

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

NEUROHUMORAL TRANSMISSION

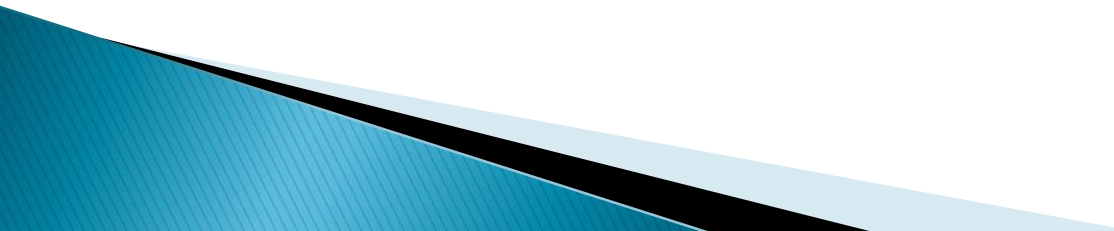
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INTRODUCTION

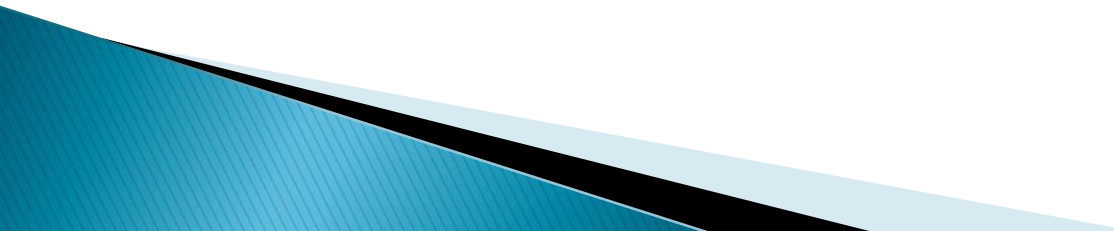
- ▶ The transfer of nerve impulse from presynaptic to post synaptic neuron by means of a humoral agent e.g. biogenic amine, an amino acid or a peptide.
 - ▶ E.g Acetylcholine and Norepinephrine are major neurotransmitters of nervous system.
 - ▶ This process involves several steps, i.e. biosynthesis, storage, release, receptor interaction and inactivation of the transmitter.
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Steps involved in neurotransmission

▶ **Junctional Transmission**

The arrival of the action potential at the axonal terminals initiates a series of events that trigger transmission of an excitatory or inhibitory impulse across the synapse or neuroeffector junction.

1. Storage and release of the transmitter

- ▶ The neurotransmitters are largely synthesized in the region of the axonal terminals and stored there in synaptic vesicles.
 - ▶ The action potential causes the synchronous release of neurotransmitter. Depolarization of the axonal terminal triggers this process.
 - ▶ The contents of the vesicles, including enzymes and other proteins, then are discharged to the exterior by a process termed exocytosis.
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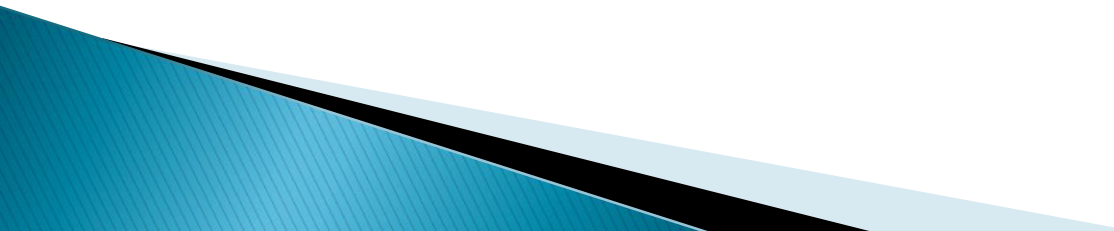
- ▶ Synaptic vesicles may either fully exocytose with complete fusion and subsequent endocytosis or form a transient pore that closes after transmitter has escaped.

2. Combination of the transmitter with postjunctional receptors and production of the postjunctional potential.

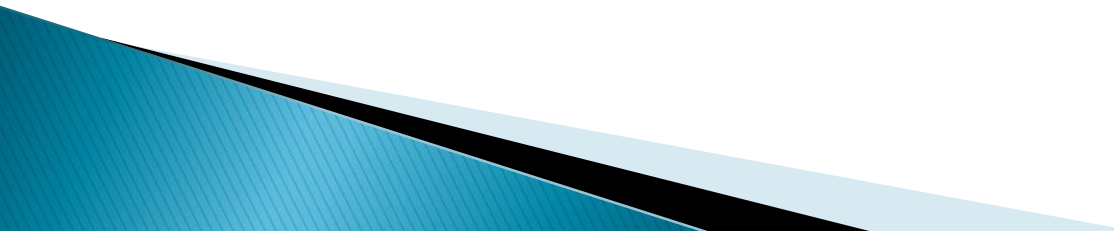
- ▶ The transmitter diffuses across the synaptic or junctional cleft and combines with specialized receptors on the postjunctional membrane; this often results in a localized increase in the ionic permeability, or conductance, of the membrane.
- ▶ With certain exceptions, one of three types of permeability change can occur:
- ▶ **(a)** a generalized increase in the permeability to cations (notably Na^+ but occasionally Ca^{2+}), resulting in a localized depolarization of the membrane, i.e., an excitatory postsynaptic potential (EPSP);

