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Mitochondrial matters of the brain: the role in Huntington's disease

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Abstract Even before the discovery of the mutant *htt* gene as the cause of Huntington's Disease (HD), abnormal energy metabolism and mitochondrial dysfunction had been suggested as a possible pathogenic mechanism in HD. These initial investigations described defects in energy metabolism using Positron Emission Tomography (PET) and Nuclear Magnetic Resonance (NMR) Spectroscopy in symptomatic and pre-symptomatic HD patients. Concurrently, 3-nitroproprionic acid, a mitochondrial complex II inhibitor, was found to replicate many of the pathological and clinical features of HD when administered to animals. Subsequently, reductions in mitochondrial respiratory chain enzyme activities in HD brain and muscle, HD mice models and cellular HD models were discovered and confirmed impaired mitochondrial function as an important component of pathogenesis. A unifying hypothesis linking chronic ATP depletion, oxidative stress and mitochondrial dysfunction culminated in the "slow excitotoxic theory" of HD pathogenesis. More recently, the localization of mutant htt within mitochondria and the association between transcriptional dysregulation caused by impaired PGC-1α activity with abnormal mitochondrial biogenesis and function has provided further links with additional potential pathogenic mechanisms.

Keywords Huntington's Disease · Mitochondria · PGC-1α · Oxidative stress · Excitotoxicity

This review will briefly summarise the evidence for mitochondrial dysfunction in HD and how this may affect strategies for future treatments.

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Introduction

Huntington's Disease (HD) is caused by an expansion in the CAG repeats of the huntingtin gene(*htt*) on chromosome 4. *Htt* encodes for a ubiquitously expressed 348 kDa protein called huntingtin(htt). HD is associated with a progressive movement disorder with dementia and is predominantly associated with degeneration of striatal and cortical neurons. Mutant htt forms intranuclear and cytoplasmic N-terminal htt inclusions. There are several postulated mechanisms by which mutant htt may cause neurodegeneration including toxicity of htt aggregates, transcriptional dysregulation, defective cellular transport, excess free radical formation and mitochondrial dysfunction. This review will summarize the main findings linking mitochondrial dysfunction to HD and how this may be translated into potential therapies.

The mitochondrial hypothesis in neurodegeneration

Mitochondria are subcellular organelles in eukaryotic cells which have several roles in maintaining cellular homeostasis, such as transient storage of intracellular calcium, fatty acid oxidation, the Kreb's cycle and iron metabolism (McBride et al. 2006 for review). Mitochondria also have a key role in the regulation of apoptosis (Dejean et al. 2006

for review). One of the most important roles of mitochondria is to catalyze the phosphorylation of the majority of cellular adenosine diphosphate (ADP) to adenosine triphosphate (ATP). Neurons require a high level of ATP production to maintain ionic homeostasis. The mitochondrial hypothesis in neurodegeneration postulates that defects in mitochondrial metabolism may lead to chronic mitochondrial dysfunction and eventually to depletion of cellular ATP, increased free radical generation, calcium dysregulation and potentially, defective mitochondrial fission/fusion. (Schapira 2006). It is notable that disorders of mitochondrial function caused by mutations in mitochondrial DNA, mitochondrial proteins or the presence of mitochondrial inhibitors have a role in several neurodegenerative diseases (Morgan-Hughes et al. 1988; Schapira et al. 1988; Owen et al. 1996).

