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Mini-Review

Glycogen: The Forgotten Cerebral Energy Store

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The brain contains a significant amount of glycogen that is an order of magnitude smaller than that in muscle, but several-fold higher than the cerebral glucose content. Although the precise role of brain glycogen to date is unknown, it seems affected by focal activation, neurotransmitters, and overall electrical activity and hormones. Based on its relatively low concentration, the role of brain glycogen as a significant energy store has been discounted. This work reviews recent experimental evidence that brain glycogen is an important reserve of glucose equivalents: (1) glial glycogen can provide the majority of the glucose supply deficit during hypoglycemia for more than 100 min, consistent with the proposal that glial lactate is a fuel for neurons; (2) glycogen concentrations may be as high as 10 μmol/g, substantially higher than was thought previously; (3) glucose cycling in and out of glycogen amounts to ~1% of the cerebral metabolic rate of glucose (CMR_{glc}) in human and rat brain, amounting to an effective stability of glycogen in the resting awake brain during euglycemia and hyperglycemia, (4) brain glycogen metabolism/concentrations are insulin/glucose sensitive; and (5) after a single episode of hypoglycemia, brain glycogen levels rebound to levels that exceed the pre-hypoglycemic concentrations (supercompensation). This experimental evidence supports the proposal that brain glycogen may be involved in the development of diabetes complications, specifically impaired glucose sensing (hypoglycemia unawareness) observed clinically in some diabetes patients under insulin treatment. It is proposed further that brain glycogen becomes important in any metabolic state where supply transiently cannot meet demand, such conditions that could occur during prolonged focal activation, sleep deprivation, seizures, and mild hypoxia.

Key words: brain glycogen; hypoglycemia; ^{13}C NMR spectroscopy

Glycogen represents the largest store of glucose equivalents in the brain and is present in concentrations that exceed by several times the normal concentration of total brain glucose. Although brain glycogen seems vital for normal brain function, its role as an energy reserve has been discounted in the textbook literature, based on its low concentration compared to that in muscle and liver. One aim of this review is to outline recent evidence that supports a role for glycogen as an important store of glucose equivalents also for the brain.

Of course, under conditions of insufficient oxygen supply, glycogen is expected to be rapidly depleted. Indeed, glycogenolysis is rapid in global hypoxic-ischemia, (see Swanson, 1992; Choi et al., 1999, and references therein). The postmortem instability of glycogen in brain makes its measurement difficult using biochemical methods. Recent studies suggest that rat brain glycogen content may have been underestimated previously (Cruz and Dienel, 2002; Kong et al., 2002).

These difficulties in measuring glycogen in extracted brain tissue can be avoided altogether when using localized ^{13}C nuclear magnetic resonance (NMR), which was shown recently to be capable of quantifying brain glycogen metabolism (Choi et al., 1999, 2000; Choi and Gruetter, 2003; Oz et al., 2003). Localized ^{13}C NMR spectroscopy is non-invasive and thus brain glycogen metabolism can be followed in a single animal for several hours. Insights into the regulation of glycogen metabolism in animals and humans alike should now be possible.

This article provides an overview of recent insights into brain glycogen metabolism already gained with this emerging method, and a mechanism for regulation of glycogen metabolism in relation to hypoglycemia is proposed. Furthermore, a role for brain glycogen in the syndrome of hypoglycemia unawareness is proposed.

