

Information Transmission in G Protein-Coupled Receptors

Subjects: Cell & Tissue Engineering

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G protein-coupled receptors (GPCRs) are the largest class of receptors in the human genome and constitute about 30% of all drug targets. The concept of information capacity can be used to measure researcher's understanding of GPCR computation. Capacity is the maximum amount of information that can be transmitted by a system.

Keywords: G protein-coupled receptors ; information transmission

1. Introduction

Most papers on G protein-coupled receptors (GPCRs) start out with some variation of the sentence, "GPCRs are the largest class of receptors in the human genome and constitute about 30% of all drug targets [1]". The foreseeable practical applications of this class of proteins are well established. The long-term practical and scientific applications may be even more interesting, however. GPCRs are molecular microprocessors, or perhaps more accurately "nanoprocessors," that transmit, process, and compare information among and about the environments on each side of the cell membrane and within the membrane itself [2][3]. GPCRs are important examples of molecular computation that may shed light on the mechanisms of information processing in all adaptable biological processes. If that is true, then it may be scientifically and practically profitable to regard GPCRs within the context of general information theory and statistical physics, two disciplines with connections to broad sets of general principles.

Figure 1 is a schematic of the GPCR complex. The core of the complex is composed of seven transmembrane (7TM) alpha helices that form a barrel. There is an eighth intracellular helix that plays an important role in information transmission. A ligand in the extracellular region can bind to a pocket in the barrel and allosterically affect the conformation of the intracellular portion of the core. The intracellular portion of the complex is composed of a collection of molecular switches that can take two forms: (1) a $G\alpha$ switch that involves the $G\alpha$ subunit of a G protein and (2) a collection of phosphorylation sites can form phosphorylation dephosphorylation cycles [4]. The phosphorylation sites form a barcode [5][6] that transmits information to β arrestin (β arr), which directs downstream responses to the ligand.

