Mitochondrial Dysfunction, Metabolic Deficits, and Increased Oxidative Stress in Huntington's Disease

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Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, characterized by an array of different psychiatric manifestations, cognitive decline and choreiform movements. The underlying molecular genetic defect is an expanded trinucleotide (CAG)n repeat encoding a polyglutamine stretch in the N-terminus of the huntingtin protein. The mechanisms by which mutant huntingtin causes neuronal dysfunction and degeneration are not fully understood. Nevertheless, impaired ubiquitin-proteasome activity, defective autophagy-lysosomal function, transcriptional dysregulation, oxidative stress, apoptosis, mitochondrial and metabolic dysfunction, and abnormal protein-protein interaction have been shown to play important roles in the pathogenesis of HD. Neurons are energy-demanding and more susceptible to energetic failure and oxidative damage than other types of cell. Given that mitochondria play a central role in both processes of metabolism and oxidative stress, and increasing direct evidence shows mitochondrial abnormalities in both HD mouse models and patients, this article will review the studies of mitochondrial dysfunction, metabolic deficits, and increased oxidative stress in HD, and discuss the potential therapeutics targeting these abnormalities. *(Chang Gung Med J 2011;34:135-52)*

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Huntington's disease (HD) is an autosomal dominant, progressive neurodegenerative disorder, characterized by an array of different psychiatric manifestations, cognitive decline and choreiform movements.[1] Two forms of HD, juvenile HD and adult HD, have been arbitrarily divided by the age of disease onset. The term 'juvenile HD' is generally applied to cases of HD with onset before 20 years of age. Presentation of juvenile HD commonly shows symptoms of mental disturbance and rigidity rather than choreic movements, while HD presenting in mid life more frequently shows a relatively pure movement disorder, usually chorea. The psychiatric problems include a variety of conditions that range from antisocial personality, psychosomatic disorder, delusional disorder, and affective disorder to schizophrenia. Although chorea is a cardinal sign of HD, other motor abnormalities such as rigidity, bradyki-

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nesia, dystonia, cerebellar ataxia and myoclonus are common in juvenile HD and occasionally present in the late stage of adult HD. Family studies of HD in the pre-genetic era had documented that most juvenile and early-onset cases of HD were paternally transmitted and that there appeared to be anticipation, i.e. progressively earlier onset in successive generations. HD is a relentlessly progressive disease, and survival ranges between 10 and 17 years from the age at onset.

The causative gene mutation for HD is an unstable CAG trinucleotide repeat sequence encoding a polyglutamine (polyQ) tract in the huntingtin (htt) protein[2] resulting in neuronal dysfunction and death predominantly in the striatum and cortex.[3] The CAG repeat region shows a range of 11-35 repeats in normal individuals, while a repeat number of greater than 35 indicates a very high probability of developing HD.[4] The expanded CAG repeats tend to be unstable and show both somatic and germline instability, frequently expanding rather than contracting in successive transmissions through the generations of a family. This is called intergenerational mutation instability.[5] Anticipation results from intergenerational mutation instability and its corresponding impact on phenotype.[6] A significant inverse correlation was found between age at onset of symptoms and CAG repeat number, a trend that is even stronger within the juvenile group.[7,8] It was also observed that the severity and progression of disease is correlated to the length of CAG repeats.[9,10]

Animal models of HD

The transgenic and knock-in mouse models of HD have been generated to investigate the disease pathogenesis.[11] When mouse models are compared, it appears that full-length mutant htt is less pathogenic than polyQ-containing N-terminal htt fragments, and transgenic models have earlier and more severe phenotype than the knock-in when they carry a similar length of CAG repeats.[12-14] The R6/2 transgenic mice that express *exon* 1 of the human HD gene with around 150 CAG repeats have been extensively used to explore the pathogenesis of HD.[12] Knock-in mouse models showed mild and late onset of behavioural phenotypes and late occurrence of intracellular inclusions without overt neuronal death, suggesting that they are modelling early stages of human HD.[13-15] *Hdh*$^{(CAG)150}$ knock-in mice that express an endogenous full length mouse htt with a 150Q tract has been commonly used to reveal early pathological changes.[13]

Misfolding and aggregation of mutant htt

The polyQ expansion can cause a conformational change in the mutant protein leading to intranuclear and intracytoplasmic aggregates (beta pleated sheet protein formed by hydrogen bond), which is a pathological hallmark in the brains of both HD patients and mouse models.[16,17] The aggregates may play a role in HD pathogenesis, although whether the aggregates are toxic to neurons is still debatable.[18-21] It also remains to be determined whether the oligomer of the mutant htt or the inclusion is the toxic species.[22]

The misfolded htt aggregates require ubiquitin-proteasome system to degrade. In addition to ubiqutitin, intracellular aggregates have been shown to contain chaperone proteins, including heat shock proteins HSP40 and HSP70, and components of the proteasome system.[16,17] HDJ-2 chaperone and HSC70 also co-localize with aggregates in brains of R6/2 HD mice and over-expression of HDJ-1 and HSC70 can suppress the formation of aggregates and cellular toxicity in cell culture.[23] Hence, most of the studies support the postulation that aggregates accumulate when the capacity of the ubiquitin-proteasome system to degrade misfolded htt is exhausted and over-expression of some chaperones may promote the degradation of misfolded htt and reduce cell toxicity.

