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Basic Principles of Pharmacolgy

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Pharmacology

- Can be defined as the study of substances that interact with living systems through chemical processes, especially by binding to regulatory molecules („drug receptors“) and activating or inhibiting normal body processes.
- Medical Pharmacology (substances used to prevent, diagnose, or treat diseases)
- Toxicology (deals with the undesirable effects of chemicals on living systems)

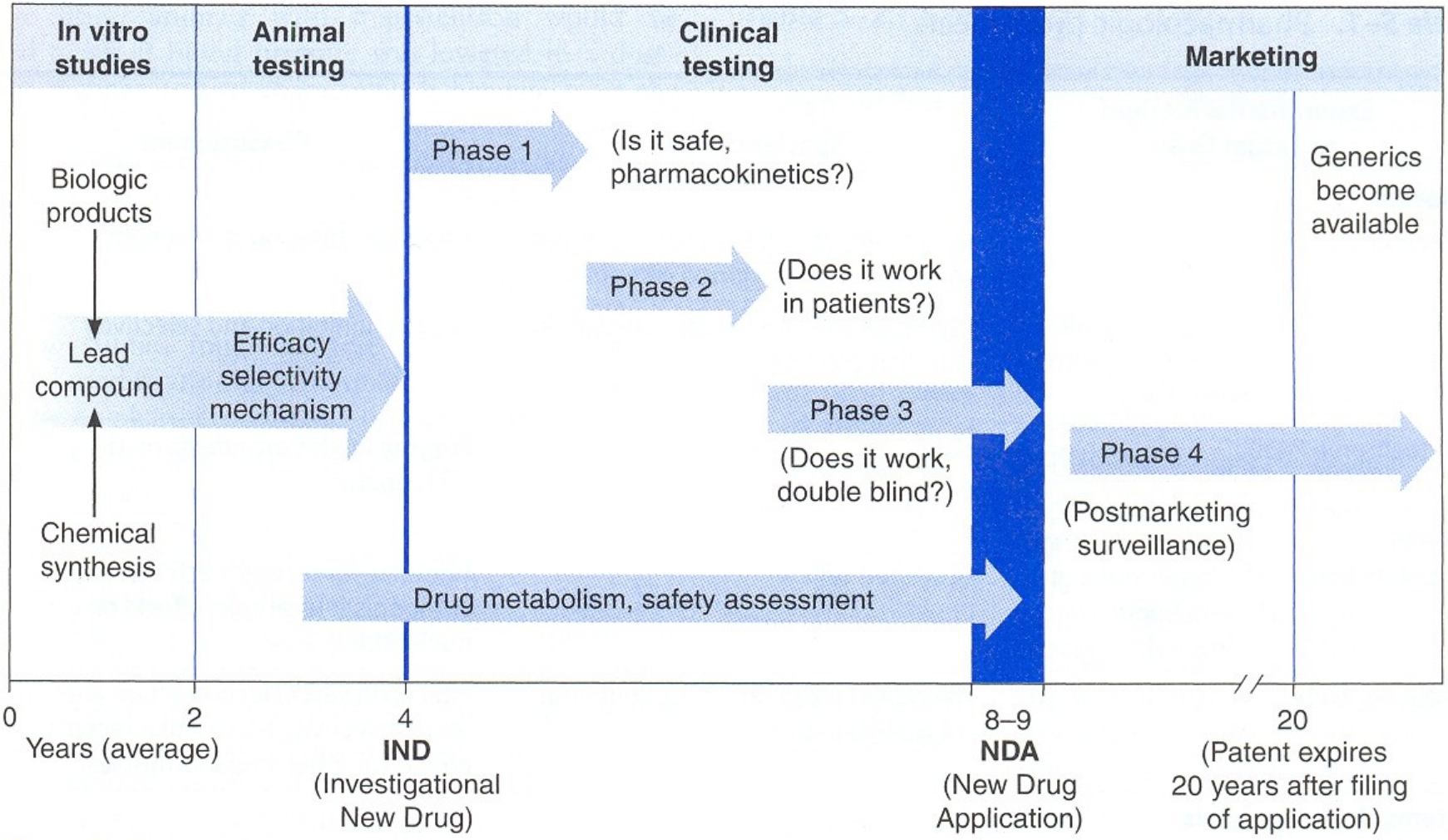


Figure 5–1. The development and testing process required to bring a drug to market in the USA. Some of the requirements may be different for drugs used in life-threatening diseases.

Two general principles that one should always remember

- That all substances can under certain circumstances be toxic (Paracelsus)
- All dietary supplements and all therapies promoted as health-enhancing should meet the same standards of efficacy and safety

Alle Dinge sind Gift

und nichts ohn Gift;

allein die Dosis macht,

daß ein Ding kein Gift ist.

Paracelsus

Drug Size

- The molecular size of drugs varies from very small (lithium ions, MW 7) to very large (e.g. alteplase = tPA, a protein of MW 59,050)
- Most drugs have molecular weights between 100 and 1000

Drug-Receptor Bonds

- **Covalent** (aspirin; DNA-alkylating agents)
- **Electrostatic** (more common, but weaker)
- **Hydrophobic** (quite weak, highly lipid soluble drugs)
- Drugs that bind through weak bonds to their receptors are generally more selective than drugs that bind by means of very strong bonds.
  (Weak bonds require a very precise fit of the drug to its receptor if an interaction is to occur)

Pharmacodynamic processes = actions of the drug on the body

Pharmacokinetic processes = actions of the body on the drug

Drug Receptors & Pharmacodynamics

- Receptors largely determine the quantitative relations between dose or concentration of drug and pharmacologic effects (affinity and maximal effect)
- Receptors are responsible for selectivity of drug action
- Receptors mediate the actions of both pharmacological agonists and antagonists

Macromolecular Nature of Drug Receptors

- **Regulatory proteins** (best characterized; mediate actions of endogenous chemical signals such as neurotransmitters, autacoids and hormones)
- **Enzymes** (e.g. dihydrofolate reductase is inhibited by methotrexate)
- **Transport proteins** (Na^+/K^+-ATPase is inhibited by digitalis glycosides)
- **Structural proteins** (e.g. tubulin is the receptor for colchicine)

Receptors (Selection)

Acetylcholin	nikotinisch: (N)
Acetylcholin	muskarinisch: M_{1-5}
Adenosin	A_1, A_2, A_3
Angiotensin	AT_1, AT_2
Bradykinin	B_1, B_2
Cannabinoide	CB_1, CB_2
Catecholamine	α_1, α_2; β_1, β_2, β_3
Chemokine	CCR_{1-8}, $CXCR_{1-5}$
Cholecystokinin	CCK_1, CCK_2
Dopamin	D_1, D_2, D_3, D_4, D_5
Endothelin	ET_A, ET_B
GABA	$GABA_A$, $GABA_B$

Glutamat (ionotrop)	NMDA, AMPA, Kainat
Glutamat (metab.)	$mglu_{1-4}$
Histamin	H_1, H_2, H_3
Serotonin (5-HT)	$5\text{-}HT_{1-7}$
ATP (extrazell.)	$P2X_{1-7}$, $P2Y_{1,2,4,6,11}$
Opioide	DOP (δ), KOP (κ), MOP (μ)
Prostaglandine	$DP_{1,2}$, EP_{1-4}, FP, IP_{1-3}, TP
Leukotriene	BLT, $CysLT_1$, $CysLT_2$
Somatostatin	SST_{1-5}
Steroidhormone	GR, MR, PR, AR
Tachykinine	NT_1, NT_2, NT_3
Vasopressin	V_1, V_2, V_3

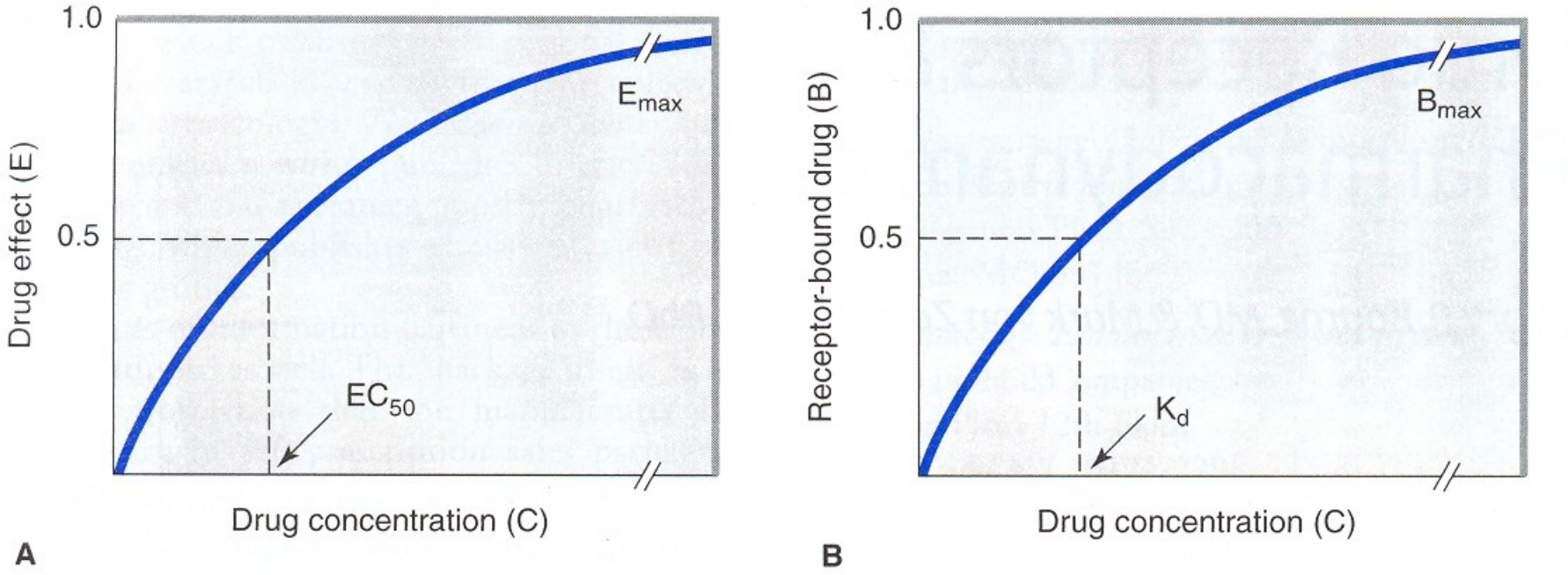
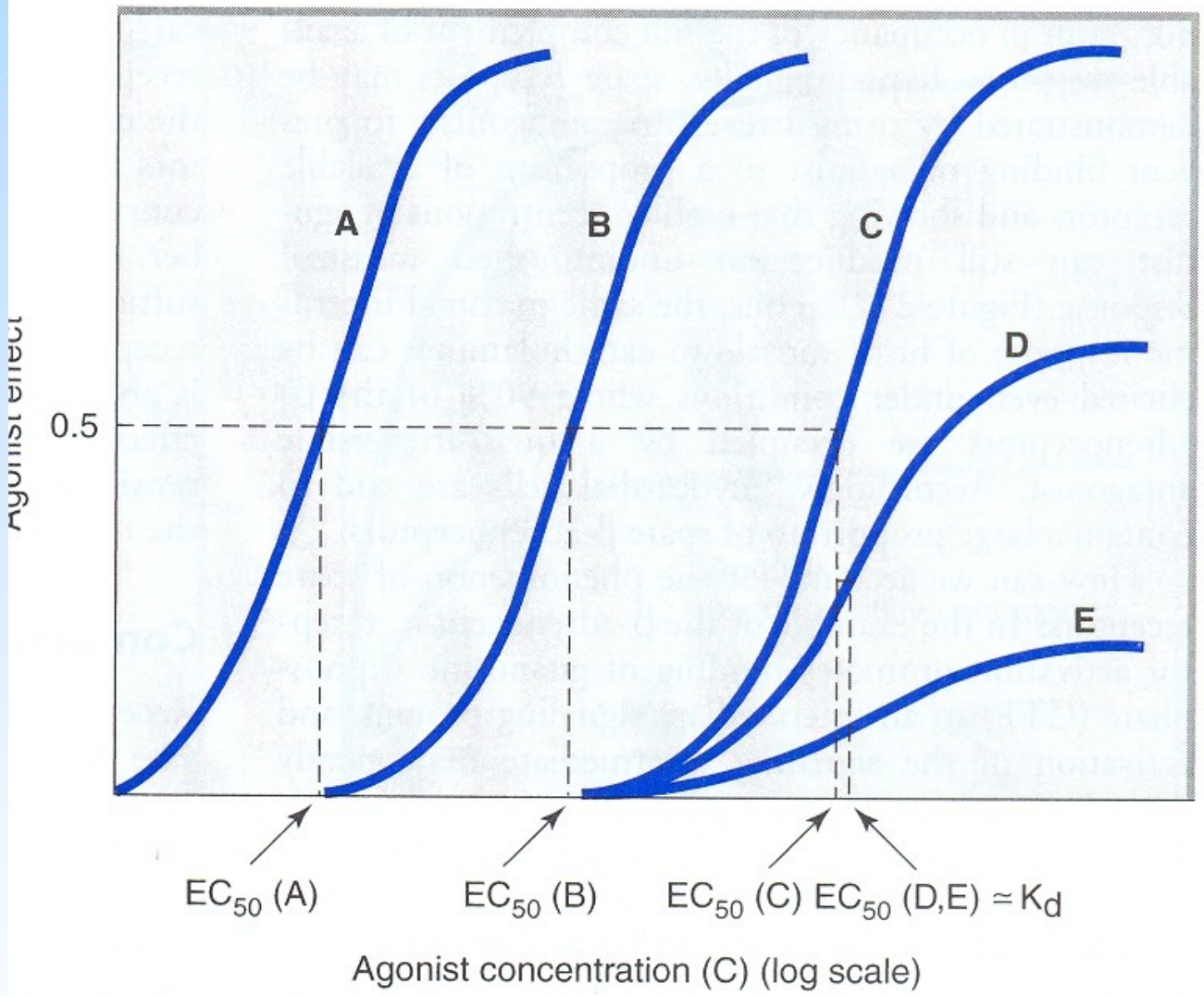


