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Swanson, Raymond A

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Perspective article

A thermodynamic function of glycogen in brain and muscle

Raymond A. Swanson[a,b]

[a] Neurology Service, San Francisco Veterans Affairs Health Care System, San Francisco, CA 94121, USA
[b] Dept. of Neurology, University of California San Francisco, San Francisco, CA 94143, USA

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ABSTRACT

Brain and muscle glycogen are generally thought to function as local glucose reserves, for use during transient mismatches between glucose supply and demand. However, quantitative measures show that glucose supply is likely never rate-limiting for energy metabolism in either brain or muscle under physiological conditions. These tissues nevertheless do utilize glycogen during increased energy demand, despite the availability of free glucose, and despite the ATP cost of cycling glucose through glycogen polymer. This seemingly wasteful process can be explained by considering the effect of glycogenolysis on the amount of energy obtained from ATP ($\Delta G'_{ATP}$). The amount of energy obtained from ATP is reduced by elevations in inorganic phosphate (Pi). Glycogen utilization sequesters Pi in the glycogen phosphorylase reaction and in downstream phosphorylated glycolytic intermediates, thereby buffering Pi elevations and maximizing energy yield at sites of rapid ATP consumption. This thermodynamic effect of glycogen may be particularly important in the narrow, spatially constrained astrocyte processes that ensheath neuronal synapses and in cells such as astrocytes and myocytes that release Pi from phosphocreatine during energy demand. The thermodynamic effect may also explain glycolytic super-compensation in brain when glycogen is not available, and aspects of exercise physiology in muscle glycogen phosphorylase deficiency (McArdle disease).

1. Introduction

Large, rapid increases in local energy demand, correlating with bursts of neuronal activity, are a defining feature of brain energy metabolism. The metabolic demands posed by these increases are met in part by increases in local blood flow. However, changes in local blood flow occur on a time scale that is orders of magnitude slower than changes in local brain activity, resulting in transient mismatches between local energy demand and substrate delivery. These mismatches are accommodated several ways, including increased ATP production from local glucose and phosphocreatine reserves (see Text Box). Skeletal muscle likewise exhibits large, rapid fluctuations in energy demand associated with bursts of activity, and like brain, muscle responds to these fluctuations with a combination of blood flow and metabolic responses. Among these metabolic responses is rapid utilization of glycogen.

Glycogen is stored in cells as granules comprised of highly branched glucose polymer (Fig. 1). Both brain and muscle contain millimolar concentrations of glucose stored as glycogen, and in both tissues glycogen utilization is time-linked to increases in energy demand. It is thus widely assumed that glycogen in these tissues functions to buffer mismatches between glucose supply and demand. However, this concept does not account for several fundamental aspects of glycogen metabolism. Glycogen utilization occurs continuously in normal brain, despite the fact that use of glucose derived from glycogen entails a net ATP cost relative to use of free glucose. In skeletal muscle, glycogen is required for rapid and efficient contraction even when free glucose is available; and in both brain and muscle, local glucose concentrations rarely if ever fall to levels that could be rate-limiting for energy metabolism; instead, glycogen is consumed *despite* an excess of usable glucose.

Prevailing concepts of glycogen metabolism also ascribe differing and somewhat conflicting roles for glycogen in muscle and brain. Muscle glycogen is considered a source of glucose for the myocytes themselves, whereas astrocyte glycogen is instead widely viewed as a source of lactate that is exported to neurons for use as an energy metabolite. However, lactate cannot be used for ATP production if oxygen availability is insufficient, as is the case whenever glucose availability is insufficient (excepting profound hypoglycemia). Moreover, quantitative studies indicate that most lactate derived from astrocyte glycogen is released to the blood stream (Dienel, 2012, 2019), in the same manner as lactate generated from exercising muscle. Also as in muscle, there is no evidence that glucose consumption in brain can outstrip normal glucose supply under physiological conditions. These

Abbreviations: ADP, adenosine diphosphate; AMP, adenosine monophosphate; ATP, adenosine triphosphate; $\Delta G'_{ATP}$, Gibbs free energy of ATP hydrolysis; Km, Michaelis-Menten constant; NAD^+, nicotinamide adenine dinucleotide; PCr, phosphocreatine; Pi, inorganic phosphate ($H_2PO_4^-$); UDP, uridine diphosphate

E-mail address: raymond.swanson@ucsf.edu.

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Text Box:
Cellular responses to graded energy demands: glycogen, phosphocreatine, and adenylate kinase.

Relationships between energy demand and energy supply can be divided into three stages.

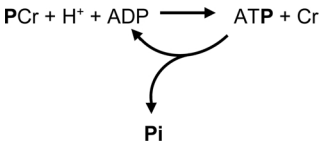
1 At rest or moderate exercise, glycolysis and mitochondrial oxidative phosphorylation together regenerate ATP at a rate sufficient to meet demand, and there is no net increase in ADP or Pi concentrations. Mitochondrial oxidative phosphorylation is fueled by several substrates, including lipids, amino acids, ketone bodies, and the lactate or pyruvate generated by glycolysis.

2 With increasing energy demand, a point is reached at which the rate of mitochondrial oxidative phosphorylation is maximal, but the rate of glycolytic ATP production can further increase. The excess pyruvate resulting from the mismatch between glycolytic and oxidative metabolism is converted to lactate in order to regenerate the NAD^+ consumed by glycolysis, and the lactate is either exported to the blood stream or used locally, after conversion back to pyruvate, when energy demand is lessened. Glycolysis can be fueled either by glucose or glycogen stores, but there is a net cost of one ATP per glucose moiety cycled on and off of glycogen polymer (Fig. 2).

3 With extreme or very rapid onset energy demand, ATP consumption outstrips the maximal rate that ATP can be produced even with maximal glycolytic flux. Under these conditions, cells consume phosphocreatine (PCr) through the creatine kinase reaction:

$$PCr + ADP \leftrightarrow ATP + Cr \quad (A.1)$$

This reaction both increases ATP and lowers ADP concentrations, but the relative effect on ADP is far greater because cytosolic ATP > > ADP. All cell types also use PCr to facilitate intracellular dispersion of ATP and ADP equivalents (Wallimann, 1994), but skeletal muscle and brain uniquely contain high levels of cytosolic PCr to permit a net consumption of PCr during intervals of rapid ATP hydrolysis. During net PCr consumption, there is an equimolar production of Pi, as the ATP is cycled back to ADP.



(A.2)

Cells experiencing extreme levels of energy demand also employ the adenylate kinase reaction:

$$ADP + ADP \rightarrow ATP + AMP \quad (A.3)$$

This reaction likewise has a far greater relative effect on lowering ADP levels than on increasing ATP levels. The adenylate kinase pathway can be utilized for only limited intervals because the excess AMP it generates is rapidly degraded to inosine and ammonia, consequently depleting the total adenylate pool (ATP + ADP + AMP).

interleaving considerations warrant a reassessment of the basic observations and assumptions pertaining to glycogen metabolism in both brain and muscle. This perspective will review the bioenergetics of glycogen metabolism, identify conflicts between current concepts and experimental data, and argue that the primary function of glycogen is the same in both brain and skeletal muscle: to maintain maximal energy yield from ATP.

