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The role of astrocytic glycogen in supporting the energetics of neuronal activity

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Abstract

Energy homeostasis in the brain is maintained by oxidative metabolism of glucose, primarily to fulfil the energy demand associated with ionic movements in neurons and astrocytes. In this contribution we review the experimental evidence that ground a specific role of glycogen metabolism in supporting the functional energetic needs of astrocytes during the removal of extracellular potassium. Based on theoretical considerations, we further discuss the hypothesis that the mobilization of glycogen in astrocytes serves the purpose to enhance the availability of glucose for neuronal glycolytic and oxidative metabolism at the onset of stimulation. Finally, we provide an evolutionary perspective for explaining the selection of glycogen as carbohydrate reserve in the energy-sensing machinery of cell metabolism.

Keywords

brain glycogen; neurometabolic coupling

Most research is largely based on the work of others. Ours is not an exception, and among them we are profoundly indebted to Prof. Leif Hertz, to whom this special issue of the Journal is dedicated. Prof. Hertz was the first to suggest a role for astrocytes in brain potassium homeostasis [1], and one of those pioneering the studies on the possible involvement of astrocytic glycogen in potassium clearance from the extracellular space after neuronal activity (reviewed in [2]). In this paper, we would like to provide further arguments of discussion about the role of astrocytic glycogen, hoping that this might be of interest for future experimental works.

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The authors declare no conflict of interest.

A specific role for astrocytic glycogenolysis in supporting the rapid clearance of extracellular potassium during enhanced neuronal activity

At the organ level, the ubiquitous P-type Na^+/K^+-activated adenosine triphosphatase (NKA) is the principal source of ATP hydrolysis related to signaling in the brain ([3] and references therein). At the cellular level, the sodium pump is responsible for the neuron-astrocyte metabolic interactions that form the basis for the coupling between neuronal activity and energetics. In particular, while NKA in neurons is engaged in extruding the large amount of Na^+ entering these cells during action and postsynaptic potentials, astrocytic NKA supplements neuronal NKA in fueling the rapid removal of neuroactive compounds, such as K^+ and transmitter molecules, from the extracellular space [2]. This distribution of functions is believed to stem from two important mechanisms for ion movements in neurons and astrocytes after neuronal activity. First, the specific cellular expression of NKA subunits would give neuronal and astrocytic enzymes very different kinetic properties in terms of intra- versus extracellular ion binding site affinity for Na^+ and K^+ in the physiological range. Specifically, neuronal NKA appears to be activated by increases in intracellular Na^+ concentrations, while being largely independent on increases in extracellular K^+ concentrations; the opposite is true for the astrocytic NKA, which seems to be exquisitely sensitive to increases in extracellular K^+ [4,5]. This is largely due to expression of the neuron specific α3 catalytic subunit, which has a several-fold lower K_m (i.e. higher affinity) for extracellular K^+ and a much higher K_m (i.e. lower affinity) for cytoplasmic Na^+ relative to α1 and α2 isoforms [6]. The difference of K_m values for the effect of extracellular K^+ on NKA suggests that neuronal NKA is already saturated at normal extracellular K^+ level, whereas astrocytic NKA can be stimulated by above-normal concentrations of K^+ in the extracellular space. Consistent with the different response of neuronal and astrocytic NKA, previous assays of respiration rate in isolated neurons and astrocytes reported substantial astrocytic but not neuronal stimulation upon exposure to K^+ [7,8]. Stimulation of astrocytic but not neuronal NKA activity at its extracellular K^+-sensitive site was then repeatedly supported in cultured or isolated cells [9–13]. Second, distribution and kinetic properties of electroneutral neuron specific outward K^+/Cl^- cotransporter (KCC) and ubiquitous inward $Na^+/K^+/2Cl^-$ cotransporter (NKCC) would favor sequestration of extracellular K^+ by astrocytes while maintaining intra- and extracellular K^+ and Cl^- homeostasis [2]. In particular, a trans-membrane Na^+ cycle in astrocytes was proposed to be the result of the combined action of astrocytic NKA and NKCC [14]. Although not previously hypothesized, the requirement of extracellular K^+ by the neuronal NKA, while activated at the intracellular Na^+-sensitive site, strongly suggests the existence of a corresponding trans-membrane K^+ cycle in neurons generated by neuronal NKA and KCC. Return of K^+ to neurons might occur during recovery by efflux from astrocytic K^+ channels and reversal of neuronal KCC [15,5].

