Pharmacodynamics - The Mechanisms of Drug action

I. Most drugs cause their effects by interacting with specific drug receptors
   A. Drugs (and hormones and neurotransmitters) are molecules that have unique chemical structures that give them such properties as shape, electrical charge

   B. Receptors are structures on cells that interact with a particular drug because they have chemical structures that "match" the shape, charge, of the drug(s), much like the relationship between a key and the lock it opens (or a substrate and the enzyme that acts on the substrate)

      1. The receptor is often named to indicate the type of drug/chemical that interacts best with it (e.g., a receptor for histamine is called a histamine receptor)

      2. Drug + Receptor <------> drug -Receptor Complex ----> Effect (response)

      3. Cells may have tens of thousands of receptors for certain drugs (or hormones or neurotransmitters)

      4. Cells may have different types of receptors, each of which is specific for a particular type of drug(or hormone or neurotransmitter)

   C. Some drugs have shapes(structures) that "match" the shape of the receptor better or worse than others, and so activate the receptor better or worse, causing more or less of a response on that receptor

      D. When there is a poor (or no) "match" between specific drug molecules and the types or receptors on a particular cell, the drug-receptor interaction may lead to a weaker response, or no response at all (depending on how well the drug’s shape and the receptor's shape "match-up")

   E. Some drugs have shapes that allow them to interact with more than one type of receptor

      1. Example: drugs like diphenhydramine seem to interact with certain receptors for histamine and certain receptors for the neurotransmitter, acetylcholine

II. Agonists
   A. Defined as a drug(or hormone or neurotransmitter) that interacts with receptors on cell(s) and causes a response by changing the function of that cell

   B. Agonists have two main properties

      1. Affinity: the ability of the agonist to "bind to" (attach to) the receptor

      2. Efficacy: the ability to cause a response via the receptor interaction
III. The Dose-Response Relationship
A. The bigger the dose of a given drug, the greater the effect

B. Bigger dose means that more drug molecules are available and able to interact with the many receptors on target cells, each interaction --> a small response, but collectively leading to a bigger response than with a lower dose

C. Efficacy - the ability to cause a response via the receptor interaction
   1. The ability of a single drug to cause a response (regardless of the intensity of the response; see II.A.2. above)
   2. The maximum intensity of response to several other wise-similar drugs: if drug A causes a greater intensity of response than drug B (regardless of dose), then drug A is more efficacious than drug B
   3. ED50 (effective dose-50%)
      a. Defined as the dose of a drug needed to cause 50% of the maximum effect (response) that the drug can cause
      b. Different drugs that are agonists for the same receptor can have different ED50s: they can cause the same intensity of the same response(s), it just takes different doses of the drug(s) to do that

D. Potency
   1. Is a comparison of the ED50s of two or more drugs that cause the same responses via interacting with the same receptor
   2. The drugs being compared must be able to cause the same maximum intensity of response (i.e., they have equal efficacy), regardless of the doses needed to cause that maximum response
   3. Potency is not defined as the ability of one drug to cause a bigger response than another
   4. Is a term that's often misused (confused with efficacy) and given too much importance ("Our drug is more potent than Brand X")

IV. The two most important properties of any drug used (or being considered for use in) human or veterinary medicine are:

A. Efficacy
   The ability to cause a response via the receptor interaction

B. Safety
Lacks serious adverse effects, at least at doses needed to cause the desired effects

C. Manufacturers of prescription and nonprescription drugs (and drug products) must provide suitable proofs of efficacy and safety to the Food and drug Administration (FDA) before the drug can be approved for use.

D. With non prescription drugs, safety is usually assured but efficacy may be poor.

E. One way for manufacturers of nonprescription products to "get around" the need to show efficacy is not to claim their product is a drug, but rather something like a "nutritional supplement"

V. LD50 (lethal dose-50%)
A. Defined as the dose of a drug needed to cause a lethal effect (kill) in 50% of a test population of subjects

B. Depending on the drug(s), the LD50 may be close to, or much greater than, the ED50 (but obviously the LD50 of a clinically used drug can never be smaller than the ED50, or it would kill more people / animal than it would help)

VI. Therapeutic index
A. Defined as LD50/ED50

B. Reflects the "margin of safety " for a drug how likely an overdose might cause serious toxicity or death how far above the average effective dose you would have to go (if someone made a mistake) to start killing animal with the drug

C. The bigger the therapeutic index or margin of safety the more relatively safe a drug is compared to another drug with a lower therapeutic index

D. Differences between drugs' therapeutic indexes (margins of safety)
1. For some drugs the therapeutic index is so small that a toxic dose is barely above the average effective dose (examples: digoxin, for heart failure; theophylline, used for asthma)
2. For others, the therapeutic index is so great that it's almost impossible to kill (or seriously poison) a patient by giving too much (example: penicillin)

E. Other factors can change the therapeutic index (margin of safety), making a drug"less safe" than it would be under other conditions, e.g.
1. presence/use/administration of other interacting drugs
2. changes in drug absorption, distribution, metabolism, excretion

VII. Pharmacologic antagonists (also generally called receptor blockers)
A. Properties of antagonists
1. Have affinity (can bind to a receptor)
2. Have no efficacy -- they do not cause a response of their own; any "effect" you see after giving an agonist results only from their counteracting the effects of an agonist

B. Two main types of pharmacologic antagonists
1. Competitive antagonist (surmountable) - the most common, most worthy of your attention and understanding
2. Noncompetitive antagonist - relatively uncommon

C. Competitive antagonists (examples: atropine, propranolol)
1. Clinically, these are the most common type of antagonists
   a. Often used (given afterwards) to overcome excessive or toxic effects of agonists, whether the agonist is a drug, hormone, or neurotransmitter
   b. Sometimes given before an agonist to prevent one or several specific unwanted effects of an agonist that is capable of causing multiple effects
2. Compete with agonist for the same receptor sites
3. When bound to the receptor(s), the antagonist prevents the agonist from binding and so prevents the agonists from causing an effect
   a. Cause an apparent increase in the ED50 of the agonist – a bigger dose of agonist is needed to cause a response of the same intensity as would be caused by a lower dose if the agonist were not present -- that is, whether the antagonist merely weakens the effects caused by an agonist, or abolishes the agonist's effects altogether, depends on the dose of both the agonist and the antagonist
4. Effects of competitive antagonist can be overcome (surmounted) by giving a greater dose of the agonist so the agonist molecules can "out compete" the antagonist
   a. Competitive antagonists do not reduce the maximum effect caused by the agonist - provided the agonist's dose is increased enough

D. Noncompetitive antagonists
1. "Permanently" occupy or change receptor so agonist can't interact with it
2. Effects of noncompetitive antagonist cannot be overcome by increasing the dose of the agonist
3. Much less common, in terms of clinical use, than competitive antagonists