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Review Article

A REVIEW ON RECEPTORS

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Abstract

A molecule that binds to a receptor is called a ligand, and can be a peptide or another small molecule such as a neurotransmitter, hormone, pharmaceutical drug, toxin, or parts of the outside of a virus or microbe. Regardless of the nature of the initiating signal, the cellular responses are determined by the presence of receptors that specifically bind the signaling molecules. Binding of signal molecules causes a conformational change in the receptor, which then triggers the subsequent signaling cascade. A large number of these receptors have been identified and are grouped into three families defined by the mechanism used to transduce signal binding into a cellular response. **Categories of cellular receptors:** Membrane-impermeant signaling molecules can bind to and activate either channel linked receptors, enzyme linked receptors, or G protein coupled receptors. Membrane permeant signaling molecules activate intracellular. The cholinergic receptors includes muscarinic and nicotinic receptors and also adnergic, histaminic, prostanoid, dopamine, opiod, imidazoline receptors used in the various activity in the body.

Key Words: receptors, enzyme & channel linked receptors, cholinergic, adnergic, dopamine.

Introduction: In biochemistry and pharmacology, a receptor is a protein-molecule that receives chemical-signals from outside a cell. When such chemical-signals bind to a receptor, they cause some form of cellular/tissue-response, e.g. a change in the electrical-activity of a cell. In this sense, a receptor is a protein-molecule that recognises and responds to endogenous-chemical signals, e.g. an acetylcholine-receptor recognizes and responds to its endogenous-ligand, acetylcholine[1]. However, sometimes in pharmacology, the term is also used to include other proteins that are drug targets, such as enzymes, transporters and ion channels. Receptor proteins are embedded in all cells' plasmatic membranes; facing extracellular, cytoplasmic, or in the nucleus. A molecule that binds to a receptor is called a ligand, and can be a peptide or another small molecule such as a neurotransmitter, hormone, pharmaceutical-drug, toxin, or parts of the outside of a virus or microbe. While numerous receptors are found in most cells, each receptor will only bind with ligands of a particular structure, much like how locks will only accept specifically shaped keys. When a ligand binds to its corresponding receptor, it activates or inhibits the receptor's associated biochemical pathway. The structures of receptors are very diverse and can broadly be classified into the following categories:

Type 1: Lonotropic receptors: These receptors are typically the targets of fast-neurotransmitters such as acetylcholine and GABA activation of these receptors results in changes in ion-movement across a membrane[2]. They have a hetero structure. Each subunit consists of the extracellular ligand binding domain and a transmembrane domain where the transmembrane domain in turn includes four transmembrane alpha helixes. The ligand-binding cavities are located at the interface between the subunits.

Type 2: G protein-coupled receptors: This is the largest family of receptors and includes the receptors for several hormones and slow transmitters e.g. dopamine, metabotropic-glutamate. They are composed of seven transmembrane alpha helices. The loops connecting the alpha-helices form extracellular and intracellular domains[3]. The binding-site for larger peptidic ligands is usually located in the extracellular domain whereas the binding-site for smaller non peptidic ligands is often located between the seven alpha-helices and one extracel-

lular loop. The aforementioned receptors are coupled to different intracellular effector systems via G proteins.

Type 3: Kinase linked and related receptors: Receptor tyrosine kinase, and Enzyme linked receptor They are composed of an extracellular domain containing the ligand binding site and an intracellular domain, often with enzymatic function, linked by a single transmembrane alpha helix. e.g. the insulin receptor [4].

Type 4: Nuclear receptors: While they are called nuclear-receptors, they are actually located in the cytosol and migrate to the nucleus after binding with their ligands. They are composed of a C terminal ligand binding region, a core DNA binding domain and an N terminal domain that contains the activation function region. The core region has two zinc fingers that are responsible for recognising the DNA sequences specific to this receptor. The N terminal interacts with other cellular-transcription factors in a ligand independent manner and depending on these interactions it can modify the binding/activity of the receptor [5].

Receptor Types: Regardless of the nature of the initiating signal, the cellular responses are determined by the presence of receptors that specifically bind the signaling molecules. Binding of signal molecules causes a conformational change in the receptor, which then triggers the subsequent signaling cascade. Given that chemical signals can act either at the plasma membrane or within the cytoplasm of the target cell, it is not surprising that receptors are found on both sides of the plasma membrane [6]. The receptors for impermeant signal molecules are membrane-spanning proteins that include components both outside and inside the cell surface. The extracellular domain of such receptors includes the binding site for the signal, while the intracellular domain activates intracellular signaling cascades after the signal binds. A large number of these receptors have been identified and are grouped into three families defined by the mechanism used to transduce signal binding into a cellular response.