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BRAIN GLYCOGEN IS A SIGNIFICANT ENERGY RESERVE

Based on a small concentration of brain glycogen and a total glucose metabolic rate ranging between 0.3 μmol/g/min in humans to 1.4μmol/g/min in rodents, it has been argued that 3μmol/g of glycogen can sustain glycolysis for at most 10 min, which is generally taken as an argument that glycogen does not serve as an important glucose reservoir (Siesjo, 1978; Siegel and Agranoff, 1999). Glycogen need only account for part of the glucose supply deficit during hypoglycemia, however, and hence can survive longer periods of sustained hypoglycemia. This shall be illustrated with the following argument that is based on specific kinetic constants of brain glucose transport (it should be recognized that the conclusions do not depend critically on the specific values being used.): The apparent Michaelis-Menten constant of glucose transport across the blood-brain barrier (BBB), K_t, is 1–3 mM (Gruetter et al., 1998; Choi et al., 2001; de Graaf et al., 2001; Seaquist et al., 2001), within experimental accuracy of the Michaelis-Menten constant K_m of the ubiquitous glucose transporter at the blood-brain barrier (BBB), i.e., GLUT-1. The low K_t implies that over much of the physiological glucose concentrations, glucose transport can operate at close to maximum capacity. It also implies that when plasma glucose concentrations approach K_t, the glucose transport capacity decreases and at some point (see below) becomes rate-limiting for metabolism, in a manner that depends on the rate of glucose utilization, CMR_{glc}. Glucose becomes rate-limiting for metabolism when its concentration approaches that of the K_m of hexokinase (~50 μM). Therefore, brain glucose concentrations measured by NMR that are close to zero indicate metabolism limited by the glucose available to the brain cell. Even at a brain glucose concentration close to zero, however, glucose is transported across the BBB. For example, using recent kinetic constants derived in the α-chloralose anesthetized brain, where K_t~3 mM and the relative apparent maximal glucose transport rate T_{max}/CMR_{glc} = 2.7 (Choi et al., 2001), glucose transport provides ~90% of the resting CMR_{glc} at 1.5 mM plasma glucose concentrations. Assuming a basal glucose consumption of 0.4 μmol/g/min, a 10% deficit in glucose supply corresponds to a compensatory glycogenolytic rate of 0.04 μmol/g/min, which would completely deplete brain glycogen only after about 120 min of such hypoglycemia. Experimentally, it was very difficult to completely eliminate all brain glycogen during 2 hr of hypoglycemia (Fig. 1). The presence of substantial brain glycogen levels even after periods of profound hypoglycemia supports the hypothesis that brain glycogen is a significant store of glucose equivalents, protecting the brain in periods of glucose need under normoxic conditions.

Interestingly, glycogen degradation started at a brain glucose concentration of 0.1 ± 0.1 μmol/g (vertical dashed line in Fig. 1) (Choi et al., 2003), and cerebral blood flow (CBF) was acutely increased (Choi et al., 2001). This is the point at which brain glucose content became rate-limiting for metabolism (Gruetter et al., 2000; Choi et al., 2003) and thus points to insufficient glucose phosphorylation being important in activating cerebral defenses against a deficiency in fuel supply. Together with the apparent stability of glycogen in the non-stimulated brain at euglycemia or hyperglycemia (see below), these data suggest that brain glucose plays an important, yet most likely indirect, regulatory role in cerebral glycogenolysis. Whether the regulation is at the level of glucose phosphorylation or is a downstream consequence of inadequate glucose-6-phosphate generation remains to be determined. The proposed role and control of glial glycogen is illustrated in the scheme in Figure 2.