- ▶ **(b)** a selective increase in permeability to anions, usually Cl^- , resulting in stabilization or actual hyperpolarization of the membrane, which constitutes an inhibitory postsynaptic potential (IPSP);
- ▶ or **(c)** an increased permeability to K^+ . Because the K^+ gradient is directed out of the cell, hyperpolarization and stabilization of the membrane potential occur (an IPSP).

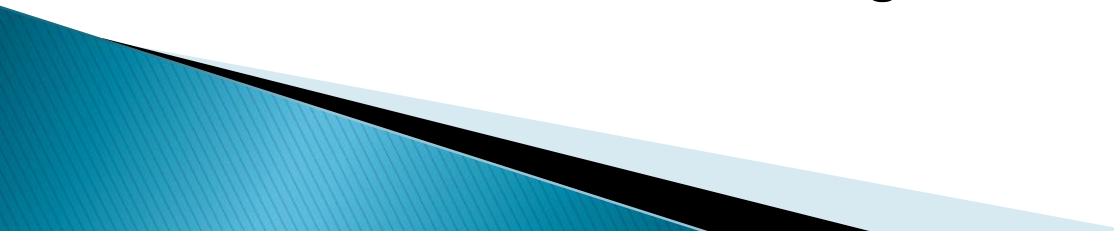
3. Initiation of postjunctional activity.

- ▶ If an EPSP exceeds a certain threshold value, it initiates a propagated action potential in a postsynaptic neuron or a muscle, in skeletal or cardiac muscle by activating voltage-sensitive channels in the immediate vicinity.
 - ▶ An IPSP, which is found in neurons and smooth muscle but not in skeletal muscle, will tend to oppose excitatory potentials simultaneously initiated by other neuronal sources.
 - ▶ Whether a propagated impulse or other response ensues depends on the summation of all the potentials.
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4. Destruction or dissipation of the transmitter.

- ▶ At cholinergic synapses involved in rapid neurotransmission, high and localized concentrations of acetylcholinesterase (AChE) are available for this purpose.
 - ▶ On inhibition of AChE, removal of the transmitter is accomplished principally by diffusion.
 - ▶ Rapid termination of norepinephrine occurs by a combination of simple diffusion and reuptake by the axonal terminals of most of the released norepinephrine.
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Signal Transduction

- ▶ Drugs act as signals, and receptors act as signal detectors.
 - ▶ Receptors transduce their recognition of a bound agonist by initiating a series of reactions that ultimately result in a specific intracellular response
 - ▶ The regulatory actions of a receptor may be exerted directly on its cellular target(s), on effector protein(s), or on intermediary cellular signaling molecules called transducers.
 - ▶ Ultimate physiological target is an enzyme, ion channel, or transport protein that creates, moves, or degrades a small molecule (e.g., a cyclic nucleotide, IP3) or ion (e.g., Ca^{2+}) termed a second messenger.
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EXTRACELLULAR
FLUID

CYTOPLASM

Plasma membrane

1 Reception

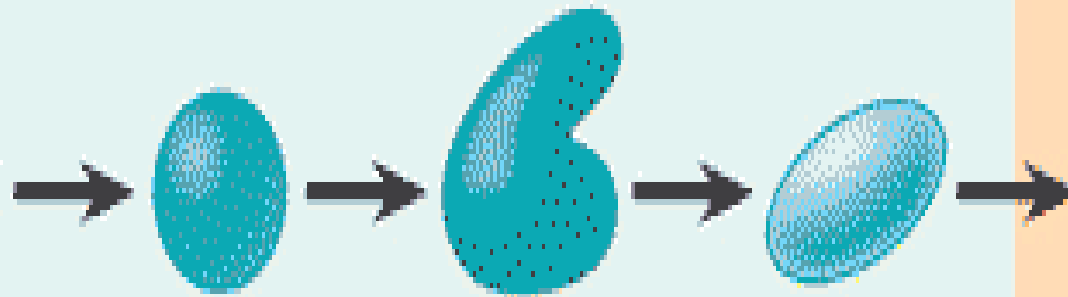
2 Transduction

3 Response

Receptor



Signal
molecule



Relay molecules in a signal transduction
pathway

Activation
of cellular
response

Types of receptors

- ▶ There are two types of receptors

1. Intracellular cell receptors

1.1 Cytoplasmic receptors

1.2 Nuclear receptors

2. Cell Surface receptors

2.1 Ligand-gated ion channels (Ionotropic Receptors)

2.2 Enzyme-linked receptors

2.3 G protein– coupled receptors (Metabotropic Receptors)

➤ Receptors

- **INTRACELLULAR RECEPTORS :-**
 - 1) Cytoplasmic
 - 2) Nuclear receptors
- **CELL SURFACE RECEPTORS:-**



