Pharmacodynamic Phase

This phase describes the mechanisms of drug action by which a drug molecule causes its effect on the body.

Overview
Overview

- Pharmacodynamics
  - describes what the drug does to the body
    - remember
      - no drug exerts a simple isolated action solely on the diseased part of an abnormal organ
      - the safest drugs are those that produce side effects only when administered in dosages larger than normally given
      - virtually all drugs carry the possibility of side effects or toxicity

Overview

- most drugs exert their effects by binding to protein targets including
  -
  -
  -
  - some drugs exert their effects by interacting directly with DNA (anti-viral, anti-cancer)

Structure-Activity Relations
Structure-Activity Relations

- Structure-Activity Relation
  - the relationship between a drug's chemical structure and its clinical effect
    - isoproterenol and albuterol are both beta adrenergic agents but the difference in the chemical structures leads to differences in clinical effects
      - some of these differences are due to the way the drugs are absorbed and metabolized
      - some are due to the fact that the difference in structure leads to a difference in receptor selectivity

Isoproterenol
- Catecholamine
- relaxes bronchial smooth muscle
- peak effect = 20 min.
- duration = 1.5-2 hrs.
- side effect = increased heart rate

Albuterol
- Saligenin
- relaxes bronchial smooth muscle
- peak effect = 30-60 min.
- duration = 4-6 hrs.
- side effect = little or no increase in heart rate

Drug Receptors
Drug Receptors

• Drug receptors are proteins, or polypeptides

• Drug receptor proteins include

Drug Receptors

• Process of drug attachment to a receptor transduces a signal from the drug into an intracellular sequence that controls or alters cell function

• The drug most commonly attaches to a receptor on the cell membrane, creating a “transmembrane signalling”

Drug Receptors

• There are four known mechanisms of this “transmembrane signalling”
  1. Lipid soluble drugs cross the cell membrane

  2. Drug attaches to the extracellular portion of a protein receptor
Drug Receptors

- There are four known mechanisms of this "transmembrane signalling"
  1. Drug attaches to a surface receptor
  2. Drug attaches to a transmembrane receptor

Dose-Response Relations

- Response to a drug is proportional to the drug concentration
  - As the concentration increases, so does the number of occupied receptors
  - There is, however, a maximal response, beyond which increasing drug concentration does not increase response. Graphing this dose-response produces a sigmoid curve with a midpoint (ED$_{50}$) and a maximal effect plateau.
Dose-Response Relations

- **ED$_{50}$** actually has two definitions
  - when plotting a dose-response curve or determining drug potency, ED$_{50}$ is defined as the effective dose that provides 50% of a drug's maximal effect - it is also referred to as EC$_{50}$ or the effective concentration that provides 50% of a drug’s maximal effect
  - when determining the Therapeutic Index (TI) of a drug, ED$_{50}$ is defined as the effective dose at which 50% of the test subjects improve

Dose-Response Relations

- **Potency vs. Maximal Effect**
  - these two concepts are used to characterize and compare drugs
  - potency can be determined with a comparison of the ED$_{50}$ of 2 drugs (drug A and drug B) using this formula

\[
\text{ED}_{50}(B)/\text{ED}_{50}(A)
\]

In this example: ED$_{50}(B)/$ED$_{50}(A) = 5$mg/1mg = 5
Drug a is 5 times more potent than drug B because drug B requires 5 times the amount of drug A to produce 50% of its maximum effect
Dose-Response Relations

\[ \frac{\text{ED}_{50}(B)}{\text{ED}_{50}(A)} = \frac{5\text{mg}}{1\text{mg}} = 5 \]

- in the previous example, drug A is 5 times more potent than drug B because drug B requires 5 times the amount of drug A to produce 50% of its maximum effect.
- maximal effect is the greatest response that can be produced by a drug, a dose above which no further response can be elicited.
- in the following example, drugs B and C have the same potency, but drug B has a greater maximal effect.

Dose-Response Relations

- Therapeutic Index (TI)
  - based on the dose-response curve
  - instead of effect in a subject, TI looks at toxicity and/or death in a subject
  - TI: the ratio of the LD_{50} to the ED_{50} of a drug, with LD_{50} and ED_{50} indicating half of the test subjects rather than a 50% clinical response.
    - \( \text{ED}_{50} \) represents the dose at which half of the subjects improve.
    - \( \text{LD}_{50} \) represents the dose that is lethal to half of the subjects.
Dose-Response Relations

- **Therapeutic Index (TI)**
  - TI represents the safety margin of a drug
  - the smaller the TI the greater the chance of reaching a toxic level
  - example: LD$_{50}$ = 6 gms and ED$_{50}$ = 4
    - TI = LD$_{50}$/ED$_{50}$
    - TI = 6/4
    - TI = 1.5
    - meaning the toxic dose is 1.5 times the therapeutic dose

- **Examples**
  - Penicillin has a TI of >100
  - Digitalis has a TI of 1.5-2
Dose-Response Relations

- Agonists and antagonists
  - an agonist is a drug that binds to a receptor and initiates a response
  - an antagonist is a drug that binds to a receptor, but causes zero effect - since it is occupying a receptor site it blocks other drugs (agonists) from the site thereby inhibiting or blocking a response

Dose-Response Relations

- Drug interactions
  - antagonism
  - synergism - 2 drugs act on a target organ by different mechanisms with the effect being greater than the sum of the separate effects of the drugs
  - additivity - 2 drugs act on the same receptors and the combined effect is the sum of the 2 drugs' effects, up to a maximum effect
  - potentiation - type of synergism in which one drug has no effect but can increase the effect of the other drug

Dose-Response Relations

- Drug responsiveness
  - idiosyncratic effect - effect that is opposite to or unusual or no effect compared to what was expected
  - hypersensitivity - allergic or immune-mediated reaction to a drug
  - tolerance - decreasing intensity of response to a drug over time
  - tachyphylaxis - a rapid decrease in responsiveness to a drug
Pharmacogenetics

The study of hereditary or genetics differences between patients in their responses to drugs.

- Genetic variations may not be manifested as an abnormality until the patient is challenged with the drug
- Examples:
  - isoniazid - antituberculosis drug varies in its rate of metabolism with rapid and slow inactivation; difference seem to be along race lines
  - succinylcholine - normally metabolized by pseudocholinesterase in about 5 min. - 1 in 3000 are deficient in this enzyme and may take hours to begin breathing on their own