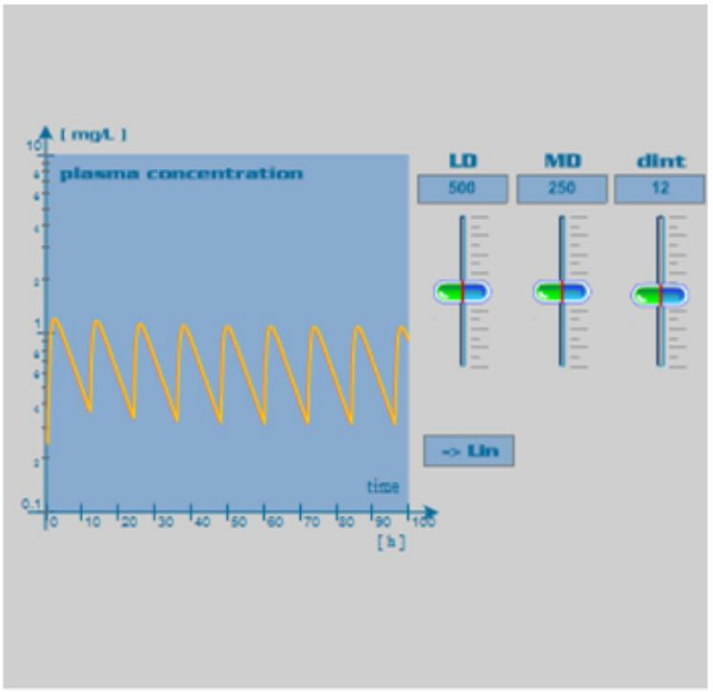
PHARMACODYNAMICS

The study of the relationship between the concentration of a drug and its pharmacological effect.

DRUG-DOSING REGIMEN

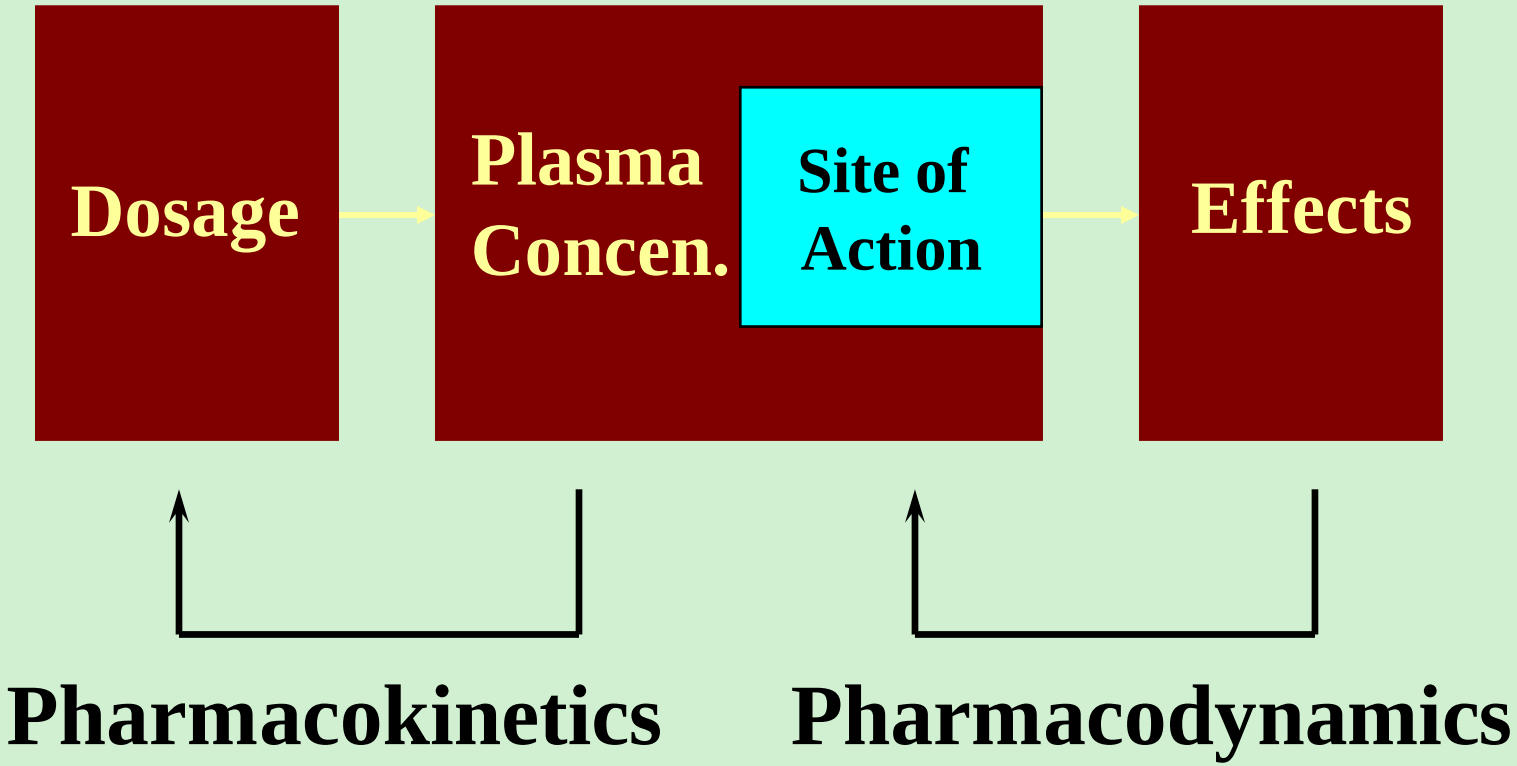
- *Route of administration*
- Galenic formulation
- Unit dose
- Frequency
- Loading dose
- Length of treatment



LD = Loading Dose

MD = Maintenance

dint = dosing interval


Dosage
Plasma Concen.
Site of Action
Effects
Pharmacokinetics
Pharmacodynamics

PHARMACODYNAMICS (PD)

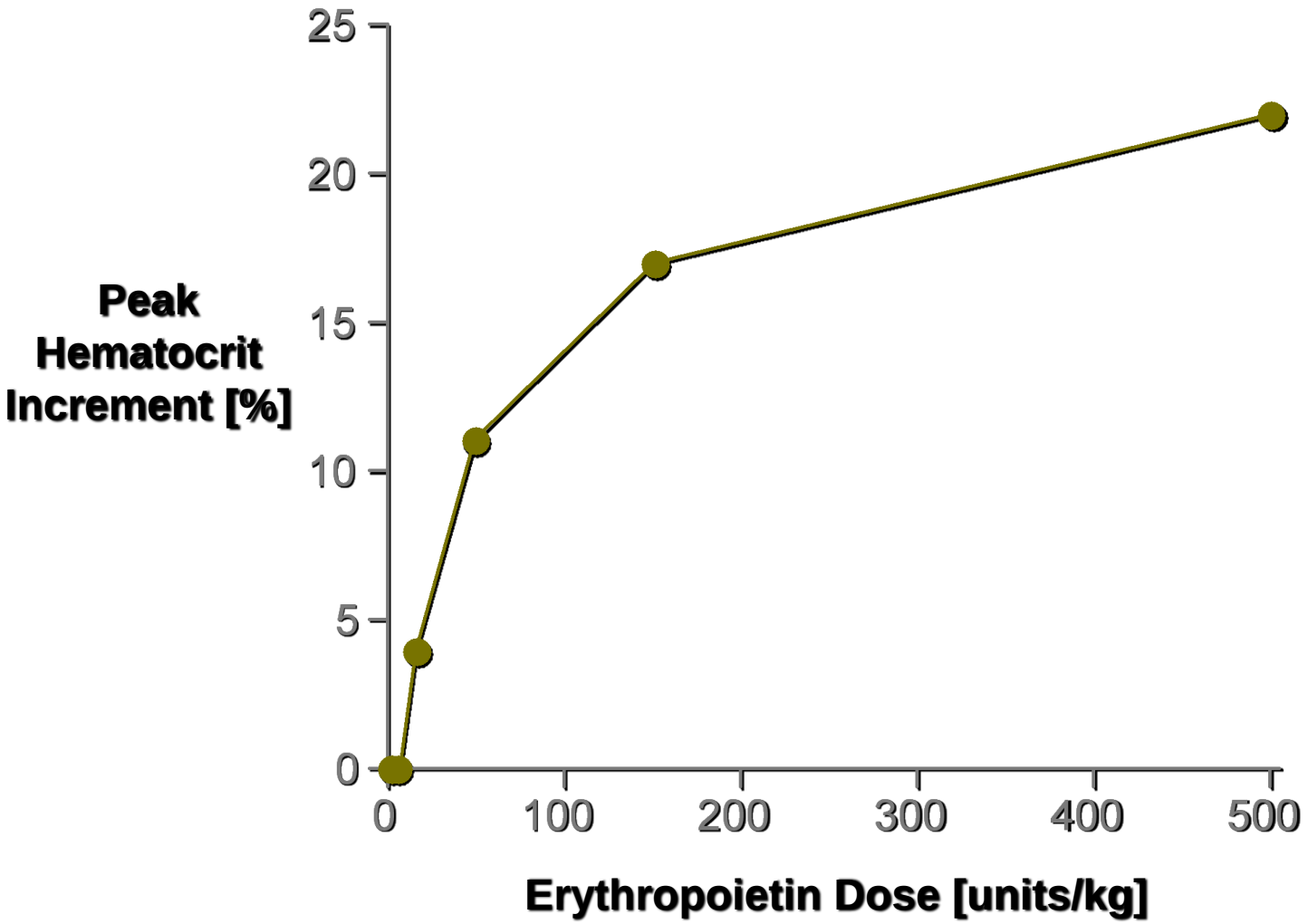
a drug *effect* on the body over a time-course

- **E MAX: MAXIMAL EFFECT ATTAINABLE DUE TO THE DRUG**

- **EC50: The concentration at which half of the maximal effect is observed – DRUG POTENCY.**

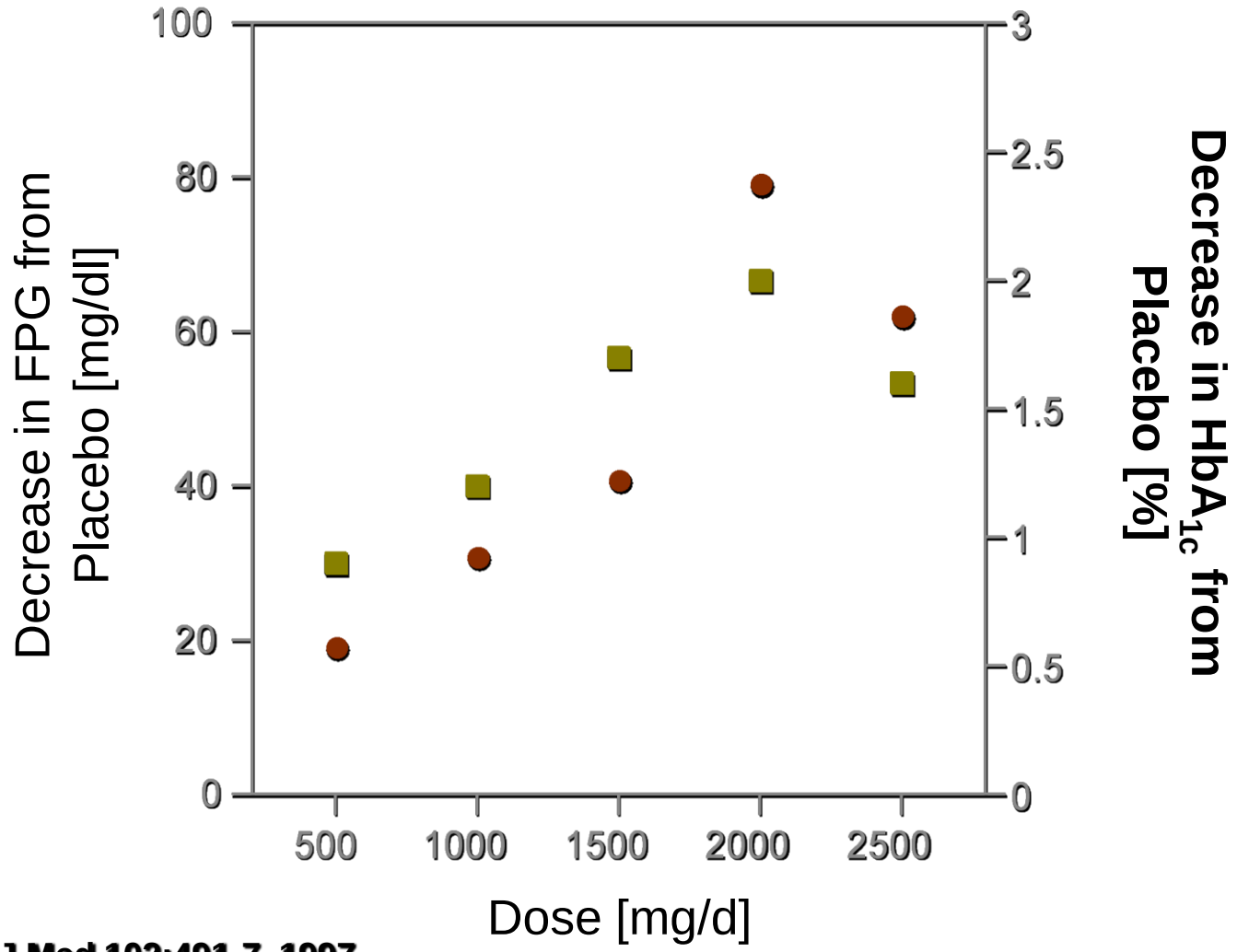
$$\text{EFFECT} = \frac{E_{MAX} * \text{CONCENTRATION}}{EC50 + \text{CONCENTRATION}}$$

