Membrane Receptors: The Basic Structure and Functions

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Abstract

Membrane receptors are special protein molecules in cell membranes to which changes in the function of cells are triggered, signal communication and various molecules outside the cell bind. Communication between cells takes place in three ways: direct physical contact from surface to surface, gap junction and chemical signaling between cells. Signals that do not cross the cell membrane bind to specific receptors in the membrane and direct cellular events. The identification of new receptors and providing important information, particularly on cell growth, differentiation and activity, has led to significant advances in cell typing and drug design. Membrane receptors are composed of integral glycoproteins ranging from 140 to 150kDa. A receptor molecule consists of three parts: the ligand, the hydrophobic region crossing the membrane, and the cytoplasm-facing region that provides signal transduction. In terms of structural properties, membrane receptors are divided into three groups as catalytic receptors, receptors containing ion channels and receptors containing intracellular messenger molecules. Using monoclonal antibody technology, mutant receptors can be detected by producing monoclonal antibodies to various parts of the receptor. Gene therapy is possible by identifying mutations in their genes to receptors.

Keywords: Membrane receptors; Structure; Messenger systemb

Introduction

For cell growth and differentiation in multicellular organisms, the cells need to receive various signals and develop the appropriate response to ensure inter-tissue harmony. Intercellular signaling allows for a broader integration of metabolism and generally produces a slower response to changes that occur within the cell [1]. Intercellular communication is provided in three ways;

A. Direct physical contact from surface to surface

B. Gap junction allowing direct communication with the cytoplasm of neighboring cell

C. Indirect interaction as a result of chemical signaling between cells

Signals that do not cross the cell membrane bind to specific receptors in the membrane and direct cellular events. The signal is usually chemical but follows a similar path in light stimulation. Structures of membrane receptors, ligand binding properties have been the subject of many studies, the structure of many receptors has become clear with new methods developed. Ligand binding studies have led to significant improvements in pharmacology. Studies have generally focused on the transmission and amplification of receptor stimulation into the cell. The identification of new receptors and providing important information, particularly on cell growth, differentiation and activity, has led to significant advances in cell typing and drug design [2-4].

Structure of Membrane Receptors:

Membrane receptors are integral membrane glycoproteins with molecular weights ranging from 140 to 150kDa. The receptor molecule has three basic parts [5,6].

A. Part outside the ligand-binding cell

B. Hydrophobic section crossing the membrane

C. The section facing the cytoplasm that provides signal transmission

In terms of structural properties, membrane receptors are examined in three groups;

A. Catalytic receptors

B. Receptors containing ion channels in their structures

C. Receptors containing intracellular messenger molecules

A. Catalytic receptors: Receptors in this group naturally possess enzymatic activity in part of their structure. In many instances, enzyme activity is tyrosine-specific protein kinase. The receptors of insulin and growth factors are examples of such receptors [7]. They may be monometric, such as the EGF (Epidermal Growth Factor) receptor, or they may consist of subunits such as insulin and IGF I (Insulin like growth factor I). Extracellular regions of this group of receptors contain cysteine-rich regions. These zones allow sub-units to be held together. The cysteine-rich regions at the monomeric receptors formed rings (cysteine fingers) to clarify the ligand binding site. Binding of the ligand to receptors stimulates intrinsic tyrosine kinase activity, which transfers the terminal phosphate group of ATPs to the hydroxyl groups of specific tyrosines in the target proteins and the receptor itself [8-12].

B. Receptors containing ion channels in their structures: These receptors are directly connected to the ion channels of the membrane. Nicotinic acetylcholine receptors of muscles and nerves, glutamate, gamma-amino butyric acid (GABA) and glycine receptors commonly found in the central nervous system are among such receptors. The acetyl choline receptor contains the Na+ channel and its components that control the channel. One type of glutamate receptors that leads to rapid cellular response is cation channels. The selective permeable channel to Na+, K+, and Ca++ is opened depending on the receptor activity [8,13].

C. Receptors containing intracellular messenger molecules: The hydrophobic portion of the receptor molecule is long enough to cross the membrane several times. The peptide chain folds the membrane seven times in the alpha-helix structure, with the amino end outside the cell. The similarity between species in the amino acid sequence at such receptors has been shown in several studies Especially the hydrophobic parts were preserved during evolution. Examples of such receptors are the beta-adrenergic receptor schematized. Intracellular messenger systems serve as signal amplification. At this stage, an activated receptor molecule causes its activation in many effector molecules [8,13,14].

