Mitochondrial Dysfunction in Brain and Muscle Pathology of Huntington's Disease

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Contents

Abstract

Huntington's disease (HD) is an autosomal dominant, typically late-onset neurodegenerative disease characterized by a heterogeneous phenotype involving involuntary choreiform movements, metabolic deficits, loss of motor skills, and psychiatric and cognitive impairment. Substantial evidence suggests that increased oxidative stress and mitochondrial dysfunction occur in brain and peripheral tissues of HD patients and HD experimental models. However, the precise mechanisms by which mutant huntingtin cause

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neurological damage remain unclear. This chapter reviews recent literature regarding the role of reactive oxygen species in mitochondrial dysfunction and HD pathogenesis with special attention on the brain and the skeletal muscle.

Keywords
Brain • DNA repair • Huntington's disease • Mitochondrial DNA • Mitochondrial dysfunction • Oxidative stress • Skeletal muscle

Introduction

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by mutations involving abnormal expansions of CAG trinucleotide repeats in the huntingtin gene, resulting in atypically long N-terminal polyglutamine (polyQ) stretches in the huntingtin protein (Gusella et al. 1983; Huntington's Disease Collaborative Research Group 1993). When the number of CAG repeats exceeds 36, the disease manifests and CAG repeat instability increases in future generations (Kremer et al. 1994; Goldberg et al. 1995; McMurray 1999). Longer CAG repeat expansions are associated with earlier disease onset (Kremer et al. 1994; Andrew et al. 1993; Duyao et al. 1993; Snell et al. 1993), greater severity, and faster progression (Butterworth et al. 1998; Furtado et al. 1996; Ravina et al. 2008; Foroud et al. 1999). Although the genetic cause of HD is known, no pharmacological interventions are yet available to cure the disease. However, a recent report shows that administration of a mitochondria-targeted antioxidant suppresses motor dysfunction, weight loss, and mitochondrial oxidative DNA damage in a knock-in mouse model of HD (Xun et al. 2012). HD patients typically develop behavioral abnormalities, cognitive impairment, psychiatric symptoms, metabolic deficits, and loss of motor skills, symptoms that worsen over time as the disease progresses (Martin and Gusella 1986; Paulsen and Conybeare 2005; Kumar et al. 2010; Shannon 2011; Folstein et al. 1987; Burns et al. 1990). Motor problems involve both involuntary and voluntary movements. The most common clinical manifestation of HD is chorea, an involuntary and irregular dance-like movement. Dystonia (a disruption of voluntary movement) is also observed in HD (Shannon 2011; Anderson 2011) and may manifest as interrupted gait (Koller and Trimble 1985; Delval et al. 2008) and abnormal voluntary eye movements (Peltsch et al. 2008). The heterogeneous HD phenotype results in death approximately 15–25 years after clinical diagnosis, with the most common causes of death mainly associated with choking, aspiration pneumonia, and heart disease (Shannon 2011; Lanska et al. 1988).

Huntingtin, a ubiquitous, multifunctional protein, is expressed in both neuronal and nonneuronal cells of the central nervous system (CNS) and in peripheral tissues including skeletal muscle, lung, testis, and ovary (Li et al. 1993). The mechanisms by which mutant huntingtin causes neurological damage remain unclear, but significant evidence from both human HD patients and experimental

HD models supports an important role for oxidative stress and mitochondrial dysfunction in HD pathology. In this chapter, we review the literature regarding the role of reactive oxygen species (ROS) in mitochondrial dysfunction and HD pathogenesis, with particular emphasis on the brain and skeletal muscle. The heterogeneity of HD pathology and its varied clinical phenotypes suggest that therapeutics should target both neurological defects and skeletal muscle dysfunction.