The capacity of cells to carry out energy-dependent processes depends not only on their capacity to maintain ATP concentrations, but also to maintain the *amount* of energy obtained from ATP hydrolysis to ADP and Pi. This energy amount, termed $\Delta G'_{ATP}$, is not a constant but is instead influenced by the ratios of the reactants and products of the ATP hydrolysis reaction. In simplified form, $\Delta G'_{ATP}$ varies in proportion to the ratio [ADP]·[Pi] : [ATP]. As this ratio rises the $\Delta G'_{ATP}$ becomes smaller, and at the extreme condition no energy can be obtained from ATP regardless of ATP abundance (Nicholls and Ferguson, 2013). Crucially, the first step of glycogen mobilization *subtracts* inorganic phosphate (Pi) from the cytosol, thereby preserving $\Delta G'_{ATP}$. This thermodynamic function of glycogenolysis is likely particularly important for cells that that intermittently consume phosphocreatine (which indirectly generates free Pi), and for cells such as astrocytes in which ATP hydrolysis occurs in extremely narrow, confined spaces.

2. Regulation and bioenergetics of glycogen metabolism

Glycogen concentrations vary considerably across cell types, being highest in liver, brain and skeletal muscle, and much lower in smooth muscle and other tissues (Table 1). Liver has a special role as a systemic glycogen storage depot. To this end, hepatocytes express glucose-6-phosphatase for generating exportable free glucose from glycogen-derived glucose-6-phosphate. Brain and muscle have only negligible expression of glucose-6-phosphatase (Dringen et al., 1993; Gamberucci et al., 1996), and correspondingly do not have a role analogous to hepatocytes as a source of free glucose for use by other cells.

As illustrated in Fig. 1, the glucose residues in glycogen are joined as linear chains by α-1,4-glycosidic bonds, with branch points formed by α-1,6-glycosidic bonds approximately every 10–14 glucose residues (Calder, 1991). Glycogen synthesis requires uridine diphosphate glucose (UDP-glucose) as a substrate, which is produced from uridine triphosphate and glucose-1-phosphate by UDP-glucose pyrophosphorylase. The α-1,6-glycosidic branch points are subsequently produced by glycogen branching enzyme (1,4-α-glucan-branching enzyme). Glycogenolysis, by which glucose residues are detached from glycogen, is mediated by glycogen phosphorylase, which hydrolyzes glucose residues at α-1,4 linkage points to generate glucose-1-phosphate. Glycogen debranching enzyme acts at the α-1,6 branch points to provide a linear substrate for glycogen phosphorylase (Nakayama et al., 2001).

Mammals express three isoforms of glycogen phosphorylase: a liver isoform, a muscle isoform and a brain isoform, each termed by the tissue in which it is predominately expressed. Astrocytes contain both the brain isoform (PGYB) and the muscle isoform (PGYM), and low levels of the brain isoform also detectable in some neurons (Pfeiffer-Guglielmi et al., 2003). The isoforms differ in response to various regulatory influences (Mathieu et al., 2017). Glycogen phosphorylase is regulated by changes in energy state through allosteric effects of ATP and glucose-6-phosphate, which slow enzymatic activity, and AMP, which accelerates activity. Glycogen phosphorylase is also regulated by

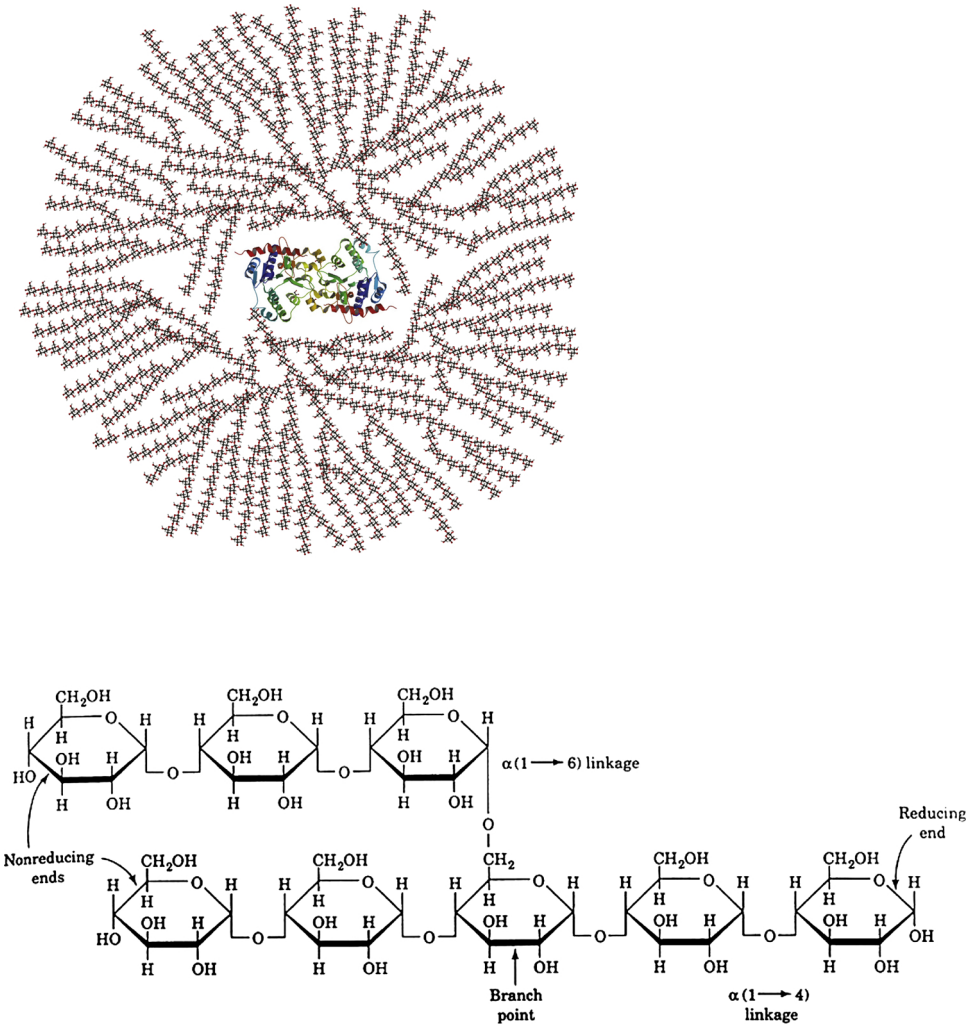


Fig. 1. Schematic two-dimensional cross-sectional view of glycogen. A core protein of glycogenin is surrounded by branches of glucose units. The entire globular granule may contain up to 30,000 glucose units. The individual glucose moieties of glycogen are linked by α-1,4-glycosidic bonds, with α-1,6-glycosidic branch points every 10 - 14 glucose residues. The exposed ends of all glycogen chains are non-reducing. Image from (Haggstrom, 2014).

glycogen phosphorylase kinase, which is in turn responsive to several signaling pathways. For example, stimulation of ß-adrenergic receptors activates glycogen phosphorylase kinase through the cAMP / protein kinase A pathway. This provides a mechanism for "anticipatory" glycogen mobilization prior to any actual perturbation in cellular energy state. Glycogen phosphorylase kinase can also be activated by Ca^{2+} binding to its calmodulin subunit, a mechanism particularly important in skeletal muscle, where contraction is initiated by release of Ca^{2+} from the sarcoplasmic reticulum.

The immediate product of glycogen phosphorylase is glucose-1-phosphate, which exists in equilibrium with glucose-6-phosphate. Glucose-6-phosphate is also produced from free glucose in the initial step of glycolysis (Fig. 2), but there are significant bioenergetic differences between these two pathways. First, there is a net cost of one ATP

Table 1
Tissue glycogen concentrations.