Strong evidence for a major contribution of active astrocytic K^+ uptake to clearance of the ion comes from the tight link between astrocytic membrane potential and extracellular K+ reported in rat cortex in vivo, whereby depolarization of astrocytes was found to closely follow the rise in extracellular K^+ during excitation [16]. This was further confirmed by the finding that intracellular K^+ increases in astrocytes and decreases in neurons by nearly the

same amount during rise in extracellular K^+, consistent with the notion of concomitant neuronal release and astrocytic uptake of K^+ during enhanced neuronal activity [17 and references therein]. The importance of active astrocytic K^+ clearance from the extracellular space was also shown theoretically, as the absence of astrocytic K^+ transport is incompatible with the maintenance of low (<6 mM) extracellular K^+ at moderate to high (e.g. 6 Hz to 30 Hz) neuronal firing rates [18].

Although the role of astrocytes in the clearance of extracellular space from K^+ should be regarded as common knowledge, the notion that these cells accounts for most of active K^+ uptake is unfortunately still poorly acknowledged [2]. As a result, the energy demand of astrocytes during neuronal signaling is substantially underestimated when based only on the ATP-dependent reactions involved in glutamate-glutamine cycling [3]. Since glycogen as well as glycogen phosphorylase activity is confined to astrocytes [19,20], quantitative estimate of energy consumption by these cells is all-important for assessing the possible functional role of astrocytic glycogenolysis to neuroenergetics (see also [21]). The first report of K^+-induced glycogenolysis, which dates back to 1978, showed substantial glycogen mobilization after depolarization of mouse cerebral cortical slices with 50 mM K^+ [22]. Similarly, glycogenolytic responses of astrocytes to supraphysiological K^+ concentrations (25–50 mM) were observed in mouse cortical slices and cultured astrocytes [23,24]. Stimulation of glycogen metabolism by physiological concentrations of K^+ (from 2.5–3.5 mM under resting conditions to 10–12 mM during neuronal activation) was first documented in studies on the nerves of leech (*Haemopsis sanguisuga*) and snail (*Planorbis corneus*) ganglia [25]. Shortly thereafter, several in vitro studies confirmed that physiological levels of K^+ could produce, in a concentration-dependent manner, rapid (seconds to minutes) mobilization of glycogen stores that could be largely prevented by inhibiting NKA with the cardiac glycoside ouabain [26–28]. Interestingly, these experiments showed that a large fraction of the glycogenolytic effect of K^+ is inhibited by calcium (Ca^{2+}) channel blockers, indicating that K^+-induced depolarization of astrocytes triggers opening of voltage-gated Ca^{2+} channels. Increase in intracellular Ca^{2+} stimulates astrocytic NKCC [29], thus accelerating removal of extracellular K^+ and energy consumption by NKA, which in turn further stimulates glycogenolysis [2]. Calcium per se has an inhibitory effect on glycolysis only at concentrations >0.1 mmol/L, which is therefore not of physiological significance [see 30], as normal intracellular Ca^{2+} level is below 1 μmol/L. Rather than preventing glucose use, Ca^{2+} directly or indirectly stimulates glycogen breakdown [24,26–28]. How glucose phosphorylation can be inhibited by glycogenolysis is described later in the next section.

The effective mobilization of brain glycogen during physiological stimulation appears to be well documented [31]. In particular, sensory stimulation was found to induce ~20% net glycogen breakdown in rat cerebral cortex [32,33]. Moreover, inhibition of glycogen mobilization in conscious rats during sensory stimulation caused regional compensatory increase in utilization of blood glucose up to 50% [34]. A series of experiments conducted in adult rat optic nerve, a white matter tract of myelinated axons, demonstrated the involvement of glycogen provided by periaxonal astrocytes at internodes ([35] and references therein). Studies on neonatal chicks also showed glycogen utilization during

processing and formation of memory (reviewed in [36]). However, measurement of glycogenolysis in human primary visual cortex after visual stimulation showed no detectable changes [37]. A possible explanation for such discrepancy has been suggested elsewhere, and relates to the highly heterogeneous, tier-dependent process of label incorporation into glycogen [38].

