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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.

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Contents

1. Introduction . . . 1085
2. Huntington's disease . . . 1085
 2.1. Description . . . 1085
 2.2. Pathogenesis . . . 1085
3. Mitochondrial disorders and mitochondrial toxins suggest preferential vulnerability of the striatum . . . 1086
4. General mechanism of mitochondrial defects in HD patients . . . 1086
 4.1. Mitochondrial enzymes and high energy phosphates . . . 1086
  4.1.1. Defects in respiratory chain enzymes . . . 1086
  4.1.2. Levels of high energy phosphates . . . 1087
 4.2. Mitochondrial membrane potential . . . 1087
 4.3. Mitochondrial Ca^{2+} buffering capacity . . . 1087
 4.4. Abnormal dynamics and unbalanced fusion/fission mechanisms . . . 1088
 4.5. PGC-1 alpha, NRF and PPARγ, PPARδ . . . 1088

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4.6. Tim23 and mitochondrial import 1088
4.7. Mitophagy 1088
5. Possible integrated mechanisms of mitochondrial dysfunction in HD 1089
6. In vivo evidence for energy/mitochondrial impairment in HD 1089
6.1. Pioneering studies using brain imaging methods in patients and animal models 1089
6.2. Recent imaging studies using brain imaging methods in patients and animal models 1089
6.2.1. Brain metabolite measurement by ^{1}H MRS 1089
6.2.2. A novel MRI method to establish brain map of glutamate: gluCEST imaging 1090
6.2.3. ^{31}P-MRS for high energy phosphates 1090
6.3. What MRS could bring to HD patients? 1091
Acknowledgements 1091
References 1091

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

[41]. In addition, the mutation in the HTT gene also leads to toxic mechanisms not produced by expression of mutant Htt (or fragments) but involving (abnormal) sense and antisense non ATG translation of RNA (RAN) of expanded CAG repeats [42].

Abnormal transcription and transcription regulation have been demonstrated [29,43–45]. Mutant Htt alters macromolecular complexes regulating transcription. The mutation produces changes in protein-protein interaction between Htt and transcription factors or co-factors such as CBP, TAF4, CA150, Sp1, and p53 that can produce deleterious downstream events. Intriguingly, expression of neuronal genes, especially striatal-enriched genes is particularly reduced in HD [45,46].

For example, an important consequence of transcriptional changes involves the neurotrophin BDNF (brain neurotrophic factor). Wild type Htt regulates the expression of BDNF by sequestering REST/NRSF in the cytoplasm, avoiding repression of BDNF gene through binding at the RE1/NRSE site located in the BDNF promoter [47]. BDNF is mainly synthesized in the cortical neurons and delivered to the striatum through vesicles using axonal transport [26]. Reduced BDNF levels in the striatum would render medium size spiny neurons highly vulnerable. Early axonal transport dysfunction and alteration of vesicle trafficking have been shown [48]. In particular impaired transport of vesicles containing BDNF along the axon would further reduce the delivery of BDNF to striatal cells [26]. Additionally, the retrograde transport of the BDNF receptor, TrkB. TrkB-containing vesicles within striatal dendrites and the BDNF/TrkB-induced signaling through ERK phosphorylation and c-fos induction are decreased in neurons from an HD mouse model [49]. Impaired axonal transport might also affect organelle, including mitochondria localization (see below). Protein misfolding, proteasome dysfunction [50,51], and reduction of autophagy [52], likely play important roles in HD. Abnormal entry of Ca^{2+} through NMDA receptors and excitotoxicity has been suggested [53,54]. Defective cytosolic Ca^{2+} buffering by mitochondria and ER have been observed [55–57].

There exists a large body of studies focus on the transcriptomic defects in post mortem samples of the striatum and cerebral cortex of HD patients, and genetic rodent models. Additional set of data has been recently provided from the characterization of neurons differentiated from human neural stem cells (hESC) or induced pluripotent stem cells from HD gene carriers (e.g. Ref. [58]). These different dataset point to the variety of the potential consequences of transcriptional defects, and underscore that the associated mechanisms of neuronal dysfunction/neurodegeneration are probably highly complex. Many comprehensive reviews can be read on this aspect of HD pathogenesis.

An integrated RNAseq analysis of transcriptional changes in the striatum, cerebral cortex and cerebellum of different knock-in HD mouse models with increasing CAG repeat length at different ages recently provided a global picture on how several cellular functions are early disturbed in the HD striatum including transcription and chromatin factors, cell death pathways, DNA damage repair, proteostasis and mitochondria [59].

There is a number of excellent detailed reviews on the “mitochondrial” hypothesis for HD that have been released in the past [60–62] and more recently [63–67]. Each presents an overview of many different types of mitochondrial defects (and more generally defects in energy metabolism) in HD. The mechanisms underlying these defects are ill-defined. Mutant Htt can interact functionally with the outer mitochondrial membrane [68–71], possibly through a set of mitochondrial proteins [5,65]. Besides mechanisms linked to a direct interaction with mutant Htt, transcriptional changes induced by mutant Htt indirectly disturb the regulation of mitochondrial/energy homeostasis. Deregulation of post-transcriptional modification of mitochondrial proteins may also be involved (ubiquitination, acetylation, nitrosylation, protease-mediated cleavage, phosphorylation …).

