Pharmacodynamics

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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.

- Important thing to know about areas of pharmacology

They aren't separate areas, they are actually highly connected and meet multiple times in the course of the drug.

Absorption, distribution, metabolism, elimination, mechanism of action, those processes don't happen sequentially but at the same time.

for example, a part of the drug is being absorbed and distributed into circulation then it reaches its target, while other parts may still be in the biotransformation phase or are being eliminated.

So the processes are in equilibrium.

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.

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

By knowing the mechanism of action of a particular drug, we'll be able to deduce the indications and the side effect of the drug

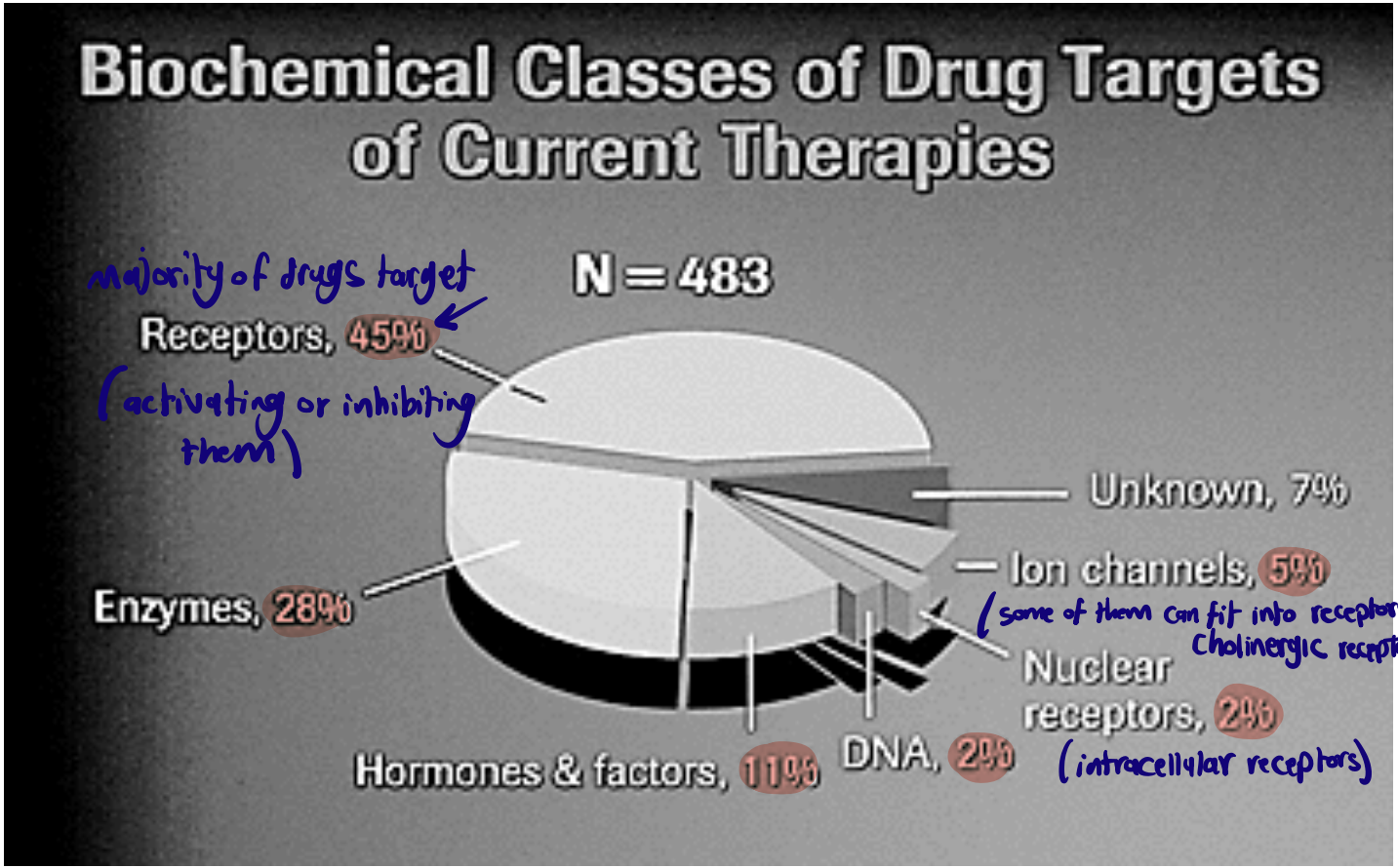
- The study of the relationship of drug concentration to drug effects.

