Technical and comparative aspects of brain glycogen metabolism

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Original submission Jan 10, 2019; Revised submission April 14, 2019

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Abstract

It has been known for over 50 years that brain has significant glycogen stores, but the physiological function of this energy reserve remains uncertain. This uncertainty stems in part from several technical challenges inherent in the study of brain glycogen metabolism, and may also stem from some conceptual limitations. Factors presenting technical challenges include low glycogen content in brain, non-homogenous labeling of glycogen by radiotracers, rapid glycogenolysis during postmortem tissue handling, and effects of the stress response on brain glycogen turnover. Here, we briefly review aspects of glycogen structure and metabolism that bear on these technical challenges, and discuss ways these can be overcome. We also highlight physiological aspects of glycogen metabolism that limit the conditions under which glycogen metabolism can be useful or advantageous over glucose metabolism. Comparisons with glycogen metabolism in skeletal muscle provide an additional perspective on potential functions of glycogen in brain.

1. Introduction

It has been known for over 50 years that brain has significant glycogen stores, but the physiological function of this energy reserve remains uncertain. This uncertainty stems in part from several technical difficulties inherent in the study of brain glycogen metabolism, and may also stem from some conceptual limitations. This chapter will briefly outline basic structural and bioenergetic aspects of glycogen metabolism, discuss how these lead to certain technical challenges for the study of brain glycogen, and compare what is known about glycogen metabolism in brain with skeletal muscle.

2. Glycogen structure and distribution

Glycogen is a large, branched polymer of glucose. The polymer form eliminates the high osmolarity that would result from an equimolar concentration of free glucose. It also protects the otherwise free "reducing" ends of glucose from auto-oxidation (Figure 1), and provides a means of intracellular localization of the energy store. Glycogen polymers are roughly spherical and organized into concentric tiers, with the inner tiers composed by chains that normally contain two branches, and the outer tiers composed of unbranched chains (Gunja-Smith et al. 1970). The linear chains of glucose residues are joined by α-1,4-glycosidic bonds, with branch points at approximately every 10 - 14 glucose residues linked by α-1,6-glycosidic bonds (Calder 1991). The exposed ends of all glycogen chains are non-reducing. Mathematical modeling suggests that the size of a glycogen molecule is limited to 12 tiers, which means a total of approximately 53,000 glucose residues and a radius of 21 nm. In accordance with this modeling, the glycogen particles found in the mouse brain and resting human skeletal muscle ranged from 10 to 44 nm in diameter (Cataldo and Broadwell 1986; Wender et al. 2000; Marchand et al. 2002). The average diameter of these glycogen particles is 20 - 30 nm, which is estimated to be 7 - 8 tiers (Goldsmith et al. 1982; Melendez-Hevia et al. 1993).

Glycogen polymers ("granules") are present in the cytosol, endoplasmic reticulum (ER)/ sarcoplasmic reticulum (SR) and lysosomes (Cardell 1977; Stapleton et al. 2010; Geddes et al. 1992). In liver cells, approximately 10% of all glycogen particles are found in lysosomes (Jiang et al. 2010), where they undergo slow degradation by acid maltase. Almost all tissues contain some detectable glycogen, but the relative amounts of glycogen vary enormously. Glycogen levels in the adult rat under physiological conditions are as follows: liver >> skeletal muscle > cardiac muscle > brain > kidney (Table 1). Glycogen in mammalian brain is localized primarily to astrocytes (Cali et al. 2016; Cataldo and Broadwell 1986; Wender et al. 2000; Koizumi 1974), but much smaller amounts are also found in meningeal cells, endothelial cells, and other cell types. Neurons contain appreciable amounts of glycogen during

development, but this falls to very low levels in the mature brain except in certain brainstem neurons (Koizumi 1974; Ibrahim 1975; Cavalcante et al. 1996; Saez et al. 2014; Cataldo and Broadwell 1986; Borke and Nau 1984; Oe et al. 2016).

3. Glycogen metabolism

The synthesis of a *de novo* glycogen granule is thought to be initiated by glycognenin, although recent studies with glycogenin deficient mice indicate other mechanisms of glycogen initiation are likely possible (Testoni et al. 2017). Glycogenin glycosylates itself at a tyrosine residue and catalyzes the extension of glucan chains (Smythe and Cohen 1991; Cao et al. 1993). The glucan chains serve as primer for glycogen synthetase, which catalyzes the formation of α-1, 4-glycosidic linkages of glycogen. Glycogen synthesis requires uridine diphosphate glucose (UDP-glucose) as a substrate, which is formed from uridine triphosphate and glucose 1-phosphate by UDP-glucose pyrophosphorylase (Figure 2). α-1, 6-glycosidic branch points are subsequently produced by glycogen branching enzyme (1,4-alpha-glucan-branching enzyme) at approximately every 12 glucose residues.

