

G Protein-Coupled Receptor, an Important Target for Drug Design and Screening

Daniel Chikere Ali¹, Humphrey Ochinn², Cheng Peng¹ and Ye Boping^{1*}

¹Department of Microbiological and Biochemical Pharmacy, School of Life Science, China Pharmaceutical University, Nanjing, China

²Clinical Center for Reproductive Medicine, First Affiliated Hospital, Nanjing Medical University, Nanjing, China

*Corresponding Author: Ye Boping, Department of Microbiological and Biochemical Pharmacy, School of Life Science, China Pharmaceutical University, Nanjing, China.

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Abstract

G protein-coupled receptor as a targeting receptor is prevailed by peptide and a small molecule in which antibody has performed vital functions over such molecules by the way of its specific abilities, restricted penetration and dosing frequency. Moreover, GPCR has functional familiarities like structural function, sequence and they are known based on their physiological functions such as pain, appetite, synaptic transmitter and mood, which were considered in drug discovery. Studies revealed that ligand and receptors are the major player in GPCRs functional selectivity for targeting because conformation changes depend on them and in the accessory protein for interactions. However, GPCR modelling is generally used as a practical alternative in the absence of crystallographic data because it can produce vital information about the different technological development and its effective functions in the structural-based drug discovery. This results due to its binding site targets for rationalization, cost-effectiveness, and efficiency in drug design.

Keywords: 7-Transmembrane; Cell Surface Receptor; GPCR Selectivity; Drug Design and Screening; Antibody

Introduction

G protein-coupled receptors (GPCR) is the largest family of cells surface receptor protein, and it contains 4% of the protein coding in human genome [1]. Following the importance of the GPCRs physiological function, it was found to be one of the most pursued targets for drug development and it shows that over 19% of the approved drug-targeted portion of the genome [2]. GPCR is also the richest source of targets in the pharmaceutical field [3]. G-Protein coupled receptor has three basic characteristics which are identified as having an extracellular N-terminal, intracellular C-terminus and 7-transmembrane spanning domains (TMDs). It has been shown that within 7-transmembrane, there are a number of motifs in which its characteristics are highly protected within the subfamily, and the homology between subfamilies are very limited [4]. These receptors were able to regulate several physiological processes as pharmaceutical targets in the treatment of many diseases such as pain, obesity, cancer, pulmonary diseases, endocrine and neurological cardiovascular disorder [5]. GPCR superfamily targets potential drugs efficiently more than any other protein family and it is most dynamic and occurs at equilibrium between different conformational states. GPCR is one of the receptors that plays an important role in biological process through signal transduction of several extracellular signals across cell membrane in cytosolic site such as enzymes, lipid, hormone, neurotransmitters, peptides which occurs via physiological process of endogenous extracellular interactions with the binding site that initiates conformational changes that carries signal from plasma membrane-spanning 7TM region and stimulation of intracellular cascade through heterotrimeric G proteins [6]. It is the most drug targeted receptors expressed on the cell surface and half of them remains the most noticed drug targets from Pharmaceutical industries and other research group.

A report from National Institute of Health (NIH) Molecular Libraries Program (MLP) carried large-scale screening capabilities to identify new drug targets and GPCR were one of the targets involved in high-throughput screening HTS in the MLP [7]. GPCR has about

860 members known according to phylogenetic analysis studies [8]. Reports revealed that its specific responsibilities are signal transduction from cytosol to the cell interior. However, 350 out of the receptors were considered as drug targets while 100 is regarded as orphan receptors but neither endogenous ligand nor their physical function is known [9]. GPCR depends on structurally related functions that share heptahelical transmembrane receptor. It is the base target for sight, smell and taste with very relative low expressions level due to extractions in the crystallization of GPCR that contributes in the measurement of structural functions that was first discovered in the structure of bovine rhodopsin in the year 2000. The β_2 adrenergic receptor as the second structural crystalline in 2007 which shows that functional and structural activities of GPCR is known.

GPCR has structural, sequence and functional familiarities, and they are divided into five major classes such as rhodopsin, adhesion, secretin, metabotropic glutamate and frizzled which plays physiological function [10]. The class Secretin (GPCR class B) and 15 receptor of peptide hormone has vital drug targeting abilities in human diseases such as diabetes, osteoporosis, cardiovascular disease, cancer, neurodegeneration, headache including psychiatric disorder. Large N-terminal extracellular domain (ECD) and transmembrane domain (TMD) is made up of receptor proteins. It consists of GPCR 7transmembrane spanning α -helices that contribute to the signaling of heterotrimeric G proteins which increases the intracellular cAMP level through the activation of adenylated cyclase that in turn increases the inositol phosphate and intracellular calcium rate [11].