3. Mitochondrial disorders and mitochondrial toxins suggest preferential vulnerability of the striatum

The striatum is extremely vulnerable to the impairment in oxidative energy metabolism [60,62]. Genetic mitochondrial defects can lead to striatal degeneration and, clinically, to choreoathetosis and dystonia. Point mutations in mitochondrial genes coding for several subunits of complex I (NADH: ubiquinone oxidoreductases) can lead to putaminal degeneration and dystonia, in association with other severe alterations such as epilepsy, stroke and optic nerve atrophy. Nuclear genes encoding for mitochondrial proteins [e.g. complex II (SDHA, Fp subunit and SDHAF1); complex III, (subunit VII); MR-1 (Myofibrillogenesis regulator-)] can also lead to neurological abnormalities reminiscent of Leigh syndrome [72–75].

Reported cases of accidental (or suicidal) poisoning with mitochondrial toxins (e.g. cyanide, methanol, 3-nitropropionic acid) also show that the striatum is extremely sensitive to acute blockade of oxidative energy metabolism. In man, the ingestion of the mitochondrial toxin 3-nitropropionic acid (3-NP) produces putaminal necrosis and delayed dyskinesias and dystonia [76,77]. Systemic administration of 3-NP produces in rats [78,79] and in non-human primates [80] causes preferential degeneration in the caudate/putamen, abnormal movements and frontal type cognitive deficits that are highly reminiscent of HD [81,82]. The mechanisms of 3-NP toxicity in vivo involve impaired Ca^{2+} homeostasis, calpain and caspase activation, and JNK activation that are also involved in HD pathogenesis [82]. However, 3-NP does not produce transcriptional changes and abnormal protein aggregation and disruption of proteostasis that are comparable to those found in transgenic and knock-in mice expressing mutant Htt [83,84].

4. General mechanism of mitochondrial defects in HD patients

4.1. Mitochondrial enzymes and high energy phosphates

4.1.1. Defects in respiratory chain enzymes

Defects in the respiratory chain in HD have been observed in early biochemical studies. Severe reduction in the activity of complex II/III and milder reduction of complex IV were found in post mortem samples of the caudate/putamen in HD patients [85–89]. Analysis of subunits of the mitochondrial complexes in striatal samples from small cohort of HD patients indicated preferential (profound, ~-70%) reduction in the expression of complex II subunit Ip (SDHB) [90]. Interestingly, SDHB or SDHA mRNA in HD caudate are not reduced [91]. The cerebral cortex showed minor changes in respiratory chain enzymes [86,88,90,92]. Massive loss of aconitase activity has been found in the caudate (~90%), and putamen (~70%) [92,93]. Loss of the pyruvate dehydrogenase complex was also found [87,94]. No changes were found in samples from patients at early stages of the disease [95].

In a transgenic mouse model of HD (R6/2) with limited cell loss, aconitase and pyruvate dehydrogenase have been found to be decreased to various extents [96]. It seems that in addition to presenting reduced levels, many proteins are modified by oxidative stress in these transgenic models [97]. Proteomics analysis of R6/2 brain showed that the expression of a number of proteins related to brain energy metabolism/mitochondrial proteins are changed [98]. However, the changes can be seen in young animals and undetectable in severely symptomatic mice or the other way around. Change in expression of mitochondria complexes have also studied

in transgenic mice expressing a short N-terminal fragment of mutant Htt with 82 polyglutamines (N171-82Q mice). Blue native gel analysis of mitochondrial complex showed reduced levels of complex II [99]. Loss of complex II (activity, levels of Ip protein) was found in R6/1 mice and in the rat model using lentiviral vectors to express mutant Htt in the striatum [99]. In mice expressing a short (N-ter-171 a.a.) mutant Htt fragment only in the striatum (D9-N171-98Q), reduction in complex II activity was also found in young non-symptomatic mice, while the activity of the complex increases in older symptomatic mice [100]. In primary culture of striatal neurons, overexpression of a N-terminal domain of mutant Htt using lentiviral vectors also leads to a progressive loss of complex II subunit Ip protein, while the levels of Fp protein were relatively preserved [90]. This loss of Ip protein was not correlated with reduction in SDHB mRNA, indicating a post-transcriptional mechanism. The re-expression of complex II subunits using lentiviral vector in these in vitro and in vivo rat models was shown to significantly block the death of striatal neurons, indicating that the loss of Ip subunit could be causal in mutant Htt toxicity [90,99,101]. Reduced activity of complex II-III or levels of complex II proteins were reported in a few other cellular models (Neuro2A and HeLa cells expressing Htt exon 1 [102] and interestingly also in yeast expressing mutant Htt [103]. Reduction of complex II, seen in the "aggressive" (R6/1, N171-82Q) mouse and rat (LV) models of mutant Htt toxicity, was not seen in rodent models with more progressive adult BACHD mice, and knock-in 140CAG mice (Damiano, Malgorn, Francelle, Brouillet, unpublished results). Different groups studied complex II protein levels in other genetic animal models of HD and could not find major modifications [e.g. Refs. [104–106]]. Thus, preferential loss/disruption of complex II is likely a relatively late event associated to actual neurodegeneration/death of neurons. In some mice models with no obvious neuronal cell loss, the changes in complex II could be only transient, and could be rapidly compensated with age and disease progression.

