Published in final edited form as:

Mol Neurobiol. 2016 July ; 53(5): 2944–2953. doi:10.1007/s12035-015-9188-0.

Mutant Huntingtin and Elusive Defects in Oxidative Metabolism and Mitochondrial Calcium Handling

Nickolay Brustovetsky[1,2]

[1]Department of Pharmacology and Toxicology, Indiana University School of Medicine

[2]Department of Stark Neuroscience Research Institute, Indiana University School of Medicine

Abstract

Elongation of a poly-glutamine (polyQ) stretch in huntingtin protein (Htt) is linked to Huntington's disease (HD) pathogenesis. The mutation in Htt correlates with neuronal dysfunction in the striatum and cerebral cortex, and eventually leads to neuronal cell death. The exact mechanisms of the injurious effect of mutant Htt (mHtt) on neurons are not completely understood, but might include aberrant gene transcription, defective autophagy, abnormal mitochondrial biogenesis, anomalous mitochondrial dynamics and trafficking. In addition, deficiency in oxidative metabolism and defects in mitochondrial Ca^{2+} handling are considered essential contributing factors to neuronal dysfunction in HD and, consequently, in HD pathogenesis. Since the discovery of the mutation in Htt, the questions whether mHtt affects oxidative metabolism and mitochondrial Ca^{2+} handling and if it does, what mechanisms could be involved, were in focus of numerous investigations. However, despite significant research efforts, the detrimental effect of mHtt and the mechanisms by which mHtt might impair oxidative metabolism and mitochondrial Ca^{2+} handling remain elusive. In this paper, I will briefly review studies aimed at clarifying the consequences of mHtt interaction with mitochondria and discuss experimental results supporting or arguing against the mHtt effects on oxidative metabolism and mitochondrial Ca^{2+} handling.

Keywords

mutant huntingtin; mitochondria; respiration; calcium uptake; permeability transition pore

Huntington's disease (HD) is a neurodegenerative disorder that belongs to the family of polyglutamine (polyQ) diseases [1] and manifests in motor, cognitive, psychiatric, and behavioral abnormalities [2]. In 1993, a mutation in huntingtin (Htt), a 350 kDa cytosolic protein that is ubiquitously expressed in various tissues was found and linked to HD pathogenesis [3]. In healthy individuals Htt contains up to 35 glutamines in a polyQ stretch near the N-terminus. The mutation in exon 1 of *huntingtin* gene leads to increased number of CAG repeats that results in elongation of polyQ stretch in Htt beyond 35Qs with 40 or more

Correspondence: Dr. Nickolay Brustovetsky,Department of Pharmacology and Toxicology, Indiana University School of Medicine, 635 Barnhill Dr. Medical Science Bldg 547, Indianapolis, IN 46202, Phone 317-278-9229, Fax 317-274-7714, nbrous@iu.edu.

Conflict of Interest Statement

There is no conflict of interest.

Qs leading to HD with full penetrance [4]. The elongated polyQ stretch in Htt correlates with neuronal dysfunction in the striatum and cerebral cortex, and eventually results in neuronal loss [5]. The precise mechanisms of the detrimental effect of mutant Htt (mHtt) on neurons are not clear, but may include aberrant gene transcription [6], defective autophagy [7] as well as abnormal mitochondrial biogenesis [8], mitochondrial dynamics [9,10,11], and trafficking [8,12]. In addition, bioenergetic deficiency and mitochondrial Ca^{2+} handling defects are considered to be important contributing factors to neuronal dysfunction in HD [13,14]. Since the discovery of the Htt mutation, numerous studies have been conducted to elucidate the mHtt effect on oxidative metabolism and mitochondrial Ca^{2+} handling. However, despite significant efforts, the question whether mHtt impairs mitochondrial functions remains controversial and not completely understood. In this paper, I briefly review experimental data that demonstrate mHtt effects or the lack thereof on oxidative metabolism and mitochondrial Ca^{2+} handling highlighting existing contradictions.

