بسم الله الرحمٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pharmacology | Lecture 3

Pharmacodynamics

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Pharmacodynamics

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Learning Objectives

- Define pharmacodynamics and its scope in pharmacology.
- Differentiate pharmacodynamics from pharmacokinetics.
- Describe how drugs act on biological targets to produce effects.
- Identify major drug targets: receptors, enzymes, ion channels, and transporters.

Introduction

- Pharmacology is the study of the biochemical and physiological aspects of the drug effects including absorption, distribution, metabolism, elimination, toxicity and specific mechanism of action.

- The main areas of pharmacology are :

  - **Pharmacokinetics**: the way the body handle drug absorption, distribution, biotransformation, and excretion.

  - **Pharmacodynamics**: the study of the biochemical and physiological effect of the drugs and their mechanism of action.

Definitions

Drug: It is any chemical that affect living processes. It modifies an already existing function, and does not create a new function.

Pharmacodynamics is what the drug does to your body

Pharmacokinetics is what your body does to the drug

A drug is a chemical which has a physiological effect on the body

Pharmacodynamics

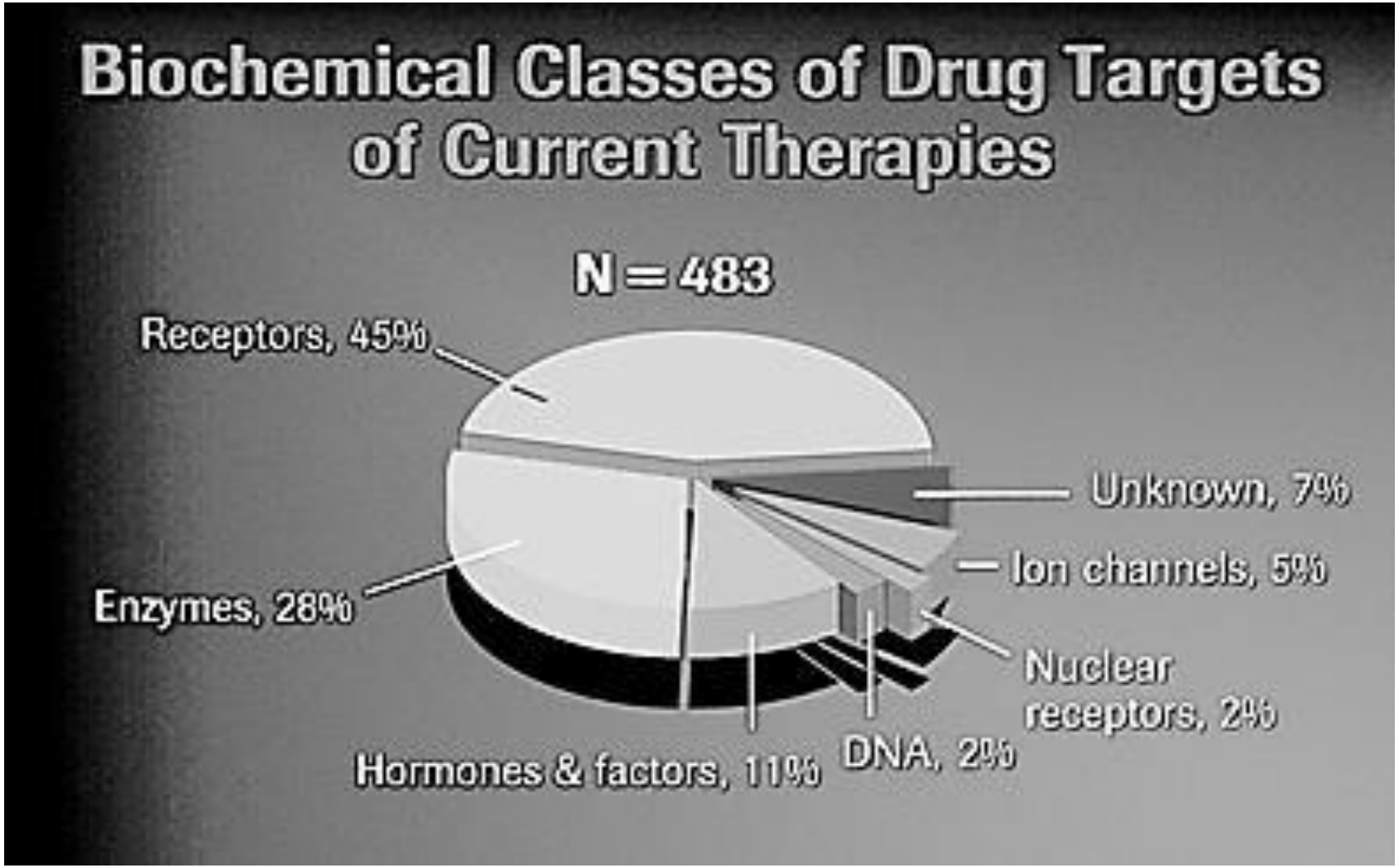
- Drug targets are usually receptors or enzymes. The drug needs to bind a sufficient number of target protein at a reasonable dose, so the drug should be potent .