4.1.2. Levels of high energy phosphates

The effect of mHtt on ATP levels was studied in isolated mitochondria from HD mouse models of HD. ATP has been also studied in cellular models expressing mHtt. In living cell, ATP lifetime is short and ATP concentrations can drop in a matter of seconds when the source of nutriment such as glucose is suppressed, the respiratory chain is blocked, proton-force disrupted or oxygen supply cut. Measurement of ATP by extraction in cultured cells is relative easy and reliable since proteins using ATP can be rapidly inactivated and extracted ATP reflect levels in the living cells. In addition, new fluorescent probes for ATP, give the possibility to determine ATP levels using video-microscopy in living cells expressing mHtt. In most studies, levels in ATP at rest are not markedly changed in neurons expressing mHtt [e.g. Refs. [104,106]). However, ATP levels (or ATP/ADP ratio) have been found reduced in peripheral HD lymphoblast along with increased phosphocreatine levels, immortalized cells from HDhQ111 knock-in mice and cultured neurons from YAC128 [107,108]. Differences in experimental protocols might explain the existence of discrepancies between different studies.

In vivo, measurement of brain levels of ATP and phosphocreatine (PCr) are difficult for this reason. Rapid decapitation, even using freeze camp techniques, always underestimates actual concentrations. One way to bypass this limitation of ATP assessment is to use microwave methods were all the proteins that degrade/use ATP (including creatine kinase) are destroyed in a few second. Then precise measures of metabolites can be achieved after HPLC separation. This difficult method has been used recently by Mochel and collaborators to measure ATP and its metabolites in brain regions of R6/2 mice at different ages. Results showed that ATP concentration was decreased in striatum, hippocampus and cerebral cortex of R6/2 [109]. These decreases were found to be associated with increased PCr at 8 and 12 weeks of age. Even at 4 weeks of age, when mice are considered "presymptomatic", PCr concentration was increased in their brain. Similar trends have been observed in non-symptomatic 4-month-old knock-in HDhQ111/+ mice. These early changes in PCr and increased levels of brain levels were associated with reduced levels of brain creatine kinase (BB-CK) and activation of the AMP-dependent protein kinase (AMPK) signaling. Upregulation of the PCr may reflect adaptive response mechanisms attempting to counteract the early energy deficit prior to the decrease in ATP known as a late marker of cell distress.

The only way to look at ATP levels in a non-invasive manner in vivo is to use magnetic resonance spectroscopy of ^{31}P nucleus. This method is very challenging because the signal/noise ratio is very low, especially in small animal (mice or rats) where the brain is small. A few key studies in vivo in patients and rodent HD models are presented and discussed later.

4.2. Mitochondrial membrane potential

There are a number of studies that showed that mitochondria from cells expressing mutant Htt show decreased membrane potential, especially when cells are challenged with toxic stimuli. Lympoblasts derived from lymphocytes from HD patients showed increased stress-induced apoptotic cell death, which is associated with great mitochondrial membrane potential loss [71,110]. Loss of mitochondrial membrane potential was recently reported by Rego's group and collaborators [107]. Clonal cells derived from knock-in mice harbouring a pathologically expanded CAG repeat tract (STHdhQ111/Q111) show reduced mitochondrial membrane potential [111,112] and show high sensitivity to Ca^{2+}-induced mitochondrial permeability transition [68,113]. This sensibility was confirmed in mitochondria isolated from HD transgenic rats [114]. STHdhQ111/Q111 cells also show higher vulnerability to permeability transition and death when treated with the 3-NP, an effect that could be prevented by cyclosporine-A [115] or expression of hMTH1, a human hydrolase that degrades oxidized purine nucleoside triphosphates [111]. It has also been demonstrated that recombinant mutant Htt (short N-terminal fragment) could directly trigger loss of membrane potential and permeability transition, likely through an interaction with the outer mitochondrial membrane [68,116]. In situ studies using fluorescent dyes (JC-1, MitoTracker Red) also showed that neuronal cells expressing mutant Htt could display reduced mitochondrial membrane potential at rest [90,117]. However, loss of mitochondrial membrane potential at rest is not seen in all models of HD. In unchallenged isolated mitochondria prepared from Ki105CAG mice, no modification of mitochondrial membrane potential was observed [106].