ERYTHROPOIETIN AND ANEMIA



Eschbach et al. NEJM 316:73-8, 1987

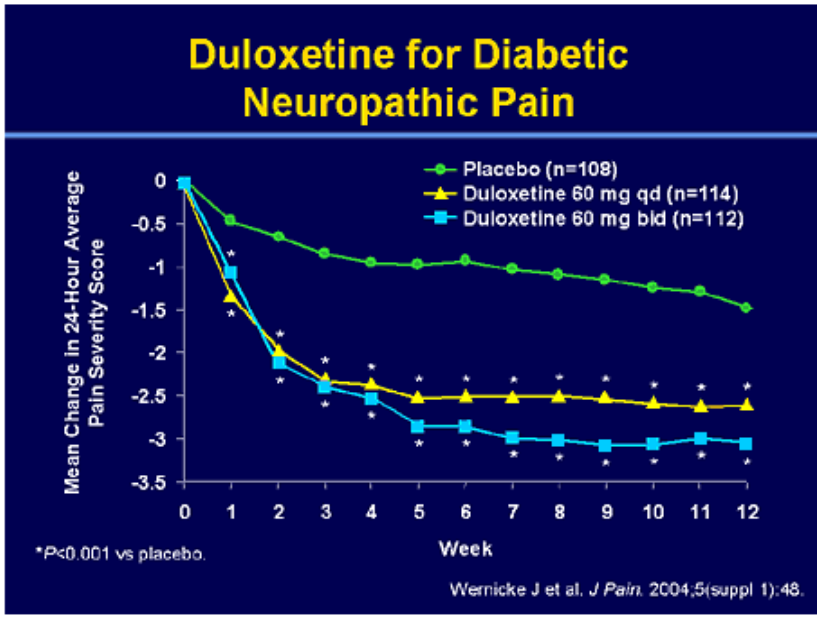
METFORMIN DOSE-RESPONSE



Garber et al. Am J Med 102:491-7, 1997

Diabetic peripheral neuropathy - Pain

1) The recommended dose of duloxetine for the treatment of neuropathic pain associated with diabetic peripheral neuropathy is 60 mg orally once daily. The maximum recommended dose is 60 mg once daily**. There is no evidence that doses higher than 60 mg/day provide additional significant benefit.** A lower starting dose may be considered for patients in whom tolerability is a concern. Efficacy beyond 12 weeks of treatment has not been evaluated in placebo-controlled trials [1].



53.

Duloxetine for Diabetic Neuropathic Pain

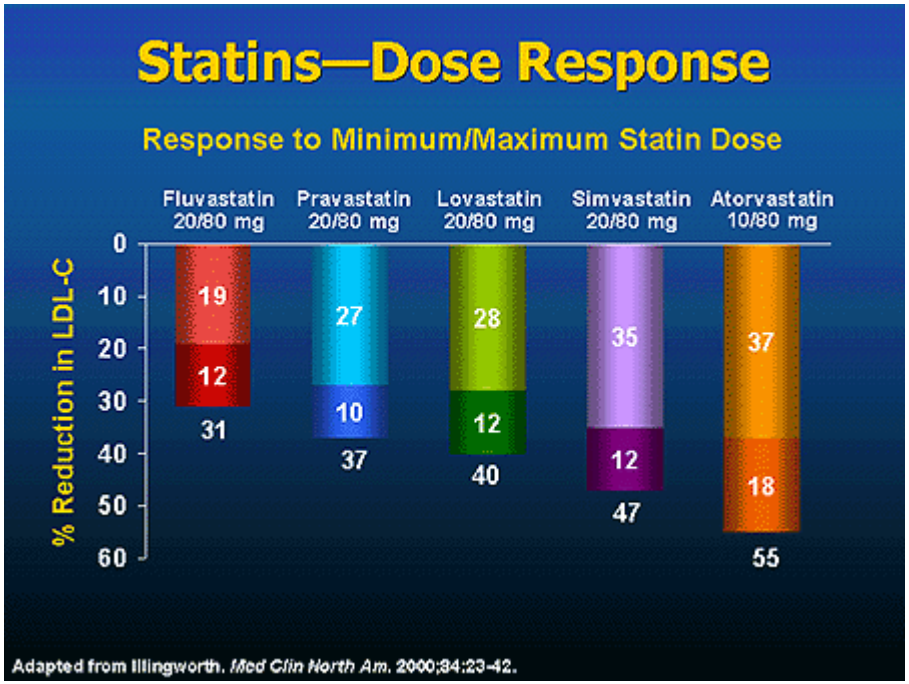
DOSE-EFFECT PARAMETERS

POTENCY: The sensitivity of an organ or tissue to the drug

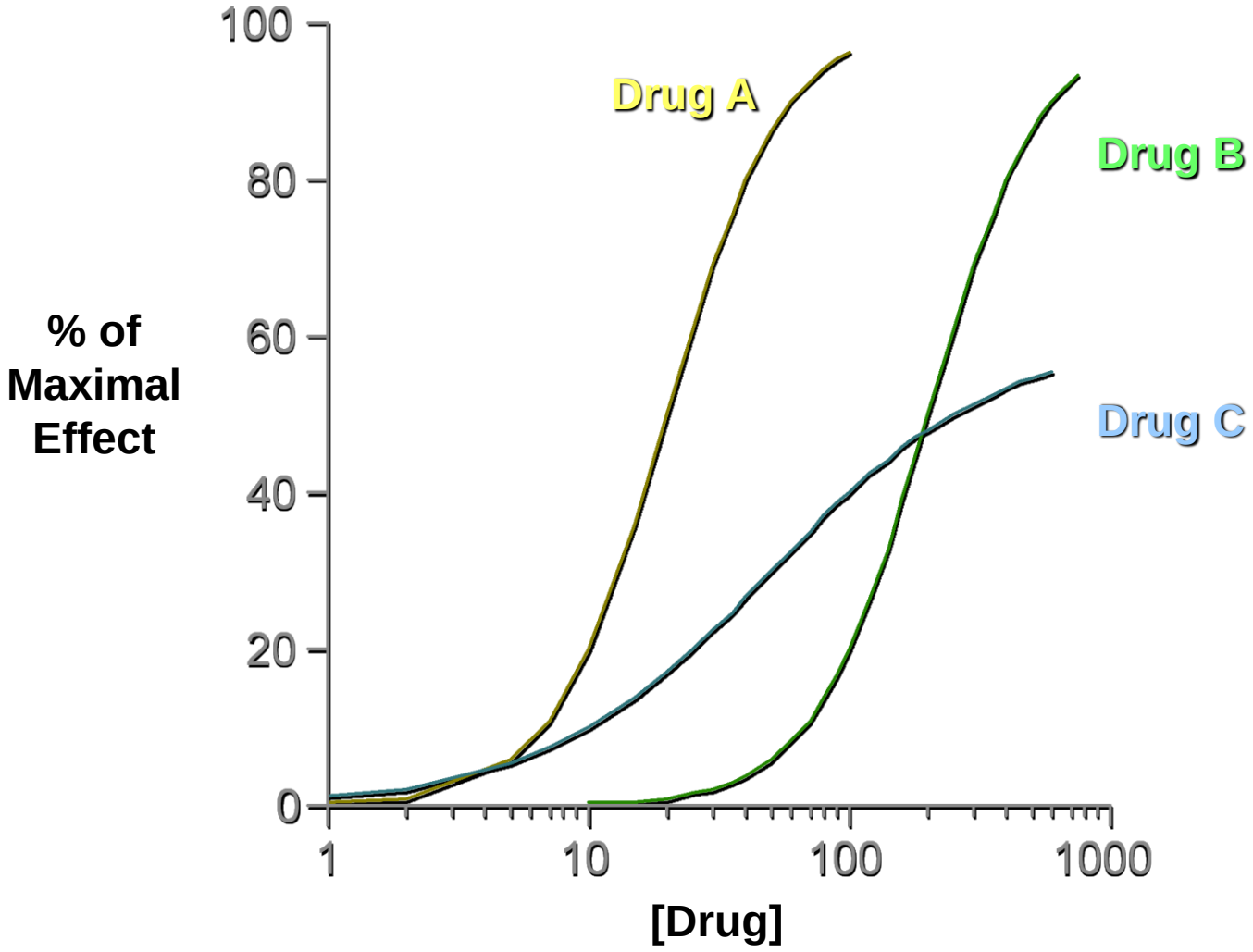
EFFICACY: The maximum effect

Table 3 – Equivalent statin doses

Lovastatin	Pravastatin	Simvastatin	Fluvastatin	Atorvastatin	Rozuvastatin
20 mg	20 mg	10 mg	40 mg	--	--
40 or 80 mg	40 mg	20 mg	80 mg	10 mg	--
80 mg	80 mg	40 mg	--	20 mg	5 or 10 mg
--	--	80 mg	--	40 mg	--
--	--	--	--	80 mg	20 mg
--	--	--	--	--	40 mg



COMPARING DOSE-EFFECT CURVES



HOW IS PD EFFECT ACHIEVED?

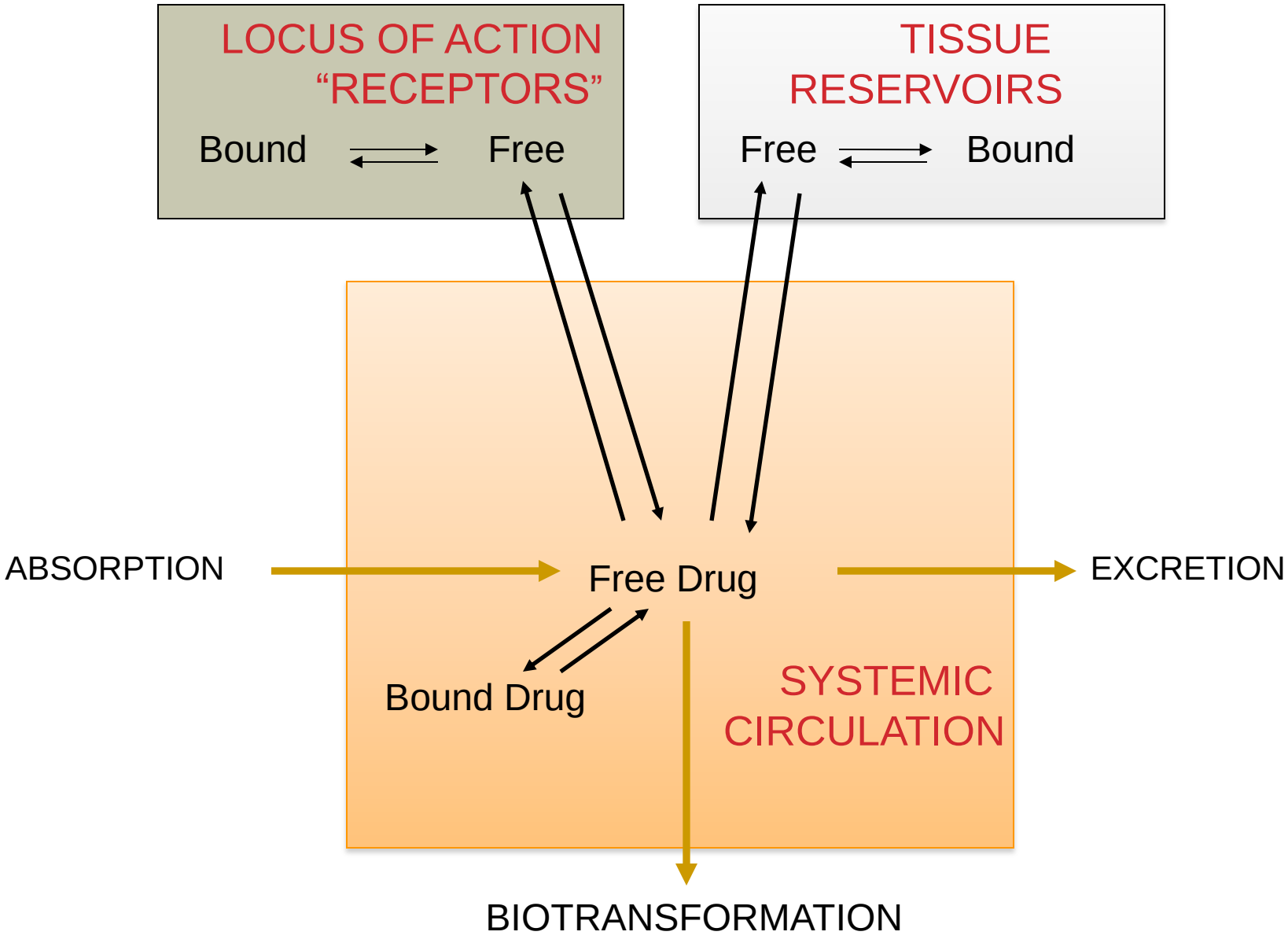
Drug concentration in plasma or tissue fluid drives a **reversible** interaction with a protein:

receptor,

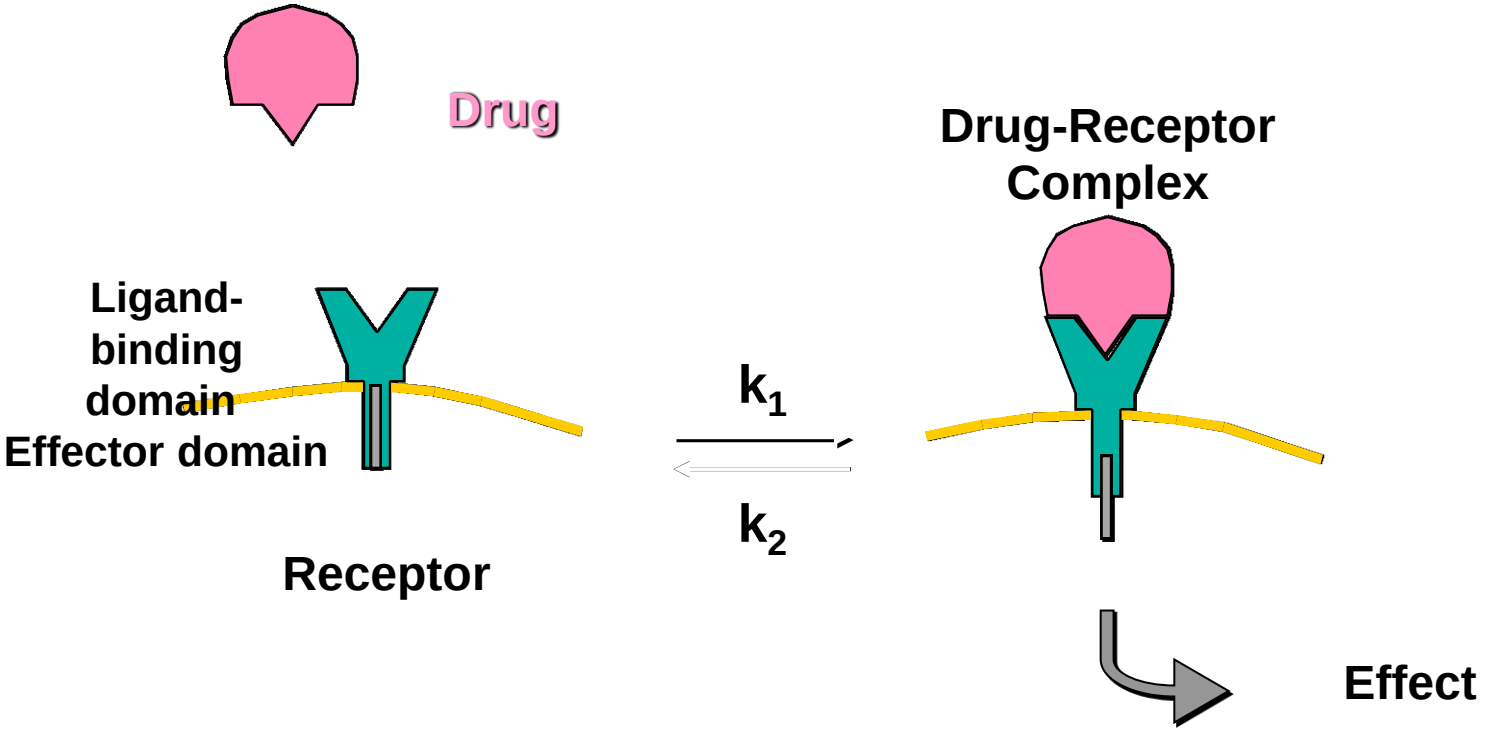
enzyme,

ion channel

DRUG RECEPTOR INTERACTIONS


LOCUS OF ACTION
"RECEPTORS"
Bound
Free
TISSUE
RESERVOIRS
Free
Bound
ABSORPTION
Free Drug
EXCRETION
Bound Drug
SYSTEMIC
CIRCULATION
BIOTRANSFORMATION

DRUG-RECEPTOR INTERACTIONS



DRUG –RECEPTOR BINDING

rate dependent on the concentration of the drug and receptor, and the resulting *drug–receptor complex* breaks down at a rate proportional to the number of complexes formed

$$[D] + [R] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [DR]$$

k_1 = association rate constant
k_2 = disassociation rate constant

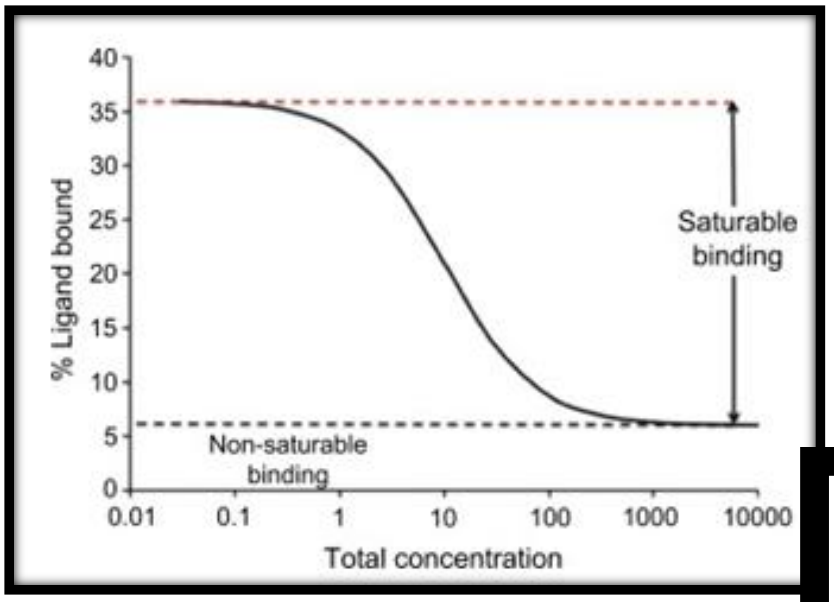
$$K_A = \text{association equilibrium constant} = \frac{[DR]}{[D][R]}$$

$$K_D = \text{disassociation equilibrium constant} = \frac{[D][R]}{[DR]} = \frac{1}{K_A}$$

FIGURE 3.3

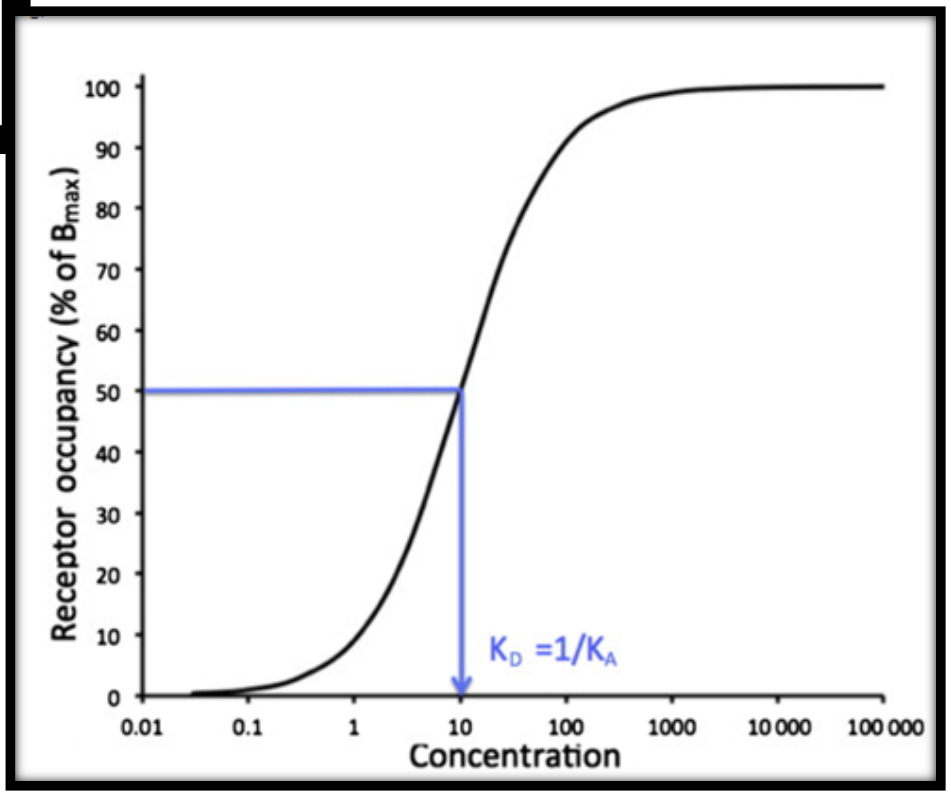
Mass-action equations describing reversible interaction between a ligand (drug, toxin) and a receptor.

MAXIMUM BINDING CAPACITY



radioligand displacement from a receptor as non-radioactive ligand increases

concentration–receptor occupancy curve



RECEPTOR OCCUPANCY MODELING

- attempts to link the action of a drug to the proportion of receptors occupied by that drug at equilibrium

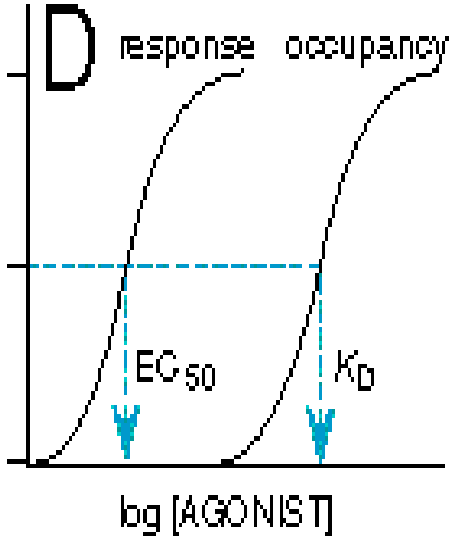
  - insulin stimulates maximum glucose oxidation in adipocytes with only 2-3% of receptors bound

  - LH stimulates maximum testosterone production in Leydig cells when only 1% of receptors are bound

WHY ARE THERE SPARE RECEPTORS?

