**PHARMACODYNAMICS**

**Receptor theory:** A receptor is a component of a cell or organism that interacts with drugs which results in a sequence of events which lead to an observed change in function. Receptors determine the quantitative relationship between dose or concentration of the drug and the pharmacological effects. Receptors are responsible for the selectivity of the drug function. Receptors mediate the actions of pharmacological agonists and antagonists. Katzung pg 15, Miller pg 215

Evidence for the presence of receptors is inferred from the biological response of tissues to drugs, from genome sequencing and from molecular biology.

Classic receptor theory describes interaction between ligand and receptor based on the laws of mass action. In simplest form this can be represented by the following formula:

\[
\text{[Drug]} + \text{[Receptor]} \rightarrow \text{[Drug-Receptor]}
\]

**Kd** may also be represented graphically as shown here. Again it represents 50% occupancy of the maximum number of receptors (Bmax).

**EC50** represents the concentration of the drug which results in 50% of the maximal effect (Emax).

**Responses to drugs can be either graded or quantal.** In a graded response there is an increasing magnitude of response with increasing dose. In a quantal response once a certain number of receptors are occupied there is an all-or-nothing response (examples include mortality or loss of consciousness).

The frequency of response in the population is the important variable in quantal effects. This can be plotted as a gaussian distribution curve or more commonly as a sigmoid plot against concentration (either standard or log). The 50% of population with a quantal response represents the \( ED50 \) (effective dose). Animal studies are used to determine the 50% lethal dose \( LD50 \) (or 50% toxic dose \( TD50 \)).

The **therapeutic index** represents the ratio of LD50 to ED50. The higher the therapeutic index the greater the range of safety. Hemmings pg 98-99 Katzung pg 30-31

**AGONISTS and ANTAGONISTS**

Receptors exist in activated and inactivated states, and the intrinsic efficacy of a drug is determined by the extent to which it stabilizes the active form of the receptor (i.e., agonists such as midazolam), the inactive form (i.e., inverse agonists such as metoprolol and bisoprolol), or displaces agonists from the binding site without favoring either form (i.e., neutral antagonists such as flumazenil). Agents that are only partly as effective as agonists no matter the dose employed are termed partial agonists (such as buprenorphine).

Competitive antagonism, more agonist is required to get to \( E_{max} \). With an irreversible antagonist even with very high doses of agonist the system is unable to get to \( E_{max} \).

A chemical antagonism works by directly binding to another drug which renders it inactive. An example of this is protamine which forms an ionic bond with heparin.

**Physiologic antagonism** works by producing a countering effect by other pathways to reduce the effect of a drug. It is less specific and sometime difficult to control.

**QUANTIFYING AGONISM**

Relative potency implies that in two agonists with equal efficacy, a smaller dose of one agonist is required to achieve maximal effect.

Relative efficacy that the maximal effect of one agonist is greater than the other.