DRUG REPONSE RELATIONSHIP

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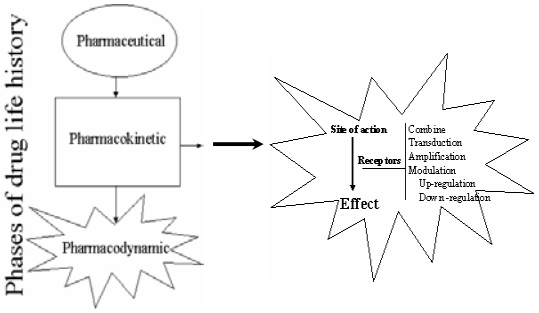
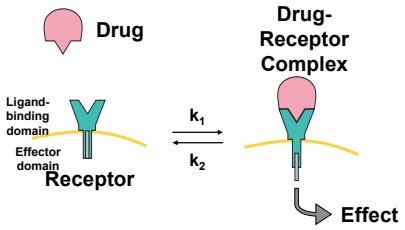
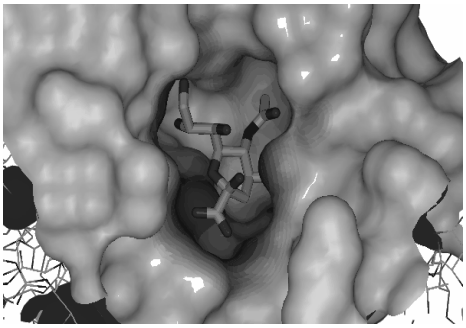
Life History of A Drug



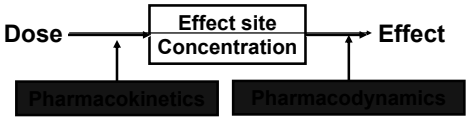
Drug-Receptor Interactions



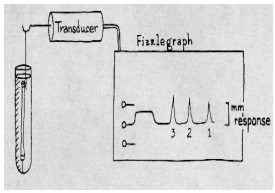
Hypothetical Drug in Receptor Site

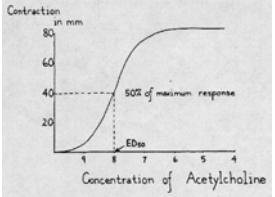


From Dose to Effect

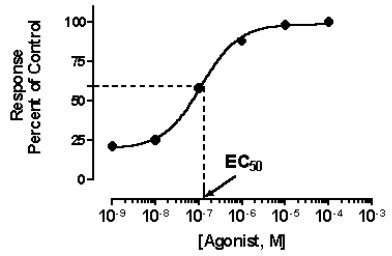


DOSE EFFECT RELATIONSHIP





Dose-Response Curve



Type of Dose-Response Curves

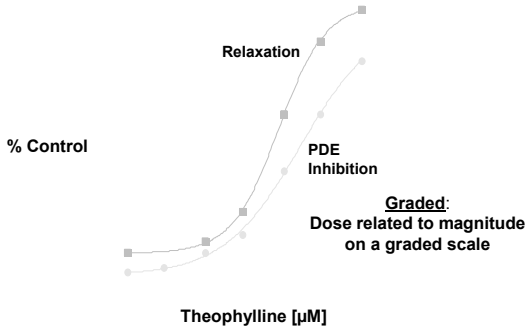
Graded

- Measured in a single biologic unit
- Continuous scale (↑dose → ↑effect)
- Relates dose to intensity of effect

Quantal

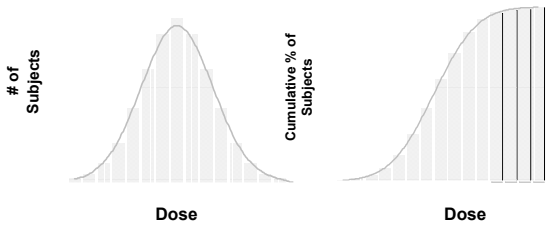
- Population studies
- All-or-none pharmacologic effect
- Relates dose to frequency of effect