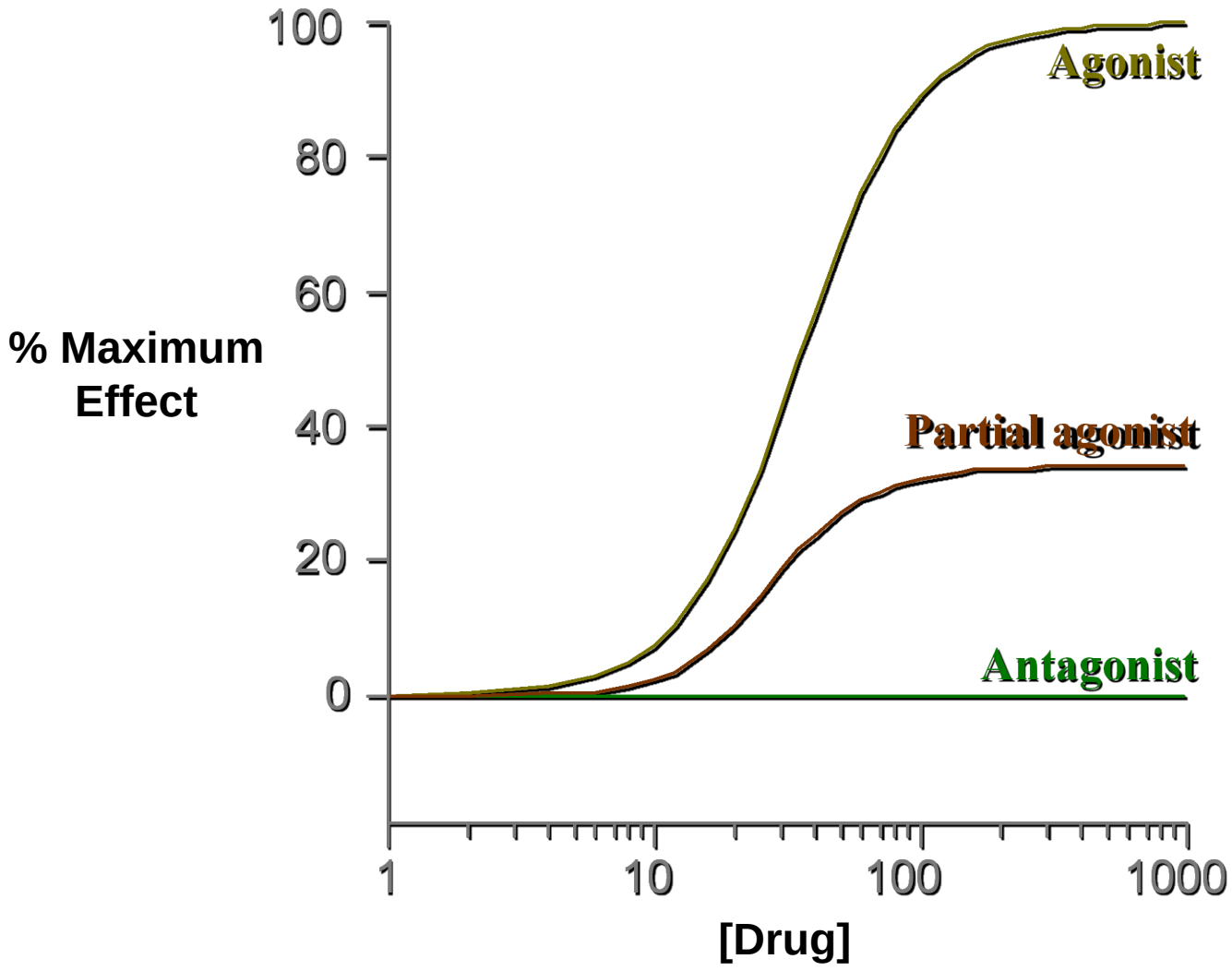
- **allow maximal response *without* total receptor occupancy – increase sensitivity of the system**

- **spare receptors can bind (and *internalize*) extra ligand preventing an exaggerated response if too much ligand is present**



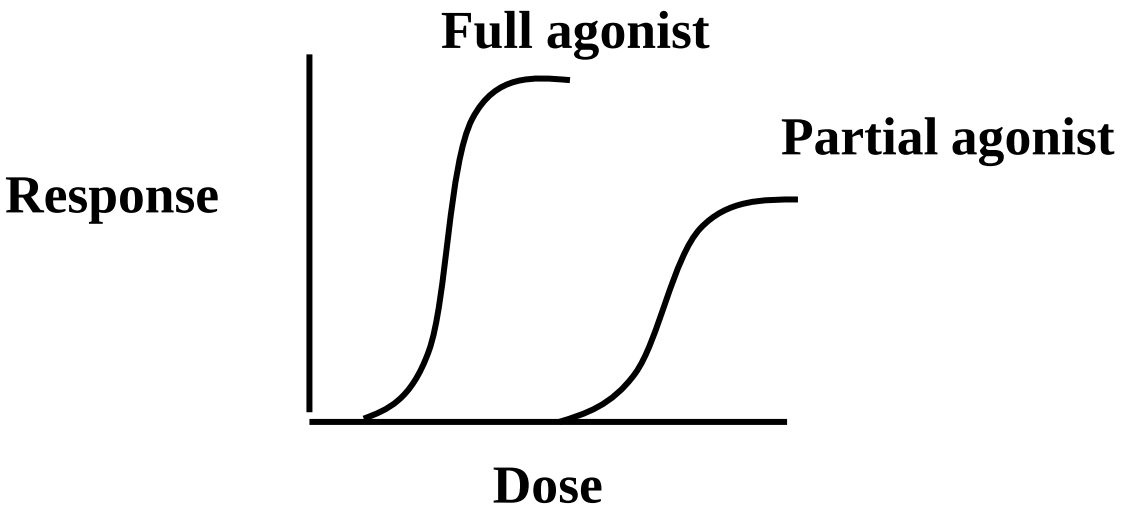
The receptor theory assumes that all receptors should be occupied to produce a maximal response. In that case at half maximal effect EC50=kd. Sometimes, full effect is seen at a fractional receptor occupation

RECEPTOR-MEDIATED EFFECTS



AGONISTS

Stimulate the response from the receptor



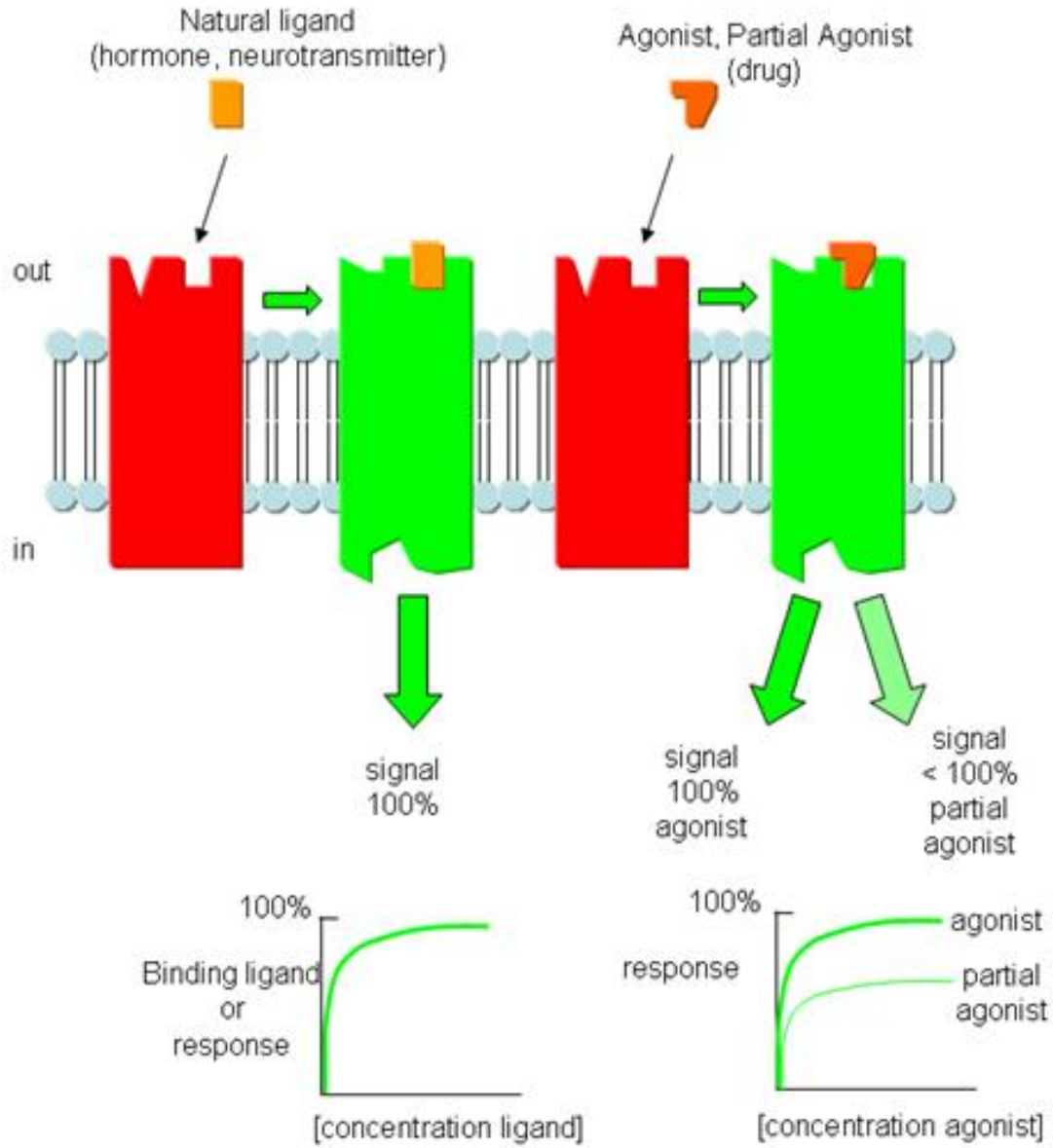
drugs that interact with and activate receptors; they possess both affinity and efficacy

