Introduction & General Principle of Pharmacology

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Pharmacology

It is the science that deals with the interaction between the living system & small molecules particularly chemicals.

or

Study the physical and chemical properties of drugs as well as their biochemical and physiological effects.

Medical Pharmacology: The science of substances which are used for the prevention, diagnosis and treatment of diseases.

Pharmacy: It is the science that deals with the preparing & dispensing the drugs

Drug: It is the chemical molecules which alter biochemistry & physiology of the living system when introduced inside the body

The Physical Nature of Drugs

Drugs may be

- Solid at room temperature (e.g. aspirin, atropine)
- Liquid (e.g. nicotine, ethanol)
- Gaseous (e.g. nitrous oxide)

These factors often determine the best route of administration.

Routes of administration, bioavailability and general characteristics

Route	Biovailability (%)	Characteristics
Intravenous (IV)	100 (by definition)	Most rapid onset
Intramuscular (IM)	75 to ≤ 100	Large volumes often feasible; may be painful
Subcutaneous (SC)	75 to ≤ 100	Smaller volumes than IM; may be painful
Oral (PO)	5 to < 100	Most convenient; first-pass effect may be important
Rectal (PR)	30 to < 100	Less first-pass effect than oral
Inhalation	5 to < 100	Often very rapid onset
Transdermal	80 to ≤ 100	Usually very slow absorption; used for lack of first-pass effect; prolonged duration of action

Drugs may be:

- Synthesized within the body (e.g. hormones)
- Chemicals *not* synthesized in the body, ie, xenobiotics (from the Greek *xenos*, meaning stranger).
- Poisons are drugs that have almost exclusively harmful effects.
- Toxins are poisons of biologic origin, ie, synthesized by plants or animals, in contrast to inorganic poisons such as lead.

Drugs may be

- Organic compounds (carbohydrates, proteins, lipids, and their constituents). Organic drugs are weak acids or bases. This fact has important implications for the way they are handled by the body, because pH differences in the various compartments of the body may alter the degree of ionization of such drugs
- Inorganic elements, e.g. iron

Drug Size

- The molecular size of drugs varies from very small (MW 7) to very large (MW 59,050).
- most drugs have molecular weights between 100 and 1000.
- Drugs much larger than MW 1000 do not diffuse readily between compartments of the body (Therefore, very large drugs (usually proteins) must often be administered directly into the compartment where they have their effect. In the case of alteplase, a clot-dissolving enzyme, the drug is administered directly into the vascular compartment by intravenous or intra-arterial infusion

Drug Reactivity & Drug-Receptor Bonds

Drugs interact with receptors by means of chemical forces or bonds. There are three major types

1. Covalent
2. Electrostatic
3. Hydrophobic

Covalent Bonds

Very strong (not broken) and in many cases not reversible under biologic conditions.

EXAMPLE: the covalent bond formed between the acetyl group of aspirin and its enzyme target in platelets cyclooxygenase

Electrostatic Bonds

Weaker than covalent bonds.

Hydrophobic Bonds

Quite weak and are probably important in the interactions of highly lipid-soluble drugs with the lipids of cell membranes

Drug Shape

The shape of a drug molecule must be permit binding to its receptor site via the bonds, the drug's shape is complementary to that of the receptor site in the same way that a key is complementary to a lock.

Drug-body Interactions

The interactions between a drug and the body are divided into two classes.

Pharmacodynamic

What a drug does to the body,such as mechanism of action and therapeutic and toxic effects.

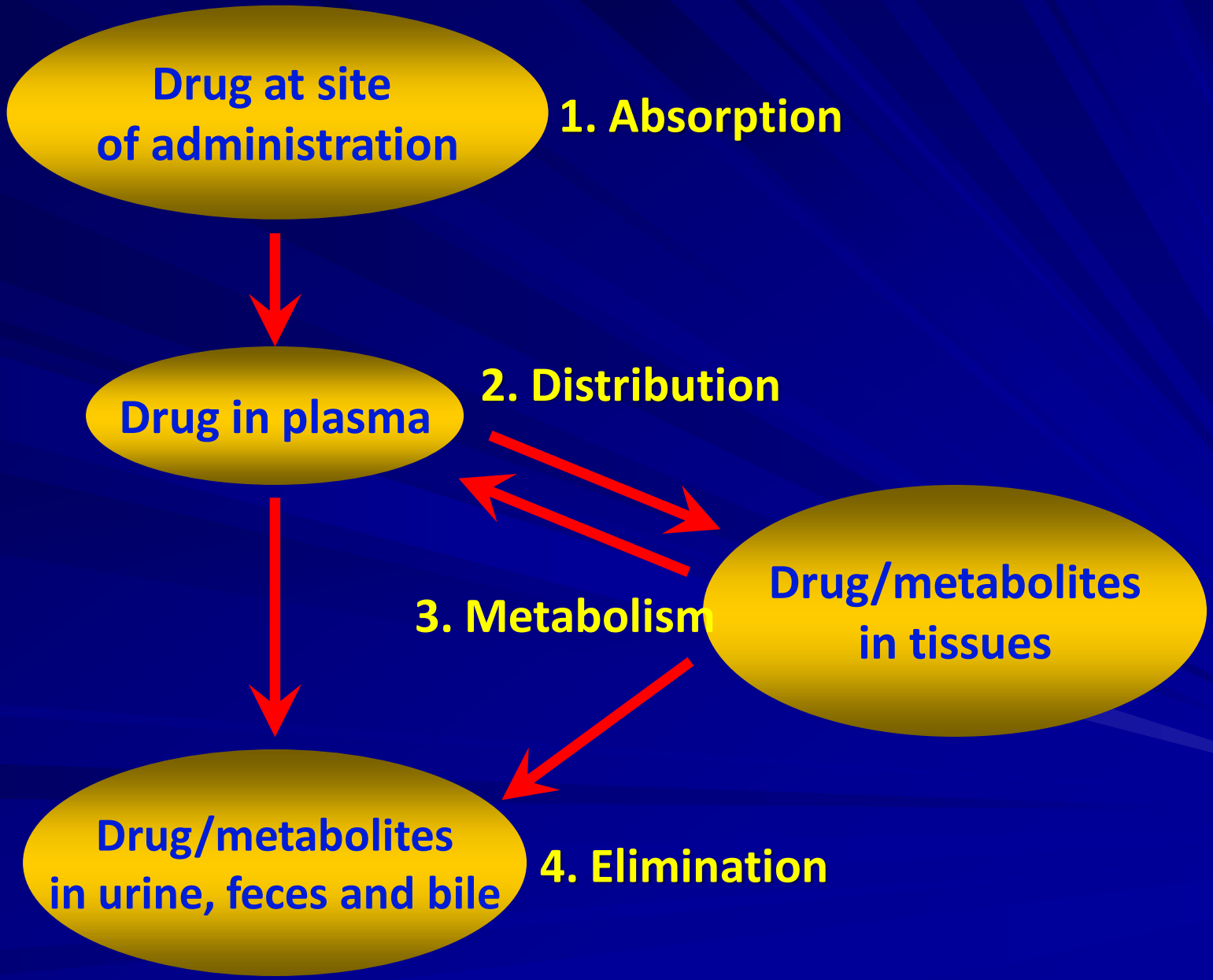
Pharmacokinetic

What the body does to the drug or how the body deals with the drug or the fate of the drug in the body

Pharmacokinetics processes are

Absorption, Distribution, Metabolism and Excretion

What Happens After Drug Administration?



