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Mitochondria in Huntington's disease

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Abstract

Huntington's disease (HD) is an inherited progressive neurodegenerative disorder associated with involuntary abnormal movements (chorea), cognitive deficits and psychiatric disturbances. The disease is caused by an abnormal expansion of a CAG repeat located in exon 1 of the gene encoding the huntingtin protein (Htt) that confers a toxic function to the protein. The most striking neuropathological change in HD is the preferential loss of medium spiny GABAergic neurons in the striatum. The mechanisms underlying striatal vulnerability in HD are unknown, but compelling evidence suggests that mitochondrial defects may play a central role. Here we review recent findings supporting this hypothesis. Studies investigating the toxic effects of mutant Htt in cell culture or animal models reveal mitochondrial changes including reduction of Ca²⁺ buffering capacity, loss of membrane potential, and decreased expression of oxidative phosphorylation (OXPHOS) enzymes. Striatal neurons may be particularly vulnerable to these defects. One hypothesis is that neurotransmission systems such as dopamine and glutamate exacerbate mitochondrial defects in the striatum. In particular, mitochondrial dysfunction facilitates impaired Ca²⁺ homeostasis linked to the glutamate receptor-mediated excitotoxicity. Also dopamine receptors modulate mutant Htt toxicity, at least in part through regulation of the expression of mitochondrial complex II. All these observations support the hypothesis that mitochondria, acting as "sensors" of the neurochemical environment, play a central role in striatal degeneration in HD.

Key words: Huntington's disease, mitochondria, excitotoxicity, calcium, glutamate, NMDA receptors, dopamine.

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1. Introduction

Basic research has demonstrated that mitochondria are key actors in cell survival by controlling energy metabolism, apoptosis pathways and Ca^{2+} homeostasis [1-4]. The hypothesis that mitochondria could play a role in neurodegenerative diseases arise from the observation that mitochondrial defects and oxidative stress can be detected in biological materials from patients with neurodegenerative conditions. In addition, a number of cell biology experiments demonstrated that mitochondria play an active role in the complex cascade of events leading to cell demise in various models of neurodegenerative disorders [5, 6]. However, the question as how mitochondrial defects could be involved in the region specific pattern of degeneration is unclear. It has been known for a long time that the striatum is extremely sensitive to impairment in energy metabolism. Acute poisoning with mitochondrial toxins (cyanide, sodium azide, 3-NP) are often associated with striatal degeneration in man and laboratory animals [7, 8]. Mitochondrial defects of genetic origins (e.g. mutation or deletion of mitochondrial DNA or nuclear DNA) can lead to striatal degeneration [7]. In Huntington's disease, recent studies have highlighted the particular mechanisms that directly link mitochondrial defects with the preferential vulnerability of the striatum, the brain region which displays the earliest and most striking neuropathological changes in patients.

2. Huntington's disease

2.1. Description

Huntington's disease (HD) is an autosomal dominant inherited neurodegenerative disorder of midlife onset caused by an abnormal expansion of a CAG repeat located in the exon 1 of the gene encoding for the Huntingtin protein (Htt) [9]. HD is characterized by involuntary abnormal movements and postures (chorea, dyskinesia, dystonia) of the legs, trunk and face [10]. Speech disturbance (dysarthria) is often seen. Other highly alienating symptoms consist of mood, psychiatric disturbances and cognitive deficits characterized by a perseverative behaviour and impaired strategy and planification. With the progression of the disease, motor rigidity and dementia predominate. The disease is fatal within 15-20 years after onset. Although several cerebral regions show signs of neurodegeneration in HD, the most striking neuropathological hallmark of this disorder is the atrophy of the striatum as seen using post mortem histological evaluation [11] or non-invasive brain magnetic resonance imaging (MRI) [12-14]. Detection of pre-symptomatic patients (i.e. carrying the mutation but asymptomatic) demonstrated significant atrophy of the caudate and putamen [12-14]. This suggests that degenerative events (cell shrinkage or loss) begin

years before the occurrence of clinical symptoms. The disease preferentially affects the GABAergic medium size spiny neurons of the striatum that project to substantia nigra reticulata and pallidum. Intriguingly, large cholinergic interneurons and medium size aspiny interneurons are preserved in the HD striatum [15, 16]. Cortical atrophy and early degeneration of the hypothalamus are also important aspects of HD pathogenesis, and late stage HD patients show widespread brain degeneration [17]. However, the severity of striatal alterations is correlated with the degree of motor, cognitive and psychiatric perturbations [18], suggesting that striatal degeneration is an important aspect of HD physiopathology.

Many genetic models of HD have been generated in mice [19, 20]. Transgenic mice express N-terminal fragments of different sizes, the R6/2 mice which overexpress human exon 1 of the HD gene, have a very strong behavioural phenotype with short life span and has been the most studied model so far. Other transgenic models that express the entire mutant human gene show a milder and more progressive neurological phenotype (BACHD, YAC128Q). One transgenic rat model expressing two thirds of the gene shows relatively mild degeneration but develops motor and cognitive symptoms. The mouse models that are genetically the most relevant to HD are the knock-in models where a CAG expansion is inserted in the mouse homologue HD gene (HDh111, HDh140, HDh150). Excellent reviews have been released for a comprehensive view of characteristics of the mouse models that have been generated and are still currently used for research [21-23]. The different types (summarized in table 1) of mitochondrial defects which have been observed in these animal models will be discussed below.

2.2. Pathogenesis

The mutation induces both a loss of function and a gain of function. Wild type Htt plays an important role in cell survival by controlling apoptosis pathways, regulating intracellular transport machinery, vesicle trafficking and secretion [24-26].

