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Role of Oxidative DNA Damage in Mitochondrial Dysfunction and Huntington's Disease Pathogenesis

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Abstract

Huntington's disease (HD) is a neurodegenerative disorder with an autosomal dominant expression pattern and typically a late-onset appearance. HD is a movement disorder with a heterogeneous phenotype characterized by involuntary dance-like gait, bioenergetic deficits, motor impairment, and cognitive and psychiatric deficits. Compelling evidence suggests that increased oxidative stress and mitochondrial dysfunction may underlie HD pathogenesis. However, the exact mechanisms underlying mutant huntingtin-induced neurological toxicity remain unclear. The objective of this article is to review recent literature regarding the role of oxidative DNA damage in mitochondrial dysfunction and HD pathogenesis.

Keywords

Huntington's disease; mitochondrial dysfunction; oxidative stress; DNA repair; mitochondrial DNA; mitochondrial bioenergetics

Introduction

Huntington's disease (HD) is a neurodegenerative disease of genetic origin with an autosomal dominant inheritance pattern. The HD gene was cloned in 1993 and found to be an abnormal expansion of cytosine, adenine and guanine (CAG) trinucleotide repeats in the huntingtin gene [1, 2]. The abnormal CAG expansion results in the expression of an unusually long N-terminal polyglutamine stretch in the huntingtin protein [1, 2]. The number of pathogenic CAG repeats correlates with the severity and age of onset of the disease. In individuals carrying 39–60 repeats, HD typically exhibits a late-onset appearance. In individuals with more than 60 CAG repeats, the disease manifests in an earlier, juvenile onset form with increased severity [3–10].

The HD mutation triggers a heterogeneous, progressive clinical phenotype comprising symptoms mainly associated with the central nervous system but also with peripheral tissues. The most common clinical manifestation of HD is chorea, an involuntary and irregular dance-like gait, but the effects of the HD mutation go beyond the loss of motor abilities and include emotional and personality changes, depression, cognitive impairment,

loss of body weight and bioenergetic deficits [11–16]. Although the HD mutation is ubiquitously expressed [17], it appears to be particularly toxic to brain tissue. Neuropathologically, the disease is characterized predominantly by the loss of medium-sized spiny neurons in the neostriatum. With disease progression, neuropathology is also observed in other brain regions including the cerebral cortex, the globus pallidus, thalamus and cerebellum [18–20]. At present, no pharmacological interventions are available to reverse or delay the onset and progression of HD, whose symptoms progressively worsen over time, with typical disease duration of 15–20 years after its clinical diagnosis followed by death. However, a recent report shows that a synthetic mitochondrial-targeted antioxidant prevents oxidative damage to the mitochondria and delays disease progression in the *HdhQ150 knock-in mouse model of HD* [21].

Despite remarkable progress in the understanding of the processes underlying HD pathogenesis, the molecular mechanisms by which mutant huntingtin causes disease progression remain uncertain. However, compelling evidence from studies in both human HD patients and experimental HD models link oxidative stress and mitochondrial dysfunction to the pathophysiology of HD. The focus of this review is on the role of oxidative DNA damage and mitochondrial dysfunction in HD neurodegeneration.

Evidence for dysfunctional mitochondrial bioenergetics in HD

Consistent with an impaired energy metabolic state in HD, both presymptomatic and symptomatic HD patients show significant losses in body weight [22–24] as well as muscle wasting [25], especially during late stage disease. The possibility of a mitochondrial energy deficit in HD was suggested by early nuclear magnetic resonance spectroscopic analyses of mitochondrial function, which demonstrated increased lactate levels in the striatum and cerebral cortex of HD patients compared to healthy individuals [26] that correlated with the polyglutamine repeat length [27]. Neuroimaging studies using positron emission tomography show decreased glucose metabolism in the caudate putamen and cortex of presymptomatic HD patients [28, 29], also suggesting a mitochondrial metabolic deficit in HD. Furthermore, biochemical studies reveal reductions in the activities of the mitochondrial electron transport chain complexes II, III and IV in postmortem caudate putamen and cerebral cortex of HD affected individuals [30–33]. The importance of mitochondrial complex II deficiency in HD is evidenced by the significant reductions in the expression of two complex II subunits in the caudate putamen from symptomatic HD patients compared to controls [34]. Indeed, over-expression of either subunit rescues complex II activity and prevents death of mutant huntingtin-expressing primary striatal mouse neurons [34].

Reductions in the activity of other key mitochondrial metabolic enzymes emphasize the role of mitochondrial dysfunction in HD. Postmortem tissue from the caudate nucleus of late stage HD patients exhibits significant reductions in the activity of pyruvate dehydrogenase [35], an enzyme involved in converting pyruvate into acetyl CoA for use in oxidative phosphorylation. Moreover, a significant decrease in the activity of creatine kinase, an enzyme that catalyses the phosphorylation of creatine to phosphocreatine to generate ATP, occurs in human HD caudate putamen and cortex compared to healthy controls [36]. Additional analyses by the authors show that the activity of both cytosolic and mitochondrial creatine kinase isoenzymes are decreased in human HD brain [36]. Decreased creatine kinase activity is observed in the brains of two transgenic mouse models of HD compared to wild type controls [36], and there is decreased pyruvate dehydrogenase expression *in the striatum of the R6/2 transgenic mouse model of HD expressing exon 1 of the huntingtin gene* [37] and in enzyme activity in HD human cybrid lines [38]. Thus, the activity of

metabolic enzymes associated with mitochondrial function and ATP synthesis is impaired in HD brain.

