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A Review on Structure of Drug-Receptor Complex

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Abstract: Drug-receptor complexes, fundamental to molecular pharmacology, consist of a drug molecule interacting with specific receptor proteins located on the surface or within cells. These interactions underpin the pharmacological effects of drugs by altering the chemical and biochemical properties of biological tissues. The mechanisms of drug action can be broadly categorized into passive physicochemical modifications and chemical interactions with tissue constituents. Receptors, characterized by specificity, saturability, high-affinity binding, and reversibility, play a pivotal role in mediating the therapeutic and toxic effects of drugs. The dynamic ligand-receptor interaction forms the basis of pharmacodynamics, influencing drug efficacy and selectivity. Various types of drug-receptor interactions hydrophobic, electrostatic, covalent, and hydrogen bonding are critical to understanding drug action and are central to the drug-design process. Theories like the occupation, induced-fit, and two-state models provide deeper insights into receptor behavior, aiding the development of novel therapeutic agents. This review article comprises different types of drug-receptor complexes, the structure of drug-receptor complexes, binding sites and conformational changes upon ligand binding along with mechanisms and application of drug-receptor complexs.

Keywords: Drug-receptor complexes, High-resolution structures, Conformational dynamics, Binding kinetics, Allosteric modulation, Computational Modeling.

1. Introduction

A drug-receptor complex in molecular pharmacology is made up of a drug molecule and a particular receptor protein that can be found inside or on the surface of a cell. The only way to understand how a medicine affects a living tissue chemically is to consider how the drug molecule changes that tissue's chemical properties or interferes with its biochemical processes. Because we can only think about a drug in physical or chemical terms, pharmacological events must also be understood in those terms. This requires us to explore what happens at the molecular level when a drug interacts with the extremely complex chemical organization of biological tissues. We can now consider the drug as a substance that interferes with or disturbs the balance of the normal state if we assume, as we have good reason to do, that the resting state of any organ or tissue is the result of a dynamic equilibrium between numerous biochemical reactions that are constantly taking place. A priori, we can distinguish two main ways in which drugs may do this: 1) Drugs with the appropriate physicochemical qualities, such as lipophilic solubility, surface active characteristics, etc., but without a high degree of structural specificity, may passively modify the normal physicochemical state of living cells. This type of effect, known as "physical toxicity," is common to numerous opioids, some disinfectants, and general anaesthetics. In other words, activity behaves similarly to any physical property that depends on the distribution of the drug molecule between two phases, with homologous series of such drugs typically exhibiting a geometrical increase in activity (up to a limiting value) as the number of C-atoms increases arithmetically. 2) A chemical interaction that forms between specific tissue constituents and drugs may be the cause of those drugs' effects. Such combinations may be real covalent ones, which may be rather stable, or they may be complexes due to relatively weak interactions, such as polar or ionic forces, hydrogen bonding, or dispersion (van der Waals or London) forces.

Because they can only combine with a restricted subset of tissue constituents, medications whose pharmacological effects depend on chemical interactions with tissue constituents (of any kind) are likely to have localized and focused effects. A "receptor" is the term used to describe the component of a tissue that a drug is intended to interact with to have a pharmacological effect [1]. Receptors, which can be found on the cell surface membrane or in the cytoplasm, are macromolecules that play a role in chemical signaling between and inside cells. Receptor activation controls cellular biochemical processes directly or indirectly (eg, protein phosphorylation, ion conductance, enzymatic activity, and DNA transcription) [2]. The drug receptors are distinguished by four features: a) Specificity: A target molecule must show specificity of binding to be categorized as a receptor; this means that only certain drugs with comparable structural relationships can attach to the molecule and produce an effect, but the drugs, structurally unrelated relationships cannot. The basis for the specificity of therapeutic action is its selectivity, which also explains why different medications can have multiple effects even though they target the same physiological function. b) Saturability: Drugs that particularly bind to the receptors according to their structures can saturate drug receptors since they are expressed in finite quantities and are therefore by definition able to withstand such a load. c) Binding with high affinity: Receptors have a high affinity for the medications they are designed to bind, making it possible to saturate them with low drug doses. d) Reversibility: Structurally specific medications engage with their receptors by creating chemical bonds, and these interactions are typically reversible. Yet, certain drugs establish covalent interactions with their receptors to create essentially irreversible, non-reversible drug-receptor complexes [3].

Many of the drugs interact with the molecular targets, or receptors, to produce therapeutic and toxic effects. The drug molecule interacts with the receptor to start a series of biochemical and physiological processes that result in the drug's apparent effects. Therefore, Pharmacodynamics is the term used to describe this ligand-receptor interaction and its effects [1]. The receptor theory has significant practical significance for medication development. It provides a basis for understanding pharmacological effects and therapeutic applications. The quantitative relationships between drug dose or concentration and pharmacologic effects are mostly determined by receptors. The amount of drug needed to generate a substantial number of ligand-receptor complexes depends on the receptor's affinity for binding the drug, and the total number of receptors may set a limit on the maximum effect a medication can have. The selectivity of a drug's activity is governed by receptors. Among the numerous chemically distinct binding sites present in the patient, a drug's size, shape, and electrical charge decide whether it will attach to a particular receptor.

Likewise, a drug's affinity for various classes of receptors can be greatly increased or decreased by modifications to its chemical structure, which can modify the drug's therapeutic and harmful effects. However, the processes behind the therapeutic effects of numerous medications frequently involve receptor activation and inhibition. The three-dimensional structure of the receptor site makes it possible for the medicine to bind there in a certain way. The amount of time the drug-receptor complex remains in the body also affects the pharmacologic effect. Dynamic processes (conformation modifications) that regulate the rate of drug interaction and dissociation from the receptor have an impact on the drug-receptor complex's lifespan. A prolonged pharmacologic impact is explained by a longer residence time. Part of the reason why a medication has an affinity for a receptor site is due to its complementary structure. A complementary drug-receptor complex is shown in **Figure 1**.

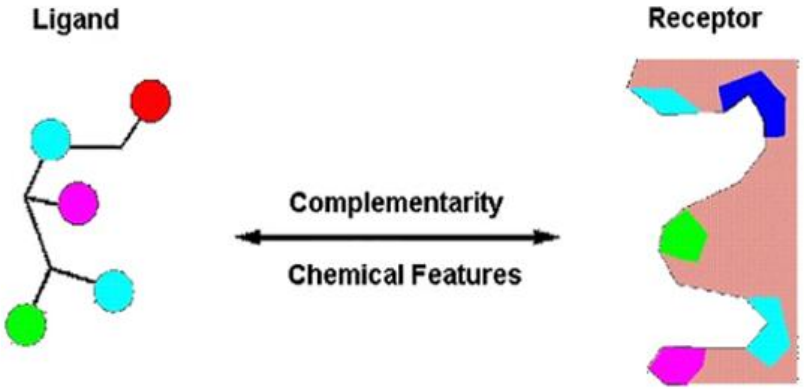

Figure 1: Specificity of a drug-receptor complex or complementary drug receptor structure.

There are three main types of interactions involved between drug and receptor complexes, i.e. hydrophobic, electrostatic, and covalent bond interactions. Covalent interactions are powerful and frequently irreversible in biological systems. Electrostatic bonds are more prevalent, more common, and frequently reversible than covalent ones. The hydrophobic interactions between lipid-soluble drugs and hydrophobic "pockets" of receptors include the weakest connections, which are also likely to be the most significant. The other interactions such as hydrogen bonding, ionic, ion-dipole, dipole-dipole interactions, and pi-pi interactions are of equal importance, especially in the drug-designing process [4]. Various theories also explain the drug receptors' complex behaviour like occupation theory, rate theory, induced-fit theory, macromolecular perturbation theory, activation-aggregation theory, and two-state models of receptor activation [5].

