The structure and function of cell membrane receptor

Zihan Gao*

Ballarat Clarendon College, Ballarat, Australia

*Corresponding author: dfrye81677@student.napavalley.edu

Abstract. Cell membrane receptors play a key role in regulating cell communication and maintaining cell homeostasis. This paper explores the complex relationship between the structure and function of cell membrane receptors, and elucidates their multiple roles in signal transduction, cellular response, and disease pathways. Different receptor types, including as G protein-coupled receptors (GPCRs), ligand-gated ion channels, receptor tyrosine kinases (RTKs), and cytokine receptors, have varied structural properties that serve different biological purposes and are necessary for cell division, proliferation, and metabolism. The function of membrane receptors that translate extracellular signals into intracellular responses is diverse. The organization of lipid rafts and other receptors within membrane microdomains can influence signal transduction efficiency and specificity. There are inseparable interactions among receptor internalization, recycling and degradation, and regulating the duration and intensity of receptor signaling is closely related to the treatment of diseases. In summary, the current research status of cell membrane receptor structure and function is reviewed in this paper. It contributes to a broader understanding of how receptors regulate important cellular processes at the molecular level. Understanding the nuances of receptor structure-function relationships holds great promise for developing new therapeutic strategies and advancing drug discovery for a variety of diseases.

Keywords: membrane receptor, ligands, signaling.

1. Introduction

Cell surface receptors, also known as membrane receptors or transmembrane receptors, refer to proteins embedded within the cell's plasma membrane, which play an essential role in intercellular communication and transcellular transport regulation. Glycoproteins and lipoproteins, two transmembrane proteins that can be categorized based on their tertiary structure, are among the many receptors. The three main types of cell membrane receptors that are found in living organisms are those that are related to ion channels, G-proteins, and enzymes. The channels can open when ligands bind to ion channel-linked receptors. They make it possible for specific ions to cross cell membranes. G protein-coupled linked receptors have the ability to activate the G protein when they bind to ligands. These cells are found only in eukaryotic ones. Humans have more than 700 GPCRs, of which 150 are unknown ligands. Transmembrane receptors, commonly referred to as catalytic receptors, are the second most common form of cell-surface receptor and are enzyme-linked receptors. In order to catalyze intercellular processes, they first attach to external ligands [1].

Cell communication is mainly for four reasons: survive, growth and division, differentiation and death and they always happen in a very short period of time. Different pathways of cell communication involving different cell membrane receptors. The signaling pathways have characteristics of specificity, amplification and modularity. The active sites of receptors should be complementary to signal molecules. The molecules they bind to are called ligands. There are many kinds of ligands such as hormones, neurotransmitter etc. Molecules can be ligand without restriction on size or polarity, such as large, hydrophillic molecules can be ligands, since they do not need to cross the cell membrane. Ligands initiate biological response and they can either carry information or essential cell nutrients. They will operate differently due to different distances between signaling cells and target cells.

There are 10 types of activities involving membrane receptors: signal transduction, cell communication, hormone regulation, neurotransmission, immune response, nutrient uptake, cell adhesion, sensory perception, apoptosis and survival and cell growth and proliferation.

In real life, about half of all known drugs work on GPCRs or their pathways. Until 2017, there are approximately ~700 drugs target GPCRs (G protein- coupled receptors) which occupy 35% of approved drugs. As of 2020, 36% of drugs approved by FDA are designed to target mainly GPCRs [2]. This paper introduces structure and functioning mechanism of 3 major types of membrane receptors together with specific examples of each type. We highlight how these receptors work individually or cooperatively to regulate cells' activities. And we also emphasize how the specific function of receptors can be utilized on drug development.

2. The structures of three types of cell membrane receptors

2.1. The structure of ion channel-linked receptor

Ion channel receptor, also referred to ligand-gated ion channel, is usually multimeric protein that exist within plasma membrane. It is constructed by multiple copies of polypeptide protein chains that are encoded by genes. It is attached on the ion channel which is they reason why it is called ion channel-linked receptor. The ion channel receptor provides passageway for movements of specific ions from one side of plasma membrane to the other. Ligand-gated ion channel, also known as chemical-gated ion channel, is a kind of ion channel, that is opened by the combination of specific transmitter, which is different ligands, and the binding site on the ion channel receptor. The type of transmitter which can activate ion channel is depends on amino acids in the channel and the width of the channel. Cys-loop receptors, ionotropic glutamate receptors, and ATP-gated channels are the three types of ligand-gated ion channels. They have different functions but they share similar structural subunits.