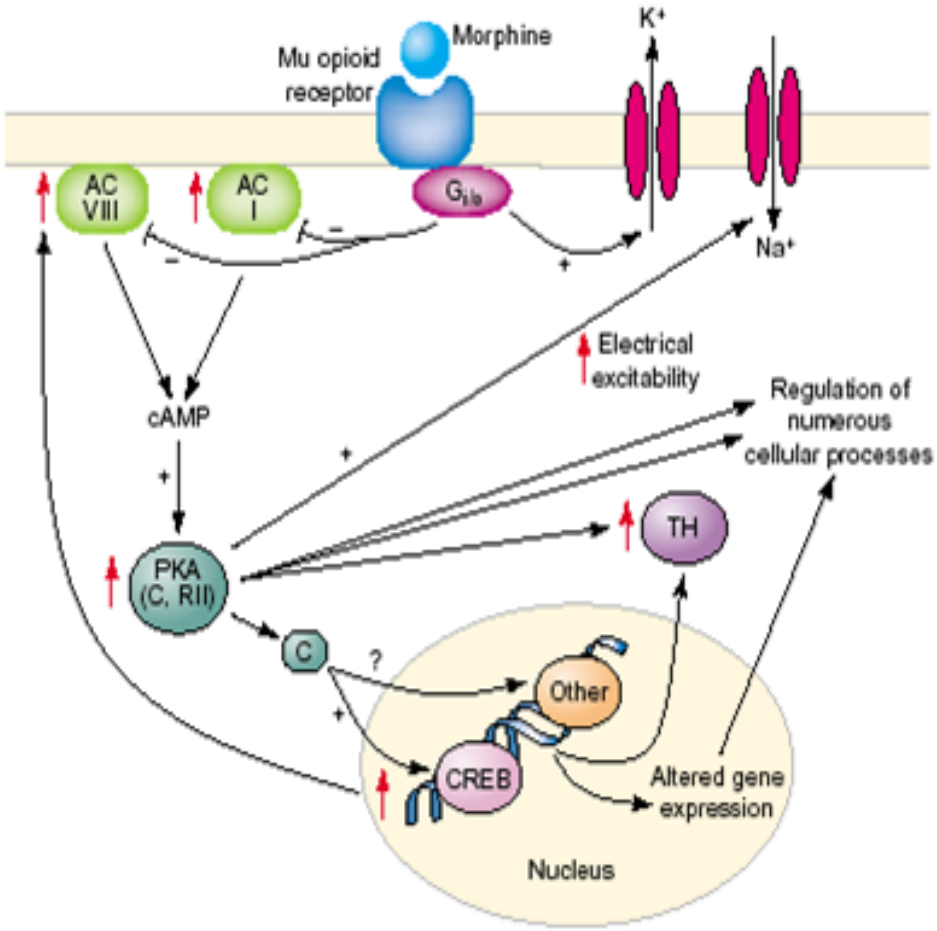
two types

Full – an agonist with maximal efficacy

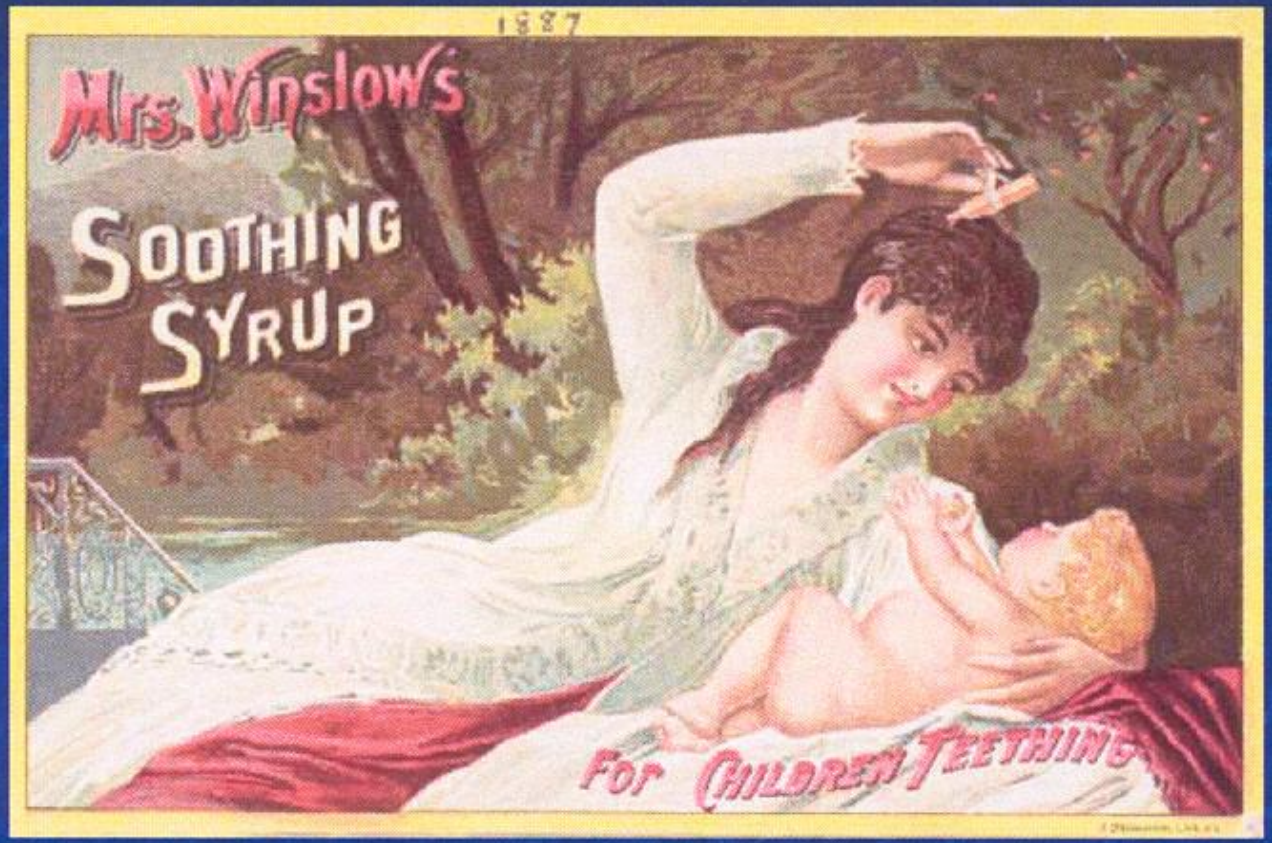
Partial – an agonist with less then maximal efficacy

Agonists


Natural ligand
(hormone, neurotransmitter)
Agonist, Partial Agonist
(drug)
out
in
signal
100%
signal
100%
agonist
signal
< 100%
partial
agonist
100%
Binding ligand
or
response
[concentration ligand]
100%
response
agonist
partial
agonist
[concentration agonist]


Morphine
Mu opioid receptor
K+
Na+
AC VIII
AC I
Gi/o
cAMP
PKA (C, RII)
C
?
Other
CREB
Altered gene expression
Nucleus
TH
Electrical excitability
Regulation of numerous cellular processes

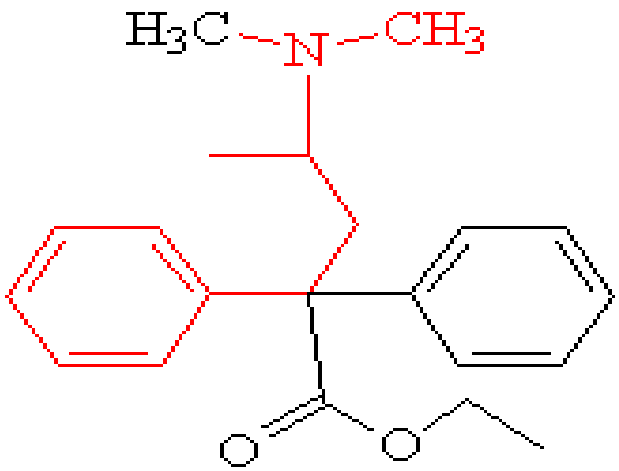
Mrs Winslow's Soothing Syrup



For children teething. Greatly facilitates the process of Teething, by softening the gums, reducing all inflammation; will allay ALL PAIN and spasmodic action, and is SURE TO REGULATE THE BOWELS. Depend on it, Mothers, it will give rest to yourselves and RELIEF AND HEALTH TO YOUR INFANTS. Sold by all chemists, at 1s 1/2d per bottle."

Source: http://www.opioids.com/images/soothingsyrup.html

METHADONE

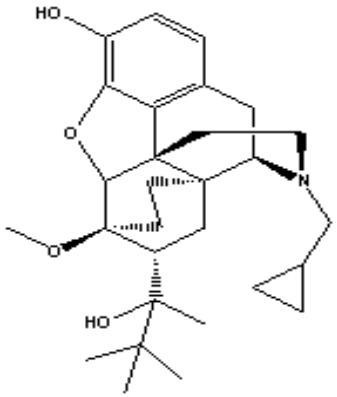


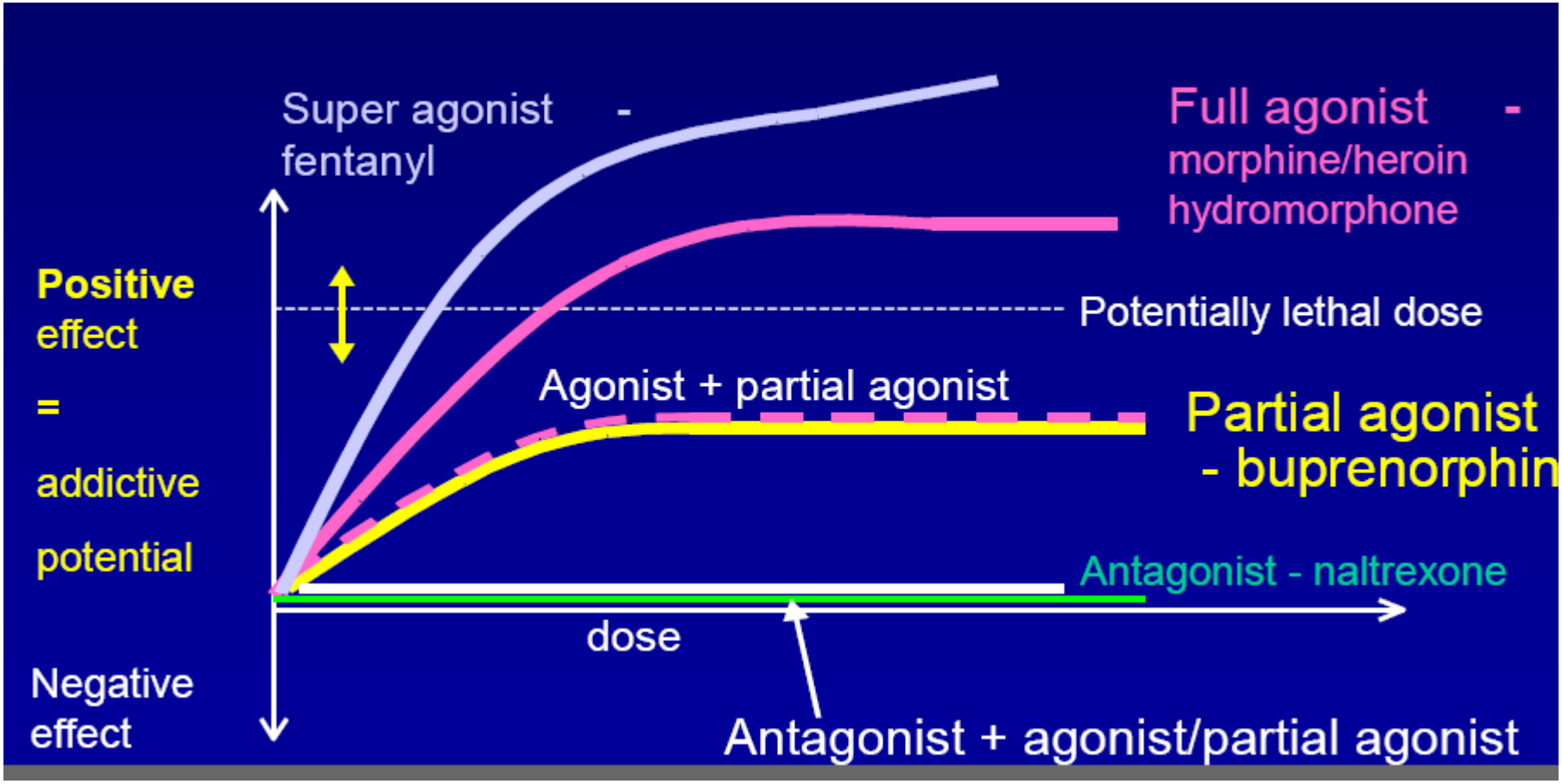
pure mu-agonist

differs from morphine by an additional noncompetitive antagonist activity at the N-methyl-D-aspartate (NMDA) receptor

BUPRENORPHINE

Buprenorphine hydrochloride is a derivative of the morphine alkaloid **thebaine**.