Mutant huntingtin also impacts mitochondrial metabolism in tissues other than brain. HD mitochondria from human lymphoblasts are more susceptible to reductions in mitochondrial membrane potential [39, 40], and mitochondrial ATP production and ADP uptake are reduced in human HD lymphoblastoid cell lines [41]. Both the perturbed mitochondrial membrane potential and low ATP levels correlate with increasing CAG repeat length in HD patients [39, 41]. Electron microscopic analysis showed increased numbers of mitochondria of abnormal size and morphology in lymphoblastoid cell lines from HD patients compared to healthy controls [42]. Moreover, expression of mutant huntingtin but not normal huntingtin reduces ATP levels in HeLa cells, and increases oxidative stress-induced mitochondrial fragmentation [43]. Mitochondrial spare respiratory capacity is a measure of the ability of mitochondria to generate energy beyond that required for sustaining the basic metabolic needs of the cell, and is critically important for maintaining homeostasis and survival of neurons [44–46]. Interestingly, the mitochondrial spare respiratory capacity of a primary culture of HD diploid skin fibroblasts is significantly reduced than in control human fibroblasts [47], further indicating that mitochondrial function is compromised in HD. *Mitochondrial dysfunction has also been reported in skeletal muscle of HD patients, another tissue that is highly dependent on ATP utilization. Increased lactate production, ATP depletion and reduced ability to generate phosphocreatinine (a high-energy phosphate metabolite and energy reservoir used for the rapid generation of ATP), are found in muscle from HD patients* [48–50]*. ATP levels are significantly reduced in skeletal muscle from NLS-N171-82Q HD transgenic mice compared to wild type mice and ATP and phosphocreatinine levels are further decreased when mice are under chronic energy deprivation conditions* [51]. *Skeletal muscle from HD patients shows disrupted mitochondria and myoblasts cultures from the same patients exhibit increased lactate production compared to age-matched controls* [50]. *Moreover, myoblasts from heterozygous and homozygous HD patients show a 19 and 29% increase in disrupted mitochondria, respectively, as shown by abnormal cristae structure and loss of matrix substance as compared to controls* [52]. *Myoblasts from presymptomatic and symptomatic HD individuals show loss of mitochondrial membrane potential and increased apoptosis* [53] *whereas apoptotic and autophagic signaling is increased in skeletal muscle from the R6/2 transgenic mouse model of HD* [54]. *Thus, these results further support a role for mutant huntingtin in promoting mitochondrial dysfunction in HD.*

Consistent with human HD studies, evidence from animal and cultured cell models of HD strongly support the idea of defective mitochondrial bioenergetics in HD. Systemic administration of 3-nitropropionic acid (3-NPA) and malonate, selective inhibitors of complex II activity, induce in rodents and nonhuman primates striatal lesions and behavioral and motor deficits like those seen in the human HD phenotype [55, 56]. Significant age-dependent increases in lactate levels occur in the striatum of *HD72 knock-in mice expressing full-length mutant huntingtin* [57] and a significant impairment of mitochondrial complex IV activity is observed in the striatum and in the cerebral cortex from the R6/2 transgenic HD mouse model [58]. Interestingly, a recent study using microwave fixation of whole brain showed a significant decrease in ATP levels in the striatum, hippocampus and cerebral cortex of a transgenic mouse model of HD and in the striatum of the 3-NPA chemical model of HD [59]. Moreover, that study showed that the ATP deficit in HD transgenic mice is dependent on the length of pathogenic CAG repeats, thus underscoring a link between mitochondrial dysfunction and disease severity.

Further evidence supporting defective mitochondrial bioenergetics in HD is revealed by the direct interaction of mutant huntingtin with brain mitochondria [40, 60–62]. The localization

of mutant huntingtin to brain mitochondria correlates with age and disease progression in *the HdhQ150 knock-in mouse model of HD* [62], and results in disruption of fast axonal transport [63, 64], mitochondrial trafficking [57, 62] and calcium homeostasis [60, 65] and in reduction of mitochondrial ATP generation in synaptosomal membranes [62]. Interestingly, in postmortem HD brains and primary neurons from *transgenic BACHD mice,* mutant huntingtin has been shown to interact with dynamin-related protein 1, a mitochondrial protein involved in mitochondrial fragmentation, leading to defective mitochondrial axonal transport and synaptic degeneration in primary neurons [66, 67]. Expression of mutant huntingtin within immortalized striatal neuronal progenitor cells derived from the *HdhQ111 knock-in mouse model of HD* decreases complex II activity and increases the sensitivity of cells to calcium-induced decreases in oxygen consumption and mitochondrial membrane potential, whereas overexpression of complex II prevents mitochondrial dysfunction and cell death [34, 65]. Striatal mouse cells exhibit ATP depletion and reduced oxygen consumption rate when compared with wild type cells [68]. Furthermore, a recent study shows a significant reduction in spare respiratory capacity in human HD skin fibroblasts and in immortalized mutant huntingtin-expressing mouse striatal cells compared to wild type cells, supporting a toxic role of mutant huntingtin on mitochondrial function [47]. Interestingly, the study shows that treatment of striatal neurons with hydrogen peroxide results in further reductions in mitochondrial spare respiratory capacity, suggesting that mutant huntingtin renders neurons more sensitive to oxidative-induced decreases in mitochondrial function.

