RECEPTORS OVERVEW

Dr Issam Skaba

LECTURE OVERVIEW

1-intruduction

2-receptors in general

3-G protein receptor .why?

4-signal transduction pathways

-cAMP pathway

-IP3/DAG

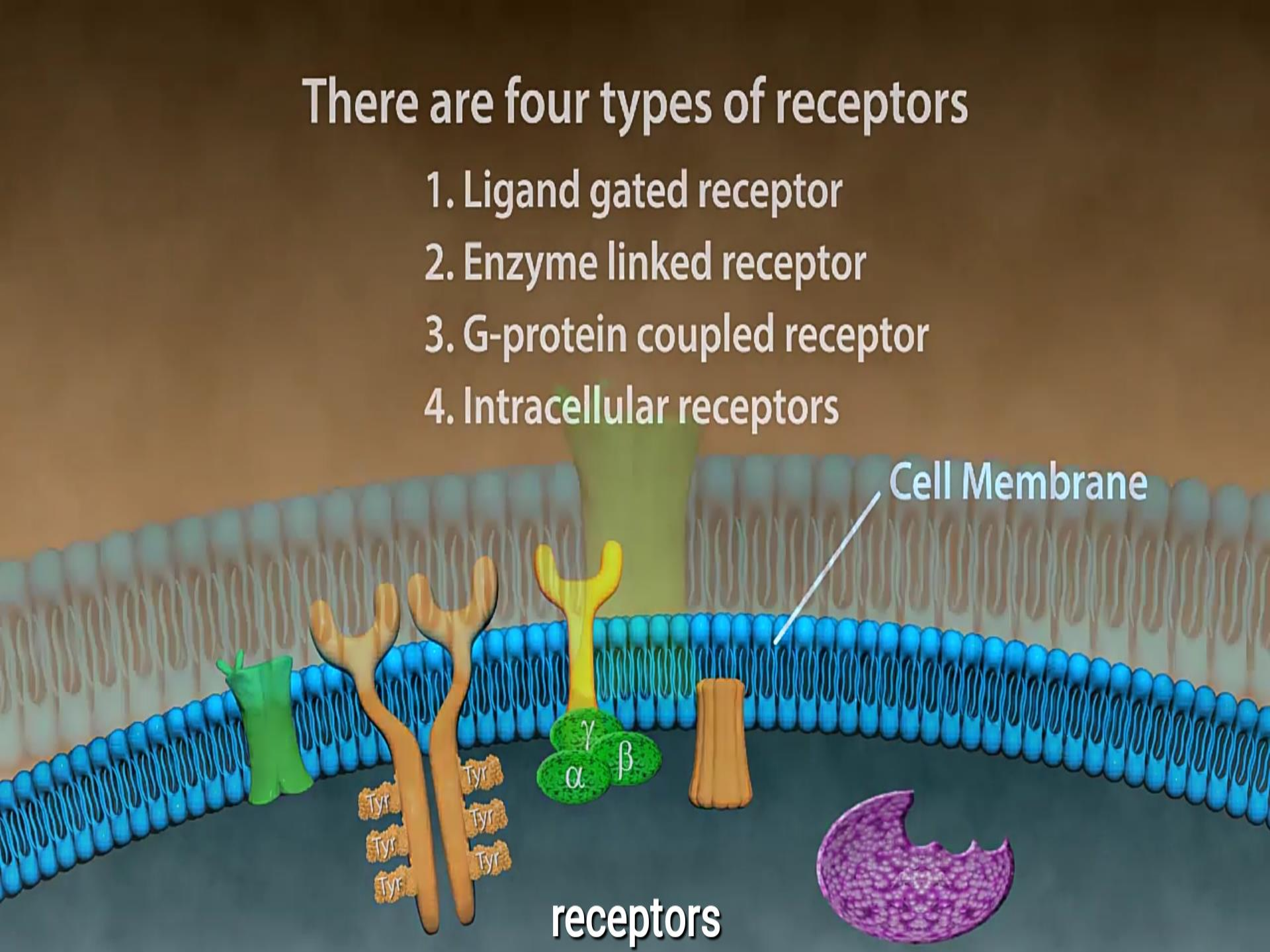
5-moscarinic , adrenergic dopamin histamin vasopressin receptors