2. Types of Drug-Receptor Complexes

The study of how medications, pharmaceuticals, and other xenobiotics interact with receptors is known as receptor pharmacology. Certain fundamental concepts of receptor theory must be considered to comprehend the molecular mechanism underpinning a ligand's impact on physiological or therapeutic cellular responses. They consist of target accessibility, affinity, effectiveness, and potency. They also comprise the number of occupied receptors, association and dissociation rates, and residence times. These targets react to the binding of chemical messengers to change a cellular response. These diverse messengers include chemokines, hormones, neurotransmitters, and exogenous medicinal substances. Drugs that mimic or compete with endogenous mediators can be used to target receptors. There are many kinds of receptors, including ligand-gated ion channels, tyrosine kinase-coupled, enzyme-linked, hormonal intracellular, and G-protein coupled receptors (GPCRs). We will be explaining these receptors one by one for better clarity.

2.1 Ligand-gated Ion Channels

Ligand-gated ion channels (LGICs) (**Figure 2**) are membrane proteins that are structurally integral and feature a pore that permits the controlled passage of particular ions across the plasma membrane. The electrochemical gradient for the permeable ions drives the passive ion flux. The quickest cellular reactions to receptor activation involve ligand-gated ion channels. These transmembrane receptors are made up of many peptide subunits, each of which has four membrane-spanning domains. These receptors are also called ionotropic receptors. These are a class of transmembrane ion-channel proteins that open to permit the passage of ions like Na+, K+, Ca2+, and/or Cl in response to the interaction of a chemical messenger (i.e., a ligand), such as a neurotransmitter.

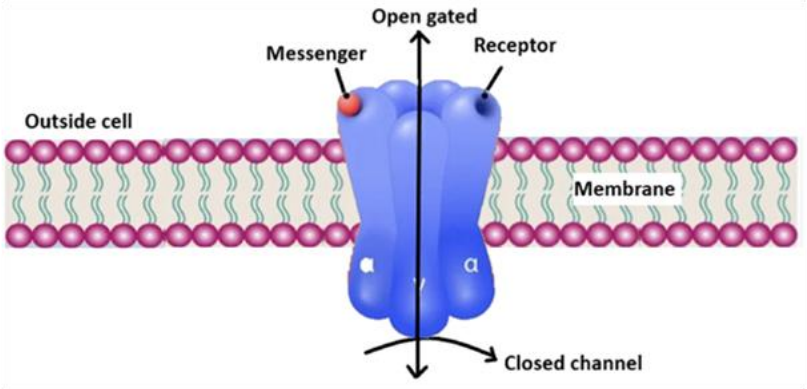

Figure 2: Ligand-gated ion channels.

The binding of neurotransmitters to one or more orthosteric sites causes a conformational shift that leads to the conducting state, which opens or gates the channels. The binding of endogenous or foreign modulators to orthosteric sites can modify gating. On a millisecond time scale, LGICs mediate rapid synaptic transmission in the neurological system and at the somatic neuromuscular junction. This type of transmission entails the release of a neurotransmitter from a pre-synaptic neuron and the subsequent activation of post-synaptically situated receptors that mediate a quick, phasic electrical signal (the excitatory, or inhibitory, post-synaptic potential). A neurotransmitter is discharged from vesicles into the synaptic cleft by an activated presynaptic neuron. After that, the neurotransmitter attaches to receptors on the postsynaptic neuron. If the receptors in question are ligand-gated ion channels, the ensuing conformational shift causes the ion channels to open, allowing ions to flow across the cell membrane.

A depolarization for an excitatory receptor response or a hyperpolarization for an inhibitory response, respectively, follow. These receptor proteins typically contain two or more distinct domains: an extracellular domain that contains the ligand binding site and a transmembrane domain that contains the ion pore (an allosteric binding site). However, it is now known that some LGICs play a role in tonic neuronal control in addition to their historical function in phasic neurotransmission, which occurs from the activation of extra-synaptic receptors by background levels of neurotransmitter. Non-excitable cells' expression of various LGICs may have extra functions. It is considered an important class of membrane proteins which are essential for mediating cell-cell communication and cellular excitability [6, 7]. Many LICs are also affected by membrane potential, ions, channel blockers, allosteric ligands, and channel blockers. The three superfamilies of LICs—cys-loop receptors, ionotropic glutamate receptors, and ATP-gated channels—are not related in any way evolutionarily.

2.2 Cys-loop Receptor

The cys-loop receptors got their name from a distinctive loop in the N terminal extracellular domain that was created by a disulfide link between two cysteine residues. They belong to a larger family of pentameric ligand-gated ion channels that typically do not have this disulfide link [8]. In vertebrates, a binding site in the extracellular N-terminal ligand-binding domain confers receptor specificity for (1) acetylcholine (AcCh), (2) serotonin, (3) glycine, (4) glutamate, and (5) -aminobutyric acid (GABA). The receptors are categorized into families according to the endogenous ligand and further according to the type of ion that they conduct (anionic or cationic). The nicotinic acetylcholine receptor is the prototype ligand-gated ion channel. The structural components of cys-loop receptors are well conserved, and they have a large extracellular domain (ECD) that contains an alpha-helix and ten beta-strands [9]. There are two types of Cyc-loop receptors: anionic receptors and cationic receptors. Examples of Cationic receptors are serotonin (5-HT), Nicotinic acetylcholine, and zinc-activated ion channels, whereas anionic receptor examples are: GABAa and glycine.

2.3 Ionotropic Glutamate Receptors

It’s a significant class of heteromeric ligand-gated ion channels (CNS). The majority of excitatory neurotransmission in the vertebrate central nervous system is mediated by ionotropic glutamate receptors (iGluRs), [10], WormBook, ed. The C. elegans Research Community, WormBook,). The glutamate, a neurotransmitter, is bound by ionotropic glutamate receptors. Each subunit of these tetramers contains a transmembrane domain (TMD, which forms the ion channel), an extracellular ligand binding domain (LBD, which binds glutamate), and an extracellular amino-terminal domain (ATD, which is involved in the assembly of the tetramer and binds glutamate). Based on their pharmacological specificity, these transmembrane proteins can be roughly divided into two groups: those that belong to the N-methyl-D-aspartate (NMDA) class and those that do not, i.e. non-NMDA class. The ionotropic glutamate receptors are divided into four subtypes, namely AMPA, NMDA, Kainate, and Delta receptors, based on their affinity for ligands other than glutamate [11].

2.4 ATP-gated Channels

ATP-gated channels open in response to ATP nucleotide binding. The C and N termini are both on the intracellular side, and each subunit has two transmembrane helices. Adenosine triphosphate (ATP) is widely distributed in the cytosol and is used to drive energy-intensive processes because ATP hydrolysis releases energy. It is therefore referred to as the energy currency of cells. ATP-gated cation channels known as P2X receptors play significant roles in a variety of pathophysiological diseases. Extracellular adenosine 5'-triphosphate (ATP) produced during synaptic transmission serves as the ligand for the cation channel P2X receptors [12].

2.5 Tyrosine Kinase-coupled Receptor

Receptor tyrosine kinases (RTKs) are transmembrane proteins found on the surface of cells that function as signaling receptors (**Figure 3**). They control vital biological functions like metabolism, differentiation, apoptosis, and cell division. These are the collection of membrane-bound receptors that are crucial to cells' regular operation. By phosphorylating tyrosine residues on essential intracellular substrate proteins, they serve as signal transducers that facilitate cell-to-cell communication.