Figure 2–1. Relations between drug concentration and drug effect (panel **A**) or receptor-bound drug (panel **B**). The drug concentrations at which effect or receptor occupancy is half-maximal are denoted EC_{50} and K_d, respectively.


A
B
C
D
E
0.5
EC50 (A)
EC50 (B)
EC50 (C) EC50 (D,E) ≃ Kd
Agonist concentration (C) (log scale)

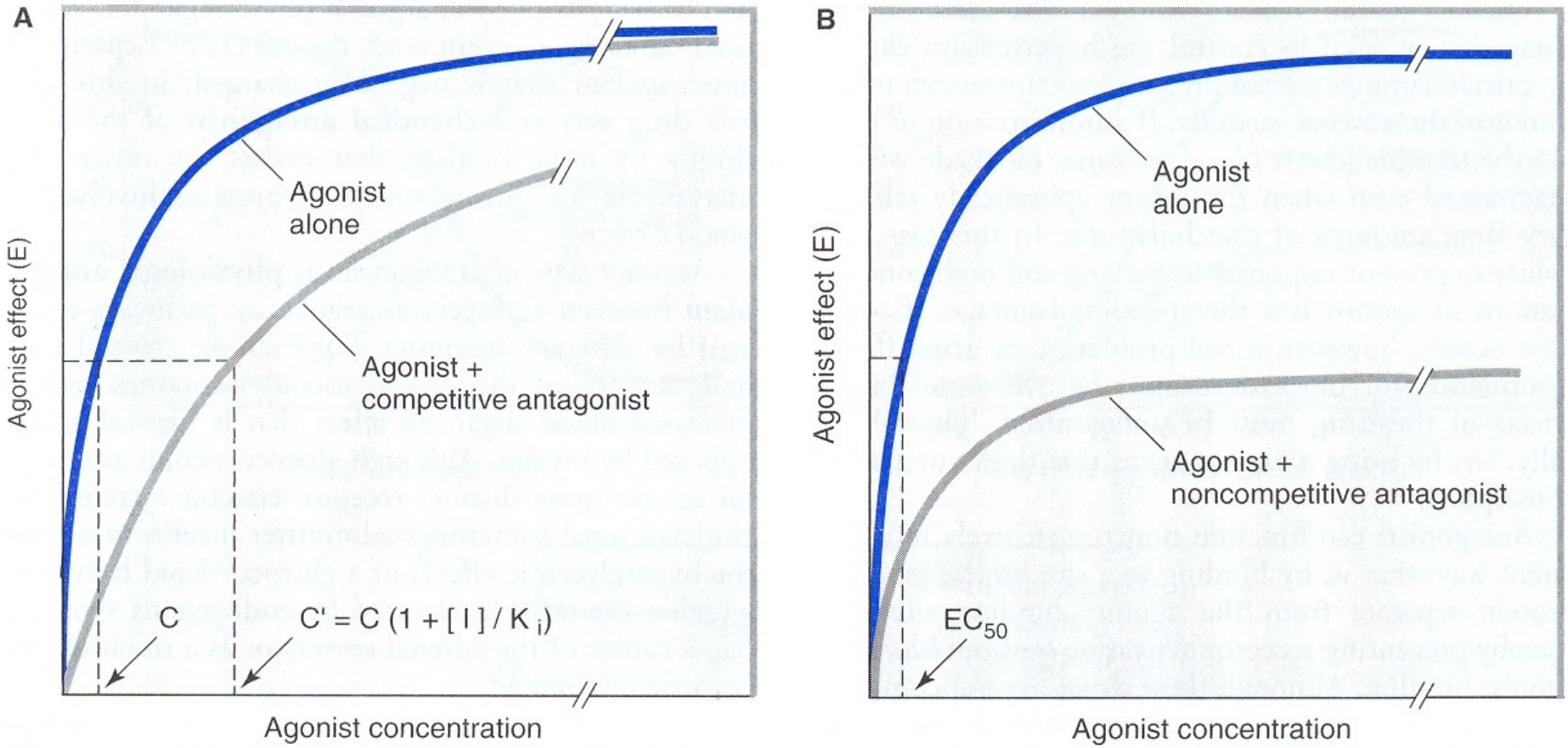
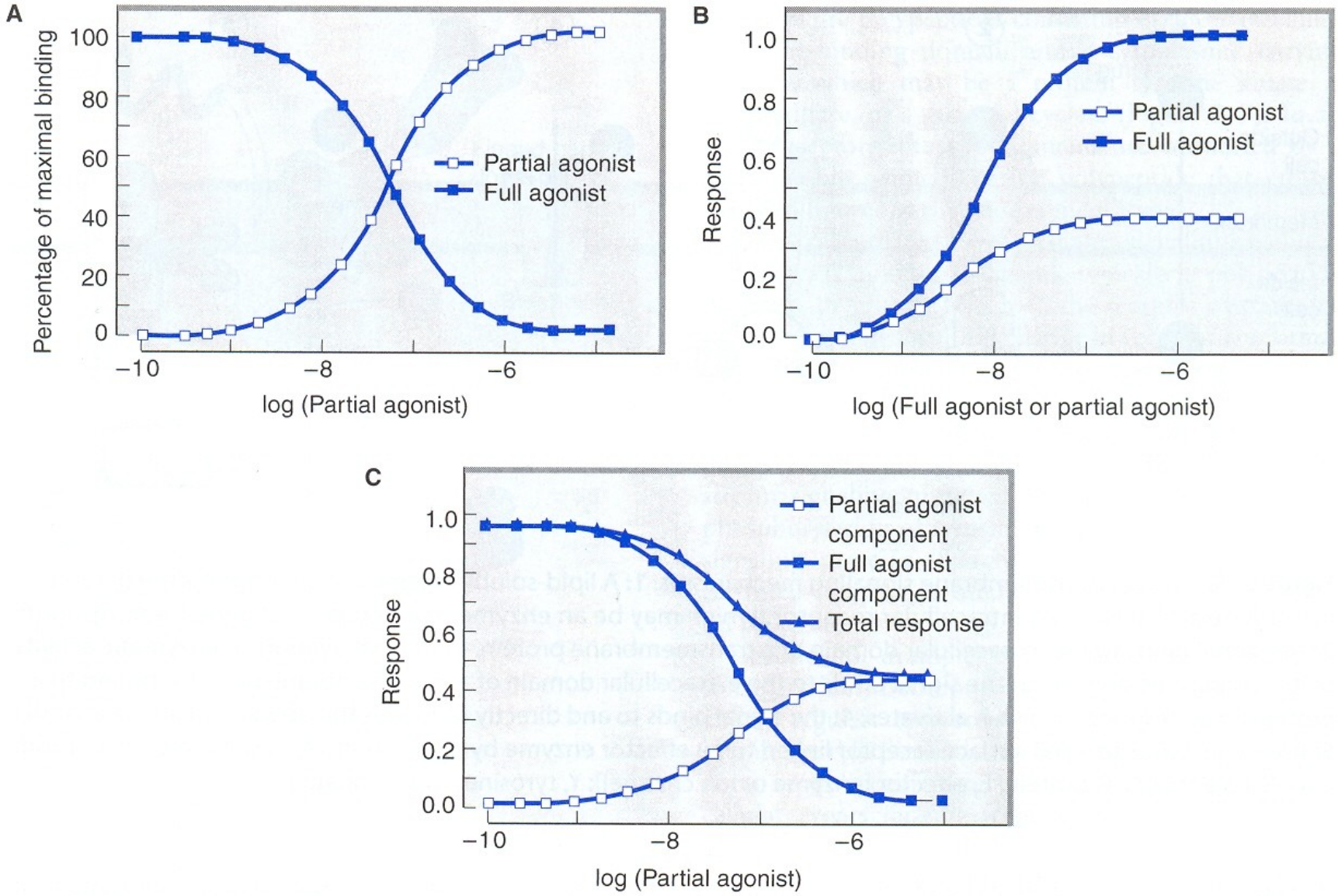


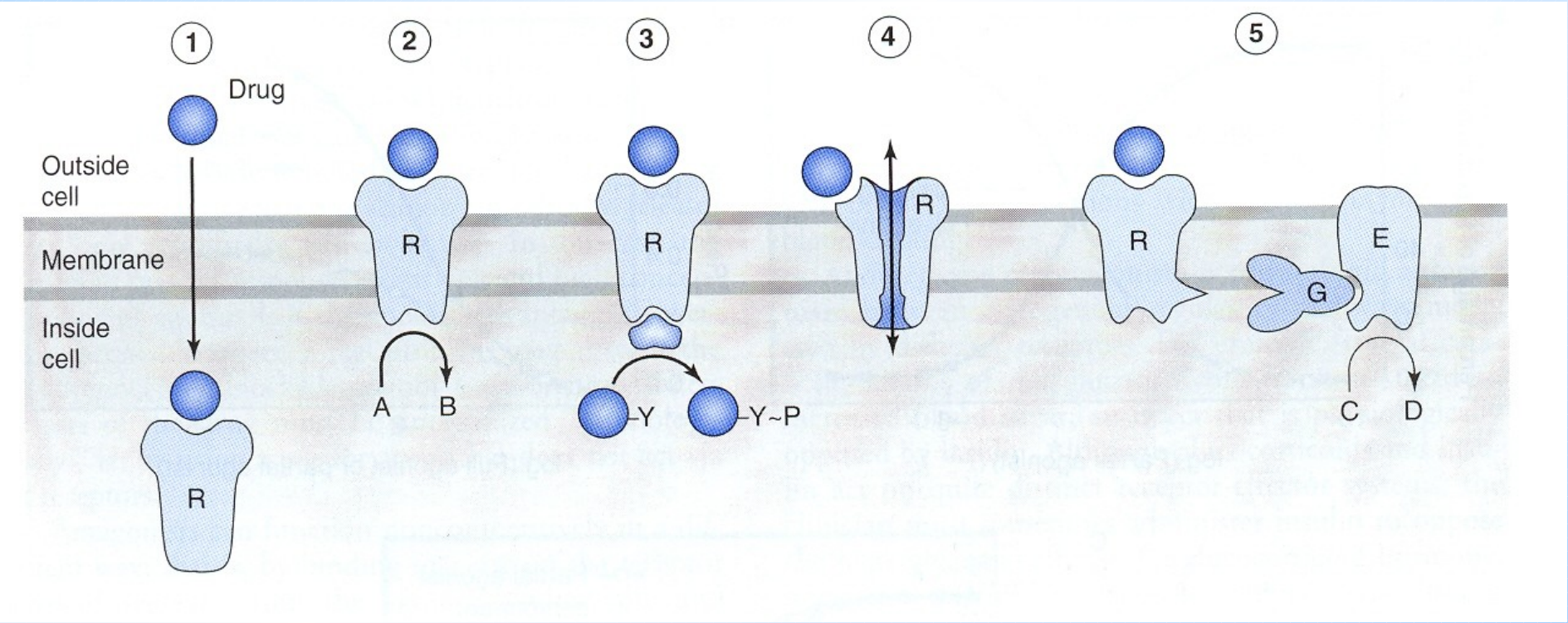
Figure 2–3. Changes in agonist concentration-effect curves produced by a competitive antagonist (Panel **A**) or by an irreversible antagonist (Panel **B**). In the presence of a competitive antagonist, higher concentrations of agonist are required to produce a given effect; thus the agonist concentration (C′) required for a given effect in the presence of concentration [I] of an antagonist is shifted to the right, as shown. High agonist concentrations can overcome inhibition by a competitive antagonist. This is not the case with an irreversible (or noncompetitive) antagonist, which reduces the maximal effect the agonist can achieve, although it may not change its EC_{50}.

