Principles of Pharmacokinetics and Pharmacodynamics

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PHARMACOKINETICS
"The actions of the body on the drug…"

VS

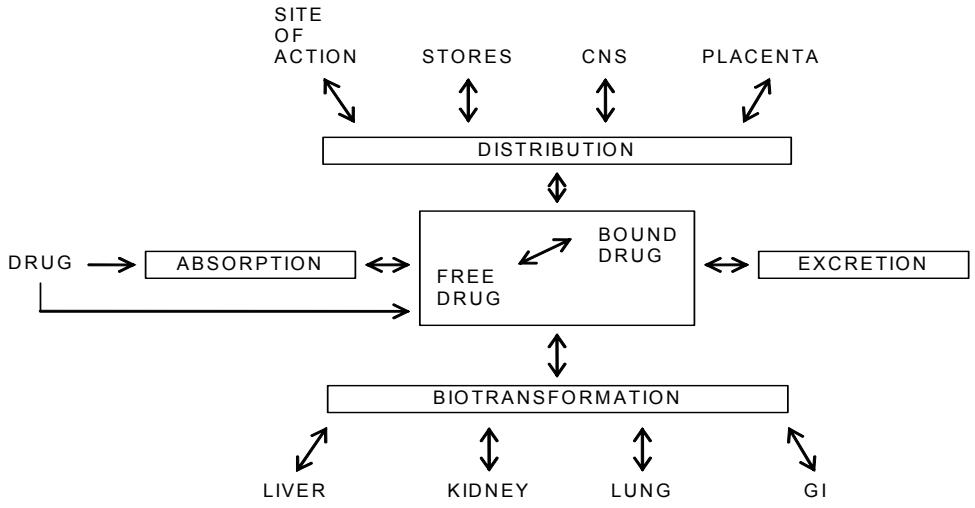
PHARMACODYNAMICS
"The actions of the drug on the body…"

Katzung, 8th ed., pg. 4

PHARMACOKINETICS:	PHARMACODYNAMICS
Absorption	Mechanism(s) of action
Distribution	Organ System Effects
Metabolism	Therapeutic Effects
Elimination	Side Effects / Toxicities

PHARMACOKINETICS

Pathways of Drug Disposition



Drug Absorption

Drugs cross biological membranes via one or more of the following mechanisms:

- Passive Diffusion
- Active Transport
- Facilitated Diffusion
- Pore Transport

Absorption of Drugs

- Most lipid-soluble drugs pass through biological membranes by simple diffusion
- Fick's law (Equation 1)

$$\frac{dD}{dt} = \frac{KA(C_m - C_s)}{X}$$

where:

dD/dt	=	rate of diffusion
K	=	a constant with units of cm^2/min
A	=	area of the membrane exposed to the drug solution
C_m	=	drug concentration in the GI lumen
C_s	=	drug concentration in the GI blood
X	=	thickness of the membrane

Henderson-Hasselbalch Equation

$$pKa - pH = log\left(\frac{protonated}{unprotonated}\right)$$

Two variations of the Henderson-Hasselbalch equation are:

For acidic drugs

$$pK_a - pH = \log(D_u / D_i)$$

For basic drugs

$$pK_a - pH = \log(D_i / D_u)$$

where:

pK_a	=	the dissociation constant of the drug
pH	=	pH of the milieu in which the drug is dissolved
D_u	=	the concentration of un-ionized drug
D_i	=	the concentration of ionized drug

Partition Coefficient

Table 1

The Effects of Partition Coefficient on Absorption of Drugs with Similar pK_a

	pKa	Partition Coefficient	% Absorbed
Barbital	7.8	0.7	12
Aprobarbital	7.5	4.9	17
Phenobarbital	7.4	4.8	20
Cyclobarbital	7.5	11.7	24
Pentobarbital	8.0	28.0	30
Secobarbital	7.9	50.7	40

Characteristics of Active Transport

1) movement occurs against a concentration gradient.

2) rate is proportional to drug concentration only when the carrier is not saturated.

3) specificity for a particular type of chemical structure.

4) occurs from a specific site in a limited segment of the small intestine.

5) competitive inhibition for structurally similar substrates transported by the same transport mechanism

6) inhibited noncompetitively by substances that interfere with cell metabolism.

Facilitated Diffusion and Pore Transport

- Facilitated Diffusion

  Substrate is not transported against a concentration gradient

- Pore Transport

  Diffusion via an aqueous-filled pore or channel

Factors Influencing Drug Distribution

- physiochemical characteristics of the drug
- cardiac output
- regional blood flow
- Tissue-dependent factors:

  pH gradient, active transport, non-specific binding, dissolution in fat

Drug Reservoirs

- Plasma proteins

  binding primarily to albumin

  binding is usually reversible

  organic acids and bases bind different sites

  prior to equilibrium reduces free drug concentration in plasma

  nonselective and competitive binding

Drug Reservoirs

- Cellular Reservoir
  - accumulation may be the result of binding or active transport
  - binding is generally reversible
- Fat
  - important reservoir for lipid-soluble drugs
  - may affect onset and duration of action

Distribution across blood-brain barrier

- CNS capillaries are not fenestrated
- CNS capillaries are surrounded by a astrocytic sheath
- resists the movement of water-soluble and ionized drugs into CNS
- CSF proteins do not function as drug reservoir

Distribution across placenta

- Placenta is highly permeable to drugs
- Distribution primarily by simple diffusion
- Nutrients, as wells as drugs of abuse (e.g., alcohol, cocaine), readily cross placenta

Drug Metabolism

- Primary site of biotransformation is the liver
- Products generally have lower biological activity
- Products are usually more polar, facilitating renal excretion
- Two major categories: phase I and phase II

First-pass effect (first-pass elimination)

- Biotransformation (usually to a less active compound) of a drug prior to its entry into the systemic circulation is termed “first-pass effect.”
- The most common site of first-pass effect is the liver; drugs absorbed from the GI tract are transported via the portal blood to the liver, where they may be metabolized.

Drug Elimination

- Primary site of drug elimination is the kidneys
- Several other sites exist; excretion into bile is most important of these secondary sites
- In most cases, the rate of elimination is proportional to the free drug concentration in the plasma.

Drug Interactions

- May yield increased or decreased drug effects
- Three types:
  1. physicochemical
  2. pharmacodynamic
  3. pharmacokinetic

PHARMACODYNAMICS

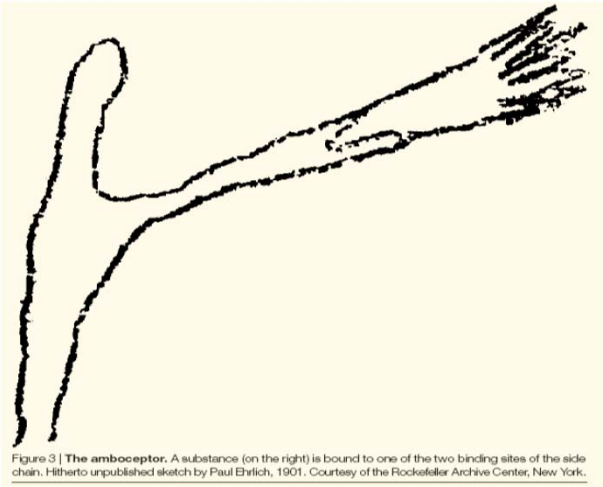


Figure 3 | **The amboceptor.** A substance (on the right) is bound to one of the two binding sites of the side chain. Hitherto unpublished sketch by Paul Ehrlich, 1901. Courtesy of the Rockefeller Archive Center, New York.