Transcriptional dysregulation

Evidence from cellular and animal models indicates that nuclear localization of mutant htt is important in toxicity.[24] It is possible that nuclear localization of mutant protein interferes with nuclear transcription factors and co-factors leading to cellular toxicity. CBP [cAMP-responsive element binding protein (CREB)-binding protein], a cofactor for CREB-dependent transcriptional activation, has been shown to co-localize with the mutant htt in cells co-transfected with expression plasmids containing both genes.[25] Furthermore, CBP has been found in nuclear inclusions formed in HD mice[25,26] and in human HD brains.[25] Several lines of evidence also suggest the possibility that expanded polyQ repeats could cause aberrant transcriptional regulation

through their interaction with nuclear transcription factors. The binding of $TAF_{II}130$ (a cofactor for CREB-dependent transcriptional activation) to expanded polyQ stretches has been shown in a cell culture model of polyQ disease to strongly suppress CREB-dependent transcriptional activation.[27] A further study using cell lines expressing N-terminal mutant htt suggests that increased susceptibility to cell death and decreased neurite outgrowth is partly due to an impaired cAMP-responsive element (CRE)-transcriptional response.[28] A reduction of CRE-mediated transcription is likely in human HD, since reduced levels of the CRE-response genes such as corticotrophin-releasing hormone, proenkephalin and substance P are seen in HD brain tissue compared to control brain tissue.[29,30] This pathway is also likely to be impaired in HD mouse models, since cAMP-responsive genes are down-regulated in R6/2 mice.[31]

Other transcription factors could also be inactivated by an expanded polyQ tract. At least 12 such proteins have been identified.[32] Interestingly, many of these factors are involved in histone acetylation. A recent *Drosophila* study also demonstrated that progressive neurodegeneration and early adult lethality, caused by expression of an expanded polyQ tract in htt, were arrested by feeding flies with histone deacetylase inhibitors (HDAC).[33] Transfection of mutant htt causes cell toxicity and CBP depletion accompanied by histone hypo-acetylation, both of which can be rescued by CBP overexpression.[34] HDAC inhibitors are now seen as a novel therapeutic approach to HD.[35] A new HDAC inhibitor, 4b, has been shown to ameliorate the disease phenotype and transcriptional abnormalities in HD transgenic mice.[36]

In addition to reduced CRE-mediated transcription, other transcript expression appears to be altered in polyQ diseases. Nuclear proteins that interact with expanded polyQ stretches include p53. It was demonstrated that mutant htt with expanded polyQ binds to p53, up-regulates levels of nuclear p53 as well as p53 transcriptional activity in neuronal cultures, and genetic deletion of p53 suppresses neurodegeneration in HD flies.[37] *In vitro* studies have recently demonstrated that mutant htt binds strongly to specificity protein 1 (Sp1), a transcription factor, inhibiting the Sp1-dependent transcription of genes such as nerve growth factor receptor.[38] Co-expression of Sp1 and $TAF_{II}130$ in cultured striatal cells from wild-type and HD transgenic mice reverses the transcriptional inhibition of the dopamine D2 receptor gene caused by mutant htt, as well as protects neurons from htt-induced cytotoxicity.[39] Further *in vivo* studies demonstrated that soluble mutant htt inhibits Sp1 binding to DNA in post-mortem brain tissues of both pre-symptomatic and affected HD patients, suggesting that inhibition of Sp1-mediated transcription may be an early molecular event in HD.[39] Mutant htt can selectively target Sp1 and multiple components of the core machinery (TFIID and TFIIF) to interfere with the transcription process.[40] Nuclear mutant htt fragments are sufficient to cause transcriptional dysregulation *in vivo*,[41] suggesting a model whereby mutant htt interacts directly with DNA, altering DNA conformation and transcription factor binding, and thus ultimately leads to transcriptional dysregulation.[42] RE1 (repressor element 1)-silencing transcription (REST) is a master regulator of neuronal genes, repressing their expression. Many of its direct target genes are known, or suspected to have, a role in HD pathogenesis, including BDNF (brain-derived neurotrophic factor). Recent evidence has also shown that REST regulates transcription of regulatory microRNAs (miRNAs), many of which are known to regulate neuronal gene expression and are dysregulated in HD. Zuccato and colleagues have shown that wild-type htt in neural cells binds to REST in the cytoplasm, preventing REST repression of BDNF.[43,44] The presence of mutant htt leads to reduced interaction between mutant htt and REST, nuclear levels of REST subsequently increase and levels of BDNF correspondingly decrease.[43,44] All of these suggest the presence of transcriptional dysregulation in HD.

