REVIEW

AMPK in the central nervous system: physiological roles and pathological implications

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Abstract: 5′ AMP-activated protein kinase (AMPK) is considered the master metabolic regulator in all eukaryotes, as it maintains cellular energy homeostasis in a variety of tissues, including the brain. In humans, alterations in AMPK activity can lead to a wide spectrum of metabolic disorders. The relevance of this protein kinase in the pathogenesis of diabetes and metabolic syndrome is now well established. On the contrary, correlations between AMPK and brain physiopathology are still poorly characterized. The aim of this review is to summarize and discuss the current knowledge about the prospective involvement of AMPK in the onset and the progression of different neurological diseases.

Keywords: AMPK, brain, neurodegeneration, stroke, tumor, autophagy

Introduction

The maintenance of energy homeostasis is guaranteed by the tight regulation of molecular and functional mechanisms involved in energy intake and expenditure. The AMP-activated protein kinase (AMPK) is a sensor of AMP:ATP ratio and mediates adaptive changes as a function of low energy conditions. AMPK is considered the metabolic regulator of the whole organism, and it has become the leading factor in the study of obesity, diabetes, cachexia, and other metabolic disorders. However, during the last decade, increasing evidence sustains a pivotal role for AMPK also in the physiopathology of the central nervous system (CNS). AMPK is implicated in several neuronal aspects, such as neuronal proliferation and differentiation, synaptic connectivity, and neuroprotection. Thus, alterations in AMPK could easily lead to the onset of different neurological and neurodegenerative diseases.

AMPK: a pivotal metabolic regulator of the whole organism

Structure and regulation

In most species, AMPK exists as a heterotrimeric protein complex, containing α, β, and γ subunits in equal stoichiometry. The α subunit is responsible for the catalytic kinase activity, whereas the β and γ are regulatory subunits. In particular, mammalian γ subunits contain four cystathionine-β-synthase (CBS) domains, which occur as tandem pairs and function as nucleotide-binding sites for AMP or ATP.[1] When intracellular ATP levels are low, AMP or ADP directly and mutually bind to the γ regulatory subunits of AMPK, thus inducing a conformational change that leads to AMPK activation.[2,3] High AMP levels also protect AMPK from dephosphorylation events operated by the

major classes of serine/threonine phosphatases (PP1, PP2A, and PP2Cα). The activatory phosphorylation of AMPK is mainly mediated by liver kinase B1 (LKB1), which phosphorylates the α catalytic subunit at Thr172.[4] However, several studies have demonstrated that AMPK can be also phosphorylated on Thr172 in response to intracellular calcium levels by calcium/calmodulin-dependent protein kinase kinase 2 (CAMKK2).[5–8] (For extensive review, see works by Hardie[5] and Moussa and Li[8]).

There are two genes encoding the α catalytic subunits (α1 and α2), two β genes (β1 and β2), and three γ genes (γ1, γ2, and γ3). Some of these isoforms display a tissue-specific expression pattern, and several experimental data also highlight functional distinctions for the two catalytic α subunits, which reflect in AMP- and LKB1-responsiveness and nuclear localization. AMPKα2 isoform is particularly abundant in the nucleus, even though AMPKα1 is able to translocate to the nucleus under distinct and peculiar conditions.[9,10] Moreover, the myristoylation of the β isoforms is an essential prerequisite for AMPK activation and its localization to membranes.[11]

Even though all the AMPK subunits are expressed in the brain, interesting findings underlie a specific distribution pattern of the various subunit isoforms among cell types in the CNS. For instance, the α2 represents the dominant catalytic subunit in neurons. On the other hand, α subunits are not generally expressed in glial cells at basal conditions, but only in activated astrocytes. The γ1 subunit is mainly expressed in neurons but absent in astrocytes, and the amount of β1 and β2 subunits also differs according to the brain cell type (for extensive review, see Turnley et al[12]).

AMPK orchestrates autophagy and cell proliferation

Eukaryotic cells adaptively respond to low-nutrient conditions by blocking cell growth and proliferation. These events are mediated by AMPK through the activation of p53, the inhibition of the mammalian target of rapamycin (mTOR) complex 1 (mTORC1), and the induction of autophagy. The inhibition of cell-cycle progression-induced by AMPK occurs via MDMX phosphorylation on Ser342, which leads to an increased binding of MDMX to 14-3-3. The subsequent inactivation of MDMX is responsible for the enhanced stability and activation of p53, which provokes a cell-cycle checkpoint.[13]

Beyond effects on p53, AMPK directly phosphorylates the tumor suppressor tuberous sclerosis complex 2 (TSC2) thus stimulating its GAP activity toward Rheb, which in turn leads to the inactivation of mTORC1 and the inhibition

of cell proliferation.[8,14] AMPK also blocks the positive trophic effects of mTORC1 through the direct phosphorylation of regulatory associated protein of mTOR (raptor) (Figure 1).[15]