For the clinician this has important therapeutic implications:

- **The degree of inhibition produced by a competitive antagonist depends on the concentration of antagonist.** Different patients receiving a fixed dose of propranolol, exhibit a wide range of plasma concentrations due to differences in clearance of the drug – the dose must be adjusted
- **Clinical response to a competitive antagonist depends on the concentration of agonist that is competing for binding to receptors**. A dose of propranolol that decreases resting heart rate may not be sufficient when epinephrine and norepinephrine increase with exercise, or emotional stress


A
Percentage of maximal binding
100
80
60
40
20
0
−10
−8
−6
log (Partial agonist)
Partial agonist
Full agonist
B
Response
1.0
0.8
0.6
0.4
0.2
0.0
−10
−8
−6
log (Full agonist or partial agonist)
Partial agonist
Full agonist
C
Response
1.0
0.8
0.6
0.4
0.2
0.0
−10
−8
−6
log (Partial agonist)
Partial agonist component
Full agonist component
Total response

Five Basic Mechanisms of Transmembrane Signaling



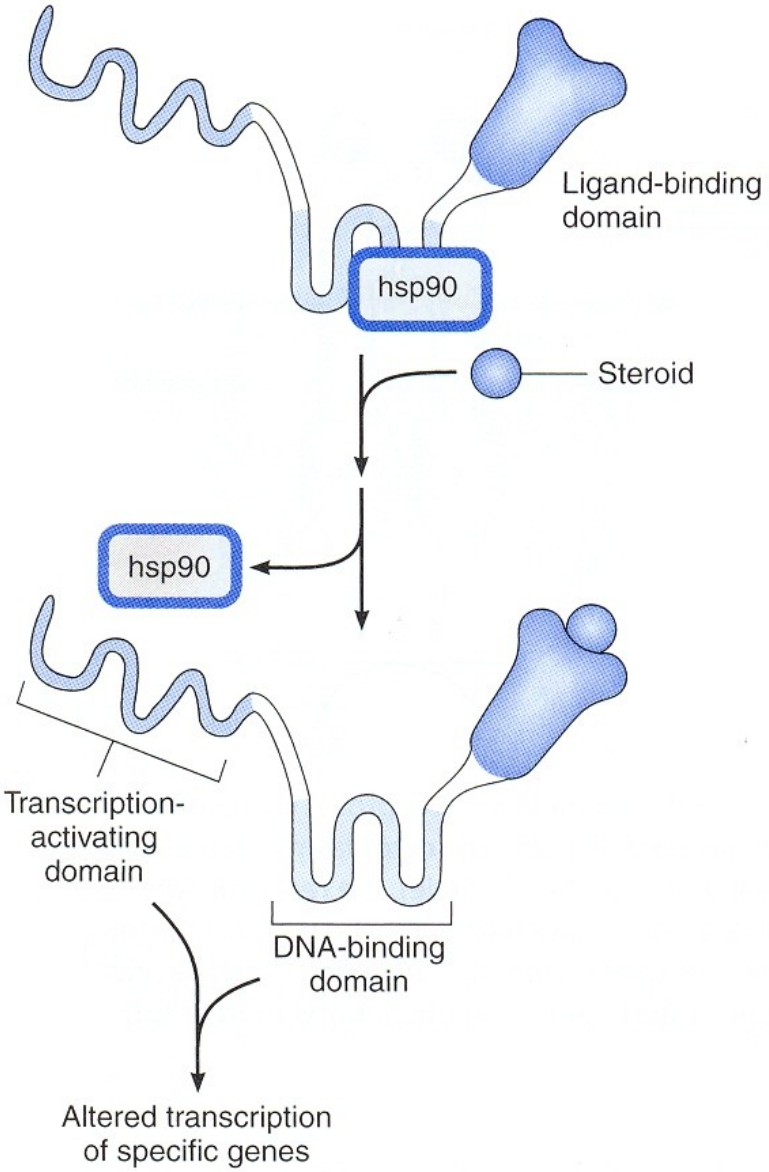
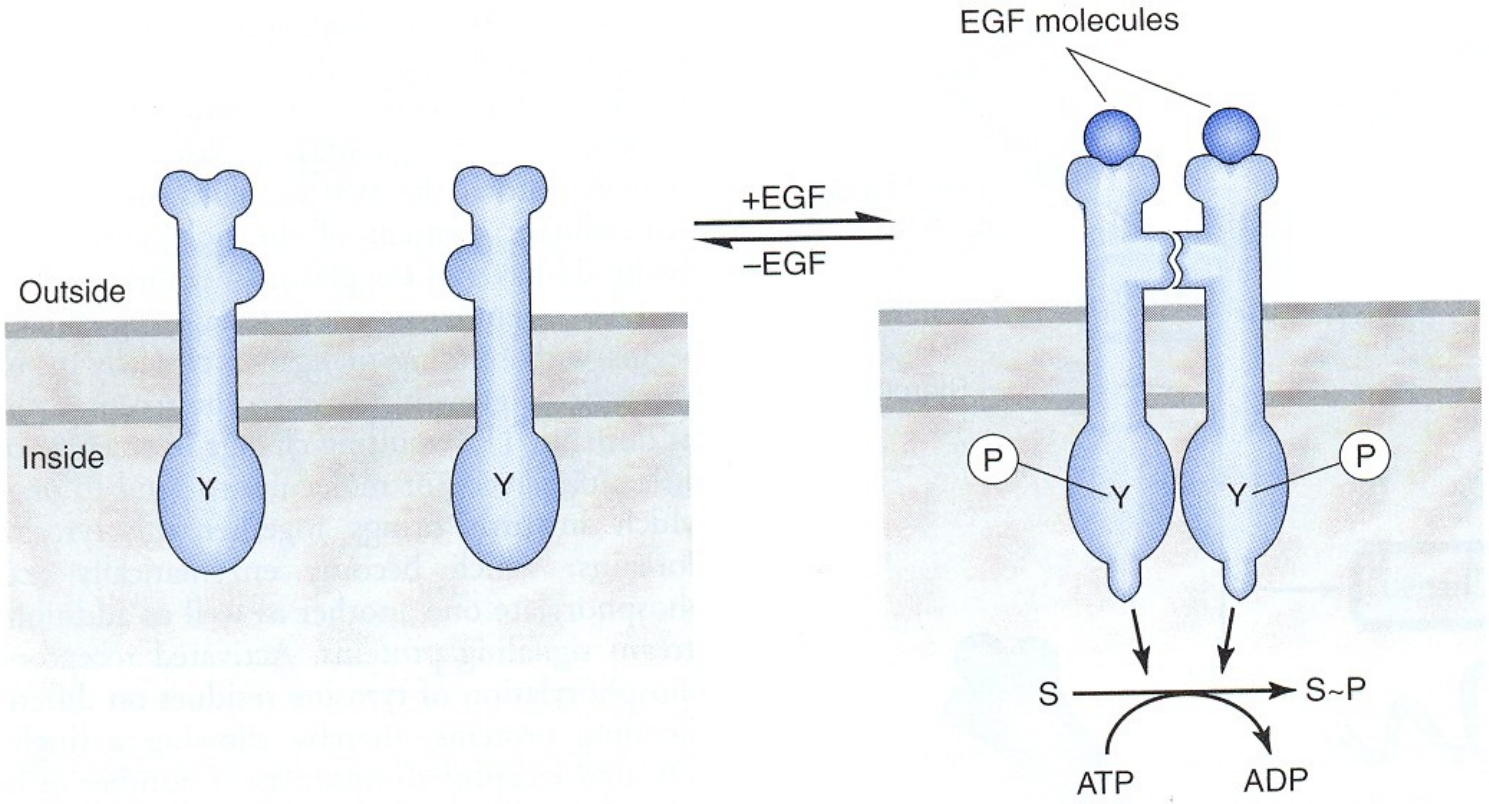
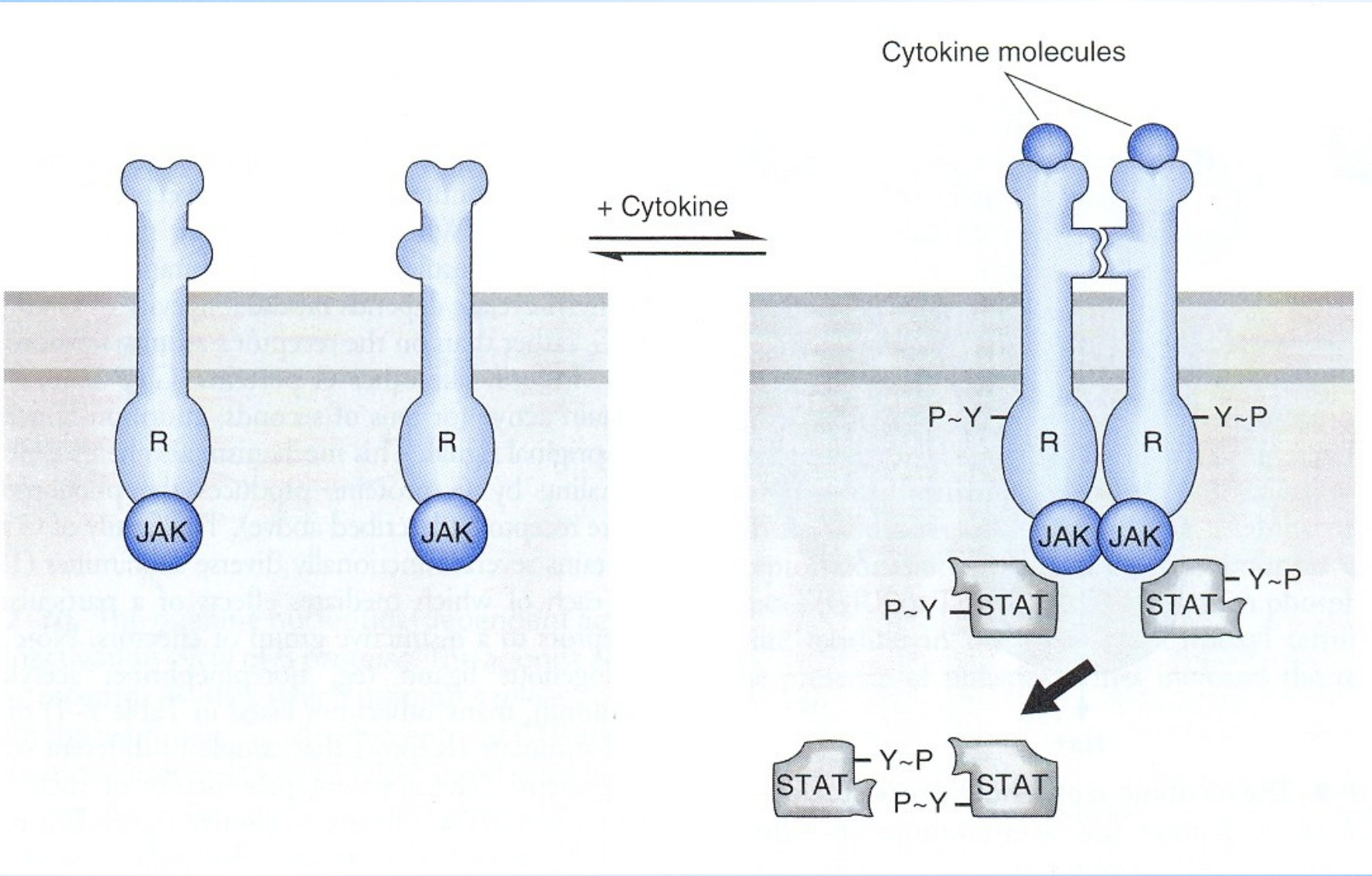