A conformational change that leads to activation of cellular molecule

- The study of the biochemical and physiological effect of the drugs and their mechanism of action.

  To get to know their effect and toxicity

- The study of the relationship of drug concentration to drug effects .


Biochemical Classes of Drug Targets of Current Therapies
N = 483
Receptors, 45%
Unknown, 7%
Ion channels, 5%
Enzymes, 28%
Nuclear receptors, 2%
Hormones & factors, 11%
DNA, 2%

- The most common drug target is receptors

The receptors are usually on the cell surface because not all molecules get to cross the membrane .
Other receptors can be intracellular (cytosolic , nuclear)
Ion channels can also be receptors like nicotinic receptors that are originally Na+ channels , they bind to the ligand (acetylcholine) , which leads to muscle contraction
Nuclear receptors are present in cytoplasm and translocate to the nucleus as they target DNA and modulate what happens there,
An example on nuclear receptors are steroid receptors (vitamin receptors, T3, T4)

- Tyrosine kinase (an enzyme) binds to insulin thus some enzymes can be considered receptors

Mechanism of drug action

- Most drugs exert their effect by interacting with a specialized target macromolecules, called receptors, present on the cell surface or intracellularly.

- The receptors will transduce the binding into a response by causing a conformational changes or biochemical effect.

Mechanism of drug action

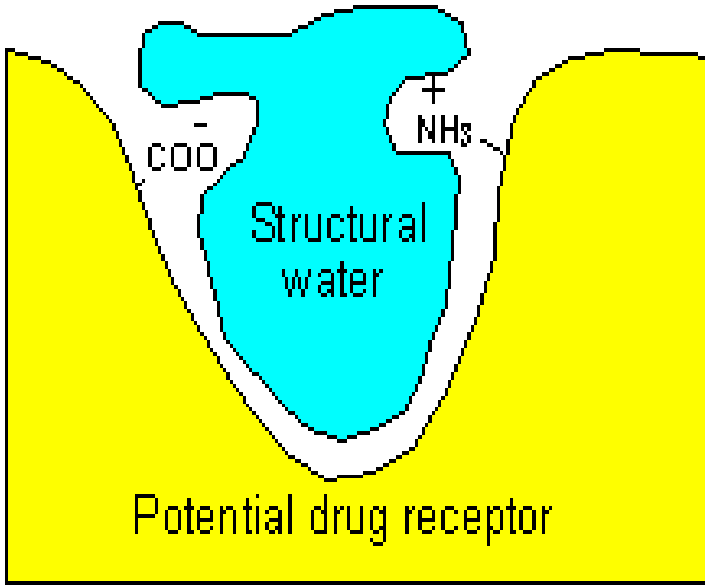
- **Receptors** are large macromolecules with a well-defined 3D shape .