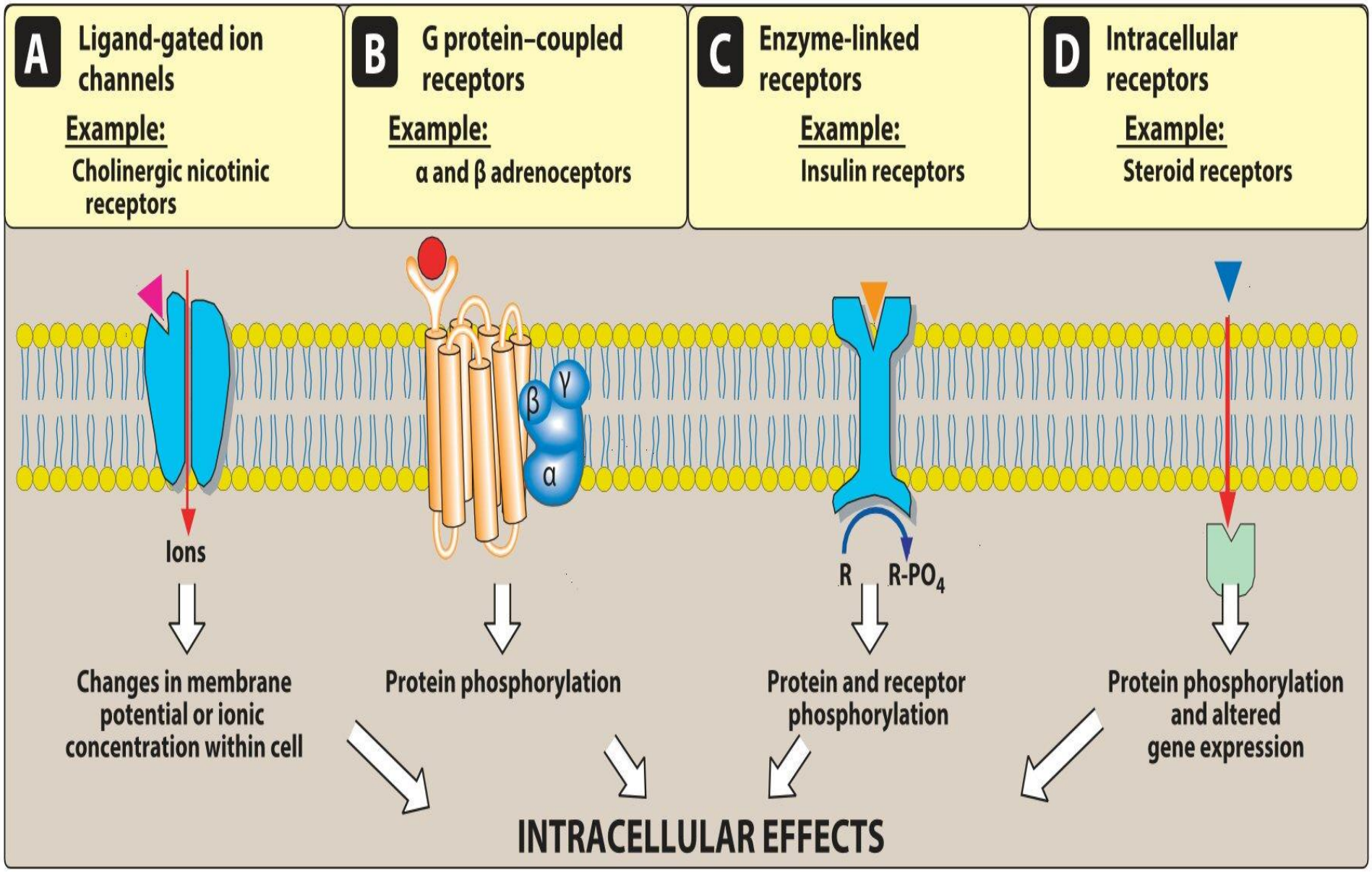
6-MNEMONICS

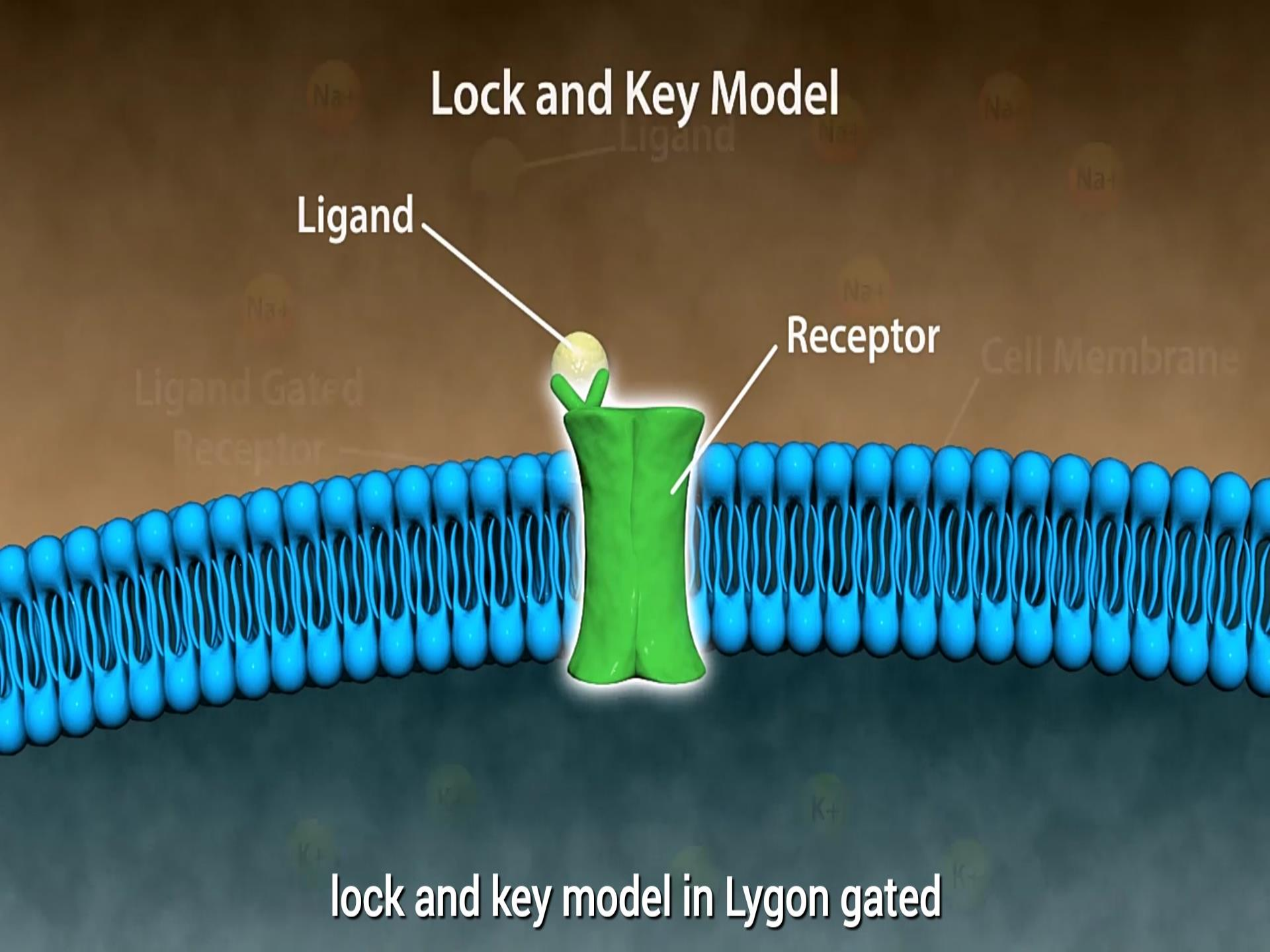
7-Agonists & antagonists

There are four types of receptors

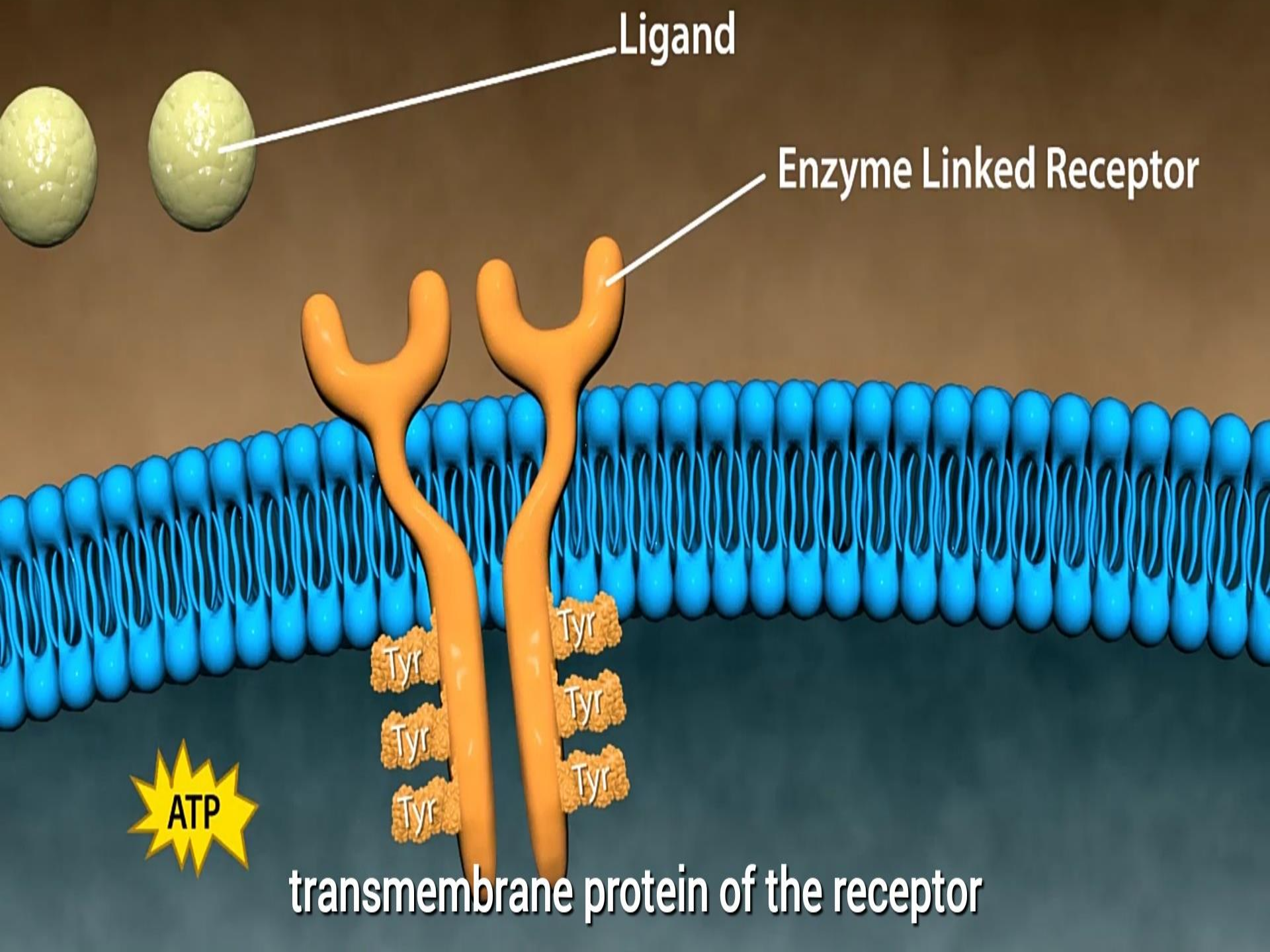
1. Ligand gated receptor
2. Enzyme linked receptor
3. G-protein coupled receptor
4. Intracellular receptors