Besides the regulation of cell growth and proliferation, mTORC1 suppresses the autophagic flux through the inhibition of uncoordinated 51-like kinase 1 (ULK1) complex.[16] Autophagy is required for the breakdown of cellular organelles and the recycling of cellular components under nutrient deprivation, as well as for the selective clearance of damaged organelles. In contrast to the inhibitory regulation operated by mTORC1, a variety of experimental evidence demonstrated that AMPK promotes autophagy by direct phosphorylation of ULK1 at several serine residues (eg, Ser317, Ser555, and Ser777).[17,18] AMPK-dependent stimulation of ULK1 complex seems to appear as a universal event for the induction of autophagy, as it occurs under different conditions such as nutrient starvation, hypoxia, and drug administration. This route of activation results in the promotion of not only nonselective autophagy (known as bulk autophagy) but also selective autophagy: for instance, AMPK triggers
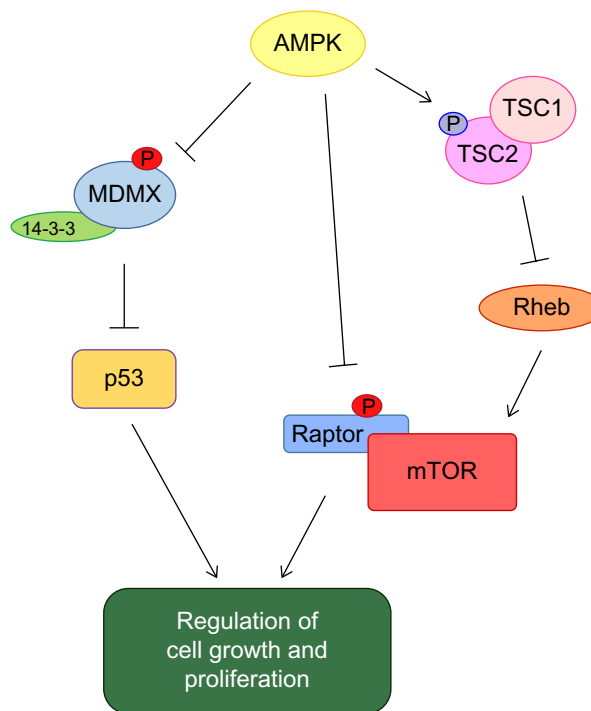

Figure 1 AMPK modulates cell-cycle progression and cell growth.
Notes: Cell growth inhibition is mainly achieved by regulating one of the most well-known anabolic pathways, which involves mTORC1. AMPK activates TSC1/2 complex, leading to the downregulation of mTORC1, composed by mTOR itself and the associated protein, raptor. AMPK is also able to inactivate mTORC1 through the direct phosphorylation of raptor. In addition, AMPK blocks the activity of MDMX, thus leading to the stabilization of p53 and the subsequent cell-cycle arrest. Inhibitory phosphorylations are shown in red and activating phosphorylations in blue.
Abbreviation: AMPK, AMP-activated protein kinase.

mitophagy through the phosphorylation of ULK1 during stress conditions, and this pathway is also required for the clearance of damaged mitochondria in physiopathological states.[19–24] In addition, recent data showed that AMPK phosphorylates Beclin1 at Ser91/94, and this event is essential for the induction of autophagy in nutrient stress response.[25] An interesting study published by Sanchez et al sustains that AMPK also determines, at least in skeletal muscle, the FoxO3-dependent increase of autophagy-related proteins, such as LC3B, GABA-RAPL1, and Beclin1.[26] Another research supports these findings, since AMPK directly activates FoxO3 transcription through the phosphorylation of different serine residues (eg, Ser413, Ser588).[27] Collectively, these data highlight that AMPK drives autophagy at multiple levels (Figure 2).

AMPK maintains energy homeostasis through short- and long-term regulation of metabolic targets

AMPK was originally discovered as the main protein kinase involved in the short-term modulation of key enzymes controlling fatty acid and cholesterol biosynthesis. In particular, AMPK was found to be responsible for the rapid regulation of acetyl-CoA carboxylase (ACC) and HMG-CoA reductase (HMGR), as the inhibitory phosphorylation mediated by this kinase is able to strongly suppress the activity of both the enzymes.[28,29]

In highly specialized cells of metabolic organs, such as skeletal muscle and adipose tissue, AMPK regulates glucose metabolism promoting the phosphorylation of AS160 and Tbc1d1 and the subsequent binding to 14-3-3. These events lead to an enhancement of GLUT4 translocation on the cell membrane.[30] In addition, AMPK drives lipid mobilization by directly phosphorylating hormone-sensitive lipase (HSL) and adipocyte triglyceride lipase (ATGL).[31,32] Recently, these mechanisms have been shown to be involved not only during homeostasis maintenance in physiological conditions but also in the development of metabolic disorders such as cancer-associated cachexia.[33]

The adaptive changes in energy homeostasis induced by AMPK are not limited to the short-term regulation of enzymes, as this kinase orchestrates a profound metabolic reprogramming through transcriptional control. For instance, AMPK phosphorylates a variety of transcriptional factors and cofactors, such as PGC1α, p300, histone deacetylase 5 (HDAC5), and sirtuin1, thus leading to the long-term regulation of genes involved in gluconeogenesis, lipogenesis, and mitochondrial biogenesis (for details, see Mihaylova and Shaw[19]). Of note, AMPK also suppresses the activation of SREBP1 and SREBP2. The inhibitory phosphorylation mediated by AMPK is a pivotal prerequisite to prevent the proteolytic processing and activation of SREBPs. SREBPs are crucial transcription factors involved in the regulation of lipogenic genes, such as *ACC* and *HMGR*.[34] As a result, AMPK controls lipid metabolism regulating both the activity and the protein levels of enzymes implicated in fatty acid and cholesterol biosynthesis (Figure 3).
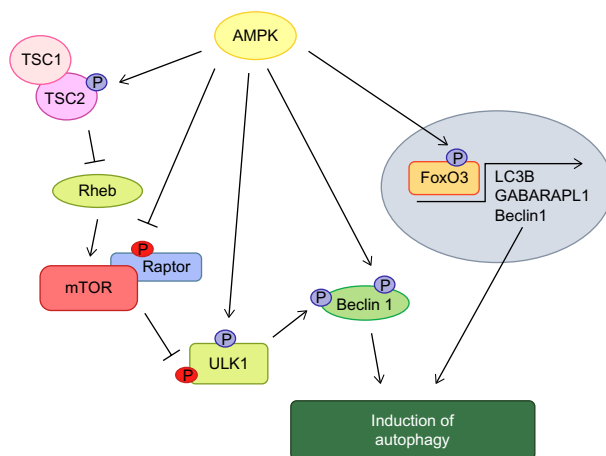
Physiological roles of AMPK in the CNS
AMPK regulates brain cell metabolism, proliferation, and morphology