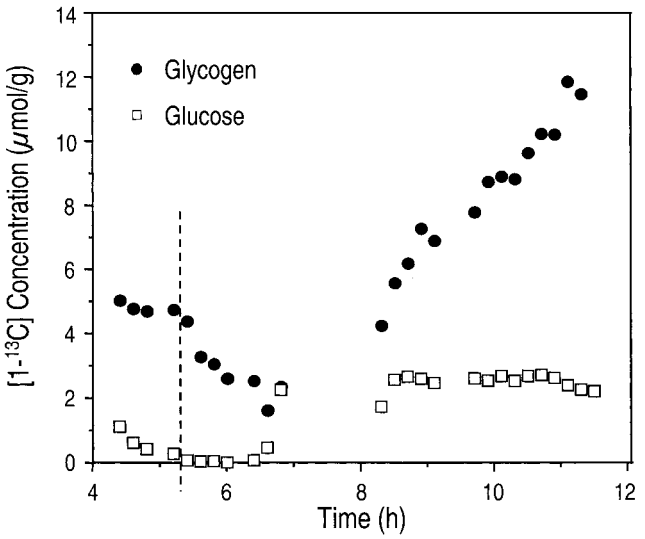

Fig. 1. Brain glycogen metabolism in the rat. Time-course of glycogen C1 and glucose C1 before, during and after hypoglycemia, which was induced by administering insulin. During hypoglycemia, plasma glucose concentration was below 2 mM for 2 hr. The vertical dotted line indicates the start of glycogenolysis during hypoglycemia, which coincided with the time point where brain glucose approached zero. Adapted from (Choi et al., 2003).

It was interesting to note that the rate of brain glycogen degradation observed experimentally was ~0.04 μmol/g/min and accounted for the majority of the estimated glucose supply deficit of 0.15 CMR_{glc} during the hypoglycemic period, 0.06 μmol/g/min (Choi et al., 2003). Because in vivo most oxygen metabolism is reported to occur in neurons (Cruz and Cerdan, 1999; Gruetter et al., 2001; Bluml et al., 2002; Lebon et al., 2002), this result implies that a net transfer of fuel must have occurred from glial glycogen to neuronal oxygen metabolism (Fig. 2), consistent with the recent proposal that lactate generated by astrocytes is a fuel for neurons whose metabolism is linked to that of astrocytes (Magistretti and Pellerin, 1996) and a constant brain lactate concentration during hypoglycemia (unpublished observation).