The toxic functions acquired by mutant Htt may involve the full length Htt and the short N-terminus fragments produced by the cleavage performed by different proteases, all of which have not been identified yet. Cleavage by calpain [27-32] and caspases has been demonstrated [33-35]. Experimental approaches have shown that the N-terminus fragments of mutant Htt recapitulate several aspects of the full-length mutant protein's toxicity. Of interest, reducing the caspase-6-dependent cleavage of full length mutant Htt markedly slows down the progression of symptoms and neurodegeneration in a transgenic mouse model of Huntington's disease [34]. However, it cannot be totally ruled out that the C-terminal part of full length mutant Htt could trigger toxic

events. In a recently developed transgenic mouse model of HD (bacterial artificial chromosome HD – BACHD) expressing the full length human mutant gene, neuronal dysfunction starts early while the accumulation of N-terminal Htt fragment is minimal [36].

Abnormal transcription and transcription regulation have been demonstrated [37, 38]. Mutant Htt alters macromolecular complexes regulating transcription. The mutation produces changes in protein-protein interaction between Htt and transcription factors or co-factors such as CBP, TAF4, CA150, Sp1, and p53, that can produce deleterious downstream events. Mutant Htt could also lead to increased transglutaminase activity thus producing an abnormal covalent link between proteins [39].

It has been shown that wild type Htt regulates the expression of BDNF by increasing REST/NRSF at the RE1/NRSE site located in the BDNF promoter [40]. BDNF is an important factor contributing to neuronal survival in the striatum. It is mainly synthesized in the cortical neurons and delivered to the striatum through vesicles using axonal transport [24]. Reduced BDNF levels in the striatum would render medium size spiny neurons highly vulnerable.

Early axonal transport dysfunction and alteration of vesicle trafficking have been shown [41]. In particular impaired transport of vesicles containing BDNF along the axon would further reduce the delivery of BDNF to striatal cells [24]. Impaired axonal transport might also affect organelle, including mitochondria localization (see below). Protein misfolding, proteasome dysfunction [42, 43], and reduction of autophagy [44], likely play important roles in HD. Abnormal entry of Ca^{2+} through NMDA receptors and excitotoxicity has been suggested [45, 46]. Defective cytosolic Ca^{2+} buffering by mitochondria and endoplasmic reticulum (ER) have been observed [47].

In the present review, we aim to provide an overview of how mitochondrial dysfunction in HD could play a central role in cell degeneration in HD [48, 49]. How mitochondrial defects could contribute to striatal degeneration is however debated. One important point is that mutant Htt can interact with the outer mitochondrial membrane [50-53]. Besides the direct interaction, the transcriptional changes induced by mutant Htt and excitotoxicity could modify some mitochondrial functions. The eventual energy failure would render striatal cells more fragile, and eventually trigger the irreversible cascade of events leading to cell death.

3. Preferential vulnerability of the striatum in human mitochondrial disorders

It has been known for a long time that the striatum is extremely vulnerable to the impairment in the OXPHOS system. Primary genetic mitochondrial defects can lead to striatal degeneration and associated motor and cognitive symptoms. For example deletions or mutations in several mitochondrial genes may lead to Leigh syndrome, characterized by various degrees of basal ganglia damage, and possibly striatal necrosis and, clinically, by choreoathetosis and dystonia. Point mutations in mitochondrial genes coding for several subunits of complex I (NADH: ubiquinone oxidoreductases) can lead to putaminal degeneration and dystonia, in association with other severe alterations such as epilepsy, stroke and optic nerve atrophy. Mutations in mitochondrial DNA encoded ND1 [54] genes produce Leber hereditary optic neuropathy and spastic dystonia. Mutations in ND3 [55] can also produce Leigh syndrome.

More rarely, nuclear genes encoding for mitochondrial proteins or assembly factors can lead to neurological abnormalities reminiscent of Leigh syndrome. Defects in succinate oxidation [56] were associated with bilateral striatal degeneration and dystonia. Loss of function in the gene coding one of the succinate dehydrogenase (SDHA) determines Leigh syndrome [57]. A recent work reported striatal atrophy resulting from homozygous point mutation in subunits VII of complex III, ubiquinol-cytochrome c reductase [58].

Mutations in nuclear genes that encode for mitochondrial proteins that are indirectly associated with OXPHOS can also lead to basal ganglia dysfunction. For instance, mutation in the Myofibrillogenesis regulator-1 (MR-1) gene is the cause of the Paroxysmal non-kinesigenic dyskinesia (PNKD) a rare autosomal-dominant movement disorder characterized by paroxysmic episodes of dystonia and chorea [59].

4. General mitochondrial and OXPHOS defects in HD patients and HD models

4.1. Mitochondrial enzymes

Defects in the respiratory chain in HD have been observed in early biochemical studies. Severe reduction in the activity of complex II/III and milder reduction of complex IV were found in post mortem samples of the caudate/putamen in HD patients.[60-64]. No changes were observed in pre-symptomatic patients [65]. The cerebral cortex showed minor changes in respiratory chain enzymes [61, 63, 66]. No change was observed in blood cells. Reduced activity of other enzymes of oxidative metabolism in the striatum was also reported. In particular massive loss of aconitase

activity has been found in the caudate (~90%), and putamen (~70%) [66, 67]. Loss of the pyruvate dehydrogenase complex was also shown [62, 68]. Those defects were observed in symptomatic patients with caudate/putamen atrophy. Thus, whether they are a consequence of striatal degeneration, or they play a pivotal role in it, remains to be determined.