3 levels of consideration

1. Molecular Level :
   Drug-Receptor Interactions
2. Cellular and Tissue Physiology Level :
   Graded Dose-Response Curves
3. Clinical Therapeutics Level :
   Quantal Dose-Response Curves

1. Molecular Level :
Drug-Receptor Interactions

RECEPTOR

- A structure that recognizes endogenous or exogenous compounds (ligands) with high selectivity.
- Binding of the appropriate ligand to a receptor initiates (or terminates) a physiologic process.

AGONIST & ANTAGONIST

- **AGONIST:** A drug that mimics the effects of the endogenous ligand for a receptor
- **ANTAGONIST:** A drug, which does not itself have intrinsic activity, but which interferes with the binding of the endogenous ligand (or an agonist) to a receptor

BONDING FORCES

5 Van der Walls

4 Hydrophobic

3 Hydrogen

2 Ionic

1 Covalent

weakest

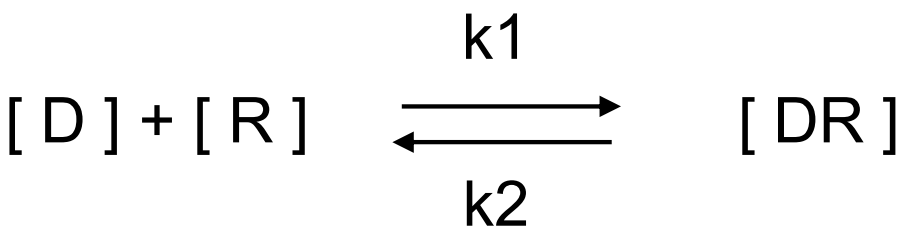
strongest

AFFINITY

The affinity of a receptor for a particular drug is determined by:

1. The number of interacting sites
2. The types of forces that are involved in the binding interactions

EQUATION DESCRIBING REVERSIBLE DRUG – RECEPTOR INTERACTION



Equations describing the dissociation constant (Kd); note that the Kd is also called the "affinity" constant

$K_d = k_2 / k_1$

K_d = rate of DR dissociation / rate of DR association

K_d = "off" rate / "on" rate

It can be shown that, when [DR] = 0.5 X [R_{total}],

K_d = [D]

Thus, the K_d is the concentration of drug at which one-half of the total # of receptors are bound by drug

AFFINITY

The affinity (K_d) of a drug for a receptor is the concentration of drug that occupies half of the total number of available receptors [R_T].

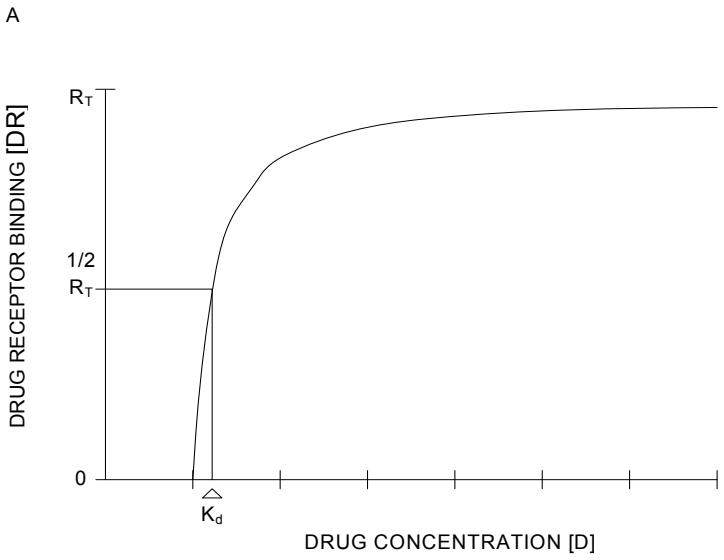
The lower the molar concentration value of K_d for a given drug, the higher that drug's affinity for the receptor.

