# Glycogen: a Trojan horse for neurons

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**Neural activity leads to the mobilization of energy from glycogen in astrocytes. A new paper reports that neurons have an ambivalent relationship with glycogen: they can synthesize it themselves, but that synthesis induces apoptosis. Presumably for this reason, neurons normally inhibit glycogen synthesis through two redundant pathways.**

Glycogen, the single largest energy reserve of the brain[1], is mobilized by neuronal activity[2], probably to match the increased energy requirements associated with it. Glycogen metabolism provides a clear example of neuron-glia metabolic coupling. Glycogen is almost exclusively localized in astrocytes, whereas the neurotransmitters and neuromodulators that mobilize glycogen are released by active neurons[3].

Glycogen is regulated by two key enzymes, glycogen synthase and glycogen phosphorylase. Phosphorylation inhibits glycogen synthase and increases the activity of glycogen phosphorylase, resulting in glycogenolysis. In cortical slices, glycogenolysis is triggered by noradrenaline, vasoactive intestinal peptide, adenosine and ATP[1] through cyclic AMP– or calcium-dependent intracellular signaling. During glycogenolysis, astrocytes release lactate as an energy substrate for neurons[4–6]. This is a nice story, to which Vilchez *et al.*[7] add an unexpected and very instructive chapter in this issue.

The authors provide evidence that neurons also have the enzymatic machinery for synthesizing glycogen, as they express glycogen synthase, but that its activity is kept silent by a series of well-coordinated intracellular mechanisms. They go on to show that failure to keep glycogen synthase under control, resulting in glycogen synthesis, damages neurons by triggering apoptotic signaling. In addition, the glycogen that neurons synthesize is abnormal and causes the accumulation of granular deposits that cannot be mobilized. Such deposits, dubbed Lafora bodies, are characteristic of a form of progressive myoclonus epilepsy, Lafora disease.

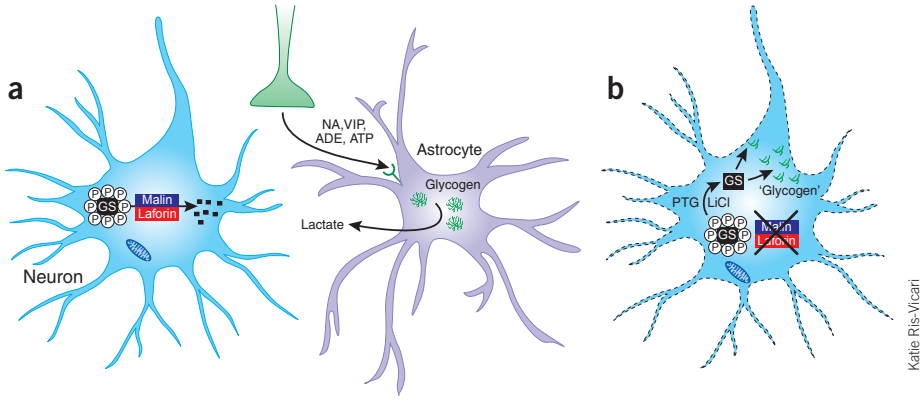


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**Figure 1** Glycogen metabolism in the brain and its dysregulation in Lafora disease. (**a**) Under normal circumstances, astrocytes synthesize and store glycogen. Neurotransmitters such as noradrenaline (NA), vasoactive intestinal peptide (VIP), adenosine (ADE) or ATP trigger the breakdown of glycogen to enable the release of lactate, which is taken up as fuel by neurons. In neurons, glycogen synthase (GS) is hyperphosphorylated and thereby inactivated. The malin-laforin complex targets hyperphosphorylated GS for ubiquitin proteasome–dependent degradation. No glycogen is synthesized in neurons. (**b**) In Lafora disease, either malin or laforin is mutated. Thus, hyperphosphorylated GS escapes degradation and can be activated by dephosphorylation. Vilchez *et al.*[7] show that either inhibition of glycogen synthase kinase by LiCl or by overexpression of the protein phosphatase 1 regulatory subunit PTG can activate GS in neurons, leading to the accumulation of abnormally branched glycogen species that are toxic to neurons (as indicated by the dashed cell outline.)

Vilchez *et al.*[7] also unravel the mechanisms that go astray when neurons synthesize glycogen. First the authors show that glycogen synthase is present in cultured neurons in a highly phosphorylated, and thus inactive, state. When dephosphorylation is induced by LiCl, an inhibitor of glycogen synthase kinase (the main kinase that keeps glycogen synthase phosphorylated), neurons synthesize large amounts of glycogen. The authors show that overexpression of protein targeting to glycogen (PTG), a regulatory subunit of protein phosphatase 1 that activates glycogen synthase by stimulating its dephosphorylation[8,9], also leads to abnormal glycogen accumulation in neurons (**Fig. 1**).