Human Pathology

Mitochondrial Dysfunction in HD Brain

Traditionally, HD has been considered a CNS disorder, which has been extensively reviewed (Anderson 2011; Vonsattel et al. 2011) and discussed above. Briefly, the brains of HD patients show prominent neuronal loss, mainly in the neostriatum and cerebral cortex (Harper 1991; Vonsattel et al. 1985). Although the underlying basis for disease is complex, there is substantial evidence in humans, mice, and in cells that supports the idea that mitochondrial dysfunction not only occurs in HD but also contributes significantly to pathophysiology. Truncated forms of mutant huntingtin associate directly with brain mitochondria (Panov et al. 2002; Choo et al. 2004; Petrassch-Parwez et al. 2007) in an age-dependent fashion and correlate with disease progression in HD model mice (Orr et al. 2008). Aberrant mitochondrial morphology accompanies disease progression and occurs in both brain and peripheral tissues of HD patients (Squitieri et al. 2006; Mihm et al. 2007). Moreover, the activities of the mitochondrial electron transport complexes II, III, and IV decrease in the caudate/putamen of HD patients (Brennan et al. 1985; Gu et al. 1996; Browne et al. 1997; Tabrizi et al. 1999), and pyruvate dehydrogenase activity decreases in the caudate nucleus of patients with advanced disease (Butterworth et al. 1985). Indeed, expression of Ip and Fp subunits of complex II is reduced in striatum from grade 1–2/3 HD patients (Benchoua et al. 2006). Overexpression of either of these subunits in cultured rat striatal neurons expressing mutant huntingtin restores complex II activity and protects cells from death. These findings underscore the importance of deficient complex II in HD toxicity. An increase in lactate levels in the cerebral cortex of symptomatic HD patients (Koroshetz et al. 1997) provides further evidence of mitochondrial dysfunction and correlates with disease duration (Jenkins et al. 1993). Consistent with a mitochondrial defect, positron emission tomography imaging reveals glucose hypometabolism in the caudate/putamen of preclinical HD patients (Feigin et al. 2001). Paradoxically, defects in glucose metabolism are not accompanied by alterations in oxidative phosphorylation in presymptomatic patients (Powers et al. 2007), and no changes in the activity of complexes I–IV are observed in the neostriatum or cerebral cortex of presymptomatic and grade 1 HD patients (Guidetti et al. 2001). These findings imply that deficits in mitochondrial respiration may not occur in early phases of disease progression in the brain.

Animal and cell models of HD have also provided compelling evidence for mitochondrial dysfunction in HD. Decreased activities of complex IV and of aconitase, an enzyme involved in the Krebs cycle, are observed in the striatum and cerebral cortex of the R6/2 mice (Tabrizi et al. 2000) as well as in HD brain (Tabrizi et al. 1999). The decreased activity of aconitase suggests that the generation of superoxide is increased in R6/2 mice (Hausladen and Fridivich 1994). While superoxide is not very reactive, it can damage iron/sulfur centers liberating iron from aconitase and other iron-containing proteins (Fridovich 1986) and leading to the generation of the highly potent hydroxyl radical via the Haber-Weiss/Fenton reaction (Graf et al. 1984; Burkitt and Gilbert 1990). Indeed, mutant huntingtin-expressing immortalized mouse striatal neuronal progenitor cells derived from a knock-in mouse model of HD show a 23 % increase in basal levels of mitochondria-generated superoxide relative to wild-type neurons (Siddiqui et al. 2012). Deficient mitochondrial respiration and decreased ATP production were seen in immortalized striatal neuronal progenitor cells derived from a knock-in model of HD (Gines et al. 2003; Milakovic and Johnson 2005). Direct association of soluble N-terminal fragments of mutant huntingtin with brain mitochondria of HdhQ150 knock-in mice results in age-dependent increases in lactate levels (Trushina et al. 2004). Mutant huntingtin also disrupts mitochondrial motility and mitochondrial trafficking along axons (Trushina et al. 2004) and reduces synaptosomal mitochondrial ATP production (Orr et al. 2008). Mutant huntingtin localized to mitochondria causes mitochondrial calcium-handling abnormalities (Panov et al. 2002; Choo et al. 2004; Rockabrand et al. 2007) and sensitizes striatal neurons to calcium-induced decreases in state 3 respiration and mitochondrial membrane potential (Milakovic et al. 2006). Additional evidence of disruption of Ca^{+2} homeostasis in HD is found in HD striatal cells (Lim et al. 2008).

Muscle Pathology in HD

In contrast to the brain, mitochondrial dysfunction appears to precede the onset of symptoms in peripheral tissues such as skeletal muscle (Lodi et al. 2000; Saft et al. 2005) of HD patients. For example, weight loss and skeletal muscle wasting are hallmark phenotypes in HD patients (Sanberg et al. 1981; Farrer and Yu 1985; Stoy and McKay 2000; Djousse et al. 2002; Trejo et al. 2004). Weight loss occurs in both presymptomatic and in symptomatic HD patients and correlates with the length of CAG repeats (Aziz et al. 2008). Muscle wasting is accompanied by reductions in muscle strength (Busse et al. 2008) and work capacity (Ciammola et al. 2011). An increase in apoptosis occurs in primary muscle cell cultures from both presymptomatic and symptomatic HD subjects (Ciammola et al. 2006), suggesting that muscle is vulnerable to the toxic effects of mutant huntingtin.