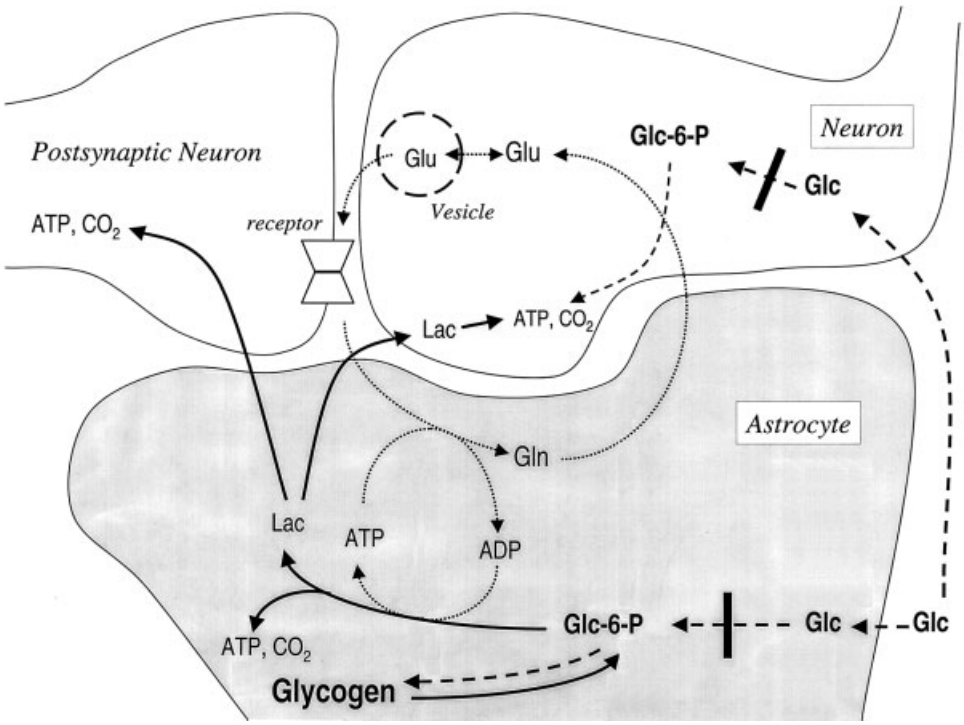

Fig. 2. Scheme depicting a potential role for astrocytic glycogen in neuroprotection during hypoglycemia. When glucose phosphorylation is limited by the low brain glucose concentration, astrocytic glycogenolysis can provide the necessary glucosyl units to maintain ATP synthesis in the glial compartment (thick solid lines), which can maintain glutamate uptake into the astrocyte to avoid glutamate excitotoxicity (dotted lines). Glycogen can provide fuel to neurons in the form of lactate during hypoglycemia and thus reduce the energy deficit in the neuronal compartment (Dringen et al., 1993; Magistretti and Pellerin, 1996). When glucose supply is sufficient and in the presence of insulin, glucose is stored in glial glycogen (dashed lines).

INSULIN, DIABETES AND BRAIN GLYCOGEN

In contrast to other tissues, bulk brain glucose metabolism is considered largely insulin-insensitive. As in other tissues, however, brain glycogen metabolism and possibly concentrations have been shown to be affected strongly by plasma insulin and/or glucose concentrations (see Choi et al., 1999, 2003 and references therein). Insulin can exert its control over brain glycogen metabolism by being transported across the BBB, by insulin receptors in the brain and possibly at the endothelial cell. Whatever the precise mechanism of regulation, the apparent role as an energy reserve during hypoglycemia and its insulin-sensitivity make brain glycogen a likely player in the cerebral sequelae of iatrogenic hypoglycemia encountered frequently in diabetes.

Tight glycemic control has been shown to reduce complications of diabetes, however, an increased frequency of hypoglycemia is a major problem in the intensive insulin treatment of diabetes. Sudden drops in plasma glucose are prevented normally by an interaction of pancreas, liver, muscle, and brain resulting in hormonal regulation ("counterregulation") to maintain a close to normal plasma glucose concentration. Counterregulation is known to be defective after a single episode of insulin-induced hypoglycemia in patients and normal individuals alike (hypoglycemia unawareness), whether they are awake or not (Veneman et al., 1993). Hypoglycemia unawareness leads to a vicious cycle of increasing frequency and severity of hypoglycemia, the reversal of which requires strict avoidance of hypoglycemia for 1–2 weeks (Cryer, 2002).

After a single hypoglycemic episode, measurements (Fig. 1) indicated that brain glycogen increased above the basal level and beyond. This rebound or supercompensation seemed unabated several hours after restoring glycemia in many studies, reaching levels up to three times the normal brain glycogen concentration (Fig. 1). Supercompensation of brain glycogen has been observed after sleep deprivation (Kong et al., 2002) or hypoxic ischemia (Brucklacher et al., 2002). Studies in astrocyte-neuronal co-cultures preloaded with glycogen and in the postnatal rat have reported that preloaded brain glycogen results in increased neuroprotection (Swanson and Choi, 1993; Brucklacher et al., 2002), consistent with neuroprotective effects of glycogen on axons in aglycemia (Brown et al., 2003). It has been proposed that brain glycogen metabolism may be a factor involved in the mechanism of the hypoglycemia unawareness syndrome observed clinically in patients with type I diabetes (Choi and Gruetter, 2003; Choi et al., 2003). Specifically, we hypothesize that because of the importance of brain glycogen as a fuel reserve in the brain, excess brain glycogen will have a neuroprotective effect in subsequent episodes of hypoglycemia. We hypothesize further that such neuroprotection occurs due to increased glucose release during subsequent episodes of hypoglycemia, which can interfere with proper recognition of hypoglycemia. A possible mechanism by which increased release of glucose equivalents from glycogen in neighboring glia could interfere with the operation of glucose-sensing neurons would be through the release of more fuel in the form of lactate from glycogen (Fig. 2).

