G PROTEIN-COUPLED RECEPTORS

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Summary

G protein-coupled receptors are an important group of membrane proteins. They consist of seven tightly packed transmembrane domains and are also often called the seven transmembrane receptors. G protein-coupled receptors mediate extracellular signals into intracellular events. They are essential for the function of several of our senses (vision, taste and smell), hormone action and neurotransmission. The receptors developed early in the process of evolution. Not only vertebrates but also insects, plants and even

protozoa utilize these signaling molecules. A G protein-coupled receptor needs its signaling partner, a heterotrimeric G protein (guanine nucleotide binding protein) to activate effector proteins inside the cell. These effectors can be enzymes or ion channels, which in turn regulate various signaling pathways inside the cell. G protein-coupled receptors are usually classified in about 100 receptor families, which form five receptor superfamilies. The total number of different G protein-coupled receptors in vertebrates is estimated to be close to 1000. Receptor number and function are constantly regulated, which is essential for the cell to achieve a proper function. Due to their importance in various physiological processes, G protein-coupled receptors are currently the most important targets of clinically marketed drugs and ongoing drug discoveries in the pharmaceutical industry.

1. Introduction

The cells that form a multicellular organism must be able to communicate with each other. Sometimes the communication must be rapid, like in the case of neuronal signaling, and sometimes slower and possibly prolonged responses are desirable.
In most cases, communication occurs with the help of signal molecules which bind receptor proteins in the cells. Receptors were traditionally classified in four categories according to their functional properties. This classification has been validated by the cloning of receptor genes, which supports the existence of four major receptor groups (Table 1). The opening and closing of an ion channel receptor is the most rapid signal transduction mechanism, which responds in milliseconds to the changing concentration of signal molecules. Ion channel receptors are required for neural transmission and they also regulate muscular contraction. The effects conveyed by G protein-coupled receptors (GPCRs) typically appear in seconds, while the responses to tyrosine kinase receptor or nuclear receptor activation usually take from a few hours to a few days to appear. Tyrosine kinase receptors mediate their signals through phosphorylation of tyrosine residues in specific target molecules. Many growth factor receptors belong to this class. Steroid hormones and some other lipophilic molecules have nuclear receptors. When activated, these receptors bind to the regulatory elements in the DNA to activate their target genes. Another type of signaling is mediated by gases like NO and CO. They diffuse freely across cell membranes and affect their target molecules directly, without depending on receptors.

	Ion channel receptors	**G protein coupled receptors**	**Tyrosine kinase receptors**	**Nuclear receptors**
Location	Plasma membrane	Plasma membrane	Plasma membrane	Nucleus
Effector	Ion channel	Enzyme or ion channel	Enzyme	Gene activity regulation
Time scale	milliseconds	seconds - minutes	minutes - hours	hours - days
Examples	Nicotinic receptors	Adrenergic receptors	Insulin receptor	Steroid receptors
	$GABA_A$ receptors	rhodopsin	EGF receptor	vitamin D receptor

Table 1. Four receptor classes

G protein-coupled receptors are integral cell membrane proteins that convey extracellular signals into intracellular events. When activated, the receptors activate heterotrimeric guanyl nucleotide binding proteins, G proteins—a property after which they have been named.

The 1994 Nobel Prize in Physiology or Medicine was awarded to Alfred G. Gilman and Martin Rodbell *"for their discovery of G-proteins and the role of these proteins in signal transduction in cells"*. Today, three decades after the initial discovery of G proteins and two decades after the cloning of the first GPCRs, the importance of these molecules in cellular signaling is well recorded.

About 30% of commonly prescribed medicines work through GPCRs (see section 8.). Genome projects are revealing that the GPCRs form the largest class of receptors with about 1000 members in the human genome.

The receptors play hundreds of roles in our body. Several sensations (vision, taste, smell) are initiated by the action of the GPCRs. They are also important in tasks in the regulation of growth, death, metabolism and differentiated functions of the cells.

Stimuli that can activate GPCRs (agonists) are in most cases hormones, peptides or other chemicals (see section 5). In the special case of photoreceptors in the retina (rhodopsin and the cone opsins), the receptor is covalently bound to its ligand, retinal.

Isomerization of retinal upon absorption of photons of light leads to activation of these receptors. In lower eukaryotes like yeast and slime mold, other extracellular agents, such as mating factors and cyclic AMP, also interact with GPCRs.

GPCRs have several common structural features (see Figure 1). The receptors have an extracellular N-terminus, seven membrane-spanning transmembrane domains connected by extra- and intracellular loops, and an intracellular C-terminus.

The amino acids in the transmembrane domains are thought to form structures called alpha helices. Based on the structural features of the GPCRs, this receptor group is also called seven-transmembrane receptors or serpentine receptors.

The receptors are classified into approximately 100 subfamilies according to the sequence homology, ligand structure and receptor function. To date, the crystal structure of only one prototypical GPCR, rhodopsin, has been resolved and the structural modeling of other GPCRs relies on the rhodopsin template.