In a transgenic mouse model of HD (R6/2) with limited cell loss, aconitase and pyruvate dehydrogenase have been found to be decreased to various extents [69]. It seems that in addition to presenting reduced levels, many proteins are modified by oxidative stress in these transgenic models [70]. Thus abnormalities in mitochondrial proteins related to energy metabolism might not simply result from the loss of mitochondria due to the neuronal loss. Experiments using the mitochondrial toxin 3-NP and recent studies on mitochondrial complex II support the hypothesis that complex II dysfunction (alteration), in conjunction with oxidative damage to mitochondrial proteins might be causal in HD-linked striatal cell death (see below).

4.2 Brain examination using non invasive methods

Other indications for energy metabolism problems in HD patients were reported. In particular, early striatal hypometabolism was detected in vivo using positron emission tomography and [¹⁸F]fluorodeoxyglucose [7, 71]. Increased lactate concentrations were found in the cortex of symptomatic HD patients using proton NMR spectroscopy [72, 73]. Lactate/pyruvate ratio was elevated in the CSF of HD patients [74]. In one NMR study, half of the pre-symptomatic HD patients examined showed increased lactate concentration in the striatum [73]. In muscle, phosphorus NMR spectroscopy showed reduced ATP production [75].

4.3 Mitochondrial membrane potential

Mitochondria isolated from cells expressing mutant Htt show decreased membrane potential. As first reported by Sawa and collaborators, lymphoblasts derived from lymphocytes from HD patients showed increased stress-induced apoptotic cell death [76]. When subjected to apoptotic stress, lymphoblasts from patients displayed increased mitochondrial membrane depolarisation as compared to control lymphocytes. This aggravated loss of potential was correlated with CAG repeat expansion. Other studies also suggest abnormal mitochondrial membrane potential in cell expressing mutant Htt. Others have reported similar observations in lymphocytes/lymphoblasts

[53]. In neural cells, particularly in studies performed on clonal cells derived from knock-in mice harbouring a pathologically expanded CAG repeat tract (STHdhQ111/Q111), showed high sensitivity to Ca^{2+} induced permeability transition [50]. This sensibility was confirmed in many recent studies, specifically when using mitochondria isolated from HD transgenic rats [77]. STHdhQ111/Q111 cells also show higher vulnerability to permeability transition when treated with the 3-NP, an effect that could be prevented by cyclosporine-A [78]. It has also been demonstrated that recombinant mutant Htt (short N-terminal fragment) could directly trigger loss of membrane potential and permeability transition, likely through an interaction with the outer mitochondrial membrane [50, 79]. In situ studies using fluorescent dyes (JC-1, MitoTracker Red) that accumulate in the mitochondria as a function of the membrane potential confirmed that neuronal cells expressing mutant Htt could display reduced mitochondrial membrane potential at rest [80, 81].

4.4. Mitochondrial Ca^{2+} buffering capacity

Increased cytoplasmic Ca^{2+} levels are toxic to neurons [82]. Impaired Ca^{2+} homeostasis in HD might have different causes. Although it may originate from various extra-mitochondrial origins (see below), mechanisms related to mitochondrial dysfunction have received the closest attention. The Ca^{2+} buffering capacity of cells expressing mutant Htt can be reduced. This was first shown by Panov and collaborators in lymphoblasts derived from lymphocytes of HD patients [53]. Similarly, reduced Ca^{2+} loading capacity was found in the brains of YAC72Q mice [53]. Compared to mitochondria from control cells (STHdhQ7/Q7), the mitochondria from clonal striatal cells with mutant Htt (STHdhQ111/Q111) undergo permeability transition at a lower Ca^{2+} concentration when treated with increasing Ca^{2+} loads and have a reduced capacity to take up Ca^{2+} [83]. Isolated mitochondria from transgenic rats expressing mutant Htt, show reduced rates of Ca^{2+} accumulation compared to control rats [77]. However, not all HD models show reduced brain mitochondrial Ca^{2+} loading capacity. The latter was found increased in 12 week old R6/2 mice and 12 month old YAC128Q while no changes were found in knock-in 150Q mice [84]. One possibility is that changes in mitochondrial Ca^{2+} loading capacity are transient in HD mice. Aging processes and cell substitution may occur in later stages thus hiding the original defect.

5. Complex II defects in Huntington's disease

5.1. 3-nitropropionic acid, a complex II inhibitor replicating many aspects of Huntington's disease

In man the ingestion of the mitochondrial toxin 3-nitropropionic acid (3NP) produces putaminal necrosis and delayed dyskinesias and dystonia [85, 86]. Systemic administration of 3NP produces in rats [87, 88] and in non-human primates [89] preferential degeneration in the striatum, abnormal movements and frontal type cognitive deficits that are highly reminiscent of HD [8, 48]. The 3NP models strongly suggest that complex II defects detected in the striatum of HD patients may participate to cell demise. Alongside the similar phenotype, studies on 3NP toxicity also showed that mitochondrial defects and mutant Htt toxicity share common pathogenic pathways, such as impaired Ca^{2+} homeostasis, calpain and caspase activation, and JNK activation [48]. However, 3NP does not produce transcriptional changes that are comparable to those found in transgenic and knock-in mice expressing mutant Htt [90, 91]. The 3NP model should be considered as an excellent model to study the consequences of chronic mitochondrial impairment and oxidative stress in vivo. As a model of HD, it presents several limitations compared to transgenic animals [48].