Metabolic deficits in HD

3-nitropropionic acid (3-NP)-induced HD animal models

The basal ganglia are particularly susceptible to mitochondrial toxins such as 3-nitropropionic acid (3-NP), which is an inhibitor of succinate dehydrogenase. Accidental ingestion of 3-nitropropionic acid (3-NP) in man produces selective basal ganglia lesions and dystonia.[45] Extensive behavioural and neuropathological evaluations have shown that a partial but prolonged energy impairment induced by 3-NP in rodents and non-human primates is sufficient

to replicate most of the clinical and pathophysiological hallmarks of HD, including choreiform movements, cognitive deficits, and progressive selective striatal degeneration.[46-48]

Metabolic deficits revealed by functional neuroimage

Studies of cerebral glucose metabolism using F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) provide strong evidence for an impairment of energy metabolism in HD. In HD patients, and those at risk of developing this disorder, decreased cerebral metabolic rates for glucose were shown in the caudate and putamen as well as in the frontal and parietal cortex.[49-53] A further study showed that impaired basal ganglia metabolism is highly correlated with the functional capacity of individual patients and the degree of their motor dysfunction.[51] Using magnetic resonance spectroscopy (MRS) imaging, increased lactate levels were observed in the striatum and occipital cortex of HD patients, suggesting a compensatory glycolytic response to impaired mitochondrial function.[54] Recently, a proton MRS study of cerebrospinal fluid from HD patients showed reduced levels of both lactate and citrate, suggesting an impairment of both glycolysis and tricarboxylic acid cycle function in HD patients.[55] Energy metabolism shown by phosphocreatine recovery after exercise in the skeletal muscle is impaired in manifest HD patients and asymptomatic mutation carriers.[56] A FDG-PET study showed significant increased glucose metabolism in the cerebellum and thalamus accompanying decreased metabolism in basal ganglion and cerebral cortex in pre-manifest HD gene carriers.[57] The study followed patients for 4 years and showed that the glucose metabolism in the thalamus fell to subnormal levels, while the glucose metabolism in the cerebellum kept increasing in the pre-manifest subjects who developed symptoms 4 years later. It was proposed that the increased glucose metabolism is a compensatory response to maintain neuronal function.

Weight loss

In the late stages of HD, weight loss or cachexia is a frequent although not invariable symptom. Weight loss can also be seen in the early stages of HD.[58] It has been reported that weight loss occurs in patients with HD despite an adequate diet and feeding.[59] Further supportive evidence for a metabolic deficit in HD comes from transgenic mouse studies that report progressive weight loss despite increased caloric intake.[12] HD patients at early stage with a higher CAG repeat number had a faster rate of weight loss which is likely to result from a hypermetabolic state.[60]

A pro-catabolic profile was found in the peripheral blood of both HD mice and HD patients, which may account for the weight loss frequently seen in HD patients.[61] Proton nuclear magnetic resonance (NMR) spectroscopy on plasma of HD patients has found low levels of the branched chain amino acids (BCAA), valine, leucine and isoleucine. BCAA levels were correlated with weight loss and importantly, with disease progression and triplet repeat expansion size in the HD gene.[62] Two circulating hormones, leptin and ghrelin, acting oppositely on the hypothalamus to control energetic balance, have been studied to investigate their roles in weight loss in HD. The adipocyte-derived circulating hormone leptin, is a satiety factor that signals the amount of body energy stores (in the form of fat) to the neural pathways involved in food intake.[63] Plasma levels of leptin are directly proportional to the existing fat reserves. Reductions in plasma levels of leptin activate feeding behavior, slow the metabolism and help conserve energy stores. Leptin receptor activation in the hypothalamus stimulates orexigenic neurons expressing neuropeptide Y (NPY) and agouti-related peptide as well as anorexigenic neurons expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART).[64] Ghrelin is an endogenous ligand for the growth hormone (GH) secretagogue/ghrelin receptor (GHS-R) and stimulates feeding behavior and GH levels in rodents and humans.[65] High circulating ghrelin and low leptin levels in HD patients suggest compensatory responses to a state of negative energy balance.[66] While baseline levels of GH, insulin growth factor-1 (IGF-I), insulin and glucose in HD patients did not differ from those in healthy subjects in the study done by Popovic et al., elevated GH and IGF-1 levels in serum of HD patients were associated with severity of functional impairments.[67] The study also suggests that the somatotropic axis is overactive even in patients with early disease, and could be related to the weight loss seen in HD patients. Reduced levels of leptin and adiponectin can also be found in both

R6/2 transgenic and CAG140 knock-in mouse strains.[68] In contrast, Aziz and colleagues have shown that after correcting for fat mass, mean plasma leptin concentration as well as basal, pulsatile and total secretion rates increased with the size of the CAG repeat mutation.[69] In addition, both higher pulsatile leptin secretion and higher mean adiponectin levels were associated with a greater degree of motor and functional impairment in HD patients. The high fat, high sugar-fed R6/2 mice were found to have obesity accompanied by increased serum leptin.[70] The ability of insulin to stimulate leptin release from isolated epididymal adipose tissue was also enhanced in R6/2 mice. In contrast, the ability of isoproterenol to inhibit leptin release was reduced in adipose tissue from R6/2 mice, as was the lipolytic effect of isoproterenol, implicating obesity observed at 8-9 weeks in R6/2 mice which may stem from a defect in fat breakdown by adipocytes. While the findings in the level of leptin in HD patients are not consistent, its involvement in weight loss is evident.

