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A Glance through Receptors: Its Types and Their Mechanism of Action

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ABSTRACT

The largest number of drugs do not bind directly to the effectors such as enzymes, channels, transporters, structural proteins, template biomolecules, etc. but act through specific regulatory macromolecules that control the above-listed effectors. These regulatory macromolecules or the sites on them which bind and interact with the drug are called receptors. Intracellular receptors are located in the cytoplasm of the cell or the nucleus and are activated by hydrophobic ligand molecules that can pass through the plasma membrane. Cell-surface receptors bind to an external ligand molecule and convert an extracellular signal into an intracellular signal. ion -channel, G- protein, and enzyme-linked protein receptors are cell surface receptors. This review aims to convey some basic definitions and the mechanism of action of various receptors.

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INTRODUCTION

RECEPTORS: Receptors are defined as the macromolecules or binding sites that are located on the cell surface /inside the effector cell that serves to recognize the signal molecule or drug and initiates a response to it, but itself has no other function [1].

Ligand: Any molecule which attaches selectively to particular receptors or sites. The ligands are of various types based on two properties: ***Affinity:*** It is the ability to bind with the receptor. ***Intrinsic activity***: It is the ability to elicit a physiological effect by inducing a functional change in the receptor.

Drug + Receptor ↔Drug receptor complex→Biological response

Agonist: An agent that activates a receptor to produce an effect similar to that of the physiological signal molecule *(I.A=1).* Eg: Adrenaline on adrenergic receptors, Histamine on histaminergic receptors

Inverse agonist: An agent that activates a receptor to produce an effect in the opposite direction to that of the agonist *(I.A = -1).* Eg: β carbolines with benzodiazepine receptors produce anxiety, increased muscle tone, etc, which are opposite to that produced by diazepam(agonist).

Antagonist: An agent that prevents the action of an agonist on a receptor but does not have any effect of its own *(I.A=0).* Eg: Propranolol on adrenergic receptors, atropine on cholinergic receptors

Partial agonist: An agent that activates a receptor to produce submaximal effect but antagonizes the action of a full agonist (*I.A= between 0-1).*Eg: Pentazocine on μ opioid receptor

RECEPTOR REGULATION [2-4]

Receptor regulation is the homeostatic increase or decrease in receptor activity or number, in response to activation or blockade.

Downregulation is the process by which a cell decreases the quantity of a cellular component. The repeated or persistent drug-receptor interaction results in the removal of receptors from sites where subsequent drug-receptor interaction may occur. It is called

receptor downregulation. The receptor down-regulation maybe because of phosphorylation or internalization of the receptor. Several mechanisms are responsible for down-regulation :(1) Phosphorylation of the receptors, destruction of the receptors, relocalization, sequestration (isolation of receptors) (2) Decreased synthesis, and several receptors. Eg: chronic use of isoprenaline for the asthmatic patient the bronchial relaxation effect will be decreased.

An increase of a cellular component is called upregulation. The continued use of antagonists/denervation may result in the synthesis of additional receptors. Upregulation is connected with an increase of sensitization for chronic use of an antagonist or having symptoms induced by withdrawal of drugs. Eg: After chronic use of propranolol for the hypertensive patient, suddenly stoppage of its use will induce a rebound increase of blood pressure.

CLASSIFICATION OF RECEPTORS

- **G – protein-coupled receptors(GPCR)**
- **Ion channel receptors**
- **Transmembrane enzyme-linked receptors**
- **Transmembrane JAk – STAT binding receptor**
- **Receptors that regulate transcription factors**

G – PROTEIN – COUPLED RECEPTORS (GPCR) [5-9]

Most common receptors in the biological system. Also known as metabotropic receptors. It is a cell surface receptor. The receptor is a larger protein and consist of two-component:

1. Receptor molecule: It is a single larger polypeptide chain of 400-500 amino acid residues. It possesses 7α-transmembrane helices, with an extracellular $–NH_2$ terminal and intracellular –COOH terminal. The helices are connected by alternative intracellular and extracellular loops. There are 3 intracellular and 3 extracellular loops in the receptor structure.

2. G-protein: It is a heterotrimeric protein. It is named so as it can bind with the guanine nucleotides GTP and GDP. The G- protein interacts with the receptor through the third intracellular loop and the –COOH terminal. It is attached to the cytoplasmic face of the

plasma membrane through a fatty acid chain by a process known as prenylation. The subunits are α, β, and γ. The αβγ complex exit together in the resting state. The α – subunit is having a GTP/GDP binding site and it is having GTPase activity.

