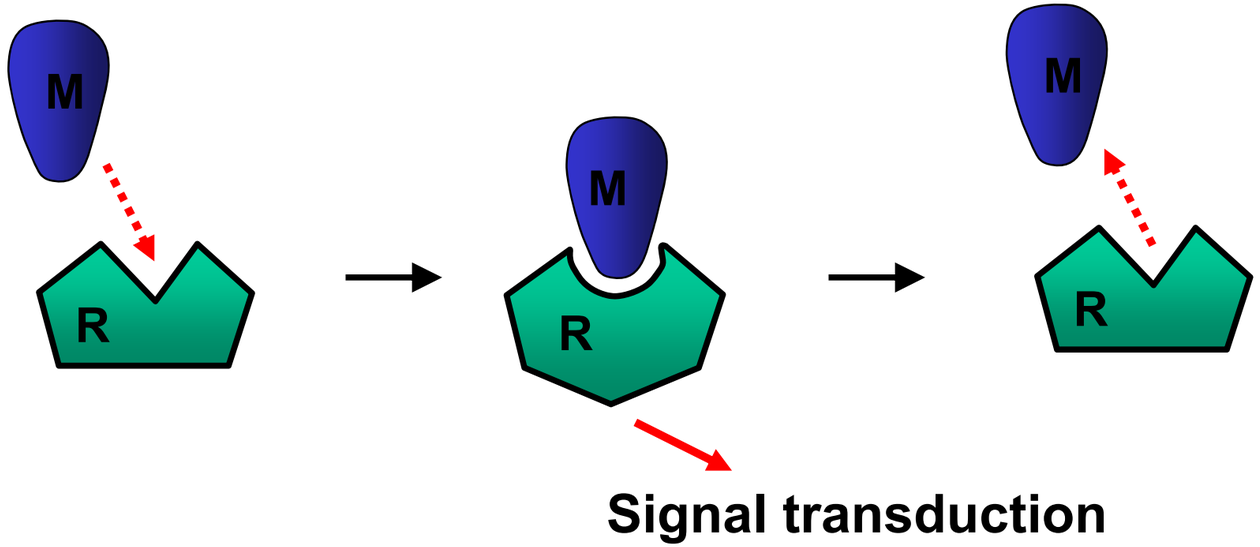
Medicinal Chemistry

Chapter 7

RECEPTOR AS DRUG TARGETS

Contents

In General



Signal transduction

Notes on drug design

• Agonists are drugs designed to mimic the natural messenger

• Agonists should bind and leave quickly - number of binding interactions is important

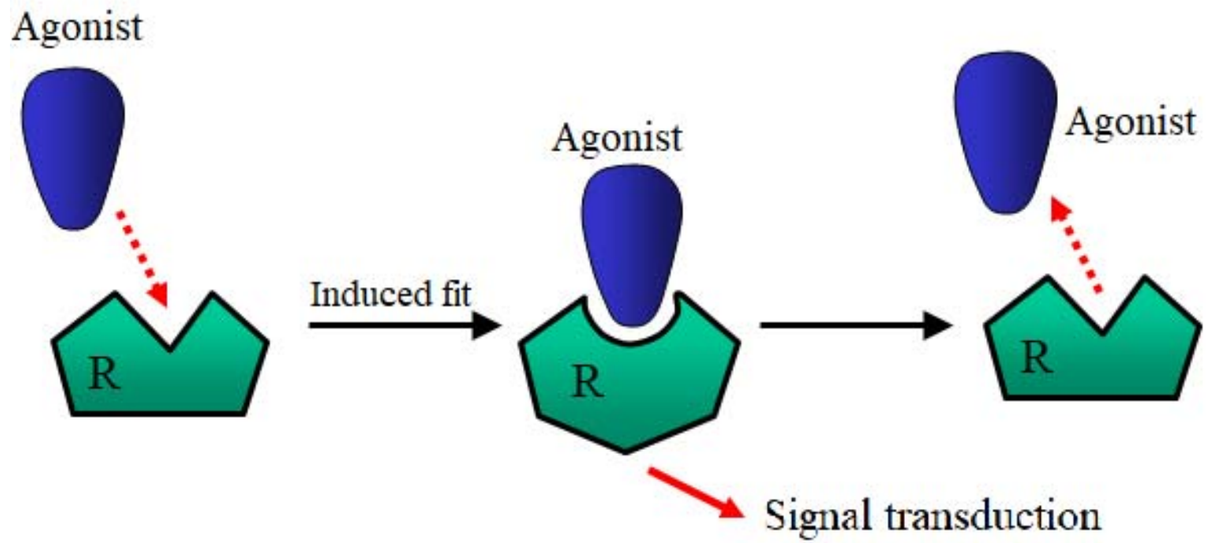
• Antagonists are drugs designed to block the natural messenger

• Antagonists tend to have stronger and/or more binding interactions, resulting in a different induced fit such that the receptor is not activated.

Design of Agonists

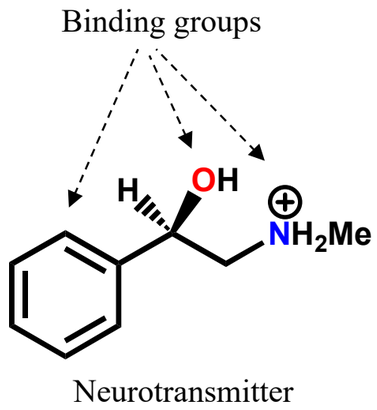
Introduction

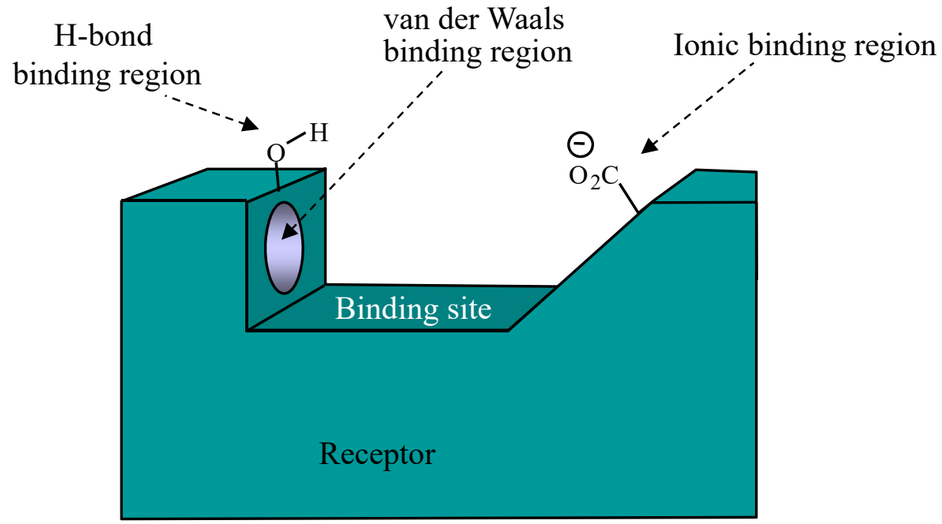
- Agonists mimic the natural messenger of a receptor
- Agonists bind reversibly to the binding site and produce the same induced fit as the natural messenger receptor is activated
- Similar intermolecular bonds formed as with natural messenger
- Agonists are often similar in structure to the natural messenger