Impaired energy production

Reduced cAMP and ATP/ADP ratio is a consequence of mutant htt, which has been shown in the striatum of a knock-in HD mouse model carrying 111 CAG repeats, HD postmortem brains, and the lymphoblastoid cells of HD patients.[71] In this study, mitochondrial enzyme activity was significantly reduced by ~30% in mutant striatal cells compared with the wild-type cells. Another study using PET showed increased oxygen utilization relative to glucose utilization and selective defect of in vivo glycolysis rather than defect in mitochondrial oxidative metabolism in the striatum of early HD patients.[72] Increased oxygen consumption along with up-regulated uncoupling protein 2 (UCP-2) mRNA was found in brown adipose tissue in R6/2 HD mice, which may suggest that a mitochondrial deficit resulting in inefficient coupling of electron transport to ATP production could underlie the increased whole body energy expenditure.[73] In that study, levels of hypothalamic peptides including the body weight decreasing peptides POMC and CART, as well as the weight increasing peptides ghrelin and MCH (melanin-concentrating hormone) in R6/2 HD mice at 12 weeks of age were decreased. A *Drosophila* model of HD shows that energetic metabolism is involved in mutant htt-induced glial alterations and that increasing glucose metabolism by overexpression of UCPs may be beneficial to rescue abnormal glia-to-neuron communication in HD.[74] In contrast to most of the speculation in the literature, another study found that increased energy metabolism with increased ATP level were associated with the neuronal damage in brain tissues of transgenic N171-82Q mice, where activities of mitochondrial enzymes were not impaired.[75] Similarly, no change in the activity of mitochondrial complexes I–IV was found in full-length mutant htt cDNA transgenic mice, and pre-symptomatic and pathological grade 1 HD cases, although a loss of complexes II, III, and IV in late-stage HD brains was observed, which could be explained by neuronal loss.[76]

Peroxisome proliferator-activated receptor γ (PPARγ) coactivator 1α (PGC-1α), a transcriptional coactivator that works together with combination of other transcription factors like PPARγ in the regulation of several metabolic processes, including mitochondrial biogenesis and respiration, has been shown to play an important role in the pathogenesis of HD. Cui et al. have found that mutant htt inhibits transcription of PGC-1α by interfering with the CREB/TAF4 acting on the PGC-1α promoter.[77] They also showed reduction of PGC-1α mRNA specifically in the striatal spiny neuron of a knock-in HD mouse model, Hdh^{Q111}, but not in other parts of brain. Furthermore, recombinant adenovirus-mediated expression of PGC-1α in striatal neuron cell from Hdh^{Q111} mice significantly reversed the mitochondrial defect and lentiviral-mediated delivery of PGC-1α in the striatum provides neuroprotection in the transgenic HD R6/2 mice, suggesting that upregulation of PGC-1α can rescue the effect of mutant htt on mitochondrial function. Mutant htt could interfere with transcription of PGC-1α–regulated genes including PGC-1α itself and its target genes NDUFS3, CYCS, COX7C, NDUFB5, ACADM and LDHB, which has been shown in the striatum of HD N171-82Q mice and human HD patients.[78] Because uncoupling protein-1 (UCP-1) that is exclusively expressed in brown adipose tissue (BAT) is the effecter of PGC-1α, the authors also have shown that PGC-1α transcription interference caused disrupted PGC-1α-UCP-1 circuit that would lead to profound thermoregulatory defects with abnormal mitochondrial energy production in BAT and striatum of HD transgenic mice.[78] Impaired expression of fat storage

genes in adipocytes of HD mice can be recapitulated by expression of an inducible mutant htt transgene in an adipocyte cell line, where mutant htt inhibits transcriptional activity of the PGC-1α in adipocytes, which may contribute to aberrant gene expression.[68] Chaturvedi and colleagues have recently shown reduced PGC-1α and target gene expression in muscle of HD transgenic mice, and that the response of AMP kinase (AMPK), which in turn activates PGC-1α, to a catabolic stressor β-guanidinopropionic acid (GPA), was reduced in NLS-N171-82Q HD mice.[79] They also showed that adenoviral mediated delivery of PGC-1α resulted in increased expression of PGC-1α and markers for oxidative muscle fibers and reversal of blunted response to GPA in HD mice. In addition, such findings are also present in the brain, liver and brown adipose tissue of the NLS-N171-82Q HD mice.[79] They concluded that impaired function of PGC-1α plays a critical role in muscle dysfunction in HD, and that treatment with agents to enhance PGC-1α function could exert therapeutic benefits. Chiang et al. have shown that the transcript of PPARγ, a transcription factor that is critical for energy homeostasis, was markedly down-regulated in multiple tissues of a mouse model (R6/2) of HD and in lymphocytes of HD patients, which was due to inhibited function of PPARγ by mutant htt.[80] Stimulation of PPARγ promotes mitochondrial biogenesis via the induction of the PGC-1α.[81] Interestingly, the authors also found that PGC-1α, one of the downstream target genes of PPARγ, was significantly altered in the subcutaneous and abdominal white adipose tissue of R6/2 HD mice.