OXIDATIVE MEATBOLISM

In early papers concerning HD-associated alterations in mitochondrial bioenergetics, even before discovery of mutation in Htt, investigators reported some defects in mitochondrial respiratory activity. In postmortem brain tissues from HD patients, decreased respiratory activity of caudate mitochondria was found [15], and defects in mitochondrial Complexes II, III, and IV were described [16,17]. However, it was not obvious whether these respiratory defects contributed to HD pathogenesis or they were a result of the late stage of HD pathology. To resolve this issue, various experimental models of HD have been developed and utilized in search of a mechanistic link between mutation in Htt and HD pathology. The effects of mHtt on oxidative metabolism have been examined with polyQ-GST fusion proteins as surrogates for mHtt [18,19], with cell models expressing mHtt [20] as well as with numerous HD rodent models that express full-length or fragments of endogenous or human mHtt with different length of polyQ stretch [21,22].

The polyQ-GST fusion proteins were generated and tested in experiments with isolated mitochondria from wild-type (WT) animals. In experiments with Q62-GST fusion protein applied to liver mitochondria isolated from WT mice, investigators found a slight inhibition of ADP-stimulated respiration, but no inhibition of respiratory complexes, ATP synthase, and adenine nucleotide translocase [18]. Another mHtt substitute, GST-51Q exon 1 fusion protein, resulted in depolarization in isolated rat brain cortical mitochondria accompanied by a significant increase in oxygen consumption by the organelles, suggesting mitochondrial uncoupling but not inhibition of mitochondrial respiratory complexes [19]. Interestingly, in this study GST-20 exon 1 fusion protein with an unexpanded polyQ stretch produced similar effects, arguing against the role of an expanded polyQ stretch in the observed mitochondrial defects.

The opportunities to investigate the effects of mHtt on cell physiology and biochemistry were significantly expanded with the advent of conditionally immortalized, mutant $STHdh^{Q111/Q111}$ striatal neuronal progenitor cells [20]. Using these cells, Milakovic and Johnson, although observed reduced respiration and ATP production, found no difference in activities of mitochondrial Complex I-IV in mutant $STHdh^{Q111/Q111}$ cells compared with

STHdh$^{Q7/Q7}$ cells [23]. The authors concluded that mHtt may impair mitochondrial bioenergetics via different mechanisms that do not directly affect respiratory Complexes. In line with this conclusion, Seong et al. found lower cellular ATP in STHdh$^{Q111/Q111}$ cells compared with STHdh$^{Q7/Q7}$ cells [24]. The authors found inhibition of ADP uptake by mitochondria from mutant cells; however, activity of adenine nucleotide translocase that catalyzes ADP/ATP exchange across the inner membrane remained unchanged. Mitochondrial membrane potential was decreased whereas intracellular Ca^{2+} was elevated in mutant cells. The elevated intracellular Ca^{2+} was proposed to be responsible for inhibition of ADP transport into mitochondria. Indeed, inhibition of Ca^{2+} influx into STHdh$^{Q111/Q111}$ cells with EGTA in the bath solution or NMDA receptor antagonist MK801 significantly increased ATP/ADP ratio in these cells, suggesting improvement in ADP translocation into mitochondria [24]. Recently, in experiments with STHdh$^{Q111/Q111}$ cells, Siddiqui et al. found slightly reduced maximal respiratory activity without any difference in basal respiration [25]. The authors obtained a similar result with primary cultures of HD diploid skin fibroblasts. Consistent with these findings, in experiments with hetero- and homozygous STHdh$^{Q111/Q7}$ and STHdh$^{Q111/Q111}$ striatal neuronal progenitor cells, Napoli et al. found deficient oxidative phosphorylation and decreased Complex I and IV activities as well as a decrease in F_0F_1-ATPase activity [26]. It has to be noted, however, that immortalized neuronal progenitor cells may differ functionally and morphologically from primary neurons and, therefore, mHtt effects on oxidative metabolism in these cells should be taken cautiously, especially, bearing in mind negative results produced in numerous experiments with primary neurons, brain slices, and whole HD animals.