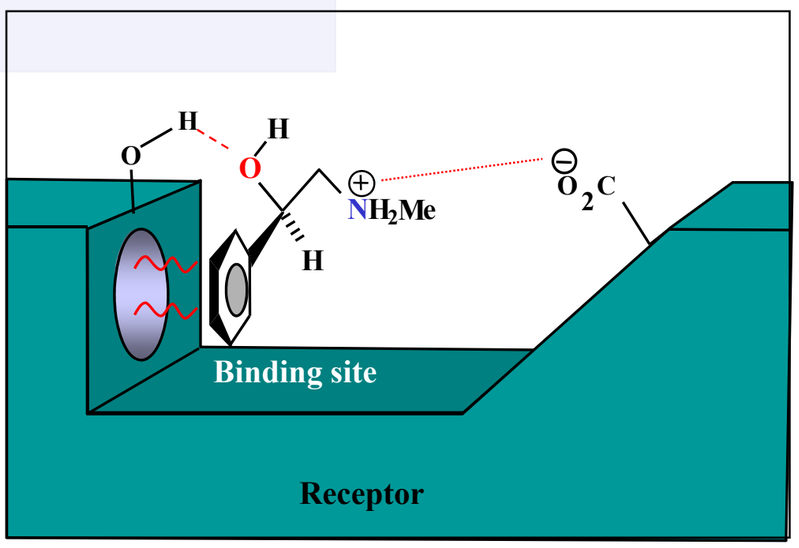


Requirements

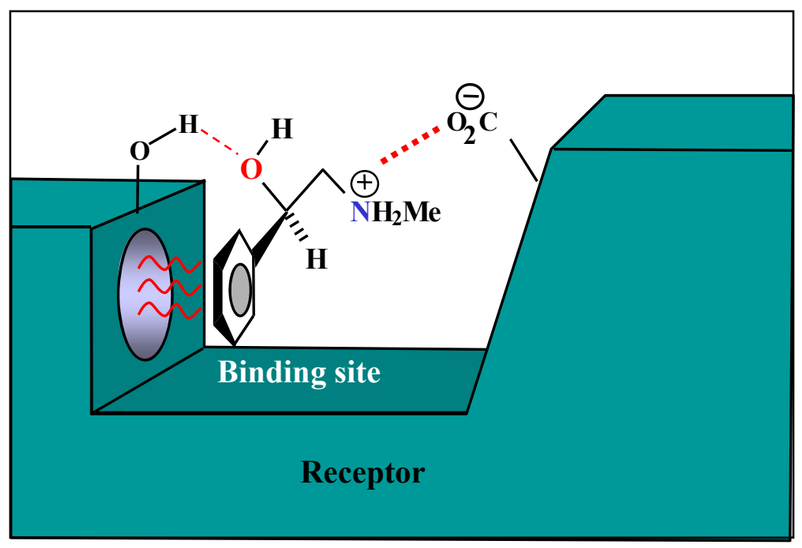
- The agonist must have the correct binding groups
- The binding groups must be correctly positioned to interact with complementary binding regions
- The drug must have the correct shape to fit the binding site







INDUCED FIT

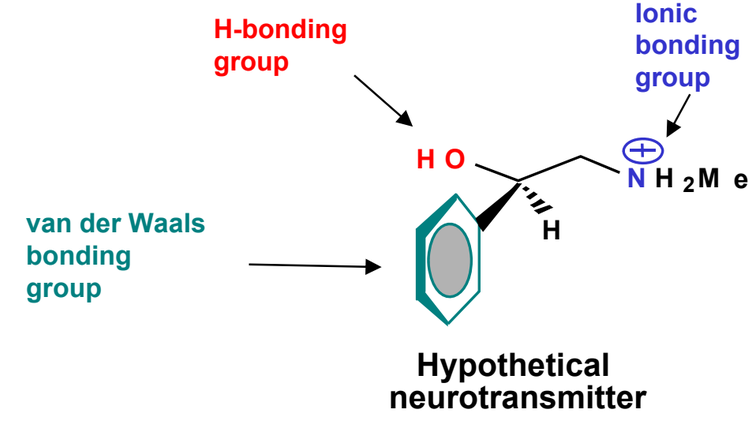


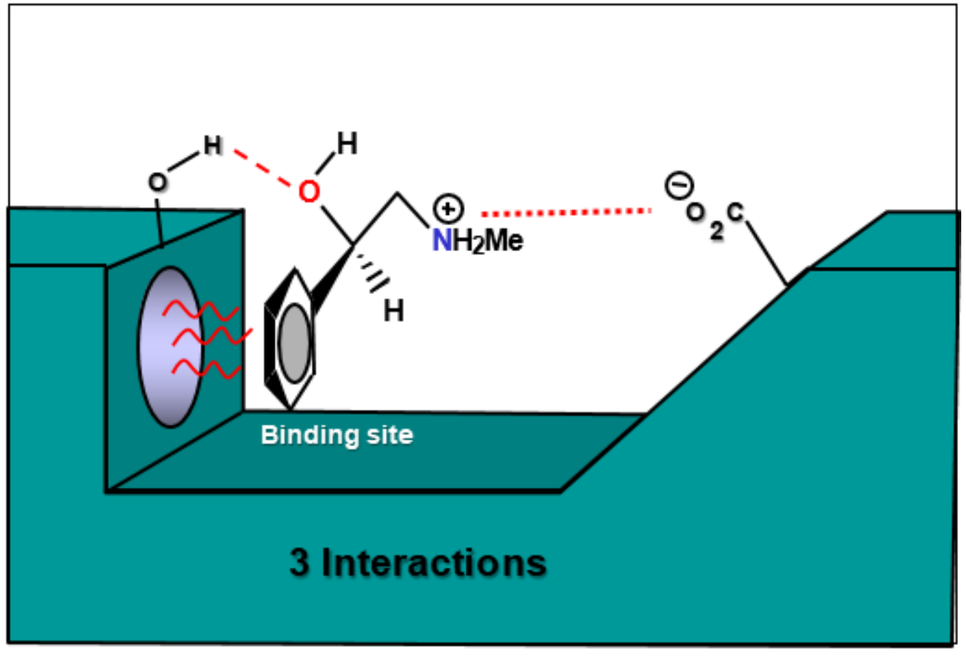
Induced fit allows stronger binding interactions

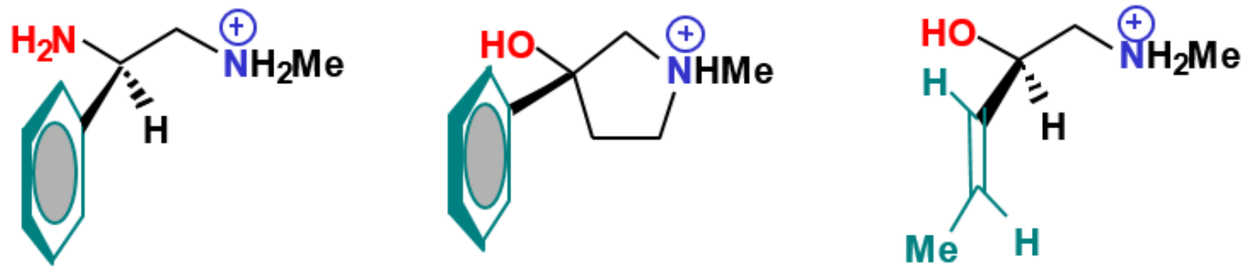
Design of Agonists

Correct binding groups

If we know the structure of the natural chemical messenger and can identify the functional groups that form important interactions with the binding site, then we might reasonably predict which of a series of molecules would interact in the same way.

