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G proteins: Introduction of its history, structure, function, and drug development

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Abstract. G protein-coupled receptor can be written in GPCR, it has a big great family and this species include 800 human genes, it become the important part of human body. Although each species has their own unique skills, it can make different kind of medicine that can save human's life. And then there's the G-protein-coupled receptor mechanism. The GPCR desensitization regulator - arrestin was further analyzed, and researchers discovered that GPCRs could be activated not only through the G-protein-dependent pathway but also through the non-G-protein-dependent pathway, known as the -inhibitor pathway, to control the ingestion and desensitization throughout vivo and even start a new wave of signal transduction. The development of G-protein-coupled receptor drugs followed. GPCR is strongly associated to pathological conditions and has an essential function in cell signal transmission. More than 40% of the medicines on the market today target GPCR, which is the reached a high point family of pharmacological targets. The intracellular effector proteins (G proteins, etc.) that are activated by the GPCR play an important role in the regulation of its physiological function.

Keywords: G protein-coupled receptor (GPCR), medicines, signal transduction, pharmacological targets, intracellular effector proteins.

1. Introduction

G-proteins are a family of signal transduction proteins playing a quite critical role in the transmission of extracellular signals into the cell [1]. They are involved in numerous physiological processes, including vision [2], olfaction [3], hormone secretion [4], and neurotransmitter release [5]. G-protein coupled receptors (GPCRs) is the largest kind of cell surface receptors and are responsible for G-protein activation on ligand binding [6]. The downstream effects of G-protein signalling vary widely, including alterations in ion channel activities [7], second messenger production [8], and gene expression [9][9=]. Given their importance in cellular signaling, G proteins have been the subject of intense research over the past few decades.

The discovery of G proteins dates back to the 1960s [10], when it was first observed that the binding of epinephrine to certain receptors in the plasma membrane of cells leads to the activation of an unknown intracellular signaling pathway. It was later discovered that this pathway involves the activation of a trimeric G protein complex, which consists of three subunits: alpha, beta, and gamma

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[11]. Substantial progress has been made in understanding the architecture since, function, and regulation of G proteins. This has led to the development of a wide range of drugs that target G protein signaling, including beta-blockers, antipsychotics, and antidepressants.

In this review, we provide a comprehensive overview of G proteins, including their history, structural characteristics, signal transduction mechanisms, and drug research and development. We begin by exploring the history of G proteins, from their initial discovery to the latest research on their evolution and diversity. We then delve into the structural features of G proteins, including their various subtypes, domains, and interactions with other proteins. Finally, we review the latest research on drug development targeting G proteins, including small molecule inhibitors and activators, as well as potential therapeutic applications. Altogether, this review aims to provide a comprehensive and up-to-date summary of the role of G proteins in cellular signal transduction and highlights their potential as targets for drug development.

2. History of G proteins

GPCR was researched to be expressed for the first time in the rat small intestine in 1998 [12]. Subsequent studies have shown that GPR35 is displayed in a number of tissues, including the intestinal tract [13], the central nervous system [14], the cardiovascular system [15], the liver [16], and the spleen [17]. For their studies on the operation of G-protein-coupled sensors, Robert Lefkowitz and Laurence Kobilka received the Nobel Prize of the field of chemistry in 2012 [18].

GPCR's primary structure is made up of seven helices that span the plasma membrane [19]. Ye and the three rings play a crucial role in the interaction seen between receptor and its ligand outside of the cell. The contact between the GPCR protein and the downstream G protein, which facilitates intracellular signal transduction, depends heavily on the third ring and the C-terminal, both of which are intracellular. A second messenger, like as Ca^{2+} or cAMP, is created when a ligand binds to a GPCR, and it is this second messenger that carries the intracellular signal from the transcription factor downstream late receptors [20]. GPCRs can, however, also facilitate signal transduction without the involvement of G proteins, for instance through the molecular control of downstream pathways.

3. Characteristics of G proteins

Alpha, beta, and gamma subunits make up the G protein.[11] The most adaptable subunit, the alpha, is in charge of binding and hydrolyzing GTP, which is needed for the G protein to be activated and inhibited [21]. The beta and gamma subunits engage with the alpha subunit and other effector proteins to form a closely bound heterodimer. Figure 1 shows the classical structure of one G protein.