5.2. *The SDH-Complex II molecular evidence in HD*

The main component of complex II is the enzyme succinate dehydrogenase (SDH) [92]. Complex II/SDH is composed of four nuclear-encoded subunits: the 70 kDa Fp subunit that catalyses the oxidation of succinate, the 30 kDa Ip subunit which transfers electrons to the ubiquinone via its iron centers, and two small subunits (SDH-D and SDH-C) that anchor the complex to the internal mitochondrial membrane. Thus, complex II/SDH plays a central role in the respiratory chain, in the tricarboxylic acid cycle and probably in the control of free radical production [92, 93].

The expression of the 30 kDa iron-sulfur (Ip) subunit and of the 70 kDa FAD (Fp) subunit was preferentially decreased in the striatum of HD patients, compared with controls [81]. Other mitochondrial proteins were examined including subunit IV of complex IV, alpha subunit of the F1-ATPase, BclXL, a protein of the mitochondrial outer membrane, and cytochrome c. None showed significant changes in the striatum of HD patients, suggesting that the defective expression of complex II is not only the consequence of mitochondrial loss, secondary to neuronal death. In the cortex and cerebellum there was no decrease in SDH subunits [81].

Despite these observations, the possible role of complex II in HD is questioned by the fact that many attempts to detect significant reduced enzymatic activity have failed in transgenic mouse models of HD [71]. We also initially failed to find reduced activity or expression of complex II when studying R6/2 and N171-82Q mice at relatively advanced symptomatic stages (Brouillet, Benchoua, personnel communication). The reason for this is not totally understood but recent findings strongly suggest that transient changes in SDH expression might occur in transgenic HD

mouse models. Careful longitudinal analysis of R6/2 mice using well-controlled proteomics methods showed expression changes of the Ip subunit [94]. A significant 34% decrease was seen in the 2 week old R6/2 mice. In the same model, a 50% increase was observed in 4 week old animals, before gross brain atrophy and severe symptoms. Increased activity of many glycolysis and OXPHOS enzymes was also observed in R6/2 mice at 4 weeks. At 6 weeks no changes were observed in the Ip subunit. At 8 weeks, in contrast, Ip was again reduced by 37%. We also found reduced levels of SDH Ip and Fp subunits in the striatum of R6/1 mice at 16 weeks of age while at 32 weeks, changes were less pronounced [95]. Cortex showed no change at either ages. The apparent "wavy" changes in Ip expression in R6/2 mice [94] may result from changes in cellular composition of the brain tissue (i.e. neurons and astrocytes) especially considering that reactive gliosis is a physiological phenomenon that follows neuronal loss.

SDH activity was also reduced in the striatum of rats injected with lentiviral vectors coding the 171 N-terminal part of Htt with 82 glutamines (Htt171-82Q) [95, 96]. This was observed along with reduced regional glucose consumption as assessed using quantitative ^{14}C -2-deoxyglucose autoradiograph [95, 96]. Depletion of activity was in the 50% range at 8 weeks post infection in the region expressing mutant, but not wild type Htt fragment. Blocking mutant Htt using siRNA strategy prevented the SDH and regional glucose consumption reduction [95, 96].

Only few studies report complex II changes in cells expressing mutant Htt in culture. Complex II activity was found reduced in Neuro2A and HeLa cells expressing Htt exon 1 [97]. Interestingly, in yeast, mutant Htt can be cytotoxic through alteration of OXPHOS, in particular reduced function and amount of mitochondrial respiratory chain complex II+III [98]. The potential role of SDH /complex II in HD has been examined in striatal neurons in primary culture using infection with lentiviral vectors coding for the N-terminus part of huntingtin (Htt) with either a pathological (Htt171-82Q) or physiological (Htt171-19Q) polyglutamine tract [81]. A longitudinal biochemical analysis after infection showed that, compared with Htt171-19Q, expression of Htt171-82Q decreased the levels of Ip followed by Fp subunits and reduction of the dehydrogenase activity of the complex. Other mitochondrial proteins remained unchanged. Of interest, the Htt171-82Q-induced loss of complex II did not result from a decrease in mRNA levels. Thus reduction of SDH subunits may be the result of a post-transcriptional problem. Overexpression of Ip or Fp subunit restored complex II levels, blocked mitochondrial dysfunction and prevented striatal cell death induced by Htt171-82Q in primary neurons [81]. These results provide evidence that complex II/SDH subunits are critical for the execution of mutant Htt-induced cell death.

6. Possible mechanisms of mitochondrial dysfunction in HD

As discussed above, mutant Htt (N-terminal small fragments) can possibly directly interact with the outer mitochondrial membrane. This may destabilize mitochondrial membrane, increase the sensitivity of the mitochondrial permeability transition pore (mPTP) to Ca^{2+} or other apoptotic stimuli. Mitochondrial changes that have been hypothesised to play a role in other neurodegenerative diseases could also be involved in HD. In particular a shift in the fusion/fission equilibrium might occur [99]. Reduced mitochondrial mobility could reduce the incorporation of certain proteins leading to mitochondrial dysfunction [100]. An elegant study using live cell video microscopy showed that aggregates impair mitochondrial movements along neuronal processes. Mitochondria may remain embedded in the aggregate formations in the somato-dendritic compartment [101]. A very interesting observation in this study is that full length mutant Htt, more than the short N-terminal fragments, impairs mitochondrial mobility. Radical oxygen species (ROS), which production is thought to be increased in HD patients and HD mouse models [67, 71, 102, 103] could also lead to mitochondrial impairment, particularly by increasing the vulnerability of the mPTP in presence of Ca^{2+} .

