Course: Drug discovery

Introduction to Pharmacodynamics

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Pharmacodynamics

- Drug actions at receptor sites and the physiological/chemical/behavioral effects produced by these actions
  - Studies of drug mechanisms of action at the molecular level
  - Provides basis for rational therapeutic uses and the design of new, superior therapeutic agents

Drug Receptors and Pharmacodynamics (how drugs work on the body)

The action of a drug on the body, including receptor interactions, dose-response phenomena, and mechanisms of therapeutic and toxic action.

Pharmacodynamics
(how drugs work on the body)

- **many drugs inhibit *enzymes***

Enzymes control a number of metabolic processes

A very common mode of action of many drugs

  - **in the patient (ACE inhibitors)**
  - **in microbes (sulfas, penicillins)**
  - **in cancer cells (5-FU, 6-MP)**

- **some drugs bind to:**
  - **proteins (in patient, or microbes)**
  - **the genome (cyclophosphamide)**
  - **microtubules (vincristine)**

Drug Receptor

- A macromolecular component of a cell with which a drug interacts to produce a response
- Usually a protein

Types of Protein Receptors

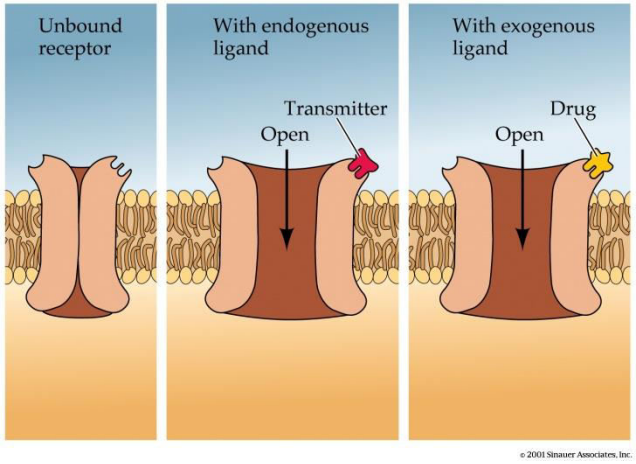
1. Regulatory – change the activity of cellular enzymes
2. Enzymes – may be inhibited or activated
3. Transport – e.g. Na^+ /K^+ ATP'ase
4. Structural – these form cell parts

Drug-Receptor Interactions

- Receptors found on membrane spanning proteins
  - Continuous series of amino acid loops
- Ligands (neurotransmitters, drugs) attach inside spaces between coils, held by ionic attractions
  - Reversible ionic binding of ligand activates receptor by changing protein structure.
  - Intensity of transmembrane signal is determined by percentage of receptors occupied.
- Drugs may influence transmembrane signal by binding to neurotransmitter receptor or to nearby site.

Drug-Receptor Interactions

- Drug/Receptor Binding
  - Mimic actions of neurotransmitter at same site (agonist)
  - Bind to nearby site and facilitate neurotransmitter binding (agonist)
  - Block actions of neurotransmitter at same site (antagonist)



Receptor Structures

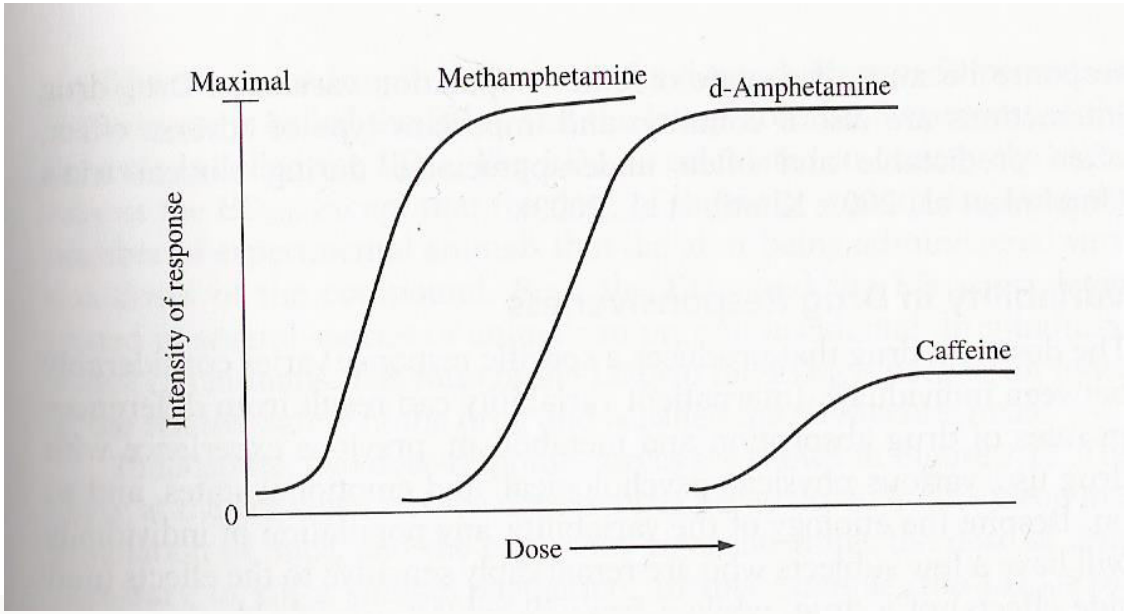
- Ion Channel Receptors
- Carrier Proteins
- G Protein-Coupled Receptors
- Enzymes