GPCRs were identified as the first protein interaction found in the regulation of GPCR or G protein coupling in which GPCR kinase (GRK) and arrestin exist. GRKs plays a vibrant central role in regulating GPCR signaling through the following three ways; G-protein-independent mechanisms, endocytosis of GPCRs to endosomes for GPCR dephosphorylation and resensitization, and uncoupling (desensitization) of GPCR/ G-protein signaling [12]. The mechanism of receptor-ligand and activation of class B GPCR have been extensively studied so that drug design by structure-based method be more effective. The X-ray crystallography and Nuclear Magnetic resonance (NMR) structure of the large N-terminal extracellular domains of class B receptors coupled with peptide ligand contribute to the structural mechanism of ligand selectivity. Class A GPCR(rhodopsin) has recorded more success but there is the need for more focus on understanding the conformational changes in TMD when Class B receptor is activated and to determine the ways of designing small molecules modulators for good drug targeting [11].

It is no doubt that Transmembrane of GPCR protein was found to be more difficult to explain the nature of its structural stands, but globular proteins were clear due to the discovery of bovine rhodopsin structure where no X-ray structure of GPCR type is known. Moreover, Rhodopsin structural nature helps in pharmaceutical drug design. In 2012, GPCRs were estimated 40 to 50% of drugs marketed act on GPCRs and as therapeutic drugs. Also for drug development, the orthosteric site has a better advantage insolubility of ligands and no metabolism from CYP450 and little interaction with available protein in the central nervous system (CNS), because each GPCR has a good binding site for endogenous ligand [13]. GPCRs has functional characteristics of the receptors in signal transductions like orthosteric, ligand, allosteric and its mechanism of action has gradually been understood because GPCR have properties like variation and side effect found in clinical trials, where GPCR is acting directly in many drugs that are already approved by the indirect action of GPCR such as selective serotonin reuptake inhibitor (SSRI). Other inhibitors and the way in which GPCR is acting via modulations of a signal in regulating pathways through activation of GPCR within its level of interactions [14]. In this review paper, we focused on the structural-based function of GPCRs, GPCR used as an antibody, GPCRs functional selectivity and their roles in the drug design and screening.

***In silico* screening for drug discovery**

The structural-based drug design is the process that involves ligand binding to its target receptor to derive new drug against the target. Generally, the ligand mainly exists as small molecule such as an endogenous ligand and been identified as high throughout and virtual screening for the system [15]. For the past 100 years of research in pharmacology and pharmaceutical development, receptors have been discovered to possess the ability to bind compound known as a ligand to obtain chemical information contained in these compound and convert them into a biological response which leads to the changes in their activities [8]. In evaluating the wide steps involving development and computation of drug discovery, GPCR modelling was reported to be used in the structural-based drug discovery due to its bind-

ing site targets for rationalization, cost-effectiveness and efficiency of drug design. Studies have revealed that GPCR depends on HTS for proper recognition by *in silico* screening that accounts on a common combination for time and cost management. This will minimize the compound that supposed to be tested for each experiment and expand the lead compound identification rate. *In silico* screening, drug discovery is available in both ligand-based and structural based applications. Structure-based screening is said to be effective with 3D structure in protein targeting because of heterogeneity of receptor's family and lack of crystallographic. Table 1 explains the vital functions of GPCR structural based-drug design [16]. Moreover, crystallographic studies of GPCRs remains a difficult issues because they have the ability to produce only microcrystals and up to date, most GPCR structures obtained using crystallization from membrane-mimetic environment of lipidic cubic phase (LCP) which proved successful in acquiring high-resolution structure of different membrane proteins such as transporters, enzymes and ion channel [17]. Due to the advance contributions of GPCR crystallography, it has significantly changed the landscape of GPCR homology modelling because multiple template strategies can be used in constructing models [18]. However, GPCR modelling is generally used as a practical alternative in the absence of crystallographic data because it can produce more important information about different technological developments. This can lead to the formation of numerous new GPCR structure like β 2 adrenergic receptor, A2a adenosine receptor, dopamine D3 receptor, Histamine H1 receptor and CXCR4 chemokine receptor in which the β 2 adrenergic receptor and G α s was the first structure found. Ligand-based screening strategies reported being the most effective and reproductive in GPCR drug discovery that stands as the major computational methods in studying more information of GPCR ligand.

