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Synaptic activity and bioenergy homeostasis: implications in brain trauma and neurodegenerative diseases

Natasha Khatri [1,2] ***and Heng-Ye Man*** [1,2] ******

[1] *Department of Biology, Boston University, Boston, MA, USA*

[2] *Department of Pharmacology and Experimental Therapeutics, Boston University School of Medicine, Boston, MA, USA*

Edited by:

Guoqiang Xing, Lotus Biotech.com, Gaithersburg, USA

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****Correspondence:***

Heng-Ye Man, Department of Biology, Boston University, 5 Cummington Mall, Boston, MA 02215, USA

e-mail: hman@bu.edu

Powered by glucose metabolism, the brain is the most energy-demanding organ in our body. Adequate ATP production and regulation of the metabolic processes are essential for the maintenance of synaptic transmission and neuronal function. Glutamatergic synaptic activity utilizes the largest portion of bioenergy for synaptic events including neurotransmitter synthesis, vesicle recycling, and most importantly, the postsynaptic activities leading to channel activation and rebalancing of ionic gradients. Bioenergy homeostasis is coupled with synaptic function via activities of the sodium pumps, glutamate transporters, glucose transport, and mitochondria translocation. Energy insufficiency is sensed by the AMP-activated protein kinase (AMPK), a master metabolic regulator that stimulates the catalytic process to enhance energy production. A decline in energy supply and a disruption in bioenergy homeostasis play a critical role in multiple neuropathological conditions including ischemia, stroke, and neurodegenerative diseases including Alzheimer's disease and traumatic brain injuries.

Keywords: glucose metabolism, glutamatergic neurotransmission, AMPK, mitochondria, Alzheimer disease, traumatic brain injury, stroke

INTRODUCTION

The brain is the most energy-demanding organ in our body. It consumes 20% oxygen and 25% of total glucose supply, equivalent to approximately 20% of total ATP production (1–5). Given that the brain accounts for only 2% of our body weight, its energy consumption is impressive – 10 times that of other organs on average. The high cost in energy is not solely due to a large number of cells in the brain, with an estimated 100 billion neurons and many fold more glia, because organs with a comparable number of cells such as the liver have a much more modest energy bill (6). In contrast to peripheral tissues, neurons depend almost entirely on glucose for ATP production (1). Notably, the brain lacks cellular mechanisms to store energy or energy-generating sources such as glycogen or fat. Rather, energy must be produced continuously in order to maintain neuronal activity. Therefore, neurons are extremely sensitive to energy decline occurring during hypoxia, ischemia, stroke, and other forms of neurotrauma. Indeed, decreased glucose metabolism and mitochondrial energy production dysfunction have been associated with neurodegenerative diseases such as Alzheimer's, Parkinson's, and Huntington's disease. Alzheimer's and Huntington's patients exhibit reduced glucose energy metabolism even at early stages of disease, possibly caused by reduced glucose uptake through transporters, mitochondrial dysfunction, or changes in mitochondrial motility. Traumatic brain injuries are becoming increasingly concerning in populations due to recent wars and the discovery of Chronic Traumatic Encephalopathy (CTE) in athletes. These conditions also cause rapid declines in neuronal glucose levels and associated long-term damaging effects, such as increased intracellular calcium, production of free radicals, and depolarization of the mitochondrial membrane. Recent studies have elucidated mechanisms in energy sensing and the role of synaptic events in energy metabolism and neuronal energy homeostasis, which shed light on our understanding of the pathogenesis of neurological diseases. In addition, proteins and pathways involved in neuronal energy metabolism are being investigated as therapeutic targets for neurodegenerative diseases and traumatic brain injuries.

GLUTAMATERGIC EXCITATORY SYNAPTIC TRANSMISSION IS A PRIMARY ENERGY-CONSUMING EVENT

Although glia outnumber neurons, the latter account for 85% of energy consumption (1). Among many neuronal cellular events, action potential-mediated neuronal communication is believed to be a major process of energy consumption. However, in contrast to a long-held belief, recent studies have revealed that the propagation of action potentials is highly energy efficient (7), consuming only 11% of brain ATP (8). Instead, energy cost mainly comes from synaptic activity, including transmitter release, but primarily postsynaptic receptor activation (9). In the brain, most of the synaptic activity is mediated by glutamate, thus, the excitatory glutamatergic system represents the single largest energy consumer, consuming 50% of ATP in the brain (4, 8, 10, 11). In addition to glutamate receptor channel activity, other glutamate-related events including glutamate synthesis, vesicle filling, release, uptake, and recycling, as well as receptor trafficking and signaling, are also energy consuming.

At the presynaptic terminals, glutamate is enriched in synaptic vesicles (SVs), powered indirectly by a proton pump on the vesicle membrane, at a concentration of 100 mM. During synaptic

transmission, a single vesicle release can cause a rapid rise of glutamate in the synaptic cleft to concentrations as high as 1 mM (12). Under normal conditions, ambient glutamate in the extracellular environment is maintained by the constant activity of glutamate transporters at the plasma membrane of both neurons and glia (12, 13). Glial transporters often surround synapses to ensure an efficient uptake of released transmitter and prevent glutamate spillover.