Even though the brain constitutes 2% of the total body weight, it utilizes 50% of the entire glucose supply. The energy consumption by brain cells is very high and, unlike other peripheral cells, neurons use only glucose as a source of energy. As neurons are not able to synthesize and store a sufficient amount of glycogen, it is indispensable to ensure themselves a constant and continuous source of glucose.[35] During the last few years, several research groups highlighted a crucial role for AMPK in the regulation of energy production and consumption in neurons. Synaptic activation is followed by a number of molecular and cellular events characterized by high energy consumption, such as sodium pump activity, neurotransmitter receptor translocation/recycling, synaptic transport, cytoskeleton remodeling, and metabolic processes. In the light of these observations,

Figure 2 AMPK drives autophagy through short- and long-term mechanisms.
Notes: AMPK directly phosphorylates and activates proteins involved in the initiation and nucleation steps of autophagy, such as ULK1 and Beclin1. The permissive action of AMPK on autophagy is also mediated by the inhibition of mTOR pathway. Furthermore, AMPK phosphorylates FoxO3, leading to increased transcription of autophagy-related genes. Inhibitory phosphorylations are shown in red and activating phosphorylations in blue.
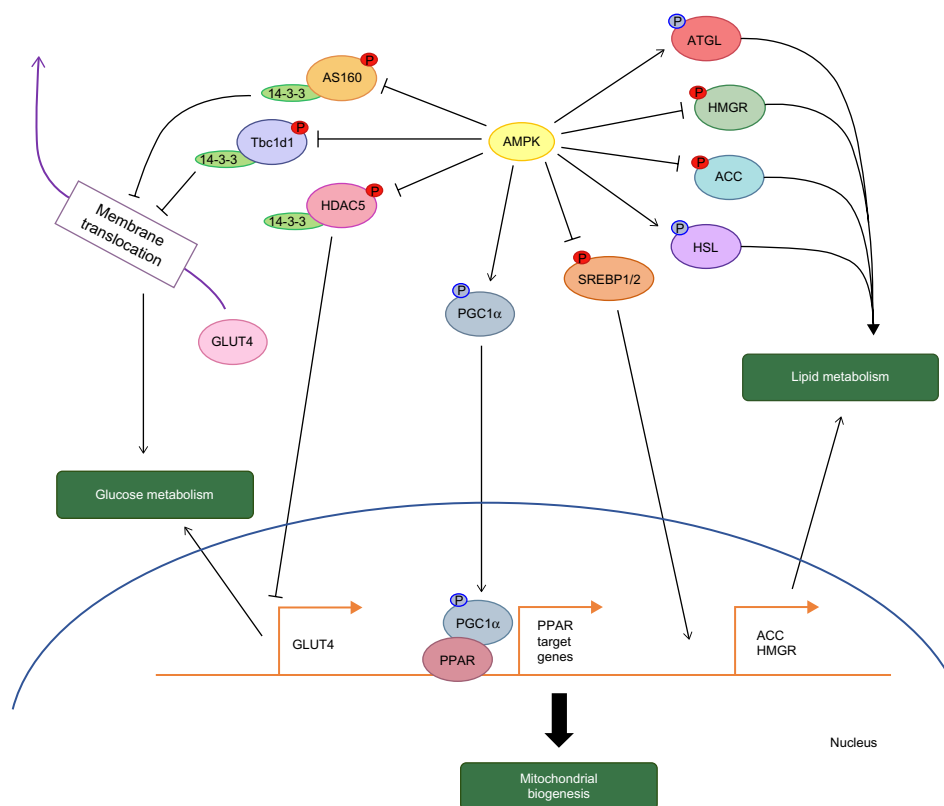**Abbreviation:** AMPK, AMP-activated protein kinase.

Figure 3 AMPK controls cell metabolism.
Notes: AMPK phosphorylates/activates HSL and ATGL, thus leading to increased lipolysis. On the contrary, the inhibitory phosphorylations on HMGR and ACC are responsible for the reduction in lipid biosynthesis. This kinase also affects the transcription of lipogenic genes through the direct phosphorylation of SREBP transcription factors. AMPK regulates mitochondrial biogenesis, as it activates PGC1α and the subsequent transcription of PPAR target genes. In addition, AMPK controls the membrane translocation and the protein expression of GLUT4 by inhibiting Rab GTPase activating proteins (AS160 and Tbc1d1) and HDAC5, respectively. Inhibitory phosphorylations are shown in red and activating phosphorylations in blue.
Abbreviation: AMPK, AMP-activated protein kinase.

it was demonstrated that the decrease in ATP levels following glutamate stimulation is able to strongly phosphorylate AMPK, and the activation of glutamate transmission enhances the translocation of the glucose transporter GLUT3 on cell surface. Notably, the increase of GLUT3 on cell membrane is mediated by AMPK, as the pharmacological inhibition or the knockdown of this kinase is able to completely prevent the glutamate-induced GLUT3 translocation.[36]