Muscle wasting is also evident in transgenic mouse models of HD (She et al. 2011). R6/2 mice expressing an N-terminal huntingtin truncation fragment display a robust symptomatic phenotype and have skeletal muscle atrophy throughout their life span (She et al. 2011; Sathasivam et al. 1999; Ribchester et al. 2004). Abnormal morphology of neuromuscular junctions is prominent particularly in older mice as age-dependent reductions in muscle fiber diameter as well as alterations in the ratio

of type I to type II fibers (Ribchester et al. 2004). Muscle wasting appears to be responsible for the bulk of age-related weight loss in R6/2 mice, with weight reductions of 38 % and 33 % observed in the gastrocnemius and quadriceps, respectively (She et al. 2011). Exacerbated age-related quadriceps atrophy is also observed in the HdhQ150 knock-in HD mouse model in which the full-length mutant huntingtin is inserted into the endogenous murine HD promoter (Moffitt et al. 2009). Thus, motor dysfunction in HD patients and HD model mice likely results not only from the loss of CNS control of motor function but also from direct effects of skeletal muscle pathology.

Mitochondrial Dysfunction in HD Skeletal Muscle

As measured by magnetic resonance spectroscopy, the reduction in ATP synthesis observed in resting muscle has suggested that there are deficits in oxidative mitochondrial metabolism in HD patients (Koroshetz et al. 1997; Lodi et al. 2000). Furthermore, there is a decrease in phosphocreatine recovery in muscle of HD patients and asymptomatic mutation carriers compared to age-matched controls (Saft et al. 2005). The maximum ATP production rates drop by 35 % and 44 % during exercise recovery in asymptomatic and symptomatic HD patients, respectively (Lodi et al. 2000). Mitochondrial impairment is similar in asymptomatic and symptomatic HD patients, again suggesting that mitochondrial dysfunction in muscle is an early event in HD pathogenesis (Saft et al. 2005). Consistent with this idea, myopathic symptoms emerged before neurological ones in an asymptomatic HD carrier after endurance exercise (Kosinski et al. 2007). Analysis of a muscle biopsy from this patient reveals that there is a complex IV deficiency, and analysis of the patient's fibroblasts shows decreased mitochondrial oxygen consumption (Kosinski et al. 2007). Defects in complex I and increased numbers of abnormal mitochondria have been reported in muscle biopsy specimens from HD patients, which correlated with CAG expansion length (Arenas et al. 1998). Interestingly, multiple species of mitochondrial DNA (mtDNA) deletions are present in the patient with the greatest complex I defect and the highest repeat expansion (Arenas et al. 1998). Abnormally shaped mitochondria and increased lactate levels are observed in muscle cell cultures from HD patients, further indicating inadequate mitochondrial oxidative respiration (Ciammola et al. 2011). Moreover, primary muscle cell cultures from both presymptomatic and symptomatic HD subjects have lower mitochondrial membrane potential and are subject to increased apoptosis relative to those of control patients, as evidenced by increased cytochrome c release and caspase activation (Ciammola et al. 2006). Paradoxically, in another study, no significant differences were found in the activities of complexes I–IV in muscle biopsies of HD patients compared to the controls (Turner et al. 2007). Thus, there is not yet universal agreement on the underlying mechanisms of these muscle mitochondrial defects.

The mitochondrial dysfunction observed in human HD is recapitulated in the muscles of R6/2 transgenic mice that are characterized by fiber atrophy, an increase in fuchsinophilic aggregates, a decrease in cytochrome c oxidase activity, and an increase in the Ca^{2+}-induced opening of the permeability transition pore

(Gizatullina et al. 2006). A decrease in oxidative fibers is also observed in soleus muscle of HD mice (Chaturvedi et al. 2009). Together, these results support a role for mitochondrial dysfunction in HD muscle pathology. Importantly, these findings also suggest skeletal muscle mitochondrial abnormalities as potential biomarkers for HD progression.

Oxidative Stress in HD

Oxidative Stress and Responses Associated with HD Pathology

It is clear from the studies discussed above that mitochondria-associated dysfunctions manifest in skeletal muscle as well as the brain in HD patients. In the brain, a decrease in mitochondrial function parallels neuronal loss and the emergence of neurological symptoms during disease progression. In contrast, impaired mitochondrial function in muscle appears to precede the onset of symptoms. A question that remains to be answered is what causes mitochondrial dysfunction in HD. Several lines of evidence suggest that oxidative stress and ROS play a central role in the HD-associated cellular dysfunction.

