

BASICS OF NEUROBIOLOGY

METABOTROPIC RECEPTORS

ZSOLT LIPOSITS

Basics of Neurobiology: Metabotropic receptors

CHARACTERISTICS OF METABOTROPIC RECEPTORS

SYNONYM FOR METABOTROPIC RECEPTOR IS G PROTEIN-COUPLED RECEPTOR

THE BINDING OF THE LIGAND TO THE RECEPTOR RESULTS IN G PROTEIN ACTIVATION THAT TRIGGERS DOWNSTREAM EFFECTORS, MAINLY ENZYMES AND ION CHANNELS

THE G PROTEIN-COUPLED RECEPTOR FAMILY HAS MORE THAN 1000 MEMBERS

THE RESPONSE EVOKED VIA METABOTROPIC RECEPTORS HAS A SLOWER ONSET AND LONGER DURATION (FROM 0.1 s TO HOURS).

CERTAIN CLASSIC TRANSMITTERS UTILIZE BOTH THE FAST IONOTROPIC (RESPONSE TIME IS IN MILLISECONDS) AND THE SLOWER METABOTROPIC RECEPTORS FOR COMMUNICATION.

PEPTIDES USE G PROTEIN-COUPLED RECEPTORS EXCLUSIVELY

THE RECEPTORS BELONG TO SUBFAMILIES LIKE:

METABOTROPIC GLUTAMATE TYPE

RHODOPSIN-BETA ADRENERGIC TYPE

SECRETIN-VIP TYPE

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CHARACTERISTICS OF METABOTROPIC RECEPTORS

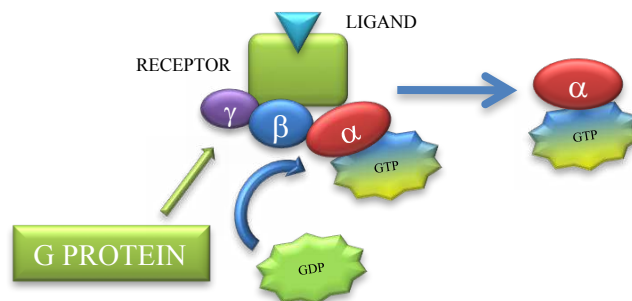
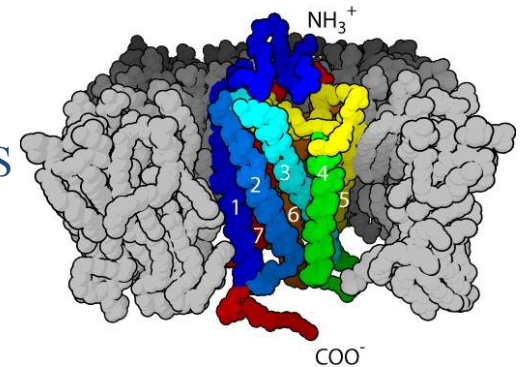
THE RECEPTOR POSSESSES 7 TRANSMEMBRANE DOMAINS

LIGANDS COMPRISE LIGHT-SENSITIVE COMPOUNDS, ODORS, PHEROMONES, HORMONES, NEUROTRANSMITTERS, PEPTIDES AND LARGER PROTEINS

THE ACTIVATED GPCR CAN TURN ON AN ASSOCIATED G-PROTEIN BY EXCHANGING ITS BOUND GDP FOR A GTP

THE G PROTEIN HAS ALPHA, BETA AND GAMMA SUBUNITS. THE ALPHA SUBUNIT TOGETHER WITH THE BOUND GTP DISSOCIATES AND AFFECTS SECOND MESSENGERS

