PHARMACODYNAMICS

Receptor theory: A receptor is a component of a cell or oganism 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 a the following formula;

$$[\text{Drug}] + [\text{Receptor}] \underset{\text{K association}}{\overset{\text{K dissociation}}{\rightleftharpoons}} [\text{Drug-Receptor}]$$

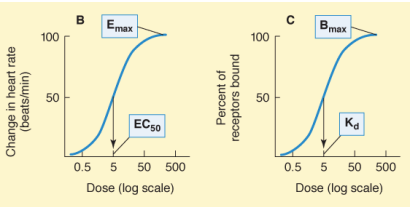
rearranged: (@ steady state)

$$\frac{[D][R]}{[D\text{-}R]} = \frac{\text{K dissociation}}{\text{K association}} = K_D$$

This is the dissociation constant! It is the concentration when 50% of receptors are occupied

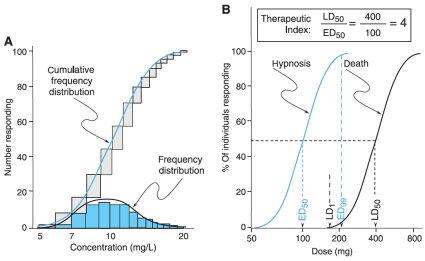
A low Kd value indicates that less drug is required to occupy 50% of the receptors, implying that each molecule of drug is tightly associated with the receptor. A high Kd value indicates that more drug is required to occupy 50% of receptors, implying a weak binding to the receptor. Kd has been determined for many of the drugs administered during anesthesia. The reciprocal of Kd is Ka - the association constant. Ka is a measure of the affinity of the drug for the receptor. A drug with a low Kd value has a high Ka value and therefore high affinity for the receptor.

K_d may also be represented graphically as shown here . Again it represents 50% occupancy of the maximum number of receptors (B_{max})



EC_{50} represents the concentration of the drug which results in 50% of the maximal effect (E_{max})

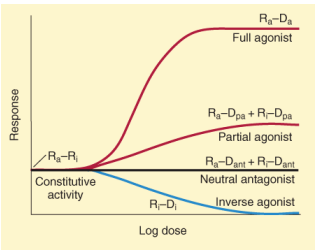
GRADED, QUANTAL DOSES AND THERAPEUTIC INDEX



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 ED_{50}. (effective dose). Animal studies are used to determine the 50% lethal dose LD_{50} (or 50% toxic dose TD_{50}).

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

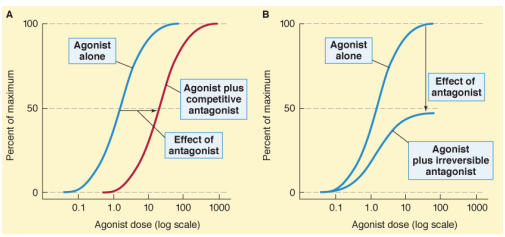


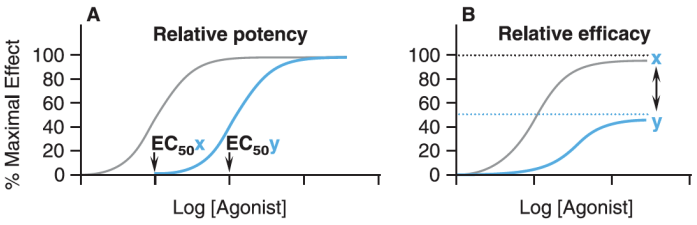
AGONISTS and ANTAGONISTS

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 midazolm), 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 flumanezil). 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 anatagonist even with very high doses of agonist the system is unable to get to E_{max}.

A chemical anatagonism 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 that the other