The Gi and Gs protein-coupled μ-opioid-galanin Gal1 receptor heterotetramer

E. Moreno1, P.A. De Oliveira2, N. Casajuana-Martin3, V. Casadó-Anguera1, N.S. Cai2, G.A. Camacho-Hernandez4, H. Zhu5, A. Bonifazi4, M.D. Hall5, D. Weinshenker6, A.H. Newman4, D.E. Logothetis7, L.D. Plant7\*, L. Pardo3\*, S. Ferré2\*, V. Casado1\*.

1University of Barcelona, Department of Biochemistry and Molecular Biomedicine- Faculty of Biology, Barcelona, Spain.

2National Institute on Drug Abuse- Intramural Research Program- National Institutes of Health, Integrative Neurobiology Section, Baltimore, United States.

3Autonomous University of Barcelona, Laboratory of Computational Medicine- Biostatistics Unit- Faculty of Medicine, Bellaterra, Spain.

4National Institute on Drug Abuse- Intramural Research Program- National Institutes of Health, Medicinal Chemistry Section, Baltimore, United States.

5National Center for Advancing Translational Sciences- National Institutes of Health, Division of Preclinical Innovation, Rockville, United States.

6Emory University School of Medicine, Department of Human Genetics, Atlanta, United States.

7School of Pharmacy at the Bouvé College of Health Sciences and College of Science-Northeastern University, Departments of Pharmaceutical Sciences- Chemistry and Chemical Biology and Center for Drug Discovery, Boston, United States. \*Co-senior authors.

Recent studies indicate that heteromers of μ-opioid receptors (MORs) and galanin Gal1 receptors (Gal1Rs) constitute a predominant population of the MOR localized in the ventral tegmental area and mediate the dopaminergic effects of opioids. Allosteric mechanisms in the MOR-Gal1R heteromer determine the ability of Gal1R ligands to decrease the affinity and efficacy of opioids and, importantly, a specific decrease in the potency of methadone. This MOR-Gal1R heteromer-dependent pharmacodynamic property of methadone provided a mechanistic explanation for its weaker dopaminergic effects, blunted euphoric properties, and lower addictive liability as compared with morphine and other opioids. Thus, targeting the MOR-Gal1R heteromer provides a logical approach to fighting the opioid epidemic. However, we do not have any knowledge about its quaternary structure. The present study reports converging evidence, using a peptide-interfering approach combined with biophysical and biochemical techniques, including total internal reflection fluorescence microscopy, for a predominant homodimeric structure of MOR and Gal1R when expressed individually, and for their preference to form functional heterotetramers when co-expressed. Results show that a heteromerization-dependent change in the Gal1R homodimeric interface leads to a switch in G-protein coupling from inhibitory Gi to stimulatory Gs proteins. The MOR-Gal1R heterotetramer, which is thus bound to Gs via the Gal1R homodimer and Gi via the MOR homodimer, provides the framework for a canonical Gs-Gi antagonist interaction at the adenylyl cyclase level. These novel results shed light on the intense debate about the oligomeric quaternary structure of G protein-coupled receptors, their predilection for heteromer formation, and the resulting functional significance.

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