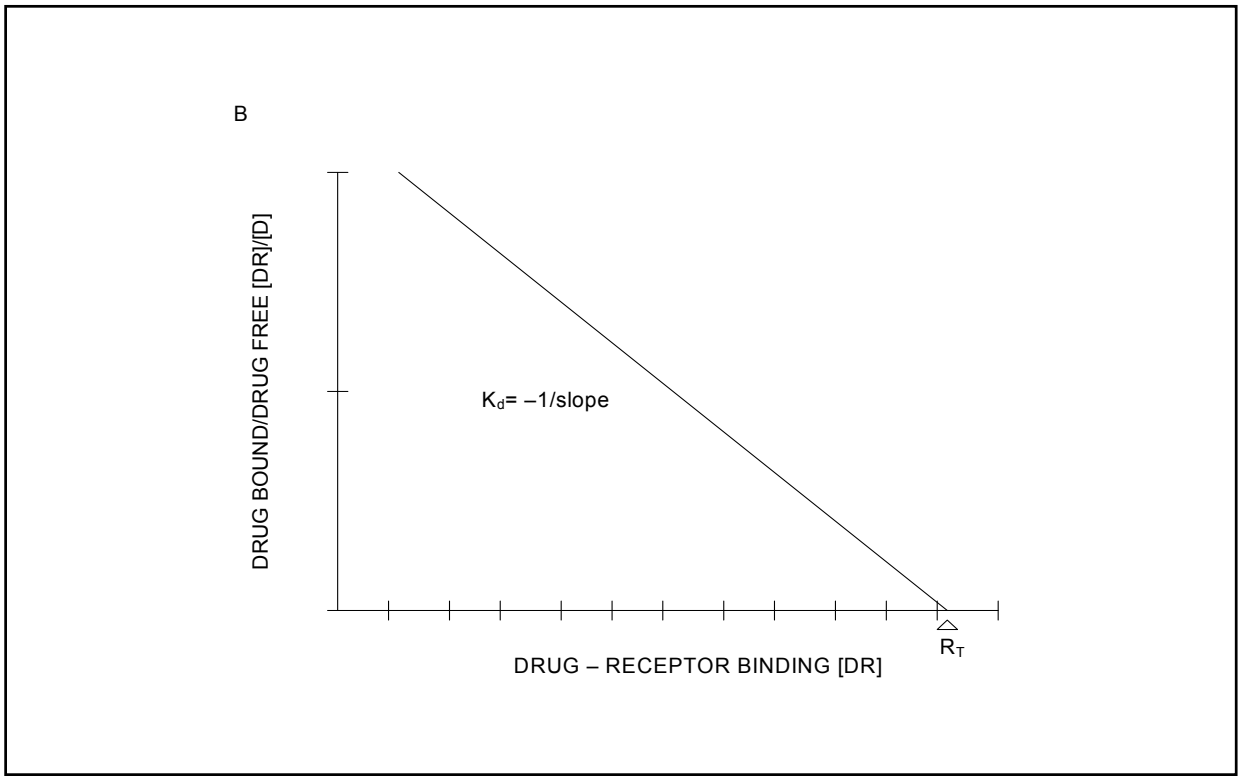
Kd values

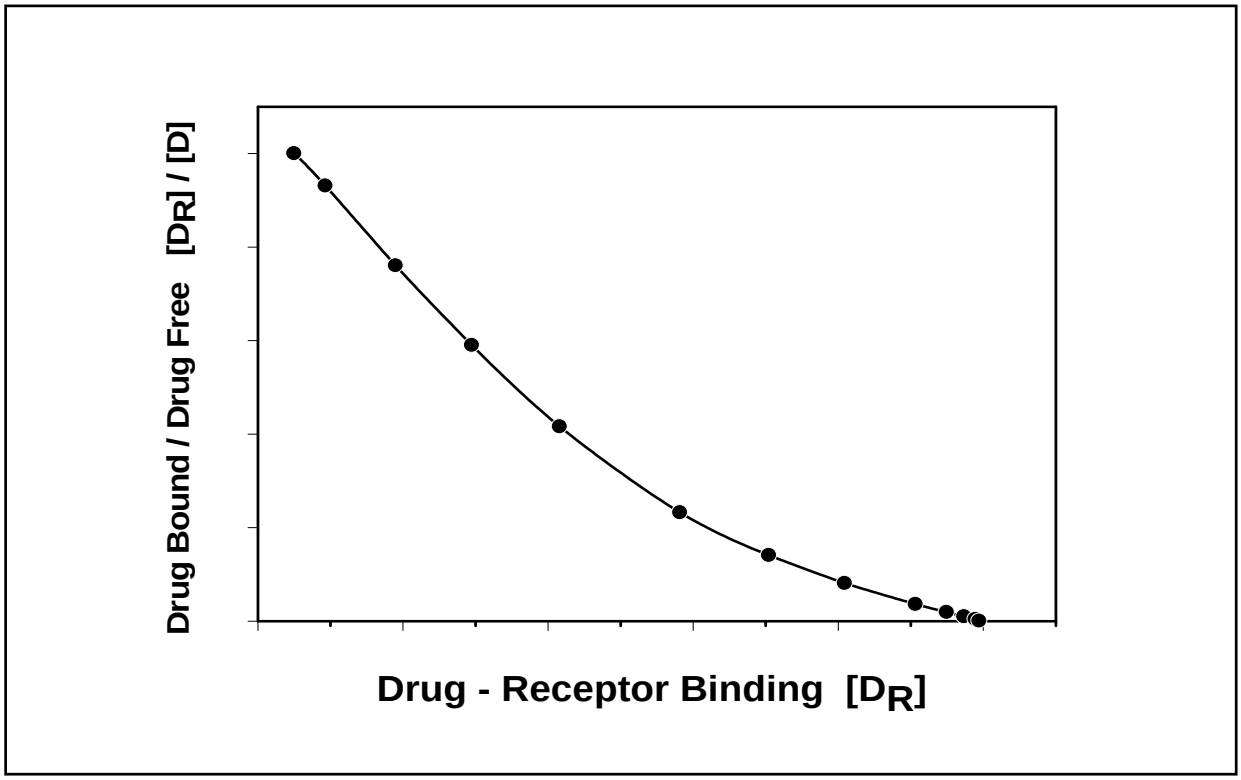
Which of the following drugs has a higher affinity for the (same) receptor?

- Drug A $K_d = 10^{-8}$ M
- Drug B $K_d = 10^{-7}$ M
- Drug C $K_d = 3 \times 10^{-8}$ M
- Drug D $K_d = 10^{-6}$ M

$$DR = \frac{([R_T])([D])}{(K_d) + ([D])}$$

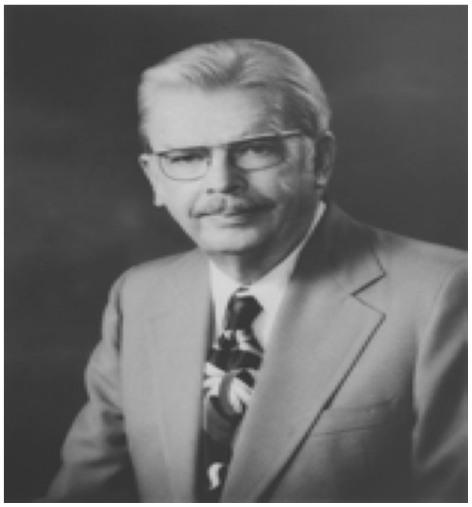



B
DRUG BOUND/DRUG FREE [DR]/[D]
K_d= –1/slope
R_T
DRUG – RECEPTOR BINDING [DR]


Drug Bound / Drug Free [D_R] / [D]
Drug - Receptor Binding [D_R]

Raymond P Ahlquist (1914-1983); concept of receptor subtypes

- In 1948 Ahlquist noted that the relative potencies of (-)-noradrenaline and (-)-adrenaline differed and proposed the existence of α- and β-subtypes of adrenergic receptors.



Decreasing Response to Drugs With Sustained Exposure

RECEPTOR DESENSITIZATION

Time Course : Seconds to Minutes
Mechanism : Receptor Phosphorylation
Effect : Decreased Affinity

RECEPTOR DOWN-REGULATION

Time Course : Hours to Days
Mechanism : Receptor Turnover
Effect : Decreased Receptor Number

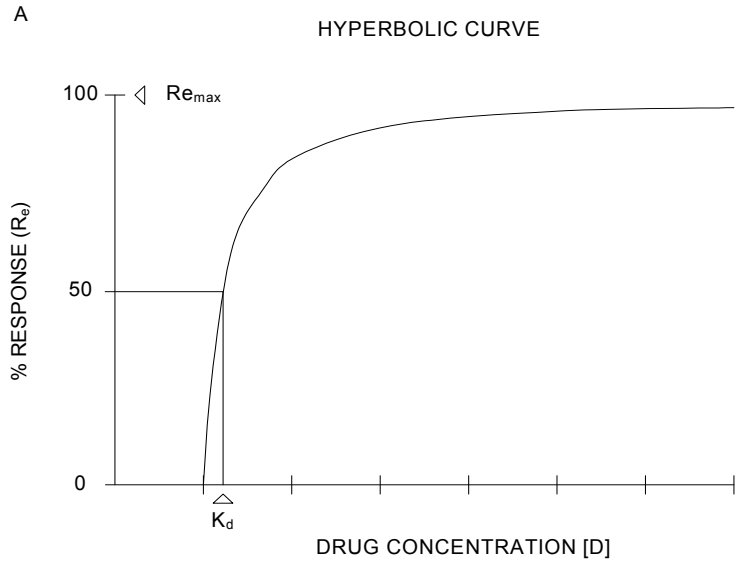
2 Cellular and Tissue Physiology Level :
Graded Dose-Response Curves