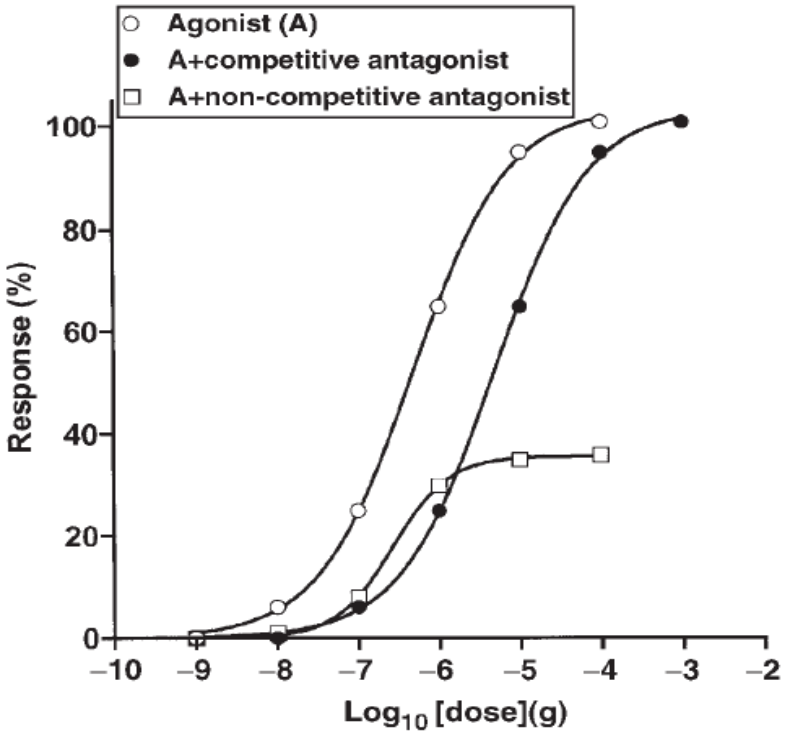
ANTAGONISTS

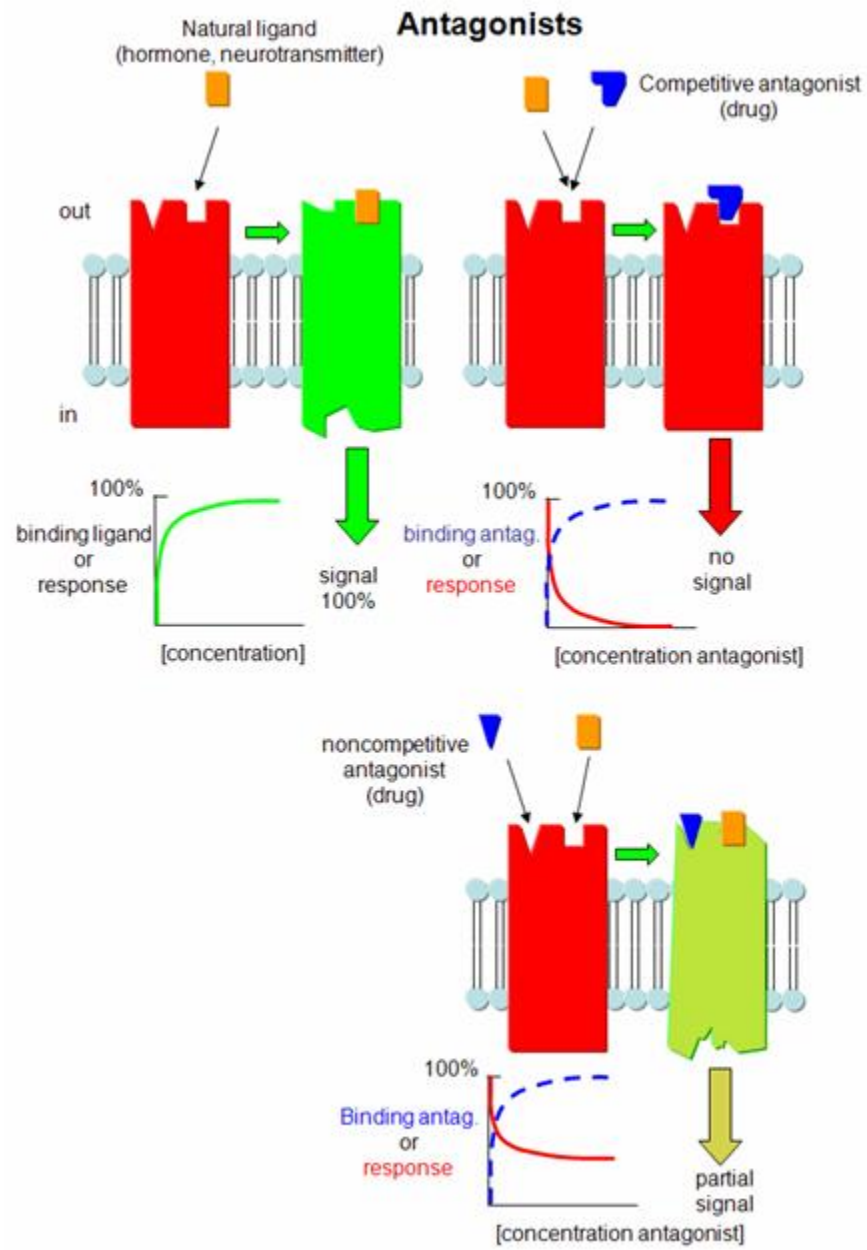
Antagonists interact with the receptor but
do NOT change the receptor
they have affinity but NO efficacy

two types

Competitive – NALOXONE

Noncompetitive - OMEPRAZOLE




Antagonists
Natural ligand
(hormone, neurotransmitter)
Competitive antagonist
(drug)
out
in
100%
binding ligand
or
response
signal
100%
[concentration]
100%
binding antag.
or
response
no
signal
[concentration antagonist]
noncompetitive
antagonist
(drug)
100%
Binding antag.
or
response
partial
signal
[concentration antagonist]

RECEPTOR DOWN REGULATION

• continued use and stimulation of receptors by agonist drugs may decrease the number and sensitivity of receptors

•Constant use of beta-2 agonist salbutamol inh reduces therapeutic response in ASTHMA

RECEPTOR UP REGULATION

- continued use and inhibition of receptors by antagonists may increase the number and sensitivity of receptors

- Sudden withdrawal of propranolol may precipitate angina

TOLERANCE AND DEPENDENCE

Tolerance – it is increasing of the dose of a drug required to produce the same effect.

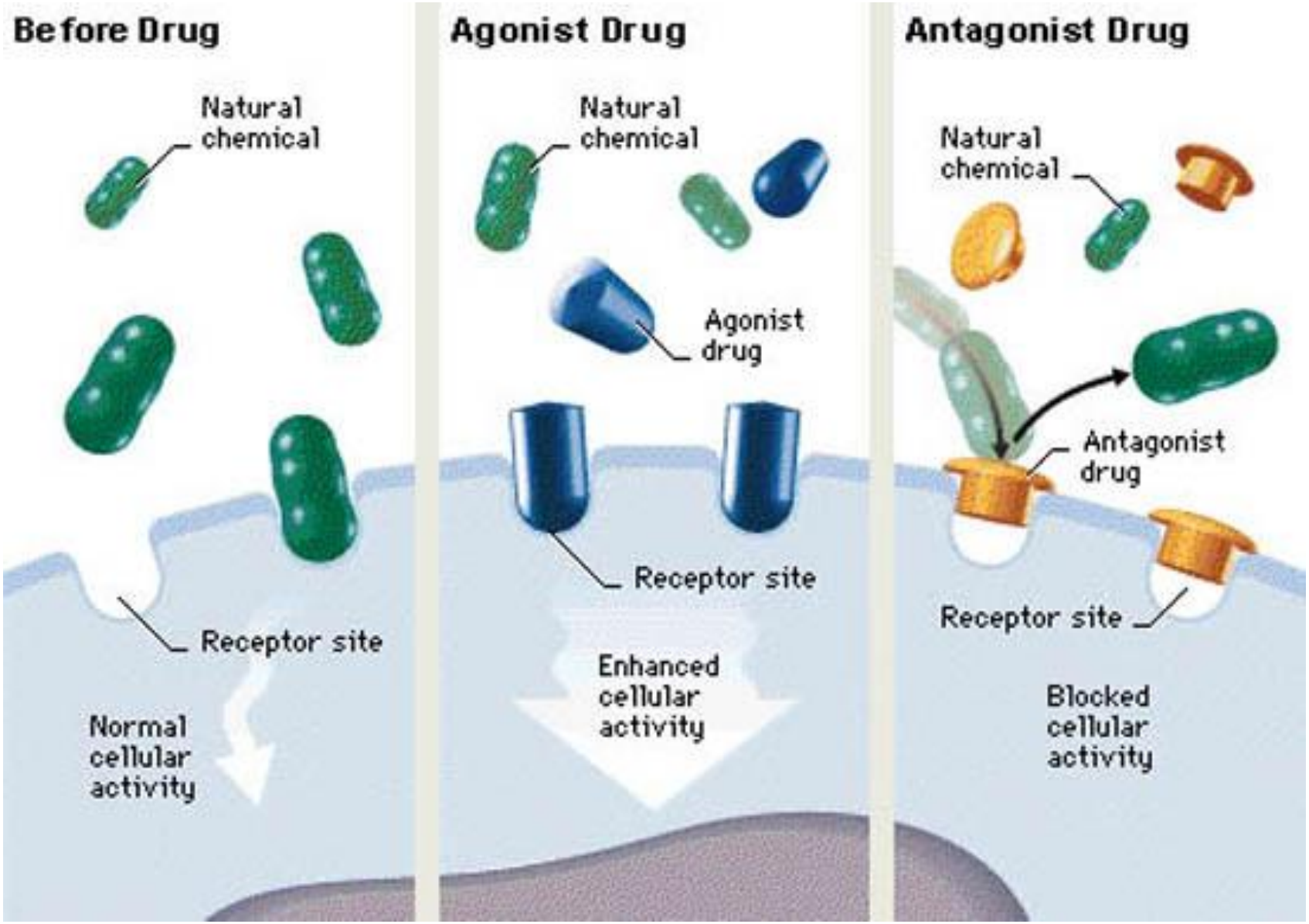
It occurs rapidly with opioids (with morphine 12–24 hours, e.g. the hot plate test – in mice, after 3 days the dose of morphine required for analgesia increases 5-fold).

Important in drug addiction – may need to increase dose 50-fold.

WHY DOES TOLERANCE OCCUR?

There are several potential reasons:

- **Increased metabolism of the drug**
-
- **Decreased receptor affinity**


Before Drug
Natural chemical
Receptor site
Normal cellular activity
Agonist Drug
Natural chemical
Agonist drug
Receptor site
Enhanced cellular activity
Antagonist Drug
Natural chemical
Antagonist drug
Receptor site
Blocked cellular activity