Prodrug

- A chemical that is administered, absorbed and distributed and then converted to the active drug by biologic processes inside the body.

Drug Receptors

Coupling

The overall transduction process that links drug occupancy of receptors and pharmacologic response is called coupling

Agonist

Drug or endogenous regulatory molecule that occupies a receptor& make conformational changes &produce a pharmacologic response.

Agonists can be divided into

- **Full agonists** produce maximal pharmacologic response
- **Partial agonists** produce a lower response, at full receptor occupancy, than do **full agonists.**

Note: Partial agonists produce concentration-effect curves that resemble those observed with full agonists in the presence of an antagonist that irreversibly blocks some of the receptor sites

Receptor Antagonists

Bind to receptors but do not activate them; the primary action of antagonists is to reduce the effects of agonists

Antagonist Drugs

- Competitively
- Noncompetitively

Note: Some drugs mimic agonist drugs by inhibiting the molecules responsible for terminating the action of an endogenous agonist

Example:

- Acetylcholinesterase inhibitors, Inhibit acetylcholinesterase enzyme (the enzyme responsible for the destruction of endogenous acetylcholine, cause cholinomimetic effects (resemble the actions of cholinoceptor agonist)

Antagonist Drugs

- Competitively
- Noncompetitively

Pharmacologic Antagonist

- Drugs activate the agonist binding site, by binding to a receptor, compete with and prevent binding by other molecules.

Example

- Atropine (acetylcholine receptor blockers) are antagonists because they prevent access of acetylcholine to the acetylcholine receptor site and they stabilize the receptor in its inactive state (or some state other than the acetylcholine-activated state).

Allosteric Modulators

Drugs that bind to the same receptor but do not prevent binding of the agonist , may enhance or inhibit action of the agonist molecule.

- Allosteric inhibitors (Non competetive antagonists) (negative allosteric modulators) bind very tightly to the receptor site in an irreversible or pseudoirreversible fashion and cannot be displaced by increasing the agonist concentration (by increasing the dose of agonist)

Example of Irreversible α-Adrenoceptor Antagonist

Phenoxybenzamine, an irreversible α-adrenoceptor antagonist, is used to control the hypertension caused by catecholamines released from pheochromocytoma, a tumor of the adrenal medulla. If administration of phenoxybenzamine lowers blood pressure, blockade will be maintained even when the tumor releases very large amounts of catecholamine.

- Allosteric activators (positive allosteric modulators) may increase the efficacy of the agonist or its binding

Example:

Benzodiazepines bind noncompetitively to ion channels activated by the neurotransmitter γ-aminobutyric acid (GABA), thereby enhancing the net activating effect of GABA on channel conductance

Note: Allosteric antagonists do not bind to the agonist receptor site; they bind to some other region of the receptor molecule that results in inhibition of the response to agonists, they do not prevent binding of the agonist. In contrast, pharmacologic antagonists bind to the agonist site and prevent access of the agonist, High concentrations of agonist displace or prevent the binding of a pharmacologic antagonist but not an allosteric antagonist.

Antagonism by Receptor Block (Receptor Antagonist)

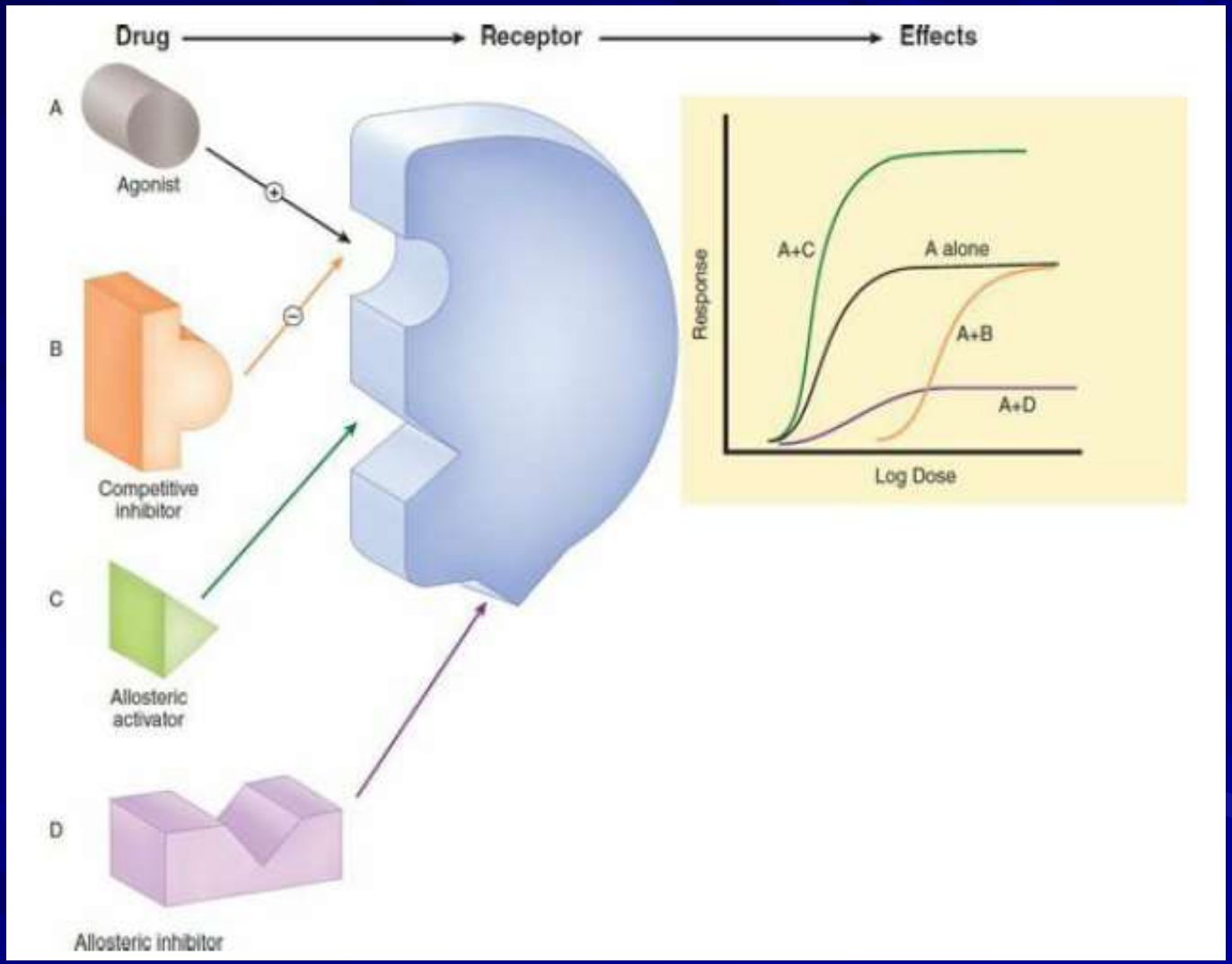
- Competitive: They compete for the binding site