Types of Dose-Response Curves: Graded

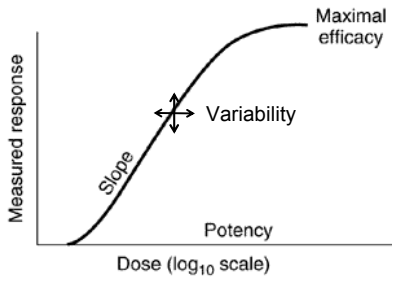


Types of Dose-Response Curves: Quantal

Dose related to % of subjects showing a specified "all-or-non" response



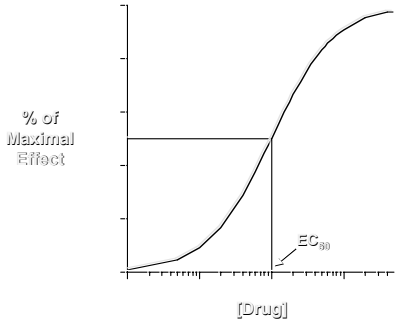
Characteristics of A Dose-Response Curve



POTENCY

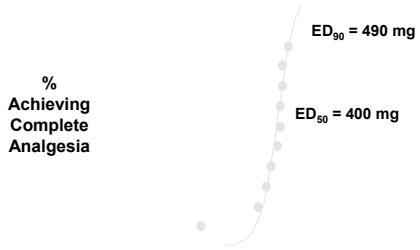
- Amount of a drug needed to produce a given effect
- Determined mainly by the affinity of the receptor for the drug
- Potency affects drug dosage
- Relatively unimportant in clinical use of drugs
- Are more potent drugs superior therapeutic agents?
- Expressed as EC50 (μM) or ED50 (mg/kg)
  - Graded= 50% of the maximal effect
  - Quantal = 50% population studied (LD50, TD50)

Potency: Graded Responses



ED50 or EC50 = Dose needed to produce 50% of the maximal effect.

Potency: Quantal Responses



Ferrante et al. Anesth Analg 82:91-7, 1996

Potency: Quantal Responses

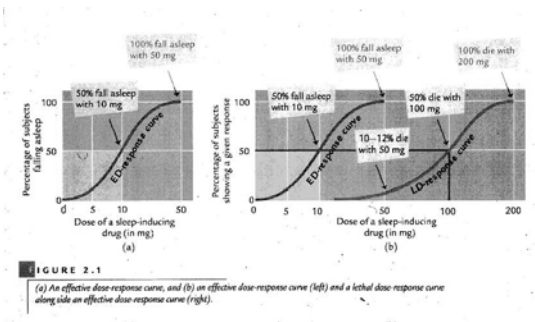


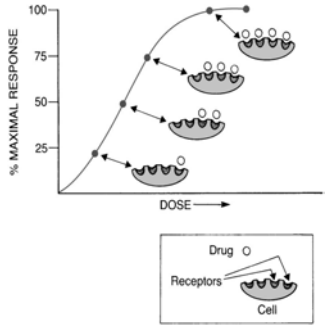
FIGURE 2.1

(a) An effective dose-response curve, and (b) an effective dose-response curve (left) and a lethal dose-response curve alongside an effective dose-response curve (right).

EFFICACY

- **The maximal effect that can be produced by a drug**
- **Determined mainly by the properties of the drug and its receptor-effector system**
- **Important clinical measure**
- **Partial agonist have lower maximal efficacy than full agonists**

Dose-Response Curves and Efficacy

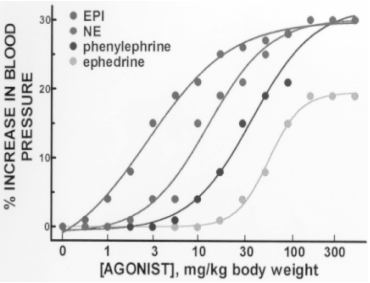


Dose-Response Curves and Partial Agonists

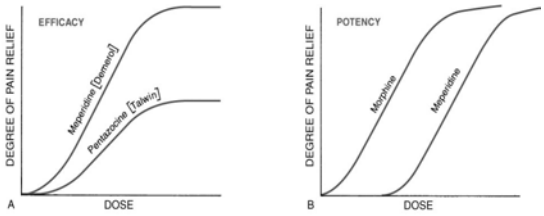
The full agonist can induce a conformational change in the receptor leading to a maximal effect. The ability to induce changes in receptor conformation leading to activation is a measure of the intrinsic activity.

