LSL60101 compound reduces neuroinflammation and improves cognition

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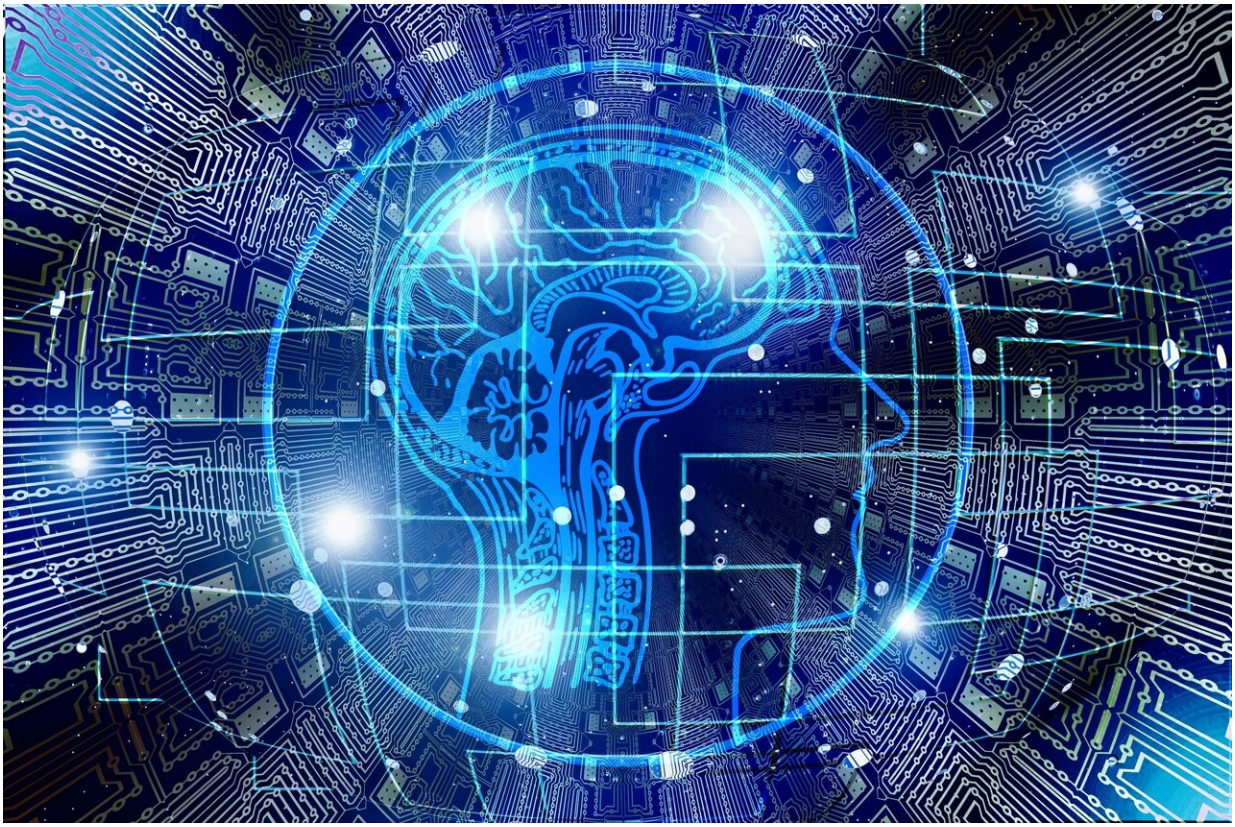

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The LSL60101 compound, a specific ligand of the I2-IR receptors in the brain, could shed light on the development of future strategies against Alzheimer's disease. This is stated in the recent studies by the Research

Group on Medicinal Chemistry and Pharmacology of Neurodegenerative Diseases of the University of Barcelona, published in the journals *European Journal of Medicinal Chemistry* and *British Journal Pharmacology*. In studies carried out with mice, LSL60101 has improved the cognitive deficit and the biomarkers related to the disease in these animal models.

