= Receptor antagonist =

A receptor antagonist is a type of receptor ligand or drug that blocks or dampens agonist @-@ mediated responses rather than provoking a biological response itself upon binding to a receptor . They are sometimes called blockers ; examples include alpha blockers , beta blockers , and calcium channel blockers . In pharmacology , antagonists have affinity but no efficacy for their cognate receptors , and binding will disrupt the interaction and inhibit the function of an agonist or inverse agonist at receptors . Antagonists mediate their effects by binding to the active orthosteric (= right place) site or to allosteric (= other place) sites on receptors , or they may interact at unique binding sites not normally involved in the biological regulation of the receptor 's activity . Antagonist activity may be reversible or irreversible depending on the longevity of the antagonist ? receptor complex , which , in turn , depends on the nature of antagonist ? receptor binding . The majority of drug antagonists achieve their potency by competing with endogenous ligands or substrates at structurally defined binding sites on receptors .

= = Receptors = =

Biochemical receptors are large protein molecules that can be activated by the binding of a ligand (such as a hormone or drug) . Receptors can be membrane @-@ bound , occurring on the cell membrane , or intracellular , such as on the nucleus or mitochondrion . Binding occurs as a result of noncovalent interaction between the receptor and its ligand , at locations called the binding site on the receptor . A receptor may contain one or more binding sites for different ligands . Binding to the active site on the receptor regulates receptor activation directly . The activity of receptors can also be regulated by the binding of a ligand to other sites on the receptor , as in allosteric binding sites . Antagonists mediate their effects through receptor interactions by preventing agonist @-@ induced responses . This may be accomplished by binding to the active site or the allosteric site . In addition , antagonists may interact at unique binding sites not normally involved in the biological regulation of the receptor 's activity to exert their effects .

The term antagonist was originally coined to describe different profiles of drug effects . The biochemical definition of a receptor antagonist was introduced by Ariens and Stephenson in the 1950s . The current accepted definition of receptor antagonist is based on the receptor occupancy model . It narrows the definition of antagonism to consider only those compounds with opposing activities at a single receptor . Agonists were thought to turn " on " a single cellular response by binding to the receptor , thus initiating a biochemical mechanism for change within a cell . Antagonists were thought to turn " off " that response by ' blocking ' the receptor from the agonist . This definition also remains in use for physiological antagonists , substances that have opposing physiological actions , but act at different receptors . For example , histamine lowers arterial pressure through vasodilation at the histamine H1 receptor , while adrenaline raises arterial pressure through vasoconstriction mediated by alpha @-@ adrenergic receptor activation .

Our understanding of the mechanism of drug @-@ induced receptor activation and receptor theory and the biochemical definition of a receptor antagonist continues to evolve . The two @-@ state model of receptor activation has given way to multistate models with intermediate conformational states . The discovery of functional selectivity and that ligand @-@ specific receptor conformations occur and can affect interaction of receptors with different second messenger systems may mean that drugs can be designed to activate some of the downstream functions of a receptor but not others . This means efficacy may actually depend on where that receptor is expressed , altering the view that efficacy at a receptor is receptor @-@ independent property of a drug .

= = Pharmacodynamics = =

= = = Efficacy and potency = = =

By definition , antagonists display no efficacy to activate the receptors they bind . Antagonists do not maintain the ability to activate a receptor . Once bound , however , antagonists inhibit the function of agonists , inverse agonists , and partial agonists . In functional antagonist assays , a dose @-@ response curve measures the effect of the ability of a range of concentrations of antagonists to reverse the activity of an agonist . The potency of an antagonist is usually defined by its EC50 value . This can be calculated for a given antagonist by determining the concentration of antagonist needed to elicit half inhibition of the maximum biological response of an agonist . Elucidating an EC50 value is useful for comparing the potency of drugs with similar efficacies , however the dose @-@ response curves produced by both drug antagonists must be similar . The lower the EC50 the greater the potency of the antagonist , and the lower the concentration of drug that is required to inhibit the maximum biological response . Lower concentrations of drugs may be associated with fewer side @-@ effects .