Glycogenolysis is mediated by glycogen phosphorylase, which hydrolyzes glucose residues at α-1, 4 linkage points to generate glucose 1-phosphate. Glycogen debranching enzyme linearizes glycogen chains near the α-1, 6 branch points to provide linear substrate for glycogen phosphorylase (Nakayama et al. 2001). Glycogen phosphorylase is thought to be the rate limiting enzyme in glycogen breakdown. The activity of glycogen phosphorylase is regulated by changes in energy state through allosteric actions of AMP, which accelerates activity; and by ATP and glucose-6-phosphate, which slow enzymatic activity. Glycogen phosphorylase is also regulated by its phosphorylation state, through the action of glycogen phosphorylase kinase. Glycogen phosphorylase kinase is in turn regulated by a variety of signaling pathways through phosphorylation and allosteric interactions. These regulatory actions provide a mechanism for "anticipatory" glycogen mobilization to prevent any actual decline of cellular energy state. For example, glycogen phosphorylase kinase is activated by epinephrine through epinephrine-induced elevations in cAMP and activation of protein kinase A. Glycogen phosphorylase kinase can also be partly activated by elevated levels of Ca^{2+}, via binding to its calmodulin subunit. This mechanism is particularly important in skeletal muscle where muscle contraction triggers the release of Ca^{2+} from the sarcoplasmic reticulum.

Glycogen phosphorylase liberates glucose residues from glycogen as glucose-1-phosphate, which is freely converted to glucose-6 phosphate (Figure 2). The shuttling of each glucose moiety on and off glycogen requires one ATP equivalent (consumed at the UDP pyrophosphorylation step). This

bioenergetic expense has implications for the potential physiological functions of brain glycogen, as discussed later in this chapter. It may also be significant that formation of glucose-6 phosphate from glycogen does not consume ATP, unlike the initial hexokinase step of glycolysis.

4. Brain-specific aspects of glycogen metabolism

Although neurons are thought to be the primary energy consuming cells in brain, astrocytes contain the vast majority of brain glycogen. Electron microscopy identifies glycogen granules throughout astrocyte cell bodies and processes, particularly near around axonal boutons and dendritic spines (Cali et al. 2016). Glutamate uptake is an energy-intensive astrocyte function, and interestingly glycogen phosphorylase has been found to be associated with the astrocyte glutamate transporter, GLT-1 (Genda et al. 2011). Astrocyte glycogen is quickly degraded under conditions of energy failure (Swanson et al. 1989; Suh et al. 2007a; Lowry et al. 1964), as would be expected. Glycogen metabolism in astrocytes is also induced by a several neurotransmitters and other signaling molecules, including vasoactive intestinal peptide (VIP), noradrenaline, arachidonic acid, glutamate, cAMP, and K^+ (Magistretti 1988; Sorg et al. 1995; Cummins et al. 1983; Cambray-Deakin et al. 1988a, b; Subbarao et al. 1995; Subbarao and Hertz 1990; Walls et al. 2009). These signaling molecules serve to couple astrocyte glycogen metabolism to neuronal activity. For VIP and noradrenaline in particular, the anatomical organization of these inputs provides a framework for coordinated signaling. The narrow radial pattern of arborization of intracortical VIP neuron and the tangential intracortical trajectory of the noradrenergic fibers suggests that these two systems may function in a complementary fashion: VIP regulating energy metabolism locally, within individual columnar modules, and norepinephrine exerting a more global effect (Magistretti et al. 1981).

Direct autoradiographic and biochemical measures of glycogen turnover show it to be increased by sensory neuron stimulation in the awake rat (Swanson et al. 1992; Dienel et al. 2007). Conversely, conditions causing focally or globally reduced neuronal activity lead to a corresponding local or global increases in glycogen content, suggesting reduced glycogen utilization (Swanson 1992b). These conditions include focal brain injury, anesthetics, slow wave sleep, and hibernation (Pudenz et al. 1975; Nelson et al. 1968; Phelps 1972; Watanabe and Passonneau 1973; Swanson 1992b).