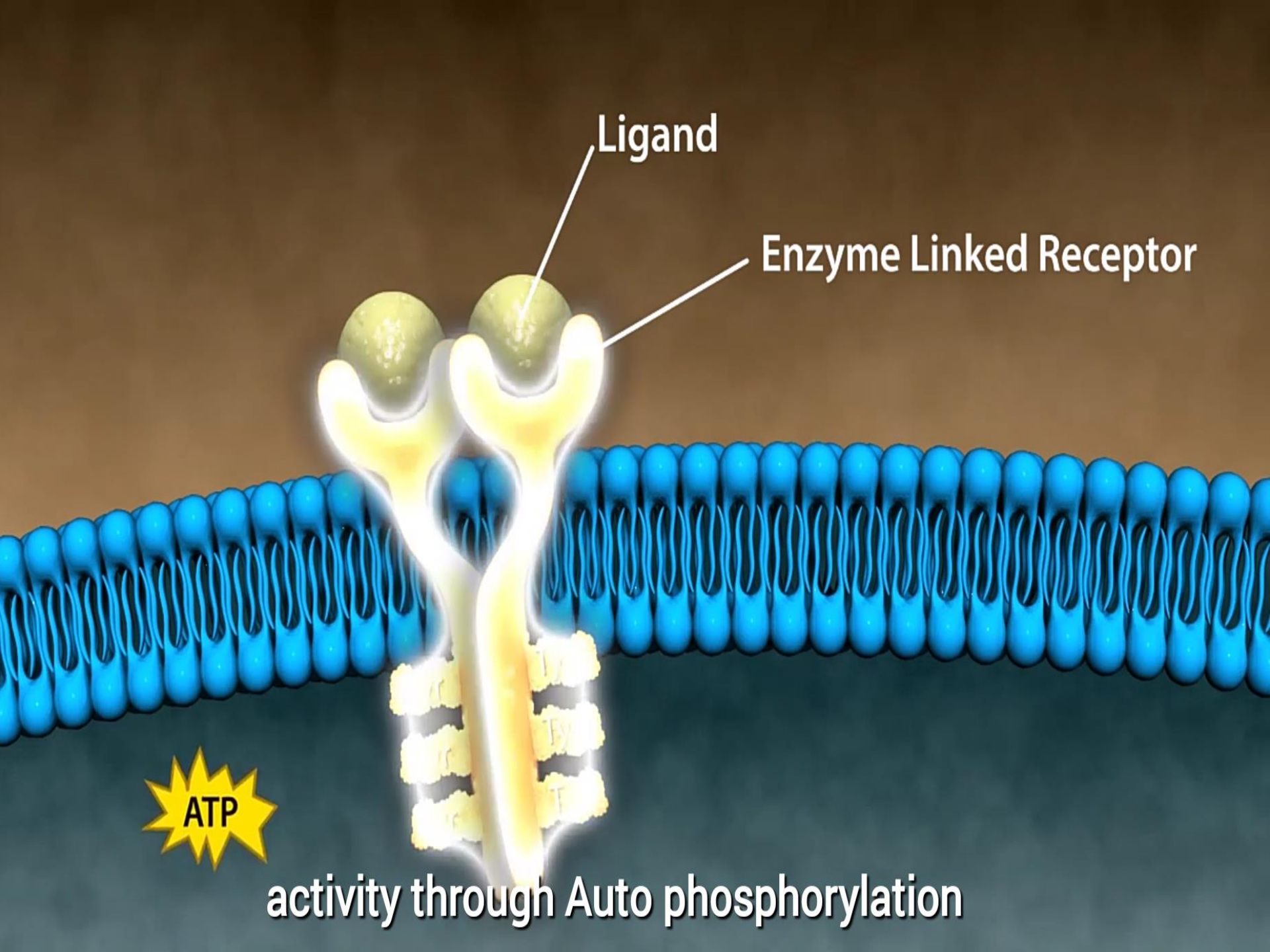


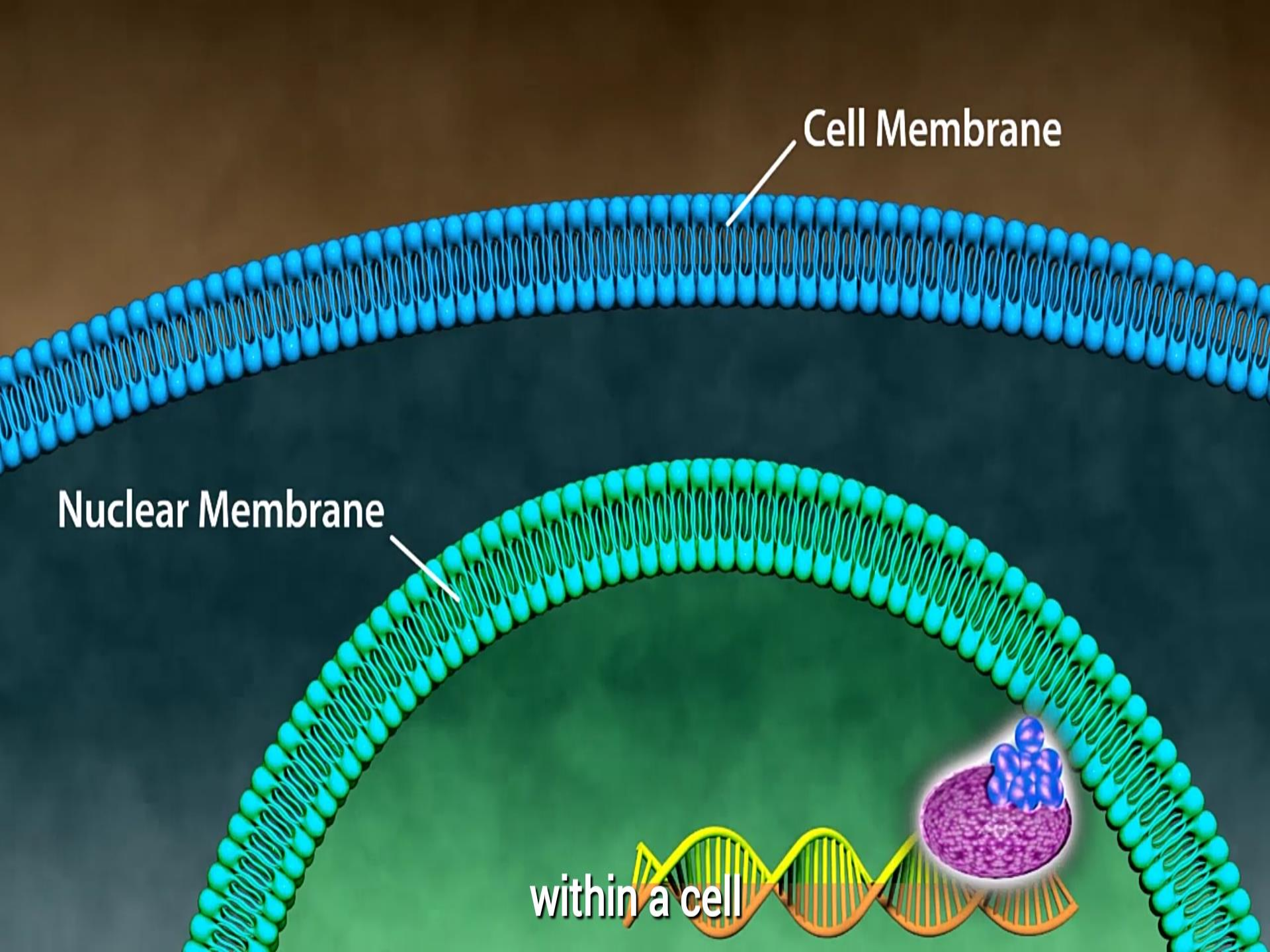

A
Ligand-gated ion channels
Example:
Cholinergic nicotinic receptors
B
G protein–coupled receptors
Example:
α and β adrenoceptors
C
Enzyme-linked receptors
Example:
Insulin receptors
D
Intracellular receptors
Example:
Steroid receptors
β
γ
α
Ions
R
R-PO4
Changes in membrane potential or ionic concentration within cell
Protein phosphorylation
Protein and receptor phosphorylation
Protein phosphorylation and altered gene expression
INTRACELLULAR EFFECTS

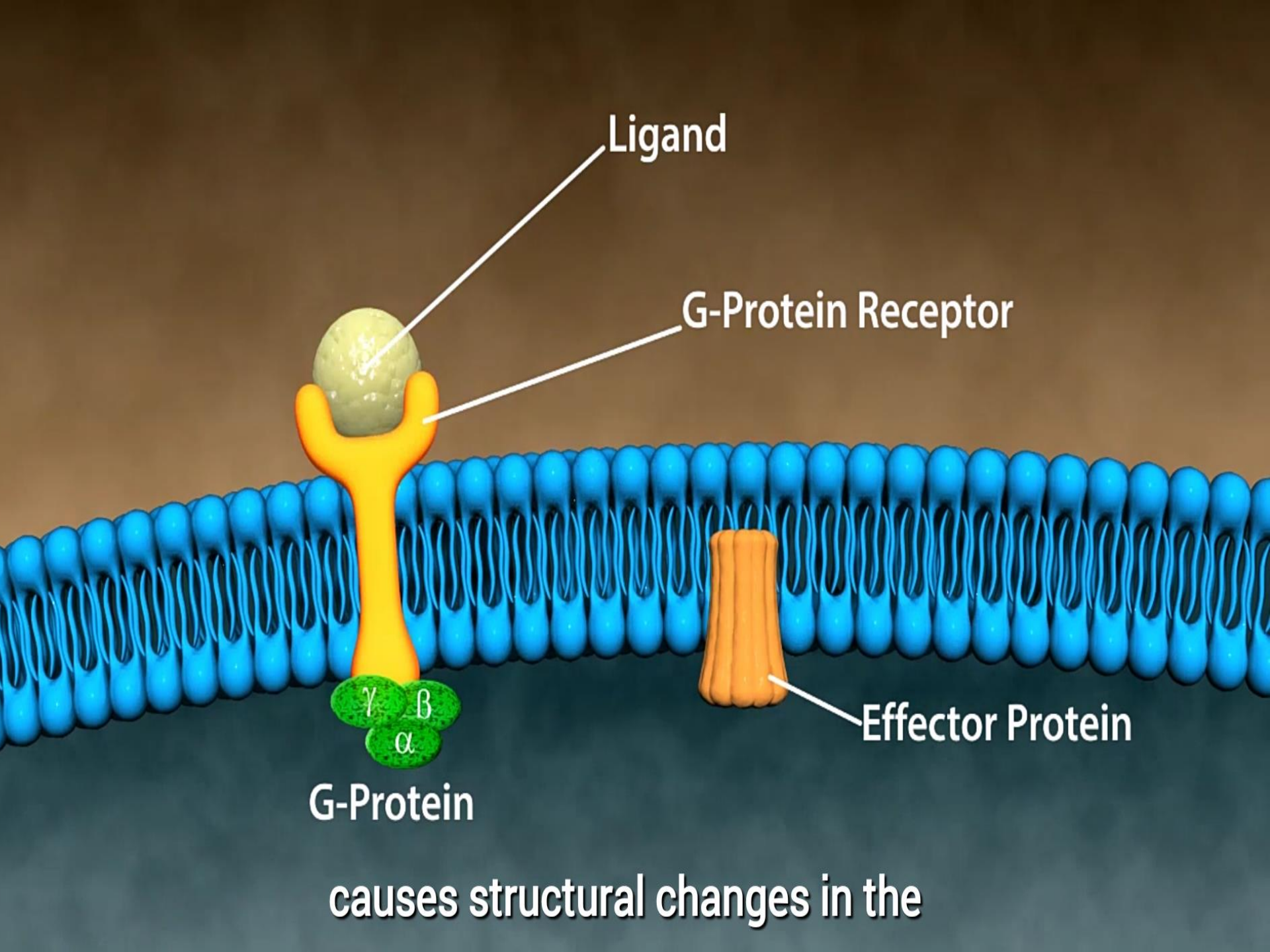


lock and key model in Lygon gated


Ligand
Enzyme Linked Receptor
Tyr
Tyr
Tyr
Tyr
Tyr
Tyr
ATP
transmembrane protein of the receptor


Ligand
Enzyme Linked Receptor
ATP
activity through Auto phosphorylation


Cell Membrane
Nuclear Membrane
within a cell



causes structural changes in the

Some characteristics of signal transduction

Signal transduction has two important features:

1) The ability to amplify small signals (1

ligand may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. a fraction of the total receptors (may need to be occupied to elicit a maximal response (insulin 99% spare receptors).(human heart 5-10% of B AD R are spare i.e. little functional reserve in failing heart.

2) mechanisms to protect the cell from excessive stimulation.