In summary, because of the kinetic profile of ion channels and transporters in neurons and astrocytes, the clearance of extracellular space from K^+ appears to be a specific astrocytic function. Accordingly, analysis of the current literature suggests that most of the K^+ uptake after stimulation onset occurs into astrocytes [15–17,39]. Furthermore, accumulated experimental evidence on cultured cells and tissue slices indicates that K^+ removal by astrocytes is largely fueled by glycogen [2]. Notably, glycogen appears to be mobilized during physiological activity in vivo (for a comprehensive review, see [32]).

A specific role for mobilization of astrocytic glycogen in supporting the increase of neuronal metabolism at the onset of stimulation

Given the high energy demand of both neurons and astrocytes (see above), this means that these cell types compete for the extracellular, paracellularly diffused blood-borne glucose [40,41]. We have recently proposed, based on metabolic modeling studies, that the provision of glucose to neurons is controlled by a mechanism requiring glycogenolysis in astrocytes [38,21]. In particular, during conditions of high extracellular K^+ the combined action of astrocytic NKA/NKCC and phosphagen kinases (see below) triggers glycogen mobilization as part of the short-term energy-sensing response. Glycogenolysis generates glucose-6-phosphate (Glc-6-P) in astrocytes at a rate several-fold higher compared with uptake and phosphorylation of glucose, thereby transiently increasing Glc-6-P concentration. Intracellular accumulation of Glc-6-P reduces the substrate flow through hexokinase (HK) due to product-inhibition (i.e. detachment of the enzyme from mitochondrial membrane), which in turn prevents any gradient-driven glucose uptake by these cells [38]. Temporal dependence on the proposed glycogenolysis-induced suppression of glucose phosphorylation is difficult to establish with current knowledge, but it is probable that it remains confined to few seconds after stimulation onset, which identify the dependence of extracellular K^+ clearance on astrocytic glycogenolysis [2]. Accordingly, efficient re-synthesis of glycogen, possibly simultaneous to degradation [34,42], prevents shortage of the available glycogenolytic response [43].

Common sense would suggest that the main importance underlying glycolysis or glycogenolysis is the rapidity of ATP production compared with respiration, a notion that is sometimes used to rationalize the uncoupling between metabolism of carbohydrates and oxygen in the stimulated brain. However, this is not the case for the following reasons. First, respiration provides far more ATP (30–31 ATP for each glucose equivalent processed) per unit time per glucose than both glycolysis (2 ATP) and glycogenolysis (3 ATP), regardless of the activation state [44]. In particular, the rate of glycolysis should increase more than 15-fold to overwhelm ATP production by respiration, which is largely beyond the experimentally observed increase in cerebral glucose utilization ranging from +30% to +50% [44]. Second and most importantly, up-regulation of cerebral oxidative metabolism at

the tissue level is quicker than anaerobic processing of glucose. The shorter rise-time of respiration compared to glycolysis is evidenced by the findings that concentrations of nicotinamide adenine dinucleotide [45,46] and lactate [47,48] in the brain decrease within seconds after the onset of sustained stimulation. Specifically, the early increase in mitochondrial respiration was found to be located to neuronal dendrites [45]. This is likely to be the result of the selective expression of ubiquitous mitochondrial creatine kinase (CK) in neurons but not astrocytes, whereas both cell types express cytosolic CK [49]. Indeed, mitochondrial CK triggers rapid energy-status signaling from cytosolic sites of ATP hydrolysis (e.g. plasma membrane NKA) to mitochondria via diffusion of creatine (which is many-fold higher than diffusion of ADP) [50,51]. In other words, re-phosphorylation of ADP by cytosolic CK results in accumulation of creatine that is quickly directed to mitochondrial CK in neurons. This cannot happen in astrocytes, as both degradation and formation of phosphocreatine is accomplished by CK in the cytosol.