Figure 2–6. Mechanism of glucocorticoid action. The


EGF molecules
+EGF
–EGF
Outside
Inside
Y
Y
P
Y
Y
P
S
S~P
ATP
ADP


Cytokine molecules
+ Cytokine
R
R
JAK
JAK
P~Y
Y~P
R
R
JAK
JAK
P~Y
STAT
STAT
Y~P
STAT
Y~P
P~Y
STAT

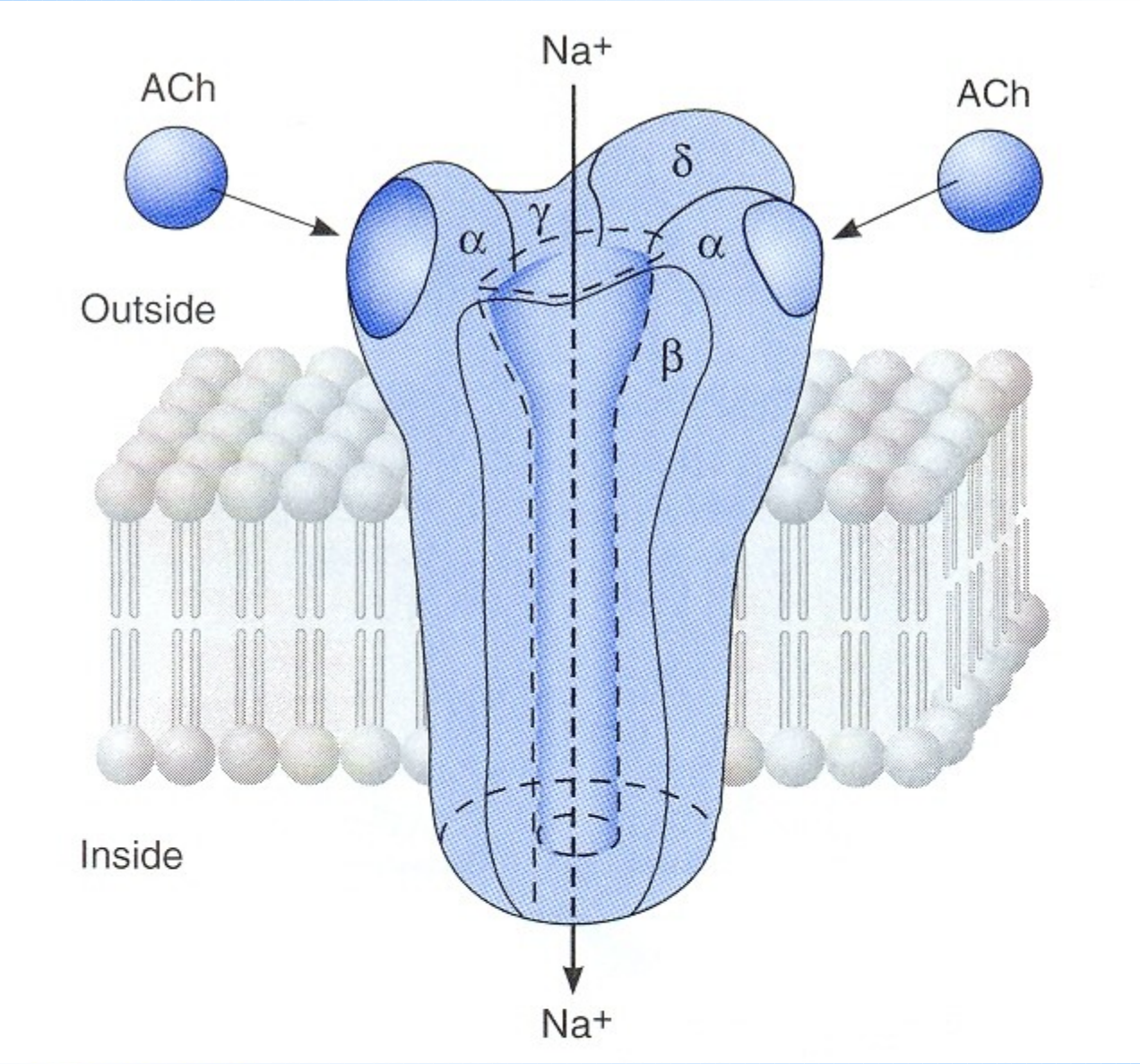
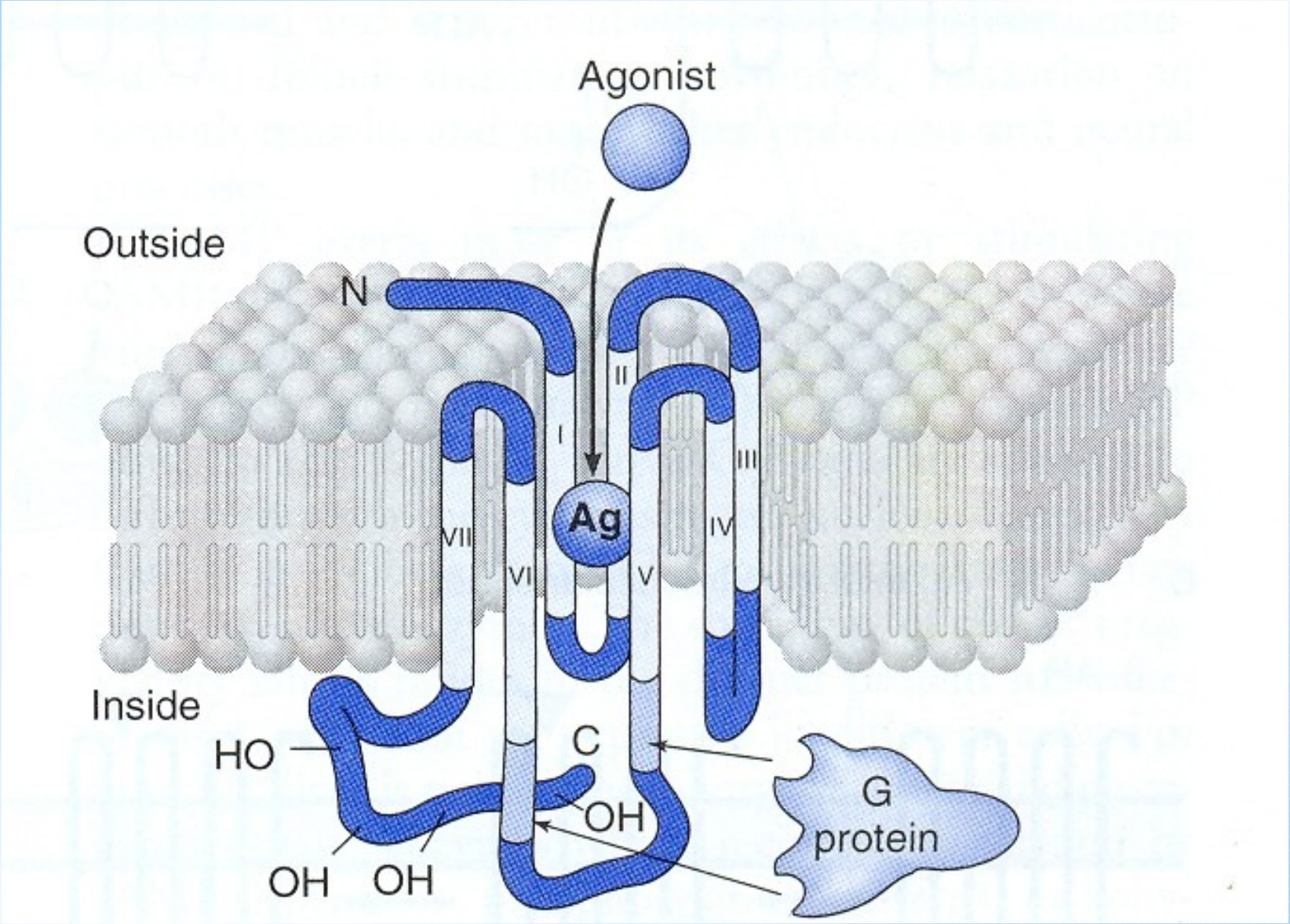
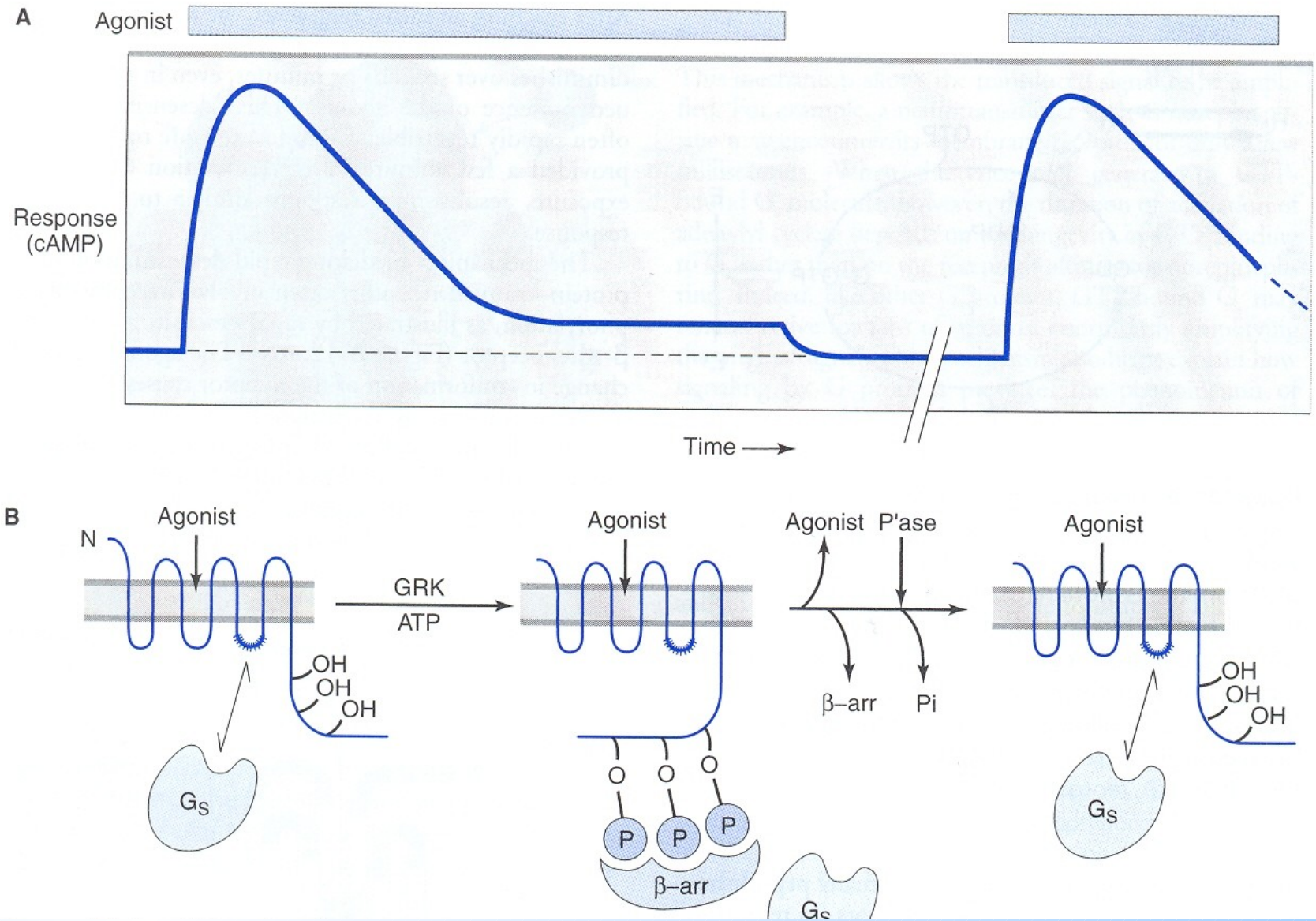

