligomer formation and toxicity.

Using immunostaining analysis of mutant Htt oligomers (detected by the A11 antibody) [40], the Reddy lab recently found significantly increased numbers of mutant Htt oligomers in the cortical tissues from postmortem brains of patients at stages HD3 and HD4, relative to control subjects. These proteins ranged from 15–50 kDa [21]. Our immunostaining analysis of mutant Htt mitochondrial marker, cytochrome oxidase 1 (COX1) revealed that mutant Htt oligomers are colocalized with COX1, suggesting that mutant Htt oligomers may promote mitochondrial toxicity, oxidative stress and neuronal damage in HD patients [22]. Very recently, we (22) and others [23] found mutant Htt interaction with the mitochondrial protein, Drp1 selectively in affected regions of the brain from the postmortem brains of HD patients and BACHD transgenic mice, and in peripheral cells from the brain tissues of HD patients (see upcoming section for details).

3. Cellular Changes in Huntington's Disease

The selective, premature death of striatal projection neurons has been reported in HD patients and HD transgenic mice [1,2,13–15,62]. As shown in Fig. 2, several cellular pathways have been proposed and extensively investigated to explain premature neuronal death in HD progression, but this neuronal death is not well understood. The following cellular changes have been reported to involve HD pathogenesis: 1) transcriptional dysregulation [63–66], 2) expanded polyglutamine repeat proteins interacting with other CNS proteins [67], 3) caspase activation [68–73], 4) NMDAR activation [74–78], 5) calcium dyshomeostasis [28, 79–85], and 6) abnormal mitochondrial bioenergetics and axonal trafficking [33,86–89]. The most compelling evidence from these studies implicates abnormal mitochondrial bioenergetics and defective axonal transport in the selective synaptic degeneration and neuronal damage in HD.

4. Defective mitochondrial bioenergetics

Multiple lines of evidence suggest that abnormal mitochondrial bioenergetics is involved in HD progression: 1) The loss of body weight is a major factor in HD progression in HD patients and HD mouse models [90–93]. 2) Studies using magnetic resonance imaging (MRIs) of postmortem brains from HD patients revealed a progressive atrophy of the striatum, compared to brain images of age-matched control subjects [94–95]. Several other studies of HD brains utilizing MRIs found atrophy in the caudate nucleus, putamen, globus pallidus, and thalamus [96–98]. 3) Using positron emission tomography in functional studies of the brains of HD patients and control subjects, researchers found a marked decrease in the amount of glucose utilized in the striatum [99–103]. These same studies found decreased glucose metabolism to correlate with reduced performance of HD patients on several cognitive tasks, including immediate recall memory, verbal associative learning, and executive functions, suggesting that cerebral glucose metabolism is defective in HD patients [99–103]. 4) Biochemical studies of mitochondria in striatal neurons from brain tissues of late-stage HD patients revealed reduced activity of several components of oxidative phosphorylation, including complexes II, III, and IV of the electron transport chain [86–87]. In studies of HD transgenic and knockin mice, and in experimental HD rodent models, decreases in enzyme activities of complexes I, II, III, and IV were found in brain tissues [104], suggesting that mitochondria are somehow involved in HD pathogenesis. And 5) recent studies of HD knock-in striatal cells and lymphoblasts from HD patients revealed

expanded polyglutamine repeats associated with low levels of mitochondrial ATP and decreased mitochondrial ADP-uptake, suggesting that HD mutation is associated with mitochondrial functional defects [105].

Overall, findings from these studies suggest that defective mitochondrial bioenergetics plays a large role in the progression and pathogenesis of HD.