Partial agonists can induce some degree of receptor activation but not of sufficient magnitude for a maximal response

Dose-Response Curves and Efficacy

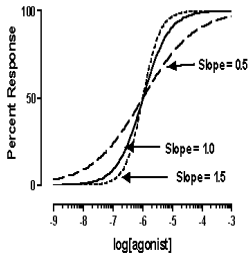


Dose-Response Curves Showing Efficacy & Potency

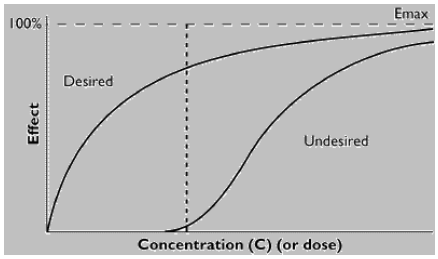


SLOPE

- The shape of the curve describe drug binding to receptors
- Indicator of useful dosage range (steepness of the curve)
- The slope have more theoretical than practical use

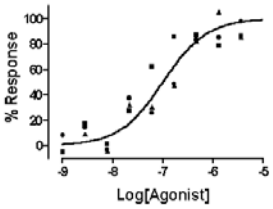


Slopes of Dose-Response Curves

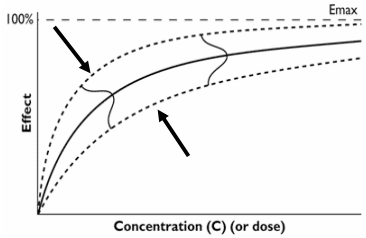


VARIABILITY

- Curves usually represent the mean response of a sample of population
- Effect may vary considerably
- "Start Low, Go Slow"
- Expressed as 95% Confidence limits



Confidence Limits of Dose-Response Curves



Value of Dose-Response Curves

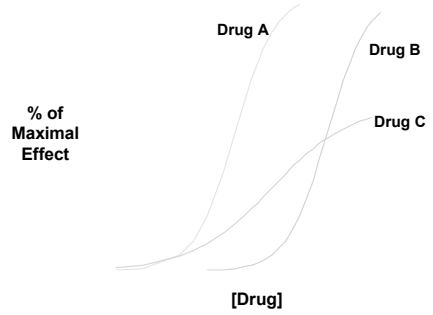
⇒ **Determining if a drug produces a certain desired effect**

⇒ **Determining potency or dose required in producing effect**

⇒ **Comparing one drug with others:**

1. ***Efficacy***
2. ***Potency***
3. ***Safety***

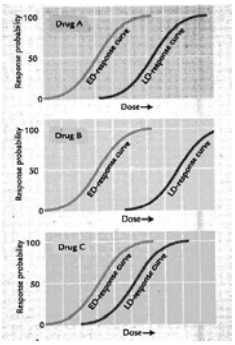
Comparing Dose-Response Curves



Relative Safety of A Drug

- **Dose-response curves help estimating the safety of a drug**
- **Therapeutic Index: TI= LD50/ED50**
  - *** LD50= the median lethal dose of a drug in animals**
  - *** Statement on selectivity of desired effects vs toxic**
- **More general concept: The Median Toxic Dose (TD50)**
  - **** No drug produce a single effect: example of Codeine***
  - **** Severity of the disease***
  - **** Concentration vs dose***

Therapeutic Index



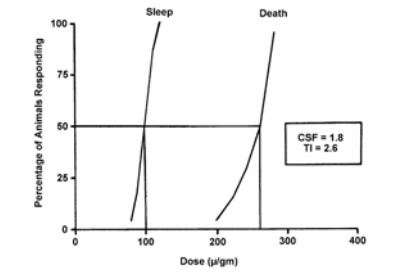
Examples of TI

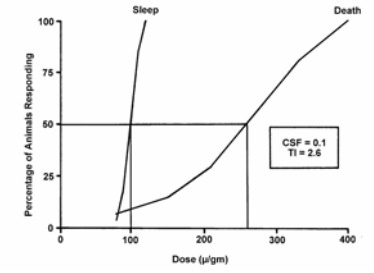
Substance	safety margin
Alcohol	1:4 - 1:10
Aspirin	1:50
Caffeine	1:100
Marijuana	1:400-1:1800

Certain Safety Factor

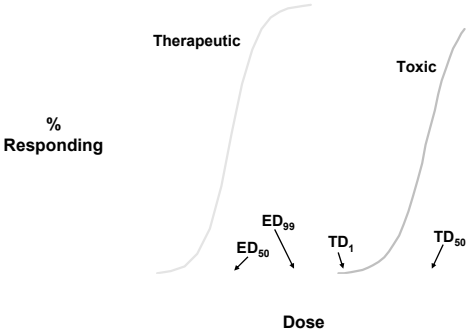
- **Problems with TI:**
  - **Comparison of the mid-points of DRC**
  - **Overlap of DRC**
- **Determination of Certain Safety Factor:**
  - **Compare the extremes of the DRC**
  - **Important concept: used to determine a Therapeutic Window**
  - **99% and 1% are not absolutes**

