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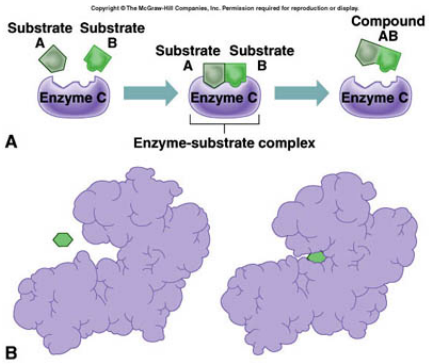
- ✓ **Definition of the word 'Drug':** *Drugs are chemicals that prevent disease or assist in restoring health to diseased individuals*
- ✓ **Langley and Ehrlich's receptor hypothesis**
  - ➢ *100 years ago, Langley rationalized why only certain molecules produced a specific therapeutic response … certain cells contain receptor molecules that served as hosts for the drugs … the new supermolecule had properties that produced the therapeutic effect*
  - ➢ *Ehrlich coined the term 'receptive substance' or 'receptor'.*
- ✓ **Receptor:** *Most drugs combine with specific sites on macromolecules by precise physiochemical and steric interactions between specific chemical groups of the drug. These sites are termed receptors.*
- ✓ **Types of Receptors:** *There are several types of receptors. G-protein coupled receptors, ion-gated channels, enzyme-linked receptors, intracellular receptors.*
- ✓ **Receptor d***efinition is changing … DNA and RNA are also being recognized as receptors …carbohydrate molecules on cell surfaces are also thought of nowadays as receptors … enzymes? Yes free floating enzymes can also be <u>thought of</u> as receptors, however in the common literature one does not typically refer to them as such*
- ✓ **Theory of Receptor Action**

Fischer's Lock and Key hypothesis: *The drug and its receptor were thought to be rigid and pre-crafted to fit into each other perfectly. The drug is a key that fits the target ('the corresponding lock') specifically and productively … when the fit is appropriate, the desired therapeutic response is achieved … when the fit is not appropriate, the door cannot be opened*

The theory does not fully explain why some keys open door partially (partial agonist or antagonist) or why some keys produce an antagonist action or why some keys bring about the formation of the lock!

- ✓ **Induced-fit hypothesis**
  - ➢ *Complexities regarding receptors*
  - ➢ *Neither the drug nor the receptor need to be rigid … the zipper model*
  - ➢ *Intermediate cases … rigid ligand – flexible receptor and flexible ligand – rigid receptor … the induced-fit model*
  - ➢ *At least two steps …an initial interaction between the drug and the receptor followed by a conformational change in either the drug or the receptor or both that results in tight binding*

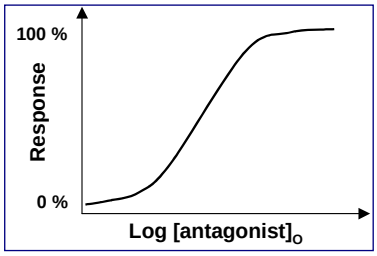


- ✓ **Measuring Drug Action**
  - ➢ *Interaction measured in two fundamental ways – affinity of interaction (K_I) and concentration of the drug that effects a 50% decrease in the physiological signal (IC_{50})*
  - ➢ *The case of enzyme + substrate and the enzyme + inhibitor reactions … measuring the K_I through chromogenic substrate hydrolysis*
  - ➢ *Definitions of **agonist, antagonist, partial agonist, partial antagonist, activator, inhibitor,** examples of these words*
  - ➢ ***K_A, K_D, K_I, IC_{50},** units of these constants, profiles of constants with respect to concentration of the drug*
- ✓ **Quantifying Drug Action and Dose – Response Curves**
  - ➢ *Basic principles enunciated for enzyme inhibition remain same for binding to receptors.*

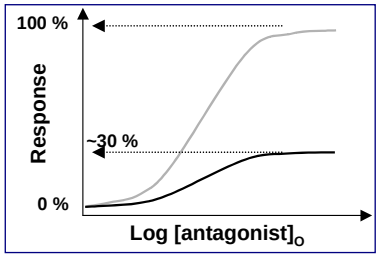
$$R + D \underset{k_2}{\overset{k_1}{\Leftrightarrow}} RD \xrightarrow{k_3} \text{Response}$$

fraction bound (fb) =

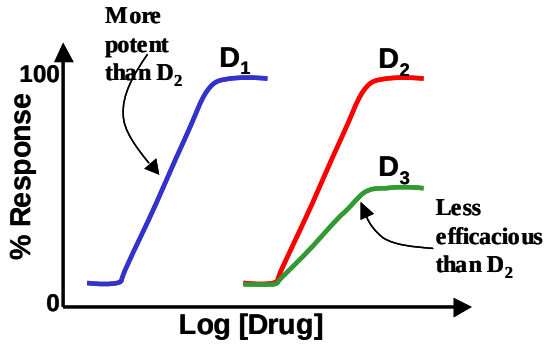
$$\frac{[RD]}{[R]+[RD]} = \frac{K_D[R][D]}{[R]+K_D[R][D]} = \frac{[D]}{K_D+[D]}$$



- *Thus, a plot of fb versus [D] will be hyperbolic and when fb = 0.5, $K_D = [D]_{0.5}$*

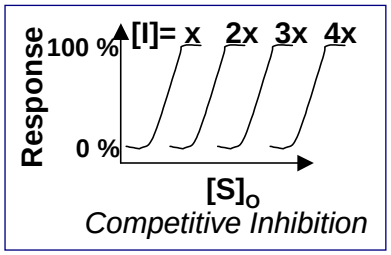


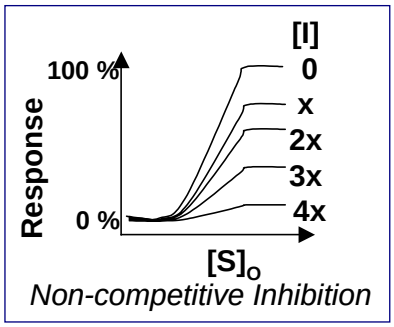
- ***Antagonist**: A molecule that prevents the normal action of a receptor, that prevents a normal response. This is equivalent to the use of term inhibitor for enzymes.*
- ***Agonist**: An agent that facilitates the normal action of the receptor. This is equivalent to the use of term activator for enzymes.*
- ***IC_{50}** is not the same as **K_I**. Units of both terms are same.*
- *Partial agonists: Partial agonists bind to the receptor, they do generate an agonist response, however they do not generate the full agonist response. They are weak agonists. So they reduce the overall agonist activity.*
- *Potency and Efficacy*



✓ **Types of Drug – Receptor Interactions**

- *Inhibition (or agonism or antagonism) could be either competitive or non-competitive; competitive inhibition involves the displacement of substrate **S** from the active site, while non-competitive inhibition involves the simultaneous binding of **S** and **I** to the same enzyme molecule.*





- *Non-competitive inhibition may also be allosteric inhibition. Allos = other. Thus allosteric inhibition involves the inhibition through binding at other sites.*
- *Irreversible inhibition is a process of inhibiting an enzyme through the formation of an breakable chemical bond*