Collectively, the studies discussed above in human HD and in animal and cellular models of HD show that markers of energy metabolism are altered in HD, and point to a link between mutant huntingtin toxicity and mitochondrial dysfunction. Despite these significant observations, it remains unclear how mutant huntingtin toxicity leads to mitochondrial dysfunction. A possible mechanism by which mutant huntingtin may contribute to mitochondrial dysfunction and neuronal toxicity is by the induction of oxidative stress.

Mitochondrial dysfunction and oxidative stress in HD

The main function of mitochondria is the generation of ATP by means of oxidative phosphorylation, which in turn results in the production of reactive oxygen species (ROS) as byproducts of the normal metabolic process [69]. Mitochondria are the principal sources of endogenous cellular ROS, as unpaired electrons in the respiratory chain are donated to molecular oxygen to generate the superoxide anion, which in turn can be converted to hydrogen peroxide by the action of the mitochondrial enzyme manganese superoxide dismutase. When iron and other transition metals are present, hydrogen peroxide can be further converted to the highly reactive hydroxyl radical via the Fe^{2+}-mediated Fenton reaction. Mitochondrial dysfunction leads to the overproduction of ROS, which in HD may cause failure of mitochondrial bioenergetics. *Increased ROS levels are detected in mutant huntingtin-containing aggregates in transfected African green monkey kidney COS-7 cells and neuronal SK-N-SH and PC12 cells, suggesting that aggregates/inclusion bodies are associated to increased oxidative stress* [70]. Oxidative stress associated with the CAG repeat pathogenic expansion mediates neuronal and non-neuronal cell death and is prevented by treatment with antioxidants [71–73]. Hands and coworkers showed that huntingtin aggregation directly leads to increased ROS production and precedes death in HeLa and inducible PC12 cells expressing exon 1 of mutant huntingtin relative to control cells [74]. Moreover, the study shows that ROS production correlates with increasing CAG repeat length and that inhibition of huntingtin aggregation prevents ROS generation. Another study shows increased generation of ROS in mutant huntingtin expressing neuroblastoma cells compared to cells transfected with a control construct [75]. Thus, expression of mutant huntingtin results in increased ROS generation and cell toxicity.

The effects of mutant huntingtin on the antioxidant response in human brain and in mouse and *in vitro* models further supports the hypothesis of increased oxidative stress in HD. Proteomic analysis of postmortem human HD striatum and cortex shows increased expression of the antioxidant enzymes peroxiredoxines 1, 2, and 6 and glutathione peroxidases 1 and 6 and increased activity of the mitochondrial superoxide dismutase and catalase relative to control samples [76], suggesting ongoing responses to oxidative stress in HD. Moreover, inducible PC12 cells expressing a pathogenic repeat of huntingtin exon 1 and immortalized mouse striatal cells treated with 3-NPA show decreased expression and hyperoxidation of peroxiredoxin 1, whereas mutant huntingtin toxicity is attenuated by overexpression of peroxiredoxin 1 [77]. Overexpression of Cu/Zn superoxide dismutase in cells expressing mutant huntingtin suppresses huntingtin aggregation, ROS-induced proteasomal dysfunction and cell death [78]. Results observed in the brain, and in skin fibroblast cultures show that the activities of catalase [79] and of erythrocyte Cu/Zn-superoxide dismutase and glutathione peroxidase [80] are reduced in individuals affected with HD. Another study shows decreased levels of reduced glutathione in both presymptomatic and symptomatic patients [81].

Further evidence suggesting that mutant huntingtin expression involves a response to oxidative stress and antioxidant status shows that up-regulation of NF-E2-related factor 2 (Nrf2)-antioxidant response element (ARE)-responsive transcripts, a pathway that confers protection against oxidative stress, occurs in an inducibIe PC12 model of HD [82]. Moreover, activation of the Nrf2-ARE system prevents 3-NPA-induced striatal degeneration and increases in oxidative markers in mice [83]. Along this line, induction of the Nrf2-ARE pathway improves motor performance, attenuates striatum degeneration and oxidative stress and increases survival in transgenic HD mice [84].

