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REVIEW

Energy dysfunction in Huntington's disease: insights from PGC-1α, AMPK, and CKB

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Abstract Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by a CAG trinucleotide expansion in the *Huntingtin* (*Htt*) gene. When the number of CAG repeats exceeds 36, the translated polyglutamine-expanded Htt protein interferes with the normal functions of many types of cellular machinery and causes cytotoxicity. Clinical symptoms include progressive involuntary movement disorders, psychiatric signs, cognitive decline, dementia, and a shortened lifespan. The most severe brain atrophy is observed in the striatum and cortex. Besides the well-characterized neuronal defects, recent studies showed that the functions of mitochondria and several key players in energy homeostasis are abnormally regulated during HD progression. Energy dysregulation thus is now recognized as an important pathogenic pathway of HD. This review focuses on the importance of three key molecular determinants (peroxisome proliferator-activated receptor-γ coactivator-1α, AMP-activated protein kinase, and creatine kinase B) of cellular energy homeostasis and their possible involvement in HD pathogenesis.

Keywords AMP-activated protein kinase · Brain-type creatine kinase · Huntington's disease · Peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α · Polyglutamine

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Introduction

Huntington's disease (HD) is an inherited autosomal dominant neurodegenerative disease caused by a CAG trinucleotide expansion in exon 1 of the *Huntingtin* (*Htt*) gene, which is located on the short arm of human chromosome 4 (4p63). Major symptoms include progressive involuntary movement disorders, psychiatric signs, cognitive decline, dementia, and eventual death [1]. When the number of CAG repeats exceeds 36, the translated polyglutamine (polyQ)-containing Htt protein (mutant Htt) alters many important physiological functions and several types of cellular machinery, and causes cytotoxicity [2–4]. Accumulation of polyQ-expanded mutant Htt leads to aggregate formation in neurons, astrocytes, microglia, and many different types of peripheral cells (e.g., liver cells, hair cell, adipocytes, and muscle cells) [2, 5–7].

Mutant Htt is known to impair the function of proteasomes, interfere with normal transcription, elevate oxidative stress, and cause energy dysfunction [5, 8–10]. In addition to neuronal dysregulation, which has been extensively studied and reviewed [11–16], metabolic abnormalities were reported in patients with HD and have recently attracted much attention [7, 17–26]. Specifically, hyperglycemia and abnormal glucose metabolism were found in several mouse models of HD and in HD patients [18, 19]. Contributions of deficiencies of a few other metabolic pathways (e.g., cholesterol biosynthesis and urea cycle metabolism) to the HD pathogenesis are also well documented [7, 20–26].

At the cellular level, the major cause of energy deficiency triggered by mutant Htt is mitochondrial abnormalities [27–29]. The effects of mutant Htt on mitochondria are likely to be direct because it exists in mitochondrial membranes [30]. Expression of mutant Htt leads to increased mitochondrial fragmentation, lower

mitochondrial membrane potentials, poor mitochondrial calcium handling, dysregulated mitochondrial biogenesis, and impaired mitochondrial trafficking [30–34].

The production of adenosine triphosphate (ATP) by mitochondria is mediated by the mitochondrial oxidative phosphorylation system (OXPHOS), which converts energy released from the oxidation of nutrients to produce ATP. In eukaryotes, the OXPHOS is composed of five protein complexes: NADH-coenzyme Q oxidoreductase (complex I), succinate-Q oxidoreductase (II), Q-cytochrome c oxidoreductase (III), cytochrome c oxidase (IV), and ATP synthase (V). Deficiencies in the OXPHOS are observed in many neurodegenerative diseases, including HD. A few studies demonstrated that activities of oxidative phosphorylation enzymes in the basal ganglia of HD patients [35, 36] and striatal cells expressing mutant Htt [37] were lower than those of controls, and thus contributed to the impaired production of ATP. Because mitochondria are the main source of ATP and free radicals, such mitochondrial impairment is critical for HD and many other degenerative diseases. Indeed, treatments with coenzyme Q10 or antioxidants (e.g., *N*-acetyl-L-cysteine, α-lipoic acid, and tauroursodeoxycholic acid) can delay disease progression in HD mice [38–42].

Another important function of mitochondria is the regulation of intracellular calcium homeostasis. Mitochondria are major organelles that mediate the uptake and release of calcium. Expression of mutant Htt interferes with the mitochondrial calcium-handling ability, and leads to deficient respiration, a lower mitochondrial Ca^{2+} capacity, increased sensitivity to calcium, Ca^{2+}-induced cellular dysfunctions, and neuronal toxicity [such as NMDA receptor-mediated excitotoxicity and overactivation of AMP-activated protein kinase (AMPK)] [32, 43, 44]. Given the importance of mitochondria in generating ATP and controlling calcium homeostasis, mitochondrial trafficking is crucial for neuronal functions and survival [45, 46]. Formation of mutant Htt aggregates interferes with the trafficking of mitochondria and is recognized as an early pathogenic event of HD [47].