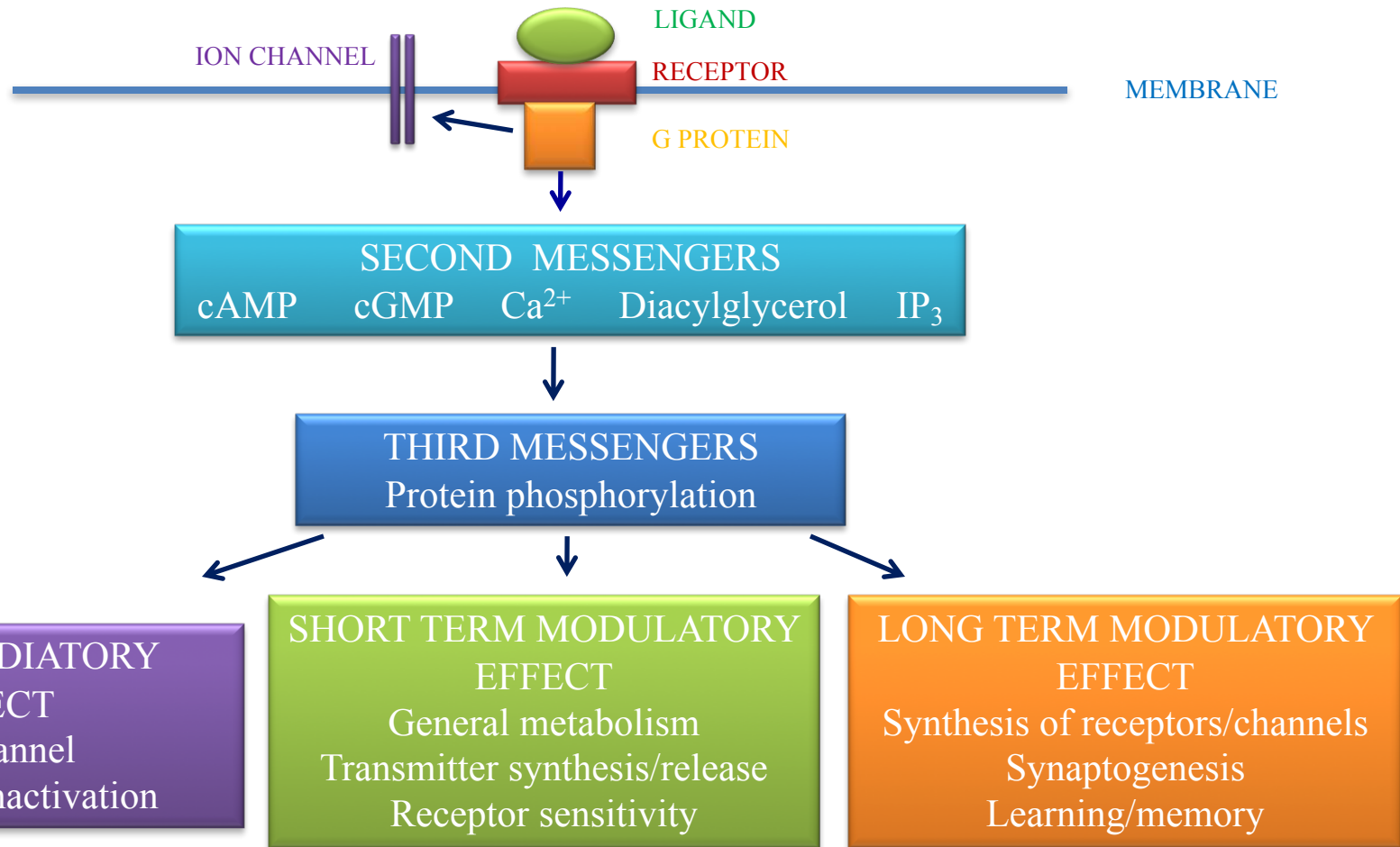
GPCRs UTILIZE cAMP AND PHOSPHATIDYLINOSITOL SIGNAL TRANSDUCTION PATHWAYS



G PROTEIN ACTIVATION BY LIGAND BINDING OF THE RECEPTOR

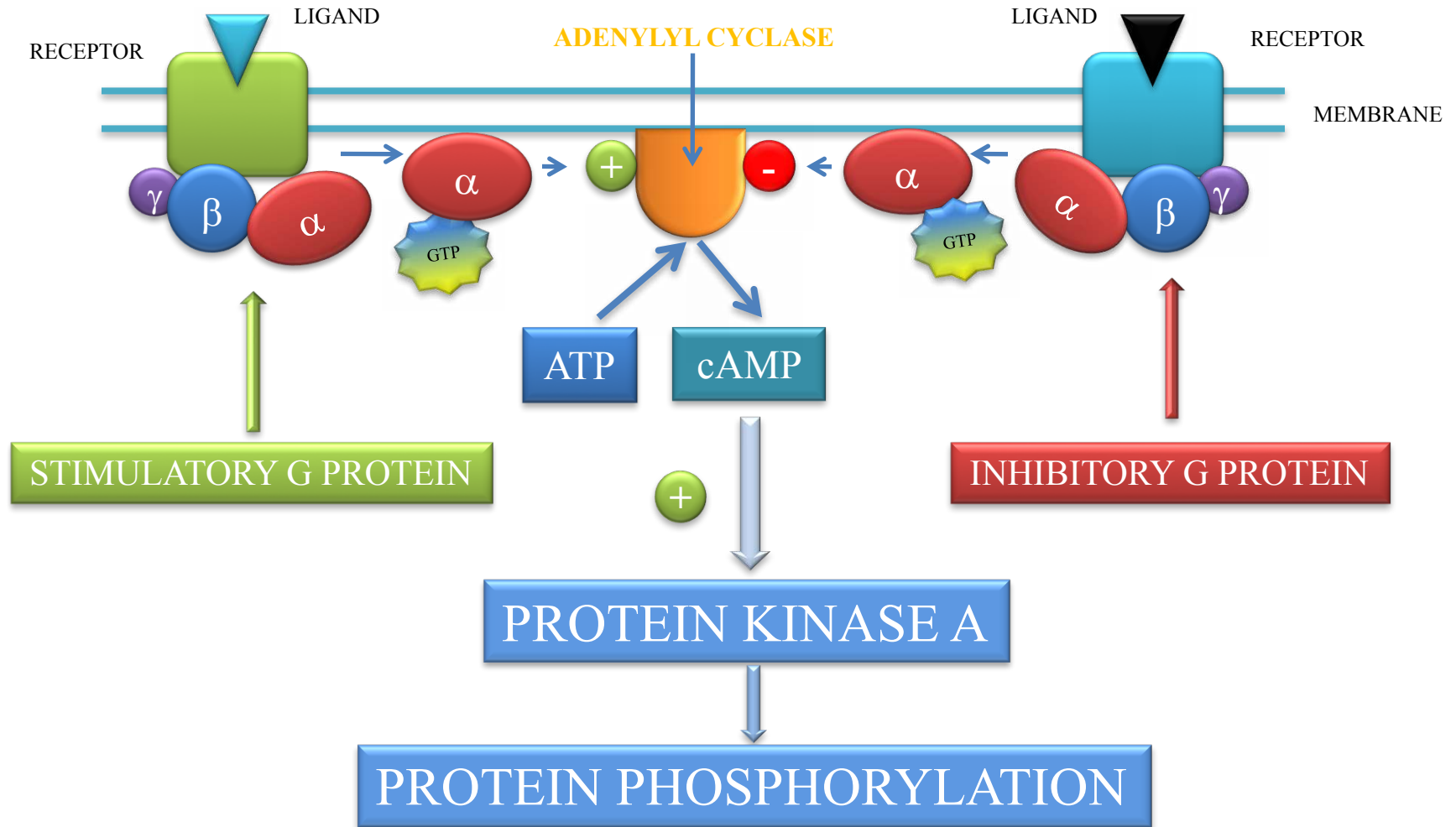
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METABOTROPIC SIGNAL TRANSDUCTION



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STIMULATORY AND INHIBITORY G PROTEIN ACTIONS



Metabotropic receptors

TABLE 21-2 Some Neurotransmitter and Neuropeptide Receptors That Are Coupled to G Proteins

CLASSIC NEUROTRANSMITTERS

Acetylcholine* (muscarinic receptors)
Adenosine
ATP
Dopamine
Epinephrine, norepinephrine

GABA* (B-class receptors)
Glutamate*
Histamine
Serotonin* (5HT₁, 5HT₂, 5HT₄ receptors)

NEUROPEPTIDES

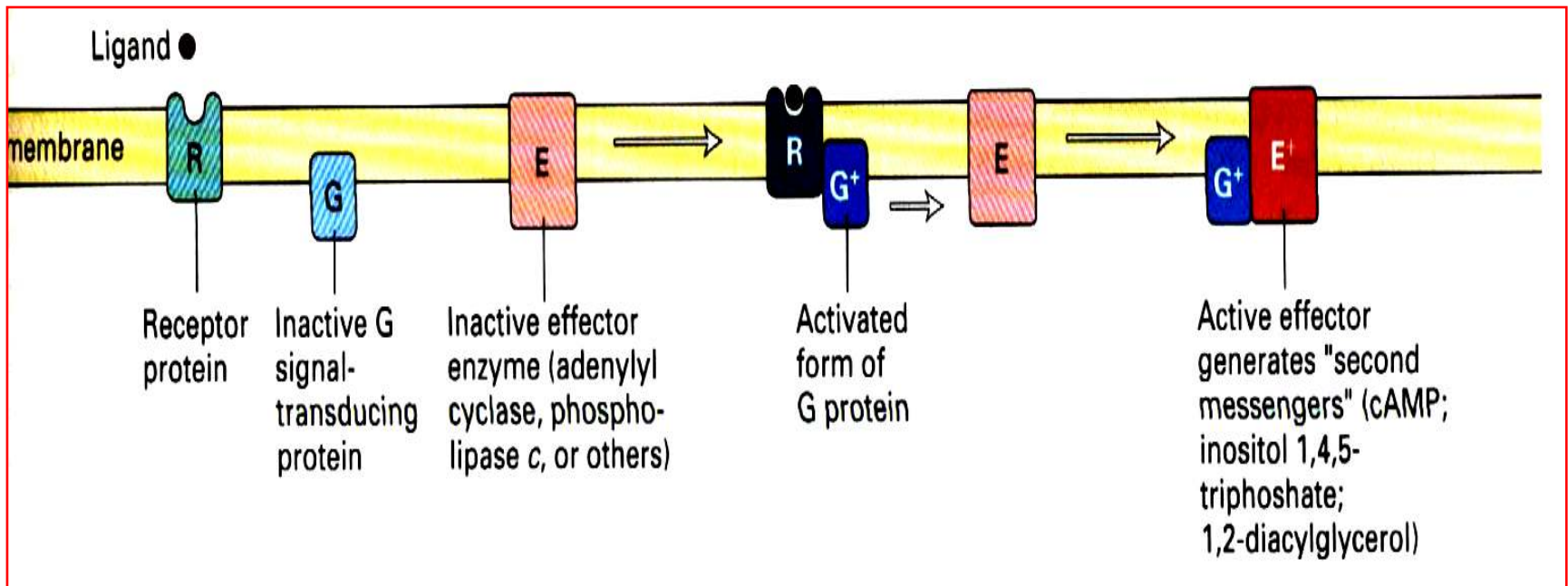
Adrenocorticotrophic hormone (ACTH)
Bradykinin
Cholecystokinin (CCK)
Endothelin
Gastrin
Luteinizing hormone-releasing hormone (LHRH)

Opioids (e.g., β -endorphin)
Oxytocin
Tachykinins (e.g., substance P)
Thyrotropin-releasing hormone (TRH)
Vasoactive intestinal peptide (VIP)
Vasopressin

*These neurotransmitters also bind to other receptors that are ligand-gated ion channels (see Table 21-1).
Their G protein-coupled receptors are indicated in parentheses.

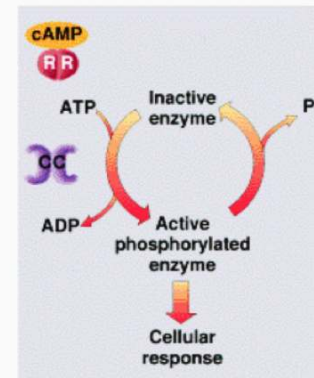
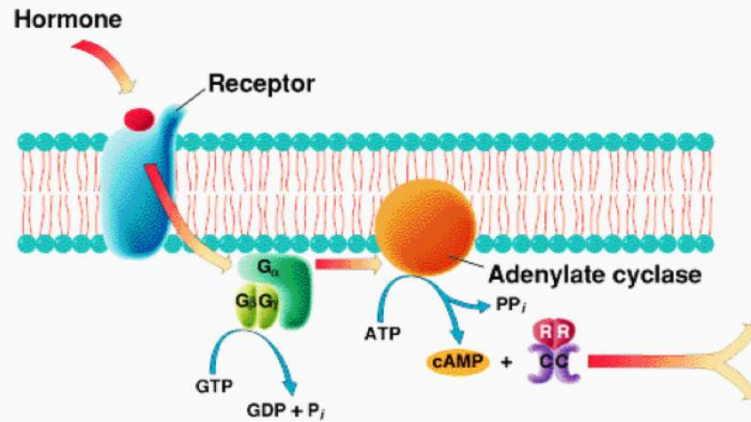
SOURCE: R. LEH, 1993, 81, 81-87.

