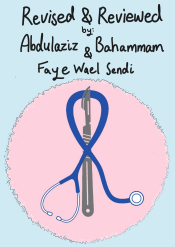


MED441
KING SAUD UNIVERSITY

Receptors families

Important
Main Text
Male slides
female slides
Extra information
Doctors notes

For any future corrections Editing file

If you didn't understand any part from this lecture Click here

Objectives

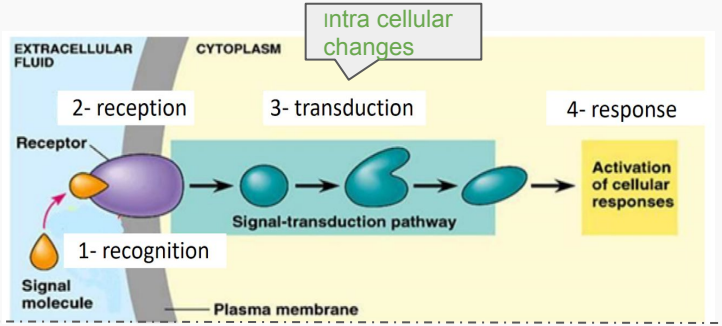
- Classify receptors into their main superfamilies
- Recognize their different transduction mechanisms
- Identify the nature & time frame of their response

Main Receptor Classes (Receptor Families)

Boys slides

- Effect Persistency of drugs
- Cellular mechanism of the drugs
- Selectivity of drugs
- Development of new drugs

The drug will produce its action in 4 steps:



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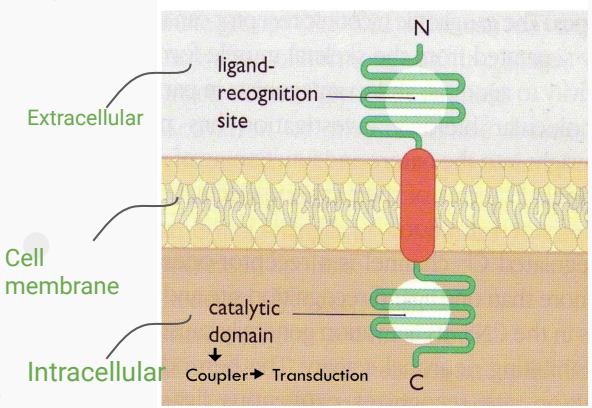
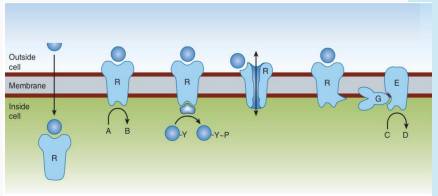
A Receptor structure :

- Ligand(signal molecule) recognition site.
- Inner catalytic domain (catalysis>break down).



1,2 and 3 are surface receptors(on the cell membrane). Type 4 is intracellular receptor

Receptor Families



Nuclear receptor>has to be lipid soluble

Type I	Type II	Type III	Type IV
(Ion Channel-Linked receptors)	(G-Protein coupled receptors)	(Enzyme-Linked receptors)	(Receptors linked to gene transcription)