5. Experimental and technical considerations in study of brain glycogen

Low glycogen content in brain. Several aspects of glycogen structure and regulation in brain pose unique challenges for experimental observation. First among these is the relatively low concentration of

glycogen in brain. Many of the classical histochemical methods for detecting glycogen were developed using liver or muscle tissues, in which glycogen content is far higher than in brain. For example, the periodic acid schiff (PAS) method of staining polysaccharides works well in liver and muscle, but it in brain the low glycogen content and relatively higher content of glycoproteins and glycolipids, which also react with PAS, makes this approach less useful, even when coupled with dimedone blocking of aldehydes (Cammermeyer and Fenton 1981). Immunohistochemical methods using glycogen antibodies are far more sensitive (Oe et al. 2016). Nonspecific glycogen labeling by either of these methods can be identified as label that persists in tissues after digestion with amylase or rendered ischemic for a few minutes prior to fixation. Low glycogen levels similarly pose a challenge for magnetic resonance studies of glycogen, as recently reviewed (Soares et al. 2017).

Use of radiotracers to assess glycogen turnover. A challenge common to many studies of metabolism is that there is no fixed relationship between the metabolite flux and measured metabolite concentrations. Glycogen turnover in particular — i.e. the breakdown and resynthesis of individual glycogen molecules — may accelerate, decelerate, or stop altogether with little or no change in net glycogen content (Figure 3). Radiolabeled or isotope enriched substrates are therefore widely used for assessments of metabolic rates. However, accurate quantification by these approaches requires that the labeled molecules be homogenously distributed among the unlabeled molecules. This is difficult to achieve in glycogen because individual glucose moieties are sequentially added to and removed from the outer glycogen tiers, and have widely variable dwell times in the glycogen polymer (Youn and Bergman 1987; Elsner et al. 2002). The relationships between rates of glycogenolysis and label release therefore depend upon the patterns of glycogen synthesis and breakdown at the level of individual glycogen granules (as diagrammed in Figure 4). These limitations do not render assessments of glycogen turnover impossible, but they do limit the precision of these measures and often require certain assumptions. For example, very prolonged administration of tracers can be used to improve homogeneity of glycogen labeling, and this can be further refined by modeling patterns of glycogen turnover (DiNuzzo 2013; Oz et al. 2015; Soares et al. 2017).

The use of radiolabeled glucose to monitor glycogen metabolism is also complicated by the fact that normal glucose metabolism rapidly distributes the label to amino acids, lipids and many other cell constituents other than glycogen. This problem can be surmounted in part by physical isolation of glycogen prior to isotope analysis, or by the use of 2-deoxyglucose, which is incorporated into and released from glycogen but is much more slowly metabolized to other molecules (Nelson et al. 1984; Kai

Kai and Pentreath 1981). Glucose labeled at the 3 or 4 carbon positions also mitigates this problem (Swanson et al. 1992), because glucose entering the tricarboxylic acid cycle (from which most other metabolites are formed) loses the 3 and 4 carbons in the pyruvate dehydrogenase reaction. In vivo magnetic resonance spectroscopy studies can in some cases use native ^{13}C abundance to assess brain glycogen concentrations, but the low abundance of ^{13}C coupled with low concentrations of glycogen in brain currently limit the temporal and spatial resolution of this approach (Soares et al. 2017).

Rapid post-mortem glycogenolysis. Glycogenolysis is triggered by very small elevations in AMP, befitting its role as an emergency energy store. This process begins almost instantly with cessation of blood flow, and continues until the brain is frozen, acidified, or otherwise treated to inactivate glycogen phosphorylase. (For frozen brains, the process resumes upon thawing unless other measures are also taken.) This presents a major challenge to histochemical detection of glycogen, particularly with the low concentration of glycogen in brain. Post-mortem glycogenolysis can be prevented by "funnel freezing" with direct application of liquid nitrogen to the animal skull (Ponten et al. 1973; Dienel et al. 2002), or more conveniently by high-energy microwave fixation of brain *in situ*, in which brain temperature is elevated to levels that denature glycogen metabolizing enzymes within 1 second or less (Medina et al. 1975; Sagar et al. 1987). The microwave approach has limitations, however. The high heat induced by and required for microwave fixation can reduce the water content of the brain, thus artificially elevating the glycogen content expressed per gram wet weight. This can be avoided by normalizing to mg protein rather than to wet weight, but special care must be taken to ensure that the fixed (denatured) protein is fully solubilized for protein determination. Failure to correct for brain dehydration or fully solubilize proteins leads to erroneously elevated glycogen measurements in microwave fixed brain (Swanson and Sagar, unpublished observations). A second limitation is that the heating and water vapor formation often distort normal cell architecture and destroy immunoreactivity of many antigens; however, these problems can be overcome by careful titration of microwave power (Oe et al. 2016; Oe et al., this volume).