Tissue	Glycogen (mg / g)	Citation
Liver	29.02 ± 2.40	(Vissing et al., 1989)
Liver	41.39 ± 5.28*	(Kusunoki et al., 2002)
Muscle (gastrocnemius-plantaris-soleus complex)	5.70 ± 0.24[a]	(Baker et al., 2005)
Muscle (white gastrocnemius)	6.73 ± 0.16	(Vissing et al., 1989)
Brain (cortex)	2.01 ± 0.26	(Cruz and Dienel, 2002)
Brain (whole brain)	1.98 ± 0.20	(Oe et al., 2016)
Heart	4.33 ± 0.32	(Vissing et al., 1989)
Heart	3.99 ± 0.22	(Conlee et al., 1989)
Kidney	0.06 ± 0.01	(Khandelwal et al., 1979)
Kidney	0.03 ± 0.01*	(Nannipieri et al., 2001)

Data are from adult rat or mouse under rest, non-fasted conditions. Values are means ± SEM or means ± SD (*). Glycogen in brain is restricted primarily to astrocytes, which comprise less than 25 % of brain volume (Gundersen et al., 2015). The glycogen content within astrocytes is thus roughly 4 times the measured brain value.
[a]Reported as mmol / kg dry weight; converted here using 76 % as the water content of muscle.

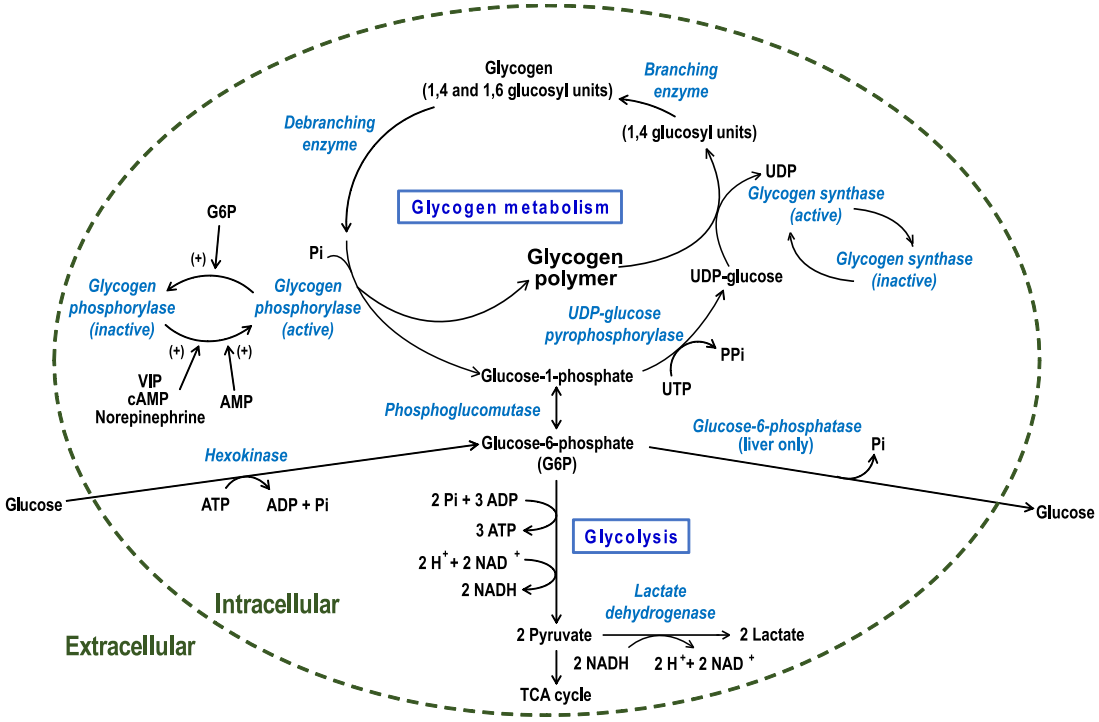


Fig. 2. Bioenergetics and regulation of glycogen metabolism. Glycogen synthase extends an existing glucosan chain of α-1,4-glycosidic linkages using UDP-glucose as substrate. Glycogen branching enzyme subsequently forms α-1,6-glycosidic bonds to create branch points. Glycogenolysis is mediated by debranching enzyme and glycogen phosphorylase. Glycogen phosphorylase is regulated allosterically in response to neurotransmitters and hormones, by changes in energy metabolites (AMP, glucose-6-phosphate, and others), and by second messengers such as cAMP. The immediate product of glycogen phosphorylase is glucose-1-phosphate, which is freely converted to glucose-6-phosphate. Hepatocytes (but not other cell types) can rapidly dephosphorylate glucose-6-phosphate to generate free glucose for export. There is a net cost of one ATP per molecule of glucose-6-phosphate that is cycled onto and off of the glycogen polymer, as 2 ATP equivalents are consumed in forming UDP-glucose from glucose-1-phosphate and only 1 ATP equivalent is gained back at the formation of glucose-1-phosphate at the glycogen phosphorylase step. The formation of glucose-1-phosphate from glycogen (but not from glucose) removes Pi from the cytosol.

for each glucose residue shuttled onto and off glycogen polymer, as two ATP are consumed in forming UDP-glucose and only one ATP equivalent is regained with the formation of glucose-1-phosphate (Fig. 2). Second, glycogen metabolism to glucose-1-phosphate has the immediate effect of removing Pi from the cytosol, whereas formation of glucose-6-phosphate from free glucose does not. These two differences have fundamental implications for the functions of brain and muscle glycogen.

2.1. Special aspects of glycogen metabolism in brain

The importance of glycogen in brain function is less widely recognized than its role in muscle. Astrocytes contain most of the glycogen in brain, with much smaller amounts also detectable in meningeal cells, endothelial cells, and other cell types (Cali et al., 2016; Cavalcante et al., 1996; Ibrahim, 1975; Koizumi, 1974). Neurons contain appreciable amounts of glycogen during development, but this falls to low (but non-zero) levels in the mature brain except in certain brainstem neurons (Borke and Nau, 1984; Oe et al., 2016; Saez et al., 2014). Astrocytes maintain homeostasis of brain extracellular space through active, energy-dependent processes (Kettenmann and Ransom, 2012). They form a syncytium through gap junctions, and extend innumerable fine processes that function independently of one another as metabolic microdomains (Grosche et al., 1999). Electron microscopy identifies glycogen granules throughout astrocyte cell bodies and processes, particularly near axonal boutons and dendritic spines (Cali et al., 2016). After accounting for the fact that almost all brain glycogen is in astrocytes, and astrocytes comprise less than 25 % of brain volume (Gundersen et al., 2015), the estimated glycogen concentration in astrocytes is roughly comparable to that in skeletal muscle (Table 1).

Glucose is by far the primary energy substrate used by brain, and glucose metabolites liberated from astrocyte glycogen can support neuronal survival for limited periods of time during brain ischemia or profound hypoglycemia (Kilic et al., 2018; Seidel and Shuttleworth, 2011; Suh et al., 2007; Swanson and Choi, 1993; Swanson et al., 1990; Wender et al., 2000). However, several factors indicate that this is not the primary function of brain glycogen. These factors include continuous turnover of brain glycogen during normal brain activity, suppression of glycogen turnover during anesthesia or hibernation (Swanson, 1992), the location of most glycogen in astrocytes rather than neurons, and the complex neuromodulatory influences that regulate astrocyte glycogen metabolism. Brain glycogen turnover (utilization and re-synthesis) accelerates in response to local neuronal activity (Swanson et al., 1992; Watanabe and Passonneau, 1973) to rates that can match or exceed activity -induced increases in local utilization of free glucose (Dienel, 2019; Shulman et al., 2001). Glycogen turnover is stimulated by neurotransmitters and other signaling molecules including serotonin, norepinephrine, arachidonic acid, glutamate, and K^+ (Magistretti, 1988; Quach et al., 1982; Subbarao et al., 1995; Walls et al., 2009).

