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The interrelationship between mitochondrial dysfunction and transcriptional dysregulation in Huntington disease

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Abstract Huntington disease (HD) is an inherited neurodegenerative disease caused by an abnormal expansion of the CAG repeat region in the huntingtin (Htt) gene. Although the pathogenic mechanisms by which mutant Htt (mHtt) causes HD have not been fully elucidated, it is becoming increasingly apparent that mHtt can impair mitochondrial function directly, as well as indirectly by dysregulation of transcriptional processes. mHtt causes increased sensitivity to Ca^{2+}-induced decreases in state 3 respiration and mitochondrial permeability transition pore (mPTP) opening concurrent with a reduction in mitochondrial Ca^{2+} uptake capacity. Treatment of striatal cells expressing mHtt with thapsigargin results in a decrease in mitochondrial Ca^{2+} uptake and membrane potential and an increase in reactive oxygen species (ROS) production. Transcriptional processes regulated by peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α), which are critical for mitochondrial biogenesis, have been shown to be impaired in HD. In addition, the PPARγ signaling pathway is impaired by mHtt and the activation of this pathway ameliorates many of the mitochondrial deficits, suggesting that PPARγ agonists may represent an important treatment strategy for HD.

Keywords Mitochondria · Huntingtin · PGC-1α/PPARγ · Ca^{2+} · Respiration

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Introduction

Huntington disease (HD) is an autosomal dominant inherited disease caused by an abnormal expansion of CAG repeats in exon 1 of the huntingtin (Htt) gene located on chromosome 4p16.3, resulting in a pathological elongation of polyglutamine in the Htt protein. HD is one of nine polyglutamine diseases with the only common feature being the expansion of a polyglutamine domain in the disease-specific protein (Orr and Zoghbi 2007; Shao and Diamond 2007). HD patients exhibit neuronal degeneration predominantly in striatum and at the later stage of disease in cerebral cortex. GABAergic medium size spiny neurons (MSNs) undergo neurodegeneration, whereas interneurons survive in striatum of HD patients (Ferrante et al. 1991). Clinical manifestations of HD consist of progressive behavioral and motor abnormalities, psychiatric disturbance, and cognitive disorder. Although the mutation in Htt gene was discovered more than 17 years ago (The Huntington's Disease Collaborative Research Group 1993), the molecular role of Htt in the cell and the pathological mechanisms that result from the presence of mutant Htt (mHtt) are still under investigation. When intraneuronal aggregates containing mHtt were first discovered in the brain of HD patients and HD mouse models it was suggested that they had a causative role (Davies et al. 1997; DiFiglia et al. 1997; Scherzinger et al. 1997). However, more recent studies indicate that the aggregates in HD may not be a causative factor per se, and in fact may actually play a protective role, findings that have led investigators to concentrate on other pathogenic aspects in HD (Slow et al. 2006). A growing number of studies provide evidence that mHtt results in mitochondrial impairment such as defects in the electron transport chain (ETC) activity, reduced Ca^{2+} uptake capacity, and increased sensitivity of mitochondria to Ca^{2+}-induced

permeability transition pore (mPTP) opening. Furthermore, data now indicate that the translocation of mHtt into nucleus and transcriptional dysregulation likely play an important role in the pathogenic process (Saudou et al. 1998), and more specifically these events have a significant impact on mitochondria (Greenamyre 2007; Ross and Thompson 2006).

Indications of mitochondrial dysfunction in HD patients

Energetic impairment in HD patients has been observed in many studies by a variety of methods. For example, positron emission tomography (PET) scans that utilize ^{18}F-2-deoxyglucose (^{18}F-2-DOG) showed a significant reduction in glucose uptake in cortex and striatum of HD patients even prior to striatal neuronal loss and pathological symptoms (Gil and Rego 2008). Paradoxical increases in lactate have been observed in the cortex of symptomatic HD patients and in the striatum of presymptomatic HD patients using ^{1}H-magnetic resonance spectroscopy (MRS) (Jenkins et al. 1998). Furthermore, most HD patients suffer weight loss and muscle wasting in spite of constant food intake (Djousse et al. 2002; Kirkwood et al. 2001; Sanberg et al. 1981). These studies clearly indicate the involvement of bioenergetic deficits in HD.

