



Astrocytic glycogen metabolism in the healthy and diseased brain

Published, Papers in Press, March 23, 2018, DOI 10.1074/jbc.R117.803239

Lasse K. Bak^{1,2}, Anne B. Walls^{1,3}, Arne Schousboe, and Helle S. Waagepetersen

From the Department of Drug Design and Pharmacology, Faculty of Health and Medical Sciences, University of Copenhagen, 2 Universitetsparken, 2100 Copenhagen, Denmark

Edited by Roger J. Colbran

The brain contains a fairly low amount of glycogen, mostly located in astrocytes, a fact that has prompted the suggestion that glycogen does not have a significant physiological role in the brain. However, glycogen metabolism in astrocytes is essential for several key physiological processes and is adversely affected in disease. For instance, diminished ability to break down glycogen impinges on learning, and epilepsy, Alzheimer's disease, and type 2 diabetes are all associated with abnormal astrocyte glycogen metabolism. Glycogen metabolism supports astrocytic K⁺ and neurotransmitter glutamate uptake and subsequent glutamine synthesis—three fundamental steps in excitatory signaling at most brain synapses. Thus, there is abundant evidence for a key role of glycogen in brain function. Here, we summarize the physiological brain functions that depend on glycogen, discuss glycogen metabolism in disease, and investigate how glycogen breakdown is regulated at the cellular and molecular levels.

Glycogen in the brain is mostly but not exclusively confined to astrocytes (1), and astrocytic glycogen metabolism is vital for a number of fundamental processes in the brain. For instance, brain glycogen is affected in hypoglycemia (2). Curiously, the glycogen level rebounds to a higher level following a single but not repeated hypoglycemic episodes in humans (2, 3). Interestingly, it has repeatedly been reported that the ability to synthesize or break down brain glycogen is important in learning and memory formation (4–7), and maladaptive learning, measured as the conditioned response to cocaine in mice, is reduced when glycogen breakdown is blocked (8). Thus, a linkage exists between breakdown of glycogen and the neural plasticity involved in both learning and addiction. In addition, glycogen breakdown is essential for key astrocytic processes, such as uptake of K⁺ and neurotransmitter glutamate, and the subsequent synthesis of glutamine as part of the glutamate–glutamine cycle (9–11). However, several details regarding the role and regulation of glycogen metabolism in physiology and

pathology are still obscure. The importance of astrocyte glycogen is somewhat enigmatic in light of the fact that the ample supply of extracellular glucose would appear to be sufficient to serve the brain's energetic needs. Hence, two questions are as follows. (i) What is it about glycogen that gives it this prominent position in brain biochemistry and physiology? (ii) what extracellular and intracellular cues regulate these processes? As will be evident from the discussions below, we are really just beginning to understand this at the cellular and molecular levels.

Glycogen in health and disease

Historically, brain glycogen was thought to be vestigial due to the limited amount present (12). Later, glycogen was considered to constitute an emergency fuel, which was degraded only when there was a discontinuation in the cerebral glucose supply. Now we know that degradation of glycogen is crucial for sustaining a number of physiological processes. It should be noted that alterations in glycogen metabolism may be a consequence of the changes related to disease, rather than the underlying cause of disease. The altered glycogen metabolism may, of course, bring about new complications because glycogen breakdown is a key process involved in many aspects of proper brain function.

Implication of glycogen in learning, memory, and Alzheimer's disease

Degradation of glycogen is important for learning and memory formation, as well as long-term memory consolidation (4, 5, 13, 14). Disruptions of glycogen metabolism have also been linked to Alzheimer's disease, potentially due to overactivation of GSK-3 and a resulting inhibition of glycogen synthase (15). Moreover, mice lacking glycogen synthase in the brain display a significant deficiency in the acquisition of an associative learning task (4). Furthermore, intracerebral injection of β -amyloid (A β (1–42)) into 1-day-old chicks caused memory loss, which could not be rescued by stimulation of glycogen breakdown likely because β -amyloid impairs glycogen synthesis via activation of GSK-3 (15). Impairments in glycogen synthesis could reduce brain glycogen levels, hampering the physiological flux of glucose units through glycogen, which is important for learning and memory. In line with the importance of noradrenergic regulation of flux through the glycogen shunt (11), noradrenergic dysfunction was proposed to be an important component of Alzheimer's disease (16–18). The importance of glycogen with regard to Alzheimer's disease is underlined by a recent study

This work was supported by the Hørslev Foundation and the Faculty of Health and Medical Sciences at University of Copenhagen (to L. K. B.) and Lundbeck Foundation Grant R165-2013-15334 (to A. B. W.). This is the third article in the Thematic Minireview series "Brain glycogen metabolism." The authors declare that they have no conflicts of interest with the contents of this article.

¹ Both authors contributed equally to this work.

² To whom correspondence may be addressed. E-mail: laba@sund.ku.dk.

³ To whom correspondence may be addressed. E-mail: abw@sund.ku.dk.

This is an Open Access article under the [CC BY](https://creativecommons.org/licenses/by/4.0/) license.

that found facilitated spatial learning and increased glycogen stores in an Alzheimer's disease model fed a diet containing pyruvate (19).

Implication of glycogen in seizures and epilepsy

The involvement of glycogen in glutamatergic neurotransmission has repeatedly been demonstrated. Glycogen may be converted to lactate that can be released to the extracellular space and used by neurons or other cells as fuel (20, 21). Furthermore, glycogen degradation fuels glutamate transport in astrocytes (11, 22) or glycogen in astrocytes can be used for synthesis of glutamine, thus serving as precursor for biosynthesis of neurotransmitter glutamate (13). In line with this, it has been suggested that reduced glycogen degradation contributes to the imbalance of glutamatergic and GABAergic neurotransmission associated with epilepsy and seizures (24). Some findings indicate that epileptic animals contain alternatively structured glycogen molecules that are resistant to degradation (24), consistent with the increased levels of hippocampal glycogen detected in epileptic patients (25). Compatible with this, epileptic seizures are the symptomatic hallmark of Lafora disease characterized by abolished glycogen degradation (see Minireview by Gentry *et al.* (39)).

In contrast to epilepsy involving repetitive seizures, acute kainate-induced seizures led to a dose-dependent decrease in cerebral glycogen content (26). This indicates that under this condition glycogen can be degraded and contributes to the maintenance of cerebral energy homeostasis. Furthermore, based on mathematical modeling, it was recently concluded that glycogen is mobilized as an early event after induced spreading of depression in rats, an event that, like seizure activity, leads to synchronized activity in brain encompassing a drastic increase in local energy demand to restore ion homeostasis (28). This may be explained by excessive neuronal activity being associated with efflux of K^+ , which is subsequently removed from the extracellular space by active transport into astrocytes (23). In primary astrocyte cultures, glycogen is involved in fueling the removal of K^+ from the extracellular space (11), and in line with this, it has been suggested that glucose is spared for neuronal energy metabolism when glycogen is used for fueling astrocytic K^+ clearance (27). In conclusion, altered glycogen metabolism seems to be clearly involved in seizure activity and epilepsy, although the two scenarios appear to affect glycogen metabolism differently.

