Semester I.
Seminar 1.

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Exam topics 1-2

1.

- Pharmacodynamic principles. Receptors and subtypes
- General description of parasympathetic nervous system from pharmacological point of view (neurotransmitters and receptors)
- Antihypertensive mode of action of thiazide diuretics and the side effects, osmotic diuretics

2.

- Dose-response relationships. Efficacy and potency
- Directly acting parasympathomimetics
- Calcium channel blockers

What is pharmacology?

- Pharmacon = active substance, agent, drug
- …-logy = the study of …

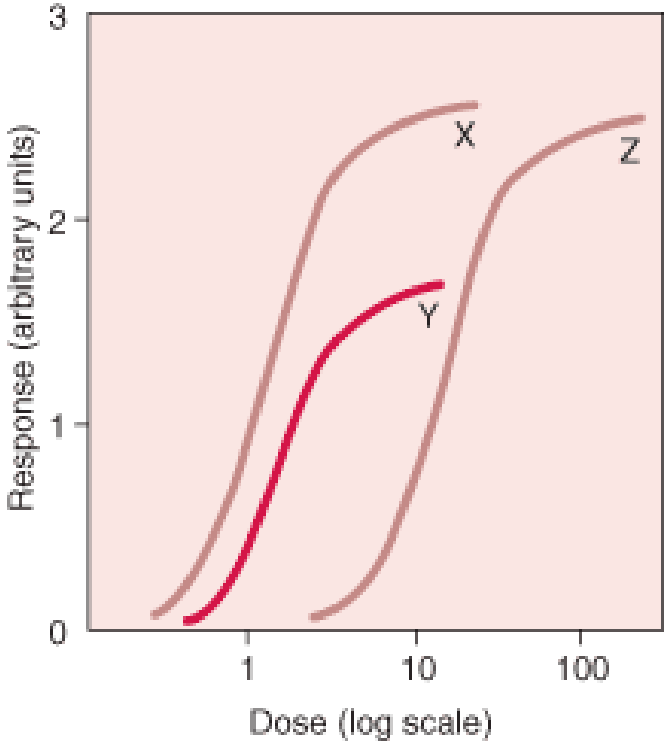
- Pharmacology can be defined as the study of the interactions between drugs and the function of living systems

<u>It can be distinguished into two main branches:</u>

- Pharmacodynamics: how drugs (pharmacons) act on the organism (body) – dose-response relationships. (‘what the drug does to the body’)

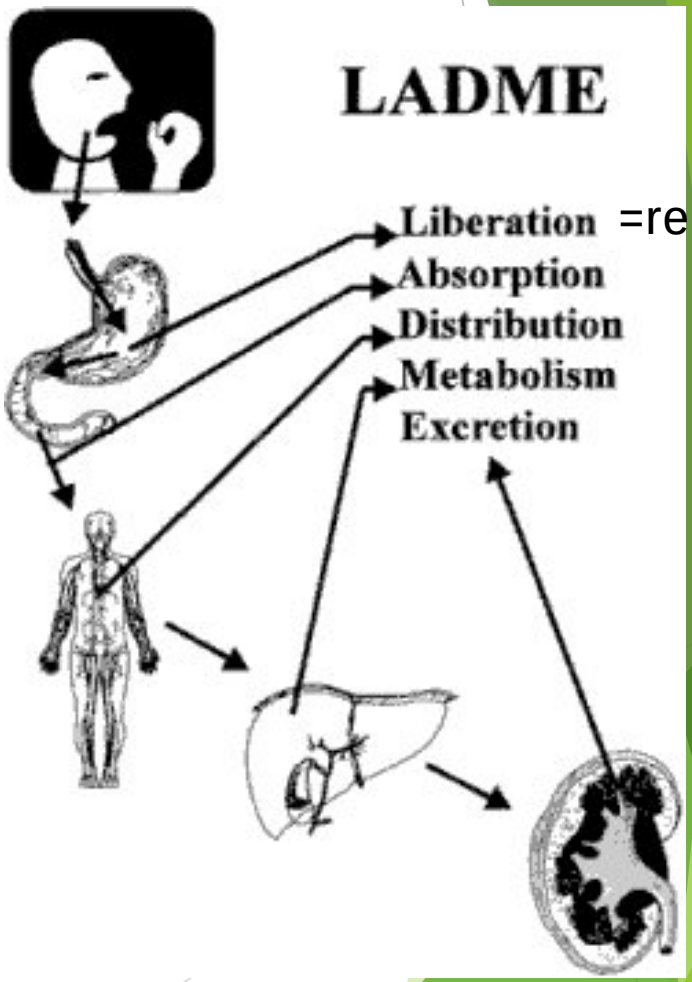
- Pharmacokinetics: Pharmacokinetics may be defined as the measurement and interpretation of changes of drug concentrations in time in different regions of the body in relation to dosing (‘what the body does to the drug’).

Pharmacodynamics



e.g: Epinephrine acts on beta1 receptors and increases heart rate by elevating cAMP levels"

Pharmacokinetics



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Related disciplines

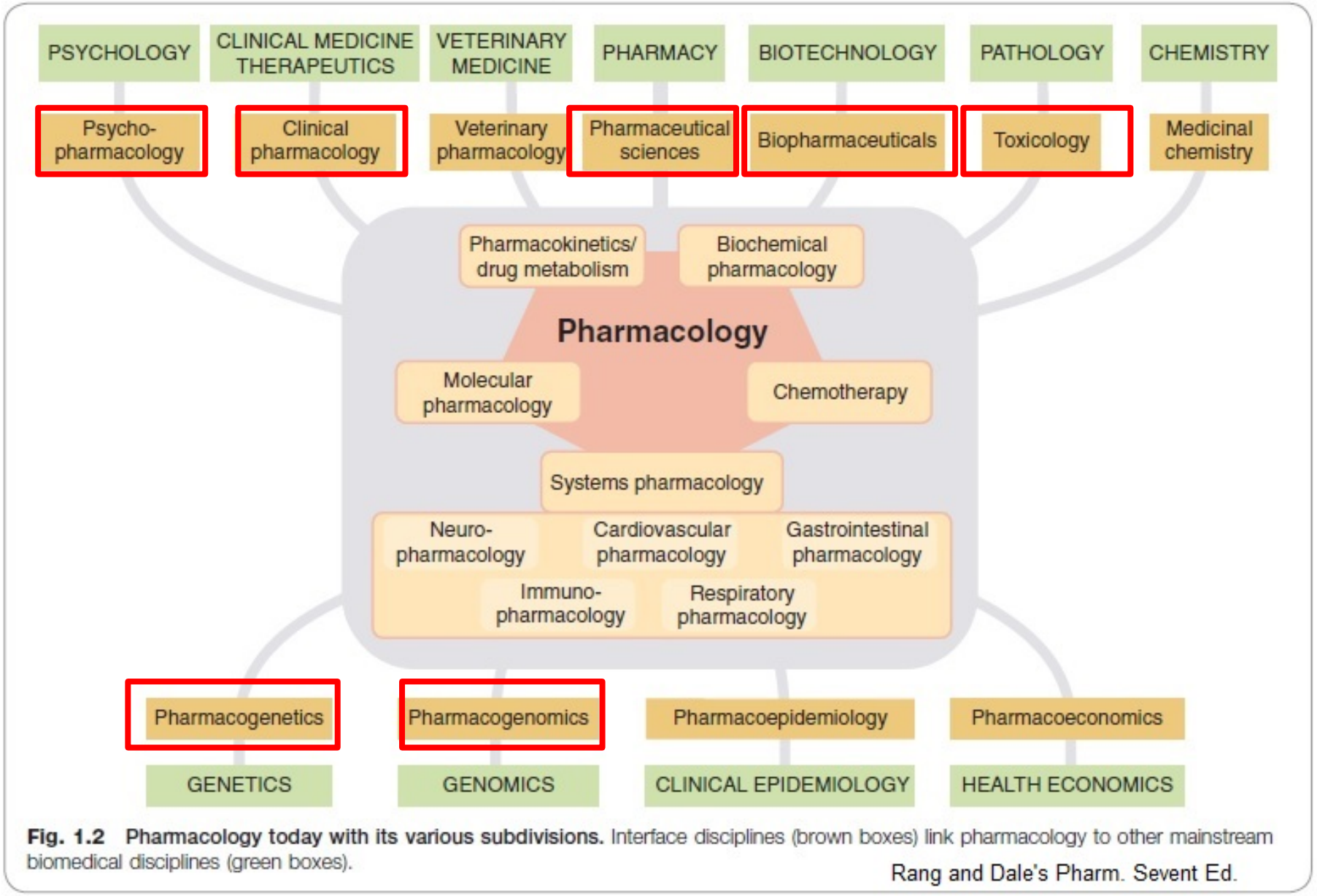


Fig. 1.2 Pharmacology today with its various subdivisions. Interface disciplines (brown boxes) link pharmacology to other mainstream biomedical disciplines (green boxes).