4.3. Mitochondrial Ca^{2+} buffering capacity

Increased cytoplasmic Ca^{2+} levels are toxic to neurons, at least in part through mitochondrial mechanisms [30,57,118]. Impaired Ca^{2+} homeostasis in HD might have different causes. Alteration of mitochondrial Ca^{2+} homeostasis may also result from different extra-mitochondrial origins, especially increased entry of Ca^{2+} in the cell and increased release/reduced uptake from intracellular store, such as the ER. There is one abnormality/change related to mitochondria and Ca^{2+} that appears to be consistently observed across most of HD models: The Ca^{2+} buffering capacity of cells expressing mutant Htt is reduced. This was first demonstrated by Panov and collaborators in lymphoblasts derived from lymphocytes of HD patients [71]. Similarly, reduced Ca^{2+} loading capacity was found in the brains of YAC72Q mice [71]. Compared to

mitochondria from control cells (STHdhQ7/Q7), the mitochondria from clonal striatal cells with mutant Htt (STHdhQ111/Q111) undergo permeability transition at a lower Ca^{2+} concentration when treated with increasing Ca^{2+} loads and have a reduced capacity to take up Ca^{2+} [119]. Isolated mitochondria from transgenic rats expressing mutant Htt, show reduced rates of Ca^{2+} accumulation compared to control rats [114]. In neuronal cultures expressing the N-terminal part of Htt with a 104 glutamine repeat, calcium overload induced by thapsigargin resulted in a significant decrease in mitochondrial calcium uptake compared to wild type cells which showed a transient increase in mitochondrial calcium [113]. However, not all HD models show reduced brain mitochondrial Ca^{2+} loading capacity. The latter was found increased in 12 week old R6/2 mice and 12 month old YAC128Q while no changes were found in knock-in 150Q mice [120]. More recently, Chang and collaborators observed a higher level of mitochondrial Ca^{2+} loading in embryonic fibroblasts from YAC128 mice compared to wild type mice [121]. All results on this aspect are not always congruent depending on the animal/cell models and laboratory. This has been precisely reviewed recently [67].

4.4. *Abnormal dynamics and unbalanced fusion/fission mechanisms*

Changes in organelle dynamics have been hypothesized to play a role in neurodegenerative diseases especially in HD [122]. Two types of modification can be depicted: motility or morphology. First, reduced mitochondrial mobility could reduce the incorporation of certain proteins leading to mitochondrial dysfunction [105]. An elegant study using live cell video microscopy showed that aggregates impair mitochondrial movements along neuronal processes. Mitochondria may remain embedded in the aggregate formations in the somato-dendritic compartment [123]. A very interesting observation in this study is that full length mutant Htt, more than the short N-terminal fragments, impairs mitochondrial mobility. More recently mitochondrial motility defects were observed in primary neurons from rat expressing mutant Htt-containing exon1 [124] or from BACHD mice [125].

On the other hand, mitochondrial morphological changes can also result in dysfunction. In primary cultures of cortical neurons treated with 3-NP, mitochondrial fission occurs and is preceded by an ATP drop and a ROS increase, the latter being blocked by a NMDA antagonist, leading to neuronal rescue [126]. Mitochondrial fission increase and fusion decrease has been shown in different models of cell lines or primary cultures expressing wild type or mutant Htt [124,125,127–129]. This mitochondrial fission was associated with an increase of Dynamin Related Protein (Drp1) and Fis1 and a decrease of Mitofusins-1 and -2 expression [129]. This GTPase, Drp1, interacts with mutant Htt resulting in an increase of its activity and overexpression of an inactive form of Drp1 leads to the blockade of mitochondrial fission [124,125]. Interestingly, treatment of HD transgenic mice with an inhibitor of Drp1 (p110-TAT) blocks Drp1 association with mitochondria, reduced motor deficits, and mortality in mice [130]. Costa and collaborators demonstrated that overexpression of OPA1 or inactive Drp1 but not Mitofusin-1 rescue mitochondrial cristae remodelling and the increased susceptibility to apoptosis of mutant Htt-expressing cells [189]. Other mechanisms playing a role in mitochondrial fission were also described such as Cdk5 [131], p53 [130] or S-nitrosylation [127].