It is often useful to express glycogen measurements in terms of glucose molecule equivalents. The molecular weight of glucose is 180.16 g/ mol; however, the molecular weight of each glucose moiety in glycogen is somewhat less, because the glycosidic linkages between the glucose moieties in glycogen each subtract the equivalent of one H_2O from their molecular weight. There is one α-1,4 glycosidic bond between each glucose moiety in the linear chains, and there is in addition one α-1,6 glycosidic bond at each branch point, which occurs approximately every tenth glucose residue. The calculated molecular

weight for glycogen can thus be estimated to be 160.3 g/ mol glucose equivalent. The true value will vary slightly depending upon the degree of polymer branching.

Hormonal and neurotransmitter effects on glycogenolysis. This aspect of glycogen metabolism may be uniquely problematic for studies of glycogen in brain because it involves sensory experience of the subject. There is a generally inverse relationship between neuronal activity and glycogen levels, as evidenced by elevated brain glycogen levels during anesthesia, hibernation, and slow wave sleep. Conversely, as outlined above, glycogen phosphorylase is activated by a number of signaling molecules to initiate glycogenolysis in anticipation of actual energy demand. For example, epinephrine and norepinephrine released during the stress response are potent glycogenolytic signaling molecules. It follows that animals that are stressed during the interval before brain harvest may have regionally lower brain glycogen levels than non-stressed animals. Experimental evidence supports this concern (Cruz and Dienel 2002). This observation suggests that, like glucose utilization, glycogen levels and turnover rates are likely influenced in a regionally discrete manner by the subject experience and response near the time of the observation.

6. Physiological functions of glycogen in brain

Function under energy failure conditions. There is no question that glycogen can serve as an energy reserve in brain. Electrophysiology experiments using optic nerve and corpus callosum have shown that astrocyte glycogen can sustain axon function during glucose deprivation or during high frequency stimulation (Wender et al. 2000; Brown et al. 2005; Brown et al. 2012). These and other studies also suggest that lactate or pyruvate derived from astrocyte glycogen can be used by neurons for oxidative metabolism (Dringen et al. 1993; Poitry-Yamate et al. 1995; Pellerin et al. 1998; Tekkok et al. 2005). Other studies have demonstrated that increased glycogen in astrocytes improves survival of neurons under conditions of oxygen deprivation or glucose deprivation, both in culture and *in vivo*.

The total glycogen store in brain is approximately 3 mM (as expressed in glucose equivalents). Given estimates of basal brain glucose utilization rate (Sokoloff et al. 1977), this amount of glycogen would be expected to fuel brain metabolism for less than 15 minutes if it were the only energy supply available. However, there is a compensatory reduction in the rate of glucose utilization and synaptic activity during energy compromise (Suda et al. 1990). In addition, it is rare to have a complete absence of other energy metabolites. During severe insulin-induced hypoglycemia, for example, the flux of glucose from blood to

brain is reduced but not zero, and brain glycogen is consumed very gradually (Ratcheson et al. 1981; Choi et al. 2003). A quantitative analysis suggests that normal levels of astrocyte glycogen should be able to support brain metabolism for about 100 minutes during hypoglycemia (Gruetter 2003). In agreement with this assessment, an experimental study demonstrated that an 80% increase in rat brain glycogen at the onset of severe hypoglycemia extended the period of brain electrical activity by 90 minutes (Suh et al. 2007b). The rats with elevated initial brain glycogen concentrations also had improved neuronal survival.

Glycogen is far less useful as an energy store in brain under ischemic conditions, in which only anaerobic (glycolytic) energy metabolism is possible. Under these conditions each glucose molecule stored in glycogen can generate only 3 ATP, as opposed to the 34-36 ATP generated under aerobic conditions. Accordingly, glycogen stores are very rapidly depleted (within 3 minutes) during complete ischemia (Lowry et al. 1964). Moreover, there is no possibility of transferring usable energy substrates from astrocytes to neurons under anoxic conditions because substrates that can exit from astrocytes, such as lactate and pyruvate, can only be metabolized aerobically. However in focal ischemia (as results from occlusion of a cerebral artery), there is often a border zone area with partially preserved blood supply in which energy metabolism is barely adequate to maintain cell viability. Spreading depression from the ischemic core can strikingly increase energy demands in this "penumbra" area and exacerbate ischemic injury (von Bornstadt et al. 2015). Astrocyte glycogen stores are rapidly consumed during spreading depression (Feuerstein et al. 2016), and increased glycogen stores delay its advancing wave front (Seidel and Shuttleworth 2011). A study of focal brain ischemia showed reduced infarct size in rats that had elevated brain glycogen content (Swanson et al. 1990).