(for example, high concentrations of calcium, initiate cell death)

1.Desensitization and down-regulation of receptors.

receptors internalized

and sequestered within the cell, unavailable for further agonist interaction

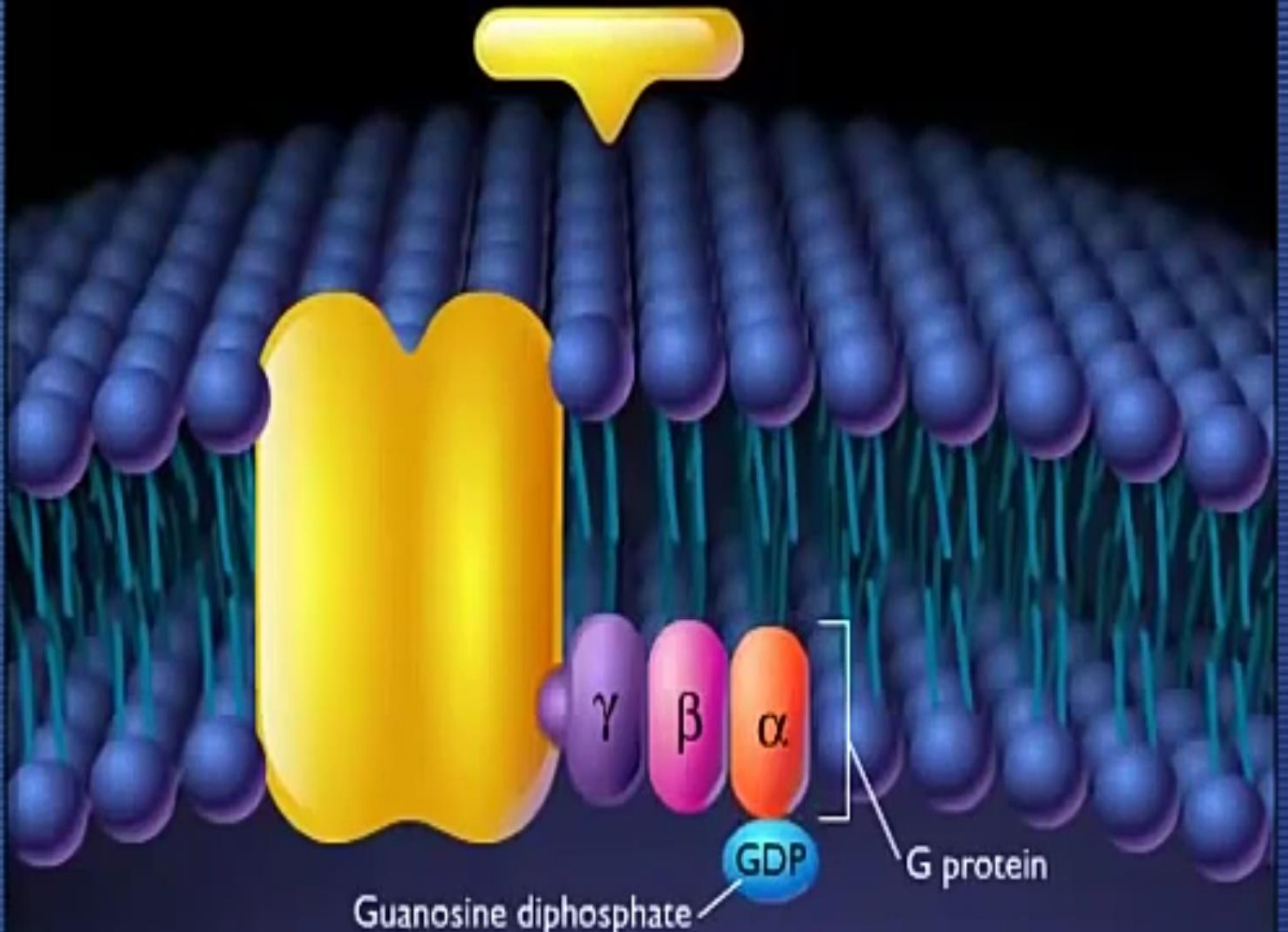
what r G proteins

- Heterotrimeric GTP-binding proteins,composed of 3 subunits
- Guanine nucleotid-binding protiens

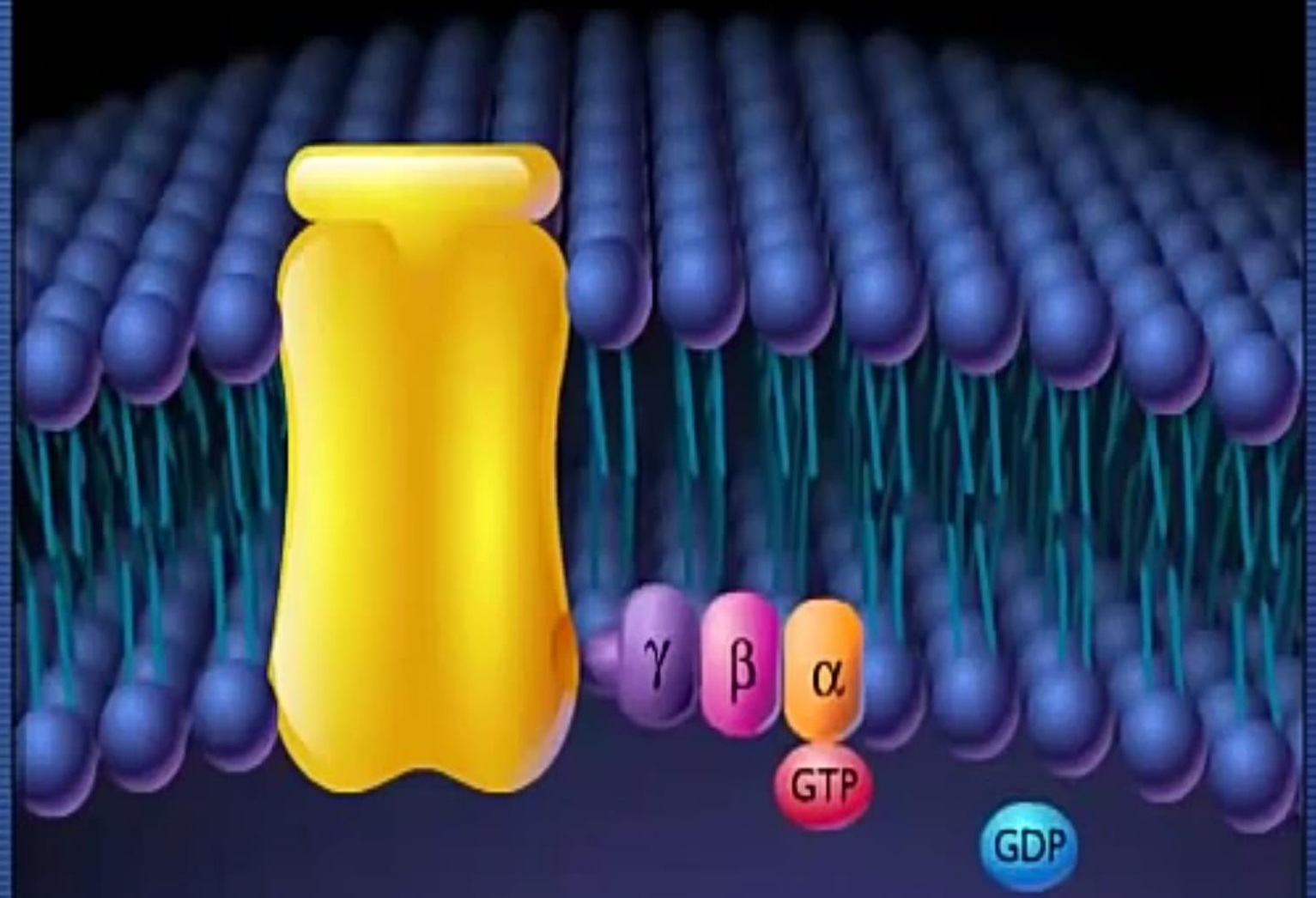
There are many kinds of G proteins (for

example, Gs, Gi, and Gq), but they all are composed of three protein subunits. The α subunit binds guanosine triphosphate (GTP),and the β and γ subunits anchor the G protein in the cell membrane

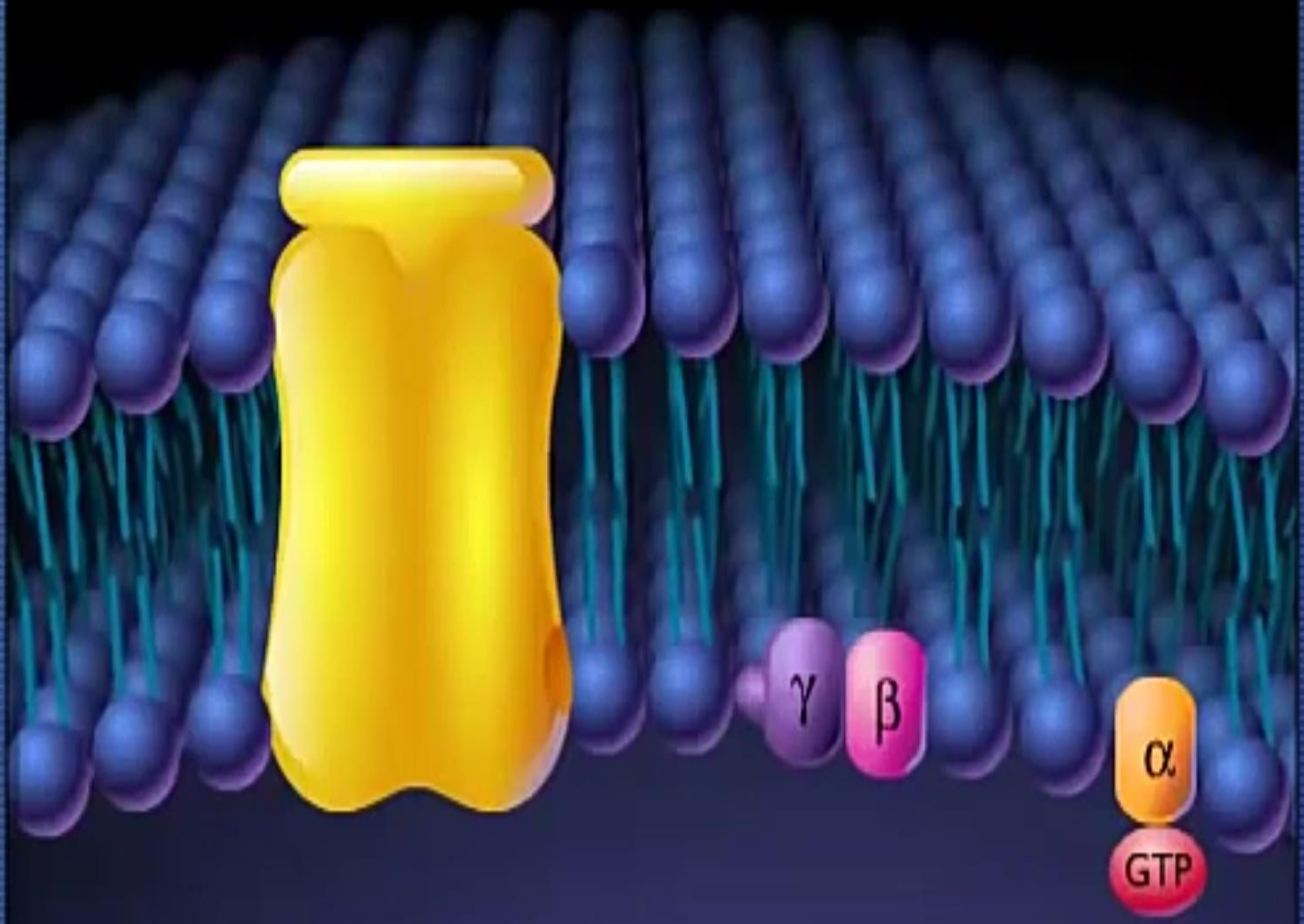
- Guanosine triphosphate = GTP
- Guanosine diphosphate = GDP