+ ibuprofen

for example: paracetamol (The scientific name of panda pandol and revanin) is an analgesic drug (pain killer) its mechanism of action to inhibit an enzyme called cycloxygenase (The target of the drug) preventing the production of prostaglandins (which causes inflammatory responses like fever, redness, pain)

⇐

Another thing to know about the pharmacodynamics of "ibuprofen" is its adverse effects ⇒ it causes gastric irritation (since it inhibits prostaglandins that is responsible for decreasing the stomach acid secretions as well as increasing the protecting mucous secretions (So I would never give the drug to peptic ulser patient)


Biochemical Classes of Drug Targets of Current Therapies
N = 483
majority of drugs target
Receptors, 45%
(activating or inhibiting them)
Unknown, 7%
Ion channels, 5%
(some of them can fit into receptors like Cholinergic receptor)
Enzymes, 28%
Nuclear receptors, 2%
(intracellular receptors)
Hormones & factors, 11%
DNA, 2%

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. → like opening an ion channel allowing the passage of ions

The purpose of having receptors in our body is that we have endogenous ligands (neurotransmitters, hormones, ...) that will utilize this receptor for maintaining homeostasis and producing physiological effect (ex. we need adrenaline for heart rate, constriction of the blood vessels) But we also utilized those receptors and we targeted them with exogenous ligands (drugs). Now why did we choose receptors?

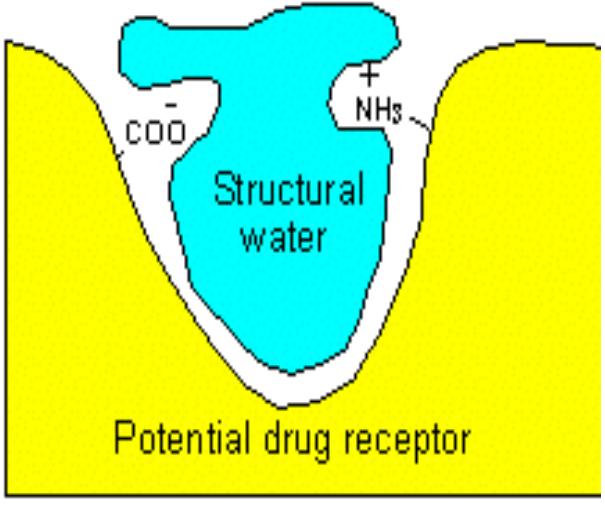
- macromolecules
- present on the cell surface so they transmit the signal from outside the cell to the inside (not all drugs can enter the cell)
- specificity

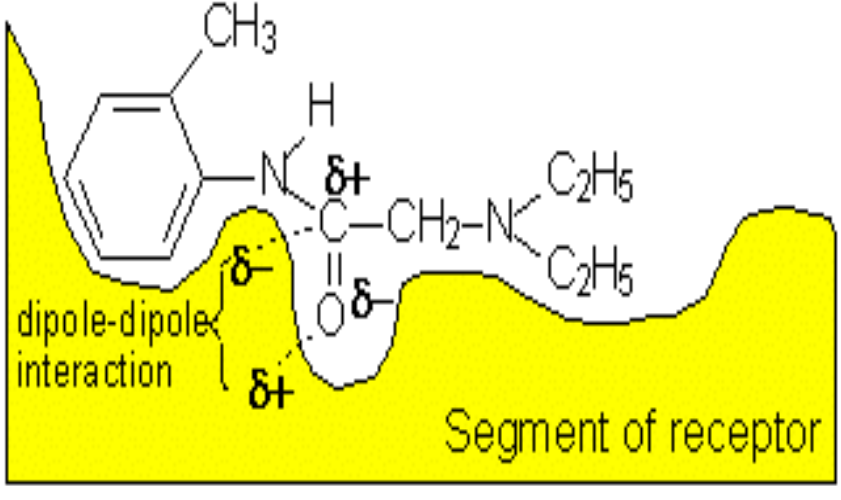
Mechanism of drug action

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

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

Lock and key


COO⁻
NH₃⁺
Structural water
Potential drug receptor


CH3
H
N
δ+
C
CH2
N
C2H5
C2H5
O
δ−
δ−
δ+
dipole-dipole interaction
Segment of receptor

Receptors

- determine specificity of drug action
- *most* are proteins (more than 99%.)
- Most drugs bind reversibly (noncovalent)
- not all "drugs" use receptors

important for an ideal drug, we don't want the drug to stay permanently.

