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Mitochondrial functional alterations in relation to pathophysiology of Huntington's disease

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Abstract Huntington's disease (HD) is an autosomal dominant neurodegenerative disease which is characterized by psychiatric symptoms, involuntary choreiform movements and dementia with maximum degeneration occurring in striatum and cerebral cortex. Several studies implicate mitochondrial dysfunction to the selective neurodegeneration happening in this disorder. Calcium buffering imbalance and oxidative stress in the mitochondria, critically impaired movement across axons and abnormal fission or fusion of this organelle in the cells are some of the salient features that results in the loss of mitochondrial electron transport chain (ETC) complex function in HD. Although several models involving mutant huntingtin, excitotoxins and mitochondrial complex-II inhibitors have been used to explore the disease, it is not clear how disturbances in mitochondrial functioning is associated with such selective neurodegeneration, or in the expression of huntingtonian phenotypes in animals or man. We have carefully assessed various mitochondrial abnormalities observed in human patient samples, postmortem HD brains, cellular, vertebrate and invertebrate models of the disease, to conclude that ETC dysfunction is an integral part of the disease and justify a causal role of mitochondrial ETC dysfunction for the genesis of this disorder

Keywords Mutant Huntington · Oxidative stress · Mitochondrial membrane potential · Electron transport chain · Calcium imbalance · Mitochondrial trafficking · Contribution of dopamine

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Huntington's disease (HD) is a progressive neurodegenerative disease inherited in an autosomal dominant manner. The disease is caused due to an expansion of an unstable trinucleotide CAG repeat region which codes for polyglutamines (polyQ) and occurs within the first exon of the gene "*IT 15*" in HD patients (The Huntington's Disease Collaborative Research Group 1993). The glutamine tract in the mutant huntingtin (mhtt) is polymorphic, with 8 to 37 glutamine repeats in the normal population and 41 or more in HD (Rubinsztein et al. 1996). Several brain areas show signs of neuropathology in HD, with the maximum degeneration occurring in the nuclei of caudate and putamen and in cerebral cortex (Vonsattel et al. 1985).

Reports available in literature reveal affection of various aspects of mitochondrial function in HD. Brain imaging of HD patients showed defects in energy metabolism, indicating mitochondrial abnormalities in the brain (Koroshetz et al. 1997; Powers et al. 2007). The mhtt has been shown to directly interact with mitochondrial membranes leading to deficits in the normal functioning of the organelle (Panov et al. 2002; Choo et al. 2004). Huntington (htt) is expressed in brain and other tissues (Strong et al. 1993). Several studies conducted on peripheral tissues of patients, including platelets (Parker et al. 1990), lymphocytes (Sawa et al. 1999) and muscles (Arenas et al. 1998; Turner et al. 2007), showed mhtt to be linked to mitochondrial abnormalities.

Besides, mitochondrial electron transport chain (ETC) inhibitors such as 3-nitropropionic acid (3-NP) and malonate have been shown to reproduce neuropathological features of HD in rodents and primates (Beal et al. 1993; Brouillet et al. 1995; Pandey et al. 2008).

Intense research over years carried out in different models of HD as well as studies from HD patients have produced voluminous data, yet it is a challenge to decipher an active role of mitochondria in the pathophysiology of the disease. The greater involvement of this cytoplasmic organelle in other neurodegenerative diseases has also spurred research for understanding its diverse roles in different aspects of cell malfunctioning in HD. In the present review a critical assessment is made on the roles of mitochondria and its dysfunction in relation to HD pathogenesis based on the accumulated findings in HD patients as well as in cellular and animal models of the disease. Various models made available for the disease research is provided in Table 1.