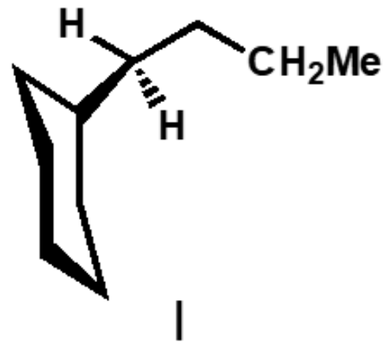




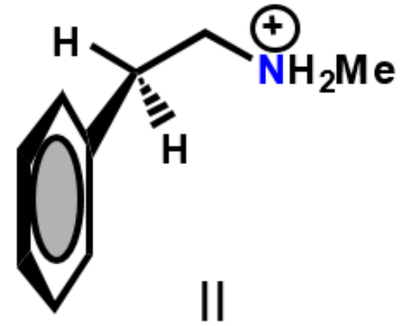


Possible agonists with similar binding groups

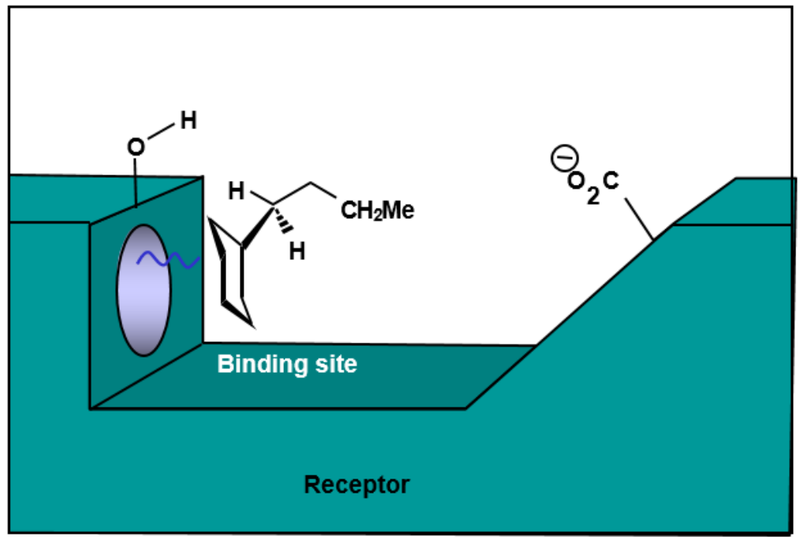
They lack one or more of the required binding groups and should, therefore, have poor activity. We would expect them to drift into the binding site, then drift back out again binding only weakly, but might be effective even though it lacks a suitable hydrogen bonding group.



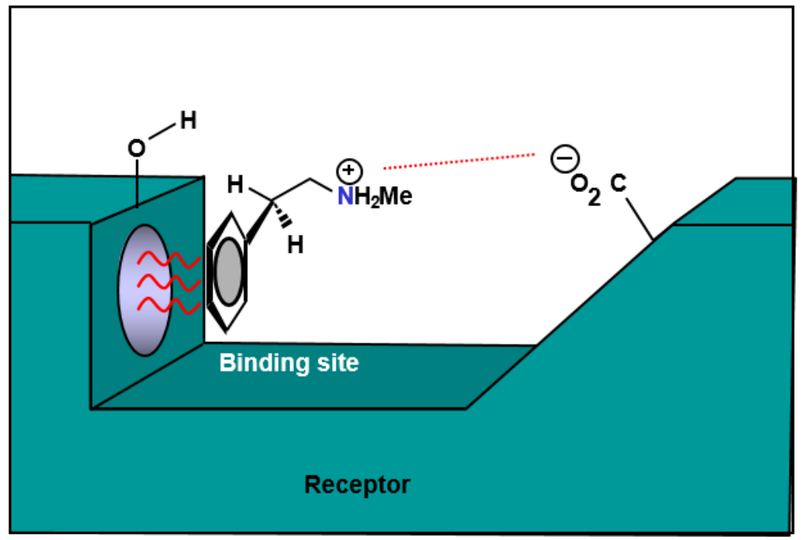
I



II



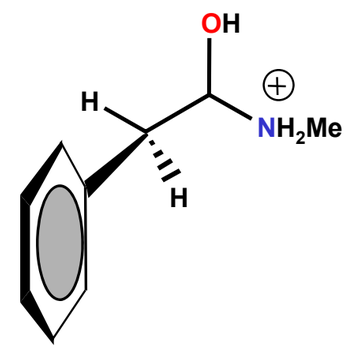
Structure I has one weak binding group - negligible activity