Other abnormal metabolic profiles such as hyperglycemia, deficient urea-cycle activity, and disturbed cholesterol biosynthesis have also been reported in several HD mouse models and in HD patients.[82-85]

Increased oxidative stress in HD

A role for oxidative damage in HD, is gathering increasing experimental support. Damage caused by oxidative stress includes lipid peroxidation, protein oxidation, and DNA mutation and oxidation. A significantly increased 8-hydroxydeoxyguanosine (8-OHdG), an oxidized DNA marker, has been shown in the caudate of HD patients.[86] In addition, a significant increase in 8-OHdG in mitochondrial DNA (mtDNA) of the parietal cortex was found in late stage (Vonsattel grade 3-4) of HD patients, while no such increase was found in frontal cortex or cerebellum.[87] Similarly, 8-OHdG was higher in forebrain tissue and striatum of R6/2 mice at 12 and 14 weeks of age.[88,89] Increased concentrations of 8-OHdG were found in the urine, plasma and striatal microdialysates of the R6/2 HD mice at 12 and 14 weeks of age.[89] Both our[90] and Hersch's studies[91] have documented increased oxidative damage to DNA outside the brain of HD patients by demonstrating increased 8-OHdG in HD peripheral blood. Elevated levels of MDA, a marker of lipid peroxidation, has also been shown in HD brain[92] and in the R6/2 HD mouse brain.[88,93] An increase in lipid peroxidation products in HD blood has also been shown, although its correlation with HD severity is not known.[94] Compatible with these studies, our study shows increased levels of MDA in the peripheral blood of HD patients, which correlates significantly with disease severity.[90] A 23% decrease of Cu/Zn-superoxide dismutase (Cu/Zn-SOD) has been shown in R6/1 HD transgenic mice, at the age of 35 weeks, when the mice have shown a severe phenotype.[95] We also found reduced activities of erythrocyte Cu/Zn-SOD in HD patients.[90] Although reduced Cu/Zn-SOD was not found in skin fibroblast cultures of HD patients, lower catalase activity and coenzyme Q10 levels in HD skin fibroblasts was shown.[96] The dichlorofluorescein (DCF) level, an index of reactive oxygen species (ROS) formation, was significantly increased in R6/1 HD mice from the age of 11 to 35 weeks, while R6/1 HD mice started to develop clasping behavior at 19 weeks of age.[97] Oxidative stress caused by N-terminal fragments of mutant htt could be suppressed by overexpression of heat shock protein 27 in a HD cellular model.[98] Oxidative stress could promote mutant htt aggregation and mutant htt-induced cell death by impairing proteasomal function.[99] Increased carbonylation of the mitochondrial enzymes results in decreased mitochondrial enzyme activity and then impaired energy production has been shown in striatum of Tet/HD94 conditional HD mice.[100] All of the evidence suggests that oxidative damage plays an important role in HD pathogenesis.

Mitochondrial abnormalities in HD

Abnormalities of mitochondrial DNA and enzymes

Mitochondrial DNA (mtDNA) that encodes 13

subunits of mitochondrial respiratory enzyme complex is particularly susceptible to oxidative damage, due to its proximity to the respiratory chain, limited repair mechanisms, few non-coding sequences, and absence of histones.[101] If increased oxidative stress occurs in HD, it is reasonable to expect that mtDNA as well as nuclear DNA might be compromised. Indeed, a marked increase in mtDNA deletion levels has been reported in the temporal and frontal cortex of HD patients.[102] Decreased expression levels of cytochrome c oxidase I mRNA has been recently shown in striatum, external globus pallidus and putamen of HD brain.[103] Acevedo-Torres and collaborators have shown that mtDNA damage is an early biomarker for HD-associated neurodegeneration supporting the hypothesis that mtDNA lesions might contribute to the pathogenesis observed in HD.[104] We have also shown increased amounts of mtDNA deletion in peripheral leucocytes of HD patients.[90]