Imaging energetic defects

^{18}Fluoro-deoxyglucose positron emission tomography (PET) studies in symptomatic HD patients have demonstrated a defect in energy utilization in HD striatum and cortex (Kuwert et al. 1990; Martin et al. 1992) and in the striatum in pre-symptomatic HD patients (Grafton et al. 1990; Kuwert et al. 1993). ^{1}H Nuclear magnetic resonance (NMR) spectroscopy demonstrated elevated lactate levels in the occipital cortex (Jenkins et al. 1993), frontal cortex and striatum of symptomatic and some pre-symptomatic HD patients (Harms et al. 1997; Jenkins et al. 1998). The levels of lactate correlated with the length of the CAG repeats and disease duration which suggested a relation between disease severity and abnormal energy metabolism. The striatal levels of N-acetyl aspartate (NAA), a putative neuronal marker, was also reduced and choline (Ch), a putative glial marker, was elevated. This suggested that there was striatal neurodegeneration and gliosis in regions of elevated lactate formation and therefore a greater dependence on anaerobic metabolism (Martin et al. 1996; Sanchez-Pernaute et al. 1999). The absence of a reduction in the NAA/Ch ratio in pre-symptomatic HD patients in spite of an elevation in lactate levels, suggested that defects in energy metabolism occurred before gross neuronal loss and before phenotypic expression (Harms et al. 1997). NMR spectroscopy has also demonstrated a more widespread defect in energy metabolism in symptomatic and pre-symptomatic HD patient's skeletal muscle (Koroshetz et al. 1997; Lodi et al. 2000).

Mitochondrial respiratory chain function in HD tissues

The major studies of oxidative phosphorylation in HD are shown in Table 1. The more recent studies have demonstrated a consistent defect in mitochondrial complex II/III activity and to a lesser extent complex IV activity in regions associated with significant neurodegeneration. In addition, the abnormalities found in HD lymphoblasts and muscle (Turner et al. 2007) have suggested that expression of mutant huntingtin outside the CNS, also induces a mitochondrial respiratory chain defect.

Mitochondrial dysfunction and the R6/2 mouse

The R6/2 HD transgenic mouse model exhibited progressive neurological disease from 2 months of age and both the light microscopic and ultrastructural pathology were similar to those seen in the HD brain. These neuropathological features occur approximately 4 weeks prior to a progressive movement disorder and muscle wasting, and 10 weeks before neuronal cell death in selected brain regions. This suggested that, in this model at least, neuronal dysfunction is responsible for the initial phenotype rather than cell death. A reduction in complex IV in the striatum and cerebral cortex of 12 week old R6/2 mice and a reduction in aconitase in the striatum have been described (Tabrizi et al. 2000). These changes were associated with increased immunostaining for inducible nitric oxide synthase (iNOS) and nitrotyrosine (a marker of increased peroxynitrate generation) in the mouse brains (Tabrizi et al. 2000). These results suggested that complex IV deficiency and elevated nitric oxide and superoxide radical generation precede neuronal death in the R6/2 mouse and may have contributed to subsequent neurodegeneration. An increase in the lesion size produced by 3-NP in the R6/2 mice and increased striatal 3,4-dihydroxybenzoic acid (a marker of ROS) also support a role for mitochondrial dysfunction and free radical damage in the R6/2 model (Bogdanov et al. 1998).

Mitochondrial respiratory chain dysfunction in cell models of HD

There have been four studies investigating mitochondrial respiratory chain activities in N-terminal htt cell models (Table 2). Wyttenbach et al. (2001), did not find any reduction in respiratory chain activities in their cell model, in contrast to Solans et al (2006) and Fukui and Moraes (2007) who described reductions in complex II/III:CS ratios, and Benchoua et al. (2006) who described a reduction in complex II specific activities (corrected for protein). These models suggested that a reduction in complex II/III activity is a consistent abnormality following early expression of highly truncated and expanded mutant htt.

Table 1 The major studies of oxidative phosphorylation in HD

Respiratory chain defect	Authors
↓ complex II	Stahl et al. 1974, Butterworth et al. 1998
↓ caudate cytochrome oxidase (COX) and cytochrome aa3 (complex IV subunit)	Brennan et al. 1985
↓ caudate complex II/III	Mann et al. 1990
↓ complex I in platelet mitochondria	Parker et al. 1990
↓ caudate complex II/III and IV	Gu et al. 1996, Tabrizi et al. 1999
↓ caudate and putamen complex II/III and putamen complex IV	Browne et al. 1997
↓ skeletal muscle complex I	Arenas et al. 1998
↓ skeletal muscle complex II/III correlated with ↓ UHDRS cognitive subscale	Turner et al. 2007
↑ apoptosis with cyanide (complex IV inhibitor) in HD lymphoblasts	Sawa et al. 1999

