Energy Metabolism in Huntington's Disease

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1. Introduction

Neurodegenerative diseases are pathological processes characterized by neuronal death and morbid evolution leading to occupational injury and serious neuropsychiatric disorders. The natural course of neurodegenerative diseases does not show regression of symptoms or cure and current treatments are far from producing a real improvement in the quality of patient's life. Several studies have been conducted in an attempt to find causes of cellular disturbances focusing new pharmacological targets priming to successful therapeutic interventions. Studies have been directed to investigate possible changes in energy metabolism pathways. Indeed, some disturbances in glycolytic pathway and mitochondrial dysfunctions have been associated with Huntington's Disease and other neurodegenerative diseases and are often related to the events of cell death. In this section, an overview of the energy metabolism pathways will be presented and the particular aspects of energetic metabolism in Huntington's Disease will be discussed.

2. Glucose transport

Under ordinary conditions, the basic substrate for brain metabolism is glucose. In the resting state, adults use about 20% of whole-body glucose for brain metabolism. The brain has an exquisite dependence on glucose for energy production and as an important carbon source for biosynthesis of a variety of simple and complex molecules (Siegel et al., 1999). Such dependence is well demonstrated and a transient decline in the metabolism of glucose would cause a serious disruption of brain function (Oliveira et al., 2007). As glucose is a water-soluble substance its entry into brain from blood is greatly restricted (Vannucci et al., 1997). The major reason for that is the presence of an anatomical-physiological barrier – so called Blood-Brain-Barrier (BBB). The BBB is a specialized barrier made up of microvascular endothelial cells that are held together by tight junction complexes that effectively avoid the paracellular diffusion of solutes (Wilhelm et al., 2011). Even small molecules do not simply

diffuse across this physical barrier. To manage this problem, not only for glucose but also for other metabolites important to brain metabolism, there are a large family of specific membrane transporters responsible to carry these molecules across the BBB by means of facilitated diffusion through the luminal and ablumenal endothelial membranes (Vannucci et al., 1997).

It is established that transport and uptake of glucose is performed by a super-family of glucose transporters belonging to the GLUT gene family. The GLUT family includes 12 genes encoding 12 GLUT proteins (Vannucci et al., 1997; Klepper and Voit, 2002). Various members of this membrane protein family have been detected in brain (GLUT-1, GLUT-3 and GLUT-5), but the initial glucose transport step across the BBB is mediated exclusively by the facilitative glucose transporter protein type 1 (GLUT-1) (Lund-Andersen, 1979; Pardridge et al., 1990; Klepper and Voit, 2002). Important to note is the fact that despite such facilitative transport mechanism, the actual concentration of glucose in brain is lower than it is in structures lacking a barrier, e.g. peripheral nerves. There is, then, no safety device to supplement carbohydrate reserve during hypoglycemia episodes making the regulation of GLUTs extremely relevant for brain physiology.

Following entry into the brain glucose is transported from the interstitial fluid into neurons primarily via GLUT-3 and into glia primarily via GLUT-1 transporters. GLUT-5 protein is known to be present in brain microglia, although its function in these cells remains unclear. This transport into the intracellular compartment is relatively rapid, making the BBB the rate-limiting step for glucose entry into brain cells (Pardridge et al., 1990).

Glucose, entering the neuronal cells, is phosphorylated irreversibly to glucose-6-phosphate (G-6~P) and metabolized in the pentose phosphate shunt or the Embden-Meyerhoff pathway, or converted to glycogen. The Embden-Meyerhoff metabolic pathway permits glycolytic conversion of glucose to pyruvate. Glycogen synthesis provides a source of fuel during periods of metabolic stress (3.3 mmol/kg rat). Evidently a decreased entry of glucose into the brain limits these three pathways and potentially contributes to the development of innumerous neuronal pathologies.

Brain metabolic needs are demanding and the way in which it circumvents this situation has long remained unclear. For the past 15 years authors are looking for a more universal explanation but it turns out to be rather complicated. The subject is controversial and the field is still very active.

Neurons and astrocytes, the two major types of brain cells, are largely responsible for the massive consumption of O_2 and glucose in the brain. Just to point out how important they are, under resting conditions, astrocytes release ~85% of the glucose they consume as lactate. On the contrary, neurons contribute minimally to glucose consumption by the brain. Thus, despite their shared localization, neurons and astrocytes exhibit a different preference for glucose consumption and utilization (Nehlig and Coles, 2007).

The ATP-dependent phosphorylation of glucose to G-6~P is the first step of glycolysis and it is catalyzed by hexokinase (HK) (Berg et al., 2006). The reaction is practically irreversible and has been recognized as a key point in the regulation of carbohydrate metabolism in brain. This whole process concomitantly generates local ADP which is important as a recycling mechanism. Important to note that hexokinase activity in neurons and in other cell

types also participates in various essential processes including ATP production, apoptosis, controlling glutathione levels, and preventing neuronal oxidative unbalance (Saraiva et al., 2010). In the brain, HK-1 is the major expressed enzyme isoform. It localizes into cytosol or firmly attached to outer mitochondrial membrane. The bound enzyme is more active and the extent of binding is thought to be inversely related to the ATP/ADP ratio (Siegel et al., 1999). Interestingly, conditions where energy utilization is greater than the substrate supply there is a shift in the solubilization equilibrium towards the membrane-bound enzyme form which per se provokes a greater potential to ignite glycolysis to meet the energy demand.