Reversible

1. Antagonist binds with the same receptor as the agonist
2. Antagonist resembles chemically with agonist
3. Antagonist reduces affinity of agonist
4. Intensity depend on conc. Of both agonist and antagonist

- **Non-Competitve**
  1. Antagonist binds to another binding site of the recepter
  2. Not resembles chemically with agonist
  3. Antaginist reduces efficacy of agonist
  4. depend only on concentration of antagonist

Some antagonists exhibit “**inverse agonist**” activity, because they also reduce receptor activity below basal levels observed in the absence of any agonist at all (activate the recepter to produce an effect in the opposite direction to that of the agonist


Drug
Receptor
Effects
A
Agonist
B
Competitive inhibitor
C
Allosteric activator
D
Allosteric inhibitor
Response
A+C
A alone
A+B
A+D
Log Dose

Constitutive Activity (Basal Signal):

The receptor is able to have 2 states

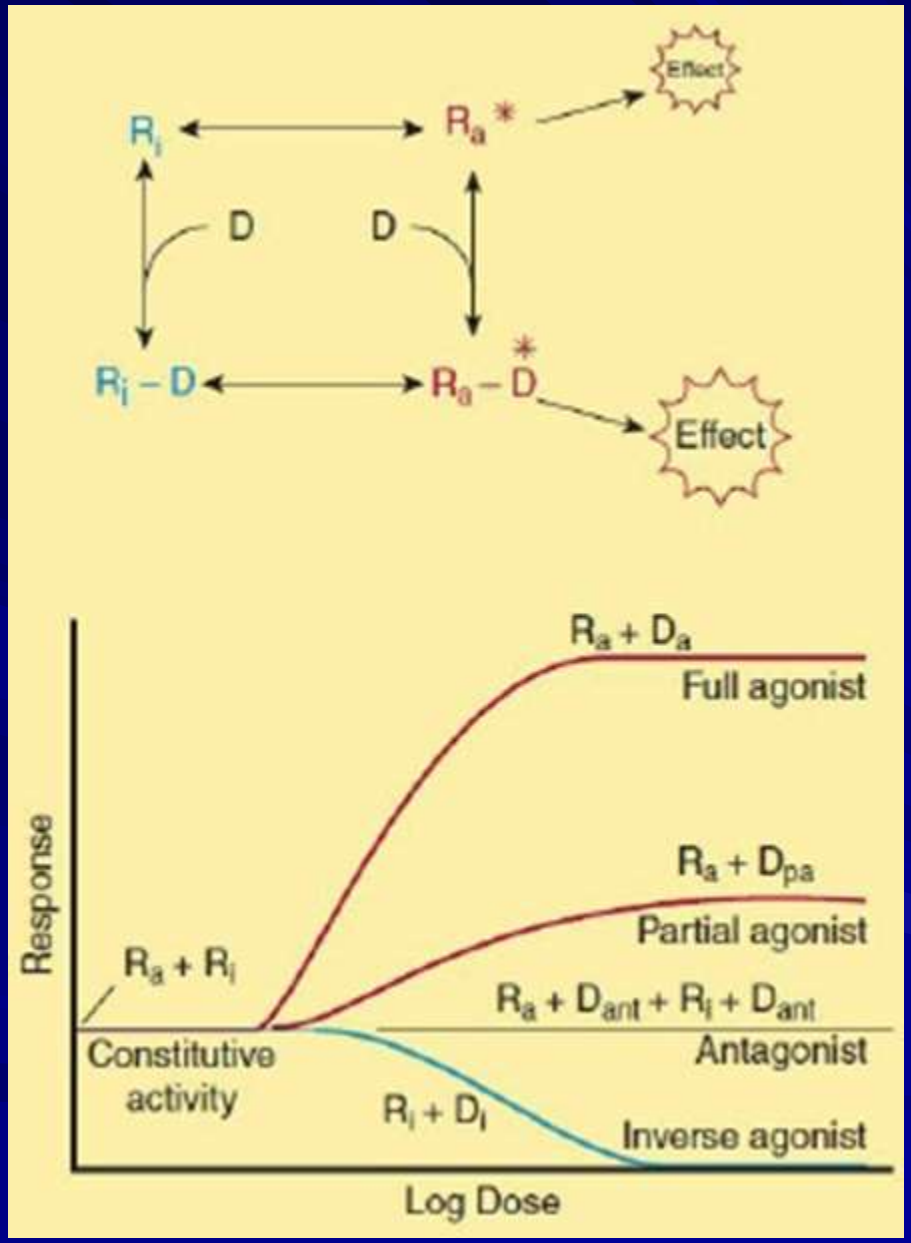
Ri & Ra

- **Ri** state, it is inactive and produces no effect (nonfunctional), even when combined with a drug (D) molecule.
- **Ra** state, it activates its effectors and an effect is recorded, even in the absence of ligand.

- In the absence of drug, the equilibrium between Ri and Ra determines the degree of constitutive activity.
- Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity

- A full agonist drug (Da) has a much higher affinity for the Ra than for the Ri receptor conformation, and a maximal effect is produced at sufficiently high drug concentration.
- A partial agonist drug (Dpa) has somewhat greater affinity for the Ra than for the Ri &produces less effect, even at saturating concentrations.
- A neutral antagonist (Dant) binds with equal affinity to both receptor conformations and prevents binding of agonist.
- An inverse agonist (Di) binds much more to the Ri receptor conformation, prevents conversion to the Ra state, and reduces constitutive activity

- The receptor is exist in the inactive, nonfunctional form (Ri) and in the activated form (Ra).
- Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist-induced activity.
- This effect, occurring in the absence of agonist, is termed constitutive activity.