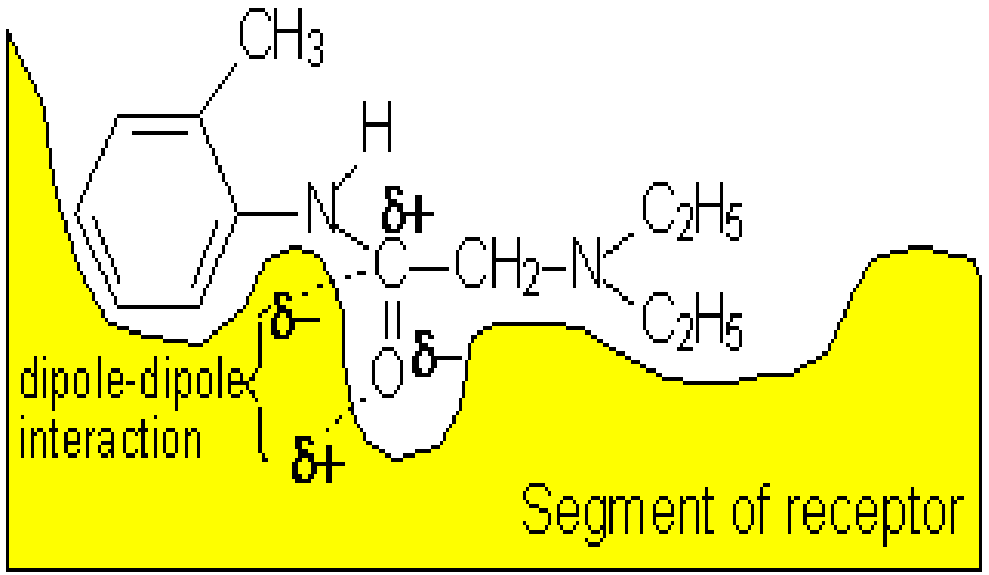
  The 3D shape gives complementarity to the receptor, that only specific molecules can bind to the receptor

  The 3D structure might have undergone post transitional modifications for eg : phosphorylation, glycosylation ; that gives shape complexity -> specificity -> complementary

- The two fundamental properties underlying specificity in drug-receptor interactions are <u>complementarity of shape</u> between drug and receptor, and complementarity between the <u>electrostatic, hydrophobic, and hydrogen bonding</u> surfaces of each component .

Lock and key





Shape complimentarity

Electro-chemical structure (charge, chemical group) that forms different bonds

Receptors

- determine specificity of drug action

- *most* are proteins

Some are lipids.

DNA can be considered a receptor because some drugs go to the nucleus and bind to the DNA and modulates what happens there

- Most drugs bind reversibly (noncovalent(
- not all “drugs” use receptors

Reversible non-covalent bonding allows more control on the effect in the body

Some drugs might bind to the receptor covalently but it's not preferable, as it is irreversible, and those drugs have different characteristics and a longer term of binding

Characteristics of Drug-Receptor Interactions

- Chemical Bond: ionic, hydrogen, hydrophobic, Van der Waals, and covalent.
- Saturable
- Competitive
- Specific and Selective
- Structure-activity relationships
- Transduction mechanisms

Receptors are an Excellent Drug Target

- Activated receptors directly, or indirectly, regulate cellular biochemical processes within and between cells to change cell function.
- Recognition sites are precise molecular regions of receptor macromolecules to which the ligand binds providing:
- Specificity
- Selectivity
- Sensitivity

An example on selective drugs is SSRI (selective serotonin re-uptake inhibitor) and celebrex

We have receptors as 45% of drug targets because they are highly specific (can only bind to a specific number of ligands which they already have affinity to)

COX 1 is working all the time , and COX 2 is present in specific inflammatory sites (only work when there is an inflammation.

Paracetamol and Ibuprofen are both COX inhibitors that inhibit prostaglandins (inflammatory mediators; responsible for all the events we see in cascade of inflammation)
Once I stop COX, I stop all this , but those prostaglandins have an effect on the stomach; they increase mucus secretion, so stopping COX using these two drugs will have side effects and they can't be used by people with gastric ulcer.
So we need a drug that only blocks COX 2 = Celecoxib (known commercially as Celebrex)

We have two types of adrenergic receptors: Alpha and Beta.
Beta receptors are also subdivided into : Beta1 Beta2 Beta3...
Beta1 is present in the heart , while beta2 is present mostly in the lungs
(Mnemonic: One heart two lungs)
If there is an adrenaline rush, heart rate and contractility will increase (fight or flight reaction)
Lungs at the other side will need more oxygen so bronchi will dilate and be more relaxed.
Notice how we have opposite reactions from the two organs even though they have same receptor's type? This is because they differ in the sub-receptor beta1 and beta2 .
This is an example on selectivity
As selectivity reduces side effects, for eg beta blockers treat heart conditions, if I block beta receptors I block both beta1 and beta2 receptors if the drug wasn't selective. Then bronchi will contract . If the patient is asthmatic this will increase asthmatic attacks. Eg on non selective blocker is propranolol