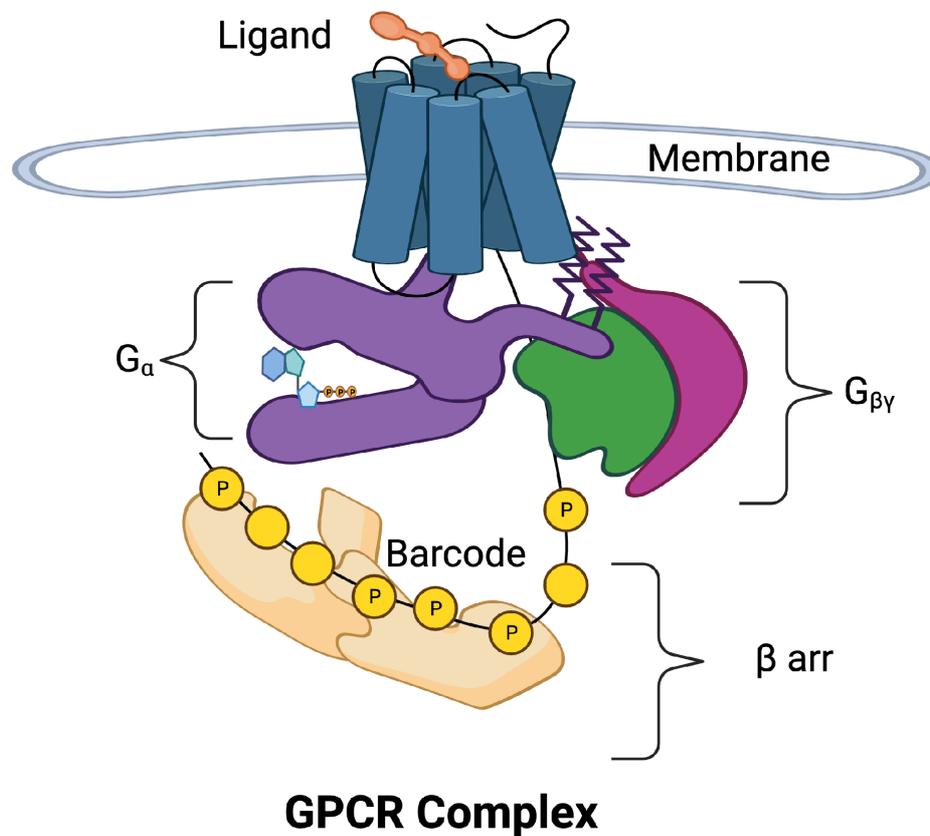


Figure 1. The 7-transmembrane GPCR is illustrated with blue cylinders representing the seven α helices that span the cell membrane. The extracellular ligand (orange) binds to the binding site of the GPCR inducing movement in the α helices. The helices allosterically alter the conformation of the intracellular domains of the GPCR complex. The intracellular portion of the complex has been separated for visibility. Two pathways may be activated, the $G\alpha$ pathway (purple) and the β arr pathway (tan). The $G\alpha$ subunit is a part of the G protein also composed of subunits β (green) and γ (magenta). The β arr pathway is composed of additional response pathways determined by phosphorylation sites on the C tail of the GPCR and intracellular loops that form a barcode that encodes signals for downstream processes.

Even at this basic level, the picture of the GPCR complex is mysterious and unsatisfying. Intuitively, researchers see that a small amount of information is associated with the binding of a ligand to the GPCR, and perhaps the concentration of the ligand is translated into a larger amount of information that requires a barcode to store and transmit all the response options. Precision/personalized/stratified medicine attempts to identify the individual prognosis and targeted treatment at the right time for the right patient, or at least for smaller and more homogeneous groups [7][8][9]. The nuances of the information transmission across the membrane must be clear.

The study of information transmission is taking place on three scales. The largest scale studies take place at the level of the human organism, the clinical level (e.g., [10][11]). Here, approved drug treatments are applied to patient populations and advanced statistical tools are used to tease out the individual patient characteristics that respond differentially to specific treatments. This is a coarse approach to precision drug discovery.

At the smallest scales are detailed observations of GPCR structure (e.g., [6][12]). Here, portions of the GPCR complex are studied in isolation. This may involve, for instance, isolation of the C tail of the GPCR [5] or isolation of the GPCR core [12]. Often, synthetic nanobodies are used to mimic missing parts of the complex. Function and interaction among the complex of components is inferred from the structural observations.

Assay experiments (e.g., [13][14]) take place on intermediate scales. Here, GPCR complexes that are intact, or at least chimeric, are treated with ligands and the downstream responses are observed. Precision drug targets in the complex must be inferred.

Proper characterization of information transmission in the control of downstream response requires that the observations on all three scales be glued together into a single coherent picture. If physics is taken as an example, this glue is provided by theory that is able to fill in gaps in the picture. Recently a theory has been developed, the BOIS Model [15], that may be a candidate for filling in some of the unobserved gaps in the multi-scale observations. The model combines standard principles of statistical mechanics [16] with speculations on natural selection to make a series of predictions, some of which are testable and some of which lie in the gaps of the unobservable.

2. Observations of Information Transmission across the Cell Membrane

2.1. Direct Measurement of Information Transmission in GPCRs

Information capacity can be measured from assay experiments. However, an important challenge to the measurement of information flow in these experiments is removing signal from noise. Accurate measurements require the application of multiple ligand concentrations to a single cell [14][17]. Ref. [14] focused on the muscarinic acetylcholine receptor (M3R). The muscarinic receptor-induced calcium response measured in individual HEK293 cells was repeatedly stimulated with the ligand acetylcholine. Using this approach, single cell assays in human embryonic kidney 293 (HEK293) cells found a capacity greater than two bits of information [14][18].

These results are in contrast with some previous studies using cell populations that provided lower values for the information capacity of the GPCR pathways [9]. Lower capacity measurements were a consequence of increased noise due to variable responses among cells and the fact that individual cells were only exposed to a single value of ligand concentration [14][17].

2.2. Observations of Information Transmission in Assay Experiments

Bias between two downstream response pathways was examined in Ref. [13]. The authors focused on two receptors, the adrenergic receptor $\beta 2AR$ and the angiotensin II receptor $AT_{1A}R$. Eleven different ligands were applied to $\beta 2AR$, whereas ten were applied to $AT_{1A}R$. The measured downstream responses were β -arrestin (βarr) recruitment to the GPCR as well as cAMP for $\beta 2AR$ and IP_1 for $AT_{1A}R$ for the $G\alpha$ pathway. To reduce noise in βarr response, the C terminus of the human $\beta 2AR$ was replaced with the C-terminal tail of the V2 vasopressin receptor tail. In addition to the bias observations this study identified various values of half maximal effective concentration (EC_{50}) for the responses. The EC_{50} for each response can be used to identify the ligand concentration at which the response is activated. This is in agreement with Ref. [14] where information about the ligand concentration was identified in the information transmission.