Other proteins that have been linked to the regulation of energy metabolism, lifespan extension and, more recently, to HD-associated mitochondrial dysfunction and oxidative stress are the sirtuins (Sirt), a family of nicotinamide adenine dinucleotide (NAD)-dependent protein deacetylases. Brain-specific knockout of Sirt1, a sirtuin implicated in neuroprotection, aging and metabolism [85], exacerbates motor deficits and striatal atrophy *in the R6/2 transgenic mouse model of HD* [86], whereas overexpression of Sirt1 attenuates striatal and neocortex atrophy and improves motor performance *in R6/2 and in N171-82Q and BACHD mice expressing full-length mutant huntingtin* [86, 87]. In addition, Sirt1 overexpression alleviates mutant huntingtin-mediated hyperglycemia and insulin resistance in *N171-82Q HD mice* and restores ATP levels in mutant huntingtin expressing immortalized striatal mouse cells to levels similar to wild type [87]. In mutant huntingtin-expressing striatal mouse neurons, the expression levels of the mitochondrial Sirt3 (a sirtuin involved in mitochondrial metabolism and ROS production [88]) are reduced, ROS levels are increased, and mitochondrial membrane potential is lowered relative to cells expressing normal huntingtin [89], further suggesting a link between mitochondrial dysfunction and oxidative stress in HD. In a yeast model of HD, oxidative stress-induced by mutant huntingtin expression leads to impaired activities of mitochondrial complexes II and III and increased ROS production [90]. Sir2 activation decreases the formation of mutant huntingtin-associated aggregates and protein oxidation levels [91], while increasing mitochondrial biogenesis restores mitochondrial membrane potential and cellular respiration to levels similar to wild type yeast cells [92].

Mutant huntingtin may also affect mitochondrial energy metabolism by repressing the expression of the peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1 α (PGC-1α), a transcriptional coactivator implicated in the regulation of mitochondrial biogenesis, mitochondrial respiration and ROS metabolism [93, 94]. Striata from HD patients, *HdhQ140 knock-in mice and transgenic NLS-N171-82Q mice* [95, 96] show

reduced PGC-1α mRNA expression compared to controls. Expression of PGC-1α in the striatum of *R6/2 mice prevents* mutant huntingtin associated atrophy of striatal neurons [95]. Moreover, activation of PGC-1α improves motor impairment in the *R6/1 HD transgenic mouse model* [97] and upregulation of PGC-1α in immortalized mouse striatal cells results in protection against mutant huntingtin mitochondrial dysfunction and cell death [95], suggesting that PGC-1α may mediate mutant huntingtin-induced mitochondrial toxicity. *Interestingly, overexpression of PGC-1α in N171-82Q HD transgenic mice not only suppresses the neurological phenotype but prevents mutant huntingtin protein aggregation by activating autophagy* [98]. *The authors also show that overexpression of PGC-1α attenuates hydrogen peroxide-induced protein aggregation and oxidative stress in Neuro2a cells coexpressing a toxic huntingtin fragment* [98]. PPARγ also promotes mitochondrial biogenesis through the induction of PGC-1α. Activation of PPARγ rescues expression levels of PGC-1α, nuclear respiratory factor (NRF)-1, NRF-2 and mitochondrial transcription factor A (proteins involved in the regulation of mitochondrial respiration and biogenesis), and of the antioxidant enzymes superoxide dismutase 1 and 2 and glutathione peroxidase 1 in cortex from *the R6/2 transgenic mouse model of HD* [75]. Furthermore, the study also shows that activation of PPARγ in mutant huntingtin expressing neuroblastoma cells significantly improves mitochondrial biogenesis.

Consistent with high levels of oxidative stress and mitochondrial dysfunction in HD, the ROS-sensitive, Krebs cycle mitochondrial enzyme aconitase is decreased in postmortem caudate/putamen and cerebral cortex from HD patients [33, 76]. Furthermore, mitochondrial creatine kinase, citrate synthase and ATP synthase are significantly oxidized in human HD brain striatum [99]. Increased striatal ROS formation [100] and significant levels of oxidative damage to aconitase and creatine kinase is also seen *in the R6/2 transgenic mice* relative to wild type mice [37]. Overall, studies in various HD models suggest a link between oxidative damage and defective mitochondrial energy metabolism in HD pathogenesis.

Oxidative damage to the nuclear and mitochondrial genomes in HD

It is clear from the studies discussed above that mutant huntingtin expression is associated with increased oxidative stress and impaired mitochondrial bioenergetics. A fundamental question that remains to be answered is how oxidative stress and ROS production lead to HD-associated mitochondrial dysfunction and disease progression. Compelling evidence suggests that mutant huntingtin provokes oxidative damage to nuclear and mitochondrial DNA, which in turn may lead to impairment of mitochondrial bioenergetics and, thus, HD pathology. Markers of oxidative stress increase in human HD and in animal models of the disease. Increased oxidative damage to nuclear DNA, in the form of 8-hydroxydeoxyguanosine (8-OHdG), occurs in postmortem caudate from HD patients [32], and significant elevations in 8-OHdG occur in serum [101] and leukocytes [80] from affected individuals. Moreover, oxidative lesions to nuclear DNA are significantly increased in postmortem grade 3 HD caudate putamen compared to age-matched controls [47]. Interestingly, concentrations of plasma 8-OHdG are significantly increased in HD patients with mild symptoms compared to control individuals [102]. *"Furthermore, the rate of 8-OHdG accumulation increases with disease progression in HD individuals relative to controls* [102], *suggesting that plasma levels of 8-OHdG may be considered a marker for HD development".* In accordance with these observations, HD patients supplemented with creatine, an antioxidant and a compound critical for the maintenance of ATP levels in brain and muscle, show decreased concentrations of serum 8-OHdG to levels comparable to those of control individuals [101] and a delay in the progression of cortical atrophy [103].