The rapid up-regulation of respiration in neurons has important consequences for the activity of glucose-phosphorylating enzymes of the glycolytic pathway and hence for the channeling of glucose to neuronal glycolysis. Indeed, respiration requires substrates to run, which can occur only at the expense of energy for substrate-level phosphorylation of glucose. Remarkably, the initial ATP expended by the preparatory phase of glycolysis or glycogenolysis is important to prevent depletion of the ADP generated by mitochondrial bound kinases [52,53]. These kinases control both the membrane potential of mitochondria and the generation of reactive oxygen species (ROS). Active HK, PFK and ubiquitous mitochondrial CK are targeted to the inner and/or outer membrane of mitochondria, where they have access to mitochondrially-generated ATP [54–57,50]. In this manner, mitochondrial bound HK, PFK and CK constantly provide substrate (i.e. ADP) for phosphorylation by F_1F_0 ATP synthase, thus generating a cycling of ADP/ATP that reduces electron leak and hence mitochondrial ROS generation [52,53]. Disruption of this ADP-recycling mechanism would be detrimental for neurons, as they have high rates of respiration and corresponding ROS production through electron transport chain, which makes them especially sensitive to oxidative stress (reviewed in [58]). Furthermore, neurons strongly depend on the processing of Glc-6-P through pentose phosphate pathway (before eventually re-entering glycolysis) for regeneration of the antioxidant system of ascorbate/glutathione [59]. Importantly, neurons are capable of Glc-6-P synthesis only via phosphorylation by HK, while astrocytes can produce Glc-6-P through glycolytic, glycogenolytic and gluconeogenic routes (for a review, see [21]). Taken together, these arguments strongly suggest that glucose phosphorylation is mandatory for neurons to maintain mitochondrial ADP concentration during the initial phase of highly increased respiration rate.

In summary, the metabolic response of the brain to activation is most likely initiated by the activation of neuronal mitochondrial bound kinases. Kinase activity is required to (i) provide substrates to respiring mitochondria, (ii) maintaining mitochondrial ADP-recycling mechanism, and (iii) channeling glucose into pentose phosphate pathway. These events allow substantial up-regulation of ROS-generating oxidative metabolism in neurons, which is especially relevant at stimulation onset. Astrocytes are “good scouts” [60] as they help supporting substrate delivery to neurons in the short-term. Specifically, the lack of

ubiquitous mitochondrial CK and the presence of glycogen in astrocytes prevents the competition for oxygen and glucose, respectively, with activated neurons. Notably, neither neurons nor astrocytes are required to have a preferred substrate during the course of neuronal activation [61].

A specific role for glycogen metabolism in sensing cellular energy status: a perspective from evolution

Glycogen represents the most widespread form of carbohydrate storage in living cells, as it is found in Archaea, Bacteria and Eukaryotes. The selection pressure for glycogen metabolism is thought to reflect a trade-off between the requirements of rendering large amounts of glucose osmotically less active than e.g. unbranched malto-oligosaccharides, and the requirements to make the carbohydrate storage readily hydrosoluble for rapid mobilization (as opposed to starch) [62]. It is likely that the accumulation of carbohydrate in the form of glycogen served first as glucose reserve in case of nutrient deprivation, and subsequently as substrate buffer for local energy demand. This is suggested by the high degree of conservation of the binding site for the inhibitor Glc-6-P, but not for the activator phosphorylation/AMP, as well as associated dimer contact networks in glycogen phosphorylase (GP) of lower organisms [63]. Accordingly, allostery of the enzyme is proposed to have evolved from the earlier control by Glc-6-P to the ability of being fully activated by either phosphorylation or AMP, thus specializing according to different physiological roles towards activation rather than inhibition [63].