G-protein-coupled receptor



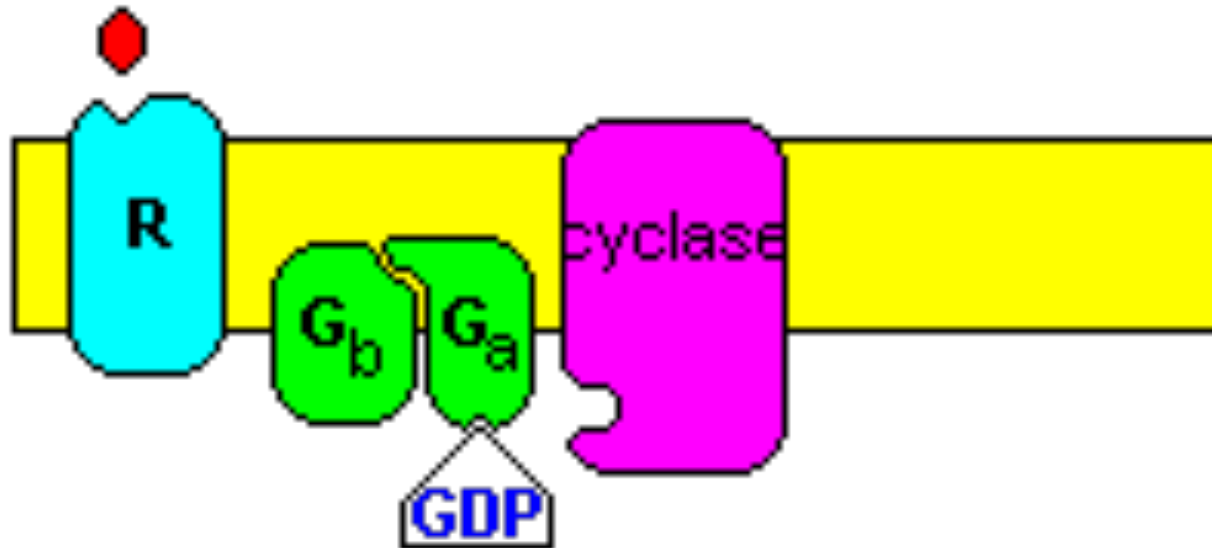
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Campbell, Biochemistry, 3/e
Text Figure 20.05



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G-protein coupled receptor */gif animation/*

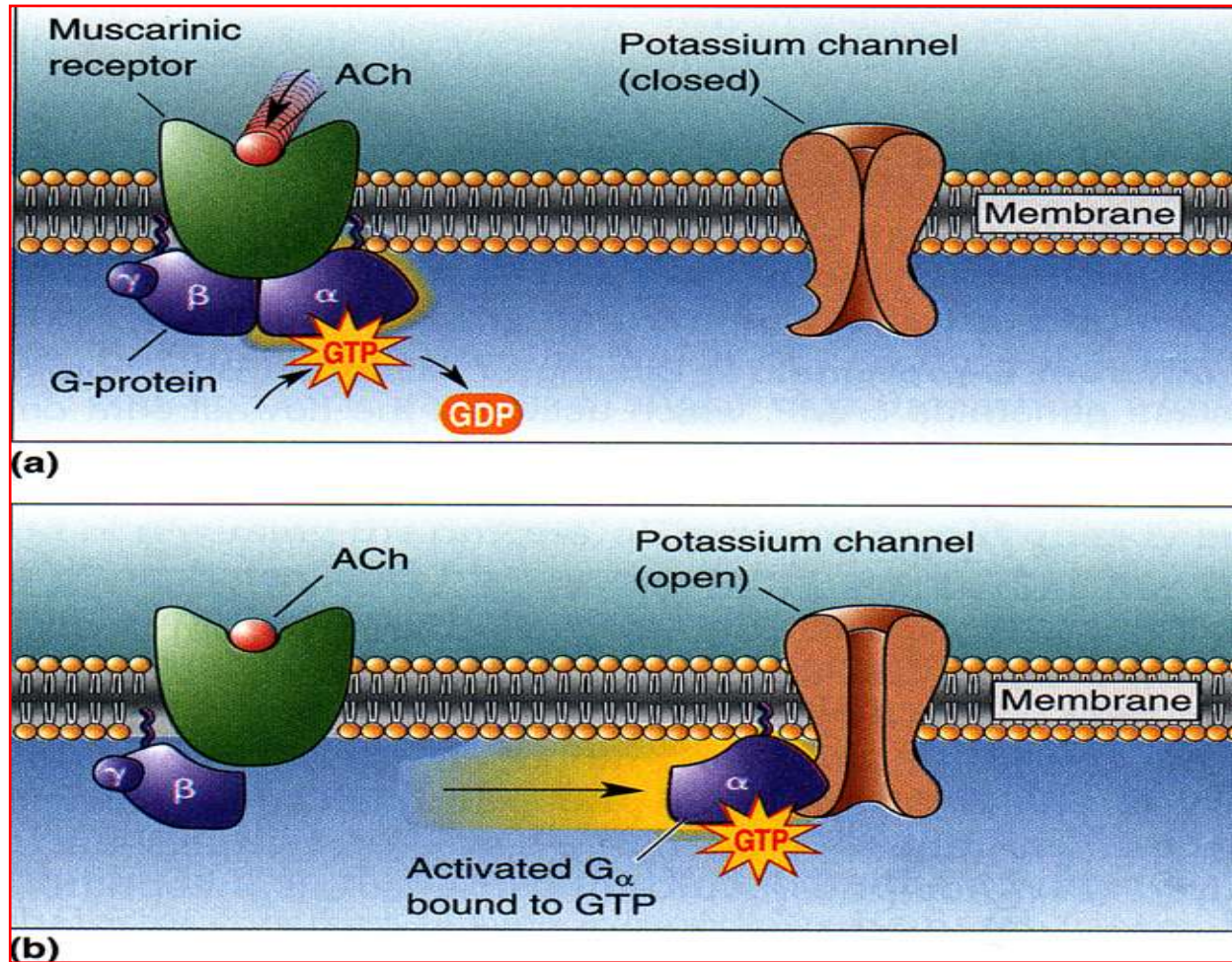


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MUSCARINIC ACETYLCHOLINE RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	MUSCARINIC ACETYLCHOLINE RECEPTOR
STRUCTURE	7 TRANSMEMBRANE
SUBTYPES	FIVE SUBTYPES HAVE BEEN DETERMINED, NAMED M1-M5
EXPRESSION TYPES	M1: CNS, EXOCRINE GLAND, M2: HEART, M3: SMOOTH MUSCLE OF BLOOD VESSELS. LUNG, M4, M5: CNS. PRE- AND POSTSYNAPTIC RECEPTOR LOCATIONS IN THE BRAIN
LIGAND BINDING	HIGHER AFFINITY FOR MUSCARINE THAN NICOTINE
BASIC ROLE(S)	M1, M3, M5 COUPLE TO G PROTEINS THAT STIMULATE PHOSPHOLYPASE C M2, M4 COUPLE TO G PROTEINS THAT REGULATE POTASSIUM AND CALCIUM CHANNELS, INHIBIT ADENYLYL CYCLASE
AGONISTS	MUSCARINE, PILOCARPINE, BETANECHOL
ANTAGONISTS	ATROPINE, SCOPOLAMINE, PIRENZEPINE
FUNCTIONAL ROLES	REGULATION OF CNS NETWORKS AND AUTONOMIC NERVOUS SYSTEM
DISEASES	COGNITIVE DECLINE IN ALZHEIMER DISEASE DUE TO DIMINUTION OF ACETYLCHOLINE

