Life History of A Drug

Drugs-Receptor Interactions

Hypothetical Drug in Receptor Site

From Dose to Effect

Dose Effect site Concentration Effect
Dose-Response Curve

![Dose-Response Curve Image]

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

- Dose related to magnitude on a graded scale

% Control

Relaxation

PDE Inhibition

Graded: Dose related to magnitude on a graded scale

Theophylline [µM]

Types of Dose-Response Curves: Quantal

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

Cumulative % of Subjects

Dose

Characteristics of A Dose-Response Curve

![Characteristics of A Dose-Response Curve Image]

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

$ED_{50}$ or $EC_{50} = \text{Dose needed to produce 50\% of the maximal effect.}$

Potency: Quantal Responses

$ED_{90} = 490 \text{ mg}$

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

The shape of the curve describes drug binding to receptors.

Indicator of useful dosage range (steepness of the curve).

The slope has more theoretical than practical use.

SLOPE

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

Examples of TI

<table>
<thead>
<tr>
<th>Substance</th>
<th>safety margin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>1:4 - 1:10</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1:50</td>
</tr>
<tr>
<td>Caffeine</td>
<td>1:100</td>
</tr>
<tr>
<td>Marijuana</td>
<td>1:400-1:1800</td>
</tr>
</tbody>
</table>

Certain Safety Factor

⇒ Problems with TI:
  o Comparison of the mid-points of DRC
  o Overlap of DRC

⇒ Determination of Certain Safety Factor:
  o Compare the extremes of the DRC
  o Important concept: used to determine a Therapeutic Window
  o 99% and 1% are not absolutes

Certain Safety Factor = LD1/ED99
Therapeutic and Toxic Effects

- Therapeutic
- Toxic

% Responding

Dose

ED_{50}  ED_{10}  TD_{1}  TD_{50}

Drug Interaction & Dose-Response Curves

- Agonist
- Partial agonist
- Antagonist
- Inverse Agonist

Log [Drug]

Receptors, Agonists & Antagonists

A) Competitive Antagonists

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

Non-Competitive Antagonist Effects on Dose-Response Curves
Thank you for your attention