= = = Affinity = = =

The affinity of an antagonist for its binding site (Ki) , i.e. its ability to bind to a receptor , will determine the duration of inhibition of agonist activity . The affinity of an antagonist can be determined experimentally using Schild regression or for competitive antagonists in radioligand binding studies using the Cheng @-@ Prusoff equation . Schild regression can be used to determine the nature of antagonism as beginning either competitive or non @-@ competitive and Ki determination is independent of the affinity , efficacy or concentration of the agonist used . However , it is important that equilibrium has been reached . The effects of receptor desensitization on reaching equilibrium must also be taken into account . The affinity constant of antagonists exhibiting two or more effects , such as in competitive neuromuscular @-@ blocking agents that also block ion channels as well as antagonising agonist binding , cannot be analyzed using Schild regression . Schild regression involves comparing the change in the dose ratio , the ratio of the EC50 of an agonist alone compared to the EC50 in the presence of a competitive antagonist as determined on a dose response curve . Altering the amount of antagonist used in the assay can alter the dose ratio . In Schild regression , a plot is made of the log (dose ratio @-@ 1) versus the log concentration of antagonist for a range of antagonist concentrations . The affinity or Ki is where the line cuts the x @-@ axis on the regression plot . Whereas , with Schild regression , antagonist concentration is varied in experiments used to derive Ki values from the Cheng @-@ Prusoff equation , agonist concentrations are varied . Affinity for competitive agonists and antagonists is related by the Cheng @-@ Prusoff factor used to calculate the Ki (affinity constant for an antagonist) from the shift in IC50 that occurs during competitive inhibition . The Cheng @-@ Prusoff factor takes into account the effect of altering agonist concentration and agonist affinity for the receptor on inhibition produced by competitive antagonists .

= = Types = =

= = = Competitive = = =

Competitive antagonists (also known as surmountable antagonists) reversibly bind to receptors at the same binding site (active site) as the endogenous ligand or agonist , but without activating the receptor . Agonists and antagonists " compete " for the same binding site on the receptor . Once bound , an antagonist will block agonist binding . The level of activity of the receptor will be determined by the relative affinity of each molecule for the site and their relative concentrations . High concentrations of a competitive agonist will increase the proportion of receptors that the agonist occupies , higher concentrations of the antagonist will be required to obtain the same degree of binding site occupancy . In functional assays using competitive antagonists , a parallel rightward shifts of agonist dose ? response curves with no alteration of the maximal response is observed .

The interleukin @-@ 1 receptor antagonist , IL @-@ 1Ra is an example of a competitive antagonist . The effects of a competitive antagonist may be overcome by increasing the concentration of agonist . Often (though not always) these antagonists possess a very similar chemical structure to that of the agonist .

=== Non @-@ competitive ===

The term " non @-@ competitive antagonism " (sometimes called non @-@ surmountable antagonists) can be used to describe two distinct phenomena : one in which the antagonist binds to the active site of the receptor , and one in which the antagonist binds to an allosteric site of the receptor . While the mechanism of antagonism is different in both of these phenomena , they are both called " non @-@ competitive " because the end @-@ results of each are functionally very similar . Unlike competitive antagonists , which affect the amount of agonist necessary to achieve a maximal response but do not affect the magnitude of that maximal response , non @-@ competitive antagonists reduce the magnitude of the maximum response that can be attained by any amount of agonist . This property earns them the name " non @-@ competitive " because their effects cannot be negated , no matter how much agonist is present . In functional assays of non @-@ competitive antagonists , depression of the maximal response of agonist dose @-@ response curves , and in some cases , rightward shifts , is produced . The rightward shift will occur as a result of a receptor reserve (also known as spare receptors , see in pharmacodynamics) and inhibition of the agonist response will only occur when this reserve is depleted .
An antagonist that binds to the active site of a receptor is said to be " non @-@ competitive " if the bond between the active site and the antagonist is irreversible or nearly so . This usage of the term " non @-@ competitive " may not be ideal , however , since the term " irreversible competitive antagonism " may also be used to describe the same phenomenon without the potential for confusion with the second meaning of " non @-@ competitive antagonism " discussed below .
The second form of " non @-@ competitive antagonists " act at an allosteric site . These antagonists bind to a distinctly separate binding site from the agonist , exerting their action to that receptor via the other binding site . They do not compete with agonists for binding at the active site . The bound antagonists may prevent conformational changes in the receptor required for receptor activation after the agonist binds . Cyclothiazide has been shown to act as a reversible non @-@ competitive antagonist of mGluR1 receptor .