Selectivity

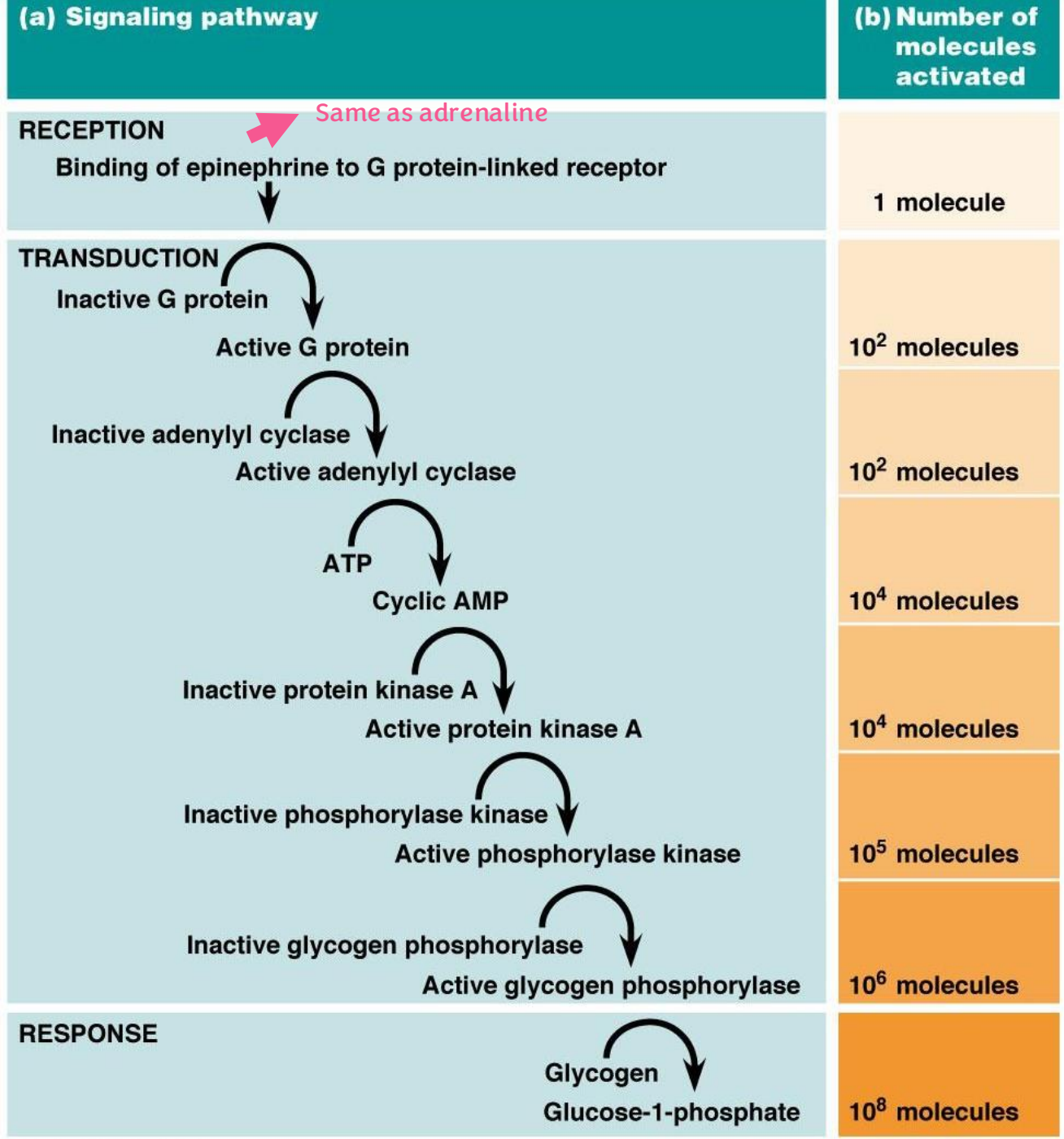
We benefit a lot from the fact that receptors are selective and We use selectivity to help us limit the side effects.

All receptors of the same subtype, like beta receptors, have the same shape. They all have the same structure, so adrenaline is able to identify these receptors and bind to them. But why is the effect different when the receptor structure and the ligand are similar? Because the signaling cascade that is coupled to the beta-1 receptor is different from the signaling cascade that is coupled to the beta-2 receptor. One of them increases cyclic AMP production and the other one decreases it.

