Pharmacodynamic Phase

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

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

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
      - differences are due to

Drug Receptors
- Drug receptors are proteins, or polypeptides, whose shape and electric charge provide a match to a drug's corresponding chemical shape or charge
- Drug receptor proteins include receptors on cell surfaces and within cells, as well as enzymes
  -
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

Drug Receptors

- There are four known mechanisms of this "transmembrane signalling"
  1. lipid soluble drugs cross the cell membrane and act on intracellular receptors (corticosteroids, vitamin D, thyroid hormone)
  2. drug attaches to the extracellular portion of a protein receptor, which projects into the cell cytoplasm, activating an enzyme system (insulin, platelet-derived growth factor)

Drug Receptors

- There are four known mechanisms of this "transmembrane signalling"
  3. drug attaches to a surface receptor, regulating the opening of an ion channel (acetylcholine receptors and gamma-aminobutyric acid [GABA])
  4. drug attaches to a transmembrane receptor which is coupled to an intracellular enzyme by a G protein, or guanine nucleotide regulating protein (beta adrenergic agents and acetylcholine at parasympathetic nerve endings)

Dose-Response Relations

- Response to a drug is proportional to the drug concentration
  - as the concentration increases
  - there is, however, a maximal response

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
    \[
    \frac{ED_{50}(B)}{ED_{50}(A)}
    \]
  - In this example: \( \frac{ED_{50}(B)}{ED_{50}(A)} = \frac{5mg}{1mg} = 5 \)

  - 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: 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.
      - \( ED_{50} \) represents the dose
      - \( LD_{50} \) represents the dose
**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
    \[
    TI = \frac{LD_{50}}{ED_{50}} = \frac{6}{4} = 1.5
    \]
  - meaning the toxic dose is 1.5 times the therapeutic dose

- **Agonists and antagonists**
  - agonist
  - antagonist

- **Drug interactions**
  - Other mechanisms of antagonism
    - Functional antagonism
      - can occur when two drugs each produce an effect, and the two effects cancel each other
      - example: methacholine can stimulate parasympathetic (muscarinic) receptors in the airways, causing bronchoconstriction; epinephrine can stimulate $\beta_2$ receptors in the airways, causing bronchodilation
    - Competitive antagonism
      - occurs when a drug has affinity for a receptor, but no efficacy, and at the same time blocks the active agonist from binding to and stimulating the receptor
      - example: fexofenadine is a competitive antagonist to histamine on specific receptors (H$_2$) on bronchial smooth muscle and the nasopharynx and therefore is used to treat allergies to pollens
Dose-Response Relations
- Drug interactions
  - synergism
- additivity
- potentiation

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

Pharmacogenetics
- 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

• Self-assessment questions; page 34
• Clinical scenario; page 34