Na+
ACh
ACh
δ
γ
α
α
Outside
β
Inside
Na+

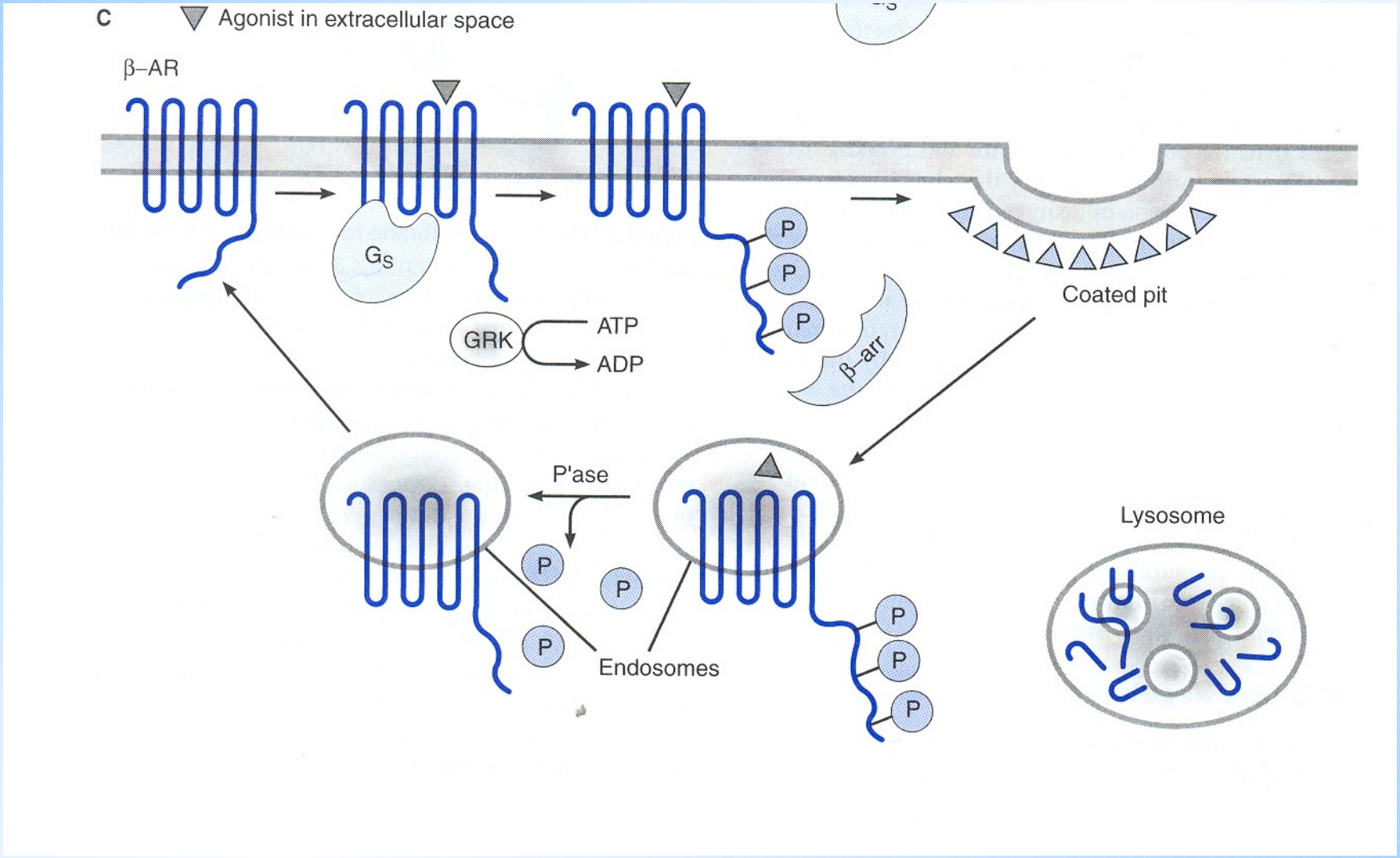
Table 2–1. G proteins and their receptors and effectors.

G Protein	Receptors for:	Effector/Signaling Pathway
G_s	β-Adrenergic amines, glucagon, histamine, serotonin, and many other hormones	↑ Adenylyl cyclase → ↑ cAMP
G_{i1}, G_{i2}, G_{i3}	α_2-Adrenergic amines, acetylcholine (muscarinic), opioids, serotonin, and many others	Several, including: ↓ Adenylyl cyclase → ↓ cAMP Open cardiac K^+ channels → ↓ heart rate
G_{olf}	Odorants (olfactory epithelium)	↑ Adenylyl cyclase → ↑ cAMP
G_o	Neurotransmitters in brain (not yet specifically identified)	Not yet clear
G_q	Acetylcholine (muscarinic), bombesin, serotonin ($5\text{-}HT_{1C}$), and many others	↑ Phospholipase C → ↑ IP_3, diacylglycerol, cytoplasmic Ca^{2+}
G_{t1}, G_{t2}	Photons (rhodopsin and color opsins in retinal rod and cone cells)	↑ cGMP phosphodiesterase → ↓ cGMP (phototransduction)

Key: cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate.

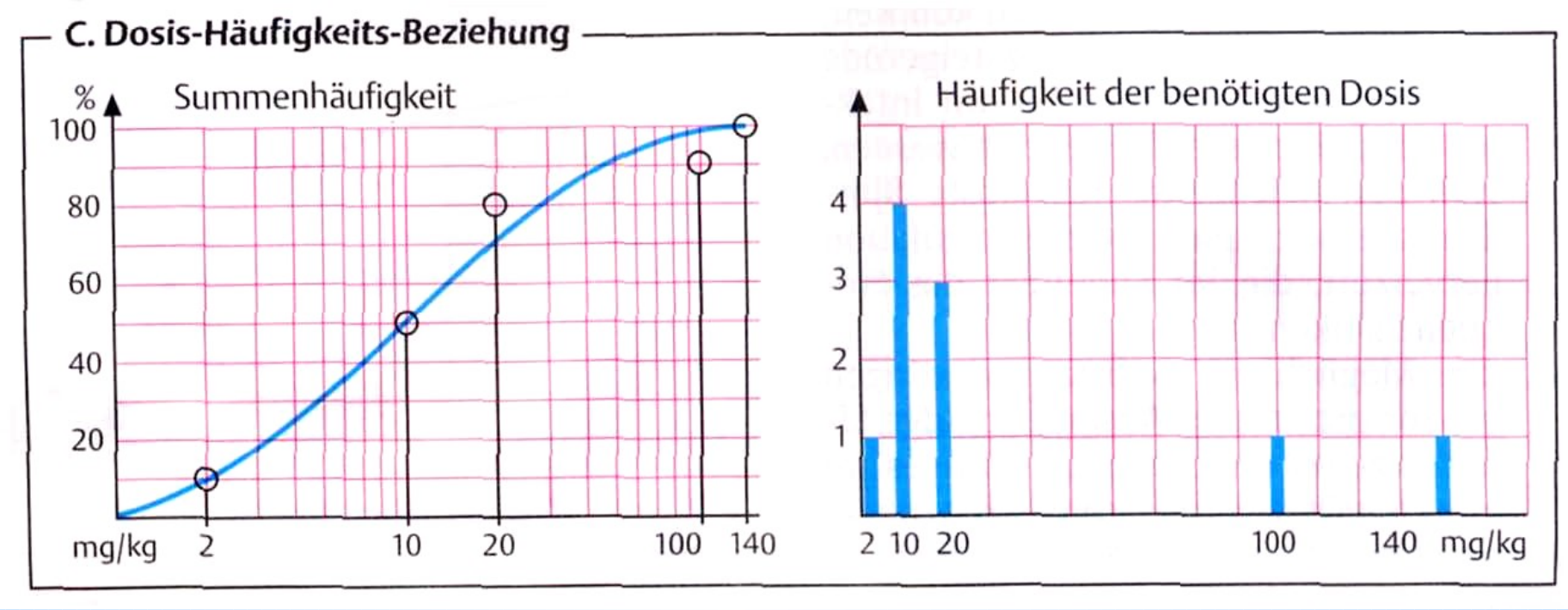

Agonist
Outside
N
I
II
III
IV
V
VI
VII
Ag
Inside
HO
C
OH
OH
OH
G
protein


A
Agonist
Response
(cAMP)
Time
B
Agonist
N
OH
OH
OH
GS
GRK
ATP
Agonist
O
O
O
P
P
P
β–arr
Agonist
P'ase
β–arr
Pi
Agonist
OH
OH
OH
GS


C
Agonist in extracellular space
β–AR
G_S
GRK
ATP
ADP
P
P
P
β–arr
Coated pit
P'ase
P
P
P
Endosomes
P
P
P
Lysosome

Relation Between Drug Dose & Clinical Response

- When faced with a patient who needs treatment, the prescriber must make a choice among a variety of possible drugs and devise a dosage regimen that is likely to produce maximal benefit and minimal toxicity.
- The prescriber must know the relative pharmacologic potency and maximal efficacy of the drugs in relation to the desired therapeutic effect



- Es wurden 140 mg/kg für die maximale Antwort benötigt.
- Es wurden individuelle Dosen (2 - 140 mg/kg) benötigt, um eine Antwort auszulösen.

Ursachen vielfältig: z.B.

- Unterschiede in der Rezeptorzahl
- Unterschiede im Metabolismus des Arzneistoffs ➔ **Pharmakokinetik**