3-nitropropionic acid (3-NP): a complex II inhibitor

3-NP is a widely distributed plant and fungal neurotoxin that causes damage to the basal ganglia, hippocampus, spinal tracts and peripheral nerves in animals (Alexi et al. 1998). 3-NP is an irreversible inhibitor of succinate dehydrogenase (SDH) or complex II. Reports from Northern China have suggested that 3-NP caused putaminal necrosis and delayed dystonia and chorea in children who ate mildewed sugar cane (Ludolph et al. 1991). The intrastriatal administration of 3-NP to rats caused neuronal loss in the striatum (Beal et al. 1993a). This neuronal loss was ameliorated by decortication of the rats and suggested that the glutaminergic input from the corticostriatal pathway may be required to cause excitotoxic damage in 3-NP-mediated cell death (Beal et al. 1993a). NMDA receptor antagonists, such as MK-801, also block the toxic effects of 3-NP indicating that mitochondrial respiratory chain dysfunction and impaired energy metabolism may predispose to excitotoxic damage (Beal et al. 1993b). The chronic systemic administration of 3-NP in rats produced an animal model displaying lesions that closely resembled the neuropathological features of HD with selective loss of striatal medium spiny neurons. This suggested that the cell population that was most vulnerable in HD was sensitive to energy impairment (Beal et al. 1993a).

The systemic administration of 3-NP to primates caused spontaneous dystonia and dyskinesia accompanied by lesions in the caudate and putamen on MRI. The histopathology was similar to HD with depletion of calbindin-positive neurons, gliosis, sparing of NADPH-diaphorase neurons, and growth-related proliferative changes in dendrites of spiny neurons (Chyi and Chang 1999). Serial ^{1}H-NMR spectroscopy in 3-NP treated baboons (Dautry et al. 1999) demonstrated a region-selective increase in lactate and progressive decrease in NAA, creatine and choline in the striatum in association with the formation of a lesion in the dorsolateral putamen on T2-weighted MRI. The selective decrease in NAA and creatine in the striatum suggested that there was preferential vulnerability of the striatum to impairment of mitochondrial function by 3-NP. It is postulated that the impairment of mitochondrial function in HD, especially complex II, may therefore cause selective neuronal loss within the basal ganglia in HD patients.

Huntingtin localisation to mitochondria

The direct association of htt with mitochondria was first described by Panov et al. (2002) who demonstrated by electron microscopy that N-terminal MT htt localised to

Table 2 Summary of HD N-terminal cell models and MRC activities

Study	Cell type	Induction	PolyQ (WT/MT)	Htt	Time/hrs	Complex CS ratios in MT clones
Wyttenbach et al. (2001)	PC12	Yes	23/74	Exon 1	18	No difference compared to WT
Solans et al (2006)	Yeast	Yes	25/103	Exon 1	4–6	↓CxII/III CxIV normal
Fukui and Moraes (2007)	143B	Yes	25/103	Exon 1	72	↓CxII/III ↑Cx IV
Benchoua et al. (2006)	Primary rat striatal	No (Constitutive)	19/82	171aa	1008	↓CxII (specific activity)

mitochondria in the brain of an HD transgenic full length htt mouse model. Subsequently, in SH-SY5Y and clonal striatal cells established from "knock-in" HD mice embryos, full length htt was present in the purified mitochondrial fraction and was associated with the outer membrane of mitochondria (Choo et al. 2004). Htt inclusions have been described in association with mitochondria in a rat transgenic model of HD (Petrasch-Parwez et al. 2007). The functional relationship of htt to mitochondria is still uncertain and a direct toxic role of mutant htt on mitochondria has not been excluded.