binding usually takes about milliseconds

Some of them utilize other mechansim of action

for example, adrenaline will bind to the adrenergic receptors on the heart increasing its contraction. Simply I utilize this complementarity to make a drug that's very similar to the structure of adrenaline, so it will fit into that lock and bind to the receptor, and it will either activate it or inhibit it

Some drugs bind irreversibly and they form covalent bond, so it will be so hard to break and it will stay longer in my body, so I have to take that into consideration when I use this drug

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 ⇒ Controls the degree of effectiveness of a drug so when receptor sensitivity changes, the same concentration of a drug will produce a greater or lesser physiological response.

- Small amount of a sensitive drug causes amplification of signal on the other hand we need a big amount of a non-sensitive drug to cause effect

The most important characteristics of receptors

- specificity: They have recognition sites that are precise molecular regions to which the ligand or the drug binds (lock and key)
- selectivity: refers to the extent to which a receptor binds with a particular drug rather than other molecules. Selectivity depends both on the receptor and on the size, shape, and bioelectrical charge of the drug molecule.

example: adrenergic receptors ($\alpha_{1,2}$, $\beta_{1,2,3}$) Both bind to the same ligand (adrenaline) but causes different physiological effects in the body

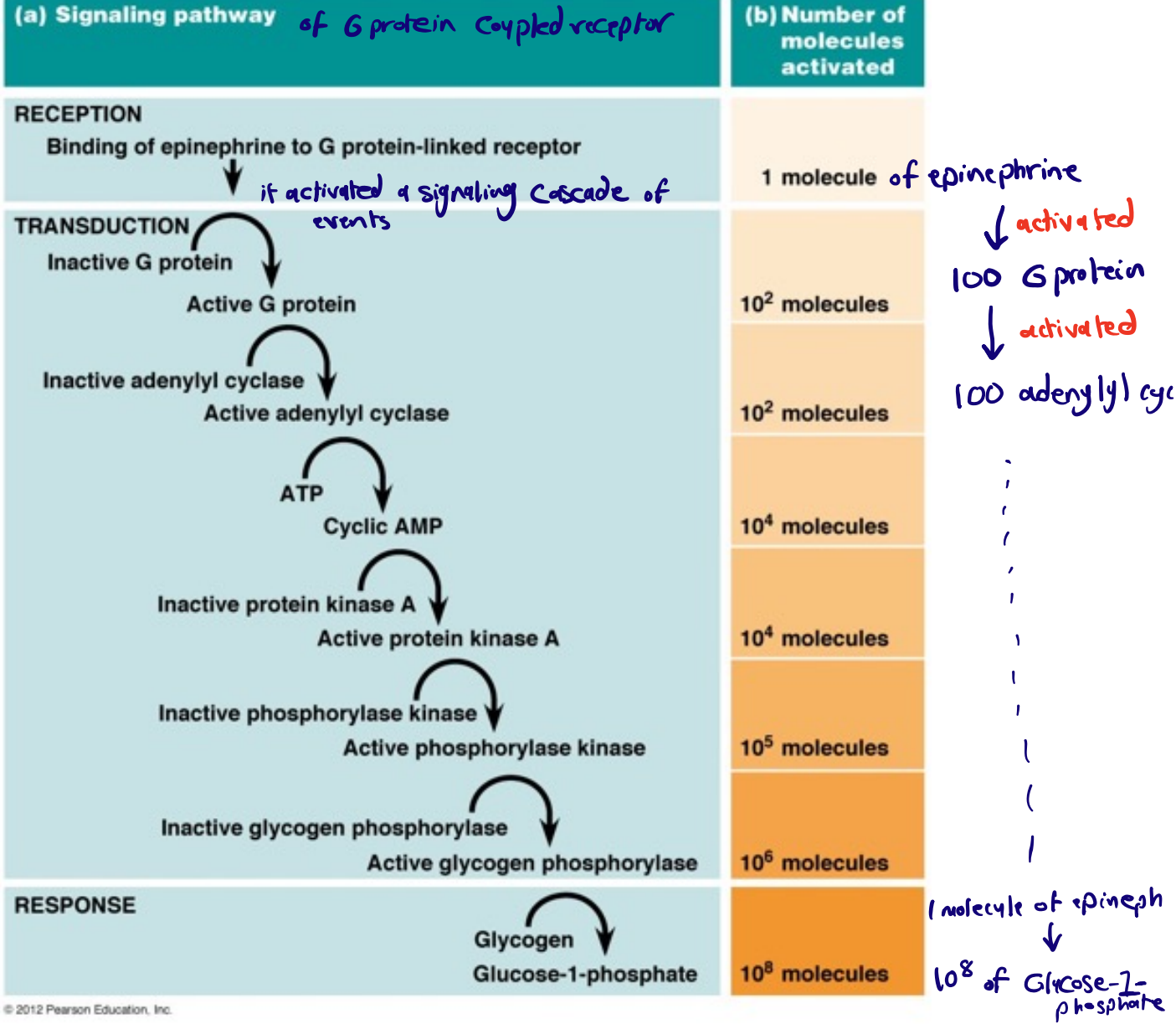
adrenaline binding to β_1 → causes contraction of the heart and increases heart rate