Severe defects in the activities of the mitochondrial respiratory chain, especially complex II/III, have been identified in caudate and putamen of HD patients, but not in cortex, cerebellum or fibroblasts.[86,105-107] In addition, aconitase activity is decreased by 92% in caudate, 73% in putamen, and 48% in cortex, but is normal in cerebellum and fibroblast of HD patients.[107] Aconitase is particularly vulnerable to free radicals such as $NO^{\cdot}$ and $ONOO^{-}$, and the decrease of aconitase activity is more prominent than that of complex II/III activity when cells are exposed to $NO^{\cdot}$. Therefore, the decreased aconitase activity in HD striatum may be caused by $NO^{\cdot}$, $ONOO^{-}$ and other free radicals usually generated through excitotoxicity. The decreased aconitase expression, caused by increased oxidative damage, was further found in the striatum of post-mortem HD patients[108] and in the striatum of R6/2 HD mice[109] using a proteomics approach. We have also recently shown that aconitase activity is reduced in leucocytes of HD patients, which correlates significantly with disease severity indicated by Unified Huntington's Disease Rating Scale (UHDRS) as well as disease duration, although not with repeat length and age onset (unpublished data). Milakovic and collaborators have shown that striatal cells derived from a knock-in mouse model of HD demonstrates significantly diminished oxidative phosphorylation as indicated by lower respiration and mitochondrial ATP production rates compared with the wild-type cells. However, the activities of respiratory complexes and sensitivity to mitochondrial inhibitors were not different between the two cell lines, suggesting reduced mitochondrial ATP production is not through the impairment of the respiratory complexes.[110] In their study, the rather low respiratory thresholds for complexes I, II, and III in the striatal cells suggest that the striatum may be more sensitive to mitochondrial inhibitors, which leads to the selective neuronal loss of striatum in HD.

Abnormalities of mitochondrial permeability transition pore (mPTP) and calcium-handling

A recent study has also shown that the striatal vulnerability may be an increased susceptibility of striatal mitochondria to induction of the permeability pathways by calcium.[111] Since the pathology of HD is mainly in the striatum, defects in mitochondrial permeability transition pore and calcium-handling may contribute to the neuronal dysfunction of HD. The N-terminal mutant htt accumulating on neuronal mitochondrial membranes has been shown by electronic microscope, and the mitochondrial calcium defect was seen in normal mitochondria incubated with a fusion protein containing an abnormally long polyQ repeat, as well as in those of human patients and transgenic animals.[112] This study suggests that early mitochondrial calcium-handling defects in HD are a direct effect of polyglutamines.[112]

Mitochondria isolated from knock-in HD mice with 150 polyQ show an increased sensitivity to calcium-induced mPTP opening with mitochondrial swelling and binding of htt to outer mitochondrial membrane.[113] Sawa et al. have shown that lymphoblasts from HD patients, when treated with cyanide (a mitochondrial enzyme complex IV inhibitor), manifested a considerable increase in mitochondrial depolarization correlated with increased polyQ length.[114] Lymphocyte mitochondria from HD patients have a lower membrane potential,[115] and depolarize at lower calcium loads than do controls.[112,116] Lim and co-workers reported that mutant htt expression induced mPTP opening and disruption of mitochondrial Ca^{2+} homeostasis.[117] Similar results were obtained in mitochondria isolated from striatal cells expressing mutant htt containing 150Q[118] and from muscle of R6/2 mice.[119] Mitochondrial NAD^{+}-linked state 3 respiration and complex I activity were found to be compromised in

the cerebral cortex of the 3-NP-induced rat model of HD.[120] Mitochondria from a HD rat model expressing htt containing 51 poluglutamine (htt51Q) exhibited a diminished membrane potential stability in response to Ca^{2++}, lower capacities of Ca^{2++} accumulation, and a decreased Ca^{2++} threshold for mPTP in a substrate-independent but cyclosporin A-sensitive manner.[121] Furthermore, htt51Q mitochondria showed a deficient state 3 respiration and a higher susceptibility to Ca^{2++}-dependent inhibition.[121] The authors therefore suggest that interactions between htt and the permeability transition pore may underlie mitochondrial dysregulation leading to energetic failure and cell dysfunction in HD. Contrarily, Brustovetsky and colleagues have shown that in R6/2 mice, striatal and cortical mitochondria were equally resistant to Ca^{2+}, while striatal mitochondria from littermate controls were more susceptible.[121] No increases in calcium sensitivity were observed in the mitochondria from HD mice compared to controls. Neither motor abnormalities, nor expression of cyclophilin D corresponded to the changes in mitochondrial sensitivity. PolyQ expansions in htt produced an early increased resistance to calcium in striatal mitochondria suggesting mitochondria undergo compensatory changes in calcium sensitivity in response to the many cellular changes brought by polyQ expansion.[122] Determination of in situ respiratory function of mitochondria from R6/2 mice (12–13 weeks) and 12 months YAC128 shows much higher respiratory control ratios and exhibits increased resistance to Ca^{2+}-loading when compared with respective wild-type littermates. However, when challenged with energy-demanding stimuli (NMDA-receptor activation), neurons from Hdh^{150} knock-in mice are more vulnerable to Ca^{2+}-deregulation than neurons from their wild-type littermates.[123] Failure to observe resistance to Ca^{2+}-loading in Hdh^{150} knock-in mice may be related to the slower progression of the disease in these mice. The results done by Oliveira et al. and Brustovetsky et al. conflict with those previously obtained with isolated HD mitochondria, where HD animal and htt containing cells are more sensitive to Ca^{2+}-loading.[112,113,118] Therefore, the effects of mutant htt on mitochondrial Ca^{2+}-handling are still debatable.

