Free Radical Biology and Medicine 62 (2013) 37–46

Contents lists available at SciVerse ScienceDirect

Free Radical Biology and Medicine

journal homepage: www.elsevier.com/locate/freeradbiomed

Review Article

PGC-1α, mitochondrial dysfunction, and Huntington's disease

Ashu Johri*, Abhishek Chandra, M. Flint Beal

Department of Neurology and Neuroscience, Weill Medical College of Cornell University, New York–Presbyterian Hospital, New York, NY 10065, USA

ARTICLE INFO

Available online 19 April 2013

Keywords:
PGC-1α
PPARs
SIRT1
SIRT3
Mitochondrial dysfunction
Huntington's disease
Oxidative stress
Energy metabolism
Mitochondrial dynamics
Mitophagy
Neurodegeneration
Therapeutics

ABSTRACT

The constant high energy demand of neurons makes them rely heavily on their mitochondria. Dysfunction of mitochondrial energy metabolism leads to reduced ATP production, impaired calcium buffering, and generation of reactive oxygen species. There is strong evidence that mitochondrial dysfunction results in neurodegeneration and may contribute to the pathogenesis of Huntington's disease (HD). Studies over the past few years have implicated an impaired function of peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α), a transcriptional master coregulator of mitochondrial biogenesis, metabolism, and antioxidant defenses, in causing mitochondrial dysfunction in HD. Here we have attempted to discuss in a nutshell, the key findings on the role of PGC-1α in mitochondrial dysfunction in HD and its potential as a therapeutic target to cure HD.

Contents

Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by the expansion of a CAG repeat in the gene encoding the protein huntingtin, leading to expression of mutant huntingtin with expanded polyglutamine repeats [1]. The expansion of polyglutamine repeats results in acquisition of an altered conformation by mutant huntingtin, which in turn causes the protein to aggregate. The function of normal huntingtin protein has not been fully elucidated yet, but it is known to be associated with synaptic vesicles and microtubules, and is an essential scaffold protein regulating axonal transport of vesicles including brain-derived neurotrophic factor (BDNF) [2–7]. The huntingtin protein was recently shown to play a role linking the glycolytic enzyme GAPDH to vesicles, to supply energy from glycolysis for fast axonal transport [8]. Both a gain-of-function (for mutant huntingtin) hypothesis and a loss-of-function (for normal huntingtin) hypothesis have been put forward to explain HD pathogenesis. Patients with HD have CAG repeat lengths above

Abbreviations: BAT, brown adipose tissue; HD, Huntington's disease; HNE, 4-hydroxynonenal; MBP, myelin basic protein; MDA, malondialdehyde; NOX-NADPH, oxidase; 3-NP, 3-nitropropionic acid; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; OXPHOS, oxidative phosphorylation; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PPAR, peroxisome proliferator-activated receptor; ROS, reactive oxygen species.

* Corresponding author. fax: +1 212 746 8276.
E-mail addresses: johri.ashu@gmail.com, asj2002@med.cornell.edu (A. Johri).

0891-5849/$ - see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.freeradbiomed.2013.04.016

36, with variable penetrance of repeat lengths 36–39 and complete penetrance above 39 repeats; longer repeat lengths (>60) have been associated with juvenile-onset HD [9]. Disease manifestations can begin at any time in life; the most common age range of onset is between 30 and 50 years old, although it occurs in children and the elderly as well. The juvenile variant of HD usually results from paternal transmission and is associated with increased severity as well as with a more rapid progression of the disease.

HD is characterized by progressive motor impairment, personality changes, psychiatric illness, and gradual intellectual decline. Pathologically, there is a preferential and progressive loss of the medium spiny neurons (MSNs) in the striatum, as well as cortical atrophy, and degeneration of other brain regions later in the disease. There are no currently available treatments to delay disease onset or retard its progression, and the focus of medical care is limited to symptom management and maximizing function. Transcriptional dysregulation, protein aggregation, mitochondrial dysfunction, and enhanced oxidative stress have been implicated in the disease pathogenesis. A key feature of HD patients is pronounced weight loss, despite sustained caloric intake. Deficits in energy expenditure have been linked with mitochondrial dysfunction in HD. The evidence for mitochondrial dysfunction in HD has been reviewed earlier [10–12]; we have summarized a few key findings in the following discussion.

Mitochondrial dysfunction in HD

There is extensive evidence for bioenergetic deficits and mitochondrial dysfunction in HD, such as a pronounced weight loss despite sustained caloric intake, nuclear magnetic resonance spectroscopy showing increased lactate in the cerebral cortex and basal ganglia, decreased activities of oxidative phosphorylation (OXPHOS) complexes II and III, and reduced aconitase activity in the basal ganglia, abnormal mitochondrial membrane depolarization in patient lymphoblasts, abnormal ultrastructure of mitochondria in cortical biopsies obtained from patients with both juvenile and adult-onset HD, and pathologic grade-dependent reductions in numbers of mitochondria in HD postmortem brain tissue; and in striatal cells from mutant huntingtin-knockin mice, both mitochondrial respiration and ATP production are significantly impaired (reviewed in [11]). It was shown that ATP production is decreased as a function of CAG repeat length in human HD lymphoblastoid cell lines [13]. Studies of mitochondria isolated from HD patients and mice indicated that HD mitochondria depolarize at decreased calcium ion levels, and mutant huntingtin protein may directly interact with mitochondria to exert this effect [14–16].