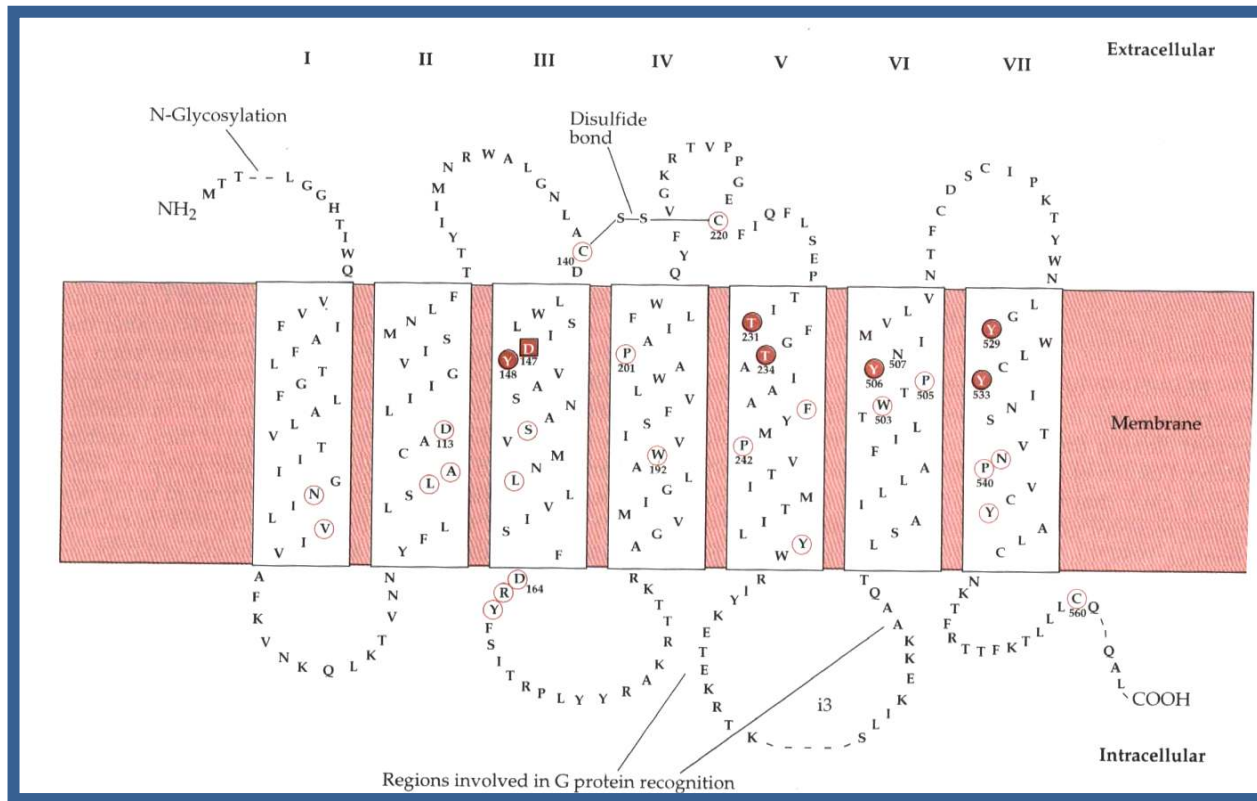


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mAChR



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Table 7.1 Effector Mechanisms Associated with Specific Muscarinic Receptor Subtypes^a

Subtype	Mechanism
m1, m3, m5	Stimulate PI hydrolysis Increase intracellular Ca^{2+} Increase cAMP levels Release arachidonic acid Inhibit M-current (K^+) Activate Ca^{2+} -dependent K^+ and Cl^- currents
m2, m4	Inhibit adenylyl cyclase Stimulate inward-rectified K^+ current Inhibit Ca^{2+} currents

^aNot all reported effects of muscarinic receptor activation are shown here (see text).

Source: After Richards, 1991; Hulme, Birdsall, and Buckley, 1990

mAChR

Table 7.2 Distribution of Nicotinic and Muscarinic Receptors in Peripheral Neurons and Effector Organs

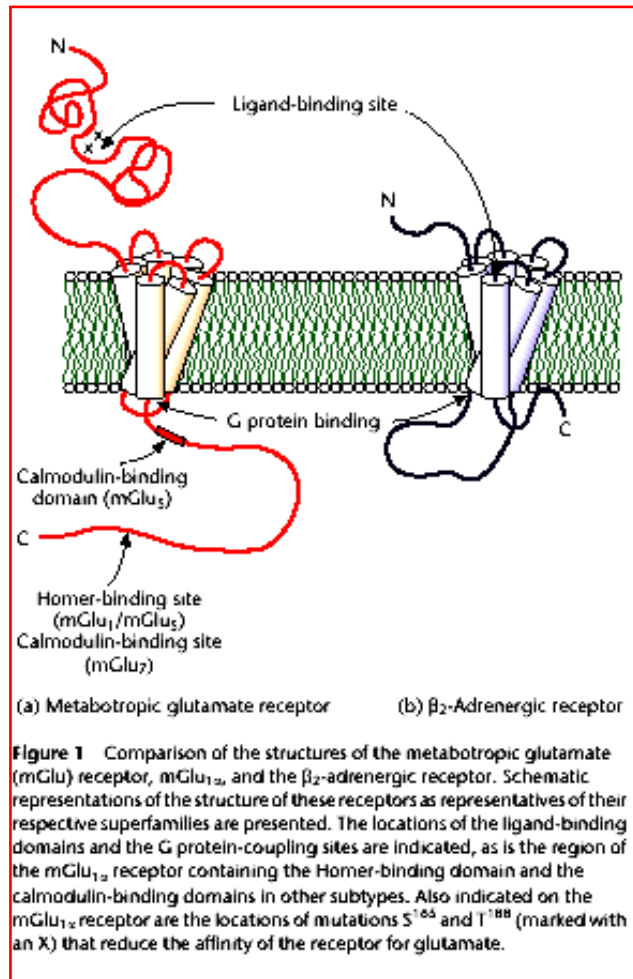
Receptor type	Distribution
Nicotinic	All striated muscles Postganglionic sympathetic and parasympathetic neurons ^a Adrenomedullary chromaffin cells ^a
Muscarinic	Parasympathetically innervated cardiac and smooth muscles (heart, iris, stomach, bronchioles, intestines, bladder, urogenital organs, etc.) Salivary, tear, and sweat glands

^aThese cells also possess muscarinic receptors.

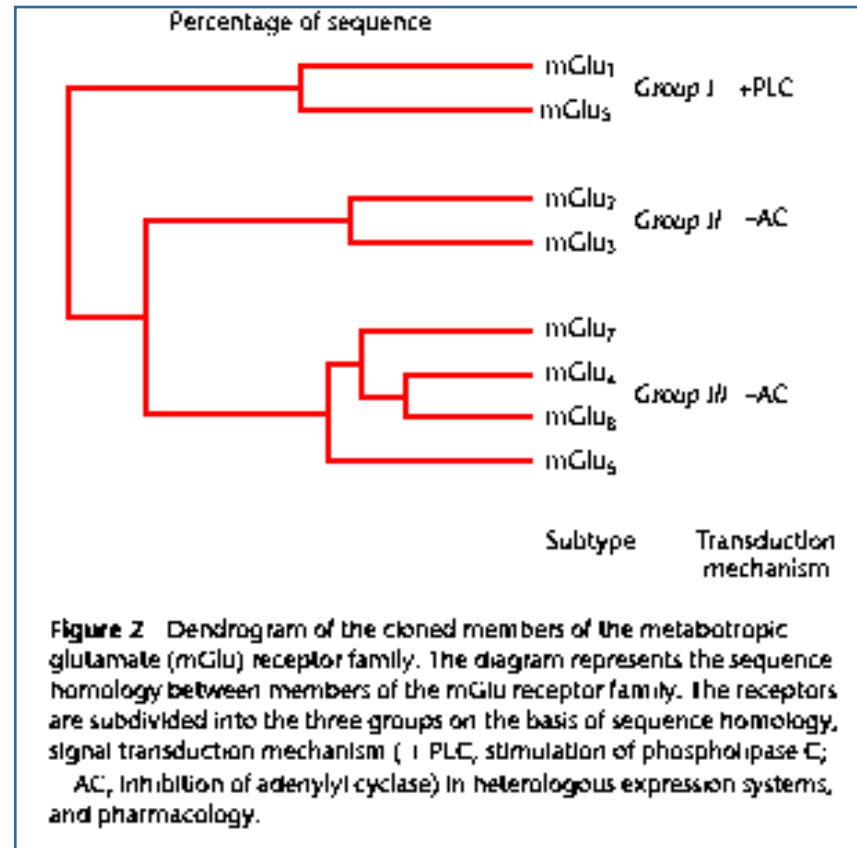
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METABOTROPIC GLUTAMATE RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	METABOTROPIC GLUTAMATE RECEPTOR
STRUCTURE	7 TRANSMEMBRANE
SUBTYPES	EIGHT SUBTYPES DIVIDED INTO THREE GROUPS GROUP I: mGluR ₁ and mGluR ₅ Group II: mGluR ₂ and mGluR ₃ GROUP III: mGluR ₄ and mGluR ₆₋₈
EXPRESSION TYPES	WIDE DISTRIBUTION IN THE BRAIN, PRE- AND POSTSYNAPTIC RECEPTOR LOCATIONS, INHIBITORY, PRESYNAPTIC AUTORECEPTORS
LIGAND BINDING	AT EXTRACELLULAR N TERMINUS PART OF THE RECEPTOR
BASIC ROLE(S)	GROUP I: STIMULATION OF PHOSPHOLIPASE (PLC) C GROUP II: INHIBITION OF ADENYLYL CYCLASE GROUP III: INHIBITION OF ADENYLYL CYCLASE
AGONISTS	2-CHLORO-5-HYDROXYPHENYLGLYCINE, (S)-3,5-DIHYDROXYPHENYLGLYCINE
ANTAGONISTS	4-CARBOXYPHENYLGLYCINE, 1-AMINOINDAN-1,5-DICARBOXYLIC ACID
FUNCTIONAL ROLES	REGULATION OF CNS NETWORKS
DISEASES	mGluR ₁ INVOLVED IN SYNAPTIC PLASTICITY, LTP AND LTD

