G PROTEIN-COUPLED RECEPTORS

Overview:- The completion of the Human Genome Project allowed the identification of a large family of proteins with a common motif of seven groups of 20-24 hydrophobic amino acids arranged as α-helices. Approximately 800 of these seven transmembrane (7TM) receptors have been identified of which over 300 are non-olfactory receptors (see Frederikson *et al*., 2003; Lagerstrom and Schioth, 2008). Subdivision on the basis of sequence homology allows the definition of rhodopsin, secretin, adhesion, glutamate and Frizzled receptor families. NC-IUPHAR recognizes Classes A, B, and C, which equate to the rhodopsin, secretin, and glutamate receptor families.

The nomenclature of 7TM receptors is commonly used interchangeably with G protein-coupled receptors (GPCR), although the former nomenclature recognises signalling of 7TM receptors through pathways not involving G proteins. For example, adiponectin and membrane progestin receptors have some sequence homology to 7TM receptors but signal independently of G-proteins and appear to reside in membranes in an inverted fashion compared to conventional GPCR. Additionally, the NPR-C natriuretic peptide receptor has a single transmembrane domain structure, but appears to couple to G proteins to generate cellular responses. The 300+ non-olfactory GPCR are the targets for the majority of drugs in clinical usage (Overington *et al*., 2006), although only a minority of these receptors are exploited therapeutically.

Signalling through GPCR is enacted by the activation of heterotrimeric GTP-binding proteins (G proteins), made up of α, β and γ subunits, where the α and βγ subunits are responsible for signalling. The α subunit (tabulated below) allows definition of one series of signalling cascades and allows grouping of GPCRs to suggest common cellular, tissue and behavioural responses. Gβγ subunits (tabulated below) also are able to signal, in a manner independent of the Gα subunits. Recently, the concept of agonist bias, or functional selectivity, has arisen (see Kenakin & Miller, 2010), which suggests that particular agonists, or allosteric modulators, may be able to promote post-receptor signalling through one cascade at the expense of an alternative. This has complicated the scenario for classification of GPCR. For the purposes of the Guide to Receptors and Channels, “Principal transduction” is limited to the predominant established Gα signalling.

$G\alpha_s$ family: β_1-adrenoceptors in the heart couple principally through $G\alpha_s$ to activate adenylyl cyclase activity and elevate intracellular cyclic AMP levels. This in turn leads to activation of protein kinase A and the consequent phosphorylation and enhancement of function of voltage-gated calcium channels ($Ca_v1.2$). This, in turn leads to the observed action of noradrenaline (norepinephrine) or adrenaline (epinephrine) in increasing cardiac rate and force of contraction. The identification of other G_s-coupled GPCR in the heart would allow prediction of a similar effect on heart rate and force through the same mechanisms. In other tissues, G_s-coupled receptors would be predicted to evoke smooth muscle relaxation (e.g. β_2-adrenoceptors in bronchioles), enhance secretion (e.g. H_2 histamine receptors in gastric parietal cells), stimulate lipolysis in adipocytes (e.g. β_3-adrenoceptors) and inhibit platelet aggregation (e.g. IP prostanoid receptors).

Nomenclature	HUGO nomenclature	Other names	Ensembl ID
α_s	GNAS	Stimulatory G protein	ENSG00000087460
α_{olf}	GNAL	Olfactory type	ENSG00000141404

$G\alpha_i$ family: M_2 muscarinic acetylcholine receptors in the heart couple *via* $G\alpha_i$ subunits to inhibit adenylyl cyclase activity. Vagal innervation targets these receptors, primarily in the atria, to counteract the effects of noradrenaline and adrenaline in the cardiac myocyte, leading to a reduction in heart rate and force of contraction. In addition, $G\alpha_i$ subunits and Gβγ subunits (see below) enhance potassium channel opening ($K_{iR}2.x$). The ensuing hyperpolarization of the cardiac myocyte leads to a reduction in voltage-gated L-type calcium channel activity and a consequent inhibition of rate and force of cardiac contraction - the manifestation of vagal nerve stimulation. In other tissues, G_i-coupled receptors would be predicted to inhibit neurotransmitter release (e.g. μ opioid receptors on parasympathetic nerve terminals in the small intestine), inhibit lipolysis in adipocytes (e.g. A_1 adenosine receptors) and enhance platelet aggregation (e.g. $P2Y_{12}$ receptors).

In the retina, transducin (α_t) subunits allow coupling to a cyclic GMP-specific phosphodiesterase, PDE6. This reduces cellular cyclic GMP levels leading to a reduction of currents through cyclic nucleotide-gated channels (CNG) and subsequent decrease of the ‘dark’ current.