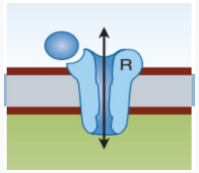
*overview

Receptors Families

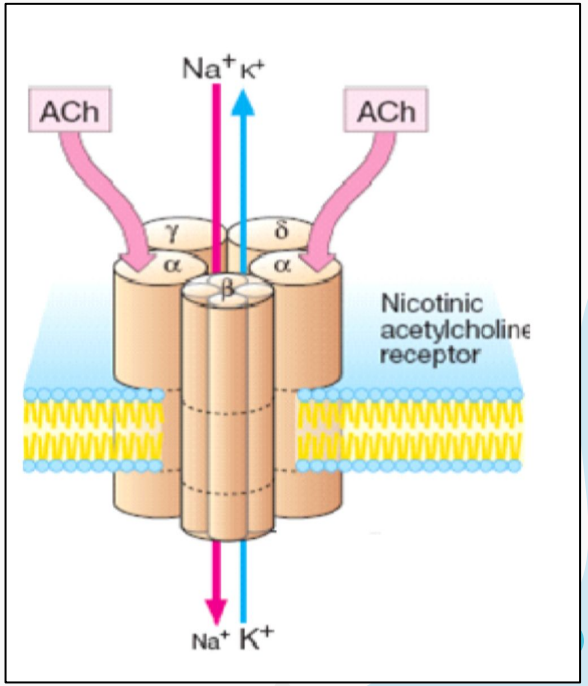
	Type I	Type II	Type III	Type IV
Location	Membrane	Membrane	Membrane	Nucleus
coupling	Direct	G-Protein	Direct	Via DNA
Synaptic transmission	Very Fast	fast	slow	Very slow
Response	milliseconds	Seconds	minutes	Hours or days
Examples	Nicotinic receptors	-Muscarinic receptors -Adrenergic receptors	Insulin receptors	Estrogen Steroid receptors
Effectors	channels	Channels/ Enzymes	Enzymes	DNA

Notes from
*436 & 437

Type I : ion channel-linked receptor (ligand gated ion channel)-(ionotropic receptor)

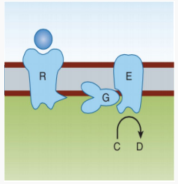


- Located at cell membrane (as it's on the cell membrane, it doesn't require to be lipid soluble).
- Directly activated by ligand binding. (no second messenger needed)
- Directly related to ion channels (when the drug starts produce its effect, the effect will directly change the ion channel, open or close the channel).
- Involved in very fast synaptic transmission.
- Response occurs in milliseconds.
- E.g: nicotinic acetylcholine receptor that is activated by occupancy of a ligand as acetylcholine



Type II

(G-Protein coupled receptors)



- The largest family that accounts for many known drug targets.
- Located at cell membrane .
- Coupled to G-protein Response through ion channels or enzymes
- (not direct)
- Involved in rapid transduction Response occurs in seconds.
- Eg: 1-Muscarinic receptors of Ach (M) .
  2- Adrenergic receptors of Noradrenaline (α and β)

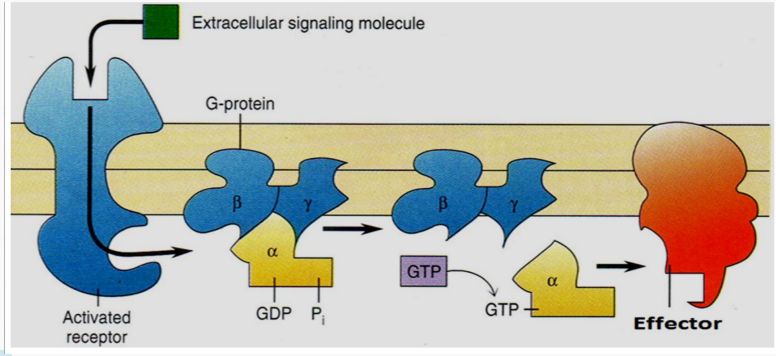
G-protein (Guaninenucleotide-binding proteins)

- Regulatory proteins (regulation for intracellular events)
- Comprise of three subunits (αβγ), α subunits possess GTPase activity.
- G proteins belong to the larger group of enzymes called GTPases.
- Regulate guanine nucleotides GDP, GTP.
- They bind and hydrolyze guanosine triphosphate (GTP) to guanosine diphosphate (GDP).
- They are active 'on' when they are bound to GTP.
- They are inactive 'off' when they are bound to GDP.

Mechanism

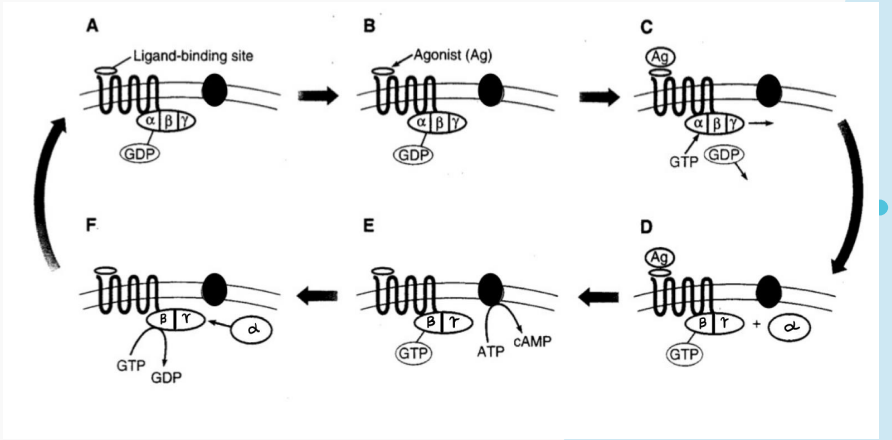
Receptors in this family respond to agonists By:

- promoting the binding of GTP to the G protein alpha (α) subunit.
- GTP activates the G protein and allows it, in turn, to activate the effector protein
- The G protein remains active until it hydrolyzes the bound GTP to GDP and returns to its ground (inactive) state.



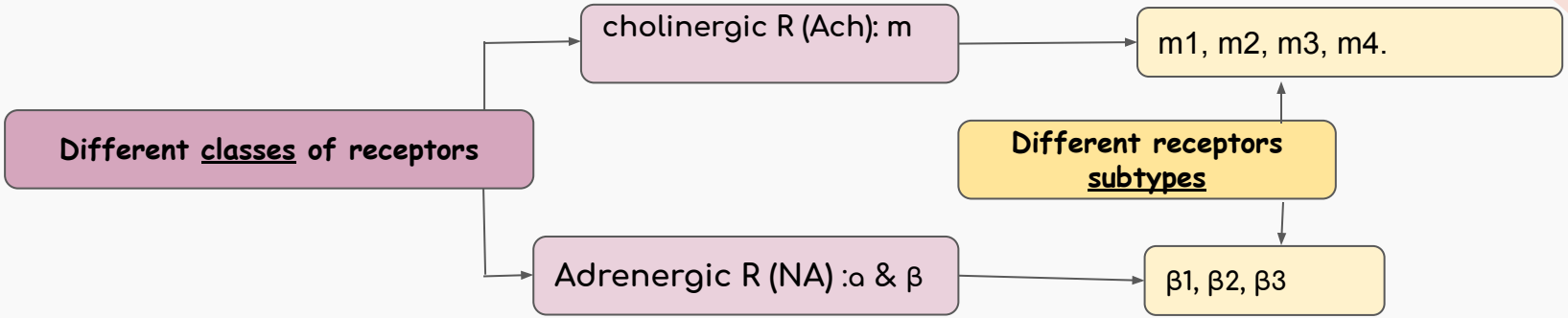
-When the G-protein trimer (αβγ), binds to agonist-occupied receptor , the a-subunit dissociates & is then free to activate an effector.

-Activation of the effector is terminated when the bound GTP molecule is hydrolyzed to GDP which allow α-subunit to recombine with (βγ) and returns to its inactive state.



Type II receptors (G-Protein-Coupled Receptors)

Are the Most Abundant Type



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(Guanine nucleotide-binding proteins) are divided according to their α-subunits into:		
Gs: stimulation of the effector Linked to the CAMP-dependent pathway	Gi: Inhibition of the effector Linked to the CAMP-dependent pathway	Gq: (activation, linked to Inositol phosphate system).

*More details in slides 10+11

Type II : G-Protein coupled receptors

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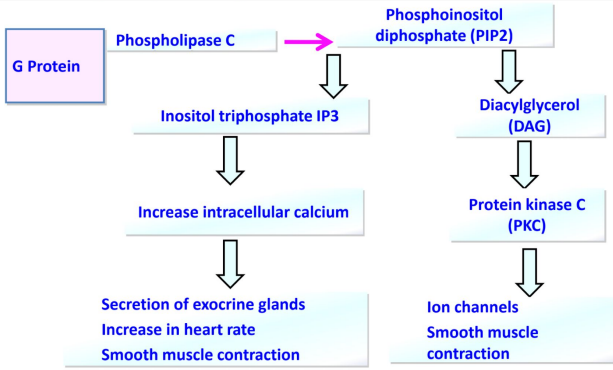
Enzymes (To give Second messengers)