Transgenic mice lacking brain glycogen synthase further demonstrate a role for glycogen metabolism in normal brain function. These mice are overtly normal, but have increased susceptibility to hippocampal seizures following the administration of kainate or stimulation of Schaffer collaterals (Lopez-Ramos et al., 2015). These mice also exhibit impaired synaptic plasticity, as evidenced by decreased long-term potentiation in the hippocampus and impairment in an associative learning task (Duran et al., 2013). Studies using inhibitors of glycogen phosphorylase likewise suggest a role for glycogen in memory consolidation (Gibbs et al., 2006; Gibbs and Hutchinson, 2012; Gibbs et al., 2007; Newman et al., 2011). Electrophysiology recordings from *ex vivo* optic nerve and corpus callosum show that the capacity of axons to

maintain conductance during high frequency stimulation varies in proportion to astrocyte glycogen content in these structures (Brown et al., 2012, 2005; Wender et al., 2000). These and other studies also suggest that lactate derived from astrocyte glycogen can be metabolized by neurons (Dringen et al., 1993; Tekkok et al., 2005; Tsacopoulos and Magistretti, 1996); however, lactate metabolism is ubiquitous (Veech, 1991), and there remains controversy as to whether this is a significant mechanism by which astrocytes support neuronal function *in vivo* (Dienel, 2019; Dienel and Cruz, 2004). It should also be noted that lactate cannot normally serve as an energy metabolite under conditions under which local blood delivery of glucose insufficient. This is because lactate must be metabolized oxidatively, and blood normally carries a considerable excess of glucose over extractable oxygen (after accounting for the 6:1 ratio of oxygen : glucose required for oxidative glucose metabolism). Accordingly, blood flow that is insufficient to provide adequate glucose will also be insufficient to provide oxygen required for lactate metabolism.

3. Current concepts of brain glycogen function

The energetic cost of shuttling glucose on and off glycogen (1 ATP per glucose moiety) strictly limits the conditions under which there can be an advantage to utilizing glycogen stores over free glucose. Accordingly, current views presume that glycogen is utilized only when glucose supply is insufficient. The concentration of glucose in blood does not fall near values affecting brain function under physiological conditions, but it has been proposed that glucose supply to locally activated regions of brain might become transiently insufficient during the brief interval between onset of local neuronal activity and subsequent increase in local blood flow (Swanson, 1992; Swanson et al., 1992). This idea was formally developed by Shulman and colleagues as the “glycogen shunt” hypothesis, to explain changes in the ratio of glucose : oxygen utilization observed during local brain activation (Shulman et al., 2001). A related idea proposes that astrocyte glycogenolysis occurs pre-emptively near active neurons to prevent reductions in neuronal access to extracellular glucose (Dienel and Cruz, 2015; DiNuzzo, 2019; DiNuzzo et al., 2010, 2011). Glycogenolysis produces glucose-6-phosphate (Fig. 2), which when elevated inhibits hexokinase and thereby inhibits glucose utilization. Glucose-6-phosphate that is generated selectively from glycogen in astrocytes could, if not rapidly consumed, selectively suppress astrocyte glucose utilization and thereby preserve extracellular glucose for neuronal consumption.

Although these concepts have gained wide support, experimental observations suggest than glucose availability is rarely if ever rate-liming for brain energy metabolism, even for short time intervals. The concentration of glucose in brain is normally 1–2 mM (de Graaf et al., 2001; Gruetter et al., 1998; Shestov et al., 2011), and reductions in this concentration cannot significantly limit glucose utilization rate unless they approach the hexokinase Km for glucose, which is 0.03 - 0.3 mM (Wilson, 2003). At a resting glucose utilization rate of 0.25 μmol /g /min, (Dienel, 2019),a brain glucose concentration of 1 mM glucose (1 μmol /g) would supply local brain metabolism for roughly 3 min by oxidative metabolism, or about 15 s by anaerobic metabolism. This appraisal matches experimental observations. The classic study by Silver and Ericińska found that spreading depression, which causes nearly simultaneous bursting of neurons at its wave front and thus approximates the maximal rate of brain energy demand, reduced extracellular glucose concentrations by only 25 % (Silver and Erecinska, 1994). Sustained pentylenetetrazole-induced status epilepticus similarly produces only minor reductions in brain glucose concentration, excluding settings in which cerebral blood flow is impaired (Folbergrova et al., 1985; Ingvar et al., 1984; McCandless et al., 1987). These findings are also consistent with the observation that the maximum rate of glucose transport into brain is more than twice the maximum rate of glucose utilization (de Graaf et al., 2001; Shestov et al., 2011). Moreover, functional MRI studies show that neither total cerebral blood flow nor local activity-induced increases in cerebral blood flow are attenuated by large (3-fold) elevation in blood glucose concentration (Gruetter et al., 2000), as would be expected if activity-induced local increases in cerebral blood flow were required to prevent insufficient glucose delivery.

In summary, the 1 − 2 mM glucose concentration in brain is itself a large buffer against transient mismatches between glucose supply and demand, measured changes in brain glucose content show only small reductions even with supra-physiological brain activity, and the measured capacity to transport glucose into brain far exceeds brain capacity to utilize glucose. These *in vivo* experimental findings argue against the idea that normal brain activity can drive local glucose concentrations below levels required to fuel neuronal or astrocyte function even for very brief time intervals, and suggest instead that glycogen must serve a purpose other than (or in additional to) a local glucose reserve. This suggestion is supported by studies using cell culture preparations, in which glucose is always available in far excess of need. In cultured astrocytes, the maximal rate of energy-dependent K^+ uptake is reduced by pharmacological inhibition of glycogen phosphorylase (Xu et al., 2013). Similarly, glycogen phosphorylase inhibition reduces miniature excitatory and inhibitory post-synaptic currents in neurons cultured with astrocytes (but not in neurons alone) despite ample glucose in the culture medium (Kaczor et al., 2015; Mozrzymas et al., 2011).

4. Current concepts of muscle glycogen function

Skeletal muscle fiber types can be classified as Type 1 “red” or Type 2 “white”, with the red fibers containing more mitochondria and white fibers containing more glycogen (Nielsen et al., 2011). At the subcellular level, muscle glycogen is concentrated within and between individual myofibrils, which are the contractile elements and major ATP consuming sites (Ortenblad and Nielsen, 2015). Glycogen is consumed during muscle activity and is re-synthesized from blood-borne glucose between muscle contractions (Nielsen et al., 2011; Shulman and Rothman, 2001). During very rapid or sustained muscle activity, glycogen consumption outpaces synthesis and is eventually depleted.

It is generally presumed that muscle glycogen is metabolized to augment circulating glucose to fuel the energy demand during the brief periods (10–40 milliseconds) of high ATP demand associated with individual myocyte contractions (Chin and Allen, 1997; Shulman and Rothman, 2001). However, glucose concentrations in muscle are in the millimolar range, far too high to be consumed in sub-second intervals. Moreover, muscle glucose content increases rather than decreases with exercise, as a result of increased blood flow (Hamrin et al., 2011; MacLean et al., 1999; Rosdahl et al., 1993; Sahlin, 1990). Although sustained muscle contraction can reduce the flow of blood through contracting muscle, this reduction is incomplete even with intense and prolonged contractions (Lanza et al., 2005; McNeil et al., 2015; Wigmore et al., 2006). Even in the absence of glucose, the 20–25 mM concentration of phosphocreatine (PCr) in muscle would be sufficient to maintain muscle ATP levels for at least several seconds (Baker et al., 2010; Bogdanis et al., 1996; Funk et al., 1989; Meyer, 1988) (see Text Box).