ION CHANNEL RECEPTOR (inotropic)

- Ligand gated ion channels
- Controlled by neurotransmitters
- Present in neurons
- Eg: Ach cation channel

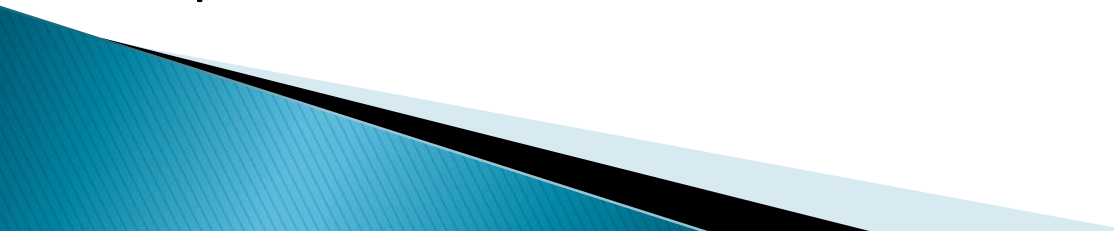
G -PROTEIN LINKED RECEPTOR (Metabotropic)

- Act via second messengers-cAMP, IP_3 , DAG, c GMP

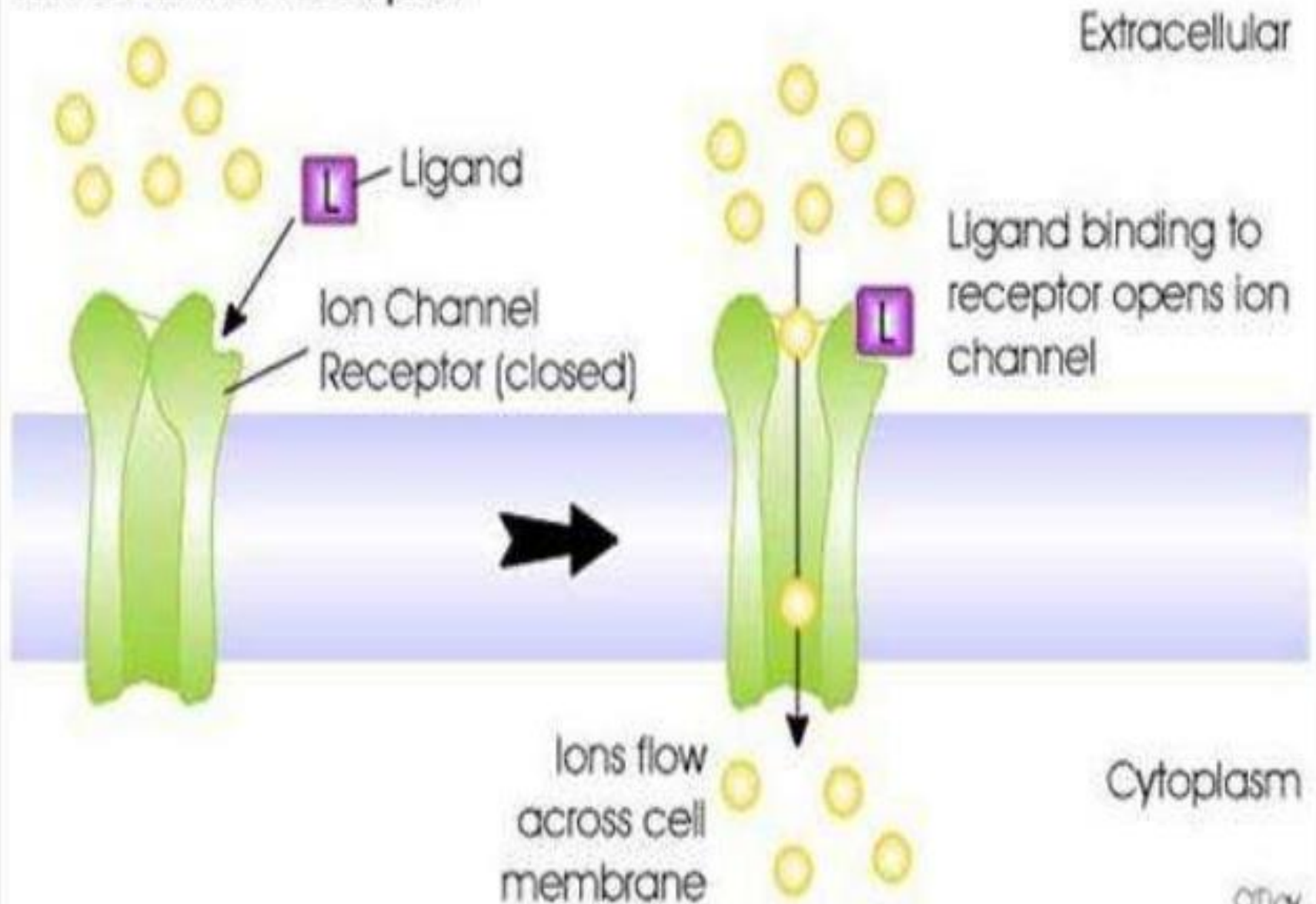
ENZYME LINKED RECEPTOR

- Eg:
 - Protein kinase
 - Tyrosine kinase
 - Tyrosine phosphatase
 - Serine/threonine kinase
 - Guanylyl cyclase
 - Histidine kinase