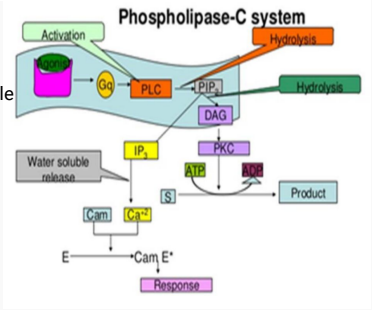
Ion channels

•Phospholipase C enzyme Inositol phosphate system (IP3+DAG)

IP3 = inositol trisphosphate
DAG= diacylglycerol

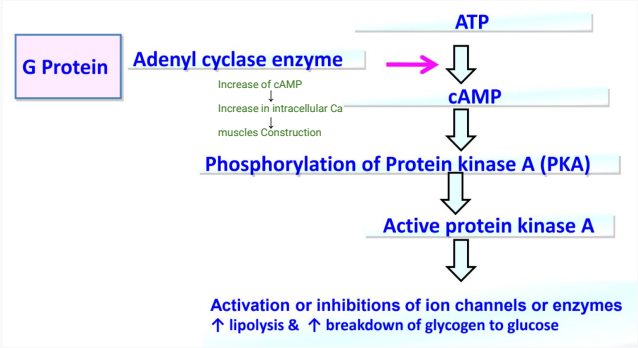


-Inositol phosphate system (IP3+DAG)
-M1 & M3 Ach receptors couple to Gq to stimulate PLC
-α1 Adrenoceptors couple to Gq to stimulate PLC.

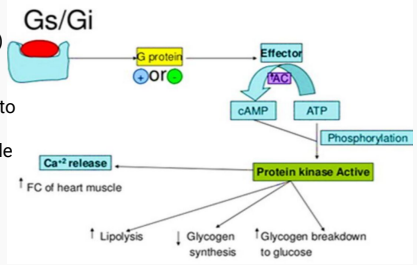


Adenyl cyclase enzyme (AC) Cyclic AMP system (cAMP)

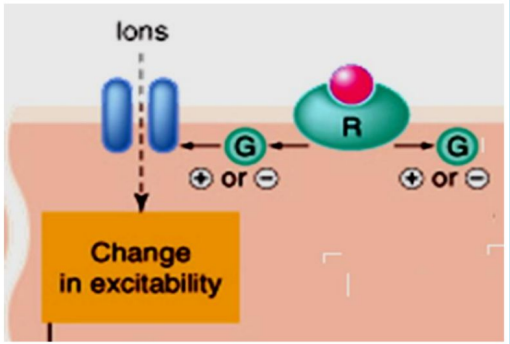
cAMP = cyclic adenosine monophosphate



Cyclic AMP system (cAMP)
-M2 & M4 Ach receptors couple to Gi to inhibit AC.
-α2 Adrenoceptors couple to Gi to inhibit AC.
-β1&2 Adrenoceptors couple to Gs to stimulate AC

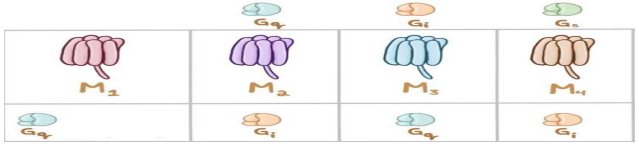


e.g. Ach acts upon muscarinic receptors in heart (opening of K-channel hyperpolarization-inactive-), to decrease heart rate(bradycardia)



*Team 439

Type II receptors (G-Protein coupled receptors classes)

Adrenoceptors (Alpha & Beta)	Cholinergic receptors (M)
α 1 Adrenoceptors couple to Gq to stimulate PLC = Contraction of smooth muscles ◄ second messenger is inositol phosphate system (IP3+DAG)	M1 & M3 Ach receptors couple to Gq to stimulate PLC. ◄ second messenger is inositol phosphate system (IP3+DAG)
α2 Adrenoceptors couple to Gi to inhibit AC. ◆ Second messengers is cyclic AMP system (cAMP)	M2 & M4 Ach receptors couple to Gi to inhibit AC ◆ Second messengers is cyclic AMP system (cAMP)
β1&2 Adrenoceptors couple to Gs to stimulate AC ◆ Second messengers is cyclic AMP system (cAMP)	
- Adrenaline binds to α2 Adrenoceptors that will activate Gi (Inhibitory) protein. Gi protein will inhibit (AC) that will decrease cAMP Concentration = Decrease contraction. - Adrenaline works on heart muscles by binding to β2 Adrenoceptors, that will activate Gs (Stimulatory) protein. Gs protein will activate (AC), that will increase cAMP Concentration = Increase muscle contraction (tachycardia) Thx for #438	- Acetylcholine works on bronchi by M3 Ach receptor that will activate Gq proteins and Gq proteins will activate (PLC) phospholipase c that will increase Ca concentration= Increase contraction of smooth muscles - Adrenaline works on smooth muscles by a 1 receptor that will activate Gq proteins and Gq proteins will activate (PLC) that will increase Ca concentration = Increase contraction