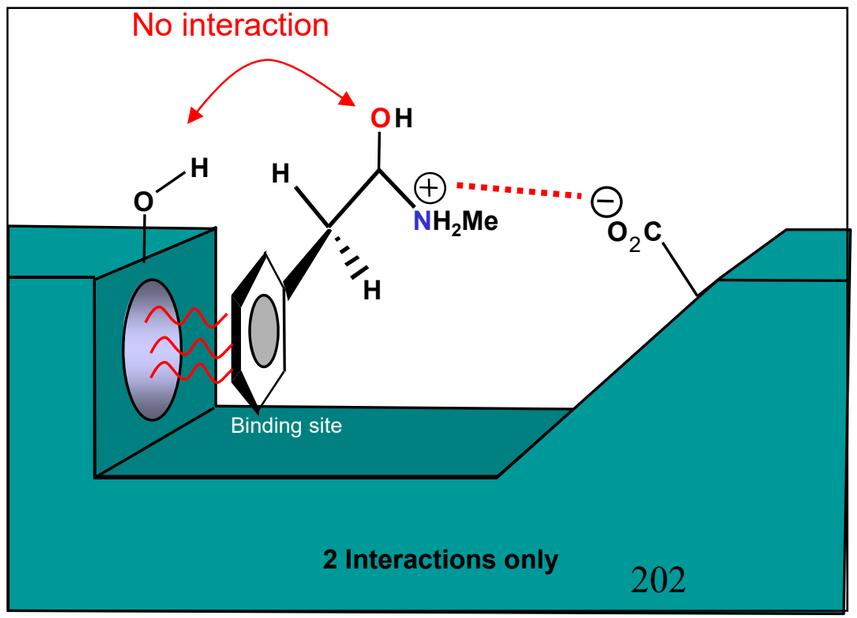


Structure II has 2 of the 3 required binding groups - weak activity

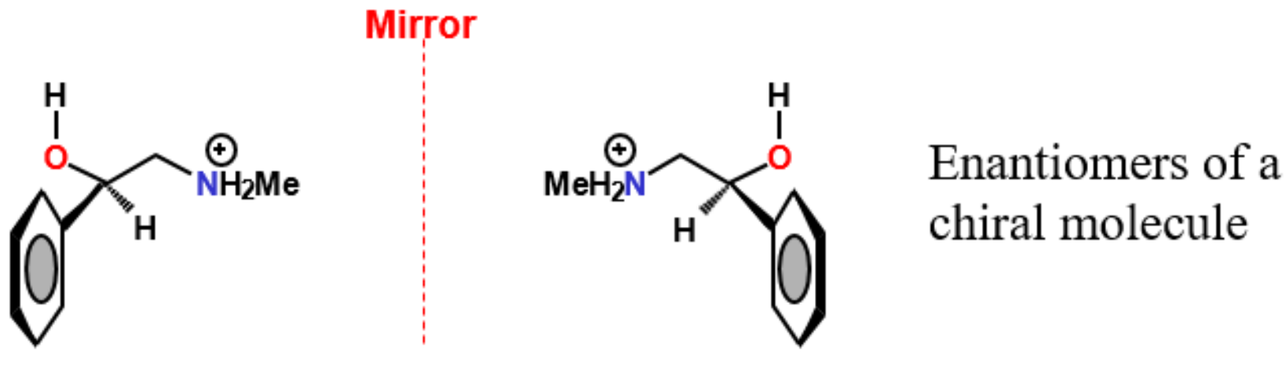
Correct position of binding groups

The molecule may have the correct binding groups, but if they are in the wrong relative positions they will not be able to form bonds at the same time. As a result, bonding would be too weak to be effective. Example has three binding groups, but only two can bind simultaneously

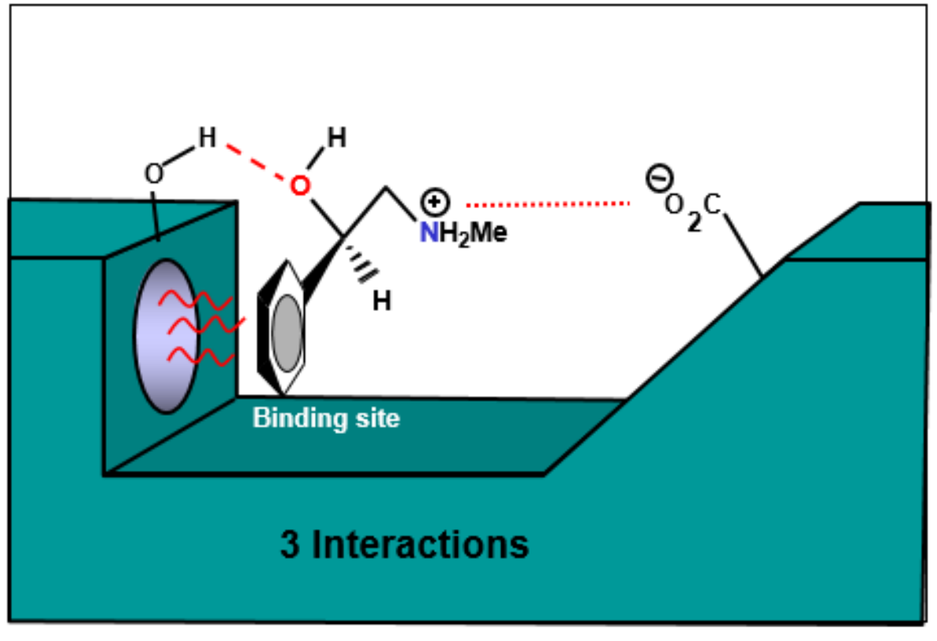


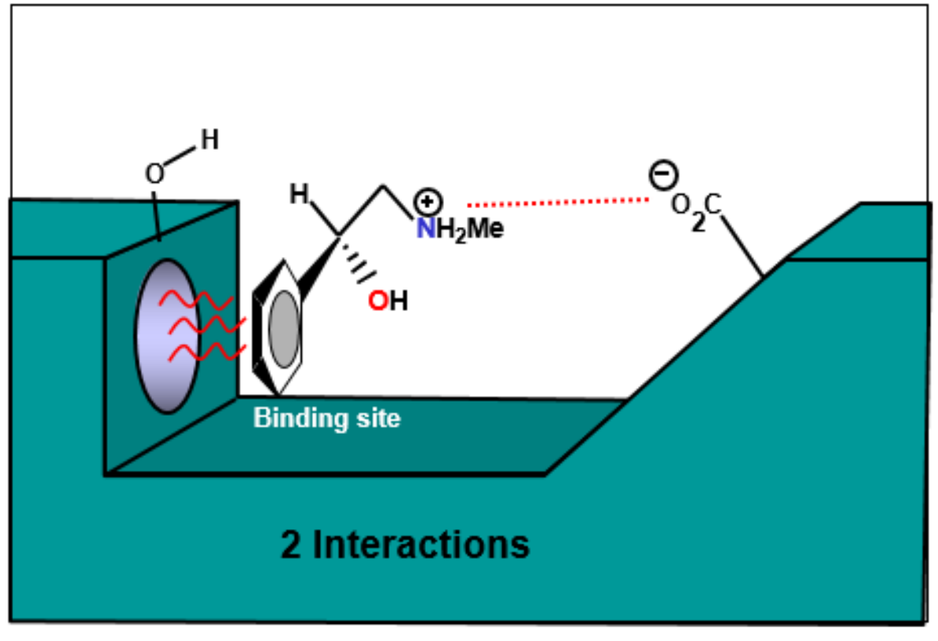


the mirror image of our hypothetical neurotransmitter would not bind strongly to the binding site, different enantiomers likely to have different biological properties