Interestingly, in mammals this specialization is also found at the individual organism level. Mammalian GPs exist as three isoforms, muscle, brain and liver that exhibit different responses to activation by phosphorylation and AMP, regardless of species [64]. In particular, muscle and brain, but not liver, GPs display phosphorylation/AMP-mediated control mechanisms that confer the enzyme the ability to respond to cellular energy status [65]. Accordingly, muscle and brain GPs are more closely related to each other than to the liver isoform [63]. Hydrolysis of ATP during energy consumption is buffered by creatine (Cr) kinase (CK) reaction ($PCr + ADP + H^+ \leftrightarrow Cr + ATP$; PCr, phosphocreatine) as well as adenylate kinase (AK) reaction ($2ADP \leftrightarrow ATP + AMP$). AK is probably the primary source of AMP in vivo, where small decreases in ATP concentration (<20%) can result in very large increases (25- to 45-fold) in AMP level [66]. Small departures of ATP homeostasis are further amplified by energy-sensor protein kinases that are ubiquitous in eukaryotic cells, such as AMP-activated protein kinase (AMPK) and cAMP-dependent protein kinase A (PKA) [65]. AMPK and PKA phosphorylate both glycogen synthase (GS) and GP leading to catalytically inactive GS and active GP [65]. Interestingly enough, genetic studies in non-mammalian AMPKs indicate that the ancestral role of this kinase was in response to glucose starvation (see [66]).

It is possible that the origin of AMP increase is due to the limited ATP buffering capacity of the PCr/CK system, which is the most labile among cellular phosphagens [67]. In particular, regeneration of ATP via CK-mediated transfer of phosphoryl groups from PCr to ADP results in the rapid depletion of PCr, thereby favoring AMP production by AK. It is often thought that PCr/CK system is especially advantageous for tissues with high and variable

energy turnover, such as muscle and brain. However, phosphagen systems are widespread in simplest organisms and cells/tissues that cannot be characterized as having high and fluctuating energy demand (e.g. low power output muscles in sea anemones, mollusks and many polychaetes capable of sustained glycogenolytic flux). Selective pressure for regulation of glycogenolysis is probably one of the early factors in the evolution of phosphagen systems [51]. In particular, PCr traps considerable amounts of inorganic phosphate (Pi), a substrate for GP reaction, which is liberated upon net ATP hydrolysis ($ATP \rightarrow ADP + H^+ + Pi$) followed by substrate-level phosphorylation by CK. The control of Pi level can thus promote glycogen breakdown during the CK-mediated ATP buffering induced by activation relative to resting conditions ([51] and references therein). A close link between CK and GP is also suggested by the putative AMP-dependent association between the two enzymes [68]. This might influence the allosteric activation of GP by AMP, which is antagonized by ATP as it competes with AMP for the same binding site [67].

In summary, the role of cellular glycogen appears to have evolved from emergency carbohydrate depot to a member of the enzymatic machinery that is exquisitely sensitive to cell energy status. As such, regulation of glycogen mobilization in tissues like muscle and brain is under the allosteric control of adenylates (ATP, ADP and AMP) via AK- and CK-mediated reactions, as well as AMP-activated and/or AMP-dependent protein kinases (AMPK and PKA).

Concluding remarks

In this paper, we summarized the experimental evidences supporting a role for astrocytic glycogen metabolism in the energetics of neuronal electrical activity. During the restoration of trans-membrane ion concentrations, extrusion of intracellular sodium and sequestration of extracellular potassium identify the principal energy demand of neurons and astrocytes, respectively. The energy demand associated with ionic movements is thus distributed between neurons and astrocytes, which however have specific metabolic needs underlying the provision of substrates to oxidative metabolism. Notably, mobilization of glycogen in astrocytes has the potential to support the availability of glucose for neuronal respiration. Carbohydrate reserve in the form of glycogen was arguably incorporated during evolution in the energy-sensing machinery of cell metabolism. For future studies, it would be of great interest to characterize how the metabolic interactions between neurons and astrocytes couple with the spatiotemporal dependence on glycogenolysis during stimulation, thus providing critical insights into the regulation of nutrient supply and utilization in the brain under physiological and pathological conditions.

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Abbreviations used

AK	adenylate kinase
AMPK	AMP-activated protein kinase
CK	creatine kinase
HK	hexokinase
Glc-6-P	glucose 6-phosphate
GP	glycogen phosphorylase
GS	glycogen synthase
KCC	K^+/Cl^- cotransporter
NKA	Na^+/K^+-Adenosine triphosphatase (sodium pump)
NKCC	$Na^+/K^+/2Cl^-$ cotransporter
PFK	phosphofructokinase
PKA	cAMP-dependent protein kinase A
ROS	reactive oxygen species

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