Increased levels of oxidative nuclear DNA damage are also found in mouse models of HD. The accumulation of oxidative DNA lesions in brain and liver of *R6/2 transgenic mice* correlates with the age-dependent extent of CAG expansion [104]. Brain, striatal microdialysates, urine and plasma of *R6/2 transgenic mice* all show significant elevations in 8-OHdG concentrations compared to control mice [105]. Immunohistochemical analysis shows increased levels of 8-OHdG in the striatum of *the N171-82Q transgenic mice expressing* an N-terminal fragment of mutant huntingtin [84], and mice treated with 3-NPA show age-dependent increases in striatal 8-OHdG relative to untreated controls [106]. Moreover, levels of oxidative nuclear DNA lesions as determined by quantitative PCR are significantly elevated in the striatum and cerebral cortex of *the R6/2 transgenic mouse model of HD* compared to wild type mice [106]. Consistent with these results, administration of the antioxidants creatine and coenzyme Q10 reduce 3-NPA-induced oxidative damage to DNA in the striatum, attenuate atrophy of striatal neurons, and improve motor function and survival *in the R6/2 and N171-82Q transgenic HD mouse models* [107–109]. Furthermore, overexpression of hMTH1, the major human enzyme that hydrolyzes the pool of oxidized purine deoxynucleoside triphosphates and thereby preventing their incorporation into DNA, confers in mice protection against 3-NPA-induced weight loss, motor dysfunction, striatal atrophy and death [110]. Thus, reduction of DNA oxidation ameliorates HD symptoms and pathology in HD mouse models.

Mitochondrial DNA (mtDNA) is also a major site of ROS-induced oxidative damage. Damaged mtDNA is not only an indicator of impaired mitochondrial bioenergetics, but also is implicated in HD neurodegeneration [111]. Mutant huntingtin-expressing immortalized mouse striatal neurons expressing 111 CAG repeats [47] and PC12 cells expressing a pathogenic polyglutamine tract [77] show significantly increased levels of mitochondrial-generated superoxide compared to wild type cells. The increased mitochondrial ROS associated with mutant huntingtin is likely to increase levels of mtDNA damage. Indeed, there is a significant increase in 8-OHdG levels in mtDNA from postmortem parietal cortex of late-stage HD subjects relative to age-matched normal individuals [112]. Moreover, postmortem striata from late-stage HD individuals exhibit significant levels of mtDNA damage as indicated by increased frequency of oxidative mtDNA lesions and significant mtDNA depletion compared to age-matched controls [47]. Similarly, depletion of mtDNA molecules occurs in leukocytes from HD patients and correlates with CAG repeat length [113], in the striatum of *the transgenic NLS-N171-82Q mouse model of HD* [96] *and in cortex from HdhQ150 knock-in* mice relative to wild type mice [21]. Moreover, immortalized mouse striatal cells expressing mutant huntingtin exhibit a significant increase in mtDNA lesions [47] and reduced mtDNA abundance [47, 89] compared to wild type cells. The increased levels in mtDNA damage precede reductions in mitochondrial spare respiratory capacity in striatal cells expressing mutant huntingtin treated with hydrogen peroxide [47]. In addition, mtDNA deletions are significantly increased in the temporal and frontal cortex of HD patients [114] and in HD leukocytes [80]. In further evidence that mtDNA damage may contribute to mitochondrial dysfunction and HD pathogenesis, striatal mtDNA is selectively vulnerable to oxidative damage in *R6/2 transgenic mice* relative to wild type mice [106]. Interestingly, treatment with an antioxidant specific to mitochondria improves function in isolated mitochondria from HdhQ150 knock-in mice and restores in vivo the mtDNA copy number to levels similar to the controls [21]. Thus, mtDNA damage in the form of oxidative lesions and mtDNA depletion may ultimately interfere with electron transport chain function, resulting in diminished mitochondrial membrane potential and ATP synthesis, increased ROS production, and exacerbation of oxidative damage to mitochondrial and nuclear DNA, thereby establishing a vicious cycle of cellular oxidation damage (Figure 1). Overall, oxidative damage to both the nuclear and mitochondrial genomes have been shown to occur in human HD brains and in mouse and cellular models

of HD are associated with defective mitochondrial bioenergetics. Thus, the accumulation of oxidative DNA damage is associated with disease onset and progression.