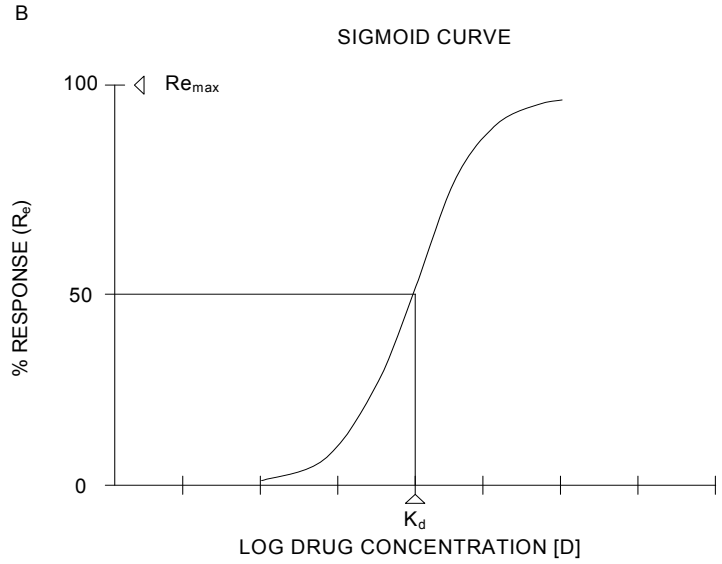
$$[DR] \xrightarrow{\gamma} \mathrm{Re}$$

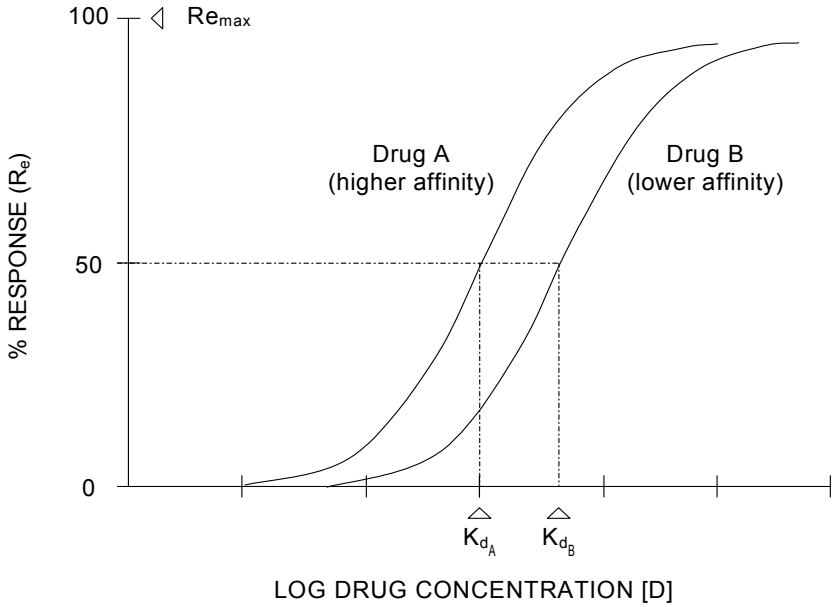
$$\mathrm{R_e} = \gamma [DR]$$

$$R_e = \frac{\gamma\left([R_T]\right)\left([D]\right)}{\left(K_d\right) + \left([D]\right)}$$

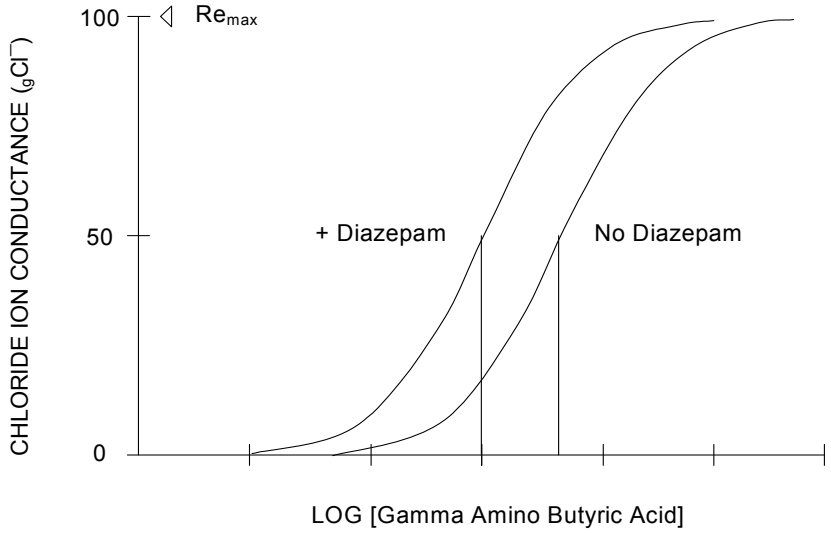
A




B
SIGMOID CURVE
100
Remax
% RESPONSE (Re)
50
0
Kd
LOG DRUG CONCENTRATION [D]


100
Remax
Drug A
(higher affinity)
Drug B
(lower affinity)
% RESPONSE (Re)
50
0
KdA
KdB
LOG DRUG CONCENTRATION [D]

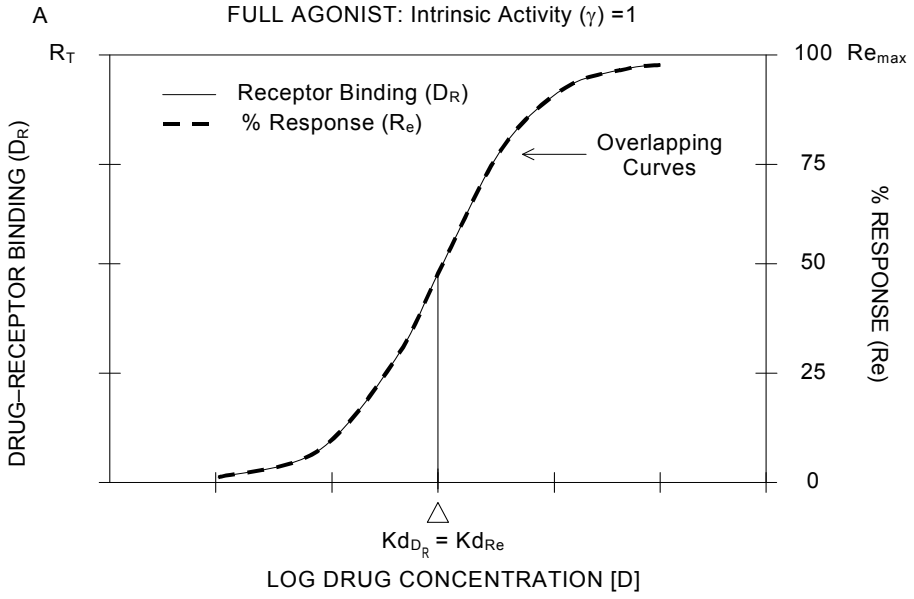
Effect of a positive allosteric modulator on an agonist log drug-response curve