Loss of mitochondrial ETC enzyme activities

Neurons in the brain have large demands of energy in the form of ATP to carry out their general functions. Decrease in activities of mitochondrial ETC enzymes can lead to energy crisis in the brain resulting in altered vital neural metabolism leading to neurodegeneration. Consistent decreases in mitochondrial complex-II/III activities have been reported in nuclei of caudate and putamen of the postmortem brain (Gu et al. 1996; Browne et al. 1997) and in lymphoblasts of HD patients (Sawa et al. 1999). It has been reported that two subunits of complex-II, the 30-kDa iron sulphur (Ip) and the 70-kDa FAD (Fp) subunits were selectively decreased in postmortem HD striatum, but not in the cerebellum or the cerebral cortex as compared to control tissues (Benchoua et al. 2006). Primary striatal cultures when infected with lentiviral vector containing N-terminal fragment (171 amino acids) of human htt having 82 polyQ repeats were found to have similar decreases in the Ip and Fp complex-II subunits as compared to 19 polyQ repeats (Benchoua et al. 2006). The striatal cells expressing 82 polyQ repeats exhibited increased toxicity in terms of decreased mitochondrial membrane potential and cell death which could be prevented by the overexpresion of the Ip and Fp subunits. They also found that there was no decrease in the expression of RNA of these subunits indicating that mhtt was able to affect these subunits at the protein level (Benchoua et al. 2006). In a follow up study, Benchoua et al. (2008) reported that dopamine (DA), a neurotransmitter found in high concentrations in striatum could lead to a decrease in mRNA transcripts of complex-II in striatal cell cultures. Additionally they found a synergistic decrease in succinate dehydrogenase activity along with reduced expression of the Ip and Fp subunits when such cultures expressing N terminal mhtt containing

Table 1 Different models of HD

Model	Form of huntingtin	References
Cell line(s)	Full length of mhtt, polyQ only, Exon1 containing polyQ repeats	Lunkes and Mandel (1998); Jana et al. (2001)
Striatal cell culture	Full length of mhtt	Hunter et al. (2007)
Lymphoblasts	Wild type and mhtt	Panov et al. (2002)
Yeast (*Saccharomyces cerevisiae*)	mhtt	Krobitsch and Lindquist (2000)
Nematode (*Caenorhabditis elegans*)	Exon 1 of human htt	Bates et al. (2006)
Fruit fly (*Drosophila* sps)	N terminal of mhtt	Gunawardena et al. (2003)
R6 transgenic line in mice	N terminal of exon 1 human htt, Larger N terminal (N171-82Q)	Mangiarini et al. (1996) Schilling et al. (1999)
HD line in mice	1 kb of human htt	Laforet et al. (2001)
	Full length of human htt	Reddy et al. (1998)
Yeast artificial chromosome model in mice	Full length human htt	Hodgson et al. (1999)
Knock in mouse	Mutated mouse htt, htt exon 1 of mouse replaced by mhtt exon 1 of human	Shelbourne et al. (1999); Levine et al. (1999)
Excitotoxin models in rats: Kainic acid, Quinolinic acid,		Beal et al. (1986); McGeer and McGeer (1976)
Mitochondrial complex-II inhibitors in rats: malonate, 3-nitropropionic acid.		Beal et al. (1993)
Mitochondrial complex-II inhibitors in Baboons *(Papio anubis)*		Brouillet et al. (1995)
Transgenic model in monkey (*Macaca* sps)	human mhtt exon 1	Yang et al. (2008)

82 polyQ repeats were exposed to DA. Several other studies reported the involvement of DA in striatal neurodegeneration (Reynolds et al. 1998; Charvin et al. 2005). In an analogous situation, we reported a synergistic increase in cytotoxic hydroxyl radical (.OH) generation in vitro in the rat cerebral mitochondria, and in vivo in the striatum when exposed to mitochondrial complex-II inhibitor, 3-NP and DA that led to huntingtonian phenotypes and striatal neurodegeneration in the rodent (Pandey et al. 2009).

While mitochondrial complex-I defects in HD was known for some time, mitochondrial complex-I deficit was first reported in platelets isolated from HD patients in 1990 (Parker et al. 1990), and thereafter in HD muscle (Arenas et al. 1998). However, several studies that followed could not reproduce such deficit in postmortem HD brains (Gu et al. 1996; Browne et al. 1997), or in HD patients' platelets (Powers et al. 2007), muscles (Turner et al. 2007), and lymphocytes (Sawa et al. 1999). Interestingly, a relatively recent study revealed significant decreases in mitochondrial complex-I activity in postmortem caudate nuclei of individuals at the early stages of the disease (Weydt et al. 2006), signifying a causative role for mitochondrial ETC complex activity in HD pathology. Contrary to this report, presymptomatic grade 1 postmortem HD brains and HD transgenic mice did not show significant alterations in mitochondrial ETC activities, but late stage HD postmortem brains revealed crucial changes in complex-I–IV enzyme activities suggesting mitochondrial perturbations as a consequence, but not a cause in HD phenotype (Guidetti et al. 2001).