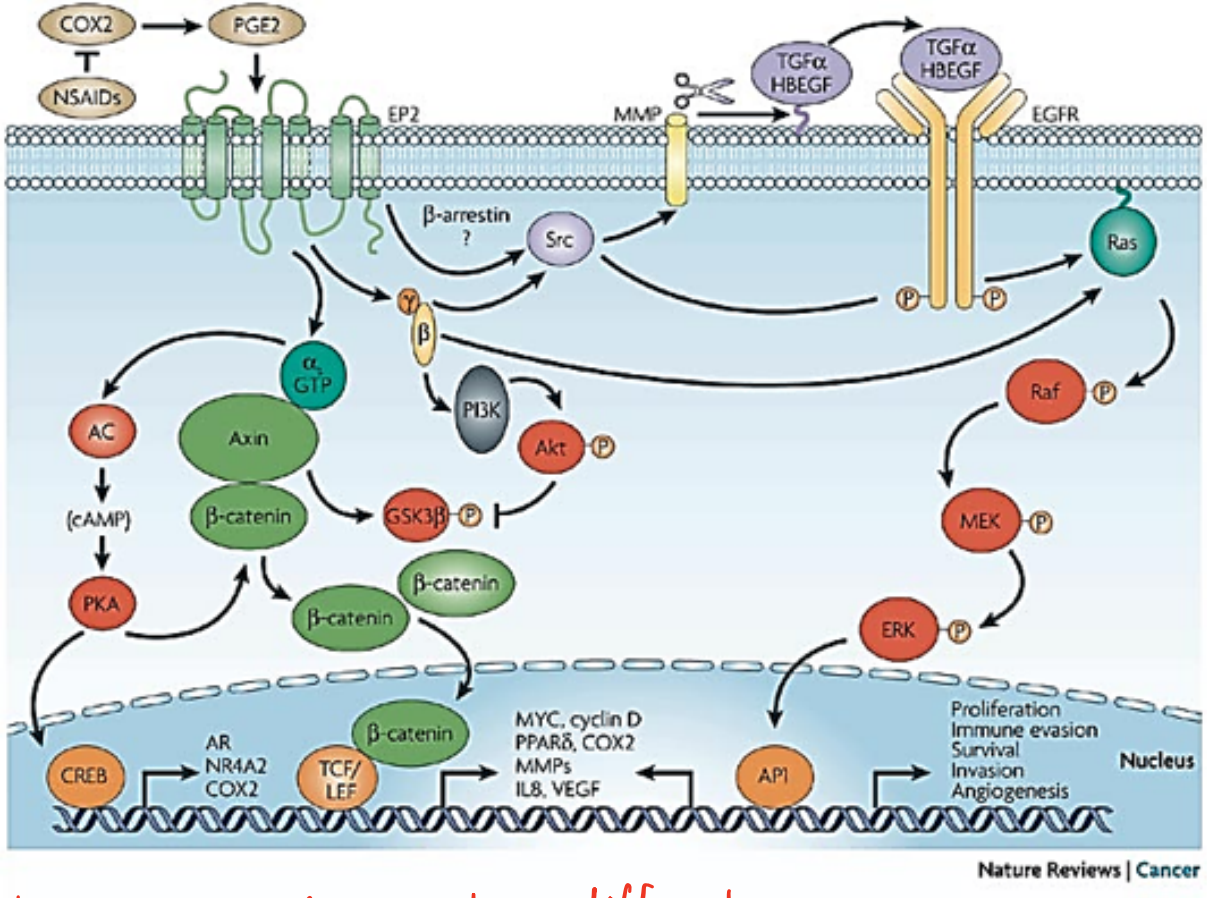
β_2 → causes relaxation of the bronchi smooth muscles (to breath more air)

So how does the same ligand causes 2 opposite effects?