Receptor Types: Regardless of the nature of the initiating signal, the cellular responses are determined by the presence of receptors that specifically bind the signaling molecules. Binding of signal molecules causes a conformational change in the receptor, which then triggers the subsequent signaling cascade [7]. The receptors for impermeant signal molecules are membrane-spanning proteins that include components both outside and inside the cell surface. The extracellular domain of such receptors includes the binding site for the signal, while the intracellular domain activates intracellular signaling cascades after the signal binds. A large number of these receptors have been identified and are grouped into three families defined by the mechanism used to transduce signal binding into a cellular response. Categories of cellular receptors. Membrane-impermeant signaling molecules can bind to and activate either channel-linked receptors (A), enzyme-linked receptors (B), or G-protein-coupled receptors (C). Membrane permeant signaling molecules activate intracellular.

Channel linked receptors also called ligand-gated ion channels have the receptor and transducing functions as part of the same protein molecule. Interaction of the chemical signal with the binding site of the receptor causes the opening or closing of an ion channel pore in another part of the same molecule [8]. The resulting ion flux changes the membrane potential of the target cell and, in some cases, can also lead to entry of Ca^{2+} ions that serve as a second messenger signal within the cell. Good examples of such receptors are the neurotransmitter receptors.

Enzyme linked receptors also have an extracellular binding site for chemical signals. The intracellular domain of such receptors is an enzyme whose catalytic activity is regulated by the binding of an extracellular signal [9]. The great majority of these receptors are protein kinases, often tyrosine kinases, that phosphorylate intracellular target proteins, thereby changing the physiological function of the target cells.

G-protein-coupled receptors regulate intracellular reactions by an indirect mechanism involving an intermediate transducing molecule, called the GTP-binding protein. Because these receptors all share the structural feature of crossing the plasma membrane seven times, they are also referred to as 7 transmembrane receptors. Hundreds of different

G-protein-linked receptors have been identified. Well known examples include the β-adrenergic receptor, the muscarininc type of acetylcholine receptor, metabotropic glutamate receptors, receptors for odorants in the olfactory system, and many types of receptors for peptide hormones [10].

Intracellular receptors are activated by cell permeant or lipophilic signaling molecules. Many of these receptors lead to the activation of signaling cascades that produce new mRNA and protein within the target cell. Often such receptors comprise a receptor protein bound to an inhibitory protein complex. When the signaling molecule binds to the receptor, the inhibitory complex dissociates to expose a DNA-binding domain on the receptor [11]. This activated form of the receptor can then move into the nucleus and directly interact with nuclear DNA, resulting in altered transcription. Some intracellular receptors are located primarily in the cytoplasm, while others are in the nucleus. In either case, once these receptors are activated they can affect gene expression by altering DNA transcription.

P1 receptors: In 1989, complementary DNAs encoding two different P1 receptor subtypes (A1 and A2) were isolated, and, shortly after, the A3 subtype was identified. Four different P1 receptor subtypes, A1, A2A, A2B and A3, have been cloned and characterised. All are members of the rhodopsin-like family of G protein-coupled receptors. Their Ntermini are relatively short as are their C termini. In the transmembrane domains (TMI-TMVII), human adenosine receptors share 39 to 61% sequence identity with each other and 11 – 18% identity with P2Y receptors. Each of the four human P1 receptor genes contains an intron within the coding region, located immediately after the end of the third transmembrane domain. Polymorphisms have been observed in theA1 and the A2A receptors. P1 receptors couple principally to adenylate cyclase [12]. A1 andA3 are negatively coupled to adenylate cyclase through the Gi/o protein a subunits, whereas A2A and A2B are positively coupled to adenylate cyclase through G.

P2X receptors: The firstcDNAs encoding P2X receptor subunits were isolated in 1994. Members of the family of ionotropic P2X1–7 receptors show a subunit topology of intracellular N- and C-termini possessing consensus binding motifs for protein kinases; two transmembranespanning regions, the first involved with channel gating and the second lining the ion pore; a large extracellular loop, with 10 conserved cysteine residues forming a series of disulfide bridges; a hydrophobic H5 region close to the pore vestibule, for possible receptor/channel modulation by cations and anATP-binding site, which may involve regions of the extracellular loop adjacent to TM1 and TM2. The P2X1 7 receptors show 30– 50% sequence identity at the peptide level [13]. The stoichiometry of P2X1 7 receptors is thought to involve three subunits, which form a stretched trimer or a hexamer of conjoined trimers. The pharmacology of the recombinant P2X receptor subtypes expressed in oocytes or other cell types is often different from the pharmacology of P2X-mediated responses in naturally occurring sites. Several contributing factors may account for these differences.Recent advances have been made by the preparation of knockout mice for P2X1, P2X2, P2X3, P2X4 and P2X7 receptors, and transgenic mice that overexpress the P2X1 receptor.