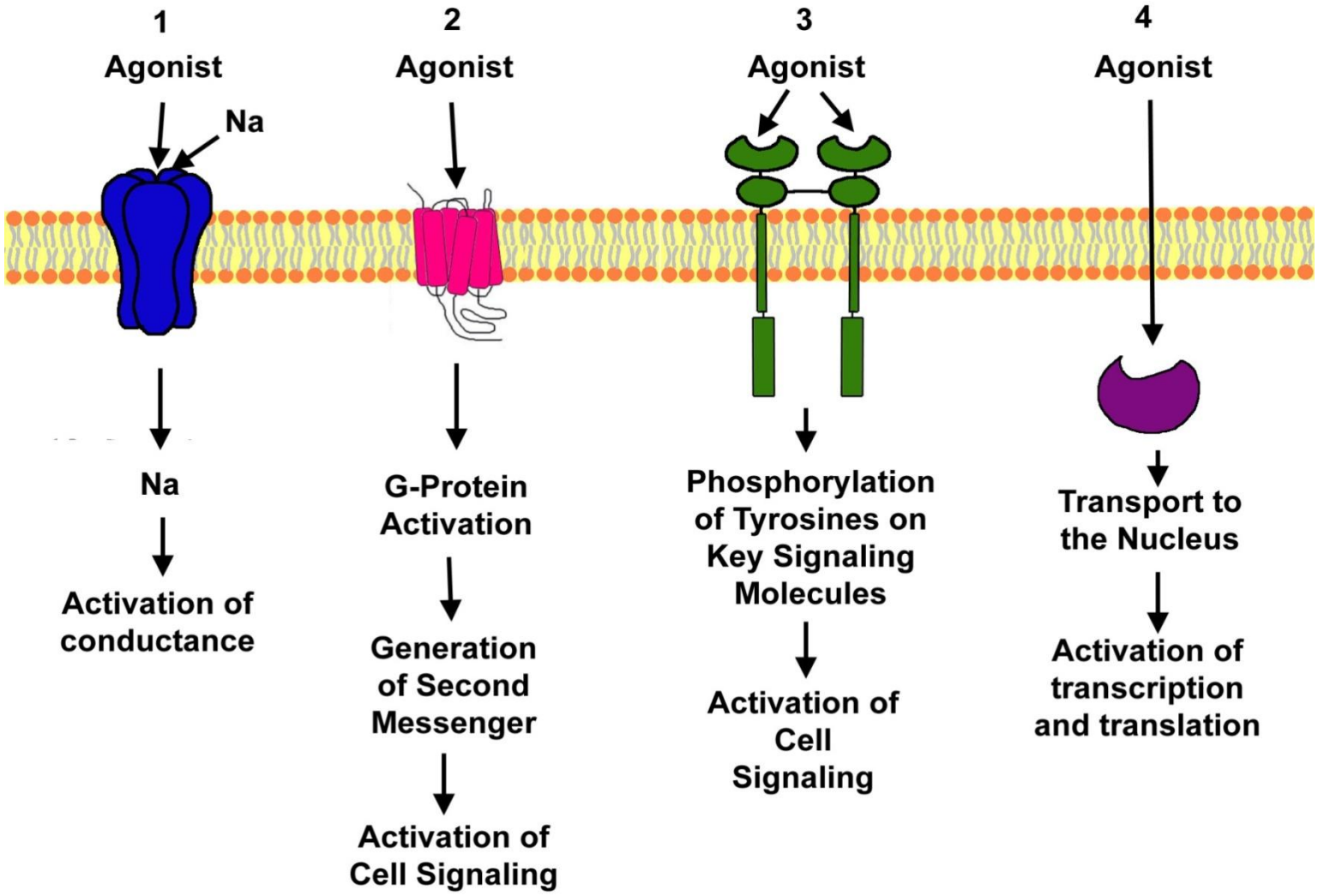
MECHANISMS OF DRUG ACTION

GENERAL CATEGORIES

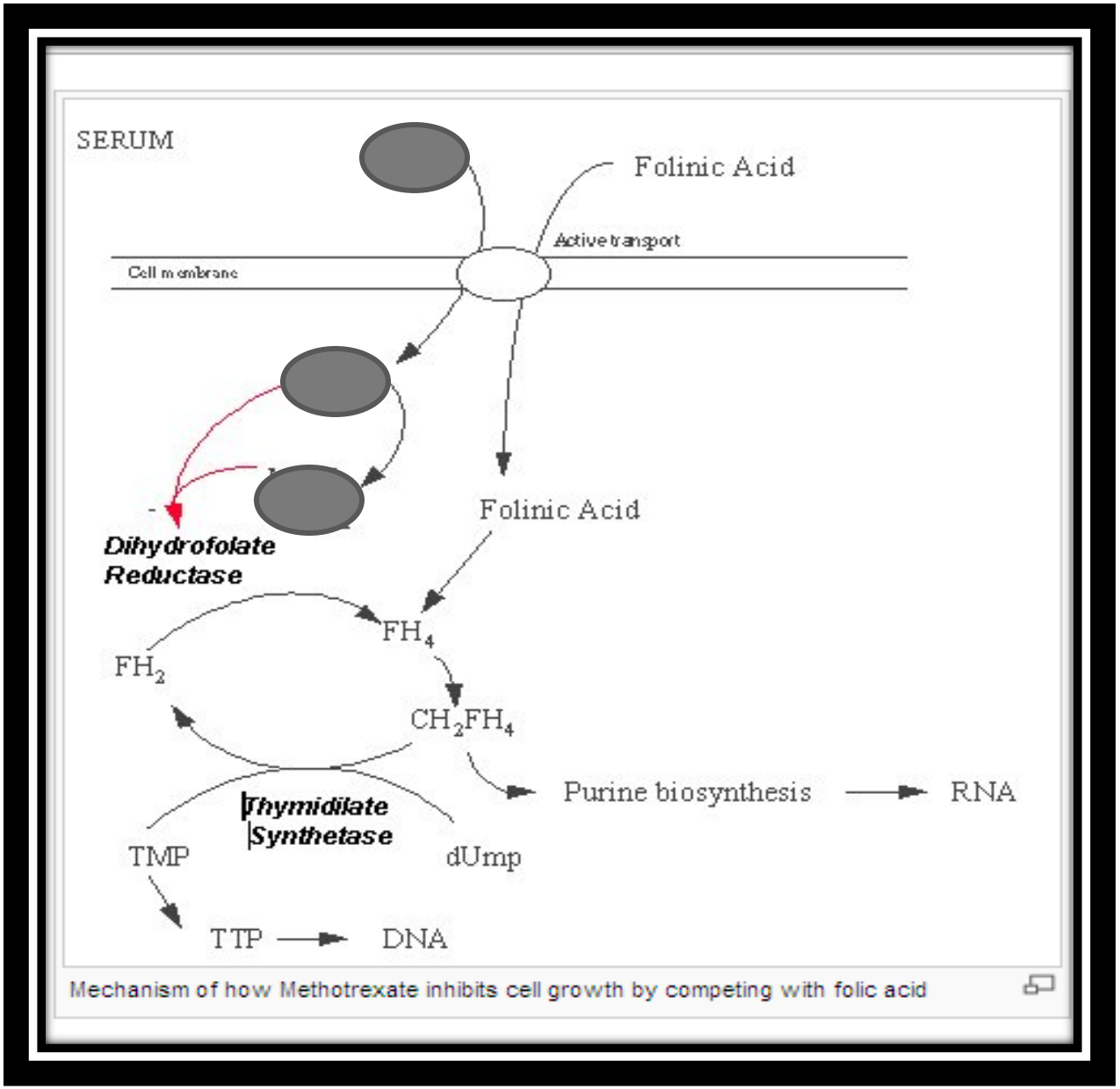
- **Physical/chemica**l (Mannitol, oral antacids)
  - alter, respectively, *osmolarity* and *pH*, but do not interact directly with cellular processes.

Biological

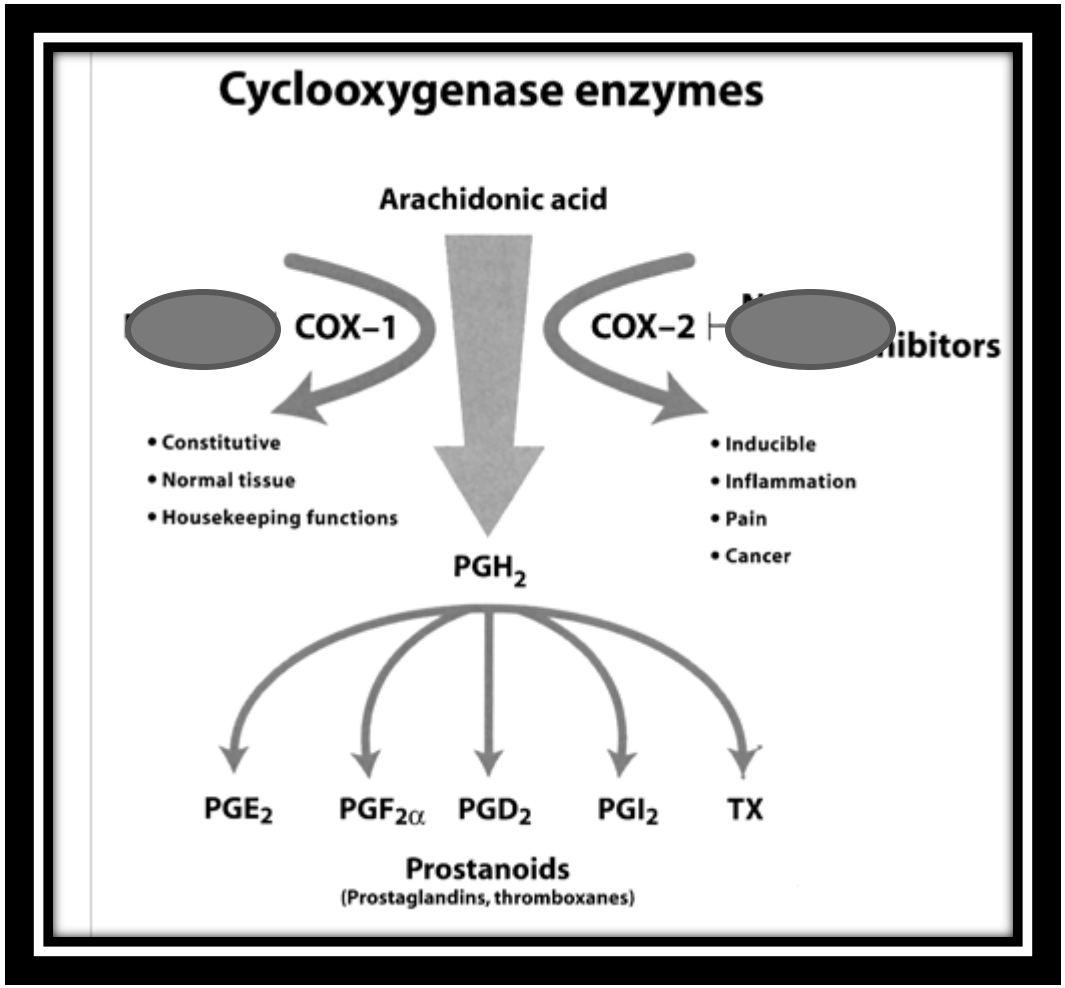
- **Receptor interaction** - alters the receptor protein's three-dimensional structure, triggering *signal transduction* processes within the cell and resulting in a biological effect
- **Non-receptor interaction** - directly target enzymes, carrier proteins like ion transporters, ion channels, DNA, and cellular structures like microtubules.


1
Agonist
Na
Na
Activation of conductance
2
Agonist
G-Protein Activation
Generation of Second Messenger
Activation of Cell Signaling
3
Agonist
Phosphorylation of Tyrosines on Key Signaling Molecules
Activation of Cell Signaling
4
Agonist
Transport to the Nucleus
Activation of transcription and translation