The activity and specific subcellular localization of neuronal HK-1 are regulated by distinct mechanisms that act synergistically to fine-tuning glycolytic flux in response to changes in cellular environment. At this point it may be important to bring up the idea that mitochondrial-bound hexokinase 1 could be neuroprotective as has been discussed by different research groups in this field.

The reaction product of HK-1 is G-6~P which represents a major branch point in metabolism because it is a common substrate for enzymes involved in glycolytic, pentose-phosphate shunt, and glycogen-forming pathways. In glycolysis, G-6~P is the substrate of isomerase producing fructose-6-phosphate (F-6~P). This reaction is promptly reversible (small free energy change), however its equilibrium ratio in brain greatly favors G-6~P accumulation. F-6~P is phosphorylated by phosphofructokinase-1 (PFK-1), which is considered one of the most regulated catalysts of the glycolytic sequence, to form fructose-1,6-bisphosphate (F-1,6-Bis~P). As observed in other regulatory biochemical reactions it is also essentially irreversible.

A number of studies focusing into this particular metabolic reaction led to the observation that astrocytes' PFK-1 is about two fold more active than in neurons under baseline conditions (Herrero-Mendez et al., 2009). One possible reason for that is the concentration of fructose-2,6-bisphosphate (F-2,6-Bis~P), an powerful allosteric modulator of PFK-1 activity, is significantly greater in astrocytes. This dramatic difference could be ascribed to the near absence in neurons of phosphofructokinase-2/fructose-2,6-phosphatase (PFK-2/F-2,6-Pase) the bifunctional enzyme responsible for the F-2,6-Bis~P synthesis and degradation (Herrero-Mendez et al., 2009).

The question to be raised is how neurons actually control PFK-2/F-2,6-Pase activity? There are four isoforms of PFK-2/F-2,6-Pase, each encoded by a separate gene [Pfkfb1, Pfkfb2, Pfkfb3, and Pfkfb4] (Okar et al., 2001). It is reasonable to suppose that each isoform displays significantly different regulatory and kinetic features and this, in turn, determines the ratio of kinase/phosphatase activity, and as a consequence the concentration of F-2,6-Bis~P in different tissues (Yalcin et al., 2009). In a well conducted study Herrero-Mendez and colleagues (2009), using RT-PCR analysis of RNA extracts from rat cortical neurons and astrocytes, indicated that Pfkfb3 mRNA was present in neurons as well as astrocytes. Importantly, the authors demonstrated that Pfkfb3 was the most abundant mRNA expressed in both cell types. The authors expected that if neurons contained the same relative abundance of Pfkfb3 mRNA as astrocytes and lower levels of the mature enzyme that the final concentration of PFK-2/F-2,6-Bis~Pase in neurons might be regulated post-transcriptionally. Some studies exploring the mechanism of such proteasomal degradation revealed that Pfkfb3, contains a KEN box that starts at position 142 (Pesin and Orr-Weaver, 2008; Herrero-Mendez et al., 2009). This motif targets proteins for ubiquitylation by the

anaphase-promoting complex/cyclosome when bound to its activator CDH1 (Pesin and Orr-Weaver, 2008). Interestingly, CDH1 silencing in neurons induced PFK-2/F-2,6-Bis~Pase accumulation and as expected increased the rate of glycolysis.

Fructose-1,6-Bis~P is split by brain aldolase to glyceraldehyde-3-phosphate (Gal-3~P) and dihydroxyacetone phosphate (DHAP). DHAP is the common substrate for both glyceraldehyde-3-phosphate dehydrogenase and triose phosphate isomerase. One important point to comment is the equilibrium between DHAP and Gal-3~P maintained by the action of triose phosphate isomerase. In brain, the equilibrium favors accumulation of DHAP. After this reaction step, glycolysis in the brain proceeds through the usual biochemical reactions to produce pyruvate (Berg et al., 2006).

As we have been discussing throughout the chapter neurons use glucose basically to maintain their antioxidant balance status. In order to do this, neurons have to downregulate glycolysis. Under this situation one the question is raised: Where does glucose go to be further metabolized? To answer this question we need to remember that pentose-phosphate pathway (PPP) uses G-6~P as substrate and that PPP is metabolic linked to glycolysis. One interesting, however somehow surprising, observation made by different laboratories is the fact that, in contrast to astrocytes, neurons do not display increased glycolytic rate upon mitochondrial inhibition as one could expect (Bolanos et al., 2008; Bolanos et al., 2010), but instead these neuronal cells entry into cell death program. These results lead us to assume that the increased glycolytic rate in astrocytes served to preserve cells from ATP depletion and cell death, most probably because glycolytic ATP was used to drive the reverse activity of ATP synthase to maintain the mitochondrial membrane potential (Nehlig and Coles, 2007; Bolanos et al., 2010; Cunnane et al., 2011). On the other hand, such treatment caused neuronal ATP depletion and apoptotic cell death (Nehlig and Coles, 2007). Based on all facts presented so far one can hypothesize that neurodegenerative diseases (including Alzheimer's Disease and Huntington's Disease) may present a diminished neuronal glycolytic activity (Oliveira et al., 2007). Data in support of this hypothesis will be discussed later.

Accumulated evidence suggest that in neurons a significant proportion of G-6~P is directed towards the PPP (Bolanos et al., 2008). Besides its role at supplying ribose-5-phosphate for nucleic acid biosynthesis, glucose oxidation through the PPP is a major component of the cytosolic NADPH regenerating cell machinery (Nelson and Cox, 2004; Bolanos et al., 2008). The rate-limiting step in PPP activity is catalyzed by glucose-6-phosphate dehydrogenase, which oxidizes G-6~P into 6-phosphogluconate, conserving the redox energy as NADPH. Next, 6-phosphogluconate is further oxidized by 6-phosphogluconate dehydrogenase, which also conserves redox energy in the form of NADPH (Nelson and Cox, 2004; Bolanos et al., 2008).