Cholinoceptors: They are two types Muscarinic, Nicotinic

Muscarinic Receptors: The Muscarinic receptors includes Subtypes: M1, M2, M3, M4, M5. These receptors are selectively stimulated by muscarine and blocked by atropine. They are located primarily on autonomic effector cells in heart, blood vessels, eye, smooth muscles and glands of gastrointestinal, respiratory and urinary tracts, sweat glands etc. in the CNS [14].

M1: The M1 plays a major role in mediating gastrisecretion,relaxation of lower esophageal shinter caused by vagal stimulation and in learning, memory, motor functions etc.

M2 Receptors:

LOCATION	FUNCTION
SA-node	Hyperpolarization- decreases rate of impulse generation
AV-node	Decreses velocity of conduction
Atrium	Shortening of action potential duration,decreses contractility
Ventricle	Decreses contractili-

	ty(slight)(receptors sparse)
Cholinergic nerve endings	Decreses Ach release
Cns	Tremor,analgesia
Visceral smooth muscle	Contraction

M3:

LOCATION	FUNCTION
Visceral smooth muscle	Contraction
Iris	Constriction of pupil
Ciliary muscle	Contraction
Exocrine glands	Secretion
Vascular endothelium	Vasodilation

NICOTINIC RECEPTORS: These receptors are selectively activated by nicotine and blocked by tubocuranine or hexamethonium. Sub types – Nm,Nn.

Nm:

LOCATION	FUNTION
Neuromuscular junction	Contraction

Nn:

LOCATION	FUNCTION
Autonomic ganglia	Depolarisation
Adrenal medulla	Catecholamine relese
Cns	Site specific excitation or inhibition

DISEASES TRETED BY TARGETING M AND N RECEPTORS:

By using anticholinestarases: It is used in the treatment of Miosis, Myasthenia gravis, Urinary retention, Cobra bite, Belladonna poisoning, Other drug overdosages like tricyclic antidepressants, phenothiazines, etc., Alzheimers disease [15].

BY USING ANTICHOLINERGIC DRUGS AND DRUGS ACTING ON AUTONOMIC GANGLIA:

AS ANTISECRETORY: Paranaesthetic medication, Peptic ulcer, Pulmonary embolism, As antispasmodic, Bronchial asthma , asthmatic bronchitis , COPD, As mydriatic and cycloplegi. As cardiac vagolytic, For central action, To antagonize muscarinic effects of drugs and poisons [16].

ADRENERGIC RECEPTORS: These are membrane bound G-protein coupled receptors.Which function primarily by increasing or decreasing the intracellular production of second messengers C-AMP or IP3/DAG. Ahlquist (1948) , on the basis of two distinct rank order of potencies of adrenergic agonists , classified adrenergic receptors into two types [17]

1. ALPHA (α)
2. BETA (β)

BY USING ADRENERGIC DRUGS:

THERAPEUTIC USES [18]:

1. Vascular uses: Hypotensive states, Along with local anaesthetic, Control of local bleeding, Nasal decongestant:- In cold, rhinitis, sinusitis, blocked nose or eustactrian tube-one of the alpha agonist is used as nasal drops, Peripheral vascular diseases.
2. Cardiac uses: Cardiac arrest, Partial or complete A-V block, Congestive heart failure (CHF)
Bronchial asthma and COPD, Allergic disorders, Mydriatic.
3.Cental uses: Attention deficit hyper kinetic disorder (ADHD), Narcolepsy Epilepsy, Parkinsonism, Obesity.
4.Uterine relaxant
5. Insulin hypo glycaemia

BY USING ANTI ADRENERGIC DRUG:

α- Adrenergic blocking drugs:

Use of α- blocking: Pheochromocytoma, Hypertension, Benign hypertrophy of prostate (BHP), Secondary shock – shock due to blood or fluid loss is accompanied by reflex vasoconstriction, Peripheral vascular diseases, Congestive heart failure (CHF), Papavarine/phenotolamine induced penile erection (PIPE) therapy for importences [19].

β- Adrenergic blocking drugs:

Uses of β blockers: Hypertension, Anginapectoris, Cardiac arrhythmias, Myocardial infarction (M_1), Congestive heart failure, Dissecting aortic aneurysm -β- blockers help by reducing cardiac contractile force and aortic pulsation. Thyrotoxicosis – propranolol rapidly controls the sympathetic symptoms (palpitation, nervous ness, tremor, fixed stare, severe myopathy and sweeting) without significantly affecting thyroid status, Migraine, Anxiety, Essential tremor, Glaucoma, Hypertrophic obstructive cardiomyopathy.