5. Mutant Htt and Abnormal Mitochondrial Dynamics

Mitochondrial shape and structure are maintained by two important but opposing forces: mitochondrial fission and mitochondrial fusion [106–110]. Mitochondrial fission is the division of single mitochondrion into two, and mitochondrial fusion is the integration of 2 mitochondria into single elongated mitochondrion. In a healthy neuron, fission and fusion balance equally. Mitochondria alter their shape and size to travel from the cell body to nerve terminals via anterograde movement, and back to the cell body via retrograde movement [19]. Mitochondrial fission and fusion are controlled by evolutionary conserved, large GTPases belonging to the family of dynamin. Mitochondrial fission is regulated by mitochondrial fission 1 (Fis1) and Drp1. Fis1 is localized to the outermembrane of mitochondria. Drp1 is localized in the cytoplasm, but a small part of Drp1 localized to the outermembrane, which promotes mitochondrial fragmentation [110]. Mitochondrial fusion is controlled by 3 GTPase proteins, 2 outermembrane proteins Mfn1 and Mfn2, and 1 innermembrane protein Opa1 [107]. The C-terminal part of Mfn1 mediates oligomerization among Mfn molecules of adjacent mitochondria and facilitates mitochondrial fusion.

Increasing evidence suggests that mitochondrial dynamics is imbalanced (increased fission and decreased fusion) in neurodegenerative diseases, including in AD [111–114], PD [110,115] and HD [20–23]. This imbalanced mitochondrial dynamics is caused by an altered expression of mitochondrial fission and fusion genes [110]. Further, in aged neurons, in neurons exposed to toxins, and in neurons that express mutant proteins, such as mutant Htt, an imbalance between fission and fusion leads to abnormalities in mitochondrial structure and function, and neuronal damage [110].

Several studies reported such abnormal mitochondrial dynamics in HD patients, HD mouse models, and cell lines that express mutant Htt [20–23]. Recently, the Reddy lab studied abnormal mitochondrial dynamics in tissues from postmortem brains of HD patients [21] and primary neurons and brain tissues from BACHD transgenic mice [22]. In a study of brain specimens from patients at HD3 and HD4 stages and from control subjects, we found increased expressions of Drp1 and Fis1 in HD4 than in HD3, and decreased levels of Mfn1, Mfn2, and Opa1 in HD4 than in HD3 [21] in the striatum and cortex (HD-affected brain regions), but not in the cerebellum (non-HD-affected brain region), indicating that abnormal mitochondrial dynamics may be related to HD [21]. Further, we also found significantly increased levels of cylophilin D (CypD) only in the striatum and cortex of the HD3 and HD4 patients relative to control subjects [21], again suggesting structurally damaged mitochondria in the HD-affected brain regions since increased CypD is known to damage mitochondrial structure.

Using recently developed BACHD mice that express the full-length (170 kb DNA) human Htt gene with 97 CAA and CAG (mixed repeats) [8], we studied mutant Htt and mitochondrial and synaptic genes. We found significantly increased mRNA levels of fission genes, Drp1 and Fis1 and matrix gene CypD, and decreased levels of fusion genes, Mfn1 and Mfn2 in 2-month-old BACHD mice relative to age-matched WT mice, suggesting that abnormal mitochondrial dynamics is an early event in HD progression [22].

Overall, findings from our lab together with earlier study by Kim et al [20] indicate a relationship between mutant Htt and impaired mitochondrial dynamics and dysfunction in HD.

5. Interaction between Mutant Htt and Drp1, and Elevated GTPase Drp1 Enzymatic Activity

To determine whether the interaction of Drp1 and mutant Htt increases as HD progresses, the Reddy lab performed co-immunoprecipitation analysis of Drp1 and mutant Htt, using a Drp1 antibody, and immunoblotting analysis, using the mutant Htt-specific antibody 1C2 and protein lysates of cortical tissues from control subjects and HD3 and HD4 patients and protein lysates from 2-month-old BACHD mice [22]. We found an 82 kDa and 40kDa mutant Htt protein in IP elutes from HD3 and HD4 patients. We also found Drp1 interaction with WT Htt, but lesser extent, in the control subjects, indicating that mutant Htt interaction with Drp1 is specific and related to disease progression.

Using cortical protein lysates from BACHD mice and WT mice, and Drp1 and 1C2 antibodies, we also performed co-IP analysis. Similar to HD brains, two bands of proteins, one with an 82 kDa and the other with 40 kDa mutant Htt proteins were found in the IP elutes of the BACHD mice, but not in those of the WT mice [22]. Overall, our lab findings together with results from Song et al [23], indicate that Drp1 interacts with mutant Htt and may participate in mitochondrial fragmentation and impaired mitochondrial biogenesis in HD neurons.