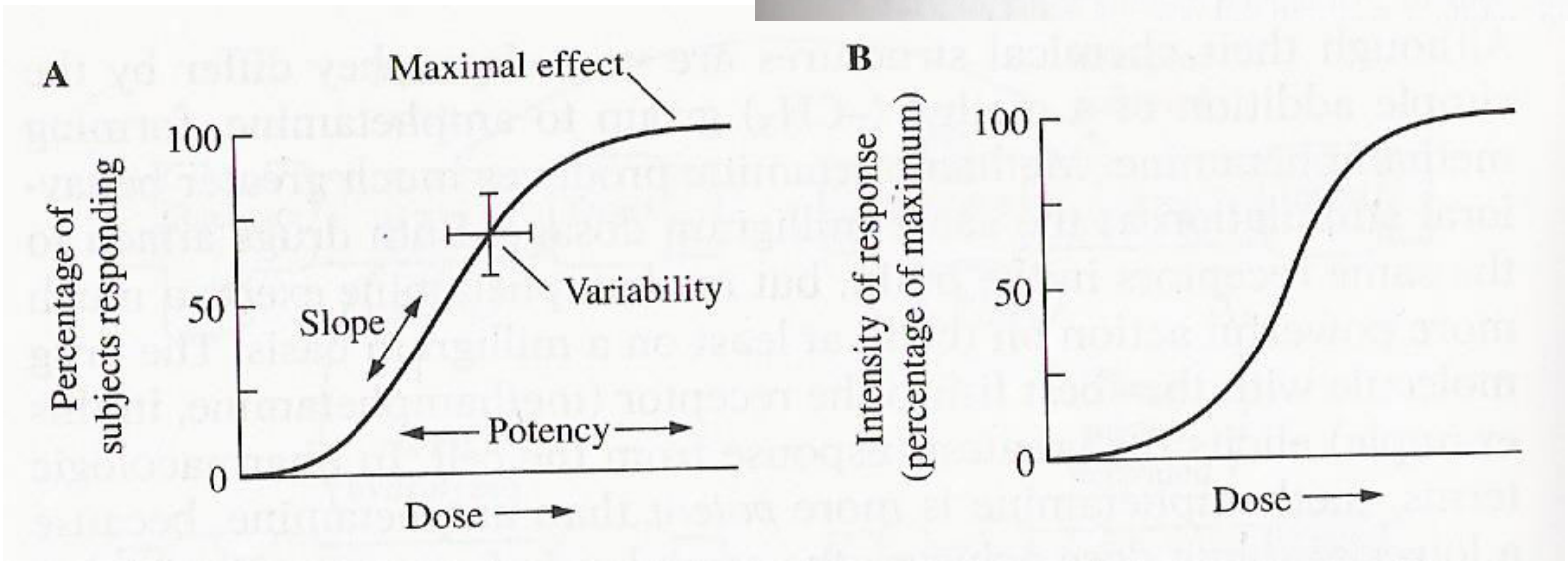
Drug-Receptor Specificity

- Alterations to a drug's chemical structure may influence potency
  - e.g., amphetamine vs. methamphetamine
- Many drugs have multiple sites of action
  - Some sites of action are responsible for side effects
  - e.g., tricyclic antidepressants: sedation, dry mouth, blurred vision

Dose-Response Relationships

- Potency
- Efficacy





Dose-Response Functions

- Efficacy (ED_{50} = median effective dose)
- Lethality (LD_{50} = median lethal dose)
- Therapeutic Index = LD_{50}/ED_{50}

The therapeutic index

- The higher the **TI** the better the drug.

- **TI's** vary from: 1.0 (some cancer drugs)

  to: >1000 (penicillin)

- Drugs acting on the same receptor or enzyme system often have the *same* **TI**: (eg 50 mg of hydrochlorothiazide about the same as 2.5 mg of indapamide)

Summary

- most drugs act through receptors
- there are 4 common signal transduction methods
- the interaction between drug and receptor can be described mathematically and graphically
- agonists have both *affinity* (k_d) and *intrinsic activity* (α)
- antagonists have affinity only
- antagonists can be *competitive* (change k_d) or
- *non-competitive* (change α) when mixed with agonists
- agonists *desensitize* receptors.
- antagonists *sensitize* receptors.

Thank you