In addition to glucose metabolism, other studies indicated that AMPK acts as a key regulator of mitochondrial function and biogenesis in neurons. In Neuro2a cell line, AMPK activation by resveratrol determines an increase in the transcripts of the mitochondrial protein marker Mitofusin 2, and a rise in the master regulators of mitochondrial biogenesis, PGC-1α and mitochondrial transcription factor A (mtTFA). AMPK inhibition suppresses the transcription of these mitochondrial-related proteins, further sustaining that AMPK exerts a pivotal role in the regulation of mitochondrial metabolism in neurons.[37,38]

Besides the direct regulation of metabolism in neurons, AMPK has been shown to be involved in neurodevelopmental

processes. For instance, AMPK maintains the genomic integrity during neural progenitor cell division in *Drosophila*, and any interference with the activity of this kinase provokes embryonic lethality.[39] This study corroborates the finding that the ablation of AMPK β1 subunit leads to a severe reduction in the number of neurons and oligodendrocytes, as well as alterations in astrocyte proliferation in mice. Indeed, defects in AMPK functionality induce aberrant proliferation and increased apoptosis of neural stem cell progenitors (NPCs). The effects of AMPK on NPC proliferation and viability are exerted through direct phosphorylation of Rb protein, whose activation is required for the normal development of CNS.[40]

Increasing evidence also suggests that AMPK plays an important role in the control of cell polarization under energy-lacking conditions. As an instance, AMPK modulates the establishment of initial neuronal polarity by affecting the processes at the root of axogenesis.[41] In addition, a recent work sustains that AMPK regulates neuronal development during dendrite outgrowth and branching. At molecular level, the effects on neuronal architecture are induced by

the AMPK-dependent suppression of both mTOR and Akt signaling pathways.[42]

In adult brain, AMPK drives the cellular events involved in the aging process. An elegant study performed in *Drosophila* demonstrated that the activation of neuronal AMPK determines a delay in systemic aging and prolongs life span. These outcomes are mediated by the AMPK-dependent activation of autophagy and the synergic reduction of insulin-like peptide signaling.[43]

Hypothalamic AMPK controls food intake and body weight

Metabolic diseases are regarded as a major health problem in many Western countries. Generally, they are caused by the lack of physical activity and are strictly associated to the presence of food intake-related disorders. From a pathophysiological point of view, metabolic diseases are characterized by obesity, insulin resistance, and several atherogenic signs, leading to disruption in energy homeostasis.[44]

Whole-body energy balance is guaranteed not only by the functionality of high metabolic peripheral tissues such as liver, skeletal muscle, and adipose tissue, but also by the control of the CNS. The hypothalamus represents the main brain area involved in regulating food intake and energy expenditure, and it is organized into several structural and functional nuclei, including the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the dorsomedial nucleus (DMN), the ventromedial nucleus (VMN), and the lateral hypothalamic area. The majority of these hypothalamic regions are involved in the production and secretion of orexigenic and anorectic neuropeptides that affect food intake and energy homeostasis. For instance, the orexigenic neuropeptides agouti-related protein (AgRP) and neuropeptide Y (NPY), as well as the anorectic neuropeptide α-melanocyte-stimulating hormone (MSH) are synthesized by the ARC.[45,46] On the other hand, the orexigenic neuropeptides melanin-concentrating hormone (MCH) and orexins are produced by the lateral hypothalamic area.[45,47] In addition, both the hypothalamic regions possess the capability to synthesize the anorexigenic neuropeptide cocaine-amphetamine regulated transcript (CART).[48]

During the last few years, a variety of hormones have been identified as powerful modulators of energy balance.[49] In this context, AMPK exerts a pivotal role in nutritional regulation and energy homeostasis, as this kinase orchestrates the hormonal signaling pathways required for the production and the release of hypothalamic orexigenic and anorectic neuropeptides.[50–52]

The orexigenic hormones induce the activation of hypothalamic AMPK. Specifically, cannabinoids exert their permissive effects on food intake by activating cannabinoid receptors expressed in the VMN, whereas ghrelin, secreted by the gastric mucosa, binds to receptors expressed in both VMN and ARC.[53,54] Different findings demonstrated that a rise in ghrelin levels is associated with an increase in food intake and body weight.[55,56]

At molecular level, the ghrelin-dependent increase of intracellular Ca^{2+} triggers CAMKK2 activity, which in turn enhances AMPK phosphorylation and the subsequent activity of AgRP/NPY and pro-opiomelanocortin (POMC) neurons.[57,58] Similar orexigenic effects are also elicited by adiponectin. This adipocyte-secreted hormone mimics the outcomes induced by ghrelin through the activation of hypothalamic AMPK.[59] However, the molecular mechanisms linking adiponectin and AMPK modulation are still not completely elucidated.