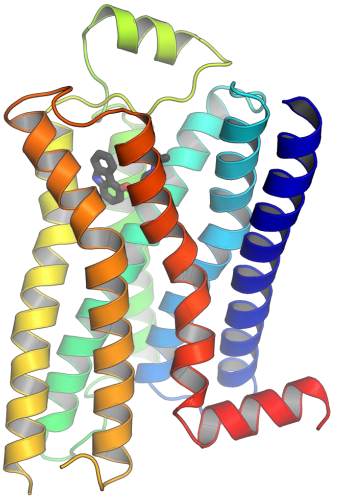

Figure 1. Representative schematic diagram of the structure of G protein.

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It consists of four parts: the N-terminal part, the switch I part, the alpha helical part and the switch II part. The N-terminal domain binds GTP, while the switch I and II regions undergo conformational changes when hydrolyzed by GTP, necessary for activation and inactivation of the G-protein. The alpha-helical domain is responsible for interaction with other proteins, including GPCRs and downstream effectors.

G proteins consist of seven and three transmembrane domains in the beta and gamma subunits, respectively. The β-sub contains an N-terminal coiled-coil domain interacting with the γ-sub and a C-terminal domain interacting with other proteins, including GPCRs and downstream effectors. The γ-subunit contains an N-terminal domain interacting with the β-subunit and a C-terminal domain interacting with other proteins, including ion channels and enzymes. [22]

In addition to their subunit composition, G proteins are regulated by a number of other proteins. These include G protein-coupled receptor kinases (GRKs) [23], which phosphorylate GPCRs and promote their desensitisation, and regulators of G protein signalling (RGSs), which accelerate the rate of GTP hydrolysis by the alpha subunit, thereby promoting G protein deactivation.

Taken together, the structural features of G proteins are complex and diverse and are critical to how they function in cellular signalling. The signalling mechanisms of G proteins, including their activation, regulation and downstream effectors, are reviewed in the next section.

4. Signal transduction mechanisms of G proteins

G-protein signalling mechanisms are complex, involving several steps [24] including receptor activation, G-protein activation and activation of downstream effectors. The process starts with the binding of the ligand to the GPCR.

After G-protein activation, H-GDP is exchanged for GTP on the alpha subunit, resulting in a change in shape of the alpha subunit and dissociation of the beta-gamma subunit complex. The alpha/beta complex then communicates with second messengers, ion channels, enzymes and other downstream effectors.

The downstream effects of G-protein signalling are diverse and include changes in the activity of ion channels, the production of second messengers and the expression of genes. For example, when Gs is activated, adenylate cyclase is stimulated and cyclic AMP (cAMP) is produced, which can activate protein kinase A (PKA) and other downstream effectors. On the other hand, activation of the Gi proteins inhibits adenylate cyclase and reduces the level of cAMP.

Collectively, the signalling mechanisms of G proteins are complex, involving several stages, but are critical for their function in cellular signalling. In the next section, we review recent research into G protein drug development, including small molecule inhibitors and activators, and potential therapeutic applications.

5. Drug research and development targeting G proteins

However, because the GPCR family is so widespread in the human body and because it performs complex functions, it has been linked, either directly or indirectly, to the growth and spread of a wide range of diseases. GPCRs and Cardiovascular/Metabolic Diseases: Members of the class A subclass of GPCRs, including the AT1Rs, AT2Rs and Mas-Rs of the angiotensin system (RAAS), one of the most important neurohormonal regulatory systems in the human organism, have been mainly implicated in cardiovascular and metabolic disorders [25]. GPCRs and inflammation: The Ccr5 family is highly expressed in various cells of the immune system and is involved in the proliferation, migration, survival and immune function of both healthy and diseased immune cells. GPCR in cancer: Research has shown that different members of the GPCR family are involved in the initiation and growth of many types of cancer. Several hormone-dependent tumours use GPCRs as hormone receptors.

6. Conclusion

In this review, we have provided a comprehensive overview of G proteins, including their discovery and evolution, structural characteristics, signal transduction mechanisms, and drug research and

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development. We began by exploring the history of G proteins, from their initial discovery to the latest research on their evolution and diversity. We then delved into the structural features of G proteins, including their various subtypes, domains, and interactions with other proteins. Next, we discussed the signal transduction mechanisms of G proteins, including their activation, regulation, and downstream effectors. Finally, we reviewed the latest research on drug development targeting G proteins, including small molecule inhibitors and activators, as well as potential therapeutic applications. Taken together, this review provides a comprehensive and timely overview of G-protein roles in cellular signalling. and highlights their potential as targets for drug development. As our understanding of the structure and function of G proteins continues to evolve, it is likely that new drugs will be developed that target these proteins with even greater specificity and efficacy, leading to new therapies for a wide range of diseases.

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