Implication of glycogen in sleep

Levels of cerebral glycogen are reduced during wakefulness, and especially during sleep deprivation, but are replenished during sleep (29, 30). However, it seems that all brain areas are not equally affected by sleep and sleep deprivation (30), and brain glycogen appears to respond distinctly to sleep deprivation in different mouse strains (31). Based on the alterations in cerebral glycogen content in response to sleep, an hypothesis was formulated proposing that glycogen (in combination with adenosine) was a key regulator of sleep (32). However, current evidence does not support a direct correlation between regulation of sleep and glycogen content (33). It should be noted that the cerebral glycogen level increases only during the first 15

min of sleep and decreases slowly 20 min after awakening (34), but otherwise the cerebral glycogen content remains quite constant compatible with a persistent flux through the glycogen shunt. Recent studies have demonstrated that pharmacological inhibition of glycogen degradation by intracerebroventricular (ICV)⁴ injection of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB; a blocker of glycogen phosphorylase and thus glycogen breakdown, see below) did not affect either rapid eye movement or nonrapid eye movement sleep in mice (33). In contrast, ICV injection of DAB led to a decrease in spontaneous locomotor activity of almost 40%, suggesting that glycogen breakdown may be linked to locomotion because sleep/a quiet wake period is induced whenever glycogen degradation is inaccessible (33).

Astrocyte glycogen in diabetes

Diabetes is characterized by a persistent high concentration of glucose in plasma, and it is unclear whether glucose transport into the brain is affected (35). In a rat model of type 2 diabetes, glycogen metabolism was impaired resulting in a lower amount of brain glycogen (36). This is further supported by the observations that cerebral glycogen levels are reduced during hypoglycemia but then rebound to even higher levels during subsequent normo- or hyperglycemic periods (37–40). Remarkably, this increase in glycogen content was observed only after the first incidence of hypoglycemia and not after recurrent episodes, which led to the conclusion that impairments in glycogen metabolism may be involved in hypoglycemia unawareness (38).

Intracellular signals regulating glycogen breakdown

Intracellular elevations in the two canonical second messengers, 3',5'-cyclic adenosine monophosphate (cAMP) and Ca^{2+} , are required to elicit glycogen breakdown. The receptor-mediated regulation of glycogen breakdown has been known for decades and has been reviewed extensively (41). However, less is known about the compartmentalization of the intracellular signals and how this influences glycogen breakdown. We predict this to be an important area of future research, and thus we devote most of this section to explore this topic, rather than attempting to reproduce what has been previously discussed in the review literature.

Glycogen phosphorylase

Very briefly, astrocytes express two of the three known isoforms of GP, *i.e.* the brain form, bGP, and the muscle form, mGP (42, 43). As outlined in Fig. 1, cAMP and Ca^{2+} may elicit glycogen breakdown because phosphorylase kinase (PhK) that phosphorylates, and thus activates, GP is itself activated by Ca^{2+} and phosphorylation by protein kinase A (PKA) (41, 44). Activity of GP is also linked to the energetic status of the cell, because AMP activates GP allosterically, although of the two isoforms of GP in astrocytes, bGP responds more strongly to

⁴The abbreviations used are: ICV, intracerebroventricular; PK, pyruvate kinase; TCA, tricarboxylic acid cycle; DAB, 4-dideoxy-1,4-imino-D-arabinitol; SOCE, store-operated Ca^{2+} entry; GPCR, G protein-coupled receptor; AC, adenylate cyclase; PhK, phosphorylase kinase; GP, glycogen phosphorylase; bGP, brain GP; mGP, muscle GP; IP₃, inositol 1,4,5-triphosphate; TRPC, transient receptor potential channel.

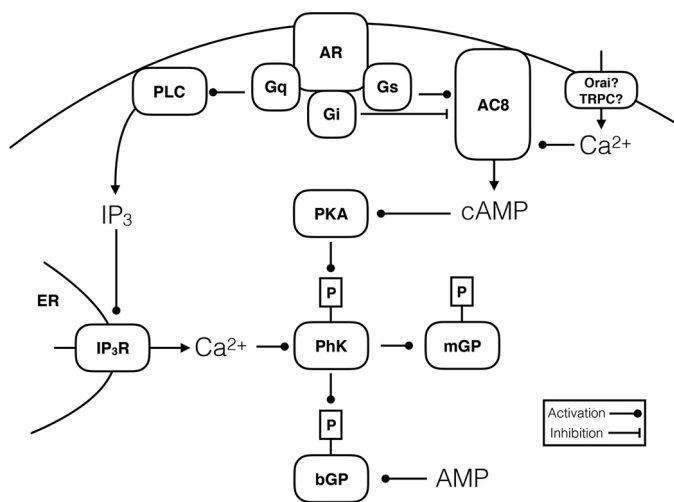


Figure 1. Cartoon depicting the two major signaling pathways regulating breakdown of glycogen. Glycogen phosphorylase brain (*bGP*) or muscle (*mGP*) forms are both activated by phosphorylation by a dedicated kinase, phosphorylase kinase (*PhK*). In addition, *bGP* is only fully active in the presence of ample levels of AMP. *PhK*, in turn, is activated by Ca^{2+} and phosphorylation by protein kinase A (*PKA*), and both signals are needed for full activation. In astrocytes, cAMP may be generated by plasma membrane-bound adenylate cyclase (*AC*), which in turn is regulated by the $\text{G}\alpha_s$ or $\text{G}\alpha_q$ protein-coupled adrenergic receptors (*AR*; see text for details). Depending on the isoform of *AC* expressed, Ca^{2+} flowing in via *Orai* or *TRPC* channels activated during store-operated Ca^{2+} entry may activate or inhibit the cAMP signal adding to the complexity; *AC8* is activated by Ca^{2+} and is expressed in astrocytes. Finally, $\text{G}\alpha_q$ -coupled $\alpha 1$ -adrenergic receptors may regulate glycogen breakdown via phospholipase C (*PLC*)- IP_3 mediated release by IP_3 receptors (*IP}_3\text{R}*) in the endoplasmic reticulum (*ER*).

AMP than does *mGP* (41, 45, 46). For a further description of astrocytic glycogenolysis, see Minireview by Nadeau *et al.* (97).

Generation of receptor-coupled cAMP and Ca^{2+} signals in astrocytes

In astrocytes, cAMP and Ca^{2+} signals may arise following activation of G protein-coupled receptors, and mouse brain astrocytes express $\alpha 1$, $\alpha 2$, and $\beta 1$ and possibly low but functionally important amounts of $\beta 2$ -adrenergic receptors (47, 48). This is essential because astrocytes are thought to be a major target of noradrenergic signaling stemming from the locus coeruleus regulating (among others) glycogen metabolism, *e.g.* in relation to the circadian rhythm, arousal, and emotional stress (47). Thus, norepinephrine may promote or inhibit cytosolic cAMP signaling via $\text{G}\alpha_s$ -coupled β -adrenergic receptors or $\text{G}\alpha_i$ -coupled $\alpha 2$ -adrenergic receptors, respectively, and induce cytosolic Ca^{2+} signals via $\text{G}\alpha_q$ -coupled $\alpha 1$ -adrenergic receptors (Fig. 1) (47). The effects of activating the different adrenergic receptors on astrocytes for glycogen breakdown have been studied extensively, although some studies show somewhat conflicting results (41). Concomitant Ca^{2+} and cAMP signals are needed (at least in muscle) to elicit glycogen breakdown via activation of *PhK*, which might explain the presence of both $\text{G}\alpha_q$ - and $\text{G}\alpha_s$ -coupled noradrenergic receptors on astrocytes. The remaining part of this section will deal with what we know and, more importantly what we need to know about these intracellular signals.