Mitochondria are essential organelle that are involved in many vital processes such as energy production through oxidative phosphorylation (Oxphos) via the tricarboxylic acid (TCA) cycle, fatty acid oxidation and the electron transport chain (ETC), thermogenesis, cell death mechanisms, defense against reactive oxygen species (ROS), and Ca^{2+} buffering. Early ultrastructural studies using cerebral cortical tissue obtained from HD patients revealed abnormal neuronal mitochondrial morphology (Goebel et al. 1978; Tellez-Nagel et al. 1974). In addition, functional defects have been observed. For example, deficits in succinate dehydrogenase activity, a component of complex II of ETC as well as the TCA cycle, were observed in postmortem HD brains in 1974 (Stahl and Swanson 1974). Reduced expression of complex II subunits has been observed in striatum of HD patients (Benchoua et al. 2006). The activities of complex III in the caudate and putamen and complex IV in the putamen are also significantly decreased in HD cases (Gil and Rego 2008). The activity of aconitase, an essential enzyme in the TCA cycle, has been reported to be significantly decreased in the striatum and cerebral cortex (Tabrizi et al. 2000), and loss of the pyruvate dehydrogenase complex was observed in symptomatic patients with caudate/putamen atrophy (Butterworth et al. 1985; Sorbi et al. 1983). Concurrent with these changes in mitochondrial morphology and function, there is a significant decrease in mitochondrial DNA in the cerebral cortex of HD patients (Horton et al. 1995).

Although studies have focused primarily on the brain, mitochondrial abnormalities have been observed outside of the brain in HD cases. A deficit in complex I was first reported in muscle of HD patients (Arenas et al. 1998), although another recent study showed no significant differences in the activities of complexes I and IV (Turner et al. 2007). However, in this latter study, significant correlations between the activity of complexes II–III and disease duration/progress were noted, along with evidence of inclusion formation in HD muscle (Turner et al. 2007). ^{31}P-MRS showed significantly reduced ATP production in muscle of presymptomatic and symptomatic HD patients (Lodi et al. 2000). Other groups found out abnormal morphologies as well as decreased membrane potential in mitochondria from peripheral tissues including lymphoblasts and muscle of HD patients (Panov et al. 2002; Squitieri et al. 2006, 2010). As in the brain, mitochondrial DNA in leukocytes from HD patients was depleted (Liu et al. 2008).

Mitochondrial impairment in cell and mouse models of HD

Numerous studies in cell and mouse models of HD have revealed mitochondrial impairment. The hypothesis that mitochondrial dysfunction contributes to the pathogenesis of HD was first tested pharmacologically by using 3-nitropropionic acid (3-NP), an irreversible-, and malonate, a reversible inhibitor of succinate dehydrogenase. Administration of these inhibitors to animals results in pathological characteristics of HD such as marked increases in striatal lactate concentration and striatal lesions (Beal et al. 1993; Brouillet et al. 1993; Frim et al. 1993). In addition, mitochondria isolated from the striatum of adult rats are more sensitive to Ca^{2+}-induced mPTP opening than mitochondria from the cerebral cortex of adult rats (Brustovetsky et al. 2003). These and other findings suggest that mitochondria in striatal neurons, especially MSNs, are selectively vulnerable to metabolic stress which may contribute to the selective loss of these neurons in HD.

The first mouse model of HD, the R6/2 line, was produced by expressing exon 1 of the Htt gene with an expanded CAG repeat (Mangiarini et al. 1996). These mice have been used extensively in HD studies and exhibit mitochondrial abnormalities. R6/2 transgenic mice exhibit increases in mitochondrial DNA damage (Acevedo-Torres et al. 2009), and a significant reduction in aconitase and complex IV activities in striatum and complex IV activity in cerebral cortex (Tabrizi et al. 2000). A decreased stability of muscle mitochondria against Ca^{2+}-induced mPTP opening and an increased sensitivity of complex I-dependent respiration against Ca^{2+}-induced inhibition have been found

in R6/2 mice, leading to energetic deficits and muscle atrophy (Gizatullina et al. 2006).