HISTAMINE RECEPTORS: The Four types of histaminergic receptors have now been clearly delineated and cloned [20]. Histaminergic receptors were classified by asch and schild (1966) into H1 and H2, H3 receptor , which serves primarily as an auto receptor controlling histamine release from neurons in brain was identified in 1983. Molecular cloning has revealed yet another (H4) receptor in 2001. Eosinophils, mast cells and basophils are the primary cells expressing H4 receptors. Activation of H4 receptors enhances chemotaxis of these cells. The receptor may be playing a role in allergic inflammation. H4 antagonists are being explored as potential drugs for allergic inflammatory conditions like rhinitis and asthma. Intestines and brain are the other sites where H4receptors have been located.

ALPHA (A)RECEPTORS:

	ALPHA 1	**ALPHA 2**
LOCATION	Postjunctional on effector Organs	Prejunctional on nerve ending (alpha 2A) , also postjuctional in brain , pancreatic beta cells and extrajunctional in certain blood vessels , platelets.
FUNCTION OBSERVED	GU smooth muscle contration , vasocontraction , gland-secretion , gut –relaxation, liver –glycogenolysis , heart-arrythmia	Inhibition of transmitter , release vasoconstriction ,decreased central sympathetic flow , decreased insulin release , platelet aggregation.

BETA (β) RECEPTORS:

	BETE 1	BETA 2	BETA 3
LOCATION	Heart , JG cells in kidney	Bronchi , blood vessels , uterus , liver , GIT , urinary tract , eye.	Adipose tissue

	H1	H2	H3
Distribution in body and actions mediated	a)smooth muscle (intestine,air way, uterus)-contraction b)blood vessels: i)Endothelium: Release of NO and PGI_2vasodilatation. Widening of gap junctions-increased capillary permeability. ii) Smooth muscle of larger vessels-vasoconstriction. c) Afferent nerve ending-stimulation d) Ganglionic cell- stimulation. e) Adrenal medulla- release of CAs. f) Brain- transmitter.	a) Gastric glands- acid secretion b) Blood vessels (smooth muscle)- dilation. c) Heart Atria: +ive chornotropy. Ventricles: +ive inotropy d) Uterus (rat)-relaxation e) Brain- transmitter.	a) Brain (presynaptically)- inhibition of histamine release- sedation b) Lung, spleen, skin, gastric mucosa- decrease histamine release. c) Ileum- inhibition of Ach release from myenteric plexus neurons. d) Certain blood vessels-inhibit NA release- vasodilation.

H_1 ANTAGONIST:

Uses: Allergic disorder, Other conditions improving histamine, Pruritides, Common cold, Motion sickness, Vertigo, Preanaesthetic medication, Cough, Parkinsonism, Acute muscle dystonia, As sedative, hypnotic, auxiolytic.

H_2 ANTAGONIST [21]:

Uses: Peptic ulcer, Gastro esophageal reflux and other gastric hyper secretory states, Duodenal ulcer, Gastric ulcer, Stress ulcer&gastritis, Zollinger-ellisim syndrome, Gastro esophageal reflux diseases (GERD), Prophylaxis of aspiration pneumonia

SEROTONERGIC (5-HT) RECEPTORS: Gaddum & picarelli (1957) classified 5-HT receptor into musculotropic (D type) and neurotropic (M type) based on their blocked by dibentyline (phenoxy benzamine) and morphine. Four families of 5-HT receptors (5-HT_1,5-HT_2, 5-HT_3,5-$HT_{4\text{-}7}$,) comprising 14 receptors subtypes have so far been recognized. All 5-HT receptors (except 5-HT_3) are G- protein coupled receptor which function through decreasing (5-HT_1)or increasing (5-HT_4,5-HT_6, 5-HT_7) CAMP production or by generating IP_3/ DAG (5-HT_2) as second messengers [22]. The 5-HT_3 is a ligand gated cation (Na^+, K^+) channel which on activation elicits fast depolarization.

5-HT_1 receptor: Five subtypes (5-$HT_{1A, B, D, E, F}$) have been identified. The most important location of 5-HT_{1A}, receptor is somato dendritic synapses in raphe nuclei of brain stem, their activation serves to reduce firing of raphe neurons. Hippocamps is auother important site. The 5-$HT_{1D/1B}$ to cause constriction of cranial blood vessels.

5-HT_2 receptor: There are three sub types of 5HT_2 receptors. The 5HT_{2A} is the most widely expressed post junctional 5-HT receptor located on vascular and visceral smooth muscle, platelets and cerebral neurons especially prefrontal cortex. It mediates most of the direct actions of 5-HT like vasoconstriction intestinal, uterine and bronchial contraction, platelet aggregation and activation of cerebral neurons [23]. Contraction of rat gastric fundus is mediated by 5-HT_{2B} receptor. The 5HT_{2C} receptor is located on vascular endothelium elicits vasodilatation through EDRF release. Choroid plexus expresses large number of 5HT_{2C} receptors which may regulate CSF formation.

