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Energy defects in Huntington's disease: Why “in vivo” evidence matters

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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 most striking neuropathological change in HD is the early atrophy of the striatum. While the disease progresses, other brain structures also degenerate, including the cerebral cortex. Changes are also seen outside the brain, in particular weight loss/cachexia despite high dietary intake. The disease is caused by an abnormal expansion of a CAG repeat in the gene encoding the huntingtin protein (Htt). This mutation leads to the expression of a poly-glutamine stretch that changes the biological functions of mutant Htt (mHtt). The mechanisms underlying neurodegeneration in HD are not totally elucidated. Here, we discuss recent results obtained in patients, animal and cellular models suggesting that early disturbance in energy metabolism at least in part associated with mitochondrial defects may play a central role, even though all data are not congruent, possibly because most findings were obtained in cell culture systems or using biochemical analyses of post mortem tissues from rodent models. Thus, we put a particular focus on brain imaging studies that could identify biomarkers of energy defects in vivo and would be of prime interest in preclinical and clinical trials testing the efficacy of new therapies targeting energy metabolism in HD.

Contents

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1. Introduction

Mitochondria play central roles in cell survival by controlling energy metabolism, apoptosis pathways and Ca^{2+} homeostasis [1–4]. The hypothesis of a role of mitochondria in Huntington's disease (HD) has been initially substantiated by the observation of biochemical anomalies in the respiratory chain enzymes in mitochondria prepared from the striatum of HD patients. It was also shown that mitochondrial toxins could produce preferential striatal degeneration. Since these pioneering studies in the 80's and early 90's, the mutation responsible for HD has been identified, the gene (HTT) cloned, and many genetic animal models have been studied to decipher the pathogenesis of HD. Since, accumulating evidence indicate that mitochondria are key players in HD pathogenesis [5].

In the first part of the present review, we will provide a brief overview of the mitochondrial defects that are suspected to play a key role in HD, with a focus on the most recent studies. The core of many convincing findings was mostly obtained using genetic models of HD in cells or animals using biochemical, cellular biology and transcriptomic studies. These studies improved our understanding of the "mitochondrial" hypothesis. However, in vivo observations of energy defects in patients or animal models are scarcer. Thus, in a second part, we will review data obtained by non-invasive imaging and spectroscopy methods in the brain. These challenging approaches could improve the follow up of energy metabolism in vivo in the brain of animal models and human HD gene carriers. This would be of major interest in preclinical and clinical trials testing the efficacy of novel therapeutics, especially those targeting the mitochondria.

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 in the exon 1 of the gene encoding for the Huntingtin protein (Htt) [6]. HD is characterized by involuntary abnormal movements and postures (chorea, dyskinesia, dystonia) [7]. Other symptoms consist of mood, psychiatric disturbances and cognitive deficits characterized by a perseverative behavior 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. Several cerebral regions show signs of neurodegeneration in HD. However, the most striking neuropathological hallmark of this disorder is the atrophy of the striatum as seen using post mortem histological evaluation [8]. Non-invasive brain magnetic resonance imaging (MRI) [9–12] confirmed severe striatal atrophy in patients with symptoms. MRI studies in large cohort of mutant HTT gene carriers with no detectable symptoms (i.e. pre-symptomatic or pre-manifest) showed that the caudate and putamen are atrophied even ten years before onset [9–11]. The disease preferentially affects the GABAergic medium size spiny neurons of the striatum that project to substantia nigra reticulata and pallidum whereas large cholinergic interneurons and medium size (aspiny) interneurons are preserved in the HD striatum [13,14]. Cortical atrophy and early degeneration of the hypothalamus are also important aspects of HD pathogenesis, and late stage HD patients show widespread brain degeneration [15].

Many genetic models of HD have been generated in flies, worms and mammals (mice, rats, pigs, sheep, monkeys) [16–18]. Among all these animal models, rodent models are the most commonly studied [19,20]. The R6/2 and R6/1 transgenic mouse models of HD which overexpress human exon 1 of the HD gene have a very strong behavioral phenotype with short life span and has been the most studied model so far. Other transgenic models express the entire mutant human gene under its own promoter (YAC128Q mice, BACHD mice and rats) show a milder and more progressive neurological phenotype with limited/absent neurodegeneration [21]. 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, zQ175). Excellent reviews have been released for a comprehensive review of these models, all very different but complementary depending on the research to be conducted [20,22–25].

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 [26–29].

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 including calpain [30–34] and caspases [35–37]. Other proteases, all of which have not been identified yet play also key roles [38,39]. Compelling evidence has shown that the N-terminus fragments of mutant Htt recapitulate several aspects of the full-length mutant protein's toxicity [40]. 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 [21]. And recently, it has been demonstrated that the C-terminal part of Htt generated by cleavage of the full length mutant Htt is toxic. By binding and inactivating dynamin 1, the C-terminal part of mutant Htt generates endoplasmic reticulum (ER) dilation and cell toxicity