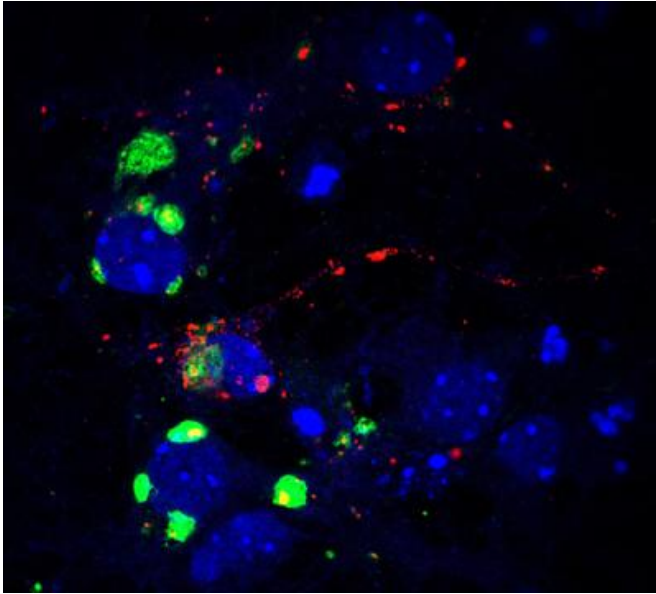


Researchers reveal the dual role of brain glycogen

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Neurons accumulate glycogen in small amounts, which is beneficial for them. Glycogen synthase is shown in green, and glycogen accumulation is shown in red. Credit: Isabel Sáez, Institute for Research in Biomedicine

In 2007, in an article published in *Nature Neuroscience*, scientists at the Institute for Research in Biomedicine (IRB Barcelona) headed by Joan Guinovart, an authority on glycogen metabolism, reported that in Lafora Disease (LD), a rare and fatal neurodegenerative condition that affects adolescents, neurons die as a result of the accumulation of glycogen—chains of glucose. They went on to propose that this accumulation is the root cause of this disease.

The breakthrough of this paper was two-sided: first, the researchers established a possible cause of LD and therefore were able to point to a plausible therapeutic target, and second, they discovered that neurons have the capacity to store glycogen—an observation that had never been

made—and that this accumulation was toxic.

Some scientists sceptical about the article upheld that the glycogen deposits were not cause by the neurodegeneration but were a consequence of another, more important, cell imbalance, such as a down deregulation of autophagy—the cell recycling and cleaning programme. In several articles, Guinovart's "Metabolic engineering and diabetes therapy" group has recently brought to light evidence of the toxicity of glycogen deposits for LD patients, and has now provided irrefutable data.

In an article published at the beginning of February in *Human Molecular Genetics*, with the associate researcher Jordi Duran as first author, the scientists show that in LD the accumulation of glycogen directly causes neuronal death and triggers cell imbalances such a decrease in autophagy and synaptic failure. All these alterations lead to the symptoms of LD, such as epilepsy.

Glycogen, a Trojan horse for neurons?

There was still a greater mystery to be solved. Was glycogen synthase truly a Trojan horse for neurons, as apparently established in the article in *Nature Neuroscience*? That is to say, was the accumulation of glycogen always fatal for cells, thus explaining why their glycogen synthesis machinery is silenced? The inevitable question was then why these cells had such machinery.

In another paper published in *Journal of Cerebral Blood Flow & Metabolism*, part of the Nature Group, the researchers provided the first evidence that neurons constantly store glycogen but in a different way: accumulating small amounts and using it as quickly as it becomes available. In this regard, the scientists set up new, more sensitive, analytical techniques to confirm that the machinery responsible for glycogen synthesis and degradation existed. In summary, they showed that, in small amounts, glycogen is beneficial for neurons.

"For example, while the liver accumulates glycogen (IRB Barcelona) in large amounts and releases it slowly to maintain blood sugar levels, above all when we sleep, neurons synthesise and degrade small amounts of this polysaccharide continuously. They do not use it as an energy store but as a rapid and small, but constant, source of energy," explains Guinovart, also senior professor at the University of Barcelona (UB).

To observe the action of glycogen, the scientists forced cultured mouse neurons to survive under oxygen depletion. They demonstrated that the first cells to die were those in which the capacity to synthesise glycogen had been removed. The same experiments were performed in collaboration with Marco Milán's "Development and growth control" group in the in vivo model of the fruit fly *Drosophila melanogaster*. These tests led to the same conclusions.

The researchers postulated that glycogen is a lifeguard under oxygen depletion, a condition that leads the brains to shut down and that often occurs at birth and in cerebral infarctions in adults, which leads to severe consequences, such a cerebral paralysis.

"It is the first function of glycogen that we have discovered in neurons, but we still have to identify its function in normal conditions and establish how the mechanism works," says Jordi Duran. Postdoctoral researcher Isabel Saez is the first author of the article out today, which involved the collaboration of ICREA Research Professor Marco Milán's lab.

The beneficial and toxic roles of brain [glycogen](#) are currently the focus of main research lines conducted by Joan Guinovart's lab.

More information: *Human Molecular Genetics* (2014)1–10. AOP 4 february, [DOI: 10.1093/hmg/ddu024](#)
Nature NeuroScience (2007) [DOI: 10.1038/nn1998](#) (2007)

Provided by Institute for Research in Biomedicine

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