While the aggregate evidence that glycogen can serve as an emergency energy store in brain is convincing, it nevertheless does not establish this as the physiological, evolutionarily directed function of brain glycogen. (As an analogy, the catabolism of skeletal muscle to support nutrition during extreme starvation does not demonstrate this as the primary function of muscle.) In fact, several aspects of brain glycogen are poorly explained by this interpretation. These include the continuous turnover of brain glycogen under normal conditions; the complex neuromodulatory influences that promote astrocyte glycogenolysis in the absence of energy failure; and perhaps most fundamentally, the location of glycogen in astrocytes rather than in neurons.

Given the energetic cost of shuttling glucose into and out of glycogen polymers, it is useful to delineate the conditions under which this might carry advantages over direct glucose utilization. One obvious condition would be to provide buffering for transient, local insufficiencies in glucose supply, as might happen for example in the brief interval between a burst of neuronal activity and subsequent

increase in local blood flow (Figure. 3). This idea was proposed by Swanson (Swanson 1992a) and more formally developed by Shulman and colleagues as the "glycogen shunt" hypothesis (Shulman et al. 2001; Shulman and Rothman 2001). A related idea proposes that astrocyte glycogenolysis occurs preemptively in activated tissues as a glucose sparing mechanism, to prevent reduction in available glucose that would otherwise occur (Dienel and Cruz 2015; DiNuzzo et al. 2010). Although these concepts have gained wide support, there is uncertainty as to when or if such a transient glucose insufficiency occurs under physiological conditions. Glucose concentration will not become rate-limiting for energy metabolism unless it falls near the glucose Km of hexokinase, which is less than 0.1 mM (Thompson and Bachelard 1977). Glucose concentration in normal rodent brain is approximately 2-2.5 mM, which can also be taken as the approximate concentration of glucose in the intracellular space. (Values for humans are about 30% lower). Can neuronal activity outstrip supply to the extent that local glucose concentrations fall near the hexokinase Km value? The classic study by Silver and Ericińska (Silver and Erecinska 1994) showed that spreading depression, which causes nearly simultaneous bursting of neurons at its wave front, reduced extracellular glucose concentrations from 2.4 mM to 2 mM, a value well above the hexokinase Km. Similarly, studies of brain energy metabolites during pentylenetetrazole-induced status epilepticus showed reductions in brain glucose concentration to no lower than 0.9 mM (McCandless et al. 1987; Folbergrova et al. 1985; Ingvar et al. 1984), excluding settings in which cerebral blood flow was impaired. Though not definitive, these results obtained using spreading depression and seizure activity, both of which massively increase brain energy demands, cast some doubt on the concept that changes in brain glucose utilization resulting from normal activity could require buffering by local mobilization of glycogen stores.

7. Comparisons to liver and skeletal muscle

Assessment of glycogen functions in other tissues may suggest alternative possible roles for glycogen utilization in brain. Liver has a specialized role as a glycogen storage depot for systemic use. Hepatocytes express high concentrations of glucose-6-phosphatase for liberating free glucose into the blood circulation for use by other organs. However, astrocytes do not have high levels of glucose-6-phosphatase, and it follows that astrocytes do not have a role analogous to hepatocytes as a store of free glucose for use by other cells. Skeletal muscle contains glycogen levels intermediate between liver and brain, and like brain the stored glycogen in muscle undergoes continuous turnover and is not released to the systemic circulation. Skeletal muscle fiber types can be classified as Type 1 "red" or Type 2 "white", with the red fibers containing far more mitochondria and white fibers containing far more glycogen (Nielsen et al. 2011). The Type 2 white fibers contract more quickly but fatigue more rapidly than Type 1 red fibers.

Muscle glycogen turnover increases during exercise (Nielsen et al. 2011; Shulman and Rothman 2001), similar to the glycogen turnover increase induced by neuronal activity in brain. However, contracting muscle has repetitive intervals of ischemia corresponding to muscle contractions, during which glycolytic metabolism is essential for ATP production, and this does not have a correlate in brain. Moreover, glycogen in muscle is localized to the contacting myocytes themselves, and there is no evidence that glycogen is metabolized in one cell to fuel activity in another cell as has been proposed to occur in brain.