Besides mitochondrial abnormalities, regulation of several major players in energy homeostasis by mutant Htt was reported. This review focuses on recent findings of several key molecular determinants of cellular energy homeostasis and their possible involvement in HD pathogenesis.

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α)

Basic properties and functions of PGC-1α

The best-characterized regulator of mitochondrial biogenesis is PGC-1α. It is a transcriptional co-activator that controls the expression of genes involved in mitochondrial biogenesis, cellular respiration, and glucose/fatty acid metabolism [7, 48, 49]. Specifically, PGC-1α stimulates mitochondrial biogenesis via enhancing the expression and functions of uncoupling protein (UCP)-2 and nuclear respiratory factors (NRFs), and thus increases the expression of mitochondrial transcription factor A (mtTFA), which controls the replication and transcription of mitochondrial DNA [50].

Importantly, PGC-1α also regulates many transcriptional regulators that are not directly involved in mitochondrial biogenesis. Partners of PGC-1α include peroxisome proliferator-activated receptors (PPARα, -β/δ, and -γ), nuclear receptors [estrogen receptor, estrogen-related receptors, thyroid hormone receptor, retinoid receptors, glucocorticoid receptor, mineralocorticoid receptor, sterol-regulatory-element-binding protein-1 (SREBP1), and hepatic nuclear factor (HNF)-4α], and several non-nuclear receptors [forkhead box O1 (FOXO1) and myocyte enhancer factor 2 (MEF2)] [51–57]. These proteins are also important in metabolism regulation. For example, FOXO1 and HNF-4α modulate genes of gluconeogenesis [55, 58]. MEF-2 is critical for glucose transport [56, 59]. SREBP1 regulates genes involved in lipid and cholesterol metabolism [56, 59]. Moreover, PPARα promotes insulin resistance in the liver [60]. Besides controlling mitochondrial energy metabolism, PGC-1α also modulates multiple metabolic pathways.

The function of PGC-1α can be regulated by post-translational modifications (including acetylation, phosphorylation, methylation, and sumoylation). Acetylation of PGC-1α is critical for its localization within the nucleus and transcriptional activity [61]. Phosphorylation of PGC-1α by several kinases [e.g., AMPK and p38 mitogen-activated protein kinase (MAPK)] enhances the function of PGC-1α [62, 63]. Methylation of PGC-1α at several arginine residues in its C-terminal region by a protein arginine methyltransferase potentiates its co-activator activity [64]. On the contrary, sumoylation of PGC-1α by small ubiquitin-like modifier 1 protein suppresses its translational activity without altering its cellular localization [65].

PGC-1α in HD

Recent studies showed that the expression of PGC-1α is downregulated in mice and patients with HD. This suppression of PGC-1α by mutant Htt is mediated by interfering with the function of the CREB and TAF4 on the PGC-1α promoter [66]. Consistent with the above findings, many PGC-1α target genes in the caudate nucleus of HD patients were lower than those in non-HD subjects [67]. Likewise, expression of mutant Htt is also associated with

impairment of PGC-1α in the striatum and soleus muscle of HD mouse models (N171-82Q and NLS-N171-82Q, respectively) [67, 68]. In oligodendrocytes, suppression of PGC-1α by mutant Htt leads to inhibition of genes involved in myelination and causes aberrant myelination in HD brains, further supporting a pathogenic role of the impairment of PGC-1α in HD [69]. In addition, genetic removal of PGC-1α in mice leads to defects similar to several clinical features (e.g., impaired mitochondrial functions, hyperkinetic movement disorder, and striatal degeneration) of HD patients [66, 70–72]. Conversely, exogenous expression of PGC-1α rescues the mitochondrial membrane depolarization evoked by 3-NP in striatal cells expressing mutant Htt [67], and prevents neurodegeneration in HD mice (R6/2) [66]. Similarly, activation of PGC-1α using a well-characterized PPARγ agonist (thiazolidinedione) enhances mitochondrial biogenesis in the brain and peripheral tissues, reduces mutant Htt aggregate formation, and rescues motor deterioration of HD mice (R6/2 mice) [73–75]. In addition, deacetylation of PGC-1α by overexpression of Sirtuin-1 (SIRT1) was shown to protect neurons from mutant Htt-induced toxicity in a mouse model of HD (N171-82Q) [76, 77]. Those studies collectively suggest that PGC-1α is an attractive drug target for HD.

AMPK

Basic properties and functions of AMPK

AMPK is a major energy sensor that maintains cellular energy homeostasis [78]. It is a Ser/Thr kinase that stimulates pathways that promote energy production or inhibit energy expenditure [78, 79]. For example, activation of AMPK is known to enhance glucose uptake and glycolysis, increase fatty acid oxidation, and promote mitochondrial biogenesis [80, 81]. Ample evidence suggests that AMPK regulates cellular energy homeostasis by multiple mechanisms including the induction of PGC-1α [68], activation of FOXO3 transcriptional activity [82], and promotion of SIRT1 and its downstream signaling pathways [83].