In addition to experiments with polyQ-GST fusion proteins and immortalized neuronal progenitor cells, experiments with isolated mitochondria and cells in culture derived from HD animal models provided important information about the possible effects of mHtt on oxidative metabolism. Tabrizi et al., using biochemical assays, found a significant decrease in activities of Complex IV and aconitase in the striatum of R6/2 mice [27]. In line with these findings, Bae et al., using the same methodology, reported decreased activity of Complex IV in striatum of N171-82Q transgenic mice [28]. Later, Kim et al. found significant reduction in States 3 and 4 respiration of succinate-fueled striatal mitochondria from pre-symptomatic transgenic D9-N171-98Q mice, also known as DE5 mice, compared with their age-matched controls, suggesting Complex II impairment [29]. On the other hand, Complex I and IV activities as well as activity of ATP synthase, were not altered in the striatum of young and old DE5 mice compared with WT littermates. Interestingly, succinate-supported respiration in States 3 and 4 as well as maximal FCCP-stimulated respiration were found to be increased in symptomatic DE5 mice compared with presymptomatic animals [29]. Damiano et al. also reported defects in respiration of mitochondria isolated from forebrains of N171-82Q transgenic mice [30]. With malate/glutamate (Complex I substrates) or succinate (Complex II substrate) supplemented with glutamate, ADP-stimulated respiration of mitochondria from 2-3 month old N171-82Q transgenic mice was lower compared to respiration of mitochondria from control N171-Q18 mice. Recently, Aidt et al. measured respiration of striatum homogenates from 12-week old R6/2 mice and found a slight but statistically significant decrease in Complex II and Complex IV flux control ratios defined as respiratory rates normalized to the maximal uncoupled respiration [31]. The

authors interpreted these data as an indication of respiratory impairment in striatal mitochondria of R6/2 mice. However, how mHtt, a 350 kDa cytosolic protein that binds to the outer mitochondrial membrane, but cannot cross it [32], impairs the respiratory chain in the inner mitochondrial membrane remains not completely understood. One possibility is that mHtt might decrease expression and mitochondrial import of proteins, involved in oxidative metabolism. Indeed, loss of Complex II activity was found in the postmortem striatum of HD patients and associated with a decreased expression of two subunits of Complex II, iron-sulfur subunit Ip (30 kDa) and FAD subunit Fp (70 kDa) [33]. Similarly, Damiano et al. demonstrated preferential loss of Complex II in mitochondria isolated from forebrains of N171-82Q transgenic mice [30]. Recently, Yano et al. reported mHtt-mediated inhibition of mitochondrial protein import [34]. On the other hand, no decrease in Complex II levels (judged by the levels of 30 and 70 kDa subunits of Complex II) was found in brain mitochondria isolated from Hdh150Q knock-in mice [35] and in mitochondria of STHdh$^{Q111/Q111}$ cells [23]. Possible alterations in oxidative metabolism could decrease ATP production in cells, expressing mHtt. Lim et al. reported a significant decrease in ATP level in cortex of R6/1 mice compared with WT control [36]. Although in HD striatum is considered the most vulnerable region of the brain [5], a decrease of ATP in striatum was much less pronounced and was not statistically significant [36].

In addition to studies, reporting mHtt-induced impairment of oxidative metabolism, there are numerous studies that demonstrate the lack thereof. Trushina et al. discovered a reduction in mitochondrial motility due to sequestration of trafficking motors components by mHtt aggregates, but did not find signs of mitochondrial dysfunction in striatal neurons derived from YAC72 mice [12]. Mitochondrial morphology was not altered in these neurons and the levels of ATP and lactate (an indicator of glycolytic activity) were similar in neurons from WT and YAC72 mice. Olah et al. reported that the activities of Complexes I-IV in brain mitochondria from 20-week old transgenic N171-82Q mice were not decreased compared with mitochondria from WT animals [37]. Interestingly, the authors found that ATP levels in the homogenate of the posterior brain regions of N171-82Q mice were significantly higher than in brains from WT mice. In addition, the authors noticed an increased glycolytic rate in cytosolic extracts from brain tissue of N171-82Q mice [37]. Based on these observations, the authors concluded that expression of the N-terminal fragment of mHtt is not accompanied by decreased activity of the mitochondrial respiratory chain or decline in glycolytic rate. Consistent with this, Guidetti et al. did not find any changes in mitochondrial electron transport through Complexes I-IV in the striatum and cerebral cortex of HD48 and HD89 mice, expressing full-length mHtt with either 48 or 89 Qs in polyQ stretches, compared with WT animals [38]. Moreover, these investigators failed to find changes in the activity of Complexes I-IV in the neostriatum and cerebral cortex in pre-symptomatic and pathological Grade 1 HD cases. Oliveira et al. reported that respiration of cultured striatal neurons derived from heterozygous knock-in Hdh$^{150/+}$ mice and their WT littermates was similar [39]. Later, Gouarne et al. measured respiration of cultured striatal neurons from heterozygous transgenic BACHD rats and found no difference compared with WT neurons, when cells were incubated in the presence of 25 mM glucose and 1 mM pyruvate [40]. However, when neurons were incubated in low glucose (2.5 mM) medium, the authors observed a modest decrease in maximal, FCCP-stimulated respiration of mHtt expressing