4.5. *PGC-1 alpha, NRF and PPARγ, PPARδ*

Another very interesting mechanism that has recently been proposed to be involved in HD-linked striatal degeneration is the PGC-1alpha pathway. Reduced expression of PGC-1alpha has been reported in HD models [132,133]. PGC-1alpha is a nuclear co-activator that plays a major role in mitochondrial biogenesis [132,133]. Mice that are nullizygous for PGC-1alpha display abnormalities related to energy metabolism and strikingly develop striatal lesions [134]. Increasing PGC-1alpha expression is neuroprotective against mutant Htt toxicity and, on the contrary, when PGC-1alpha is knocked down, neurons are highly vulnerable to mutant Htt toxicity in cell culture and in vivo [133]. Other family members (PGC-1beta and PGC-1 Related co-activator −PRC), also known to regulate important aspects of mitochondrial biogenesis and of respiratory enzymes, could be also involved [135]. In line with this, it cannot be excluded that downstream targets of PGC-1alpha, the nuclear respiratory factors, NRF-1 and NRF-2 [136] could also participate in HD-linked mitochondrial dysfunction. More recently, the ligand-activated transcription factor named peroxisome proliferator-activated receptors (PPARs) downstream targets of PGC-1alpha were involved in HD pathogenesis. Activation of PPARγ or PPARδ by agonists could block Htt-induced neurotoxicity [137,138], or restore the expression of PGC-1alpha and Bcl2, and the mitochondrial mass in the brain of HD mice [139]. Administration of bezafibrate, a pan-PPAR agonist, increases the expression of PGC-1alpha and mitochondrial biogenesis, and improves phenotype and survival in R6/2 transgenic mice, it also restores PPARγ, PPARδ, PGC-1alpha signaling pathway and enhanced mitochondrial biogenesis in BACHD mice [140].

4.6. *Tim23 and mitochondrial import*

Another mechanism potentially involve in mitochondrial dysfunction in HD can be mitochondrial import. In fact, as 99% of the mitochondrial proteins are encoded by the nuclear genome, once synthetized these proteins need to be translocated to the mitochondrial membranes and matrix. This function is provided by a group of proteins named translocators in the outer (TOM) or inner (TIM) mitochondrial membrane. In 2014, Yano and collaborators demonstrated that mutant Htt interacts with TIM23 which inhibits protein import in vitro [141]. Moreover, protein import defects have been pinpointed in mitochondria from brain synaptosomes of presymptomatic HD mice or primary neurons expressing mutant Htt. Finally, this group demonstrated that overexpression of TIM23 complex subunits in mutant Htt-expressing neuronal primary cultures decreases import defects and neuronal death [141].

4.7. *Mitophagy*

Autophagy is a self-degrading process (protein degradation and organelle turnover) necessary to the cell physiology but which has also been involved in human diseases. Impaired autophagic function may be considered as a possible mechanism in neurodegeneration [142] and the pathogenesis of several neurodegenerative disorders including Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and Huntington's disease [143]. If we focus on mitochondria, the autophagic process involved in mitochondrial clearance is named mitophagy. Mitophagy can be useful to selectively degrade dysfunctional mitochondria in order to maintain a healthy mitochondrial network. In MEFs from mutant Htt knock-in mice, starvation−induced macroautophagy is deficient compared to those from wild type htt knock-in mice. In addition, both HD neuronal and MEF cells expressing mutant Htt show a higher percentage of depolarized mitochondria when compared their corresponding wild type cells [144]. Later, a beginning of understanding on which mechanisms lead to mitophagy has been made. It was shown that, in HdhQ111 striatal cells, mHtt alters mitophagy through blockade of mitochondria-containing autophagosome formation. This defect

can be partially restored by PINK1 overexpression [145]. Moreover, Holzbaur's team demonstrated that Htt and HAP1 co-localize with LC3-II-containing autophagosomes to control autophagosome dynamics. Expression of mutant Htt inhibits autophagosome/lysosome fusion leading to inefficient autophagosome maturation and finally resulting in defective clearance of both polyQ-htt aggregates and dysfunctional mitochondria [146]. A new mechanism, named “micro mitophagy”, was highlighted in 2015. Under oxidative stress, glyceraldehyde-3-phosphate dehydrogenase (GAPDH) undergoes oxidative modifications and becomes catalytically inactive. Oxidized GAPDH detects and associates with damaged mitochondria for degradation by lysosomes. In mutant Htt-expressing cells, inactivated (oxidized) GAPDH interacts with mutant Htt at the outer mitochondrial membrane which results in blockade of engulfment by lysosomes and a consecutive defect in micro mitophagy with accumulation of damage mitochondria deleterious for the cells [147].

5. Possible integrated mechanisms of mitochondrial dysfunction in HD

As discussed above, mutant Htt (N-terminal small fragments) can possibly directly interact with the outer mitochondrial membrane and mitochondrial proteins to alter mitochondrial function and indirectly mHtt could disrupt mitochondrial homeostasis. How the different/multiple effects of mHtt (or loss of function of wild type Htt) act in concert and participate to neuronal degeneration is uncertain. As mentioned earlier, defects in respiratory chain enzymes may be considered relatively late events is this processes. It is likely that transcriptional changes happen relatively early in HD patients and mouse models. Transcriptional changes can be reverted by HDAC inhibitors, and interestingly, HDAC inhibitors have been shown to revert some of the functional mitochondria defects in neurons expressing mHtt [148]. Whereas at rest/basal conditions, HD mitochondria may function normally, many experiments indicate that their capability to cope with different types of challenges (such as Ca^{2+} load; oxidative stress; full stimulation to produce ATP) appears reduced. In the neurons *in situ*, especially in the striatum, where the mitochondria are constantly stimulated for basal energy demand linked to glutamatergic synaptic transmission, this particular susceptibility could translate into a progressive cascade of events more and more deleterious, with eventually activation of cell death molecular machinery.

