Medicinal Chemistry & Drug Discovery
Section 2.3.1 – Receptor Ligands

Learning goals

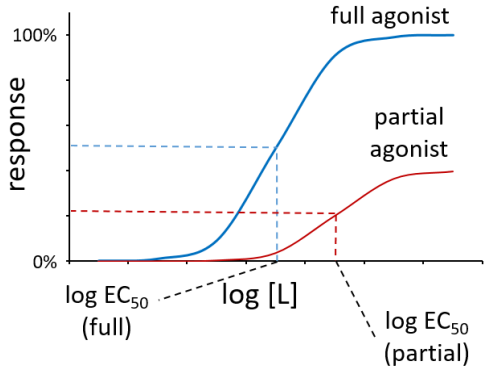
- list the different types of receptor ligands
- interpret receptor response curves

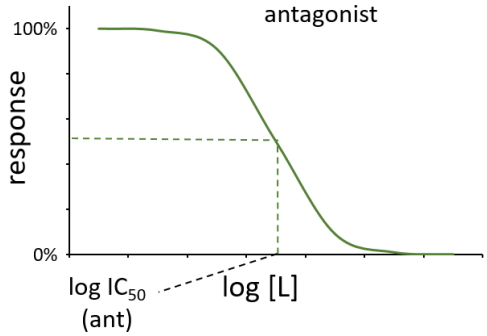
Vocabulary

- receptor
- ligand
- agonist
- full agonist
- partial agonist
- antagonist
- EC_{50}
- IC_{50}
- endogenous ligand
- exogenous ligand

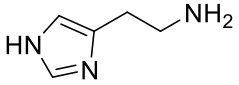
Receptors are proteins that control responses in biological pathways. Ligands are molecules that bind a receptor and turn the receptor on or off. Ligands that turn "on" a receptor are **agonists.** There are different degrees of being turned on. Some agonists fully activate a receptor. These are **full agonists**. Ligands that do not fully activate a receptor are called **partial agonists**. Ligands that block the action of agonists are called **antagonists**. There are other types of receptor ligands, but full agonists, partial agonists, and antagonists cover most drugs that target receptors.

The activity of ligands on receptors is measured with graphs. The y-axis is the response, and the x-axis is the logarithm of the ligand concentration – log[L]. For full agonists, at low concentration, the response is 0%. At high concentration, the response is 100%. In between, the response rises with a sigmoidal shape. At the point of inflection, log[L] equals log[$\mathbf{EC_{50}}$] – the ligand concentration that gives 50% effect. Partial agonists look similar except the response rises to a value less than 100%. The inflection point, although not at 50% effect, is still called the EC_{50} for partial agonists. The response is 50% (half) of the maximum possible for the partial agonist. For antagonists, the receptor is mixed with a full agonist, so the response starts at 100%. As more and more antagonist is added, the response drops to 0%. The curve is again sigmoidal. Response drops to 50% when log[L] equals log[$\mathbf{IC_{50}}$]. Antagonists inhibit response so the concentration is IC_{50}, not EC_{50}. Antagonists alone do not cause a response.

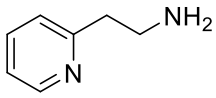




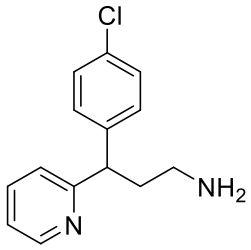
Receptors are named after their natural ligand, or **endogenous ligand**. The histamine H1 receptor naturally binds to histamine. An excellent approach to designing unnatural ligands, or **exogenous ligands**, is to imitate the endogenous ligand. 2-Pyridylethylamine and chlorpheniramine are both exogenous ligands for the histamine H1 receptor. 2-Pyridylethylamine closely resembles histamine and is also a full agonist. Chlorpheniramine is similar enough to bind but does not cause a response and blocks the action of histamine. Chlorpheniramine is an antagonist. Both of these are competitive ligands because each binds to the receptor at the same site as the endogenous ligand.



histamine



2-pyridylethylamine



chlorpheniramine