cells. Interestingly, this difference between mutant and WT cells was observed only with striatal but not cortical neurons. The authors proposed that mHtt expression results in a dysfunction in glycolysis that might precede defects in mitochondrial respiration [40]. Yano et al. reported that respiration of synaptic and non-synaptic mitochondria from forebrains of pre-symptomatic and mid-stage disease R6/2 mice (the authors used two distinct R6/2 strains: 150 CAG R6/2 and 195CAG R6/2) was not different from that of mitochondria from WT littermates [34]. Consistent with this, in a recent study with neurons and astrocytes from BACHD mice, Boussicault et al. found no evidence for direct effect of mHtt with 97 Qs on oxidative metabolism in these cells *in vitro* [41]. In this study, mHtt did not affect the glycolytic rate in single cells as measured by FRET and did not decrease mitochondrial membrane potential in neurons assessed with Rhodamine 123. Taken together, these data obtained with isolated mitochondria and cells in culture argue against mHtt-induced impairment of oxidative metabolism in animal models of HD.

In addition to isolated mitochondria and cells in culture, experiments with animal brain slices and whole animals *in vivo* provided further insights into the possible effect of mHtt on respiratory activity. Weydt et al. reported that oxygen consumption measured by indirect calorimetry of the whole animals was slightly increased in transgenic HD N171-82Q mice at baseline, especially during fasting [42]. The oxygen consumption rates (OCRs) in brain slices from 11-week-old, pre-symptomatic N171-82Q mice incubated with 20 mM glucose were similar. However, when brain slices were incubated with 5 mM lactate and 1 mM pyruvate, OCRs for HD slices were significantly lower [42]. Thus, the ability of lactate to be converted to pyruvate and subsequently undergo oxidative metabolism in the citric acid cycle appeared to be impaired in brains of N171-82Q mice. At the same time, respiration of brain slices fueled by succinate was normal, indicating the lack of impairment of the respiratory chain. Goodman et al. reported that 8-week-old R6/2 mice had oxygen consumption, energy expenditure, and respiratory exchange ratio (RER, CO_2 release rate/ oxygen consumption rate) similar to WT animals [43]. With 14-week-old R6/2 mice, the authors found significantly increased oxygen consumption and energy expenditure, while RER was not significantly different. Van der Burg et al. found elevated oxygen consumption in 6- to 12-week-old R6/2 mice compared with WT littermates [44]. In elegant *in vivo* experiments with magnetic resonance spectroscopy (^{31}P MRS), Tkac et al. found no significant change in ATP concentration in the brain of knock-in Q111 mice [45]. ADP concentration and a relative rate of ATP synthase were increased in brain of Q111 mice at 6 weeks, but returned to nearly normal level at 13 weeks. In R6/2 mice, however, these parameters remained normal. The authors proposed that brain energy homeostasis in these HD mouse models is maintained from early ages until the pathological symptoms become apparent. Overall, these data argue against an overt inhibitory effect of mHtt on oxidative energy metabolism.

The experiments with cell and animal models generate important information about HD, but only studies with human tissues and HD patients provide an ultimate test to the hypotheses generated in animal studies. Severe reduction in the activity of mitochondrial respiratory chain Complexes was found in caudate/putamen from human post-mortem brain tissue, suggesting that these abnormalities may underlie HD pathology [15,16,17]. However, *in vivo* measurements of oxygen consumption and glucose metabolism with positron emission

tomography in early-stage HD patients demonstrated that, while glucose consumption was somewhat reduced in striatum, its respiratory capacity was not significantly altered [46]. Consistent with this, the mid-stage HD patients do not show energy imbalance *in vivo* compared to age-matched healthy individuals as judged by indirect calorimetry in a human respiratory chamber [47]. Turner et al. studied the respiratory chain function in skeletal muscle biopsies from HD patients and also failed to find a significant difference in the activities of Complexes I-IV compared with age-matched controls [48]. Powers et al. investigated platelet mitochondrial citrate synthase and Complex I and I/III activities in HD patients and found no difference compared with healthy controls, whereas striatal volume was already significantly reduced in patients with HD [49]. In another study, using positron emission tomography applied to live HD patients with manifested striatal atrophy, Powers et al. obtained data inconsistent with a defect in mitochondrial oxidative metabolism due to reduced activity of the mitochondrial respiratory chain [46]. Because HD pathology was already manifested by striatal atrophy, the authors concluded that a deficit in energy production due to impairment of mitochondrial respiratory chain is not important for the mechanism of neuronal death in early HD.