Effect
R_i
R_a *
D
D
R_i – D
R_a – D
*
Effect
Response
$R_a + D_a$
Full agonist
$R_a + D_{pa}$
Partial agonist
$R_a + R_i$
$R_a + D_{ant} + R_i + D_{ant}$
Antagonist
Constitutive activity
$R_i + D_i$
Inverse agonist
Log Dose

A Model of Drug-receptor Interaction.

- The receptor is able to assume two conformations. In the Ri conformation, it is inactive and produces no effect, even when combined with a drug molecule.
- In the Ra conformation, the receptor can activate downstream mechanisms that produce a small observable effect, even in the absence of drug (constitutive activity).
- In the absence of drugs, the two isoforms are in equilibrium, and the Ri form is favored.
- Conventional full agonist drugs have a much higher affinity for the Ra conformation, and mass action thus favors the formation of the Ra-D complex with a much larger observed effect.

- **Partial Agonists** have an intermediate affinity for both Ri and Ra forms.
- **Conventional Antagonists**, according to this hypothesis, have equal affinity for both receptor forms and maintain the same level of constitutive activity.

Inverse Agonists

have a much higher affinity for the Ri form, reduce constitutive activity, and may produce a contrasting physiologic result

Examples:

- γ-aminobutyric acid (GABA) receptor-effector (a chloride channel)
- GABA (endogenous transmitter) causes inhibition of postsynaptic cells.
- Benzodiazepines also facilitate the &cause GABA-like inhibition (cause sedation)
- This sedation can be reversed by neutral antagonists such as flumazenil (Inverse agonists of this receptor system cause anxiety and agitation (the inverse of sedation)

Properties of an Ideal Drug

Effectiveness

Safety

Selectivity

Reversible action

Ease of administration

Freedom from drug Interactions

Low cost

Chemical Stability

Efficacy

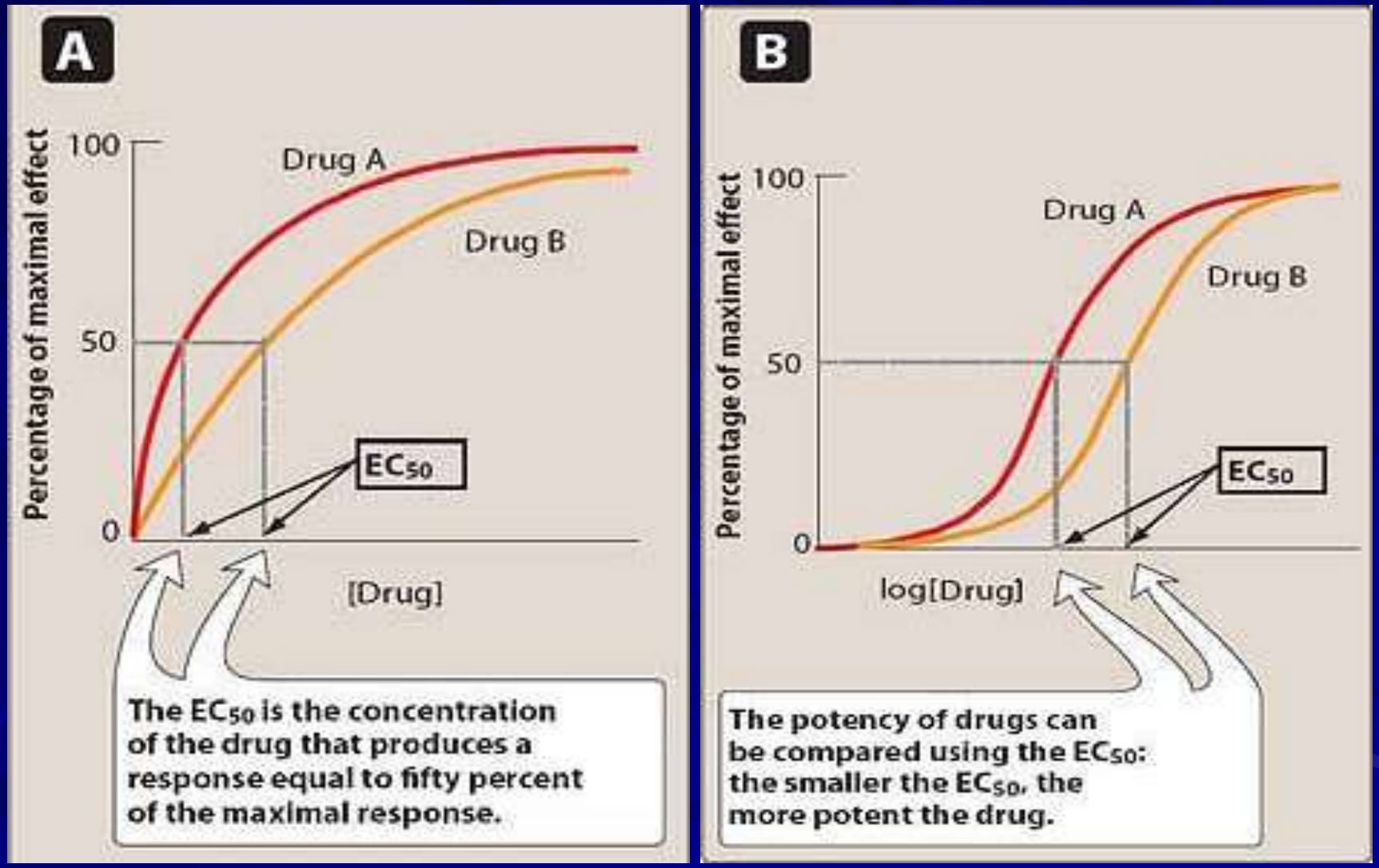
Is the capacity of a drug to produce a specific effect

