ABSTRACT

MNS 2022 Dubrovnik, Croatia

- Symposium S19 - Understanding the role of GPCR heteroreceptor complexes and their adaptor proteins in the neuronal networks of the brain in health and mental disorders

On the balance of D2R-MOR and D4R-MOR in the dorsal and ventral striatum. Putative link to morphine dependence and addiction.

Ramon Fores-Pons[1, 2], Manuel Narvaez[1], Lakshmi Vasudevan[3], Minerva Crespo-Ramirez[4], Alicia Rivera[5], Miguel Perez de la Mora[4], Christophe Stove[3], Kjell Fuxe[2] and Dasiel O. Borroto-Escuela[1,2]

[1] *Receptormics and Brain Disorders Lab, Department of Physiology, Faculty of Medicine, University of Malaga, Malaga, Spain. e-mail:* rforespons@gmail.com.

[2]*Department of Neuroscience, Karolinska Institutet, Retzius väg 8, 17177 Stockholm, Sweden.*

[3]Laboratory of Toxicology, Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Ghent University, Belgium

[4]Instituto de Fisiología Celular, Universidad Nacional Autónoma de México, Mexico City, Mexico.

[5]Department of Cell Biology, University of Malaga, Instituto de Investigación Biomédica (IBIMA). Malaga, Spain.

Abstract

The widespread distribution of heteroreceptor complexes with allosteric receptor-receptor interactions in the CNS represents a novel integrative molecular mechanism in the plasma membrane of neurons and glial cells. It was proposed that they form the molecular basis for learning and short-and long-term memories. This is also true for drug memories formed during the development of substance use disorders like morphine and cocaine use disorders. Herein, we discuss and propose how an increase in opioid heteroreceptor complexes, containing MOR-DOR, MOR-D4R and MOR-D2R, and their balance with each other and A2AR-D2R complexes in the striatal-pallidal enkephalin positive GABA antireward neurons, may represent markers for development of morphine use disorders. We suggest that increased formation of MOR-DOR complexes takes place in the striatal-pallidal enkephalin positive GABA antireward neurons after chronic morphine treatment in part through recruitment of MOR from the MOR-D2R and/or MOR-D4R complexes due to the possibility that MOR upon morphine treatment can develop a higher affinity for DOR. As a result, increased numbers of D2R monomers/homomers in these neurons become free to interact with the A2ARs found in high densities within such neurons. Increased numbers of A2AR-D2R heteroreceptor complexes are formed and contribute to enhanced firing of these antireward neurons due to loss of inhibitory D2R protomer signaling which finally leads to the development of morphine use disorder. Altogether, we propose that these altered complexes could be pharmacological target to modulate the reward and the development of substance use disorders.