Unit IV: Pharmacodynamics:

Receptors and receptors subtypes

A receptor can be defined loosely as 'a macromolecule in the membrane or inside the cell that recognizes specifically (chemically) a second small molecule (ligand/drug) whose binding brings about the regulation of a cellular process…in the unbound state a receptor is functionally silent'. This definition states that a receptor binds specifically a particular ligand (e.g. bombesin binds to bombesin receptors and not vanilloid receptors) but in reality selectivity is a more accurate definition as in some cases high concentrations of ligands will bind to multiple receptor types.

The binding of a drug to receptor depends on types of chemical bonds that can be established between drug and receptor. The strength of this chemical bonds (covalent, ionic, hydrogen, hydrophobic) determine the degree of affinity of ligand to receptor.

Ligands (drugs) that attracted the receptors may be classified as

1) **Agonists** and
2) **Antagonists**.

Agonists produce the biological response as a results of receptor –ligand interactions therefore agonists posses efficacy. On the contrary antagonists did not provoke any biological activity after binding to its receptor.

There are different types of receptors:

1. **Transmembrane ion-channels receptors**
2. **Transmembrane G-protein-coupled receptors**
3. **Transmembrane receptors with cytosolic domain**
4. **Intracellular (cytoplasm or nucleus) receptors**

1) Transmembrane ion-channels receptors

The most rapid cellular responses to receptor activation are mediated via **ligand-gated ion channels**. These kind of transmembrane receptors composed of multiple peptide subunits and each of it contains four membrane-spanning domains (Figure 1).

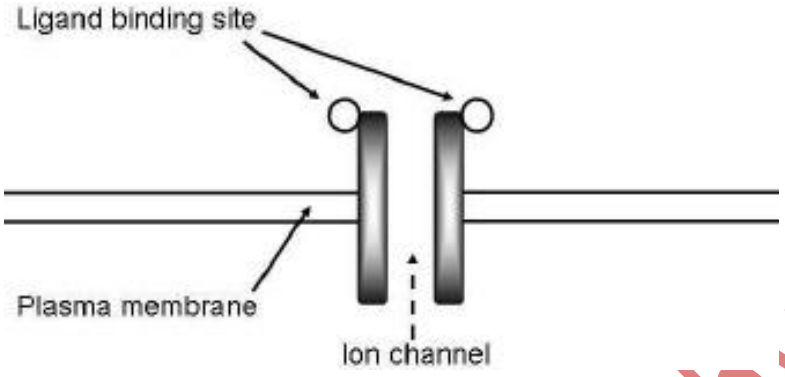

Figure 1: Ion-channel receptors

The ligand binding causes the conformational changes of receptor and ion channel forming. The binding of acetyl choline (Ach) to each of four subunits of acetyl choline receptor (AchR) induces change in receptor and opening the sodium selective channel through the centre of the receptor protein. It causes the depolarisation of surrounding membrane. In this type of receptors belong nicotinic acetylcholine receptors and receptors for GABA, serotonine and some other neurotransmitters.

2) Transmembrane G-protein-coupled receptors

The most abundant type of drug receptors are **G-protein coupled receptors** (GPCR). This are family of (over 100 different) transmembrane receptors which share a well conserved structure and transduce their signals via activation of intracellular guanidine nucleotide binding protein (G-protein) (Figure 2). A variety of ligands for these receptors include biogenic amines (Ach, noradrenalin, serotonin), amino acid neurotransmitters (glutamat, glycine) and

peptide hormones (angiotensinII, somatostatin). There are multiple GPCR types for a single ligand. The result is the possibility that single ligand can activate a variety of transduction pathways. Thus receptor is defined not only just by which ligands binds to it but also by second messenger systems (cAMP, PLC, Na/H exchange) and signal transduction pathway, which is activated by receptor activation.

