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Mitochondrial matters in Huntington disease

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Abstract Huntington Disease (HD) is a relatively common inherited neuropathy with characteristic cognitive and behavioral features. HD usually has a late onset and often is not recognized until the third or fourth decades of life. Transmitted as an autosomal dominant trait, HD has become a prototype for understanding a group of neurogenetic disorders. As a class, HD and the others are manifestations of the expansion of a trinucleotide repeat within the gene coding or structural region. In HD expansion of the $(CAG)_n$ repeat in the first exon from an average of 18 (normal) to a median of 44 is the underlying molecular biologic change. In affected individuals, the mutant HD protein (*Huntingtin,* mHtt) thus contains an extended polyglutamine repeat. Clinical and neuropathic changes in the caudate and putamen nuclei occur relatively early with other brain regions being affected later. Mitochondrial structure, altered electron transport and increased brain lactate levels have implicated mitochondria in HD pathophysiology. There is also evidence that reduced transcription of the peroxisome proliferator-activated receptor-γ coactivator (PGC-1α) leads to altered downstream gene regulation. Further evidence for mitochondrial involvement is presented in the following reviews. Clarifying mitochondrial derangements has led to some possibilities for therapeutic intervention.

Keywords Huntington · DNA amplification · DNA repeat · Movement disorder · Mitochondrion · Neuropathy · Reactive oxygen species · PGC-1α

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Introduction

Although there were earlier descriptions, the American George Huntington described this disorder, which he and his father had observed in several patients, in 1872. He noted concentration of the disorder in families and also noted that if a family member failed to develop the symptoms he or she would not have affected offspring. Huntington Disease (HD, OMIM #143100) is usually well-recognized and is one of the most frequently encountered forms of hereditary neuropathy in referral centers.

As is common in many autosomal dominant conditions, the clinical picture of HD is pleiotropic and varies within a recognized spectrum of presentations. The earliest manifestations often are psychologic with depression, mood changes and even psychosis. Suicide has been noted in affected individuals. Memory and poor attention often develop relatively early but may progress very slowly. The most easily recognized feature is usually the movement disorder. Sometimes restlessness or "fidgeting" is all that is noted but the characteristic chorea (from Gk "dance") almost always becomes prominent over time. The movements vary in complexity but are widespread, involuntary and uncoordinated.

Progressive neuropathologic changes include loss in mass in the heads of caudate and putamen nuclei. More moderate atrophy of frontal and temporal gyri can develop, usually later. The medium-size spiny neurons appear particularly susceptible. Perinuclear densities also accumulate.

The relatively late onset of HD symptoms (often in 4th decade and later) and the autosomal dominant inheritance pattern has led to the development of large kindreds with affected members over many generations. A large US kindred has been traced from 17th century immigrants and likely included affected members de-

scribed by Huntington. Studying a particularly large kindred near lake Maracaibo in Venezuela led to the first genetic marker mapping for a neurologic disorder. Gusella et al. (1983) identified a polymorphic marker near the terminus of human chromosome 4 (4p16.3) that cosegregated with the HD phenotype, marking a new era in the application of molecular genetics to neurology. The gene and its mutation proved difficult to characterize more fully, however, and it took ten years for the gene (*Huntingtin*) to be identified (The Huntington's Disease Collaborative Research Group 1993). The actual mutation proved to be a surprise because it was not a simple nucleotide change (with a corresponding amino acid alteration). Instead, the first exon of the gene contains an in-frame $(CAG)_n$ trinucleotide repeat, coding for glutamine$_n$. The length of the $(CAG)_n$ domain was found to be genetically unstable and susceptible to expansion. Very long tandem repeats were found in affected individuals. This pattern of amplification of trinucleotide repeats has now been identified in multiple neurogenetic disorders. Identifying this genetic mechanism now permits both prenatal and presymptomatic diagnosis for HD because the median number of repeats in unaffected individuals is 18 while affected individuals have 36–121 repeats (median 44) (Kremer et al. 1994). Expansion of the $(CAG)_n$ repeat appears more likely to occur in individuals with certain haplotype variants on chromosome 4 (Warby et al. 2009). This is consistent with the relatively high frequency of these haplotypes in Western Europeans (where HD is more common) in comparison with Asians and Africans.