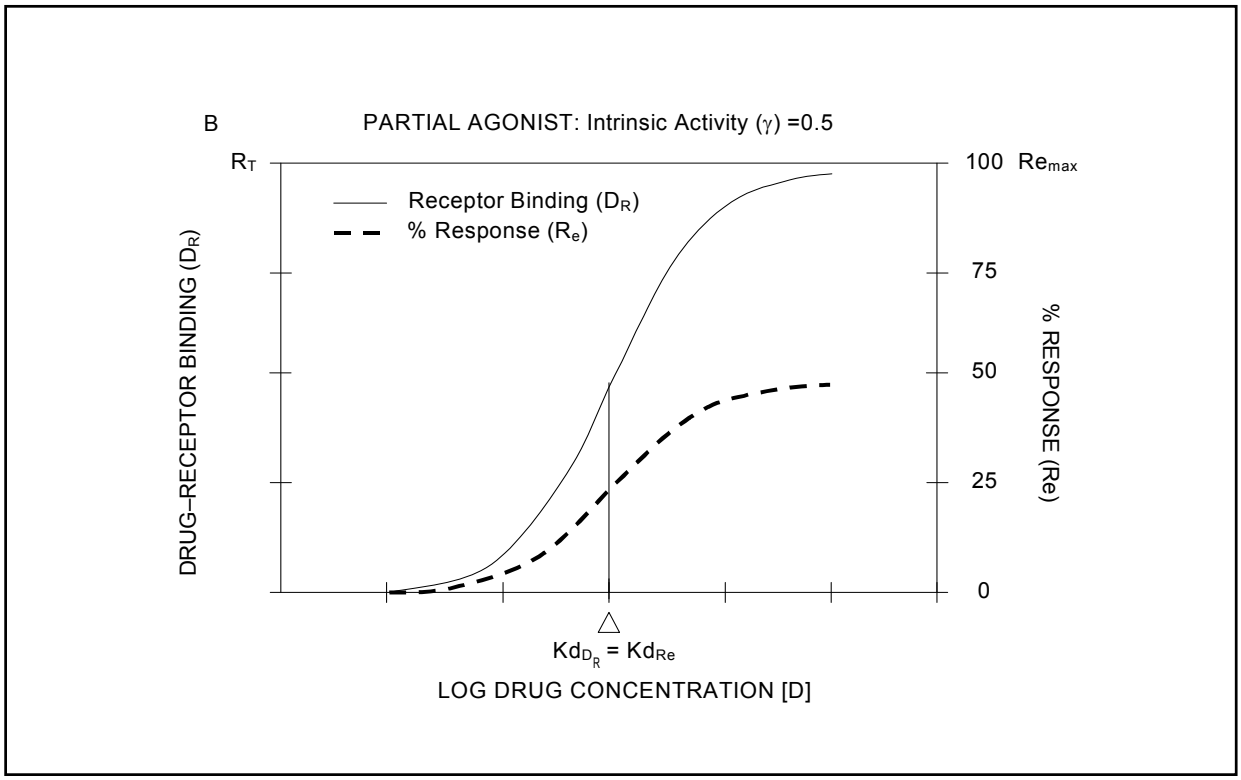


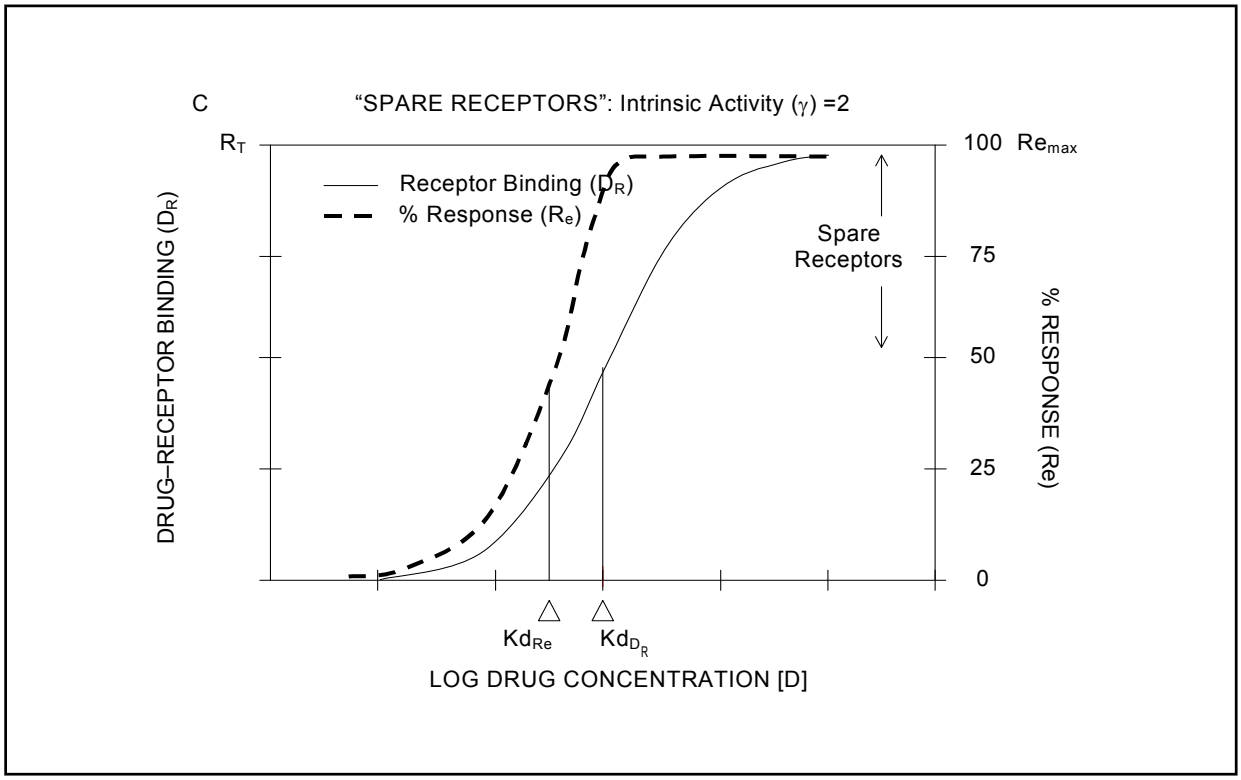
$$R_e = \frac{\gamma\left([R_T]\right)\left([D]\right)}{\left(K_d\right) + \left([D]\right)}$$

AGONIST

By definition, a drug that is capable of eliciting a response after interaction with a receptor has an intrinsic activity greater than zero. Drugs that have an intrinsic activity greater than zero are called *agonists*.