AMPK comprises three subunits (α, β, and γ) [84, 85] (Fig. 1). The α subunit of AMPK is the catalytic subunit and has two different isoforms (α1 and α2) [86]. AMPK-α1 is widely expressed in the entire body and is predominantly expressed in the cytoplasmic region, while AMPK-α2 is mainly expressed in nuclei of liver, heart, and skeletal muscles [87, 88]. Recent studies showed that AMPK can be directly activated by many upstream kinases, such as liver kinase B1 (LKB1), calmodulin-dependent protein kinase kinase (CaMKK), ataxia telangiectasia mutated (ATM), and TGF-β-activated kinase 1 (TAK1) via phosphorylating threonine^{172} within the catalytic domain of the α subunit (Fig. 1). Activation of AMPK by LKB1, a tumor-suppressor kinase, is mainly triggered by an increase in the cellular ratio of adenosine monophosphate (AMP)/ATP [89]. Activation of AMPK by CaMKK is triggered by stimulation of intracellular calcium signals [90, 91]. Based on pharmacological analyses using inhibitors of calcium/calmodulin-dependent kinases, Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) might also lie upstream of AMPK and positively regulate its phosphorylation and activation [44, 92]. It remains to be determined whether CaMK II regulates AMPK by direct phosphorylation. ATM is a serine/threonine protein kinase. Purified ATM from insulin-like growth factor (IGF)-1-treated cells was shown to phosphorylate and activate AMPK in vitro [93]. Activation of AMPK by TAK1 was first reported in the cardiac system with little knowledge of the detailed mechanism [94]. Conversely, phosphorylation of AMPK-α1 at Ser^{173} and Ser^{485} by cAMP-dependent kinase (PKA) leads to inhibition of AMPK [95, 96]. Most interestingly, AMPK can be activated or inhibited by a few hormones (such as adiponectin and leptin) in a tissue-specific manner [97].

In addition to regulating cellular energy metabolism, AMPK also phosphorylates many other proteins involved in a wide variety of cellular functions, including transcription, insulin secretion, formation of reactive oxygen species (ROS), and apoptosis/survival [98–101]. For example, AMPK-α1 phosphorylates importin-α1 and controls the nuclear-cytoplasmic shuttling of an RNA-binding protein (HuR) [102]. In addition, AMPK phosphorylates a motor protein (Kif5), and interferes with the interaction between Kif5 and phosphatidylinositol 3-kinase (PI3 K), which subsequently blocks the targeting of PI3 K to the tips of axons and suppresses axonal polarization and growth [103].

The role of AMPK in controlling cell survival during stresses was actively investigated. In pancreatic β cells, prolonged stimulation of AMPK causes activation of c-Jun-N-terminal kinase (JNK) and caspase-3, and leads to apoptosis in pancreatic β cells [100, 101]. Such detrimental effects of AMPK activation can be prevented by stimulation with Akt, which enhances the mammalian target of rapamycin (mTOR)-translation pathway [104]. In the brain, overactivation of AMPK suppresses the expression of a survival gene (Bcl-2) in striatal neurons and accounts for neuronal atrophy in HD mice [44]. Activation of AMPK was also found to cause apoptosis by induction of p53 at the transcription level and promotion of p53 phosphorylation at Ser^{46} [105]. Interestingly, elevated expression of AMPK-β1 (the regulatory subunit that targets the AMPK holoenzyme to the appropriate cellular location) is closely associated with the suppression of cell growth in carcinoma cell lines through a p53-independent pathway [106],