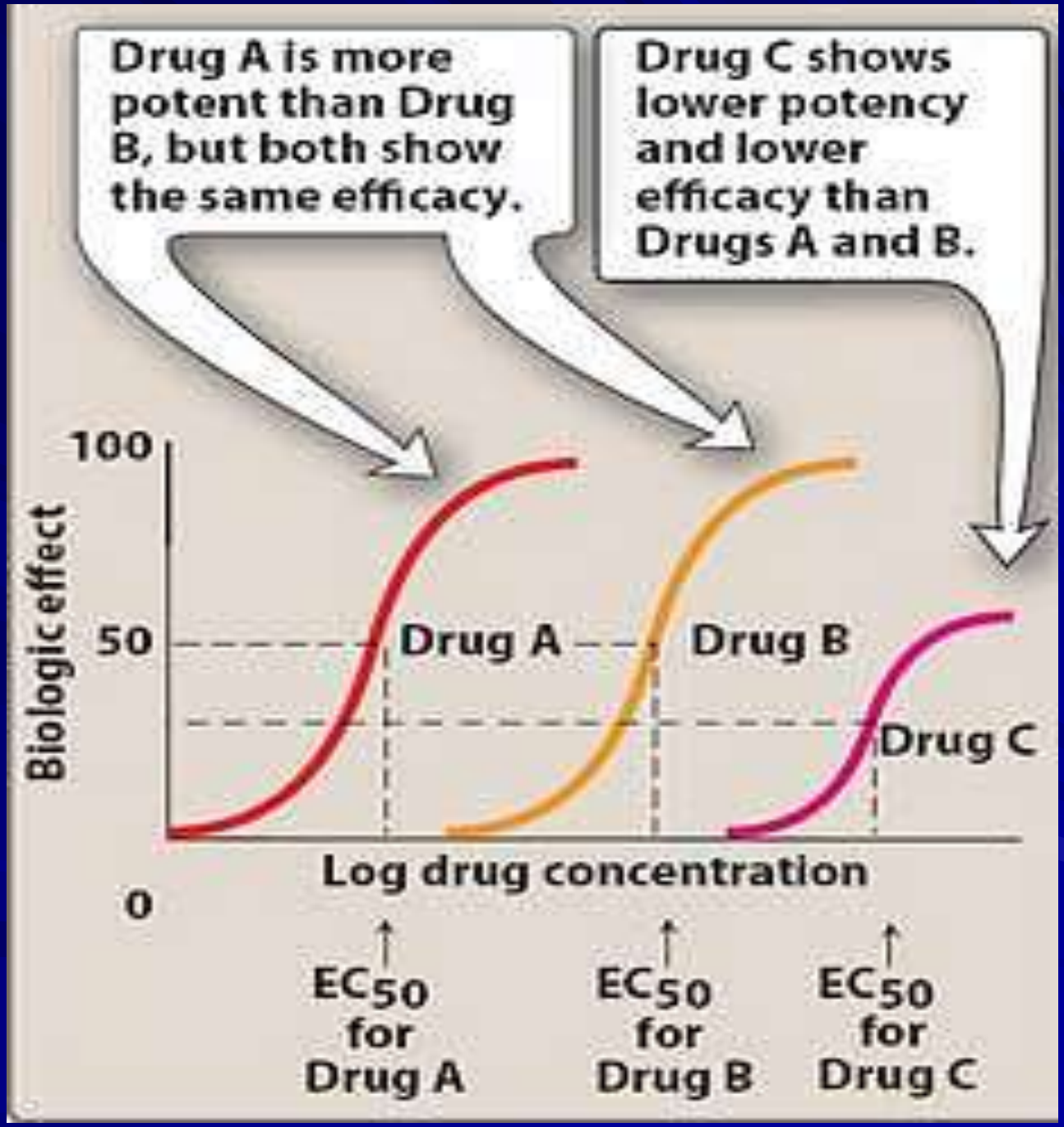
Potency

Refers to the amount of drug (in weight) that give an effect

Example

Morphine 10mg can relief severe pain, meperidine 100 mg can relief the same degree of pain relived by morphine, so morphine is more potent than meperidine.


A
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
[Drug]
The EC50 is the concentration of the drug that produces a response equal to fifty percent of the maximal response.
B
Percentage of maximal effect
100
50
0
Drug A
Drug B
EC50
log[Drug]
The potency of drugs can be compared using the EC50: the smaller the EC50, the more potent the drug.


Drug A is more potent than Drug B, but both show the same efficacy.
Drug C shows lower potency and lower efficacy than Drugs A and B.
100
50
0
Biologic effect
Drug A
Drug B
Drug C
Log drug concentration
EC50 for Drug A
EC50 for Drug B
EC50 for Drug C

Toxicology

It is part of pharmacology which deals with the undesired or toxic effect of drugs.

The therapeutic index

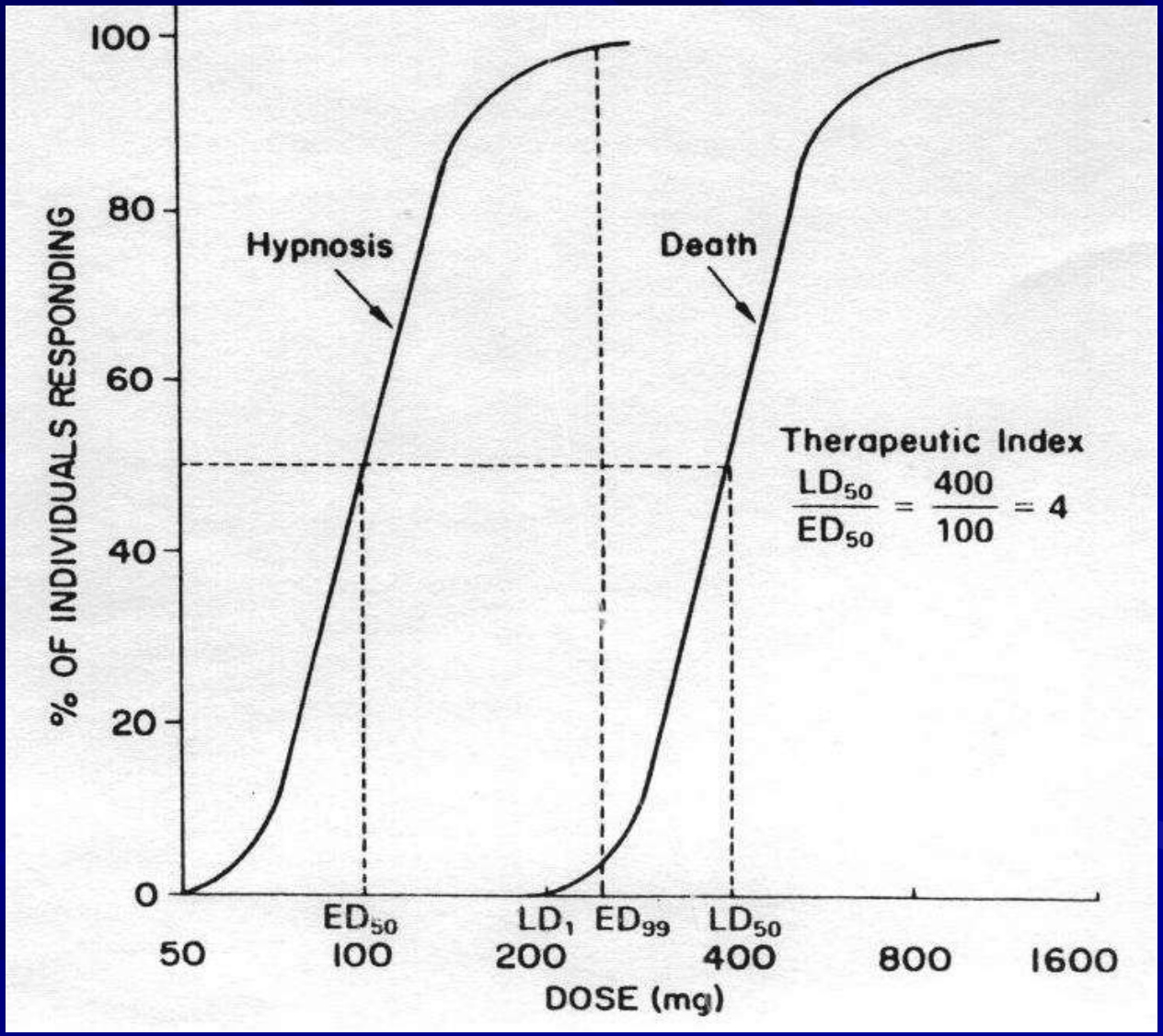
The ED 50 and LD50 are used to calculate an important value in pharmacology, the ratio of a drug's LD 50 and its ED 50 --- the higher the value, the safer the medication