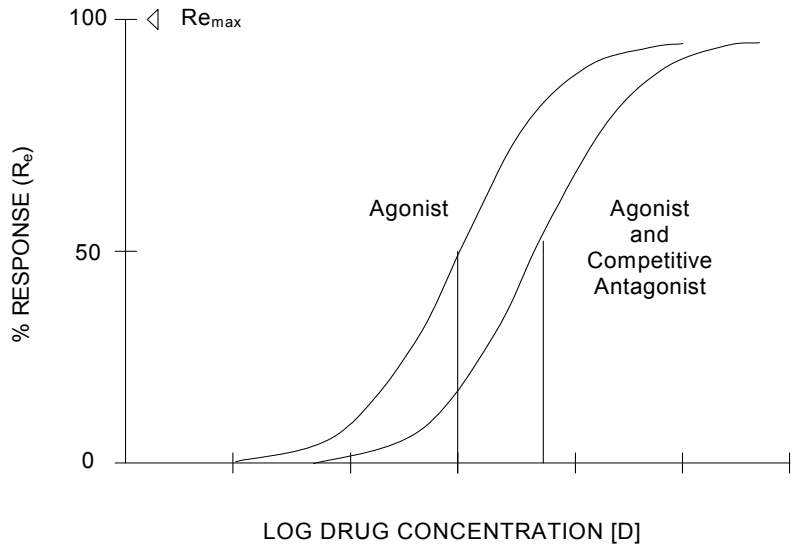

B
PARTIAL AGONIST: Intrinsic Activity (γ) =0.5
R_T
100 Re_{max}
Receptor Binding (D_R)
% Response (R_e)
DRUG–RECEPTOR BINDING (D_R)
% RESPONSE (Re)
75
50
25
0
$Kd_{D_R} = Kd_{Re}$
LOG DRUG CONCENTRATION [D]

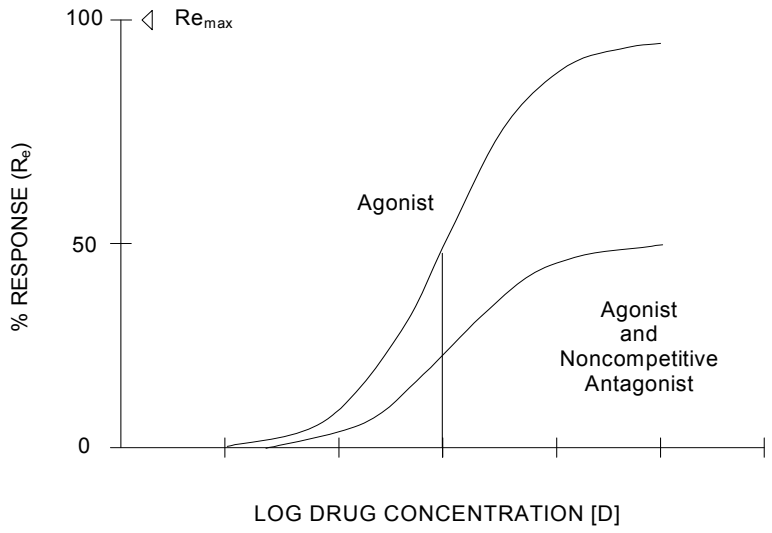

C
"SPARE RECEPTORS": Intrinsic Activity (γ) =2
R_T
100 Re_{max}
Receptor Binding (D_R)
% Response (R_e)
Spare
Receptors
DRUG–RECEPTOR BINDING (D_R)
% RESPONSE (Re)
75
50
25
0
Kd_{Re}
Kd_{D_R}
LOG DRUG CONCENTRATION [D]

RECEPTOR ANTAGONIST

An *antagonist* is a drug that can bind to a receptor but has an intrinsic activity of zero.

It occupies a receptor, but does not elicit a response.





OTHER FORMS OF "ANTAGONISM"

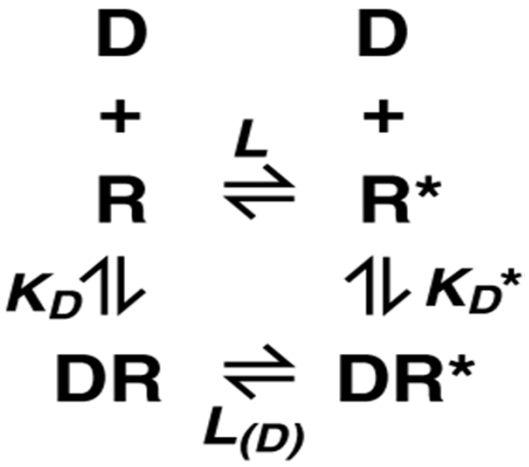
1. PHYSIOLOGICAL

2. "THERAPEUTIC WINDOWS"

More complex model of drug-receptor interactions: concepts of inverse agonists and agonist-directed trafficking of receptor signaling

Two-state receptor model

- A schematic representation of the two-state receptor model. R, R*, DR and DR* are in constant equilibrium, where D is the drug, R is the receptor in the inactive state, R* is the receptor in the active state, and DR and DR* are the respective drug-receptor complexes (drug-bound receptor). K_D, K_D*, L and $L_{(D)}$ are kinetic constants describing the equilibrium between the respective states. In particular, K_D and K_D* describe the affinity (binding power) of the drug for the receptor in its inactive and active states, respectively



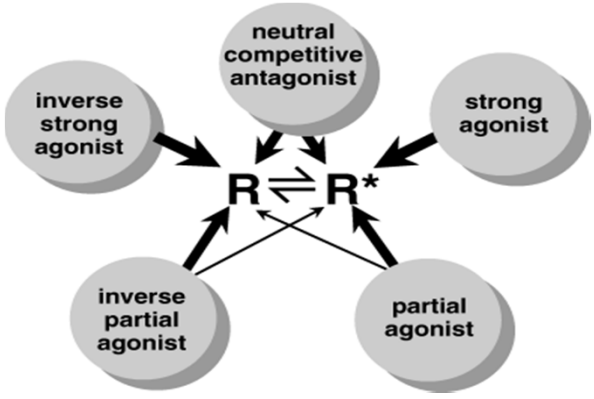
Brink et al 2004 Br J Clin Pharmacol

Inverse agonist

- The binding of an inverse agonist to a receptor that has constitutive (basal, ligand-independent) activity results in inhibition of the agonist-independent activity. Constitutive activity corresponds to the R^* conformation in the two-state receptor model (see next slide).
- Long-term treatment with an inverse agonist may lead to receptor up-regulation.