There are three types of ligand-gated ionotropic glutamate receptors, including AMPA receptors (AMPARs), NMDA receptors (NMDARs), and kainate receptors (KRs) (14–16). AMPARs are sodium channels that are the major components responsible for synaptic transmission, whereas NMDARs play an essential role in the formation of synaptic plasticity, mainly via regulation of AMPAR trafficking and synaptic localization. More importantly, the high permeability of NMDARs to calcium enables the receptor to initiate a series of calcium-dependent signaling cascades, including those for energy-dependent protein modification and metabolic regulations (17). Of note, although NMDARs show high permeability to calcium and are often mistakenly considered a calcium channel, more than 80% of NMDA currents are actually carried by sodium (18). Since NMDA synaptic currents have a long-lasting time course compared to that of AMPARs, NMDARs contribute a large amount of sodium influx during synaptic activities.

A large amount of energy consumption results from the maintenance of ionic gradients via the sodium pump. Neuronal activity and synaptic transmission cause rises in intracellular sodium. Compared with the intracellular sodium concentration of about 10 mM at resting conditions, an action potential can increase spine sodium concentrations to 35–40 mM, and tetanus stimulation for the induction of long-term potentiation (100 Hz stimulation for 1 s) leads to sodium levels as high as 100 mM in the spine (19). Inhibition of the sodium pump activity abolishes glutamate-induced ATP reduction (20), indicating the sodium pump as the major cellular machinery attributing to glutamate-related energy spending. Membrane depolarization by glutamate stimulation induces firing of action potentials, which also leads to sodium influx via voltage-gated sodium channels. However, consistent with the notion that action potentials are energy efficient, blockage of sodium channels by tetrodotoxin (TTX) does not affect glutamate-induced ATP reduction, indicating that glutamate receptors are the primary source of intracellular sodium.

SENSING OF CELLULAR ENERGY BY AMPK SIGNALING

When ATP is hydrolyzed to release energy to enable cellular processes, a rise in the AMP:ATP ratio is sensed by the bioenergy detector AMP-activated protein kinase (AMPK). Once activated, AMPK utilizes its serine/threonine kinase activity to increase the rate of cellular catabolism (glucose utilization, fatty acid oxidation, etc.) while simultaneously inhibiting anabolic processes (cell biosynthesis), resulting in a net increase in ATP production. AMPK is a heterotrimeric protein composed of α, β, and γ subunits in equal stoichiometry. The α subunit constitutes the catalytic domain, conferring kinase activity, while the γ subunit enables AMPK to monitor cellular energy status through two AMP/ATP binding domains, referred to as Bateman domains, that bind AMP or ATP in a mutually exclusive manner (21–23). An increase in the concentrations of AMP, an indicator of energy insufficiency, will facilitate AMP binding to the AMPK Bateman domains, leading to a change in molecular structure, and exposure of an activation loop in the α subunit. This conformational alteration allows AMPK to be phosphorylated at the α subunit Threonine 172 residue by upstream kinases, causing a 50–100-fold increase in the catalytic activity of AMPK (24). Conversely, a high concentration of intracellular ATP promotes ATP/Bateman domain binding and produces an antagonistic effect on AMPK activation. Given that neurons have a high degree of metabolic activity and energy demand, it is expected that AMPK plays a critical role in maintaining energy homeostasis within the brain.

AMPK can be phosphorylated by two upstream kinases including liver kinase B1 (LKB1) and the calmodulin-dependent protein kinase kinases, CaMKKα, and CaMKKβ (25–28). LKB1 was originally found as the tumor suppressor mutated in the genetically inherited susceptibility to human cancer, coined Peutz–Jeghers Syndrome (PJS) (29). In peripheral tissues, LKB1 has been shown to be necessary for AMPK phosphorylation and activation (30, 31). Despite both LKB1 and AMPK being ubiquitously expressed in mammalian cells, there is evidence to suggest that AMPK may be acted upon by different AMPKKs in a tissue-specific manner. For instance, LKB1 has been demonstrated to be the major upstream activator of AMPK in muscle and liver cells (32, 33), however a study utilizing LKB1 knockouts found that LKB1 deficient neurons had similar levels of phosphorylated AMPK as compared to wild-type cells under normal physiological conditions (34). In neurons, AMPK is more likely to be regulated by calcium-dependent signaling. In rat brain slices, intracellular increases in Ca^{2+} results in CaMKK-dependent AMPK phosphorylation. Importantly, membrane depolarization causes AMPK phosphorylation in the absence of an obvious change in cellular AMP:ATP ratio, indicating that AMPK can be regulated in a Ca^{2+}-dependent, AMP-independent manner (35). Thus, glutamatergic synaptic activity can signal neurons for energy production via calcium-mediated AMPK activation.

COUPLING OF SYNAPTIC ACTIVITY AND ENERGY HOMEOSTASIS

In the brain, glutamate is the major neurotransmitter mediating most synaptic transmission. Multiple molecular events occurring during synaptic activation, including sodium pump activity, receptor trafficking, cytoskeletal rearrangements, signaling, and metabolic processes make synaptic activity an energetically costly process (8). Thus, coordinated cellular processes are necessary to convey synaptic signals to bioenergy metabolic activities (**Figure 1**).