Rang and Dale's Pharm. Sevent Ed.

Basic terms

- DRUG: „a drug can be defined as *a chemical substance of known structure - other than a nutrient or an essential dietary ingredient - which, when administered to a living organism, produces a biological effect"*

- PHARMACON: synonym for drug, scientific term ⇔ drug is also a legal term

- MEDICINE: A *medicine is a chemical* preparation, which usually but not necessarily contains one or more drugs, administered with the intention of producing a therapeutic effect.
  Medicines usually contain other substances (excipients, stabilisers, solvents, etc.) besides the active drug, to make them more convenient to use. (Medication is a synonym.)

- *(Rang and Dale Ph. 7th Ed.)*

Classification of drugs

	Groups	Notes, Examples
Based on occurence	a.) physiologic b.) xenobiotic	Synthetized in organism (e.g. cortisol, insulin, adrenaline) Not synthetized by organism (e.g.penicilline)
Based on creation	a.) natural b.) semi-synthetic c.) synthetic	e.g. herb extracts e.g. penicilline e.g. ranitidine

Other examples:

natural alkaloid: morphine

Semi-synthetic: heroine

Synthetic: loperamide

Classification of drugs based on origin

Natural:

- Mineral origin: vaselin, paraffin, white clay
- Animal origin: pepsin, cod liver oil, beeswax
- Herbal origin: chamomile flower, rosehip, catnip (valerian) (herbal drug: the part of the plant used for medical purposes)
- Biochemical origin: antibiotics, vitamin B12

Natural/Artificial (?):

- Biotechnologically produced: insulin
- Genetechnologically produced: therapeutic DNS encapsuled into viral vector

How does a drug molecule act?

- First a drug molecule must get to the tissue, in the appropriate concentration
- Then it may interact with some macromulecule of the organism
- Target molecules:
  - Proteins
    - **Receptor**
    - Enzyme
    - Carrier molecule
    - Ion channel
  - Lipids
  - DNA, RNA
  - (exeptions: antimicrobals, bisphosphonates, biopharmaceuticals)

What is a receptor?

- Receptor:
  - A macromolecule,
  - which can identify a specific ligand by binding it (”cognitive function”),
  - and if this ligand is activating (agonist), the receptor generates a specific change in containing cell (”transduction function”, effect-generation)

- In broader sense ‘Receptor’ is sometimes used to denote *any target molecule*
- E.g: Na+ channel is the *receptor* for lidocain molecule

Receptor types and families

Receptor Classification

Depending on their placement,

- **peripheral membrane** proteins.
  attached to the cell membrane from the outside.

- **transmembrane proteins**:
  embedded in the phospholipid bilayer of cell membranes,

- **intracellular receptors**

According to function:

- **Metabotropic receptors**
  initiate a **metabolic change** in the cell.
  They are either:
  * coupled to G proteins
  * or they have enzymatic functions themselves.

- **Ionotropic receptors**
  contain a central pore which functions as a ligand-gated ion channel. Indicate faster response.

Receptor Classification II.

The most commonly used classification is as follows:

According to localisation, structure, signal transduction method and endogenous ligand

Receptors can be grouped into:

- Receptor superfamilies consist of
- Receptor families, that are composed of
- Receptor classes, that contain
- Receptor types, that comprise
- Receptor subtypes.

E.g.: G-protein-coupled receptors (superfamily), Acetyl-choline receptors (class), Muscarinic Acetyl-choline receptors (type), M_1-ACh-receptor (subtype)

Receptor Classification III.

Receptor Superfamilies important in pharmacology:

	1. Ionotrop receptors (forming an ion-channel)	2. G-protein-coupled receptors	3. Enzyme-linked receptors	4. Nuclear receptors
Localisation	Cell-membrane	Cell-membrane	Cell-membrane (or intracellular)	Cell nucleus (or intracellular)
Effector	Ion-channel	Enzyme or Ion-channel	Enzyme	Gene transcription
Type of coupling	Direct	G-protein	Direct	DNA-mediated
Examples	nAChR, $GABA_A$, NMDA, AMPA, Kainate, $5\text{-}HT_3$, Glycine-receptors	mAChR Adrenerg receptors, Dopamine-receptors	Receptor for: Insuline, ANP, Tumor Growth Factor (or sGC)	Steroid hormone receptors, thyroid receptors

