Molecular Aspects of Medicine 46 (2015) 70–77

Contents lists available at ScienceDirect

Molecular Aspects of Medicine

journal homepage: www.elsevier.com/locate/mam

Review

Brain glycogen in health and disease

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ARTICLE INFO

Article history:
Received 21 August 2015
Accepted 21 August 2015
Available online 5 September 2015

Keywords:
Brain
Neuron
Glycogen
Glycogen synthase
Lafora disease
Corpora amylacea

ABSTRACT

Glycogen is present in the brain at much lower concentrations than in muscle or liver. However, by characterizing an animal depleted of brain glycogen, we have shown that the polysaccharide plays a key role in learning capacity and in activity-dependent changes in hippocampal synapse strength.

Since glycogen is essentially found in astrocytes, the diverse roles proposed for this polysaccharide in the brain have been attributed exclusively to these cells. However, we have demonstrated that neurons have an active glycogen metabolism that contributes to tolerance to hypoxia. However, these cells can store only minute amounts of glycogen, since the progressive accumulation of this molecule leads to neuronal loss.

Loss-of-function mutations in laforin and malin cause Lafora disease. This condition is characterized by the presence of high numbers of insoluble polyglucosan bodies, known as Lafora bodies, in neuronal cells. Our findings reveal that the accumulation of this aberrant glycogen accounts for the neurodegeneration and functional consequences, as well as the impaired autophagy, observed in models of this disease. Similarly glycogen synthase is responsible for the accumulation of *corpora amylacea*, which are polysaccharide-based aggregates present in the neurons of aged human brains.

Our findings change the current view of the role of glycogen in the brain and reveal that endogenous neuronal glycogen metabolism is important under stress conditions and that neuronal glycogen accumulation contributes to neurodegenerative diseases and to aging-related *corpora amylacea* formation.

Contents

1. Brain glycogen

Cells store glucose in the form of a branched polymer called glycogen, the main function of which is to act as

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http://dx.doi.org/10.1016/j.mam.2015.08.007
0098-2997/

energy and carbon storage in a molecular form readily available to tissues dependent on glucose oxidation. Glycogen accumulated in muscle is assumed to provide fuel for contraction during physical activity. In contrast, liver glycogen provides glucose to the rest of the body during fasting periods. Glycogen synthase (GS), the only enzyme able to catalyze the synthesis of glucose polymers in mammals, has two isoforms: one muscular (MGS, encoded by the GYS1 gene), which is found in most tissues, and one liver-specific (LGS). GS catalyzes the growth of the outer branches of the glycogen molecule by forming alpha-1,4-glucosidic bonds, while the glycogen branching enzyme introduces the alpha-1,6-glucosidic bonds that form the branching points. The coordinated action of these enzymes results in a properly branched glycogen molecule, which is soluble and can be readily degraded by glycogen phosphorylase (GP) and debranching enzyme when required. There are three tissue-specific isoforms of GP in mammals, namely the muscle (MGP), liver (LGP), and brain (BGP) isoforms. Nevertheless, in addition to BGP, MGP is also expressed in brain. Glycogen synthesis and degradation are highly regulated processes that contribute to glucose homeostasis. Several regulatory mechanisms control GS activity, including, but not limited to, phosphorylation, allosteric activation by glucose-6-phosphate, and intracellular localization. Protein targeting to glycogen (PTG, a regulatory subunit of protein phosphatase PP1) plays a key role in the activation of GS by dephosphorylation (Roach et al., 2012). GP activity is also regulated by phosphorylation and allosteric activation. MGP is activated mainly through phosphorylation and is therefore primarily tailored to respond to extracellular signals. In contrast, BGP, which is extremely sensitive to increases in AMP levels, is more adapted to providing energy for internal needs (Crerar et al., 1995).