In essence, they are at the center of intricate, interconnected signaling pathways and actively contribute to the maintenance of cellular homeostasis by controlling cell proliferation, migration, metabolism, differentiation, and other processes [13]. Several RTKs have been linked to the initiation or development of various malignancies as a result of their functions as growth factor receptors, either through receptor gain-of-function mutations or by receptor/ligand overexpression. RTK alteration or aberrant activation has frequently been seen and acknowledged as a significant component in the development of many malignancies [14]. The epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) are frequently used to treat non-small cell lung cancer (NSCLC). The tyrosine kinase domain of EGFR is inhibited by these small molecule inhibitors [15]. The insulin receptor, hepatocyte growth factor/scatter factor receptors, platelet-derived growth factor receptors, fibroblast growth factor receptors, Met (hepatocyte growth factor/scatter factor [HGF/SF] receptor), vascular endothelial growth factor receptors, fibroblast growth factor receptors (FGFRs) and ephs (ephrin receptors), are all members of the RTK family.

RTKs are crucial components of cellular signaling networks that are active during adult homeostasis and embryonic development. RTKs are type I, single-pass receptors that are found in the plasma membrane. RTKs are normally activated by ligand-induced oligomerization, which typically dimerizes the cytoplasmic tyrosine kinase domains [16]. The ensuing conformational alterations for the majority of RTKs allow for the trans-autophosphorylation of each TKD and the release of the cis-autoinhibition [17]. The TKD can take on an active conformation as a result of this conformational shift. Moreover, many downstream signaling proteins with Src homology-2 (SH2) or phosphotyrosine-binding (PTB) domains are recruited and activated by the autophosphorylation of RTKs. These domains interact with downstream mediators to spread important cellular signaling pathways by binding to particular phosphotyrosine residues within the receptor [18, 19].

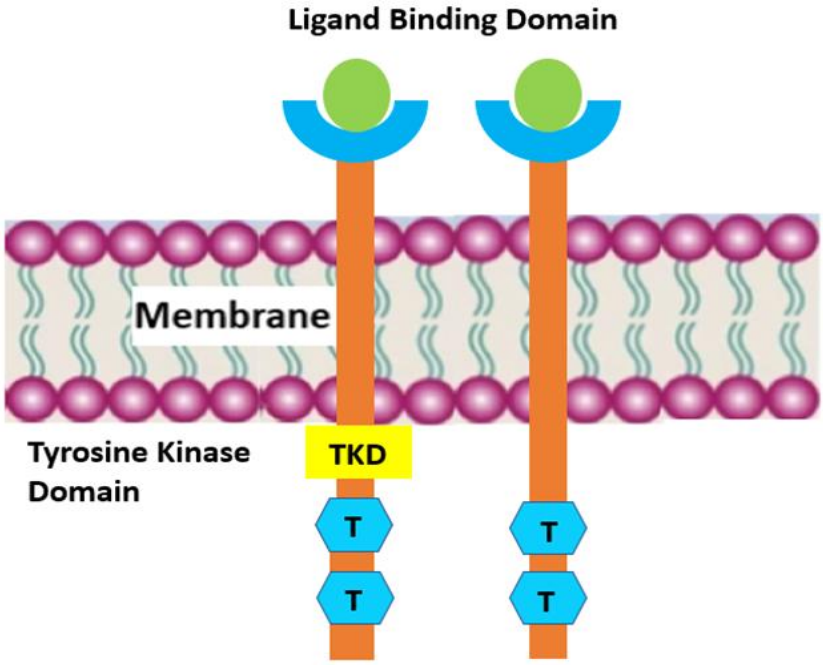

Figure 3: Structure of a Tyrosine Kinase Receptor.

2.6 Enzyme-linked Receptor

Proteins, classified as enzyme-linked receptors (**Figure 4**) function as both receptors and enzymes, activating a variety of intracellular signals. The intracellular domain of enzyme-linked receptors has an innate catalytic activity, and it is connected to an extracellular ligand-binding domain. According to their catalytic activity, this huge and diverse collection of membrane receptors can be grouped into four subfamilies: guanylate cyclase such as in atrial natriuretic factor receptor, tyrosine kinase such as in fibroblast growth factor receptor, tyrosine phosphatase, and serine/threonine kinase such as in bone morphogenetic protein [20]. They have two significant domains, an extracellular ligand-binding domain and an intracellular domain, having a catalytic function, and a single transmembrane helix. The signaling molecule attaches to the receptor outside of the cell and changes the conformation of the receptor's internal catalytic function [21].

There are numerous receptors in this group, including the RTK family of tyrosine kinases. Many hormones and growth factors bind to and activate the RTKs [22]. Tyrosine residues in the receptor of its own and occasionally related to cytoplasmic proteins are transphosphorylated as a result of ligand binding, which also promotes receptor dimerization. As explained earlier, there are up to 20 classes of RTK, which include growth factor receptors. Many of these receptors communicate with one another via proteins in the mitogen-activated protein (MAP) kinase cascade, which has an impact on gene transcription, apoptosis, and cell division. In chronic myeloid leukaemia, leucocyte proliferation is caused by constitutive overactivity of the RTK, called Bcr-Abl. The RTKs are the primary targets of medications developed for the treatment of cancer. Whereas tyrosine phosphatase receptors are highly prevalent in immune cells and dephosphorylate tyrosine on certain receptor molecules or cytoplasmic proteins. The other group of receptors i.e. Tyrosine kinase-associated receptor family (or nonreceptor tyrosine kinases), these receptors lacking with integral kinase activity but activate the separate kinase linked with the receptor, for example, inflammation-related gene expression is influenced by inflammatory cytokine receptor and signaling through the JAK/Stat pathways. The other receptor family i.e., serine-threonine kinase, is involved in the activation of serine and threonine residues in the targeted cytosolic proteins. The guanylyl cyclase family of the receptor facilitate the conversion of GTP into cGMP via a cytosolic domain [23, 24].

