Mechanism that adjusts the function of the nervous system to the metabolic state

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This important study has been carried out by Victoria García-Morales, Fernando Montero, David González-Forero, Guillermo Rodríguez-Bey, Laura Gómez-Pérez, María Jesús Medialdea-Wandossell, Germán Domínguez-Vías, José Manuel García-Verdugo and Professor Bernardo Moreno-López

Researchers at the Faculty of Medicine of the University of Cadiz, led by Professor Bernardo Moreno, have made an important finding which has recently been published in the prestigious scientific journal *Plos Biology*. The Cadiz scientists have identified a molecule, Lysophosphatidic acid (LPA), as a possible element implicated in the link between the metabolic state of an organism and its cerebral function.

To put it another way, "we have discovered that this molecule could be the missing link that regulates the activity of the nervous system depending on the metabolic state of the organism in physiological and/or pathological conditions. Production of this molecule is increased, for example, in situations of obesity, dyslipidaemias, lipodystrophies, hypercholesterolemia, insulin resistance (significant diabetes) and alcoholism, as well as in neurodegenerative diseases such as Alzheimer's and multiple sclerosis. Interestingly, all these syndromes also involve cognitive dysfunctions. It would appear that learning, memory and behaviour are all affected in this type of syndrome. We thought that LPA could be involved in linking these metabolic syndromes with dysfunctions of the nervous system," says Professor Moreno.

This finding, which opens up a new line of investigation in the area of physiopathology, has led the scientists to show that in physiological conditions, this molecule regulates communication between neurons. Therefore, "LPA regulates the function of the synapses (units specialized in communication between one neuron and another) and is also involved as a messenger in cases of neuroplasticity." This means that "the synapse is not something static but can be modified."

In order to understand this assertion better, Bernardo Moreno states that, for example, "when we acquire a new motor function, when we learn or when we store memories in our minds, it is because the synapse has modified its behaviour. In this sense, LPA could be a key mediator in

these cases of modulation of synaptic activity in learning and memory processes, and this explains the relevance of the work we have carried out."

To this end, the researchers from the Faculty of Medicine have also identified the receptor molecule that this phospholipid affects in the nervous system (the LPA1 receptor, as six different LPA receptors have already been identified in the nervous system). "Hence, we are also identifying a possible therapeutic target." But this study goes even further. In the article published in *Plos Biology*, these scientists have detailed the molecular mechanisms by which LPA regulates the inhibitory and excitatory synapses on the neurons, two mechanisms that have turned out to be totally different.

"The correct functioning of the nervous system depends on a very well-regulated balance between excitatory and inhibitory inputs received by the neurons. LPA is involved in maintaining this balance. If, in metabolic syndromes or in pathological conditions, the levels of LPA change, this also has a direct effect on this balance between excitatory and inhibitory synapses. That is to say, this balance disappears and the resulting imbalance makes the nervous system work less efficiently, or at the very least, differently, to how we are used to it working," asserts Bernardo Moreno.

This intensive study, carried out by nine researchers, "does not end here." This new line of study "leads us to ask ourselves many things, among them, whether LPA is physiologically altering neuroplasticity processes as either an anterograde or a retrograde messenger. That is to say, we wish to see if LPA acts as a messenger produced by the neuron that regulates the synaptic activity that reaches it or if, to the contrary, is produced by the synapse and acts on the neuron." According to Dr. Moreno, "this would mean an interesting advance in the knowledge of the working of the nervous system."

More information: 'Membrane-Derived Phospholipids Control Synaptic Neurotransmission and Plasticity'. *Plos Biology*. DOI: 10.1371/journal.pbio.1002153