Clonal striatal precursor cells established from striatal primordia of E16 embryos of wild-type ($STHdh^{Q7/Q7}$) and mHtt ($STHdh^{Q111/Q111}$) knock-in mice (Trettel et al. 2000) have been used in studies of mitochondrial function. Mitochondria from $STHdh^{Q111/Q111}$ striatal cells, show significantly reduced respiration and ATP production as compared with mitochondria from $STHdh^{Q7/Q7}$ striatal cells, when either glutamate/malate or succinate was used as the substrate, despite equivalent levels of ETC complex activities in the two cell lines. However, when the artificial electron donor TMPD/ascorbate for complex IV was used as the substrate, there was no difference in mitochondrial respiration between two cell lines (Milakovic and Johnson 2005). Taken together, these mouse and cell models exhibit mitochondrial impairment and metabolic deficits similar to the pathological characteristics that have been observed in HD (Damiano et al. 2010; Quintanilla and Johnson 2009). Interestingly, yeast expressing mHtt showed a significant reduction in mitochondrial Oxphos due to an alteration in complex II and III (Solans et al. 2006).

Ca^{2+} handling defects and mitochondrial membrane potential ($\Delta\Psi m$) depolarization

Panov et al. (2002) showed that mitochondria isolated from lymphoblasts of HD patients have decreased Ca^{2+}-buffering capacity and undergo mitochondrial membrane depolarization at lower Ca^{2+} concentrations. They also found similar abnormalities in mitochondria from YAC72 mice expressing full-length mHtt with a polyglutamine stretch of 72, but not from YAC18 mice expressing full-length Htt with a polyglutamine stretch of 18. Mitochondrial localization of mHtt as detected by immunocytochemistry and electron microscopy, suggested a direct interaction between mHtt and mitochondria (Panov et al. 2002). Choo et al. (2004) showed that huntingtin was present in the mitochondrial fraction purified from human neuroblastoma cells and clonal striatal cells and associated with the outer mitochondrial membrane. A recombinant truncated mHtt directly added to isolated mouse liver mitochondria significantly decreased the Ca^{2+}-threshold for mPTP opening, an effect that was abolished by cyclosporin A (CsA), an mPTP inhibitor. Mitochondria isolated from a knock-in (150/150) HD mouse showed a similar increased susceptibility to Ca^{2+}-induced mPTP opening (Choo et al. 2004). Mitochondria from $STHdh^{Q111/Q111}$ cells were more sensitive to Ca^{2+}-induced decreases in state 3 respiration and mitochondrial membrane potential than mitochondria from $STHdh^{Q7/Q7}$ cells (Milakovic et al. 2006). Importantly, mitochondria from $STHdh^{Q111/Q111}$ cells showed a significant reduction in Ca^{2+} uptake capacity compared with mitochondria from $STHdh^{Q7/Q7}$ cells (Lim et al. 2008; Milakovic et al. 2006). ADP treatment attenuated the mitochondrial membrane potential defect and CsA treatment prevented the decreases in Ca^{2+} uptake capacity (Milakovic et al. 2006). Striatal neurons from Hdh150 knock-in mice exhibit increased susceptibility to Ca^{2+}-deregulation by NMDA receptor activation than striatal neurons from wild type littermates, when pyruvate instead of glucose is used in media to emphasize Oxphos dependent bioenergetics (Oliveira et al. 2007). These findings clearly indicate that mHtt induces Ca^{2+} handling defects, respiratory deficits, and increased sensitivity to Ca^{2+}-inducded mPTP opening in mitochondria.

In addition to increasing the sensitivity of mitochondria to Ca^{2+}-induced mPTP opening, mHtt could contribute to the vulnerability of MSNs by causing increased Ca^{2+} loading. mHtt directly interacts with C-terminal region of the type 1 inositol 1,4,5-trisphosphate (InsP3) receptor (InsP3R1), resulting in increased sensitivity of InsP3R1 to activation by InsP3 (Tang et al. 2003). The implication of InsP3R1 activation for mHtt-induced toxicity was corroborated in MSN cultures from a HD mouse model using a pharmacological approach (Tang et al. 2005) and in a Drosophila HD model using genetic experiments (Kaltenbach et al. 2007). Moreover, mHtt enhances the activity of N-methyl D-aspartate receptors (NMDARs) harboring the NR2B subunit, resulting from increased NMDAR trafficking to the plasma membrane (Fan et al. 2007; Sun et al. 2001; Zeron et al. 2002). Importantly, MSNs express high levels of the NR2B subunit, implying a greater sensitivity to excitotoxicity caused by NMDAR activation (Heng et al. 2009; Rigby et al. 1996). In addition, inhibition of mPTP opening by treatment with CsA and bongkrekic acid significantly diminished NMDA-induced Ca^{2+} influx and mitochondrial membrane potential loss in MSNs of YAC128 mouse (Fernandes et al. 2007). Similarly, Htt is likely to have an effect on the function of the voltage-gated Ca^{2+} channels (VGCCs), because Htt associates with the synaptic protein interaction (synprint) region of N-type VGCC (Swayne et al. 2005) and the $\alpha2/\delta$ auxiliary subunit of VGCC (Kaltenbach et al. 2007), and MSNs from R6/2 mice at 3–6 weeks of age show increases in voltage-gated Ca^{2+} conductances (Cepeda et al. 2007). Photoreceptor neurodegeneration in an HD fly model expressing a full length of mHtt with a polyglutamine stretch of 128 was rescued by removing one copy of Dmca1D (a L-type VGCC pore subunit of Drosophila) (Romero et al. 2008).

