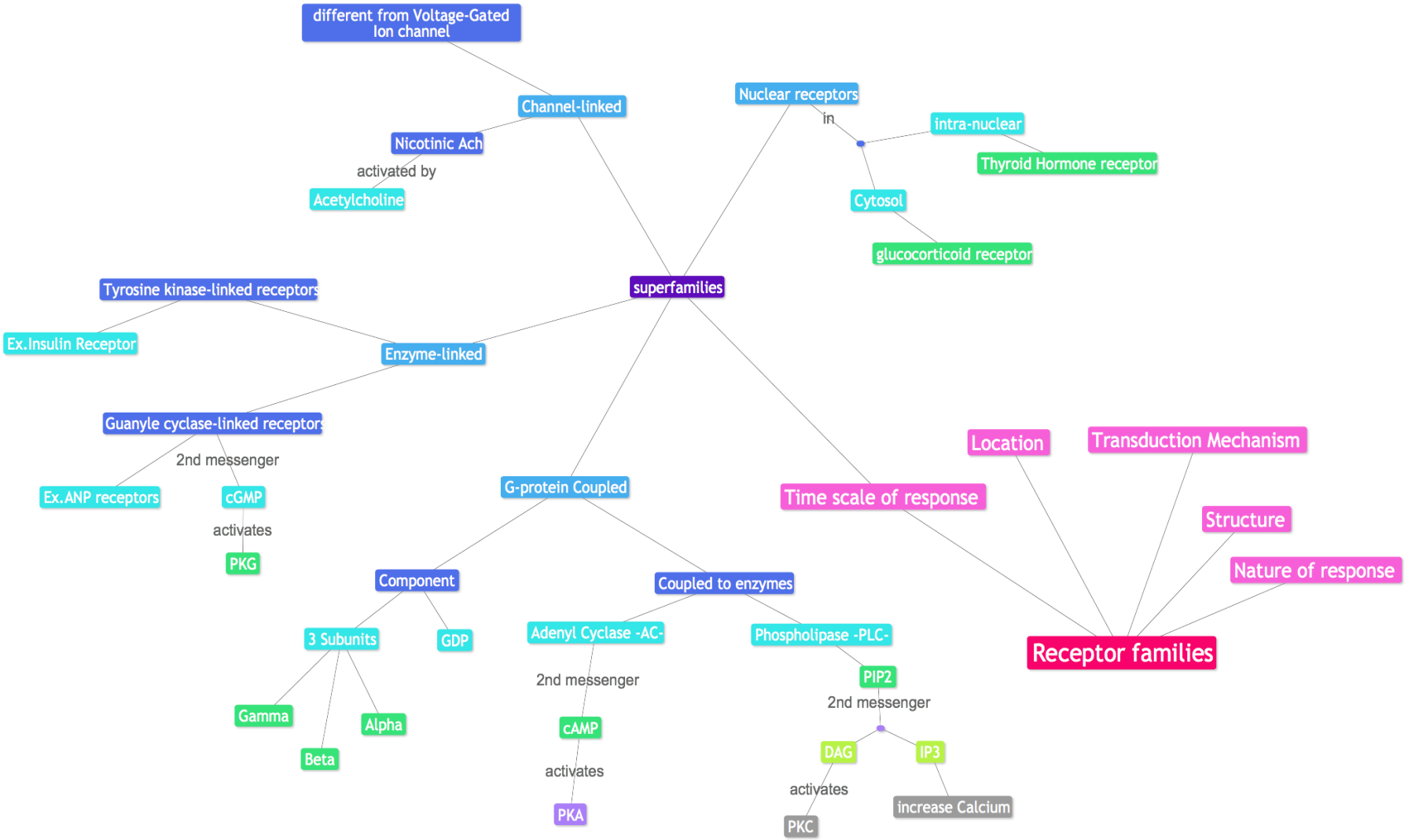
Lecture 7

Pharmacodynamics : Receptor families.