CO-ORDINATION OF SODIUM PUMP AND GLUTAMATE RECEPTOR LOCALIZATION

The sodium gradient forms the foundation for synaptic transmission and neuronal excitation. Because of the frequent perturbation of ion homeostasis due to constant neuronal activity, the workload of the Na^+/K^+ ATPase (NKA) is so high that it consumes nearly half of the ATP in the brain. NKA is a heterodimer composed of

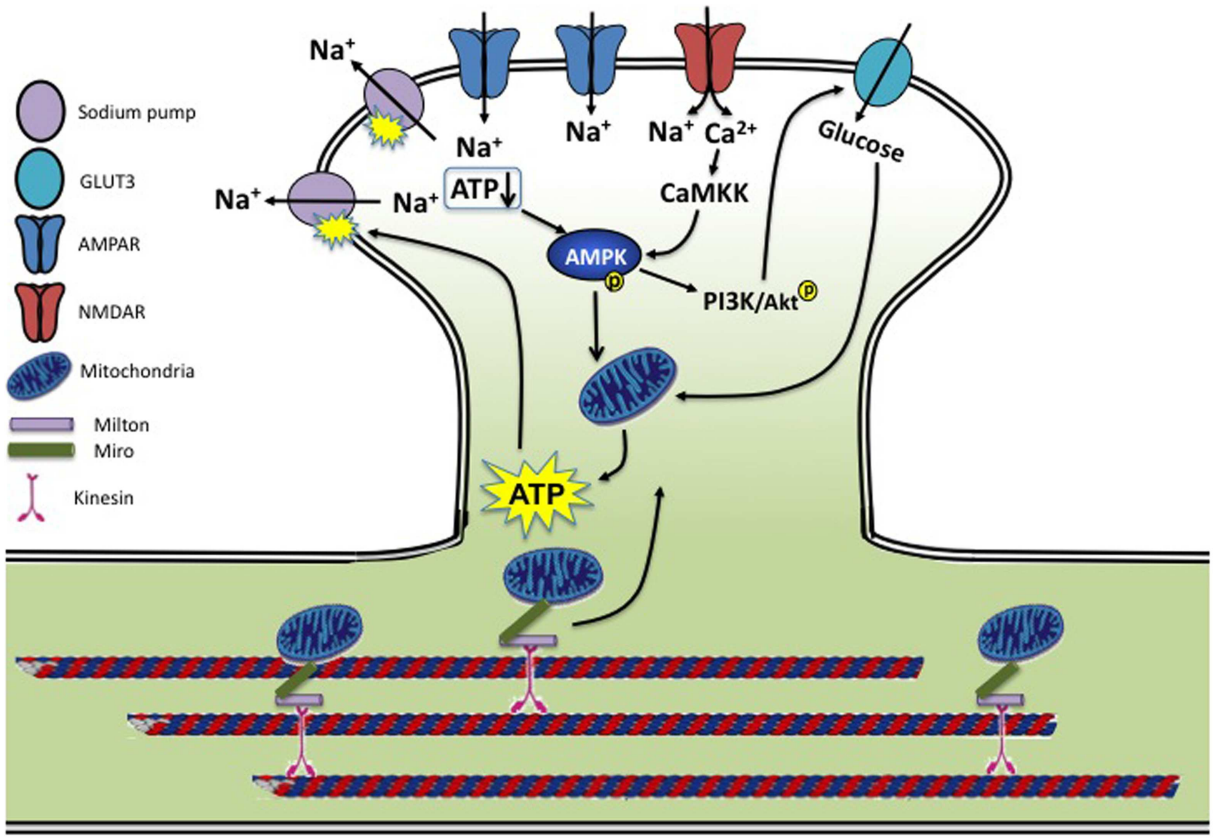

FIGURE 1 | Synaptic activity and energy homeostasis. During synaptic transmission, activation of glutamate receptors allows influx of a large amount of sodium and calcium. Rises in intracellular sodium are rebalanced by the sodium pump powered by ATP consumption. Cellular energy status is sensed by AMPK via a reduced ATP/AMP ratio and CaMKK-dependent calcium signaling, leading to enhanced mitochondria activity and ATP biogenesis. AMPK activity also activates the PI3K/AKT pathway, leading to enhanced glucose uptake by stimulating glucose transporter membrane expression and transport efficiency. Mitochondria are trafficked on microtubules into metabolically demanding synapses by binding to Milton/Miro-mediated kinesin motor complex. In conditions of neurotrauma and neurodegenerative diseases, several aspects of this regulation may be disrupted. During hypoxia, ischemia, and stroke, insufficient ATP levels cause dysfunction of the sodium pump, leading to a loss in membrane potential and neuronal function. AD brains show reduced levels of GLUT3, and both AD and HD brains have a reduced rate of neuronal glucose metabolism. Mouse models of AD and PD show mitochondrial dysfunction along with reduced mitochondrial motility, preventing proper mitochondria delivery to the synapse and leading to decreased energy metabolism. Brains of traumatic injuries show reduced ATP levels and suppressed mitochondrial function.