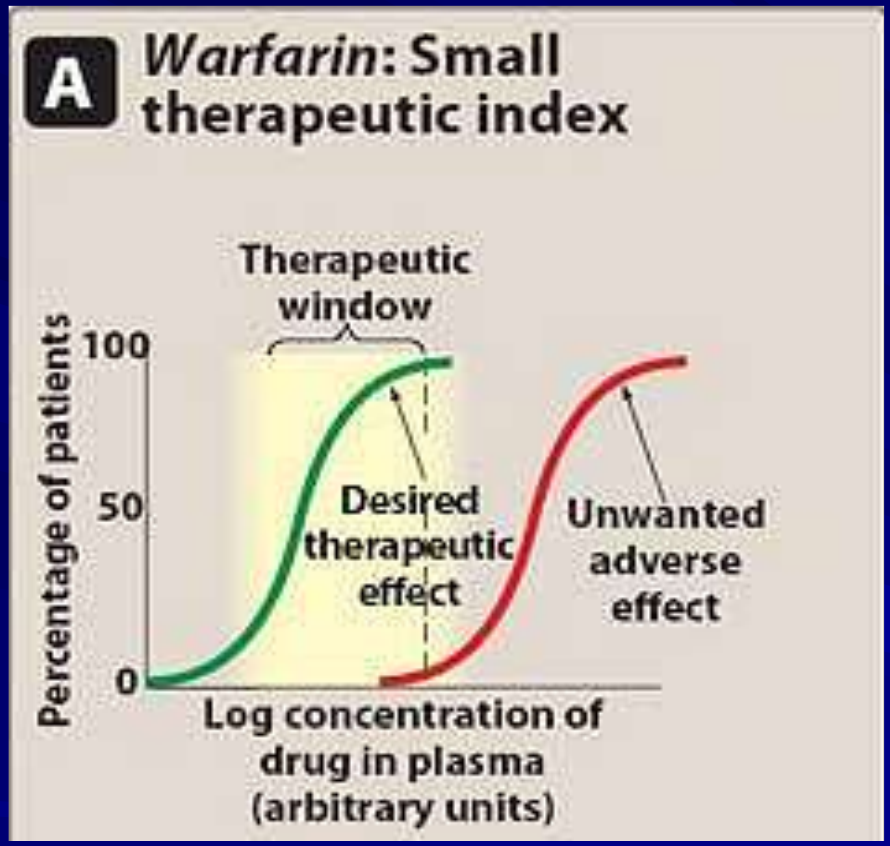
TI=LD50/ED50

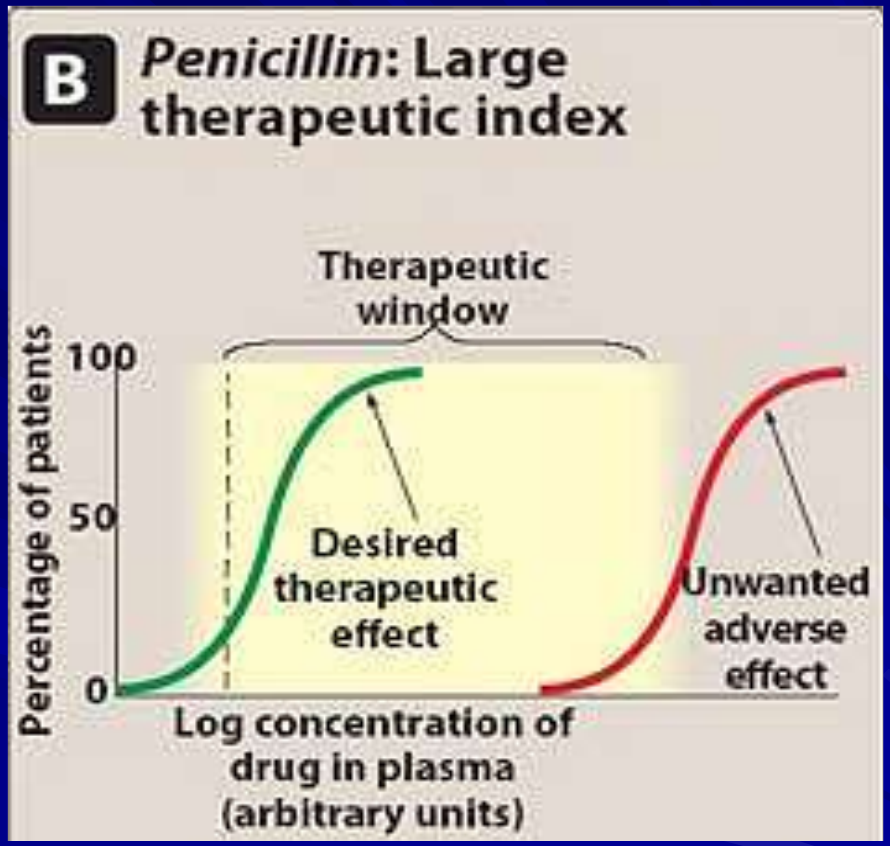
Median Lethal Dose (LD 50)

The dose of a chemical that causes death in 50% of the animals

- A large therapeutic index indicates that a drug is relatively safe.
- A small therapeutic index indicates that a drug is relatively unsafe


100
80
60
40
20
0
% OF INDIVIDUALS RESPONDING
Hypnosis
Death
Therapeutic Index
LD50 / ED50 = 400 / 100 = 4
ED50
LD1
ED99
LD50
50
100
200
400
800
1600
DOSE (mg)


A
Warfarin: Small therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)


B
Penicillin: Large therapeutic index
Therapeutic window
Percentage of patients
100
50
0
Desired therapeutic effect
Unwanted adverse effect
Log concentration of drug in plasma (arbitrary units)

Selectivity of Drug

Receptors are responsible for selectivity of drug action.