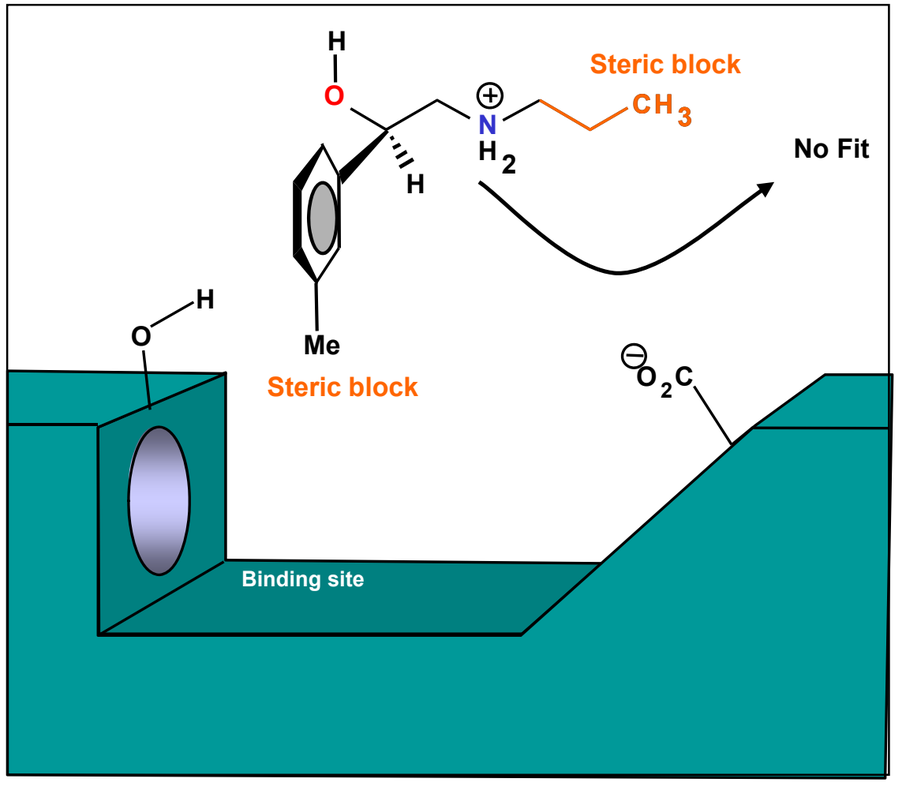
Enantiomers of a chiral molecule





Size and shape

- Agonist must have correct size and shape to fit binding site
- Groups preventing access are called steric shields or steric blocks

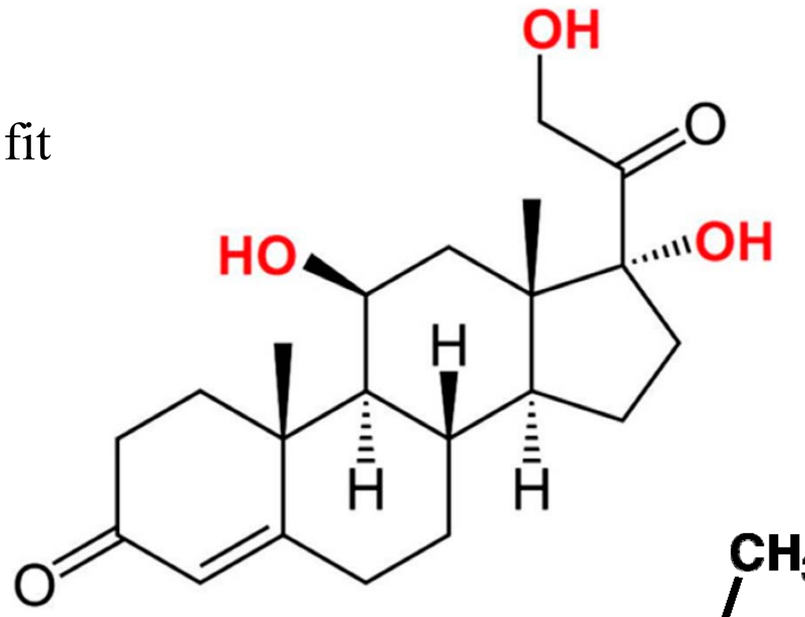


In exceptional cases, there can be quite significant alterations in the induced fit

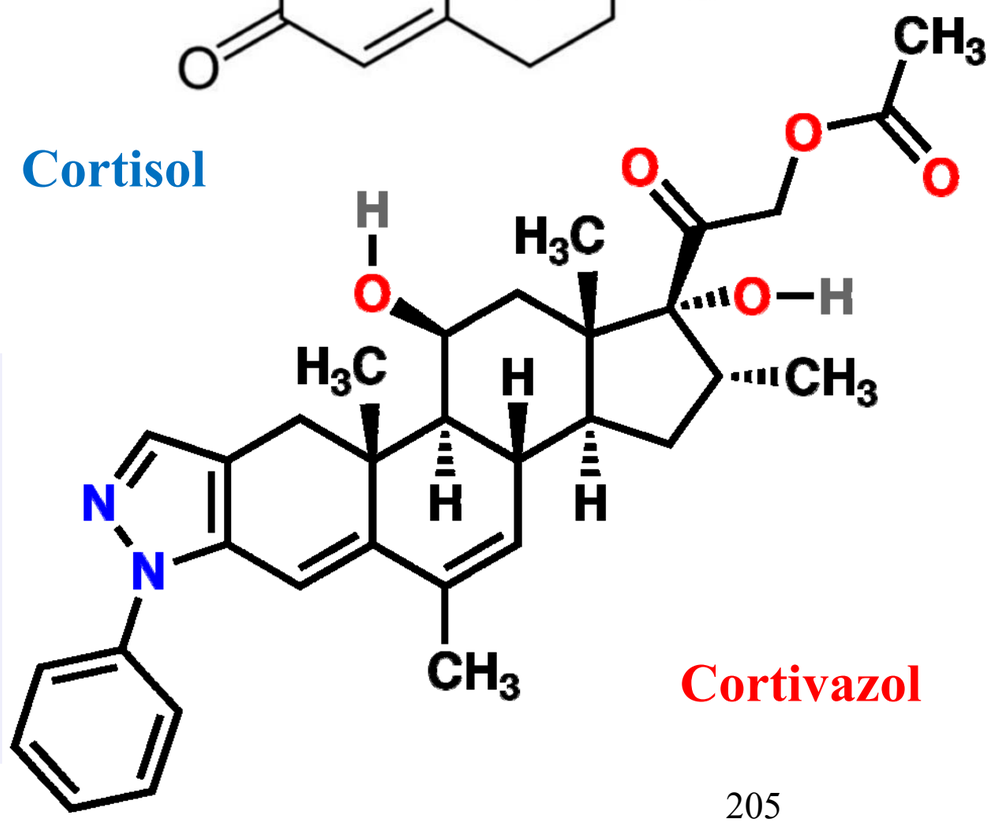
Cortisol have the correct size, shape, and binding groups to fit the binding site, and produce the required induced fit for activation the glucocorticoid receptor. And act as agonists

Cortivazol acts as an agonist, with lacking the ketone binding group and has two extra and a different induced fit had occurred from normal.

This had resulted in a new channel being opened up in the binding site that could accommodate the extra rings. Moreover, extra interactions with the rings compensated for the loss of the usually crucial ketone group.