Alternatively, glycogen might be metabolized to produce glucose-6-phosphate more quickly than it can be produced from free glucose, as the maximal flux through glycogen phosphorylase substantially exceeds maximal flux through hexokinase in mammalian skeletal muscle (Suarez et al., 1997). However, an accelerated production of glucose-6-phosphate would not significantly increase the rate of glycolytic ATP production because it is the downstream phosphofructokinase and glyceraldehyde-3-phosphate dehydrogenase steps that are rate-limiting for glycolytic ATP production, rather than glucose-6-phosphate availability (Kobayashi and Neely, 1979; Tanner et al., 2018). There is no evidence that glycogen in muscle is metabolized in one cell to fuel activity in a neighboring cell, as has been proposed for glycogen in brain astrocytes.

All of these observations argue against the idea that muscle glycogen serves as local glucose reserve to bridge brief mismatches between blood glucose delivery and glucose demand. But most conclusively, studies using "skinned" (permeabilized) muscle fibers showed that *muscle fibers depleted of glycogen are unable to attain maximal contractile force even when perfused with excess glucose, phosphocreatine (PCr), and ATP* (Stephenson et al., 1999), thereby definitively establishing that muscle glycogen must have functions other than simply a glucose store. Importantly, these authors also noted that glycogen represents a sizeable sink for Pi in contracting muscle, and this provides a biochemical link between glycogen and muscle fatigue.

Muscle fatigue is physiologically defined as a progressive decline in contractile force that largely recovers after rest (Allen et al., 2008). Fatiguing muscle also has reduced efficiency, i.e. produces less force per unit of metabolic substrate consumed (Broxterman et al., 2017; Gorostiaga et al., 2010). Muscle fatigue correlates well with glycogen depletion (Allen et al., 2008; Ortenblad and Nielsen, 2015); however, the primary biochemical factor causing muscle fatigue is not reduced ATP, but rather elevated inorganic phosphate (Pi) (Baker et al., 1993; Cooke et al., 1988; Miller et al., 1993). Elevated Pi concentrations actively suppress muscle activity, in part by inhibiting the release of calcium from the sarcoplasmic reticulum that triggers muscle fiber contraction (Allen et al., 2002; Allen and Trajanovska, 2012). Thus, the studies by skinned muscle fiber studies by Stephenson and colleagues described above suggest that Pi sequestration may be the primary function of glycogen metabolism in exercising muscle.

5. A thermodynamic function of glycogen metabolism

The capacity of cells to do work is determined not only by their levels of ATP, but also by the amount of energy obtained from each molecule of ATP consumed ($\Delta G'_{ATP}$). The $\Delta G'_{ATP}$ in mammalian cells is usually near -55 kJ / mol. The more negative the value of $\Delta G'_{ATP}$, the more energy obtained from each molecule of ATP hydrolyzed to ADP. When the $\Delta G'_{ATP}$ rises (becomes less negative), ATP hydrolysis produces less energy. It is thus important that cells maintain $\Delta G'_{ATP}$ in order to maximize both work capacity and work efficiency (i.e. work performed per substrate consumed). Omitting the terms for H^+, Mg^{2+} and H_2O for clarity (Alberty, 1969; Manchester, 1989), the simplified equation for ATP hydrolysis is

$$ATP \rightarrow ADP + Pi \quad (1)$$

and the corresponding equation for the free energy ($\Delta G'$) for ATP hydrolysis is

$$\Delta G'_{ATP} = \Delta G^{\circ\prime}_{ATP} + RT \ln([ADP]\cdot[Pi] / [ATP]) \quad (2)$$

where $\Delta G^{0\prime}_{ATP}$ is the free energy of ATP hydrolysis under defined standard conditions (1 M concentrations of all reactants and products), R is the gas constant, ln is the natural logarithm, and T is temperature. (See (Iotti et al., 2005) for a more complete description). The equation states that the amount of energy derived from ATP is influenced by the local concentrations of ADP and Pi. When the ratio of [ADP] · [Pi] / [ATP] is increased, the value of $\Delta G'$ becomes less negative and less energy is obtained from ATP consumption.

During very rapid energy demand, the rate of ATP consumption can exceed capacity for ATP regeneration. This affects cell energetics in two ways: it reduces ATP availability, and by elevating ADP and Pi it increases $\Delta G'_{ATP}$. *Of these two, it is the increase in $\Delta G'_{ATP}$ that is most immediately significant.* This is because the intracellular ATP concentration is normally 3–10 mM, and reductions in ATP concentration do not significantly limit the velocity of ATP - consuming enzymes unless they approach the enzyme ATP Km values. These values are below 20 μM for both Na^+/K^+ ATPase and myosin ATPase (Hackney and Clark, 1985; Pilotelle-Bunner et al., 2008). By contrast, any elevation in $\Delta G'_{ATP}$ immediately reduces the amount of energy derived from ATP hydrolysis. This particularly affects enzymes that operate near thermodynamic equilibrium with respect to $\Delta G'_{ATP}$, which include both Na^+/K^+ ATPase and myosin ATPase (Astumian, 2010; Ventura-Clapier et al., 1987; Wagoner and Dill, 2019; Wallimann, 1994).

The effect of Pi elevations on $\Delta G'_{ATP}$. can be substantial not only in the immediate vicinities of ATP hydrolysis, but also at the whole-cell level. Whole-cell Pi concentrations in muscle rise from about 1 mM to above 5 mM during strenuous exercise (Bogdanis et al., 1996, 1998; Gaitanos et al., 1993; Sahlin et al., 1997), and Pi elevation is the primary biochemical cause of both muscle fatigue and reduced efficiency, as noted above. Crucially, the glycogen phosphorylase reaction attenuates the rise in Pi.

$$\mathbf{Pi} + glycogen_n \rightarrow glycogen_{n-1} + \text{glucose-1-}\mathbf{phosphate} \quad (3)$$

By removing Pi from the cytosol, glycogen utilization buffers elevations in Pi that would otherwise reduce the amount of energy obtained from ATP utilization.

This effect of Pi sequestration on $\Delta G'_{ATP}$ might be spatially and temporally limited if the Pi bound as glucose-1-phosphate were rapidly liberated back to the cytosol. However, measurements from actively exercising muscle show that most of the Pi remains sequestered as millimolar concentrations of phosphorylated glycolytic intermediates, primarily glucose-6-phosphate, until exercise ends (Bendahan et al., 1990, 1992; Bogdanis et al., 1996, 1998; Gaitanos et al., 1993; Kappenstein et al., 2013).