2.3. Observations of Allosteric Mechanisms of Information Transmission

The two signaling pathways, $G\alpha$ and βarr mediate distinct physiological effects [12][20]. In the prototypical angiotensin II receptor, for instance, $G\alpha$ coupling increases blood pressure, whereas βarr coupling promotes heart protection [21][22][23]. In opioid receptors, the $G\alpha$ pathway confers pain relief whereas the βarr path may be associated with side effects such as tolerance, dependence, addiction, constipation, and respiratory depression [24][25][26][27][28].

The GPCR protein is composed of seven alpha helices arranged in a barrel conformation and one intracellular helix (Figure 2A). The helices themselves are somewhat rigid whereas the connections between the helices are flexible. The determination of which parts of the protein are flexible and which are rigid is determined by the ratio of the local bond strength to the background energy fluctuations [29][30][31][32][33][34]. At thermal equilibrium at room temperature, the background energy fluctuations are at about 0.5 kcal/mol. The amount of energy available in a single ATP is about 12 kcal/mol ([35], [Sec. 15.2]). Typical covalent bond energies are around 80 kcal/mol and greater, whereas ionic, hydrogen, and hydrophobic interaction energies are typically around 5 kcal/mol ([36], Chapter 8). Van der Waals interactions are typically 0.5–1 kcal/mol [35]. Parts of the protein with bond energy less than the fluctuation energy are unstable leading to flexibility. Parts of the protein where individual bonds, or collections of bonds, that have bonding energies greater than the fluctuation energy are rigid. The flexible and rigid parts of a protein are not fixed. If the background fluctuation level changes energy, then flexible parts of the protein can become rigid or rigid parts of the protein can become flexible. Recent observations have discovered a major hydrogen-bond network that bathes the ligand and transmits information allosterically [12].