Putative role of nonreceptor-coupled Ca^{2+} and cAMP signals

Astrocytic Ca^{2+} signals have been researched intensively for the last few decades (49), whereas the other canonical second messenger, cAMP, has received less attention, although the protein biosensors for detecting cAMP have been available for about 2 decades (50). We know that both cAMP and Ca^{2+} signals may be diffusing across the cytosol or only be present in discrete micro (or rather nano) domains within the cell (51, 52). Clearly, this spatial compartmentalization of signaling pathways must influence the functional outcomes, and it has indeed been shown to do so in different preparations (51). In Müller *et al.* (53), we provide evidence that coordinated cross-talk between Ca^{2+} and cAMP induces astrocytic glycogen degradation, potentially allowing increases in nearby neuronal activity to engage this important supportive astrocytic process (49, 54). We induced store-operated Ca^{2+} entry (SOCE) in cultured astrocytes by depleting the intracellular stores through inhibition of the sarco/endoplasmic reticulum Ca^{2+} -ATPase pumps in the absence of extracellular Ca^{2+} , and we then re-introduced extracellular Ca^{2+} to provoke SOCE (53). In this way, a cytosolic Ca^{2+} signal is generated in the absence of GPCR activation, and SOCE induced a significant breakdown of glycogen within minutes. As expected, if Ca^{2+} and cAMP-PKA jointly activate *PhK*, the breakdown was curbed by inhibition of adenylate cyclases (*AC*s); because SOCE was induced separately from GPCR activation, this indicates that the breakdown depends on Ca^{2+} -induced cAMP signaling, presumably by Ca^{2+} -activated *AC* isoform 8 (*AC8*; Fig. 1), which is present in astrocytes (48, 53). *AC8* can be activated by SOCE in the absence of GPCR activation, perhaps due in part to a physical association with *Orai1* channels (55–57), although the relative roles of *TRPC* versus *Orai* channels for mediating SOCE remains controversial (58, 59). Clearly, SOCE represents a nonreceptor-mediated way of initiating Ca^{2+} /cAMP-dependent glycogen breakdown; however, *in situ* SOCE would only occur following an initial cytosolic Ca^{2+} signal depleting intracellular Ca^{2+} stores such as a GPCR- $\text{G}\alpha_q$ - IP_3 -mediated store depletion. Thus, the *AC8*-mediated cAMP signal represents a post-signaling signal arising subsequent to the initial cytosolic Ca^{2+} signal.

Putative role of compartmentalized intracellular signals

An interesting but little explored aspect of glycogen dynamics is whether compartmentalized Ca^{2+} /cAMP-PKA signals can selectively affect glycogen breakdown. It has been shown in cardiac myocytes that activation of $\beta 1$ -adrenergic receptors produces a far-reaching cytosolic cAMP signal, whereas activation of $\beta 2$ -adrenergic receptors results in a signal that is restricted to the T-tubules (T-tubules are invaginations in the cell membrane that allow a fast cytosolic response to myocyte depolarization) (60). It is therefore likely that two different pools of glycogen are degraded upon activation of $\beta 1$ - and $\beta 2$ -adrenergic receptors, respectively. We know from electron micrographs of cultured astrocytes that glycogen granules in some places line the inside of the plasma membrane but are also present in “belts” in the cytosol (61); thus, should astrocytes show the same compartmentalization of β -adrenergic signals, one might expect very different glycogenolytic responses to $\beta 1$ -

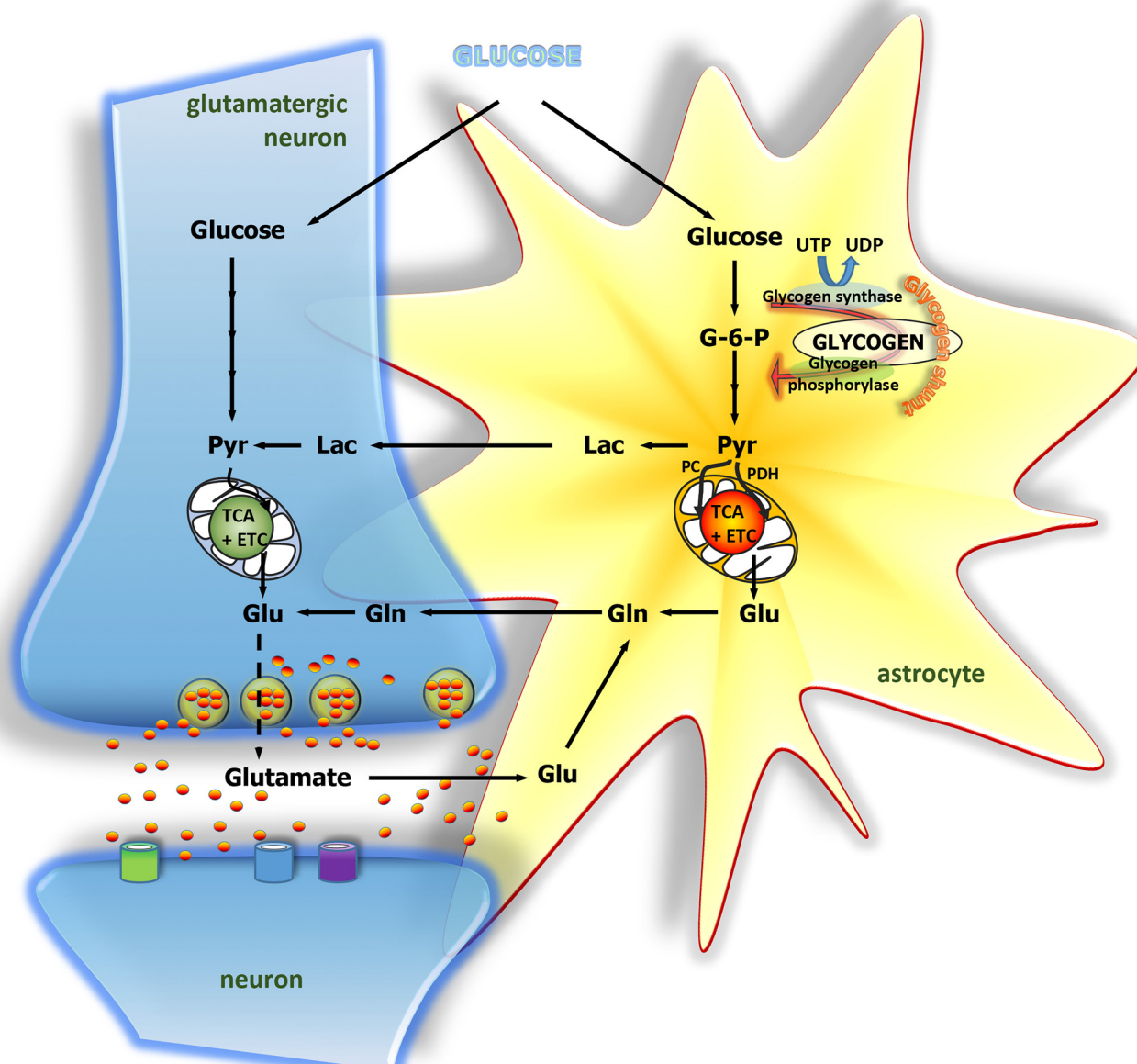


Figure 2. Cartoon depicting glucose and glycogen metabolism in the brain as well as substrate transfer between astrocytes and neurons. In astrocytes, glucose may be metabolized via glycolysis or the glycogen shunt to pyruvate, which may be converted to lactate and transferred to neurons for oxidative metabolism to occur. Alternatively, pyruvate may enter the TCA cycle either by way of pyruvate dehydrogenase (PDH) or via pyruvate carboxylase (PC). Entrance of pyruvate via both of these pathways is required for *de novo* synthesis of glutamate and glutamine. Glutamine is not neuroactive and may be transferred to neurons to serve as precursor for glutamate synthesis. Following vesicular release of glutamate and interactions with receptors in the postsynaptic membrane, glutamate is cleared from the synapse mainly by transporters located in the astrocytic membrane. Glutamate can then be converted to glutamine and transferred to neurons, thereby completing the glutamate–glutamine cycle.

versus β 2-adrenergic receptor stimulation. Thus, it would be interesting to ascertain whether populations of astrocytes functionally express either β 1- or β 2-adrenergic receptors or perhaps both receptor subtypes. For instance, one could imagine that astrocytes expressing β 2-adrenergic receptors might be tuned to release downstream metabolites from glycogenolysis, such as glutamine or lactate, whereas β 1-adrenergic receptor-expressing astrocytes may respond to norepinephrine by breaking down glycogen for internal fuel or building blocks for anaplerosis of TCA cycle intermediates. Studying these aspects is not only interesting in terms of exploring the basic neurobiology, but also in terms of revealing putative drug targets.