Intracellular Messenger Systems

Hormones or neurotransmitters act as signals and receptors act as signal detectors. Each piece serves as a transmitter for the communication between extracellular events and intracellular chemical changes. Many receptor-binding ligands deliver the recognition signal by initiating a series of reactions resulting in specific intracellular responses. Molecules named as second messengers for mediating their effects on the cell and the original message, they are part of a waterfall-like event in the conversion of hormone or neurotransmitter binding to a cellular response. The

two most commonly known second messenger systems are the adenylate cyclase system and the calcium/phosphotidylinositol system [15,16].

Adenylate Cyclase System

Recognition of a chemical signal by certain membrane receptors such as beta and alpha 2-adrenergic receptors triggers an increase or a decrease in adenylate cyclase activity. Adenylate cyclase is a membrane-bound enzyme that converts ATP to 3', 5' adenosine monophosphate. Chemical signals are often hormones or neurotransmitters and each bind to a single type of membrane receptor. Thus, there are several types of receptors in tissues that respond to multiple chemical signals, each of which may be due to adenylate cyclase. These receptors consist of an extracellular ligand-binding region, seven transmembrane helixes and an intracellular region that interacts with a G-protein [8,15,16].

G Proteins (Guainin Nucleotide Binding Proteins)

G proteins are peripheral proteins attached to the cell membrane from the cytoplasmic side. They are heterotrimetic with alpha, beta and gamma subunits. The subunits differ depending on the species and tissue from which they are obtained or due to covalent changes after translation. G proteins mediating signal transduction also provide signal amplification and inter-receptor linkage. These proteins form a link in the communication chain between the receptor and adenylate cyclase. In the absence of receptor stimulation, the active form of the G-protein binds to GDP. The stimulated receptor interacts with G-proteins and triggers the change of GDP to GTP. The trimmetric G-protein is then separated into the alpha subunit and beta-gamma dimer. The GTP-bound form of the alpha subunit moves from the receptor to adenylate cyclase and in this way adenylate cyclase is stimulated. Many stimulated G protein molecules are formed by this stimulated receptor. The ability of a hormone or neurotransmitter to inhibit or stimulate adenylate cyclase depends on the type of G protein bound to the receptor. A group of G proteins identified as Gs stimulates adenylate cyclase. Another group Gi causes inhibition of the enzyme. The effects of the G-protein –GTP complex are short-lived. G-protein has structurally GTPase activity and GTP rapidly hydrolyses to GDP. As a result, G-protein is inactivated. Such interactions involving G-proteins have been shown in particular in cholera toxin and pertussis toxin models [8,17-21].

cAMP (Cyclic Adenosine Monophosphate)

Cyclic AMP is synthesized from adenosine triphosphate (ATP) by the catalytic effect of the adenylate cyclase enzyme located in the cell membrane. t is a very important intracellular nucleotide that is converted to 5'- adenosine monophosphate and becomes inactivated by the effect of phosphophodiesterase enzyme. It is known as a second messenger that mediates the effects of many hormones and certain enzymes. However, it is accepted as an intracellular hormone by some researchers [8]. c-AMP mediating hormones as a second messenger; The binding of the hormone to the

receptor on the cell wall activates the nucleotide regulatory protein or G protein bound to GTP. And then it activates adenylate cyclase. Activation of adenylate cyclase allows the synthesis of c-AMP from ATP. c-AMP activates protein kinase in the cell. Activated protein kinase has different effects on the phosphorylation of enzymes and other proteins in the cell. It makes a decrease or an increase in the activity of the enzymes, thus changing the metabolism. Changes in the concentration of intracellular calcium ion affect the regulator system of cAMP. Phosphorylase kinase activated by c-AMP-dependent protein kinase requires Ca++ for catalytic function. The activity of many phosphodiesterases is significantly increased by Ca++ calcium binding protein [22-24].

Calcium/Phosphotidyl Inositol System

Many receptors respond to neurotransmitters or hormones by activating membrane-bound phosphodiesterase, defined as phospholipase C. G proteins are used by signal transduction via this receptor. The stimulation mechanism of this system is similar to receptor-dependent stimulation of adenylate cyclase. The induced phospholipase C breaks down membrane-bound phosphotidylinositol 1, 4, 5-triphosphate, and inositol 1, 4, 5 releases triphosphate and two parts as diacylglycerol. These molecules have synergistic effects as second messenger molecules [3,5,8].

Inositol 1, 4, 5-Triphosphate

This inositol derivative binds to receptors on the endoplasmic reticulum and causes rapid release of Ca++ from intracellular stores. As a result of the increase in the cell Ca++- allows the formation of calmodulin complex. Inositol 1, 4, 5-triphosphate is a short-term chemical signal, inositol 1, 4, which is rapidly inactive as the second messenger, is dephosphorylated to bisphosphate and inositol 1-phosphate [25,26].