Thus, the existing literature supports two different views on the interaction of mHtt with oxidative metabolism system. One group of investigators reports detrimental effects of mHtt on oxidative metabolism, whereas another group does not find evidence for such effects. This contradiction limits our understanding of HD pathogenesis and impedes the development of new treatment approaches for HD. Consequently, this contradiction has to be resolved in order to provide explicit answers to the questions of whether mHtt results in defects in oxidative metabolism and whether these defects contribute to HD pathogenesis and therefore represent a valid target for the development of effective HD therapies.

MITOCHONDRIAL CALCIUM HANDLING

One of the main hypotheses regarding HD pathology postulates that expression of mHtt results in defects in Ca^{2+} signaling in neurons [50] most likely due to alterations in activity of NMDA-subtype of ionotropic glutamate receptors [51], abnormalities in IP_3 receptor function [52], and aberrations in mitochondrial Ca^{2+} handling [14]. The inner mitochondrial membrane has a Ca^{2+} channel [53,54], historically called the Ca^{2+} uniporter [55], that mediates Ca^{2+} influx into the mitochondrial matrix driven by large membrane potential negative inside of mitochondria. The magnitude of mitochondrial Ca^{2+} uptake capacity is restricted by the sensitivity of mitochondria to the damaging effect of Ca^{2+}, manifested in an induction of the mitochondrial permeability transition pore (PTP) [56].

Several studies demonstrated mHtt-induced defects in mitochondrial Ca^{2+} uptake (defects in mitochondrial Ca^{2+} handling). An early paper by Panov et al. reported bioenergetic abnormalities and a reduction in Ca^{2+} uptake capacity by mitochondria isolated from cells and tissues expressing mHtt [14]. Mitochondria from lymphoblasts of patients with HD as well as brain nonsynaptic mitochondria from pathological YAC72 mice had a diminished membrane potential and were depolarized at smaller Ca^{2+} loads compared with mitochondria from healthy YAC18 mice. These defects appeared to be upstream of the onset of pathological or behavioral abnormalities and could be replicated by a fusion protein GST-

Q62 containing expanded polyQ repeat. It is known that Ca^{2+} uptake capacity could be increased by a combination of ADP and cyclosporin A (CsA), efficient inhibitors of the PTP [57,56]. However, Panov et al. reported that the Ca^{2+} handling defect persisted even in the presence of these PTP inhibitors [14]. Thus, the mechanism of the mitochondrial Ca^{2+} handling defect was not clarified in this study, but based on the fact that ADP and CsA failed to eliminate the difference between mitochondria from mutant and WT animals, PTP involvement could be excluded. Intriguingly, the effect of mHtt on mitochondrial Ca^{2+} uptake capacity appeared to be elusive, and in the next study Panov et al. found that "the defect in Ca^{2+} handling in brain mitochondria was consistently observed only if brain mitochondria were isolated without BSA" [58]. The authors proposed that BSA could replace mHtt in its binding sites on mitochondria, but did not provide experimental evidence supporting this hypothesis.

Soon after that, Choo et al. showed that liver mitochondria from homozygous knock-in $Hdh^{150/150}$ mice had augmented predisposition to the Ca^{2+}-induced PTP [32]. The authors also found that GST-fused N-terminal truncated mHtt (GST-exon1-Q65 or Htt65), containing 65 glutamines, and GST-Q62 fusion protein, containing 62 glutamines, significantly increased mitochondrial susceptibility to Ca^{2+}-dependent PTP induction. Htt65 reduced Ca^{2+} threshold for PTP induction and could directly stimulate Ca^{2+}-dependent PTP induction in mouse liver mitochondria [32]. Later, Milakovich et al. showed that in mitochondria isolated from conditionally immortalized striatal progenitor cells $STHdh^{Q111/Q111}$, mHtt with 111 glutamines augmented mitochondrial sensitivity to Ca^{2+}-induced decrease in ADP-activated respiration (State 3) and mitochondrial depolarization [59]. In addition, mHtt reduced mitochondrial Ca^{2+} uptake capacity that could be salvaged by a combination of ADP and CsA, the inhibitors of the PTP [57], thus linking PTP induction to the mHtt-induced Ca^{2+} handling defect. In line with this, Lim et al., using the same cell lines, demonstrated that mitochondria from the cells had reduced Ca^{2+} uptake capacity due to increased susceptibility to PTP induction [60]. In support of these findings, Gizatullina et al. observed increased propensity of skeletal muscle mitochondria from R6/2 mice to Ca^{2+}-induced PTP compared with mitochondria from WT mice [61]. In the following study, Gellerich et al. examined brain mitochondria isolated from transgenic HD rats expressing a 727 amino acid fragments of mHtt with a 51Q-stretch [62]. The authors found that the mHtt fragments reduced membrane potential stability in response to Ca^{2+}, decreased Ca^{2+} uptake capacity, and diminished Ca^{2+} threshold for PTP induction.