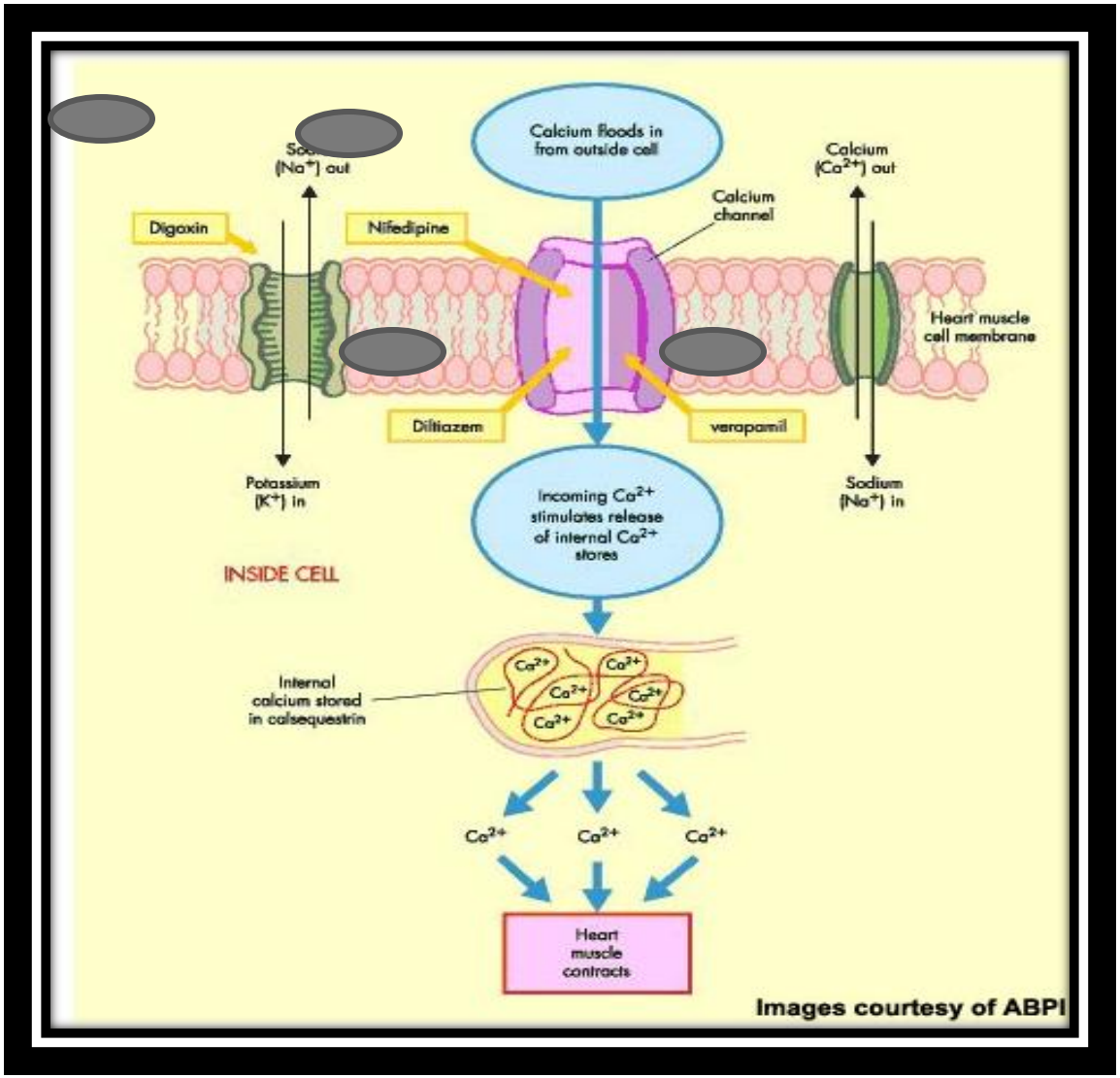
ENZYME INHIBITORS



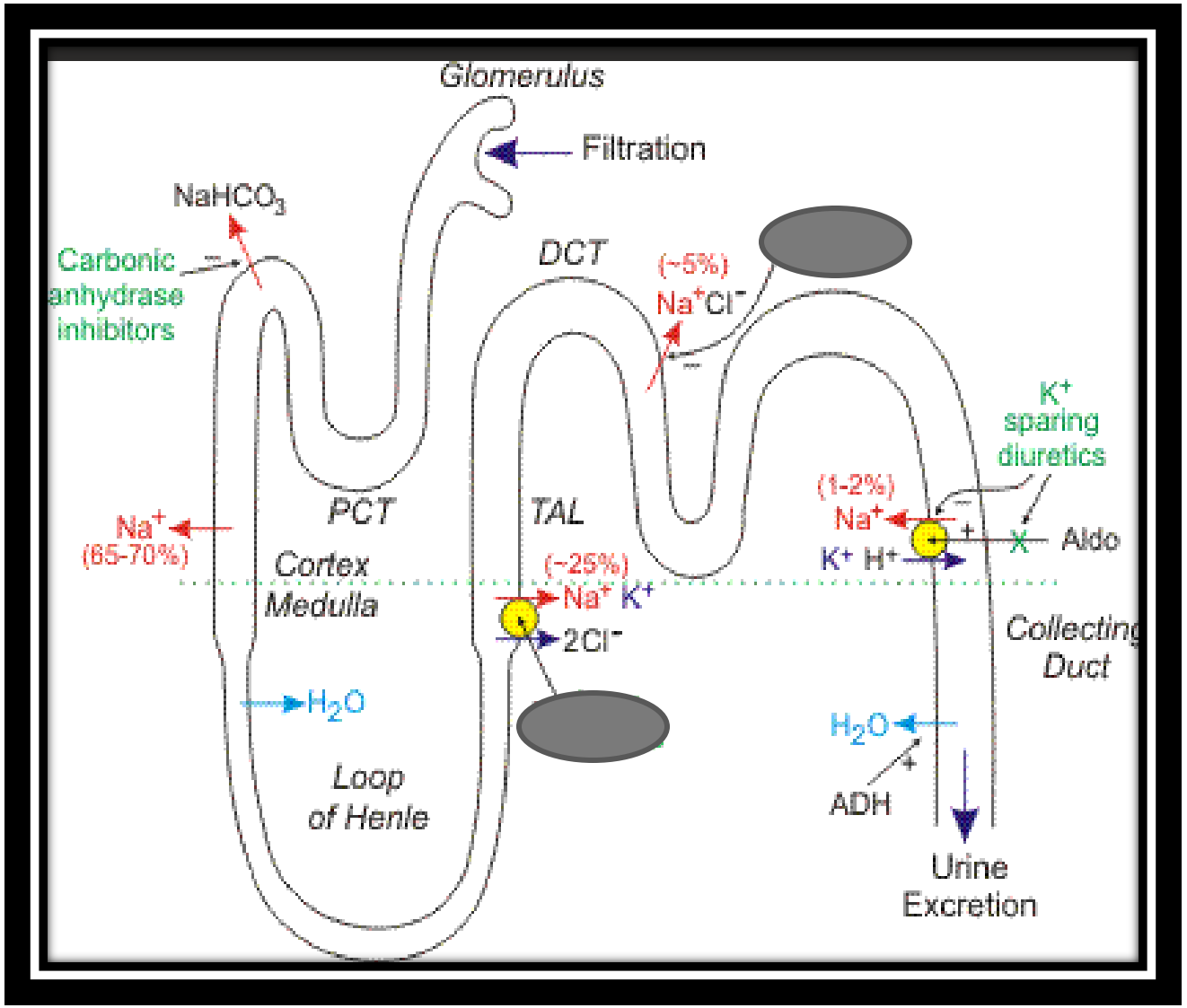
ENZYME INHIBITORS



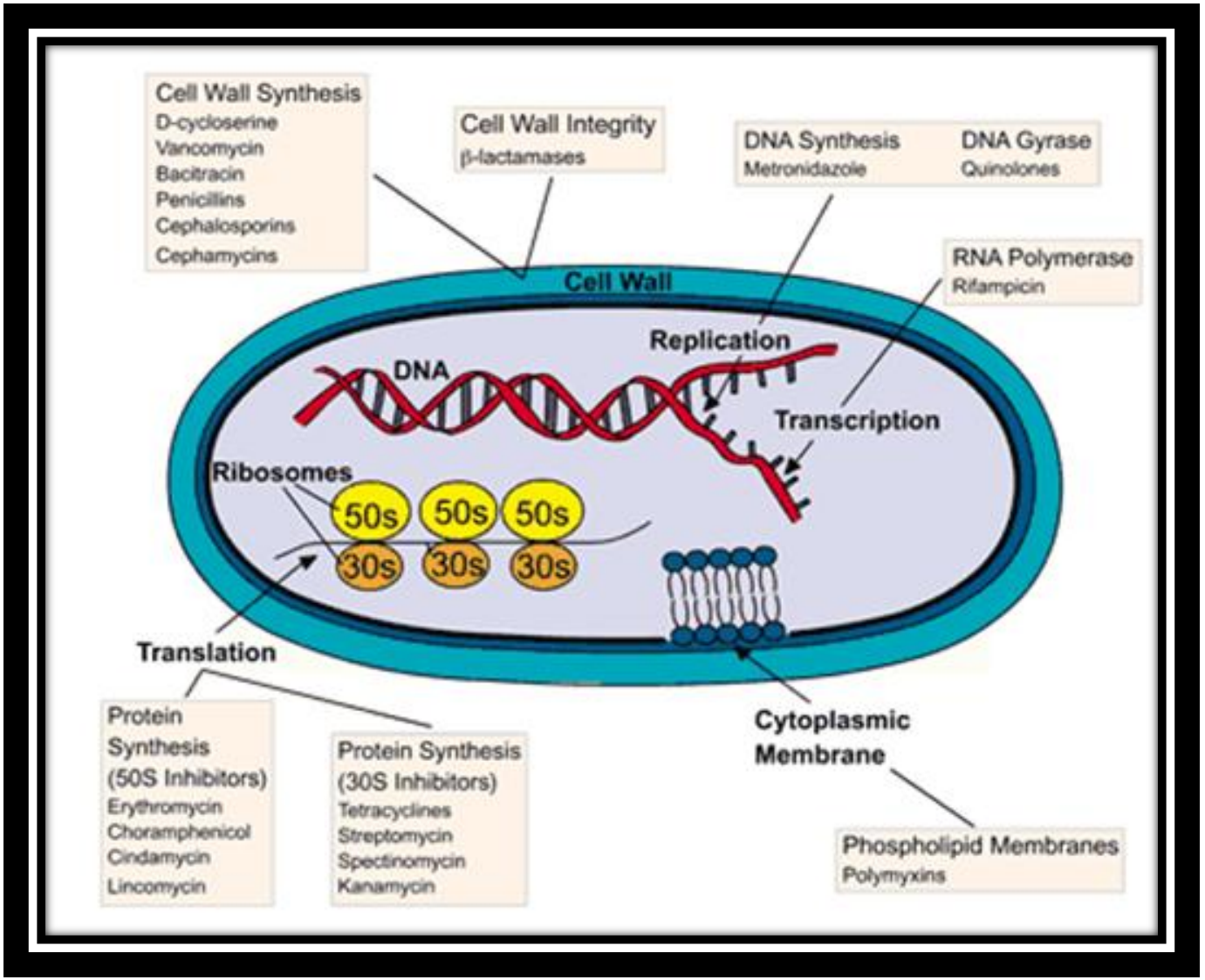
DIRECT *INHIBITORS OF ION CHANNELS*



DRUGS INHIBITING *MEMBRANE ION TRANSPORTERS*

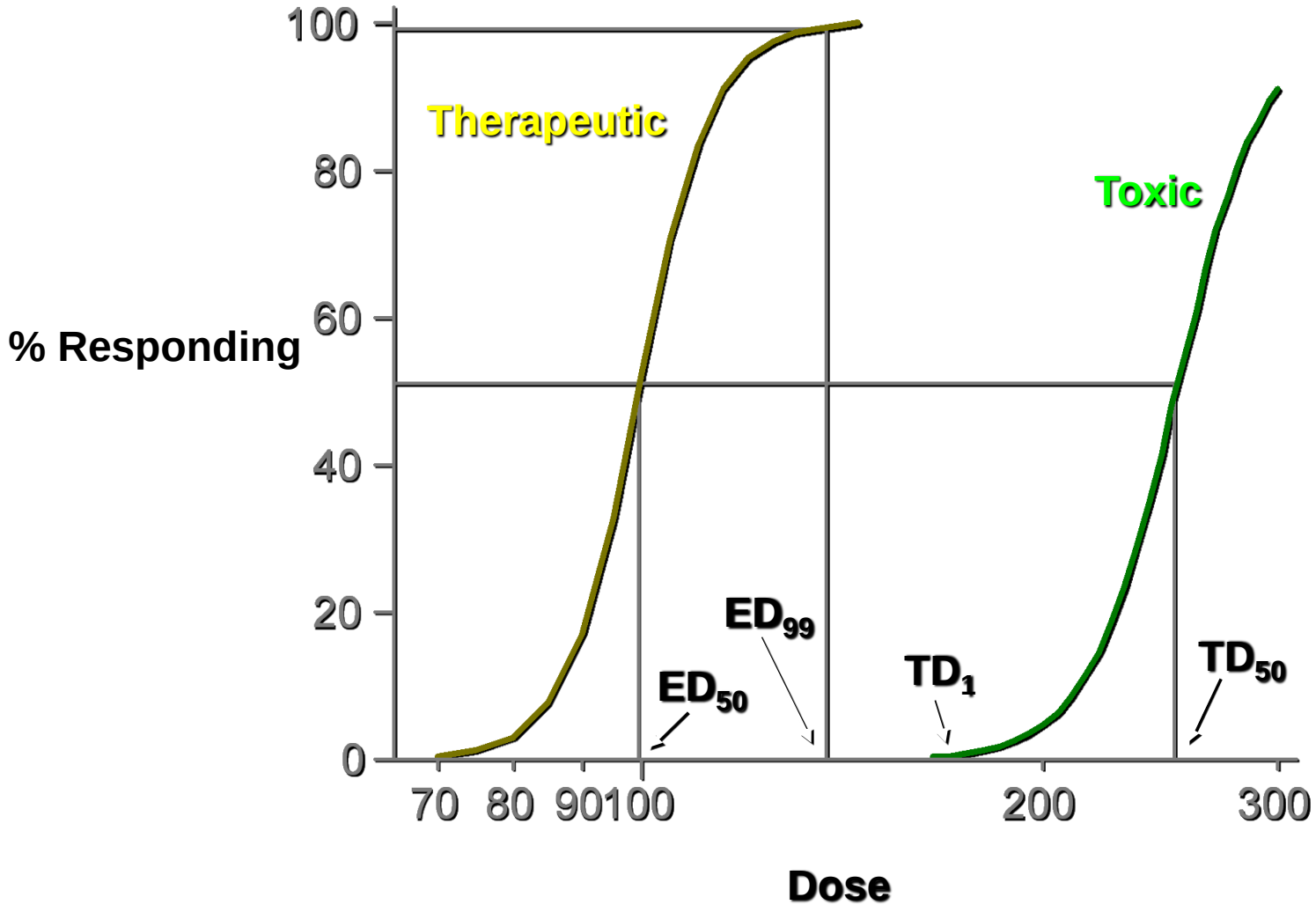


DRUGS *INTERACT WITH DNA*



ADVERSE DRUG REACTIONS

THERAPEUTIC AND TOXIC EFFECTS



ADVERSE REACTIONS

Side Effects

- Expected responses based on the pharmacologic action of the drug

Allergic Reactions

- Exaggerated immune response to a certain drug

Organ Cytotoxic Effects

- Adverse effects on organs

ADVERSE REACTIONS

Idiosyncratic Reactions

- Reaction that is particular to an individual or defined group of people

Drug-drug Interactions

- Interaction of 2 or more drugs that result in a disadvantage to a patient

Drug-food Interactions

- Interaction of a drug with food that results in an adverse patient reaction

Basic & Clinical Pharmacology & Toxicology, **109**, 156–163 Doi: 10.1111/j.1742-7843.2011.00700.x

A Population Pharmacokinetic–Pharmacodynamic Model for Simvastatin that Predicts Low-Density Lipoprotein-Cholesterol Reduction in Patients with Primary Hyperlipidaemia

Jimyon Kim[1,2], Byung-Jin Ahn[3], Hong-Seok Chae[1,2], Seunghoon Han[1,2], Kichan Doh[1,2], Jeongeun Choi[4], Yong K. Jun[4], Yong W. Lee[4] and Dong-Seok Yim[1,2]

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(Received 4 November 2010; Accepted 9 March 2011)