Objectives:

1. Classify receptors into their main superfamilies
2. Recognize their different transduction mechanism
3. Identify the nature & time frame of their response

- Additional Notes
- Important
- Explanation –Extra-


different from Voltage-Gated Ion channel
Channel-linked
Nicotinic Ach
activated by
Acetylcholine
Nuclear receptors
in
intra-nuclear
Thyroid Hormone receptor
Cytosol
glucocorticoid receptor
Tyrosine kinase-linked receptors
Ex.Insulin Receptor
Enzyme-linked
superfamilies
Guanyle cyclase-linked receptors
2nd messenger
Ex.ANP receptors
cGMP
activates
PKG
G-protein Coupled
Component
3 Subunits
GDP
Gamma
Alpha
Beta
Coupled to enzymes
Adenyl Cyclase -AC-
2nd messenger
cAMP
activates
PKA
Phospholipase -PLC-
PIP2
2nd messenger
DAG
IP3
activates
PKC
increase Calcium
Location
Transduction Mechanism
Time scale of response
Structure
Nature of response
Receptor families

Superfamilies

A Receptor

Responsible for selectively sensing & binding of a stimulus (ligand) & its coupling to a **response** via a set of signal **transduction** machinery.

***Its Structure:**

1. N terminal
2. C terminal

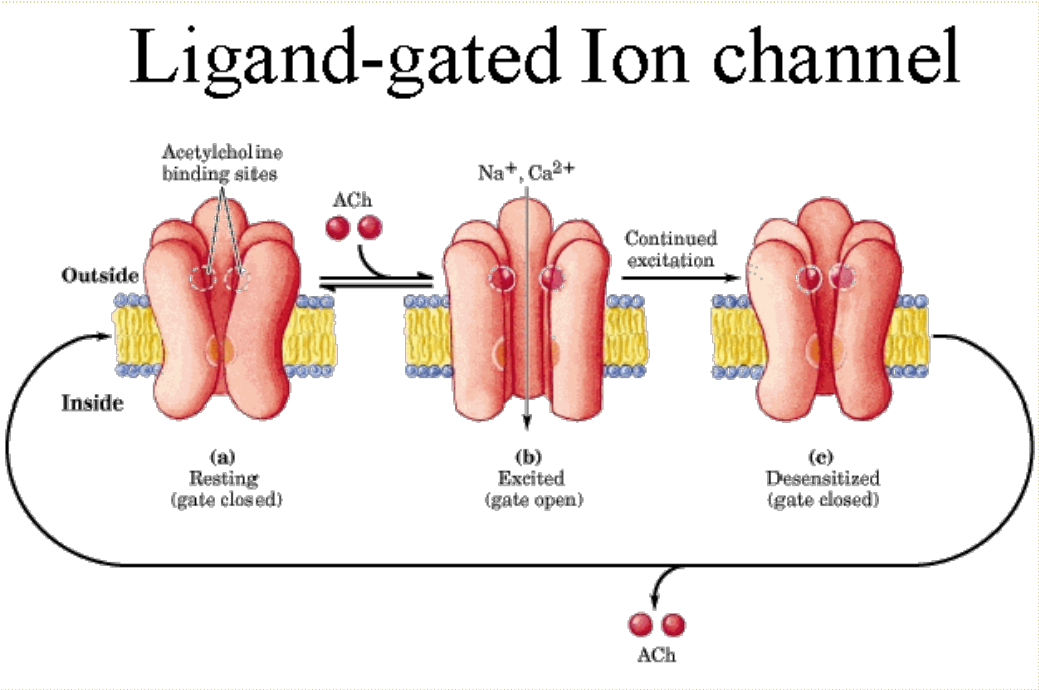
	1-Channel-Linked	2-G-Protein Coupled	3-Enzyme-Linked	4-Nuclear
Function	**Conductance**	**Cell Signal**	**Cell Signal**	**Transcription & Translation**
Time scale	Milliseconds	seconds	Minutes/ hours	Hours/days
Examples	Nicotinic Ach receptor	Muscarinic Ach receptor	Cytokine receptors	Oestrogen receptor

