Medicinal Chemistry & Drug Discovery
Section 2.4.1 – Target Binding

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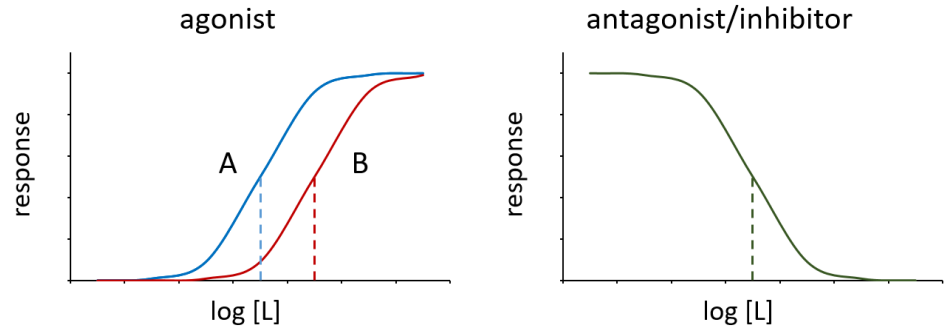
Learning goals

- describe drug-target binding as equilibria
- calculate binding energies

Vocabulary

- potency
- dissociation equilibrium constant
- inhibitory equilibrium constant
- binding energy

Potency refers to the concentration of a molecule required to exert its effect. EC_{50} and IC_{50} are both measures of **potency**. EC_{50} is a concentration – the concentration at which an agonist or partial agonist generates half, 50%, of its potential response on a graph of response vs. log ligand concentration. Molecule A has a lower EC_{50} than molecule B. Molecule A is more potent because it exerts its effect at a lower concentration. IC_{50} is a concentration – the concentration at which enzyme inhibitors and antagonists block the action of an enzyme or receptor, respectively. Molecule A is more potent because it exerts its effect at lower concentrations. Molecule A has a lower EC_{50} than molecule B.



EC_{50} (A) < EC_{50} (B) → potency (A) > potency (B)

Potency can also be discussed through equilibrium constants. Drugs (D) bind target proteins (T) reversibly, so binding is an equilibrium. The drug-target complex can reversibly dissociate into free drug and free target. The more this equilibrium favors the drug-target complex, then the greater the fraction of target will be bound by the drug, and the more potent the drug will be. In chemistry, we quantify equilibria with an equilibrium constant, K. Here is the equation for this equilibrium. For agonists, this equilibrium constant is often called K_d, the **dissociation equilibrium constant**. For enzyme inhibitors and antagonists, it is K_i, the **inhibitory equilibrium constant**. K_d and K_i can be measured through calorimetry experiments.

$$\text{D-T} \rightleftarrows \text{D} + \text{T} \qquad K = \frac{[D][T]}{[D\text{-}T]}$$

D-T: drug-target complex; D: free drug; T: free target

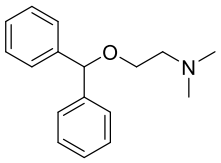
agonists → K_d = dissociation equilibrium constant

antagonists & inhibitors → K_i = inhibitory equilibrium constant

For bioactive molecules, K_d and K_i are very low. For example, *typically*, a hit from a screening program might have a K_d or K_i of 10^{-6} molar. That is 1.0 micromolar (μM). A representative drug may have a K_d or K_i of 10^{-8} molar, or about 10 nanomolar (nM). It is no surprise that drugs are more potent than hits.

Equilibrium constants are related to the **binding energy** between a molecule – ΔG_{bind} – and its target protein. K is our K_d or K_i. Note that we use 1/K because binding is the reverse of dissociation. R is the gas constant, 1.99×10^{-3} kcal/mol*K. T is the temperature, often 298 K. Diphenhydramine is a histamine H1 receptor antagonist with a K_i of 13 nM or 1.3×10^{-8} molar. (Our units must be molarity for this equation.) If we go through the calculation of ΔG, we get a binding energy of diphenhydramine for the H1 receptor of −10.8 kcal/mol. Binding energies for drugs are always negative because the binding is spontaneous.

$$\Delta G_{bind} = -2.3RT \log \frac{1}{K}$$



diphenhydramine
histamine H1 receptor antagonist
K_i = 13 nM

$$\Delta G_{bind} = -2.3 \cdot 0.00199 \frac{kcal}{mol \cdot K} \cdot 298\ K \cdot \log \frac{1}{1.3 \times 10^{-8}}$$

$$\Delta G_{bind} = -2.3 \cdot 1.99 \frac{kcal}{mol \cdot K} \cdot 298\ K \cdot 7.89$$

$$\Delta G_{bind} = -10.8 \frac{kcal}{mol}$$