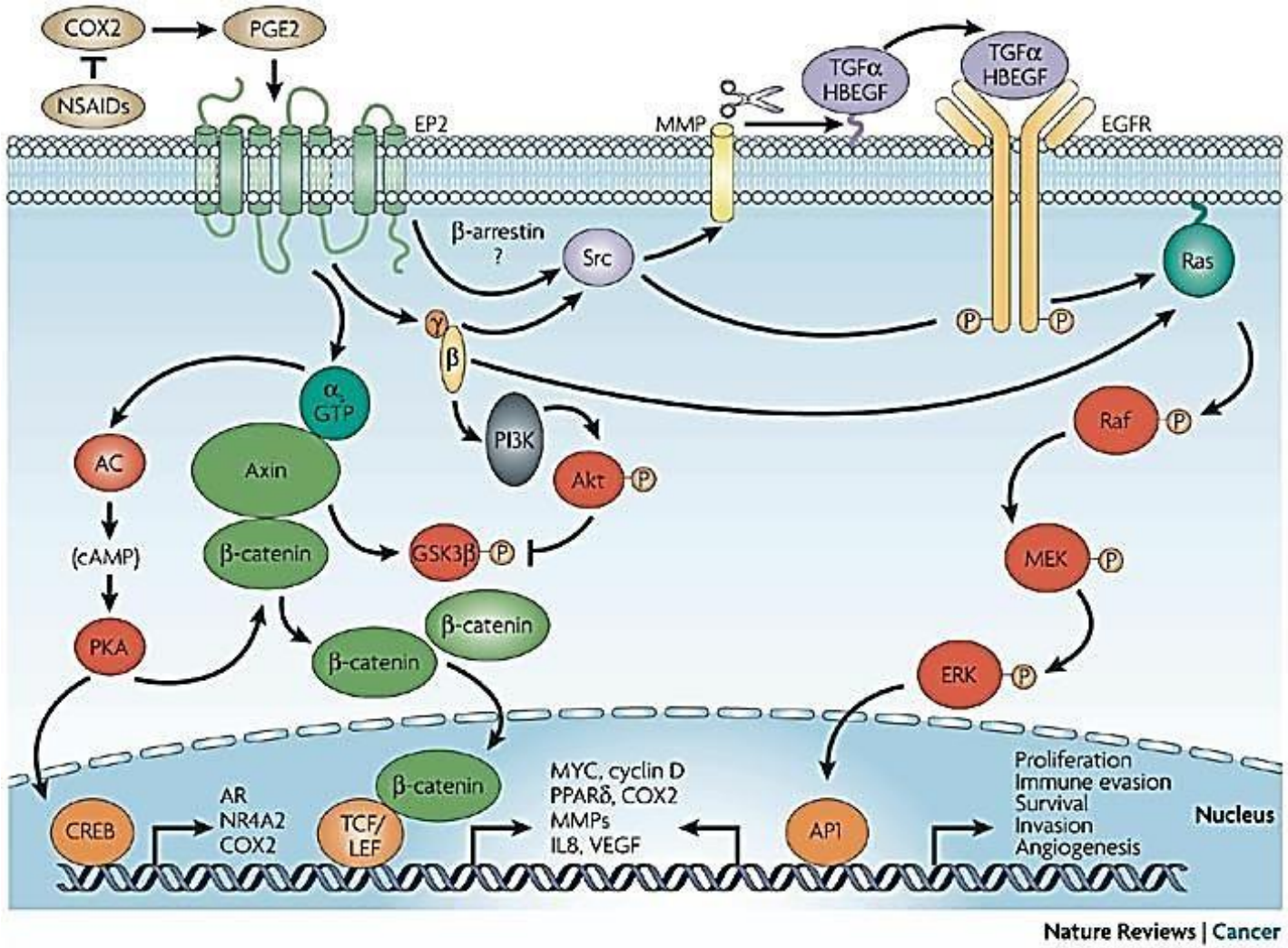
sensitivity

Sensitivity in Arabic means حساس and as the name implies it means that a small amount of the drug is gonna make a big signal (amplification of the signal)