subunit when the ligand binds to the



replaces the guanosine diphosphate on



receptor when the ligand separates from

Why G protien-linked receptors?

- Very important physiologically
- Very divers in function
- Only found in eucaryotes{حقيقي النواة}
- THE TARGET OF ABOUT 40% OF ALL DRUGS WE KNOW.

Signal Transduction Pathways

Go to Index

Two important signal pathways:

cAMP-dependent pathway.

- Gαs - "Gs" *stimulatory*
- Gαi - "Gi" *inhibitory*

IP3/DAG pathway.

- Gαq - "Gq"

Why?

He who has a why to live

Can bear almost any how

Friedrich Nietzche

He who has a why to G proteins can

Bear any mechanism

Signal Transduction Pathways

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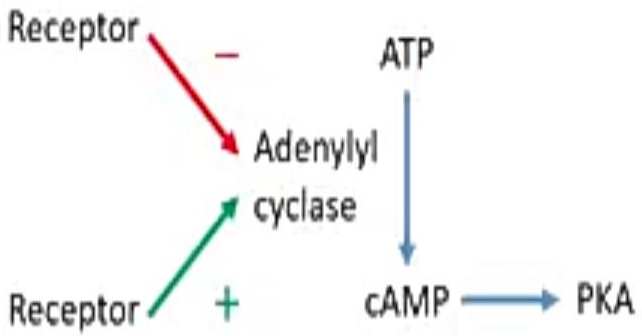
Two important signal pathways:

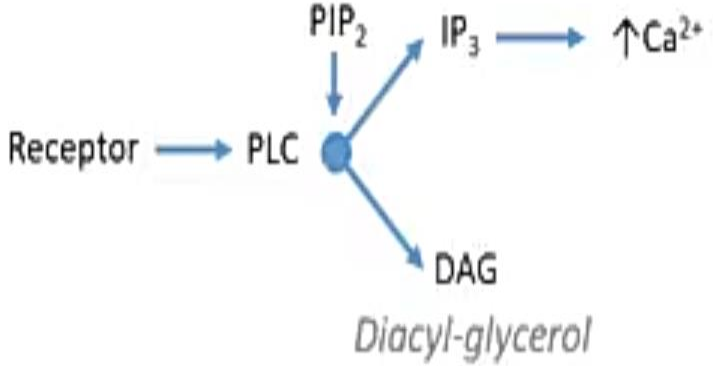
cAMP-dependent pathway.

- ↑Gs -or- ↓Gi
- Target = Adenylyl cyclase
  - ATP → cAMP → PKA



IP3/DAG pathway.

- Gq
  - Target = Phospholipase C
  - Lipids → PIP_2
    - → ↑IP_3 → ↑Ca^{2+}
    - → ↑DAG → ↑PKC



Signal Transduction Pathways

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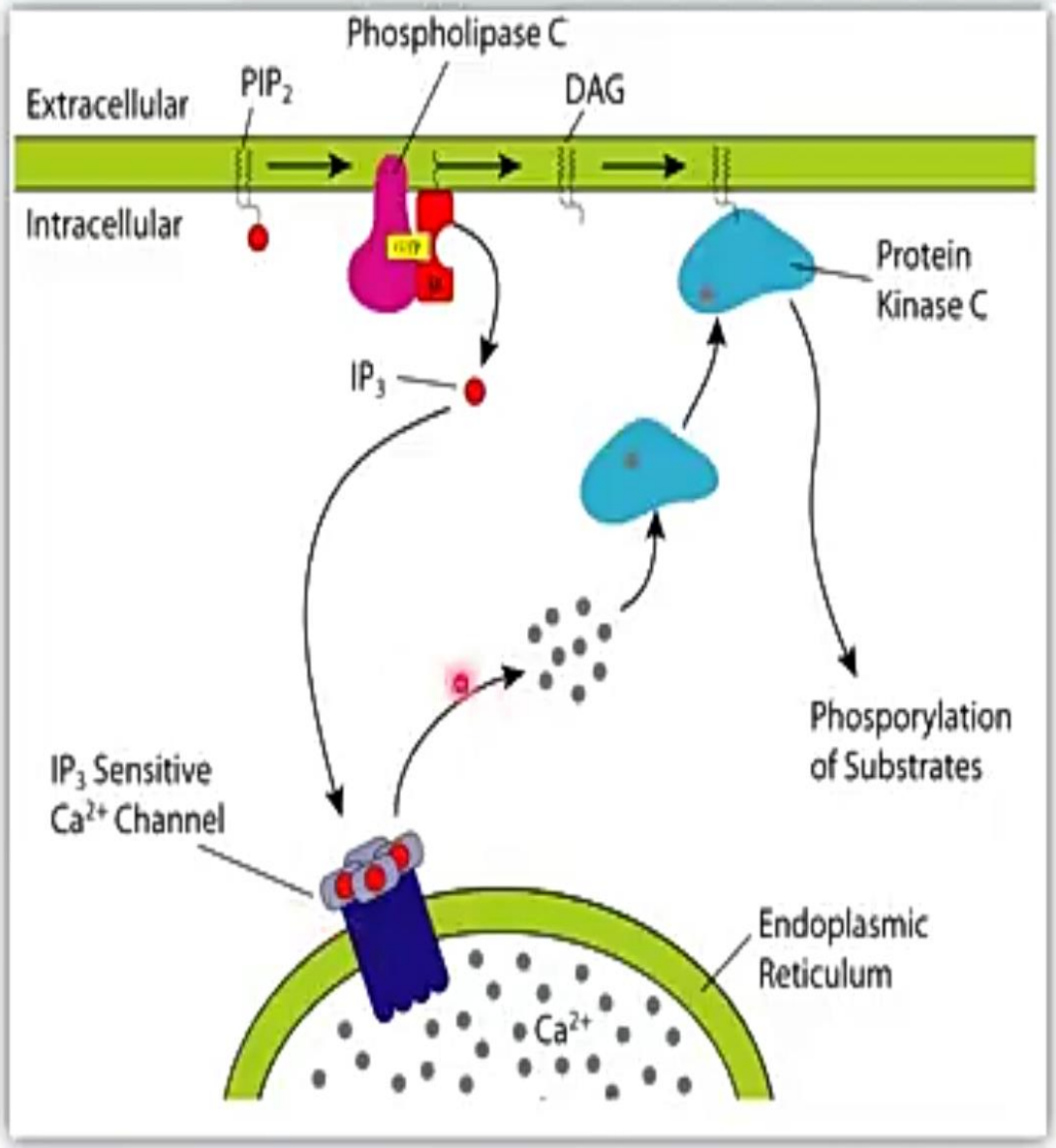
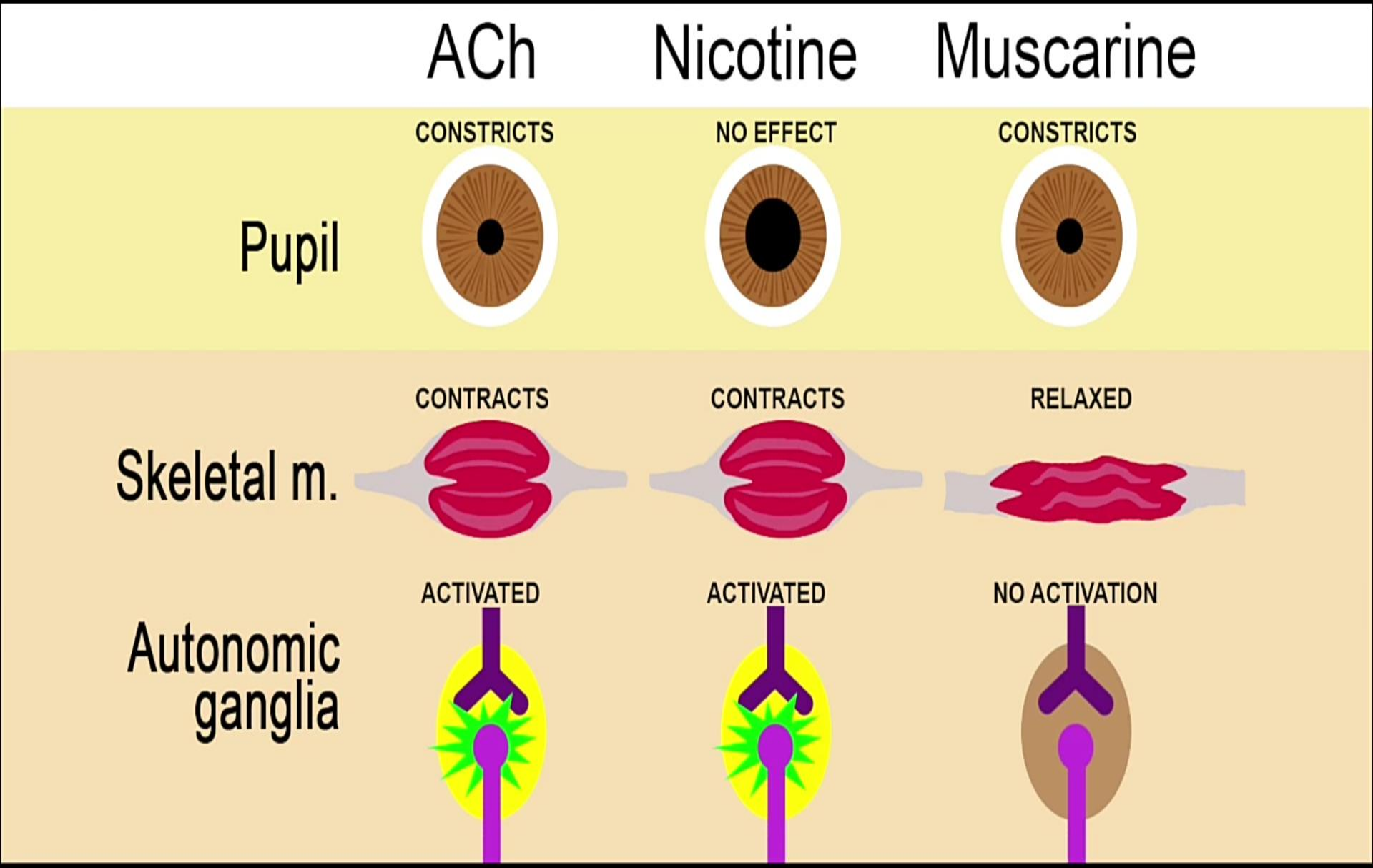