One important integrated key aspect of the probably complex/multifactorial integrated mechanisms underlying mHtt-induced mitochondrial defects is the anomalies in Ca^{2+} homeostasis. This has been discussed in many reviews in detail, and can be summarized as follows.

Mitochondria that would have a reduced capacity to cope with intracellular Ca^{2+} handling could render neurons exquisitely vulnerable to Ca^{2+} entry associated with recurrent activation of glutamatergic synapses in the striatum. Primary defects in mitochondria/energy metabolism in vivo render striatal neurons extremely sensitive to excitotoxicity, especially when depending on activation of NMDA receptors [149,150]. MHtt-induced mitochondrial defects could facilitate the deleterious effects triggered by NMDA receptors in HD. The mitochondrial Ca^{2+} defects would act in synergy with m-Htt-induced modification of Ca^{2+} homeostasis linked to activation 1 inositol 1,4,5-trisphosphate receptors (InsP(3) R1) and Ca^{2+} release from the endoplasmic reticulum (ER) [151]. Mitochondrial damages could also lead to increased ROS production which through a vicious cycle could further produce perturbation of molecular components involved in maintenance of membrane potential, protein import machinery, Ca^{2+} uptake/sequestration, production of molecules that are crucial to supply cellular energy demand such as ATP and phosphocreatine production.

6. In vivo evidence for energy/mitochondrial impairment in HD

6.1. Pioneering studies using brain imaging methods in patients and animal models

Other indications for energy metabolism problems in HD patients were reported. In particular, early striatal hypometabolism was detected in vivo using positron emission tomography and [^{18}F] fluoro-deoxyglucose [60,152]. Increased lactate concentrations were found in the cortex of symptomatic HD patients using proton (^{1}H) magnetic resonance MR spectroscopy (MRS) [153,154]. Lactate/pyruvate ratio was found elevated in the CSF of HD patients [155]. In one NMR study, half of the pre-symptomatic HD patients examined showed increased lactate concentration in the striatum [154].

Pioneering studies in rats with striatal dysfunction/degeneration associated with excitotoxic cell death after intrastriatal injection of mitochondrial toxins (malonate, quinolinate, 3-NP) or chronic systemic administration of 3-NP, evaluated the potential interest of using MRS for neurological conditions associated with metabolic defects, especially HD. These studies demonstrated that MRS was able to clearly show mitochondrial impairment in the striatum in vivo. Loss of glutamate and N-acetyl-asparte (NAA), increased lactate, were hallmarks of early effects of the mitochondrial toxins. Interestingly, these MRS studies, combined with MRI showed that while 3-NP was ubiquitously distributed in the brain after systemic administration, it preferentially impacted oxidative energy metabolism in the striatum [79,156–159]. MRS also showed in non-human primates chronically treated with 3-NP that levels of brain metabolites (NAA and glutamate) were significantly decreased as a consequence of partial blockage of mitochondrial complex II. This suggested, that changes in these metabolites could reflect mitochondria dysfunction. In addition 3-NP-induced decreases in NAA were shown to be reverted by the arrest of the 3-NP administration, indicating that these metabolic changes were reversible, and not simply the consequence of neuronal cell death. More recently ^{1}H MRS and other new MRS methods have been used to investigate metabolic changes in genetic animal models of HD as well as in HD gene carriers, which are summarized below.

6.2. Recent imaging studies using brain imaging methods in patients and animal models

6.2.1. Brain metabolite measurement by ^{1}H MRS

For several years, ^{1}H-MRS has been used in the context of neurodegenerative disease, and especially in HD, in order to identify relevant and early biological markers of the disease. This non-invasive method is promising as it can provide information at cellular level in a living organism. Striatal concentration of NAA measured by ^{1}H-MRS using clinical magnet (3T) were found to be reduced in cohorts of symptomatic HD patients [160]. Although smaller, reduction was also seen in HD gene carriers (pre-manifest) subjects [160]. The use of a 7T [161,162] permitted ^{1}H-MRS with increased detection sensitivity, allowing metabolite concentrations measurement in smaller brain regions, so that the caudate and putamen could be separately examined. Reduced NAA, glutamate and creatine concentration were measured in putamen. Intriguingly, glutamate was not found significantly reduced in the caudate nucleus [161]. This emphasizes the interest of methods that could give the possibility of studying simultaneously different brain regions in patients.

In addition, preclinical studies performed of animal models of HD are very precious as they can provide valuable information about physiopathology of the disease. Moreover, they allow a longitudinal follow-up of disease progression, which would be very hardly achievable with HD patients. The large variety of rodent models of HD permits to mimic various form of the pathology. The transgenic R6/2 mouse is a severe HD model which reproduces early onset of HD [163]. On the contrary, knock-in models such as Q111 or Ki140CAG models are more progressive models with latter onsets of symptoms [25]. The latter models are probably closer to disease progression observed in HD patients.