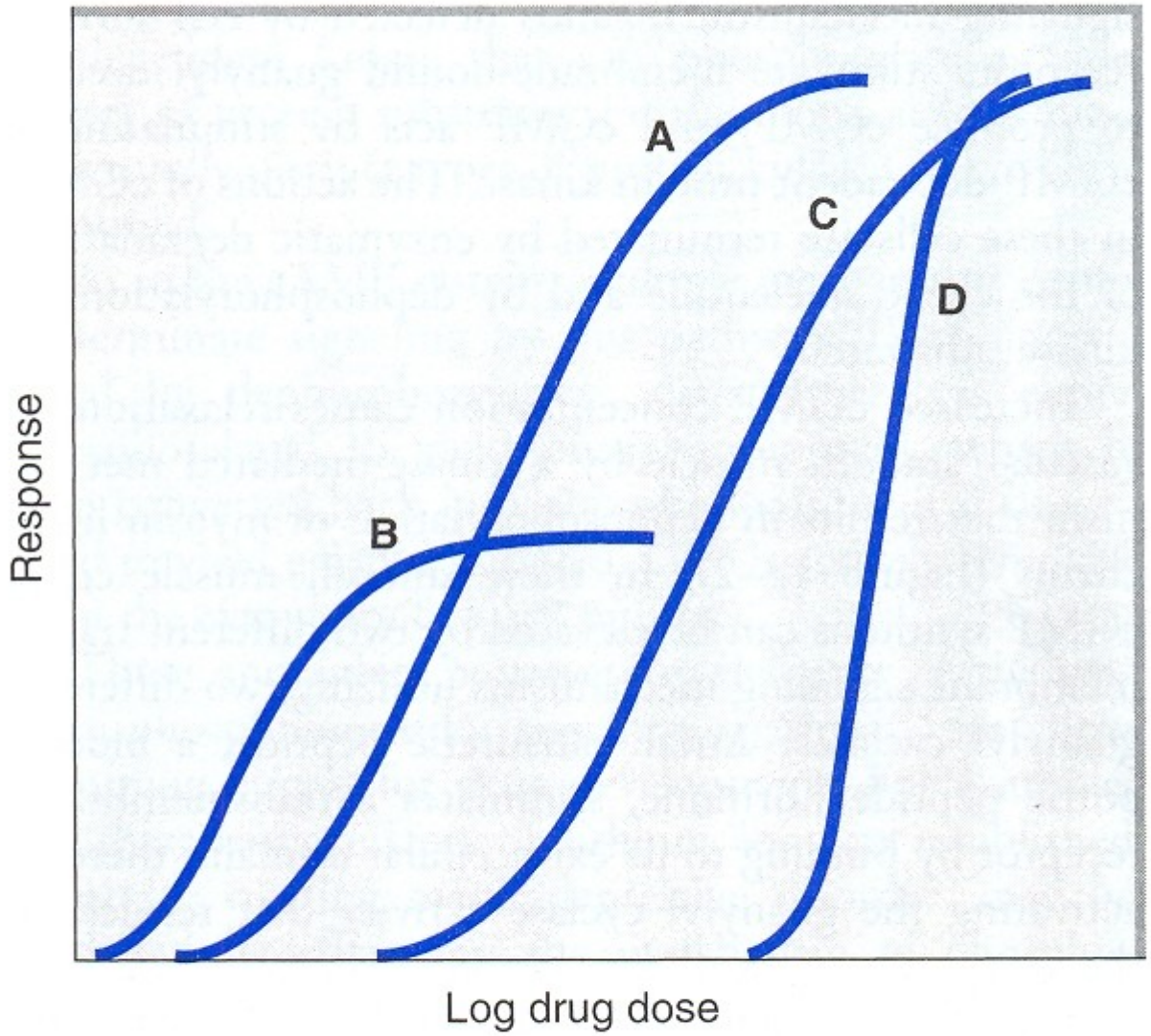
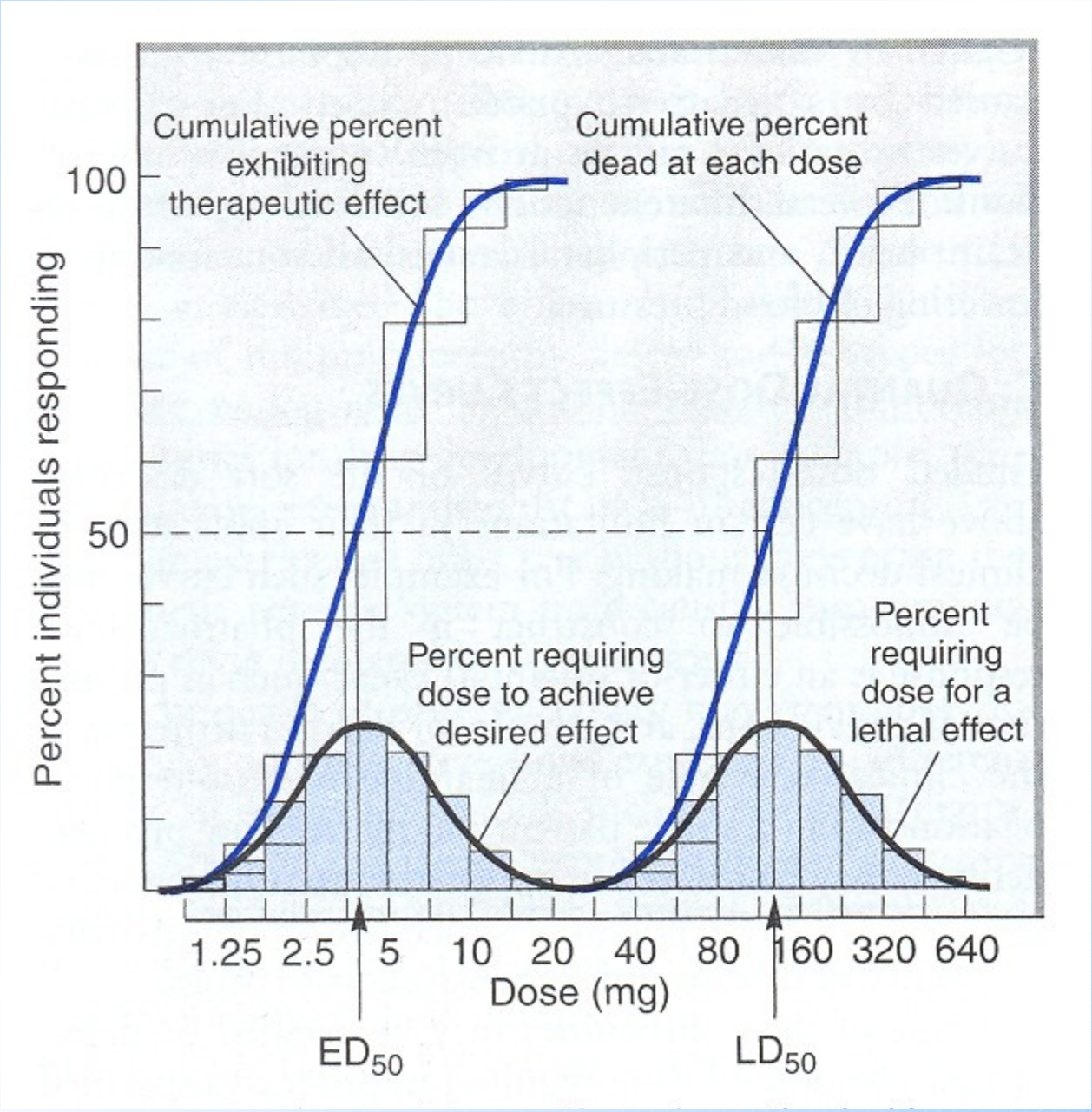


Figure 2–15. Graded dose-response curves for four drugs, illustrating different pharmacologic potencies and different maximal efficacies. (See text.)

Potency and Maximal Efficacy

- **Potency** refers to the concentration (EC_{50}) or dose (ED_{50}) of a drug required to produce 50% of that drug´s maximal effects
- The **maximal efficacy** of a drug reflects the limit of the dose-response relation on the response axis
- The **clinical effectiveness** of a drug depends not on its potency (EC_{50}), but on ist maximal efficacy and its ability to reach the relevant receptors


Cumulative percent exhibiting therapeutic effect
Cumulative percent dead at each dose
100
50
Percent individuals responding
Percent requiring dose to achieve desired effect
Percent requiring dose for a lethal effect
1.25 2.5 5 10 20 40 80 160 320 640
Dose (mg)
ED_{50}
LD_{50}

Therapeutic Index

$TD_{50} : ED_{50}$

Variation in Drug Responsiveness

- **Alteration in the concentration of the drug that reaches the receptor** (pharmacokinetic differences: age, weight, sex, disease states, liver and kidney function, genetic differences)
- **Variation in concentration of an endogenous receptor ligand** (β-adrenoceptor antagonist)
- **Alterations in number or function of receptors** (e.g. thyroid hormones increase both the number of β receptors in heart muscle and cardiac sensitivity to catecholamines; agonist ligand cause down-regulation or desensitization of its receptors → tolerance, tachyphylaxis)
- **Changes in components of response distal to the receptor** (represent the largest and most important class of mechanisms that cause variations in responsiveness to drug therapy)

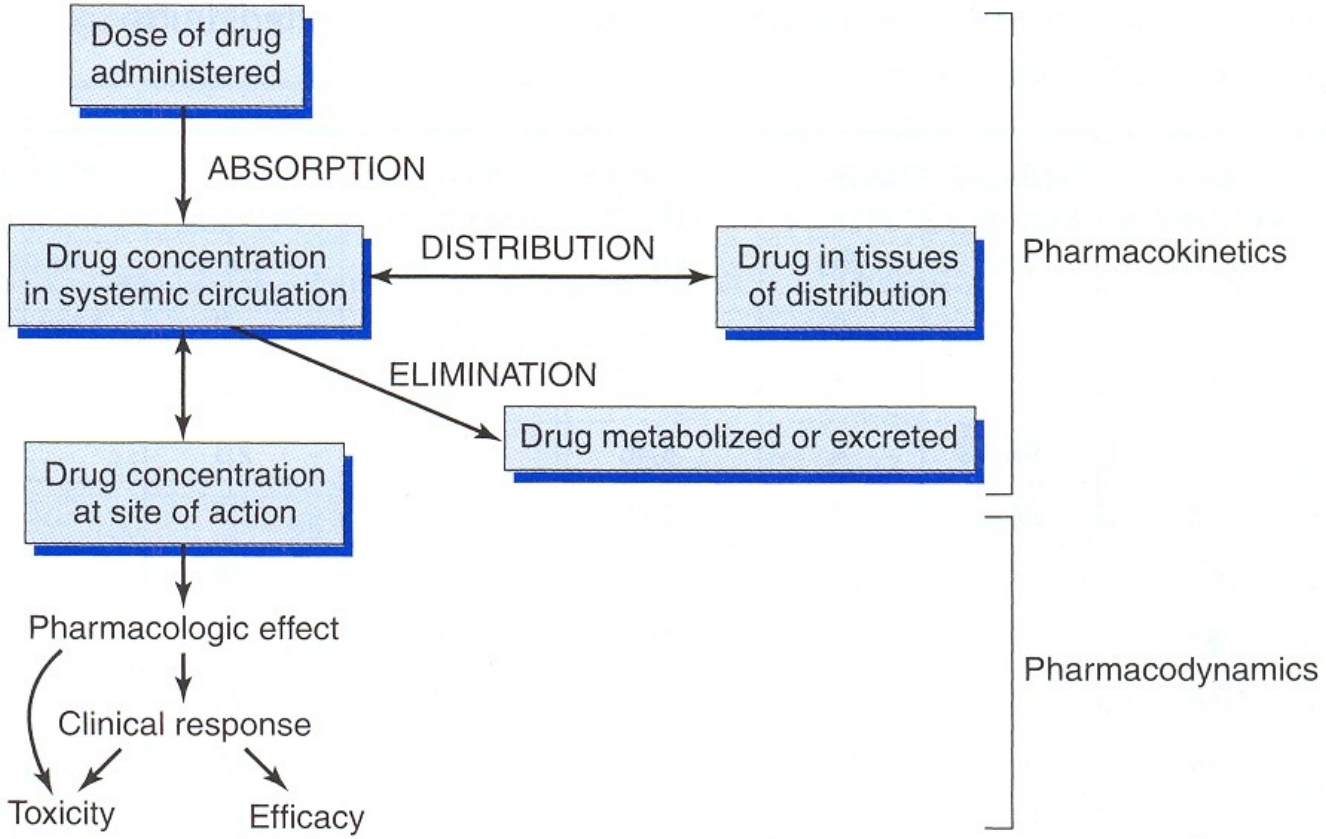
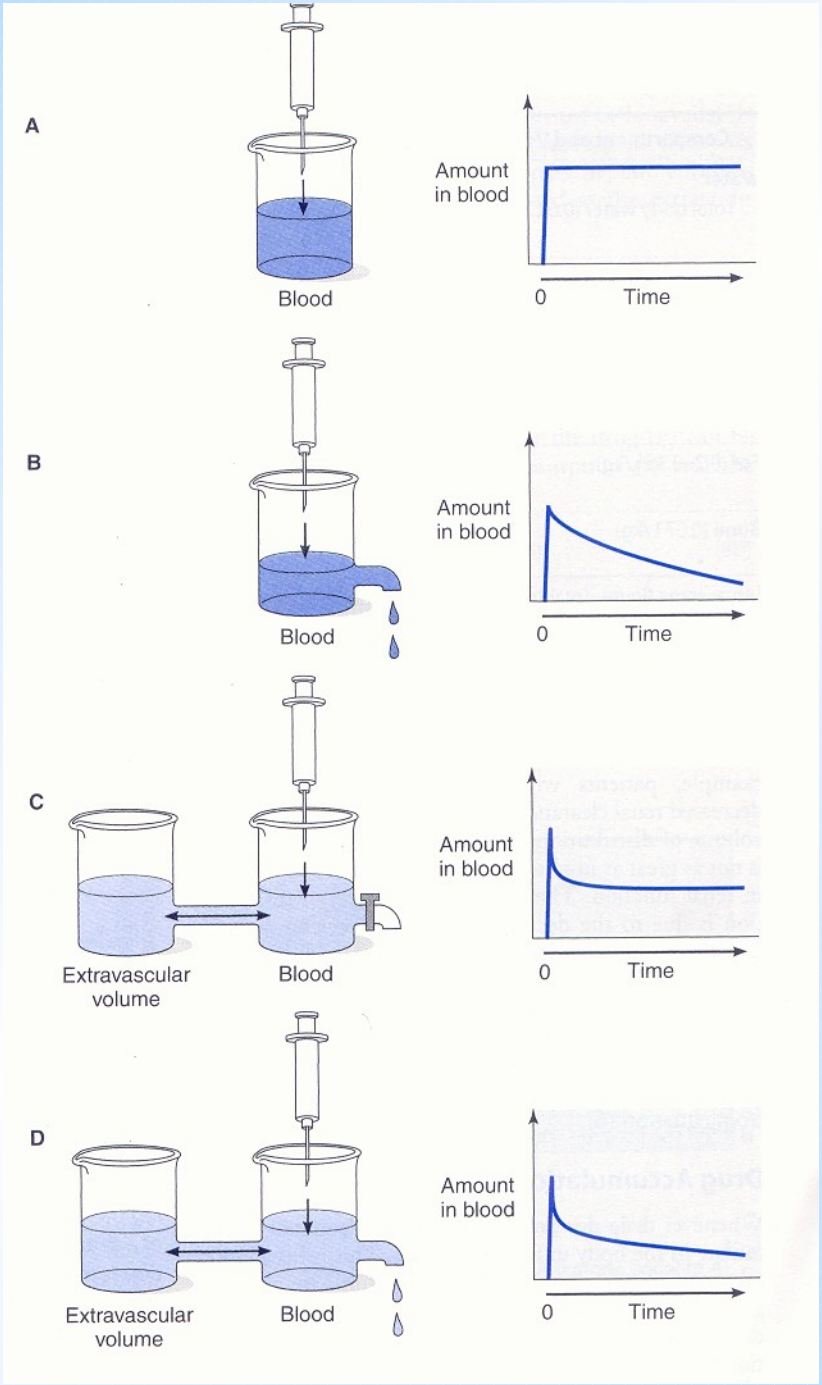