Mitochondria are the principal sources of endogenous ROS, which are generated as by-products of oxidative phosphorylation (Boveris and Chance 1979). ROS play important roles in cell signaling and homeostasis, but at high levels, ROS can cause damaging oxidation to intracellular macromolecules. Lipid peroxidation, a marker of membrane-associated oxidative stress, can be initiated by hydroxyl radical action on membrane lipids (Girotti 1998). Indeed, lipid peroxidation is prominent in plasma (Klepac et al. 2007), peripheral blood (Chen et al. 2007), human HD brain (Browne et al. 1999; Browne and Beal 2006), and in transgenic mouse models of HD (Browne and Beal 2006; Lee et al. 2010; Perez-Severiano et al. 2000). An increase in lipid peroxidation correlates with disease progression (Perez-Severiano et al. 2000) and disease severity (Chen et al. 2007). Moreover, 4-hydroxy-2-nonenal, a reactive aldehyde product of lipid peroxidation, co-localizes with mutant huntingtin inclusions in striatal neurons of R6/2 mice (Lee et al. 2010). Inhibition of lipid peroxidation by administration of an antioxidant markedly improves mitochondrial function and striatal atrophy and extends life span in these mice (Lee et al. 2010).

Cells maintain complex systems of antioxidants to control ROS levels, but these systems can fail in the face of certain environmental conditions (e.g., drugs, ionizing radiation) or pathological processes (Finkel and Holbrook 2000; Linford et al. 2006). An age-dependent increase in hydrogen peroxide formation in HD is well documented in striata from R6/1 mice (Perez-Severiano et al. 2004). In human neuroblastoma cells and in African green monkey kidney cells, levels of hydrogen peroxide increase proportionally to the number of CAG repeats (Wyttenbach et al. 2002; Firdaus et al. 2006). In HD patients, the antioxidant enzymes peroxiredoxins (Gusella et al. 1983; Huntington's Disease Collaborative Research Group 1993; Andrew et al. 1993), glutathione peroxidases (Gusella et al. 1983;

Andrew et al. 1993), catalase, and MnSOD increase in the striatum of HD patients (Sorolla et al. 2008), suggesting that the expression of mutant huntingtin induces a response to oxidative stress. These results also suggest that the increased antioxidant activity of peroxiredoxins, glutathione peroxidases, and catalase in HD likely results from increased levels of hydrogen peroxide, whereas increases in MnSOD activity would suggest the superoxide radical anion is also generated. Consistent with that hypothesis, overexpression of Cu/Zn SOD in cells expressing mutant huntingtin suppressed aggregation, ROS-induced proteasomal dysfunction, and cell death (Goswami et al. 2006). Other antioxidant pathways appear to be activated in cellular responses to mutant huntingtin. For example, the NF-E2-related factor 2 (Nrf2)-antioxidant response element (ARE) pathway controls redox and antioxidant status and confers protection against oxidative stress. Upregulation of Nrf2-ARE responsive transcripts occurs upon induction of huntingtin expression in an inducible PC12 model of HD (van Roon-Mom et al. 2008). Moreover, induction of the Nrf2-ARE system in N171-82Q HD mice improves rotarod performance, increases survival, attenuates striatal atrophy, and decreases oxidative markers (Stack et al. 2010).

Recent findings suggest that sirtuin (SIRT) proteins may also play a role in cellular responses to HD associated oxidative stress. The SIRT proteins (SIRT1-7) are members of the class III family of nicotinamide adenine dinucleotide (NAD+)-dependent histone deacetylases that regulate longevity and mitochondrial function and biogenesis in lower organisms. The SIRT proteins exhibit various levels of NAD + -dependent deacetylase activity; however, all sirtuins are not histone deacetylases. Caloric restriction, an intervention that induces SIRT1 and reduces oxidative stress in the brain, slows disease progression and increases survival of HD-N171-82Q mice (Duan et al. 2003). Similarly, induction of SIRT1 with resveratrol rescues neuronal dysfunction in HD transgenic C. elegans (Parker et al. 2005) and prevents death of striatal cells derived from HdhQ111 knock-in mice (Parker et al. 2005). Overexpression of SIRT1 alleviates brain atrophy in R6/2 mice, decreases mutant huntingtin aggregation, and extends life span (Jeong et al. 2011). In addition, overexpression of SIRT1 improves motor performance, partially attenuates striatal neurodegeneration and increases insulin sensitivity in both the N171-82Q and BACHD mouse models of HD (Jiang et al. 2012). Paradoxically, administration of SRT50-M1, a SIRT1 activator, failed to prevent striatal pathology and motor dysfunction in N171-82Q HD mice; however, it also exerted beneficial effects on glucose levels (Ho et al. 2010). Of particular importance to HD are the mitochondrial sirtuins (SIRT3-5), as they respond to changes in cellular bioenergetic demands to modulate the activity of several enzymes involved in metabolism. SIRT3, the main mitochondrial deacetylase, not only targets enzymes involved in lipid, nitrogen, and carbohydrate metabolism but also regulates the production of mitochondrial-generated ROS (Newman et al. 2012). Mutant huntingtin-expressing immortalized striatal mouse neurons exhibit reduced levels of SIRT3, decreased deacetylase activity, reduced mtDNA levels, loss of mitochondrial membrane potential, and increased levels of ROS/hydrogen peroxide (Fu et al. 2012). Together, these results indicate that mutant huntingtin causes oxidative stress and

that induction of cellular antioxidant mechanisms has protective effects on cells that express mutant huntingtin.

