**New mechanisms of GPCRs function: regulation by protein-protein interaction**

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Evidence has demonstrated that G protein coupled receptors (GPCRs) can physically interact with a variety of accessory proteins, confirming that signal transduction of these receptors is not restricted to heterotrimeric G protein activation. Such interactions can alter the effectiveness of agonist-driven cell signalling, determine the signals generated and alter the trafficking, targeting, fine tuning and cellular localization of these receptors by providing a scaffold that links the receptors to the cytoskeletal network (Georgoussi et al., 2013). Opioid receptors which belong to GPCRs modulate a variety of physiological responses in the nervous system through activation of a diverse array of effector systems ranging from adenylyl cyclase, ion channels to other signalling intermediates. Opioid administration causes activation of several transcription factors, including CREB, NF-kB, STAT3 and STAT5A/B (Tso and Wong 2003, Mazarakou and Georgoussi, 2005; Georganta et al., 2010). Such parallel manifestations of opioid receptor function suggest that these receptors are involved in different signaling circuits that lead to alterations in target gene expression in a pleiotropic fashion.

In the present study emphasis will be given to unconventional interacting partners of the μ- and δ-opioid receptors opioid receptors such as the Regulators of G protein signalling (RGS) proteins and STAT5B. Evidence will be presented on which RGS proteins opioid receptors interact; how RGS4 and RGS2 confer selectivity to the receptors to choose a specific subset of G proteins; how activation of opioid receptors result in recruitment of RGS proteins to the plasma membrane; and how RGS proteins exert a differential modulatory effect in ERK1,2 phosphorylation, agonist-driven inhibition of adenylyl cyclase and the internalization fate of opioid receptors. Moreover evidence will be presented on how STAT5B associates with the δ-opioid receptor and forms selective pairs with selective Gα and Gβγ subunits and RGS proteins; and how activation of the δ-opioid receptor with selective agonists promotes a multi-component signaling complex involving the STAT5B transcription factor and other signaling intermediates to mediate neuronal survival and neurite outgrowth. Understanding the mechanism of intercellular communication via G-protein-mediated signalling pathways in the nervous system is crucial for normal brain development and regulation of adult neural processes. Thus, defining the molecular determinants that control opioid receptor signaling is important to address problems related to phenomena such as pain perception, tolerance and dependence that occur upon chronic opiate administration and define whether disruption of such interactions may contribute to the pathophysiology of nervous system related disorders and to .the development of novel therapeutic strategies.

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