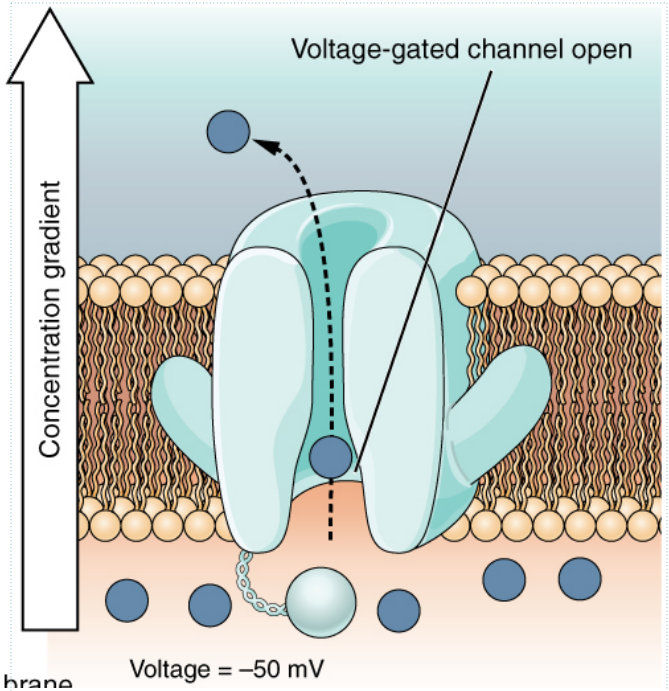
(جميع الصور في هذا العمل فقط للتوضيح)

1-Channel-Linked

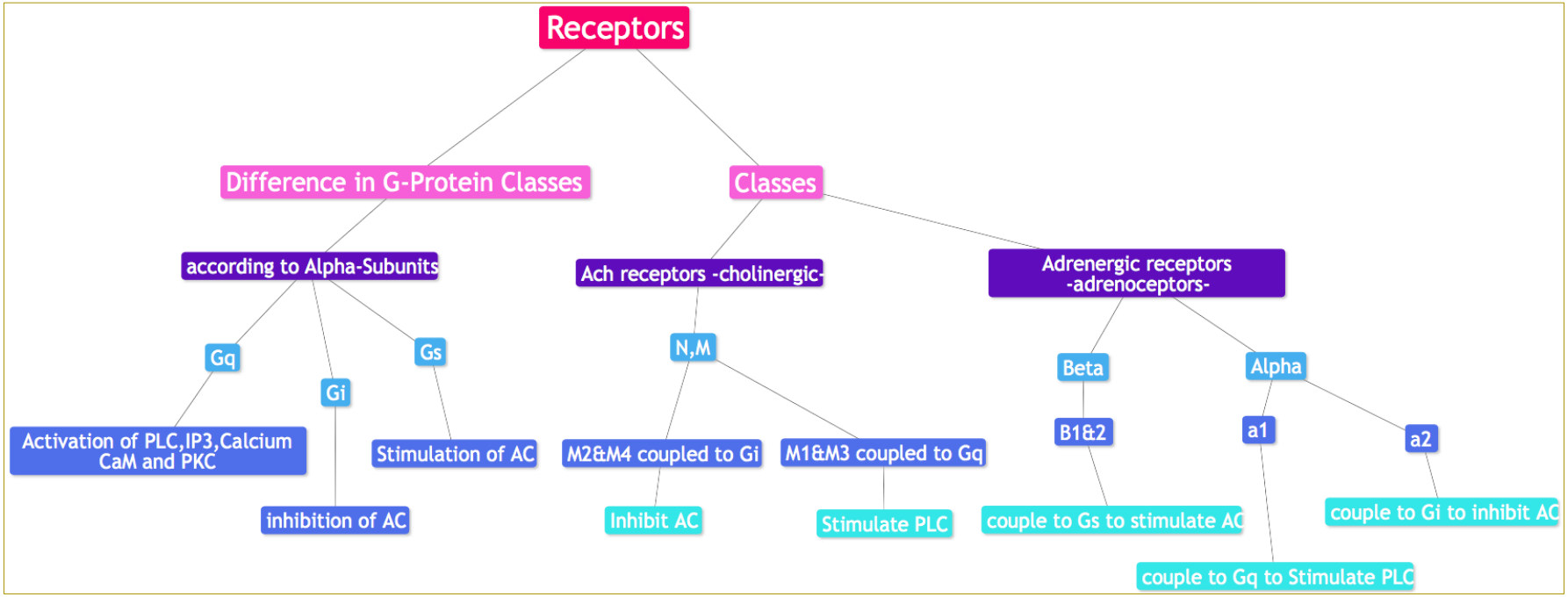
- **Function**: Involved in fast synaptic neurotransmission.
- **Time scale**: occurs over milliseconds.
- **Mechanism**: It is activated directly when a ligand binds to the receptor to open the channel that is incorporated as part of its structure.
- **Examples**: Nicotinic Ach receptor activated by Acetylcholine.