In principle, Pi sequestration as phosphorylated glycolytic intermediates could also be accomplished by metabolizing glucose, rather than glycogen. Pi sequestration in that case does not occur in the first, hexokinase step of glycolysis, but does occur after accounting for subsequent ATP re-synthesis, as shown below in the summed reactions of glycolysis.

$$\begin{aligned} &glucose + ATP \rightarrow glucose\text{-}6\text{-}phosphate + ADP \\ &glucose\text{-}6\text{-}phosphate + 2Pi + 3ADP \\ &\quad \rightarrow 3ATP + 2pyruvate \\ \text{net: } &glucose + 2Pi + 2ADP \rightarrow 2ATP + 2pyruvate \end{aligned} \quad (4)$$

However, a direct comparison between use of glycogen vs glucose as the substrate shows that glycogen metabolism removes a net one more Pi molecule per glucose moiety consumed and produces one less molecule of ADP.

$$\begin{aligned} &glycogen_n + Pi \rightarrow glycogen_{n-1} + \text{glucose-1-phosphate} \\ &\text{glucose-1-phosphate} \leftrightarrow \text{glucose-6-phosphate} \\ &\text{glucose-6-phosphate} + 3ADP + 2Pi \rightarrow 3ATP + 2\ \text{pyruvate} \\ \text{net: } &glycogen_n + 3Pi + 3ADP \rightarrow glycogen_{n-1} + 3ATP + 2pyruvate \end{aligned} \quad (5)$$

Thus, relative to free glucose utilization, glycogen utilization better maintains $\Delta G'_{ATP}$ by removing Pi from the cytosol in its initial (fastest) step, by removing a net of 1 more Pi through glycolysis, and by producing one less ADP per glucose residue metabolized. We propose that these thermodynamic advantages are crucial during rapid ATP hydrolysis, such that the immediate advantage gained in maximizing $\Delta G'_{ATP}$ more than offsets the overall ATP cost of cycling glucose through glycogen polymer.

5.1. Coupled effects of glycogen and phosphocreatine on $\Delta G'_{ATP}$

The $\Delta G'_{ATP}$ can also maintained in part by creatine kinase reaction, which limits ADP elevations while at the same time regenerating ATP.

$$PCr + ADP \leftrightarrow ATP + Cr \quad (6)$$

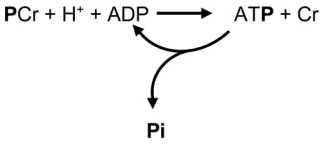
This utilization of phosphocreatine (PCr) is generally considered to be a strategy for maintaining ATP concentrations when (or where) maximal ATP synthesis falls short of demand. However, this reaction

Table 2
Estimated effect of glycogen on exercise - induced changes in whole-cell $\Delta G'_{ATP}$.

	Glycogen (mM glucose equivalents)	PCr (mM)	ATP (mM)	ADP (mM)	Pi (mM)	$\Delta G'_{ATP}$ (kJ/mol)	Change in $\Delta G'_{ATP}$ relative to rest
Measured: At rest	114	26.32	9.45	1.19	1.01	−53.6	- - -
Measured: End-exercise	80	4.41	6.86	1.37	5.67	−48.0	5.6 kJ/mol (10.5 %)
Estimated: End-exercise in the absence of glycogen	- - -	4.41	6.86	1.37	22.9	−44.4	9.2 kJ/mol (17.2 %)

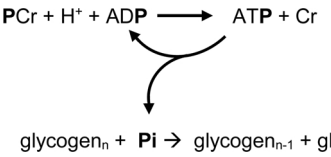
The measured metabolite values at rest and end-exercise are from biopsy studies of human quadriceps muscle: glycogen, PCr, ATP, and Pi from (Bogdanis et al., 1996), and ADP from (Sahlin et al., 1997). Similar values are reported in other studies (Bogdanis et al., 1998; Gaitanos et al., 1993). $\Delta G'_{ATP}$ values are calculated as $\Delta G^{\circ\prime}_{ATP}$ + RT ln ([ADP]·[Pi] / [ATP]), using -30.5 kJ / mol for $\Delta G^{\circ\prime}_{ATP}$ and using 2.58 kJ / mol for RT at 37 °C. For simplicity, the calculated $\Delta G'_{ATP}$ values do not account for the relatively smaller effects of Mg^{2+} and H^+ binding to the metabolites (Iotti et al., 2005). The calculations also do not account for possible changes in the ratios of free : bound metabolites during exercise. For the estimated values in the absence of glycogen it is assumed that net consumption of PCr would produce an equimolar amount of Pi. It is also assumed that rates of ATP and PCr consumption would be unaffected by the absence of glycogen, but in actual muscle the rates of PCr consumption and ATP turnover would be suppressed by increased Pi (as occurs in McArdle disease). The rise in muscle Pi during strenuous exercise reduces the energy ($\Delta G'_{ATP}$) that can be obtained from ATP hydrolysis. Pi elevations in vigorously exercising muscle are normally buffered by sequestration in glycogen-derived hexose monophosphates and other glycolytic intermediates (Bendahan et al., 1990, 1992; Bogdanis et al., 1996, 1998; Gaitanos et al., 1993; Kappenstein et al., 2013), as illustrated in Fig. 3. In the absence of glycogen, the resulting greater increase in Pi correspondingly increases $\Delta G'_{ATP}$ and decreases work efficiency and capacity.

has a far greater relative effect on ADP levels (and thus on $\Delta G'_{ATP}$) than on ATP levels because the ratio of ADP : ATP is normally very low (Wallimann, 1994). It has therefore been proposed that the primary function of PCr under steady state conditions, i.e. no net change in ATP or PCr, is to maintain $\Delta G'_{ATP}$ at sites of ATP hydrolysis by buffering the local rise in ADP (Saks et al., 2007; Ventura-Clapier et al., 1987; Wallimann, 1994). However, the effects of PCr metabolism on $\Delta G'_{ATP}$ become more complex during net PCr consumption. Under these conditions, the phosphate moieties initially bound in PCr are eventually released as free Pi.



(7)

Given that muscle cells at rest contain over 25 mM PCr and less than 2 mM Pi, complete consumption of PCr with strenuous exercise could lead to > 10-fold increase in free Pi, with a commensurate effect on $\Delta G'_{ATP}$ (see Table 2). Under these conditions, glycogen utilization can work in tandem with PCr to preserve $\Delta G'_{ATP}$ by limiting the rise in both ADP and Pi that would otherwise occur (Fig. 3).



glycogen$_n$ + **Pi** → glycogen$_{n-1}$ + glucose-1-**phosphate** (8)

It is thus noteworthy that both astrocytes and skeletal myocytes contain high levels of cytosolic phosphocreatine (Lowe et al., 2013; Manos et al., 1991; Zhang et al., 2014), along with high levels of glycogen.

5.2. Importance of glycogen metabolism for maintaining $\Delta G'_{ATP}$ in muscle

Published measurements of metabolite concentration changes in exercising muscle permit a quantitative appraisal of the effect of glycogen utilization on $\Delta G'_{ATP}$ at the whole-cell level. As shown in Table 2, phosphate sequestration in glycogen-derived metabolites can be estimated to reduce the relative change in $\Delta G'_{ATP}$ by roughly 40 % (from 9.2 to 5.6 kJ /mol) during muscle exertion that nearly depletes PCr. This estimate is based on bulk tissue measurements, which necessarily underestimate the magnitude of local subcellular changes. Pi elevations in the immediate vicinity of rapid ATP - consuming processes are likely