It is important to note: NADPH is a necessary cofactor in the regeneration of reduced glutathione and for the reductive reactions for lipid biosynthesis. This mechanism is not exclusive for neurons it also operates in astrocytes which have high concentrations of glutathione due to their high activity of γ-glutamyl cysteine synthetase. This enzyme catalyzes the rate-limiting step in glutathione synthesis providing a metabolic scenario to build a robust antioxidant system (Heales and Bolanos, 2002). As neurons have rather low concentrations of glutathione, and low activity of γ-glutamyl cysteine synthetase there are compelling evidence that glucose entry in the PPP is important to regenerate glutathione and provide an effective defense mechanism against oxidative stress.

The energy output and oxygen consumption in adult brain are associated with high levels of enzyme activity in the tricarboxylic acid cycle (TCA). The TCA is organized into a supramolecular complex that interacts with mitochondrial membranes and the electron transport chain (Berg et al., 2006). Therefore, mitochondria have a central role for the energetic metabolism, their main function is oxidation of acetyl-coenzyme A derived from carbohydrates, amino-acids and fatty acids to produce ATP (Nelson and Cox, 2004). These organelles provide energy for a plethora of cellular processes and the highest number of mitochondria is present in organs demanding the most of energy, such as brain, liver and muscles.

Actually, the processes responsible for energy production are recognized as oxidative phosphorylation which is coupled to the electron transport chain (ETC). The ETC is a set of five protein complexes sitting on the inner mitochondrial membrane. Three protein complexes (complex I, III and IV) work as a proton pump transferring protons through the membrane into the intermembrane space. Chemiosmotic theory predicts that most of the ATP synthesis comes from the electrochemical gradient across the inner membranes of mitochondria by ATP synthase. Energy saved in ATP is used in synaptic ion homeostasis and phosphorylation reactions. ATP is essential for the excitability and survival of neurons, oxidative phosphorylation is involved in synaptic signaling and is related to changes of neuronal structure and function.

The major role is given to complex I (NADH dehydrogenase [ubiquinone]) in controlling mitochondrial oxidative phosphorylation; its malfunctioning can result in mitochondrial dysfunction.(Davey et al., 1998; Hroudova and Fisar, 2011). Thus, many mitochondrial diseases originate from complex I deficiencies.

In adult brain, the enzyme succinate dehydrogenase (SDH), which catalysis the oxidation of succinate to fumarate, is tightly bound to mitochondrial inner membrane. In brain, SDH may also have a regulatory role when its steady state is disturbed. Important to note that the levels of succinate and isocitrate in brain tissue are little affected by changes in the flux of the TCA, as long as proper glucose supply is available. The highly unfavorable free-energy change of the malate dehydrogenase reaction is bypassed by the very rapid removal of oxaloacetate, which is maintained at low concentrations under steady-state conditions through the condensation reaction with acetyl-coenzyme A (Berg et al., 2006); Nelson and Cox, 2004).

3. Energetic metabolism deficit in Huntington's Disease

Huntington´s Disease patients face pronounced weight loss, despite sustained caloric intake, which was a first indication that alterations in energetic metabolism could play a role in Huntington´s Disease pathogenesis (O'Brien et al., 1990). In agreement with this hypothesis, Huntington´s Disease patients exhibit alterations in cerebral glucose consume, lactate levels, and mitochondrial enzymes activity involved in glucose metabolism. Moreover, ATP depletion was directly demonstrated in Huntington´s Disease brain tissue (Mochel et al., 2010a). Thus far, various mechanisms underlying energy deficit in Huntington´s Disease brain have been identified, including impaired oxidative phosphorylation (Milakovic and Johnson, 2005), altered oxidative stress (Tabrizi et al., 1999), impaired mitochondrial calcium handling (Lim et al., 2008), abnormal mitochondria trafficking (Li et al., 2010), and

deregulation of the transcriptional coactivator PPARγ coactivator-1α (PGC-1α), which is a crucial factor of mitochondrial biogenesis (Cui et al., 2006), and decreased glycolysis (Powers et al., 2007).

3.1 Glucose levels are reduced in Huntington's Disease patient's brain

Positron emission tomography (PET) studies revealed that glucose metabolism in the basal ganglia and cerebral cortex is markedly reduced in Huntington´s Disease patients (Kuwert et al., 1990; Andrews and Brooks, 1998). Moreover, the decrease in glucose metabolism is specific to cortical areas, caudate and putamen, and starts in the asymptomatic phase of the disease (Kuhl et al., 1985). Regardless of the severity of symptoms and despite apparent shrinkage of brain tissue, glucose utilization appears normal throughout the rest of the brain of Huntington´s Disease patients (Kuhl et al., 1985).

Furthermore, studies performed in presymptomatic Huntington´s Disease gene carriers revealed a pattern of cerebral metabolism characterized by relative increases in thalamic, occipital, and cerebellar glucose metabolism, despite reduced caudate and putamen metabolism. Following Huntington´s Disease symptoms appearance, this pattern was altered as thalamic metabolism, which was previously elevated, was reduced (Feigin et al., 2007). These data highlights the importance of the region specific alterations in glucose metabolism for Huntington´s Disease pathology.