Oxidative stress in HD

Mitochondria form the majority of intracellular reactive oxygen species (ROS) which are constantly being produced as a byproduct of aerobic metabolism. Complex III and, to a lesser extent complex I, are major sites of generation of ROS (Schapira 1995). Mitochondrial production of free radicals increases when the electron transport chain is inhibited or acquires mutations in mitochondrial DNA (Thomas et al. 1993). There is evidence in vivo and in vitro in HD of free radical damage to DNA (Butterworth et al. 1998; Alam et al. 2000), lipids (Greco et al. 2000; Perez-Severiano et al. 2000). and proteins (Browne et al. 1997; La Fontaine et al. 2000).

Aconitase is an iron-sulphur (FeS) containing enzyme that is involved in the Kreb's cycle and iron homeostasis. Aconitase activity is especially susceptible to inhibition by O_2^- and by the reaction product of O_2^- with $NO^{\cdot}$, peroxynitrate ($ONOO^-$) (Patel et al. 1996). Complexes II and III are also FeS–containing compounds and they are also susceptible to inhibition by free radicals. Aconitase deficiency has been found in HD caudate (92%), putamen (73%) and cortex (48%) but not cerebellum and this deficiency closely followed the pathology in HD (Tabrizi et al. 1999). The pattern of aconitase deficiency and the reductions in complex II/III in HD are therefore consistent with ROS having a role in the pathogenesis of the disease.

Excitotoxicity in HD

Impairment of respiratory chain function can cause a failure of maintenance of ionic gradients and partial depolarisation of the neuronal membrane. This has been shown to lead to a loss of the magnesium -dependent block of the NMDA calcium channel and enable ambient levels of glutamate to activate the receptor (Raymond 2003). This leads to elevated intracellular calcium and causes calcium entry into mitochondria which is linked with opening of the mitochondrial permeability transition pore and cell death (Rizzuto 2001). This unifying cellular mechanism, leading to apoptosis, has been called the "slow excitotoxic theory" (Albin and Greenamyre 1992).

In support of an excitotoxic mechanism in HD, Seong et al. (2005) have reported a relationship between the number of CAG repeats and mitochondrial ATP production. A potentiating effect of mutant htt on NMDA receptor activity has been described as NMDA-evoked currents and NMDA-mediated calcium transients were significantly increased in striatal neurons from YAC72 transgenic HD mice compared with WT controls leading to increased excitotoxicity (Zeron et al. 2002, 2004). Further support for the excitotoxic hypothesis comes from evidence that the striatal injection of NMDA agonists, such as quinolinic acid, into rats and primates produced lesions that closely followed the neurochemical, neuropathological and behavioural changes seen in HD (Cull-Candy et al. 2001). A study on HD post-mortem brain which showed that striatal neurons with high levels of NMDA receptor expression had increased degeneration (Albin et al. 1990). In summary, the slow progressive nature of HD could be explained by an excitotoxic mechanism involving a cycle of energy impairment and oxidative damage initiated by mutant htt. The evidence for an excitotoxic mechanism in HD is mostly indirect and a definitive study demonstrating the proposed sequence of excitotoxic events has not been demonstrated.

Weight loss and HD

HD patients suffer extreme weight loss in spite of an adequate calorific intake. A higher BMI at presentation is associated with slower disease progression (Myers et al. 1991). Weight loss was initially felt to be related to the severity of chorea but there is no relationship between the severity of chorea and energy expenditure (Pratley et al. 2000). Patient's sedentary energy expenditure was proportionately related to the severity of the movement disorder, but total energy expenditure was the same as controls because HD patients tended not to take part in as much voluntary physical activity. It therefore remains uncertain whether the weight loss observed in HD is due to a generalized metabolic defect or other causes as yet to be elucidated.

Transciptional dysregulation: PGC-1α

Transgenic mice lacking PGC-1α, a transcriptional coactivator that regulates several genes involved in mitochondrial biogenesis and respiration, show defects in brown adipose tissue as well as a pattern of neurodegeneration similar to HD (Lin et al. 2002; Leone et al. 2005). Mutant htt may cause disruption of mitochondrial function by

inhibiting expression of PGC-1α and overexpression of PGC-1α reverses the effects of mutant htt in cell models and HD transgenic mice (Cui et al. 2006). This suggests that inhibition of mitochondrial function by htt may occur at an early biosynthetic level.