Cys-loop receptors have characteristic loop formed between 2 cysteine residues by disulfide bond in between. They have N terminal extracellular domains and the binding site of on them provide their specificity. They, specifically in vertebrates, can only be activated by acetylcholine, serotonin, glycine, glutamate and gamma-aminobutyric acid. Ion channel receptors called ionotropic glutamate receptors (iGluRs) are triggered by the neurotransmitter glutamate. The receptor has subtypes based on their specificity of different ligands. However, they share common architecture. It contains subunits of extracellular domains, transmembrane domains, pore-lining helices and intracellular domains (fig 1).

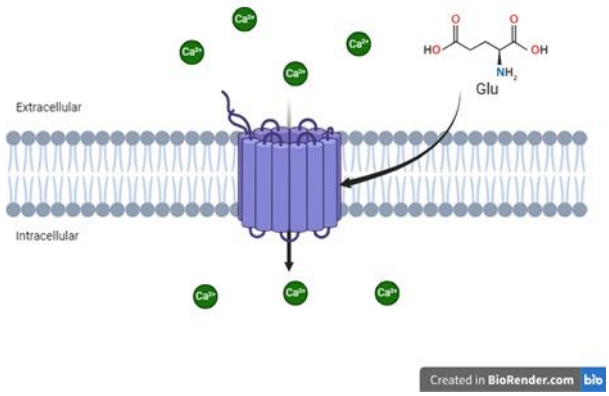

Fig. 1 The structure of glur6 ligand **binding** core in complex with glutamate

ATP-gated P2X receptor is a type of ion channel receptor that is open by binding with extracellular adenosine 5'-triphosphate and it is cation permeable. It has 380-1000 amino acyl residues per subunit. The subunits of the receptor include extracellular domain, transmembrane domain, pore-lining helices and intracellular domain [3]. The membrane domain, also referred to extracellular domain, is the site of binding between neurotransmitters and receptors. It is composed of 2 lobes and the region in between is called ATP binding pocket. The transmembrane domain consists of alpha-helices. Two membrane domains, a large extracellular loop, an intracellular carboxyl group, and the N terminus,

which marks the beginning of the polypeptide chain, are shared by all subunits. These receptor proteins often have two or more different domains: a transmembrane domain that contains the ion channel and an extracellular domain that provides an allosteric binding site for the ligand (fig 2).

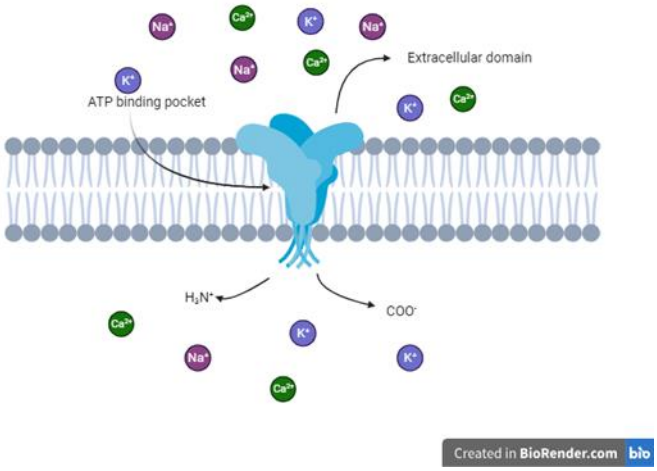

Fig. 2 The structure of the ATP-**gated** P2X receptor.