Interestingly, a recent report supports the idea that the hypothalamus, but not the basal ganglia, is the brain region responsible for the metabolic abnormalities that take place in Huntington´s Disease (Hult et al., 2011). Selective hypothalamic expression of a short fragment of mutant huntingtin was sufficient to recapitulate the glucose metabolic disturbances that occur in Huntington´s Disease patients. In addition, selective hypothalamic inactivation of the mutant huntingtin gene prevented the development of the metabolic phenotype in a Huntington´s Disease mouse model, BACHD mice (Hult et al., 2011). Further studies will be important to point all the regions involved in Huntington´s Disease metabolic alterations.

In addition to its role as an energetic molecule, glucose also plays a role as a signaling molecule. It has been demonstrated that increased intracellular glucose levels decreases aggregate formation and is neuroprotective in cultured cells transfected with a mutant huntingtin construct (Ravikumar et al., 2003). Glucose metabolism appears altered in Huntington´s Disease, as huntingtin transfected PC12 cells exhibit disturbed expression levels of four genes involved in glucose metabolism (Glut1, Pfkm, Aldolase A, and Enolase), as well as a reduction in cell death following over-expression of Glut1 and Pfkm (another key regulatory protein for glycolysis) (Kita et al., 2002). Glucose reduces phosphorylation of mTOR, which is a negative regulator of authophagy, and its downstream effector S6K1 (Ravikumar et al., 2003). Thus, glucose-mediated negative regulation of mTOR could induce autophagy and clearance of the mutated huntingtin protein, as well as influence other mTOR mediated activities involving cell survival, growth, and translation of protein transcripts. Furthermore, glucose can regulate Akt and GSK3, which influence cell growth and survival (Clodfelder-Miller et al., 2005). Importantly, Akt activation can protect against neuronal death (Datta et al., 1999; Kandel and Hay, 1999). Akt can also promote phosphorylation of mutated Htt protein, which functions to reduce Htt aggregate formation

and neuronal cell death, providing a protective pathway in Huntington´s Disease (Humbert et al., 2002; Warby et al., 2009). Highlighting the importance of Akt in Huntington´s Disease pathology, both NMDA and metabotropic glutamate receptor 5 receptors can increase Akt activation in striatal neurons from Huntington´s Disease mouse models (Gines et al., 2003a). These observations highlight the role of glucose as an important molecule not only for its energetic properties but also for its capacity to activate key molecules involved in cell survival and huntingtin clearance.

3.2 Enzymes involved in energetic metabolism are altered in Huntington´s Disease

Mutated huntingtin protein alters the function and/or expression of a number of enzymes involved in energetic metabolism and many of these alterations can have important implications in Huntington´s Disease pathology. Alteration of enzyme expression by mutated huntingtin may occur due to huntingtin-mediated regulation of transcriptional factors. For example, mutant huntingtin inhibits expression of PGC-1α, which is a transcriptional coactivator that regulates several metabolic processes, including mitochondrial biogenesis and respiration (Cui et al., 2006). Mutated huntingtin may also alter enzyme function by incorporation and sequestration of transcriptional factors and enzymes into mutated huntingtin aggregates (Yamanaka et al., 2008). The enzyme alterations caused by mutated huntingtin can have important deleterious consequence, including the metabolic deficit observed in Huntington´s Disease patients.

Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and the α-ketoglutarate dehydrogenase complex can be inactivated by long polyglutamine domains, which may cause a deficit in cerebral energy metabolism (Cooper et al., 1997). Further studies have shown that the mutated huntingtin protein alters the subcellular localization of GAPDH, increasing its nuclear localization in both human fibroblasts and in neurons from a transgenic mouse model (Mazzola and Sirover, 2001, 2002; Senatorov et al., 2003). The appearance of an abnormal high molecular weight form of GAPDH in fibroblast nuclei has also been associated with decreased glycolytic activity (Mazzola and Sirover, 2001).

Pyruvate dehydrogenase activity is decreased in basal ganglia and this deficit was significantly augmented with increasing duration of illness, possibly due to a progressive loss of neurons in Huntington's Disease caudate nucleus (Butterworth et al., 1985). Activities of the complexes II, III and IV of the electron transport chain were reduced in both Huntington´s Disease caudate and putamen of advanced grade (3 and 4) Huntington´s Disease patients (Gu et al., 1996; Browne et al., 1997). It has been shown that lactate concentration is increased in the basal ganglia and the occipital cortex of Huntington´s Disease patients (Jenkins et al., 1993; Jenkins et al., 1998). The lactate itself is not thought to be a neurotoxic metabolite, but may represent a marker for energetic changes such as reduced ATP production and excitotoxicity, which may have a direct effect on neuronal function and survival in Huntington´s Disease.

A number of studies have shown that the activity of transglutaminase 2, an enzyme primarily known for cross-linking proteins, is increased in Huntington´s Disease affected brain areas and that transglutaminase 2 causes an increase in huntingtin aggregation (Karpuj et al., 1999; Lesort et al., 1999; Karpuj et al., 2002). The most compelling evidence for a role of transglutaminase 2 in Huntington´s Disease is provided by the work of

Mastroberardino et al. (2002). These studies reported a reduction in neuronal cell death, improved behavior and prolonged survival in R6/1 X transglutaminase 2$^{-/-}$, as compared to R6/1 X transglutaminase 2$^{+/+}$. In addition to affecting huntingtin aggregation, increased transglutaminase 2 activity in Huntington´s Disease caudate may contribute to mitochondrial dysfunction by incorporating aconitase into inactive polymers and dramatically decreasing aconitase activity (Kim et al., 2005).