The contribution of oxidative stress to HD-associated muscle degeneration has received little study to date. However, skeletal muscle is very susceptible to age-dependent oxidative damage (Short et al. 2005). Oxidative stress is strongly associated with sarcopenia, the age-associated decline in mass and strength observed in skeletal muscle (Fulle et al. 2004). Although not yet thoroughly investigated in HD, the increase in mtDNA damage and loss of mtDNA copy number associated with aging of the skeletal muscle (Short et al. 2005) is reminiscent of some features of HD. During aging, skeletal muscle also displays a reduction in the levels of antioxidant enzymes and an increase in the level of protein oxidation (Szczesny et al. 2010). Overall, these findings suggest that skeletal muscle is highly susceptible to oxidative stress if ROS-scavenging enzymes are deficient.

Oxidative Damage in Nuclear and mtDNA of HD Patients

The effects of ROS are also observed in the genomes of both nuclear (n) and mtDNA. A rise in the 8-hydroxydeoxyguanosine (8-OHdG) lesion, a measure of oxidative DNA damage, occurs in the caudate of HD patients (Browne et al. 1997), in the brains of transgenic models of HD (Bogdanov et al. 2001; Stack et al. 2008), in serum (Hersch et al. 2006), and in leukocytes of HD patients (Chen et al. 2007). Moreover, agents that reduce DNA oxidation can ameliorate symptoms in transgenic HD model mice or toxin HD model mice treated with 3-nitropropionic acid (3-NPA), an inhibitor of mitochondrial complex II. For example, treatment with coenzyme Q10 (CoQ10) and creatine, agents that improve mitochondrial bioenergetics and act as antioxidants, reduces DNA oxidation and striatal lesions in rats treated with 3-NPA (Yang et al. 2009). In R6/2 mice, CoQ10 and creatine improve motor performance and extend life span (Yang et al. 2009). MTH1 is an enzyme that hydrolyzes 8-oxo-GTP to 8-oxo-GMP and, thereby, prevents nucleotide incorporation of oxidized nucleotides into DNA (Nakabeppu et al. 2006). Overexpression of human MTH1 eliminates oxidized precursors from the deoxyribonucleotide triphosphate (dNTP) pool and confers a dramatic protection in mice against 3-NPA-induced weight loss, dystonia, gait abnormalities, striatal degeneration, and death (De Luca et al. 2008).

MtDNA is a key target of oxidative damage in HD. Increases in 8-OHdG lesions in mtDNA are well documented in the parietal cortex of HD patients (Polidori et al. 1999). A significant increase in levels of oxidative mtDNA damage is present in postmortem striatum from grade 3 and grade 4 HD patients compared to healthy controls (Siddiqui et al. 2012). In striata from R6/2 transgenic mice, an eightfold higher levels of damage occurs in mtDNA relative to nDNA, suggesting that mtDNA is particularly vulnerable to huntingtin-induced oxidative stress (Acevedo-Torres et al. 2009). Moreover, mutant huntingtin-expressing striatal mouse neurons exhibit increased levels of mtDNA damage relative to wild-type neurons (Siddiqui et al. 2012). Oxidative DNA damage can lead to genomic

instability (McMurray 2010) and deletions in mtDNA as well as an increase in oxidative mtDNA lesions is observed in the temporal and frontal cortex of HD patients (Horton et al. 1995) and in HD leukocytes (Chen et al. 2007). In HD patients, there is a decrease in mtDNA molecules in leukocytes that correlates with CAG repeat length (Liu et al. 2008) and in postmortem striata from grade 3 and 4 HD patients relative to healthy individuals (Siddiqui et al. 2012). Reductions in mtDNA molecules are also observed in striatum from the NLS-N171-82Q transgenic mouse model of HD (Chaturvedi et al. 2010), in cortex from HdhQ150 knock-in mice (Xun et al. 2012), and in mutant huntingtin-expressing immortalized mouse striatal neurons relative to controls (Siddiqui et al. 2012). Thus, mtDNA oxidative damage can cause mitochondrial dysfunction and an increase in mitochondrial generated ROS.