Diacylglycerol

Phosphotidylinositol is formed by phospholipase C breakdown of 1, 4, 5-triphosphate. This product stimulates membrane-bound protein kinase C, an enzyme that phosphorylates proteins. Protein kinase C requires Ca++ for maximum activity. Protein kinase C is thought to act by increasing its affinity to Ca++ [27-29].

Synergism Between Messengers

The two second messengers, daicylglycerol and inositol 1, 4, 5, act synergistically to increase the triphosphate protein phosphorylation. Diacylglycerol stimulates protein kinase C by a process requiring Ca++, while inositol 1, 4, 5-triphosphate promotes calmodulin-dependent protein kinase to stimulate. High Ca++ levels may also be effective through other mechanisms that do not contain calmodulin [16,30].

Calmodulin

A mediator protein involved in calcium-related effects. Almost all of the intracellular effects of Ca++ are mediated by a group of proteins. Calmodulin is the most common of these proteins and is found in all cells. Structurally, it is similar to troponin C, another calcium binding protein that mediates the effect of calcium in the contraction of skeletal and cardiac muscle. The binding of four molecules of Ca++ to calmodulin triggers a structural change and stimulates the stimulated Ca++- calmodulin complex protein molecules. Most of them are enzymes. And they are inactive in the absence of Ca++- calmodulin complex. Thus, calmodulin serves as the essential subunit of many compound proteins. The list of enzymes acting through calmodulin is quite extensive and includes calmodulin-dependent protein kinases, adenylate and guanylate cyclases, phosphodiesterase and ATP-dependent Ca++ pump [8,31-33].

Other Messanger Systems

Cyclic AMP and calcium are the second most common messenger systems. Cells also contain more specialized delivery systems such as cyclic guanosine monophosphate (cGMP) and nitric oxide [34,35].

cGMP (Cyclic Guanosine Monophosphate)

The cGMP messaging system is similar to the cAMP path in many ways. It is synthesized from GTP by membrane-bound form of guanilatsiclase. This reaction is similar to the formation of cAMP by adenylate cyclase. It can stimulate protein kinase, a specific form of protein kinase, called cGMP-dependent protein kinase or protein kinase G. The effect of cGMP is terminated by phosphodiesterase, which hydrolyzes cGMP as in cAMP inactivation. However, the membrane-bound guanylate cyclase is a structural part of the enzyme receptor. Therefore, it is structurally similar to tyrosine-specific protein kinases. Unlike cAMP which has a wide range of effects; cGMP acts as a more specialized messenger and affects smooth muscle relaxation, platelet aggregation, and the visual system [36-39].

Nitric Oxide

Nitric oxide acts as a mediator for a wide variety of biological systems. It relaxes smooth muscles. It acts as a neurotransmitter and prevents platelet aggregation. It acts as a neurotransmitter and prevents platelet aggregation. It mediates the tumoruricidal and bactericidal effects of macrophages. NO is highly toxic and short-lived. It acts for 6 to 10 seconds, then is converted into nitrates and nitrites by oxygen and water. In NO synthesis, substrates for NO synthase are arginine, O_2 and NADPH. FMN, FAD is both coenzymes of the tetrahydrobioptein enzyme and are the products of the reaction in the citrulline with NO [39,40]. Two groups of enzymes were isolated. These are structural (synthesized at constant rate independent of physiological requirements) and Ca++- calmodulin dependent enzyme found in endothelial, nerve tissue, platelets [41-43]. The inducible Ca++- independent enzyme is found in hepatocytes, macrophages and neutrophils. Specific stimuli for NO synthase vary by cell type. Tumor necrosis factor and interleukin 1 have been shown to increase enzyme synthesis [44,45]. Nitric oxide is an important tool in the control of vascular smooth muscle tone.

Nitric oxide is synthesized in endothelial cells and diffuses into vascular smooth muscle cells where guanylate cyclase activates the cytosolic form. The resulting cGMP increase results in muscle relaxation by stimulating protein kinase G, which inactivates myosin light chain kinase by phosphorylating it [46]. The synthase activity of NO in macrophages is generally low, but enzyme synthesis is strongly stimulated by bacterial lipopolysaccharide and gamma-interferon released in response to infection. Stimulated macrophages form oxygen free radicals which combine with NO to form compounds that have a greater bactericidal effect than NO itself. Unlike endothelial and brain NO synthetase, macrophage NO synthase is calcium-independent [47,48].

