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The chicken or the egg: mitochondrial dysfunction as a cause or consequence of toxicity in Huntington's disease

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ABSTRACT

Mitochondrial dysfunction and ensuing oxidative damage is typically thought to be a primary cause of Huntington's disease, Alzheimer's disease, and Parkinson disease. There is little doubt that mitochondria (MT) become defective as neurons die, yet whether MT defects are the primary cause or a detrimental consequence of toxicity remains unanswered. Oxygen consumption rate (OCR) and glycolysis provide sensitive and informative measures of the functional status MT and the cells metabolic regulation, yet these measures differ depending on the sample source; species, tissue type, age at measurement, and whether MT are measured in purified form or in a cell. The effects of these various parameters are difficult to quantify and not fully understood, but clearly have an impact on interpreting the bioenergetics of MT or their failure in disease states. A major goal of the review is to discuss issues and coalesce detailed information into a reference table to help in assessing mitochondrial dysfunction as a cause or consequence of Huntington's disease.

Contents

1. Introduction

Alzheimer's (AD), Parkinson's (PD), and Huntington's disease (HD) share the property that mitochondria (MT) do not keep up with the energy demands of the cell (Arun et al., 2016; Carvalho et al., 2015; Chaturvedi and Flint Beal, 2013; Lane et al., 2015). However, AD, PD, and HD display region-specific cell death (Chaturvedi and Flint Beal, 2013; Grimm et al., 2016; Gu et al., 1996; Requejo-Aguilar and Bolanos, 2016) and even within those regions, only select cell types are targeted (Halliday et al., 1998; Reiner et al., 1988). In HD, for example, the toxic disease-causing protein is ubiquitously expressed, but initially, only the medium spiny neurons in the striatum are targeted for death (Reiner et al., 1988; Reinius et al., 2015). Regional specificity, therefore, implies that MT dysfunction develops in response to changing cellular metabolism. Mitochondrial dysfunction in cells is measurable by changes in membrane potential (de Groot and Burgas, 2015; Lane et al., 2015), low threshold for mitochondrial transition pore opening (Brustovetsky et al.,

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2003; Quintanilla et al., 2013), abnormalities in calcium dynamics (Duchen, 2012; Lim et al., 2008; Panov et al., 2002), and low ATP production (Gines et al., 2003; Seong et al., 2005), yet these well-established properties have not directly led to an obvious understanding of the age- and region-specific nature of the disease.

The early disturbances in the HD brain are likely to be the source of toxicity and the most effective point of therapeutic intervention. However, the basis for early toxicity and region-specific sensitivity is unknown, and is one of the most puzzling aspects of this disease. Impaired ATP production and bioenergetics are widely reported, but the results are often inconsistent, and vary depending on sample. e.g., the particular HD model mouse strain used, the age at the time of the measurements, and whether the system was a tissue, cell, or purified MT, and the buffer conditions under which they were measured. The effect of some of these factors on measurements has been noted previously (Brustovetsky, 2015). It remains enigmatic whether MT effects are a primary cause or a late-stage consequence of toxicity. The role of MT, therefore, needs to be clarified. In this review, we will focus on the bioenergetics in models of Huntington disease, taking note of the sample source, strain, age, and buffer conditions to address whether mitochondrial dysfunction occurs, and how much it contributes to disease progression. The major results are compiled in a Table summary (Table 1).

Due to the sheer volume of information, (1) we restrict the review to only HD, the caveat being that there may be key metabolic differences among neurodegenerative disorders, and that the discussion would not be able to include all the published work. (2) We will divide as best we can the observations in the literature into two groups; those that are directly related to metabolic dysfunction and those whose association is circumstantial, i.e. not accompanied by direct measures of mitochondrial respiration. The latter are considered to be important, but cannot be distinguished from the effects due to concomitant processes such as inflammation and/or aging. (3) Distinctions in rodent models are made between the transgenic animals with the N-terminal truncated forms of the mutant Huntington gene (mHtt) and the full-length (FL) endogenous forms, which would help highlight any distinction between these model systems.