Repair of oxidative damage of nuclear and mitochondrial DNA in HD

As discussed above, in HD, ROS induce oxidative damage to both the nuclear and mitochondrial genomes and may play a role in the onset and progression of HD. If not repaired, some DNA lesions are mutagenic and can contribute to further instability and eventually to pathogenesis. The mechanism of age-dependent increases in CAG expansions is not well understood. However, it seems to involve oxidative DNA damage and to be facilitated by the process of DNA repair. Base excision repair (BER), the mechanism responsible for the repair of most oxidative lesions [115], appears to be involved in somatic CAG expansions. Kovtun and colleagues show that age-dependent increases in oxidative nuclear DNA lesions occur in liver and brain *of R6/1 transgenic mice* [104]. They also show that *R6/1 mice* deficient in 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1), the enzyme that initiates BER to remove the 8-OHdG lesion, exhibit delayed or suppressed age-dependent somatic CAG expansions, suggesting that the expansion occurs during the removal of oxidized bases via an OGG1-dependent repair process. Interestingly, R6/2 mice deficient in another mammalian glycosylase, Nei-like 1(Neil1), also show suppressed somatic CAG expansions [116]. Treatment of fragile X premutation mice with potassium bromate, a robust oxidant that generates primarily 8-OHdG lesions, results in increased germline expansion frequency, further suggesting that removal of oxidative damage may trigger CAG expansions [117]. In addition, the hairpin loop that is formed during the process of repeat expansion may be a hotspot for oxidative DNA damage [118, 119], resulting in the accumulation of 8-OHdG in the hairpin intermediate, its incorporation into the duplex DNA, thus leading to a toxic oxidation cycle and increased CAG repeat instability [120]. Other enzymes that participate in BER seem to modulate the process of CAG instability in HD. Flap endonuclease 1 (FEN1), the enzyme responsible for flap excision and removal during BER, and DNA polymerase beta (POLβ) modulate CAG repeat expansions in mouse cell extracts [121] and block processing of CAG hairpin loops [122]. Additionally, CAG repeat expansions are prevented in a FEN1-dependent fashion [122–124]. Furthermore, the ratio of FEN1 to POLβ is lower in the striatum than in the cerebellum *of transgenic R6/1 mice*, suggesting that low expression of FEN1 may contribute to the formation of the hairpin loop and to an increase in tissue-associated repeat instability in HD [118].

Mismatch repair (MMR) is also associated with CAG repeat expansions. Deficiency of the MMR protein Msh2 in R6/1 transgenic mice prevents *in vivo* CAG instability in both somatic and germ line cells [125, 126], suggesting a role for Msh2 in CAG length modification. In addition, *HdhQ111 knock-in mice* deficient in Msh2 show a significant delay in the accumulation of nuclear full-length mutant huntingtin in the striatum [127]. *In HdhQ111 knock-in mice* Msh3 and Msh6, binding partners of Msh2, appear to affect striatal CAG repeat length and intergenerational instability [128].

Expression of mutant huntingtin causes double-strand breaks in genomic DNA thus impacting DNA strand break repair. The direct interaction of mutant huntingtin with Ku70, a protein involved in non-homologous end-joining (NHEJ) DNA repair, leads to increases in double-strand DNA breaks [129]. Moreover, overexpression of Ku70 attenuates HD-like symptoms and neuropathology *in the R6/2 mouse model of HD* [129] and rescues the mutant huntingtin-induced toxic phenotype in a *Drosophila* model of HD [130]. Consistent with the idea of oxidative DNA damage and a repair defect in CAG repeat expansion, fibroblasts from HD and SCA2 patients show activation of the ataxia telangiectasia mutated kinase (ATM) and Rad3-related kinase (ATR) double-strand break response proteins [131].

The activation of ATM/ATR is dependent on the expression of mutant huntingtin and is mediated by ROS accumulation [131]. Mutant huntingtin also induces single-strand and double-strand DNA breaks and a DNA damage response in PC12 cells expressing a truncated pathogenic HD fragment, and in striatum *of the R6/2 transgenic mouse model of HD* prior to mutant huntingtin aggregate formation [132]. Interestingly, a recent study suggests that topoisomerase 1, tyrosyl-DNA phosphodiesterase 1 and single-strand break repair are involved in the suppression of CAG repeat instability in human cells [133]. Mutant huntingtin interacts with p53, a transcription factor induced in response to DNA damage, and increases the levels and activity of p53 in mouse striatal cells, and in striatum and cerebral cortex from HD patients and *R6/2 transgenic mice* [134, 135]. Furthermore, an expanded CAG/CTG repeat activates a DNA damage response in the yeast *Saccharomyces cerevisiae* [136]. Thus, several nDNA repair mechanisms appear to be involved in the process of CAG repeat instability in HD. Together, these results support a role for nuclear DNA repair mechanisms in both the generation of the huntingtin mutation and the toxic effects of mutant huntingtin, and suggest oxidative stress as a key mediator of both processes.

While nuclear DNA damage response/repair mechanisms are clearly implicated in HD, the role of mtDNA repair processes in HD has been less well studied. The critical question of how the elevated mtDNA damage seen in HD impacts mitochondrial function is still unanswered. Moreover, how mitochondrial function is influenced by mtDNA repair remains to be determined. APE1 is the major apurinic/apyrimidinic (AP) endonuclease in BER [137], and may also play a role in somatic CAG repeat instability. APE1 is found in neuronal nuclei, cytoplasm and mitochondria [138–144], and oxidative stress induces APE1 gene activation and translocalization to mitochondria [144, 145]. Null mutations of APE1 in mice result in embryonic lethality [146–148], but APE1 heterozygous mice ($APE1^{+/-}$) live into adulthood and show increased spontaneous mutation rates in liver, spleen and spermatogenic cells [149]. In addition, spermatogenic cells from $APE1^{+/-}$ mice show increased oxidative stress [147] and age-dependent increases in nuclear and mtDNA lesions [150]. Silencing of Ape1 results in exacerbated reduced mitochondrial spare respiratory capacity in mutant huntingtin expressing mouse cells. Moreover, when striatal neurons are treated with hydrogen peroxide, APE1 localization significantly increases in the mitochondria of wild type cells but not mutant cells [47]. Thus, mutant huntingtin may impede APE1 mitochondrial import. If APE1 is necessary for the maintenance of mitochondrial function in immortalized striatal neurons derived from HdhQ111 knock-in HD mice, then deficiencies in BER may play a role in the development of mtDNA lesions and in deficient mitochondrial bioenergetics in HD. Defining whether mtDNA repair also contributes to the process of somatic CAG repeat expansion is an important future direction.

