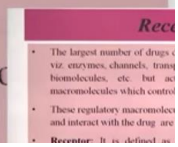
Agonist and antagonist

Receptor

- The largest number of drugs do not bind directly to the effectors, viz. enzymes, channels, transporters, structural proteins, template biomolecules, etc. but act through specific regulatory macromolecules which control the above listed effectors.
- These regulatory macromolecules or the sites on them which bind and interact with the drug are called **'receptors'.**
- **Receptor:** It is defined as a macromolecule or binding site located on the surface or inside the effector cell that recognize the signal molecule/drug and initiate the respo but itself has no other function.

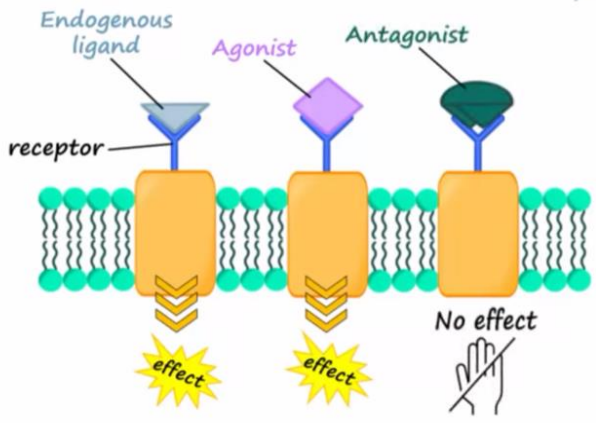


TYPES OF RECEPTORS

- Ligand Gated Ion Channels
- G-Protein Coupled receptors
- Enzyme Linked receptors
- Nuclear receptors

- **Ligand** (Latin: ligare—to bind) Any molecule which attaches selectively to particular receptors or sites. The term only indicates affinity or ability to bind without regard to functional change: agonists and competitive antagonists are both ligands of the same receptor.
- **Agonist** An agent which activates a receptor to produce an effect similar to that of the physiological signal molecule.

➢ Ligands: bind to receptors



- ➢ Endogenous ligands: made by the body & cause actions
- ➢ Agonists: cause actions
- ➢ Antagonists: prevent actions

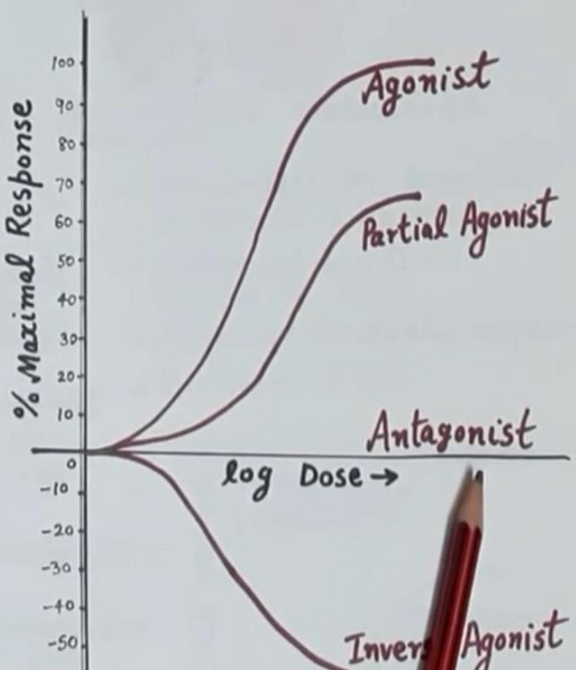
Affinity: Ability of a drug to bind with receptor

Efficacy or Intrinsic Activity: Ability of a drug to activate receptor & produce biological Response.

(a) Agonist has affinity and maximum intrinsic activity (IA=1), eg adrenaline, histamine, morphine.

(b) Partial Agonist has affinity and submaximal intrinsic activity (IA = 0 to 1) eg. Buprenorphine, Aripiprazole

(c) Inverse Agonist has affinity but intrinsic activity with negative sign (IA between 0 and -1) eg. Chlorpheniramine.

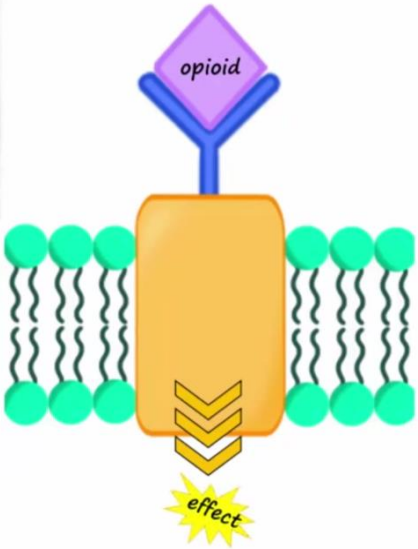


- The ability to bind with the receptor designated as ***affinity (0/1),*** and the capacity to induce a functional change in the receptor designated as ***intrinsic activity (IA)*** or efficacy are independent properties.