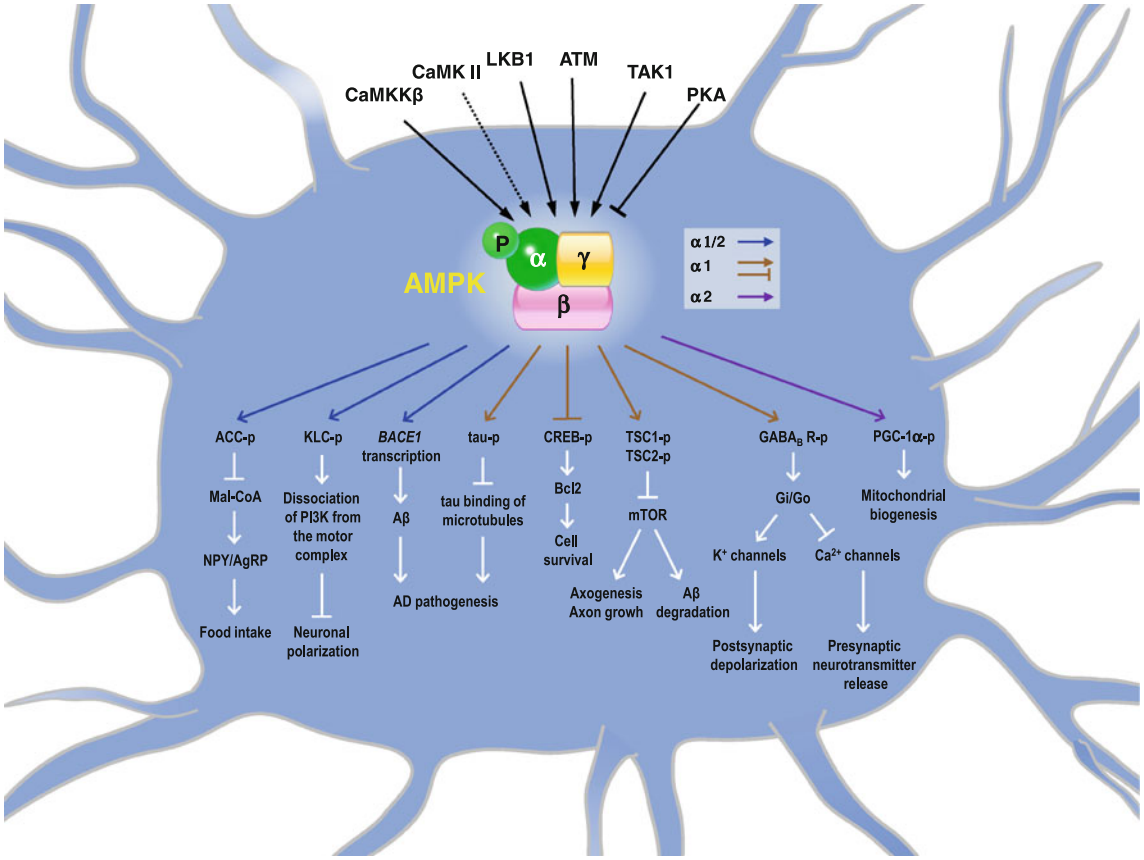

Fig. 1 Potential pathophysiological roles of AMP-activated protein kinase (AMPK) in the brain. AMPK can be activated by multiple pathways mediated by Ca^{2+}/calmodulin-dependent protein kinase kinase β (CaMKKβ) [90, 91], Ca^{2+}/calmodulin-dependent protein kinase II (CaMK II) [44, 92], liver kinase B1 (LKB1) [89], ataxia telangiectasia mutated (ATM) [93], and transforming growth factor-β-activated protein kinase 1 (TAK1) [94]. Solid lines mark direct phosphorylation of AMPK by the indicated upstream kinases. The dotted line denotes that CaMK II is proposed to lie upstream of AMPK and might be involved in AMPK activation [44, 92]. Conversely, phosphorylation of AMPK-α1 by cAMP-dependent kinase (PKA) leads to inhibition of AMPK [95, 96]. Ample evidence suggests that AMPK has a number of downstream molecular targets, which can directly or indirectly regulate specific events involved in brain pathogenesis as detailed in the text. The α subunit of AMPK is the catalytic subunit and has two different isoforms (α1 and α2) [86]. *Blue arrows* indicate pathways regulated by AMPK-α1 and/or AMPK-α2. *Brown arrows* and *lines* mark pathways regulated by AMPK-α1. The *purple arrow* indicates the pathway regulated by AMPK-α2

suggesting that specific localization of AMPK might play a critical role in regulating AMPK-evoked death signaling.

On the contrary, AMPK activation is also known to be associated with a pro-survival role against certain stresses, such as chronic hypoxia in a carcinoma cell line [107] and glutamate-induced excitotoxicity in primary hippocampal neurons [108]. Recent studies demonstrated that AMPK-α1 directly binds and phosphorylates the GABA(B) receptor, which enhances the function of GABA(B) and reduces excitotoxicity during ischemia [109, 110]. In spite of those extensive studies in recent years, the complex roles of AMPK in controlling cell death and survival remain to be further explored.

Given the importance of AMPK in regulating stress responses, it is not surprising to find that dysfunctions of AMPK signaling are associated with several brain diseases and traumas including stroke, HD, Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) [44, 111–118]. The pathophysiological roles of AMPK in regulating neuronal survival during neurodegenerative disorders are currently being actively investigated. For example, abnormal activation of AMPK was observed in cortical and hippocampal neurons of stroke patients. Inhibition of AMPK pharmacologically or by hypothermia treatment significantly reduced the size of the damaged area [112, 119, 120]. Interestingly, deletion of AMPK-α2 (but not AMPK-α1) is neuroprotective in the mouse brain undergoing ischemia [121], while activation of AMPK using metformin worsened stroke damage [122]. Those findings suggest a detrimental role of AMPK in ischemic brains. In addition, AMPK was implicated in amyloid precursor protein (APP) processing, tau phosphorylation, and enhanced autophagy in AD [123]. Chen and colleagues [124] demonstrated that an activator of