GPCR-TRANSDUCTION

a) Activation of the G-protein by the receptor: Ligand binding changes the conformation of the receptor so that it binds with the G-protein. Thus in turn causes the exchange of GDP for GTP in the α- subunit, switching it to the activated state.

b) Relay of the signal to the effector: With the bound GTP α-subunit dissociates from the βγ complex. The α can bind to its effector molecule. Binding of α causes the activation of the effector. The βγ can inturn also activate downstream effectors.

c) Ending the response: When GTP id hydrolyzed to GDP and the α – subunit rebinds to βγ, returning the complex to its inactivated state.

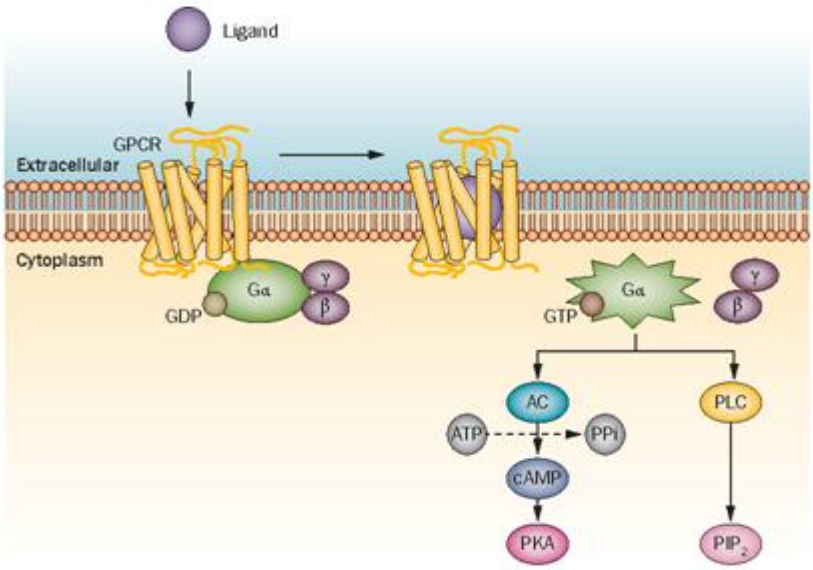

Figure No. 1: Schematic diagram of GPCR Signaling

GPCR-SECONDARY MESSENGERS

A secondary messenger is s molecule that is released in the cytoplasm following activation of a receptor. It is nonspecific and can generate a variety of responses in the cell. The second messenger systems are Adenyl cyclase/cAMP pathway, IP_3/DAG pathway, and Ion channels.

Adenyl cyclase/cAMP pathway

When an agonist bind to Gs type of receptor AC (Adenyl cyclase) is activated. The enzyme adenyl cyclase converts ATP to cAMP. The formed cAMP causes activation of protein Kinase - A. The enzyme protein kinase - A is a larger glycoprotein made up of 4 subunits – 2 catalytic sites and 2- regulatory sites. When two cAMP molecules bind to two regulatory sites of protein kinase-A, the enzyme is activated to liberate the catalytic sites. The liberated catalytic site causes phosphorylation of the target physiological structure to elicit a response.

IP_3/DAG pathway

The activation of Gq protein by a ligand stimulates an enzyme phospholipase-C.Phospholipase enzyme cleaves the plasma membrane phospholipid PIP_2 (Phosphatidylinositol 4, 5-biphosphate) to form two molecules IP_3 (inositol 1,4,5-triphosphate) and DAG (diacylglycerol). The IP_3 is transported to the cell cytoplasm and binds with the IP_3 receptor on the endoplasmic reticulum. It causes the liberation of Ca^{2+} and causes depolarization/activation of proteins. The DAG acts by: Activate protein kinase-C (It functions like protein kinase - A).

GPCR- Ion channels

The activated α-subunit may directly stimulate the transmembrane ion channels. It results in the opening of channels. G-protein gated ion channels are primarily found in CNS neurons and atrial myocytes and affect the flow of K^+, Ca^{2+}, Na^+, & Cl^- across the plasma membrane. Eg: skeletal muscle T-tubule Ca^{2+}, Cardiac myocyte Ca^{2+} channel, Sarcolemma Ca^{2+} channels in cardiac myocytes.