To determine whether Drp1 interaction with mutant Htt in affected and unaffected brain tissues from HD patients and BACHD mice enhance GTPase activity, we measured GTPase Drp1 enzymatic activity [22]. Interestingly, we found that significantly increased levels of Dp1 enzymatic activity in the cortex but not in the cerebellum of HD3 and HD4 patients relative to control subjects. We also found elevated levels of Drp1 enzymatic activity in the cerebral cortex and striatum in the BACHD mice relative to the WT mice [22]. Our findings are consistent with earlier findings from Song and colleagues who found that increased Dp1 enzymatic activity in HD neurons [23].

Overall, recent evidence indicates that Drp1 interacts with mutant Htt and enhances Drp1 enzymatic activity in HD-affected regions, leading to synaptic and neuronal damage (see Fig. 3 for summary). Further, we recently reported an increased interaction of Drp1 enzymatic activity, excessive mitochondrial fragmentation, and altered mitochondrial distribution in neurons affected by AD [113]. We also reported a similar finding in a study of HD, in which the interaction of mutant Htt with Drp1 had similar consequences and this abnormal interaction resulted in elevated Drp1 enzymatic activity, excessive mitochondrial fragmentation, and altered mitochondrial distribution in HD neurons [22]. These parallel findings for AD and HD suggest a common pathway that may be involved in triggering abnormal mitochondrial dynamics and selective neuronal damage.

6. Defective Axonal Transport of Mitochondria in HD neurons

Normal axonal transport of organelles, including mitochondria, synaptic vesicles, and proteins, is essential for synaptic activities and neural communication. In diseased neurons, such as in HD neurons, axonal transport is impaired mostly due to mutant proteins that interact with proteins localized in axons. These abnormal interactions block the transport of organelles along the axons, ultimately leading to synaptic starvation. Studies of axonal transport reported impaired mitochondrial transport in cortical neurons overexpressed with

mutant Htt [89], in HD striatal neurons [88], in rat cortical neurons, and in mouse striatal neurons transfected with N-terminal Htt [33].

Using live-cell imaging tools, primary neurons from BACHD mice and WT mice, and DsRed-mito transfections, we analyzed the mitochondrial motility in primary-neuron axonal projections from BACHD and WT mice [22]. We found significantly decreased motility in the primary neurons from BACHD mice (20.88 ± 4.86%) relative to WT neurons (with 36.73 ± 3.36%) (P = 0.015). We also found retrograde motility largely unaffected, and anterograde motility greatly affected (WT neurons 21.58±2.42 and BACHD neurons 10.04±1.78, P = 0.0009) [22].

Ours is the first study that investigated mitochondrial mass, trafficking, anterograde and retrograde movements and synaptic viability in primary neurons from BACHD mice. Our findings agree with a previous study [23], in which they studied mitochondrial transport in neurons transfected with exon 1 containing 17, 46, and/or 97 polyQ repeats. They found that neurons with exogenously expressed exon 1 Htt with 17 polyQ repeats exhibit filamentous, normal, and healthy mitochondria, whereas neurons expressing exon 1 Htt with 46 polyQ showed both elongated and round mitochondria. Neurons that exogenously expressed 97 polyQ repeats show mainly rounded, fragmented mitochondria. The findings from Song et al. [23] together with our observations of mitochondrial trafficking in BACHD mice, indicate that mutant Htt with expanded polyQ repeats are responsible for mitochondrial fragmentation in neurons affected by HD.

These findings also indicate that mutant Htt interaction with Drp1 may cause excessive mitochondrial fragmentation, leading to defective axonal transport and abnormal distribution of mitochondria in BACHD mice. Figure 4 summarizes data supporting excessive mitochondrial fragmentation and defective axonal transport of mitochondria.

7. Synaptic Damage in Huntington's disease

Synaptic damage has been extensively reported in neurodegenerative diseases, including Alzheimer's [111–114,116,117] Parkinson's [118–122] and Huntington's [22–23,123–127]. However, the precise factors that cause synaptic degeneration are not completely understood. Recent evidence from our lab [21,22] and others [20,23] revealed that abnormal interaction of mutant Htt with mitochondrial protein Drp1, cause excessive mitochondrial fragmentation that leads to defective axonal transport and abnormal mitochondrial distribution, particularly in neurites and synapse. Synapses are the sites of high ATP demand, and reduced number of mitochondria neurites and synapses produce low ATP and cause synaptic degeneration in HD neurons. These events are summarized above, and we now focus on synaptic damage and degeneration in HD neurons.