Glycogen shunt activity

Metabolism of glucose via transient incorporation into glycogen, *i.e.* with no significant change in the amount of glycogen, is known as the glycogen shunt. Following phosphorylation of glucose to glucose 6-phosphate by the first enzyme of glycolysis, hexokinase, the glucose molecule may be incorporated into glycogen, a process that consumes UTP and is hence energy-demanding (Fig. 2). The subsequent degradation of glycogen to glucose 6-phosphate via glucose 1-phosphate does not require energy. This means that glucose metabolism via the glycogen shunt produces one ATP molecule less per molecule of glucose metabolized compared with “pure” glycolysis, *i.e.* one instead of

two ATPs. However, despite being energetically unfavorable, glycogen shunt activity appears to operate persistently in muscle as well as in brain (11, 62–64). During increases in cerebral energy demand, the astrocytic glycogen content will, however, decrease (5, 64–68).

Functional importance of glycogen shunt activity

Although glycogen shunt activity has been revealed in both muscle and brain (11, 62–64), its significance and functional importance are not clear. Abolishment of glycogen degradation in cultured astrocytes exposed to ^{13}C -labeled glucose led to an increase in the percent of ^{13}C labeling in lactate, both under control conditions (without increasing the cells' energy demand) and during activation of energy requiring glutamate transport by exposure to $250\ \mu\text{M}$ D-aspartate (69). Such an increase in ^{13}C -labeled lactate results when flux through the glycogen shunt is inhibited and the amount of glucose metabolized via glycolysis exceeds the amount metabolized when both glycolysis and glycogenolysis are operational, *i.e.* glycolytic supercompensation (11). These findings propose that the ATP generated from glycolysis and from glycogen degradation, respectively, is not equivalent, which may rely on functional and/or spatial separation of these pathways. The findings may also be in agreement with the suggestion that glycolysis and glycogenolysis in astrocytes are complementary (70). Metabolic separation of these pathways was previously demonstrated by the observation that lactate derived from glycolysis and glycogenolysis contributes to distinct pools of lactate (71). Functionally distinctive roles of glycolysis and glycogenolysis have been observed *in vitro* as well as *in vivo*. Even in the presence of glucose, elimination of glycogen degradation in cultured astrocytes was demonstrated to result in reduced accumulation of D- ^3H aspartate mediated via glutamate transporters (22). This points toward a functional role of glycogen metabolism, which cannot be substituted by glycolytic activity, a finding supported by *in vivo* studies demonstrating that inhibition of glycogen degradation resulted in impairment of memory consolidation in young chickens and memory deficiency in rats, effects that could not be rescued by glucose (5, 13).

Quantitative significance of glycogen shunt activity

Although it appears that a persistent flux of glucose units through glycogen is of functional importance for proper brain function, the fraction of glucose being metabolized via the glycogen shunt is unclear. Norepinephrine is known to stimulate glycogen synthesis and degradation concomitantly, *i.e.* accelerate glycogen shunt activity (47, 72–77), and its exposure to norepinephrine ($100\ \mu\text{M}$) revealed that the glycogen shunt accounts for ~40% of total glucose metabolism under these conditions. This might be an overestimate due to the potentiation of glycogen shunt activity in the presence of norepinephrine. Nevertheless, this may be the best approach to the *in vivo* situation where norepinephrine is present in brain at concentrations ranging from 1 to $15\ \mu\text{M}$, depending on the brain area (78). It should be noted that the finding that 40% of glucose is metabolized by way of glycogen is severalfold higher than earlier reports predicting glycogen synthesis to account for only 1–6% of total cerebral glucose consumption (79, 80). Taking

the small glycogen reservoir into account (12), a functional role of the glycogen shunt with regard to sustaining cerebral activity and astrocytic neurotransmitter clearance implies that mobilization and the following reestablishment of glycogen are successive events mediated within seconds, as discussed by Shulman *et al.* (62). Such a scenario would require a high glycogen shunt activity involving only the peripheral part of the glycogen molecule, which is compatible with the finding that the cerebral glycogen content is remarkably constant under a wide range of physiological conditions (81). It should be noted that there is a dearth of data from *in vivo* studies evaluating the extent of glucose being metabolized via the glycogen shunt. Instead, a turnover time constant for brain glycogen has been estimated to be 5 and 24 h in conscious rats and humans, respectively (3, 79, 82, 83). This determines the total glycogen turnover time, *i.e.* the time needed for replacement of an amount of glycosyl units corresponding to the total brain glycogen pool at any given time. The spherical structure of glycogen and the fact that glycogen metabolism largely follows the “last-in-first-out” principle (84) would lead to the suggestion that the outer part of the molecule is much more dynamic than the inner layers. Hence, assessing a total turnover of glycogen is much more complicated than turnover of a pool of substrate exhibiting random degradation, and in addition, its relevance may be questioned.

Role of glycogen phosphorylase isoforms for glycogen shunt activity

The activity of the GP isoforms is differentially regulated, *i.e.* the muscle isoform is activated mainly via phosphorylation by PhK, whereas the brain isoform is more responsive to allosteric activation by AMP (46). This suggests that the two isoforms of GP serve different purposes; mGP elicits glycogen degradation secondary to receptor stimulation following neuronal activity, and bGP mediates glycogen breakdown as a consequence of energy fluctuations in the astrocytic microenvironment. We have recently suggested that the disproportionate augmentation of glycolysis observed when glycogen degradation was abolished, *i.e.* glycolytic supercompensation, be mediated predominantly as a result of hampered mGP activity (85). In line with this, glycolytic supercompensation *in vivo* was detected in response to whisker stimulation in conscious rats, *i.e.* as a consequence of neuronal activation (64). In contrast, the glycolytic supercompensation observed in cultured astrocytes during exposure to D-aspartate exhibits a delay of at least 30 min in onset (11). This may indicate that glycogen used to fuel glutamate transporters is degraded (at least initially) by bGP and relies on an increase in the intracellular AMP level, and only sustained exposure to D-aspartate results in phosphorylation of mGP.

Implications of glycogen in sustaining glutamatergic neurotransmission

Glycogen as energy substrate during neurotransmission

It has repeatedly been demonstrated that lactate derived from astrocyte glycogen is able to sustain neuronal activity in the absence of other energy substrates (20, 67, 68, 86–89). Although the physiological relevance of this may be questioned,

glycogen degradation was also essential for maintenance of processes related to neurotransmission in the presence of a physiological glucose concentration (22, 64, 88). However, whether the energy derived from glycogen is destined for astrocytic or neuronal purposes is unclear. Several studies have demonstrated that obstructing lactate transfer between astrocytes and stimulated neurons in the absence of an exogenous energy substrate results in accelerated neuronal failure (20, 67, 68, 87–89). It is thereby suggested that astrocytes degrade glycogen to lactate, which is then oxidatively metabolized in neurons to cover the energetic demands related to neurotransmission. This is supported by the finding that abolishing glycogen degradation led to a reduction in glutamate release that was comparable with that observed when inhibiting lactate transfer between astrocytes and neurons (22). However, the notion that glycogen is mobilized upon decrements in the energy state of the local microenvironment (*i.e.* when the intracellular AMP concentration increases) implies that glycogen sustains energy-demanding processes within the astrocytic compartment. This is supported by the observation that impeding glycogen degradation in cultured astrocytes resulted in not only a disproportionate increase in glycolytic activity, *i.e.* glycolytic supercompensation, but also led to supercompensation of TCA cycle metabolism (11). Moreover, following glutamatergic neurotransmission, glutamate clearance from the synapse is one of the energy-requiring processes related to astrocytes, and astrocytic energy shortage may lead to reversal of the transporter resulting in excitotoxic levels of glutamate in the synapse (90). This, in turn, may result in neuronal failure (91, 92). It should be noted, however, that these scenarios are not mutually exclusive, and glycogen may serve as an energy substrate utilized in both astrocytes and neurons compatible with the two isoforms of GP being activated by distinct mechanisms.