Ach receptors	Couple to		
M1 stimulatory	Gq	stimulate PLC	stimulation
M2 inhibitory	Gi	Inhibit AC(↓ cAMP) Opening of K-channels	:Heart (Bradycardia) (slow heart rate)
M3 stimulatory	Gq	stimulate PLC	Contraction of Smooth muscles (bronchoconstriction)
M4 inhibitory	Gi	Inhibit AC (↓cAMP)	Inhibition

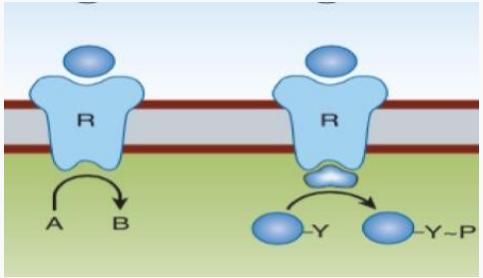
stimulate: الأعداد الفردية

Inhibit :الأعداد الزوجية

Adrenoceptors	Couple to		
β1 stimulatory	Gs	stimulate AC	Stimulation (tachycardia Increase heart rate Because ↑ Ca)
α1 stimulatory	Gq	stimulate PLC	Contraction of smooth muscles

*Extra information Team 437

Type III (Enzyme-Linked receptors) (Tyrosine Kinase-linked receptor)



- Located at cell membrane
- Linked to enzyme (with intrinsic enzymatic activity) (They control many cellular functions as metabolism and growth)
- Tyrosine Kinase-linked receptor

- Involved in response to hormones, growth factors.
- They control many cellular functions as metabolism and growth.
- Response occurs in minutes to hours.

- Activation of kinases as **tyrosine kinase** with **phosphorylation of tyrosine residue** on their substrates and activation of many intracellular signaling pathways in the cell.

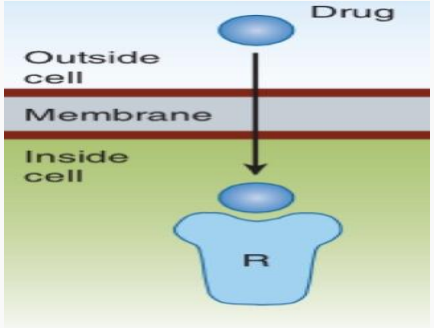
E.g. Insulin receptors

* Kinase enzyme make phosphorylation (adding phosphate) to the tyrosine. Tyrosine located in the intracellular protein, like enzyme

*Extra information Team 437

Type IV: Nuclear receptors
Gene transcription receptors

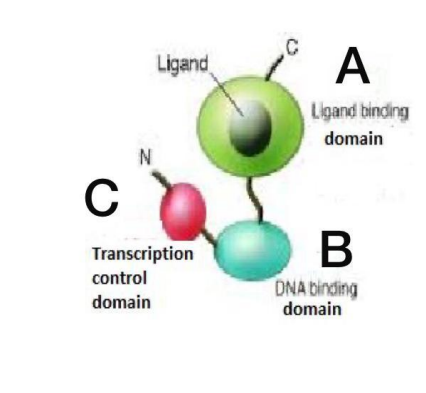
- Located intracellularly (so that the drug has to be lipid soluble).
- Directly related to DNA (Gene transcription).
- Activation of receptors either increase or decrease protein synthesis.
- Response occurs in hours or days and persists longer.
- Their natural ligands are lipophylic hormones; steroids,thyroids, estrogen.

