Huntington’s disease and mitochondrial alterations: emphasis on experimental models

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Abstract Huntington’s disease (HD) is an inheritable neurological disorder coursing with degeneration of basal ganglia and producing chorea and dementia. One common factor accounting for neurodegeneration in this disorder is mitochondrial deterioration at both morphologic and functional levels. The development of experimental models in animals or cell preparations to resemble pathologic and pathogenic conditions of this disorder has served for more than four decades to describe part of the mechanistic alterations that could be occurring in mitochondria of HD patients, and the subsequent design of therapeutic alternatives where mitochondrial alterations are the primary target. In this minireview we describe some of the most relevant studies at the experimental level, giving support to the hypothesis that mitochondria play a central role in HD pathogenesis.

Keywords Huntington’s disease • Mitochondrial alterations • Energy depletion • Neurodegeneration • Experimental models

Mitochondria and neuronal damage: basic concepts

Mitochondrial structure and function are regulated by biogenesis, fission, fusion, transport and degradation. Mitochondria are responsible for major biochemical functions needed for cellular homeostasis, and represent the main source of ATP. An adequate balance in these processes (mitochondrial dynamics) is essential for neuronal signaling, plasticity and neurotransmitter release. In addition, mitochondria are considered as mediators of cell survival and death since their proteins are factors regulating apoptosis. Indeed, mutations or abnormal expression of these factors are linked to neurodegenerative disorders (Büeler 2010).

In neuronal cells, maintenance of the respiratory chain complexes ensures the preservation of resting membrane potential (Martin et al. 1994). The appropriate maintenance of resting potential clearly depends on the activity of membrane ATPases, which in turn preserve the electrostatic gradient by modulating ion flux in cells. Mitochondria are recognized as essential for neuronal function because these cells possess a limited glycolytic capacity, turning them highly dependable on mitochondrial oxidative phosphorylation (OXPHOS) to fulfill the high energy requirements. Therefore, neuronal viability can be affected either by alterations in the capacity of neurons to maintain basal levels of energy, or simply through a sudden necessity to quickly respond to major energetic requirements (Lees 1993). OXPHOS is the major source of free radicals, including hydrogen peroxide ($\text{H}_2\text{O}_2$), hydroxyl radical ($\text{OH}$) and superoxide anion ($\text{O}_2^-\cdot$), all of them being byproducts of the cell respiratory cycle (Lemasters et al. 1999). Reactive oxygen species (ROS) generated by mitochondria have shown to target different molecules, including diverse mitochondrial components (lipids, proteins, DNA, etc.). In fact, the low reparative capacity of mtDNA makes itself a preferential target for further oxidative damage. Hence, mitochondrial dysfunction is a key event during the pathogenic cascade leading to necrotic or apoptotic cell death (Lemasters et al. 1999; Kroemer and Reed 2000). Upon oxidative stress and excessive cytoplasmic $\text{Ca}^{2+}$ upload conditions, mitochondria suffer a considerable loss.
of impermeability at the internal membrane, thereby leading to a full collapse of mitochondrial membrane potential ($\Delta \psi_m$), in a process currently known as permeability transition (PT). When PT is accompanied by mitochondrial swelling and cytochrome c release into the cytoplasm, the whole event activates certain caspases accounting for cell death (Murphy et al. 1999; Kroemer and Reed 2000). Under normal conditions, antioxidant defense systems are capable of reducing the deleterious actions of ROS; however, an accelerated production of ROS induced by altered mitochondria can decrease or even block these systems, leading to loss of ATP caused by transmembrane ATPases’ disruption, and further necrotic cell death by osmotic collapse (Dykens 1997, 1999). Moreover, a severe loss of mitochondrial function initiates apoptosis in response to a wide variety of stressors. For instance, excitotoxicity comprises excessive stimulation of glutamate receptors, including N-methyl-D-aspartate (NMDA) and other voltage-dependent and metabotropic receptors. Glutamate-mediated enhanced levels of intracellular calcium during excitotoxic episodes modify mitochondrial integrity and accelerate: ROS formation, leading to cell death (Dykens et al. 1987; Dykens 1994). Altogether, this evidence has served to suggest mitochondria as a key modulator for neuronal viability or death during excitotoxicity (Simpkins et al. 2010).