Agonists and antagonists in the context of the two-state model

- A schematic representation of how the two-state receptor model relates to the action of drugs as strong agonists, partial agonists, neutral competitive antagonists, inverse agonists, and inverse partial agonists. The inactive and active receptor conformations (R and R*, respectively) are in constant equilibrium. A strong agonist binds selectively to R*, driving the equilibrium between R and R* in favour of R*, resulting in enhanced response. A partial agonist has higher affinity for R* than for R, but with less selectivity than the strong agonist. The neutral competitive antagonist binds with equal affinity to both R and R*, so that it does not disturb the resting equilibrium and therefore does not alter basal response. An inverse strong agonist binds selectively to R, driving the equilibrium between R and R* in favour of R, resulting in decreased response, that is, when there is significant constitutive activity (basal response). An inverse partial agonist has higher affinity for R than for R*, but with less selectivity than the strong inverse agonist



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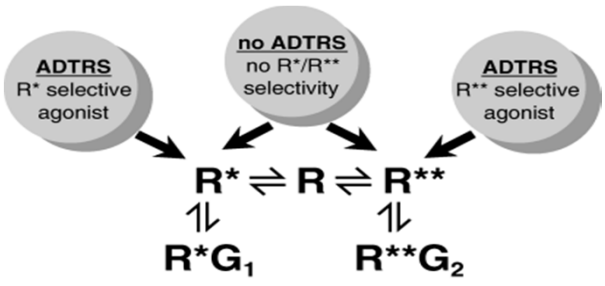
Concept of agonist-directed trafficking of receptor signaling

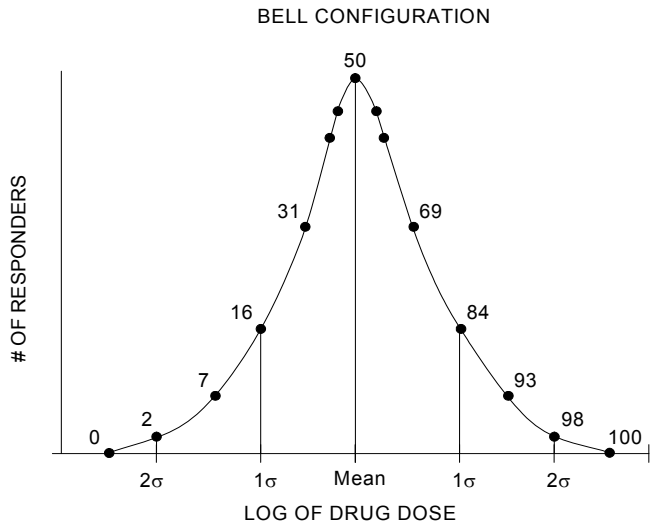
- Some receptors (e.g., certain GPCRs) have been shown to couple to more than one signal transduction pathway (e.g., to more than one G-protein).
- Some agonists at these receptors differentially control the coupling of these receptor to these differing signaling pathways (e.g., by promoting coupling of the receptor to a G_s protein, rather than a G_i protein).
- The actions of these ligands can be explained by using a model of drug-receptor interactions that includes differing activation states of the receptor (R^* and R^{**}). These differing activation states couple to different signaling pathways and likely represent differing conformational states of the ligand-receptor complex.

Three-state model and agonist-directed trafficking of receptor signaling

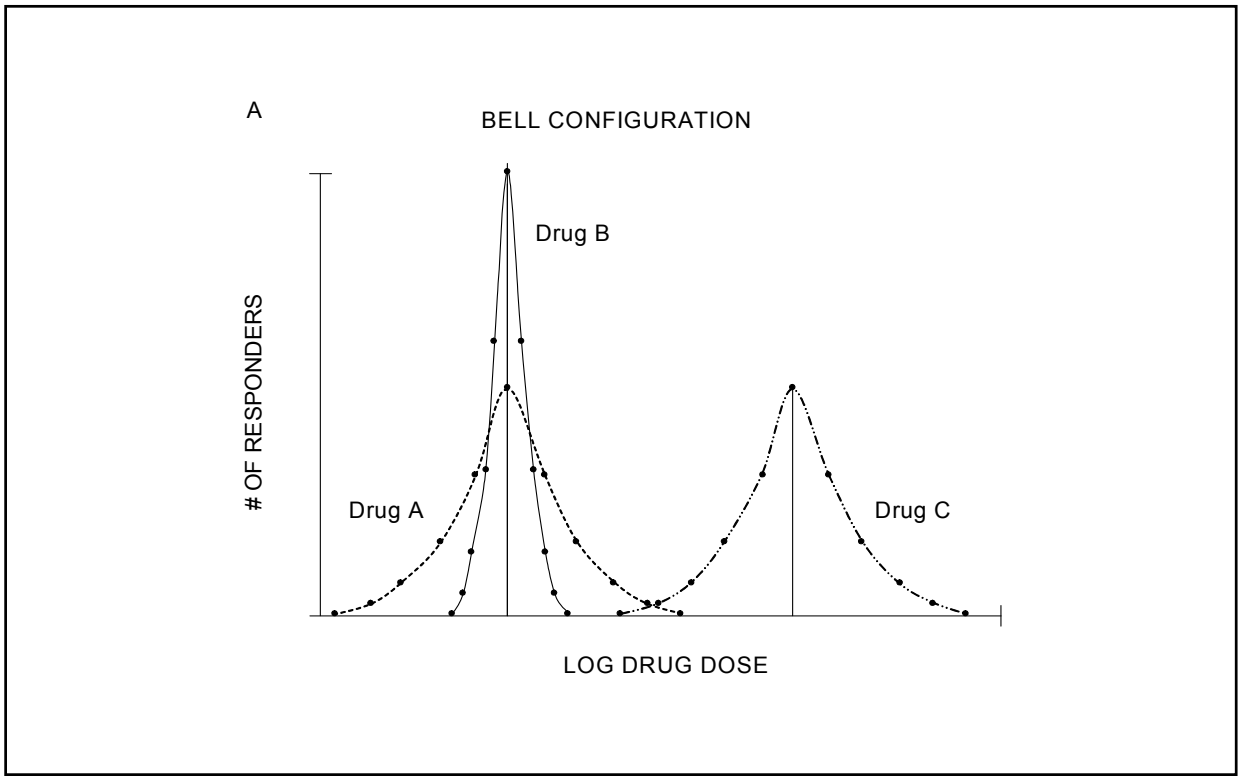
- A schematic representation of how the three-state receptor model for GPCRs explains the phenomenon of agonist-directed trafficking of receptor signalling (ADTRS). R is the inactive receptor state, R* the active receptor state coupling to and activating G-protein type 1 (G1) and R** is a second active receptor state coupling to and activating G-protein type 2 (G2). R, R* and R** are in constant equilibrium. Agonists that binds equally well to R* and R** will not display ADTRS, whereas agonists with selective binding to either R* or R** will favour coupling of the GPCR to either G1 or G2, respectively, thereby selectively activating one signal transduction pathway and therefore displaying ADTRS