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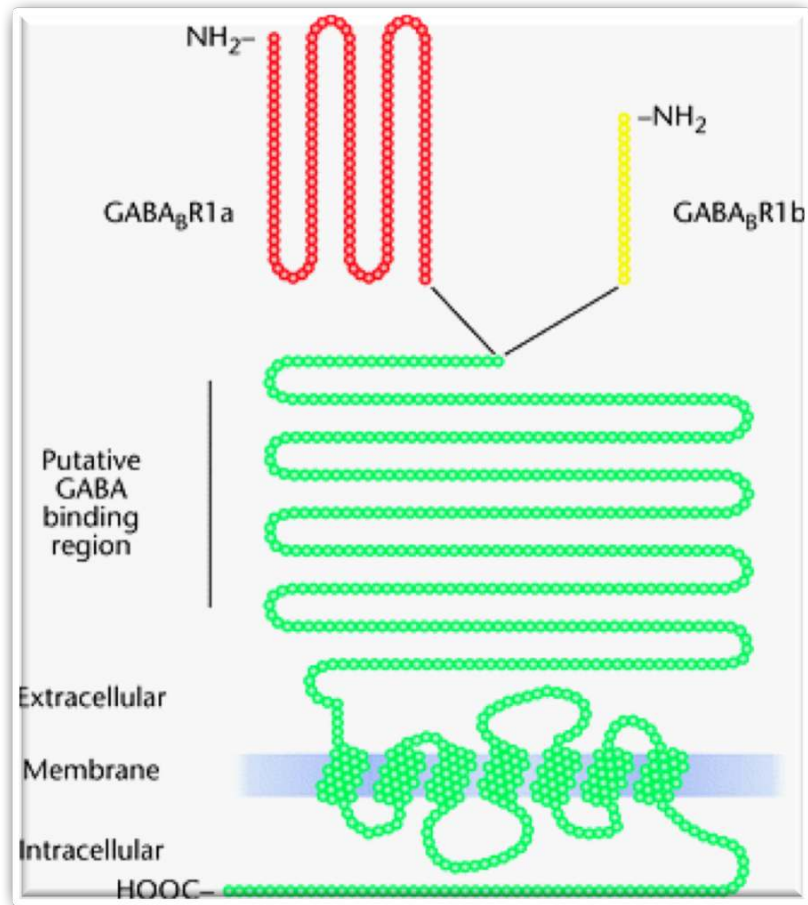
mGlu



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METABOTROPIC GABA RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	METABOTROPIC GABA RECEPTOR (GABA B RECEPTOR)
STRUCTURE	7 TRANSMEMBRANE, LARGE SIMILARITY WITH THE METABOTROPIC GLUTAMATE RECEPTOR
SUBTYPES	TWO SPLICE VARIANTS ARE KNOWN (GABA _B R ₁ , GABA _B R ₂)
EXPRESSION TYPES	WIDE DISTRIBUTION IN THE BRAIN, PRE- AND POSTSYNAPTIC RECEPTOR LOCATIONS,
LIGAND BINDING	THE EXTRACELLULAR N TERMINUS PART OF THE RECEPTOR
BASIC ROLE(S)	ACTIVATION OF GABA B RECEPTORS LEADS TO AN INCREASE IN K ⁺ CONDUCTANCE, A DECREASE IN CA ²⁺ CONDUCTANCE AS WELL AS TO CHANGES IN THE LEVELS OF SECOND MESSENGERS (cAMP)
AGONISTS	BACLOFEN
ANTAGONISTS	SACLOFEN
FUNCTIONAL ROLES	REGULATION OF CNS NETWORKS
DISEASES	PAIN, EPILEPSY

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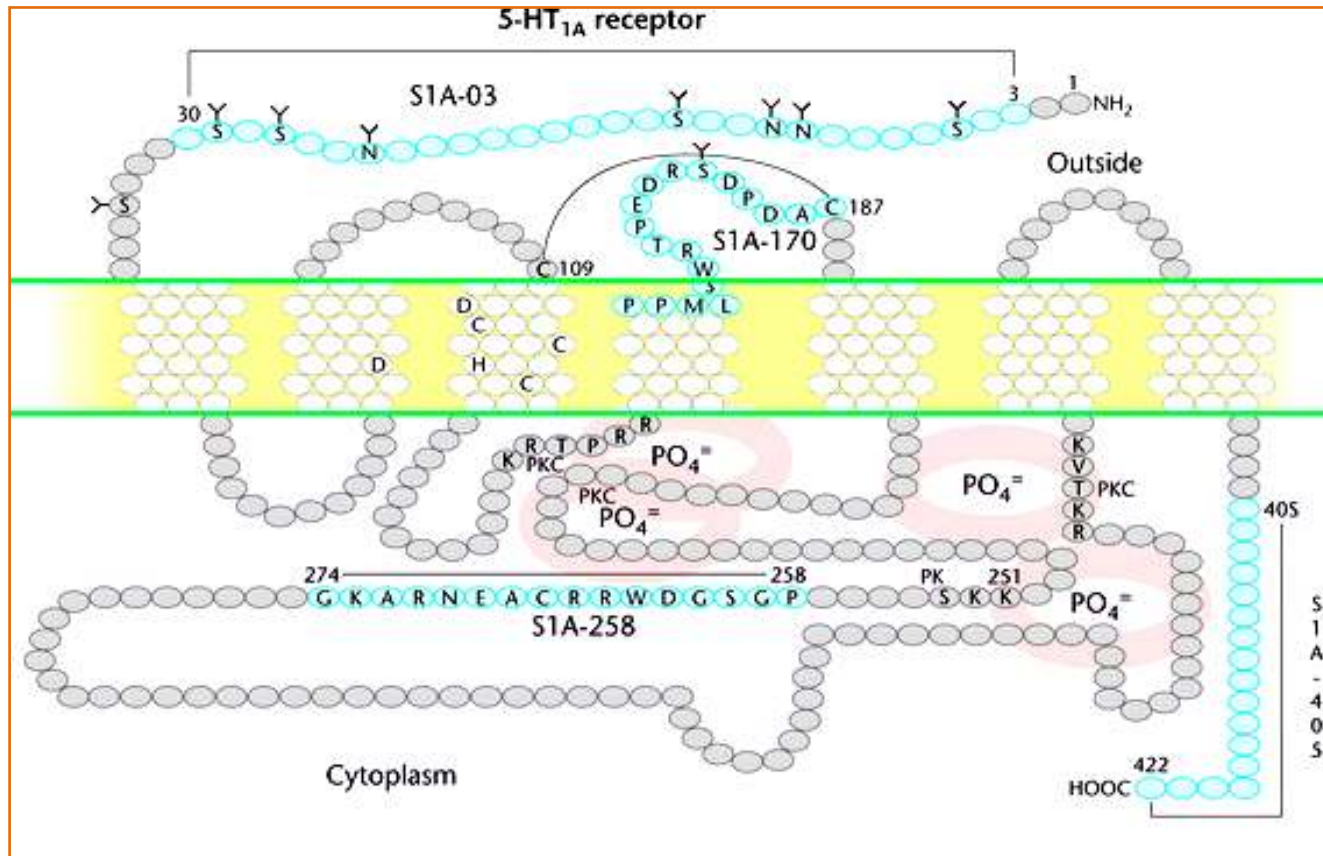