The anorexigenic hormones leptin and insulin control food intake and body weight by suppressing hypothalamic AMPK. The effects promoted by leptin are mediated through the modulation of neuropeptides in the ARC and PVN, whereas multiple hypothalamic regions are affected by insulin. An interesting study demonstrated that MC4 transduction pathway is required for AMPK inhibition by these hormones, and the expression of the constitutively active AMPKα2 isoform completely prevents the effects on food intake and body weight elicited by leptin.[60] Tri-iodothyronine (T3) represents another anorexigenic hormone able to regulate the whole-body energy balance through the inhibition of AMPK in neurons located at the VMN. As for leptin, T3 determines norepinephrine/epinephrine release from sympathetic nerves, which stimulates fatty acid mobilization from white adipose tissue and heat production in brown adipose tissue.[61] AMPK inhibition mediates the effects of anorectic hormones at least by two different mechanisms: the former involves the activation of ACC and the subsequent increase in fatty acid biosynthesis, which culminates in the translocation of fatty acids across the mitochondrial membrane; the latter is related to the activation of mTOR and the consequent phosphorylation of p70S6 kinase (p70S6K) and 4EBP1. The modulation of these pathways leads to the suppression of orexigenic AgRP/NPY neurons and the activation of anorectic POMC/CART neurons.[60,62–65]

Pathological involvement of AMPK in neurological conditions
AMPK in neurodegenerative disorders

Given the importance of AMPK in regulating stress responses, it is not surprising that dysfunctions of AMPK signaling are associated with several brain diseases including Alzheimer's

disease (AD), Huntington's disease (HD), and Parkinson's disease (PD). Here, we summarize the current knowledge about the pathophysiological roles of AMPK in regulating neuronal survival during neurodegenerative disorders.

AMPK in AD

AD is the most common form of dementia, characterized by progressive neurodegeneration, particularly affecting cortical and hippocampal brain regions. Histopathological features of AD are senile plaques, composed of β-amyloid (Aβ) peptide polymers, and intracellular neurofibrillary tangles, formed by hyperphosphorylated Tau protein.[66]

AD has been identified as a protein misfolding disease and is caused by accumulation of abnormally folded Aβ in the brain.[67] Aβ peptides originate from the proteolysis of amyloid precursor protein (APP) – amyloidogenic pathway – by the sequential enzymatic actions of beta-site amyloid precursor protein-cleaving enzyme 1 (BACE-1, or β-secretase) and a protein complex with presenilin 1 at its catalytic core (γ-secretase).[68,69]

AMPK has been identified to play an important role in the development of AD. This hypothesis was initially supported by different evidence highlighting the hyperphosphorylation of AMPK in the brains of both AD patients and AD mouse models.[70–72] Moreover, a different AMPK subcellular localization is present in the brains of AD patients when compared with control subjects.[70] It is now well established that AMPK is a key regulator of Aβ generation. Vingtdeux et al showed that the activation of AMPK by resveratrol lowers extracellular Aβ accumulation.[73] The same research group demonstrated that this polyphenol inhibits the AMPK target mTOR, triggering autophagy and lysosomal degradation of Aβ.

Studies conducted on cultured rat cortical neurons revealed that Aβ production is significantly reduced after stimulation with the AMPK activator 5-aminoimidazole-4-carboxamide-1-D-ribofuranoside (AICAR). On the contrary, Aβ peptide levels are increased when AMPKα2 is knocked out, thus indicating the crucial involvement of AMPK in amyloidogenesis.[74] AMPK controls Aβ generation through the modulation of neuronal cholesterol and sphingomyelin levels, which regulate APP distribution in lipid rafts.[67] In addition, leptin-induced AMPK activation is associated with a reduction in Tau phosphorylation.[75]

Despite these findings, other evidence sustains an opposite role for AMPK in AD. Interestingly, the activation of AMPK by metformin is protective in females but increases memory dysfunction in males, suggesting a sex-divergent cognitive effect in a murine model of AD.[76] Moreover, chronic treatment of AD mice with the same compound was reported to enhance the generation of Aβ via the upregulation of β-secretase at transcriptional level.[77] Noteworthy AMPK inhibitor compound C (CC) is able to correct Aβ-induced inhibition of long-term potentiation (LTP) and the enhancement of long-term depression (LTD). Similarly, LTP impairments in APP/PS1 transgenic mice are improved by CC treatment.[78]

AMPK in HD

HD is an age-related neurodegenerative disorder, characterized by motor and cognitive impairment, and caused by a CAG trinucleotide expansion in exon 1 of the *Htt* gene. When the number of CAG repeats is 36 or more, the translated polyglutamine-expanded Htt protein interferes with the normal functions of cellular machinery and causes cytotoxicity. The major characteristic of HD is the selective loss of neurons in the neostriatum, nigrostriatal tract, and cortex, which leads to movement disorders, dementia, and eventual death.[79]

Recent research showed that mitochondria and several key molecular players in energy homeostasis are altered during HD progression. Notably, mutated Htt (mHtt) forms aggregates on mitochondrial membranes. This aberrant association impairs calcium homeostasis and triggers Ca^{2+}-induced oxidative stress, decreases the activity of mitochondrial respiratory complexes (II and III), and alters mitochondrial fission and fusion, globally disrupting the neuronal energy homeostasis. In this scenario, AMPK could represent one of the leading actors in modulating metabolic events.[80,81] Indeed, AMPK was found to be abnormally activated in the striatum of a transgenic mouse model of HD (R6/2).[82] Ju et al highlighted that the activation of AMPKα1 in striatal neurons is closely associated with mHtt-induced cell death.[79] The induction of neurotoxicity requires the nuclear translocation of AMPKα1 to suppress the expression of the survival gene *Bcl2* in striatal neurons.[79] Furthermore, AMPK activation by AICAR in HD mice induces neuronal apoptotic activation and worsens motor function.[79,81] The same research groups showed that the induction of cAMP/PKA signaling reduces AMPK activity, thus preventing the detrimental effect of AMPKα1 in the nuclei of striatal neurons.