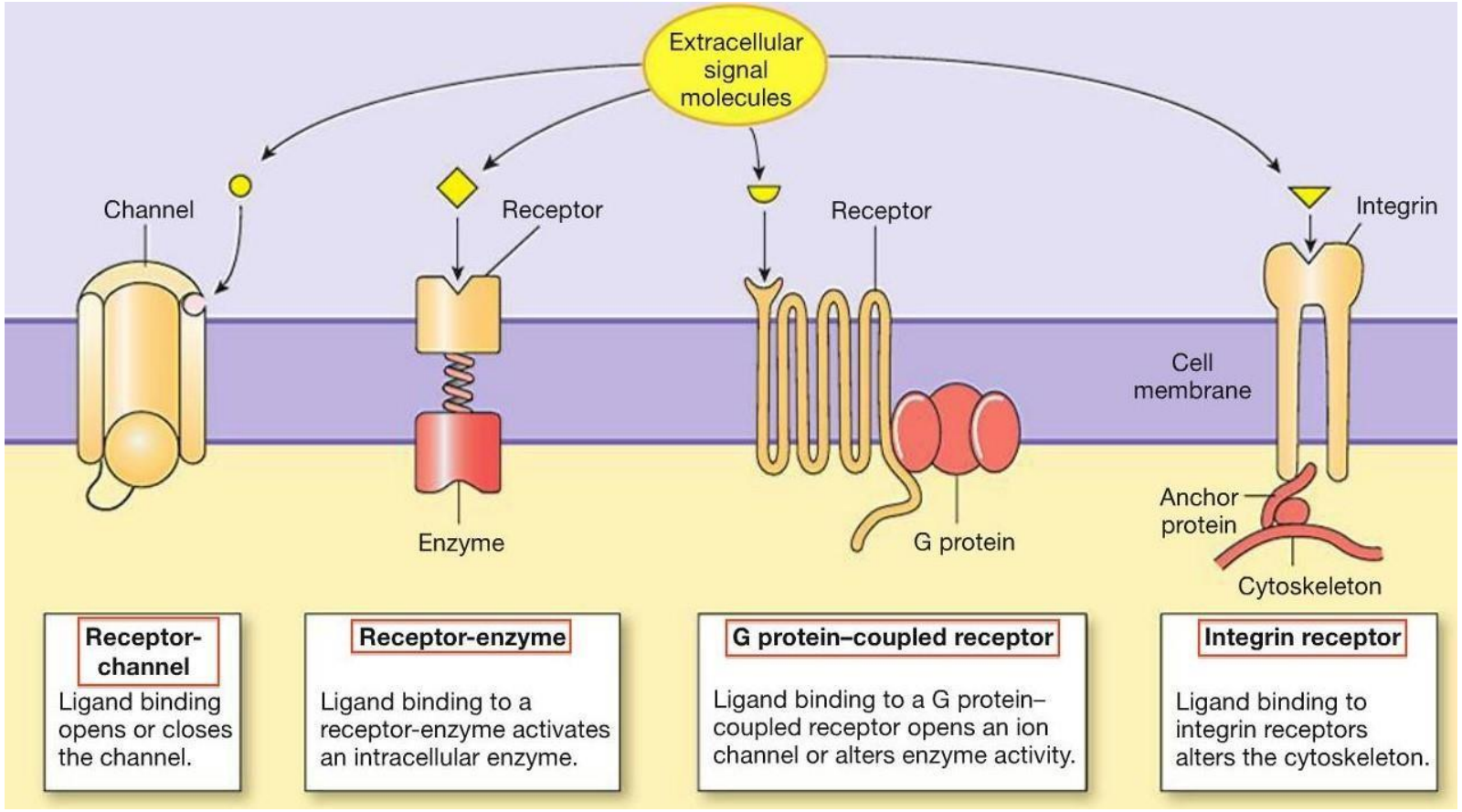
For example, only one single molecule of epinephrine binded to one receptor results in 10^8 molecules of the affect I want



Here we have different types of receptors..... (the details are not required). You just have to know that most of the receptors are sensitive.