A cellular function that is severely altered in HD and could lead to mitochondrial dysfunction is transcription. The vulnerability of mitochondria to Ca^{2+} loads and induction of permeability transition have been recently studied by Oliveira and co-workers [104, 105]. In this accurate study, the authors show that mitochondria of STHdh111Q/111Q cells derived from knock-in HD mice, as well as primary striatal neurons from YAC128 mice, have reduced Ca^{2+} handling capacity, when compared to control cells. These changes were prevented by applying HDAC inhibitors [104]. This suggests that, at least in part, mitochondrial defects are secondary to impaired nuclear transcription. Indeed mitochondrial biogenesis, and import of matrix and membrane proteins, are under the control of several nuclear transcription factors and co-activators [106]. Reduced CREB-dependent transcription in HD could have specific consequences on mitochondrial physiology. For example, CREB regulates respiratory chain proteins (e.g. COX-IV and cytochrome c) [107]. Recently, Ryu and collaborators demonstrated that CREB could directly bind mtDNA on CRE binding sites, a process that is stimulated by mitochondrial PKA [108]. Interestingly, the regulation of CREB phosphorylation in mitochondria may involve Ca^{2+} -dependent phosphatase in neurons [109]. Thus, transcriptional problems produced by mutant Htt could lead to disruption of Ca^{2+} homeostasis, which in mitochondria may further reduce CREB-dependent expression of OXPHOS proteins, and result in energy failure and apoptotic cell death.

It has been demonstrated that the accumulation of p53 plays a role in mitochondrial dysfunction and HD-linked degeneration [80]. The strong interaction between p53 and mutant Htt causes p53 accumulation in the nucleus thus inducing p53 dependent transcription. Reducing p53 activity using siRNA or gene deletion is neuroprotective against mutant Htt. Knocking down p53 rescues striatal cells from mutant Htt-induced mitochondrial dysfunction (loss of mitochondrial membrane potential and COX activity) [80]. It is currently unknown whether the transcriptional effect of p53 plays a direct or indirect role on cytosolic proteins that can regulate apoptosis such as Puma.

Another very interesting mechanism that has recently been proposed to be involved in HD-linked striatal degeneration is the PGC-1alpha pathway. Reduced expression of PGC-1alpha has been reported in HD models [110, 111]. PGC-1alpha is a nuclear co-activator that plays a major role in mitochondrial biogenesis [110, 111]. Mice that are nullizygous for PGC-1alpha display abnormalities related to energy metabolism and strikingly develop striatal lesions [112]. Increasing PGC-1alpha expression is neuroprotective against mutant Htt toxicity and, on the contrary, when PGC1-alpha is knocked down, neurons are highly vulnerable to mutant Htt toxicity in cell culture and in vivo [111]. Other family members (PGC1beta and PGC-1 Related co-activator –PRC), also known to regulate important aspects of mitochondrial biogenesis and of respiratory enzymes, could be also involved [113]. In line with this, it cannot be excluded that downstream of PGC-1alpha, the nuclear respiratory factors, NRF-1 and NRF-2 [114] could also participate in HD-linked mitochondrial dysfunction. The possible mechanisms through which mutant Htt could impair mitochondrial function is likely multifactorial and highly complex.

How could mutant Htt produce the loss of complex II/SDH activity? The loss of SDH subunits may not directly be produced by transcription regulation. The Fp SDH subunit possesses a CRE consensus sequence in its promoter [115]. However it is unknown whether this site is active or not. The mRNA expression for SDH-A and SDH-B is not markedly reduced in the brain of HD patients [116], while there is dramatic loss of the proteins as assessed using western blots [81] and activity assay [61, 63]. Using cultured striatal neurons, we showed that expression levels of mRNA coding for SDH subunits were not modified by mutant Htt while protein expression and activity was reduced [81, 117]. Mutant Htt could decrease the import of the Ip subunit into mitochondria, increase its degradation, or disturb its assembly into a functional complex. Mutant Htt can bind to the outer mitochondrial membrane [50, 53]. This could modify the molecular machinery for the SDH import. It is also possible that loss of membrane potential could reduce or alter the incorporation of the FAD prosthetic group to the Fp subunit and eventually induce complex II disassembly. Another interesting possibility is related to the Ip protein mRNA structure [81] which

presents an un-translated region (UTR) named IRE (Iron Responsive Element). Oxidative stress or imbalance in iron metabolism could modify Ip expression through the binding of IRP-1 and IRP-2 [118].

7. Environmental factors underlying striatal vulnerability through mitochondrial mechanisms

Obviously, reduced energy production, anomalies in the control of apoptosis and reduced cytosolic Ca^{2+} handling capacity can affect cell survival. Why is the striatum particularly vulnerable to mitochondrial dysfunction in HD? The general hypothesis is that striatal vulnerability to impairment in energy metabolism is caused by many factors. In particular, neurotransmission systems which modulate activity of striatal medium sized spiny neurons could play a role.

7.1 Glutamate, excitotoxicity and mitochondria

Whereas purely mitochondrial changes (protein expression, mitochondrial membrane potential, Ca^{2+} loading capacity) are not always consistently observed in all experimental models (cell types, mouse lines), one consistent observation is that in neurons, mitochondrial Ca^{2+} handling is reduced, upon stimulation of glutamate receptors *in situ*. The cause of this defect is not totally understood but elegant studies try to explain how HD-induced mitochondrial dysfunction could transform a physiological effect into an excitotoxic one.

There are mainly two studied mechanisms able to lead to impaired Ca^{2+} homeostasis within striatal neurons: 1) increase in Ca^{2+} entry, and 2) impaired Ca^{2+} sequestration/release into/from intracellular stores. In fact the two mechanisms could co-exist and synergistically exacerbate Ca^{2+} deregulation thus triggering cell death.