AMPK in PD

PD is the most common neurodegenerative movement disorder and the second most common neurodegenerative disease after AD. Clinically, it is characterized by tremor, rigidity, and bradykinesia, and pathologically by the loss of dopaminergic neurons in the substantia nigra. During the last few years, a plethora of studies identified different genes involved in

familial forms of PD, and implicated aberrant mitochondrial homeostasis as one of the key contributors to PD.[83] Among the disease-associated genes, recessive mutations in several genes such as *α-synuclein*, *DJ-1*, *PINK*, *parkin*, and dominant mutations in *LRRK2* (especially the G2019S variant) are directly or indirectly associated with mitochondrial dysfunction in PD.[84]

In this pathology, AMPK activation is similarly a double-edged sword, promoting or aggravating neurodegeneration under different circumstances.[85] Indeed, AMPK exerts a neuroprotective role as demonstrated in mice treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which represents the most common experimental model used to investigate the pathogenesis of PD. Recent findings sustain that AMPK is activated by MPTP in mice and MPP(+) in SH-SY5Y cells, and the inhibition of AMPK by CC resulted in an increase of neuronal cell death.[86] In addition, AMPK acts with parkin in a functionally converging manner to guarantee the quality control of organelles.[85] Hence, the activation of AMPK may prevent neuronal cell death and play a role as a survival factor in PD.

In contrast to these findings, Kim et al described that poly (ADP-ribose) polymerase-1 (PARP-1) promotes ATP depletion and the subsequent activation of AMPK, which mediates the degeneration of dopaminergic neurons.[87]

Impact of AMPK on cancer cell fate and brain tumors

A variety of tumor types, including brain tumors, are characterized by uncontrolled and rapid cell growth. In order to sustain the enhanced rate of mitosis, tumor cells undergo profound changes in their metabolism, a phenomenon known as "Warburg effect".[88]

It has been demonstrated that AMPK regulates cell growth arrest and cell death interacting both with mTOR and p53 in normal cells. Furthermore, the modulation of AMPK represents an important prerequisite for the induction and maintenance of cell proliferation under abnormal nutrient conditions in cancer cells. The role of AMPK in brain tumors is still poorly understood and controversial hypotheses have been proposed. Glioma represents a large group of common brain tumors that comprises glioblastoma and astrocytoma.[89] Rios et al observed that AMPK is hyperactivated both in astrocytes expressing HRasV12 (common mutation in human astrocytoma) and in glioblastoma cell lines compared to control cells. High phospho-AMPK levels were also detected in samples derived from glioblastoma patients, whereas normal brain tissue was completely negative. CC treatment and the genetic deletion of AMPK lead to a strong decrease of cell proliferation and to a reduction of Rb phosphorylation, suggesting that AMPK could play a critical role in tumor growth by regulating Rb and, consequently, cell-cycle progression.[90] Furthermore, it has been shown that AMPK activity is necessary to provide metabolic support during early stages of tumor growth.[91] The relevance of AMPK in oncology has been demonstrated not only for cell growth but also for cell migration. Indeed, AMPK inhibition antagonizes the ghrelin-mediated migration of rat C6 and human U251 glioma cells, suggesting that AMPK activation is an obligatory event in ghrelin-induced glioma migration.[92] In a retrospective clinical analysis, it has been revealed that high-grade human glioma expresses higher levels of AMPKα2 subunit if compared to low- and mid-grade gliomas. The α2 subunit is selectively induced in hypoxic conditions and significantly contributes to vascular endothelial growth factor (VEGF) expression in human glioma cells, thus improving neoangiogenesis and underlying the pivotal role of AMPK in glioma progression.[93] In addition, the resistance to antiangiogenic therapies in glioblastoma may depend on the autophagic flux induced by the activation of hypoxia-inducible factor-1α (HIF-1α)/AMPK axis after hypoxia and lack of nutrients.[94] Even though all these data sustain a protumor effect of AMPK, other researchers suggest that AMPK acts as an oncosuppressor. Guo et al showed that AMPK activation by AICAR blocks EGFR-activated glioma proliferation through the modulation of mTORC1 signaling and lipid biosynthesis.[95] The antitumor effects of AMPK were also demonstrated by the induction of apoptosis in mouse astrocytoma cell line following AICAR administration.[96] This finding corroborates the outcomes induced by metformin, which is able to inhibit tumor cell growth and to enhance the sensitivity of glioblastomas to chemotherapy.[97]

The use of different biological models (ie, different cell lines or mouse models, and different cancer mutations) may lead to the contrasting evidence about the prospective role of AMPK in glioma. In addition, AMPK activators or inhibitors may have AMPK-independent effects on cancer cells, making it more difficult to dissect the specific role of this kinase in brain tumors.[98,99] Furthermore, AMPK could not show a unique behavior; conversely, it may play a protumoral or antitumoral role depending on the energetic and the genetic status of the tumor.

Another aggressive brain tumor is neuroblastoma, the most common extracranial solid tumor in children.[100] Although only little knowledge is available about its role in neuroblastoma, AMPK is believed to act as an oncosuppressor. In particular, AMPK activity may lead to

apoptosis via p38^{MAPK}/p53 pathway in neuro2a and SH-SY5Y neuroblastoma cell lines.[101,102] However, research in this field is still limited and more detailed analysis will be necessary to specifically assess the involvement of AMPK in the onset and progression of neuroblastoma.