Ligand gated ion channel

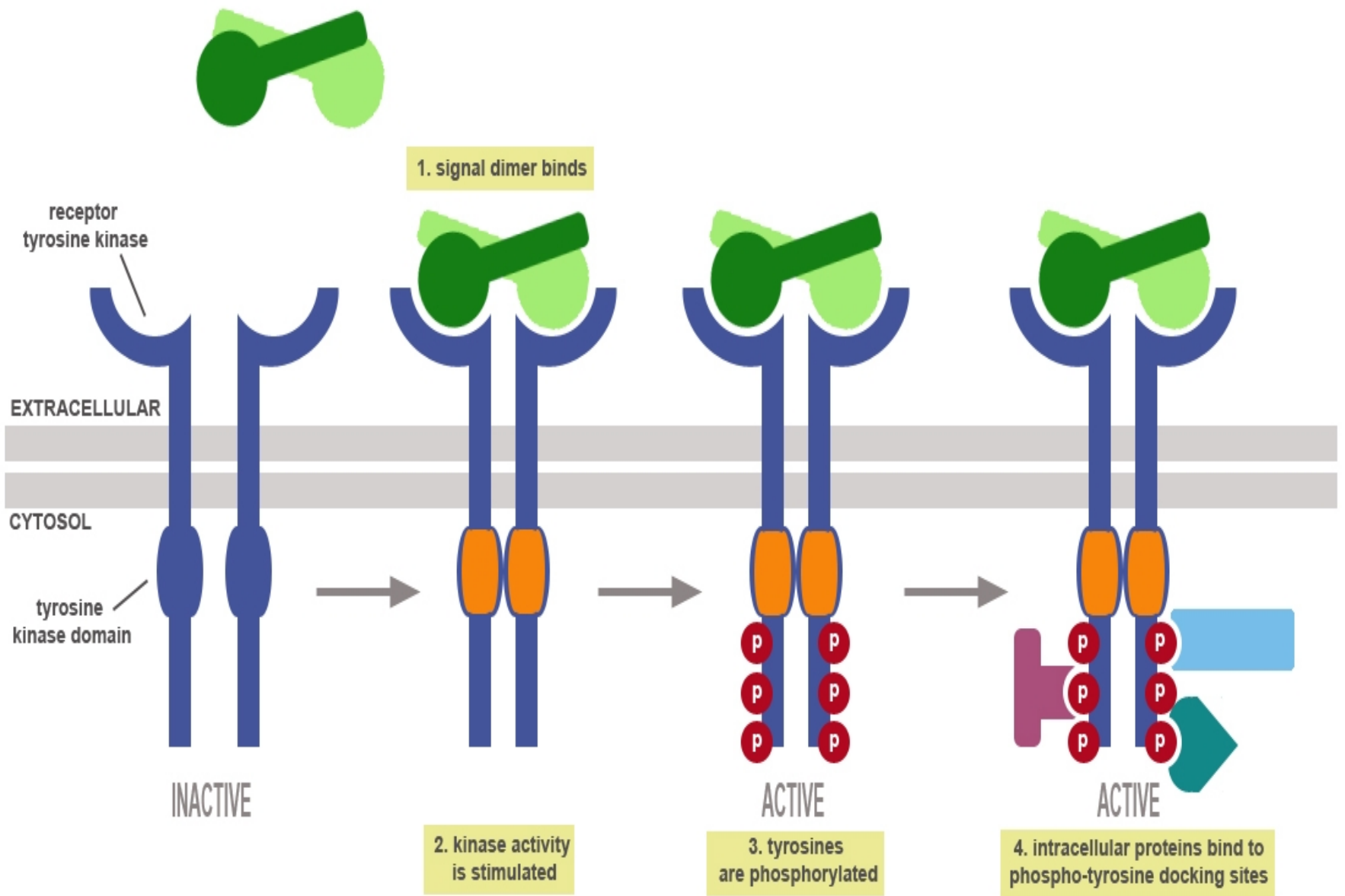
- ▶ They are ion channel (including cation and anion channels). Na K Cl Ca themselves constitutes a large family of transmembrane proteins.
 - ▶ Opening and closing of ion channel are controlled by neurotransmitters.
 - ▶ **E.g** Acetylcholine binds to site on the α subunits, a conformational change occurs that results in the transient opening of a central aqueous channel, through which sodium ions penetrate from the extracellular fluid into the cell, cell depolarized, action potential occur.
 - ▶ No intermediate biochemical steps in the transduction process
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Ion Channel Receptor