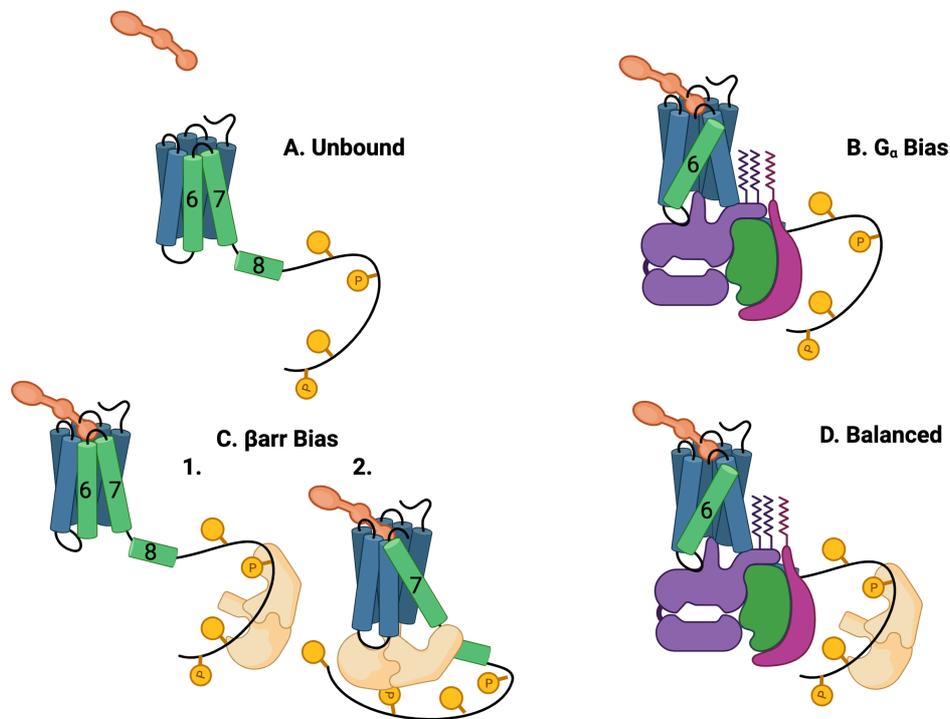


Figure 2. Five theoretically possible GPCR complex configurations, assuming that $G\alpha$ and β arr cannot occupy the intracellular core pocket simultaneously. **(A) Unbound:** The GPCR is composed of seven transmembrane (7TM) alpha helices and one intracellular helix labeled (8). The alpha helices are rigid and are connected by flexible amino-acid chains. The C tail of the GPCR may be quite long and contain multiple phosphorylation sites. Particularly important helices are in green. **(B) $G\alpha$ bias:** The ligand (orange) and the G protein (purple, green, and violet) may bind to the 7TM in a ternary reaction in which both the ligand and the G protein alter the 7 TM conformation. The most common conformational indicator is the rotation and extension of helix 6 (green). This configuration is G biased. **(C) β arr bias:** β arr may bind to the C tail of the GPCR (1) or β arr may also replace the G protein in the intracellular binding pocket (2). The conformation is characterized by a rotation and extension of helix 7. This conformation blocks the G-protein downstream response pathways. The C tail may also bind to the β arr that may select β arr downstream responses. This conformation is β arr biased. **(D) Balanced:** Another possibility is that the G protein and the β arr are both bound to the 7TM, the G protein bound to the 7TM pocket, and the β arr bound to the C-tail phosphorylation sites.

Another part of the GPCR, the C tail, is very flexible at room temperature and can take on many different conformations ([37][38][39]). The flexible/rigid nature of the complex conformations indicates that the complex can occupy multiple active quasi-stable states (Figure 2) [40].

Typically, binding of $G\alpha$ and β arr to the intracellular pocket of the GPCR is mediated by helices 6, 7, 8, and 5 [41] and the intracellular loops [42]. The 7TM conformation is altered from its baseline configuration (Figure 2A) when a ligand and a G protein form a ternary bond (Figure 2B) with the transmembrane portion of the GPCR [20]. This altered conformation transmits information from the extracellular environment to the intracellular environment. The G protein responds by activating downstream responses. The typical allosteric signature of this event is the rotation and extension of helix 6 [43]. Since only downstream responses triggered by the G protein are activated, this event is known as $G\alpha$ bias after the relevant α subunit of the G protein. It has recently been found from mutation studies that receptor sites $N111^{3,35}A$ and $N294^{7,45}A$ induce biased signaling to $G\alpha$ and β arr, respectively, [12]. AngII is a balanced agonist that activates both $G\alpha$ and β -arrestin signaling pathways. AngII can be modified to generate AT1R-biased agonists, which could preferentially activate either signaling pathway [21][44][45].

The binding of the beta arrestin (β arr) to the GPCR is observed to have more conformations than G-protein binding [6] as well as having more interactions with the membrane environment [46]. The β arr interacts simultaneously with the core GPCR in a ternary reaction [47][48][49]. Two distinct binding processes for β arr have been identified, dubbed “core-engaged” (Figure 2(C2)) and “tail-engaged” (Figure 2(C1)) for recruitment to the core and tail, respectively, [40][48]. This is illustrated in Figure 2C,D where a G protein occupies the core pocket in Figure 2D that is occupied by β arr in Figure 2(C2). The conformation of the β arr is different in the two binding paths [50]. Interestingly, β arr may continue to trigger downstream responses even after dissociation from the GPCR [39][51][52]. A typical signature for the β arr core-binding (Figure 2C) is the rotation and extension of helices 7 and 8 [43].

2.4. Information Transmitted to the Barcode

The barcode structure indicates that much more information may be stored in the barcode than the approximately two bits of information transmitted to the barcode [3][5][6][12][38][53][54][55][56][57]. As suggested in Ref. [14], this extra information may be about the details of the ligand concentration. This information may not be observed in the experiments [12][13][14] because of the focus on only the $G\alpha$ pathway and a single β arr recruitment pathway. In many cases, in these experiments, chimeric receptors were used that completely replaced the C tail of the receptor with a foreign C tail [13]. Except for the recruitment site, the phosphorylation sites on the foreign tail need not correspond with sites on the native tail. The use of the foreign tail removes information-storage capacity in the tail. The number of downstream pathways observable from a chimeric receptor would be two.

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