AMPK regulation in stroke

Ischemic stroke is one of the most frequent leading causes of death worldwide.[103] Recently, different studies showed that AMPK is rapidly activated in an energy-deprived status such as that which follows a stroke. Ischemic stroke promotes the activation of oxidative and cell death pathways, leading to cellular energy imbalance, that increases the phosphorylation of AMPK in an attempt to restore ATP levels through the enhancement of glycolysis and fatty acid oxidation, increment of glucose transport, and inhibition of glycogen synthesis.[104–106] Thus, AMPK plays a crucial role in regulating ischemic stroke phenotype, but it is unclear whether its activation would be detrimental or beneficial. In vivo studies using the transient middle cerebral artery occlusion (MCAO) model in mice have shown that AMPK activation is damaging, because the pharmacological inhibition of AMPK with CC causes a reduction in stroke volume, whereas the treatment with AICAR leads to a more severe injury, suggesting that inactivation of AMPK during ischemia may be neuroprotective.[107] The mechanisms through which acute AMPK activation exacerbates stroke injury are still unclear. It has been suggested that AMPK activation enhances astrocytic glycolysis which leads to progressive lactic acidosis, exacerbating lactate accumulation, and inhibits the ability of neurons to use lactate as an energy source, contributing to neuronal death. Moreover AMPK activation is responsible for the aberrant neuronal nitric oxide synthase activity, which in turn produces peroxynitrite, the strongest oxidizing agent. These data support the hypothesis that AMPK activation in the acute phase of stroke is associated with injury.[108] To corroborate the idea that AMPK activation is harmful in ischemic stroke, preclinical studies demonstrated that mice deficient in AMPKα2 have less injury and show a reduced total infarct volume compared with wild-type littermates in an MCAO reperfusion model. AMPKα1-knockout mice have no difference in injury compared with wild-type mice, suggesting that AMPKα2 isoform plays a more significant role in the damaging response of AMPK activation in ischemic brain.[109] On the contrary, recent clinical trials report that metformin significantly reduces the risk and incidence of stroke by actions that are independent of its glucose-lowering effects.[110–112] The chronic treatment with metformin offers potent neuroprotective effects similar to preconditioning, a phenomenon by which exposure to sublethal ischemia stimulus leads to protection of the organism from subsequent severe ischemic insults.[113,114] In particular, it was observed that chronic metformin treatment is able to significantly downregulate stroke-mediated brain injury, increase phospho-AMPK levels, reduce lactate formation, improve infarct damage, enhance angiogenesis, and alleviate inflammatory responses by a negative feedback mechanism, blunting ischemia-induced AMPK activation.[115,116] Interestingly, only a chronic metformin treatment is beneficial for the prevention of ischemic disease and the change from a chronic to an acute regimen worsens ischemic injury and functional outcome in otherwise healthy animals, by enhancing AMPK activity and lactic acidosis.[115] In addition, a recent study showed that acute metformin treatment in diabetic rats worsens the infarct size and caused significant neurological deficiencies if compared to untreated diabetic animals.[117] Thus, metformin has negative effects on the severity of neurovascular injury when used acutely, but chronic treatment is protective against fatal cerebral ischemia. The explanation of these divergent results may be dependent on the extent of AMPK manipulation in vivo, on timing and amount of its activation, and on different animal strains and models.[118] As ischemic stroke is a condition of severe energy depletion and AMPK is a master energy regulator, future investigations are needed to provide new information about the therapeutic potential of acute and/or chronic AMPK modulation in stroke.

AMPK in genetic and chromosomal disorders

Although a direct involvement is still unclear, different genetic and chromosomal aberrations strongly suggest a role for AMPK in the development of mental disabilities in genetic disorders. Mutations in the *PRKAG2* gene (AMPKγ2 subunit) have been associated with hereditary cardiac arrhythmias (Wolff–Parkinson–White syndrome, OMIM 194200), familial hypertrophic cardiomyopathy (OMIM 600858), and glycogen storage disease of the heart (OMIM 261740).[119–121] Interestingly, a polymorphism in the *PRKAG2* gene has been also linked to cognitive impairments in elderly people.[122]

PRKAB2 gene (AMPKβ2 subunit), which maps on chromosome 1q21.1, is included in chromosomal rearrangements causing the chromosome 1q21.1 deletion (OMIM 612474) and duplication (OMIM 612475) syndromes. Deletions or duplications (copy number variations [CNVs]) of 1q21.1 chromosomal region have been associated with variable phenotypes, which include intellectual disability and/or autism, schizophrenia, congenital heart anomalies, dysmorphic features, or a normal phenotype.[123] The crucial role of AMPK in brain function is particularly empathized

in 1q21.1 CNV carriers, as they manifest some form of learning disabilities.[123] Notably, AMPK inhibits the mTOR pathway, which is required for the modulation of learning and memory processes.[124]

The involvement of AMPK in brain functioning is further supported by recent studies demonstrating that 1q21.1 CNVs (candidate gene *PRKAB2*) were most frequently associated with schizophrenia.[125,126]

It has been shown that AMPKβ2 protein levels change in concordance with the 1q21.1 copy number state in patient-derived lymphoblastoid cell lines (LCLs).[123] This imbalanced expression affects AMPK activity, as the basal levels of phospho-AMPKα in both 1q21.1 Del and Dup expressing cells are significantly different in comparison to wild-type cells.[123] Furthermore, the AICAR-induced phosphorylation of the AMPK substrates ACC and raptor is suboptimal in 1q21.1 Del and Dup LCLs with respect to wild type, but it is more evident in the 1q21.1 Del-containing cells, demonstrating that the reduced availability of a regulatory β-isoform could affect AMPK activity to a greater extent than its overabundance.[123]