WHY IMPORTANT 2 KNOW ALL ABOUT RESCEPTORS

- The more specific you can make a drug to selectively bind a spesific receptor (in a specific organ) the less side effects you will have

	ACh	Nicotine	Muscarine
Pupil	CONSTRICTS	NO EFFECT	CONSTRICTS
Skeletal m.	CONTRACTS	CONTRACTS	RELAXED
Autonomic ganglia	ACTIVATED	ACTIVATED	NO ACTIVATION



Mnemonics #2

Go to Index

- α_1 q
- α_2 i
- β_1 s
- β_2 s
- β_3 s
- M_1 q
- M_2 i
- M_3 q
- D_1 s
- D_2 i
- H_1 q
- H_2 s
- V_1 q
- V_2 s

H = Histamine Receptors

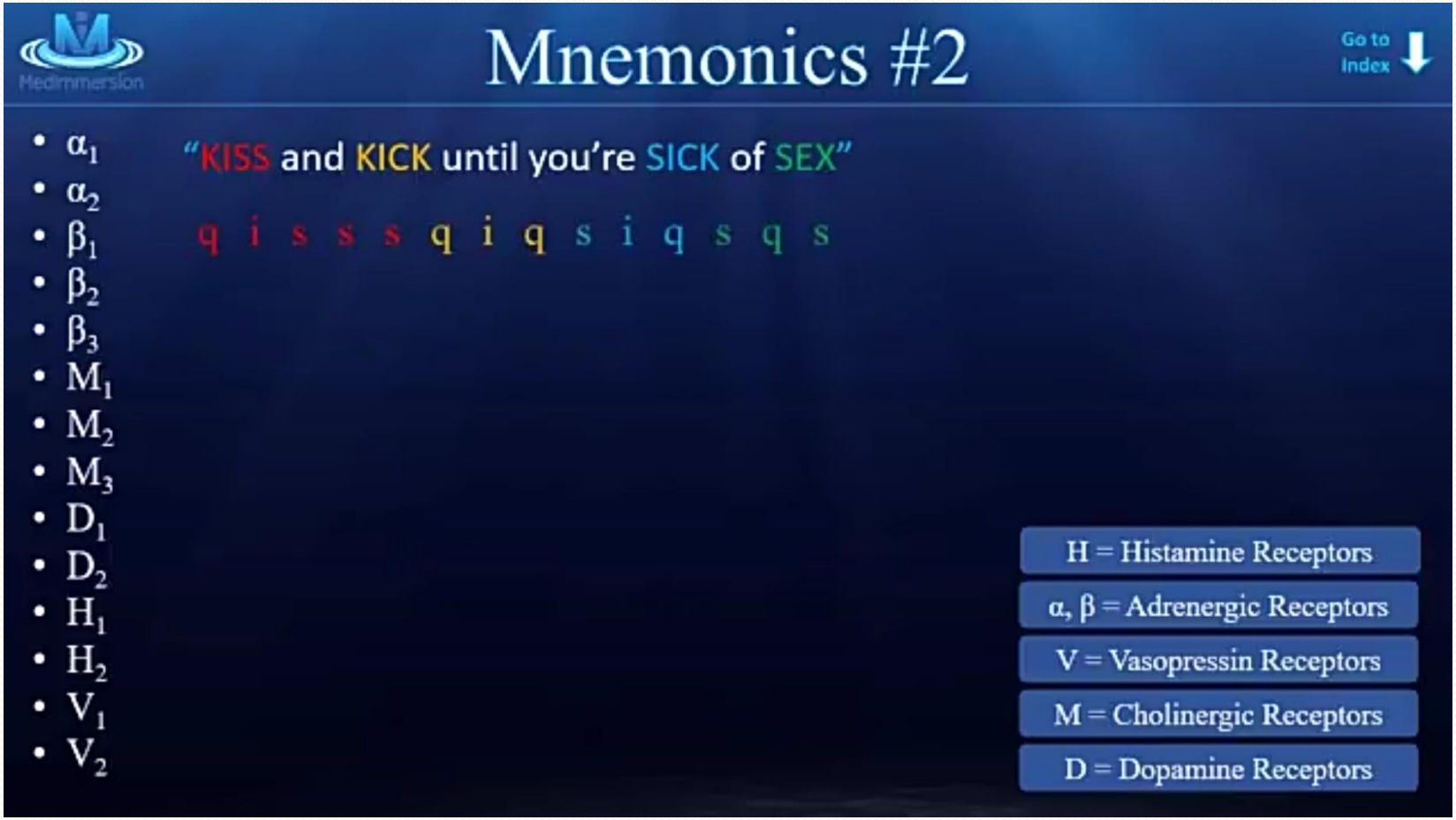
α, β = Adrenergic Receptors

V = Vasopressin Receptors

M = Cholinergic Receptors

D = Dopamine Receptors

KISS &KICK TILL UR SICK OF SEX



Mnemonics #2

Go to Index

- α_1 q
- α_2 i
- β_1 s
- β_2 s
- β_3 s
- M_1 q
- M_2 i
- M_3 q
- D_1 s
- D_2 i
- H_1 q
- H_2 s
- V_1 q
- V_2 s

H = Histamine Receptors

α, β = Adrenergic Receptors

V = Vasopressin Receptors

M = Cholinergic Receptors

D = Dopamine Receptors

Mnemonics #2

Go to Index

- α_1 q - Vasoconstriction, Mydriasis, ↑Sphincter contraction (GI, Urinary)
- α_2 i - ↓SNS tone, ↓Insulin release, ↓Lipolysis, ↓Aqueous humor
- β_1 s - ↑Chronotropy, ↑Inotropy, ↑Renin, ↑Lipolysis
- β_2 s - Vasodilation, Bronchodilation, ↑Lipolysis, ↑Insulin release, Tocolysis, Meiosis
- β_3 s - ↑Lipolysis
- M_1 q - CNS, Enteric nervous system
- M_2 i - ↓Chronotropy, ↓Inotropy of atria
- M_3 q - ↑Exocrine secretions, ↑Bladder contraction, Bronchoconstriction, Meiosis
- D_1 s - Renal vasodilation
- D_2 i - Modulates neurotransmitter release
- H_1 q - ↑Mucus production, ↑Vascular permeability
- H_2 s - ↑Gastric acid secretion
- V_1 q - Vasoconstriction
- V_2 s - ↑Insertion of H_2O channels in the collecting tubules

H = Histamine Receptors

α, β = Adrenergic Receptors

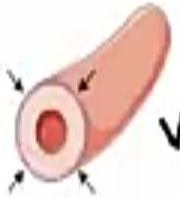
V = Vasopressin Receptors

M = Cholinergic Receptors

D = Dopamine Receptors

α Receptors

α 1 (Gq)



vasoconstriction

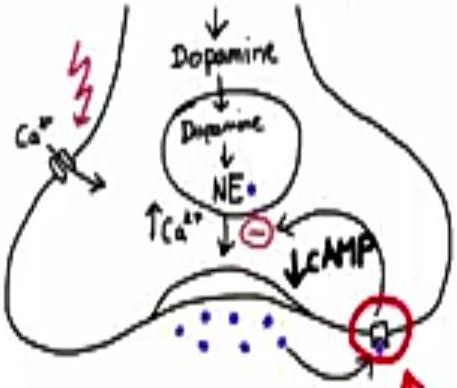
mydriasis

contraction & urinary retention

Glycogenolysis

Renin

α 2 (Gi)



↓ insulin

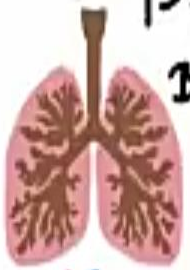
β Receptors (Gs)