Glycogen as a precursor for the neurotransmitter glutamate

In addition to its role as an energy substrate, glycogen serves as a precursor for glutamate and glutamine synthesis (7, 13). In order for glycogen to provide the entire carbon skeleton of glutamate/glutamine, the entrance of pyruvate into the TCA cycle must occur by means of pyruvate carboxylase as well as via pyruvate dehydrogenase (Fig. 2). Because of the importance of the glutamate–glutamine cycle for replenishment of neurotransmitter pools (69, 93–95), inhibition of glycogen degradation may lead to decrements in neuronal glutamate synthesis. In agreement with this, it was demonstrated that glutamate–glutamine cycle activity (Fig. 2) is impaired in an obese rat model displaying hampered glycogen metabolism in combination with a reduction in cerebral glycogen content (36). As filling of glutamatergic vesicles depends upon the cytosolic glutamate concentration (96), this may ultimately lead to impairments in neuronal glutamate release upon depolarization. Hence, it may be speculated that a lower vesicular glutamate release from neurons upon inhibition of glycogen degradation arises as a consequence of deficits in astrocytic glutamine synthesis and not (only) because of energy deficiency.

Concluding remarks

Astrocyte glycogen plays a vital role in a number of brain functions and is aberrant in not only neurological diseases but also type 2 diabetes. An increased understanding of the regulation and functional roles of astrocyte glycogen in health and disease will likely uncover novel drug targets for the potential benefit of patients.

References

- Öz, G., DiNuzzo, M., Kumar, A., Moheet, A., and Seaquist, E. R. (2015) Revisiting glycogen content in the human brain. *Neurochem. Res.* **40**, 2473–2481 [CrossRef Medline](#)
- Öz, G., DiNuzzo, M., Kumar, A., Moheet, A., Khowaja, A., Kubisiak, K., Eberly, L. E., and Seaquist, E. R. (2017) Cerebral glycogen in humans following acute and recurrent hypoglycemia: implications on a role in hypoglycemia unawareness. *J. Cereb. Blood Flow Metab.* **37**, 2883–2893 [CrossRef Medline](#)
- Oz, G., Kumar, A., Rao, J. P., Kodl, C. T., Chow, L., Eberly, L. E., and Seaquist, E. R. (2009) Human brain glycogen metabolism during and after hypoglycemia. *Diabetes* **58**, 1978–1985 [CrossRef Medline](#)
- Duran, J., Saez, I., Gruart, A., Guinovart, J. J., and Delgado-García, J. M. (2013) Impairment in long-term memory formation and learning-dependent synaptic plasticity in mice lacking glycogen synthase in the brain. *J. Cereb. Blood Flow Metab.* **33**, 550–556 [CrossRef Medline](#)
- Suzuki, A., Stern, S. A., Bozdagi, O., Huntley, G. W., Walker, R. H., Magistretti, P. J., and Alberini, C. M. (2011) Astrocyte–neuron lactate transport is required for long-term memory formation. *Cell* **144**, 810–823 [CrossRef Medline](#)
- Gibbs, M. E., Lloyd, H. G., Santa, T., and Hertz, L. (2007) Glycogen is a preferred glutamate precursor during learning in 1-day-old chick: biochemical and behavioral evidence. *J. Neurosci. Res.* **85**, 3326–3333 [CrossRef Medline](#)
- Hertz, L., O'Dowd, B. S., Ng, K. T., and Gibbs, M. E. (2003) Reciprocal changes in forebrain contents of glycogen and of glutamate/glutamine during early memory consolidation in the day-old chick. *Brain Res.* **994**, 226–233 [CrossRef Medline](#)
- Boury-Jamot, B., Carrard, A., Martin, J. L., Halfon, O., Magistretti, P. J., and Boutrel, B. (2016) Disrupting astrocyte–neuron lactate transfer persistently reduces conditioned responses to cocaine. *Mol. Psychiatry* **21**, 1070–1076 [CrossRef Medline](#)
- Xu, J., Song, D., Xue, Z., Gu, L., Hertz, L., and Peng, L. (2013) Requirement of glycogenolysis for uptake of increased extracellular K⁺ in astrocytes: potential implications for K⁺ homeostasis and glycogen usage in brain. *Neurochem. Res.* **38**, 472–485 [CrossRef Medline](#)
- Sickmann, H. M., Walls, A. B., Bouman, S. D., Schousboe, A., and Waagepetersen, H. S. (2009) Functional significance of brain glycogen in sustaining glutamatergic neurotransmission. *J. Neurochem.* **109**, Suppl. 1, 80–86 [CrossRef Medline](#)
- Walls, A. B., Heimbürger, C. M., Bouman, S. D., Schousboe, A., and Waagepetersen, H. S. (2009) Robust glycogen shunt activity in astrocytes: effects of glutamatergic and adrenergic agents. *Neuroscience* **158**, 284–292 [CrossRef Medline](#)
- Clarke, D. D., and Sokoloff, L. (1999) in *Basic Neurochemistry* (Siegel, G. J., ed) 6th Ed., pp. 637–670, Lippincott-Raven Publishers, Philadelphia, PA DOI not found. PMID not found.
- Gibbs, M. E., Anderson, D. G., and Hertz, L. (2006) Inhibition of glycogenolysis in astrocytes interrupts memory consolidation in young chickens. *Glia* **54**, 214–222 [CrossRef Medline](#)
- Newman, L. A., Korol, D. L., and Gold, P. E. (2011) Lactate produced by glycogenolysis in astrocytes regulates memory processing. *PLoS One* **6**, e28427 [CrossRef Medline](#)
- Gibbs, M. E. (2015) Role of Glycogenolysis in memory and learning: regulation by noradrenaline, serotonin and ATP. *Front. Integr. Neurosci.* **9**, 70 DOI not found. [Medline](#)
- Hertz, L. (1989) Is Alzheimer's disease an anterograde degeneration, originating in the brainstem, and disrupting metabolic and functional inter-