GABA-B receptor

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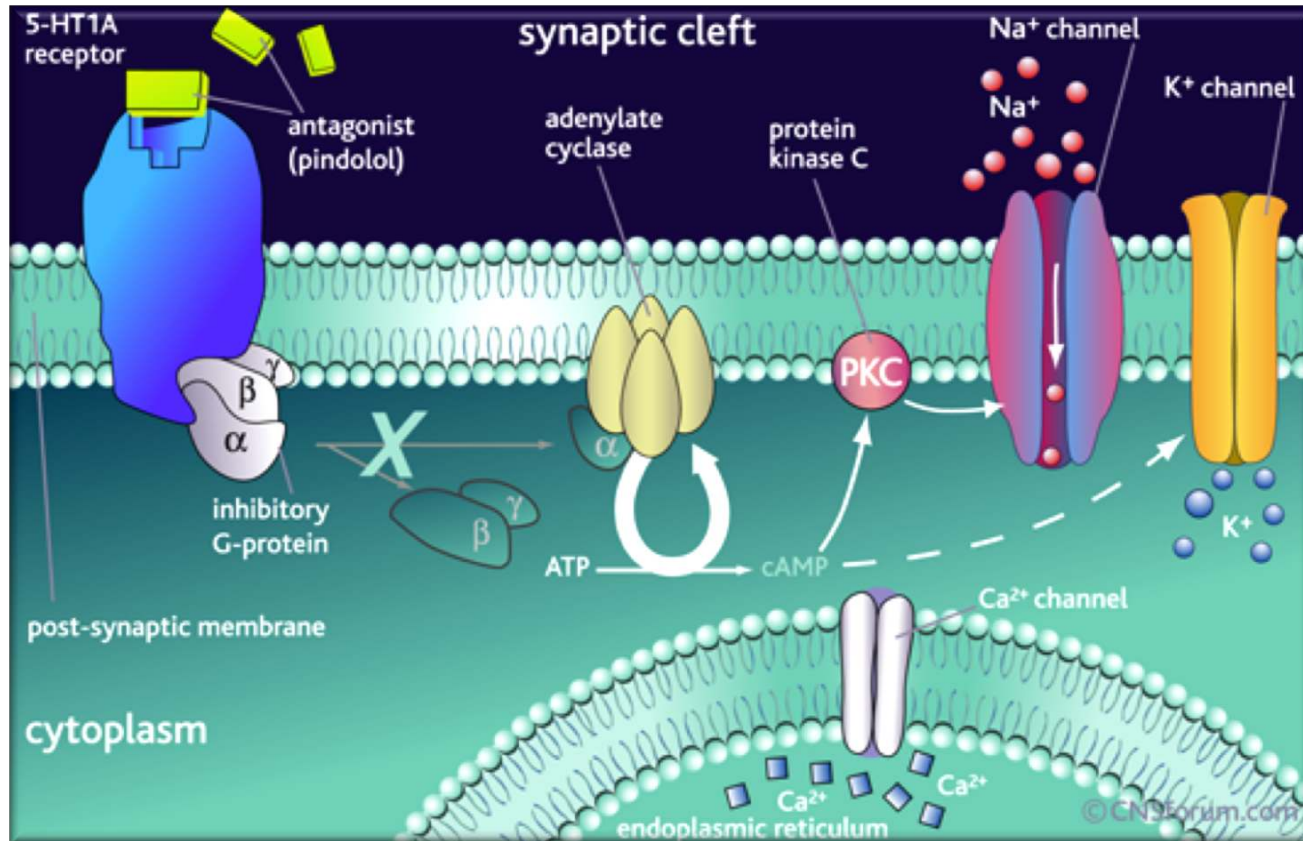
METABOTROPIC SEROTONIN RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	METABOTROPIC SEROTONIN RECEPTOR
STRUCTURE	7 TRANSMEMBRANE
SUBTYPES	13 SUBTYPES, CATEGORIZED INTO 6 GROUPS (5HT ₁ , 5HT ₂ , 5HT ₄ , 5HT ₅ , 5HT ₆ , 5HT ₇)
EXPRESSION TYPES	WIDE DISTRIBUTION IN THE BRAIN
LIGAND BINDING	THE EXTRACELLULAR N DOMAIN OF THE RECEPTOR
BASIC ROLE(S)	INCREASING CELLULAR LEVELS OF cAMP: SUBTYPES 4,6,7 DECREASING CELLULAR LEVELS OF cAMP: SUBTYPES 1,5 INCREASING CELLULAR LEVELS OF IP3 AND DAG: SUBTYPE 2
AGONISTS	LARGE SCALE OF SUBTYPE SPECIFIC AGONISTS ARE KNOWN
ANTAGONISTS	LARGE SCALE OF SUBTYPE SPECIFIC ANTAGONISTS ARE KNOWN
FUNCTIONAL ROLES	REGULATION OF CNS NETWORKS
DISEASES	ANXIETY, AGGRESSION, ADDICTION, MOOD, MEMORY, SLEEP

Szerotonin 1A receptor



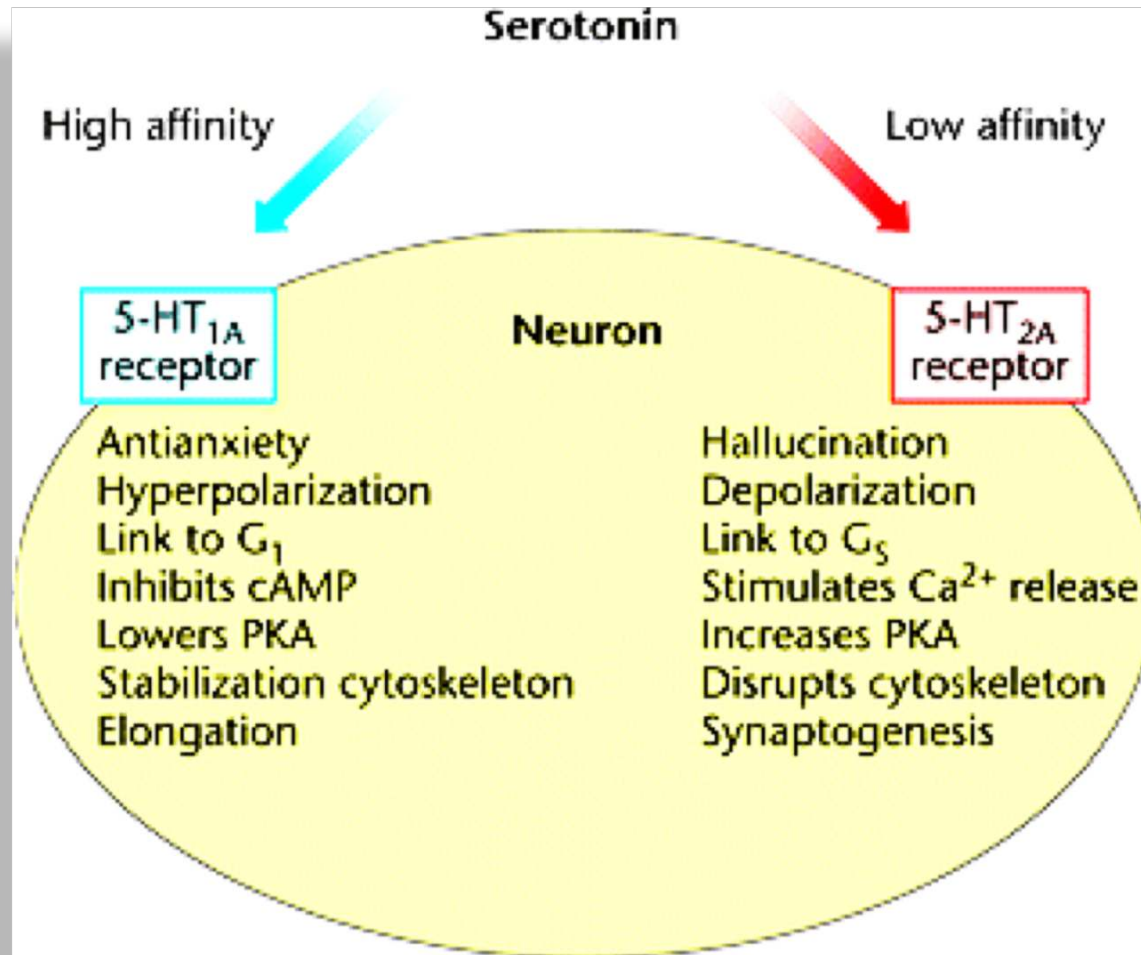
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ACTION OF 5HT_{1A} RECEPTOR ANTAGONIST