Muscle fatigue correlates with glycogen depletion (Allen et al. 2008; Matsui et al. this volume), but, surprisingly, the mechanistic link between these events has not been established (Allen et al. 2008; Ortenblad et al., 2013). This point is exemplified by observations in McCardle's disease, an inherited condition caused by a genetic deficiency in muscle glycogen phosphorylase. Individuals with MCardle's disease are generally well, but develop early fatigue with exercise. This occurs even though myocyte glucose levels *increase* with exercise (MacLean et al. 1999; Sahlin, 1990). Moreover, muscle performance in McCardle's disease is not significantly improved by hyperglycemia, as should occur if glycogen serves only to buffer intervals of reduced glucose availability. The biochemical defect in these muscles appears not to be a simple lack of glycolytic substrate, but rather a reduced capacity to sequester inorganic phosphate along with other changes that reduce the free energy ($\Delta G'$) provided by ATP hydrolysis (Malucelli et al. 2011).

8. Summary

Studies of brain glycogen metabolism are complicated by factors that stem directly from specific structural and regulatory features of glycogen. These factors must be addressed and considered in interpreting study results. Bioenergetic aspects of glycogen metabolism place certain constraints on the settings under which glycogen utilization may be advantageous to brain. These aspects, in conjunction with some aspects of muscle glycogen metabolism, suggest that current concepts of brain glycogen physiology may need to be expanded.

Table 1

Tissue	Glycogen (mg/g tissue)	Citation
Liver	30.23 ± 2.5	Vissing et al. 1989
Liver	43.12 ± 5.5 *	Kusunoki et al. 2002
Liver	32.3 ± 2.0	Khandelwal et al. 1979
Heart	4.51 ± 0.33	Vissing et al. 1989
Heart	4.16 ± 0.23	Conlee et al. 1989
Kidney	0.06 ± 0.01	Khandelwal et al. 1979
Kidney	0.03 ± 0.01 *	Nannipieri et al. 2001
Muscle (GPS) [c]	5.94 ± 0.25 [a]	Baker et al. 2005
Muscle (white gastrocnemius)	5.79 ± 0.72	Garetto et al. 1984
Muscle (white gastrocnemius)	7.01 ± 0.17	Vissing et al. 1989
Brain (cortex)	0.68 ± 0.03 [b]	Sagar et al. 1987
Brain (cortex)	0.60 ± 0.03	Kong et al. 2002
Brain (cortex)	2.09 ± 0.27 *	Cruz and Dienel 2002
Brain (whole brain)	2.06 ± 0.21	Oe et al. 2016

Glycogen content in adult rat or mouse tissues under physiological conditions were shown in the table. Data are reported as means ± SD (*) or means ± SEM.

[a] Reported as mmol/kg dry weight; converted here using values of 160.3 mg /mmol as molecular weight of glycogen and 76% as the water content of muscle (Pivarnik and Palmer 1994).

[b] Reported as mmol/mg protein; converted here using values of 122 mg protein / gram wet weight in brain (Banay-Schwartz et al. 1992).

[c] GPS: gastrocnemius-plantaris-soleus muscle complex

Figure Legends

Figure 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 around 30,000 glucose units. The individual glucose moieties of glycogen are linked by α-1, 4 -glycosidic bonds, with branch points at approximately every 12 glucose residues linked by α-1, 6-glycosidic bonds. The exposed ends of all glycogen chains are non-reducing. Image from (Haggstrom 2014)

Figure 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. Glycogen degradation is mediated by debranching enzyme and glycogen phosphorylase. Glycogen phosphorylase is regulated allosterically in response to hormones, e.g. norepinephrine and vasoactive intestinal peptide (VIP); by changes in energy state (AMP, glucose-6-phosphate (G6P), 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 2ATP equivalents are consumed in forming UDP glucose from glucose-1-phosphate and 1 ATP equivalent is gained back at the formation of glucose-1-phosphate from a glucose residue and inorganic phosphate (Pi) at the glycogen phosphorylase step.

Figure 3. Schematic relationship between neuronal activity and astrocyte glycogen metabolism. Short bursts of neuronal activity induce mobilization of astrocyte glycogen. The glycogen is resynthesized between bursts, resulting in glycogen turnover with no net change in glycogen content over time. It has been proposed that glycogenolysis is triggered by neuronal activity to provide substrate for increased glycolytic demand over intervals too short to be met by changes in local blood flow.

Figure 4. Results of radiolabeling tracer experiments are influenced by the mode of glycogen polymer growth and breakdown. Schematic diagram showing distribution in glycogen of labeled glucose (filled circles) injected early during glycogen synthesis. Each column of circles represents an

individual glycogen polymer. In one scenario, all polymers simultaneously add glucose moieties. In the opposite scenario, each polymer is synthesized to its maximum size before a second one begins to expand. Many other intermediates or more complex patterns are also possible, as are differing patterns of glycogen polymer breakdown. These differing patterns produce a different relationship between rates of glycogen turnover and rates of label release. Redrawn from (Youn and Bergman 1987).