ION CHANNEL RECEPTORS [10-12]

These are surface receptors**.** Also known as ionotropic receptors. These receptors are proteins. The receptor contains a ligand-binding site and an intrinsic ion channel. When the agonist binds to the ligand-binding domain of the receptor, the receptor undergoes a conformational change and the ion channel opens. The inflow of ion changes the potential of the cell to initiate a physiological response. Eg: Nicotinic Ach receptor(Nm), GABA receptor, Glutamate receptor

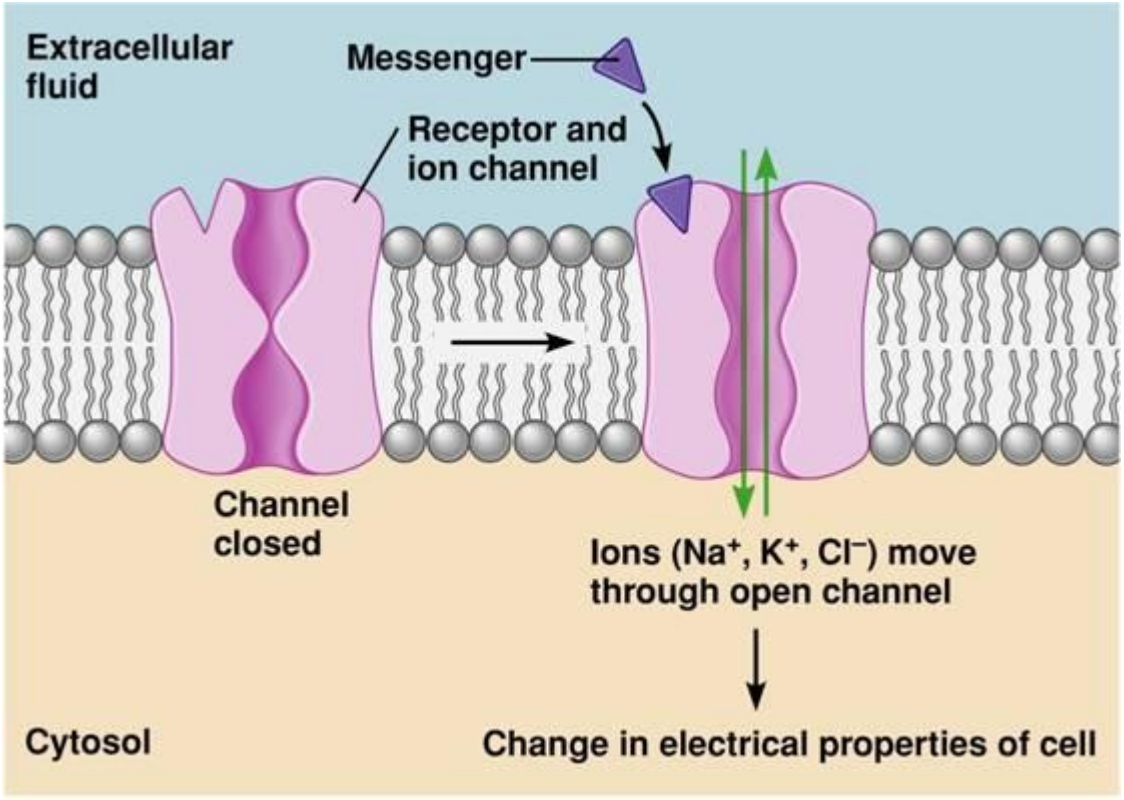

Figure No. 2: Ion channel receptors

Nm receptor: It is located in the skeletal muscle endplate. The agonist is acetylcholine. It is a heteromeric glycoprotein complex made up of 5 integral membrane subunits. Centrally it holds a Na+ channel. The subunits are 2α, 1β, 1 δ, and 1 γ. Each of these subunits forms the wall of the ion channel. The receptor contains 2 Ach binding between these subunits. When two molecules of Ach binds to the receptor, the receptor undergoes a conformational change .Opening of Na+ channel and inflow of Na+ ions causes depolarization in skeletal muscle, which results in muscle contraction.