A study employing the 3-NP model of HD in rats, administration of coenzyme Q_{10} (an important component of ETC) in combination with an antioxidant, vitamin E did not show any protective effects in the brain mitochondria when analyzed polarographically for complex-I linked state-3 respiration (Kasparová et al. 2006). However, we found a significant decrease in mitochondrial complex-I activity and defects in complex-I linked state-3 respiration in the 3-NP model of HD in rats, but with no changes in the expression of complex-I subunits, ND5 and ND6 (Pandey et al. 2008). In the R6/2 transgenic model of HD it has been reported that the mitochondrial complex-I was severely affected, where the expression of mitochondrial ND5 and ND6 subunits were decreased due to disruption of mitochondrial cyclic AMP (cAMP) response element binding (CREB) protein (Lee et al. 2005), which confirmed the earlier report that cAMP concentrations were significantly decreased in post-mortem HD brains as compared to age matched controls (Gines et al. 2003).

To understand the root cause of the mitochondrial functional deficiency in HD, Hdh Q111 knock-in mice having 109 polyQ repeats in murine huntingtin to 111 amino acid residues were used for comparing them to wild type littermates Hdh Q7 and found reduced CREB signaling and cAMP levels in cerebral cortex and the striatum of the mutant mice (Gines et al. 2003). They also found decreased mitochondrial respiratory activity and loss in ATP levels, a substrate for adenyl cyclase. These changes could be observed almost 6 months prior to formation of amino terminal aggregates and intranuclear inclusion which led to reactive gliosis and neuronal death. The study suggested that selective mitochondrial impairment due to mhtt precedes neuropathological and clinical symptoms in HD. In another study, intrastriatal administration of quinolinic acid in rat brain led to decreased expression of active phosphorylated CREB in parvalbumin and calretinin-positive striatal interneurons, which are known to be affected in HD, emphasizing the role of a defective CREB mediated energy crisis in HD (Giampà et al. 2006).

Decreased expression of the transcription factor coactivator peroxisome proliferator activator receptor (PGC)–1α was found in both transgenic N171-82Q HD mice, as well as in postmortem HD brains (Weydt et al. 2006). PGC-1α is a transcriptional coactivator that regulates several metabolic processes including mitochondrial biogenesis and oxidative phosphorylation (Puigserver and Spiegelman 2003). PGC-1α promoter has been shown to associate with mhtt, and to interfere with the CREB/TAF4 dependent transcriptional pathway, which is important for PGC-1α expression (Cui et al. 2006). Cross breeding of PGC-1α knock out with mhtt knock in mouse led to increased degeneration of striatal neurons and increased motor deficits in the animals (Cui et al. 2006). This underscored the importance of PGC-1α in striatal mitochondrial function, and its direct relation to expression of huntingtonian phenotypes. A recent report that PGC-1α levels were found to be reduced in muscles of HD patients and in transgenic HD mice NLS N171-82 Q containing 82 polyQ repeats as compared to wild type littermates confirmed the active involvement of this transcriptional coactivator in HD pathology (Chaturvedi et al. 2009).

Fukui and Moraes (2007) found that human osteosarcoma 143B cells or neuronal progenitor RN33B cells expressing mhtt had a lower complex-III, higher complex-IV activity and mhtt aggregate formation due to proteasomal inhibition as compared to cells expressing wild type htt. Pharmacological inhibition of complex-III by its blocker antimycin A also led to significant mhtt aggregation as compared to inhibition of complex-I by rotenone or complex-IV blockade by KCN. Moreover, treatment of these cells with antioxidants N-acetyl cysteine or resveratrol failed to reduce any aggregate formation ruling out the involvement of reactive oxygen species in decreased proteasomal activity.