To determine the effect of mutant Htt on synapses in HD, using cortical tissues from BACHD mice and quantitative real-time RT-PCR, the Reddy lab measured mRNA levels of presynaptic protein, synaptophysin and postsynaptic protein, PSD95 [22]. They found a significant reduction in the mRNA fold changes for the synaptic genes, synaptophysin (-1.2 fold) and PSD 95 (-1.3 fold) relative to WT mice.

Further, to determine the effects of mutant Htt on synaptophysin and MAP2 levels, they also performed immunostaining analysis of BACHD neurons using 10 DIV neurons from BACHD mice and WT mice. They found significantly decreased immunoreactivity of synaptophysin in the BACHD neurons relative to WT neurons [22]. Similar to synaptophysin, immunoreactivity of MAP2 was significantly decreased in the BACHD neurons relative to WT neurons, indicating that mutant Htt may be involved in synaptic degeneration [22].

Overall, our recent studies of mitochondrial transport, mitochondrial dynamics, expression of synaptic genes in BACHD mice together with earlier studies, indicate that synaptic damage is an early event in disease process and may be linked to mutant Htt and abnormal mitochondrial distribution at synapses in HD.

8. Therapeutic Strategies for HD

Based on cellular changes observed in HD pathogenesis and progression, multiple therapeutic strategies have been developed and tested in experimental cell, animal models, and even clinical trials, to stop or delay disease progression. As shown in Fig. 5, these strategies include: reducing mutant Htt allele expression (RNA silencing), inhibit oligomer formation, inhibiting the interaction of polyQ with other proteins in the central nervous system, enhancing the expression of endogenous transcription factors, enhancing autophagy, increasing molecules that enhance axonal transport, reducing abnormal mitochondrial dynamics, and increasing healthy mitochondrial biogenesis.

8.1. Reducing mutant Htt allele expression

Extensive research reveled that soluble mutant Htt aggregates and oligomers are toxic, cause synaptic degeneration and neuronal damage in HD. Therefore, reducing the expression of mutant Htt allele is a direct and upstream approach to treat HD. This approach involves silencing the post-transcriptional mutant Htt allele using small, anti-sense RNA molecules. Currently, RNA silencing (shRNA) technology is being used to reduce mutant Htt allele [128–136]. RNA silencing is tested in cell and mouse models of HD [137–139].

Further, delivery of short hainpin RNA using adeno-associated viral (AAV) vectors is successful in HD truncated mice (N171-82Q). Mice that received shRNA showed decreased mutant Htt aggregates and improved rotorod performance and gait [140]. This approach has been tested in BACHD mice and other mouse models. Further research is still needed to target selectively mutant Htt allele in the presence of both WT and mutant Htt alleles in HD neurons.

8.2. Inhibition of mutant oligomer formation

Several researchers around the world are using cell and animal models, high throughput screening, and inhibitors of oligomers and apoptotic cell death to determine molecules that reduce and/or prevent mutant Htt oligomer formation in HD neurons [35,36,53–61].

8.3. Inhibiting the interaction between mutant Htt and mitochondrial protein, Drp1

As described above, polyQ protein is sticky and likely to interact with other CNS proteins [67] and participate in oligomers, fibrils, protofibrils and ultimately fibrillogenesis formation [35–39]. The soluble mutant Htt aggregates are toxic and interact with axonal proteins, including Drp1, impair axonal transport and cause synaptic degeneration. Regarding mutant soluble Htt aggregates and their interaction with Drp1, further research is still needed in order to determine which domain of Drp1 protein interacts with mutant Htt aggregates and cause mitochondrial fragmentation, and neuronal damage. Therefore, identifying the molecules that inhibit abnormal interactions between mutant Htt and Drp1 is an interesting therapeutic approach.