– Simply because we have 2 substrates of receptors –

So we took advantage of the presence of these substrates of receptors to make a drug that selectively targets one of these substrates to deal with a specific problem. For example, instead of giving an asthma patient adrenaline that will cause both (contraction of the heart and relaxation of bronchi) I give him a drug that will selectively bind to β_2 (causing relaxation of bronchi, without increasing its heart rate)





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This photo indicates how we have different signaling mechanisms in the cell (each receptor is coupled to a different signaling mechanism)

Major receptor families

- Ligand-gated ion channels
- G protein-coupled receptors
- Enzyme-linked receptors
- Intercellular receptors

Ligand-gated ion channels

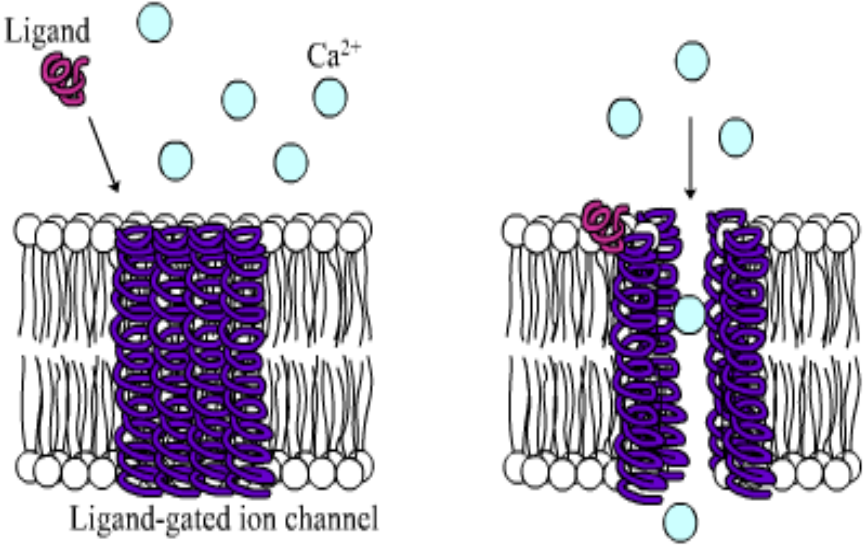
- Responsible for regulation of the flow of ions channels across cell membranes.

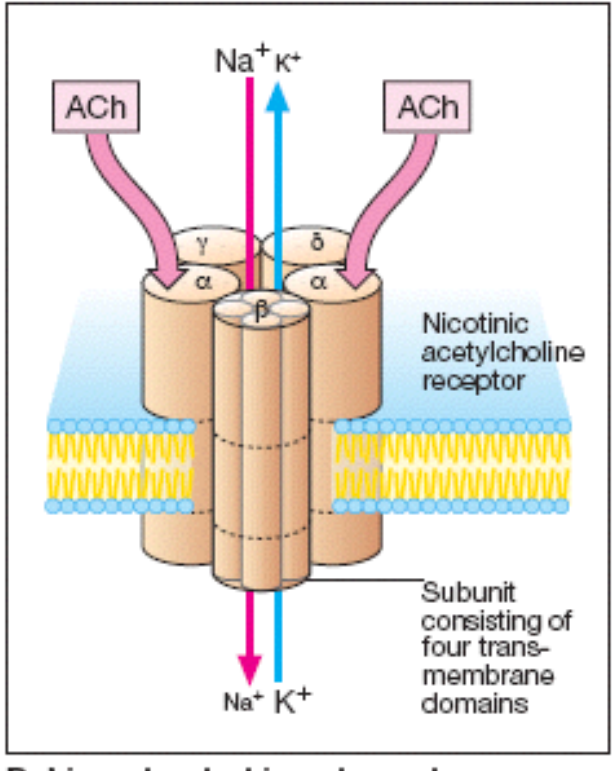
- Regulated by binding of a ligand to the channels.

- 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 → causes depolarization of the cell (muscle cell)

activated muscle cell by acetylcholine ⇒ depolarization of the cell ⇒ increasing the Ca^{+2} influx ⇒ causing contraction

we can make a drug that is either activator or inhibitor of this channel. inhibitor ones are going to bind to the nicotinic receptor preventing its activation (by preventing Ach from binding) causing muscle relaxation





B. Ligand-gated ion channel