Identification of molecule capable of reducing neurodegenerative processes in the elderly

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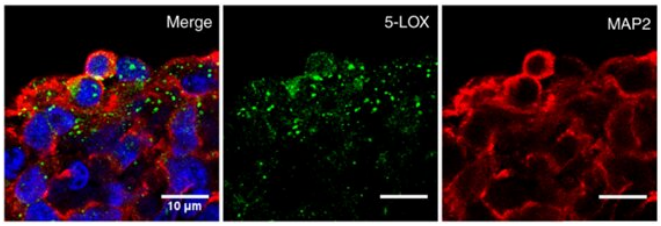

In green, it shows the presence of 5-LOX. In red, MAP2 (microtubule-associated protein 2, essential for the structure of neuronal cells). In blue, the nuclei of these cells. Credit: The D'Or Institute for Research and Education (IDOR)

Researchers from the D'Or Institute for Research and Education (IDOR) have just published a study in *Translational Psychiatry* that elucidates the mechanisms involved in the cognitive deficits of human aging. The research considers the action of molecules that can fight inflammatory processes in neurodegenerative diseases such as Alzheimer's and potentiate the endocannabinoid system.

This substance, known as lipoxin A4, has been studied by researchers for years and this is its first application against neurodegenerative diseases linked to aging, with potential developments in the diagnostic field. This study was carried out in partnership with the Oswaldo Cruz Foundation (Fiocruz), Federal University of Rio de Janeiro (UFRJ), Federal University of Espírito Santo (UFES), Federal University of Latin American Integration (UNILA) and The Broad Institute of MIT and Harvard.

Inflammation is part of the body's defense, but its unregulated action plays an important role in chronic and neurodegenerative diseases, including Alzheimer's. The control of the inflammatory response occurs, among other factors, by lipid mediators such as lipoxins, which act in the natural resolution of inflammation. For example, when a skin cut heals, these molecules are responsible. This active protection also happens in the central nervous system, but it is more difficult to visualize. The central hypothesis of the published work is that the loss of this inflammatory control could lead to chronic problems and, ultimately, to neurodegeneration.

The main interest of the research was to understand the natural dynamics of the reduction of lipoxin levels that occur in the body during aging, a phenomenon that could be related to the brain's vulnerability to cognitive impairment and neurodegenerative diseases.

Bearing in mind that the effects of lipoxin A4 (LXA4) on the brain were not very clear, the researchers evaluated the possible effects of this bioactive on the brain environment and its activity, mainly correlating it with aging. They evaluated the presence of the molecule in the brain of mice, in human neural cells developed in the laboratory, and in cerebrospinal fluid (liquor) extracted from elderly patients with dementia and other neurodegenerative diseases. This was the first study to demonstrate the origin of LXA4 in the central nervous system, pointing to its presence in neurons and microglia (inflammatory cells) of humans and mice.

Laboratory-developed brain organoids, which have a biochemical profile and structural organization similar to the embryonic human brain, were also used to confirm this information. In addition, immunofluorescence (another technique that allows assessing the distribution of antigens in a sample) demonstrated the presence of 5-lipoxygenase (5-LOX), the enzyme responsible for the production

of LXA4 in brain organoids developed in the laboratory. This dataset raises the possibility that neurons and microglia are involved in the delivery of LXA4 to the human brain.

There was controversy in the scientific literature, with another research group associating the presence of 5-LOX with synaptic dysfunction observed in animal models of Alzheimer's disease. This study proposes the opposite and clarifies that the lipoxin produced by 5-LOX in the brain is an important aspect that contributes to neuroprotection.

In the experiments with mice, the focus was to understand the relationship between the LXA4 and the aging process in the animal model, with the hypothesis that reducing levels of this substance would weaken the body's defenses, making the brain vulnerable to neurodegeneration. It was observed that the levels of LXA4 in blood plasma and in the brain were shown to be reduced in 12-month ("old") mice compared to three-month ("young adult") mice. In older mice, reduced learning ability and short-term memory loss were also demonstrated, indicating that reduced levels of LXA4 are accompanied by cognitive deficits in older animals.

"This study makes an important contribution in establishing the local presence of lipoxin in the central nervous system, as well as the decline in its levels with aging. This is something that has long been debated by the scientific community. Considering the findings in the previous article by our group, we were able to define that this substance has a very important anti-inflammatory protection factor in the human brain, probably preventing the occurrence of neurodegeneration in individuals who age healthily," says Dr. Fabrício Pamplona, associate researcher at IDOR and UNILA and first author of the article.

The study also evaluated whether injecting LXA4 could have a protective effect against memory changes induced by an inflammatory lesion in mice. It was observed that after seven days of injection with LXA4 there was a cognitive stabilization and reduction of inflammatory molecules in the blood plasma of rodents, which led the researchers to evaluate the relevance of this lipoxin in humans with different diagnoses of neurological impairment due to dementia or neurodegeneration.

In this experiment, it was observed that LXA4 decreases in the liquor following the patients' aging and the severity of cognitive impairment. This means that the older they are and the greater their cognitive impairment is, the lower will be the level of LXA4 in the liquor. The decrease in LXA4 in the cerebrospinal fluid has also been shown to be related to the accumulation of beta-amyloid protein (A?42) in the brain, one of the neurotoxic markers of Alzheimer's Disease.

An interesting novelty of this study is that LXA4 has an innovative mechanism, involving a potentiation of the endocannabinoid system. This system promotes the body's balance (known as homeostasis), making a fine control of neurotransmission, and impacting a series of physiological processes ranging from appetite control, hormone release, cognition, pain and inflammation, among others. According to the group's line of research, LXA4 promotes a neuroprotective action when interacting with CB1-type cannabinoid receptors, resulting in better transmission of the endocannabinoid anandamide.

"CB1 receptors are the main key to the endocannabinoid system, which promotes fine regulation of brain neurotransmission systems. Knowing that lipoxin promotes activation of the endocannabinoid system, as we have already characterized in another study, the information that these molecules are produced and released by immune cells in the brain (microglia) allows us to place its action in a scenario of interaction between the central nervous system and immune system. This regulation is yet another key role of the endocannabinoid system, showing that inflammatory balance is essential for the health of our brain, particularly during aging," says Dr. Pamplona.

Thus, LXA4 would be a naturally occurring substance with dual, anti-inflammatory and protective action, whose decline with aging would cause the brain to be "vulnerable" to neurodegeneration. The findings indicate that

prevention against the decrease in LXA4 can preserve the health of the brain environment and cognition, in addition to being an important discovery for the development of future therapies aimed at neurodegenerative diseases. The authors report that further studies are needed to clarify the mechanisms of LXA4 activation and to assess how stimulating the production of this molecule could be effective in slowing cognitive decline in the elderly population.

More information: Fabricio A. Pamplona et al, Age-linked suppression of lipoxin A4 associates with cognitive deficits in mice and humans, *Translational Psychiatry* (2022). DOI: 10.1038/s41398-022-02208-1

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