GPCRs	GPCR structural function based-drug design	Reference
1	It helps to recognize different diffusible orthosteric ligand including monoamine (β 2-AR), acetylcholine (M3 receptor), nucleosides (A2A receptor) etc. and this assist the hydrophobic core of protein	[20]
2	It facilitates the conformational changes in the cytoplasmic function like B2-AR which help in computation methods to estimate active-state binding pockets from inactive state crystal structure and allow structure-based docking to identify new agonist.	[20]
3	The structural-based design have succeeded in over ten marketed drugs such as renin with aliskiren and against hepatitis C virus protease with telaprevir	[21]
4	The current cardiovascular therapeutic targets only a small subset of cardiac GPCR while its deficiency has become more apparent in the post-genomic with the development of high-throughput technology which allows the profiling of GPCR expression in cell and tissues.	[22]
5	Cardiovascular homeostasis is regulated by hormones and neurotransmitters by GPCRs expressed throughout the heart	[22]
6	<i>In silico</i> method is used to create the model used in discovery and optimization of novel molecules with affinity to a target, distribution, excretion, metabolism, the clarification of absorption and toxicity properties	[23]
7	It is a vital tool for biased drug development in cardiovascular diseases via biased agonism	[24]

Table 1: Explains the vital functions of GPCR structural based-drug design.

The homology model was reportedly used *in silico* virtual screening for drug discovery and currently, it is the most successful method for identifying small molecule ligand such as DRD3. Applying homology model of DRD3 by using β 2-adrenergic receptor as a template was able to dock over 3million of compounds. GPCR homology model was used to study the structural feature of the orphan receptor but still not popularly applied *in silico* drug screening while GPRI7 were shown to be successfully used *in silico* compounds screening for an orphan receptor [19]. According to research, it revealed that homology modelling at the first time was based on the structure of rhodopsin as the popular technique used effectively to explain the relationship of structure-function of the receptor and initiate the discovery of chemicals that are capable of modulating its activities. It was very successful as it was able to generate enough data in biochemical and medicinal chemistry when used *in silico* methods and it can also generate so complexly between the small molecule and ligand [18].

The impact of β 2-adrenergic receptor in drug discovery ligands based

β 2-adrenergic receptor (β 2-AR) and rhodopsin has similar conformation changes during activation and the crystal structure of rhodopsin which is a network of hydrogen bond groups in form of water molecule from the retinal binding pocket to the cytoplasmic ends of helices found in the G-Protein coupling. The β 2-adrenergic receptor (β 2-AR) and rhodopsin have similar conformation changes during activation and the crystal structure of rhodopsin which is a network of hydrogen bond groups in form of a water molecule from the retinal binding pocket to the cytoplasmic ends of helices found in the G-Protein coupling. However, crystallography is generally known as tools in drug discoveries for soluble protein target. The crystal structure can be used for *in silico* screening to check lead compound. Moreover, the structure of the β 2-AR bound to ligands with different efficacies such as partial agonist, full agonists and neutral antagonists would help to determine if the ligands binding pocket is altered by the bound ligand [25]. The GPCRs crystallizations play a vital role such as antibody, fusion protein and lipidic cubic phase [26]. The β 2-AR peptide interface is dominated by electrostatic interactions and β 2-AR-Gas interaction shown electrostatic interactions between a β 2-AR cytosolic pocket and a charge Gas C-terminus [27].