$$\text{Certain Safety Factor} = \frac{LD1}{ED99}$$

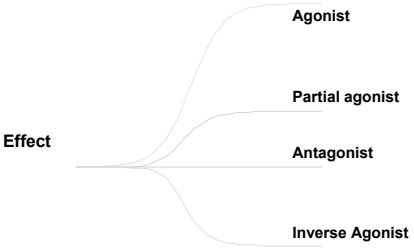




Therapeutic and Toxic Effects



Drug Interaction & Dose-Response Curves



Receptors, Agonists & Antagonists

A) Competitive Antagonists

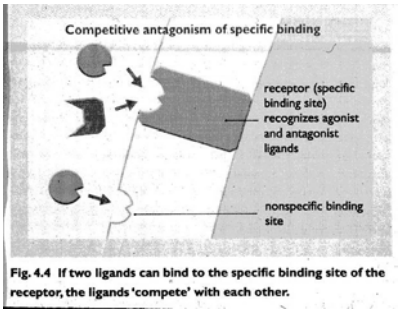
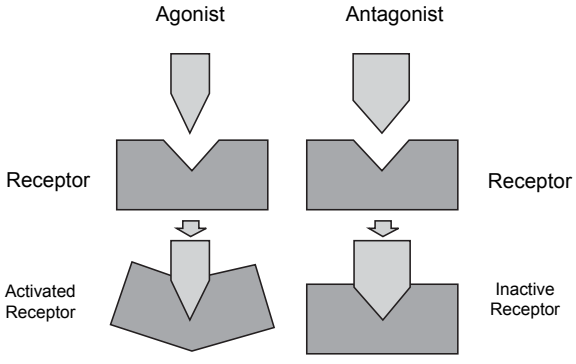
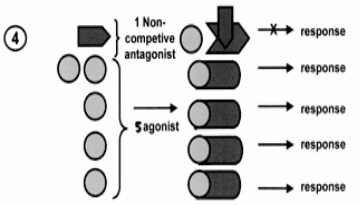


Fig. 4.4 If two ligands can bind to the specific binding site of the receptor, the ligands 'compete' with each other.



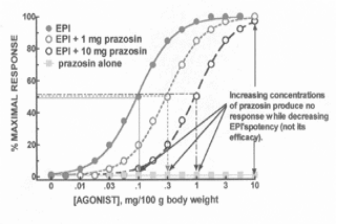
Receptors, Agonists & Antagonists

A) Non-Competitive Antagonists



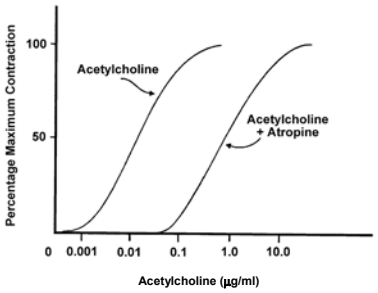
Antagonist Effects on Dose-Response Curves

A) Competitive Antagonists



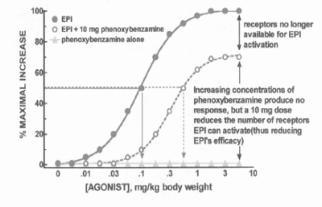
Antagonist Effects on Dose-Response Curves

A) Competitive Antagonists



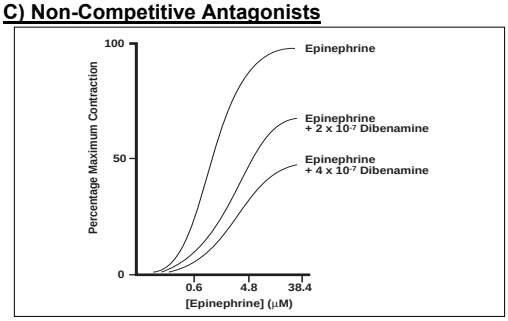
Antagonist Effects on Dose-Response Curves

C) Non-Competitive Antagonists



Antagonist Effects on Dose-Response Curves

C) Non-Competitive Antagonists



Non-Competitive Antagonist Effects on Dose-Response Curves

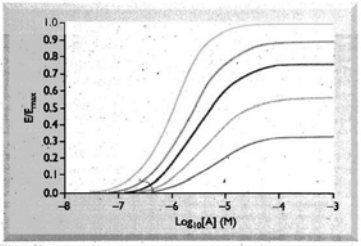


Fig. 4.14 Dose–response curves for an agonist (A) in the presence of different concentrations of a noncompetitive antagonist (D).

Thank you for your attention