3.3 Mitochondrial deficit in Huntington´s Disease

Studies published so far suggest that mitochondrial defects play a major role in Huntington´s Disease etiology, underlined by decreased mitochondrial biogenesis, oxidative stress, ATP deficit, increased apoptosis, and, ultimately, a central and peripheral energy deficit (Browne and Beal, 2004).

Degenerated mitochondria have been detected in the striatum of symptomatic Huntington´s Disease mice (R6/2, R6/1, N171-82Q, and Hdh150CAG mice) and could be detected before other neuronal pathological changes and concomitant with symptom onset (Yu et al., 2003). These degenerating mitochondria exhibit swelling, disruption of the cristae and mitochondrial membranes, and eventual condensation and lysosomal engulfment. Interestingly, this study shows that neuronal cell death aspects due to motichondrial alterations varied among different Huntington´s Disease mouse models (Hickey and Chesselet, 2003; Yu et al., 2003).

Mutated huntingtin protein destabilizes mitochondrial Ca^{2+} regulation (Panov et al., 2002; Choo et al., 2004). Mitochondrial Ca^{2+} abnormalities occur early in Huntington´s Disease pathogenesis and appear to be caused by a direct effect of mutant huntingtin, as incubation of normal human lymphoblast mitochondria with a fusion protein containing a long polyglutamine repeat recapitulates the mitochondrial calcium defect observed in Huntington´s Disease (Panov et al., 2002). Further studies have also demonstrated that the huntingtin protein binds to the outer membrane of mitochondria from human neuroblastoma cells and from cultured striatal cells from WT and transgenic mice (Choo et al., 2004). Moreover, binding of mutated huntingtin protein, but not of wild type, increases sensitivity to calcium-induced opening of the mitochondrial permeability transition (MPT), leading to the release of cytochrome c in normal liver mitochondria (Choo et al., 2004).

Mitochondria play an important role in buffering cytoplasmic calcium and increased neuronal calcium modifies mitochondrial ATP production by uncoupling oxidative phosphorylation (Nicholls, 2009). Calcium overload may result in discharge of the mitochondrial membrane potential, opening of the MPT pore, release of cytochrome c, and activation of cell death pathways (Nicholls, 2009). Mutated huntingtin protein causes sensitization of both the NMDA receptor and the inositol-1,4,5-triphosphate (IP3) receptor, increasing entrance of extracellular Ca^{2+} and the release of Ca^{2+} from intracellular stores, respectively (Chen et al., 1999; Sun et al., 2001; Tang et al., 2005). The final result is an increase in intracellular Ca^{2+} levels. The role of NMDA receptors on mitochondrial biogenesis has been further characterized, as the reduced mitochondrial ATP levels and decreased ATP/ADP ratio found in mutant Htt-containing striatal cells is normalized by blocking NMDA receptor-mediated calcium influx (Seong et al., 2005). Moreover, mitochondria isolated from both lymphoblasts of Huntington´s Disease patients and brains

of transgenic mice have a reduced membrane potential and depolarize at lower Ca^{2+} concentrations than control mitochondria (Panov et al., 2002).

Thus, data obtained so far points to a close relationship between mitochondria deficit and NMDA-mediated excitotoxicity. The glutamatergic system plays a substantial role in neuronal cell death and there are consistent data implicating NMDA receptor activation with the excitotoxic neuronal loss that takes place in Huntington´s Disease (Zeron et al., 2002; Schiefer et al., 2004). Selective depletion of NMDA receptors has been found in Huntington´s Disease striatum, suggesting that neurons expressing NMDA receptors are preferentially vulnerable to degeneration (Dure et al., 1991). Prior to the identification of the genetic mutation responsible for Huntington´s Disease, a Huntington´s Disease mouse model was developed by the introduction of quinolinic acid, which is an NMDA receptor agonist that produces excitotoxic striatal lesions that closely resemble those seen in Huntington´s Disease brain (Beal et al., 1986). Moreover, some studies suggest that the sensitization of the NMDA receptor containing the subunit NR1/NR2B by the mutated Htt protein is responsible for causing the selective cell death of the medium sized spiny neurons present in the striatum, since these neurons express high level of this NMDA receptor subtype (Chen et al., 1999; Zeron et al., 2001).

Mitochondrial toxins that deplete ATP production can also mediate excitotoxic processes (Schulz et al., 1996; Browne and Beal, 2002). Systemic administration of 3-nitropropionic acid, which is a mitochondrial toxicant that inhibits succinate dehydrogenase, results in striatum lesions similar to those observed in Huntington´s Disease (Wullner et al., 1994). Nevertheless, 3-nitropropionic acid and malonate lesions can be prevented by NMDA antagonists, such as MK-801 and memantine (Wullner et al., 1994). Taken together these observations suggest that mitochondrial-mediated excitotoxicity is promoted by secondary mechanisms involving glutamate receptors. It has been shown that omission of glucose, exclusion of oxygen, or inclusion of inhibitors of oxidative phosphorylation or of the sodium/potassium pump, enables glutamate to express its neurotoxic effects via NMDAR (Novelli et al., 1988; Henneberry et al., 1989; Zeevalk and Nicklas, 1991). Thus, in a context of reduced intracellular energy levels an otherwise harmless amount of glutamate becomes toxic.

Studies performed with Huntington´s Disease transgenic models have implicated decreased transcription of genes regulated by cyclic adenosine 3',5'-monophosphate (cAMP) responsive element (CRE) binding protein (CREB) to Huntington´s Disease pathology (Luthi-Carter et al., 2000; Shimohata et al., 2000; Steffan et al., 2000; Nucifora et al., 2001; Wyttenbach et al., 2001). These genes include brain derived neurotrophic factor (BDNF) (Zuccato et al., 2001) and a host of others involved in diverse processes ranging from neurotransmission (Bibb et al., 2000; Luthi-Carter et al., 2000) to cholesterol metabolism (Sipione et al., 2002).