Cortisol



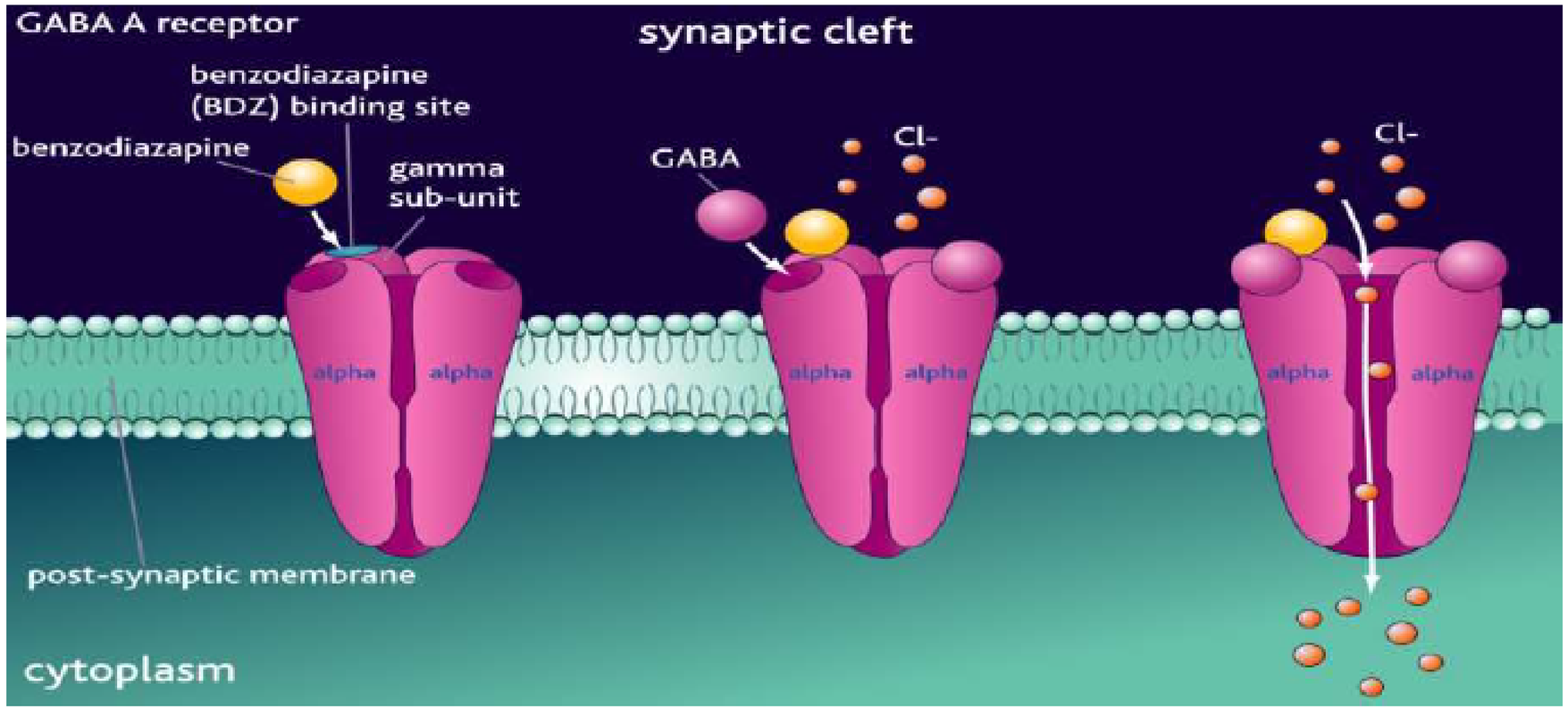
Cortivazol

Allosteric modulators

Agents which enhance receptor activity by binding to an allosteric binding site rather than the messenger binding site