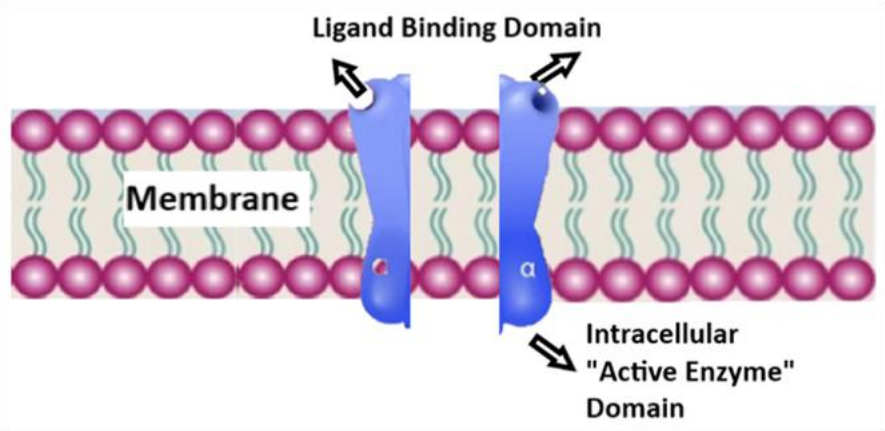

Figure 4: Structure of Enzyme-linked Receptor

2.7 Hormonal Intracellular Receptor

The globulous protein receptors called intracellular receptors (**Figure 5**) are found inside cells as opposed to on the cell membrane. The term "intracellular" refers to "Inside or within a cell". It is common for nonpolar, occasionally tiny molecules to pass a cell membrane and connect with a receptor. Ligands are another name for these compounds. Aldosterone, steroid, thyroid, and other hormones use intracellular receptors [25]. The nuclear receptors, located in the cell nucleus and cytoplasm, and the inositol triphosphate (IP3) receptor located in the endoplasmic reticulum are examples of this class. The ligands that bind to them are often extracellular lipophilic hormones like steroid hormones and intracellular second messengers like inositol trisphosphate (IP3). There are intracellular receptors for a few intracrine peptide hormones as well. Nuclear receptors are a different name for cytoplasmic receptors. Particularly, these receptors are proteins that are found in cells and oversee the identification of thyroid and steroid hormones. Along with other proteins, they control the organism's metabolism, gene expression, and homeostasis. They also can attach themselves straight to DNA. The thyroid receptor is a crucial example of a nuclear receptor. As a calcium channel, the inositol triphosphate receptor activates InsP3. The cerebellum contains a significant number of these receptors, which are distributed widely throughout tissues. The endoplasmic reticulum contains them primarily integrated. Many pharmacological and cellular processes must always be controlled by InsP3R. Due to hormone binding to receptors, when a hormone is released in excess, the number of receptors for that hormone declines, then this is called downregulation. When there is a shortage of hormones, the number of receptors increases, which is known as upregulation. Endocytosis allows the hormone to reach the target cell as a hormone-receptor complex and carry out the desired actions [26]. Occasionally these hormonal intracellular receptors are also categorized into type 1 and type 2, where type 1 receptors include steroid hormone receptor in the cytoplasm and type 2 receptors includes thyroid hormone receptor, which bind to their DNA response elements within the nucleus [27].

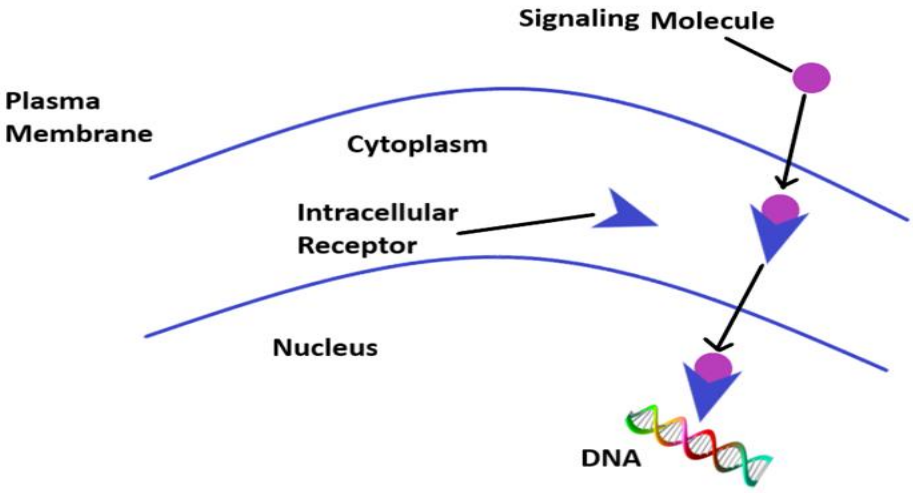

Figure 5: Structure of Hormonal intracellular receptor

2.8 G-protein Coupled Receptors (GPCRs)

These are the most abundant and diverse membrane receptors found in eukaryotes. It also known as guanine nucleotide-binding protein, is an intracellular molecule that receives signals from external molecules through a protein found in the cell membrane. Many different types of animals, including mammals, plants, microbes, and invertebrates, have GPCRs (**Figure 6**) in their cell membranes. The messages carried by light energy, peptides, lipids, carbohydrates, and proteins are received by these cell surface receptors like an inbox. These transmissions provide information sent by other cells or inform cells about the presence or absence of nutrients or light that support life in their surroundings. G protein-coupled receptors (GPCRs), also referred to as 7TM receptors, seven-(pass)-transmembrane domain receptors, serpentine receptors, heptahelical receptors, and G protein-linked receptors (GPLR), comprise a significant family of evolutionarily related proteins that function as cell surface receptors to identify molecules outside the cell and to trigger cellular responses. GPCRs are involved in a staggering variety of processes in the body, and better knowledge of these receptors has made a significant impact on modern medicine [28]. All GPCRs are fundamentally distinguished by the presence of seven membrane-spanning -helical segments, which are spaced apart by alternate intracellular and extracellular loop sections. Unsurprisingly, organisms with multiple cells use GPCRs for a lot more purposes. The traditional function of GPCRs is to relate the association of agonists to the stimulation of heterotrimeric G proteins, which then influences effector proteins downstream. As an illustration, the human β2AR is activated when adrenaline and noradrenaline bind to cells in the target tissues of sympathetic neurotransmission. This activation results in the activation of the stimulatory subunit of the heterotrimeric G protein (Gs), stimulation of adenylyl cyclase, accumulation of cyclic AMP (cAMP), activation of cAMP-dependent protein kinase A (PKA), and phosphorylation of proteins involved [29]. The G protein-coupled receptors are primarily involved in two signal transduction pathways: the phosphatidylinositol signal route and the cAMP signal pathway [30]. GPCRs are frequently divided into many subfamilies according to the structural and physiological characteristics of the protein. The GPCRs are divided into six groups using the A-F categorization system, four of which are composed of mammalian GPCRs: Class A Rhodopsin-like, which comprises around 80 percentage of GPCRs; Class B Secretin receptors; Class C Metabotropic glutamate-like receptors; and Class F Smoothened/ Frizzled. Non-mammalian GPCRs make up the Class D and Class E families. Fungal mating pheromone receptors belong to the Class D family, while cAMP receptors from slime moulds are found in the Class E family. Another classification of mammalian GPCRs has been put up recently. Based on their evolutionary tree, the GRAFS System classifies mammalian GPCRs into 5 families: adhesion (A), frizzled/taste2 (F), glutamate (G), rhodopsin (R), and secretin (S). The Adhesion family and Secretin family are the two groups into which the Class B GPCR family is divided by the GRAFS system, which is the main distinction between the A-F and GRAFS systems. The pharmacological mechanism of GPCRs is significantly noted with the occurrence of a conformational shift in the seven-transmembrane region of the receptor when a GPCR meets a ligand. By doing so, the C-terminus is activated, which attracts a substance which in response stimulates the G protein linked to the GPCR. When the G protein is activated, a sequence of intracellular processes begins and eventually produces an impact, such as a faster heartbeat in response to epinephrine or alterations in vision in response to low light [31].

However, human disease can result from both inherited and acquired mutations in the GPCR-encoding genes. For instance, numerous inflammatory cells, such as dendritic cells, lymphocytes, monocytes, and neutrophils express GPCRs, and these cells have significant immunological functions. The increased synthesis of GPCR ligands by tumour and stromal cells, abnormal overexpression, gain-of-function alterations, changes in downstream effector molecules, and changed GPCR signaling have all been linked to altered GPCR signaling in many malignancies.

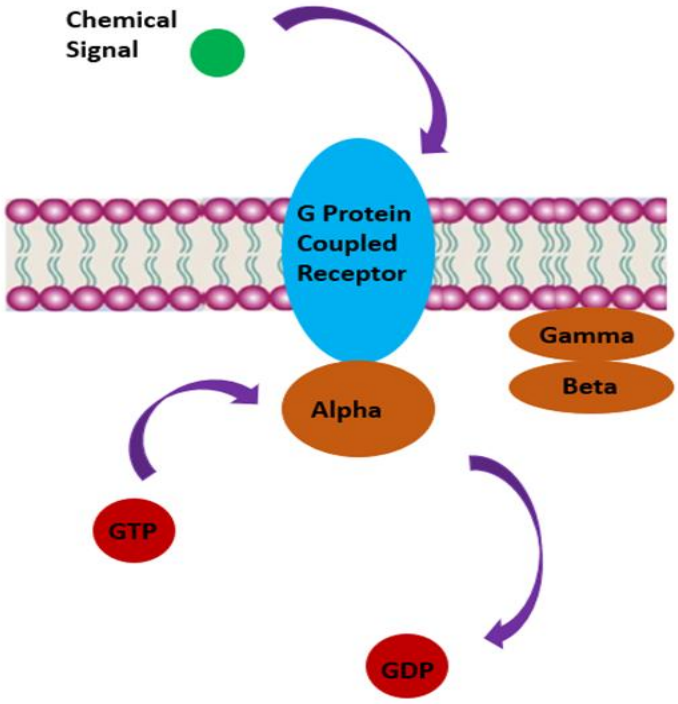

Figure 6: Structure of G-protein coupled receptors

3. Structure of Drug-Receptor Complexes

Protein structure is defined as a three-dimensional arrangement of atoms where polymer of amino acids (**Figure 7**) joined by peptide bonds.

