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Study Published in *Science* Unveils Critical Mechanism for Brain Development

A study published in the prestigious journal *Science*, which involves two dozen Portuguese, Spanish and French researchers, reveals an essential mechanism for the organization of the brain in the first years of life, providing clues for the development of new therapeutic approaches for diseases such as autism, depression, schizophrenia or Alzheimer's disease.

The discovery is the result of more than a decade of research, started in 2007 by Rodrigo Cunha, co-author of the scientific article and professor at the Faculty of Medicine of the University of Coimbra (FMUC).

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Understanding how the brain develops in the first years of life is critical, as problems that arise at this stage can have consequences for life. When we are born, our brain's network of neurons is not yet organized, it is a highly plastic network. Synapse selection, the focus of this study, is one of the central mechanisms, as synapses are responsible for communication between neurons.

In the process of brain development “about five times more synapses are generated than our nervous system needs. This happens with the objective of selecting one in five, that is, choosing the synapses that are optimal for carrying out the functions of our brain», explains Rodrigo Cunha, also a researcher at the Center for Neuroscience and Cell Biology at UC.

In particular, the researchers studied, in mice, the stability of synapses at the stage when they are most plastic, with a corresponding period in humans between six months and four years of age, the period when the greatest selection of synapses occurs. If, at this point, “failures appear in the selection of synapses, we are more susceptible, for example, to depression, to have an excessive consumption of psychoactive drugs or to develop epilepsy. This is already scientifically demonstrated. Therefore, it is so important to study the multiple mechanisms involved in brain development», observes Rodrigo Cunha.

It was already known that there is a competition between the synapses and that the most active ones are the selected ones. However, until now, it was unknown how this selection process takes place, a critical aspect to redefine the organization of synapses, aiming to correct dysfunctions in brain diseases.

Rodrigo Cunha's team, together with researchers from Spain and France, discovered precisely the main mechanism involved in synapse selection: the ATP molecule – which works as our organism's energy currency and also as a signal of activity between cells in the nervous system – is the key molecule in this process.

Scientists have found that as a synapse becomes more active, it releases more signals. One of the signals present in particularly high amounts during this initial phase of synapse selection is ATP. In other words, explains Rodrigo Cunha, «the more active the synapses are in the nervous system, the more ATP they release, and this ATP is much more quickly converted into adenosine, which is something we have been working on for about two decades, such as flag between cells. In this work we show that it is essential, it is critical, that the receptor activated by adenosine be stimulated for the synapse to remain stable. When the activity of a synapse decreases, the release of ATP decreases, this receptor for adenosine is not sufficiently activated and the synapse literally dismembers, that is, the entire organization is destroyed».

The researchers further detailed all the mechanistic processes involved in this complete synapse disaggregation. «We observed, for example, that a synapse can be around 20 minutes without working, but if it exceeds this time, it is usually eliminated. It is an irreversible process after 20 minutes », he highlights.

The results of this study provide information that can be very relevant for the development of future drugs, because, as Rodrigo Cunha explains, «in order to try to correct failures in equipment, it is first necessary to know how it works normally. Our work is part of the so-called fundamental science, which opens new doors for immediate applicability».

The next step in the investigation, says the scientist at the UC, will be to carry out new experiments on animal models, to study ways to «manipulate this synapse selection system, aiming to reduce the incidence of certain diseases. For the first time, we show the main system that allows synapse selection. So, in any situation where there are problems related to synapse selection, we now know which target we have to use».

With the discovery now published in Science, he concludes, “any group, anywhere in the world, can draw on this knowledge to develop and test new drugs for neurodevelopmental disorders and diseases.

Cristina Pinto

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