5-HT_3 receptors : It mediates the indirect and reflex effects of 5-HT at:

Somatic and autonomic nerve endings pain, itch coronary chemo reflex (bradycardia, fall in BP due to with drawal of sympathetic tone, respiratory stimulation or apnoea elicited by stimulation of receptors in the coronary bed) other visceral reflexes [24]. Nerve endings in myenteric plexess – aumentation of peristatis, emetic reflex. Area postrema and nucles tractus soli tarious in brain stemnausea, vomiting.

5-$HT_{4\text{-}7}$ receptors: It is also located in brain, especially hippocampus and the colliculi where it causes slow depolarization by decreasing k^+ conductance. These are mainly located in specific brain areas, but their functional role is not known.

PROSTANOID RECEPTORS: PGs, TX and prostacyclin act on their own specific receptors located on cell membrane. Five families of prostanoid receptors. All prostanoid receptors are G-protein coupled receptors which can be functionally categorized into excitatory or contractile and inhibitory or relaxant groups [25]. The contractile group EP,FP,TP. The relaxant group DP, EP_2.EP_4 and IP. The major characteristics of subtypes of prostanoid receptors are: **DP**: Two subtypes DP_1 and DP_2 have been identified, but both have limited distribution in the body. **DP_1:** DP_1 is a relaxant receptor which dilates certain blood vessels and inhibits platelet aggregation. This receptor has strongest affinity for PGD_2, but PGE_{2F} can activate it. **DP_2:** The DP_2 receptor couples with G_i protein and inhibits CAMP generation. This receptor is characterized by highest affinity for PGE_2. Four subtypes have recognized:

EP_1: Ep_1 is a contractile receptor- contracts visceral smooth muscle, but is less abundant in the body. EP_2 and EP_4 are relaxant in nature ,act by increasing CAMP in smooth muscle, but the same second messenger enhances Cl^- and water secretion by the intestinal mucosa. While EP_2 is present in present in two organs, EP_4 has wide distribution [26]. EP3: EP3 is inhibitory, decreases CAMP generation by coupling wiyh G_i protein.Distribution of PGE3 receptor in the body is wide. FP: This contractile receptor is highly expressed in the female genital tract, and is present in many other organs. It exhibits strong affinity for $PGE_{2\alpha}$

IP: This relaxant receptor is defined by highest affinity for PGE_2, But PGE_2 also acts on it. It is expressed in heart, lungs, kidney, platelets (antiag-

gregatory) etc. But the highest is in the vasculature. TP: Charecterized by high affinity for $T_{XA2\gamma}$ this contractile receptor is abundant in platelets (aggregatory), cardiovascular system, immune cells and many other organs. PGH_2 can also activate TP.

LEUCOTRIENE RECEPTORS : Two subtypes $cysLT_1$ and $cysLT_2$ of the cysteinyl LT receptor have been cloned. Separate receptors for LTB_4(BLT_1 and BLT_2) and for cysteinly LTS(LTC_4,LTD_4) have been defined.

The $cysLT_1$ receptor is mainly expressed in bronchial and intestinal muscle and has higher affinity for LTC_4. The primary location of $cysLT_2$ receptor is leucocytes and spleen.

USES : Priming(ripening), Postpartum haemorrhage(PPH), Peptic ulcer, Glaucoma, To maintain patency of ductus arteriosus, To avoid platelet damage, Asthma.

CANNABINOID RECEPTORS: 1990 teo cannabinoid receptors CB1 (in CNS) and CB2 (in peripheral tissues) have been identified and cloned.

DOPAMINE RECEPTORS: Two sub types of DA receptors (D_1,D_2) were originally described. Three more (D_3,D_4,D_5) have now been identified and cloned. All are G-protein coupled receptors and are grouped into two families. D_1 like (D_1, D_2) are excitatory: act by increasing CAMP formation and PIP_2 hydrolysis there by mobilizing intracellular ca^{+2} and activating protein kinase C through IP_3 and DAG. D_2 like (D_3, D_4, and D_5) are inhibitory: act by inhibiting adenyllyl cyclase/opening K^+ channels/ depressing voltage sensitive ca^{+2} channels [27]. The various subtypes of DA receptors are differentially expressed in differentent areas of the brain, and appear to play distinct roles. The dopamine receptor in SN-PC and in pituitary is also of D_2 type. The D_3 receptors predominate in nucleus accumbans and hypothalamus, but are sparse in caudate and putamen, while D_4 and D_5 are mostly distributed in neocortex, midbrain, medulla and hippocampus.

OPIOID RECEPTOR: Morphine and other opioids exert their action by interacting with specific receptors present on neurons in the CNS and in peripheral tissues. Radioligand binding studies divided the opioid receptors into three types (μ, *k, and δ*). Each has a specific pharmacological profile and pattern of anatomicaldistribution in the brain, spinal card and peripheral tissues (mainly gut, blood vessels, heart, lungs and immune cells) [28].