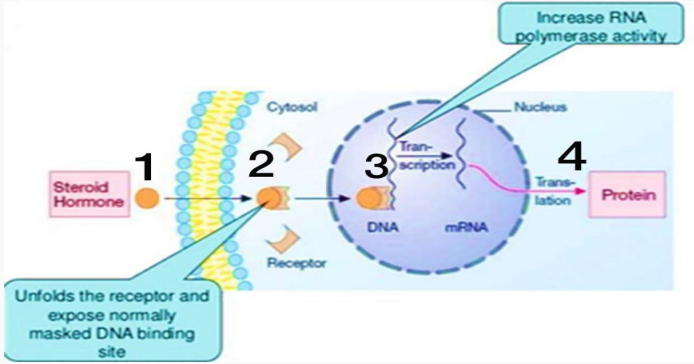


- They possess an area that recognizes specific DNA sequence in the nucleus which can bind it. This sequence is called a Responsive Element [RE] .(the place where the drug will bind is the DNA, especially in some sequence of the DNA which we called it Responsive Element)
- This means that the activated receptors are acting as TRANSCRIPTION FACTORS [TF] → expressing or repressing target genes.
- **E.g.Estrogen Steroid receptors**

*Boys Doctor Notes

Type IV: Gene transcription receptors





A-المنطقة التي سيجلس عليها Ligand

B-المنطقة التي تهبط على DNA

C-المسؤول عن زيادة او نقص gene transcription

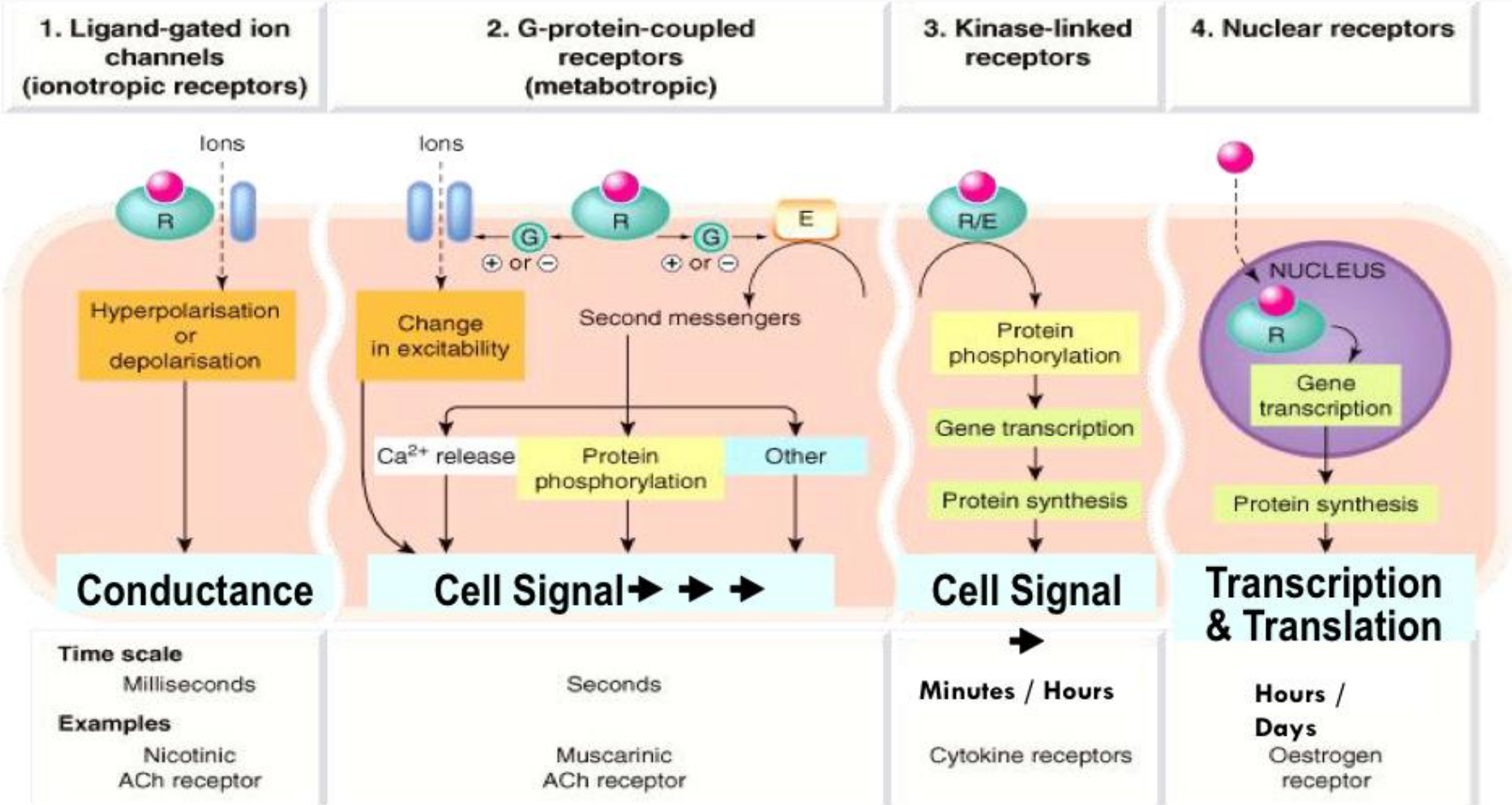
1- لازم ligand يكون lipophilic hormones ليستطيع اختراق cell membrane