The *Huntingtin* protein is 348 kD and widely expressed. Despite progress in characterizing the molecular genetics of HD, the pathophysiology of the mutant protein (mHtt) remains unsettled. Proteomic studies imply that mHtt slows proteosomal degradation (to some degree proportional to increased mHtt length). This likely explains the perinuclear densities noted above. The proposed disease pathways are not necessarily mutually exclusive and there is reason to suspect that all may participate in the final picture. mHtt binds the cyclic AMP response element (CREB)-binding protein and thus can alter CREB-regulated gene expression. Similarly, it can interfere with Sp1-mediated transcription.

An important recent observation is that Rhes, a small guanine nucleotide-binding protein, localized to the striatum, binds to mHtt at physiologic concentrations. In cultured cells, Rhes induces sumoylation of mHtt and cytotoxicity (Subramaniam et al. 2009). This observation can account for the relatively localized neuropathologic changes in HD.

That mHtt has effects on mitochondria is supported by findings that include altered mitochondrial structure(s), altered electron transport, elevated brain lactate levels and other features. In 2006 Cui et al. showed that mHtt binds to the promoter and interferes with transcription of the peroxisome proliferator-activated receptor-γ (PPARγ) co-activator 1α (PGC-1α). Interestingly, this transcription is CREB-dependent so mHtt could achieve this effect in two ways. HD was associated with reduced expression of PGC-1α-regulated genes in the striatum (including proteins in the electron-transport chain) by Weydt et al. (2006) and overexpression of PGC-1α by lentiviral induction reduced the striatal neuronal atrophy that normally occurs in HD-transgenic mice (Cui et al. 2006). These observations implicate defective PGC-1α gene regulation as central to the neuropathology of HD. They do not, by themselves, unequivocally distinguish brain regions in terms of susceptibility.

Brief overview of contributions to this minireview series

The reviews in this issue examine several aspects of mitochondrial physiology in HD. Oliveira (2010) reports in situ studies showing reduced failure to recover from NMDA receptor activation and altered calcium buffering in HD cells. Altered mitochondrial morphology was found in HeLa cells transgenic for mHtt. The data presented indicate that striatal astrocytes have reduced striatal synaptic glutamate clearance.

Jin and Johnson (2010) review mHtt effects in neurons. These include altered calcium handling, respiratory changes and increased sensitivity to calcium-induced mPTP opening. There also is a decrease in state 3 respiration. They recount the earlier evidence for impaired PPARγ signaling in HD and raise the interesting possibility that thiazolidinediones might have beneficial (?therapeutic) effects as agonists.

Pandey et al. (2010) report finding mHtt on the outer mitochondrial membrane. Increasing $(CAG)_n$ length is associated with increased mitochondrial depolarization in HD lymphoblasts. Reduced electron transport (Complex I), net respiration and ATP levels appear to antedate neuropathic changes in HD-knock-in mice. Both neuronal mitochondrial trafficking and mitochondrial integrity (altered fusion and fission) appear altered in HD. There also is reduced calcium loading capacity in HD mitochondria.

Perez-de la Cruz et al. (2010) note that PET studies have shown changes in caudate, putamen and cortex in both HD and presymptomatic HD individuals. They also describe two interesting animal toxicity models and their parallels to the pathophysiology of HD. 3-nitropropionic acid leads to succinic dehydrogenase (SDH) inhibition and altered mitochondrial energetics. Interestingly, the NMDA inhibitor MK-801 can minimize some of these effects. Quinolinic

acid leads to altered mitochondria, ATP levels and calcium physiology.

Turner and Schapira (2010) review the basic metabolic changes in HD brains. The recall that lactate production level and choline levels increase with (CAG) repeat length with complementary reduction of striatal N-acetyl aspartate. Additional localization was supported by effects of reactive oxygen species on aconitase levels—lowest in striatum, next in putamen and finally in the cortex. They also review the useful R6/2HD transgenic mouse and its use in studies of possible therapeutic effects of creatine, ubiquinone and remacemide.

Clearly, mitochondrial physiology is central to the manifestations of HD. There are several features that make these studies promising for possible therapeutic inventions. First, HD is usually readily recognizable in kindreds. Second, presymptomatic diagnosis of HD can now be achieved by molecular assays. Third, there is a prolonged presymptomatic period (measured in decades) implying extended time for intervention(s). Fourth, PGC-1α is part of a recognized pathway for which pharmacologic agents are being developed (and some already are in use). These and other characteristics help delineate useful directions for study.

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