Mitochondrial cytochrome c oxidase activity was found to be decreased in HD putamen (Brennan et al. 1985;

Browne et al. 1997), and the mRNA expression of cytochrome oxidase I subunit has been shown to be lower in postmortem HD striatum and globus pallidus, compared to age-matched controls (Gourfinkel-An et al. 2002). Similar observations were made in the brain of rats made huntingtonian by the treatment of 3-NP (Bizat et al. 2003a, b; Pandey et al. 2008). Recently, Singh et al. (2009) reported an increase in the activity of cytochrome c oxidase isoform IV-2 at the expense of increased mitochondrial peroxide production, resulting in astrocytes demise. However, no significant alterations were reported in complex-IV mediated mitochondrial respiration using TMPD/ascorbate substrates in striatal cells containing htt with polyQ111 and polyQ7 repeats (Milakovic and Johnson 2005). Although no significant alterations in mitochondrial ETC activities were found in early stage postmortem HD brains, late stage postmortem HD brains revealed significant changes in complex-I to complex-IV enzyme activities (Guidetti et al. 2001), which implied no causal role for mitochondrial ETC complex dysfunction in the pathogenesis of HD.

Mitochondrial genome encodes for a total of thirteen subunits of ETC enzymes and alterations in their expression patterns, deletions or mutations in the mitochondrial DNA may lead to abnormal ETC activities causing free radical generation and cell death, as shown in other neurodegenerative diseases such as Parkinson's disease (Borland et al. 2009). Mitochondrial DNA damage due to oxidative stress has been observed in parietal cortex of postmortem HD brains (Polidori et al. 1999), and in the striata and cerebral cortices of transgenic R6/2 and 3-NP models of HD (Bogdanov et al. 2001; Acevedo-Torres et al. 2009). In a study employing cybrid cell lines from HD patients' platelets, Swerdlow et al. (1999) have reported normal ETC activities, oxidative stress and calcium homeostasis as compared to human control cybrids. Interestingly, a recent study reported heightened vulnerability to 3-NP induced oxidative stress, mitochondrial cytochrome c release and expression of apoptosis inducing factor and cell death in HD cybrids as compared to control cybrids (Ferreira et al. 2010). This suggested loss of mitochondrial ETC complex activity as a prerequisite for neuronal death in HD.

Mitochondrial aconitase, an enzyme sensitive to superoxide generation, and which aids in the generation of this free radical (Vasquez-Vivar et al. 2000) was found to be inhibited in post-mortem HD brains (Tabrizi et al. 1999; Sorolla et al. 2008). Coenzyme Q_{10}, an important component of ETC complex-I was found to be decreased in serum of HD patients (Andrich et al. 2004), and replenishing this lost cofactor exogenously was shown to decrease cortical lactate concentrations significantly in HD patients (Koroshetz et al. 1997). Interestingly this beneficial effect was momentary and coenzyme Q_{10} dependent, since the lactate levels became reversed to HD values once the therapy was discontinued (Koroshetz et al. 1997).

Studies on the mitochondrial ETC complexes in various cellular and animal models, taken together with the data from presymptomatic and long-term HD patients contributed to a deeper understanding of the mitochondrial involvement in HD neuropathology. However, controversial results in both models of the disease as well as patient data make it difficult to conclude whether mitochondrial ETC deficits, ATP decrease and the consequent abnormal signaling events are causal or effect in nature.

Mitochondrial calcium imbalance

Mitochondria play a vital role in the regulation of intracellular calcium dynamics and act as intracellular calcium sinks. Mitochondrial calcium can alter the energy metabolism directly by modulating the mitochondrial enzymes located in the matrix leading to ATP synthesis or by regulating the cytosolic calcium in turn altering cellular functions which are dependent on cytosolic calcium levels (Brini 2003). Excitable cells like neurons require activation of voltage gated calcium channels, which are major routes for calcium entry into the cell. Cytosolic calcium can also be mobilized from the endoplasmic reticulum (ER), which is another major store of intracellular calcium. Usually inositol-3-phosphate (IP3) signaling helps in the release of calcium from the ER stores. Any deficits in the mitochondrial membrane potential can lead to a decreased uptake of calcium in mitochondria leading to elevated levels of cytosolic calcium. Abnormal signaling of excitatory neurons though NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) or kainate receptors can also lead to increased levels of cytosolic calcium which causes overloading of calcium in cells leading to cytotoxicity.