Other mitochondrial defects

Htt aggregates impaired the passage of mitochondria along neuronal processes, causing mitochondria to accumulate adjacent to aggregates and become immobilized and functional-impaired.[124] Furthermore, N-terminal mutant htt was shown to be associated with mitochondria, which would impair mitochondrial trafficking and lead to neuronal dysfunction.[125] Taken together, increasing evidence suggests that mitochondrial dysfunction plays a central role in HD pathogenesis.

Potential therapy based on metabolic deficits, increased oxidative stress, and mitochondrial dysfunction

Antioxidants

Since increased oxidative stress plays an important role in the pathogenesis of HD, several antioxidants have been tested in animal models with some success, such as coenzyme Q10,[126] tauroursodeoxycholic acid, TUDCA,[127] N-acetylcysteine,[128] and BN82451.[129] Although a multicenter, blinded, randomized study employing early HD patients receiving 300 mg coenzyme Q10 twice daily failed to produce a significant change in the primary measure of total functional capacity (TFC) between baseline and 30 months, a trend in slowing the decline of TFC was found.[130] Since a dosage of 2,400 mg/day may provide the best balance between tolerability and blood level achieved in HD patients,[131] a higher dose of coenzyme Q10 (2400 mg) for HD is now in phase III of clinical trial. TUDCA is now in phase I of clinical trial for HD. Since indole-3-propionic acid (OXIGON), an antioxidant, has been demonstrated to be an inhibitor of beta-amyloid fibril formation and to be a potent neuroprotectant against a variety of oxidotoxins,[132] it is a potential therapy for HD. Dimebon (latrepirdine), a potent antioxidant, might be effective in preventing the death of brain cells in animals and improving thinking and memory in Alzheimer disease also in HD.[133] Results of a HD study in the United States and United Kingdom showed that dimebon 60 mg per day was safe and well tolerated and suggested that dimebon may improve cognition (the Mini-Mental State Examination MMSE) in individuals with HD.[134]

The NF-E2-related factor-2 (Nrf2)/antioxidant response element (ARE) signaling pathway is an important pathway involved in antioxidant and anti-inflammatory responses.[135] Synthetic triterpenoids, which are derived from 2-Cyano-3,12-Dioxooleana-

1,9-Dien-28-Oic acid (CDDO) has been shown to up-regulate Nrf2/ARE induced genes in the brain and peripheral tissues, reduce oxidative stress, improve motor impairment and increase longevity in N171-82Q HD mice.[136] Eriodictyol, a flavonoid found in citrus fruits, induces the nuclear translocation of Nrf2, enhances the expression of heme-oxygenase-1 (HO-1) and quinone oxidoreductase 1 (NQO-1), and increases the levels of intracellular glutathione,[137] all of which may suggest its potential use as a treatment for HD.

Nutritional supplements

Nutritional supplements, creatine has been shown to be beneficial for HD mice.[138,139] Although one year of creatine intake did not improve functional and cognitive status in HD patients,[140] a 2-year pilot study of high-dose creatine therapy for HD disease demonstrated no significant difference at 2 years from baseline in total motor score, functional capacity, and the UHDRS.[141] The study of Creatine Safety and Tolerability in Premanifest HD (PRECREST) is in the process of a clinical trial. The TREND-HD study showed that at 6 months, the total motor score change for patients receiving Ethyl-Eicosapentaenoic Acid (EPA) did not differ from that for those receiving placebo.[142] However, total motor score change did not worsen for those who received active treatment for 12 continuous months compared with those who received active treatment for only 6 months (2.0-point worsening; $p = .02$), suggesting the potential of the EPA treatment for HD.

Enhancing mitochondrial biogenesis through pharmacological or metabolic modulation of the PPAR/PGC-1α pathway