-Different from (Voltage-Gated) Ion Channel: Is activated by a change in action potential not by occupancy of a ligand.

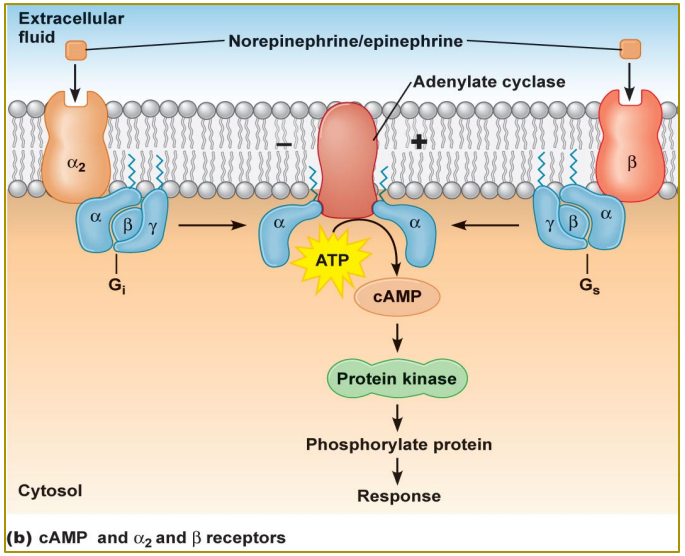




2- G-Protein Coupled

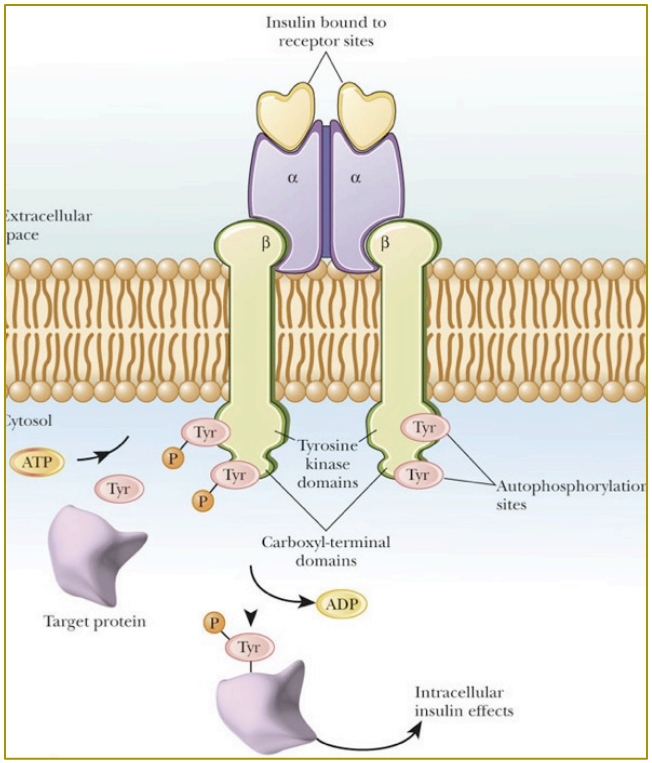


	Adenyl cyclase (AC)	Phospholipase C (PLC)	
2nd messenger	Cyclic adenosine monophosphate (cAMP)	Inositol triphsph (IP3)	Diacyl Glycerol (DAG)
Activates a kinase	Protein Kinase A (PKA)	↑Ca intacellular CaM dependent PK (CAMPK)	Protein Kinase (PKC)
PHOSPHORYLATION OF TARGET PROTEINS			
RESPONSE			