two subunits: the catalytic α subunit that contains ATPase activity and the regulatory β subunit that is required for the enzymatic activity of NKA. At the single-neuron level, immunostainings have shown widespread localization of NKA in the soma and the dendrites (36, 37). During synaptic transmission, AMPAR-mediated currents are carried by sodium ions that flow into the cytosol of the neuron, typically within a microspace of the spine $<1\,\mu m^3$. In hippocampal neurons, one action potential can cause a several-fold increase in intraspinal sodium. The frequent and often large rises in intraspinal sodium must be exuded efficiently in order to maintain synapse electrophysiology, a task achieved via the activity of NKA. Therefore, there should exist cross-talk between AMPARs and the NKA to coordinate their functions. Indeed, we have shown that sodium pumps are enriched at the synapse and physically associate with AMPARs via interactions between the pump and receptor intracellular C-terminals. AMPAR surface localization and thus activity intensity are controlled to match the functional capacity of the pump. When sodium pump activity is decreased, AMPARs undergo a translocation from the plasma membrane to intracellular compartments via endocytosis, which are then directed to the proteasome for degradation. Presumably, the adjustment in surface glutamate receptor number can help prevent drastic toxicity caused by sodium and calcium accumulation due to sodium pump insufficiency. It remains unclear whether and how changes in glutamate receptor activity lead to corresponding regulation of NKA. However, changes in sodium pump levels correlating with glutamate receptor density have been documented. In the macaque retina, TTX treatment for 4 weeks caused a significant reduction in NMDARs; this reduction was paralleled by a lower level of NKA, suggesting that glutamate activity regulates NKA levels (38).

SYNAPTIC ACTIVATION REGULATES GLUCOSE UPTAKE

Glucose is the sole source for ATP production in neurons (1). Therefore, it is of physiological significance to have synaptic activity coupled with glucose uptake. Both neurons and glia are

equipped with glucose utilization machinery, including glucose transporters and regulators, however higher glucose demands seem to be fulfilled with the assistance from glia. Glucose is first taken up by glia to be converted into lactate via glycolysis, which is then released and retaken by neurons where lactate is used for oxidative ATP genesis in mitochondria. Processes of astrocytes grow in the close proximity to neurons, often wrapping the synaptic cleft, as evidenced by a concentration of the astrocytic glucose transporter GLUT1 around synapses, where glutamate released during synaptic transmission is sensed by the glia and stimulate glial glucose uptake (39, 40).

In addition to the glia-coupled glucose delivery to neurons, synaptic activity can directly stimulate neuronal glucose uptake (41). However, exposure of neurons to glutamate results in a reduction in cellular ATP levels (20) and glucose uptake in neurons (42), indicating distinct signaling and cellular responses to synaptic vs. non-synaptic glutamate receptor activation.

AMPK is implicated in glutamate-induced glucose uptake. In neurons, AMPK signaling leads to activation of the PI3K/Akt pathway. We have shown that in cultured hippocampal neurons application of the AMPK activator AICAR causes a marked increase in phosphorylated Akt (43). This effect results directly from AMPK activation, as introduction of the AMPK antagonist successfully blocks AICAR-induced Akt phosphorylation. Furthermore, addition of a PI3K inhibitor also abolishes AICAR-induced Akt phosphorylation, indicating that the AMPK effect on Akt activation is mediated via PI3K (43) Interestingly, glutamate treatment activates AMPK, and pharmacological activation of AMPK leads to increased amounts of glucose transporters at the cell surface (44). We have recently found that in hippocampal neurons, AMPK activation causes higher levels of membrane GLUT3 and enhances glucose uptake (unpublished data). How AMPK activates PI3K remains unclear. Upon AICAR treatment, AMPK activation has been shown to phosphorylate IRS-1, the upstream component in the PI3K signaling pathway (45), suggesting IRS-1 as the intermediate factor linking AMPK to PI3K/Akt activation. Considering that glutamate-induced ATP reduction is a typical condition for AMPK activation (20, 46), the AMPK-PI3K-mediated enhancement in glucose uptake may function to prevent energy depletion and neuronal excitotoxicity. In addition, phosphorylated Akt may have a stimulatory effect on respiration by translocating to the mitochondria and increasing ATP synthase activity (47).

GLUTAMATE TRANSPORTER AND GLUTAMATE RECEPTOR ACTIVITY IN NEURONAL ENERGY CONSUMPTION

Glutamate is an extremely ample neurotransmitter, ranging to levels of 5–10 mmol/kg of brain tissue (48) and reaching millimolar concentrations within the synaptic cleft during synaptic transmission (49). However, glutamate levels are maintained in the micro- to nano-molar concentration in the extracellular milieu (50), many fold against its concentration gradient (12, 51–53). Unlike some neurotransmitters such as acetylcholine, which are efficiently removed by enzymatic digestion at the synaptic cleft, such disposal mechanism for glutamate does not exist. Instead, following release, glutamate is rapidly taken up by glia and neurons via membrane-distributed glutamate transporters (12, 54). By rapidly binding and transporting glutamate from the synaptic cleft, transporters limit the amount of glutamate receptor-permitted calcium influx and the subsequent excitotoxicity, a principal process involved in neuronal damage and neurodegeneration (55–57).