We showed that the phenotypic and neuropathologic features of HD can be modeled in rodents and primates, with the mitochondrial toxin 3-nitropropionic acid (3-NP) [17]. We and others have shown impaired brain creatine kinase activity and significant alterations in levels of high-energy phosphate intermediates in transgenic mouse models of HD [18,19]. We also found a reduction in numbers and size of mitochondria identified by a reduction in immunohistochemical markers for cytochrome c oxidase subunit 2, superoxide dismutase 2, and cytochrome *c* (Cyt c) in the preferentially vulnerable striatal calbindin-positive neurons in moderate-to-severe grade HD patients, which worsened with increasing disease severity [20]. Using electron microscopy, we showed small degenerating and/or degenerated mitochondria and a reduced mitochondrial density in the striatum of the R6/2 transgenic mouse model of HD [21]. Abnormal mitochondrial morphology was seen in neurons expressing mutant huntingtin exon1-Q46 or Q97, as opposed to normal mitochondrial morphology observed in wild-type huntingtin exon1-Q17-expressing neurons [22]. Abnormal morphology and an increased mitochondrial fragmentation were also observed in fibroblasts from juvenile and adult-onset HD patients [22]. We also showed irregular mitochondrial morphology and distribution in muscles of NLS-N171-82Q and R6/2 transgenic mouse models of HD [21,23].

We and others have shown abnormalities in mitochondrial dynamics: Dynamin-related protein 1 (Drp1, involved in mitochondrial fission) was found to be significantly increased and mitofusin 1 (Mfn1, involved in mitochondrial fusion) was significantly decreased [20,22,24,25]. A direct interaction of mutant huntingtin with mitochondria or with various protein complexes has also been proposed to play an important role in disease pathogenesis, by regulating mitochondrial fission–fusion events, mitochondrial trafficking along axons and dendrites, and mitochondrial distribution [22,25–29] (Fig. 1). Expression of mutant huntingtin causes abnormal mitochondrial ultrastructure, impaired calcium buffering, bioenergetic defects, and mitochondrial DNA (mtDNA) deletions, all of which may be a consequence of a failure to maintain a balance between mitochondrial fission and fusion.

Mitochondrial turnover is dependent on autophagy, which declines with age and is frequently dysfunctional in neurodegenerative diseases [30]. Mitochondrial reactive oxygen species (ROS) production and oxidation of mitochondrial lipids have been shown to play a role in autophagy. Mitophagy denotes the degradation of mitochondria through macroautophagy. Through mitophagy, cells regulate mitochondrial number in response to their metabolic state and also implement a quality control system for selective elimination of damaged/defective mitochondria. Changes in mitochondrial dynamics that redistribute defective mitochondrial components, and/or increase fission or decrease fusion, facilitate isolation of damaged mitochondria and their subsequent elimination by mitophagy. Defective mitochondrial fission can yield uneven products, with one depolarized daughter mitochondrion and one hyperpolarized mitochondrion [31]. Such depolarized mitochondria are much less likely to fuse, have reduced levels of OPA1 protein, and are eventually autophagocytosed. Excessive fusion, on the other hand, prevents autophagic mitochondrial degradation and protects mitochondria from massive degradation by starvation-induced autophagy [32,33]. When mitophagy is compromised, oxidized proteins accumulate, and cellular respiration decreases. As mitochondrial energy production and metabolic pathways supply energy for ion exchange pumps whose function is to maintain an electrochemical gradient across the mitochondrial membrane, defective energy metabolism could translate into an enhanced susceptibility of HD mitochondria to undergo depolarization and eventually mitophagy. A number of studies have evaluated this, and have found that mitochondria from HD patients are exquisitely sensitive to depolarizing stresses. In one study, treatment of HD lymphoblasts with complex IV inhibitors resulted in mitochondrial depolarization and apoptotic cell death involving caspase activation [34]. In another study, electrical measurements of HD lymphoblast mitochondria yielded lower than normal membrane potentials and depolarization in response to modest Ca^{2+} loads [15]. More recently, Martinez-Vicente et al. [35] have shown that HD pathology is associated with autophagic cargo recognition defects that lead to slower turnover, functional decay, and accumulation of damaged mitochondria in the cytoplasm.

Oxidative damage in HD

Mitochondria are both targets and important sources of ROS. Increased levels of ROS including superoxide ($O_2^{\bullet-}$), hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\bullet}OH$), and reactive nitrogen species such as peroxynitrite ($ONOO^-$) impair cellular function by degrading proteins, lipids, and nucleic acids. It has been shown that oxidative stress stimulates mitochondrial fission; the addition