μ- receptor:- The μ-receptor is characterized by its high affinity for morphine. High density of μ receptor has been detected in periaqueductal gray, thalamus, and nucleus tractus solitarious, nucleus ambiguces and area postrema. Two subtypes of μ receptor have been proposed:-

$\mu_1$receptor: This has higher affinity for morphine, mediates super spinal analgesia and is selectively blocked by naloxonazine.

$\mu_2$receptor: This has lower affinity for morphine, mediates spinal analgesia, respiratory depression and constipating action.

***K* receptor:-** Two subtypes of *K* receptor k_1 and k_3 are functionally important. Analgesia caused by k-against is primarily spinal (through k_1 receptor). However, k_3 receptors mediate lower ceiling supraspinal analgesia [29].

δ-receptor:- The limbic areas are rich in δ receptor, suggesting role of these receptor in the affective component of supraspinal analgesia, reinforcing action and dependences. It thus appears that μ and δ receptor responses are quite similar, but those exerted through k receptors are distinct. In certain areas k actions are antagonistic to μ actions [30].

σ (Sigma) receptor: The σsigma receptor is no longer considered and Opioid receptor, because it is neither activated by morphine nor blocked by naloxone.

EGF (EPIDERMAL GROWTH FACTOR RECEPTOR):- Epidermal growth factor (EGF) receptor is a transmembrane receptor-tyrosine - kinase which regulates growth and differentiation of epidermal cells. Binding of ligand (EGF) to the extracellular domain of the receptor induces dimerization leading to activation of tyrosine kinase activity of the intracellular domain auto phosphorylation of the kinase and phosphorylation of several cytoplasmic regulatory proteins which modify gene transcription to regulate growth [31]. Certain epithelial cancers over express EGF receptors are have an active EGFR mutation, and their growth is critically dependent upon activation of this receptors.

GABA receptor:- The GABA receptors have been divided into: $GABA_A$ receptor : Intrinsic in channel receptor which increases cl^- conductance; blocked by bicuculline ; facilitated by BZD's. $GABA_B$ receptor : G-protein coupled receptor ; hyperpolarizes neurons by increasing K^+ conductance and altering ca^{+2} flux. USES: Acute muscle spasms, Torticollis, lumbago, backache, neuralgias, Anxiety and ten-

sion, Spastic neurological diseases, Tetanus, Electroconvulsive therapy, Orthopedic manipulations [32].

ESTROGEN RECEPTORS: The recent discovery of two estrogen receptors (ER_α and ER_β).

Antiestrogens: USES: To aid in vitro fertilization, Oligozoospermia.

SELECTIVE ESTROGEN RECEPTOR MODULATORS (SERMS) :

USES: Treatment of osteoporosis in postmenopausal women, Alternative option for secondary prevention and treatment of vertebral fractures i.e. in those who have already suffered a fracture

ANGIOTENSIN RECEPTORS: There is two types angiotensin receptors AT_1, AT_2.

Uses of ARB's: CHF, Myocardial infraction, Diabetic nephropathy, Hypertension.

DOPAMINE RECEPTOR [33]: Two subtypes of DA receptors (D_1, D_2) were originally described. Three more (D_3,D_4,D_5)have now been identified and cloned. All are G protein coupled receptors and are grouped into two families: D_1 like (D_1, D_2) are excitatory: act by increasing cAMP formation and PIP_2 hydrolysis thereby mobilizing intracellular ca^{2+} and activating protein kinase C through IP_3 and DAG. D_2 like (D_2, D_3, D_4) are inhibitory: act by inhibiting adenylyl cyclase/depressing voltage sensitive ca^{2+} channels.

The various subtypes of DA receptors are differentially expressed in different areas of the brain, and appear to play distinct roles.Both D_1 and D_2 receptors are present in the striatum and are involved in the therapeutic response to levodopa. They respectively regulate the activity of two pathways having opposite effects on the thalamic input to the motor cortex. Thus, stimulation of excitatory D_1 as well as inhibitory D_2 receptors in the striatum achieves the same net effect of smoothening movements and reducing muscle tone. Dopamine receptor in sn-pc and in pituitary is also of D_2 type. The D_3 receptors predominate in nucleus accumbans and hypothalamus, but are sparse in caudate and putamen, while D_4 and D_5 are mostly distributed in neocortex, midbrain, medulla and hippocampus.

IMIDAZOLINE RECEPTORS [34]: Imidazoline receptors which are distinct from α_2 receptors and are present in the brain as well as periphery. Activation of medullary imidazoline receptors also causes dcreased sympathetic outflow and fall in BP.