To date, five excitatory amino acid transports (EAAT1–5) have been identified in glia and neurons. The glial transporters EAAT1–2 are primarily localized to the plasma membrane of specialized domains in astrocytic processes (58, 59). The distribution of the neuronal transporters shows cell type specificity. EAAT3 is expressed in most neurons, including hippocampal and cortical neurons, whereas EAAT4 is mainly localized in cerebellar Purkinje cells and EAAT5 is restricted to the ribbon synapses of rod bipolar cells in the retina (60, 61). The majority of glutamate re-uptake is conducted by the glial transporters EAAT1 and EAAT2 (62, 63) which are expressed abundantly at the glial plasma membrane (59, 64) located in close proximity to synaptic release sites (65).

Glutamate transport by EAATs is powered indirectly by the sodium gradient across the membrane. During one complete cycle of glutamate transport, an EAAT brings one glutamate molecule against its concentration gradient, together with three Na^+ ions and one H^+ ion into the cell, meanwhile counter-transporting one K^+ ion out of the cell, thereby resetting the transporter to the outward-facing conformation (66, 67). During stroke and brain trauma, a large amount of glutamate release is coupled with elevated activity of EAATs attempting to restore extracellular glutamate concentration. Despite EAAT activity being an ultimately energy consuming event, glutamate removal prevents overexcitation of glutamate receptors including AMPARs and NMDARs, which are ion channels with higher energy cost, and thus reduces net energy consumption. Indeed, inhibition of EAATs results in a decrease in ATP amount, which can be completely blocked by the glutamate receptor antagonists, indicating that local glutamate stimulation at synaptic sites causes ATP reductions similar to that caused by global glutamate application (20). Interestingly, glutamate uptake is powered mainly by glycolytic metabolism both in glia and neurons (68).

An additional layer of co-ordination exists between synaptic activity and glutamate receptor trafficking. In response to glutamate release and binding, glutamate receptors, especially the primary synaptic mediator AMPARs, undergo rapid translocation from the plasma membrane to the cytosolic domain via receptor internalization (69, 70). Elevated neuronal network activity or synaptic glutamate accumulation as a result of transporter suppression lead to AMPAR internalization (71). AMPAR trafficking has been extensively studied as a mechanism for synaptic plasticity and learning, but it may also play a role in energy homeostasis, especially in neurotraumatic conditions to prevent receptor overexcitation and rapid depletion of cellular energy store.

SYNAPTIC ACTIVITY AND MITOCHONDRIA FUNCTION AND TRANSLOCATION

Mitochondria are responsible for generating and providing energy in the form of ATP in eukaryotic cells. In addition to converting glucose into ATP, mitochondria are involved in calcium signaling, apoptosis, and the metabolism of reactive oxygen species (ROS). With such high energy demands, neurons rely heavily on the proper functioning of mitochondria. The

significance of this organelle in neurons has been shown by the implication of mitochondrial dysfunction in several neurodegenerative diseases (72). Mitochondria are also involved in other neurobiological processes including neural differentiation, neurite outgrowth, neurotransmitter release, and dendritic remodeling (73).

Because regions of highest energy consumption in the neuron are located at the synapses, mitochondrial transport and distribution are critical, since diffusion of ATP from the center of the neuron would be too slow and inefficient (74). Mitochondrial movement in dendrites is increased in areas with high levels of ATP and decreased in areas containing higher levels of ADP, suggesting that low levels of ATP signal the mitochondria to remain in the area so as to increase local energy supply (75). Dendrites contain a greater proportion of highly charged, more metabolically active mitochondria than axons to match energy demands of local activity. In accordance, axonal mitochondria are more mobile compared to those in the dendrites (76). This activity-dependent mitochondrial stopping results from NMDAR-gated calcium rises, which lead to a recruitment of mitochondria to the synapse (77). Mitochondria use the dynein and kinesin motor complexes to move in the retrograde and anterograde directions, respectively. Specifically, the core of this motor/adaptor complex is made up of kinesin-1, the protein Miro that is anchored to the outer surface of the mitochondria, and Milton, which links kinesin and Miro. A fine balance and regulation of the movements based on these complexes determine where mitochondria will be static or motile to provide adequate ATP for neuronal activity. Elevation of cytosolic Ca^{2+}, which arises from activation of glutamate receptors in dendrites, stops both the anterograde and retrograde movement of mitochondria in neurons (77), which may be regulated by a Ca^{2+} binding site on Miro (78). How this regulation occurs remains unclear, although proposed mechanisms have included a conformational change in the complex triggered by Ca^{2+} (77), and direct binding of Ca^{2+} to kinesin, thereby preventing Miro from interacting with microtubules to allow mitochondrial movement (79).

Although less than synapses, axons themselves are also energy-demanding sites, as they are responsible for generating and conducting action potentials along the length of the neuron. In the peripheral nervous system, the nodes of Ranvier harbor the highest density of Na^{+} channels to sustain saltatory conduction (80). During action potentials, mitochondria are recruited to the nodal region and their mobility is reduced to provide more ATP (81). In addition, mitochondria motility seems to be crucial for axon growth and branching. A recent study shows that LKB1-NUAK1 signaling immobilize mitochondria in the axon where locally produced energy presumably supports formation of axon branches (82).

