Mechanism behind the lack of effectiveness of certain antagonist drugs discovered

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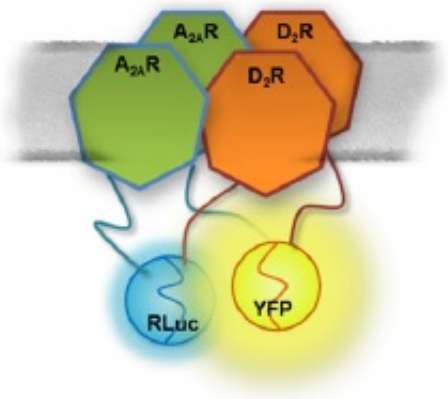

The tetrameric structure formed by these receptors explains the discrepancies observed when administering antagonist drugs.

Researchers have published a study in the journal *Proceedings of the National Academy of Sciences* (*PNAS*) about the formation of G protein-coupled receptors (GPCRs) which allows understanding the unexpected behaviour of some antagonists that block physiological responses.

The study, carried out with mice and human cell lines, has been led by Vicent Casadó and Enric I. Canela, experts in the Department of Biochemistry and Molecular Biology and members of the Research Group of Molecular Neurobiology of the UB. UB experts Jordi Bonaventura, Verònica Casadó, Gemma Navarro, Estefania Moreno,

Marc Brugarolas, Carme Lluís, Josefa Mallol and Antoni Cortés also collaborate in the study, together with the research teams led by Sergi Ferré (National Institute on Drug Abuse, United States), and Serge Schiffmann (Free University of Brussels, Belgium).

Potential drugs to fight against Parkinson's disease

The team has determined that adenosine A2A receptors bind dopamine B2 receptors and form a tetrameric structure (a homodimer of A2A together with a homodimer of D2). The former binding, produced at brain's basal ganglia, was known, but its structure remained unknown. It is one of the mechanisms involved in the control of movement. If it does not work correctly, it produces severe movement disorders leading to hypokinesia and hyperkinesia, movement alterations that characterise disorders like Parkinson's disease, schizophrenia or Huntington's disease. Considering the interaction between these receptors, it has been suggested that antagonists of receptors A2A are potential drugs to fight against Parkinson's disease.

The article published in *PNAS* describes another significant discovery: The tetrameric structure formed by these receptors explains the discrepancies observed when administering these antagonist drugs because they sometimes produce motor activation, but other times, they worsen motor inhibition.

Beyond the traditional agonist-antagonist model

The tetrameric model discovered by authors explains that a certain concentration of an antagonist drug of adenosine receptors A2A —for instance, caffeine, consumed by a large part of population— blocks movement inhibition caused by adenosine, which is produced in an endogenously. In higher doses, the antagonist may no longer block the

effect of endogenous adenosine and imitate the role played by adenosine, thus limiting the function of dopamine D2 receptors. Therefore, it will not be an effective drug but one that damages movement control. The discovery contradicts the traditional point of view that describes antagonists as inactive ligands that only compete with endogenous agonists to bind receptors and block their intracellular activity.

The study of the physiological basis of addiction

Results can be extrapolated to studies of the effect that antagonist drugs have on other receptors that also bind to form heteromers, like the ones that produce addiction to drugs, food and other substances. In fact, the study has proved that the association of many GPCRs receptors forms heteromers with new pharmacological and functional properties, different from individual receptors.

The UB research group, pioneer in the study of these interactions, affirms that "the binding of receptors of hormones, neurotransmitters and neuromodulators forming tetrameters may explain the contradictory results obtained in therapies based on the use of an antagonist drug of a receptor to alter the action of the other receptor and underlines that the success of this type of treatments relies on administering an appropriate dose of the drug".

More information: "Allosteric interactions between agonists and antagonists within the adenosine A2A receptor-dopamine D2 receptor heterotetramer." *Proceedings of the National Academy of Sciences*, vol. 112, jul 2015. DOI: 10.1073/pnas.1507704112

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