Receptor Kinetics

Membrane receptors bind their ligands specifically and with high affinity. The binding reaction is fast and often reversed. Receptor ligand binding is similar to enzyme-substrate reactions in terms of formation and specificity of weak bonds. The equilibrium dissociation coefficient (kd) is generally used to define the affinity of the receptor to the ligand [6,8,9,49]. Receptors can bind similar molecules, but affinity is different. For example, the insulin receptor binds insulin-like growth factors with low affinity. The receptors may have more than one binding site at different affinities. There is a negative or positive relationship between the binding sites or receptors. Due to the limited number of receptors in the membrane, binding reaches saturation at high ligand concentrations. Using this, the number of receptors is calculated. A cell may contain 1000-10, 000 receptor molecules. However, this amount constitutes only a small portion of membrane proteins. Therefore, the isolation of receptors is quite difficult. Investigation of the dynamics of receptors located in artificial membrane (liposome) systems can give misleading results. Therefore, information on receptor dynamics comes mostly from research on cells or membranes with radioactive ligands [3,5,8].

Control of Membrane Receptor Dynamics and Activity

Membrane receptors, like other membrane proteins, have lateral mobility in the membrane. Receptors interact with lipids and signaling membrane molecules within this mobility. Membrane fluidity of membrane cholesterol content has an effect on receptor activity. Ligand-linked regions generally shift to clathrin-coated regions and aggregate to 2-10 receptors in these regions. This is necessary for many ligand-receptor complexes and is required in endocytosis [50]. Endocytosis is an important mechanism in the number and lifetime of the receptor in the membrane. The rate of endocytosis and synthesis of the receptors is adjusted according to incoming stimuli. For example, IL-2 synthesis is increased in T lymphocytes in the presence of antigen or mitogen. İnsulin receptors in fasting state, transferrin receptor number in transformed cells is increased. Depending on the ligand concentration, the receptor level can be controlled [51,52].

This control is provided by up or down regulation. Decrease in receptor number and affinity in increasing ligand concentrations can occur in several ways:

A.   The rate of uptake of the receptor into the cell increases the rate of expression.

B.   Ligand binding to the receptor reduces the affinity of other receptors or binding sites to the ligand.

C.   Ligand binding to the receptor increases its sensitivity to proteases.

Down-regulation of membrane receptors is mainly the first two ways. The constant high level of cholesterol in the blood down-regulates the complex, low-density lipoprotein (LDL) receptors in which cholesterol is transported. Thus, the entry of cholesterol into cells is reduced and cholesterol accumulates in the blood [53]. Cholesterol suppression of LDL receptors is being examined for its role in the formation of atherosclerosis. Insulin and growth factor receptors have trosine kinase activity. In addition to phosphorylating various receptors from tyrosine amino acids, they dephosphorylate orophosphorylation sites in their cytoplasmic regions. Such receptors are able to control their autophosphorylation activity. When bound to the insulin receptor, the tyrosine kinase effect of the receptor is stimulated, increasing the affinity of the receptor by phosphorylating itself [54,55]. Receptor activity can also be controlled by intracellular kinases [56]. For example: Tumor necrosis factor (TNF) is not effective in all cells. The reason for this insensitivity, which constitutes an important obstacle to the use of TNF in cancer treatment, it is thought that intracellular kinases are caused by downregulation of TNF receptors. Protein kinase C, which is stimulated by many oncogen products and growth factors, the idea that TNF receptor causes down-regulation was supported [57].

Expected Advances in Receptor Molecular Biology and Applications

Obtaining abundant receptor molecules by recombinant DNA technology, it provided a great convenience for the study of receptors. Antibodies generated against various portions of the receptor using monoclonal antibody technology have been useful in identifying mutant receptors. The use of X-ray crystallography and simulation techniques in the investigation of receptor structure and binding site has provided invaluable information agonist and or antagonist ligand analogs to receptors have facilitated the development of new drugs [58-60]. There are some diseases that occur due to receptor. For example; Autoantibodies develop against muscle acetylcholine receptors in myasthenia gravis disease and thyroid stimulating hormone receptors in graves' disease [61]. The binding site of the receptor is examined with monoclonal antibodies. Diseases that develop against certain receptors occur due to disturbances in the receptor gene, synthesis or function [62]. The identification of mutations in receptor genes is thought to be the basis for correcting them with gene therapy in the future. Receptors have significant potential for cancer diagnosis and treatment. For example; The number of receptors in tumor cells is increasing. The development of radioactive or toxin-bound ligands directed to these receptors

is a promising approach in chemotherapy [63,64]. In addition, the development of drugs targeting receptor signaling proteins in cancer chemotherapy is being studied. Clarification of the various aspects of receptors at the molecular level will give new approaches to drug planning, diagnosis and treatment of many diseases.

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