Reduced PGC-1α and PPAR-γ have been shown in the striatum of R6/2 HD mice. PPAR/PGC-1α pathway plays an important role in regulating cellular energy metabolism. PGC-1α induces mitochondrial biogenesis and respiration in muscle cells and regulates several aspects of adaptive thermogenesis by increasing expression of nuclear-encoded electron transport chain components, metabolic enzymes, and uncoupling proteins.[143-145] PGC-1α–null mice show reduced mitochondrial function and reduced thermogenic capacity.[146] PGC-1α is also required for the induction of many ROS-detoxifying enzymes, including GPx1 and SOD2.[147] Increasing PGC-1α levels dramatically protect neural cells in culture from oxidative stressor-mediated death.[147] The cAMP pathway is key in activating PGC-1α transcription in many tissues through promoting the binding of cAMP response element binding protein (CREB) or activating transcription factor 2 (ATF-2) to the PGC-1α promoter, thus activating its transcription. The association of mutant htt with CREB and hence interference with CREB expression may underlie the reduced PGC-1α in the tissues of HD mice. Activation of PPAR/PGC-1α and its downstream targets is a possible approach to treat HD. Two metabolic sensors, AMP-activated protein kinase (AMPK) and situin-1 (SIRT1) have been described to directly affect PGC-1alpha activity through phosphorylation and deacetylation, respectively.[148] The NAD^+ -dependent deacetylase SIRT1 belongs to the sirtuin family (class III histone deacetylases) and has been shown to deacetylate multiple lysine sites on PGC-1α, thus leading to its activation.[149] Treatment with resveratrol can rescue early neuronal dysfunction induced by mutant htt in Caenorhabditis elegans via activation of SIRT1 and PGC-1α.[150] Sirtuins also modify fundamental mechanisms in neurodegenerative diseases, including protein aggregation, oxidative stress, mitochondrial homeostasis, and inflammatory processes.[151] The potential of targeting sirtuin pathways therapeutically in HD is promising. Metformin can enhance the PGC-1α expression and mitochondrial biogenesis possibly at least in part via AMPK phosphorylation in the skeletal muscle.[152] The therapeutic effects of metformin on HD warrants further studies. FGF21 can induce PGC-1α and regulates carbohydrate and fatty acid metabolism during the adaptive starvation response,[153] suggesting a role of FGF21 in increasing mitochondria biogenesis.

Thiazolidinediones (TZDs) are potent synthetic agonists of PPAR-γ. TZDs increased the expression of NRF-1, TFAM and MnSOD mRNA and promoted mitochondrial biogenesis by activating PGC-1α.[154] TZDs may potentially be beneficial to HD patients. Indeed, rosiglitazone (one of the TZDs) has been shown to prevent mitochondrial dysfunction in mutant htt expressing cells and in R6/2 HD mice.[80,155] A recent study has shown that fibrates enhance PPARγ and increase the mRNA, protein and activities of mitochondrial respiratory enzyme.[156] Another study has shown that bezafibrate delays the

onset of the mitochondrial myopathy through increasing mitochondrial biogenesis and ATP generation.[157] Therefore, fibrates have the potential as a therapeutic agent for HD, which await further studies using HD animal models.

Inhibitors of mPTP opening

Apart from its function of regulating mitochondrial biogenesis, PGC-1α selectively reduces mitochondrial Ca^{2+} responses to cell stimulation by reducing the efficacy of mitochondrial Ca^{2+} uptake sites and increasing organelle volume, and thus preventing mPTP opening and subsequent cell dysfunction.[158] Evidence of neuroprotection seen with cyclosporine in neurodegenerative diseases has been shown.[159] The neuroprotective properties of cyclosporin A (CsA) are mediated by its ability to prevent mPTP opening during exposure to high levels of calcium or oxidative stress and CsA treated 3-NP-lesioned rats displayed significantly protection from 3-NP toxicity.[160] In addition to its antioxidant properties, TUDCA also inhibits mitochondrial permeability transition, cytochrome c release, Bax translocation, and caspase activation.[161,162] Inhibitors of mPTP opening may serve as potential therapeutics for HD.

Conclusion

Several pathogenic mechanisms of HD have been implicated. Among them, increased oxidative stress, metabolic deficits, and mitochondrial abnormalities play an important role. Therapeutics targeting these pathogenic pathways may be beneficial to HD patients. Although some compounds that modify these pathways have shown some impacts on HD patients, most of them are still awaiting clinical trials.

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粒線體功能失常，代謝異常，及氧化壓力在漢丁頓氏病之致病機轉

陳瓊美

漢丁頓氏病是一顯性遺傳且進行性的神經疾患。它的特徵包括精神病病癥、心智功能退化及舞蹈症。此疾病的基因突變是在漢丁頓基因上第一外轉因子含有一擴充的重複三核苷酸。漢丁頓基因的產物是一未知功能的蛋白質稱漢丁頓蛋白。擴充的重複三核苷酸製造一擴充的多麩胺酸鏈。此擴充的多麩胺酸鏈會造成毒性導致神經細胞的功能異常或死亡。雖然突變的漢丁頓蛋白如何導致某特定神經元功能異常的機轉還不是非常清楚，然而很多研究已顯示異常的泛素-蛋白解體酶及溶小體功能、轉錄功能失常、氧化壓力、細胞凋亡、粒線體及代謝異常以及不正常的蛋白質與蛋白質之間的作用在漢丁頓致病機轉均扮演重要角色。因爲神經元對代謝異常及氧化壓力特別敏感，再加上粒線體在前二者扮演中心角色。因而此篇綜述主要討論粒線體及代謝異常及氧化壓力和漢丁頓疾病的相關研究及探討針對這三種致病機轉所發展出的可能的治療策略。(長庚醫誌 2011;34:135-52)

關鍵詞：漢丁頓氏病，代謝異常，粒線體功能失常，氧化壓力，治療策略

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