Figure 3–1. The relationship between dose and effect can be separated into pharmacokinetic (dose-concentration) and pharmacodynamic (concentration-effect) components. Concentration provides the link between pharmacokinetics and pharmacodynamics and is the focus of the target concentration approach to rational dosing. The three primary processes of pharmacokinetics are absorption, distribution, and elimination.

Table 3–1. Pharmacokinetic and pharmacodynamic parameters for selected drugs. (See Speight & Holford, 1997, for a more comprehensive listing.)

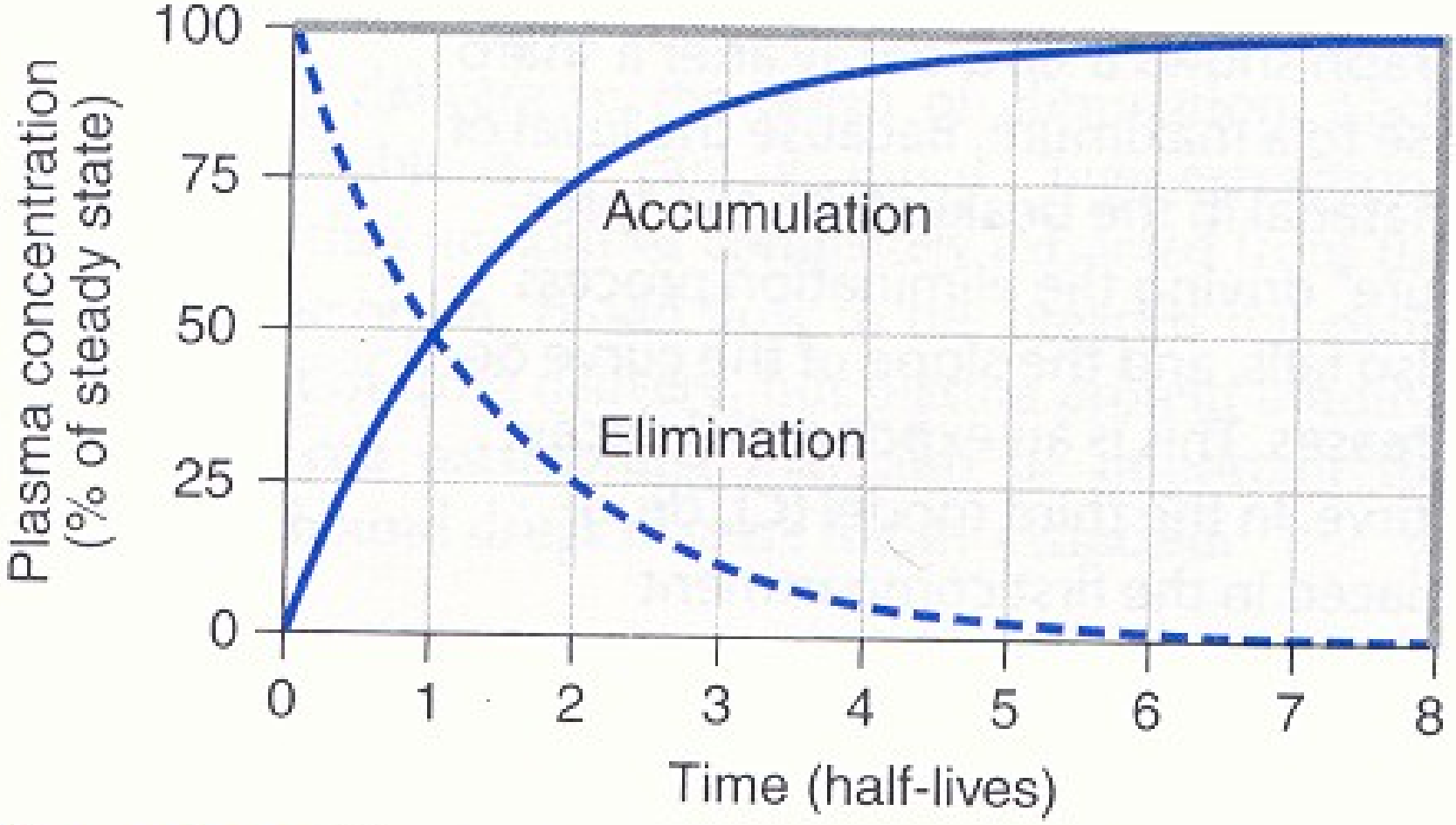
Drug	Oral Availability (F) (%)	Urinary Excretion (%)	Bound in Plasma (%)	Clearance (L/h/70 kg)[1]	Volume of Distribution (L/70 kg)	Half-Life (h)	Target Concentrations	Toxic Concentrations
Acetaminophen	88	3	0	21	67	2	15 mg/L	>300 mg/L
Acyclovir	23	75	15	19.8	48	2.4	...	...
Amikacin	...	98	4	5.46	19	2.3	...	...
Amoxicillin	93	86	18	10.8	15	1.7	...	...
Amphotericin	...	4	90	1.92	53	18	...	...
Ampicillin	62	82	18	16.2	20	1.3	...	...
Aspirin	68	1	49	39	11	0.25	...	...
Atenolol	56	94	5	10.2	67	6.1	1 mg/L	...
Atropine	50	57	18	24.6	120	4.3	...	...
Captopril	65	38	30	50.4	57	2.2	50 ng/mL	...
Carbamazepine	70	1	74	5.34	98	15	6 mg/L	>9 mg/L
Cephalexin	90	91	14	18	18	0.9	...	...
Cephalothin	...	52	71	28.2	18	0.57	...	...
Chloramphenicol	80	25	53	10.2	66	2.7	...	...
Chlordiazepoxide	100	1	97	2.28	21	10	1 mg/L	...
Chloroquine	89	61	61	45	13000	214	20 ng/mL	250 ng/mL
Chlorpropamide	90	20	96	0.126	6.8	33	...	...
Cimetidine	62	62	19	32.4	70	1.9	0.8 mg/L	...
Ciprofloxacin	60	65	40	25.2	130	4.1	...	...
Clonidine	95	62	20	12.6	150	12	1 ng/mL	...
Cyclosporine	23	1	93	24.6	85	5.6	200 ng/mL	>400 ng/mL
Diazepam	100	1	99	1.62	77	43	300 ng/mL	...
Digitoxin	90	32	97	0.234	38	161	10 ng/mL	>35 ng/mL
Digoxin	70	60	25	7	500	50	1 ng/mL	>2 ng/mL
Diltiazem	44	4	78	50.4	220	3.7	...	...
Disopyramide	83	55	[2]	5.04	41	6	3 mg/mL	>8 mg/mL
Enalapril	95	90	55	9	40	3	>0.5 ng/mL	...
Erythromycin	35	12	84	38.4	55	1.6	...	...
Ethambutol	77	79	5	36	110	3.1	...	>10 mg/L
Fluoxetine	60	3	94	40.2	2500	53	...	...
Furosemide	61	66	99	8.4	7.7	1.5	...	>25 mg/L
Gentamicin	...	90	10	5.4	18	2.5	...	...
Hydralazine	40	10	87	234	105	1	100 ng/mL	...

(continued)


A
Blood
Amount in blood
0
Time
B
Blood
Amount in blood
0
Time
C
Extravascular volume
Blood
Amount in blood
0
Time
D
Extravascular volume
Blood
Amount in blood
0
Time

Compartment and Volume	Examples of Drugs
Water	
Total body water (0.6 L/kg[1])	Small water-soluble molecules: eg, ethanol.
Extracellular water (0.2 L/kg)	Larger water-soluble molecules: eg, gentamicin.
Blood (0.08 L/kg); plasma (0.04 L/kg)	Strongly plasma protein-bound molecules and very large molecules: eg, heparin.
Fat (0.2–0.35 L/kg)	Highly lipid-soluble molecules: eg, DDT.
Bone (0.07 L/kg)	Certain ions: eg, lead, fluoride.

[1]An average figure. Total body water in a young lean man might be 0.7 L/kg; in an obese woman, 0.5 L/kg.