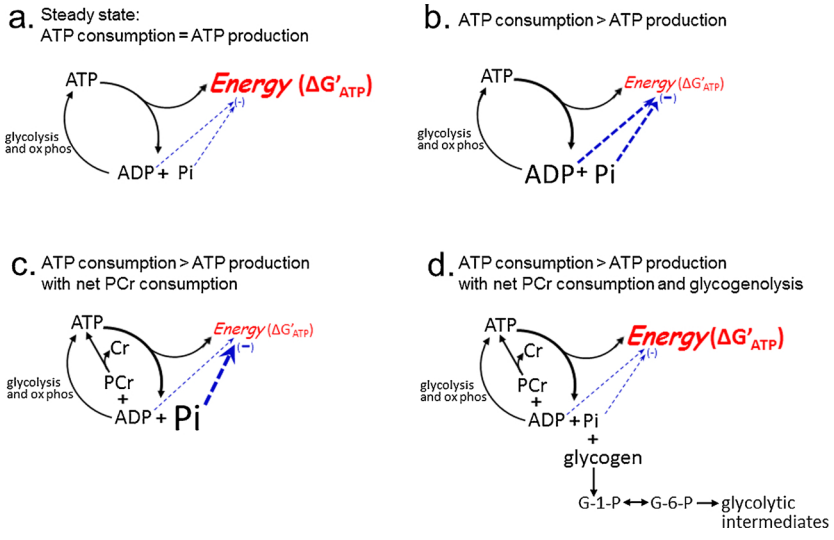


Fig. 3. Combined effects of glycogen and phosphocreatine on $\Delta G'_{ATP}$. The amount of energy obtained from the hydrolysis of each ATP molecule ($\Delta G'_{ATP}$) is reduced by elevations in either ADP or Pi. **a)** At steady state, ATP hydrolysis is matched by ATP re-synthesis through glycolysis and oxidative phosphorylation, with no net change in ATP or ADP concentrations. **b)** When ATP consumption exceeds the maximal rate of ATP re-synthesis, the resulting elevations in ADP and Pi reduce the amount of energy that can be obtained from each molecule of ATP. **c)** Cell types that contain cytosolic phosphocreatine (PCr) can consume PCr to convert ADP into ATP, thereby suppressing the rise in ADP. However, the effect of this ADP buffering on $\Delta G'_{ATP}$ is offset by a further increase in Pi as phosphate moieties in the newly formed ATP are subsequently released by ATP hydrolysis. Resting muscle contains approximately 26 mM PCr, 9 mM ATP, 1 mM ADP, and 1 mM Pi, such that complete consumption of PCr could increase Pi by over 20-fold (see Table 2). **d)** Glycogen metabolism to glucose-1-phosphate (G-1-P) removes Pi from the cytosol, thereby minimizing the effect of Pi on $\Delta G'_{ATP}$. G-1-P is in turn metabolized to glucose- 6-phosphate and other phosphorylated intermediates. In exercising muscle, phosphate remains trapped in these intermediates until ATP consumption rate falls below ATP synthesis rate and PCr levels are normalized.

faster and larger than estimated by the bulk tissue measurements, with a proportionately greater impact of Pi sequestration on subcellular $\Delta G'_{ATP}$ values. The increased efficiency provided by glycogen Pi sequestration also means that proportionately less ATP and energy substrates need be consumed to perform the same amount of work. To place these effects in context, even very small changes in work capacity can translate to significant differences in competitive advantage; e.g. the difference in the 100-meter sprint times between Olympic gold medalists and fourth place finishers is typically less than 1.5 %.

The thermodynamic effect of glycogen metabolism is also evidenced in McArdle disease, in which genetic deficiency in muscle glycogen phosphorylase (PGYM) prevents the utilization of skeletal muscle glycogen (Nogales-Gadea et al., 2016). Individuals with McArdle disease have no difficulty with moderate levels of exercise such as walking, but develop early onset muscle fatigue with strenuous exercise, followed by muscle cramps (sustained, electrically silent contractions) and myocyte disruption if exercise is continued. Importantly, the ATP concentration in exercising muscle of these individuals does not fall significantly lower than in normal subjects (or in resting muscle), but Pi concentrations rise faster and further than in normal muscle (Bendahan et al., 1992; Lofberg et al., 2001; Malucelli et al., 2011). This rise can be directly attributed to the absence of phosphate binding in glycogen-derived intermediates because, in contrast to normal muscle, the rise in Pi is nearly equimolar with the fall in PCr, and because there is no increase in phosphorylated glycolytic intermediates as in normal muscle (Bendahan et al., 1990, 1992; Rowland et al., 1965). These observations also indicate that glycogen is by far the primary mechanism used by myocytes to buffer Pi elevations.

The overall efficiency of muscle contraction – i.e. the work produced relative to the energy substrate consumed – is reduced in McArdle disease (O'Dochartaigh et al., 2004). Correspondingly, the calculated $\Delta G'_{ATP}$ in McArdle disease muscle is less negative (lower) after exercise than in normal muscle (Malucelli et al., 2011). McArdle disease muscle also forms inosine and ammonia with even moderate exercise (Kazemi-Esfarjani et al., 2002). Inosine and ammonia are products of AMP degradation, and their elevation after exercise is indicative of AMP formed by activation of adenylate kinase (Tullson and Terjung, 1991; see Text Box). While the adenylate kinase reaction generates only small increases in ATP, it generates a proportionately far greater reduction in ADP (given that ATP > > ADP), and thereby serves to maintain the normal $\Delta G'_{ATP}$. Activation of the adenylate kinase reaction thus illustrates the biological importance of maintaining muscle $\Delta G'_{ATP}$, because this incurs the unsustainable cost of depleting the total adenylate pool as (ATP + ADP + AMP) as AMP is degraded.

An additional feature of McArdle disease has long been unexplained: the absence of any net increase in lactate or H^+ production (aerobic glycolysis) in exercising muscle (Bendahan et al., 1992; Kazemi-Esfarjani et al., 2002; Lofberg et al., 2001), despite adequate glucose delivery (Berger et al., 1975; Hamrin and Henriksson, 2008; Hamrin et al., 2011; Henriksson and Knol, 2005; MacLean et al., 1999; Rosdahl et al., 1993), and even with induced hyperglycemia (Haller and Vissing, 2002; Lewis et al., 1985). Given that elevated Pi suppresses muscle contraction (Allen et al., 2002; Allen and Trajanovska, 2012), the failure to increase aerobic glycolysis may reflect a lack of metabolic demand induced by elevated Pi, rather than impaired capacity of the muscle fibers to increase use glucose utilization. This concept is supported by the strikingly attenuated increase in blood flow in exercising McArdle disease muscle (Jehenson et al., 1995), an observation that is difficult to explain except by reduced metabolic demand. Of interest, there is evidence for increased epilepsy incidence in McArdle disease (Mancuso et al., 2011), though otherwise there is no indication of brain dysfunction. This is presumably because astrocytes normally express the brain form of glycogen phosphorylase, PGYB, in addition to the muscle PGYM form.

The importance of maintaining $\Delta G'_{ATP}$ is most evident under extreme conditions such as intense exercise and McArdle disease, but it is relevant at all levels of energy metabolism to the extent that processes operating at an elevated (less negative) $\Delta G'_{ATP}$ must consume more substrate to achieve equal amounts of work. Moreover, as demonstrated with the skinned muscle fiber preparation, maximal force cannot be achieved in the absence of glycogen even when glucose, PCr, and ATP are available (Stephenson et al., 1999). Myosin ATPase is near thermodynamic equilibrium, meaning that the probability of forward movement of the actin/myosin motor is at all times influenced by existing the $\Delta G'_{ATP}$ (Astumian, 2010). This is similarly true of other ATPases, including the Na^+/K^+ ATPases that drive transmembrane ion transport in brain and other tissues (Ventura-Clapier et al., 1987; Wagoner and Dill, 2019; Wallimann, 1994). By contrast, the functions of these enzymes are minimally affected by the magnitude of changes in ATP concentration that occur under physiological conditions.