The study[7] also provides a molecular link between neuronal accumulation of abnormal glycogen deposits and Lafora disease. This autosomal recessive form of epilepsy—characterized by tonic-clonic, myoclonus and absence seizures progressing to dementia, vegetative state and death within a decade of its inception during adolescence—is associated with mutations in two genes encoding the enzymes laforin and malin. Patients with mutations of either laforin or malin express

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similar clinical manifestations, suggesting that these two proteins operate through common mechanisms[10]. Laforin is a phosphatase that interacts with PTG[11] and has a functional carbohydrate-binding domain. Malin is a ubiquitin ligase that causes ubiquitination and proteasome-mediated degradation of laforin[12].

In a series of elegant experiments, Vilchez *et al.*[7] brought the pieces of the puzzle together. They showed that the massive induction of glycogen synthase activity and of abnormal glycogen deposition induced in neurons when PTG is overexpressed is abolished by the concomitant overexpression of both laforin and malin. (Overexpressing either one alone had no effect.) They also demonstrated that the malin-laforin complex markedly decreases PTG and glycogen synthase protein levels, thus inactivating the glycogen-synthesizing machinery, through a mechanism mediated by activation of the ubiquitin-proteasome pathway. If a form of malin containing a mutation observed in individuals with Lafora disease is cotransfected in neurons with laforin instead of the wild-type malin, the inhibitory effect on PTG and glycogen synthase expression and activity is lost.

These results provide an explanation for previous puzzling observations of glycogen synthase in neurons *in situ*[13], although glycogen could not be observed in these cells in the adult brain. Vilchez *et al.*[7] report that neurons have the capacity to synthesize glycogen. However, glycogen spells trouble for neurons as it triggers a proapoptotic program. Accordingly, neurons have effective and redundant mechanisms for inhibiting glycogen synthesis. The first mechanism is to keep glycogen synthase in a phosphorylated (inactive) state. The second is to degrade PTG and glycogen synthase in a tonic, proteasome-dependent manner involving the malin-laforin complex. Mutations in the genes encoding these enzymes are found in individuals affected by Lafora disease, a condition that is histopathologically characterized by the presence of glycogen-like deposits in neurons. Thus it appears that neurons have an ambivalent relationship with glycogen; they benefit from it as long as it is localized in astrocytes and so long as they are provided with energy substrates deriving from it, most likely lactate. Increasing astrocytic glycogen has a neuroprotective effect in experimental stroke[5,14]. However, when synthesized inside of neurons, glycogen acts as a Trojan horse, triggering mechanisms that lead to neuronal dysfunction and eventually death.

Although Vilchez *et al.*[7] bring some new insights to the regulation of brain glycogen metabolism, this report raises several questions. For example, through what mechanism(s) does accumulation of abnormally branched glycogen trigger apoptosis? Why are astrocytes 'immune' to the destructive effects of glycogen accumulation? The actual link between glycogen accumulation in neurons and the clinical phenotype of Lafora disease still remains to be elucidated. Most curiously, why are neurons endowed with the potential for glycogen synthesis, but then activate complex protein-protein interaction mechanisms to keep this potential inhibited? Paradoxically, this inhibitory mechanism is likely to consume energy. One possibility raised by the authors is that glycogen synthase has other, yet undiscovered, roles in neuronal functions. This article is likely to bring a renewed attention to the study of glycogen regulation in the brain, a field that has evolved in a low-key but steady fashion over the last 25 years and is likely to still bring surprising insights into neuron-glia physiology and pathology in the years to come[3].


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# A step toward optimal coding in olfaction

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**Receptor neurons may not encode sensory information in an efficient manner. A new paper supports the idea that the brain achieves optimal encoding downstream of sensory transduction through additional processing.**

Sensory information is converted into neural activity by receptor neurons and then shaped by subsequent processing stages into a neural representation that can direct behavior. Our understanding of early steps along this pathway has been guided by the concept of optimal coding. Receptor neurons, having to handle the complexities of sensory transduction, may not be able to respond in ways that optimally encode information for particular tasks. According to the idea of optimal coding, subsequent processing may involve a transformation to a more efficient representation. In this issue, Bhandawat *et al.*[1], reporting on the *Drosophila* olfactory system, provide strong support for this idea and also raise interesting questions.

In the fly olfactory system, sensory transduction takes place in olfactory receptor neurons (ORNs), and olfactory signals are relayed in the antennal lobe (the insect analog of the olfactory bulb) through glomeruli that receive direct sensory input from ORNs that all express the same olfactory receptor gene[2,3]. Output from the antennal lobe is carried by projection neurons that each receive their input from a single glomerulus. Intrinsic projection-neuron response characteristics, properties of the synaptic connections made by ORNs and projection neurons, and features of the circuitry in and between glomeruli can all contribute to making projection neurons respond differently than ORNs (**Fig. 1a**). However, ORNs not directly connected to a given projection neuron can only influence that projection neuron through interglomerular connections within the antennal lobe. Recent studies[4–7] have revealed interesting features of interglomerular interactions, but their functional role has remained unclear. Bhandawat *et al.*[1] provide

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