The regulation of mitochondrial function occurs both presynaptically and postsynaptically in the brain. In the presynaptic zone, the cycle of SVs in neuronal synapses involves steps regulated by cytosolic calcium concentrations and dependent on mitochondrial function. Upon the arrival of an action potential at the nerve terminal, voltage-gated Ca^{2+} channels open and allow an influx of calcium into the terminals. The elevated cytosolic calcium negatively affects mitochondria transport along microtubules, causing them to pause, and accumulate close to the active zones where SVs will fuse to the membrane (83). Synapses tend to have an accumulation of mitochondria that have high electrical potential across their inner membranes and are capable of enhanced ATP production (84).

Regulation of mitochondrial function in the postsynaptic region of the dendrite involves responses to glutamate to increase glucose uptake and ATP production. Synaptic activity increases surface expression of GLUT3 leading to an elevation of intracellular glucose (85). This effect is NMDAR-dependent and involves nNOS phosphorylated by Akt. As glutamate itself is utilized by mitochondria to produce ATP, the transport of glutamate into mitochondria is also regulated by activity. Interestingly, EAAT3 (EAAC1) has been shown to be expressed in neuronal and glial mitochondria where it participates in glutamate-stimulated ATP production (86).

ENERGY DYSREGULATION IN ISCHEMIA AND STROKE

Under normal conditions, high glutamate concentrations only occur at the synaptic cleft; ambient glutamate concentrations are maintained at very low levels (50). However, during traumatic brain injury (TBI) or stroke, massive glutamate release can lead to a marked increase in extracellular glutamate and hyperactivity of the overall glutamate system, causing additional acute and delayed neural pathology. Energy depletion plays a key role in glutamate-induced neurotoxicity (87–90). Glutamate stimulation causes more severe cell death when cellular energy homeostasis is impaired (88). A lack of sufficient ATP undermines a large number of energy-dependent cellular processes including kinase/enzymatic activity, proteasomal protein turnover, transmembrane biochemical gradients, and membrane potentials, all leading to a collapse of cellular functional integrity and deterioration of cell conditions. As the primary energy user consuming half of the ATP in the brain, sodium pump activity is highly sensitive to ATP levels. Under energy deficient conditions such as hypoxia, ischemia, and stroke, NKA dysfunction is often a major early pathological response (91, 92), which leads to a loss in membrane potential and neuronal function.

Ischemic stroke-induced energy depletion is sensed by the master metabolic regulator AMPK. AMPK activation has been observed in glutamate-treated neurons and a variety of ischemia/stroke models both *in vitro* (93) and *in vivo* (94). Because AMPK activation results in enhanced catalytic and suppressed anabolic metabolism, AMPK activity helps to relieve energy stress and is beneficial for neuronal conditions. Studies have shown that in cultured neurons AMPK activation reduces neuronal cell death caused by ischemia/hypoxia (93), whereas AMPK inhibition during energy stress stimulation leads to more severe damage (95). However, there are also studies showing deleterious effects of AMPK. *In vivo* ischemia model shows that blockade of AMPK by Compound C suppressed neural injury (96). Consistently, knockout of AMPK α2 results in a reduction of brain damage (97). Mechanisms for the detrimental effects of AMPK are not clear. Possibly, when cells are under conditions of metabolic stress, forced energy production pushes the metabolic machinery over its limits, causing a collapse of the system and irreversible structural and functional failure.

ALTERATIONS OF BIOENERGY METABOLISM IN NEURODEGENERATIVE DISEASES

Given that the brain is the major energy consumer in the body, and neurons rely heavily on ATP production for development and function, even a slight impairment in energy metabolism can have drastic effects on the brain. In line with this, mitochondria and bioenergy defects have long been proposed as the mechanism underlying chronic neuronal dysfunction and death, and an increasing amount of evidence has been accumulated in support of the hypothesis (**Figure 1**).

Alzheimer's Disease (AD) is a neurodegenerative disease characterized by progressive memory loss and cognitive deficits. Its pathological hallmarks are neuronal loss, extracellular plaques consisting of Aβ aggregates and intracellular neurofibrillary tangles made up of hyperphosphorylated tau. Although the exact cause of neuronal death has not yet been determined, many studies suggest that dysfunction of energy metabolism may be responsible for neuronal deficits contributing to cell death. Indeed, AD patients exhibit reduced glucose energy metabolism, even at an early stage of disease. Positron emission tomography (PET) imaging with the 2-[18F]-fluorodeoxyglucose (FDG) tracer has long been used to track AD-related changes in the brain by estimating the cerebral metabolic rate of glucose (CMRglc). FDG-PET studies in AD show consistent and progressive CMRglc reductions. Compared to age-matched healthy controls, AD patients show metabolic reductions in the parieto-temporal and posterior cingulated cortices in early and late-onset AD (98, 99), and in the frontal areas in advanced disease (99–102). These changes in glucose metabolism could be caused by a reduction of glucose uptake through glucose transporters, mitochondrial dysfunction, or changes in mitochondrial movement.