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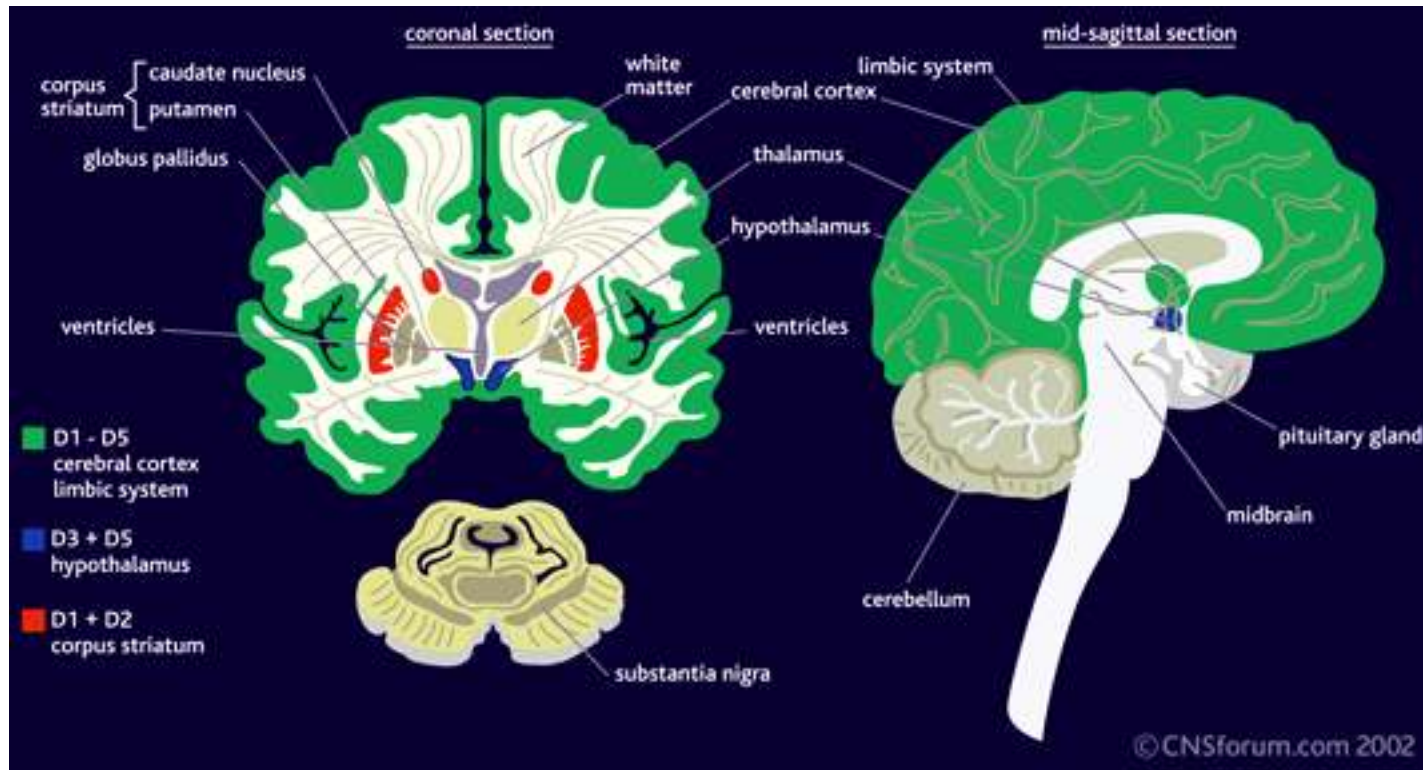
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DOPAMINE RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	DOPAMINE RECEPTOR
STRUCTURE	7 TRANSMEMBRANE
SUBTYPES	D1-LIKE AND D2-LIKE FAMILIES D1-LIKE,: D1, D5 RECEPTORS D2 LIKE: D2, D3, D4 RECEPTORS
EXPRESSION TYPES	WIDE DISTRIBUTION IN THE BRAIN. DOMINANT IN STRIATUM, N. ACCUMBENS, CORTEX
LIGAND BINDING	TRANSMEMBRANE SEGMENTS
BASIC ROLE(S)	D1-LIKE FAMILY ACTIVATES ADENYLYL CYCLASE D2-LIKE FAMILY INHIBITS ADENYLYL CYCLASE
AGONISTS	ROPINIROLE , PRAMIPEXOLE
ANTAGONISTS	CLOZAPINE, RISPERIDONE, OLANZAPINE, QUETIAPINE
FUNCTIONAL ROLES	REGULATION OF CNS NETWORKS, CONTROLLING MOVEMENT, MOOD, ADDICTION
DISEASES	PARKINSON DISEASE, SCHIZOPHRENIA, ATTENTION-DEFICIT HYPERACTIVITY DISORDER

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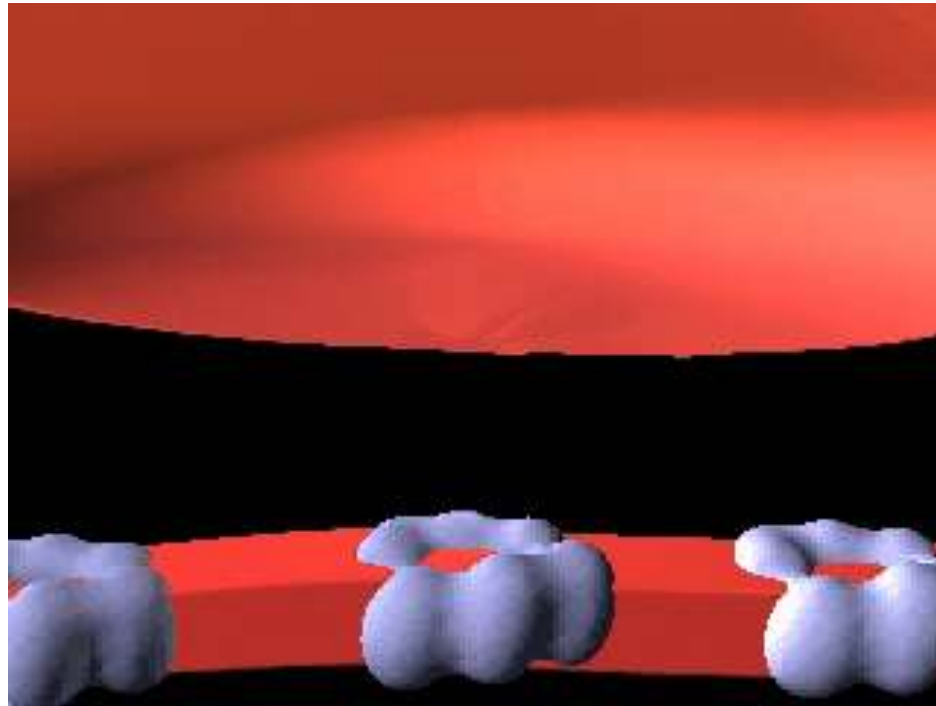
DISTRIBUTION OF D1-D5 RECEPTORS IN THE HUMAN



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Metabotrop D1 receptor



<http://www.williams.edu/imput/IIIB1.html>

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ADRENERGIC RECEPTOR	
ATTRIBUTE	DESCRIPTION
NAME	ADRENERGIC RECEPTOR. BINDS BOTH ADRENALINE AND NORADRENALINE
STRUCTURE	7 TRANSMEMBRANE
SUBTYPES	3 FAMILIES, ALPHA 1, ALPHA 2 AND BETA. SUBCLASSES IN EACH FAMILY
EXPRESSION TYPES	WIDE DISTRIBUTION IN THE BRAIN, HYPOTHALAMUS, CEREBRAL CORTEX IN THE CNS, ALPHA2A AND BETA 1 RECEPTORS ARE THE MAIN ADRENERGIC RECEPTORS ALPHA2A RECEPTORS PERFORM AS AUTORECEPTORS
LIGAND BINDING	THE EXTRACELLULAR DOMAIN OF THE RECEPTOR
BASIC ROLE(S)	ALPHA-2 ADRENERGIC RECEPTOR DECREASE CYCLIC AMP BETA ADRENERGIC RECEPTORS INCREASE CYCLIC AMP
AGONISTS	ISOPROTERENOL (SPECIFIC FOR BETA)
ANTAGONISTS	PROPRANOLOL (BETA), PHENTOLAMINE (ALPHA, WITH SOME BETA ACTION)
FUNCTIONAL ROLES	REGULATION OF CNS AND PNS FUNCTIONS
DISEASES	ANXIETY, POSTTRAUMATIC STRESS DISORDER (PTSD)

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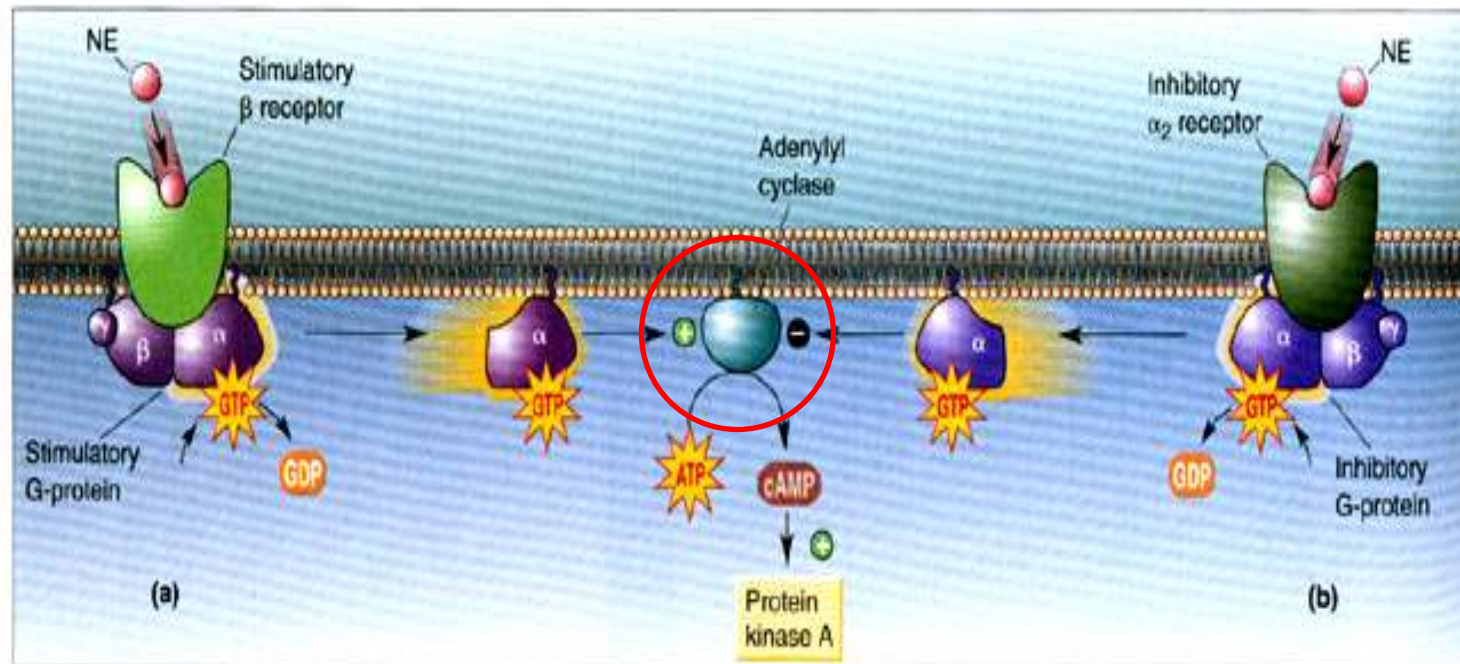