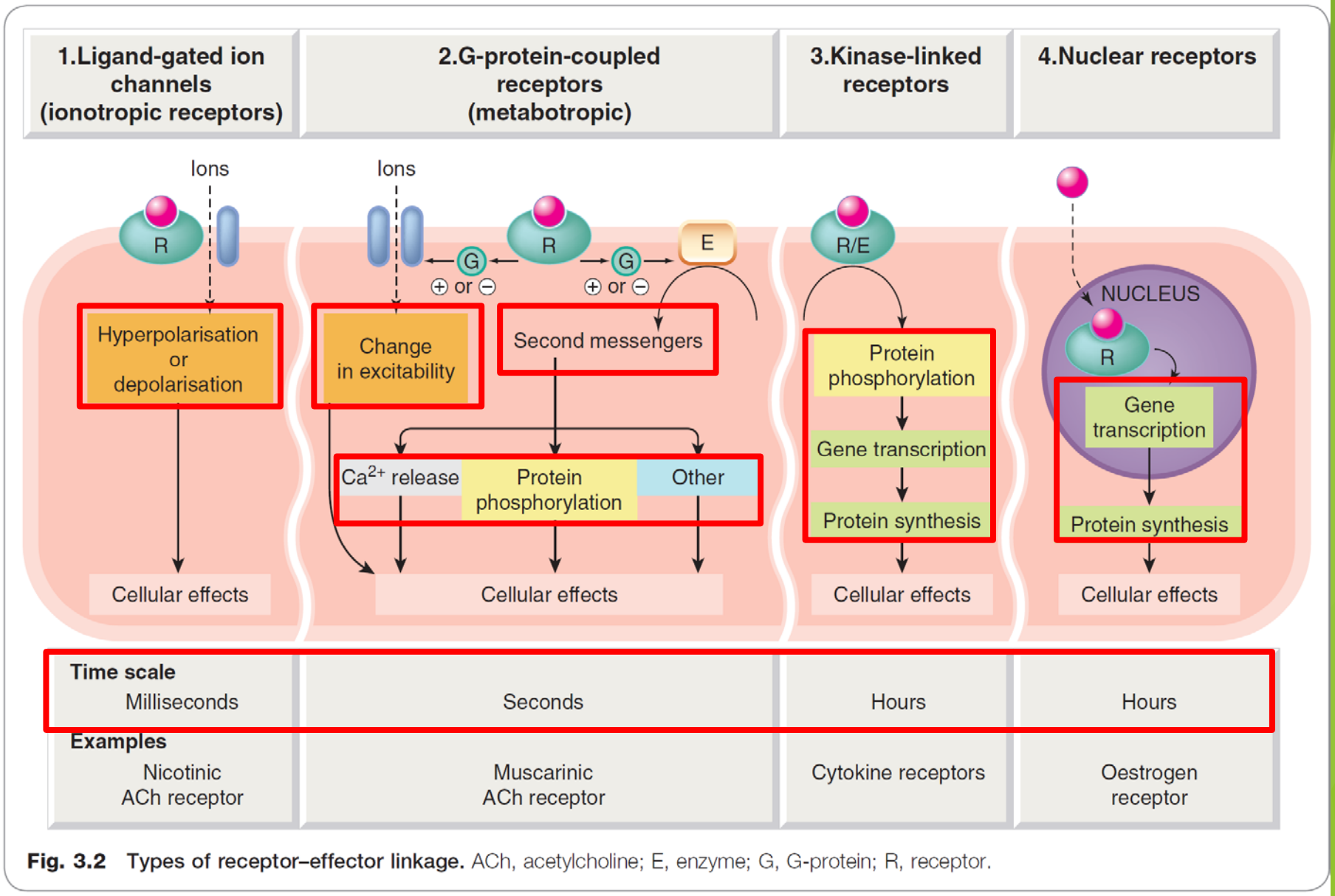
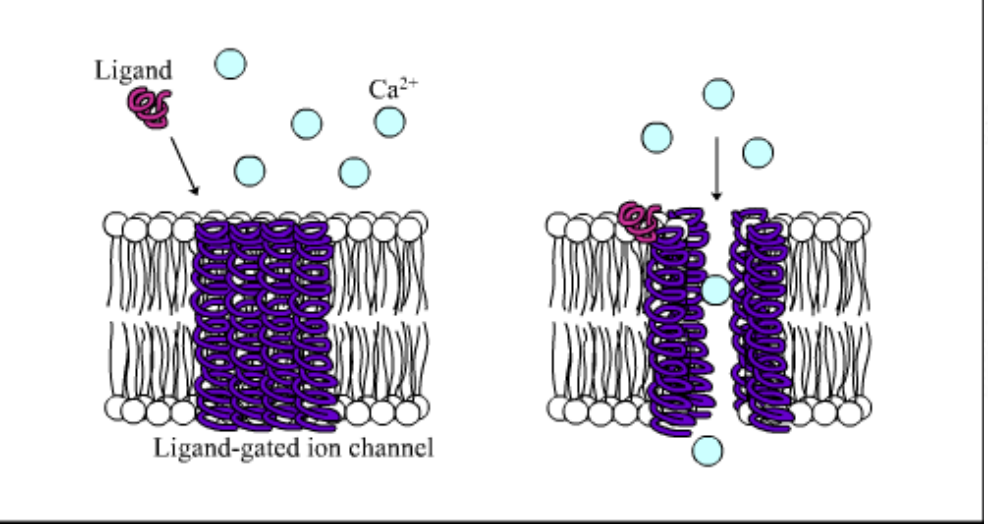
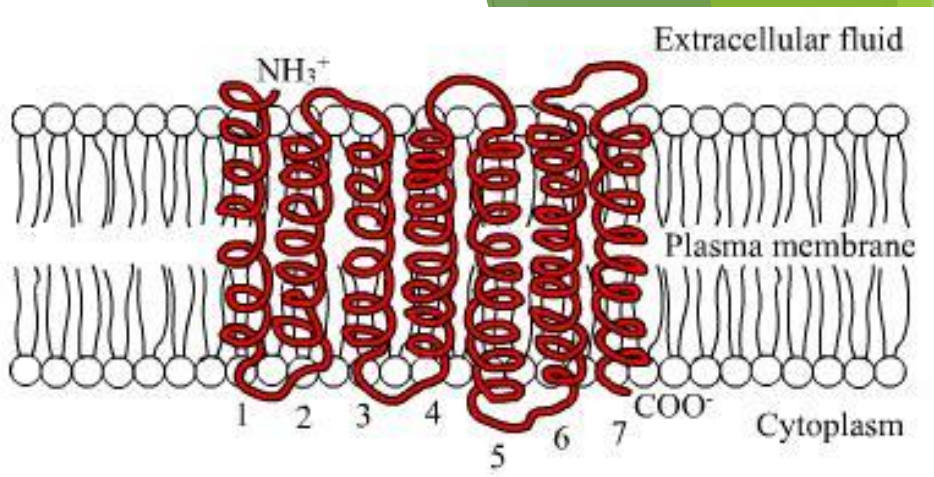
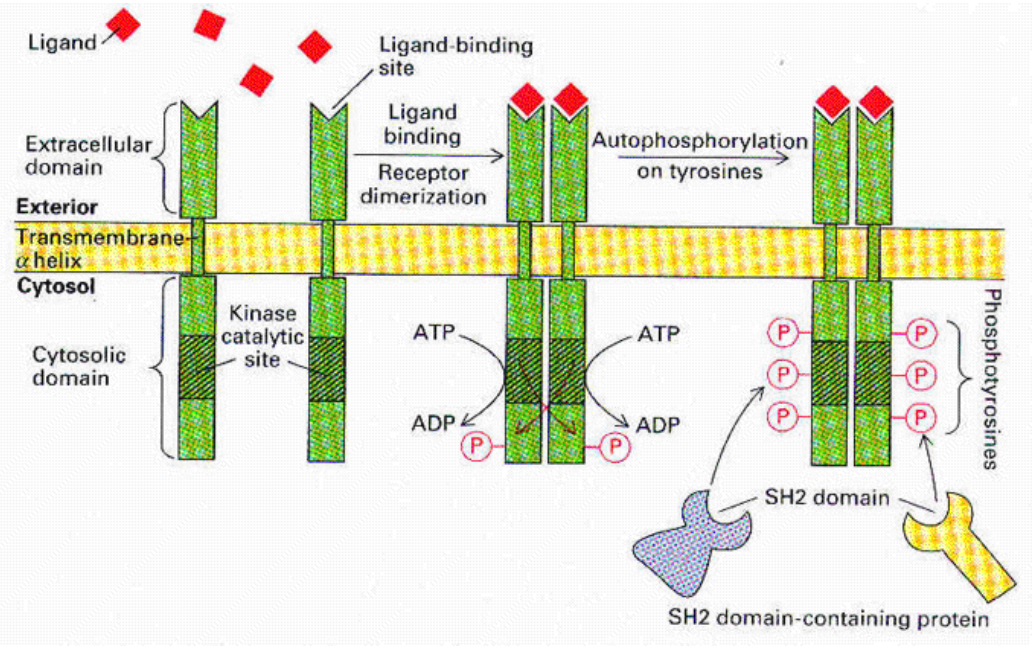
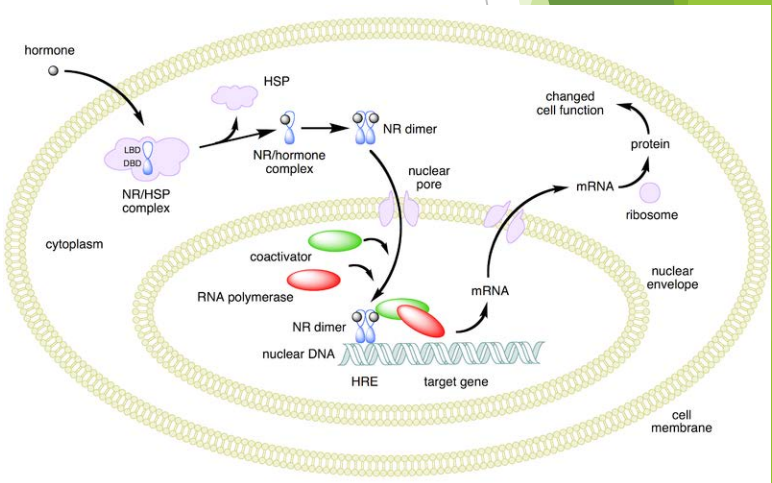


Fig. 3.2 **Types of receptor–effector linkage.** ACh, acetylcholine; E, enzyme; G, G-protein; R, receptor.