The neuronal glucose transporter GLUT3 level is reduced in the AD brain (103). Full-length cAMP response element binding protein (CREB), which is reduced in AD brain along with an increase in the truncated form, regulates the expression of GLUT3. Calpain I proteolyses CREB at Gln28-Ala29 to generate a 41-kDa truncated CREB, which is less active in promoting GLUT3 expression, supported by the observation that activation of calpain I itself also reduces GLUT3 expression. It has been suggested that overactivation of calpain I by calcium overload proteolyses CREB, resulting in a reduction of GLUT3 expression, and consequently impairing glucose uptake and metabolism in AD brain (104). AMPK, as a sensor and regulator of cellular energy metabolism, has been shown to decrease with aging, and may contribute to decreased mitochondrial function in AD (105). A study using quercetin, a natural flavonoid and activator of AMPK, showed that activation of AMPK reduces oxidative stress, improves mitochondrial dysfunction and impaired glucose uptake in AD, and slows down Aβ accumulation (106).

Characterization of mitochondrial dynamics and function in three mouse models of familial AD (FAD) (APP, PS1, and APP/PS1) revealed mitochondrial dysfunction before the onset of memory phenotype and the formation of amyloid plaques (107). Movement of mitochondria in both anterograde and retrograde directions in FAD neurons was significantly inhibited compared to wild-type neurons. This reduced motility correlated with increased excitotoxic neuronal cell death by NMDA in all three FAD mouse models, consistent with the essential role for mitochondrial motility and positioning in proper calcium buffering (83). Additionally, similar effects were seen in mouse hippocampal neurons treated with the Aβ(23–35) peptide. Compared to the control neurons, which showed approximately 35% mobile mitochondria, motile mitochondria in the Aβ-treated neurons were significantly reduced to 20%, suggesting that the Aβ(25–35) peptide impairs axonal transport of mitochondria in AD neurons. This reduction in mitochondrial dynamics also correlated with, and was suggested to be causing, a reduction in synaptic proteins synaptophysin and MAP2. In the Tg2576 AD mouse model, where a significant decrease in mitochondrial movement was also seen (108), the mitochondria-targeted antioxidant SS31, which reduces intracellular free radicals (109), restored mitochondrial transport and synaptic viability, and decreased the percentage of defective mitochondria, implicating the important role of mitochondrial function in the disease. A recent report, however, found no consistent presynaptic bioenergetic deficiencies in three mouse models of AD pathogenesis (J20, Tg2576, and APP/PS1) (110). APP/PS1 cortical synaptosomes showed an increase in respiration associated with proton leak, but calcium handling and membrane potentials of synaptosomes were not consistently impaired. The disparities between these studies may be due to the mouse models used and the age of the animal when mitochondrial dysfunction was examined. In transgenic Drosophila expressing human tau, RNAi-mediated knockdown of Milton or Miro enhanced tau-induced neurodegeneration and increased tau phosphorylation at the AD-related site Ser262. Correlated with pathological conditions implicated in AD, a reduction in the number of axonal mitochondria was also observed, and knockdown of Miro alone was sufficient to induce late-onset neurodegeneration in the fly brain (111).

Parkinson's disease (PD) is characterized pathologically by the selective degeneration of dopaminergic neurons in the substantia nigra pas compacta and the presence of Lewy bodies, intraneuronal aggregates comprised primarily of alpha-synuclein (α-syn). A mutation in α-syn, A53T, has been identified to cause familial Parkinson's disease (112), and α-syn transgenic PD models display impaired mitochondrial function and decreased mitochondrial movement (113, 114). In addition, mutations in other Parkinson related proteins, such as PINK1, parkin, and DJ-1, are also believed to be involved in the regulation of mitochondrial function (115–117).

Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by motor and cognitive impairment and caused by a trinucleotide repeat expansion encoding an elongated glutamine tract in the Huntingtin (htt) protein (118). Reduced energy metabolism has been well documented in HD patients. PET scan analysis of HD patients revealed diminished rates of cerebral glucose metabolism in parts of the cortex and throughout the striatum (119). Additionally, HD patient material was found to have significant reductions in the enzymatic activities of complexes II, III, and IV of the mitochondrial oxidative phosphorylation pathway in caudate and putamen (120, 121). BACHD mice of mutant Htt were found to have abnormal mitochondrial dynamics, supposedly due to the interaction of mutant Htt with the mitochondrial protein Drp1, resulting in defective anterograde

movement (122). A major player implicated in mitochondrial dysfunction in Huntington's, as well as Parkinson's, is PPARγ co-activator-1α (PGC-1α). As a transcription co-activator, PGC-1α regulates the expression of various genes to promote mitochondrial biogenesis and oxidative phosphorylation. Impaired PGC-1α function is a likely contributor to HD pathology, as demonstrated by reduced PGC-1α target gene expression in HD transgenic mice (123). PGC-1α transcriptional activity is also repressed in a conditional knockout model of parkin (124), and activation of PGC-1α could rescue dopaminergic neuron loss induced by mutant α-syn (125). Consistently, PGC-1α has been suggested as a promising therapeutic target for HD and PD, either by boosting PGC-1α expression by viral delivery, or by modulating the upstream activators of PGC-1α activity, such as SIRT1 and AMPK (126).