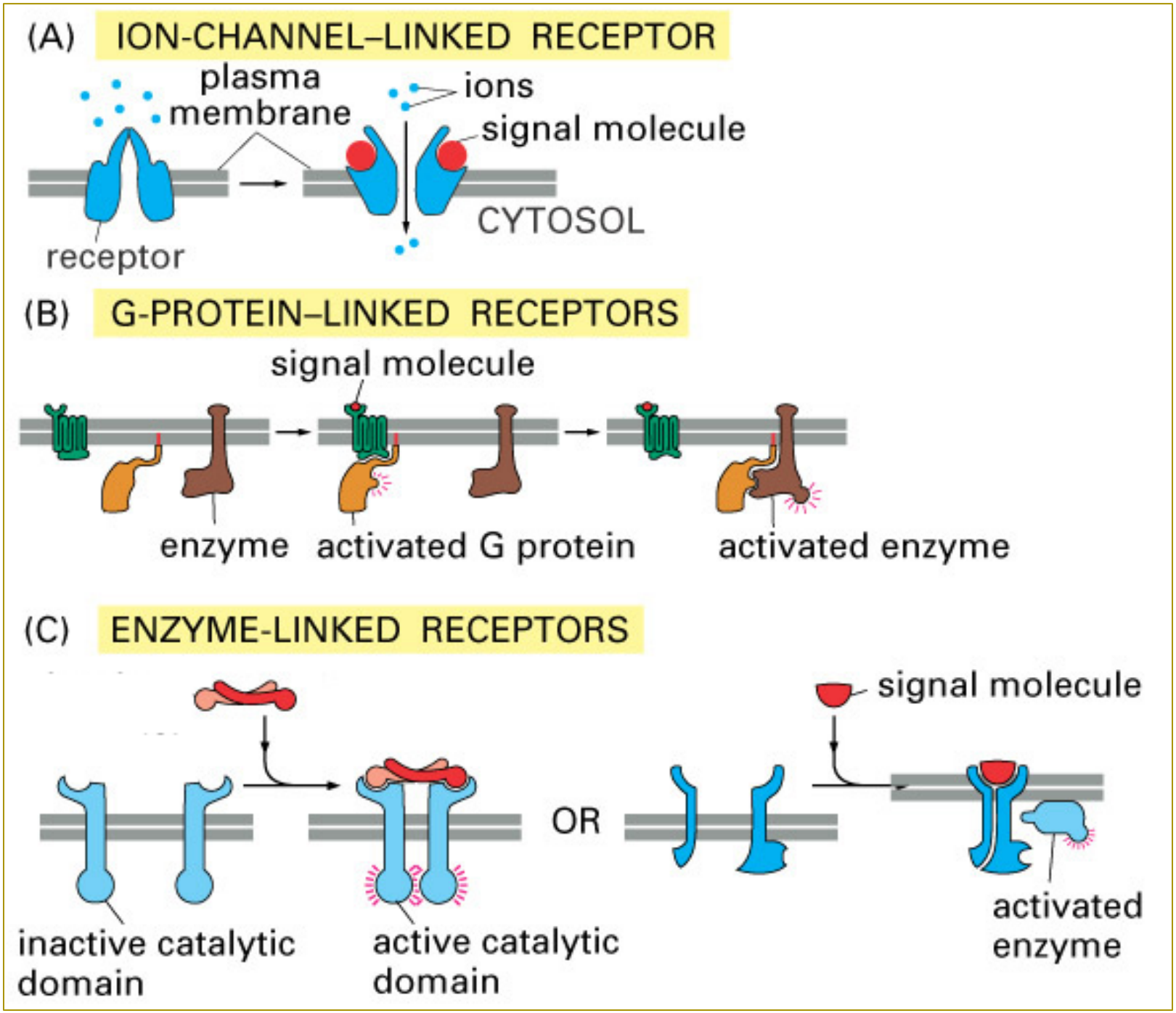


3-Enzyme-Linked

- **Function**: 1- Involved in slow action of; hormones (insulin), growth factors, cytokines, ….
  2-They control many cellular functions as motility, growth, differentiation, division & morphogenesis.
- **Time scale**: This usually require many intracellular signaling steps that take time [min. to hrs.] to process.
- **Examples**: [ANP] Receptor and Insulin Receptor