In addition, abnormal release of Ca^{2+} from ER likely exists in neurons expressing mutant Htt. Mutant Htt facilitates activity of type 1 inositol 1,4,5-trisphosphate receptors (InsP(3)R1) [119]. This is an important aspect since, in presence of impaired mitochondrial Ca^{2+} handling, and upon the pathologic stimulation of NMDA receptors, the increased Ca^{2+} release from the ER could further increase cytosolic Ca^{2+} up to excitotoxic levels and thus cause neuronal apoptosis.

Compelling evidence shows that abnormal activation of NMDA receptors likely plays a role in HD pathogenesis [45, 46, 120, 121]. Pioneering studies show that intrastriatal injection of NMDA

receptor agonists, including NMDA and quinolinate in laboratory animals produces axon-sparing lesions which are reminiscent of HD [8]. In particular, while medium-sized spiny neurons preferentially degenerate, interneurons (large cholinergic interneurons and medium size aspiny GABAergic neurons expressing nNOS, somatostatin and neuropeptide Y) are spared [122, 123]. More recently, several approaches have shown that mutant Htt can directly modify NMDA-receptor function through its interaction with PSD95 [124, 125]. In particular, mutant Htt increases the sensibility of neurons to excitotoxicity associated to stimulation of NMDA receptors harbouring the NR2B subunits [126, 127]. Degeneration is exacerbated in mice with CAG expansion in the Htt homologue gene (knock-in Hdh150Q) and overexpressing NR2B [128]. NMDA currents are increased in the striatum of transgenic mice overexpressing full length Htt [124, 127, 129]. Decortication, which removes glutamate afferents in the striatum, protects against striatal degeneration in R6/2 mice [130]. Many electrophysiological data support the view that abnormal glutamatergic transmission in the cortico-striatal pathway is a prominent aspect of striatal degeneration (reviewed in [131]).

However, increased activation of NMDA receptors might not be a pre-requisite for excitotoxicity. Indeed, extracellular normal glutamate concentrations can trigger excitotoxic cell death in neurons with impaired energy metabolism [132]. In cell culture, pre-treatment with 3-NP exacerbates the toxicity of low NMDA or glutamate concentrations [133-135]. Three studies have demonstrated that this synergy also operates in vivo by providing evidence that the size of striatal lesions produced by NMDA is significantly increased by injecting malonate, a reversible complex II inhibitor, into the striatum [136] or by systemic administration of 3-NP [137, 138]. Potentiation of QA toxicity by inhibiting SDH/Complex II with 3-NP (in the 45% range) is observed at non toxic doses 3-NP. This effect is likely associated with increased cytosolic Ca^{2+} concentrations in vivo. Intracellular Ca^{2+} imaging studies [132, 137, 139] showed that NMDA receptors activation leads to higher cytoplasmic Ca^{2+} concentrations in 3NP-treated cultured neurons and brain slices, as compared with untreated preparations. However, results obtained from $^{45}Ca^{2+}$ experiments demonstrated that, during NMDA receptor stimulation by an agonist, Ca^{2+} entry into primary striatal neurons is similar with or without 3-NP [137]. Thus the increased vulnerability of neurons to excitotoxicity when complex II is deficient is likely due to reduced mitochondrial capacity to uptake cytosolic Ca^{2+} upon NMDA receptor stimulation [132, 137, 139]. A similar process may occur in neurons expressing mutant Htt and subjected to NMDA receptor stimulation, despite the fact that reduction in complex II is likely not a prerequisite. Complex II would further aggravate the vulnerability of mitochondria to Ca^{2+} transients. Consistent with this view, a study performed in the YAC128 mouse model indicated that during the initial phase of NMDA toxicity, NMDA receptor

current and cytosolic Ca^{2+} loading are similar to those observed in wild-type striatal neurons [140]. However, NMDA receptor-mediated Ca^{2+} load triggered a more profound loss of mitochondrial membrane potential in YAC128 neurons than in wild type cells. After removal of NMDA, YAC128 cells displayed a longer time to recover normal Ca^{2+} concentrations. This was attributed to higher sensitivity of YAC128 striatal cells to Ca^{2+} induced mitochondrial permeability transition [140]. Oliveira and collaborators studied Ca^{2+} transients after NMDA receptor stimulation in YAC128 striatal neurons in relation to the modification of mitochondrial membrane potential assessed using the fluorescent TMRM+ probe [104, 105]. They characterized the patterns of Ca^{2+} recovery after NMDA receptor stimulation in wild type cells and YAC128 striatal cells in culture. The proportion of neurons with delayed recovery (i.e. initial cytosolic Ca^{2+} peak progressively return to normal after MK801 application) was significantly higher in YAC128 neurons. Striatal neurons prepared from heterozygous Hdh150Q knock-in mouse embryos were more vulnerable to Ca^{2+} deregulation than wild type neurons [104, 105].

7.2. Dopamine and mitochondria

In addition to glutamate, other neurotransmission systems likely play a role in HD pathogenesis [48, 141, 142]. In particular dopamine, which is at high concentrations in the striatum compared to other brain areas, might play an important role in the preferential vulnerability of the striatum in HD [143], possibly through a functional interaction with mitochondria.

