UNIVERSITÀ DEGLI STUDI DI PADOVA

PROJECT

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1) Project title
NOP receptor active structure, transducerome, and biased signaling
2) Abstract (max 500 words)
G protein-coupled receptors (GPCRs) control many biological functions fostering heterotrimeric G protein dissociation and subsequent signaling. The G protein heterotrimers are composed of G alpha, G beta, and G gamma subunits. Sixteen genes are encoding for G alfa subunits, five for G beta, and fourteen for G gamma, giving the GPCR a complex array of signaling possibilities. Because some GPCR ligands, referred to as biased agonists, can stimulate GPCR signaling by specific activation of a selected subset of G proteins; recent evidence suggests that biased agonists can dissect the beneficial vs. unwanted effects deriving from GPCR activation. This observation may in turn lead to the development of biased agonists as more effective/better-tolerated drugs. The nociceptin/orphanin FQ (N/OFQ) - NOP receptor system plays a pivotal role in the CNS and periphery. In fact, NOP agonists have therapeutic potential for treating pain, anxiety, locomotor and sleep disorders, drug abuse, and cough. The aim of this Ph.D. project is to finely explore the molecular basis of biased agonism at the NOP receptor, validating and characterizing innovative ligands and assays. To this aim a wide array of truly innovative approaches will be deployed i) bioluminescence-based second messenger approaches, ii) bioluminescence resonance energy transfer (BRET) approaches to detect NOP-G protein or -β-arrestin interactions, iii) BRET methods to measure specific NOP-Gα protein preferred couples, iv) label free methodologies to evaluate the activity of the NOP receptor in natively expressing cells, v) gene overexpression and downregulation in cell lines natively expressing the NOP receptor, vi) interactomic studies, and vii) site-directed mutagenesis. All these studies, combined with a collaborative medicinal chemistry effort, will contribute to elucidating the molecular mechanism of biased agonism at the NOP receptor, and more broadly at GPCRs. This know-how will greatly contribute to improving our knowledge about biased agonism as a strategy for developing a new generation of safer/more effective drugs.