

Euro Neuropharmacology 2018: Allosteric receptor-receptor interactions in heteroreceptor complexes give a new dimension to molecular neuroscience - Kjell Fuxe - Karolinska Institute.

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Abstract:

More than 4% of the human genome encodes cell receptors; these are organized into different families including matrix receptors (e.g., integrins), ligand-gated (LGIC, 76 members in the human genome) and voltage-gated (VGIC, 143 members) ion channels, intracellular receptors, such as nuclear hormone receptors (NHRs, 48 members), enzyme-linked receptors, such as receptor tyrosine kinases (RTKs, 58 members), and G protein-coupled receptors (GPCRs). GPCRs operate as receptor complexes, suggests several different incoming signals could already be integrated at the plasma membrane level via direct allosteric interactions between the protomers that form the complex. Neuronal populations has led to the identification of a large number of RRI (Receptor – Receptor Interactions). The action of a drug involved the formation of specific complexes with molecular agents in the target cells, thereby eliciting a cell response. Allosteric interactions are the basic molecular mechanism underlying the formation of these receptor assemblies. The monomers forming these assemblies display a cooperative behavior, which is enabled by the action of orthosteric and allosteric ligands. Hence, the cell-decoding apparatus becomes endowed with elaborate dynamics in terms of recognition and signaling. In the CNS, astroglia constitutes the main glial population, and increasing evidence suggests that, at the level of excitatory synapses, neurons and astrocytes interact bidirectionally, a finding that has led to the proposal of the concept of the “tripartite synapse”. hat monomers of three class A GPCRs (namely rhodopsin, β 2-adrenergic, and μ -opioid receptors) trapped inside nanodiscs are able to signal. In addition, intrinsic plasticity has been found to characterize signaling from GPCR monomers, in that they can assume multiple active conformations because of their binding with ligands, thereby initiating different patterns of signal transduction, such as G protein, arrestin pathways. However, evidence of negative cooperativity between β -adrenergic receptors has also emerged and in the 1980 s in vitro and in vivo experiments proved that indirect biochemical and functional evidence that structural receptor-receptor interactions (RRI) could be established between GPCR monomers. RET (Resonance Energy Transfer) is a short-range, nonradiative energy transfer between donor and acceptor molecules that takes place only if the two species are in close proximity (< 10 nm) to each other. Fluorescence resonance energy transfer (FRET) and bioluminescence resonance energy transfer (BRET) methods used to study homo and heteromerization of proteins including receptors in living cells. Bioluminescence RET (BRET) a bioluminescent molecule acts as the energy donor. FRET and BRET are the methods of choice for imaging protein association inside living cells. FRET methods classified as intensity-based and decay kinetics-based methods. Intensity-based methods rely on the measurement of either the acceptor fluorescence or the acceptor:donor fluorescence intensity ratio.

However, they are not suitable for detecting low-level protein-protein interactions because their sensitivity is reduced by several factors (e.g., sample autofluorescence and overlap between donor and acceptor emission). G protein-coupled receptors interact not only with heterotrimeric G proteins but also with accessory proteins called GPCR interacting proteins. They are implicated in GPCR targeting to particular cellular compartments, in their gathering into large functional complexes called “receptosomes,” in their trafficking to and from the plasma membrane, and in the fine-tuning of their signaling properties. They generally interacts with the extreme C-terminal domain of GPCRs. The concept of hetero-dimerization demonstrated that functional GABAB receptors are heterodimers composed of GABAB R1 (GB1) and GABAB R2 (GB2) subunits. GB1 binds to the ligand but is not coupled with G-protein, whereas GB2 activates a G-protein but does not bind to the ligand. Whether only one subunit of the dimer is sufficient to activate a G-protein or it can be generalized to all GPCRs remains to be elucidated. GPCRs are important transmembrane recognition molecules for regulatory signals such as light, odors, taste hormones, and neurotransmitters. To activate guanine nucleotide binding proteins (G proteins), GPCRs associate with a variety of GPCR-interacting proteins (GIPs). GPCR-interacting proteins contain structural interacting domains which allow the formation of large functional complexes that are involved in G protein-dependent and -independent signaling. The reorganization of the homo- and heteroreceptor complexes in the postjunctional membrane of synapses leading also to changes in the prejunctional receptor complexes to facilitate the pattern of transmitter release to be learned. GPCR signalling can also be modulated by intracellular GIPs interacting through the C-terminal tail and the third intracellular loop of the receptor. Thus, GPCRs select their binding partners by recognizing structural features (i.e., protein-recognition domains) located within the target protein. Eventually, these protein-recognition domains can be highly specific such as the PDZ-, the Zinc finger- or the poly proline (PP)-binding domains which are recognized by discrete sequence motifs presented on GPCRs. The PDZ domain-containing proteins include PSD95, NHERF, Shank and MUPP1 among others, and they interact with GPCRs through their conserved PDZ ligand sequence (T/SxV) motif located at the extreme C-terminus of many receptors. Interaction with these GIPs promotes 5-HT₂CR clustering, mGluR1/5 anchoring in mature dendritic spines, prolongs mGluR5 and P2Y₁R-mediated signalling promotes the coupling of PTH1R and LPA₂R receptors to G α q protein, increases GABAB receptor stability and promotes κ -OPR and β 2-AR recycling. Long-term memory may be created by the transformation of parts of the heteroreceptor complexes into unique transcription factors which can lead to the formation of specific adapter proteins which can consolidate the heteroreceptor complexes into long-

lived complexes with conserved allosteric receptor-receptor interactions. The new pattern of release can be facilitated by the reorganization of the prejunctional receptor complexes through the altered temporal pattern of the transmitters in the synaptic cleft and its surround changing the formation or disrupting the receptor complexes through agonist dependent processes. Extracellular signals such as light, odors and taste, or intercellular signals such as hormones and neurotransmitters are mainly, although not exclusively, detected by seven transmembrane cell surface G protein-coupled receptors (GPCRs). The allosteric receptor-receptor interactions in heteroreceptor complexes appear to indicate a new principle in biology making possible integration of signals at the level of the plasma membrane. The heteroreceptor complexes and their dynamics may be part of the molecular basis of learning and memory. By producing unique transcription factors formed from internalized heteroreceptor complexes. Long-lived heteroreceptor complexes with stabilized and conserved allosteric receptor-receptor interactions in the postsynaptic membrane can be an essential part of the molecular structure for long-term memory in the neuronal networks.