2.2. The structure of G-protein-coupled receptor

The G-protein coupled receptor (GPCR) consists of proteins that are structurally similar. G-protein coupled receptors, also referred as seven-pass-transmembrane(7TM) domain receptor and protein-linked receptors (fig 3). It is composed of a single polypeptide that the cell plasma membrane has folded into a globular shape. The receptor is called G-protein linked receptor because they coupled with G protein. G protein, which also refers to guanine nucleotide-binding protein, is specialized protein acting as molecular switches which means it can reversibly change between two or more stable states. This allows them to transmit signals from stimuli outside of cells to their interior because they have ability to stay in different environment. The structure of GPCRs has seven hydrophobic transmembrane segments which are insoluble in water. The seven segments line in a linear row along the whole width of plasma membrane. The segments are paired with extracellular amino terminus (N-terminus) and intracellular carboxyl terminus (C-terminus). N-terminus are the free amino groups that starts chains of proteins and polypeptides. C-terminus are free crboxyl group that is the end of amino acid chain. They form portions loop inside and outside the cells [4,5]. One of the most abundant protein classes in the mammalian genome. During the process of activation of GPCRs, G-proteins bind to GTP and GDP [1]. The g-protein associated with GPCR has three subunits which are alpha, beta and gamma. In the three subunits, alpha and gamma bind to lipid-linked proteins that are embedded in plasma membrane.

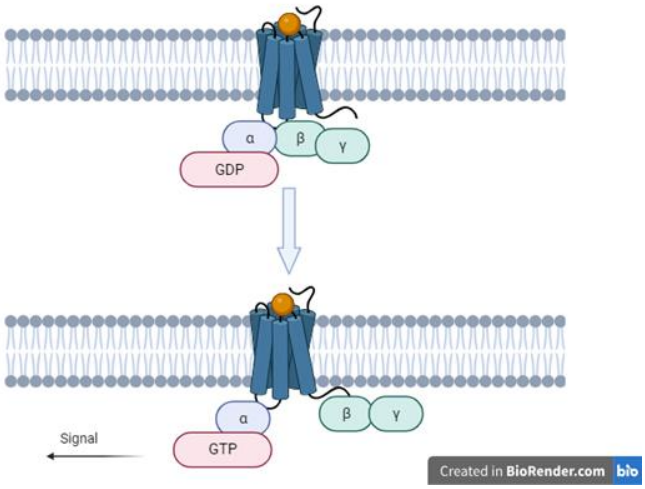

Fig. 3 Activation of the G alpha subunit **of** a G-protein-coupled receptor

2.3. The structure of Enzyme-linked receptor

The receptors are typically helical in shape, and interaction with a triggering signal causes the linking of two receptors to create dimers. The two proteins in the dimer interact with one another through their tail regions, phosphorylating one another. The polypeptide chain that makes up the enzyme-linked receptor has cytoplasmic and ligand-binding domains. The ligand binding domain, which is on the plasma membrane's extracellular face while the cytoplasmic domain is on the intracellular face, is in charge of hormone binding. The distance between the ligand binding and functional domain is separated by a single transmembrane spanning domain that is composed of 20-25 amino acid residues which are hydrophobic.

3. The Functions of three types of cell surface receptors

3.1. Ion channel-linked receptor

When neurotransmitters and ions needed to across plasma membrane arrive outside of cells, neurotransmitters bind to ion channel-linked receptors. The receptors are activated by this and the ion channel will be open to allow the ions to pass through plasma membrane.

Because they enable the quick and precise conversion of a chemical neurotransmitter message to an electrical current, ion channel-linked receptors are an essential part of nervous system signaling, notably in synaptic neurotransmission. For example, in skeletal muscle cells, there are ion channels challed nicotinic acetylcholine receptors. These ion channels are opened responding to acetylcholine binding. The result of this is depolarization of the target cell. Another example of it is heart muscle cells. In heart, cell membrane transmits signals that affect cardiac contraction and relaxation. VGICs control how ions move across cell membranes, which is crucial for the contraction of cardiac muscle cells, particularly cardiomyocytes. The receptors can control the flow of sodium ions which is necessary for depolarization of cell membrane and initiation of action potential. Furthermore, VGICs help the propagation of action potential to travel rapidly along the pathways. When the action potential reached the VGICs in cardiomyocytes, the receptor regulates the influx of Calcium ions. This can trigger a series of events that eventually can lead to heart contraction. Similar to heart relaxation, the VGICs receptors allows exit of Calcium ions from cytoplasm of cardiomyocytes can lead to heart muscle to relax [6,7]. For instance, the pancreas' insulin receptors are crucial for controlling insulin secretion. When the blood glucose level rises, pancreatic beta cells can sense the increasing of glucose level and then trigger the release of insulin. The insulin will bind the receptors on its own cell and there will be a process that helps the regulation of insulin release in order to avoid excessive release of insulin. The GPCRs also play a crucial role in pancreatic islets. They modulate the hormone release which can, for example, regulate glucagon secretion. It is also can be involved in cell communication between paracrine and other types of cells within islet.