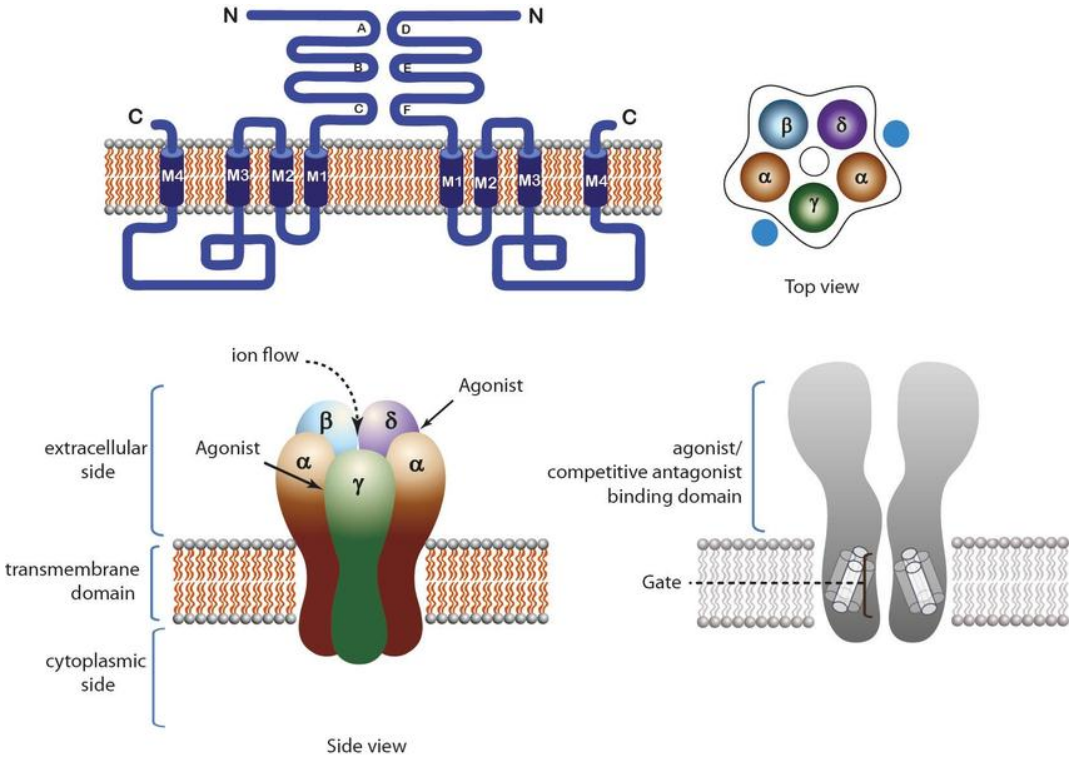

Figure No. 3: Schematic view of Nm receptors

TRANSMEMBRANE ENZYME LINKED RECEPTORS OR CATALYTIC RECEPTORS [13-15]

These are transmembrane proteins with their ligand-binding domain on the outer surface of the plasma membrane. The cytosolic domain either has an intrinsic enzyme activity or associates directly with an enzyme like *Tyrosine kinase* (TK) or *Guanylate cyclase* (GC). Insulin, Interleukins & growth factors act as agonists for TK receptors while atrial natriuretic peptide (ANP) for GC receptors. When an agonist bind to the extracellular domain (ligand-binding domain) of the receptor, it produces a conformational change. This results in the dimerization of receptors & activation of the intracellular enzyme domain (TK or GC). Only TK receptors undergo autophosphorylation i.e addition of a phosphate group & activate intracellular signaling proteins, which produces a cellular response. Receptors with intracellular GC domain produce a cellular response by producing cGMP from GTP.