A decrease in mitochondrial calcium loading capacity and lower mitochondrial membrane potential ($\Delta\Psi m$) were observed in lymphoblasts of HD patients (Panov et al. 2002). Similar defects were also observed in brain mitochondria of transgenic yeast artificial chromosome (YAC) mice expressing mhtt (Panov et al. 2002). Mhtt has been localized to the outer membrane of mitochondria, to interact and to affect the energy metabolism in mutant knock in STHdhQ111/Q111 striatal cells (Panov et al. 2002; Choo et al. 2004). In the STHdh Q111 cells (a juvenile onset HD) htt was associated with decreased ATP formation and ADP uptake in mitochondria, resulting in a lowered ATP/ADP ratio leading to a decrease in NAD^+ linked state 3 respiration. This metabolic decrease was associated with increased calcium influx in the cell that could be blocked by the NMDA antagonist MK-801 (Milakovic et al. 2006). A correlation has been observed

between increased CAG repeat length and increased mitochondrial depolarization in HD lymphoblasts (Sawa et al. 1999). Choo et al. (2004) have demonstrated that the mhtt can directly induce opening of the mitochondrial transition pore (MTP), an effect that could be reduced by blockers, cyclosporin A and ATP. It was demonstrated that mhtt could bring down the threshold levels of calcium required in MTP opening.

Subtle increases in polyglutamine repeats led to earlier swelling of mitochondria when compared to the one with fewer repeats (Choo et al. 2004). Similarly, lower threshold levels of calcium susceptibility to MTP opening was found in liver mitochondria in a CHL2 knock in mouse model of HD. This calcium induced MTP opening led to the release of cytochrome c from mitochondria, which could be blocked by cyclosporin A. A significant decrease in $\Delta\Psi m$, inability to sustain calcium load and increased mitochondrial swelling was apparent in mitochondria from liver or lymphoblasts when incubated with glutathione-S-transferase (GST)–polyglutamine (Q62) fusion proteins as compared to GST-polyglutamine (Q19) or GST alone in vitro (Panov et al. 2002). It has been demonstrated that the first 17 amino acids in the Huntington protein influence its subcellular localization to a great extent (Rockabrand et al. 2007). Using different constructs in a truncated huntingtin (Htt1exp) where the polyglutamine repeats and the flanking polyproline residues were altered, it was found that the first 17 amino acids also control its mitochondrial localization and disrupt the calcium dynamics in PC 12 cells when challenged with glutamate (Rockabrand et al. 2007). The mutant truncated protein was also involved in oxidative stress, proton leakage from the inner mitochondrial membrane and decrease in $\Delta\Psi m$.

Clonal striatal cells expressing mhtt (STHdh Q111/111) when compared to the wild type (STHdh Q7/7) showed decrease in calcium-induced state-3 respiration and in $\Delta\Psi m$ (Milakovic et al. 2006). These mitochondrial calcium loading defects were ameliorated in striatal cells expressing mhtt STHdh Q111 by treatment with the histone deacetylase inhibitors, butyrate or tricostatin A (Oliveira et al. 2006). Striatal neurons expressing mhtt were reported to be more sensitive to increased Ca^{2+} load leading to opening of mitochondrial transition pore as compared to striatal cells expressing wild type huntingtin (Lim et al. 2008). In another important study using the YAC128 mouse model of HD where full length of human htt is expressed containing 128 polyQ repeats, it was found that the mitochondria in the striatal medium spiny neurons had augmented sensitivity to NMDA-induced MPT activation (Fernandes et al. 2007).

Astrocytes are responsible for the energy requirements of neurons as well as to protect them from excitotoxicity by clearing excess excitatory aminoacids from synaptic domains (Maragakis and Rothstein 2001). It has also been shown that mitochondria from striatal astrocytes have lower buffering capacity than cortical astrocytes (Oliveira and Gonçalves 2009). This holds a lot of importance in the selective pathogenicity in HD as the medium spiny neurons, which are most vulnerable in HD (Beal 1994) and constitute 70–80% of the striatal neurons in humans, receive glutamatergic afferents from all areas of neocortex and limbic system (Parent and Hazrati 1995). In an interesting study 3-NP-induced increase in mitochondrial calcium release, reactive oxygen species generation and apoptotic cell death in astrocytes could be blocked by the MTP blocker cyclosporin A (Rosenstock et al. 2004).