Ligand
Ca^{2+}
Ligand-gated ion channel


Extracellular fluid
NH_3^+
Plasma membrane
1 2 3 4 5 6 7
COO^-
Cytoplasm

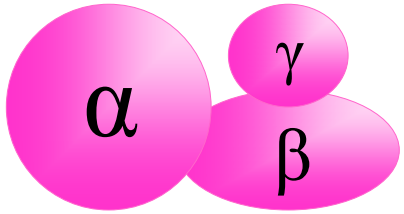

Ligand
Ligand-binding site
Extracellular domain
Ligand binding
Receptor dimerization
Autophosphorylation on tyrosines
Exterior
Transmembrane α helix
Cytosol
Kinase catalytic site
Cytosolic domain
ATP
ADP
ATP
ADP
P
Phosphotyrosines
SH2 domain
SH2 domain-containing protein


hormone
HSP
LBD
DBD
NR/HSP complex
NR/hormone complex
NR dimer
nuclear pore
changed cell function
protein
mRNA
ribosome
cytoplasm
coactivator
RNA polymerase
mRNA
nuclear envelope
NR dimer
nuclear DNA
HRE
target gene
cell membrane

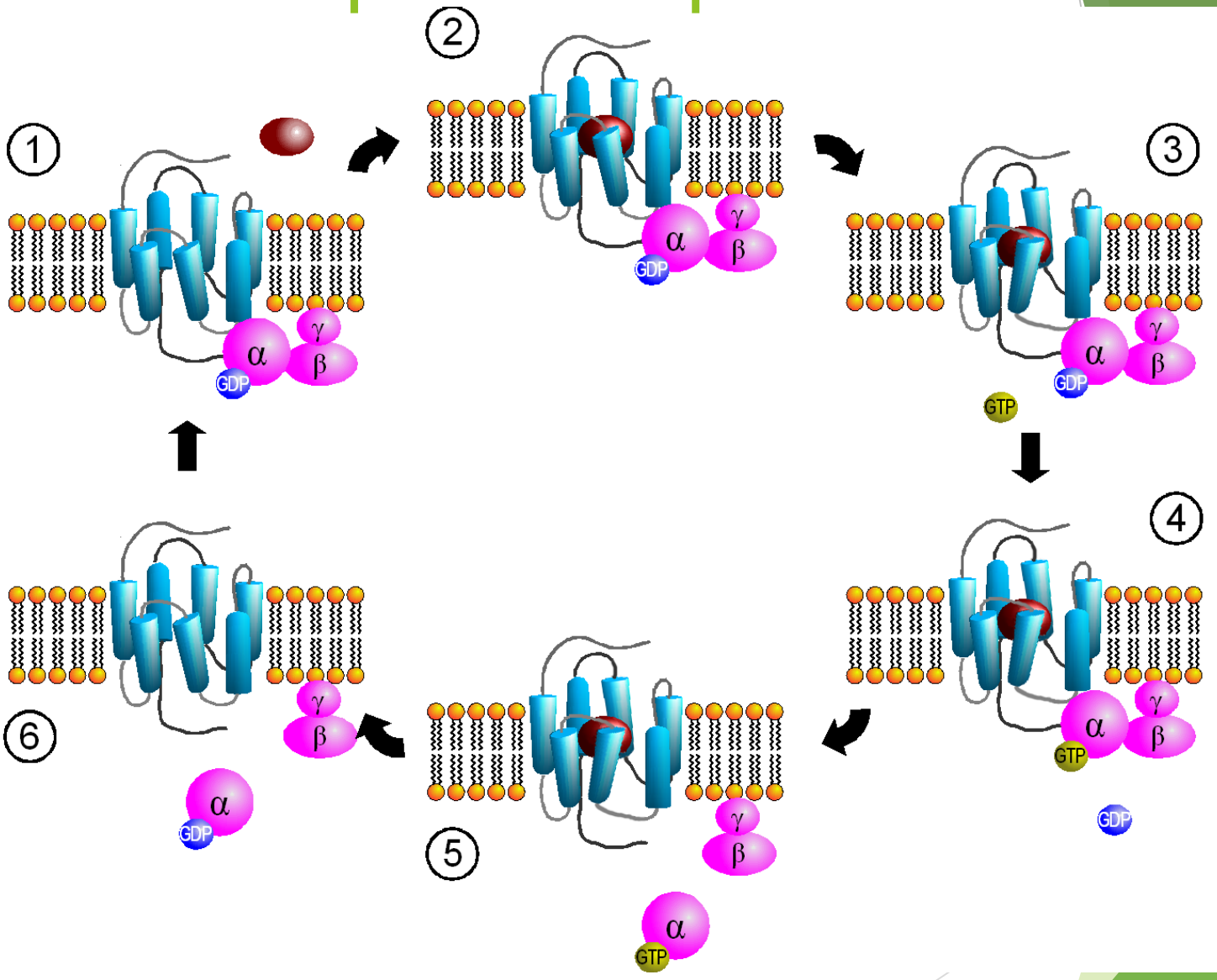
G-protein-coupled receptors I.

- Receptor = 7TM Domain receptor
- To the inner surface of 7TMD receptor a G-protein is attached.

- G protein = guanine nucleotide binding proteins
- G proteins belong to the larger group of enzymes called **GTPases**.
- G proteins consist of the G_{α} and the tightly associated $G_{\beta\gamma}$ subunits.



G-protein-coupled receptors II.

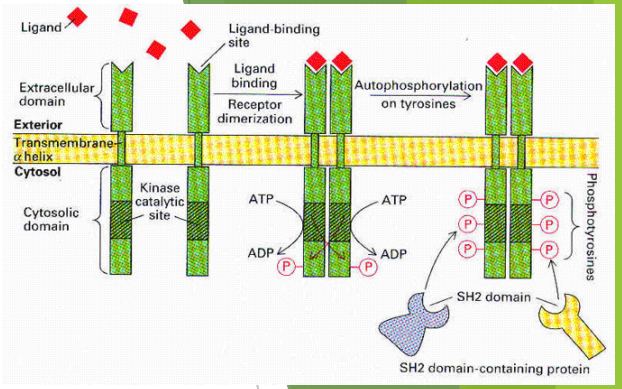


The G_α subunit will eventually hydrolyze the attached GTP to GDP by its inherent enzymatic activity, allowing it to re-associate with $G_{\beta\gamma}$ and starting a new cycle.

G-protein-coupled receptors III.

- Gα subunit actions:
  - Gs: stimulates adenylate cyclase (ATP➔cAMP) = [cAMP] ↑ ➔ PKA-activation ➔ …
  - Gi: inhibits adenylate cyclase [cAMP] ↓
  - Gq/11: stimulates membrane-bound phospholipase C (cleaves PIP2 into IP3 and DAG)
    - ➔ IP3-gated Ca-channel opens on ER ➔ [Ca2+] ↑ ➔ PKC-activation (together with DAG)
    - ➔ DAG ➔ PKC-activation (alone or together with Ca2+)
  - G12/13: through RhoGEF superfamily control cell cytoskeleton remodeling, thus regulating cell migration
- Gβγ subunit actions:
  - may activate e.g. L-type calcium ion channels

Enzyme-linked receptors



An enzyme-linked receptor is a transmembrane enzyme:
the binding of an extracellular ligand ➔
causes intracellular enzymatic activity

- Examples of the enzymatic activity include:
  - Receptor tyrosine kinase e.g. insulin receptor, leptin-receptor, growth hormone receptors etc
  - Serine/threonine-specific protein kinase e.g. tumor growth factor beta (TGF_{β}) receptor

  autophosphorylation
  - Guanylate cyclase e.g. atrial natriuretic factor (ANP) receptor