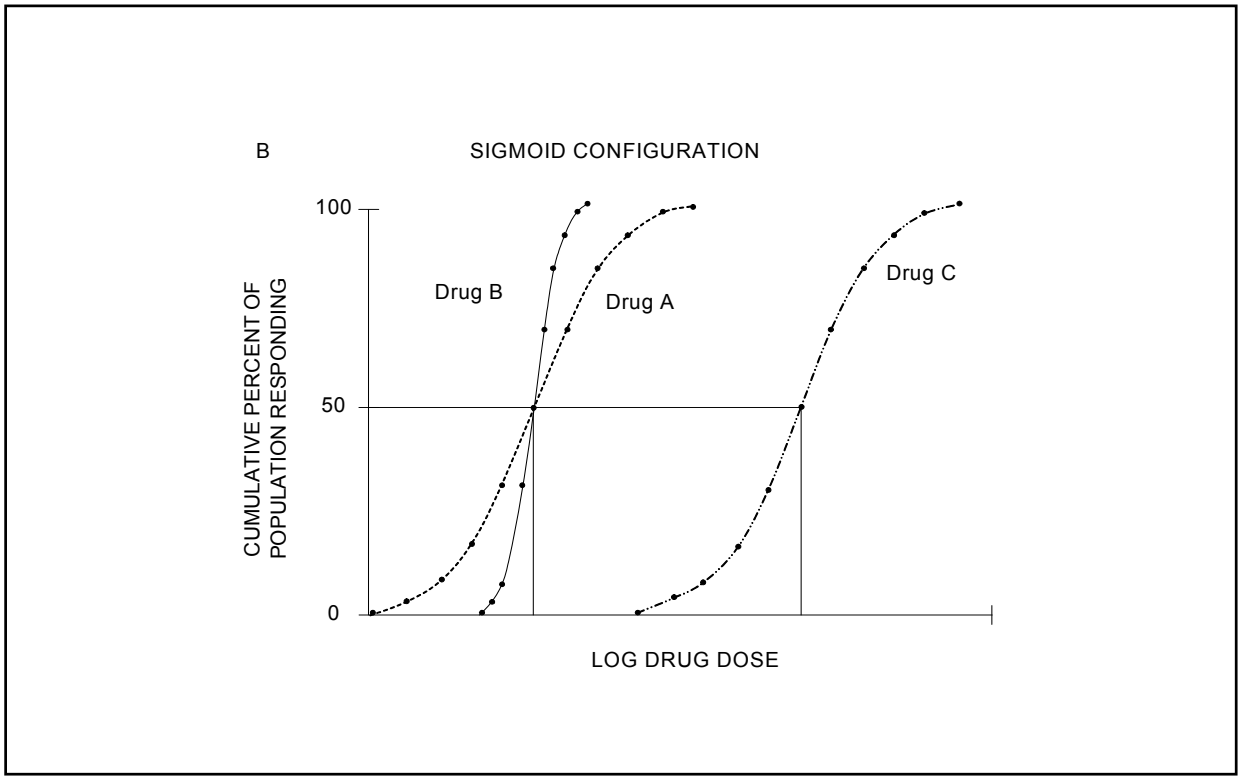


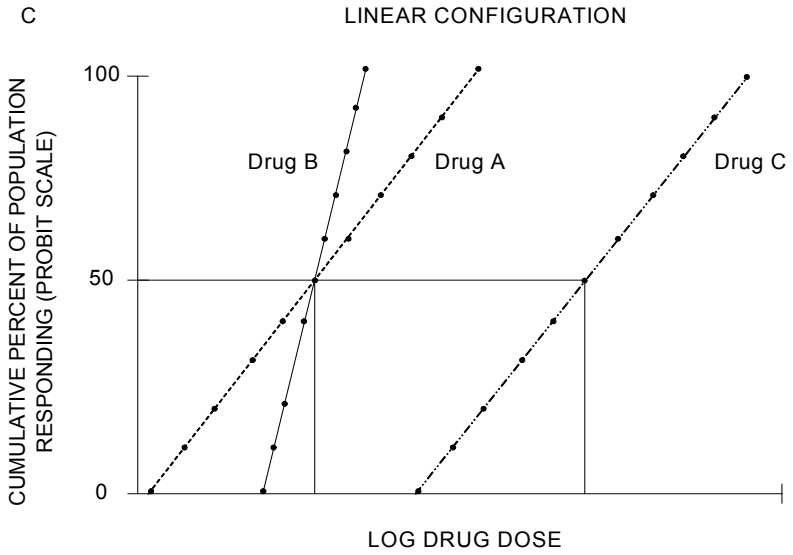
3. Clinical Therapeutics Level : Quantal Dose-Response Curves

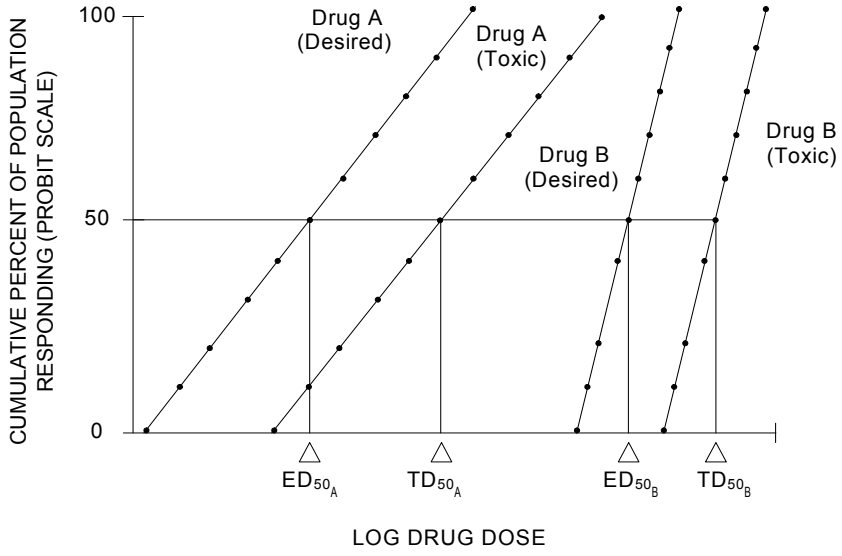


NOTE: numbers show cumulative % responding


A
BELL CONFIGURATION
OF RESPONDERS
Drug B
Drug A
Drug C
LOG DRUG DOSE


B
SIGMOID CONFIGURATION
100
50
0
CUMULATIVE PERCENT OF POPULATION RESPONDING
Drug B
Drug A
Drug C
LOG DRUG DOSE





NOTE: A and B are different than A and B in previous slides