AMPK (metformin) induced the expression of β-secretase (BACE1), promoted the biogenesis of amyloid peptides, and potentially worsened AD progression. In addition, exposure to amyloid β peptides (Aβs, the key components of senile plaques in AD) led to activation of AMPK, which phosphorylates tau at Thr^{231} and $Ser^{396/404}$, and might contribute to AD tauopathy [115, 116]. These observations suggest a pathological role of AMPK activation in AD because hyperphosphorylation of tau is a hallmark of AD. Consistently, inhibition of AMPK by treatment with either leptin or an inhibitor of AMPK (compound C) suppresses the production of Aβ and tau phosphorylation [124, 125]. Those studies suggest that activation of AMPK in AD might contribute to neurodegeneration in AD. Nonetheless, results from a few other studies argue for a beneficial role of AMPK in AD because its activity was negatively associated with amyloidogenesis [126, 127]. Moreover, activation of AMPK using an activator (5-aminoimidazole-4-carboxamide-1-d-ribofuranoside, AICAR) in primary cortical neurons reduced Aβ production, while genetically removing AMPK-α2-enhanced Aβ production [128]. Considering the seemingly contradictory effects of AMPK activation in brain diseases and trauma, future investigations of AMPK-α isoform-specific regulation and substrates deserve high priority.

AMPK in HD

The roles and regulation of AMPK in HD pathogenesis are complex (Table 1). Overactivation of AMPK-α1 was found in brains of both human HD patients and HD mice (R6/2) [44, 129]. In contrast, AMPK activity in muscles was greatly reduced [130]. In the muscle and striatum of another mouse model of HD (NLS-N171-82Q HD), levels of AMPK-α2 transcripts were slightly lower than those of WT mice [68, 131]. Those findings are important because AMPK-α2 was suggested to regulate gene expression in skeletal muscle by directly by directly phosphorylating PGC-1α at Thr^{177} and Ser^{538} [62]. Chronic energy deprivation of NLS-N171-82Q mice using a catabolic stressor β-guanidinopropionic acid (GPA) failed to elevate the expression of AMPK-α2 and mitochondrial biogenesis in their muscles, as would have been observed in WT mice, due to the deficiency of PGC-1α [68, 131].

To assess the effects of AMPK activation in HD pathogenesis, Ma and colleagues showed that systemic activation of AMPK by metformin (2 mg/ml in drinking water) extended the shortened lifespan and reduced hindlimb clasping in male R6/2 mice. Although increased activation of AMPK in the striatum of R6/2 mice was observed, those authors stated that the site of metformin's action remained unclear. Additional experiments are needed to evaluate whether the beneficial effects of metformin

Table 1 The role of AMP-activated protein kinase (AMPK) in Huntington's disease

Disease model	Age	Disease stage	Tissue/cell	AMPK-α isoform	Expression level	Activation	Subcellular localization	Pathophysiological consequence	References
HD patients	57–78 years	n.d.	Caudate/nucleus	α1	n.d.	n.d.	Nuclear enrichment	Striatal neurodegeneration	[44]
HD mice (R6/2)	12 weeks	Late	Striatum	α1	n.c.	Increase	Nuclear enrichment	Striatal neurodegeneration	[44]
HD mice (R6/2)	8 weeks	Early	Striatum	n.d.	n.c.	Increase	n.d.	Energy deficit	[163]
HD mice (Hdh^{Q111})	4 months	Early	Striatum/frontal cortex	n.d.	Decrease[a]/n.c.[b]	Increase	n.d.	Energy deficit	[163]
HD mice (NLS-N171-82Q)	26 weeks	Mid	Striatum	α2	Decrease[b]	n.d.	n.d.	Inability to activate PGC-1α	[131]
HD mice (NLS-N171-82Q)	26 weeks	Mid	Soleus muscle	α2	Decrease[b]	n.c.	n.d.	Inability to activate PGC-1α	[68]
HD mice (R6/2)	11–12 weeks	Late	Skeletal muscle	n.d.	n.c.	Decrease	n.d.	Muscle atrophy	[130]

HD Huntington's disease, *n.a.* not applicable, *n.c.* no change, *n.d.* not determined, *mid* middle