The function of cys-loop receptor is basically mediating fast synaptic transmission in the nervous system. The subtype of cys-loop receptor--nAChR is involved in cognitive functions, attention and mood regulation. The full name of nAChR is nicotinic acetylcholine receptor. nAChRs are found on skeletal muscle cells that are involved in breathing, such as the muscles of the diaphragm and intercostal muscles. Activation of these receptors by acetylcholine leads to muscle contraction, which is necessary for the expansion and contraction of the lungs during breathing [8]. GABA receptor is also a subtype of cys-loop receptor, mainly control the excitability of neurons and then maintain a balance between excitatory and inhibitory signals in brain. GABA stands for Gamma-aminobutyric acids that is an inhibitory neurotransmitter [9]. It reduces the times of neurons firing an action potential and also makes neuron less likely to produce neurotransmitter. GABA receptors can be classified into GABAa and GABAb receptors. When GABAa receptors bind with GABA molecules, it allows influx of chloride ions that hyperpolarize the membrane potential. GABAb receptors allows exit of potassium ions when they are activated (fig 4). Both receptors are activated in order to make

it less likely to fire an action potential and then reduce neuron transmission. Some drugs such as alcohols can increase GABA activity that have a sedative effect [10].

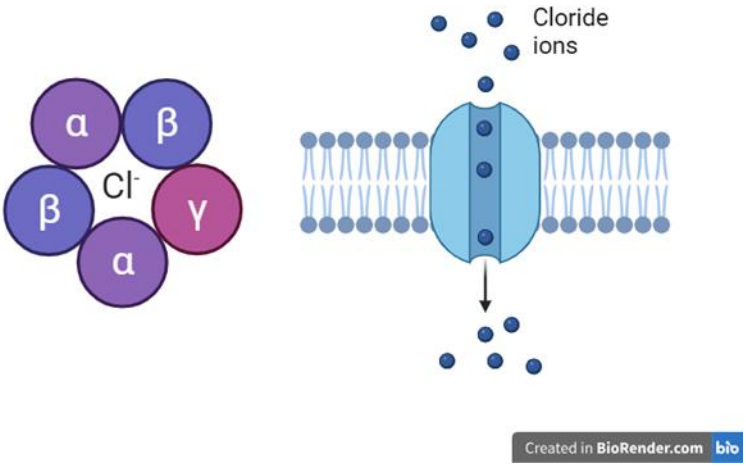

Fig. 4 GABAb receptors are activated.

The function of ionotropic glutamate receptor plays a fundamental role in mediating neurotransmission in the central nervous system. There are three types of subtypes mainly which involve AMPA receptor, kainate receptors and NMDA receptor. AMPA receptor allows rapid influx of sodium ions when the receptor is activated. Kainate receptor's function can vary differently depends on specific cell types involved. Generally, it can adjust the synaptic transmission in nervous system. The NMDA receptors take important part in synaptic plasticity.

The function of ATP-gated receptor has many functions. In nervous system, ATP-gated receptor is involved in neurotransmission. It modulates the release of neurotransmitter. When the receptor is activated, it can lead to changes in synaptic strength, and affecting Neurocommunication between neurons. The receptor also plays a significant role in immune response because activation of these cells can modulate immune response such as antigen presentation. In general, human body, the ATP-gated receptor can pass pain signaling between sensory neurons and central nervous system. As a result, these can lead to sensation on pain. In the smooth muscle cells, ATP-gated P2X receptors can trigger muscle's contraction and relaxation.