The critical role of AMPK in the CNS could also help to elucidate the mechanisms that contribute to altered neuronal function in patients affected by other genetic diseases, such as TSC (OMIM 191100 and 613254). TSC is an autosomal dominant disorder characterized by hamartomas in multiple organs and neurological manifestations such as seizures, hyperactivity and aggression, intellectual disability, or learning problems.[20] TSC is caused by mutations in the *TSC1* or *TSC2* genes, leading to the disruption of TSC1–TSC2 intracellular protein complex and to the hyperactivation of mTORC1.[127] It was reported that TSC1/2 deficiency reflects in a reduced autophagy because of the inactivation of ULK1 operated by mTORC1 in non-neuronal cells. On the contrary, a recent study demonstrated that TSC1/2 loss in neurons determines an enhanced induction of autophagy via AMPK-dependent phosphorylation of ULK1 at Ser555. Thus, despite the concomitant inhibitory effect of mTORC1 on ULK1 activity, AMPK seems to be the dominant modulator of autophagy in brain cells.[20] As a consequence, the accumulation of p62 and autolysosomes could contribute to the altered neuronal homeostasis in TSC disease.

Conclusion

The fine regulation of energy intake and expenditure is of great importance for maintaining the integrity of physiological processes in almost all eukaryotic cells. AMPK is the master regulator of metabolic stress and mediates pivotal adaptive changes as a function of nutrient deprivation. For these reasons, AMPK is considered the leading actor in several pathologies such as obesity, diabetes, cachexia, and other metabolic disorders. Recently, increasing evidence sustains a key role for AMPK also in brain physiopathology. AMPK is involved in a variety of neuronal processes, such as neuronal proliferation, differentiation, and synaptic transmission.

It is possible that alterations in AMPK activity could reflect in the development of neurological disorders (Figure 4).
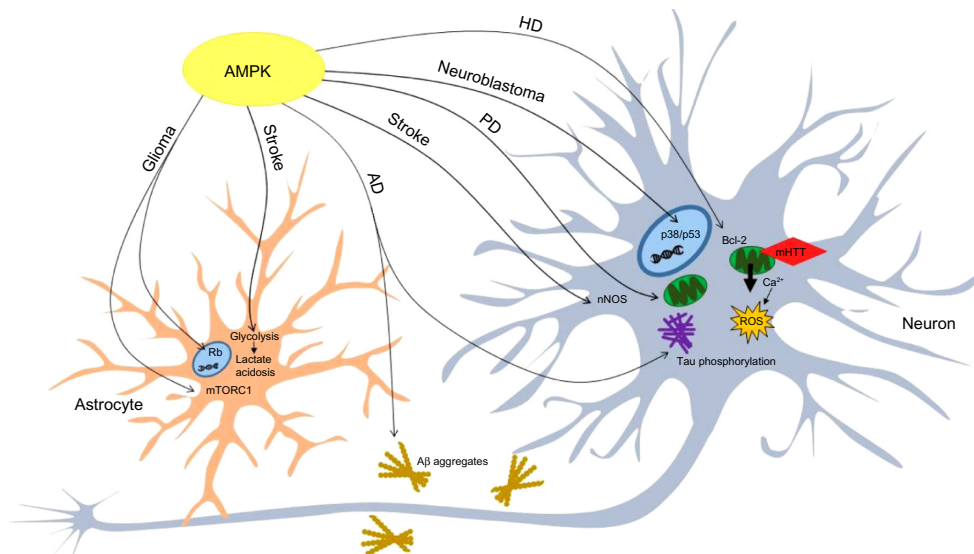

Figure 4 AMPK is involved in the manifestation of neurological conditions.
Notes: AMPK activity in the brain: a) modulates the production of β-amyloid and the formation of neurofibrillary tangles in AD; b) upregulates the expression of the prosurvival gene Bcl-2, thus preventing neurotoxicity in HD; c) orchestrates the quality control of mitochondria in PD; d) exerts pivotal roles in ischemic stroke by regulating nNOS and lactate production in neurons and astrocytes; e) is involved in brain tumor initiation and progression by modulating the oncosuppressor proteins Rb and p53.[71,73–75,77,79,81,84,85,87,90,95,101,102,107,108]
Abbreviations: AMPK, AMP-activated protein kinase; AD, Alzheimer's disease; HD, Huntington's disease; PD, Parkinson's disease; nNOS, nitric oxide synthase.

The studies reviewed here highlight intriguing relationships between AMPK and neurological diseases such as stroke, AD, HD, PD, and brain tumors, whereas other findings show emerging roles for this protein kinase in the development of mental disabilities in genetic disorders. However, even though a great knowledge about the pathological role of AMPK in the brain has been reached, literature data is far from being convincing. AMPK does not show a unique behavior in neurodegenerative diseases, and both detrimental and protective roles have been hypothesized. Indeed, while AMPK activation mediates mHtt-induced toxicity in HD striatal neurons, it prevents neuronal cell death and acts as a survival factor in PD. The role of AMPK is ambiguous in AD pathogenesis, as some reports indicate that AMPK activation is strongly associated with a reduction in amyloidogenesis, whereas other studies demonstrate that AMPK inhibition corrects the Aβ-induced impairments in LTP.[74,78] In the same way, many studies have described the divergent evidence about the involvement of AMPK in brain tumors and ischemic stroke. The presence of contradictory results indicates that further investigations are needed to better dissect the molecular mechanisms linking AMPK activity and the development of CNS diseases. A deep comprehension could provide useful information for designing novel and effective therapeutic strategies addressing a variety of neurological conditions.

Disclosure

The authors report no conflicts of interest in this work.

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