[a] Protein

[b] Transcript

were due to AMPK activation in the brain or peripheral tissues [132]. This is an important issue because AMPK activation may provide distinct functions in different tissues. Similar to what was reported by Ma and colleagues [132], we found that daily intraperitoneal injections of an AMPK activator (AICAR, 400 mg/kg body weight) for 5 weeks significantly enhanced motor functions in R6/2 mice (Ju et al., unpublished data). Note that the level of phosphorylated/activated AMPK in skeletal muscles of R6/2 mice was significantly lower than that of WT mice [130]; activation of AMPK using metformin or AICAR therefore might improve the dysregulated functions caused by inferior AMPK activity in skeletal muscles of R6/2 mice, and ameliorated the motor deterioration of R6/2 mice as described above. On the contrary, an intrastriatal infusion of AICAR (3 μg/animal/day) for 7 days worsened the motor impairment and neurodegeneration of R6/2 mice, suggesting a detrimental effect of AMPK activation in the striatum [44]. In the striatum of HD mice and striatal cell lines expressing mutant Htt, activation of AMPK using AICAR or exogenous expression of the dominant positive AMPK-α1 mutant (AMPK-α1-T172D) potentiated mutant Htt-induced cell death by suppressing a survival gene (Bcl-2). Consistent with the alteration of gene expression by AMPK-α1, its detrimental effect requires the nuclear enrichment of AMPK-α1 [44]. Blocking the activation and nuclear enrichment of AMPK-α1 using an adenosine 2A receptor ($A_{2A}R$)-selective agonist (CGS21680) via a cAMP/PKA-dependent pathway was associated with the rescue of brain atrophy [44, 129], further strengthening the involvement of AMPK-α1 in HD pathogenesis in the striatum. Note that the role of AMPK-α2 in the brain of HD patients has not been extensively investigated yet. Those studies prompted us to hypothesize that different tissues (the brain vs. muscles) might have different AMPK isoforms, which target distinct downstream pathways. Such tissue-specific regulation of AMPK and the pathophysiological consequences are of great interest and require further investigation. Those studies also call for the development of isoform-selective AMPK activators and inhibitors with specific designs on their chemical properties to control blood–brain barrier (BBB) permeability, so that these AMPK drugs can be used to treat disorders in the brain and peripheral tissues.

Creatine kinase (CK) system

Basic properties and functions of the CK/phosphocreatine (PCr) system

The CK/PCr system is one of the major machineries controlling proper energy utilization in cells (Fig. 2). CKs regulate ATP regeneration via the transfer of high-energy phosphate from PCr to adenosine diphosphate (ADP) [133, 134]. There are two cytosolic CKs [brain-type CK (CKB) and muscle-type CK (CKM)] and two mitochondrial CKs (the ubiquitous mtCK (uMtCK) and the muscle-specific sarcomeric mtCK) [135]. Tissues, which require large amounts of energy for normal functioning such as the brain and heart, usually express high levels of CKs [136]. In specialized and polarized cells (e.g., the retina, spermatozoa, and cochlear hair cells), the CK/PCr system plays a even more-important role due to differential distribution of mitochondria commonly observed in those cell types [137–139]. In addition, two creatine synthesis enzymes [L-arginine:glycine amidinotransferase (AGAT) and guanidinoacetate methyltransferase (GAMT)] and a creatine transporter (SLC6A8) are also critical for proper functioning of the CK/PCr system [135].

CKB is the cytosolic CK in the brain. A few CKB-interacting proteins that contribute to the function of CKB in the brain were identified. For example, CKB binds to the cytosolic tail of the protease-activated receptor (PAR)-1 (a seven-transmembrane G protein-coupled receptor) and positively regulates PAR-1-mediated signal transduction and Rho-A-dependent cell shape changes in astrocytes [140, 141]. It was interesting to note that activation of PAR-1 by thrombin is also known to regulate neurite extension and retraction in neuronal cell lines [142, 143], and to protect both astrocytes and neurons from elevated oxidative stresses [144]. The PAR-1/CKB complex thus might have a protective role in the brain.

Earlier studies showed that CKB directly interacts with two K–Cl cotransporters (KCC2 and KCC3), which are major routes through which K^+ and Cl^- exit from mammalian cells [145, 146] (Fig. 2). KCC2 is neuron-specific and is highly enriched in GABAergic neurons [147]. The expression of KCC3 is more ubiquitous, and can be found in the heart, kidneys, placenta, liver, and lungs [148]. Although the function of KCC3 is largely unclear, it was implicated in the hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC, Table 2), probably due to loss of interactions between KCC3 and CKB [146, 149, 150]. CKB therefore might regulate Cl^- homeostasis, neuronal excitability, and the cell volume by interacting with KCCs [145, 146, 151, 152].