3.2. G-protein-coupled receptor

In the resting state, the status of G-α proteins is determined by its interactions with G β-γ proteins and G protein-coupled receptors (GPCRs). This state changes when the receptor binds an agonist ligand. G alpha protein does not bind to GDP but to GTP, causing its activation. These receptors are located on the cell surface, detect extracellular molecules and initiate cellular responses. They transmit signals between cells through various forms of energy, including light, peptides, lipids, sugars, and proteins [11]. A GPCR's extracellular loop controls the attachment of certain molecules to it. In addition to being engaged in many physiological processes, GPCRs are essential in translating environmental information into intracellular responses. Examples of their functions include the sense of sight, taste, and smell (olfactory perception). GPCRs in taste cells are able to trigger the release of gustducin when they are responding to tastes such as sweet and bitter. Also, GPCRs take a crucial role in heart movements. There is one type of the GPCRS that is called beta-adrenergic receptors specifically respond to epinephrine and norepinephrine which are neurontransmitters. When they are binding to the certain transmitters, cAMP levels increase in cardiac muscle cells. Changing the cAMP levels overtime can enhance the contractility of heart that increase cardiac output. The other subtype of the GPCRs is called muscarinic acetylcholine receptors which respond only to acetylcholine. Activation of it can lead to a decrease in heart rate. The angiotension second receptors in the heart cells can regulate blood pressure and fluid balance by increasing sodium and water retention. It also

takes a role in cardiac remodeling. The other type of receptor is endothelin receptors. It specifically responds to endothelin. When they are activated, the vascular resistance can be increased and which lead to impact on blood flow. The insulin receptors are also a cell membrane receptor in heart cells. They mediate effects of insulin and maintain the glucose homeostasis [12].

3.3. The function of Enzyme-linked receptor

They were initially recognized for their early role in extracellular signal protein responses that enable cell growth, proliferation, differentiation, development, and survival in animal tissues. They can impact the rate of growth of stem cells and influence the properties of the cell which guide them to specific lineages. It promotes cell survival because it activates pathways that prevent apoptosis. Receptor Tyrosine Kinases is a main type of enzyme-linked receptor. The receptor is characterized by having intracellular enzymatic domain that possesses kinase anticity, which make receptors to phosphorylate specific tyrosine residues on target proteins.

4. Extention

Drug design based on cell surface receptors has believed to be a main methods of drug development. The types of drugs developed targeting cell membrane receptors include agonists, antagonists and inverse agonists. The agonists drug aims to activate cell surface receptor by mimicking the action of endogenous ligands. For instance, albuteroln is a typical agonist medication used to treat conditions like asthma. It stimulates the beta-2 adrenergic receptors on the surface of the smooth muscle cells lining the lungs' airways [13,14]. During inhalation, the albuterol binds and activates the receptor which trigger the signaling pathway leading to relaxation of smooth muscle. This increases the airflow in and out of the lungs. Antagonists is the opposite function compare to agonists. It aims to block the cell membrane receptors to prevent them being activated. They bind to the surface receptors without activating it. Among all antagonist drugs, Atenolol is a type of drug that treat hypertension. It targets β1-adrenergic receptors and block the bindings between the receptors and neurotransmitter epinephrine in heart. The receptors are a part of sympathetic nervous system. Once it is activated, heart rate will increase and the force of contraction will increase. Therefore, blocking them can decrease blood pressure and cardiac workload [15]. Inverse agonists have the opposite effect of agonists. They reduce the basal activity of receptors when they bind to the ligand-binding site of activated receptor. They stabilize the receptors in an inactivate state [16].

5. Conclusion

In conclusion, the complex interplay between the structure and function of cell membrane receptors emphasizes their fundamental importance in coordinating various physiological processes that control cell behavior. This review article illustrates the remarkable progress made in unraveling the mysteries of receptor structure, providing a glimpse into the dynamic world of conformational changes, allosteric regulation, and complex ligand-receptor interactions. By delving into the field of signal transduction, this review highlights how receptors act as molecular translators, bridging the extracellular environment and intracellular responses. The symbiotic relationship between structure and function continues to fascinate researchers, driving the development of innovative technologies and methods that allow people to decipher the complex molecular orchestration of cell membrane receptors. As researchers delve deeper into the realm of single-molecule studies, advanced imaging techniques, and comprehensive computational methods, the scope of possibilities for unraveling the mysteries of receptors continues to expand. In a broader context, this review emphasizes that the pursuit of understanding cell membrane receptors goes well beyond academic curiosity. It has profound implications for drug discovery, precision medicine, and the design of therapies that could revolutionize the treatment of a variety of diseases.

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