Involvement of transcriptional dysregulation in mitochondrial impairment in HD

Initial studies showed that mHtt interferes with cAMP-responsive element (CRE) binding protein (CREB) mediated

transcriptional processes through direct interaction with CBP (CREB-binding protein) (Steffan et al. 2000) and with TATA box-binding protein (TBP)-associated factor TAF4/TAFII130 (Dunah et al. 2002; Shimohata et al. 2000), leading to an increase in mHtt-induced cytotoxicity (Steffan et al. 2001).

The peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) is an orchestrator of mitochondrial function via integration of signals that regulate mitochondrial biogenesis and respiration, detoxification of ROS, energy metabolism, and thermogenesis (Houten and Auwerx 2004). PGC-1α interacts with a number of transcription factors including PPARγ of the PPAR family, which regulates adipogenesis and lipid metabolism, and the nuclear respiratory factor-1/2 (NRF-1/2) which play a pivotal role in mitochondrial respiration. The expression of PGC-1α is repressed in both in vitro and in vivo models of HD, at least partially due to the fact that mHtt directly interferes with the CREB/TAF4 signaling pathway which is a predominant regulator of PGC-1α expression (Cui et al. 2006). The reduced level of cAMP in HD mice and HD patients likely contributes to the significant reduction in CREB activation (Gines et al. 2003). Since CREB is one of major transcription factors for PGC-1α, cAMP reduction may affect the expression of PGC-1α. A role for PGC-1α in the pathogenesis of HD is further supported by the studies showing that primary striatal neurons are significantly protected from mHtt-induced toxicity by exogenous expression of PGC-1α and lentiviral delivery of PGC-1α into the striatum of HD mice attenuates the atrophy (Cui et al. 2006).

PPARγ plays a central role in genes involved in fatty acid oxidation and mitochondrial function. PPARγ heterodimerizes with retinoid X receptor (RXR) in the presence or absence of ligand (Glass and Ogawa 2006). Upon ligand binding, PPARγ transactivates the target genes with the support of coactivators such as PGC-1α. Clinically important exogenous ligands of PPARγ are thiazolidinediones (TZDs) (rosiglitazone, pioglitazone, troglitazone). TZDs are used in the treatment of type II diabetes. Recent studies demonstrate that TZDs show protective effects in models of Alzheimer's disease (Heneka et al. 2005; Landreth 2006),