The use of antibody as a tool in GPCR drug targeting

The antibody is one of the most effective tools in diagnostic screening as it is able to detect conformational changes in the signal protein and also receptors. It has characteristics function like localization, purification and maintains the domain function. An antibody is used in drug research for drug development because it contains a large molecule known as organic and epitope. The antibody has modulating effect and it may be used as an allosteric drug in targeting due to its ability to control problem associated with orthosteric drugs. The major function of antibody for targeting receptors is that they act as a modulator to direct agonists, inverse agonist and antagonist. It can be designed to carry marker or toxin which is perfect for targeting cancer cell and the specific receptor dimer will directly target the cells and destroy it [10]. The antibody also plays a very diverse function in pharmacological effect more than peptide and small molecule because of its differences in extracellular interaction with a receptor when compared. GPCR antibody targeting development have encountered a lot of challenge more than any other drug target classes due to its production of enough stable GPCR immunogens and antigens that are physiologically vital to epitopes. Studies revealed that no available reproducible approach been known *in vitro* or *in vivo* method while binders were considered available but not functional. The major challenges associated with antibody GPCR targeting is that it has the ability to restrict extracellular surface and epitopes. However, it was made to be ligand-sensitive like conformation changes at the ligand binding to the receptors making it possible to mask by long-chain detergents or lipid used for stabilization of purified receptors. For efficient monoclonal antibody specificity function and signal interaction, it has some setback due to the small molecule that always show a great potential on its efforts for clearing infected cells such as tumor cells because of its high drug capacity to function than a small molecule of chemical drugs. As a result of these challenges and irrespective of the success of monoclonal antibodies which already confirm that no anti-GPCR targeting antibody has been approved by FDA and European Medicines Agency. This is because its use has functional limits but Mogamulizumab found by Kyowa Hakko got approved in 2012 which was used in Japan for the treatment of refractory Adult-T-cell leukemia-lymphoma. Moreover, 37 therapeutic antibodies were approved and marketed all over the world accounting to \$64.5billion in 2012. Out of ten best drugs sold for the year shows that six are MAbs, recording each annual sales of more than \$5billion. However, Studies of antibodies provides that there is antibody currently on the clinic that targets GPCRs such as CCR5, CCR2, CCR4, CXCR4 and C5aR [28].

The significant of selectivity of GPCR in the drug targets

GPCR has been identified as the drug targets in the treatment of psychiatric disease in selective target and the changes in the pharmaceutical world have subjected several advances in GPCR crystallization, *in vivo* pharmacology and its abilities as therapeutics that can target GPCR in a very special way during psychiatric disease treatment. The pharmacological and mathematical data available revealed that GPCR is referred as pluridimensional proteins which occupy many structural conformation and signaling site. However, GPCR has an advantage over others depending on the ligand that is involved [29]. The ability of a ligand to stabilize different receptor conformation, were reported to have effects in the application of the pharmacological method to the process involved in the new drug discovery if the concept of the efficacies should be considered as the case may be. This might be because ligands may have multiple efficacies that

could change the multiple activities observed and this could result to the breakdown of simple behavioral classifications of the following, antagonist; inverse agonist, full agonist and partial agonist [30]. The ligand and receptors type is a major player in the selectivity of GPCR targets because confirmation is determined by them and in the accessory proteins for interaction. This was simply called functional selectivity (ligand-directed signaling and biased signaling), showing that the process of ligand to direct a GPCR towards a conformation where selectivity initiates a particular stimulus to the receptor that is now generally accepted as vital to GPCR targeting in the pharmaceutical research field. It was reported that classes of GPCRs are functional selectivity *in vitro* or *in vivo* including opioid, cannabinoid, metabotropic glutamate receptors, serotonin, adrenergic and muscarinic [29]. A functional selectivity based on the ligand and induced receptor conformation for GPCR ability to direct signal via the G-protein-mediated signal pathway which results to drug effectiveness, therapeutic effect and capable of reducing drug side effect was illustrated in figure 1.