Mitochondrial trafficking

Mutant htt may disrupt the normal intracellular trafficking and distribution of mitochondria in primary cortical neurons (Chang et al. 2006). In the skeletal muscle of desmin-null mice, failure of locating mitochondria to the correct position within the cell impaired mitochondrial function (Milner et al. 2000). Solans et al. (2006) have proposed that misfolded or aggregated htt can disturb the network of actin cytoskeleton, which in turn leads to the alteration of mitochondrial distribution and an early reduction in complex II/III function.

Treatment of mitochondrial dysfunction in HD

Increasing brain levels of ubiquinone (co-enzyme Q_{10}) theoretically may delay neurodegeneration in HD. Ubiquinone has been demonstrated to protect cultured neurons against glutamate toxicity (Favit et al. 1992). Ubiquinone has anti-oxidant properties (Favit et al. 1992) and protects against malonate and 3-NP-induced striatal lesions in rats (Beal et al. 1994). The oral administration of 600 mg/day of ubiquinone for 30 months significantly reduced occipital cortex lactate levels as measured by ^{1}H MRS in 18 symptomatic HD patients. The levels of lactate returned to pre-treatment values when ubiquinone was stopped and therefore this supported a treatment-related effect (Koroshetz et al. 1997). A randomised placebo-controlled trial of 300 mg twice daily of ubiquinone and 200 mg three times daily of remacemide (a noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist) has been performed (Huntington's Disease Study Group 2001). The primary measure of efficacy was the change in total functional capacity (TFC) of the UHDRS between baseline and following 30 months of treatment or placebo. Neither drug significantly altered the decline in TFC. There was a trend towards slower disease progression (13% decline in TFC) with ubiquinone but remacemide had no clinical benefit. Unfortunately, the trial was designed to identify an approximate 35–40% slowing in functional decline and so smaller benefits would have been missed (Huntington's Disease Study Group 2001). A transgenic mouse model study with the R6/2 and N171-82Q HD mice, has demonstrated a significant benefit from remacemide and ubiquinone on the phenotype and pathology of the mice when treatment was commenced on day 21 following birth (Ferrante et al. 2002). There was an approximately 32 and 17% increase in survival in the R6/2 and N171-82Q mice respectively. Treatment of HD patients may therefore need to occur sooner and for longer before a clinical effect can be observed. It is notable that a combination of ubiquinone and vitamin E has been shown to be beneficial in a clinical trial of Friedreich ataxia patients who have a very similar pattern of mitochondrial defect to HD patients (Cooper et al. 2008; Hart et al. 2005). Creatine has been found to have a protective effect in the R6/2 mouse. Dietary creatine improved survival, slowed the development of brain atrophy and delayed degeneration of striatal neurons and the formation of intranuclear inclusions. The onset of diabetes was also delayed. NMR in these mice demonstrated delayed decreases in NAA and elevated brain creatine concentrations (Matthews et al. 1998; Ferrante et al. 2000). The mechanism causing improvement may involve increasing intracellular energy reserves in order to clear misfolded and/or aggregated MT htt. Subsequently, Tabrizi et al. (2005) have described clinical benefit to some HD patients taking 10 g creatine per day. The results of the CREST-HD trial (a large placebo-controlled double-blind study of 8 g/day creatine in HD) are awaited.

In summary, there is evidence from imaging, post-mortem, animal and in vitro studies of a metabolic defect in association with mutant htt expression and a reduction in mitochondrial respiratory chain activity. The mechanism by which this occurs may involve direct inhibition of the mitochondria by mutant htt or by an indirect effect from other pathological processes such as altered mitochondrial biogenesis, excess free radicals and excitotoxicity. The precise molecular mechanisms involved in causing the metabolic disturbance in HD and the timing of this disturbance in relationship to cell dysfunction and death remain undetermined.

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