  GTP ➔ cGMP ➔ [cGMP] ↑ ➔ **PKG**

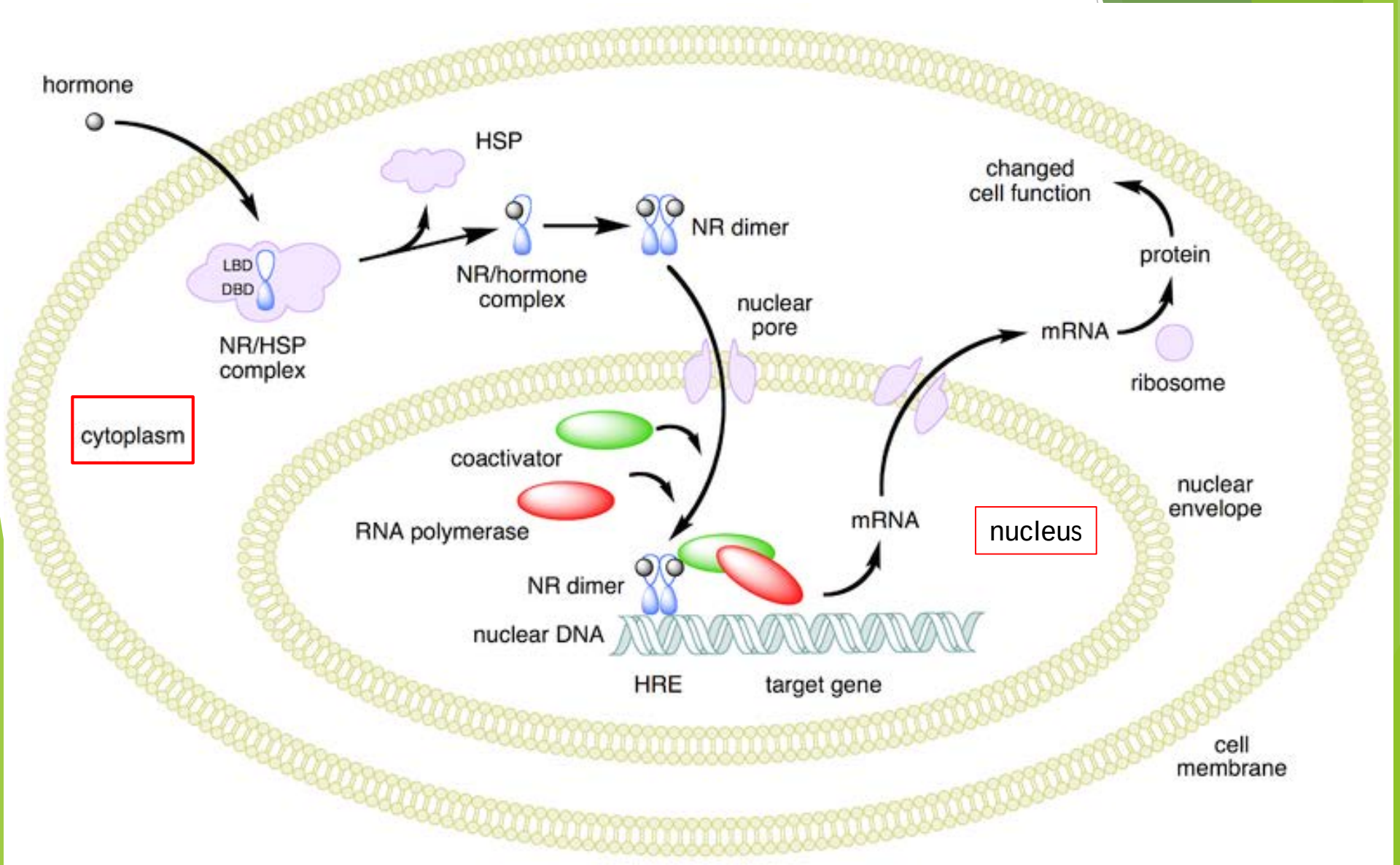
Currently two main signaltransductional way is known:

Ras/Raf/MAPkinase pathway (growth factors)

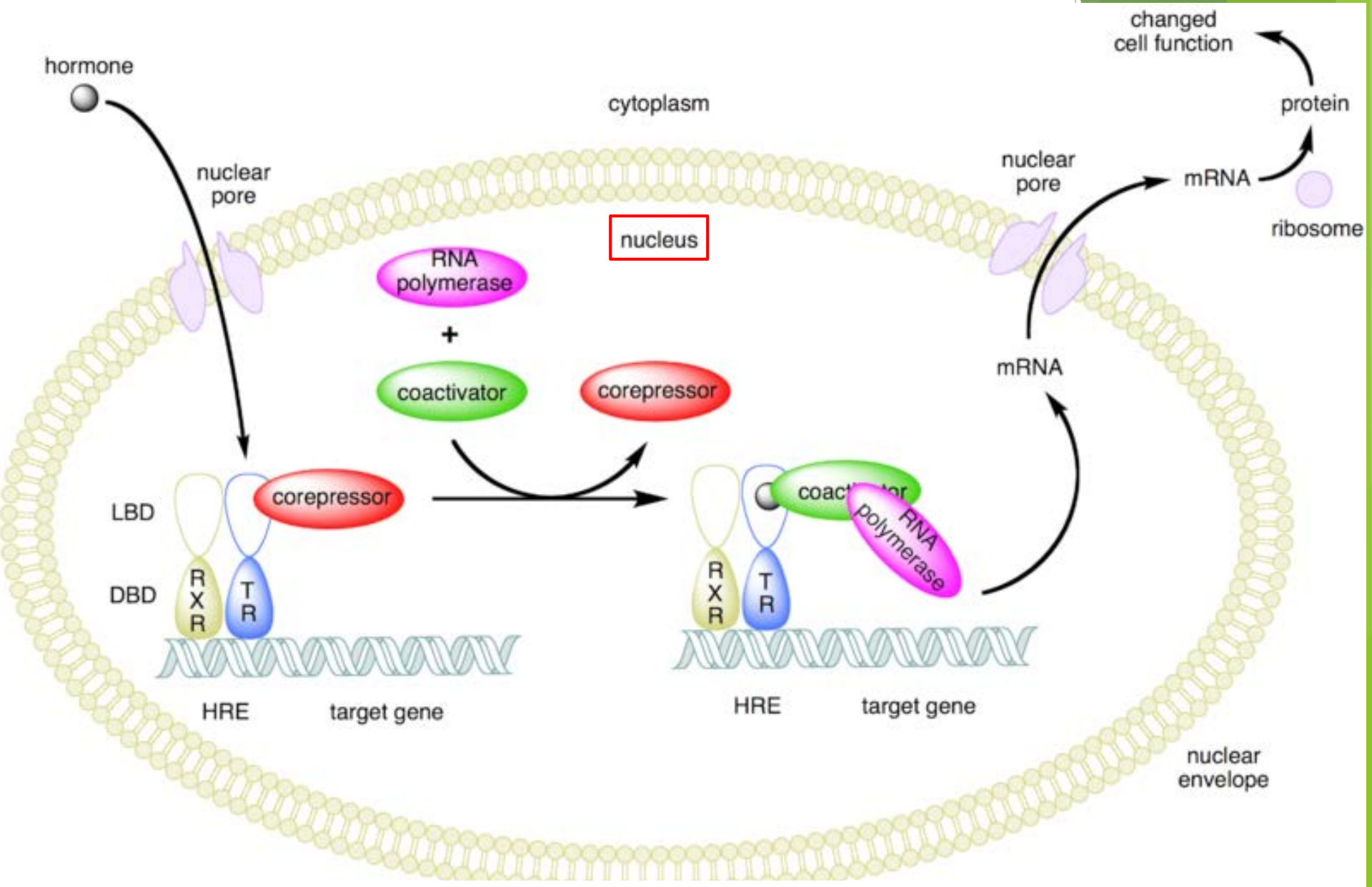
Jak/Stat pathway (cytokines)

Note: Soluble (non-transmembrane) guanylate cyclase = NO-receptor
(NO = Nitric oxide or nitrogen monoxide)

Action of type I Nuclear receptors



Action of type II Nuclear receptors



(For the purpose of illustration, the nuclear receptor shown here is the thyroid hormone receptor (TR) heterodimerized to the RXR.)

