C6. Agonist and Antagonist of Ligand Binding to Receptors - An Extension

The analysis of competitive, uncompetitive and noncompetitive inhibitors of enzymes can now be extended to understand how the activity of membrane receptors are affected by the binding of drugs. When receptors bind their natural target ligands (hormones, neurotransmitters), a biological effect is elicited. This usually involves a shape change in the receptor, a transmembrane protein, which activates intracellular activities. The bound receptor usually does not directly express biological activity, but initiates a cascade of events which leads to expression of intracellular activity. In some cases, however, the occupied receptor actually expresses biological activity itself. For example, the bound receptor can acquire enzymatic activity, or become an active ion channel.

Drugs targeted to membrane receptors can have a variety of effects. They may elicit the same biological effects as the natural ligand. If so, they are called agonists. Conversely they may inhibit the biological activity of the receptor. If so they called antagonists

Agonist

An agonist is a mimetic of the natural ligand and produces a similar biological effect as the natural ligand when it binds to the receptor. It binds at the same binding site, and leads, in the absence of the natural ligand, to either a full or partial response. In the latter case, it is called a partial agonist. The figure below shows the action of ligand, agonist, and partial agonist.

There is another kind of agonist, given the bizarre name inverse agonist. This term only makes sense when applied to a receptor that has a basal (or constitutive) activity in the absence of a bound ligand. If either the natural ligand or an agonist binds to the receptor site, the basal activity is increased. If however, an inverse agonists binds, the activity is decreased. An example of an inverse agonist (which we will discuss later) is the binding of the drug Ro15-4513 to the
GABA receptor, which also binds benzodiazepines such as valium. When occupied by its natural ligand, GABA, the protein receptor is "activated" to become a channel allowing the inward flow of Cl⁻ into a neural cell, inhibiting neuron activation. Valium potentiates the effect of GABA, which is enhanced even further in the presence of ethanol. Ro15-4513 binds to the benzodiazepine site, which leads to the opposite effect of valium, the inhibition of the receptor bound activity - a chloride channel.

![Figure 1: Agonist and Partial Agonists](https://bio.libretexts.org/Bookshelves/Biochemistry/Book%3A_Biochemistry_Online_(Jakubowski)/06%3A_TRANSPORT_AN…)

**Antagonists**

As their name implies, an antagonist inhibit the effects of the natural ligand (hormone, neurotransmitter), agonist, partial agonist, and even inverse agonists (which will not be mentioned again). We can think of them as inhibitors of receptor activity, much as we considered in the sections above inhibitors of enzyme activity. As such, there can be different types of antagonists. These include:

- **Competitive antagonist**, which are drugs that bind to the same site as the natural ligand, agonists, or partial agonist, and inhibit their effects. They would be analogous to competitive inhibitors of enzyme. One could also imagine a scenario in which an "allosteric" antagonist binds to an allosteric site on the receptor, inducing a conformational change in the receptor so the ligand, agonist, or partial agonist could not bind.

- **Noncompetitive antagonist** (or perhaps more generally mixed antagonist) which are drugs that bind to a different site on the receptor than the natural ligand, agonist, or partial agonist, and inhibit the biological function of the receptor. In analogy to noncompetitive and mixed enzyme inhibitors, the noncompetitive antagonist may change the apparent $K_d$ for the ligand, agonist, or partial agonist (the ligand concentration required to achieve half-maximal biological effects), but will change the maximal response to the ligand (as mixed inhibitors change the apparent $V_{max}$). The figure below shows the action of a competitive and noncompetitive antagonist.
• **Irreversible agonist**, which arises from covalent modification of the receptor.

**Figure 2: Antagonists: Competitive and Noncompetitive (Mixed)**

**Contributors**

- Prof. Henry Jakubowski (College of St. Benedict/St. John's University)