Plasma concentration
(% of steady state)
100
75
50
25
0
Accumulation
Elimination
0
1
2
3
4
5
6
7
8
Time (half-lives)

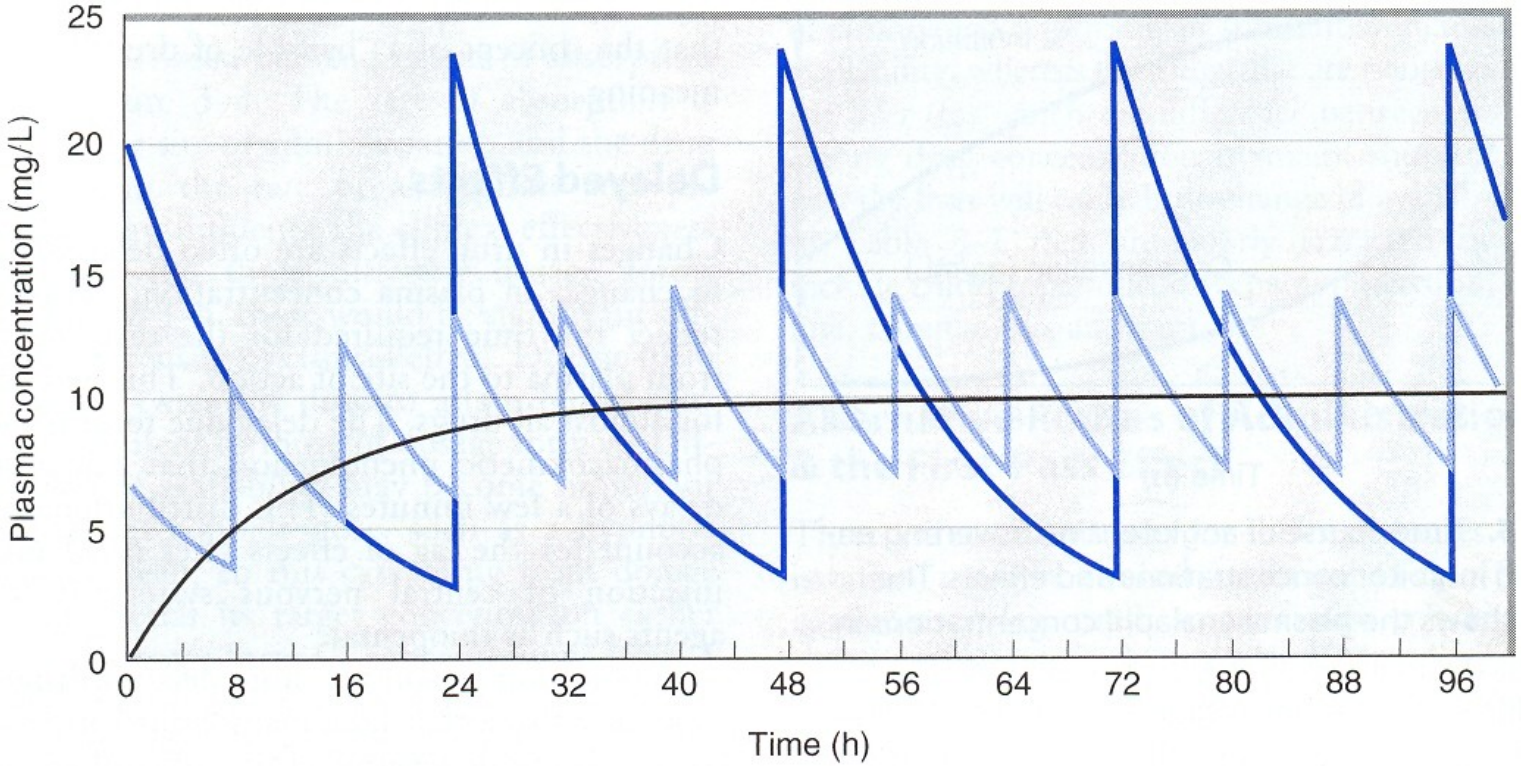


Figure 3–6. Relationship between frequency of dosing and maximum and minimum plasma concentrations when a steady-state theophylline plasma level of 10 mg/L is desired. The smoothly rising line (solid black) shows the plasma concentration achieved with an intravenous infusion of 28 mg/h. The doses for 8-hourly administration (light color) are 224 mg; for 24-hourly administration (dark color), 672 mg. In each of the three cases, the mean steady-state plasma concentration is 10 mg/L.

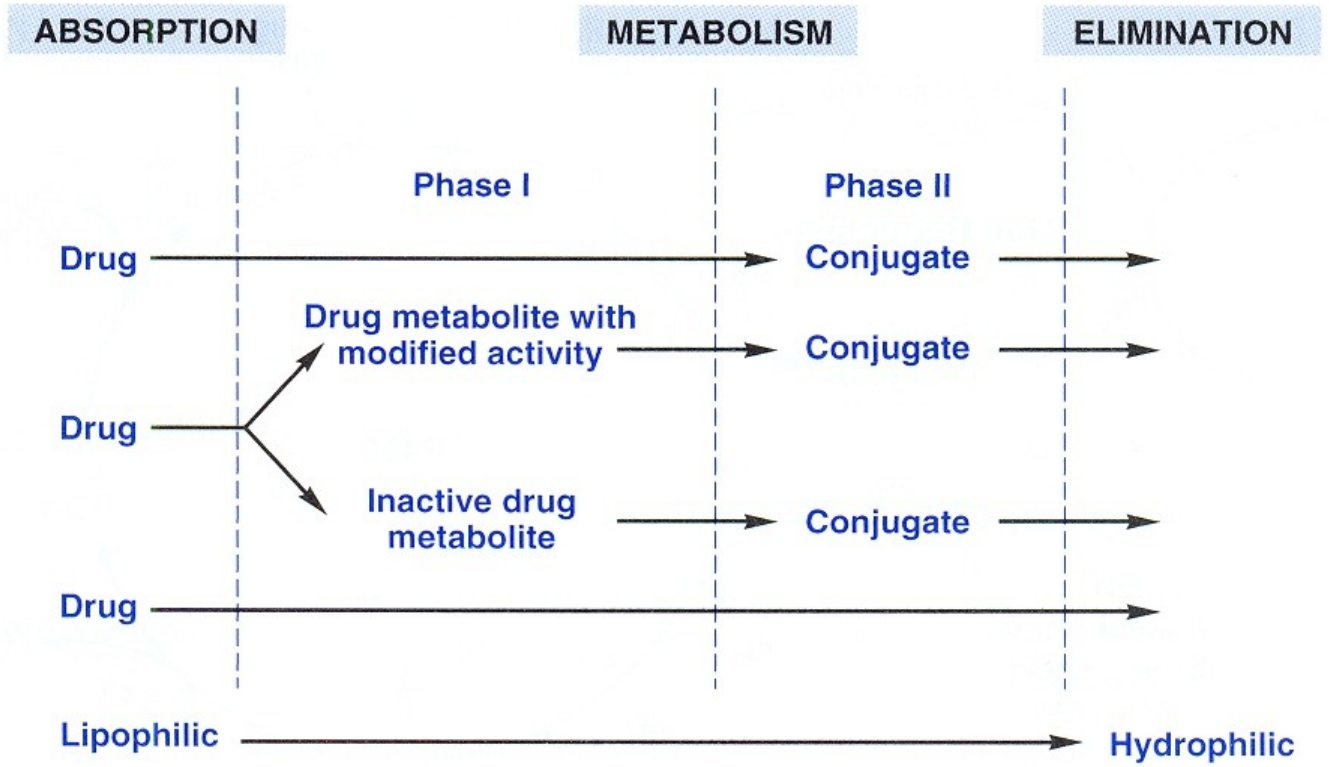
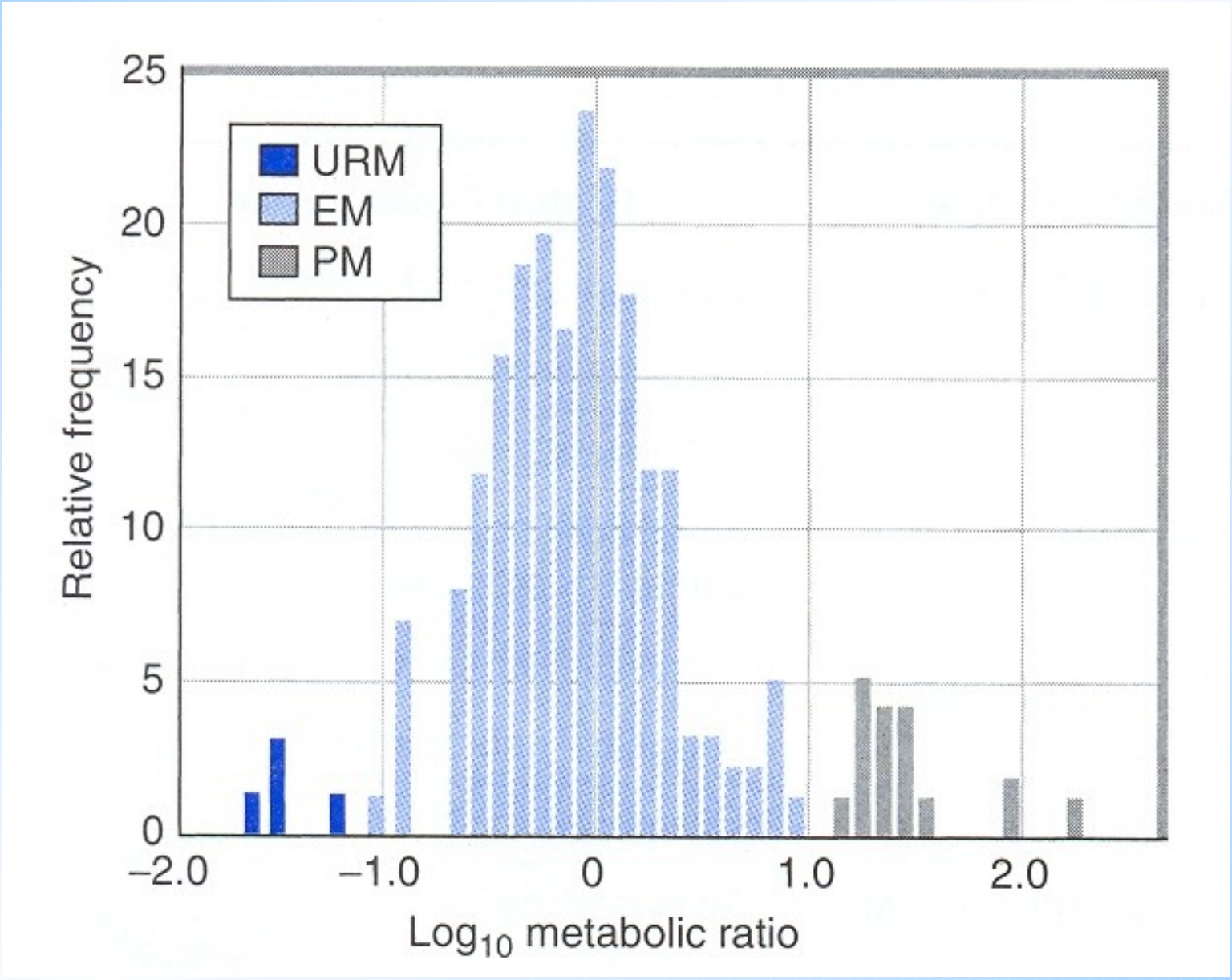


Figure 4–1. Phase I and phase II reactions, and direct elimination, in drug biodisposition. Phase II reactions may also precede phase I reactions.

Table 4–4. Some examples of genetic polymorphisms in drug metabolism.

Defect	Enzyme Involved	Drug and Therapeutic Use	Clinical Consequences[1]
Oxidation	CYP2D6	Bufuralol (β-adrenoceptor blocker)	Exacerbation of β-blockade, nausea
Oxidation	CYP2D6	Codeine (analgesic)	Reduced analgesia
Oxidation	CYP2D6	Debrisoquin (antihypertensive)	Orthostatic hypotension
Oxidation	Aldehyde dehydrogenase	Ethanol (recreational drug)	Facial flushing, hypotension, tachycardia, nausea, vomiting
N-Acetylation	*N*-acetyl transferase	Hydralazine (antihypertensive)	Lupus erythematosus-like syndrome
N-Acetylation	*N*-acetyl transferase	Isoniazid (antitubercular)	Peripheral neuropathy
Oxidation	CYP2C19	Mephenytoin (antiepileptic)	Overdose toxicity
S-Methylation	Thiopurine methyltransferase	Mercaptopurines (cancer chemotherapeutic)	Myelotoxicity
Oxidation	CYP2A6	Nicotine (stimulant)	Lesser toxicity
Oxidation	CYP2D6	Nortriptyline (antidepressant)	Toxicity
O-Demethylation	CYP2C19	Omeprazole (proton pump inhibitor)	Increased therapeutic efficacy
Oxidation	CYP2D6	Sparteine	Oxytocic symptoms
Ester hydrolysis	Plasma cholinesterase	Succinylcholine (neuromuscular blocker)	Prolonged apnea
Oxidation	CYP2C9	*S*-warfarin (anticoagulant)	Bleeding
Oxidation	CYP2C9	Tolbutamide (hypoglycemic)	Cardiotoxicity

[1]Observed or predictable.


URM
EM
PM
Relative frequency
25
20
15
10
5
0
–2.0
–1.0
0
1.0
2.0
Log10 metabolic ratio

Pharmakologie

Pharmakodynamik

Pharmakokinetik