2-لما يرتبط ligand مع receptor راح يتغير شكله ليستطيع الدخول داخل nucleus

3--يهبط على Responsive Element يا انه يزود او ينقص gene transcription

4- ينتج عندنا protein يا انه يكون صالح او طالح

Summary


1. Ligand-gated ion channels (ionotropic receptors)
2. G-protein-coupled receptors (metabotropic)
3. Kinase-linked receptors
4. Nuclear receptors
Ions
R
Hyperpolarisation or depolarisation
Conductance
Ions
G
R
G
E
⊕ or ⊖
⊕ or ⊖
Change in excitability
Second messengers
Ca2+ release
Protein phosphorylation
Other
Cell Signal
R/E
Protein phosphorylation
Gene transcription
Protein synthesis
Cell Signal
NUCLEUS
R
Gene transcription
Protein synthesis
Transcription & Translation
Time scale
Milliseconds
Examples
Nicotinic ACh receptor
Seconds
Muscarinic ACh receptor
Minutes / Hours
Cytokine receptors
Hours / Days
Oestrogen receptor

MCQs:

1- …… is the only intracellular			
A-Type IV	B-Type II	C-Type III	D-Type I

2-Nicotinic receptors activated by acetylcholine is an example for:			
A-G-Protein	B-Enzyme-Linked	C-ion channel-Linked	D- -linked to gene transcription

3-..... and ……..produce respective stimulation and inhibition of AC:			
A- Gs & Gq	B- Gi & Gq	C-Gs & Gi	D-none of above

4-Their natural ligands are lipophilic:			
A-Type I Receptors	B-Type II Receptors	C-Type III Receptors	D-Type IV Receptors

Answers:
1-A
2-C
3-C
4-D

5-Which one of these type of receptors gives the fastest response?			
A- Nicotinic receptors	B-Muscarinic receptors	C- Insulin receptors	D-estrogen steroid receptor

6-Insulin receptors are examples of :			
A- Type I	B-Type II	C- Type III	D- Type IV

7--What is the nature of the ligands that bind to type IV receptors ?			
A- amphipathic	B- hydrophilic	C- hydrophobic	D- polar ,uncharged

8-which one of the following is a target for G-protein?			
A-Adenyl cyclase enzyme (AC)	B-nucleus	C- Ach	D- A & C

Answers:
5-A
6-C
7- C
8- A

SAQ

1-When mentioning the regulate guanine nucleotides (GTP and GDP), which one is found in the active form?
2-Which enzyme configures ATP into cAMP?
3-Which system gets activated when acetylcholine binds to M2 & M4 via Gi receptor ?
4-Type IV receptors are found in ?
5-Inositol phosphate system activates which protein?

ANSWERS

1-GTP
2-Adenyl cyclase enzyme
3-Adenyl cyclase (AC)
4-Nucleus
5-Protein Kinase C

Thank you

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- Abdullah Alghamdi
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