In addition to isolated mitochondria, neurons in culture were used to study detrimental effects of mHtt on Ca^{2+} signaling and mitochondrial Ca^{2+} handling. Fernandes et al. reported that Ca^{2+} influx into cells mediated by the NMDA-subtype of ionotropic glutamate receptors resulted in augmented mitochondrial depolarization in medium spiny neurons from YAC128 mice [63]. This effect was paralleled by reduced clearance of elevated cytosolic Ca^{2+} following NMDA withdrawal. Suppression of the PTP by CsA or bongkrekic acid resulted in a decrease in cytosolic Ca^{2+} and diminished mitochondrial depolarization induced by NMDA in neurons from YAC128 mice, but not from WT mice. Based on these observations, the authors concluded that mitochondria in medium spiny neurons from YAC128 mice have increased susceptibility to PTP induction by Ca^{2+} [63]. In support of this view, Quintanilla et al. found that rat cortical neurons expressing a fragment of mHtt with

104 glutamines (Q104-GFP) are more susceptible to Ca^{2+} stress compared with neurons expressing a fragment of Htt with 25 glutamines (Q25-GFP) [64]. The authors also reported that mitochondrial defects in mutant STHdh$^{Q111/Q111}$ cells and cortical neurons expressing Q104-GFP were attenuated by CsA, suggesting an important role for PTP in mitochondrial injury induced by Ca^{2+} stress in cells expressing mHtt. Overall, these data suggest that mHtt impairs mitochondrial Ca^{2+} uptake capacity by increasing susceptibility to PTP induction. Similar to studies aimed at elucidating mHtt effects on oxidative metabolism, the major remaining question is how does mHtt, a 350 kDa cytosolic protein that binds to the outer mitochondrial membrane [32], affect mitochondrial Ca^{2+} handling and increase propensity to PTP induction, which are the processes mainly associated with the inner mitochondrial membrane.

Despite reported defects in mitochondrial Ca^{2+} handling, some investigators did not find evidence for mHtt-induced mitochondrial Ca^{2+} handling deficiency and increased propensity to PTP induction in the presence of mHtt. In our early study, we did not find an increased susceptibility to Ca^{2+}-induced PTP induction in striatal nonsynaptic mitochondria from HD mice (Q50, Q92, Q111 and R6/2 mice) compared with mitochondria from WT animals [65]. Surprisingly, we found increased resistance to Ca^{2+} in striatal mitochondria isolated from HD mice. In line with our findings, Oliveira et al. demonstrated that nonsynaptic mitochondria from R6/2 and YAC128 mice had augmented Ca^{2+} uptake capacity compared with mitochondria from WT mice whereas mitochondria from Hdh$^{150/+}$ and Hdh$^{150/150}$ mice had similar Ca^{2+} uptake capacity compared with mitochondria from WT animals [39]. The reason for the increased Ca^{2+} uptake capacity is not clear, but it may reflect compensatory adaptation to augmented Ca^{2+} influx via overactivated NMDA receptors and/or increased Ca^{2+} release from endoplasmic reticulum via abnormally activated IP_3 receptors [50]. Both, our study [65] and the study by Oliveira et al. [39], suggest that the lack of mHtt-induced impairment of mitochondrial Ca^{2+} handling argues against facilitated PTP induction in the presence of mHtt and, consequently, does not support involvement of the PTP in HD pathogenesis. Additional evidence for the lack of mitochondrial Ca^{2+} handling defects came from experiments by Chang et al. who transiently exposed cortical neurons expressing N-terminal fragment of mHtt or full-length mHtt to glutamate and used FCCP-induced mitochondrial depolarization to release Ca^{2+} accumulated in the mitochondrial matrix [66]. In these experiments, the authors failed to find significant effect of mHtt on the ability of neuronal mitochondria to accumulate Ca^{2+} following exposure of neurons to excitotoxic glutamate. Recently, Wang et al. evoked Ca^{2+} mobilization in medium spiny neurons by stimulating group I metabotropic glutamate receptors and eliciting inositol 1,4,5-trisphospahe ($InsP_3$) generation. They found significantly higher Ca^{2+} accumulation in mitochondria of neurons from YAC128 mice compared with neurons from WT mice [67]. These data argue against mHtt-induced mitochondrial Ca^{2+} handling defects. However, even if these defects exist, their role in HD pathogenesis could be non-essential. Consistent with the dispensable role of mitochondrial Ca^{2+} handling defects in HD pathogenesis, Perry et al. demonstrated that R6/2 mice crossed with cyclophilin D-knockout mice (cyclophilin D (CyD) is an important regulatory component of the PTP that sensitizes the pore to Ca^{2+} [68,69]) had augmented neuronal mitochondrial Ca^{2+} uptake capacity without any improvement in either behavioral or neuropathological characteristics [70]. The authors