Dose-response relationships, Efficacy and potency

Basic terms in Pharmacodynamics

- Dose (D) (concentration (c)): the amount of pharmacon, which is administered into a biological system (usual units: D: g, c: mmol/l).

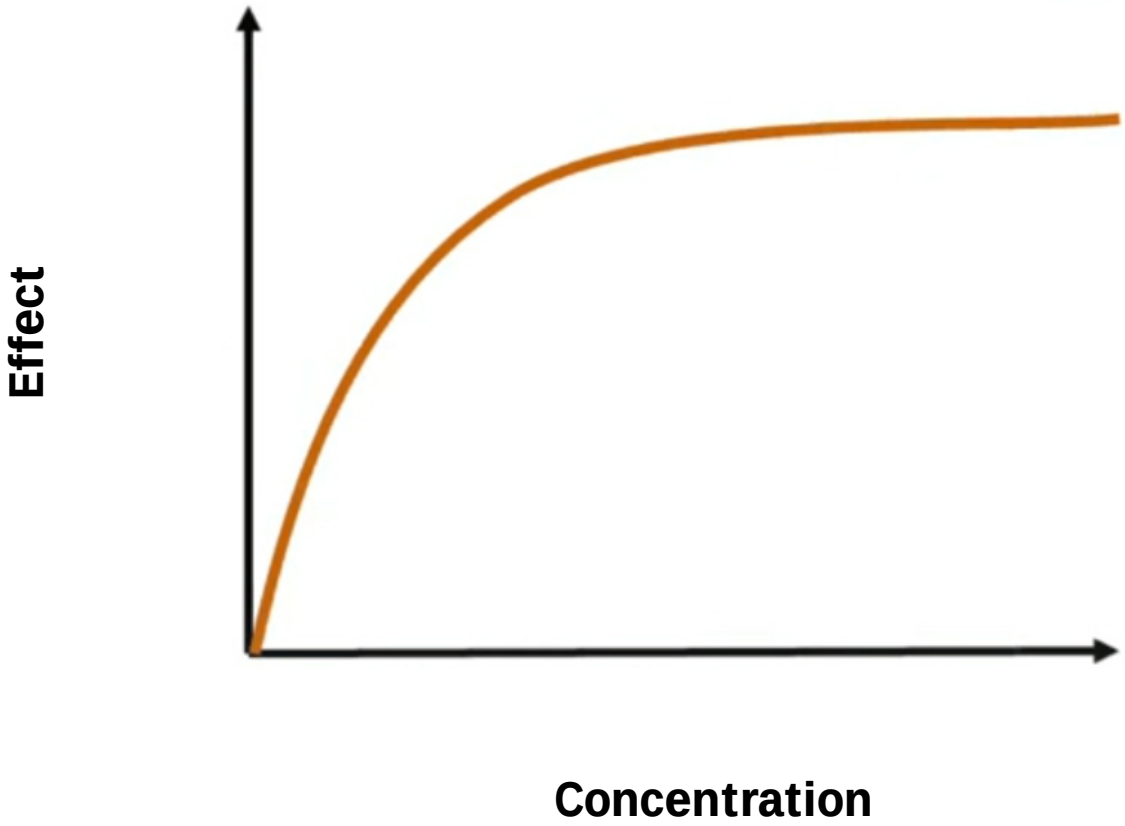
- Biological effect (E): the evoked response (which the experimental pharmacologist tries to measure)

The dose-response curve

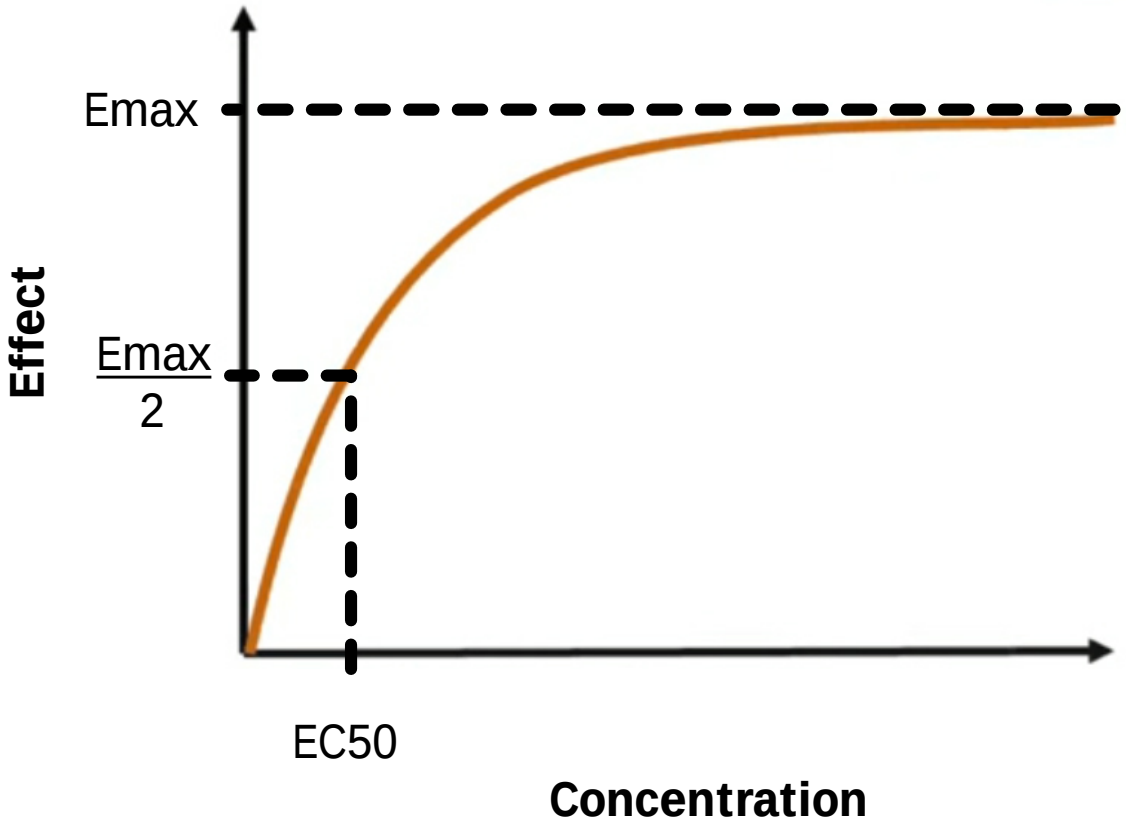
Mathematical interpretation of the drug effect, where

- X axis is the dose (or concentration)
- Y axis is the biological effect or response generated by the drug
  - The effect can be graded or quantal (see on a later seminar)
  - (The evoked effect also depends on time, to decouple it from time, we use equilibrium (=balanced) concentrations)