β1

- ↑ HR
- ↑ Contractility
- ↑ AV conduction

- ↑ Renin
- ↑ BP

β2



- Bronchodilation

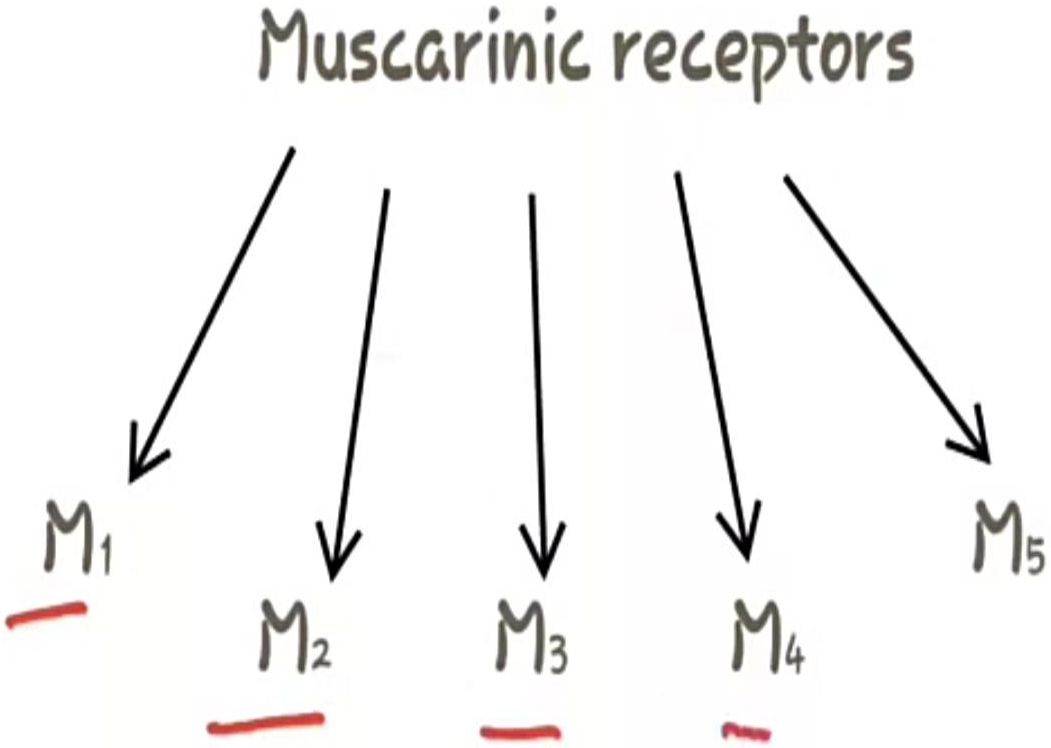
- vasodilation

- ↑ insulin
- ↓ GI motility
- Inhibition of labor

β3

- ↑ lipolysis

- Relaxation of bladder


Muscarinic receptors
M1
M2
M3
M4
M5

M_1 Receptor

Location: CNS
Gastric glands
Salivary glands

Effects: 1) CNS stimulation
2) Increase in secretion of gastric and salivary gland.

Specific agonist: 1) Pilocarpine
2) oxotremorine

M_2 Receptor

Location: 1) Heart
2) blood vessels

Effects: 1) Decrease in heart rate and force of contraction.
2) Vasodilation

Specific agonist: Methacholine.

Muscarinic Cholinergic Receptors (mAChR)

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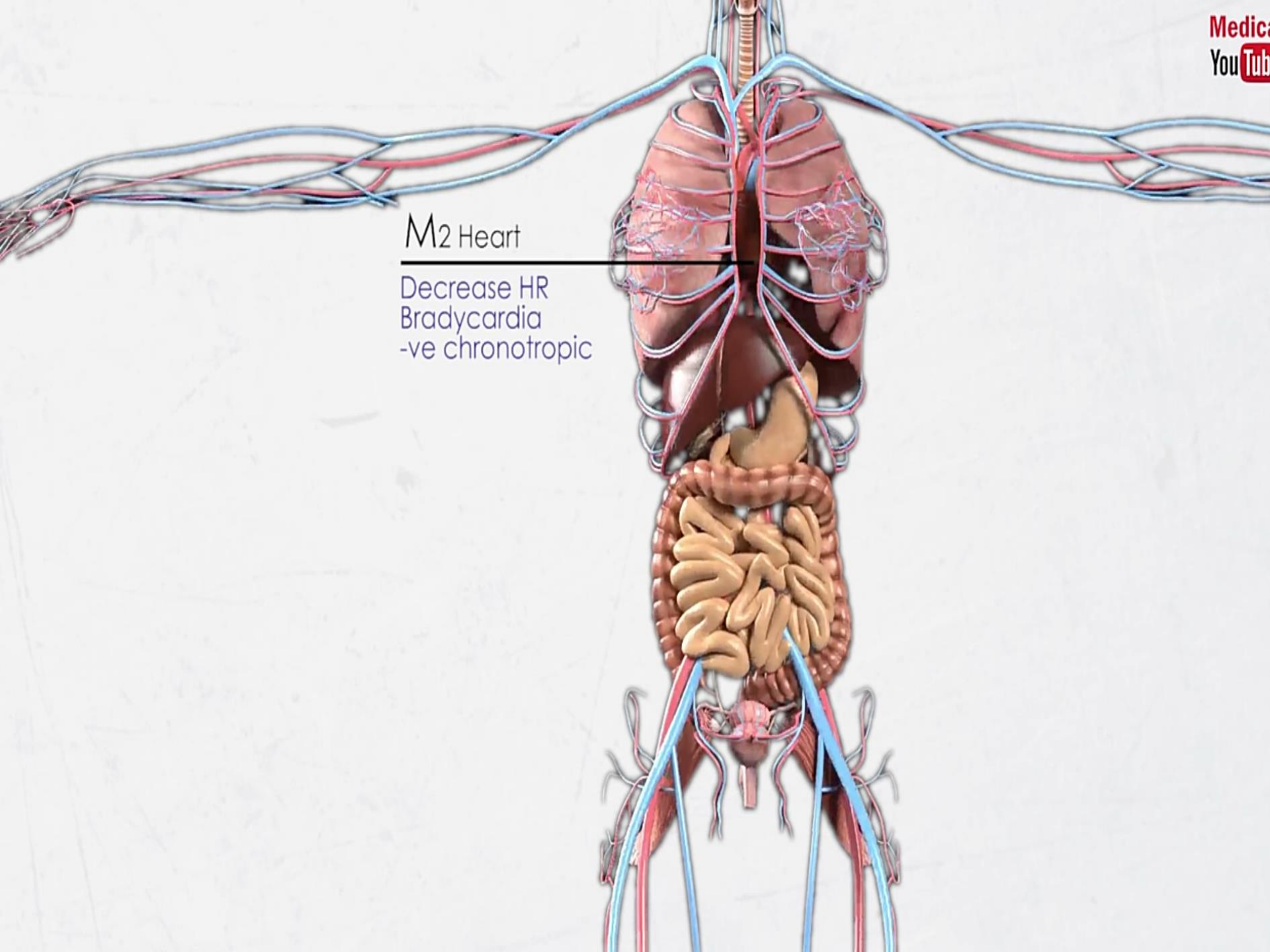
Muscarinic Acetylcholine Receptor Subtypes

- M_1
  - Gq Protein-Coupled
  - ↑Exocrine gland secretions (e.g. salivary glands, stomach)
  - Found in the CNS
- M_2
  - Gi Protein-Coupled
  - *Think: "↑Heart Parasympathetic effects"*
    - ↓Chromotropy
    - ↓Inotropy
    - ↓Dromotropy
- M_3
  - Gq Protein-Coupled
  - *Think: "↑Classic Parasympathetic effects"*
    - ↑Bronchoconstriction
    - ↑Endocrine and exocrine gland secretions (e.g. salivary glands, stomach, insulin)
    - ↑Eye accommodation
    - ↑Vasodilation

and m3 are the high-yield muscarinic


M2 Heart
Decrease HR
Bradycardia
-ve chronotropic

M_3 Receptor

Location: 1) Smooth muscles
2) Glands

Effects: 1) Contraction of smooth muscles
2) Increase in gland secretion.

Specific agonist: Bethanechol
Carbachol

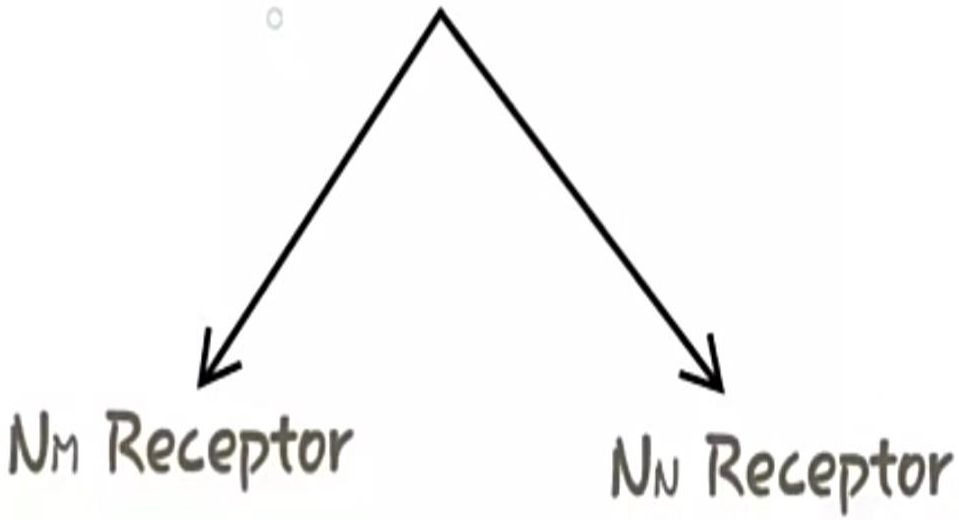
M_4 Receptor

Location: CNS

Effects: CNS inhibition

Special agonist: Not yet found.