IMPLICATIONS OF ENERGY HOMEOSTASIS IN TRAUMATIC BRAIN INJURY

Traumatic brain injury (TBI) is a complex brain damage by an external force that causes brain penetrating or closed-head injuries. Recently, TBI has become an increasing concern in the population, as almost 179,000 service members sustained a TBI during the Iraq and Afghanistan wars (127). Additionally, repeated injury to the brain, especially concussions, can lead to CTE, a neurodegenerative disease that has been discovered in brain tissues of athletes who have sustained many close head and concussions injuries over time (128, 129). The complex mechanism by which TBI triggers pathological processes and long-term neurobehavioral abnormalities are still not well understood. Mechanistic investigation is critical to guide the identification of compounds to prevent acute neuronal damage and subsequent effects.

Traumatic brain injuries cause a vast array of primary structural damages that lead to secondary effects including cellular, inflammatory, neurochemical, and metabolic alterations. In the early phases after injury, changes such as metabolic impairment, reductions in cerebral blood flow, low ATP and energy stores, severe ionic shifts, and alterations in the permeability of the blood-brain barrier are seen. Thereafter, brain lactate production increases for the first few days, indicating a shift from aerobic to anaerobic metabolism to maintain ATP production, while glucose levels decline rapidly, as measured by microdialysis in affected patients (130). High levels of lactate in the brain during this period of ischemia may cause additional harmful effects; cerebral acidosis may exacerbate calcium-mediated damage to intracellular pathways and may interfere with ion-channel function (131). ATP levels are decreased following a TBI, along with reduced availability of the nicotinic coenzyme pool, which declines proportionally with the gravity of brain insult (132). The degree of oxidative metabolism depression also correlates with the depth of coma after severe TBI, as indicated by the Glasgow Coma Scale (GSC) (133). In mice, a single blast resulted in a 20% decrease in ATP levels in the cerebral cortex at 6 h after the blast, whereas triple blasts resulted in a similar decrease as early as 1 h (134). A significant, though less severe, decrease remained 24 h after the blast. Energy failure leads to degradation of molecules of key importance to membrane and cytoskeletal integrity. It also causes a disruption in ion homeostasis, especially calcium rises, and an increase in cytosolic acidity. The rise in free cytosolic Ca^{2+} is a result of failed calcium pump function, increased membrane permeability to calcium, and decreased sequestration of intracellular calcium. Elevated calcium levels and oxidative stress lead to the opening of the mitochondrial permeability transition pore (mPTP), which depolarizes the mitochondrial membrane and leads to organelle swelling and subsequent release of cytochrome *c*, leading to caspase-dependent cell death (135, 136). Specific inhibitors of the mPTP are currently under investigation as treatment immediately after TBI to prevent neuronal damage (137).

Mitochondrial dysfunction in TBI may be caused by several mechanisms in addition to the opening of mPTP. Nitric oxide (NO) is believed to cause respiratory chain inhibition in mitochondria after TBI (138), as it has the ability to interfere with energy metabolism by inhibiting the enzymatic activity of complex IV of the electron transport chain. An increase in NO production has been observed in closed-head trauma animal models (139), caused by the increase in the production of inducible NO synthase (iNOS) (140), as indicated by the rapid upregulation of iNOS mRNA at 4 h after injury. The inhibition of pyruvate dehydrogenase (PDH) has also been implicated in causing mitochondrial damage in TBI. PDH is tightly regulated by end-product inhibition and reversible phosphorylation, and a significant decrease in both PDH enzyme levels (141) and PDH phosphorylation (142) was found in rat TBI models. In addition, activation of poly(adenosine diphosphate [ADP]-ribose) polymerase-1 (PARP-1) could be responsible for impaired mitochondrial respiration. PARP-1 senses DNA damage after injury and becomes overactivated, depletes NAD^+/NADH stores, and impairs the utilization of oxygen for ATP synthesis (143). In support of this mechanism, administration of NAD^- or the PARP inhibitor GP 6150 was found to be neuroprotective after TBI in rats (144, 145). Similar blockade of mitochondrial damage and metabolic disturbances in the early events occurring immediately after an injury are currently under investigation, which will be advanced following a better understanding of the molecular mechanisms underlying primary TBI impacts.

CONCLUSION

Excitatory glutamatergic synaptic transmission is the major energy-consuming cellular process in the brain. Therefore, it is critical for neurons to couple synaptic activities with energetic metabolism, and to have adaptive mechanisms in response to metabolic stress and neuronal overexcitation. Dysfunctions in the regulatory system and bioenergy homeostasis can lead to defects in neural development and brain function, and contribute to the pathogenesis of neurodegenerative diseases and traumatic brain injuries. It will be important to further our understandings of how synaptic activity communicates with the metabolic and energetic machineries, including energy sensing, energetic signaling, bioenergy metabolism, and mitochondria dynamics. Age-dependent changes in bioenergy homeostasis, and epigenetic control of the energetic processes are also in need of further investigation.

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