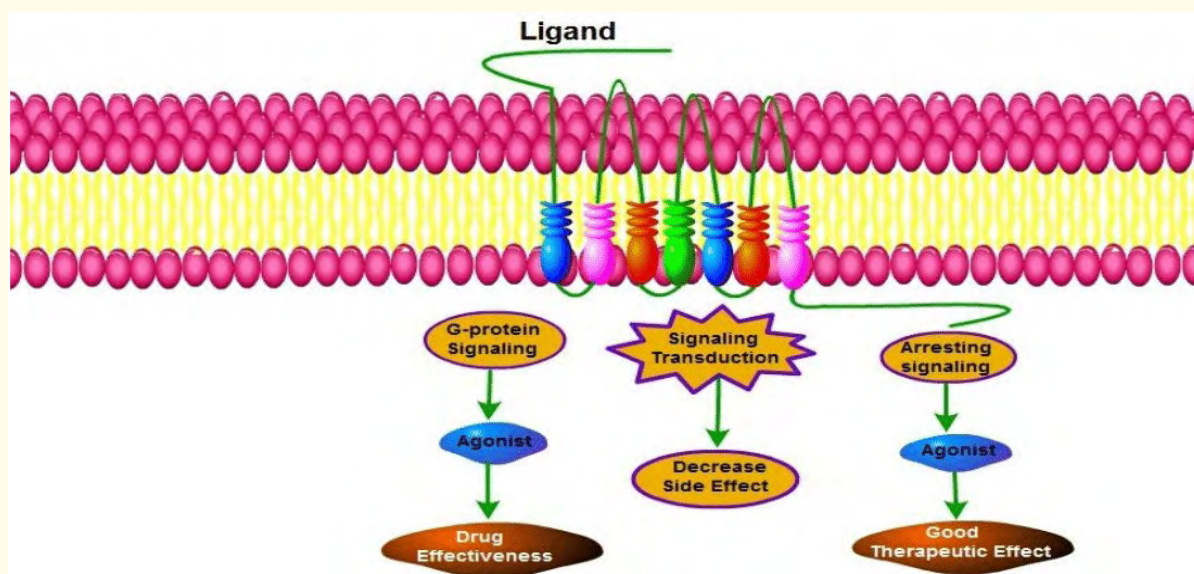


Figure 1: Functional selectivity pathway based on the ligand and induced receptor conformation for GPCR ability to direct signal via the G-protein-mediated.

Following the concern about good therapeutic drugs, functional selectivity has been considered as the major targets toward a better therapeutic drug with fewer off-target and or side effects such as the use of biased agonist pilocarpine that selectively directed on the M1 muscarinic acetylcholine receptor, showing positive therapeutic effects in different models of Alzheimer's disease [31]. The concept of functional selectivity in the pharmaceutical receptor-related case was considered as a great concern. Studies were conducted using one of the GPCR family such as serotonin (hydroxytryptamine 5-HT) receptor and ionotropic receptor [29]. It was reported that when 5-HT_{2A} receptor is activated, it will bring about the production of distinct biochemical signals identified as IP₃/diacylglycerol, 2-arachidonylglycerol (2-AG) and arachidonic acid with relative variation of ligands used and this was confirmed by measuring the two pathways using the signal transduction outputs of each of the pathways from the same cell and it showed that the ligands vary in the functional efficacy of different pathway as a result of stimulations.

However, the different ligand has the ability to activate different pathways which produce an effect on the same molecule [32]. It has become a primary target of many drug-like antipsychotics, antiemetics, antidepressants anorectics, and hallucinogens. Several ligands binding to the serotonin 2A receptors (5-HT_{2A}) and biogenic amines, like tryptamine, dopamine recreational drugs, psilocybin and ly-

sergic acid diethylamide (LSD) therapeutic or antipsychotic drugs [33]. Reports also claimed that the iloperidone has a high affinity for 5-HT_{2A} receptors than D₂ receptor and this provides its ability to be more effective than the antipsychotic compound. And this leads to no doubt that the hallucinogen psilocybin can induce schizophrenia-like psychosis in humans that was blocked by 5-HT_{2A} receptor antagonist which causes decreased in the effective doses of the psilocybin. Furthermore, it is not surprising that selective 5-HT_{2A} antagonists revealed as not effective in treating psychoses in schizophrenia but when combined with D₂ receptor blockade, the 5-HT_{2A} blockade can still provide interesting pharmacologic principles [34]. Therefore, the ligand was able to act at the 5-HT_{2A} receptor in a different way to modulate intracellular transduction cascade. There are some challenges in classifying ligand as an agonist or antagonist when a ligand at a single receptor has the ability to form heterogeneous effects on activation of signal cascade with different functional efficiency [33].

Conclusion

G protein-coupled receptor being the largest member of cell surface receptors shows that 30 to 50% of marketed drugs act on GPCR through the process of signal transduction. It was reported that ligand-based screening strategies are the most efficient, reproductive and it has an ability in providing pieces of information in GPCRs in drug discovery. GPCRs have been proved as a drug target in the treatment of some disease in selective target and functional selectivity has been the main focus of the pharmaceutical aspect of receptors. In this review, we recommend that further studies on the use of the antibody for the regulation of different signaling pathway to the 5-HT_{2A} receptor at the molecular level to determine the impact of these receptors on signal transductions cascade.

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DA contributed in designing and writing of the manuscript and HO participated in coordinating and editing of the manuscript while CP participated in designing and coordinating the manuscripts. BY contributed immensely in designing, editing and approval of the manuscript. All authors in this review have read and agreed with the contents of the final manuscript.

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