The accumulation of sugar in neurons may explain the origin of several neurodegenerative diseases

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A phenomenon considered healthy for cells, such as the accumulation of long chains of glucose (glycogen), which tissues store for energy purposes, is harmful for neurons. Published in the latest issue of *Nature Neuroscience*, this finding has been made by a team of Spanish researchers led by Joan J. Guinovart, director of the Institute for Research in Biomedicine (IRB Barcelona) and senior professor at the University of Barcelona (UB), and Santiago Rodríguez de Córdoba, research professor at the Centro Superior de Investigaciones Científicas (CSIC).

This research has been possible thanks to close collaboration between these two groups, who, in addition, have been assisted by neurobiology expert Eduardo Soriano, who is also a researcher at IRB Barcelona and senior professor at the UB.

The researchers made the discovery while studying Lafora disease, a rare pathology that causes irreversible neurodegeneration in adolescents and for which no treatment is available. Lafora disease generally presents as epileptic seizures between 10 to 17 years of age and later on as myoclonus (involuntary twitching of the arms and legs). Its evolution is marked by progressive degeneration of the nervous system which reduces the patient to a terminal vegetative state ten years after its onset. This disease is inherited from parents who are carriers of mutations in one of the two genes associated with the pathology. These genes are

called laforin (named after Dr. Lafora) and malin (from the French expression “le grand mal”, used to refer to epilepsy). The disease is characterized by the accumulation of abnormal inclusions, known as Lafora bodies, in neurons.

The study describes the function of laforin and malin, explains the origin of Lafora bodies and identifies how the neurodegenerative process of this disease arises. Joan J. Guinovart, expert in glycogen metabolism explains, “We have observed that laforin and malin act jointly as “guardians” of glycogen levels in neurons and are stimulated by the degradation of the proteins responsible for glucose accumulation. In a situation in which either of the two genes loses its function, these proteins are not degraded, glycogen accumulates and thus neurons deteriorate and cell suicide (apoptosis) ensues.

The conclusions of the study have increased expectations of finding a strategy to treat Lafora disease. One strategy consists of identifying a molecule with the capacity to inhibit glycogen synthesis in neurons.

The breakthroughs on the mechanisms that trigger and block the production of glycogen may be of great use to address the study of other neurodegenerative and neurological diseases. “We have extended the hypothesis of the study to other pathologies in which glycogen has been detected in neurons because our results suggest that this molecule is a part of the problem” comments Guinovart.

Spanish research contributions to Lafora disease have significantly improved our understanding of this pathology. These contributions date back to observations made by the physician Gonzalo Rodríguez Lafora, one of Santiago Ramón y Cajal’s students, who, in 1911, discovered the presence of “Lafora bodies” in the nervous system of patients with the disease that carries his name. In 1999, the team headed by Rodríguez de Córdoba, together with José María Serratosa, identified the laforin gene.

Source: Institute for Research in Biomedicine (IRB Barcelona)