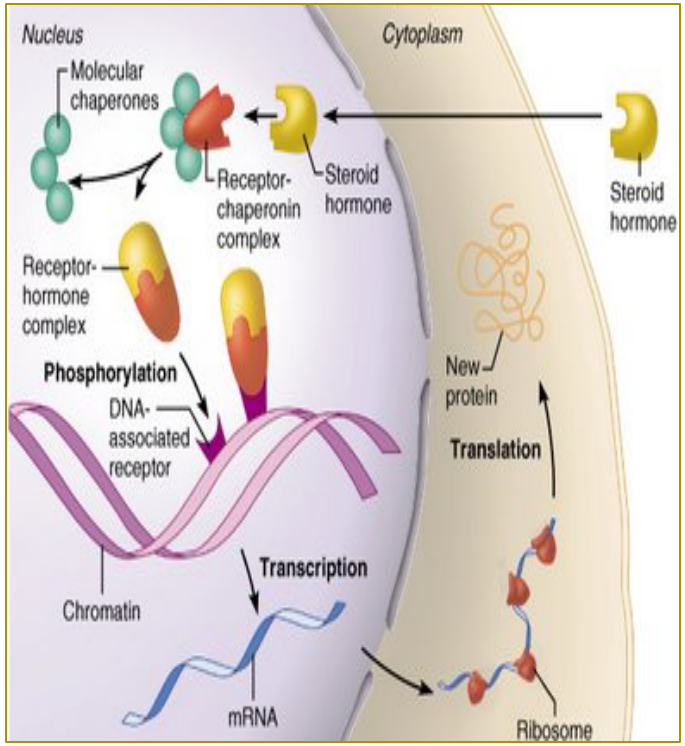


	1.Guanyle cyclase-Linked Receptors	2.Tyrosine Kinase-Linked Receptors
2nd messenger	Cyclic guanyl mono-phosph.(cGMP)	There is NO 2nd messenger because it phosphorylate itself + other proteins that bind to it
Activates a kinase	Protein Kinase G (PKG)	Auto-phosphorylated Tyrosine kinase
PHOSPHORYLATION OF TARGET PROTEINS		
RESPONSE		
Example	[ANP] Receptor	Insulin Receptor


(A) ION-CHANNEL–LINKED RECEPTOR
plasma membrane
ions
signal molecule
CYTOSOL
receptor
(B) G-PROTEIN–LINKED RECEPTORS
signal molecule
enzyme
activated G protein
activated enzyme
(C) ENZYME-LINKED RECEPTORS
signal molecule
OR
inactive catalytic domain
active catalytic domain
activated enzyme

4-Nuclear

- **Function**: 1-Involved in regulation of PROTEIN SYNTHESIS → most slowest in action.
  2-They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a **Responsive Element [RE].** This means that the activated receptors are acting as **Transcription factors [TF]** → expressing or repressing target genes.
- **Ligands usually** : lipid soluble or it could be a phosphorylated protein end product of a 2nd messenger signaling
- **Examples**: Glucocorticoid receptor and Thyroid hormone receptor



	Glucocorticoid receptor	Thyroid hormone receptor
Location	In Cytosol	Intra-nuclear
Mechanism	Once the ligand (drug) is bound to the receptor, a translocation will happen for the complex to the nucleus. In the nucleus, it binds to a certain gene sequence and it will start the process.	
	The activated GC R complex : *Up-regulates expression of **anti-inflammatory proteins.** *Represses expression of **pro-inflammatory proteins** (by preventing the translocation of their transcription factors from the cytosol into the nucleus).	_____

✸ summary

1- Classify receptors into their main superfamilies

Channel-Linked Receptor
G-Protein Coupled Receptors
Enzyme-Linked Receptors
Nuclear Receptors

2- Identify the nature & time frame of their response.