In summary, oxidative DNA damage to the nuclear and mitochondrial genomes is likely to contribute to mutant huntingtin-induced impairment of mitochondrial bioenergetics by increasing DNA instability in both genomes. In addition, repair of oxidative damage to nuclear DNA is clearly implicated in the CAG repeat expansion associated with HD. A model is proposed for mutant huntingtin-induced mitochondrial dysfunction and HD neurodegeneration caused by increases in mitochondrial ROS generation and in oxidative damage to mtDNA and nuclear DNA (Figure 2).

Conclusion

Mitochondria are fundamental to the pathogenic mechanisms underlying HD pathogenesis, as mutant huntingtin directly interacts with mitochondria and triggers increased oxidative stress and declines in mitochondrial bioenergetics. Impairment of mitochondrial function in HD in turn further elevates oxidative damage to mitochondrial and nuclear genomes.

Conditions of high energy demand on mitochondria, such as the activation of DNA repair mechanisms due to increased oxidative stress, can use all the mitochondrial spare respiratory capacity of the cell that, coupled with the expression of mutant huntingtin may render neurons more sensitive to oxidative-induced increases in mtDNA damage and exacerbated by reductions in the mitochondrial repair mechanisms. It is clear that more research is needed to explore this line of investigation. Thus, targeting mtDNA oxidative damage due to impaired mitochondrial bioenergetics may be a beneficial strategy to alter disease either before symptoms begin or during disease progression.

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Highlights

- Oxidative DNA damage in dysfunctional mitochondrial bioenergetics associated with the pathogenesis of Huntington's disease.
- Oxidative damage to DNA and to mitochondria in Huntington's disease.
- Oxidative DNA repair of both nuclear and mitochondrial genomes in Huntington's disease.

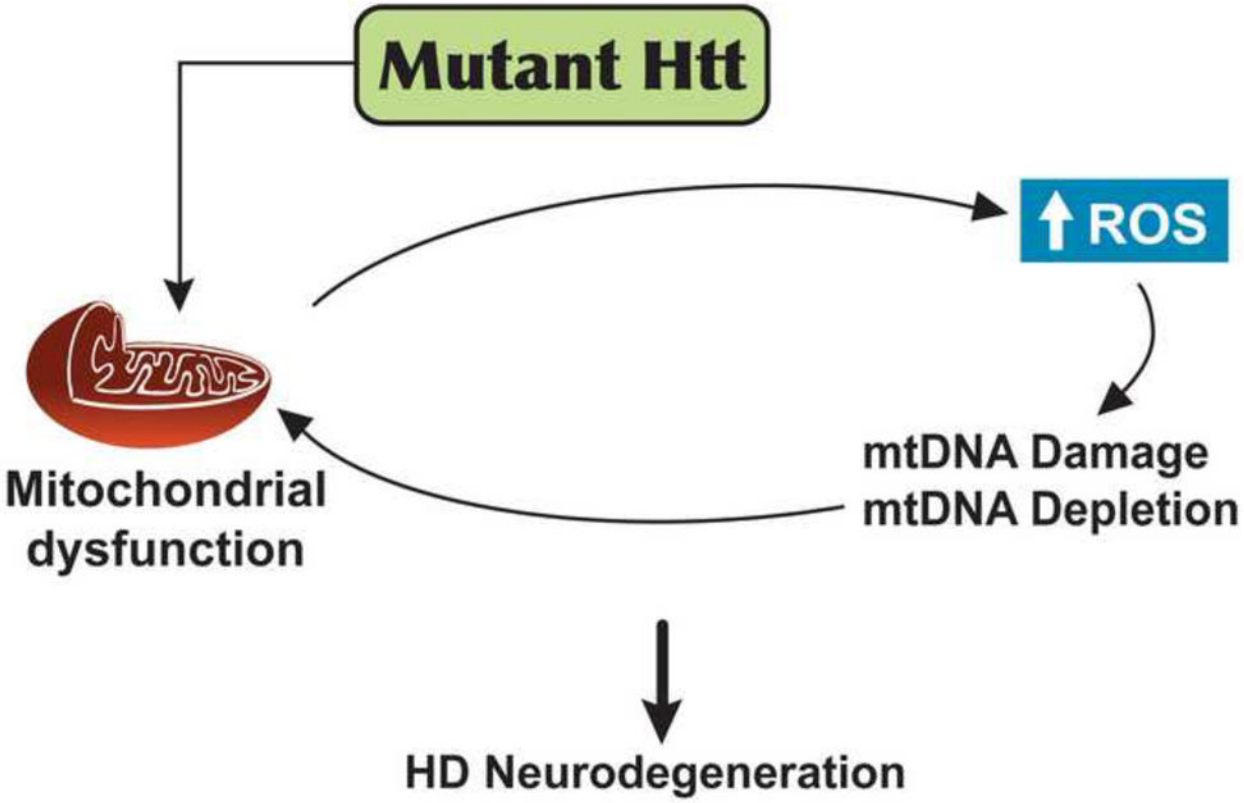

Figure 1.
Vicious cycle of mitochondrial oxidative damage in HD. Under the context of mutant huntingtin (htt) expression, mitochondria lead to overproduction of mitochondrial ROS that introduce oxidative damage to the mitochondria. Damaged mtDNA leads to dysfunctional mitochondrial bioenergetics that generate additional ROS and exacerbates oxidative damage to mtDNA, ultimately leading to HD pathophysiology. Thus, mtDNA damage in the form of oxidative lesions and mtDNA depletion may ultimately interfere with mitochondrial function resulting in diminished ATP synthesis, increased ROS production and exacerbation of oxidative damage to mtDNA.