Enzyme linked ion channel

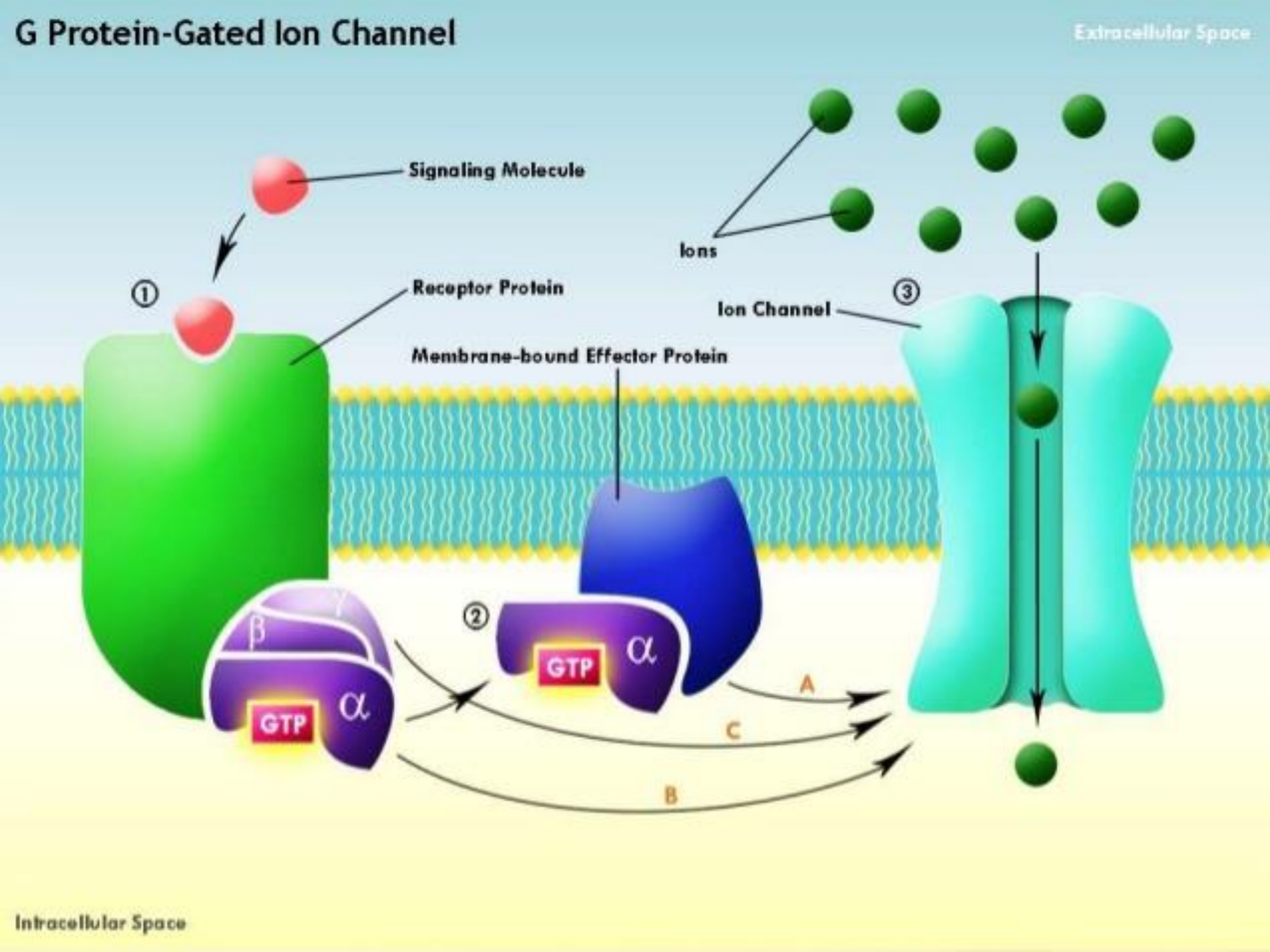
- ▶ They are either enzymes themselves, or are directly associated with the enzymes that they activate.
- ▶ The majority of enzyme linked receptors are protein kinases.



G protein coupled receptors

- ▶ These receptors activates a G protein ligand binding. G-protein is trimeric protein.
- ▶ The three subunits are called α , β and γ .
- ▶ The α subunit can bind with GDP, this cause phosphorylation of the GDP to GTP and activates the α subunit, which then dissociates from β and γ subunits.
- ▶ The activated α subunit can further affects intracellular signaling proteins or target functional proteins directly.