Reduced CREB dependent transcription of BDNF is a robust feature of Huntington´s Disease pathophysiology. By grades II and III of the disease, BDNF protein and mRNA levels in frontoparietal cortex are halved, and this effect can be mimicked by expressing full-length human mutant huntingtin in a rat CNS parental cell line (Ferrer et al., 2000; Zuccato et al., 2001). Reduced levels of cortical and striatal BDNF have been demonstrated in multiple mouse models of Huntington´s Disease expressing mutant Huntingtin (including

R6/2, N171-82Q, Hdh, and YAC-72 lines) (Luthi-Carter et al., 2000; Zuccato et al., 2001; Luthi-Carter et al., 2002; Gines et al., 2003b). Importantly, the diminished CREB-mediated gene transcription appears to be linked to energy impairment and deficient cAMP, which has been shown to be decreased in the cerebral spinal fluid of symptomatic Huntington's Disease patients (Sawa et al., 1999). Furthermore, PC12 cells stimulated with forskolin, which activates adenylyl cyclases to produce cAMP from ATP, exhibit ameliorated mutant huntingtin-fragment induced phenotypes, further supporting the hypothesis that low levels of cAMP might be implicated in Huntington's Disease pathology (Wyttenbach et al., 2001). Levels of both cAMP and CRE-signaling are decreased prior to Huntington's Disease symptoms in Hdh^{Q111} mice (Gines et al., 2003b). These data suggest that mutant huntingtin might lead to an early metabolic deficit that amplifies the disease cascade by altering cAMP-dependent processes, including CRE-mediated gene transcription (Gines et al., 2003b).

4. Treatment options for the metabolic deficit

The presence of the mutated huntingtin gene can be detected early in life which makes substrates capable of slowing disease progression an attracting therapeutic tool. A number of energy-related therapeutic approaches have been used in preclinical models and/or Huntington's Disease patients, such as coenzyme Q_{10}, creatine, antioxidant therapies, anaplerotic therapies, and PGC-1α agonists.

Creatine is an important energy molecule in the brain (O'Gorman et al., 1996). Creatine administration increases brain concentrations of phosphocreatine and inhibits activation of the MPT, both of which may exert neuroprotective effects (Hemmer and Wallimann, 1993; O'Gorman et al., 1996). Moreover, creatine appears to be neuroprotective in a rodent mitochondrial toxin model via enhancing cerebral energy metabolism (Koroshetz et al., 1997; Matthews et al., 1998). The R6/2 mice exhibit lower levels of creatine and ATP in the brain (Dedeoglu et al., 2003). In addition, pre-symptomatic dietary creatine supplementation extends survival in the R6/2 and N171–82Q transgenic Huntington's Disease mice while significantly improving the clinical and neuropathological phenotype (Ferrante et al., 2000; Andreassen et al., 2001). Creatine supplementation in symptomatic R6/2 mice also has clinical benefits (Dedeoglu et al., 2003). However, so far, clinical trials have demonstrated no substantial benefit for creatine administration to Huntington's Disease patients (Verbessem et al., 2003; Tabrizi et al., 2005). One year of creatine intake, at a rate that can improve muscle functional capacity in healthy subjects and patients with neuromuscular disease, did not improve functional, neuromuscular, and cognitive status in patients with stage I to III Huntington's Disease (Verbessem et al., 2003). Even the low levels of cerebral creatine and phosphocreatine observed in these previous studies have been disputed, as more recent studies in which in vivo concentrations of brain metabolites were preserved found increased brain levels of creatine and phosphocreatine in the same mouse model of Huntington's Disease used in previous studies (Tkac et al., 2007; Mochel et al., 2010a). Thus, it is still unclear whether creatine has a clinical benefit to Huntington's Disease patients.

Q_{10} is an antioxidant and promoter of respiratory chain function that has also been tested as a treatment for Huntington's Disease. Oral administration of Q_{10} ameliorates elevated lactate levels seen in the cortex of Huntington's Disease patients, an effect that is reversible on withdrawal of the agent (Koroshetz et al., 1997). In addition, combination of Coenzyme

Q_{10} and creatine produces additive neuroprotective effects in reducing striatal lesion volumes produced by chronic subcutaneous administration of 3-NP to rats, improves motor performance, and extends survival in the transgenic R6/2 Huntington´s Disease mice (Yang et al., 2009). However, one large-scale study assessing the potential neuroprotective effects of coenzyme Q_{10} revealed that, at the tested dosages, Q_{10} produced no significant slowing in functional decline in early Huntington´s Disease (Huntington Study Group, 2001).

Other antioxidants, such as ascorbate and BN82451, have been shown to improve motor performance and survival of R6 mice (Klivenyi et al., 2003; Rebec et al., 2003). The level of ascorbate is significantly diminished in the striatum of Huntington´s Disease mouse models, which highlights the importance of studying the effect of ascorbate supplementation to treat Huntington´s Disease (Rebec et al., 2002; Dorner et al., 2007). However further studies will be necessary to determine whether either ascorbate or other antioxidant is capable of slowing Huntington´s Disease progression in patients.

