

***Title of Lecture: drug-receptor interactions***

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***Sheet no: 9***

***Refer to slide no. :5***

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Agonists and antagonists are considered as types of drug-receptor interactions . first of all a drug binds to a receptor to produce a response then it dissociates from it, the dissociation of the drug from the receptor is followed by metabolism and excretion .

As long as the free form of the drug is present in the blood ,there’ll be binding to the receptors to produce an action until the free form ends .

\*The agonist that produces good efficacy (Full efficacy ) ,with few occupancy is known as **a full agonist** .

-In the case of a **partial agonist** the drug interacts with the receptor and produces a response and it produces Vmax but it’s lower than the Vmax produced by the full agonist .

-The doctor mentioned an example about a drug that has alpha-1 and partial alpha-2 agonistic activities . the Vmax of alpha-1 is **slightly** higher than alpha-2 .

-The same drug can have agonistic and antagonistic activities .

-the antagonistic activity on the same receptor of the full agonist is to avoid certain side effects to this full agonist .

\*Agonist-Antagonist produce good analgesia but at the same time produce addictive properties as a full agonist alone . stick the antagonistic activity to the side effects more than the desired effects . however a drug with 50% agonist and 50% antagonist is considered as a useless drug .

**-Inverse agonist** is an agonist that binds to the same receptor but produces opposite effects .

-refer to the graph in slide 45:

A and B produce an excellent potency , however Vmax is lower in B “B is a partial agonist that binds to the same receptor and back to the definition of the partial agonist ,it produces lower Vmax than the full agonist “ . Therefore both are potent by having similar ED50 .

The difference between A and C that one of them is more potent than the other . the same goes for B and D in which B is more potent than D.

-Partial agonist is utilized in specific cases .

-Refer to the graph in slide 47 : (different drugs that act on the same receptor )

It shows that the agonist produces a response , the inverse agonist produces an effect opposite to that of the agonist .

The antagonist interacts with a receptor producing a response but if it’s given with an agonist it inverses the action of this agonist .

Antagonist alone produces no effect .

\*Antagonist is used in the case of **drug toxicity** . if someone has poisoning from something ,we stop the drug and he’s given a specific antagonist .

-allergy coma (histamine mediates allergic reactions ) , histamine is released immunologically or non immunologically mediated response “ mast cell is degranulated and histamine is released to the blood stream and then reacts with specific receptors H1,H2,H3,.. this H1mediates the allergy “

\*possible targets of drugs to manage allergic conditions :

-synthesizing a drug that is an antagonist to the receptor H1 .

-histamine synthesis inhibitors to manage allergic reactions .

-drugs that release of histamine from mast cells they aren’t good drugs since they release histamine and it reaches the blood stream we cannot avoid allergic reactions except by using specific antagonist .

-prophylaxis a term used when someone has an allergy towards something and stars taking drugs two months before to avoid allergic reactions .

\*could a receptor produce a response without the binding of a specific agonist ?

The answer is yes ,it is possible in certain pathological situations .

\***Constitutive activity of a receptor** occurs in certain pathological situations as in the case of an eight years old girl and menstruating or an eight years old male child with over-sexuality and in certain cases of hyperthyroidism .

The over-activity of a receptor leads to diseases and this is know as constitutive receptor activity .

\***addition** : when you have two drugs both of them produce a response and having similar activity however they’re different drugs .( as in giving 2 drugs for heart rate ,one drug increases the HR by 50 and the other increases the HR by 50 as well and by this we have 100 as a final response ).

- one drug adds its response to the second drug .

**\*synergism**: having two drugs that produce a response , once they’re given together the final response is greater than both .” one drug synergizes the effect of another ; 50+50=150 “

-useful in the case of giving more than one drug .

**\*potentiation** :In the case of two drugs,one produces no response but enhances the response of the other one . “0+50=100”

-example: **propanacid with penicillin** . if propanacid is given with penicillin ,it interferes with the excretion of penicillin so the response has greatly increased since propanacid has no antibacterial activity . and penicillin activity has increased and this is potentiation.

The previous terms are useful in the case of a drug given alone that produces side effects and we want it to give therapeutic effects so we give another drug with it to enhance it by either addition, synergism or potentiation .

\***spare receptors** 🡪certain agonists bind to fewer number of receptors and they produce their maximal response . “ suppose we have 100 receptors ,10 of them aren’t working anymore therefore these agonists are capable of binding to the 90 receptors that are left until the regeneration of new one occur to compensate those 10 “

-as we know that Vmax is reached when we have full occupancy of the receptors and when there’s no further increase in the dose there’ll be no further increase in the response . once we increase the dose ,Vmax increases and by this we reach the toxic level that’s why we have to keep a balance .

\*many neurotransmitters and hormones as insulin occupy few number of receptors producing full response , not exceeding 10% of total number of receptors .

-slide 50 shows a graph that resembles receptor occupancy vs physiological response .

\*with or without the spare receptor theory , Vmax should be reached .

**Desensitization /down regulation** 🡪 is a decrease in the response with the frequent use correlated to the number of receptors where the chronic use resulted in a decrease in total number of receptors .

-it makes sense because once the total #of receptors decreases ,the response decreases too or if their number remained the same their sensitivity towards the agonist decreases .

This desensitization is overcome by increasing the dose a little bit .

\*Beta blockers are used for hypertension ,if you stop taking them suddenly there’ll be down regulation “beta receptors are down regulated “ but there’s another phenomenon occurs if you stop them which is up regulation(overstimulation ) .

In conclusion : -up regulation 🡪 increases the # of receptors

-down regulation 🡪decreases the # of receptors .

\*the difference between a blocker and an antagonist :

-Blocker antagonizes an endogenous substance in the body (secreted in the body )

-Antagonist reverses the effect of an exogenous agonist (from outside the body).

\*Antidote is a drug that reverses the action of a second drug but in a non receptor mediated mechanism .

\*slide 53:

-surmountable antagonism (competitive equilibrium )

When an agonist binds to the receptor and toxic level is reached ,an antagonist is given to bind to the same site on the receptor and kicks out the agonist of the binding site . now the action will be terminated since the agonist is out and the antagonist is still present .

Once the antagonist has done it’s job the agonist is required now and since we’re talking about the competitive equilibrium , the agonist kicks out the antagonist only if we increase the dose .

Can we reach the Vmax in the presence of an antagonist in the case of competitive? Yes but what we need to do is to increase the dose .

\*slide 54 :

-There’ll be no change in the total # of receptors ,if an agonist binds to a receptor and then an antagonist binds to the same one ( suppose we have 100 receptors ,an agonist binds one and what is left is 99 and when we have an antagonist it binds to the same receptor ending up with 99 receptors ).

-ED50 of an agonist increases in the presence of an antagonist in order to be able to kick out the antagonist .

\*slide 56:

Unsurmountable antagonism occurs in two ways :

They either bind to different receptors or bind to the same site on the receptor but **irreversibly .**

The most common type in unsurmountable is the non competitive in which there’s a decrease in the total # of receptors .( the agonist binds to a site and the antagonist binds to another one ; from 100 receptors we’ll end up with 98 ).

**Vmax cannot be reached in the case of a non competitive antagonist even if we increase the dose , only if the antagonist terminates it’s action .**

\*according to the graph in slide 59:

Vmax that is reached in the case of few antagonist is less than the one reached in the case of an agonist .

**The more the antagonist ,the more the downward shift curve .**

-Vmax is reached with the same ED50 but less than that of the agonist alone .