- Channel-Linked Receptor
  Milliseconds
- G-Protein Coupled Receptors
  Seconds
- Enzyme-Linked Receptors
  Minutes to Hours
- Nuclear Receptors
  Hours to Days

3- Recognize their different transduction mechanism

Channel-Linked Receptor

Activation of this receptor lead to opening of ion gate and ion influx , this will lead to (depolarization or hyperpolarization) which produce a response.

G-Protein Coupled Receptors

*Activation of G protein lead to activation of adenylyl cyclase (AC) or phospholipase C (PLC). *Activation of adenylyl cyclase : lead to activated PKA (protein kinase A). *Activation of phospholipase C, will activate CaM-PK and PKC.

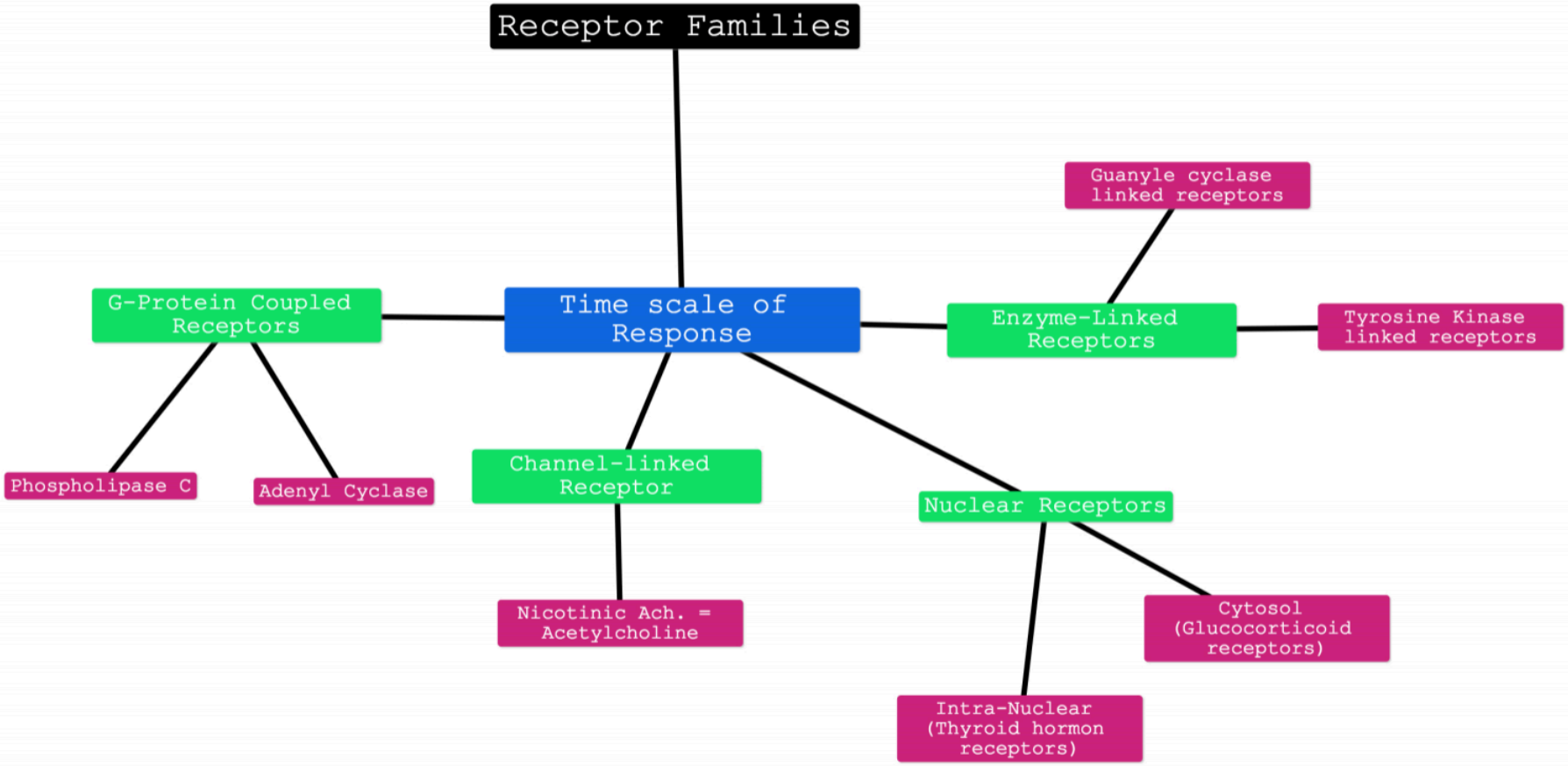
Enzyme-Linked Receptors

When agonist bind to receptor , it gets activated by two ways :- 1- activated guanyl cyclase enzyme to produce cGMP. example : Atrial Natiueretic Peptide receptor (ANP)