Interestingly, similarly to results from HD patients, a majority of animal studies suggests early metabolic changes in the brain. All studies performed in mouse models of HD showed an increase in glutamine (Gln) and a decrease in NAA [164–166], excepted in Q111 where unchanged NAA level can be explained by the relative young age of mice, whereas symptoms onset appears at more than 100 weeks [25]. Decreases in glutamate and taurine concentrations were also measured in Ki140CAG mice [165], Q111 mice [163] and of glutamate concentration in R6/2 mice [164,167]. Interestingly, in knock-in HD mice harbouring a smaller CAG expansion (HdhQ111 or Ki140CAG), no glutamate or NAA changes were found at very early ages (3–4 months), although reorganization of high energy phosphate metabolites was seen (see below) [163]. Loss of glutamate, NAA and creatine have been seen in z175 knock-in mice at 6 months of age and increased levels of glutamine were detected at 9 months of age [168,169]. These changes were more profound in 12 month-old HD mice, indicating a progression of the pathology. In most of ^{1}H-MRS studies, it is commonly admitted that glutamate and NAA are mainly located in neurons. Consequently, their concentrations can serve as a potential marker of the neuronal compartment [170–172]. A modification of their concentrations, particularly a decrease, can suggest an alteration of neuron integrity or functions. These changes suggest an astrocyte/neuron imbalance in the utilization of energy substrates.

However, modification (either increase or decrease) of brain metabolites concentration can vary depending on the type of HD model considered. In R6/2 mice, which have a more progressive phenotype, with markedly reduced life span (animal die around 12–18 weeks of age) and profound atrophy of the striatum and cerebral cortex, changes are more variable over time [166]. The changes do not follow the same trends over time. These MRS results are reminiscent of the data obtained in R6/2 on proteomic or transcriptomic characterization. This likely reflects major adaptive changes while brain atrophy progresses, when HD mice get older.

Thus, whatever the differences between models, the pattern of changes of brain metabolites clearly distinguishes HD mice from control littermate [163,173] and is consistent with defects in energy metabolism.

How these metabolic alterations seen by MRS could be related to mitochondrial anomalies is unclear. As mentioned earlier, primary mitochondrial defects induced by the mitochondrial toxin 3-NP leads to similar metabolic changes as seen by MRS in vivo. Loss of NAA is also consistent with mitochondrial defects since this metabolite is at least in part synthesized in mitochondria by the enzyme ALAT in neurons. Reduction in glutamate levels may also indicate anomalies in TCA (Krebs) cycle. Indeed, glutamate is in equilibrium with alpha-ketoglutarate in the Krebs cycle. Previous works performed in non-human primates chronically treated with the mitochondrial toxin have demonstrated that Krebs cycle defects can lead to alteration of glutamate concentration in the brain 3-NP [156,157].

6.2.2. A novel MRI method to establish brain map of glutamate: gluCEST imaging

Although very promising, one limitation of the ^{1}H and ^{31}P-MRS methods is that measurements are confined to large voxels due to the lack of sensitivity of these methods. Consequently, mapping metabolites distribution in the brain with standard ^{1}H-MRS would be very difficult and time-consuming. Chemical Shift Imaging (CSI) is able to map metabolites distribution, but the voxel size (a few μL) remains relatively large to distinguish small brain structure with few partial volume effects, especially in mice. It would be of major interest to therefore identify metabolic biomarkers that could be monitored in the entire brain and with good anatomical resolution.

Recently, CEST imaging (Chemical Exchange Saturation Transfer) has been proposed to detect dilute molecules containing labile protons. Exchangeable protons such as amine ($-NH_2$) or amide ($-NH$) groups, exhibit a resonance frequency that is shifted relative to bulk proton frequency. These exchangeable protons can be selectively saturated using radiofrequency pulse. As both pools of protons are constantly in exchange, the saturation can be transferred from one pool (shifted protons) to another (bulk protons), leading to a decrease of water signal. Interestingly, some metabolites such as glutamate, glucose of myo-inositol fulfill exchange properties to give a CEST signal [174] so that is possible to map their spatial distribution in the brain using CEST imaging.

The potential of CEST imaging to map glutamate level (gluCEST) has already been demonstrated in both rodent and human brains at high magnetic fields ($\geq$7 T) [175,176]. In a recent study, gluCEST has also been evaluated as a potential biomarker of HD [165]. In this study, a knock-in genetic mouse model of HD (Ki140CAG) with a slowly progressive appearance of the symptoms was used to evaluate glutamate levels alterations in the whole brain. Both heterozygous and homozygous mice for the gene encoding the mutant htt were compared to wild type littermates. Brain maps of glutamate were established in each group of mice using gluCEST imaging. GluCEST levels measured in homozygous mice were markedly reduced as compared with wild type littermates in most of brain structures. Surprisingly, gluCEST maps revealed that the decrease was particularly pronounced in the corpus callosum in both homozygous and heterozygous mice. As gluCEST contrast is almost proportional to glutamate concentration at physiological concentrations [175], a decrease of gluCEST contrast was consistent with a decrease of glutamate concentration. This suggests that corpus callosum which connects both hemispheres could be highly vulnerable in HD.