Nicotinic receptors



N_M Receptor

Location: Neuromuscular junction of skeletal muscle

Effects: Contraction of skeletal muscle

special agonist: phenyl trimethyl ammonium

N_N Receptor

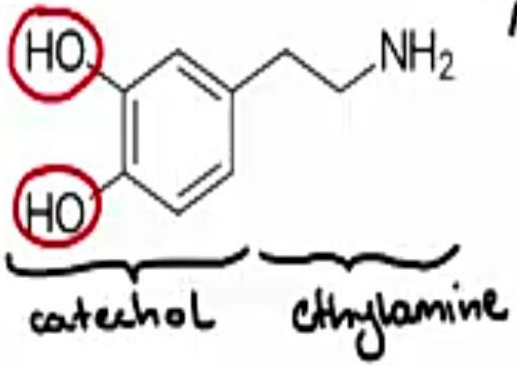
Location: Autonomic Ganglia

Effects: Stimulation of autonomic ganglia

Special agonist: Dimethyl phenyl piperazinium

Adrenergic Agonists

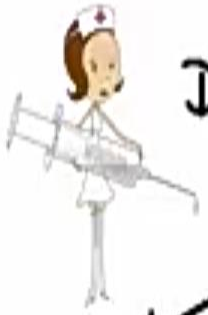
Catecholamine ← → Noncatecholamine



Ineffective ← (1) Oral usability → effective

short ← (2) Duration of action → long

poor ← (3) CNS penetration → good



Direct Acting Agonists

NON-SELECTIVE

Epinephrine

↓

vasoconstriction

↑BP

↑ cardiac output

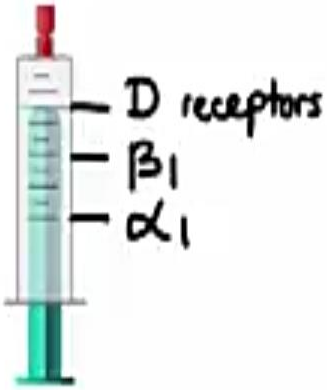
Bronchodilation

Norepinephrine

vasoconstriction

↑BP

Dopamine



Direct Acting Agonists

SELECTIVE

α_1

Oxymetazoline

Phenylephrine

α_2

Clonidine

β_1

Dobutamine

β_2

Short acting

↓

Albuterol

Terbutaline

Long acting

↓

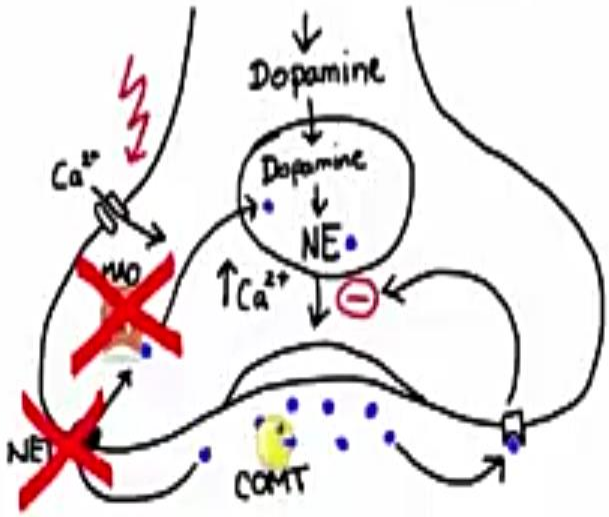
Salmeterol

Formoterol

β_3

Mirabegron

Indirect Acting Agonists

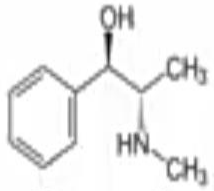


Cocaine & Amphetamine

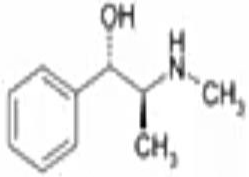
↑ BP

↑ HR

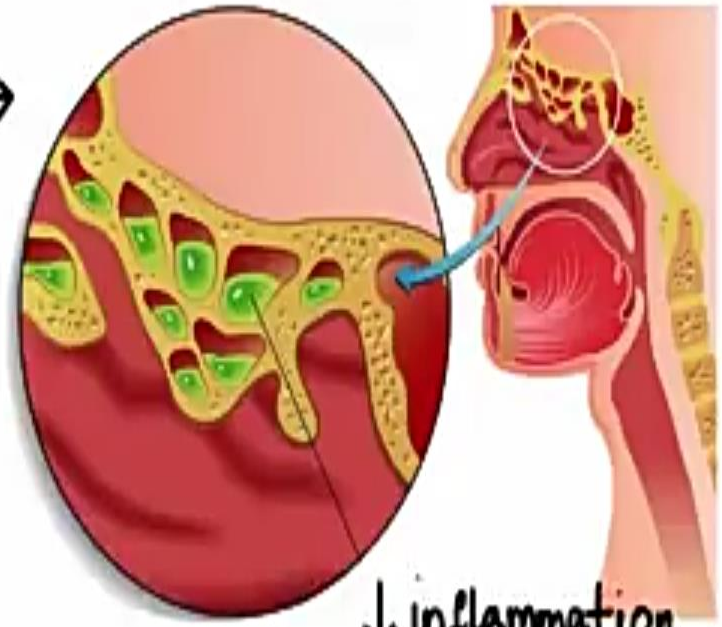
Mixed Action Agonists



Ephedrine

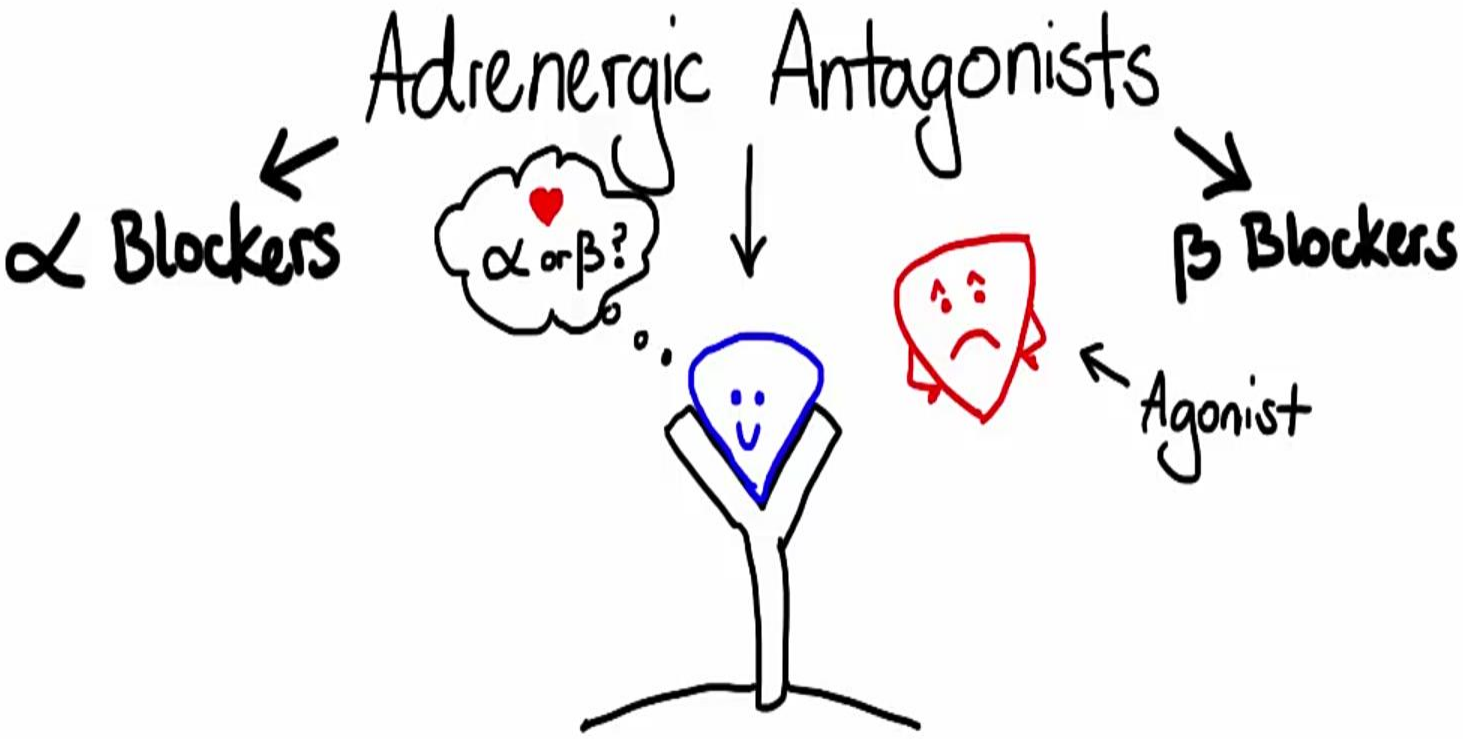


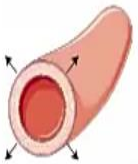
Pseudoephedrine



↓ inflammation

↓ mucus


Adrenergic Antagonists
α Blockers
β Blockers
α or β?
Agonist



α Blockers

Non-selective

Phentolamine
Phenoxybenzamine

Selective

α 1

Prazosin
Doxazosin
Terazosin

Tamsulosin
Alfuzosin
Silodosin

α 2

Yohimbine

β Blockers

1st Generation
(Non-selective)

- Propranolol
- Pindolol
- Nadolol
- Sotalol
- Timolol

2nd Generation
(β1 selective)

- Atenolol
- Acebutolol
- Bisoprolol
- Esmolol
- Metoprolol

3rd Generation

- Non-selective (β + α1)
  - Carvedilol
  - Labetalol
- Selective
  - Nebivolol (•NO)
  - Betaxolol (CCB)

Intrinsic Sympathomimetic Activity

Thanks for your listening!

The end