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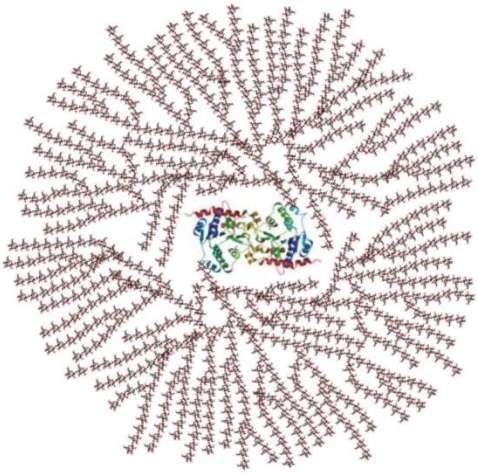
Figure 1



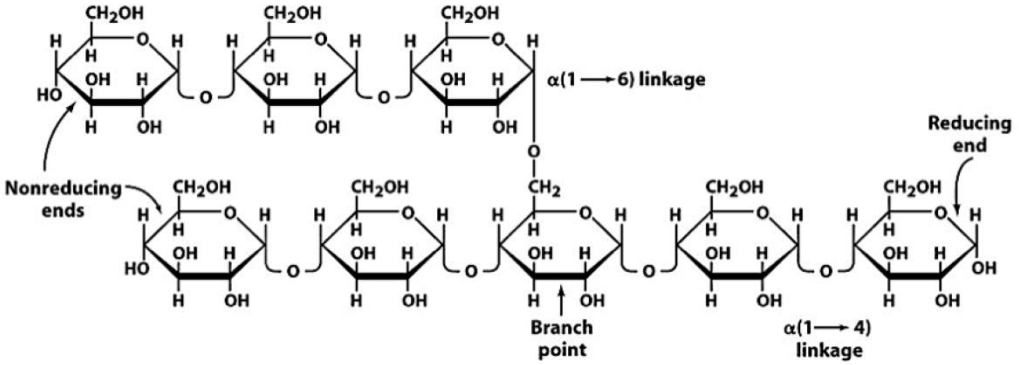

Nonreducing ends
α(1 → 6) linkage
Reducing end
Branch point
α(1 → 4) linkage

Figure 2

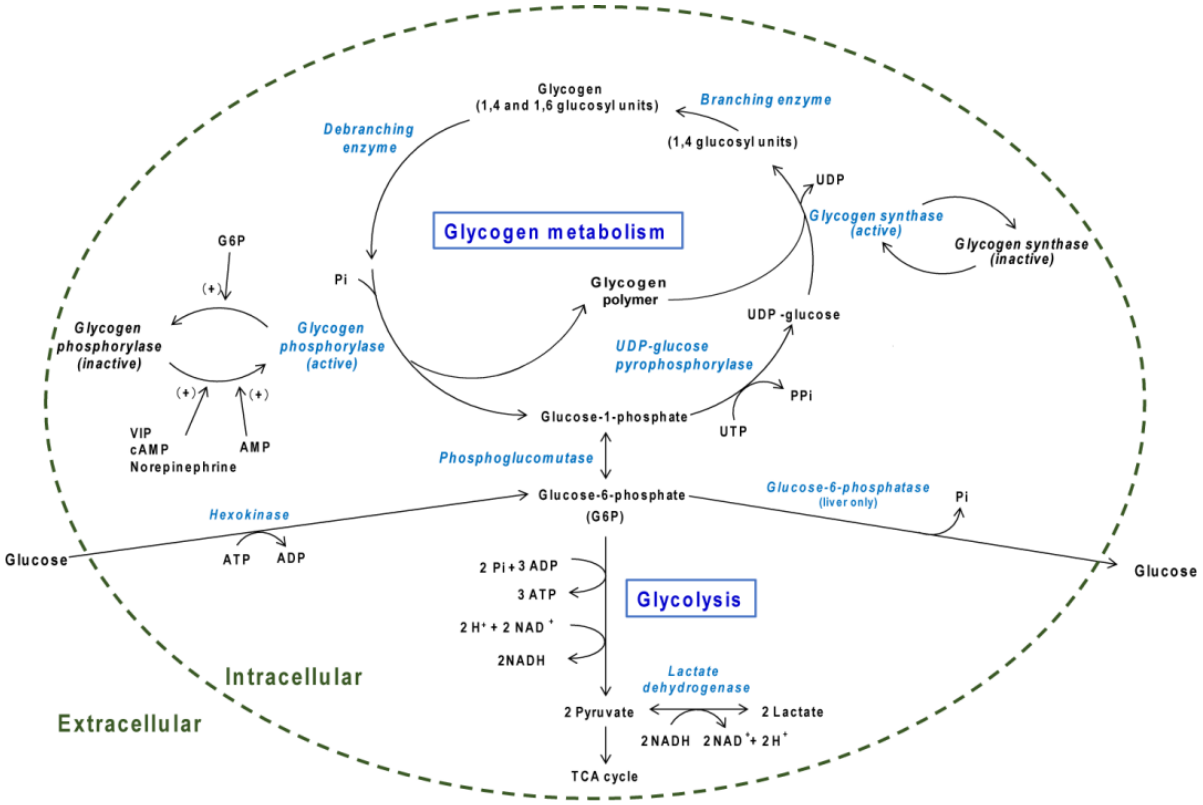

Glycogen
(1,4 and 1,6 glucosyl units)
Branching enzyme
(1,4 glucosyl units)
Debranching enzyme
UDP
Glycogen synthase (active)
Glycogen synthase (inactive)
Glycogen metabolism
G6P
Pi
Glycogen polymer
UDP -glucose
Glycogen phosphorylase (inactive)
Glycogen phosphorylase (active)