THEMATIC MINIREVIEW: Glycogen metabolism in diseased brain

- actions between neurons and glial cells? *Brain Res. Brain Res. Rev.* **14**, 335–353 [CrossRef Medline](#)
17. Marien, M. R., Colpaert, F. C., and Rosenquist, A. C. (2004) Noradrenergic mechanisms in neurodegenerative diseases: a theory. *Brain Res. Brain Res. Rev.* **45**, 38–78 [CrossRef Medline](#)
 18. Weinshenker, D. (2008) Functional consequences of locus coeruleus degeneration in Alzheimer's disease. *Curr. Alzheimer Res.* **5**, 342–345 [CrossRef Medline](#)
 19. Koivisto, H., Leinonen, H., Puurula, M., Hafez, H. S., Barrera, G. A., Stridh, M. H., Waagepetersen, H. S., Tiainen, M., Soininen, P., Zilberter, Y., and Tanila, H. (2016) Chronic pyruvate supplementation increases exploratory activity and brain energy reserves in young and middle-aged mice. *Front. Aging Neurosci.* **8**, 41 [CrossRef Medline](#)
 20. Wender, R., Brown, A. M., Fern, R., Swanson, R. A., Farrell, K., and Ransom, B. R. (2000) Astrocytic glycogen influences axon function and survival during glucose deprivation in central white matter. *J. Neurosci.* **20**, 6804–6810 DOI not found. [Medline](#)
 21. Brown, A. M., Baltan Tekkök, S., and Ransom, B. R. (2004) Energy transfer from astrocytes to axons: the role of CNS glycogen. *Neurochem. Int.* **45**, 529–536 [CrossRef Medline](#)
 22. Sickmann, H. M., Walls, A. B., Schousboe, A., Bouman, S. D., and Waagepetersen, H. S. (2009) Functional significance of brain glycogen in sustaining glutamatergic neurotransmission. *J. Neurochem.* **109**, Suppl. 1, 80–86 [CrossRef Medline](#)
 23. Nedergaard, M., and Hansen, A. J. (1993) Characterization of cortical depolarizations evoked in focal cerebral ischemia. *J. Cereb. Blood Flow Metab.* **13**, 568–574 [CrossRef Medline](#)
 24. DiNuzzo, M., Mangia, S., Maraviglia, B., and Giove, F. (2015) Does abnormal glycogen structure contribute to increased susceptibility to seizures in epilepsies? *Metab. Brain Dis.* **30**, 307–316 [CrossRef Medline](#)
 25. Dalsgaard, M. K., Madsen, F. F., Secher, N. H., Laursen, H., and Quistorff, B. (2007) High glycogen levels in the hippocampus of patients with epilepsy. *J. Cereb. Blood Flow Metab.* **27**, 1137–1141 [CrossRef Medline](#)
 26. Walls, A. B., Eyjolfsson, E. M., Schousboe, A., Sonnewald, U., and Waagepetersen, H. S. (2014) A subconvulsive dose of kainate selectively compromises astrocytic metabolism in the mouse brain *in vivo*. *J. Cereb. Blood Flow Metab.* **34**, 1340–1346 [CrossRef Medline](#)
 27. Dinuzzo, M., Mangia, S., Maraviglia, B., and Giove, F. (2012) The role of astrocytic glycogen in supporting the energetics of neuronal activity. *Neurochem. Res.* **37**, 2432–2438 [CrossRef Medline](#)
 28. Feuerstein, D., Backes, H., Gramer, M., Takagaki, M., Gabel, P., Kumagai, T., and Graf, R. (2016) Regulation of cerebral metabolism during cortical spreading depression. *J. Cereb. Blood Flow Metab.* **36**, 1965–1977 [CrossRef Medline](#)
 29. Kong, J., Shepel, P. N., Holden, C. P., Mackiewicz, M., Pack, A. I., and Geiger, J. D. (2002) Brain glycogen decreases with increased periods of wakefulness: implications for homeostatic drive to sleep. *J. Neurosci.* **22**, 5581–5587 DOI not found. [Medline](#)
 30. Gip, P., Hagiwara, G., Ruby, N. F., and Heller, H. C. (2002) Sleep deprivation decreases glycogen in the cerebellum but not in the cortex of young rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **283**, R54–R59 [CrossRef Medline](#)
 31. Franken, P., Gip, P., Hagiwara, G., Ruby, N. F., and Heller, H. C. (2003) Changes in brain glycogen after sleep deprivation vary with genotype. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **285**, R413–R419 [CrossRef Medline](#)
 32. Benington, J. H., and Heller, H. C. (1995) Restoration of brain energy metabolism as the function of sleep. *Prog. Neurobiol.* **45**, 347–360 [CrossRef Medline](#)
 33. Petit, J. M., Burlet-Godnot, S., Magistretti, P. J., and Allaman, I. (2015) Glycogen metabolism and the homeostatic regulation of sleep. *Metab. Brain Dis.* **30**, 263–279 [CrossRef Medline](#)
 34. Karnovsky, M. L., Reich, P., Anchors, J. M., and Burrows, B. L. (1983) Changes in brain glycogen during slow-wave sleep in the rat. *J. Neurochem.* **41**, 1498–1501 [CrossRef Medline](#)
 35. Sickmann, H. M., and Waagepetersen, H. S. (2015) Effects of diabetes on brain metabolism—is brain glycogen a significant player? *Metab. Brain Dis.* **30**, 335–343 [CrossRef Medline](#)
 36. Sickmann, H. M., Waagepetersen, H. S., Schousboe, A., Benie, A. J., and Bouman, S. D. (2010) Obesity and type 2 diabetes in rats are associated with altered brain glycogen and amino-acid homeostasis. *J. Cereb. Blood Flow Metab.* **30**, 1527–1537 [CrossRef Medline](#)
 37. Choi, I. Y., and Gruetter, R. (2003) *In vivo* ¹³C NMR assessment of brain glycogen concentration and turnover in the awake rat. *Neurochem. Int.* **43**, 317–322 [CrossRef Medline](#)
 38. Öz, G., Tesfaye, N., Kumar, A., Deelchand, D. K., Eberly, L. E., and Seaquist, E. R. (2012) Brain glycogen content and metabolism in subjects with type 1 diabetes and hypoglycemia unawareness. *J. Cereb. Blood Flow Metab.* **32**, 256–263 [CrossRef Medline](#)
 39. Gentry, M. S., Guinovart, J. J., Minassian, B. A., Roach, P. J., and Serratos, J. (February 26, 2018) Lafora disease offers a unique window into neuronal glycogen metabolism. *J. Biol. Chem.* **293**, 7117–7125 [CrossRef Medline](#)
 40. Duarte, J. M. N., Morgenthaler, F. D., and Gruetter, R. (2017) Glycogen supercompensation in the rat brain after acute hypoglycemia is independent of glucose levels during recovery. *Neurochem. Res.* **42**, 1629–1635 [CrossRef Medline](#)
 41. Obel, L. F., Müller, M. S., Walls, A. B., Sickmann, H. M., Bak, L. K., Waagepetersen, H. S., and Schousboe, A. (2012) Brain glycogen—new perspectives on its metabolic function and regulation at the subcellular level. *Front. Neuroenerget.* **4**, 3 [CrossRef Medline](#)
 42. Pfeiffer-Guglielmi, B., Fleckenstein, B., Jung, G., and Hamprecht, B. (2003) Immunocytochemical localization of glycogen phosphorylase isozymes in rat nervous tissues by using isozyme-specific antibodies. *J. Neurochem.* **85**, 73–81 [CrossRef Medline](#)
 43. Pfeiffer-Guglielmi, B., Bröer, S., Bröer, A., and Hamprecht, B. (2000) Isozyme pattern of glycogen phosphorylase in the rat nervous system and rat astroglia-rich primary cultures: electrophoretic and polymerase chain reaction studies. *Neurochem. Res.* **25**, 1485–1491 [CrossRef Medline](#)
 44. Brushia, R. J., and Walsh, D. A. (1999) Phosphorylase kinase: the complexity of its regulation is reflected in the complexity of its structure. *Front. Biosci.* **4**, D618–D641 [CrossRef Medline](#)
 45. Crerar, M. M., Karlsson, O., Fletterick, R. J., and Hwang, P. K. (1995) Chimeric muscle and brain glycogen phosphorylases define protein domains governing isozyme-specific responses to allosteric activation. *J. Biol. Chem.* **270**, 13748–13756 [CrossRef Medline](#)
 46. Müller, M. S., Pedersen, S. E., Walls, A. B., Waagepetersen, H. S., and Bak, L. K. (2015) Isoform-selective regulation of glycogen phosphorylase by energy deprivation and phosphorylation in astrocytes. *Glia* **63**, 154–162 [CrossRef Medline](#)
 47. Hertz, L., Lovatt, D., Goldman, S. A., and Nedergaard, M. (2010) Adrenoceptors in brain: cellular gene expression and effects on astrocytic metabolism and [Ca²⁺]_i. *Neurochem. Int.* **57**, 411–420 [CrossRef Medline](#)
 48. Holtman, I. R., Noback, M., Bijlsma, M., Duong, K. N., van der Geest, M. A., Ketelaars, P. T., Brouwer, N., Vainchtein, I. D., Eggen, B. J., and Boddeke, H. W. (2015) Glia open access database (GOAD): a comprehensive gene expression encyclopedia of glia cells in health and disease. *Glia* **63**, 1495–1506 [CrossRef Medline](#)
 49. Bazargani, N., and Attwell, D. (2016) Astrocyte calcium signaling: the third wave. *Nat. Neurosci.* **19**, 182–189 [CrossRef Medline](#)
 50. Willoughby, D., and Cooper, D. M. (2008) Live-cell imaging of cAMP dynamics. *Nat. Methods* **5**, 29–36 [CrossRef Medline](#)
 51. Ellisdon, A. M., and Halls, M. L. (2016) Compartmentalization of GPCR signalling controls unique cellular responses. *Biochem. Soc. Trans.* **44**, 562–567 [CrossRef Medline](#)
 52. Berridge, M. J. (2006) Calcium microdomains: organization and function. *Cell Calcium* **40**, 405–412 [CrossRef Medline](#)
 53. Müller, M. S., Fox, R., Schousboe, A., Waagepetersen, H. S., and Bak, L. K. (2014) Astrocyte glycogenolysis is triggered by store-operated calcium entry and provides metabolic energy for cellular calcium homeostasis. *Glia* **62**, 526–534 [CrossRef Medline](#)
 54. Volterra, A., and Meldolesi, J. (2005) Astrocytes, from brain glue to communication elements: the revolution continues. *Nat. Rev. Neurosci.* **6**, 626–640 [CrossRef Medline](#)
 55. Willoughby, D., Everett, K. L., Halls, M. L., Pacheco, J., Skroblin, P., Vaca, L., Klusmann, E., and Cooper, D. M. (2012) Direct binding between Orai1