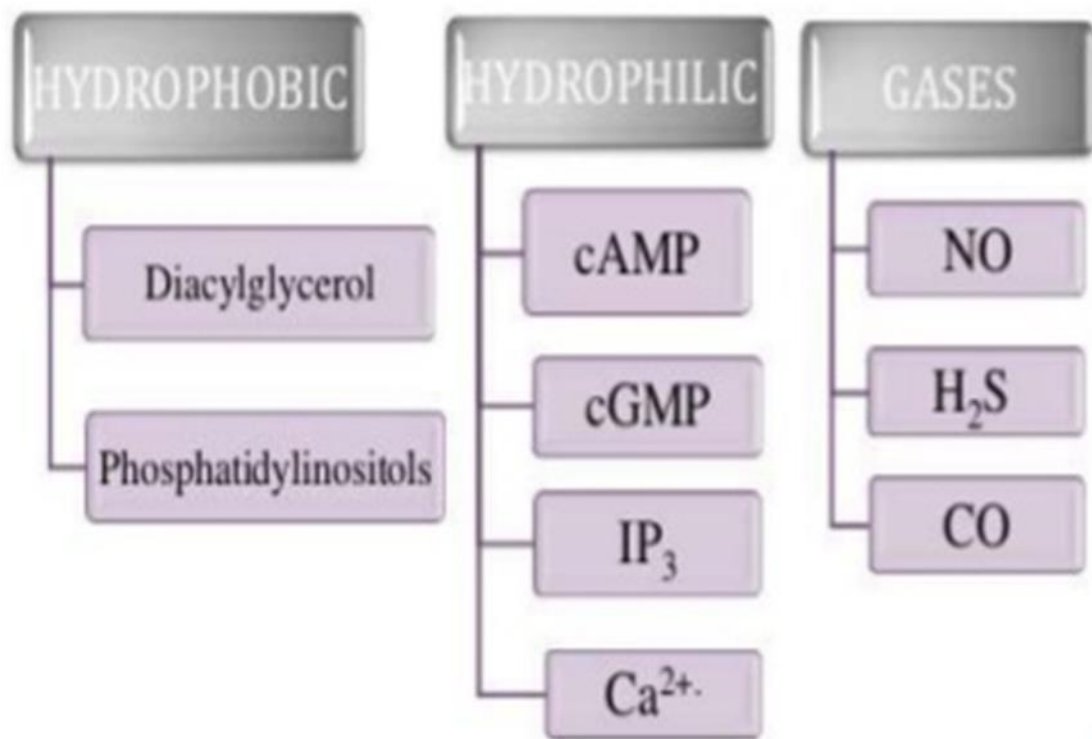
G Protein-Gated Ion Channel



Second messenger

- ▶ Second messengers are the intracellular molecule released by the cell to trigger physiological changes.
- ▶ After the receptor being activated the second messengers play a vital role in transmit signals in form of either direct cellular responses e.g cAMP, cGMP or activate further enzyme to produce responses e.g IP3, DAG signal transduction.

TYPES OF SECOND MESSENGERS



Cyclic AMP (cAMP)