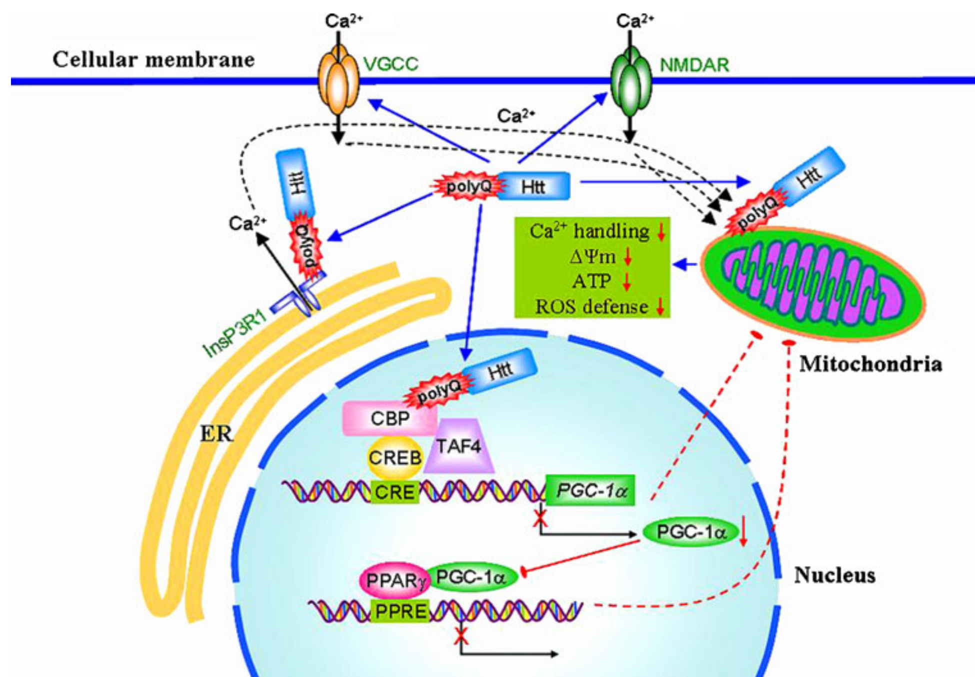

Fig. 1 Schematic Diagram of Mitochondrial Impairment Caused by Mutant Huntingtin. Mutant huntingtin (mHtt) enhances the activities of: (1) NMDA receptors (NMDARs), especially those containing NR2B subunit via increased receptor trafficking, (2) voltage-gated Ca^{2+} channels (VGCC) via association with mHtt at the cellular membrane, and (3) type 1 inositol 1,4,5-trisphosphate (InsP3) receptor (InsP3R1) via direct interaction with mHtt in the endoplasmic reticulum (ER), effects that lead to increased Ca^{2+} loading. mHtt translocates into nucleus and interferes with CREB-dependent transcriptional processes by binding to CREB-binding protein (CBP) and TBP-associated factor 4 (TAF4), which at least in part leads to transcriptional down-regulation of peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α). Impairment of the PGC-1α pathway by mHtt may give rise to the decreased activity of PPARγ. Since PGC-1α and PPARγ play a pivotal role in mitochondrial biogenesis and respiration, energy metabolism, thermogenesis, and detoxification of reactive oxygen species (ROS), the defects in PGC-1α/PPARγ pathway is likely in turn to contribute to mitochondrial impairment in HD. As a result of increased Ca^{2+} loading and impaired transcriptional processes, mitochondria in HD undergo functional deficits including Ca^{2+} handing defects, a decrease in ATP production, an increased sensitivity of mitochondrial membrane potential ($\Delta\Psi$m) loss to Ca^{2+} loading, and a decrease in ROS defense

Parkinson's disease (Breidert et al. 2002), amyotrophic lateral sclerosis (Kiaei et al. 2005), stroke (Luo et al. 2006), and multiple sclerosis (Niino et al. 2001). More importantly, we found out that STHdh$^{Q111/Q111}$ cells exhibit significant decreases in PPARγ activity, that thapsigargin induced a decrease in mitochondrial membrane potential and an increase in ROS production only in STHdh$^{Q111/Q111}$ cells, and that PPARγ activation by rosiglitazone treatment protected STHdh$^{Q111/Q111}$ cells from thapsigargin-induced mitochondrial membrane potential loss and ROS production (Quintanilla et al. 2008). These studies suggest that PGC-1α/PPARγ could be contributing factors in mitochondrial deficits in HD and the activation of PGC-1α/PPARγ could result in the protection of striatal neurons from mHtt toxicity.

Concluding remarks

The pathogenic mechanisms of HD have been shown to involve mitochondrial deficits such as increased sensitivities to Ca^{2+}-induced decreases in state 3 respiration and to Ca^{2+}-induced mPTP opening, a decrease in ATP production and in Ca^{2+} uptake capacity, and an increase in ROS production. mHtt could contribute to the vulnerability of MSNs by causing increased Ca^{2+} loading via increased activities of InsP3R1, NMDARs, and VGCCs. mHtt can impair mitochondrial function directly, as well as indirectly by dysregulation of transcriptional processes. PGC-1α/PPARγ pathway has been shown to be disrupted in HD patients and HD models, at least in part due to the interference with CREB/TAF4 signaling pathway. The activation of PGC-1α/PPARγ leads to the protective effects in HD models (Fig. 1). These findings may lead to a deeper understanding of the pathogenic mechanism of HD and suggest a potential approach of therapeutics for HD.

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