8.4. Enhancing endogenous transcription factors (PGC1α and Nrf2)

Increasing evidence suggests that transcription factors, including PGC1α and Nrf2, reduce mitochondrial oxidative damage and increase neuronal survival, in general, and HD neurons, in particular [141–143]. It is critical to increase endogenous levels of PGC1α and Nrf2 in

neurons affected by HD. Efforts are underway to enhance endogenous transcription factors that protect neurons against mutant Htt aggregates and oligomers and other oxidative insults.

8.5. Inactivating mTOR and enhancing autophagy

Growing evidence suggests that autophagy plays a large role in clearing a cell's degraded proteins and organelles in HD neurons. Further extensive literature on mammalian target of rapamycin (mTOR) suggests that cells pre-treated with rapamycin are protected against apoptotic cell death, particularly cells that express mutant Htt [144–151]. Rapamycin, a lipophilic, macrolide antibiotic, induces autophagy by inactivating the protein mTOR. Inhibition of mTOR induces autophagy and reduces toxicity of polyglutamine expansions in fly and mouse models of HD [152]. Therefore, inactivation of mTOR is another approach to treat patients with HD. Further research is still needed to understand the role of autophagy, in HD.

8.6. Developing molecules capable of enhancing axonal transport

To improve axonal transport of mitochondria and other organelles, molecules could be developed to enhance microtubule binding capacity of 'microtubule associated proteins with microtubules' and increase both anterograde and retrograde movements of organelles. The tight microtubule binding of microtubule associated proteins may enhance axonal transport of organelles may provide and supply necessary components and organelles to synapses and increase synaptic outgrowth and neural communications.

8.7. Reduction of abnormal mitochondrial dynamics and increase of healthy mitochondrial biogenesis

As discussed above, abnormal mitochondrial dynamics is an emerging and key component in neuronal damage in HD [20–23,109–110]. Maintaining the balance of mitochondrial dynamics is an important therapeutic strategy to protect neurons against the toxicity of mutant Htt oligomers and oxidative insults [21]. It is equally important to maintain healthy mitochondrial biogenesis in HD neurons. Recent research using primary neurons from AD transgenic mice and mitochondria-targeted antioxidant, SS1 revealed that SS31 appears increase the numbers of healthy mitochondria and also anterograde movement of mitochondria in primary neurons treated with SS31 [114].

9. The Current Status of Experimental Therapeutics in HD

Recent studies suggest that mitochondrial dysfunction and oxidative stress are key players in HD progression and pathogenesis. To reduce mitochondrial toxicity and abnormal mitochondrial dynamics in HD neurons, we need to develop drugs that protect mitochondria.

In the last decade, several drugs have been tested in experimental animal models of HD and also clinical trials. Several mitochondrial drugs that act to protect neurons from mitochondrial damage, including Creatine, CoQ10 and resveratrol – have shown beneficial effects in cell and animal models. Creatine and CoQ10 have shown deceased HD pathology and rotorod performance in R6/2 and N171-82Q lines of HD mice. Findings from these studies suggest that Creatine and CoQ10 boost ATP levels and increase mitochondrial function [153–156]. Further, resveratrol also has shown beneficial effects in the worm model of HD, and increased survival of striatal neurons from knockin mice indicating that resveratrol protect against age-dependent mutant Htt toxicity in HD neurons [156].

Dimebon (or Dimebolin hydrochloride or atreperdine) is an antihistamine drug that has been used clinically in Russia to reduce cognitive deficits in AD patients [157]. Based on cell culture and murine models of AD, phase III clinical trial was conducted in US and initial

findings were positive. However, a large-scale clinical trials did not show significant improved positive clinical symptoms in patients with AD. Scientists from Medication, Inc., in collaboration with clinicians and researchers in North America, conducted phase III clinical trials in HD patients, and the outcome was not positive [158–159]. These disappointing outcomes posing major challenge to HD patients and researchers.

10. Conclusions and Future Directions

Mitochondrial dysfunction and oxidative stress are critical factors in the development and progression of HD. Recent research revealed that mutant Htt aggregates and oligomers appear to interact with Drp1, to enhance GTPase Drp1 enzymatic activity, to increase mitochondrial fragmentation, and to cause abnormal mitochondrial distribution, ultimately leading to neuronal damage. These findings suggest that abnormal mitochondrial dynamics and defective axonal transport of mitochondria are mechanisms in HD pathogenesis.