- **Agonists** have both affinity and maximal intrinsic activity (IA = 1), e.g. adrenaline, histamine, morphine.
- **Competitive antagonists** have affinity but no intrinsic activity (IA = 0), e.g. propranolol, atropine, chlorpheniramine, naloxone.

- **Antagonist:**
- Does not produce a biological response on binding to a receptor but instead blocks or reduces the effect of an agonist. It may be competitive or non-competitive.
- ***Competitive antagonism*** - Drug binds selectively to a receptor without causing activation but in such a way to prevent binding of the agonist. The antagonism may be reversible; the effect can be overcome by increasing the concentration of the agonist, will lead to a shift in the equilibrium.

naloxone (Narcan) is used to reverse opioid overdoses



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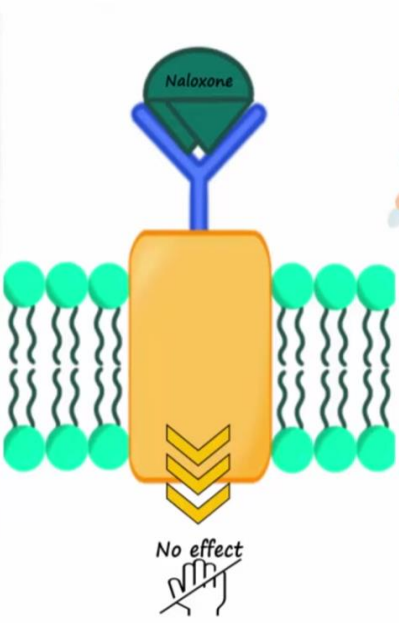
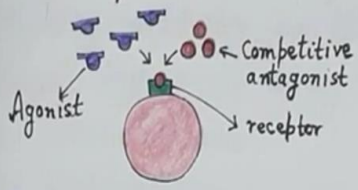


Antagonist: has affinity but no Intrinsic activity (IA=0)

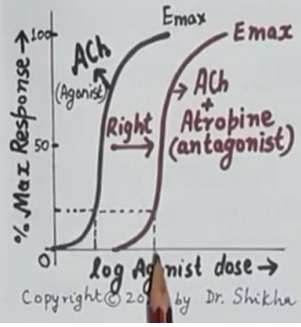
1. Competitive



→ Antagonist competes with agonist for agonist binding site.

Reversible

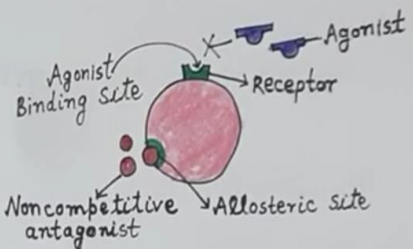
→ Antagonist binds reversibly
→ surmountable, blockade is overcome by increasing conc. of agonist.



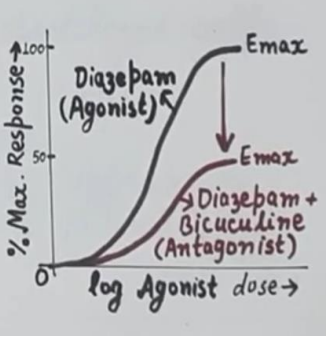
Irreversible

→ Antagonist binds covalently to agonist binding site
→ If at all antagonist dissociates - it dissociates very very slowly.
→ type of noncompetitive antagonist
→ eg Phenoxybenzamine (antagonist of Adr. at α- receptors).

2. Noncompetitive

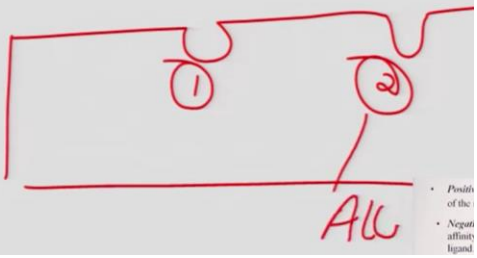


→ No competition between antagonist & agonist
→ Antagonist binds to allosteric site
→ Antagonist deactivates receptor
→ Unsurmountable.



