# 02 - 2. Receptor mechanisms

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The ‘receptor’ of a drug can be defined generally as the cellular component to which the drug binds and through which the drug initiates the pharmacodynamic effects on the body. There are 2 major superfamilies; Ionotropic or metabotropic receptors.  Ionotropic: Theses are ligand-gated ionic channels. Their activation leads to a rapid transient increase in membrane permeability to either positive cations like sodium or calcium or negative anions like chloride. It causes excitation or inhibition of the postsynaptic membrane. Examples are nicotinic acetylcholine receptors, GABA-A receptors, glutamate receptors and serotonin 5HT 3.  Metabotropic: These produce slower response involving so-called G-proteins which bind to the intracellular portion of the receptor and activate a second messenger. Altered second messenger levels result in changes in the phosphorylation state of key proteins rendering them active or inactive. Examples are Dopamine (D1-5), Noradrenaline, and Serotonin 5HT1-7 except 5-HT 3, muscarinic acetylcholine receptors and opioid receptors (mu). Ionotropic receptors result in quick response (GABAA, a benzodiazepine); G protein coupling (metabotropic) is a comparatively slower process (most antipsychotics, antidepressants. Kinetics of receptor binding: A drug can be an agonist for a receptor and can stimulate the biological activity of the receptor or could be an antagonist that inhibits the biological activity.  Full agonists produce a maximal response. The measure of the degree of response is usually measured against physiological neurotransmitter efficiency for any given receptor.  Partial agonists cannot elicit a maximal response and are less effective than full agonists. Examples are Aripiprazole, buspirone and buprenorphine. Partial agonists have a ceiling effect. The degree of response of a partial agonist depends on availability of physiological neurotransmitter in the vicinity; i.e. when maximal dopamine is available, partial agonist aripiprazole can actually inhibit the dopaminergic transmission as a less efficient molecule competes with more efficient molecule. In dopamine deficient states, the same partial agonist can enhance dopaminergic effects.  An inverse agonist is an agent that binds to the same receptor but produces the opposite pharmacological effect. No clinical drug acts via this mechanism but several have been researched especially at GABA complex.  Antagonists are drugs that interact with receptors to interfere with their activation by neurotransmitter or other agonistic molecules.

© SPMM Course Types of antagonism  Competitive antagonism can be reversed completely by increasing the dose of the agonist drug. Competitive antagonists reduce the potency (minimal dose needed to produce an effect) but not the efficacy (maximal response produced) of agonists. Examples of competitive antagonism include atropine at muscarinic receptors and propranolol at betaadrenergic receptors.  Noncompetitive antagonists alter the receptor site in some way so increasing the dose of the agonist drug can reverse the effects only partially. Non-competitive antagonism reduces both the potency and the efficacy of agonists. Therefore, non-competitive antagonists not only shift the curve to the right but also reduce the maximum effect. For example, ketamine and phencyclidine are noncompetitive NMDA antagonists. Irreversible antagonists bind irreversibly to the target site e.g. most traditional MAOIs.  Pharmacological antagonism refers to the opposing action of two molecules by acting via same receptors. Physiological antagonism refers to the opposing action of two molecules by acting via different receptors e.g. acetylcholine vs. adrenergic actions.  Chemical antagonism refers to the opposing action of two molecules by acting via chemical reactions. This is not seen in psychotropics, but heparin and protamine reaction is an example. Most drugs bind reversibly to receptors, and the response is proportional to the fraction of receptors occupied (law of mass action). As the concentration of drug increases, the responses increases until all receptors are occupied giving a dose-response curve. Receptors can be up-regulated or down-regulated by drugs. With therapeutic use, agonists may cause down-regulation (desensitivity) or reduction in receptor numbers while antagonists may have the opposite effect- upregulation (hypersensitivity) or increase in receptor numbers. The potency of a drug with receptor binding action refers to the amount of the drug needed to produce a particular effect compared to another standard drug with similar receptor profile (‘vigor’). The potency of a drug is determined by; a. The proportion of the drug reaching the receptor b. The affinity for the receptor c. Efficacy Affinity refers to the ability of the drug to bind to its appropriate receptor (‘affection’). Drugs that bind readily to a receptor are described as having high affinity for that receptor and, in general, the higher the affinity and the more receptor a drug occupies, the more potent it is.

© SPMM Course Efficacy refers to how well the drug produces the expected response i.e. the maximum clinical response produced by a drug (‘productivity’). Efficacy depends on affinity, potency, duration of receptor action in some cases and kinetic properties such as half-life, among other factors. Haloperidol is more potent than chlorpromazine as approximately 5 mg of haloperidol is required to achieve the same effect as 100 mg of chlorpromazine. These drugs, however, are comparable in the maximal clinical response achievable using them i.e. equally efficacious but not equipotent.

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