reasoned that increased Ca^{2+} capacity of neuronal mitochondria is not advantageous for R6/2 mice. Altogether, these results cast doubt on the ability of mHtt to increase susceptibility to PTP induction and to decrease mitochondrial Ca^{2+} uptake capacity. Consequently, these data question the role of mitochondrial Ca^{2+} handling defects in HD pathogenesis. Thus, there are two distinct schools of thought, where one reported mHtt-induced defects in mitochondrial Ca^{2+} uptake and increased susceptibility to PTP induction, whereas the other did not find evidence for these deleterious alterations associated with mHtt. The reason for this discrepancy is not clear, but it could be related to the use of different HD models and variations in methodological approaches. One of the major remaining problems here is to explain how 350 kDa cytosolic protein that cannot cross the outer membrane may affect mitochondrial Ca^{2+} handling that mainly depends on the processes in the inner mitochondrial membrane.

Concluding Remarks

Similar to studies of the effect of mHtt on oxidative metabolism discussed in the first half of this paper, the data about the effect mHtt on mitochondrial Ca^{2+} handling are contradictory. One group of investigators finds mHtt induced defects in mitochondrial Ca^{2+} handling, whereas another group does not. The reason for this contradiction is not clear. Consequently, additional studies are necessary to resolve this issue, and it seems very likely that a collaborative effort involving investigators from the opposite camps might be the best way to reconcile the existing contradictions and to firmly establish whether or not mHtt affects mitochondrial functions.

It is known that mHtt does not acutely damage neurons. In most cases, the HD patients remain asymptomatic until their late 30s and 40s. Different animal models of HD at the early ages demonstrate the lack of overt functional and behavioral abnormalities. Correspondingly, one of the major challenges in HD studies is to determine detrimental mechanisms that produce subtle cumulative effects leading over time to synaptic malfunction, neuronal injury, and eventually, to loss of neurons. While the findings concerning respiratory defects and Ca^{2+} handling abnormalities in the mitochondria of HD animal models are contradictory, there is a consensus about the presence of mHtt-triggered alterations in mitochondrial dynamics (balance of fission and fusion) [71,9,10,11] and motility of organelles [12,66,35,8]. Aberrant mitochondrial dynamics may affect mitochondrial quality control mechanisms, resulting in an accumulation of dysfunctional mitochondria over time. The decreased mitochondrial motility may limit the ability of neurons to adequately respond to sudden augmentation of energy demand at distant synapses. Although these alterations may not be critical for neuronal function and survival at early ages, over time they could produce detrimental changes, contributing to HD pathogenesis. Despite compelling evidence indicating aberrant mitochondrial dynamics and decreased mitochondrial motility in HD, the detailed mechanisms underlying these alterations are not completely understood. Does mHtt interact and affect individual components of mitochondrial trafficking machinery? Are there as yet unidentified proteins that might interact with mHtt and be involved in alterations of mitochondrial dynamics and/or trafficking in HD? Is there a way to mitigate the possible detrimental consequences of mHtt interference with mitochondrial dynamics and trafficking? Answering these questions

will bring us closer to understanding of the molecular mechanisms contributing to HD pathogenesis and may potentially open new avenues for developing novel HD treatments.