Repair of Oxidative DNA Damage in HD

At the DNA level, ROS causes a wide spectrum of lesions including damaged bases, with 8-oxo-G being the most common, single-strand breaks (SSB), and to a lesser extent double-strand breaks (DSB) (McMurray 2010). In all of these cases, the breaks are likely to be introduced in the process of correcting oxidative DNA damage. The cross talk among DNA repair pathways is complex (Kovtun and McMurray 2007; Fousteri and Mullenders 2008), but three major DNA repair pathways have been implicated in promoting instability arising from oxidative DNA damage in HD (McMurray 2010). In nDNA, there is substantial evidence that expansion of the CAG repeats occurs during the processing of correcting oxidative DNA damage by base excision repair (BER). Kovtun and colleagues demonstrated that the accumulation of oxidative DNA lesions in brain and liver of R6/1 transgenic mice correlates with the age-dependent degree of CAG expansion (Kovtun et al. 2007). Furthermore, the R6/1 mice deficient in 7,8-dihydro-8-oxoguanine-DNA glycosylase (OGG1), an enzyme involved in the initiation of the BER pathway, exhibited delayed or suppressed age-dependent somatic CAG expansion (Kovtun et al. 2007). These findings support the idea that expansion occurs during the process of removing oxidative DNA lesions by OGG1-dependent BER (Kovtun et al. 2007). Indeed, the level of expression of OGG1 correlates with the degree of the instability (Goula et al. 2009), and treatment with oxidizing agents increases instability of other triplet repeats in animals (Entezam et al. 2010). Other components of the BER machinery have been implicated in DNA instability. Fen-1 operates with polymerase β in BER to modulate CAG repeat expansion (Liu et al. 2009) and blocks efficient processing of the CAG hairpins (Spiro et al. 1999). APE1, the major apurinic/apyrimidinic (AP) endonuclease in BER (Demple et al. 1991), is located in the neuronal nuclei, in cytoplasm, and in mitochondria (Xanthoudakis et al. 1994; Duguid et al. 1995; Tell et al. 2005; Vasko et al. 2005; Tomkinson et al. 1988; Chattopadhyay et al. 2006; Frossi et al. 2002). Oxidative stress induces both APE1 gene activation and its translocalization to mitochondria (Frossi et al. 2002; Pines et al. 2005). *Ape1*$^{-/-}$ mice are embryonic

lethal (Xanthoudakis et al. 1996). However, there is an increase in age-dependent lesions in both nuclear and mtDNA in spermatogenic cells (Vogel et al. 2011). Recent evidence suggests that silencing Ape1 in mutant huntingtin-expressing mouse striatal neurons is associated with reduced mitochondrial bioenergetics (Siddiqui et al. 2012). Furthermore, treatment of mutant huntingtin-expressing neurons with hydrogen peroxide results in reduced localization of APE1 into mitochondria of mutant cells but not of hydrogen peroxide-treated wild-type neurons (Siddiqui et al. 2012). Although not yet thoroughly examined in HD, APE1 may also play a role in genomic instability.

Mismatched repair (MMR) causes CAG expansion in all HD mouse models tested (Manley et al. 1999; Dragileva et al. 2009; Kovtun and McMurray 2001; Wheeler et al. 2003). There is no direct evidence that MMR removes oxidized bases in cells or in animals expressing mutant huntingtin. However, 8-oxo-G paired with A is recognized by the mismatch repair systems (Modrich 2006), and it cannot be entirely excluded that MMR contributes to the genomic instability if an 8-oxo-G is inserted across an A during gap-filling synthesis at a trinucleotide repeat (TNR) tract. Removal of the lesion by the MMR system would, in this case, need to induce some kind of strand displacement to generate instability. More likely, MMR cooperates with the BER machinery in causing expansion during OGG1-mediated (or another glycosylase) removal of oxidized bases (Kovtun and McMurray 2007; Møllersen et al. 2012). Models for how this might occur have been proposed but remain controversial (McMurray 2010). We present a diagram illustrating the proposed mechanism of TNR expansion based on oxidized bases, BER and MMR (Fig. 137.1).

BER also generates DSB at sites of clustered oxidative DNA damage (Ma et al. 2009). Indeed, expression of mutant huntingtin not only elevates oxidative stress in cells but also has a direct impact on repair of DNA breaks. Mutant huntingtin directly interacts with Ku70, a protein involved in nonhomologous end-joining (NHEJ) DNA repair (Enokido et al. 2010). Moreover, overexpression of Ku70 suppresses toxicity in R6/2 mice (Enokido et al. 2010) and in fly models for HD (Tamura et al. 2011). Presumably, the beneficial effects of Ku70 act at the level of DNA. Since loss of DNA-PKcs, a Ku70 partner in NHEJ, has no effects on CAG expansion in mice (Savouret et al. 2003), accumulation of global nuclear damage rather than an increase in expansion per se is likely to contribute to the beneficial effects of Ku70 overexpression. DSB signal cell cycle checkpoints, which slow cell cycling to allow repair of the lesion. Consistent with a repair defect, expression of polyQ-expanded proteins activates ataxia telangiectasia-mutated kinase (ATM) and Rad3-related kinase (ATR) double-strand DNA break response proteins in fibroblasts from HD and SCA2 patients (Giuliano et al. 2003), and expanded CAG/CTG triggers a cell cycle check point in yeast (Sundararajan and Freudenreich 2011). ATR is most widely considered to be a marker of replication stress, while ATM is activated in part by double-strand breaks.