2. Evidence for mitochondrial dysfunction in human tissue

Early work in postmortem human brain provided the first evidence that alterations or reduction in mitochondrial electron transport chain (ETC) components or their activity were abnormal (overview of ETC and Glycolysis: Fig. 1). The most notable changes are loss of complexes II and III (Browne et al., 1997; Fukui and Moraes, 2007; Vonsattel and DiFiglia, 1998; Vonsattel et al., 1985), and to a lesser extent deficiency of complex IV in the caudate or putamen (Vonsattel and DiFiglia, 1998; Vonsattel et al., 1985). In postmortem brain specimens from 163 clinically diagnosed cases of Huntington's disease (HD), Vonsattel developed a categorization system, which ordered the macroscopic and microscopic criteria into five grades (0–4) in ascending order of severity (Vonsattel and DiFiglia, 1998; Vonsattel et al., 1985). In grade 1 disease, neuropathological changes are recognized microscopically in the medial paraventricular portions of the caudate nucleus (CN), an observation that has driven research. However, in grade 0 brains, clinically diagnosed, but pre-symptomatic HD patients display no loss of mitochondrial ETC activity, suggesting that their alterations do not precede the onset of symptoms in an obvious manner. At what stage MT "go bad" is unknown, and whether this transition is a primary cause of the pathophysiology remains enigmatic. Based on the classification work of Vonsattel et al. (1985), the general suppression of mitochondrial activity seems to occur at later stages of disease progression, but not early on.

2.1. Defects in oxygen consumption in human postmortemj brain

So, is there general agreement as to mitochondrial dysfunction at later stages in postmortem human brain? The bulk of the existing data for human brain would support the notion (Table 1). Early ultrastructural studies obtained from the cerebral cortical tissue of HD patients reveal abnormal mitochondrial morphology (Goebel et al., 1978; Tellez-Nagel et al., 1974) suggesting that they are affected in the disease state. However, as reported by others, the specific abnormalities in mitochondrial respiration of postmortem symptomatic patients do not necessarily accompany these changes, or, minimally, the relationships are inconsistent among brain samples. As judged by spectrophotometric (SPECTR) assays, the activity of the ETC enzymes are impaired in the basal ganglia of HD brains, while enzyme activities were unaltered in three regions relatively spared by HD pathology (frontal cortex, parietal cortex, and cerebellum) (Browne et al., 1997). In the most affected region of the HD brain, the striatum, complex II–III activity are markedly reduced in both caudate (−29%), while Complex II–III (−67%), and IV (−62%) are altered in the putamen (Browne et al., 1997). Another study concurred that complex III and IV are altered in human HD brains, although the regional patterns are slightly different; a decrease in activities of complex II–III occurs in the caudate and putamen, while complex IV is reduced in the putamen. Thus, it appears that mitochondrial dysfunction as indicated by loss of ETC activity, aligns with the region-specificity of degeneration, although the exact complexes that are affected are variable. Surprisingly, there is, for the most part, a failure to identify defects in ETC complex I in the HD brain. Complex I is the gateway for electron flow in the ETC, and blocking it is expected to have detrimental consequences for energy production. Thus, it is notable that complexes II–IV but not complex I are associated with human disease. It is possible that complex I defects are toxic enough to lead directly to cell death (and therefore cannot be observed). Arguing against this idea, however, are observations that rotenone inhibition of Complex I in mice is not lethal. Indeed, inhibiting it results in symptoms reminiscent of Parkinson's disease (Schapira and Gegg, 2011).

More important in HD brain seems to be the function of ETC Complex II (Benchoua et al., 2006; Gu et al., 1996; Tabrizi et al., 1999). Deficiency of respiratory chain complex II, i.e., succinate dehydrogenase (SDH), has been a focus of attention in HD due to the fact that the inhibition of succinate dehydrogenase (SDH) by 3-nitropropionate (3-NP) or malonate closely mimics the neuropathology and clinical features of HD in humans (Myers et al., 1991), in non-human primates (Palfi et al., 1996), and in rodents (Brouillet et al., 1998). Similar to humans, administration of 3-NP in rats not only inhibits complex II, but it also inactivates mitochondrial complexes III, IV and V in the striatum, without significant effect on complex I (Pandey et al., 2008). Whether impairment of complex II always inhibits the downstream complexes of the ETC chain, or always impairs electron flow through complex I is not yet clear. At least *in vitro*, classic ETC inhibitor analysis indicates that succinate stimulation of complex II is unaffected under conditions of rotenone inhibition of complex I (Oliveira et al., 2007). Complex II oxidizes succinate, which, in TCA cycle, leads to accumulation of oxaloacetate, an inhibitor of Complex II. Rotenone inhibits Complex I and maintains a high level of NADH, which prevents oxaloacetate accumulation and Complex II inhibition, suggesting that inhibition of complex I would increase the demand on complex II, but not eliminate energy production. Consistent with a critical role for complex II in HD, there is loss of its components, the 30-kDa iron-sulfur (Ip) subunit and the 70-kDa FAD (Fp), in primary striatal neurons when infected with lentiviral vectors encoding mHtt. Similarly, overexpression of Complex II components leads to significant neuroprotection (Damiano et al., 2013). Deficits in SDH have significant consequences, since it is a component of both the ETC as well