**Huntington’s disease and mitochondrial alterations**

Since a mechanistic point-of-view, one of the most fascinating neurodegenerative disorders associated with mitochondrial alterations is Huntington’s disease (HD), an autosomic dominant disease likely caused by a genetic mutation in position IT15. HD occurs when the gene for protein huntingtin (Htt), localized in region 4p16.3 at the short arm of chromosome 4, displays an expansion of cytosine-adenine-guanine (CAG) trinucleotide in exon 1, leading to the formation of mutant Htt (mHtt) which exhibits large repetitions of polyglutamine (Gusella et al. 1983; The Huntington’s Disease Collaborative Research Group 1993). In adults, HD is characterized by severe psychiatric disturbances, including irritability, aggressiveness and depression, and these signs precede involuntary motor alterations. Progression of these motor alterations—also known as choreiform movements—can be observed in three phases: 1) Slight involuntary movements are first accompanied by tremor; 2) Progressively, during the second phase (or hyperkinetic phase), patients lose coordination of the body due to the presence of abrupt involuntary movements (chorea), involving malfunction of muscles from head, thorax and limbs, thus limiting the capacities of patients to perform daily-tasks. A progressive decline in cognitive functions, accompanied by a massive loss of body weight, are characteristic of this phase; 3) In final phase, approximately 20 years after its onset, choreiform movements are replaced by rigidity and bradikinesia (Harper 1992).

The striatum is the most affected brain region in HD. Damage to this region is characterized by selective degeneration of medium-size spiny neurons, although in advanced stages the brain cortex is also affected, mostly presenting a notorious atrophy in pyramidal neurons from layers III, V and VI at motor and associative cortices (Cudkowicz and Kowall 1990; DiFiglia 1997; MacDonald and Halliday 2002). The abundant formation of inclusions, as well as a notorious loss of striatal GABAergic and cortical glutamatergic pyramidal neurons, are also evident.

A considerable amount of evidence suggests that mitochondrial dysfunction is directly or indirectly involved in HD (Reddy et al. 2009). By mean of the Positron Emission Tomography (PET), hypermetabolism has been observed in the caudate, putamen and cortex from symptomatic HD patients, as well as in non-symptomatic patients carrying the HD gene (Kuhl et al. 1982). Accordingly, glucose metabolism and $O_2$ formation are significantly decreased in basal ganglia and cerebral cortex from symptomatic patients (Kuwert et al. 1990; Beal 1992). The decreased mitochondrial metabolism is likely due to an alteration in the activity of mitochondrial complexes I and IV (Brenuan et al. 1985; Borlongan et al. 1997), a concept that is supported by ultrastructural studies in which abnormal mitochondria were observed in both early- and late-onset HD patients (Struys-Ponsar et al. 1994). In addition, defects in mitochondrial enzymes, such as succinate dehydrogenase (SDH, complex II) and aconitate, have been described in post mortem brains from HD patients (Tabrizi et al. 1999). Furthermore, Chen et al. (2007) described mitochondrial abnormalities and oxidative damage in peripheral blood from HD patients. Lim et al. (2008) also reported that mHtt expression induces mitochondrial calcium homeostasis disruption, and similar results were obtained from mitochondria isolated from cultured cells expressing mHtt (Milakovic et al. 2006), thus suggesting that mitochondrial dysfunction plays a central role in HD pathogenesis. Supporting evidence on this topic includes studies where lactate levels have been found increased in cerebrospinal fluid from HD patients (Jenkins et al. 1998), while altered enzyme activity involved in ATP production has been described in post mortem HD brain tissues: a reduction in the activity of mitochondrial complexes II, III and IV during the progression of HD was evidenced (Browne et al. 1997). More recently, a decreased metabolic ratio of brain glucose was observed in the striata of HD patients in early phases, suggesting that alterations in glycolytic metabolism is part of the initial degenerative—and probably causative-