These results obtained in a mouse model of HD constitute the first report of gluCEST as a potential biomarker of HD. Of interest, recent studies have demonstrated the feasibility of gluCEST imaging in human brain [175,177]. Even if this technic requires high magnetic fields ($\geq$7T), emergence of high field clinical scanners may open the way to clinical applications of gluCEST imaging.

6.2.3. ^{31}P-MRS for high energy phosphates

Because it is methodologically challenging, ^{31}P-MRS has been rarely used to explore energy metabolism in HD patients. One pioneering study found no major change in ATP levels in the putamen of HD patients [178]. In muscle, phosphorus NMR spectroscopy showed reduced ATP production, as seen by reduced recovery after exercise in HD patients [179]. More recently, Saft and collaborators replicated these findings in a different cohort of HD patients and further extended the research to premanifest HD gene carriers showing also defects in ATP production in these subjects [180]. In the meantime methods have been optimized to increase sensitivity for brain ^{31}P-MRS. Recently, Mochel and colleagues studied early stage symptomatic patients and age-matched controls [181]. They used ^{31}P-MRS to measure ATP, PCr and inorganic

phosphate (Pi) at rest, during activation of the occipital cortex by visual stimulation and after. At baseline, concentrations of the three metabolites in HD patients were similar to those of control subjects. They observed in control subjects a mild but significant increase (~12%) in the Pi/PCr and the Pi/ATP ratios during brain activation, reflecting utilization of ATP and increased adenosine diphosphate concentrations. The ratios return to normal levels during the recovery. Interestingly, both ratios remained unchanged in HD patients during visual stimulation. Similar findings could be replicated in another cohort of HD patients and controls, and in this cohort, ^{31}P-MRS could be repeated twice at 1 month interval [182], showing that the defect in high energy phosphate change during visual activation was stable over time in HD patients.

The use of ^{31}P-MRS in animal model is more challenging than in human, because of sensitivity limitations of the method, even at high magnetic fields. Recent measures of ATP concentration and other phosphorylated metabolites using ^{31}P-MRS led to interesting results in the knock-in HdhQ111 mouse model of HD. Although results are not totally conclusive, Tkac and collaborators found that while ATP was generally found unchanged in HD mouse brains, increased levels of calculated ADP and creatine with reduction in PCr where found at early ages (6 weeks) [163]. However these changes tended to disappear in 13 week-old mice [163]. In the same study, R6/2 mice were also characterized at 11 weeks of age (i.e. symptomatic). They showed no major alterations in high energy phosphates levels or metabolism. Preliminary studies have been reported by Tiret and collaborators [183] by ^{31}P-MRS in BACHD rats. Results obtained in a small cohort of aged rats (18 month-old) indicate that under baseline condition (anaesthetized rats) brain levels of ATP are not markedly changed in the brain of these animals when compared to wild type littermates, while those of PCr are slightly increased. However, saturation transfer ^{31}P-MRS showed that the rate of synthesis of ATP is reduced in the brain of BACHD rats suggesting a re-organization of oxidative phosphorylation (ATP synthesis), consistent with mitochondrial defects. In parallel, the rate of creatine kinase remained unchanged.

6.3. *What MRS could bring to HD patients?*

The novel results obtained by in vivo imaging in mouse and rat models of HD and cohort of HD patients suggest that early metabolic adaptation occurs in HD, to counteract potential major dysfunction. However, these brain imaging changes could constitute key “biomarkers” of energy defects. This could be of particular interest in clinical trial. Indeed functional brain imaging could help to determine whether a novel therapy rapidly produces a potentially biological effect in the brain (drug engagement). This aspect has been recently illustrated two promising studies in small cohorts of HD patients. Chronic treatment of HD patients with the dietary metabolic substrate triheptanion (a C7 fatty acid that can fuel the Krebs cycle by producing propionyl-CoA and acetyl-CoA), rapidly corrected the absence of metabolic response (ATP/PCr recovery) after exercise in muscles and during brain visual stimulation as seen with ^{31}P-MRS [182,184].

Since experimental therapies targeting the mitochondria and energy metabolism (e.g. dietary brain fuels [182,184], modulators of Sirtuins [112], antioxydants [185,186], PPAR-delta activators [137], and mitochondrial protectant such as Olesoxime [187,188]) show great promise, the use of in vivo methods to characterize energy defects in HD patients could be of prime interest. Currently, all methods cannot be directly applied in clinic, but their utilization for in vivo studied in animal models might be crucial to optimize the determination of drug efficacy/mechanisms, which constitutes an indirect asset for therapeutics research for HD gene carriers.

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