A number of in vivo and in vitro experiments showed that dopamine contributes to striatal lesions produced by the mitochondrial toxin 3-NP (see for review [48]), suggesting that dopamine could have an impact on mitochondrial function. Dopamine may act as a co-factor in mutant Htt-induced death in vitro, possibly through stimulation of autophagy [144]. However, autophagy is rather considered as neuroprotective in HD pathogenesis [145]. Increased autophagy might lead to enhanced mitochondria clearance in HD cells, and prevent the cells from entering the apoptotic cascade. The production of free radicals following dopamine oxidation [146] may also increase Htt toxicity [147].

However, direct support for the role for DA in HD comes from the recent demonstration that the toxicity of the N-terminal fragments of mutant Htt is potentiated by dopamine. Dopamine modifies the formation of Htt-containing aggregates in primary striatal neurons transfected with exon 1 of Htt gene and exacerbates mutant Htt-induced cell death [147]. Of interest, this effect involves D2 receptor signalling, since dopamine had this detrimental effect when neurons were prepared from D2 receptor null mice [147]. In addition D2 antagonists significantly reduce the effects of

dopamine. In vivo experiments also support a role for dopamine and its receptors in HD pathogenesis: DAT (dopamine transporter) knock-out (KO) mice crossed with a knock-in transgenic mouse model of HD showed enhanced motor symptoms and striatal degeneration induced by mutant Htt [148]. In YAC128 HD mice, L-dopa treatment (which elevates dopamine concentrations) accelerates striatal degeneration, whereas the neuroleptic tetrabenazine, which reduces dopamine release, was neuroprotective [149]. Chronic treatment with the D2 antagonist haloperidol significantly reduces the striatal toxicity of Htt171-82Q in vivo [150]. Stack and collaborators [130] showed that 6OHDA-induced degeneration of the nigro-striatal dopaminergic pathway prevents striatal degeneration in R6/2 HD mice.

We found that one of the underlying mechanisms of this "protoxic" effect of dopamine in mutant Htt toxicity directly involves mitochondria. Primary striatal neurons expressing Htt171-82Q were highly vulnerable to dopamine when compared to normal neurons or neurons expressing the wild type fragments [117]. This was correlated with the level of reduction of complex II/SDH activity. Indeed, incubation of striatal neurons with dopamine alone produced a significant loss of SDH activity and reduced expression of the subunits of the complex. This was related to a transient reduction of Ip and Fp complex II subunit mRNAs. This dopamine-induced loss of complex II was mediated by D2 receptors. D2 receptor antagonists blocked the effect of dopamine and D2 agonist replicated the effect of dopamine. The combined down regulation of SDH/complex II by dopamine and mutant Htt leads to cell death that can be blocked by overexpression of the Ip protein using lentiviral vector-mediated gene transfer methods [117]. How this novel mechanism could play a role in vivo in the striatum is not yet elucidated. However it could explain why the striatum is preferentially vulnerable to the complex II inhibitor 3NP and mutant Htt toxicity.

8. Therapeutic strategies from theory to proof of concept

Theoretically, if mitochondrial defects found in HD patients and HD models play a role in neuronal dysfunction and eventually death, correcting these defects may provide beneficial effects. Recent findings support this hypothesis.

Whereas gene transfer-based experiments recently led to the discovery of potential therapeutic targets that could improve mitochondria in HD (such as PGC-1alpha or the mitochondrial complex II), preclinical studies are yet required to precisely determine whether it is possible to modulate these systems in vivo. From a practical perspective, the targeting of these complex systems will

require important and long-term developments. However, a few strategies which were suggested many years ago have shown great promise in preclinical and even clinical studies. Examples are given below.

In cells expressing mutant Htt, accumulation of p53 has been showed to induce neuronal death. Reducing accumulation of p53 using RNA interference and the p53 inhibitor pifithrin- α suppress mutant Htt-induced mitochondrial depolarization. Intraperitoneal injection of pifithrin- α in 171-82Q HD transgenic mice restore levels complex IV activity to normal levels [80]. It can be speculated that pifithrin-like drugs could be neuroprotective in patients.

The loss of mitochondrial Ca²⁺ handling observed in cell lines derived from knockin mouse model can be corrected by treatment with the HDAC inhibitors trichostatin A or sodium butyrate, suggesting that acting on transcription defects could correct some of mitochondrial defects produced by mutant Htt [104]. Treatment with HDAC inhibitors in mouse models of HD reduces striatal atrophy and motor deficits [151, 152]. These beneficial effects in mice could at least in part involve amelioration of mitochondrial physiology.

Another approach consists in brain fuel supplementation. The most promising compound that could be efficacious in increasing brain energy metabolism is creatine, a compound produced endogenously and acquired exogenously through diet [153]. Diet supplementation with creatine (in the range of 600 mg/kg) in mice expressing the N-terminal part of mutant huntingtin is neuroprotective. It extends life-span in transgenic mice, and reduces motor dysfunction and striatal atrophy [154-156]. Creatine is well tolerated in patients [157]. It seems that creatine produces an actual biological effect in HD patients since blood levels of 8-hydroxy-2'-deoxyguanosine (8OH2'dG), a biomarker of oxidative stress that are elevated in untreated HD patients are near control levels in patients with creatine treatment. Ongoing clinical trials may determine within few years whether creatine treatment can slow the progression of the disease.

Production of ROS is likely increased in HD patients and HD mouse models [67, 71, 102, 103]. Reducing ROS production using compounds with anti-oxidant properties have been tested in HD models [23]. For example, ascorbate treatment in R6/2 mice ameliorates behavioural deterioration [158]. The newly developed antioxidant BN82451 protects and extends survival in R6/2 mice [159]. The most debated but still very promising compound is coenzyme Q10, which has antioxidant properties and plays an important role in the transfer of electrons in the respiratory chain [160]. Transgenic R6/2 mice treated with coenzyme Q10 alone or in association with the NMDA receptor antagonist remacemide show increased survival, attenuated weight loss, improved

motor performances, and reduced striatal atrophy when compared with untreated transgenic mice [161, 162]. Clinical trials with relatively low dose showed no major protective effects, suggesting that higher doses may be necessary.