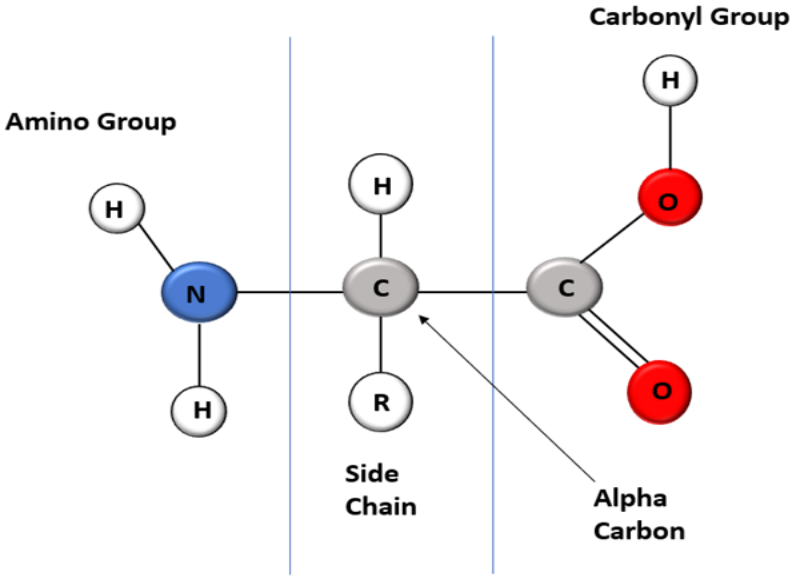

Figure 7: Structure of Amino Acids

To produce their shape and structure, amino acids go through several folding phases. Depending on their molecular makeup, proteins can have a variety of functions in the body, including structural, regulatory, contractile, and protective ones. According to the various R groups that amino acids have, there are 21 different varieties in all. Of these, 12 can be produced by the body whereas the other 9 known as essential amino acids must be obtained through diet. Proteins fold into one or more distinct spatial conformations as part of their biological activity, which is mediated by a variety of non-covalent interactions, including hydrogen bonds, ionic interactions, Van der Waals forces, and hydrophobic packing. It is frequently required to ascertain the three-dimensional structure of proteins to comprehend their molecular functions. This is the subject of the scientific discipline known as structural biology, which uses methods like X-ray crystallography, NMR spectroscopy, cryo-electron microscopy (cryo-EM), and dual polarization interferometry to ascertain the structure of proteins. When a protein performs a biological function, it typically experiences reversible structural modifications.

Different conformations of the same protein are its alternate structures, and transitions in between them are known as conformational alterations [32]. Usually, proteins can be classified into two types: Fibrous Proteins, these are the fiber-like structure, created when the polypeptide chains are arranged in parallel and are joined by hydrogen and disulfide bonds. Typically, water cannot dissolve these proteins. These proteins are not water soluble, for example: myosin, which is found in muscles, and keratin, which is found in hair, wool, and silk. The other classification is the Globular Proteins, this form develops as a result of the polypeptide chains coiling into a spherical shape. Typically, water can dissolve them. An illustration of a globular protein is albumin and insulin. Depending on its complexity, proteins can be categorized structurally into four groups: Primary, secondary, tertiary and quaternary structure.

3.1 Primary Protein Structure

The distinctive arrangement of amino acids in each of the polypeptide chains that make up a protein is known as its fundamental primary structure (**Figure 8**). Here, covalent peptide bonds are used to bind amino acids together to create a polypeptide chain. These bonds, which develop between an amino acid's N and C terminals, are extremely heat- and chemical-resistant. The protein's ability to fold correctly can be hampered by any modifications in the amino acid sequence, which might cause issues with the protein's functionality. The gene that codes for a protein determines the protein's basic structure. A particular DNA nucleotide sequence is converted into mRNA during translation, which the ribosome subsequently reads. The primary structure of a protein typically includes post-translational changes like phosphorylations and glycosylations, which cannot be read from the gene [33].

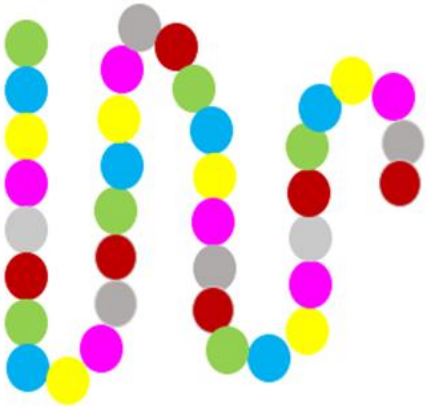

Figure 8: Primary protein structure

3.2 Secondary Structure

In the secondary protein structure (**Figure 9**), polypeptide chains are repeatedly folded by hydrogen bonds among the hydroxyl group (OH group) and a hydrogen molecule of the next amino acid, giving the protein its distinctive form. The beta-pleated sheets and alpha-helix are the two most typical examples. These hydrogen bond interactions usually occur within the protein structure. These beta sheets and alpha helix are crucial for the structural integrity of most globular and fibrous proteins [34].