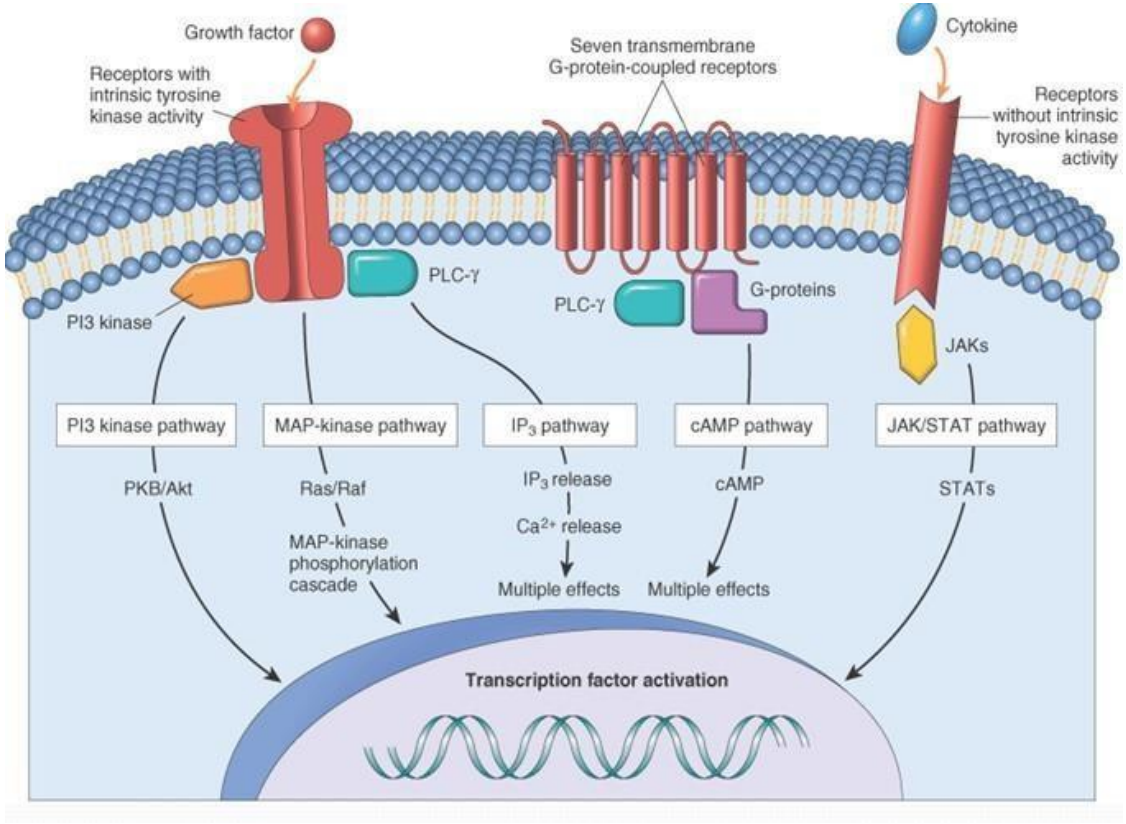


CELL SURFACE (MEMBRANE) RECEPTORS



Cell-surface (or transmembrane) **receptors** are **membrane**-anchored, or integral proteins that bind to **external ligand molecules**. This type of **receptor** spans the plasma **membrane** and performs signal transduction, converting an extracellular signal into an intracellular signal.

CELL SURFACE (MEMBRANE) RECEPTORS



This large group of membrane-bound receptors comprises the 7TM or 1TM receptor families. All recruit multiple intracellular signaling cascades known as “second messengers.”

Major receptor families

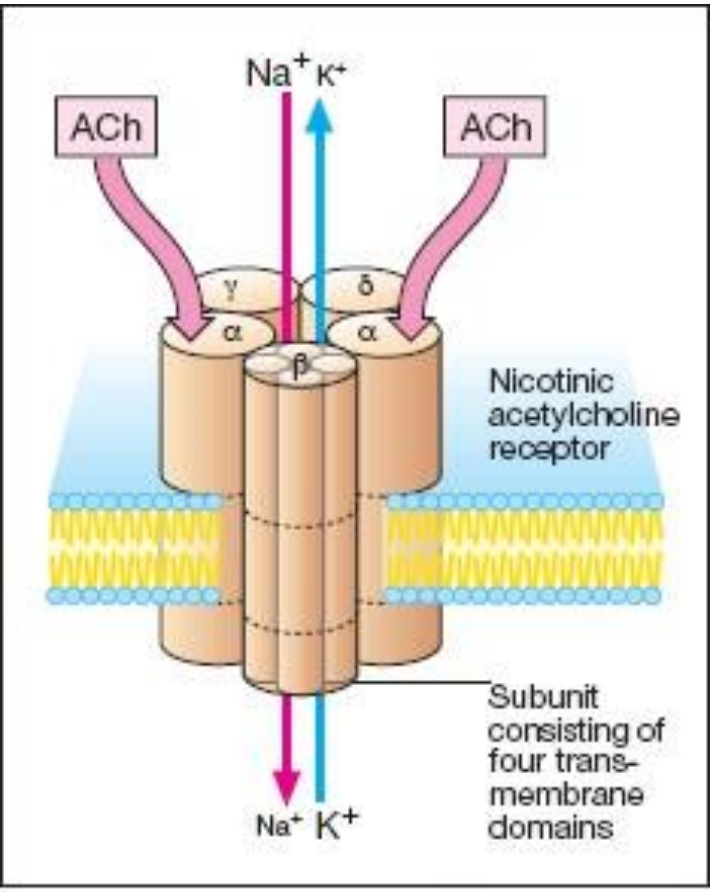
- **Ligand-gated ion channels** Ion channels are considered a separate group and not a type of receptors in some sources. Anyway, an example of a ligand-gated ion channel is the nicotinic receptor.
- **G protein-coupled receptors** Like Muscarinic Receptors
- **Enzyme-linked receptors**
- **Intercellular receptors**