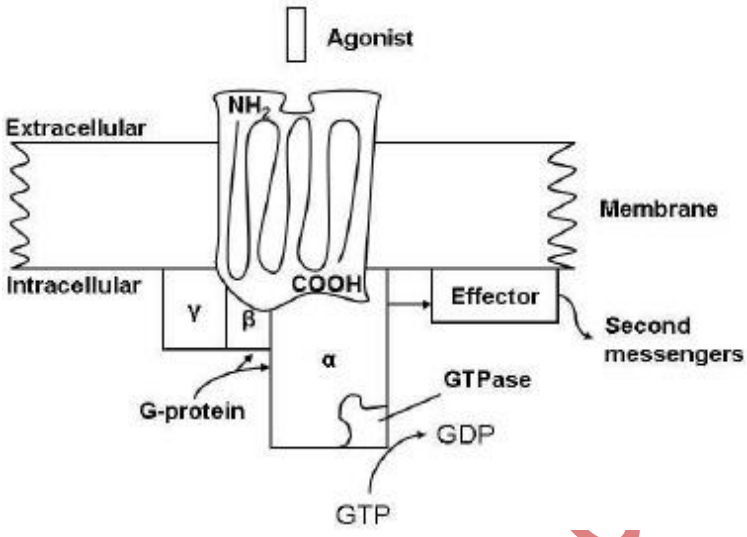

Figure 2: G-protein coupled receptors

3) Transmembrane receptors with cytosolic domain

This receptor is also known as **tyrosine kinase coupled**. The intracellular domain of this transmembrane receptor is either enzymatic active (catalytic receptors) or is bound to specific enzyme(s) in cytosol (enzyme coupled receptors). The catalytic receptors are activated predominantly by peptide hormones (insulin, growth factors, etc). Catalytic part of receptors has the protein kinase activity. Mostly dimerisation of catalytic as well as enzyme-coupled receptors is necessary for kinase activity. Phosphorilation of intracellular proteins by these receptors results in effects such as opening the ion channels, initiation of gene expression or as in the case of enzyme coupled receptors activation of signal transducers and activators like JAKs and STATs.

4) Intracellular (cytoplasm or nucleus) receptors

This is also known as **intracellular steroid receptor**. Those receptors are not associated with cell membrane. In general their protein molecule consists from three main domains: Hsp-90 and DNA and ligand binding domains. Ligands are mostly lipid soluble and passively pass cell memmbrane. Agonists include nitric oxide, steroid hormones and vitamin D. Ligand binding activates receptor and initiates the dissociation from Hsp-90. The complex then translocates to nucleus and bind to specific DNA sequences mostly located in gene promoter region (Figure 3). This kind of signal tranduction is slow, but duration of response can last long.

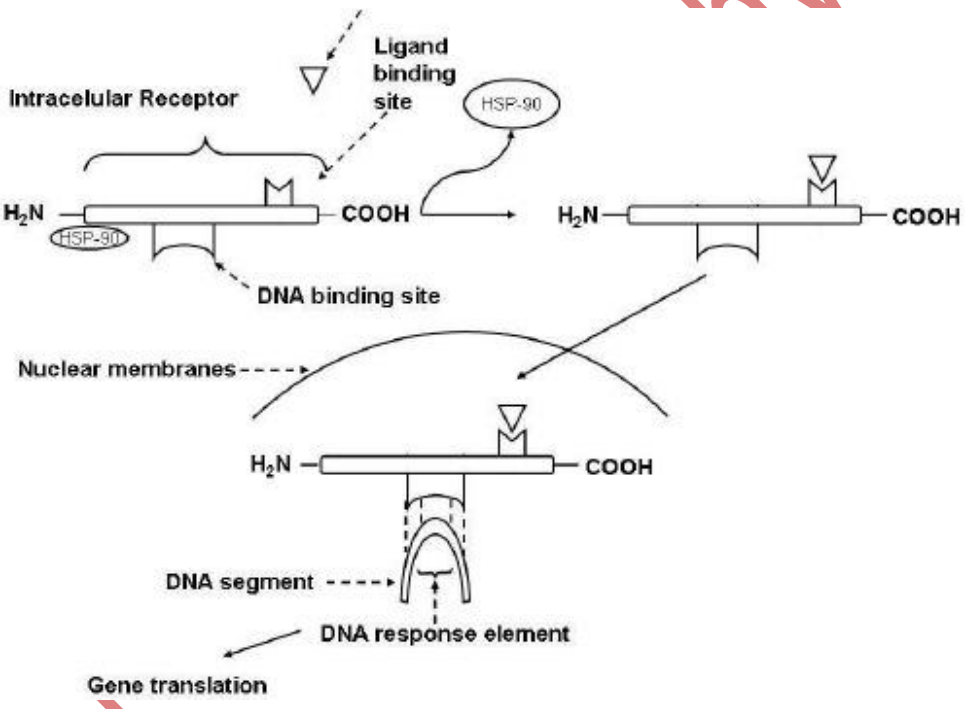

Figure 3: Schemes of nuclear receptors function

Table 1: Basic receptor characteristics

	LGIC	**TRK**	**Steroid**	**GPCR**
Location	Membrane	Membrane	Intracellular	Membrane
Main action	Ion flux	Phosphorylation	Gene transcription	2nd messengers
Example/drug	Nicotinic/NMBD	Insulin/insulin	Steroid/thyroxine	Opioid/morphine
	NMDA/ketamine	Growth factor/EGF	Steroid/oestrogen	Adrenoceptor/isoprenaline

LGIC = ligand-gated ion channel; TRK = tyrosine kinase coupled; GPCR = G-protein-coupled receptor; NMBD = neuromuscular blocking drugs; NMDA = *N*-methyl-D-aspartate; EGF = epidermal growth factor.