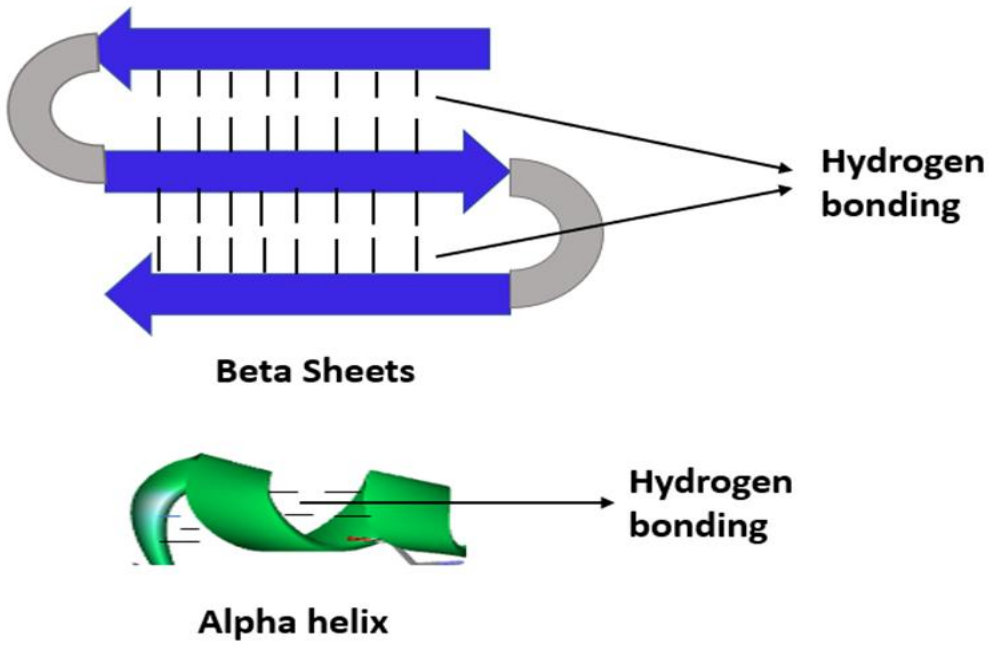

Figure 9: Secondary Protein Structure

3.3 Tertiary Structure

The point at which polypeptide chains start to operate is known as the tertiary structure (**Figure 10**). At this level, each protein is uniquely shaped in three dimensions and has functional groups on its surface that enable it to interact with other molecules and perform its specific function. The polypeptide chain is folded into a distinctive 3D structure to form the tertiary protein structure. This typically has a globular shape and a binding site enabling protein activity. The R groups of amino acids interact with one another to fold the polypeptide chain. As a result, if the links between R groups are broken, the tertiary structure can become disordered, losing its shape and its ability to perform its job. Protein denaturation is what is happening here. Hydrogen bonds, covalent bonds, hydrophobic bonds, and electrostatic or ionic bonds, are among the different types of bonding that contribute to the creation of the tertiary protein structure. When a protein, like an enzyme, loses its tertiary framework, it becomes denatured and loses its biological activity, making it incapable of performing its intended purpose. Usually, this occurs when the temperature is excessive for the protein molecule. However, the tertiary structure may be established after the temperatures are back to normal. There are various interactions, making the three-dimensional structure of a protein as hydrophobic, disulfide, ionic and hydrogen [35].

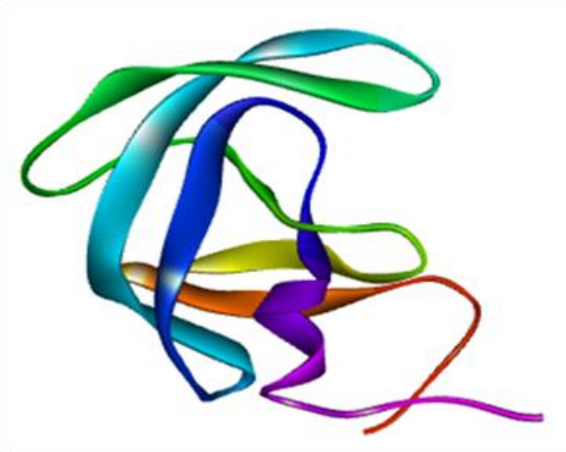

Figure 10: Tertiary Protein Structure

3.4 Quaternary Structure

The combination of many protein chains or subunits into a densely packed structure is known as the quaternary structure (**Figure 11**) of a protein. It results from the spatial arrangement of numerous tertiary structures. Each component has a unique Primary, Secondary, and Tertiary structure. Van der Waals forces and hydrogen bonding among non-polar side chains hold the subunits together [36]. Multimeric polypeptides can be stabilized by disulfide bonds and are created via the same kinds of non-covalent interactions as tertiary structures. The subunits are typically ordered symmetrically and can be unique or identical. Proteins with two subunits are generally referred to as dimers, those with three subunits as trimers, and those with four subunits as tetramers. Oligomeric proteins are proteins that have quaternary structure. Numerous biological activities, including metabolism, signal transmission, and chromosome replication, are aided by oligomeric proteins. Many different protein families, including receptor heteromers, cGMP-dependent protein kinases, transporter proteins, and the human ribonuclease H2 complex, have shown that quaternary structure may be crucial in protein function and allosteric regulation [37, 38].

Figure 11: Quaternary Protein Structure

4. Binding Sites

Local interactions between molecules that take place at specific locations, known as binding sites (**Figure 12**), enable proteins to serve the biological functions of a cell. The most crucial evidence that a medicine is acting pharmacologically is when it enters and binds to a protein's binding site. One of the main components in drug development is the identification of binding sites, which are hotspots in the pharmacological targets where the drug-like molecule is intended to bind. New approaches to therapeutic and drug discovery are made possible by the discovery of novel binding sites, expanding the genome that can be drugged [39]. Typically, drug-like compounds target either topologically different allosteric binding sites or orthosteric binding sites, where proteins interact with endogenous substances [40]. The latter is particularly interesting because, in contrast to orthosteric ligands, allosteric binding sites show a larger degree of sequence variability within protein subtypes, allowing for the development of more selective ligands [41].

A binding site is a dynamic characteristic of a protein that is mediated by its conformational changes. Proteins are flexible molecules that adopt different conformations throughout their life cycle. Since a single protein structure only makes up a small portion of the total conformational space, binding sites may be simple to miss in experimentally verified three-dimensional protein structures. In addition, many proteins carry out their tasks by assembling into oligomeric structures, and these structures can produce binding sites through the use of oligomer subunits [42]. Fragment screening and site-directed tethering, small molecule microarrays, employing antibodies, or site-directed mutagenesis and hydrogen-deuterium exchange are resource-intensive and may have unfavorable outcomes when used to experimentally identify binding sites [39]. On the other hand, computational approaches provide large-scale binding site identification, molecular dynamics simulation-based protein flexibility analysis, and virtual ligand or fragment-based screenings for chemical compound fitting. The traditional methods frequently use experimental scores based on structural details of recognized binding sites, or they include these details as features in machine learning algorithms [43].

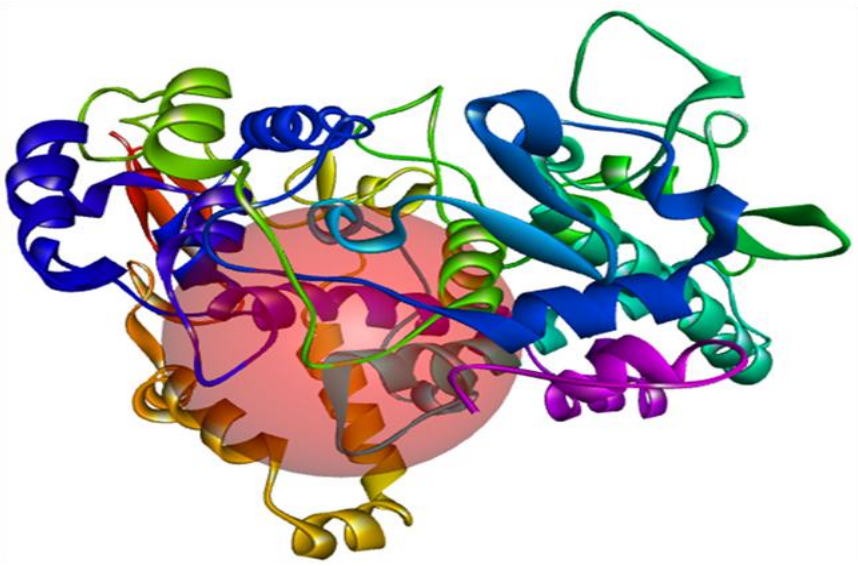

Figure 12: Binding site representation in red color

Recent developments in deep learning have shown that it is possible to identify protein binding locations without the need for manually created feature engineering. Additionally, conserved surface patterns can occasionally be used to identify the catalytic regions of enzymes. Therefore, it is usual to interpret the preservation of surface portions as a sign of functional relevance. This concept can be used to find the active-site residues in a group of related proteins, but it does not apply to protein families that employ a common framework to bind various ligands. Instead, one may speculate that such binding points will consist of variable places. The ligand is confined in the hydrophobic region after binding to the LBD changes its conformation [44]. The understanding of the biological mechanisms in the context of protein-ligand binding sites and ligand binding site residues is essential for understanding the pharmacological reactions of a drug molecule.