A decrease in branched-chain amino acid (BCAA) levels has been observed in the plasma of Huntington´s Disease patients (Mochel et al., 2007). Decreased BCAA levels might occur to compensate the energetic deficit observed in Huntington´s Disease, which is caused by impaired glycolysis, citric acid cycle and/or oxidative phosphorylation, as earlier described in this chapter (Tabrizi et al., 1999; Browne and Beal, 2004; Milakovic and Johnson, 2005). Based on this hypothesis, a short-term therapeutic clinical trial was performed using triheptanoin, a triglyceride containing seven carbon fatty acids that is metabolized to acetyl-CoA and propionyl-CoA, which is an anaplerotic compound that is a precursor of the citric acid cycle intermediate, succinate (Mochel et al., 2010b). This study shows that triheptanoin therapy can improve peripheral energy metabolism in Huntington´s Disease patients, and in particular oxidative phosphorylation in skeletal muscle (Mochel et al., 2010b). However, the benefit of anaplerotic approaches to the brain energy metabolism remains to be established.

Peroxisome proliferator-activated receptor (PPAR)γ is a member of the nuclear hormone receptor family of ligand-activated transcription factors (Rosen and Spiegelman, 2001). PPARγ is the target of the insulin-sensitizing thiazolidinediones (TZDs) drugs used to treat type II diabetes and recent studies suggest that treatment of insulin resistance with a PPARγ agonist retards the development of Alzheimer's Disease (Watson and Craft, 2003; Watson et al., 2005). There is evidence suggesting that PPARγ agonists are neuroprotective and increase mitochondrial function (Schutz et al., 2005; Hunter et al., 2007). Moreover, oral treatment with rosiglitazone, which is a thiazolidinedione drug, induces mitochondrial biogenesis in mouse brain (Strum et al., 2007). Interestingly, a significant defect in the PPARγ signaling pathway has been found in mutant huntingtin-expressing cells, as compared to cells expressing wild-type huntingtin protein (Quintanilla et al., 2008). In addition, pretreatment of mutant huntingtin-expressing cells with rosiglitazone avoids the loss of mitochondrial potential, mitochondrial calcium deregulation, and oxidative stress overproduction in response to intracellular calcium overload (Quintanilla et al., 2008). Rosiglitazone also increases mitochondrial mass levels, suggesting a role for the PPARγ pathway in mitochondrial function in striatal cells (Quintanilla et al., 2008). PPARγ protein levels are decreased in the brain and peripheral tissue of R6/2 mice and in lymphocytes of Huntington´s Disease patients, probably due to a decrease in transcription as well as recruitment of PPARγ protein to huntingtin aggregates (Chiang et al., 2010). R6/2 mice treatment with TZD results in beneficial effects on energy deficiency and on several major

Huntington´s Disease phenotypes, decreasing weight loss, lessening motor deterioration, reducing mutant huntingtin aggregate formation, improving the reduced levels of two neuroprotective factor, Bcl-2 e BDNF, and increasing mouse life span (Chiang et al., 2010). Moreover, the protective effects described above appear to have been exerted, at least partially, via direct activation of PPARγ in the brain (Chiang et al., 2010).

Peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, which is a potent co-activator of PPARγ transcriptional coactivator, is a member of a family of transcription coactivators that plays a central role in the regulation of cellular energy metabolism and stimulates mitochondrial biogenesis, participating in the regulation of both carbohydrate and lipid metabolism (Liang and Ward, 2006). PGC-1α knockout mice exhibit striatum lesions resembling Huntington´s Disease, which was first evidence that this molecule could be involved in Huntington´s Disease pathology (Lin et al., 2004). Further studies have demonstrated that downregulation of PGC-1α in Huntington´s Disease striatum affects mitochondrial energy metabolism, possibly by impairing oxidative phosphorylation (Cui et al., 2006). Moreover, over-expression of exogenous PGC-1α in Huntington´s Disease striatal neurons was protective against 3-NP treatment (Weydt et al., 2006). Decreasing levels of PGC-1α were shown to parallel markers of mitochondrial dysfunction with disease progression in Huntington´s Disease patients (Kim et al., 2010). Of note, PGC-1α polymorphisms in Huntington´s Disease patients may modify Huntington´s Disease onset age (Taherzadeh-Fard et al., 2009). Interestingly, it has been shown that mutated huntingtin protein can promote transcription repression of PGC-1alpha (Cui et al., 2006). Mutant huntingtin represses PGC-1α gene transcription by associating with the promoter and interfering with the CREB/TAF4-dependent transcriptional pathway (Cui et al., 2006). These data support a link between transcriptional deregulation and mitochondrial dysfunction in Huntington´s Disease.

Resveratrol is a polyphenol that increases the activity of SIRT1, which is an activator factor capable of increasing PGC-1α activity and mitochondrial biogenesis, as evidenced by increased oxidative-type muscle fibers, enhanced resistance to muscle fatigue, and increased tolerance to cold observed in mice treated with resveratrol (Lagouge et al., 2006). Repeated treatment with resveratrol for a period of 8 days beginning 4 days prior to 3-nitropropionic acid administration, which induces symptoms similar to Huntington´s Disease, significantly improves the 3-nitropropionic acid-induced motor and cognitive impairment (Kumar et al., 2006). When tested in the context of a transgenic mouse model of Huntington´s Disease, resveratrol increased PGC-1α mRNA levels and had protective effects in peripheral tissues, by reducing vacuolation in the brown adipose tissue and decreasing elevated blood glucose levels (Ho et al., 2010). However, there was no improvement of motor performance, weight loss, striatal atrophy and survival in Huntington´s Disease transgenic mice treated with resveratrol, which was consistent with no increase in PGC-1α mRNA levels in the striatum (Ho et al., 2010). Thus, resveratrol appears to protect against the peripheral energetic deficit in Huntington´s Disease, but it is not effective to alleviate CNS Huntington´s Disease pathology.