Mhtt has been found to be expressed in glial cells (Singhrao et al. 1998; Hebb et al. 1999) and these cells were found to have reduced expression of the glutamate transporter GLT-1 in postmortem HD brain as well as in transgenic R6/2 mice (Shin et al. 2005). In striatal brain slices of R6/2 transgenic mice it was observed that there is a reduced glutamate uptake by GLT-1 receptors that may be due to the reduced expression of these receptors and therefore the neurons may be more vulnerable to glutamate excitotoxicity. Indeed, mitochondrial calcium loading was reduced when challenged with NMDA activation in HD 150 knock-in striatal neurons when compared to wild type Hdh (Oliveira et al. 2007).

The foregoing account on mitochondrial Ca^{2+} handling ability in relation to presence of mhtt in striatal astrocytes, glial cells and neurons suggest that the neurons in this area of the brain displayed decreased ability to clear cytosolic calcium in presence of mhtt. Therefore these neurons were more vulnerable to excitotoxic insults, especially in the context of greater cell death of striatal medium spiny neurons in HD.

Impaired mitochondrial trafficking in neurons

Mitochondrial trafficking is an important event through which the cells take care of their various metabolic energy requirements, and is more important in neurodegenerative diseases when energy crisis and abnormal calcium changes inside the cells demand a major attention from healthy mitochondria to take care of its immediate requirements. This is more relevant in neurons with long axons and dendrites that connect at distant targets. Existing evidences suggest disruption of vesicles and mitochondrial trafficking by mhtt that gets sequestered to vesicular transport proteins (Gunawardena et al. 2003; Qin et al. 2004; Trushina et al. 2004; Li et al. 2010). The polyproline domain adjacent to polyQ domain of htt has been shown to be responsible in sequestering the vesicle transport proteins and thus disrupting the endocytotic process and the transport machinery

(Qin et al. 2004). A more recent report demonstrated mhtt association with microtubule based transport proteins to decrease mitochondrial transport in neurons (Orr et al. 2008). Using differential interference contrast microscopy Trushina et al. (2004) have found that movement of mitochondria was hindered in neurons in HD72 mice when compared to cells expressing normal htt. Mitochondrial mobility was significantly decreased in early embryonic stage to 1 year old HD72 mice, that accompanied with oxidative stress, ATP depletion and lactate accumulation. Mitochondria had a diminished movement in the neurites and their decreased motility correlated with their increased polyglutamine length (Trushina et al. 2004). In a follow up study Chang et al. (2006) reported that mhtt aggregates could block the movement of healthy mitochondria in cortical neurons as well. The possibility of reduced ATP levels due to mhtt leading to a decrease in mitochondrial motility across neurons also holds importance as SH-SY5Y cells treated with the complex-I inhibitor, rotenone, or parkinsonian cybrids had reduced mitochondrial movement across axons as compared to controls (Borland et al. 2008; Trimmer et al. 2009). However, inhibitors of ATP production and transport did not have any effect on mitochondrial mobility in cerebellar granule neurons (Kaasik et al. 2007a, b). Treatment of neurons with mitochondrial ETC inhibitors like sodium azide or antimycin led to swelling of mitochondria in these cells leading to a decreased axonal transport probably due to steric hindrance (Kaasik et al. 2007a, b).

Mitochondrial integrity in HD

Mitochondrial fission and fusion is a balanced process in healthy neurons. Mitochondrial fusion is dependent on two outer-membrane localized proteins Mfn1 and Mfn2, and one inner-membrane localized protein Opa, while its fission is dependent on dynamin-related protein (Drp1) and mitochondrial fission 1 (Fis1) (Reddy et al. 2009). Expression of N terminal of mhtt containing 74 and 138 polyQ repeats in HeLa cells made the mitochondria more vulnerable to oxidative stress-induced mitochondrial fragmentation and had reduced levels of ATP as compared to cells expressing 17 or 28 polyQ repeats (Wang et al. 2009). Overexpression of Drp1 (K38A), a dominant negative mitochondrial fission mutant or Mfn2 decreased the mhtt induced mitochondrial fragmentation. In *Caenorhabditis elegans* model of HD, a reduction in Drp-1 expression has been shown to rescue the motility defect associated with mitochondrial fragmentation (Wang et al. 2009).