There are various ways to identify a binding domain of a macromolecule and ligand, like, the utilization of knowledge derived from the evolutionary preservation and/or the sequence similarity of similar proteins allows sequence-based approaches to predict protein-ligand binding regions and the residues that interact with those sites, approaches that use data from 3D atomic dimensions (predicted from sequencing or obtained from experiments) are known as structure-based approaches. These techniques either forecast the position of the ligand binding site or the predicted residues that make up the ligand binding site. Presently, a large number of methods are available for predicting and analyzing protein-ligand binding sites using machine learning algorithms. These techniques combine many strategies and provide a variety of data formats, including listings for ligand binding site residues, three-dimensional molecular coordinates of ligands binding sites, lists of potential binding ligands, and more. The information driven by these in silico protein-ligand binding domains can be used to inspire additional research and generate fresh theories for solving complex biological problems.

5. Conformational Changes upon Ligand Binding

Numerous biological processes depend on molecular recognition through protein-ligand binding. As a result of their flexibility and ability to adapt to their surroundings, proteins and ligands during protein-ligand binding work together to complement one another. Almost all biological activities depend on the coupling of protein conformational changes with ligand binding. For instance, upon the interaction of an effector molecule, signaling proteins change their shape from one that is inactive to one that is active [45]. A signal can be sent to downstream members of the signaling network via a conformational alteration of the signaling protein. Enzyme conformational changes enable the binding of the substrate and release of the product by placing the residues of the catalytic enzyme in the appropriate orientation. The "induced-fit mechanism" refers to the process whereby ligand interactions lead to a structural change. When a protein is ligand-free and a ligand or substrate is bound, a new conformation is produced, according to the classical induced-fit mechanism. Nevertheless, studies using nuclear magnetic resonance (NMR), single-molecule Förster resonance energy transfer (smFRET), electron paramagnetic resonance (EPR) and other data show that proteins sample a variety of conformations both with and without bound ligands [46].

Energy-landscape perspectives, first established for protein folding, give a theoretical foundation for understanding the conformation dynamics of folded, native proteins.16–19 The change in the population of protein conformations that occurs following binding or chemical reactions and conformational selection—the idea that pre-existing, higher-energy protein conformations can be "selected" for binding by ligands—are key concepts. Already 20 models for protein allostery had key elements of these ideas [47]. In general, thermally triggered activities that necessitate the passage of free-energy barriers include both conformational shifts and binding/unbinding events. One distinguishing trait of thermally stimulated mechanisms is that the "transition time," or the actual duration for crossover of the free-energy barrier, is much shorter than the dwell periods in the phases before and following the barrier crossing. Protein conformational changes are frequently observed as "sudden jumps" across multiple conformational states in single-molecule analyses that examine these changes. The transition periods are typically beyond the resolution of the experiment [48]. The transitional period needed for bound is the duration of time it takes for a location that is physically close to the binding site to pass the energy barrier and enter the binding site. In contrast to dwell periods during the unbound state, that are correlated with the binding rate, this bonding transition period is devoid of the molecule concentrations. Contrarily, bigger ligands' conformational alterations and binding and catalytic activities can be closely connected. When the general orientation of the binding or unbinding is reversed, a conformational selection process changes into an induced-change mechanism. The conformational shift is a structural excitation from a ground-state conformation with the lowest energy to a conformation with a greater energy. Following the binding of ligands, many proteins switch from a state of open to a packed conformation. Steric effects may prevent ligands from entering or leaving closed protein conformations. Only the induced-change interaction mechanism is then able to allow the proteins to bind their ligands. Conformational modifications and binding processes can be tightly connected if proteins bind to bigger ligand molecules, such as peptides, other proteins, DNA, or RNA molecules. Computational molecular dynamics is a viable method to model such a complex connection [49].

6. Mechanisms of Ligand Binding and Activation

The process by which a ligand molecule (such as a hormone, neurotransmitter, or medication) attaches to and activates a receptor molecule on the surface or inside a cell is known as "ligand binding and activation." The criteria for specificity in this process are dictated by the structural stiffness of the ligand and its target, which also explains differences in affinity between various ligands binding to the same target or of the same ligand binding to different targets. Protein conformation changes can be caused by ligand binding. Assuming a virtually perfect form complementarity between a ligand and the binding site as a lock-and-key recognition mechanism. The principles for specificity in this process are dictated by the structural stiffness of the ligand and its target, which also explains differences in affinity between various ligands interacting with an identical target or of the same ligand interacting with different targets [50]. There are numerous ways for ligands to bind and activate targets, including lock and key, induced fit, and allosteric regulation. A drug's binding spot may be the same as or distinct from an endogenous agonist's (hormone or neurotransmitter) binding site. Allosteric agonists are occasionally used to describe agonists that interact with a receptor's neighbouring or alternative spot. Drug binding in non-receptor-designated molecular locations, such as plasma proteins, also takes place. Drug inactivation results from drug binding to non-specific locations, such as serum proteins, which prevents drug binding to the receptor. The medicine is free to attach to receptors and exert its action. There are different mechanisms involved in the activation and binding of a ligand molecule to macromolecules, like, agonists, antagonists, and inverse agonists.

6.1 Agonist and Antagonist

To get the desired reaction, agonists turn on receptors. The proportion of receptors that are activated rises when conventional agonists are used. Contrary agonists function as competitive antagonists and stabilize a receptor in its inactive state. Many hormones, neurotransmitters (such as acetylcholine, histamine, and norepinephrine), and medications (such as isoproterenol, morphine, benzodiazepines, phenylephrine, and barbiturates) have agonistic effects. Whereas the partial agonist is a chemical compound or molecule that could connect to a receptor and only minimally activate the receptor, eliciting a submaximal physiological response. Although it has the affinity property, it is not as effective on an intrinsic level as a complete agonist. On the other side, antagonists stop the activation of receptors. There are various benefits to avoiding activation. If an antagonist prevents the effect of a drug that typically causes a decline in cellular function, cellular function will increase. When an agent that ordinarily boosts cellular function is blocked, antagonists cause a decrease in cellular

activity. There are two types of receptor antagonists: irreversible and reversible. Reversible antagonists easily separate from their receptors while irreversible antagonists (e.g., through alkylation) establish a strong, long-lasting, or practically irreversible chemical link with their target. Antibodies that are supposedly irreversible slowly separate from their receptor. In competitive antagonism, the antagonist's binding to the receptor blocks the agonist's binding to the receptor. Whereas agonist and antagonist can bind together in noncompetitive antagonism, this decreases or stops the agonist's ability to exert its effects. When a stable state is reached between the agonist, antagonist, and receptor is called a reversible competitive antagonist after the agonist and antagonist form temporary connections with the receptor. By increasing the agonist's concentration, this antagonistic situation can be avoided. Agonist and antagonist qualities are typically present in structural analogues of agonist compounds; these medications are referred to as partial (low-efficacy) agonists or agonist-antagonists. Pentazocine, for instance, activates opioid receptors but prevents other opioids from also activating those receptors. Therefore, if another opioid is administered while pentazocine is still bonded, pentazocine produces opioid effects but dampens the effects of the other opioid. In some tissues, a medication that only partially agonists in others may fully agonists in those tissues.

6.2 Inverse Agonists

The inverse agonist is a substance that binds with the same kind of target as an agonist but causes a pharmacological reaction that is the opposite of the agonist's. In the absence of an agonist or inverse agonist, a neutral antagonist does not act, although it can inhibit the action of either [51]. Agonists can counteract the effects of reverse agonists by acting in the opposite ways, while antagonists can also counteract the effects of both [52]. The existence of an intrinsic (also known as intrinsic or basal) level of receptor activity in the absence of any ligand is a need for an inverse agonist response. [53]. There are inverse agonists known for the histamine, GABAA, mu-opioid, melanocortin, and beta-adrenergic receptors among other receptors. The inverse agonists have negative intrinsic activity because they preferentially bind and stabilize receptors in the inactive (Ri) state. If a disease is brought on by constitutive receptor activation, inverse agonists could be used to inhibit this activity.