As stated previously, transglutaminase 2 activity appears to be increased in Huntington´s Disease, leading to huntingtin aggregation and mitochondrial aconitase inhibition (Karpuj et al., 1999; Lesort et al., 1999; Kim et al., 2005). Based on these studies, cystamine, which is a drug capable of inhibiting transglutaminase, was tested as a therapeutic tool to treat Huntington´s Disease. Cystamine treatment prolongs the lifespan and reduces associated

tremor and abnormal movements in a Huntington´s Disease transgenic mice, possibly in part due to inhibition of transglutaminase 2 activity (Dedeoglu et al., 2002; Karpuj et al., 2002). However, cystamine does not inhibits transglutaminase 2 specifically, which might invalidate its therapeutic use (Jeitner et al., 2005). In addition to cystamine, there are a number of other transglutaminase inhibitors that have been tested in Huntington´s Disease, such as a set of irreversible peptidic inhibitors, the allosteric reversible small-molecule hydrazides, and inhibitors that bind to the guanosine triphosphate (GTP) binding site (Duval et al., 2005; Lai et al., 2008). However, each of these compounds was found to be inadequate for *in vivo* testing because of a general lack of selectivity or poor cellular potency (Schaertl et al., 2010).

Huntingtin-related proteomic studies represent an area of intense research. Proteins interacting with huntingtin pathological form exhibit altered patterns and metabolism. Mitochondrial metabolism alterations are observed in mouse models expressing various types of the mutated huntingtin (Browne, 2008). Moreover, knock-in mice models with pathogenic CAG repeats inserted into the murine homolog Hdh (e.g. Hdh^{Q111}, CAG 140, CAG 150) develop similar cerebral pathologies, including reduction of striatal-related dopamine receptor (Menalled, 2005). Protein-protein interaction studies resulted in the identification of many proteins interacting with huntingtin, characterizing it rather as a scaffolding, membrane-associated protein, involved in axonal trafficking of mitochondria and vesicles (Truant et al., 2006). From the large group of huntingtin-interacting proteins, the most research interest is focused on proteins that have a direct implication on its biological functions. Most of these proteins bind to the amino terminus of huntingtin near the polyglutamine domain (Holbert et al., 2001; Ferrier, 2002; McPherson, 2002). However, huntingtin-associated protein 40 (HAP40) which is affecting Rab5-mediated endosomal motility in complex with huntingtin, interacts with huntingtin through its carboxy-terminal domain (Pal et al., 2006).

Also, the first conserved 17 amino acids in the amino-terminal huntingtin represent possible membrane association signal, which may influence the polyglutamine expansion (Ross, 1997). It has been shown that specific cleavage (at the residue Arg[167]) and related presence of defined truncation at the N-terminus of huntingtin, mediate mutant huntingtin toxicity in Huntington's Disease (Ratovitski et al., 2009). Association of huntingtin with the production of brain-derived neurotrophic factors in cortical cells, a pro-survival factor for striatal neurons, just completes the complexity of its functions (Zuccato et al., 2001). Thus, detailed studies of huntingtin-related proteome, including the role of associated proteins in regulation of basic signaling pathways of wild type protein and mutants/polyglutamine forms in Huntington´s Disease, play an important role in research for discrepancies in energetic metabolism in Huntington's Disease and other neurodegenerative disorders, alternatively. Monospecific antibodies mapping targeting well defined epitopes on huntingtin and associated proteins may play a crucial role not only in basic research and clinical diagnostics, but also in the development of an efficient treatment for Huntington's Disease.

5. Conclusion

Despite all the efforts to obtain a drug that could overcome the energetic deficit that takes place in Huntington´s Disease, no such treatment has so far been successful to treat

Huntington´s Disease patients. However, as huntingtin protein has multiple functions in cell metabolism, it is possible that combined therapeutic approaches could improve the mutated huntingtin-mediated energy debit and slow down Huntington´s Disease course.

6. Acknowledgment

7. References

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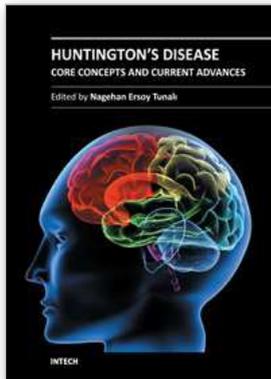
Huntington's Disease - Core Concepts and Current Advances

Edited by Dr Nagehan Ersoy Tunali

ISBN 978-953-307-953-0

Hard cover, 554 pages

Publisher InTech

Published online 15, February, 2012

Published in print edition February, 2012

Huntington's Disease is one of the well-studied neurodegenerative conditions, a quite devastating and currently incurable one. It is a brain disorder that causes certain types of neurons to become damaged, causing various parts of the brain to deteriorate and lose their function. This results in uncontrolled movements, loss of intellectual capabilities and behavioural disturbances. Since the identification of the causative mutation, there have been many significant developments in understanding the cellular and molecular perturbations. This book, "Huntington's Disease - Core Concepts and Current Advances", was prepared to serve as a source of up-to-date information on a wide range of issues involved in Huntington's Disease. It will help the clinicians, health care providers, researchers, graduate students and life science readers to increase their understanding of the clinical correlates, genetic aspects, neuropathological findings, cellular and molecular events and potential therapeutic interventions involved in HD. The book not only serves reviewed fundamental information on the disease but also presents original research in several disciplines, which collectively provide comprehensive description of the key issues in the area.

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