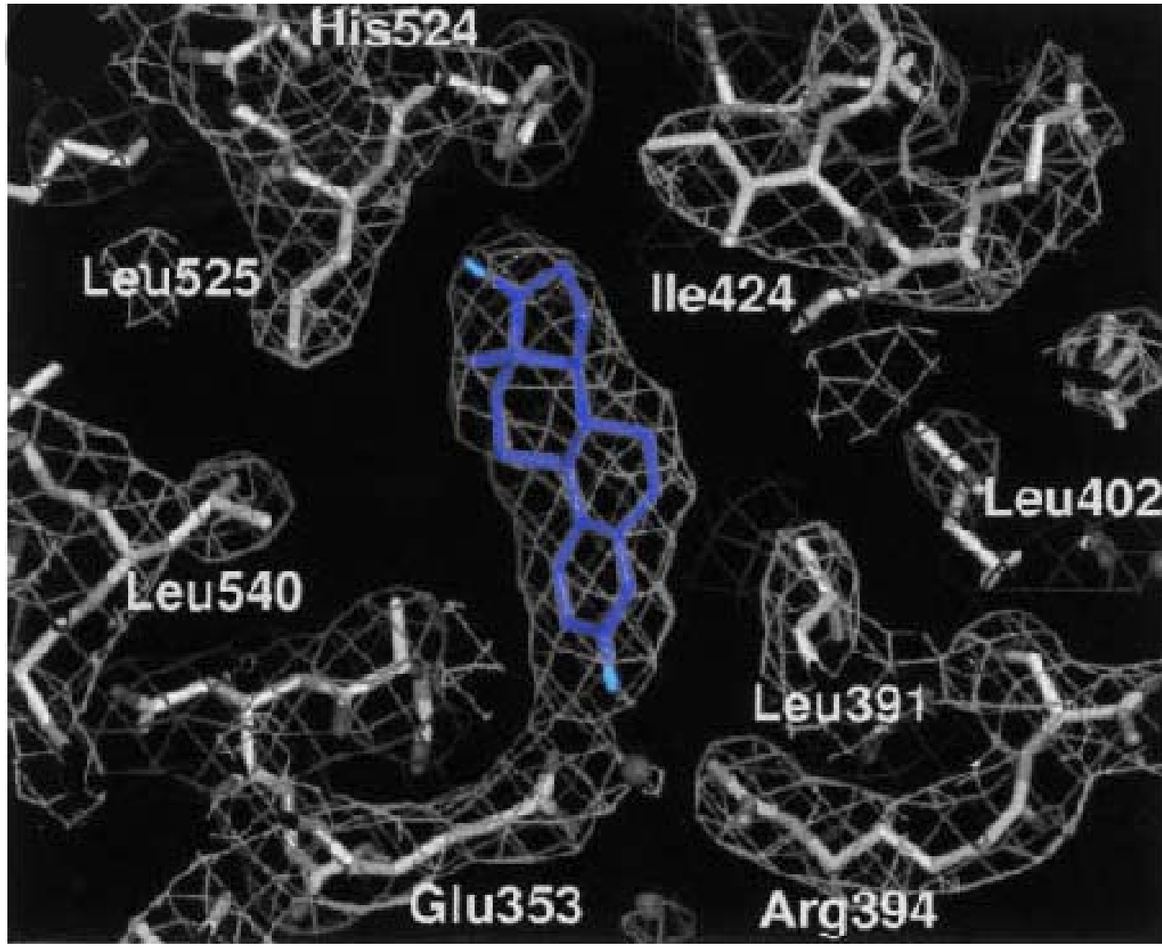
Example

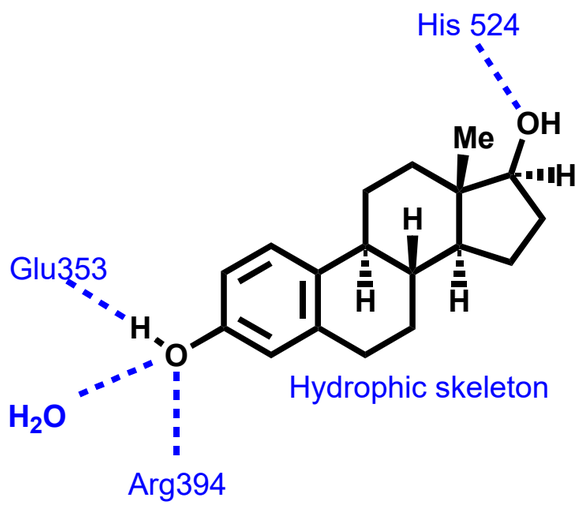
Benzodiazepines target the allosteric binding site of the $GABA_A$ receptor



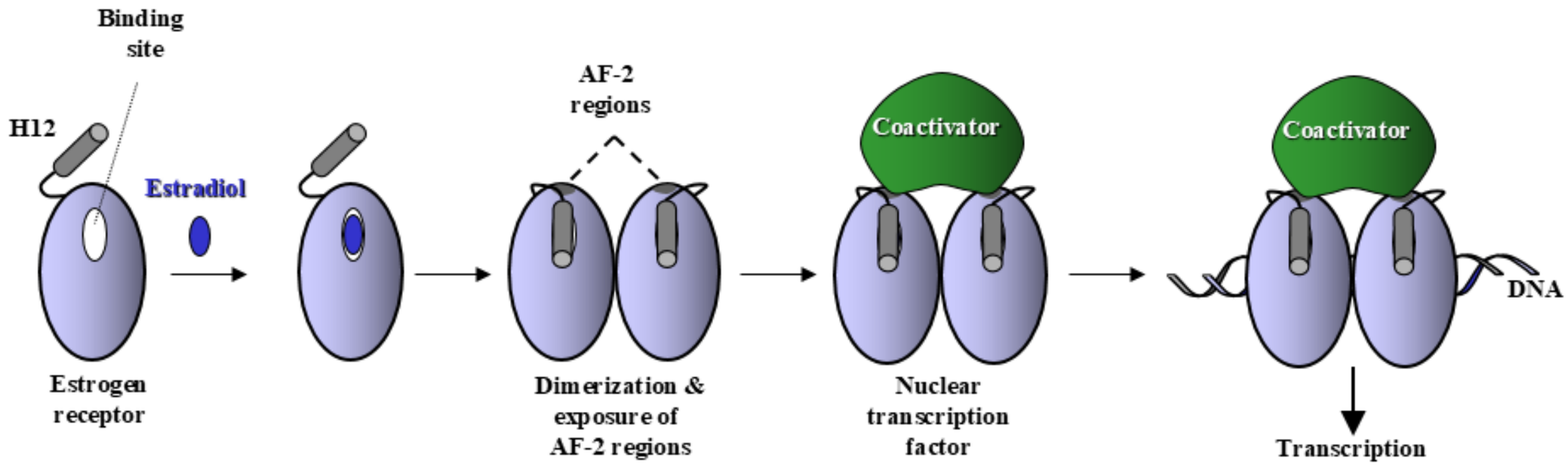
Case Study: Estradiol and the estrogen receptor “Agonists”

17β-Estradiol is a steroid hormone that affects the growth and development of a number of tissues by crossing cell membranes and interacting with the binding site of an estrogen intracellular receptor. By alcohol and phenol groups to form hydrogen bonds with the binding site, while the hydrophobic skeleton of the molecule forms van der Waals and hydrophobic interactions with other regions.





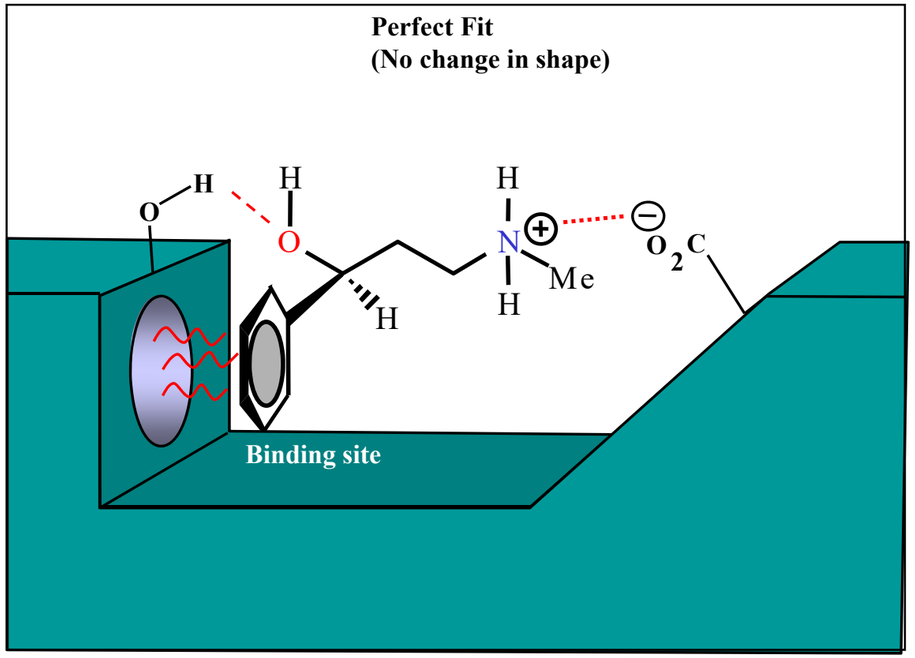
The binding induces a conformational change in the receptor which sees a helical section known as H12 folding across the binding site like a lid. This exposes a hydrophobic region called the activating function (AF-2) region which acts as a binding site for a co-activator protein. As dimerization has also taken place, there are two of these regions available and the co-activator binds to both to complete the nuclear transcription factor.