The central nervous system (CNS) is an interesting case in relation to glycogen metabolism. In embryonic stages, glycogen appears in glial and neuronal cells, but in adults this polysaccharide is found almost exclusively in astrocytes (Cataldo and Broadwell, 1986). The human brain contains around 1 g of glycogen (0.1% of the tissue weight). This concentration is 10 times lower than that in skeletal muscle and 100 times lower than that in liver (Nelson et al., 1968). Thus, it is not surprising that the contribution of brain glycogen as an energy reserve for long-term activity has been overlooked, and it is widely accepted that brain is energetically dependent on the delivery of glucose from systemic circulation (Brown, 2004). However, brain glycogen content has been proposed to be a short-term energy source that supports local and specific neural activities, such as memory formation (Suzuki et al., 2011), sensory stimulation (Brown et al., 2003; Cruz and Dienel, 2002; Swanson et al., 1992), and sleep and wake cycles (Franken et al., 2003; Gip et al., 2002; Kong et al., 2002; Petit et al., 2002; Scharf et al., 2008). Furthermore, brain glycogen is protective under stress and pathological conditions such as hypoglycemia (Brown et al., 2003; Herzog et al., 2008; Wender et al., 2000), exhaustive exercise (Matsui et al., 2012), ischemia (Brown, 2004), and seizures (Bernard-Helary et al., 2000; Cloix et al., 2010). It is also accepted that neurons – through neurotransmitters and neuromodulators – stimulate the mobilization of astrocyte glycogen reserves, which are converted into lactate to be taken up and utilized by neurons (Belanger et al., 2011).

In order to unequivocally approach the study of the role of glycogen in the brain, we generated a mouse model that lacks GS specifically in the nervous system ($GYS1^{Nestin\text{-}KO}$). We analyzed the learning capacity of these animals and checked for differences in the electrophysiological properties of the hippocampal CA3–CA1 synapse (Duran et al., 2013). Our results demonstrate the contribution of brain glycogen to associative learning and to the related changes in hippocampal synaptic strength, as well as to the experimental induction of long-term potentiation (LTP) in hippocampal synapses. Overall, we demonstrate that the lack of GS, and thus of glycogen, in the brain produces a significant deficit in learning capacity and in activity-dependent changes in hippocampal synapse strength (Fig. 1). These observations point to a key role of brain glycogen in the proper and timed acquisition of relatively difficult learning tasks.

2. Neuronal glycogen

Although glycogen is not normally detected in neurons, these cells express MGS (Inoue et al., 1988) and have the machinery to synthesize glycogen (Vilchez et al., 2007). The presence of GP in this cell type has been a matter of debate. Although the presence of GP in neurons was reported many years ago (Ibrahim et al., 1970; Pellegri et al., 1996), it was later accepted that these cells lack this enzyme (Pfeiffer-Guglielmi et al., 2003). By using a highly sensitive method, we were able show that neurons express the brain isozyme and not the muscle one, while astrocytes express both (Pfeiffer-Guglielmi et al., 2003). Furthermore, we demonstrated that – against general belief – neurons do have an active glycogen metabolism (Saez et al., 2014), which protects cultured neurons from hypoxia-induced death and *Drosophila* flies from hypoxia-induced stupor (Fig. 2). However, the glycogen content of neurons is maintained very low, which may explain why the presence of this polysaccharide in this cell population has been overlooked. These findings change the classical view of the role of glycogen in the brain and reveal that endogenous glycogen metabolism contributes to neuron survival.

Neurons keep glycogen concentrations very low because the overaccumulation of this polysaccharide induces apoptosis (Vilchez et al., 2007). We generated a mouse model conditionally overexpressing a form of GS resistant to inactivation, in which the serines whose phosphorylation causes the inactivation of the enzyme are replaced by alanine. Using this model, we demonstrated that the accumulation of glycogen in mouse and *Drosophila* neurons leads to the loss of this cell type, locomotion defects, and reduced lifespan (Fig. 3) (Duran et al., 2012). These results unveil glycogen accumulation in neurons as a direct cause of neurodegeneration. Thus, the concentration of glycogen in neurons must be tightly regulated, keeping it to low, although functional, levels.