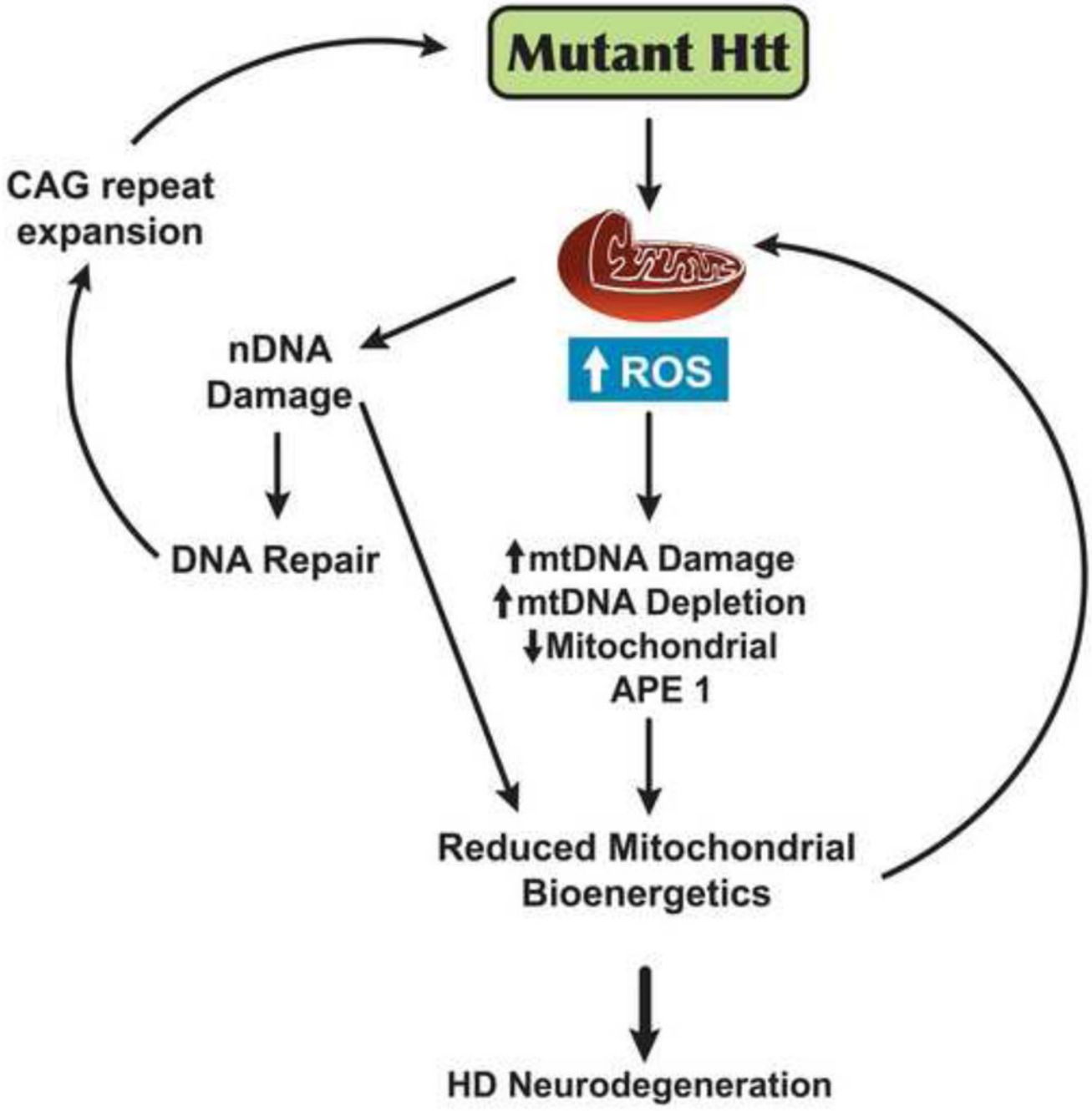

Figure 2.

Model of oxidative DNA damage and mitochondrial dysfunction in HD. A possible mechanism underlying the toxic effects of mutant huntingtin (htt) is the accumulation of mtDNA lesions and the occurrence of mtDNA depletion as a result of increases in mitochondrial ROS generation. Concurrently, mutant huntingtin affects mtDNA repair by preventing the accumulation of APE1 in the mitochondria, thus contributing to further mitochondrial damage. Consistent with this hypothesis, mtDNA damage leads to exacerbated mitochondrial dysfunction and HD-like neurodegeneration. Oxidative damage to nDNA also contributes to mitochondrial dysfunction and leads to the activation of DNA repair processes that may lead to CAG repeat expansion.