2- the receptor undergoes (autophosphorylation) which phosphorylates other protein that produce a response. example : insulin receptor.

Nuclear Receptors

The ligand (drug) has to cross the cell membrane either directly (If it is highly lipid-soluble) or through a carrier protein to act on the receptor. Once it is bound to the receptor, a translocation will happen for the complex to the nucleus. In the nucleus, it binds to a certain gene sequence and it will start the process.

summary



Check your understanding here ! –MCQ's

http://www.onlineexambuilder.com/pharmacodynamics-iii/exam-11827

Good luck!

Done by Pharmacology team 434

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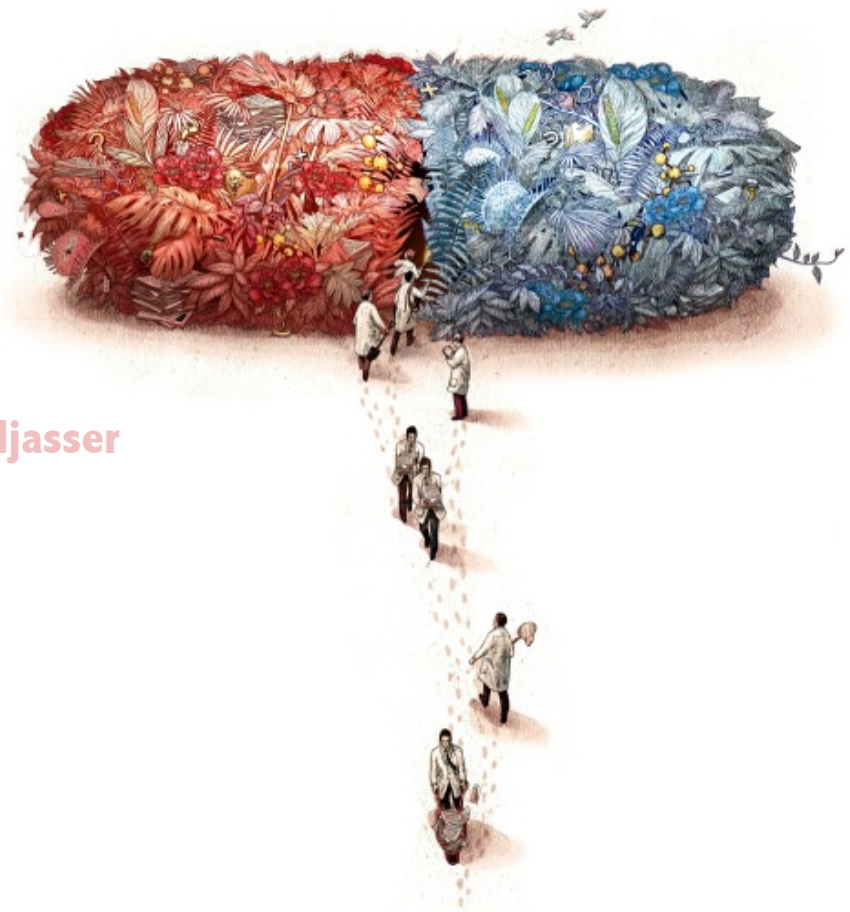

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com