Dysregulation of the CK/PCr system in HD

Downregulation of CKB was reported in numerous neurodegenerative disorders, such as AD, Pick's disease, diffuse Lewy body disease, and HD (Table 2) [153–156]. Oxidation, reduced activity, and decreased protein levels of CKB were reported in brains of mice (R6/2, 140 CAG full-length HD, and Hdh^{CAG150}) and patients with HD

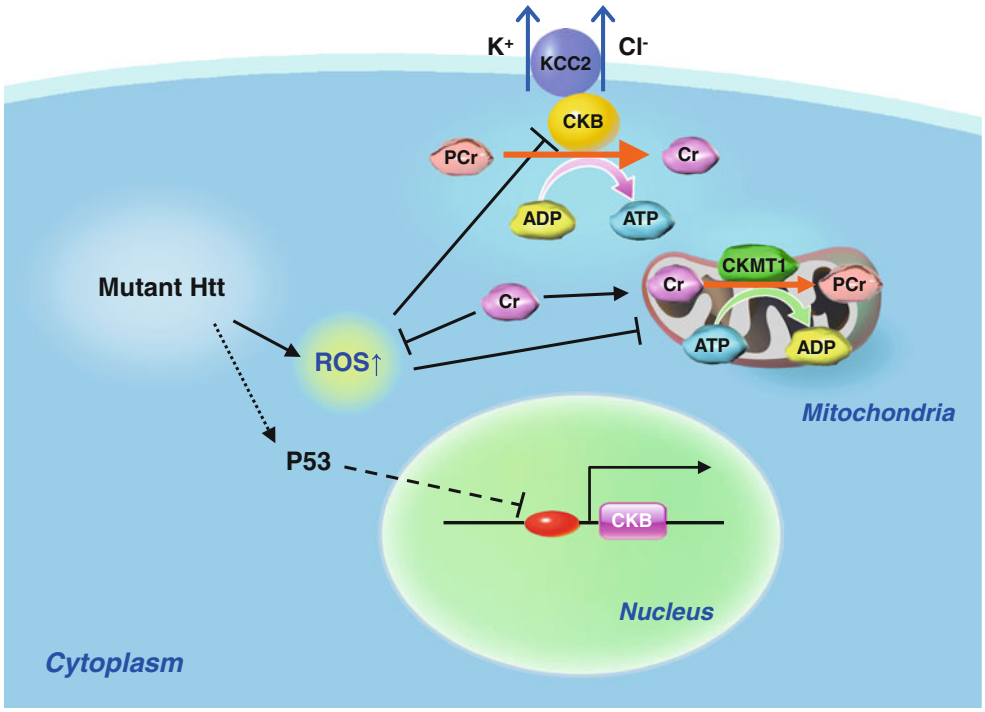

Fig. 2 Regulation of brain-type creatine kinase (CKB) in Huntington's disease (HD). Potential pathways, which mediate the regulation of the creatine kinase (CK)/phosphocreatine (PCr) system by mutant Huntingtin (Htt), are summarized. Both the expression and transcript levels of CKB are downregulated in HD. *Solid lines* represent pathways supported by experimental evidence. *Dotted lines* indicate hypothesized pathways. Mutant Htt is known to interact with and activate p53 [176], which suppresses the CKB promoter [177]. Elevation of reactive oxygen species (ROS) in HD leads to suppression of CK activity and promotes CKB degradation [178]. Creatine may provide its beneficial effect on CKB expression by reducing the level of ROS [169]. Creatine also improves mitochondrial biogenesis [6, 179]. Reduction of CKB expression in HD might compromise the functions of its interacting proteins (e.g., the neuronal K–Cl co-transporter, KCC2) [180]

[157–160]. Downregulation of CKB transcripts in the brain and muscles of HD mice (R6/2) was also demonstrated by a microarray analysis [161], suggesting that mutant Htt might also regulate CKB at the transcriptional level. Moreover, increased PCr concentrations and decreased CK activities were demonstrated in brains of HD mice (R6/2, N171-82Q, and $HdhQ^{111}$) and HD patients [162, 163]. Those studies strongly argue for a poor CK/PCr system in HD brains, which is expected to be associated with a reduced ATP-to-ADP ratio and impaired energy homeostasis. Using a microwave fixation method, accumulation of PCr and depletion of ATP were demonstrated in brains of HD mice at an early disease stage. In addition, downregulation of CKB is correlated with AMPK activation in the brain of HD mice, which might trigger a series of pathophysiological events during HD progression [163]. Those findings collectively suggest a potential cross-regulation between the CK/PCr system and AMPK, and warrant future studies on the link between these two energy-regulating systems in HD and other neurodegenerative diseases.

Besides affecting cellular energy homeostasis, suppression of CKB in HD might also compromise functions of its interacting proteins. One intriguing example is that KCC2, which directly binds to CKB and is highly expressed in GABAergic neurons, was reported to promote spine formation [164]. Selective loss of GABAergic medium spiny neurons is a major hallmark of HD. It would be of great interest to investigate whether inhibition of CKB might account for the loss of spine density and length in brains of HD mice as reported earlier [165].

We recently reported that in addition to suppressing CKB in HD brains, reduced levels of CKB protein and transcripts also occur in hair cells of the cochlea in HD mice (R6/2 and Hdh^{CAG150}) and are associated with hearing impairment in HD mice [6]. Consistent with the potential importance of CKB in peripheral tissues, a significant reduction in the CKB protein was found in the blood buffy coat of premanifest and manifest HD patients compared to those of age-matched control subjects, suggesting that CKB might serve as a peripheral biomarker of HD progression [159].