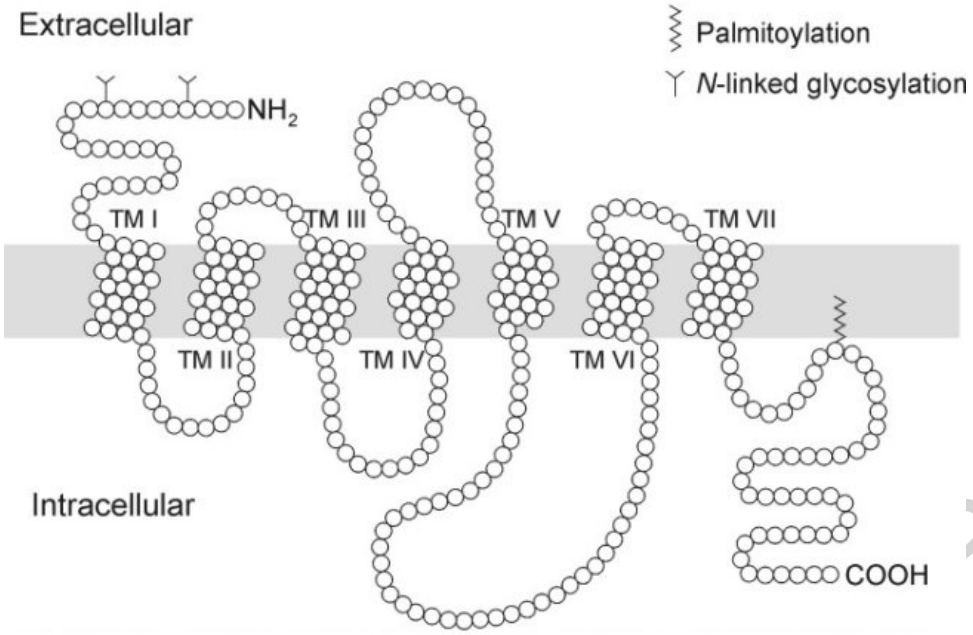

Figure 1a. Schematic representation of a prototypical G protein-coupled receptor. Putative cysteine palmitoylation site in the *C*-terminus and *N*-linked glycosylation sites in the N-terminus are shown. The gray zone represents the plasma membrane lipid bilayer through which the transmembrane alpha-helices penetrate.

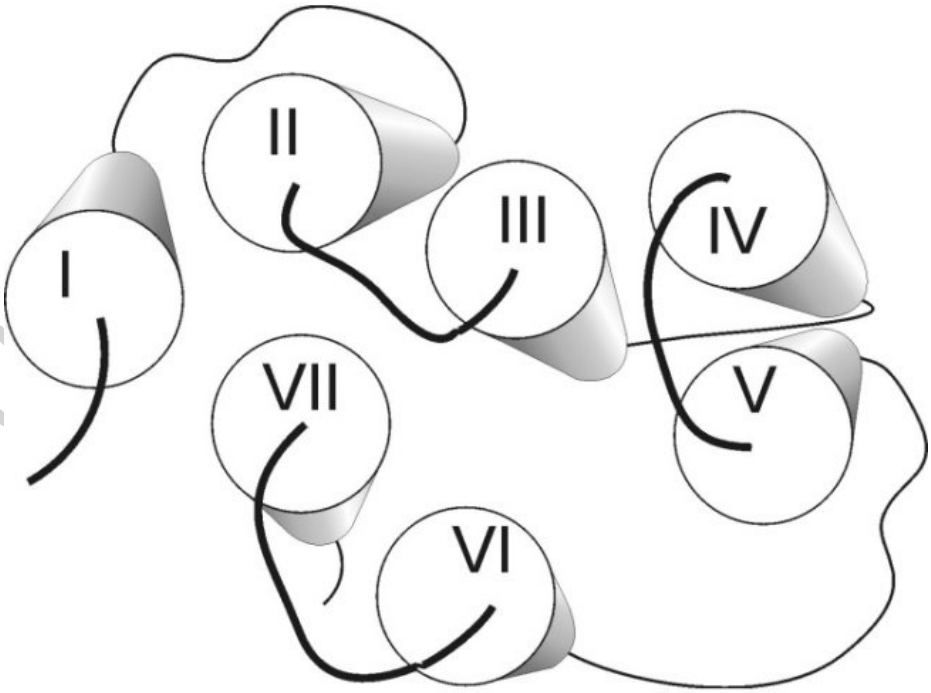

Figure 1b. Illustration of the orientation of the seven transmembrane alpha-helices (barrel-like structures) of a prototypical G protein-coupled receptor, viewed from the extracellular end. The extra- and intracellular loops connecting the transmembrane domains are shown in thick and thin lines, respectively.

For signal transduction across the plasma membrane, three components are classically required; the receptor itself, the G protein and an effector. The latter may be an enzyme or an ion channel. The receptors and effectors are transmembrane glycoproteins whereas heterotrimeric G proteins are associated with the cytoplasmic side of the plasma membrane. Conformational changes follow the agonist binding and the activation of a GPCR. These changes act as a switch to relay the signal to G proteins that in turn evoke further intracellular responses. Some intracellular regions of the receptor, including the transmembrane domain III / intracellular loop 2 interphase and the third intracellular loop, are considered to be important for receptor / G protein interaction.

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Biographical Sketch

Tarja Kokkola, Ph.D., Assistant at the Department of Physiology, University of Kuopio, Finland. She was born in 1970 at, Enontekiö, Lapland, Finland. After her childhood and school years in the quiet Vuontisjärvi village she moved to Kuopio in 1989 to study Biochemistry and Molecular Biology. She prepared her M.Sc. thesis on melatonin synthesis in rat pinealocyte primary cultures. After her graduation in 1994 her research covered various aspects of G protein-coupled melatonin receptors, including cloning novel receptors, the expression of melatonin receptors in breast cancer cells and the effect of melatonin on gene expression in target tissues. In 1996, she spent eight months working with the melatonin receptor research group at Glaxo Wellcome Medicines Research Centre in Stevenage, England. Her Ph.D. thesis, completed in 2003, concentrated on the structure and function of the human G protein-coupled MT1

melatonin receptor. Her current research deals with several G protein-coupled receptors, including muscarinic, cannabinoid and purinergic receptors.