- and AC8 mediates dynamic interplay between Ca^{2+} and cAMP signaling. *Sci. Signal.* **5**, ra29 DOI not found. [Medline](#)
56. Martin, A. C., Willoughby, D., Ciruela, A., Ayling, L. J., Pagano, M., Wachten, S., Tengholm, A., and Cooper, D. M. (2009) Capacitative Ca^{2+} entry via Orai1 and stromal interacting molecule 1 (STIM1) regulates adenylyl cyclase type 8. *Mol. Pharmacol.* **75**, 830–842 [CrossRef Medline](#)
 57. Willoughby, D., Ong, H. L., De Souza, L. B., Wachten, S., Ambudkar, I. S., and Cooper, D. M. (2014) TRPC1 contributes to the Ca^{2+} -dependent regulation of adenylyl cyclases. *Biochem. J.* **464**, 73–84 [CrossRef Medline](#)
 58. Verkhatsky, A., and Parpura, V. (2014) Store-operated calcium entry in neuroglia. *Neurosci. Bull.* **30**, 125–133 DOI not found. [Medline](#)
 59. Kwon, J., An, H., Sa, M., Won, J., Shin, J. I., and Lee, C. J. (2017) Orai1 and Orai3 in combination with Stim1 mediate the majority of store-operated calcium entry in astrocytes. *Exp. Neurobiol.* **26**, 42–54 [CrossRef Medline](#)
 60. Nikolaev, V. O., Bünemann, M., Schmitteckert, E., Lohse, M. J., and Engelhardt, S. (2006) Cyclic AMP imaging in adult cardiac myocytes reveals far-reaching beta1-adrenergic but locally confined β 2-adrenergic receptor-mediated signaling. *Circ. Res.* **99**, 1084–1091 [CrossRef Medline](#)
 61. Obel, L. F. (2011) *Energy and Amino Acid Metabolism in Astrocytes: Roles of Glycogen and Ca^{2+}* . Ph.D. thesis, University of Copenhagen
 62. Shulman, R. G., Hyder, F., and Rothman, D. L. (2001) Cerebral energetics and the glycogen shunt: neurochemical basis of functional imaging. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 6417–6422 [CrossRef Medline](#)
 63. Shulman, R. G., and Rothman, D. L. (2001) The “glycogen shunt” in exercising muscle: A role for glycogen in muscle energetics and fatigue. *Proc. Natl. Acad. Sci. U.S.A.* **98**, 457–461 [CrossRef Medline](#)
 64. Dienel, G. A., Ball, K. K., and Cruz, N. F. (2007) A glycogen phosphorylase inhibitor selectively enhances local rates of glucose utilization in brain during sensory stimulation of conscious rats: implications for glycogen turnover. *J. Neurochem.* **102**, 466–478 [CrossRef Medline](#)
 65. Swanson, R. A., Morton, M. M., Sagar, S. M., and Sharp, F. R. (1992) Sensory stimulation induces local cerebral glycogenolysis: demonstration by autoradiography. *Neuroscience* **51**, 451–461 [CrossRef Medline](#)
 66. Cruz, N. F., and Dienel, G. A. (2002) High glycogen levels in brains of rats with minimal environmental stimuli: implications for metabolic contributions of working astrocytes. *J. Cereb. Blood Flow Metab.* **22**, 1476–1489 [CrossRef Medline](#)
 67. Brown, A. M., Tekkök, S. B., and Ransom, B. R. (2003) Glycogen regulation and functional role in mouse white matter. *J. Physiol.* **549**, 501–512 [CrossRef Medline](#)
 68. Suh, S. W., Bergher, J. P., Anderson, C. M., Treadway, J. L., Fosgerau, K., and Swanson, R. A. (2007) Astrocyte glycogen sustains neuronal activity during hypoglycemia: studies with the glycogen phosphorylase inhibitor CP-316,819 ([R-R*,S*]-5-chloro-N-[2-hydroxy-3-(methoxymethylamino)-3-oxo-1-(phenylmethyl)propyl]-1H-indole-2-carboxamide). *J. Pharmacol. Exp. Ther.* **321**, 45–50 [CrossRef Medline](#)
 69. Schousboe, A., Walls, A. B., Bak, L. K., and Waagepetersen, H. S. (2015) Astroglia and brain metabolism: focus on energy and neurotransmitter amino acid homeostasis. *Morgan & Claypool Life Sciences, Milton Keynes, UK* **2**, 1–64 [CrossRef](#)
 70. Pellerin, L., Bouzier-Sore, A. K., Aubert, A., Serres, S., Merle, M., Costalat, R., and Magistretti, P. J. (2007) Activity-dependent regulation of energy metabolism by astrocytes: an update. *Glia* **55**, 1251–1262 [CrossRef Medline](#)
 71. Sickmann, H. M., Schousboe, A., Fosgerau, K., and Waagepetersen, H. S. (2005) Compartmentation of lactate originating from glycogen and glucose in cultured astrocytes. *Neurochem. Res.* **30**, 1295–1304 [CrossRef Medline](#)
 72. Subbarao, K. V., and Hertz, L. (1990) Effect of adrenergic agonists on glycogenolysis in primary cultures of astrocytes. *Brain Res.* **536**, 220–226 [CrossRef Medline](#)
 73. Subbarao, K. V., and Hertz, L. (1990) Noradrenaline induced stimulation of oxidative metabolism in astrocytes but not in neurons in primary cultures. *Brain Res.* **527**, 346–349 [CrossRef Medline](#)
 74. Sorg, O., and Magistretti, P. J. (1991) Characterization of the glycogenolysis elicited by vasoactive intestinal peptide, noradrenaline and adenosine in primary cultures of mouse cerebral cortical astrocytes. *Brain Res.* **563**, 227–233 [CrossRef Medline](#)
 75. Waagepetersen, H. S., Westergaard, N., and Schousboe, A. (2000) The effects of isofagomine, a potent glycogen phosphorylase inhibitor, on glycogen metabolism in cultured mouse cortical astrocytes. *Neurochem. Int.* **36**, 435–440 [CrossRef Medline](#)
 76. Hertz, L., Peng, L., and Dienel, G. A. (2007) Energy metabolism in astrocytes: high rate of oxidative metabolism and spatiotemporal dependence on glycolysis/glycogenolysis. *J. Cereb. Blood Flow Metab.* **27**, 219–249 [CrossRef Medline](#)
 77. Hutchinson, D. S., Summers, R. J., and Gibbs, M. E. (2008) Energy metabolism and memory processing: role of glucose transport and glycogen in responses to adrenoceptor activation in the chicken. *Brain Res. Bull.* **76**, 224–234 [CrossRef Medline](#)
 78. Mefford, I. N., Foutz, A., Noyce, N., Jurik, S. M., Handen, C., Dement, W. C., and Barchas, J. D. (1982) Distribution of norepinephrine, epinephrine, dopamine, serotonin, 3,4-dihydroxyphenylacetic acid, homovanillic acid and 5-hydroxyindole-3-acetic acid in dog brain. *Brain Res.* **236**, 339–349 [CrossRef Medline](#)
 79. Watanabe, H., and Passonneau, J. V. (1973) Factors affecting the turnover of cerebral glycogen and limit dextrin *in vivo*. *J. Neurochem.* **20**, 1543–1554 [CrossRef Medline](#)
 80. Choi, I. Y., Tkáč, I., Ugurbil, K., and Gruetter, R. (1999) Noninvasive measurements of [^{13}C]glycogen concentrations and metabolism in rat brain *in vivo*. *J. Neurochem.* **73**, 1300–1308 DOI not found. [Medline](#)
 81. Watanabe, H., and Passonneau, J. V. (1975) Cyclic adenosine monophosphate in cerebral cortex. Alterations following trauma. *Arch. Neurol.* **32**, 181–184 [CrossRef Medline](#)
 82. Oz, G., Seaquist, E. R., Kumar, A., Criego, A. B., Benedict, L. E., Rao, J. P., Henry, P. G., Van De Moortele, P. F., and Gruetter, R. (2007) Human brain glycogen content and metabolism: implications on its role in brain energy metabolism. *Am. J. Physiol. Endocrinol. Metab.* **292**, E946–E951 [CrossRef Medline](#)
 83. Morgenthaler, F. D., Lanz, B. R., Petit, J. M., Frenkel, H., Magistretti, P. J., and Gruetter, R. (2009) Alteration of brain glycogen turnover in the conscious rat after 5 h of prolonged wakefulness. *Neurochem. Int.* **55**, 45–51 [CrossRef Medline](#)
 84. Elsner, P., Quistorff, B., Hansen, G. H., and Grunnet, N. (2002) Partly ordered synthesis and degradation of glycogen in cultured rat myotubes. *J. Biol. Chem.* **277**, 4831–4838 [CrossRef Medline](#)
 85. Jakobsen, E., Bak, L. K., Walls, A. B., Reuschlein, A. K., Schousboe, A., and Waagepetersen, H. S. (2017) The enigmatic phenomenon of glycolytic supercompensation in astrocytes may be distinctly mediated via the muscle form of glycogen phosphorylase. *Neurochem. Res.* **42**, 2940–2944 [Medline](#)
 86. Swanson, R. A., and Choi, D. W. (1993) Glial glycogen stores affect neuronal survival during glucose deprivation *in vitro*. *J. Cereb. Blood Flow Metab.* **13**, 162–169 [CrossRef Medline](#)
 87. Ransom, B. R., and Fern, R. (1997) Does astrocytic glycogen benefit axon function and survival in CNS white matter during glucose deprivation? *Glia* **21**, 134–141 [CrossRef Medline](#)
 88. Brown, A. M., Sickmann, H. M., Fosgerau, K., Lund, T. M., Schousboe, A., Waagepetersen, H. S., and Ransom, B. R. (2005) Astrocyte glycogen metabolism is required for neural activity during aglycemia or intense stimulation in mouse white matter. *J. Neurosci. Res.* **79**, 74–80 [CrossRef Medline](#)
 89. Walls, A. B., Sickmann, H. M., Brown, A., Bouman, S. D., Ransom, B., Schousboe, A., and Waagepetersen, H. S. (2008) Characterization of 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) as an inhibitor of brain glycogen shunt activity. *J. Neurochem.* **105**, 1462–1470 [CrossRef Medline](#)
 90. Rossi, D. J., Oshima, T., and Attwell, D. (2000) Glutamate release in severe brain ischaemia is mainly by reversed uptake. *Nature* **403**, 316–321 [CrossRef Medline](#)
 91. Bonde, C., Sarup, A., Schousboe, A., Gegelashvili, G., Zimmer, J., and Norberg, J. (2003) Neurotoxic and neuroprotective effects of the glutamate transporter inhibitor DL-threo- β -benzyloxyaspartate (DL-TBOA) during physiological and ischemia-like conditions. *Neurochem. Int.* **43**, 371–380 [CrossRef Medline](#)
 92. Waagepetersen, H. S., Qu, H., Sonnewald, U., Shimamoto, K., and Schousboe, A. (2005) Role of glutamine and neuronal glutamate uptake