It was found that more than 54% of lymphocyte mitochondria from HD patients from homozygous patients had massive ultrastructural derangement of matrix and cristae as compared to controls (Squitieri et al. 2006). Homozygotes had giant mitochondria and heterozygotes had smaller mitochondria with minimum diameter similar to controls. Mitochondrial swelling and volume increase resulting from calcium mediated depolarization of $\Delta\Psi m$ (see above; Kaasik et al. 2007a, b), could also lead to impaired movement of mitochondria in neurites (Safiulina et al. 2006). A recent study by Liot et al. (2009) reported glutamate-mediated profound mitochondrial fission and changes in mitochondrial morphology from filamentous to punctate nature as visualized by quantitative fluorescence time-lapse microscopy in a 3-NP model of HD. This information tempt to suggest that the HD pathology resulting from mhtt aggregation definitely has a direct link to morphologically disfigured mitochondria.

Dopamine and oxidative stress

While mitochondria are a major source of oxidative stress, it is also a victim of such insults. Experimental evidences suggest that DA-induced oxidative stress has a major role in striatal neuronal death in HD. DA is metabolized by the mitochondrial enzyme monoamine oxidase B into DOPAC and H_2O_2. The production of H_2O_2 can lead to generation of highly toxic $^{\bullet}OH$ radicals through Fenton reaction (Halliwell 1992), which render the striatal area extremely vulnerable to free radical insult. DA and its oxidative metabolites including hydroxylated catecholes (Borah and Mohanakumar 2009, 2010) have been found to cause degeneration of dopaminergic neurons.

A direct evidence for DA involvement in the pathophysiology of HD stems from striking resemblance to HD symptoms of the phenotypes exhibited by DA transporter knock-out mice (Cyr et al. 2003). Excessive DA metabolism in the striatum has been found to enhance free radical generation in the presence of decreased ETC complex activities leading to behavioral abnormalities akin to HD and striatal neurodegeneration (Pandey et al. 2009). In this animal model, depletion of DA by pharmacological means (Pandey et al. 2009) or by denervation (Reynolds et al. 1998) has been shown to protect against the neurotoxin-induced neurodegeneration, aid to support the notion of neurotransmitter involvement in HD pathogenesis.

Excessive reactive oxygen species generation following distorted mitochondrial oxidative phosphorylation resulting from multiple disruptions in relation to altered $\Delta\Psi m$, calcium dynamics in this organelle and their changes in morphology and trafficking could ultimately result in severe oxidative stress. This in turn has been shown to decrease proteasomal activity, thereby enhancing mhtt aggregation and cell death (Goswami et al. 2006). Several of these oxidative stress markers (listed in Table 2) have

Table 2 Levels of oxidative stress markers in HD patients

Oxidative stress markers in HD patients	Changes	Reference
8-hydroxy-2-deoxyguanosine in mitochondrial DNA of parietal cortex	Increased	Polidori et al. (1999)
Catalase activity in skin fibroblast cultures	Decreased	del Hoyo et al. (2006)
Serum 8-hydroxy-2-deoxyguanosine	Increased	Hersch et al. (2006)
(a) plasma lipid peroxidation	Increased	Klepac et al. (2007)
(b) reduced glutathione levels	Decreased	
(a) leucocyte 8-hydroxy-2-deoxyguanosine	Increased	Chen et al. (2007)
(b) plasma malondialdehyde	Increased	
(c) erythrocyte Cu-Zn Superoxide dismutase	Decreased	
(d) erythrocyte glutathione peroxidase	Decreased	
(a) protein carbonylation in brain striatum	Increased	Sorolla et al. (2008)
(b) peroxiredoxin 1, 2 and 6 activities in brain striatum	Increased	
(c) catalase and superoxide dismutase in brain striatum	Increased	
(d) glial fibrillary acidic protein levels in brain striatum	Increased	
(e) aconitase in brain striatum	Decreased	
(a) plasma lipid peroxides	Increased	Duran et al. (2010)
(b) lipid lactate concentration	Increased	

been found to be altered in the HD brain and peripheral tissues suggesting mitochondria regulated free radical generation and oxidative stress may have a major role in striatal neurodegeneration.