The molecular size, shape and electrical charge of a drug determine, changes in the chemical structure of a drug can dramatically increase or decrease a new drug's affinities for different classes of receptors, with resulting alterations in therapeutic and toxic effects.

The sensitivity of a cell or tissue to a particular concentration of agonist depends on:

- The affinity of the receptor for binding the agonist
- The degree of spareness (the total number of receptors present compared with the number actually needed to elicit a maximal biologic response)

- Some agonists activate a single kind of receptor to produce all their biologic functions
- Others selectively promote one receptor function more than another
- Other antagonists, in addition to preventing agonist binding, suppress the **“constitutive” activity** (basal signaling) of receptors

Orphan Receptors

Their ligands are presently unknown; these may be useful targets for future drug development

Macromolecular Nature of Drug Receptors

- **Regulatory proteins**
  Which mediate the actions of endogenous chemical signals such as neurotransmitters, autacoids and hormones
- **Enzymes**
  Which may be inhibited or activated (less commonly) by binding a drug

Example

Dihydrofolate reductase, the receptor for the antineoplastic drug methotrexate)

- **Transport proteins**

Example

Na+/K+-ATPase, the membrane receptor for cardioactive digitalis glycosides)

- **Structural proteins**

Example

- Tubulin, the receptor for colchicine, an anti-inflammatory agent).

Concentration-Effect Curves & Receptor Binding of Agonists

- E is the effect observed at concentration C
- E max: is the maximal response that can be produced by the drug.
- EC50: is the concentration of drug that produces 50% of maximal effect.

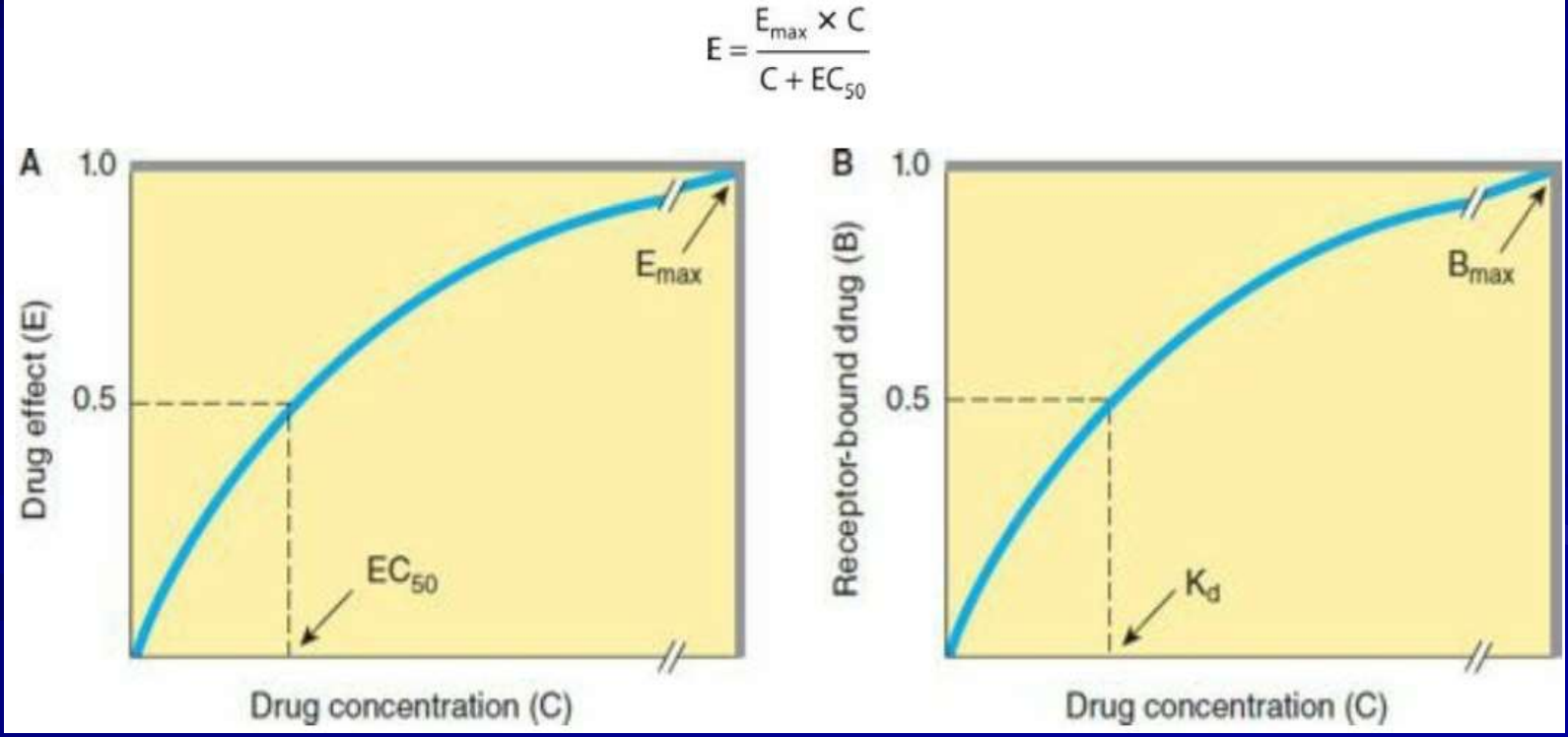
- **Kd (the equilibrium dissociation constant) : The concentration of drug that binds 50% of the receptors in the system**

Note: If the Kd is low, binding affinity is high, and vice versa.

- **Bmax**: Indicates the total concentration of receptor sites (ie, sites bound to the drug at infinitely high concentrations of free drug)

(A)Relations between drug concentration and drug effect

(B)Relations between drug concentration and receptor-bound drug



$$E = \frac{E_{max} \times C}{C + EC_{50}}$$

$$B = \frac{B_{max} \times C}{C + K_d}$$

Note:

- This relation resembles the mass action law that describes the association between two molecules of a given affinity.
- This resemblance suggests that drug agonists act by binding to ("occupying") a distinct class of biologic molecules with a characteristic affinity for the drug receptor.

The Kd of the agonist-receptor interaction determines what fraction (B/Bmax) of total receptors will be occupied at a given free concentration (C) of agonist regardless of the receptor concentration

$$\frac{B}{B_{max}} = \frac{C}{C + K_d}$$

The sensitivity of a cell or tissue to a particular concentration of agonist depends on:

- The affinity of the receptor for binding the agonist
- The degree of spareness (the total number of receptors present compared with the number actually needed to elicit a maximal biologic response

Spare Receptors

If it is possible to elicit a maximal biologic response at a concentration of agonist that does not result in occupancy of the full complement of available receptors.