THEMATIC MINIREVIEW: Glycogen metabolism in diseased brain

- in glutamate homeostasis and synthesis during vesicular release in cultured glutamatergic neurons. *Neurochem. Int.* **47**, 92–102 [CrossRef](#) [Medline](#)
93. Lebon, V., Petersen, K. F., Cline, G. W., Shen, J., Mason, G. F., Dufour, S., Behar, K. L., Shulman, G. I., and Rothman, D. L. (2002) Astroglial contribution to brain energy metabolism in humans revealed by ^{13}C nuclear magnetic resonance spectroscopy: elucidation of the dominant pathway for neurotransmitter glutamate repletion and measurement of astrocytic oxidative metabolism. *J. Neurosci.* **22**, 1523–1531 DOI not found. [Medline](#)
94. Rothman, D. L., Behar, K. L., Hyder, F., and Shulman, R. G. (2003) *In vivo* NMR studies of the glutamate neurotransmitter flux and neuroenergetics: implications for brain function. *Annu. Rev. Physiol.* **65**, 401–427 [CrossRef](#) [Medline](#)
95. Tani, H., Dulla, C. G., Huguenard, J. R., and Reimer, R. J. (2010) Glutamine is required for persistent epileptiform activity in the disinhibited neocortical brain slice. *J. Neurosci.* **30**, 1288–1300 [CrossRef](#) [Medline](#)
96. Wilson, N. R., Kang, J., Hueske, E. V., Leung, T., Varoqui, H., Murnick, J. G., Erickson, J. D., and Liu, G. (2005) Presynaptic regulation of quantal size by the vesicular glutamate transporter VGLUT1. *J. Neurosci.* **25**, 6221–6234 [CrossRef](#) [Medline](#)
97. Nadeau, O. W., Fontes, J. D., and Carlson, G. M. (February 26, 2018) The regulation of glycogenolysis in the brain. *J. Biol. Chem.* **293**, 7099–7107 [CrossRef](#) [Medline](#)