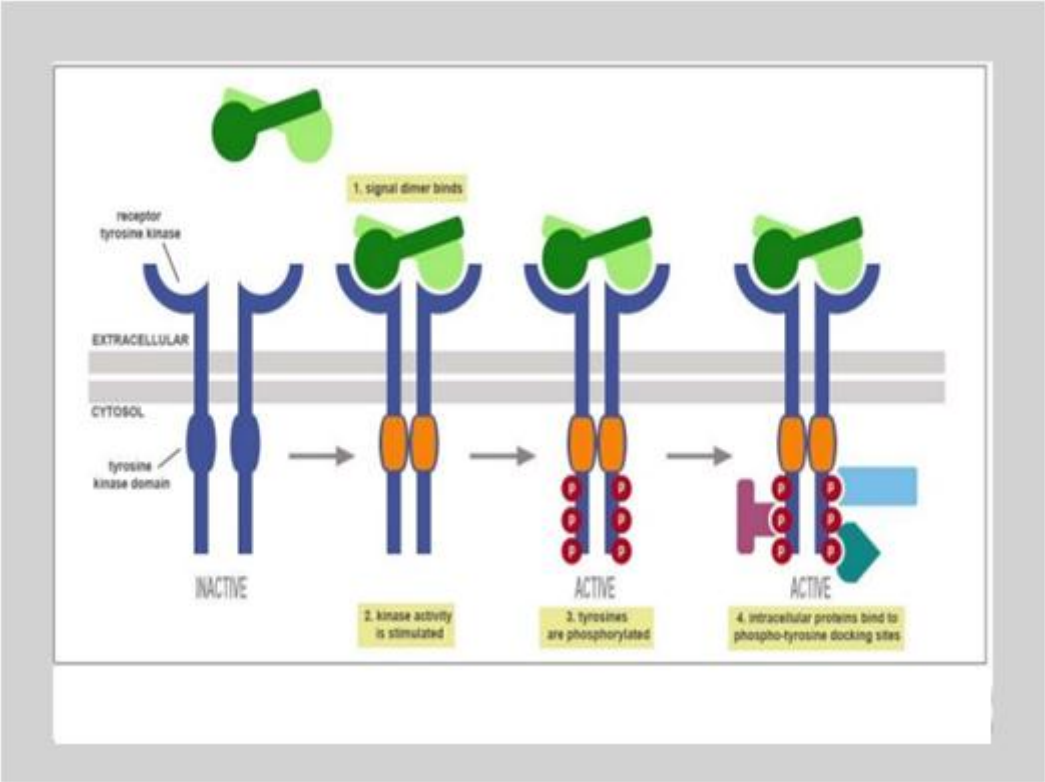

Figure No. 4: Schematic view of transmembrane enzyme-linked receptors

TRANSMEMBRANE JAK-STAT BINDING RECEPTOR [16], [17]

These receptors differ from Receptor tyrosine Kinase (RTKs) in not having any intrinsic catalytic domain. Agonist induced dimerization alters the intracellular domain conformation to increase its affinity for a cytosolic tyrosine-protein Kinase JAK(Janus Kinase).On binding, JAK gets activated & phosphorylates tyrosine residues of the receptor, which now bind another free moving protein STAT (Signal transducer & activator of transcription). This is also phosphorylated by JAK. Pairs of phosphorylated STAT dimerize & translocate to the nucleus to regulate gene transcription resulting in a biological response. Many cytokines, growth hormones, prolactin, interferons, etc act through this type of receptor.

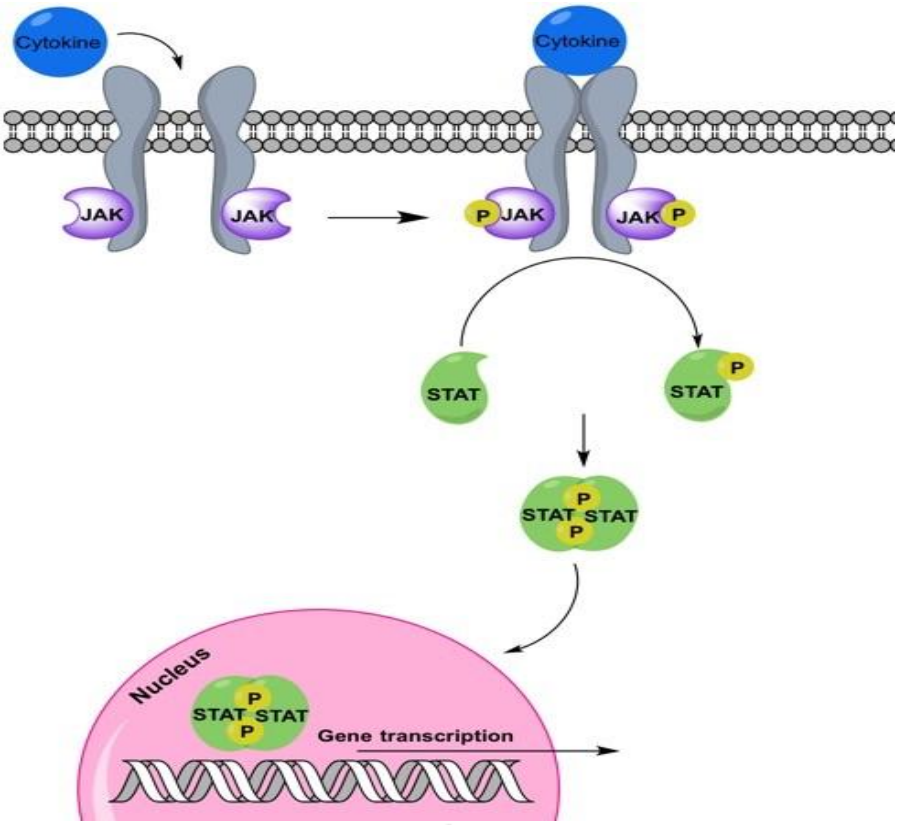

Figure No. 5: Schematic view of transmembrane Jak-Stat binding receptor

RECEPTORS THAT REGULATE TRANSCRIPTION FACTORS [18], [19]