6.3 Affinity, Efficacy and Potency

Drug effects are a function of drug concentration at the binding site, but there is a high level of complexity since individual responses to drug concentrations are frequently non-linear and because drug effects depend on dose and time. A ligand's affinity for its receptor can be used to define the degree of their binding (interaction), While clinical efficacy assesses a drug's therapeutic efficacy in people and potency is a measurement of how much drug is required to have a specific effect. If we are explaining affinity in other words, we can say that it refers to how strongly the medicine binds to the receptor. A drug that binds to the same target but has a lower affinity may compete with or replace a medicine that has a greater affinity. A drug's high affinity for a particular receptor does not guarantee that it will result in an effect. For instance, Naloxone binds to muscarinic opioid receptors with a high degree of affinity. Naloxone's affinity causes it to displace the opioid from its target and stop it from having an impact. Naloxone thereby acts to reverse the harmful side effects of an opioid overdose, such as breathing difficulties. In a lab, affinity can be calculated as the amount of a medicine that binds to 50% of the accessible receptors. The equilibrium dissociation constant (KD) is a mathematical term that was established through experimental research to gauge a drug's affinity for a particular receptor. A given mass of cell membranes with receptors is incubated with ligands (any chemical that binds a receptor) at escalating concentrations until saturation takes place to calculate KD. Saturation causes high-affinity binding to happen at low drug concentrations whereas low-affinity binding happens at high drug concentrations. On the other side, as a result of the drug binding to the receptor, it serves as a gauge for the size of the effect. The ability of the medicine to bind with receptors and the speed with which cellular responses are induced by receptor activation determine effectiveness. In pharmacology, combinations of interest are constructed using the qualities of affinity and efficacy. In some circumstances, combining two medications that individually have similar effects (identical efficacy) can result in a super-additive impact. This occurrence is referred to as synergy. For instance, doctors attempt synergy when treating cancer patients with radiation and chemotherapy or when treating heart infections with medicines like gentamicin and ampicillin. Two medications can interact in a way that increases drug B's effect by increasing drug A's affinity for the receptor. However, potency is a measurement of a drug's activity that can be defined in terms of the quantity needed to have a specific effect. A substance with high potency causes a specific reaction at low concentrations, whereas a substance with low potency causes the same reaction only at higher levels.

Greater efficacy or more negative effects do not always imply higher potency [54]. The potency of a drug should be expressed in the context of a dose, or in unit of weight. By modifying the intensity of the ligand-receptor conjunction or changing the shape of the receptor, ligand binding can change a ligand's potency. Because it can attach to and stimulate the target receptor at low doses, a ligand with a high affinity to its receptor will also have high potency. A ligand with poor affinity, on the other hand, will be less potent and require higher doses to elicit the same reaction. The natural agonist or agonists' action may be modulated positively or negatively by the allosteric interaction, which may change binding affinity and/or efficacy [55]. There are three different types of allosteric modulators: positive, negative, or neutral. Positive kinds improve the likelihood that an agonist will attach to a target (i.e. affinity), improve the agonist's capacity to stimulate the receptor (i.e. effectiveness), or both. The affinity and/or effectiveness of the agonist is decreased by negative types. Despite being able to prevent alternative regulators by binding to an allosteric site, neutral types do not impact agonist action. Allosteric agonists are another function of some modulators [56]. The efficacy and affinity of other drugs interacting on a receptor can be changed by allosteric modulators. Additionally, a modulator may boost affinities while decreasing efficacy, or vice versa. Whereas the orthosteric location is where endogenous agonists bind. Modulators do not bind to this location. They attach to any additional appropriate locations, known as allosteric sites. Upon binding, modulators often alter the receptor's conformation or three-dimensional structure. One of a receptor's typical configurations can be stabilized by allosteric modulators. Modulators alter the tissue's natural reactions and enable the targeting of certain areas with drugs.

7. Applications of Drug-Receptor Complexes

Drug receptor complexes are widely used in the development and discovery of drugs, pharmacogenetics, and personalized medicine. The Drug discovery and development processes depend on an understanding of the composition and operation of drug-receptor complexes. Researchers can discover prospective therapeutic targets and create medications that precisely bind to these targets by analyzing these complexes. This information can enhance the effectiveness and security of new medications. A person's response to medication is influenced by genetic differences. Drug receptor complexes are crucial in this area because they shed light on how genetic variants alter the way that drug targets operate. Personalized treatment plans that take into consideration a patient's unique genetic makeup can be created using this information.

A new field called personalized medicine tries to modify medical procedures to fit the specific needs of every patient. Drug receptor complexes are a crucial part of personalized medicine as well because they reveal how medications interact with body receptors. Using this data, treatment programmes may be created that are unique to each patient's needs and requirements. In conclusion, pharmacogenetics, personalised medicine, and drug discovery and development all rely heavily on drug-receptor complexes. Researchers can create more effective and individualised treatments for a variety of diseases and ailments by knowing the framework and operation of these complexes. A robust knowledge of pharmacodynamics (PD), pharmacokinetics (PK), and PGx is necessary to properly develop personalized dosage regimens for patients. Absorption, distribution, metabolism, and excretion (ADME) are the steps that each medicine takes when it enters the body. The result of all these activities is PK, which establishes the quantity of the drug required to reach the site of action and produce a successful therapeutic result. All computational research and drug designing rely on the drug target complex to determine the affinity, effectiveness, and potency of a drug-like molecule when it interacts with a target molecule. Therefore, a key factor in the development of a therapeutic candidate is to analyze the structure of a drug-receptor complex.

8. Future Directions and Challenges

The future of molecular pharmacology is poised for transformative advancements, particularly in the structural analysis of drug-receptor complexes. Techniques like cryo-electron microscopy, nuclear magnetic resonance (NMR) spectroscopy, and X-ray crystallography are being refined to achieve higher precision, enabling researchers to gain deeper insights into complex molecular interactions. Simultaneously, innovative approaches such as fluorescent markers and advanced spectroscopic methods are being developed to visualize and quantify the conformational changes induced by drug binding, which are critical for understanding drug efficacy and selectivity. The study of binding kinetics remains a focal area, with techniques like surface plasmon resonance (SPR) and isothermal titration calorimetry (ITC) becoming increasingly sophisticated. These advancements aim to unravel the mechanisms of drug interactions, including binding rates and affinities.

Another promising avenue lies in allosteric modulation, where researchers are identifying novel allosteric sites and designing drugs that specifically target these regions, potentially leading to highly selective therapies with minimal side effects. Moreover, computational modeling is anticipated to play a vital role in addressing the growing complexity of drug-receptor systems. The development of advanced algorithms and software tools will enhance predictions of drug efficacy and toxicity, accelerating the creation of next-generation pharmaceuticals. Together, these advancements mark an exciting future for molecular pharmacology, with the potential to revolutionize therapeutic approaches and improve patient outcomes.

9. Conclusion

The field of molecular pharmacology is poised for significant advancements, driven by innovations in structural biology, biophysics, and computational modeling. However, challenges such as obtaining high-resolution structures, analyzing conformational changes, and understanding allosteric interactions remain. By addressing these obstacles, researchers can deepen our understanding of drug mechanisms, paving the way for novel therapies that improve patient outcomes and expand the frontiers of medicine.

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Conflict of interest

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