Lack of cellular prion protein might cause symptoms of epilepsy and learning deficits

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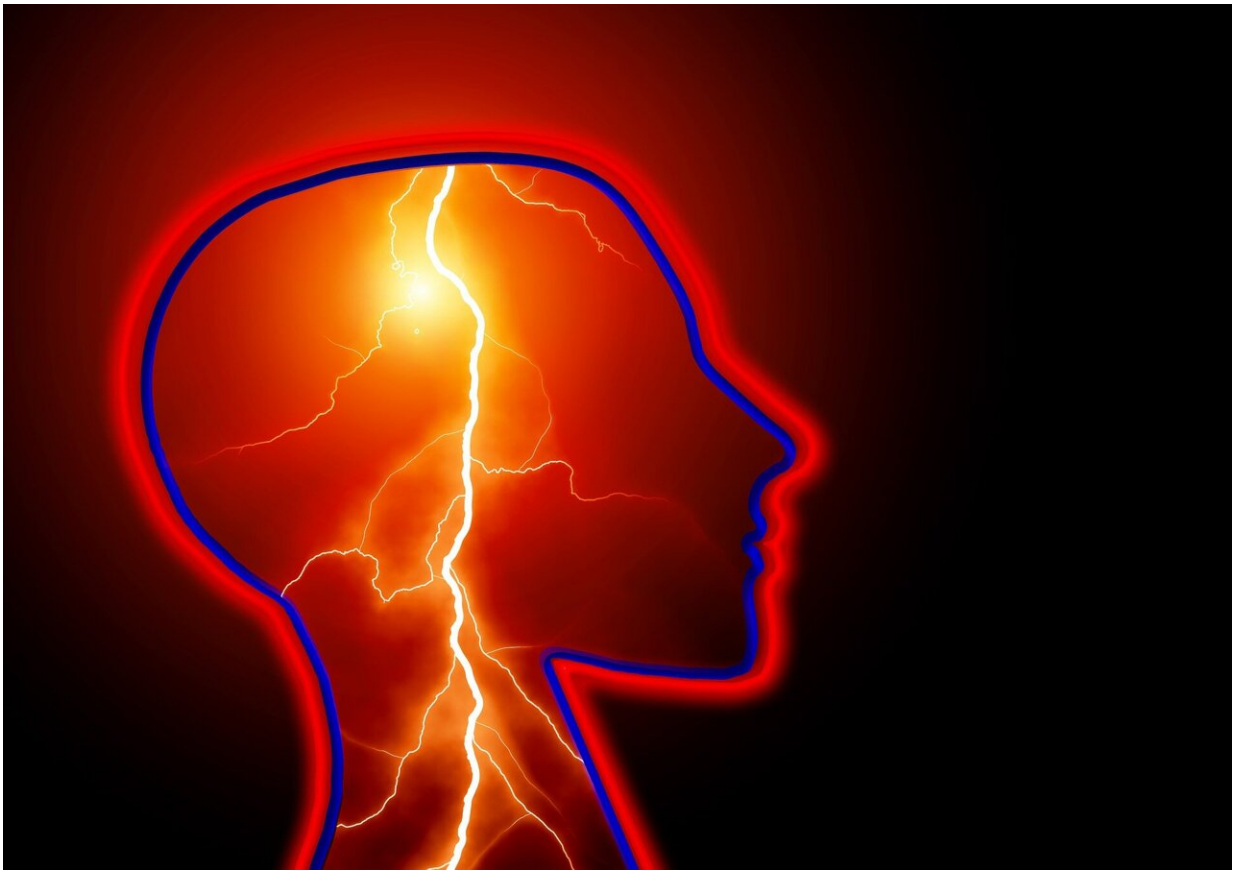

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The cellular prion protein (PrPC), a protein in the surface of the neuronal cells, is imbalanced in human patients with neurodegenerative

diseases such as Alzheimer's or Parkinson's disease. However, the knowledge on the participation of PrPC in these pathologies contrasts with many reported data on its natural and health-promoting role.

Now, a study published in the journal *BMC Biology* reveals that the lack of PrPC damages the cognitive functions such as associative learning and memory and it causes anxiety-like behaviors in mice models. According to the study, the lack of PrPC involves a higher sensitivity to epilepsy seizures in these mice.

The study was carried out by a team led by Professor José Antonio del Río, from the Faculty of Biology and the Institute of Neurosciences (UBNeuro) of the University of Barcelona (UB), the Institute for Bioengineering of Catalonia (IBEC)—with head offices at the Barcelona Science Park— and the Centre for Biomedical Research on Neurodegenerative Diseases (CIBERNED). Among the participants are teams from the Faculty of Physics, the Faculty of Medicine and Health Sciences, the Institute of Complex Systems (UBICS) of the UB, the Bellvitge Institute for Biomedical Research (IDIBELL), the University Pablo de Olavide in Sevilla, and the University Hospital of Zurich (Switzerland).

The PrPC protein: neuroprotective and regulatory role

The new paper provides new knowledge about the real role of the PrPC in neuronal physiology, a molecule described as a protector for the brain in some studies, while other studies relate its expression to a higher sensitivity to neurotoxicity. These inconsistencies are mainly explained due to the lack of proper and well-characterized mice models. In this context, the team led by Professor José Antonio del Río worked over the last five years with a new transgenic mouse model lacking PrPC, created

through the TALEN technology (Transcription Activator-Like Effector Nuclease).

"The research teams have worked for decades on altered mice with PrPC without knowing about the impact on their health due to some technical inconvenience in the previously developed models. Using TALEN generated PrPC-knockout mice, we found that the animals that do not express the protein do show epileptic-like symptoms and impaired learning and memory, which reinforce the role of the protein in these processes. These findings might help us to understand the effects of the decrease in PrPC observed in some neurodegenerative diseases in humans," notes José Antonio del Río.

As part of the study, the team carried out a series of behavioral and operant conditioning tests to assess the memory and the learning skills of mice, apart from the RNA sequencing, the analysis of neuronal network in vitro and the obtaining of in vivo electrophysiological data. The results revealed a clear decrease in mobility, impairment in the operant conditioning learning, and an anxiety-related behavior in animals lacking PrPC.

The conclusions suggest that the PrPC protein favors the formation of neuronal networks and connectivity intervenes in the synaptic function and it acts as a protector from excitotoxity. The deletion of PrPC may underlie an epileptogenic-susceptible brain that fails to perform highly cognitive-demanding tasks such as associative learning and [is prone to] anxiety-like behaviors.

More information: A. Matamoros-Angles et al, Analysis of co-isogenic prion protein deficient mice reveals behavioral deficits, learning impairment, and enhanced hippocampal excitability, *BMC Biology* (2022). DOI: 10.1186/s12915-021-01203-0

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