In terms of therapeutic approaches, multiple approaches appear to be promising, including silencing of mutant Htt allele, reducing oligomer formation, enhancing endogenous levels of transcription factors (PGC1α and Nrf2) and balancing mitochondrial dynamics and axonal transport in neurons affected by HD. Recent experimental therapeutics in cell and animal models are promising but no definitive drugs/agents are available to treat HD patients. Further research is also needed to better understand the mechanisms how mutant Htt aggregates and oligomers cause mitochondrial fragmentation and impair axonal transport in HD neurons. Further, it is worth investigating and developing the molecules that promote healthy mitochondrial biogenesis, and increase axonal transport in neurons affected by HD.

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Highlights

1. Summarized the link between mutant Htt and mitochondrial dynamics in Huntington's disease.
2. Discussed mutant Htt interaction with Drp1 in Huntington's disease neurons.
3. Highlighted possible factors of defective axonal transport in Huntington's disease neurons.
4. Discussed the therapeutic approaches for Huntington's disease.

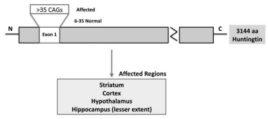

Figure 1.
Schematic illustration of expanded polyQ repeats within exon 1 of Huntington's disease gene.

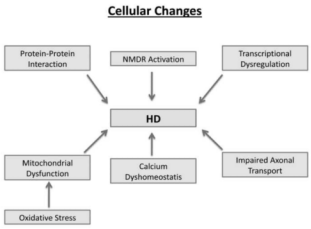

Figure 2.
Cellular changes that have been implicated in Huntington's disease pathogenesis.

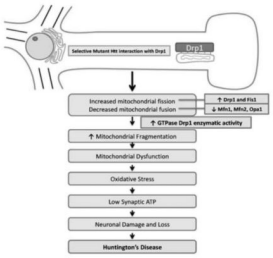

Figure 3.
Schematic illustration showing mutant huntingtin interaction with mitochondrial protein, Drp1 and subsequent pathogenic changes in HD neuron.

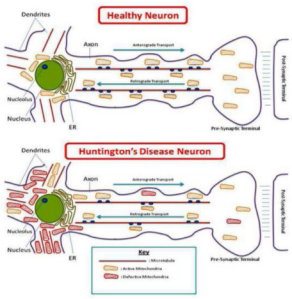

Figure 4.
Huntington's disease neuron showing excessive fragmentation of mitochondria, accumulation in cell soma, and abnormal distribution of mitochondria in neuronal processes and synapses.

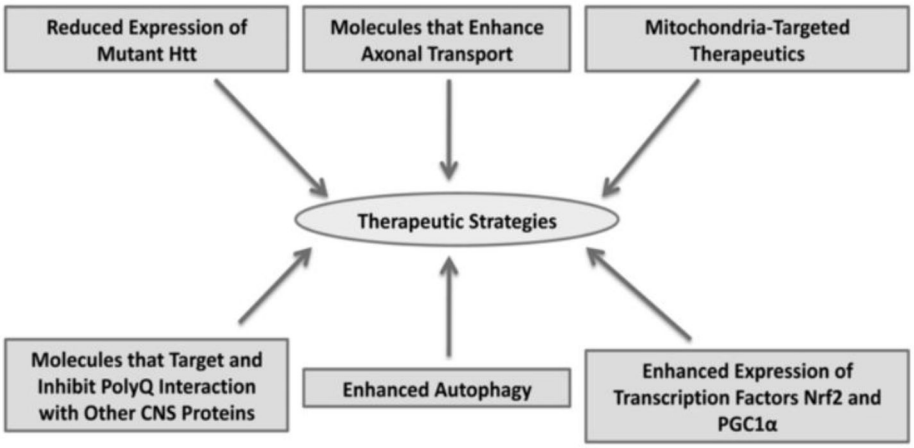

Figure 5.
Possible therapeutic approaches for Huntington's disease patients.