Transcription-coupled repair (TCR), a subpathway of nucleotide excision repair (NER), is important to lesion repair in actively transcribed genes (Hanawalt and Spivak 2008). TCR and NER differ primarily at the damage recognition step but

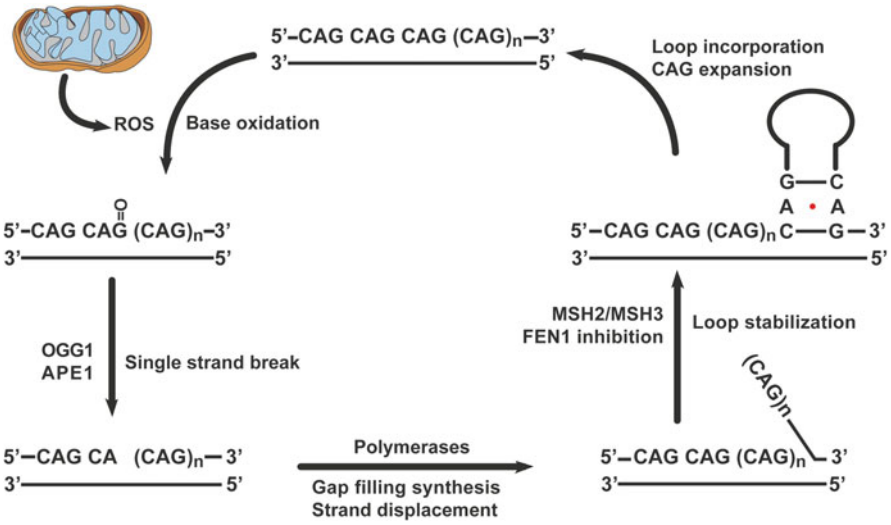

Fig. 137.1 Proposed model for the mechanism of repeat expansion based on oxidized bases, BER and MMR. Mitochondria are the principal sources of reactive oxygen species (*ROS*) contributing to nuclear DNA lesions such as the oxidation of guanine (*G=O*). Base excision repair (*BER*) is the mechanism mostly responsible for repairing oxidative lesions. In BER, participation of the DNA glycosylase OGG1 and the apurinic/apyrimidinic endonuclease 1 (*APE1*) generates a single-strand break and a 3′ hydroxyl group suitable for DNA synthesis by a polymerase, respectively. During the gap-filling synthesis, the trinucleotide repeat (*CAG*)n strand is displaced and forms a hairpin structure or loop. Binding of the mismatch repair (*MMR*) protein complex MSH2/MSH3 to the A-A mismatched bases (*red dot* in hairpin) stabilizes the repetitive hairpin loop, thereby preventing flap endonuclease 1 (*FEN1*) excision and removal. The hairpin DNA is incorporated into the duplex DNA, and CAG expansion occurs generating a "toxic oxidation cycle" in which the expanded DNA is subjected again to oxidation

share downstream machinery. Loss of the NER recognition protein XPC in mice has no impact on the CAG expansion in mice (Dragileva et al. 2009), suggesting that TCR may be more important pathway leading to instability at repetitive tracts. Loss of Cockayne's syndrome protein B (CSB) and XPG in human cells (Lin and Wilson 2007) and in flies (Jung and Bonini 2007) generates CAG instability of repeats, most often deletions. Interestingly, loss of CSB in mice has a protective effect on instability in germ cells of HD/CSB(−/−) mice and suppresses expansion in somatic cells (Kovtun et al. 2011). However, in none of these cases, there is evidence that the instability arises directly from TCR-dependent removal of oxidative DNA damage. Given that multiple pathways operate at distinct types of DNA lesions in different models, better defining the mechanisms for removal of oxidized bases from DNA will be an important future direction.