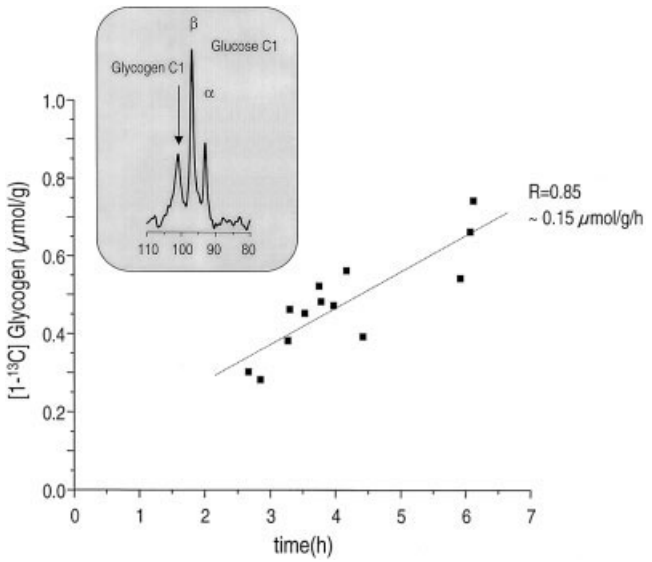

Fig. 3. Measurement of glycogen in the human brain. The inset shows the spectral region containing the glycogen C1 (arrow) and glucose C1 resonances of the ^{13}C NMR spectrum. The graph indicates a slow increase in [1-^{13}C] glycogen, which occurred at an extremely slow rate on the order of 0.15 μmol/g/hr in the human brain, containing measurements from three different studies. From Oz et al. (2003).

HUMAN BRAIN GLYCOGEN METABOLISM

Brain glycogen concentrations increase with anesthesia or depressed electrical activity (Swanson, 1992; Choi et al., 2002) and brain glycogen metabolism was reported to be changed during focal activation (Swanson, 1992; Dienel et al., 2002). Consistent with these observations, brain glycogen metabolism in the anesthetized rat brain was very slow, whether under light α-chloralose (Choi et al., 1999) or deep pentobarbital anesthesia (Choi et al., 2002). In the absence of strong focal stimulation, however, bulk brain glycogen turnover was very slow even in the awake rat brain, on the order of 0.5 μmol/g/hr (Choi and Gruetter, 2003).

Because all previous studies of brain glycogen metabolism were carried out with animals, the question remained of the magnitude of brain glycogen metabolism in the conscious human brain. Most recently, a reproducible measurement of the brain glycogen signal was reported in the normal human brain using ^{13}C NMR spectroscopy (Oz et al., 2003) (Fig. 3). Furthermore, these initial results demonstrated that brain glycogen metabolism was extremely slow (with a flux through glycogen synthase of 0.1–0.2μmol/g/hr) in subjects measured in the awake, resting condition (Fig. 3). Cycling of glucose in and out of glycogen was ~0.5% of CMR_{glc} in the conscious, unstimulated human brain at euglycemia and above. This observation was in excellent agreement with previous studies showing that under the conditions of this study (plasma glucose at euglycemia or higher and concomitant hyperinsulinemia), the brain glucose concentration is well above the K_m of hexokinase (Gruetter et al., 1998; Seaquist et al., 2001). As a consequence, a brain glycogen pool of a few μmol/g is expected to have a turnover time on the order of 2 days. Because concentration changes are induced by a mismatch in catabolic and anabolic fluxes of glycogen, elevated brain glycogen concentrations, such as the ones seen after hypoglycemia in the rat (Choi et al., 2003), may take several days to weeks to be normalized, which incidentally is consistent with the time it takes to restore the hypoglycemia unawareness syndrome (Cryer, 2002).

CONCLUSIONS

Glycogen likely is a viable and important store of glucose equivalents in the brain, whose metabolism is also affected by hormones, neurotransmitters and second messengers (Sorg and Magistretti, 1992). The sensitivity of brain glycogen metabolism to insulin, glucose and the profound effect of hypoglycemia on brain glycogen metabolism point to the potential involvement of brain glycogen in the hypoglycemia unawareness syndrome in patients with diabetes.

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