5.3. Importance of glycogen metabolism for maintaining $\Delta G'_{ATP}$ in brain

The functional effects of ΔG'ATP are more difficult to quantify in brain than in muscle, where fiber contraction provides a convenient read-out of work capacity, but evidence that glycogen metabolism is also required for optimal bioenergetic efficiency in brain comes from observations suggesting "glycolytic super-compensation" when glycogen metabolism is blocked. Glycolytic super-compensation describes an increase in glucose utilization above what is required to compensate for an absence of glucose mobilization from glycogen (Walls et al., 2009). Studies by Dienel and colleagues found that activity - induced increase in glucose utilization in rat sensory cortex was further increased by 1.7–2.9 fold by pharmacological inhibition of glycogen phosphorylase (Dienel et al., 2007). While the proportion of glucose consumed by astrocytes vs. neurons is uncertain, this result suggests a reduction in brain energetic efficiency in the absence of glycogen analogous to that observed in McArdle disease muscle (Malucelli et al., 2011; O'Dochartaigh et al., 2004).

There has been a long-standing interest in why glycogen is localized predominately to astrocytes rather than neurons. There has been less focus on why astrocytes also contain more PCr than neurons, but the answers to both questions may be gleaned by extrapolation from skeletal muscle. In muscle, PCr and glycogen are consumed during discrete episodes during which demand for ATP exceeds myocyte capacity to produce ATP. The thermodynamic role of glycogen as a Pi sink is particularly important in cells that have high levels of cytosolic PCr, because the net consumption of PCr during energy demand leads indirectly to equimolar release of free Pi (Fig. 3). Brain, like muscle, responds to rapid increases in energy demand in part by net consumption of PCr (Jost et al., 2002; Mora et al., 1991). While all cell types contain the ubiquitous mitochondrial creatine kinase, only certain tissues are enriched in cytosolic creatine kinase and cytosolic PCR. These tissues are skeletal muscle, which expresses the CKm isoform; brain, which expresses the CKb isoform; and heart, which expresses both isoforms. In brain, CKb is expressed at much higher levels in astrocytes than in neurons (Lowe et al., 2013; Manos et al., 1991; Zhang et al., 2014). The co-enrichment of cytosolic PCr and glycogen in astrocytes can thereby permit their coupled effects on $\Delta G'_{ATP}$ during intervals of rapid energy demand (Fig. 3).

Episodic energy demands on astrocytes are presumably caused by episodic activity of neighboring neurons, as supported by observations summarized in section 2.1. Glutamate is the primary excitatory neurotransmitter in mammalian brain, and it is removed from the extracellular space almost exclusively by re-uptake into astrocytes (Anderson and Swanson, 2000). Astrocytes maintain a glutamate concentration gradient of roughly 10,000:1 across their cell membranes through the activity of sodium-dependent glutamate transporters, which consume more than 2 ATP per molecule of glutamate transported against this gradient. It is thus significant that glycogen phosphorylase has been identified in a macromolecular assembly with the astrocyte glutamate transporter, GLT-1 (Genda et al., 2011). Neuronal post-synaptic

depolarizations and action potentials also release K^+ into small extracellular compartments, requiring immediate local, energy dependent K^+ uptake by astrocytes, which has been calculated to require an even greater astrocytic energy expenditure than glutamate uptake (DiNuzzo et al., 2017). Analogous to skeletal muscle, these demands on astrocytes are variable and episodic.

This alone does not, however, provide a clear explanation as to why neurons do *not* contain glycogen or high cytosolic PCr levels, given that neurons have higher energy requirements than astrocytes on average (Harris et al., 2012), and often exhibit short bursts of activity. However, these activity bursts may not necessarily require corresponding episodic bursts of neuronal energy metabolism. Measurements from cortical slices show that burst activation of neurons produces a small decrement in intracellular astrocyte glucose content, as expected, but no detectable decrease in intracellular neuronal glucose content (Mächler et al., 2019). The differing response by neurons may follow from the electrogenic distribution of neuronal repolarization over the entire neuronal surface area. The energy cost of neuronal action potentials and depolarizations occurs with the active ion transport required for membrane repolarization. Since the membrane potential is maintained over the entire surface of the neuron, the energy demand induced by repolarization after intervals of neuronal activity is distributed both spatially and temporally. By contrast, the uptake of glutamate and K^+ by astrocytes is only minimally electrogenic (Anderson and Swanson, 2000), and requires immediate, local activation of Na^+/K^+ ATPase in order to maintain the local transmembrane Na^+ gradient that drives active transport. It should also be noted that evidence from cell culture and other studies indicate that mammalian neurons do contain some glycogen (Duran et al., 2019; Pfeiffer-Guglielmi et al., 2014; Saez et al., 2014). In fact, some neuronal populations contain histochemically demonstrable glycogen comparable to that present in astrocytes (Borke and Nau, 1984; Oe et al., 2016; Saez et al., 2014). It would be of interest to know whether the activity pattern of these neuronal populations is distinctive.

A second reason that astrocytes rather than neurons require glycogen and PCr may stem from the unique aspects of astrocyte anatomy. Roughly 80 % of astrocyte surface area consists of threadlike filopodia (~0.2 μm wide) and equally thin, sheet-like lamellipodia that ensheath neuronal elements (Grosche et al., 1999; Hertz et al., 2007). These thin processes perform most astrocyte active transport, but are too narrow to contain mitochondria. Reduced mitochondrial density or proximity renders it easier for ATP consumption to outstrip ATP synthesis in these fine processes. Moreover, the spatial constraints of these processes may also limit the rate at which ADP and Pi can diffuse away from sites of ATP consumption, thereby increasing the need for local buffering.

6. Summary

There is little question that glycogen can serve as an emergency energy store in brain, that astrocyte glycogen utilization can spare glucose for neuronal use, and that lactate generated by astrocyte glycogenolysis can subsequently be used by neurons (or other cells) for oxidative energy metabolism. There is similarly little question that glycogen in muscle can serve as a local glucose reserve. However, these functions do not adequately account for several other aspects of glycogen metabolism in brain and muscle: specifically that 1) in both tissues, glycogen is metabolized even when glucose is available, despite the net ATP cost of glycogen use; (2) in both tissues, evidence suggests a reduced energetic efficiency in the absence of glycogen; (3) in both tissues, glycogen is co-localized with elevated levels of cytosolic PCr; and (4) muscle deficient in glycogen phosphorylase (McArdle disease) fails to increase glycolytic metabolism or local blood flow, but instead activates the adenylate kinase reaction to lower ADP levels. Each of these aspects of glycogen metabolism can be understood by the thermodynamic considerations presented here. The thermodynamic view holds that it is equally or more important for cells to maintain the amount of energy derived from ATP hydrolysis as to maintain ATP concentrations, because cells with less negative $\Delta G'_{ATP}$ have reduced maximal work capacity and must consume more ATP to do equivalent work. $\Delta G'_{ATP}$ is increased when ADP or Pi increase, and this can occur in cells (or in subcellular domains) that must transiently utilize ATP faster that it can be regenerated. The coupled metabolism of glycogen and PCr buffers elevations in Pi and ADP, and thereby maintains a maximal energy yield from ATP hydrolysis. This effect may be particularly important in subcellular domains such as thin astrocyte processes, where simple diffusion may be insufficient to quickly dissipate local Pi and ADP elevations during intervals of rapid ATP consumption.

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Appendix A. The Peer Review Overview and Supplementary data

The Peer Review Overview and Supplementary data associated with this article can be found in the online version: https://doi.org/10.1016/j.pneurobio.2020.101787.

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