The detailed mechanism that mediates the suppression of CKB by mutant Htt is largely uncharacterized. Because CKB is very sensitive to oxidative stress [156, 166, 167], and mutant Htt aggregates enhance ROS production in HD [35, 168], ROS are likely to mediate suppression of CKB during HD progression. Noting that creatine has antioxidant

Table 2 The creatine kinase (CK)/phosphocreatine (PCr) system in neurodegenerative disorders

Disorder	Mechanism	Impairment of the CK/PCr system	Age at onset	Symptoms	References
Guanidinoacetate methyltransferase (GAMT) deficiency	Mutation of the GAMT gene	Creatine synthesis	3 months–3 years	Mental retardation, speech delay, and epilepsy	[181]
L-arginine:glycine amidinotransferase (AGAT) deficiency	Mutation of the AGAT gene	Creatine synthesis	1–2 years	Mental retardation, speech delay, and autism-like behaviors	[182, 183]
Creatine transporter (SLC6A8) deficiency	Mutation of the SLC6A8 gene	Creatine transport	1–2 years	Mental retardation, speech delay, and autism-like behaviors	[184, 185]
Alzheimer's disease	Aberrant accumulation of β amyloid (A β)	Suppression of CKB	Mostly $\geq$65 years old	Dementia	[153, 186]
Pick's disease	Tauopathy	Suppression of CKB	40–60 years	Personality change, loss of speech, and dementia	[153]
Diffuse Lewy body disease	Accumulation of insoluble α-synuclein	Suppression of CKB	72–75 years	Dementia, hallucinations, and parkinsonism	[154, 187, 188]
Huntington's disease	Mutation of the Huntingtin gene	Suppression of CKB	35–44 years	Chorea, cognitive decline, behavioral difficulties, and hearing impairment	[6, 157, 159, 189, 190]
Hereditary motor and sensory neuropathy with agenesis of the corpus callosum (HMSN/ACC)	Mutation of the C-terminus of the KCC3 protein	Disruption of the interaction between CKB and KCC3	1 year	Progressive sensorimotor neuropathy, mental retardation, hallucinations and hearing loss	[146, 149, 191]

properties [169], we recently found that creatine supplementation significantly rescued the downregulation of CKB in the cochlea of HD mice (Fig. 2) [6], probably due to feedback regulation between the CK/PCr system and ROS. Further investigation is required to evaluate the potential feedback regulation described above.

Creatine supplementation as treatment for neurodegenerative diseases

Because impaired cellular energy homeostasis is a common pathogenic pathway for many degenerative disorders, the beneficial effects of creatine supplementation have been extensively tested and proven effective in various animal models of many degenerative disorders including HD, PD, and ALS [170]. In HD mice (R6/2, N171-82Q), dietary creatine supplementation (1–3%) was long shown to delay disease progression by improving aggregate formation, weight loss, impaired motor coordination, brain atrophy, lifespan, and hearing loss [6, 171]. Similarly, in the MPTP-treated mouse model of PD, orally administrated creatine (1 % in the diet) protected MPTP-evoked dopamine depletion and neuronal loss [172]. The beneficial effects of creatine (1–2 % in the diet) on motor performance and lifespan were also observed in a mouse model of ALS [173]. Nonetheless, results from human trials on dietary creatine supplementation (5–10 g/day) in HD patients have not been promising to date [174]. Considering the low permeability of the blood–brain barrier (BBB) to creatine [175], one possible solution is to further increase dosages of dietary creatine in human trials. A phase III clinical trial of high-dose creatine (40 g/day) for HD patients is currently recruiting participants (CREST-E, http://www.clinicaltrials.gov). In addition, suppression of CKB during the course of many degenerative diseases (including HD) inevitably limits the effect of substrate (creatine) supplementation. Future studies that enhance the activity and/or expression of CKB might greatly facilitate the therapeutic effectiveness of creatine supplementation.

Concluding remarks

Many neurodegenerative disorders (including AD, PD, and HD) are protein-misfolding diseases. Despite the tremendous efforts devoted to developing therapeutic interventions, effective treatment to delay disease progression has yet to be developed. Recent studies suggest that dysregulation of cellular energy homeostasis is a common feature of many degenerative disorders (including HD), and thus is an important pathway as a drug target. The complex role of AMPK in brains undergoing degeneration, as shown in HD and AD, call for further studies on the characterization of

AMPK isoform-specific functions and regulation. Results of those studies should provide necessary insights into the development of isoform-specific AMPK activators or inhibitors, and potential therapeutic applications of AMPK drugs. It would also be of great interest to characterize the potential cross-regulation of the two energy-regulating systems (AMPK and CK/PCr) in the brain so that a better match between energy supply and demand can be achieved in degenerative neurons.

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