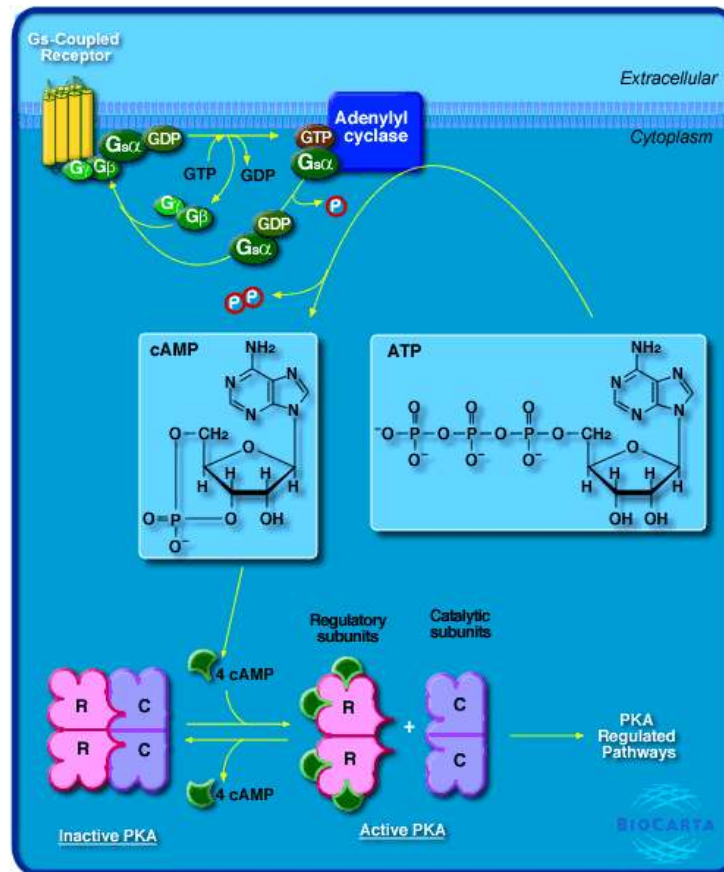
Figure 6.25

Stimulation and inhibition of adenylyl cyclase by different G-proteins. (a) Binding of NE to the β receptor activates G_s , which in turn activates adenylyl cyclase. Adenylyl cyclase generates cAMP, which activates the downstream enzyme protein kinase A. (b) Binding of NE to the α_2 receptor activates G_i , which inhibits adenylyl cyclase.

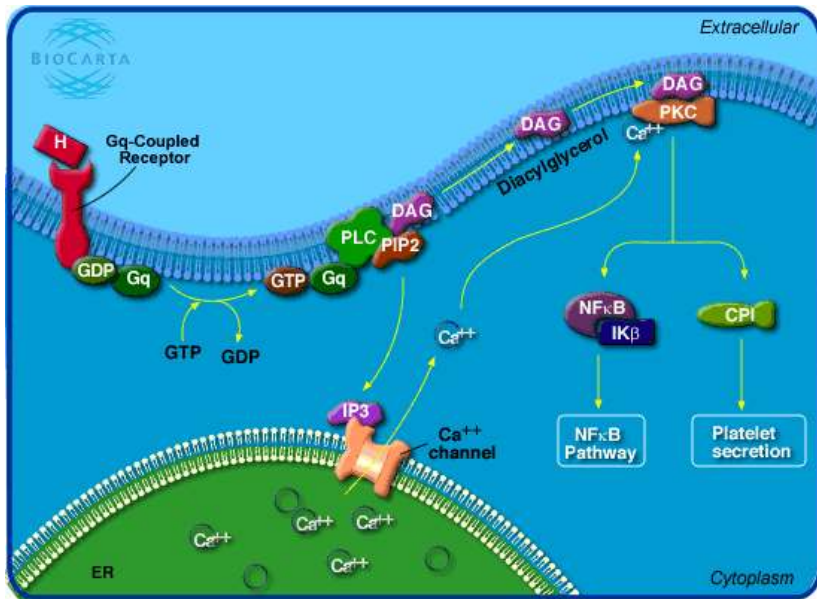
Signal Transduction Cascades

<http://www.rpi.edu/dept/bcbp/molbiochem/MBWeb/mb1/part2/signals.htm>

Activation of cAMP-dependent protein kinase, PKA



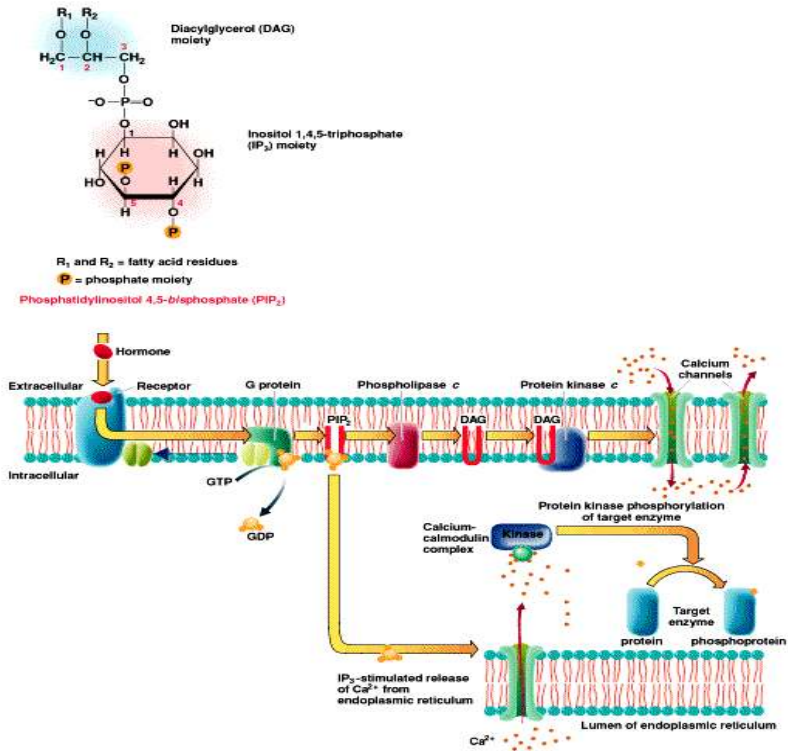
Activation of PKC through G protein coupled receptor



G-protein coupled receptors (GPCRs) transduce a variety of signals from the extracellular environment across the plasma membrane. One of the common signaling systems utilized by GPCRs activates protein kinase C (PKC), a ubiquitous family of serine/threonine protein kinases. The pathway leading to PKC activation starts with a class of GPCRs that interact with and activate Gq G-proteins when the receptor has agonist ligand bound. GPCRs that act through Gq include some muscarinic acetylcholine receptors, many peptide receptors, and the 5-HT₂ serotonin receptors. Activated Gq with GTP bound activates its downstream target phospholipase C (PLC) to hydrolyze the membrane lipid PIP₂, producing IP₃ and diacylglycerol (DAG). IP₃ is water-soluble and diffuses through the cytoplasm to the ER, where it binds to and opens a calcium channel, releasing calcium stores from inside the ER into the cytoplasm. Calcium alters many cellular processes, in part by binding to regulatory proteins such as calmodulin and calcineurin. The interaction of both DAG and calcium with PKC activates its kinase activity and the phosphorylation of many different protein targets alters their activity. The involvement of PKC in cellular proliferation and the cell cycle is indicated by the activity of tumor promoters like phorbol esters as PKC activators

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Text Figure 20.06



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MAP Kinase Signaling Pathway