USES: Central sympatholytics acts on it, Antihypertension, Clonidine: opioid withdrawal,alcohol withdrawal and smoking cessation,analgesic activity. Clonidine attenuates vasomotor symptoms of menopausal syndrome. Clonidine has been used to control loose motions due to diabetic neuropathy.

INSULIN RECEPTORS: Insulin acts on specific receptors located on the cell membrane of practically every cell, but their density depends on the cell type: liver and fat cells are very rich. The insulin receptor is a receptor tyrosine kinase (RTK) which is heterotetrameric glycoprotein consisting of 2 extracellular α and 2 tranmembrane β subunits linked together by disulfide bonds. It is oriented across the cell membrane as a heterodimer. The α subunits carry insulin binding sites, while the β subunits have tyrosine protein kinase activity.

USES: Diabetes mellitus, Diabetic coma, Hyperosmolar coma

KININ RECEPTORS: The Existence of two types of kinin receptors (B_1, B_2) has been established. Bradykinin and kallidin are metabolites generated by action of kininase I are selective agonists of B_1 receptor. Most of the kinin actions in noninflamed tissues are mediated by B_2 receptors which are constitutively present on: Visceral smooth muscle-contraction of intestine,uterus,airway. Vascular endothelium- NO release, vasodilatation, increased permeability. Sensory nerves- acute pain.

The B_2 receptor is a GPCR coupled to Gq and Gi proteins. Endothelial NO synthase is activated causing vasodilation. Certain responses to kinins, e.g. bronchoconstriction and renal vasodilatation are attenuated by pretreatment with PG synthesis inhibitors (aspirin). Kinin induced acute pain involves B_2 receptors. These responses are mediated by phospholipase A activation- release of arachidonic acid and generation of PGs. The activated Gq protein also mediates production of and triggering of MAP kinase pathway leading to generation of proinflammatory mediators. The B_1 receptor is located on the smooth muscle of large arteries and veins- mediates contraction of these vessels, but is expressed minimally in normal tissues. Inflammation induces synthesis of B1 receptors. Activated B_1receptor also transduces through Gq and Gi proteins and produces similar responses, especially enhanced PG synthesis, leukocyte recruitment, activation of inducible NOS and chronic pain in inflamed tissues.

PATHOPHYSIOLOGICAL ROLE OF KININS [35]: Mediation of inflammation, Mediation of pain, Functional hyperemia, Production of kinins is integrated with clotting, fibrinolysin and complement system, Kinins appear to plays no significant role in the regulation of normal BP. Kinins cause closure of ductus arteriosus, dilatation of foetal pulmonary artery and constriction of umbilical vessels. Kinins play a major role in the devolpment of angioedema.They are also appear to be involved in shock, rhinitis, asthma, ACE inhibitor induced cough, carcinoid, postgastrectomy dumping syndrome, fluid secretion in diarrohea, acute pancreatitis and certain immunological reactions. Because of evanescent and unpleasant actions, kinins have no clinical use.

NK_1 RECEPTOR: Realizing that activation of neurokinin (NK_1) receptor in CTZ and NTS by substance P released due to emetogenic chemotherapy and other stimuli plays a role in the causation of vomiting, selective antagonist of this receptor have been produced, and are being used as antiemetic.

PRORENIN AND (PRO) RENIN RECEPTOR: Prorenin is activated both enzymatically and non-enzymatically. Nonenzymatic and reversible activation occurs by binding of prorenin to another cell surface protein called (pro) renin receptor(PRR), because it binds renin as well. The PRR is richly expressed in heart,blood vessels, kidney, brain,eye and liver. **(pro)** renin receptor (PRR) mediated action of tissue prorenin/renin through angiotensin II (Ang II) dependent and Ang II independent pathways [36] Cell growth, Fibrosis, Apoptosis, Remodeling of myocardium/vascular muscle, Nephropathy, Retinopathy.

RETINOID RECEPTORS: Retinol and retinoic acid act through nuclear retinoid receptors which function in a manner analogous to the steroid receptors: activation results in modulation of protein synthesis. In the target cells(epithelial, gonadal, fibroblast) synthesis of certain proteins is enhanced while that of other proteins is depressed- accounting for the structural and functional changes [37]. Two distinct families of retinoid receptors, viz. Retinoic acid receptors (RARs) and Retinoid X receptors (RXRs) have been identified with differing affinities for different retinoids.

RYANODINE RECEPTOR CALCIUM CHANNEL: Two subtypes of ryanodine receptors are RyR1 and RyR2.

USES: Directly acting muscle relaxants acts on this receptors. Many susceptible subjects have an abnormal RyR1 calcium channel at the sarcoplasmic reticulum of skeletal muscles. This channel is triggered by halothane to release massive amounts of ca^{2+}intracellularly causing persistent muscle contraction and increased heat production. Treatment of congestive heart failure, cardiac arrhythmias

ADH (VASOPRESSIN) RECEPTORS [38]: These are G protein coupled cell membrane receptors; two subtypes V_1 and V_2 have been identified, cloned and structurally characterized.