These studies result from the collaboration of the research teams led by professors Carmen Escolano, from the Faculty of Pharmacy and Food Sciences and the Institute of Biomedicine of the UB (IBUB), and Mercè Pallàs, from the same Faculty and the Institute of Neurosciences (UBNeuro). Framed within a program in the CaixaImpulse program, the studies are also signed by the UB researchers Christian Griñán Ferré, Foteinin Vasilopoulou, Sergio Rodríguez Arévalo and Andrea Bagán. Among the participants are teams of the

Alzheimer's is a neurodegenerative disease without a cure yet. Despite the efforts made by the international scientific community, many initiatives in medical chemistry to find future drugs to treat it have failed, and it is postulated that this situation could be explained by the selection of unsuitable therapeutic targets. Therefore, it is important to tackle the fight against Alzheimer's from perspectives that help to shape new therapeutic targets from the side of innovation in biomedical research.

The paper published in the *European Journal of Medicinal Chemistry* describes the synthesis of a new family of compounds with high affinity and selectivity for I2 imidazoline receptors, altered in the brain of patients with Alzheimer's. The synthesis pathway of compounds, which is efficient and affordable, would allow us to apply different structural modifications to access a notable range of compounds of pharmaceutical interest.

The new family of I2-IR receptor ligands is formed by compounds with different structural features. In particular, the interaction of a representative compound—LSL60101 or garsevil—with the I2 imidazoline receptors improves the cognitive deficit in murine models with neurodegeneration and Alzheimer's. This compound, described for the first time in the scientific literature in 1995 as a specific I2-IR receptor ligand, is known for its properties in preclinical studies of pharmacokinetics, metabolism and toxicity, and presents a high affinity and selectivity regarding these receptors in the human brain.

Nowadays, the function of the I2-IR receptors under physiological conditions is unknown. However, researchers know these are altered in some neurodegenerative diseases such as Alzheimer's or Parkinson's. Moreover, the scientific bibliography features studies with ligands of these receptors as markers of the progress of Alzheimer's disease.

"Apart from fighting the formation of amyloid-beta plaques or neurofibrillary tangles, acting on the neuroinflammation mechanisms could be a suitable therapeutic strategy to stop the progression of such a complex disease like Alzheimer's," notes Professor Escolano.

LSL60101 versus donepezil: The future of a combined therapy

According to the article in *British Journal Pharmacology*, the effects of LSL60101 in laboratory animals prove to be more beneficial than those from donepezil, one of the most commercialized drugs for Alzheimer's treatments.

In the murine models with Alzheimer's, "the new compound created changes in oxidative stress markers and in neuroinflammation makers, one of the main dysfunctions present in most of the neurodegenerative diseases. In particular, LSL60101 reduced the number of amyloid-beta

plaques and the levels of this altered protein in the brain of the treated animals. Parallelly, it reduced the phosphorylation of the tau protein, another important biomarker in the progression of the diseases," says Professor Mercè Pallàs.

The results could be explained with the several action mechanisms of LSL60101 and donepezil. Donepezil increases the levels of acetylcholine—a neurotransmitter related to memory and cognitive skills—because it inhibits the enzyme in charge of its degradation (acetylcholinesterase). Also, LSL60101 is described as a I2 imidazoline receptor ligand, which have increased in the brain of people with dementia. Everything points to the fact that the interaction of this drug with its receptor is involved in the generation of proinflammatory molecules that would increase the ongoing neuroinflammation in the disease. Therefore, I2 ligands would contribute to reduce the inflammation and thus, would slow the progression of the disease.

Both compounds were efficient in the recovery of the cognitive damage, but one of the objectives of the research study was to find whether the combination could improve the success of the treatment. "The results show that the SL60101-donepezil combined therapy is more efficient in some biomarkers of the disease. Therefore, it is possible that, with the combination of the suitable dose, we could reach an additive or even synergic effect," note the researchers.

Conducting new researches in the study will be a decisive factor to focus on the relation between I2 imidazoline receptors and Alhzeimer's and other diseases, and to boost the design of new therapeutic strategies based on the use of new selective I2-IR ligands to modulate the altered receptors in neurodegenerative pathologies.

More information: Sergio Rodriguez-Arévalo et al, Benzofuranyl-2-imidazoles as imidazoline I2 receptor ligands for

Alzheimer's disease, *European Journal of Medicinal Chemistry* (2021). DOI: 10.1016/j.ejmech.2021.113540