The dose-response curve



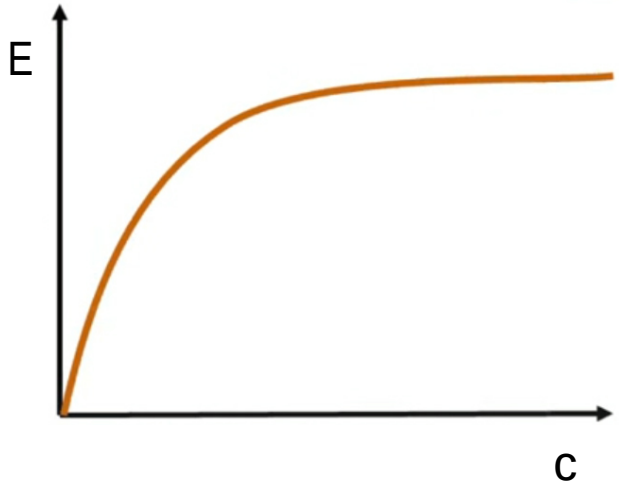
The dose-response curve



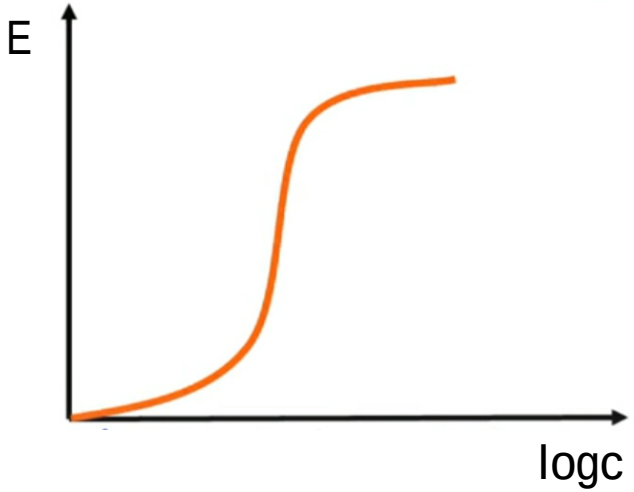
Such curves allow us to estimate *the maximal response that the drug can produce (Emax), and* the concentration or dose needed to produce a 50% maximal response (EC50 or ED50), parameters that are useful for comparing different drugs that produce similar effects

The dose-response curve

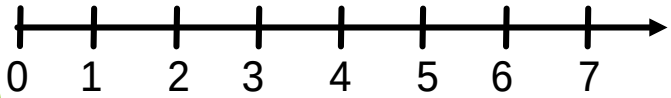
Linear scale
Hyperbolic shape



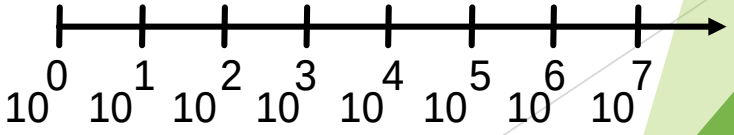
Semilogarithmic scale
Sigmoid shape



The agonist concentration is plotted in linear form

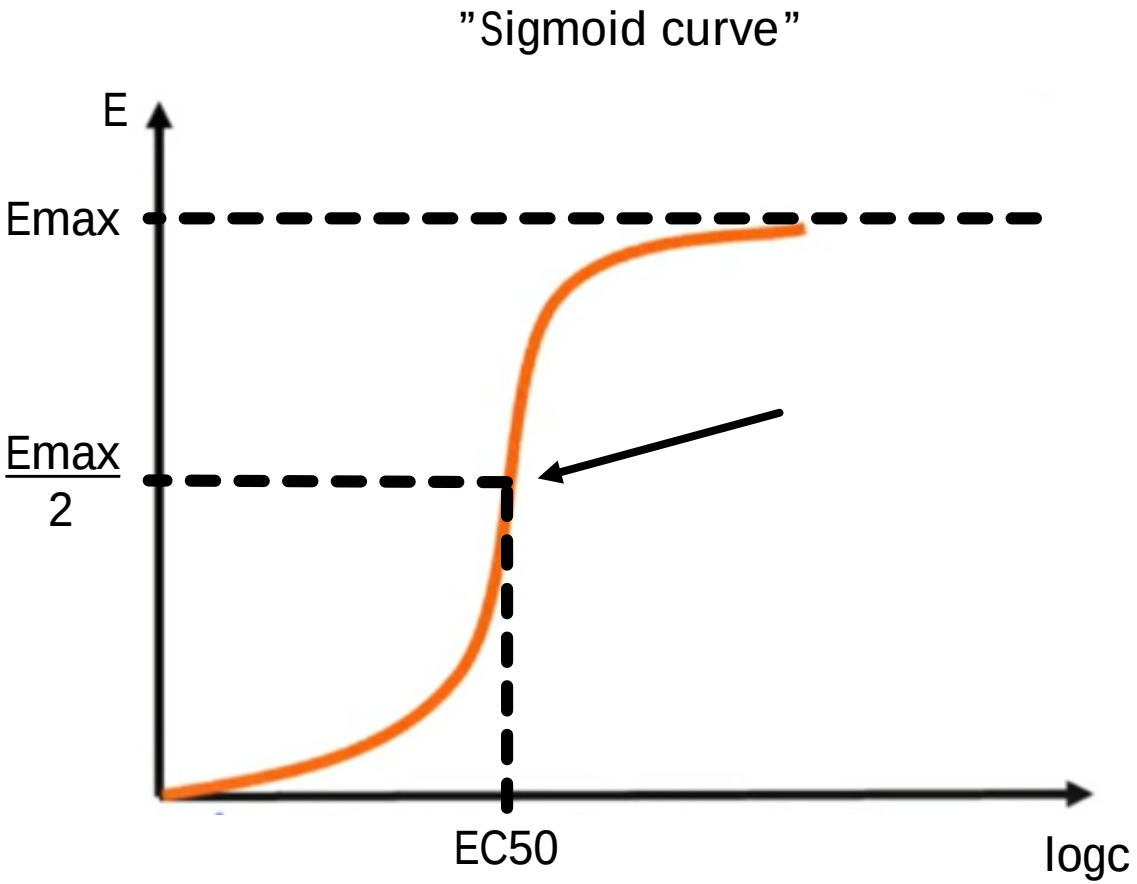


The agonist concentration is plotted in logarithmic form



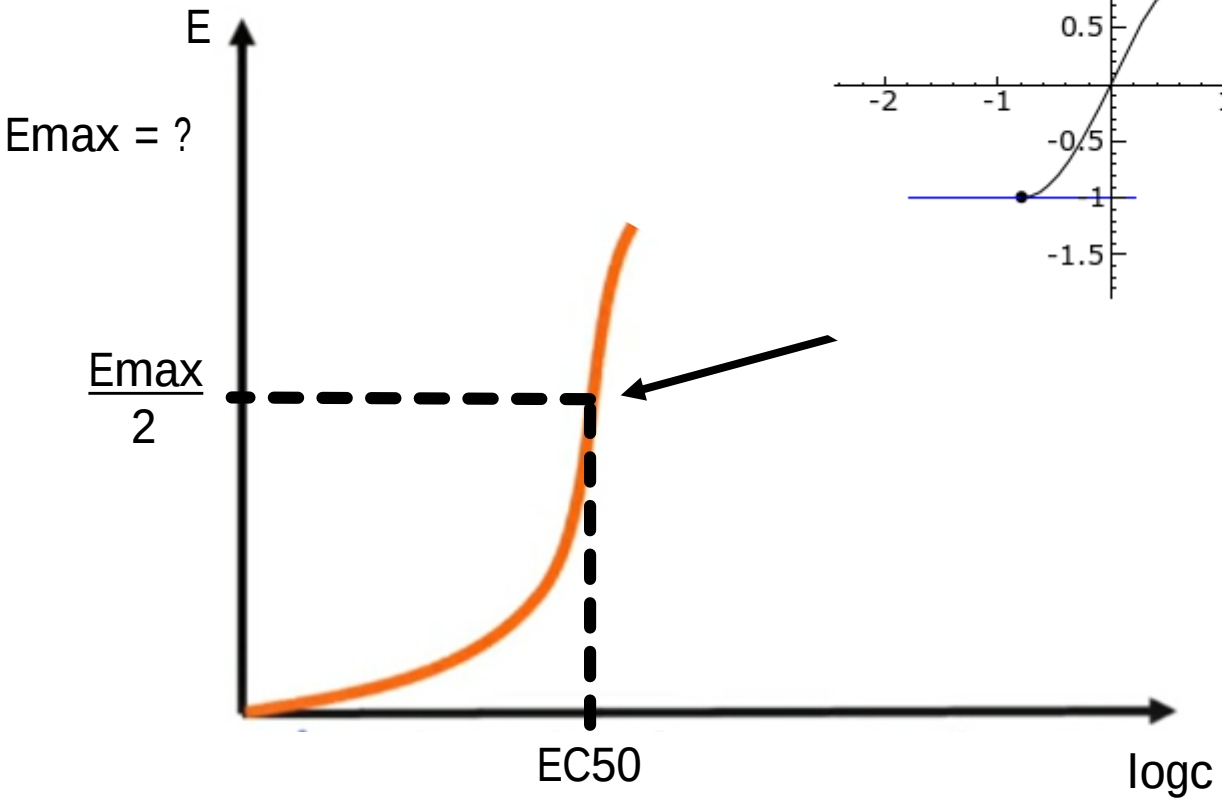
Here we use logarithm to base 10 but we could use any base to denote a logarithmic system