V_1 receptors: All vasopressin receptors except those on renal CD cells, AscLH cells and vascular endothelium are of the V_1 type. These are further divided into V_{1a} and V_{1b} subtypes:

V_{1a} receptors are present on vascular smooth muscle (including that of vasa recta in renal medulla), uterine and other visceral smooth muscles, interstitial cells in renal medulla, cortical CD cells, adipose tissue, brain, platelets, liver,etc. The V_{1b} receptors are localized to the anterior pituitary, certain areas in brain and in pancreas.

MEDIATED ACTIONS: Vasoconstriction, visceral smooth muscle contraction, glycogenolysis, platelet aggregation, ACTH release, etc. Generation of PGs and other eicosanoids. Growth of vascular smooth muscle and other responsive cells.

V_2 receptors: These are located primarily on the collecting duct (CD) principal cells in the kidney-regulate their water permeability through cAMP production. Some V_2 receptors are also present on AscLH cells which activate $Na^+K^+2Cl^-$ cotransporter. Vasodilatory V_2 receptors are present on endothelium of blood vessels. The V_2 receptors are more sensitive (respond at lower concentrations) to AVP than are V_1 receptors.

USES: Based on V_2 actions: Diabetes insipidus, Bedwetting in children and nocturia in adults. Renal concentration test, Haemophilia, von willebrand's disease. Based on V_1 actions: Bleeding esophageal varices, Before abdominal radiography

GABA RECEPTORS [39]: The GABA receptors have been divided into two types**:** $GABA_A$ receptor, $GABA_B$ receptor

$GABA_A$ receptor: Intrinsic ion channel receptor which increases cl^- conductance : blocked by bicuculline facilitated by BZD's. The $GABA_A$-BZD receptor – cl^- channel complex is composed of five α, β, γ and in some cases δ, ε, θ or π subunits as well.

Several isoforms of α, β and γ subunits have been cloned. The subunit composition of the complex differs at different sites i.e. there are multiple subtypes of BZD receptor. The ($\alpha_1 2\ \beta_2\ 2\ \gamma_2$) pentamer appears to be the most commonly expressed BZD receptor isoform. BZD receptor isoforms containing the α_1 subunit are involved in mediating sedative, hypnotic and amnesic actions of BZD's while those containing α_2 subunits mediate anxiolytic and muscle relaxant actions. The newer non-BZD hypnotics zaleplon,zolpidem, etc. have high affinity for α_1 subunit isoform of BZD receptor and exert selective hypnotic-amnesic effects but have little anti seizure or muscle relaxant property.

$GABA_B$ receptor: G- protein coupled receptor: hyper polarizes neurones by increasing k^+ conductance and altering ca^{2+} flux; bicuculline insensitive, but blocked by saclofen. Central acting muscle relaxants acts on $GABA_B$ receptor.

Uses of central acting muscle relaxants: Acute muscle spasms, Torticollis, lumbago, backache, neuralgias, Anxity and tension, Spastic neurological disease, Tetanus, Electroconvulsive therapy, Orthopedic manipulations.

Conclusion: The Muscarinic receptors includes Subtypes: M1, M2, M3, M4, M5. These receptors are selectively stimulated by muscarine and blocked by atropine. Anticholinestarases used in the treatment of Miosis, Myasthenia gravis, Urinary retention, Cobra bite. Eosinophils , mast cells and basophils are the primary cells expressing H4 receptors. Activation of H4 receptors enhances chemotaxis of these cells. The receptor may be playing a role in allergic inflammation. All prostanoid receptors are G-protein coupled receptors which can be functionally categorized into excitatory or contractile and inhibitory or relaxant groups. The contractile group EP,FP,TP. The $cysLT_1$ receptor is mainly expressed in bronchial and intestinal muscle and has higher affinity for LTC_4. The primary location of $cysLT_2$ receptor is leucocytes and spleen. Morphine and other opioids exert their action by interacting with specific receptors present on neurons in the CNS and in peripheral tissues. Radioligand binding studies divided the opioid receptors into three types (μ, *k, and δ*). The GABA receptors are used in Acute muscle spasms, Torticollis, lumbago, backache, neuralgias, Anxiety and tension, Spastic neurological diseases, Tetanus, Electroconvulsive therapy, Orthopedic manipulations. Kinins appear to plays no significant role in the regulation of normal BP. Kinins cause closure of ductus arteriosus, dilatation of foetal pulmonary artery and constriction of umbilical vessels. Kinins play a major role in the devolpment of angioedema.They are also appear to be involved in shock, rhinitis, asthma.

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