9. Conclusion

Mitochondria likely play a key role in HD, although the exact mechanisms involved are still under debate. Of interest, the striatum might be particularly vulnerable to mitochondrial defects through multiple mechanisms involving molecular factors which are selectively present in this brain region. Amongst these factors, dopamine and D2 receptors, which are present in high concentrations in the striatum likely play a role in the selective degeneration of striatal neurons expressing mutant Htt. Many other factors possibly determine striatal vulnerability and may directly regulate mitochondrial homeostasis. Beyond a better understanding of these mechanisms, there is really an urgent need to find an efficacious therapeutic strategy to slow disease progression. Many therapeutic strategies are studied at a preclinical level and several clinical trials have been carried out in HD patients. None have provided major beneficial effects. Continuing to precisely decipher the various ways by which mitochondria are involved in HD pathogenesis will certainly help to disclose new therapeutic strategies.

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Figure 1: Hypothetical mechanisms involving mitochondria in Huntington's disease pathogenesis.

Mutant huntingtin (m-Htt) produces mitochondrial impairment through different mechanisms. Mitochondria from HD patients and genetic models of HD show reduced membrane potential ($\Delta\Psi$), decreased Ca^{2+} buffering capacity, enhanced sensitivity to Ca^{2+} -induced permeability transition, and triggering of caspase-mediated apoptotic pathways involving caspases. In addition, m-Htt can produce preferential reduction of respiratory chain enzymes, in particular complex II (SDH/II) and to a lesser extent cytochrome c oxidoreductase (IV).

These mitochondrial defects may result from a direct interaction of m-Htt with the outer membrane and/or indirect modification of protein(s) expression linked to m-Htt-induced transcriptional changes. One important effect of m-Htt-induced mitochondrial defects includes deregulation of cytosolic Ca^{2+} concentrations. In striatal cells, this could act in synergy with other m-Htt-induced modification of Ca^{2+} homeostasis: m-Htt increases the activation of the InsP_3 receptor (IP3R) triggering Ca^{2+} release from the endoplasmic reticulum (ER) and enhances Ca^{2+} entry through NMDA receptors. In this scenario, glutamate is a primary cause of Ca^{2+} transients during synaptic transmission, leading to Ca^{2+} deregulation and cell death (excitotoxicity) in cells expressing m-Htt. In addition, the presence of dopamine could also render striatal cells more vulnerable to m-Htt toxicity. D1 receptors can exacerbate glutamate toxicity and D2 receptors might down regulate expression of mitochondrial complex II. Mitochondrial defects can indirectly increase the activity of proteases that cleaves Htt, leading to enhanced production of N-terminal Htt fragments. This would further exacerbate transcriptional defects which, through a vicious cycle, would further accentuate mitochondrial impairment.

Table I : Main mitochondrial defects observed in genetic models of Huntington's disease

The left column indicates the mitochondrial targets/functions found defective in HD models (indicated in the second column). The table is not exhaustive. It lists main findings in genetic models and corresponding references for further reading.

Mitochondrial target/function	Organism/model	Change (mutant/wt)	Ref.
Mitochondria membrane potential	Primary culture of striatal neurons expressing N-terminal Htt fragments	Decreased	[80, 81]
Sensitivity of permeability transition pore to Ca^{2+}	STHdhQ111/Q111 striatal cell line	Increased	[78, 104]
Induction of permeability transition	Recombinant N-terminal Htt fragments in vitro	Increased	[50, 79]
Ca^{2+} buffering capacity/handling	Mitochondrial preparation from YAC72Q tg mouse brains	Decreased	[53]
	STHdhQ111/Q111 striatal cell line	Decreased	[83]
	Mitochondrial preparation from tg HD rat brains	Decreased	[77]
	Cultured cortical cells from YAC128Q tg mice	Decreased	[104]

	Cultured cortical cells from HD150Q knock-in mice	Decreased	[104]
	Mitochondrial preparation from R6/2 tg mouse brains	Increased	[84]
	Mitochondrial preparation from YAC128Q tg mouse brains	Increased	[84]
	Mitochondrial preparation from HD150Q knock-in mouse brains	~	[84]
Aconitase	R6/2 brains	Decreased	[70]
Pyruvate dehydrogenase	R6/2 brains	Decreased	[70]
Complex II/SDH activity	Rat HD models using lentiviral vectors	Decreased	[95]
	Primary culture of striatal neurons expressing N-terminal Htt fragments	Decreased	[81, 117]
	Neuro2A cells expressing Htt exon I	Decreased	[97]
	HeLa cells expressing Htt exon 1	Decreased	[97]
	Yeast expressing full length Htt	Decreased	[98]
Expression of complex II subunits	R6/1 tg mice	Decreased	[95]
	R6/2 tg mice (depending on age)	Decreased, increased, ~	[94]
	Primary culture of striatal neurons expressing N-terminal Htt fragment	Decreased	[81, 117]
Complex IV (COX) activity	N171-82Q tg mice	Decreased	[80]
Mitochondrial movement	Cortical primary neurons expressing a N-terminal fragment and full length Htt	Decreased	[100]
Mitochondria transport machinery	Cortical primary neurons	Decreased	[101]

Fig. 1