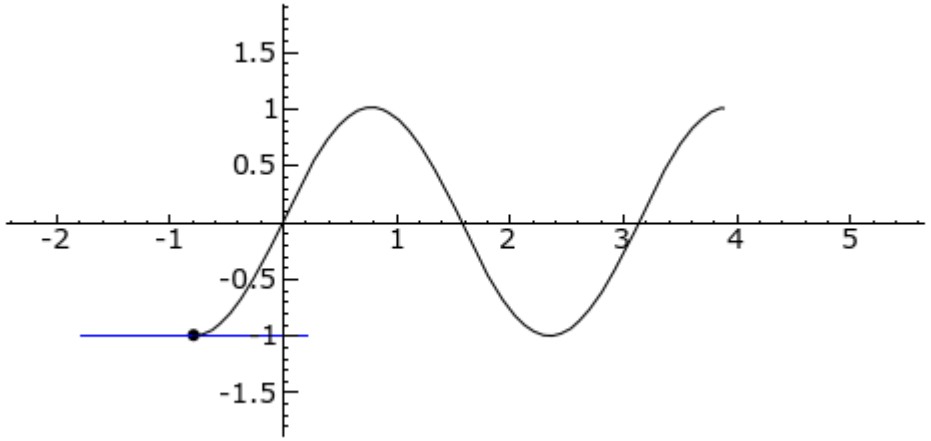
The dose-response curve



Why it is better? ➔

The dose-response curve

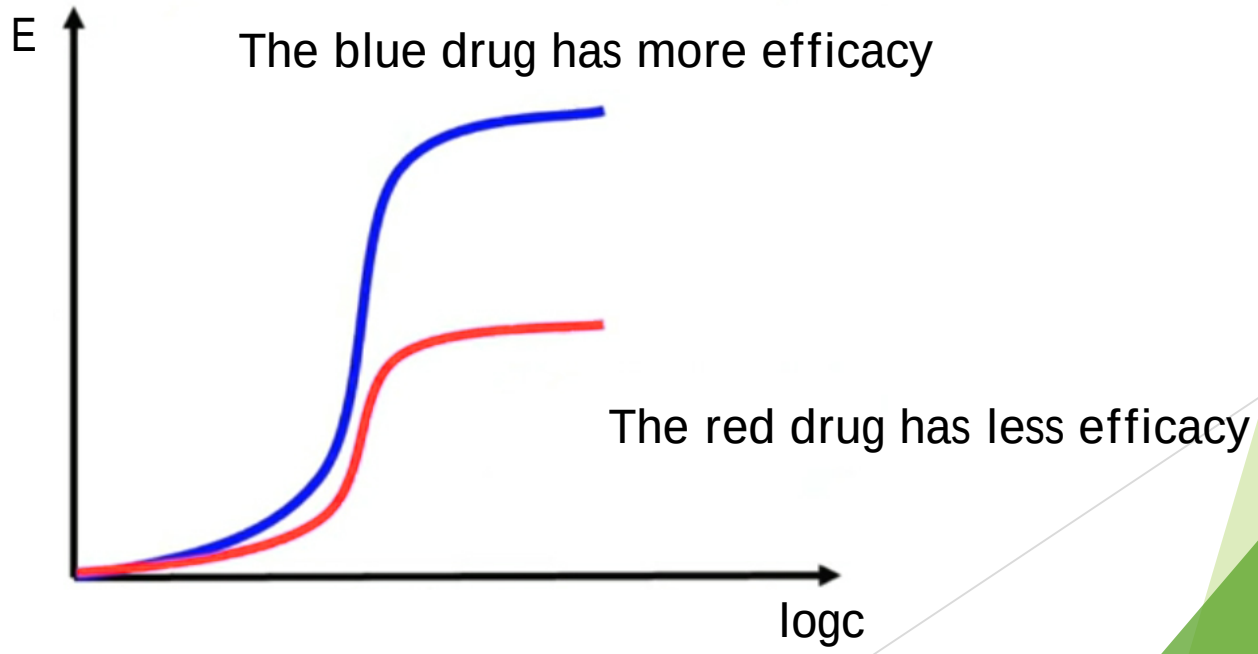




Why it is better? ➔ without the need to measure Emax, EC50 can be calculated from the inflection point of the curve

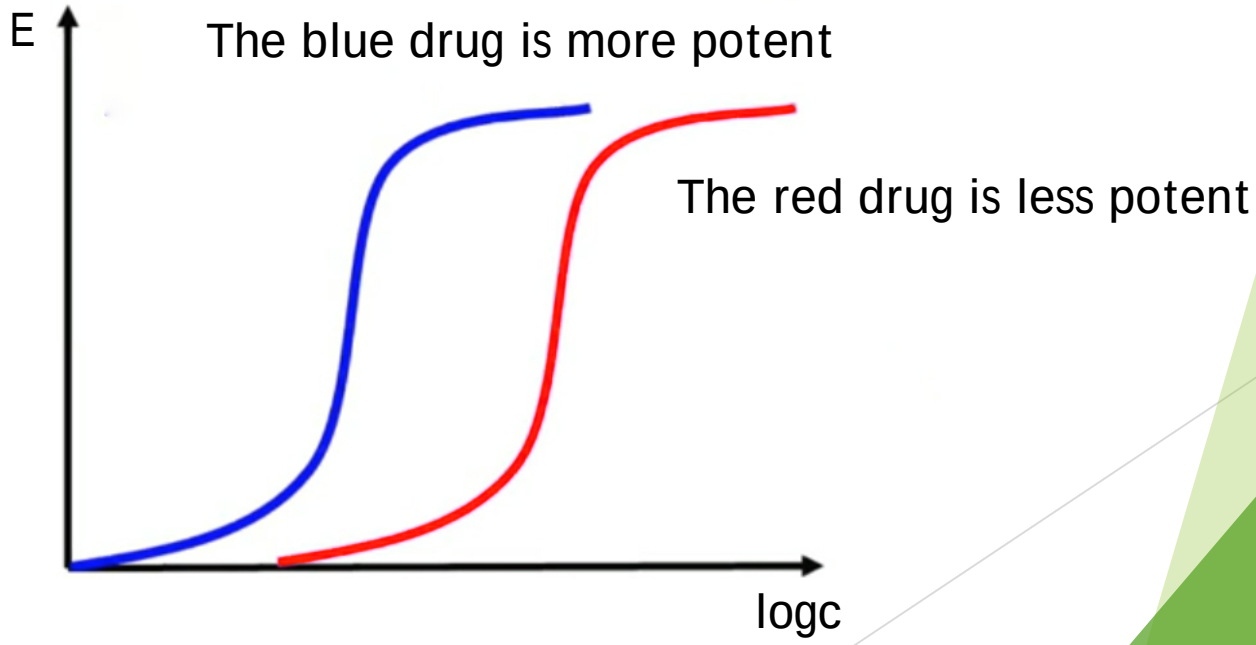
Efficacy and Potency

- **Efficacy** refers to the effect of the drug.
  The more effect (the higher the maximal effect),
  the more **efficacious** the drug.



Efficacy and Potency

- **Potency** refers to the concentration of a drug needed for the effect.
  The less the concentration required, the more **potent** the drug.



Efficacy and Potency

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