Ligand-gated ion channels

- Responsible for regulation of the flow of ions channels across cell membranes.

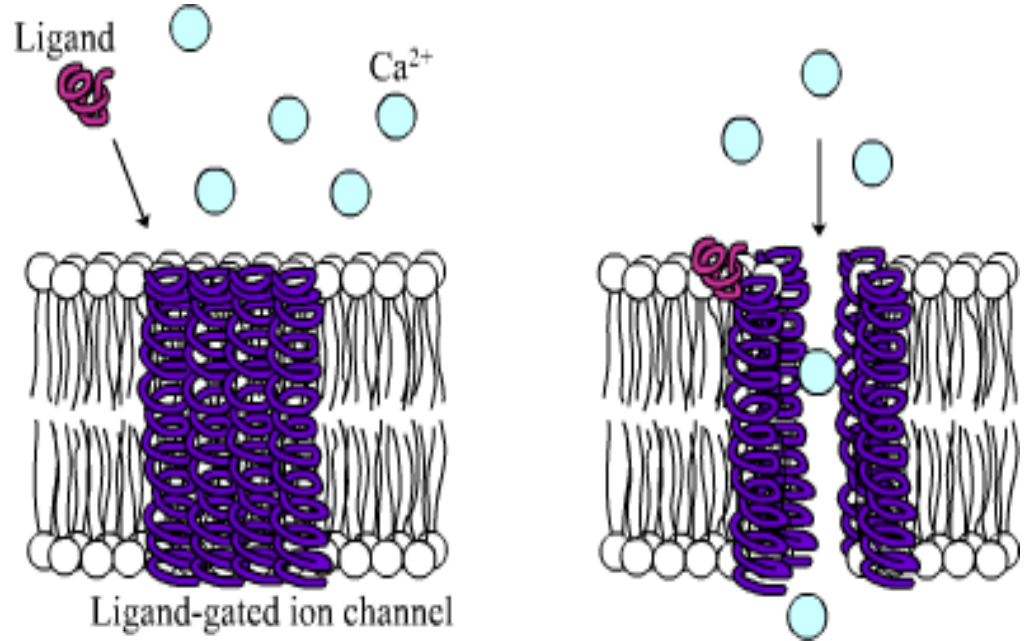
- Regulated by binding of a ligand to the channels .

- The best example being the nicotinic receptor, in which the binding of the acetylcholine results in sodium influx and the activation of contraction in skeletal muscle



B. Ligand-gated ion channel

When acetylcholine binds to the channel, a conformational change occurs, opening the channel and allowing sodium influx. This leads to depolarization, which in turn activates another channel, the calcium channel. As a result, calcium enters the cell, either via influx from outside or release from intracellular stores (Sequestration from calcium stores), increasing the intracellular calcium concentration. All of this ultimately leads to muscle contraction.



Nicotinic receptors exist in 2 locations, including 1) the autonomic ganglia and 2) skeletal muscles

. Many types of skeletal muscle relaxant drugs act on this receptor. Their mechanism is blocking the receptor and inhibiting the binding of acetylcholine, which leads to muscle relaxation

Additionally, pesticides can affect acetylcholine metabolism and may have several adverse effects.

Smokers use nicotine, which binds to nicotinic receptors in the ganglia, activating both the sympathetic and parasympathetic nervous systems. The effect depends on which system is dominant in each organ. For example, the heart and blood vessels are primarily under sympathetic control

While smoking, you stimulate the sympathetic system and cause constriction of blood vessels, which can have many negative effects, such as hypertension.

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	Slide 13 Reversible Covalent Slide 22 & 23	Covalent _____	Non-covalent New slides have been added
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