Acknowledgments

This work was supported by NIH/NINDS grant R01 NS078008.

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Table 1

Models of Huntington's disease discussed in this paper.

HD cell or mouse model	Origin or genetic construct	Effects on oxidative metabolism and mitochondrial Ca^{2+} handling
Conditionally immortalized, mutant $STHdh^{Q111/Q111}$ striatal neuronal progenitor cells [20]	Derived from knock-in mice with 111 CAG repeats in endogenous *htt* gene	Inhibited respiration, but respiratory Complexes are not affected [23] Slightly reduced maximal respiratory rate, no difference in basal respiration [25] Deficient OXPHOS and decreased Complex I and IV activities [26] Reduced Ca^{2+} uptake capacity and increased propensity to PTP induction in mitochondria isolated from $STHdh^{Q111/Q111}$ cells [59,60]
Transgenic R6/2 mice [72]	N-terminal fragment of human *htt* with 115-150 or 195 CAG repeats	Activities of Complex IV and aconitase are decreased [27] Respiratory impairment of striatal mitochondria [31] Respiration of synaptic and nonsynaptic mitochondria is not affected [34] Oxygen consumption is not affected in 8 week old mice, but increased in 14-week-old animals [43] Increased propensity to Ca^{2+} -induced PTP induction in skeletal muscle mitochondria [61] Augmented Ca^{2+} uptake capacity in brain nonsynaptic mitochondria [39]
Transgenic N171-82Q mice [73]	N-terminal fragment of human *htt* with 82 CAG repeats	Decreased Complex IV activity [28] Activities of Complexes I-IV are not decreased, glycolysis is increased [37] ADP-stimulated respiration of isolated brain mitochondria is decreased [30] Oxygen consumption by whole animals slightly increased, electron respiratory chain is not compromised [42]
Transgenic D9-N171-98Q mice, also known as DE5 mice [74]	N-terminal fragment of human *htt* with 98 CAG repeats	Decreased respiration of succinate-fueled striatal mitochondria; Complexes I and IV as well as ATP synthase are not affected [29]
Transgenic HD48 and HD89 mice [38]	Full-length human *htt* gene with 48 or 89 CAG repeats	Complexes I-IV are not affected in the striatum and cortex [38]
Transgenic YAC72 mice [75]	Full-length human *htt* gene with 72 CAG repeats	Diminished mitochondrial membrane potential, decreased Ca^{2+} uptake capacity [14]
Transgenic YAC128 mice [76]	Full-length human *htt* gene with 128 CAG repeats	Augmented mitochondrial depolarization in response to Ca^{2+} in medium spiny neurons, increased susceptibility to PTP induction [63] Augmented Ca^{2+} uptake capacity in brain nonsynaptic mitochondria [39]
Transgenic BACHD mice [77]	Full-length human *htt* gene with 97 mixed CAA-CAG repeats	No effect of mHtt on oxidative metabolism in cultured astrocytes and neurons [41]
Knock-in Q50, Q92, and Q111 mice [78]	Mouse *htt* gene with inserted 50, 92, or 111 CAG repeats in exon 1	No increase in sensitivity to Ca^{2+}-induced damage in striatal and cortical nonsynaptic mitochondria [65]
Knock-in Hdh150Q mice [79]	Mouse *htt* gene with inserted 150 CAG repeats in exon 1 in a single allele	Respiration of striatal cultured neurons from $Hdh^{150/+}$ is not affected [39]

HD cell or mouse model	Origin or genetic construct	Effects on oxidative metabolism and mitochondrial Ca^{2+} handling
	($Hdh^{150/+}$) or both alleles ($Hdh^{150/150}$)	Liver mitochondria from $Hdh^{150/150}$ mice have increased propensity to Ca^{2+} -induced PTP [32]. No change in Ca^{2+} uptake capacity in brain nonsynaptic mitochondria [39]
Transgenic BACHD rats [80]	Full-length human *htt* gene with 97 mixed CAA/CAG repeats	No difference in respiration of cultured striatal neurons incubated with high glucose and pyruvate; modest decrease in maximal respiration in the presence of low glucose; respiration of cortical neurons is not affected [40]
Transgenic HD rats [81]	Express 727 amino acids of the htt_{51Q} gene, corresponding to 22% of the full-length gene	Reduced mitochondrial membrane potential stability in response to Ca^{2+}, decreased Ca^{2+} uptake capacity, increased propensity to PTP induction [62]