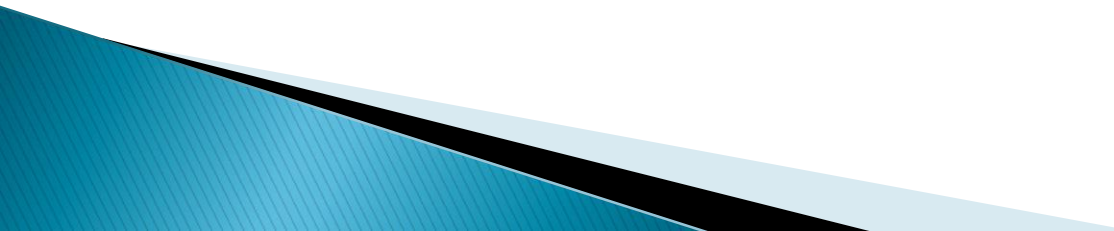
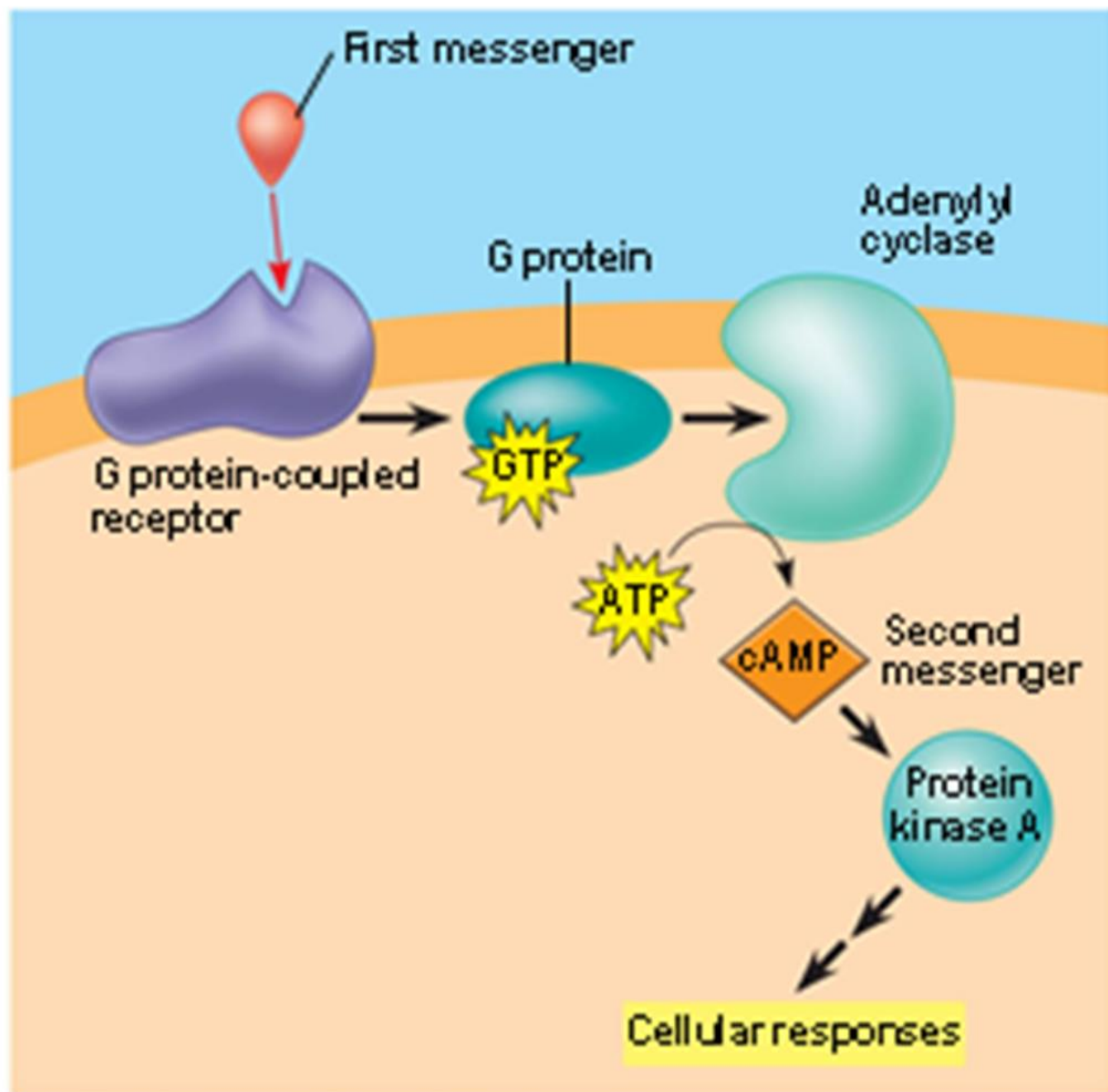
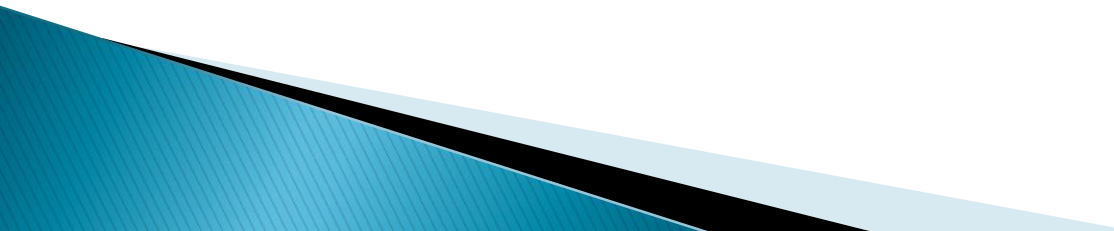
- ▶ Cyclic adenosine monophosphate (cyclic AMP or cAMP), a small molecule made from ATP. In response to signals, an enzyme called adenylyl cyclase converts ATP into cAMP.
 - ▶ Once generated, cAMP can activate an enzyme called protein kinase A (PKA), enabling it to phosphorylate its targets and pass along the signal.
 - ▶ Protein kinase A is found in a variety of types of cells, and it has different target proteins in each. This allows the same cAMP second messenger to produce different responses in different contexts.
 - ▶ E.g Adrenaline, glucagon and lutenizing hormone
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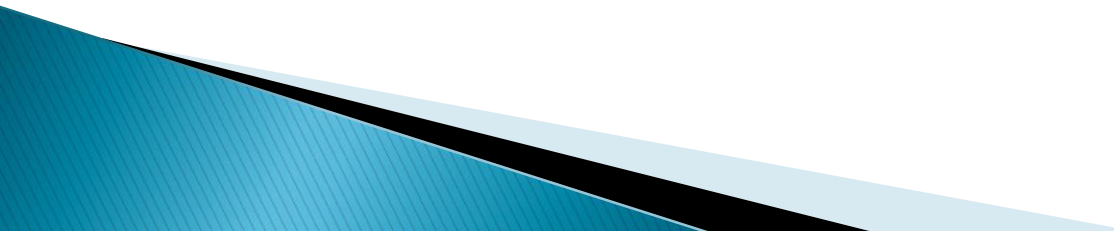
Fig. 15-11



IP3 and DAG

- ▶ In response to a signal, an enzyme called phospholipase C cleaves PIP2 into two fragments, DAG and IP3. These both act as second messenger.
 - ▶ DAG stays in the plasma membrane and can activate a target called protein kinase C (PKC), allowing it to phosphorylate its own targets.
 - ▶ IP3 diffuses into the cytoplasm and can bind to ligand-gated calcium channels in the endoplasmic reticulum, that continues the signal cascade.
 - ▶ E.g Vasopressin, thyroid stimulating hormone G-protein coupled receptor.
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Calcium ions

