Researchers determine the complex structure of the receptors related to opioid addiction

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A study published in *Pharmacological Research* reveals the oligomeric molecular structure of the MOR-Gal1R complex, a component present in the brain which is involved in the analgesic and addictive effects of

certain opioids. The study includes the participation of the experts Vicent Casadó, Estefanía Moreno and Verònica Casadó-Anguera, from the Molecular Neuropharmacology Research Group of the Faculty of Biology and the Institute of Biomedicine of the University of Barcelona (IBUB).

The study is coordinated by the experts Vicent Casadó (UB-IBUB), Leonardo Pardo (UAB), Leigh Daniel Plant (Boston Northeastern University, United States) and Sergi Ferré (National Institute on Drug Abuse, NIH, United States).This preclinical study, based on the use of cellular models and leading biophysical, biochemical and pharmacological techniques (total internal reflection fluorescence microscopy, TIRF), has been distinguished for its scientific interest on the website of the NIH's National Institute on Drug Abuse.

Receptors, macrostructures and pharmacological activity

Gal1R and MOR receptors belong to the family of G protein-coupled receptors (GPCRs) that take part in the transduction of different cellular signals and the control of essential cell functions. These structures can form dimers—homodimers or heterodimers—that determine functional and pharmacological properties that are different from those of the individual components.

The study shows different in vitro evidences that reveal the preference of Gal1R and MOR receptors to form homodimeric complexes (MOR-MOR or Gal1R-Gal1R) in cell cultures when they are expressed separately. When expressed together, tetrameric complexes (heterotetramers) are formed by homodimers of both receptors (MOR-MOR-Gal1R-Gal1R-Gal1R).

"This heterotetrameric structure is even more complex because when the homodimers of both receptors join to form the MOR-MOR macrocomplex, the interaction and corresponding signaling is maintained by means of their characteristic G protein (the G protein inhibitory to adenylate cyclase or Gi)," says Vicent Casadó, member of the Department of Biochemistry and Molecular Biomedicine and the IBUB.

"However, Gal1R-Gal1R exchanges its characteristic inhibitory G-protein for the adenylyl cyclase-stimulating G-protein (Gs). This higherorder oligomeric complex contains more than 10 protein subunits considering the four receptors, the two heterotrimeric G-proteins and the adenylyl cyclase enzyme on which both G-proteins act to up- or down-regulate the intracellular levels of the cyclic AMP messenger," adds the expert. Determining the molecular characteristics of this macrostructure would explain the molecular mechanism by which the neuropeptide galanin —which has neurotrophic and neuroprotective properties— causes a decrease in the release of dopamine into the nucleus accumbens induced by opioids, as described by the same team (*Journal of Neuroscience*, 2016).

"This would be possible because when the Gal1R ligand binds to the heteromer, it activates the Gs protein, which interacts with the same adenylyl cyclase that was inhibited by the MOR-activated Gi protein, so it counteracts the secondary effects that opioid ligands have in activating the MOR receptors in the ventral tegmental area," says researcher Estefanía Moreno, member of the Department of Biochemistry and Molecular Biomedicine and IBUB.

Searching for new non-addictive drugs

In previous studies, the team from the Faculty of Biology and the IBUB had already showed that the greater proportion of analgesic—and not euphoric—effects of methadone administration make this compound the

most indicated non-addictive option for the treatment of chronic pain (*Journal of Clinical Investigation*, 2019). This could be explained by the fact that methadone acts preferentially on MOR receptors when they do not form heteromers with Gal1R receptors, and therefore, its effect is mainly peripheral.

"Now, knowing this tetrameric macrostructure of the receptor complex—in addition to the differential capacities of opioid ligands to activate MOR depending on the formation of oligomeric complexes with other receptors—will facilitate the future design of opioid drugs that can bind with a greater affinity or can bind more effectively the signal pathways with mu-opioid receptor homodimers than with the MOR-Gal1R heterotetramers," notes researcher Verònica Casadó-Anguera.

Specifically, it would be about μ-opioid receptor drugs capable of discriminating between homodimers of these compounds and their heterotetramers with galanin receptors. "It is also possible to design a strategy that combines opioid ligands with Gal1R ligands that bind to the heterotetramer and inhibit the activation of the dopamine system and, therefore, addiction. Thus, these therapies are expected to have a greater analgesic effect and less addictive activity," concluded the research team.

More information: Paulo A. De Oliveira et al, Preferential Gs protein coupling of the galanin Gal1 receptor in the μ-opioid-Gal1 receptor heterotetramer, *Pharmacological Research* (2022). DOI: 10.1016/j.phrs.2022.106322

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