=== Uncompetitive ===

Uncompetitive antagonists differ from non @-@ competitive antagonists in that they require receptor activation by an agonist before they can bind to a separate allosteric binding site . This type of antagonism produces a kinetic profile in which " the same amount of antagonist blocks higher concentrations of agonist better than lower concentrations of agonist " . Memantine , used in the treatment of Alzheimer 's disease , is an uncompetitive antagonist of the NMDA receptor .

=== Silent antagonists ===

Silent antagonists are competitive receptor antagonists that have zero intrinsic activity for activating a receptor . They are true antagonists , so to speak . The term was created to distinguish fully inactive antagonists from weak partial agonists or inverse agonists .

=== Partial agonists ===

Partial agonists are defined as drugs that , at a given receptor , might differ in the amplitude of the functional response that they elicit after maximal receptor occupancy . Although they are agonists , partial agonists can act as a competitive antagonist in the presence of a full agonist , as it competes with the full agonist for receptor occupancy , thereby producing a net decrease in the receptor

activation as compared to that observed with the full agonist alone . Clinically , their usefulness is derived from their ability to enhance deficient systems while simultaneously blocking excessive activity . Exposing a receptor to a high level of a partial agonist will ensure that it has a constant , weak level of activity , whether its normal agonist is present at high or low levels . In addition , it has been suggested that partial agonism prevents the adaptive regulatory mechanisms that frequently develop after repeated exposure to potent full agonists or antagonists . Buprenorphine , a partial agonist of the ? @-@ opioid receptor , binds with weak morphine @-@ like activity and is used clinically as an analgesic in pain management and as an alternative to methadone in the treatment of opioid dependence .

Inverse agonists

An inverse agonist can have effects similar to those of an antagonist , but causes a distinct set of downstream biological responses . Constitutively active receptors that exhibit intrinsic or basal activity can have inverse agonists , which not only block the effects of binding agonists like a classical antagonist but also inhibit the basal activity of the receptor . Many drugs previously classified as antagonists are now beginning to be reclassified as inverse agonists because of the discovery of constitutive active receptors . Antihistamines , originally classified as antagonists of histamine H1 receptors have been reclassified as inverse agonists .

Reversibility

Many antagonists are reversible antagonists that , like most agonists , will bind and unbind a receptor at rates determined by receptor @-@ ligand kinetics .
Irreversible antagonists covalently bind to the receptor target and , in general , cannot be removed ; inactivating the receptor for the duration of the antagonist effects is determined by the rate of receptor turnover , the rate of synthesis of new receptors . Phenoxybenzamine is an example of an irreversible alpha blocker ? it permanently binds to ? adrenergic receptors , preventing adrenaline and noradrenaline from binding . Inactivation of receptors normally results in a depression of the maximal response of agonist dose @-@ response curves and a right shift in the curve occurs where there is a receptor reserve similar to non @-@ competitive antagonists . A washout step in the assay will usually distinguish between non @-@ competitive and irreversible antagonist drugs , as effects of non @-@ competitive antagonists are reversible and activity of agonist will be restored .
Irreversible competitive antagonists also involve competition between the agonist and antagonist of the receptor , but the rate of covalent bonding differs and depends on affinity and reactivity of the antagonist . For some antagonist , there may be a distinct period during which they behave competitively (regardless of basal efficiacy) , and freely associate to and dissociate from the receptor , determined by receptor @-@ ligand kinetics . But , once irreversible bonding has taken place , the receptor is deactivated and degraded . As for non @-@ competitive antagonists and irreversible antagonists in functional assays with irreversible competitive antagonist drugs , there may be a shift in the log concentration ? effect curve to the right , but , in general , both a decrease in slope and a reduced maximum are obtained .