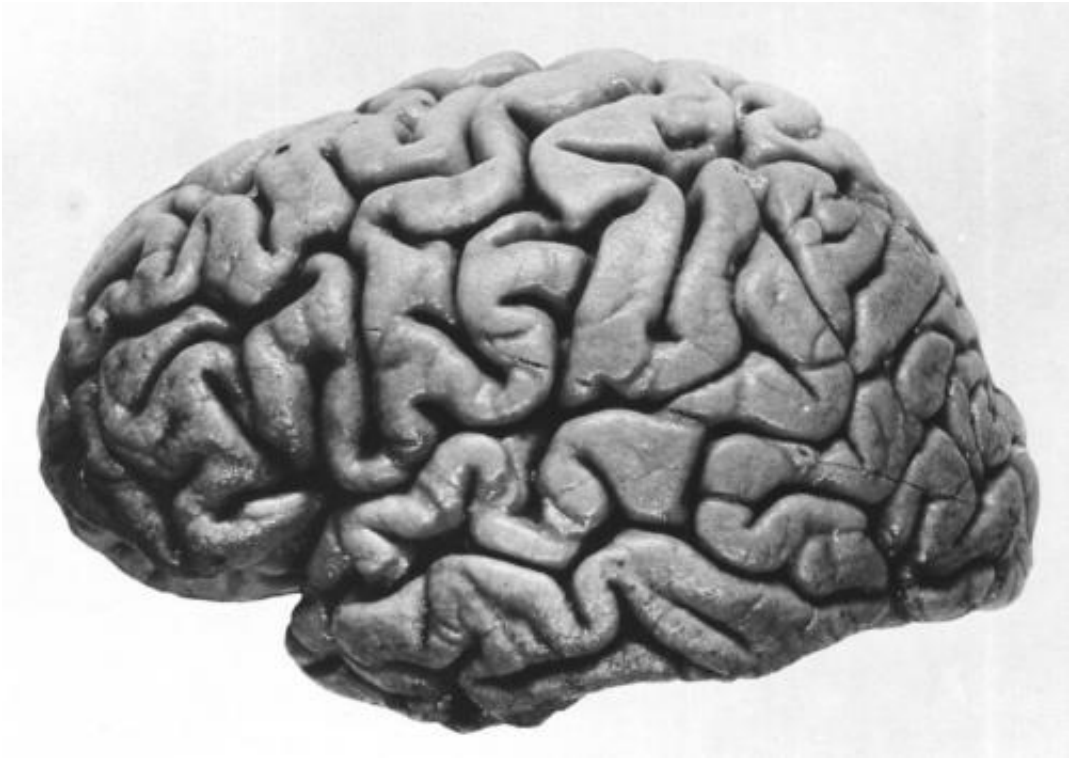
Glutamate, an essential food for the brain

October 1 2015



Left hemisphere of J. Piłsudski's brain, lateral view. Credit: public domain

Glutamate is an amino acid with very different functions: in the pancreas, it modulates the activity of the pancreatic ß-cells responsible for insulin production, whereas in the brain it is the main excitatory neurotransmitter. In recent years, it has been suspected to play an additional role in the functioning of the brain. By discovering how the brain uses glutamate to produce energy, researchers at the University of Geneva (UNIGE) confirm this hypothesis and highlight unexpected links

with the rest of the body. To read in *Cell Reports*.

Unlike other organs, the brain cannot draw its energy from lipids, an energy resource widely present in the body. The blood-brain barrier, which protects it from the pathogens and toxins circulating in the blood, indeed limits the passage of these lipids. Moreover, while most of the organs in the human body have the ability to store glucose by increasing their mass, the brain, prisoner of the cranial bones, cannot count on these variations in volume. Unable to store its food, it depends on sugar supplied in real-time by the rest of the body. This distribution of energy is controlled by the liver.

Pierre Maechler, professor at the Faculty of Medicine at UNIGE, and his team therefore decided to verify if glutamate was indeed an energy source for the brain. To do so, the researchers analyzed the role of the glutamate dehydrogenase enzyme in the brain. In mutant form, this enzyme, encoded by the Glud1 gene, is responsible for a congenital hyperinsulinism syndrome, a severe disease affecting at the same time the endocrine pancreas, the liver and the brain. Individuals affected by this syndrome suffer from intellectual disability and have a high risk of epilepsy. "We have suppressed the Glud1 gene in the brain of mice. In the absence of glutamate dehydrogenase, we observed that the brain was no longer able to convert glutamate into energy, even though the amino acid was present in the brain," explains Melis Karaca, first author of this study.

Priority to the brain

Devoid of the energy supplied by cerebral glutamate, the brain sends signals to the liver to requisition a compensatory proportion of glucose, at the expense of the rest of the body. This is why the transgenic mice also showed a growth deficit and muscle atrophy. "This clearly shows how the brain works in a just-in-time manner and that each percent of

energy resources is essential for its proper functioning," highlights Professor Pierre Maechler. "If a part of this energy disappears, the brain serves itself first and the rest of the body suffers. The liver must then make more glucose by drawing upon muscle protein, resulting in loss of muscle mass. Knowing that the brain uses glutamate as an energy resource allows us to reflect on other ways to overcome a potential shortfall. "

Scientists also suspect a correlation between the Glud1 gene and some neurodevelopmental disorders, particularly epilepsy and schizophrenia. They are currently pursuing their research by introducing in mice the same Glud1 mutation detected in epileptic patients. At the same time, another group is working with schizophrenic patients to assess the way their brain uses glutamate.

Provided by University of Geneva