Emerging evidence implicates oxidative DNA damage in loss of mtDNA. Indeed, hydrogen peroxide causes loss of mtDNA accompanied by impairment of mitochondrial function (Furda et al. 2012). Conversely, treatment with an oxygen radical scavenger in vitro improves function in isolated mitochondria from HD

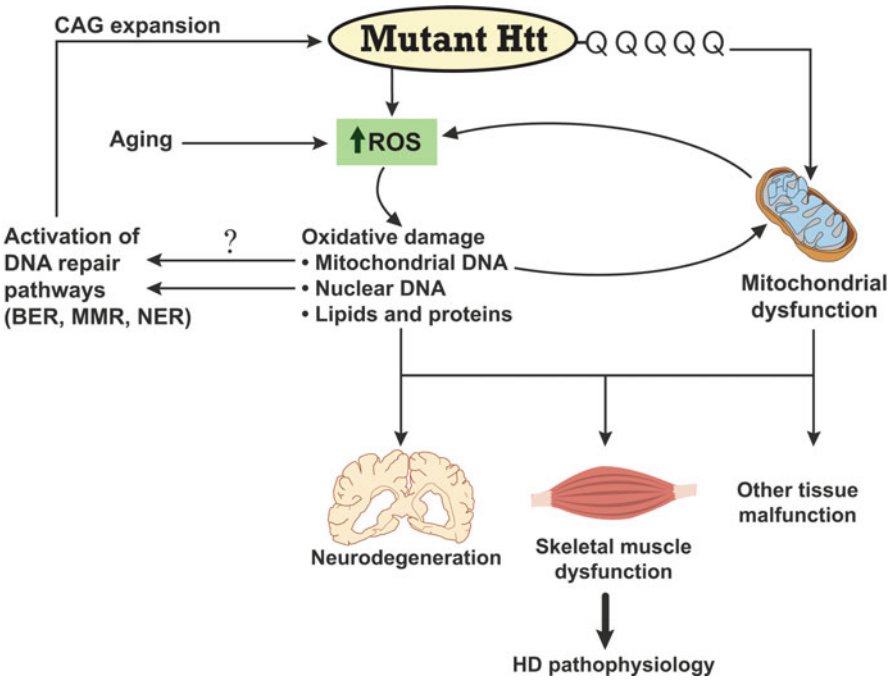

Fig. 137.2 Proposed model of oxidative damage and mitochondrial dysfunction in brain and muscle in HD. Oxidative damage in the form of modified DNA bases, strand breaks, and abasic sites may contribute to the toxic effects of mutant huntingtin in brain and muscle by leading to increased DNA instability in both the mitochondrial and nuclear genomes that in turn results in defective mitochondrial function and HD pathology. Mitochondrial dysfunction exacerbates oxidative damage to DNA, lipids, and proteins ultimately leading to HD pathophysiology. The activation of repair processes in response to oxidative DNA damage may lead to increases in the length of the CAG repeat expansion in nDNA

animals and restores the mtDNA copy number in an HD animal model to 90 % that of controls (Xun et al. 2012). Collectively, these findings imply that oxidative damage has profound effects on mitochondria structure and function.

In muscle, the activity of mitochondrial BER enzymes decreases in an age-dependent fashion in BALB/c mice, and the activity of both nuclear and mitochondrial BER enzymes is significantly lower compared to other tissues of the same mice (Szczesny et al. 2010). The observed defects in mitochondrial respiration suggest that repair of oxidative DNA damage and other pathways may correct consequent DNA breaks in mtDNA. Whatever the detailed mechanisms, collectively, DNA strand breaks are likely to contribute to the toxic effects of mutant huntingtin in both brain and muscle by increasing DNA instability in both nDNA and in mtDNA. We propose a model in which mutant huntingtin-induced ROS generation and oxidative damage to mtDNA, nDNA, lipids, and proteins may result in mitochondrial dysfunction and HD pathology (Fig. 137.2).

Conclusion

The observed defects in mitochondrial respiration suggest that oxidative DNA damage may contribute to the toxic effects of mutant huntingtin in both brain and muscle. The effects of oxidative damage in the brain are well documented. The relevance of oxidative stress to the HD phenotype in skeletal muscle remains more speculative. However, the prominent mitochondrial dysfunction observed in HD muscle and the susceptibility of aging muscle to oxidative stress strongly point to the possibility that ROS are involved in motor decline and muscular degeneration that occurs in HD. Mitochondrial dysfunction is observed in both brain and skeletal muscle in HD, providing a source for elevated oxidative damage to lipids, proteins, and to DNA. Thus, decreasing the oxidative damage due to mitochondrial respiration may be beneficial as a therapeutic approach for HD. Moreover, the importance of the peripheral changes in HD indicates that therapy should target not only the brain but also other important tissues like skeletal muscle. Muscle is more accessible than brain tissue, and alterations in the peripheral tissues like skeletal muscle may provide a useful biomarker for HD.

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