- ***Non-competitive antagonism-*** A non-competitive antagonist may affect the reaction by binding to the active site of the receptor or to an allosteric site, therefore not competing with the agonist. The magnitude of the maximal response is reduced, regardless of the amount of agonist present.
- **Allosteric modulator-** A drug that binds to a receptor at a site distinct from the active site. A conformational change is induced in the receptor, altering the affinity of the receptor for the endogenous ligand.

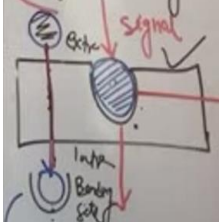
- ***Positive allosteric modulators*** - Increase the affinit of the receptor for the endogenous ligand.
- ***Negative allosteric modulators*** – Decrease th affinity of the receptor for the endogenou ligand.



Mechanism of Drug Action:- Receptor

Receptors:- These are macromolecule or binding site (1), located on the surface or (2) inside the cell, that recognize (3) the signal molecule or drug (4) and initiate the response (05).

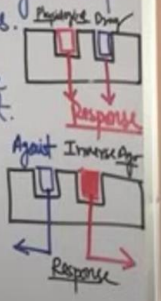
Signal / Drugs

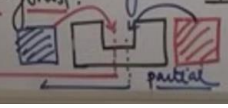


Drug + Receptor = complex → Action

Full Terms:-

1. **Agonist:-** Which activate receptor and give response as like physiological signals.
2. **Inverse Agonist** - Which activate receptor but produce response in opposit direction of agonist.
3. **Antagonist** - Which prevent the action of Agonist on receptor.
4. **partial agonist** - Which activate receptor to give submaximal effect but antagonize the action of full agonist.





5. **Legand:-** Signal (Bind selectively)

Spare Receptor = Basic Introduction

Spare = Reserve receptor. or simply unused.

Expl^{n} = Receptors may be considered as – 'spare R.' when the maximal response is elicited by an agonist at a concentration that does it produce full occupancy of the available receptors.

Simplest form = If an agonist can induce a maximum response while occupying less than 100% of available recep.

→ Unoccupied receptor = spare receptors

– Maximal response without occupying 100% receptor

Note:– spare receptor exist when max. drug response is achieved prior to saturation of all receptors.

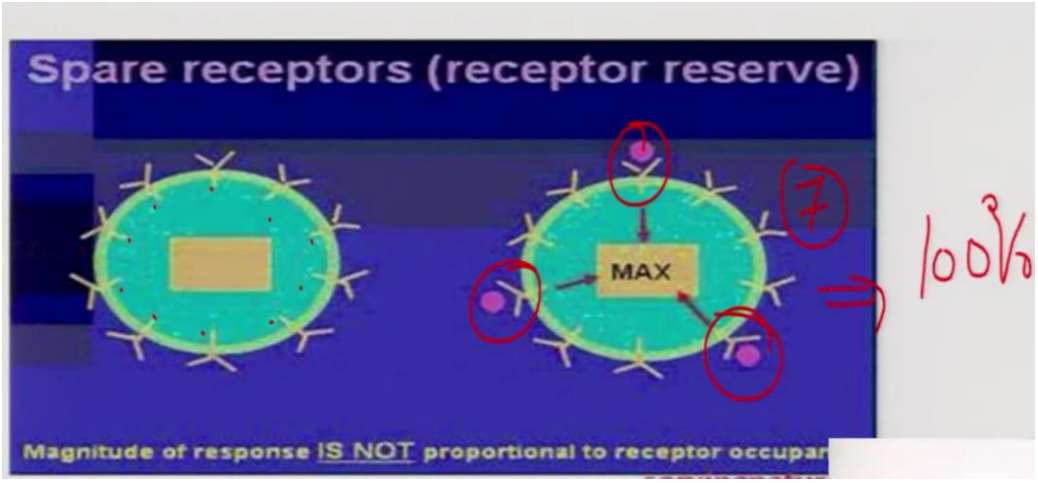
They are not hidden receptors.

Widely misunderstood as non functional

Presence of spare receptor = ↑ potency of agonist

Spare Receptor

- It has also been demonstrated that many full agonists can produce maximal response even while occupying <1% of the available receptors. A large receptor reserve exists in their case, or a number of spare receptors are present.
- Receptors are said to be spare **when, the maximal response can be elicited by an agonist at a concentration that does not result in 100% occupancy** of available receptors.


Spare receptors (receptor reserve)
MAX
7
100%
Magnitude of response IS NOT proportional to receptor occupar


1 2 3 4 5
Available receptors
1 2 3 4 5
Receptors Occupied
Max Effect
100% / Maximal