- ▶ Calcium ions are a widely used type of second messenger. In most cells, the concentration of calcium ions in the cytosol is very low, as ion pumps in the plasma membrane continually work to remove it.
 - ▶ For signaling purposes, calcium ions may be stored in compartments such as the endoplasmic reticulum.
 - ▶ In pathways that use calcium ions as a second messenger, upstream signaling events release a ligand that binds to and opens ligand-gated calcium ion channels.
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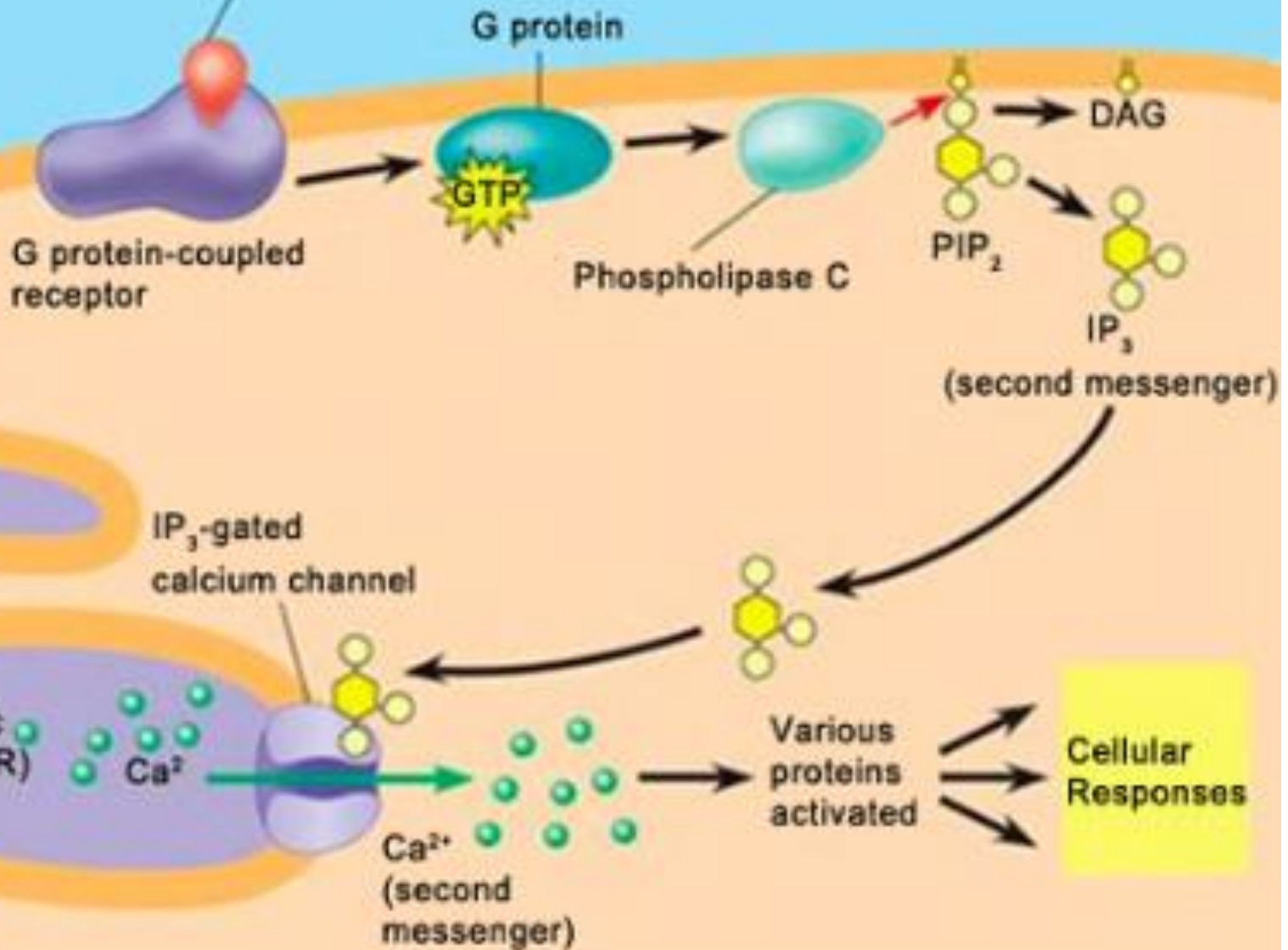
- ▶ These channels open and allow the higher levels of calcium ions that are present outside the cell (or in intracellular storage compartments) to flow into the cytoplasm, raising the concentration of cytoplasmic calcium ions.

E.g.

- ▶ muscle contractions
 - ▶ Releasing of hormones like insulin etc.
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EXTRA-CELLULAR FLUID

Signaling molecule
(first messenger)



Thank you