Nomenclature	HUGO nomenclature	Other names	Ensembl ID
α_{i1}	GNAI1	Inhibitory G protein α subunit	ENSG00000127955
α_{i2}	GNAI2	Inhibitory G protein α subunit	ENSG00000114353
α_{i3}	GNAI3	Inhibitory G protein α subunit	ENSG00000065135
α_{t1}	GNAT1	Transducin 1 α subunit	ENSG00000114349
α_{t2}	GNAT2	Transducin 2 α subunit	ENSG00000134183
α_{t3}	GNAT3	Gustducin α subunit	ENSG00000214415
α_o	GNAO1	α other	ENSG00000087258
α_z	GNAZ	-	ENSG00000128266

$G\alpha_q$ family: M_3 muscarinic acetylcholine receptors in bronchial smooth muscle couple via $G\alpha_{q/11}$ subunits to stimulate phospholipase C-β activity. This leads to an elevation of intracellular calcium ions through inositol 1,4,5-trisphosphate action at IP_3 receptors, activation of protein kinase C and the consequent smooth muscle contraction and reduced airway conductance. In other tissues, G_q-coupled receptor activation leads to increased platelet aggregation (e.g. $P2Y_1$ receptors).

Lysophosphatidic acid receptors and proteinase-activated receptors are examples of GPCR which couple through multiple G protein families, including $G\alpha_{12/13}$ leading to activation of a guanine nucleotide exchange factor, or GEF, for the Rho family of low molecular GTP-binding proteins (ENSFM00500000269651), the subsequent activation of Rho kinase and regulation of the cytoskeleton, leading to cellular shape changes and/or migration.

Nomenclature	HUGO nomenclature	Ensembl ID
α_q	GNAQ	ENSG00000156052
α_{11}	GNA11	ENSG00000088256
α_{12}	GNA12	ENSG00000146535
α_{13}	GNA13	ENSG00000120063
α_{14}	GNA14	ENSG00000156049
α_{15}	GNA15	ENSG00000060558

GNAQP1 is a pseudogene (ENSG00000214077).

Gβγ subunits: although β and γ subunits are synthesised as separate entities, they are considered to generate a complex which is essentially biologically irreversible. Acylation and prenylation ensure an association with the plasma membrane, where Gβγ subunits may regulate ion channel activities, or recruit members of the G protein-coupled receptor kinase family, also known as β-adrenoceptor kinases. Phosphorylation of particular cytoplasmic serine/threonine residues of GPCR allows binding of β-arrestin (ENSFM00250000000572). These proteins act as scaffolding partners facilitating internalization of GPCR as a mechanism of desensitization, or coupling to alternative signalling pathways (e.g. MAP kinases)

Nomenclature	HUGO nomenclature	Ensembl ID
β1	GNB1	ENSG00000078369
β2	GNB2	ENSG00000172354
β3	GNB3	ENSG00000111664
β4	GNB4	ENSG00000114450
β5	GNB5	ENSG00000069966

Nomenclature	HUGO nomenclature	Ensembl ID
γ2	GNG2	ENSG00000186469
γ3	GNG3	ENSG00000162188
γ4	GNG4	ENSG00000168243
γ5	GNG5	ENSG00000174021
γ7	GNG7	ENSG00000176533
γ8	GNG8	ENSG00000167414
γ10	GNG10	ENSG00000242616
γ11	GNG11	ENSG00000127920
γ12	GNG12	ENSG00000172380
γ13	GNG13	ENSG00000127588
γt1	GNGT1	ENSG00000127928
γt2	GNGT2	ENSG00000167083

GNB1L (ENSG00000185838) and GNB2L1 (ENSG00000204628) are described as Gβ-like proteins on the basis of sequence homology. Four Gγ pseudogenes are defined in the human genome (GNG5P1, ENSG00000213536; GNG5P2, ENSG00000133136; GNG5P3, ENSG00000254949; GNG5P5, ENSG00000234590).

Further reading:

Foord SM, Bonner TI, Neubig RR, Rosser EM, Pin JP, Davenport AP *et al.* (2005). International Union of Pharmacology. XLVI. G protein-coupled receptor list. *Pharmacol Rev* **57**: 279-288.

Fredholm BB, Hokfelt T, Milligan G (2007). G-protein-coupled receptors: an update. *Acta Physiol* **190**: 3-7.

Fredriksson R, Lagerstrom MC, Lundin LG, Schioth HB (2003). The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Mol Pharmacol* **63**: 1256-1272.

Hill SJ, Williams C, May LT (2010). Insights into GPCR pharmacology from the measurement of changes in intracellular cyclic AMP; advantages and pitfalls of differing methodologies. *Br J Pharmacol* **161**: 1266-1275.

Kenakin T (2010). Being mindful of seven-transmembrane receptor 'guests' when assessing agonist selectivity. *Br J Pharmacol* **160**: 1045-1047.

Kenakin T, Miller LJ (2010). Seven transmembrane receptors as shapeshifting proteins: the impact of allosteric modulation and functional selectivity on new drug discovery. *Pharmacol Rev* **62**: 265-304.

Kenakin TP (2009). Cellular assays as portals to seven-transmembrane receptor-based drug discovery. *Nat Rev Drug Discovery* **8**: 617-626.

Lagerstrom MC, Schioth HB (2008). Structural diversity of G protein-coupled receptors and significance for drug discovery. *Nat Rev Drug Discovery* **7**: 339-357.

Milligan G (2009). G protein-coupled receptor hetero-dimerization: contribution to pharmacology and function. *Br J Pharmacol* **158**: 5-14.

Overington JP, Al-Lazikani B, Hopkins AL (2006). How many drug targets are there? *Nat Rev Drug Discovery* **5**: 993-996.

http://www.iuphar-db.org/

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