UDP-glucose pyrophosphorylase
PPi
UTP
VIP
cAMP
Norepinephrine
AMP
Glucose-1-phosphate
Phosphoglucomutase
Glucose-6-phosphate
(G6P)
Glucose-6-phosphatase
(liver only)
Pi
Hexokinase
ATP
ADP
Glucose
Glucose
2 Pi + 3 ADP
3 ATP
Glycolysis
2 H+ + 2 NAD+
2NADH
Lactate dehydrogenase
2 Pyruvate
2 Lactate
2NADH
2NAD+ + 2H+
TCA cycle
Intracellular
Extracellular

Figure 3

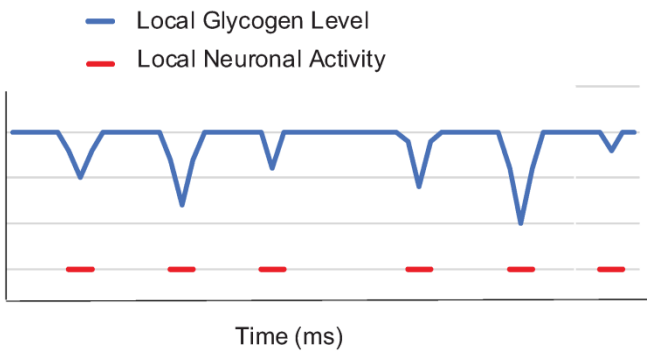
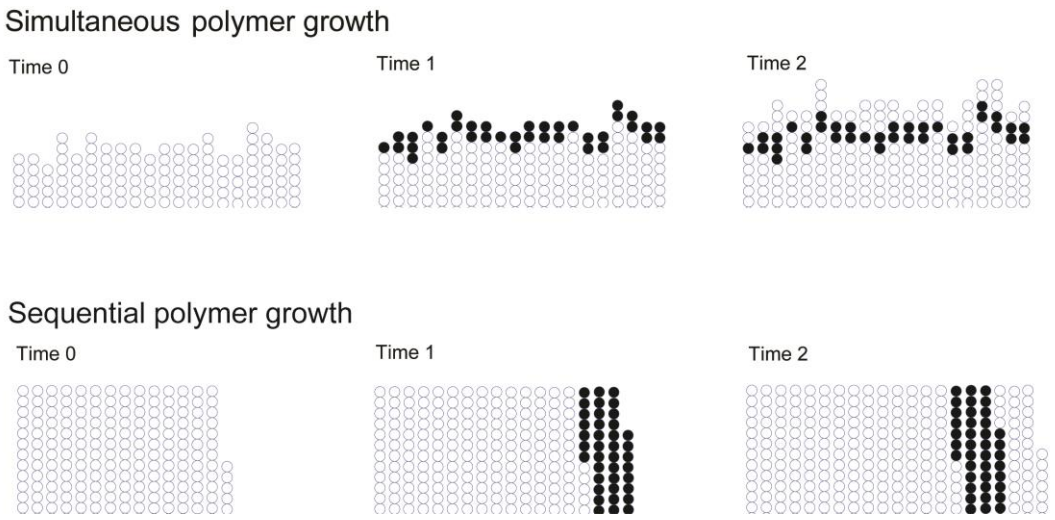


Figure 4.


Simultaneous polymer growth
Time 0
Time 1
Time 2
Sequential polymer growth
Time 0
Time 1
Time 2