These receptors are located either in the cell cytoplasm or in the nucleus. Eg: Steroid hormone receptors, Thyroid hormone receptors. Several agonists for these receptors include mineralocorticoids, glucocorticoids, estrogens, androgens, progesterone, thyroxine, Vitamin D & A. Nuclear receptors contain the following domains: **N-terminal regulatory domain**: Contains the activation function 1 (**AF-1**) whose action is independent of the presence of ligand. **DNA-binding domain** (**DBD**): Highly conserved domain containing two zinc fingers that bind to specific sequences of DNA called hormone response elements (HRE). **Hinge region**: Thought to be a flexible domain that connects the DBD with the LBD. **Ligand binding domain** (**LBD**): Moderately conserved in sequence and highly conserved in structure between the various nuclear receptors. **C-terminal domain**: Highly variable in sequence between various nuclear receptors.

STEPS: (1) The agonist that is lipid-soluble permeates into the cytosol & attach to the binding site on the receptor. (2) Binding of agonist to the receptor activates the DNA – binding site, which is otherwise inactive. (3) This complex penetrates the nucleus, where the

active DNA-binding site gets associated with genetic materials (genes), resulting in transcription. (4) mRNA synthesized results in translation i.e., production of proteins from mRNA which results in cellular response.

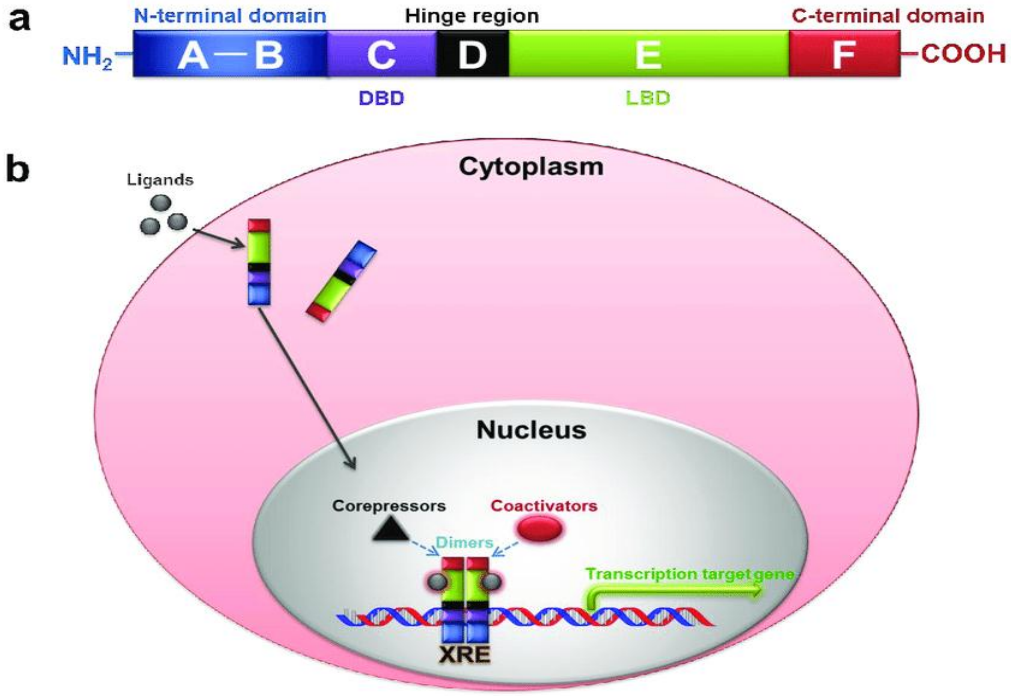

Figure No. 6: Schematic view of receptors that regulate transcription factors

SUMMARY

Signaling mechanisms that control cell growth, migration, survival, and differentiation involves plentitude types of ligands, including proteins, peptides, and certain lipids, that bind to receptors at the cell surface, and steroids and gases that can pass across the plasma membrane and bind to intracellular receptors. This review gives a hurried look into how receptors are activated after ligand binding, how they initiate signaling inside the cell, and how signaling is terminated. Signal transduction often occurs by the reversible formation of complexes and specific translocations of signaling molecules, rather than by random diffusion events. Furthermore, different signaling inputs converge on a few well-conserved intracellular pathways, several of which link to transcriptional regulation of gene programs.

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