Mitochondria and apoptosis

Postmortem HD brains (Grade 1–4) were found to have cells undergoing apoptosis in the striata when analyzed by Tdt-mediated dUTP-biotin nick end labeling (TUNEL) technique (Thomas et al. 1995). This finding strengthened a concept of apoptotic mode of cell death in this disease, as known in other neurodegenerative diseases such as Parkinson's disease (Banerjee et al. 2007). Mitochondria contain several proteins whose relocation and/or activation are critical for cell survival or death. Release of cytochrome c, an important part of the ETC has been shown to regulate apoptosis in cells by the activation of a series of cysteine proteases, the caspases. Release of apoptosis inducing factor from mitochondria has also been shown to induce the activation of caspases leading to cell death in HD (Almeida et al. 2006). Western blot analyses of cytochrome c, and caspase 9 expression and distribution revealed an increased distribution of cytochrome c in the cytosol when compared to that in mitochondria in the striatum of HD brain and in a transgenic (R6/2) mouse model of HD (Kiechle et al. 2002). Inhibitors of cytochrome c and mitochondrial transition pore blockers have been demonstrated to have therapeutic potential in cell culture and transgenic rodent model of HD (Wang et al. 2008).

Conversely, significant activation of calpains in the HD brain has been reported, and N terminal mhtt has been shown to be a substrate of calpain in HD brains (Gafni and Ellerby. 2002). Supporting this idea, both calpains and caspases have been shown to be activated in HD models (Bizat et al. 2003a, b), probably resulting from the loss of calcium homeostasis in neurons due to a decrease in calcium buffering by mitochondria in HD brains (see above). Moreover, htt is an antiapoptotic protein (Rigamonti et al. 2001; Luo and Rubinsztein 2009) and its cleavage by calpain can make the brain vulnerable to toxic insult. Targeted mutation of calpain cleavage sites in htt led to neuroprotection (Gafni et al. 2004), which suggested calpain activation in HD brain may have a major role in pathophysiology of HD.

Conclusion

It is clear from several studies that mhtt causes multiple deficits in mitochondrial function which in turn lead to a cascade of cellular events resulting in neuronal death in HD. In one way the mutant protein leads to MTP activation by directly interacting with this organelle. On the other hand it causes transcriptional dysregulation leading to decreases in several regulatory proteins, which have important functions in mitochondria. Results from various models of the disease and postmortem HD brain samples provided great advantages to us to predict presymptomatic and late stage disease events involved in neuropathology of this neurodegenerative disease.

It has been assessed that not all the models involving mhtt exhibit coherence in terms of mitochondrial abnormalities, behavioral and neuropathological deficits. Interestingly, most of the findings in different models of HD

support the fact that normal mitochondrial function is severely compromised in numerous ways in the brain as well as several other tissues in HD. It is also evident from some of these studies that the severity of mitochondrial abnormalities correlates with increasing number of polyQ repeats in mhtt, suggesting mitochondria as a major target of the mutant protein which in turn over a period of time becomes more susceptible to various toxic stimuli in discrete brain areas. Further focused studies on mitochondria in various models at different stages of the disease could render unequivocal evidences for delineating this organelle's involvement in HD neuropathology. For the purpose it is imperative for all the animal models to have a graded system depending on the behavioral and neuropathological deficits which correlates to the HD neuropathological grading system to understand the molecular events in the disease models in human disease perspectives.

Considering the various roles mitochondria play in regular neural function and the multiple ways the cells regulate to keep this proper functioning of the organelle, it is quite possible that one may not have a single target in the mitochondria to prevent mitochondrial dysfunction mediated neurodegeneration in HD. Therefore the focus of study henceforth might be on to understand the upstream events in mitochondrial functional regulation that are affected by mhtt, which could possibly narrow down the drug targets to be more specific and effective in blocking or controlling the neural cell death that lead to HD. The information that other regions of the brain are not affected to a great deal in HD as compared to striata or cerebral cortices shall be used in future research to our advantage for understanding the 'protective phenomenon' in these 'privileged' regions of the brain. Of course parallel investigations in different models of the disease, and studies on the patients' samples and postmortem brains could lead to a better understanding of the relevance of mitochondrial functioning in striatocortical neurodegeneration as seen in HD.

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