Example

The same maximal inotropic response of heart muscle to catecholamines can be elicited even when 90% of the β adrenoceptors are occupied by a irreversible antagonist, this mean myocardial cells contain a large proportion of spare β adrenoceptors.

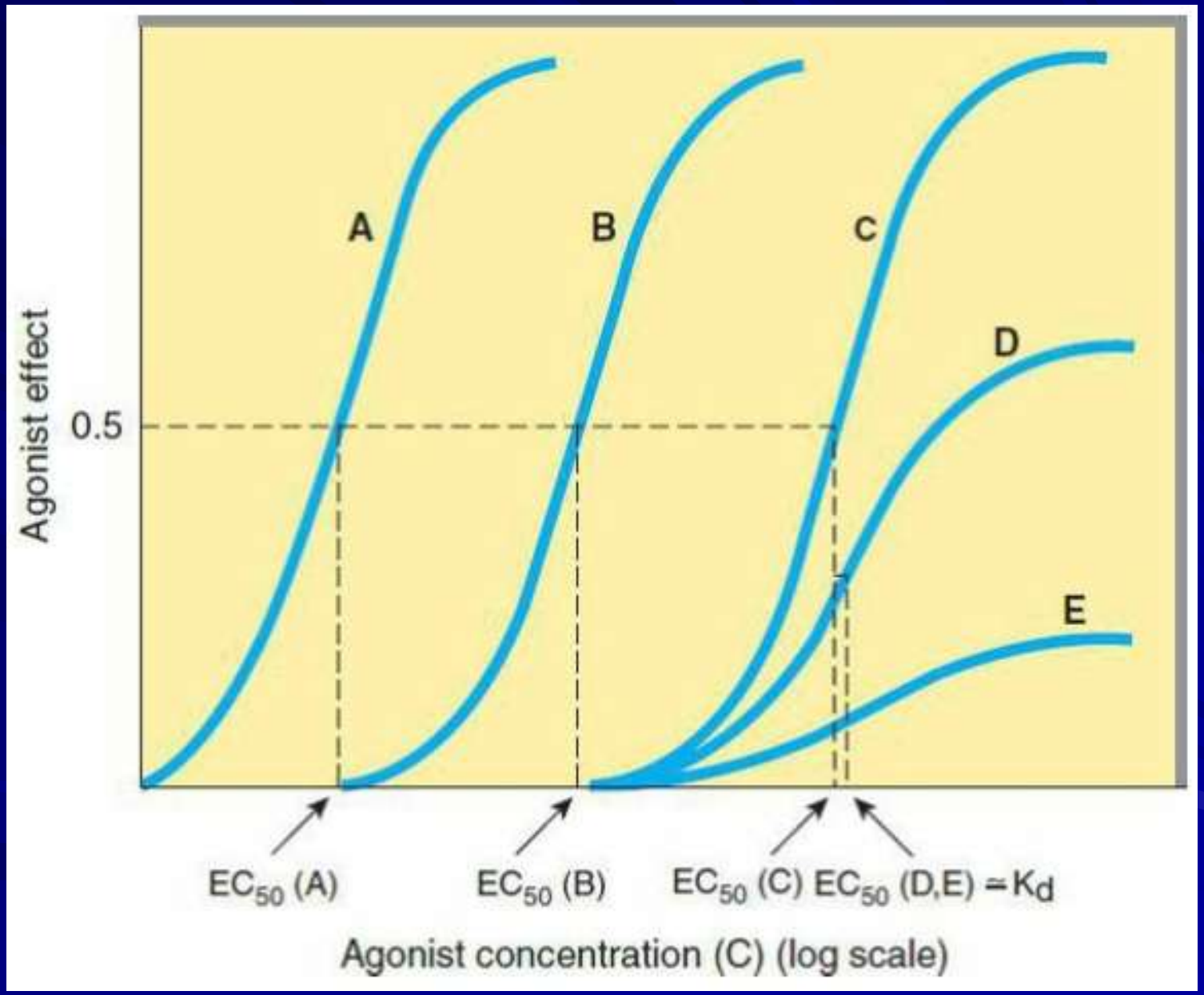
Spare receptors

Experimental demonstration of spare receptors, using different concentrations of an irreversible antagonist.

- **Curve A** shows agonist response in the absence of antagonist.
- **Curve B** After treatment with a low concentration of antagonist, the curve is shifted to the right. Maximal responsiveness is preserved, however, because the remaining available receptors are still in excess of the number required.

- Curve C produced after treatment with a larger concentration of antagonist, the available receptors are no longer “spare”; they are just sufficient to mediate an undiminished maximal response.
- Curves D and E ,Still higher concentrations of antagonist ,reduce the number of available receptors to the point that maximal response is diminished.

Note: The apparent EC50 of the agonist in curves D and E may approximate the Kd that characterizes the binding affinity of the agonist for the receptor


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

some antagonists exhibit “inverse agonist” activity ,because they also reduce receptor activity below basal levels observed in the absence of any agonist at all.

Chemical Antagonist

Some types of antagonism do not involve a receptor

Example

Protamine, a protein that is positively charged at physiologic pH, can be used clinically to counteract the effects of heparin, an anticoagulant that is negatively charged.

In this case, one drug acts as a chemical antagonist of the other simply by ionic binding that makes the other drug unavailable for interactions with proteins involved in blood clotting.

Physiologic Antagonism

mediated by different receptors

Example

Elevated glucocorticoid by endogenous synthesis (a tumor of the adrenal cortex) or as a result of glucocorticoid therapy, several catabolic actions of the glucocorticoid hormones lead to increased blood sugar, an effect that is physiologically opposed by insulin.

- The clinician administer insulin to oppose the hyperglycemic effects of a glucocorticoid hormone

Note:

Physiologic antagonist produces effects that are less specific and less easy to control than
are the effects of a receptor-specific antagonist.

Example

- To treat bradycardia caused by increased release of acetylcholine from vagus nerve endings, the physician could use isoproterenol, a β-adrenoceptor agonist that increases heart rate by mimicking sympathetic stimulation of the heart.
- Use of this physiologic more dangerous than use of a receptor-specific antagonist such as atropine (a competitive antagonist at the receptors at which acetylcholine slows heart rate).

Down Regulation:

- When the receptors of a cell are continuously exposed to an agonist, the cell usually becomes less responsive.

Up Regulation:

- Continuous exposure to antagonists has the opposite effect, causing the cell to become hypersensitive (supersensitive)