Design of Antagonists

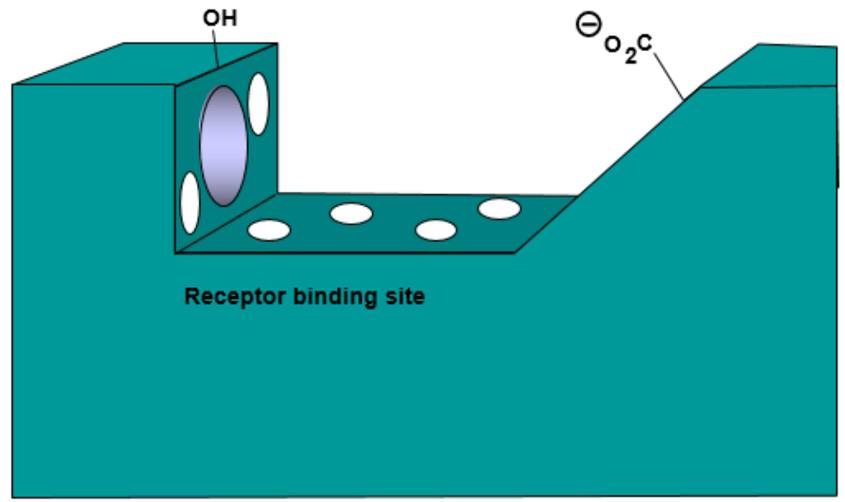
The compound fits the binding site perfectly and, as a result, does not cause any change of shape. Therefore, there is no biological effect and the binding site is blocked to the natural neurotransmitter.

So, Normal messenger is blocked from binding



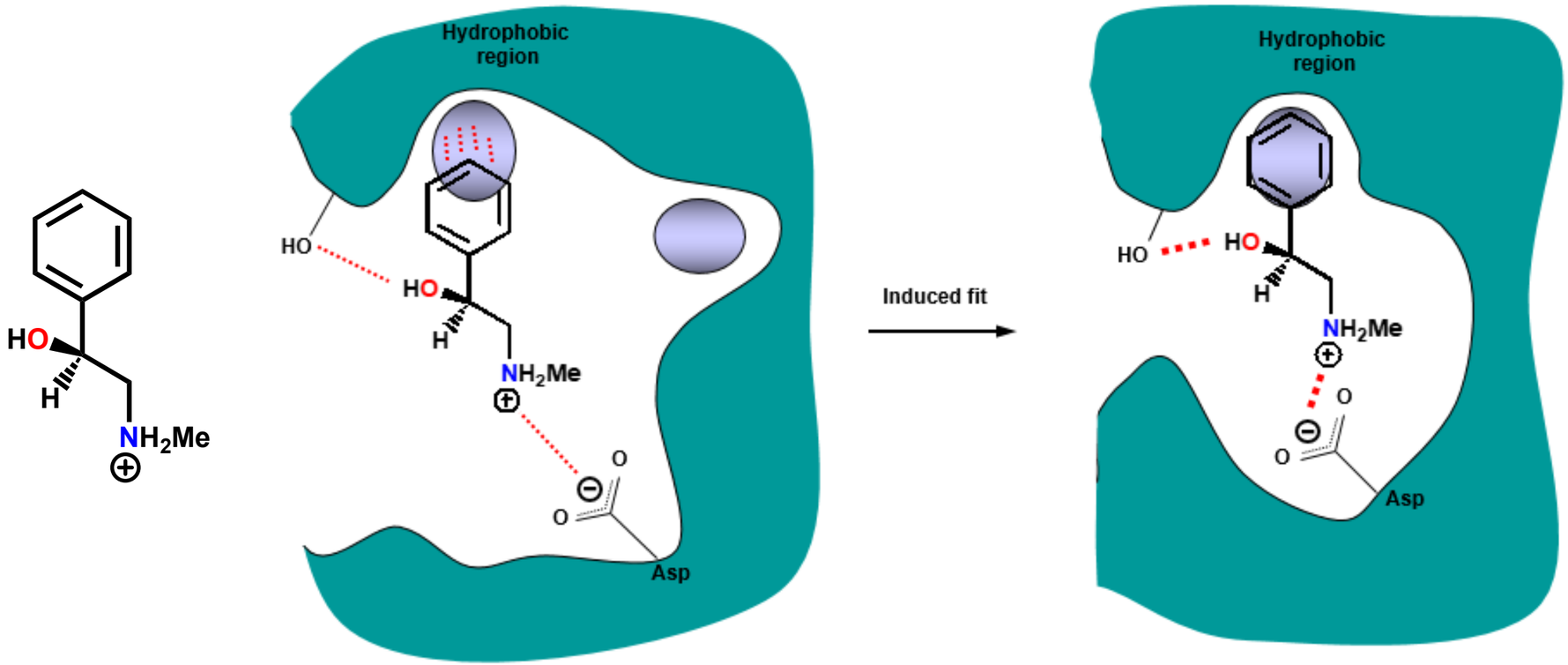
Antagonists can form binding interactions with binding regions in the binding site not used by the natural messenger.

Drugs could be designed to interact with some of these extra binding regions such that the resultant binding produces a quite different induced fit from that obtained when the natural messenger binds—an induced fit that fails to activate the receptor.



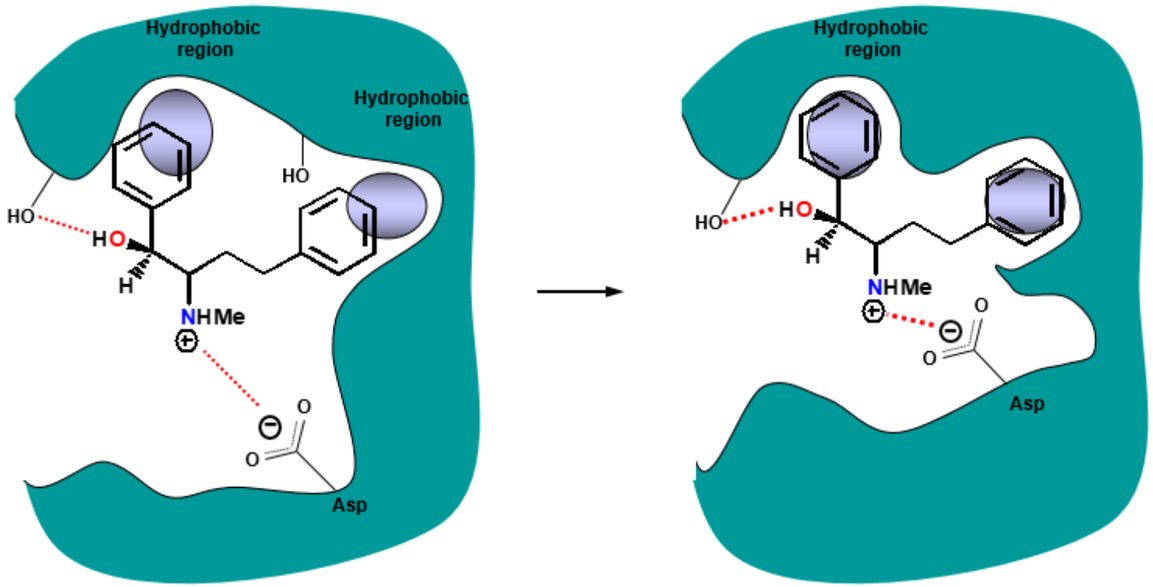
Extra binding regions do not necessarily have to be within the part of the binding site occupied by the natural messenger. It is quite common to find antagonists that are larger than the natural messenger and which access extra binding regions beyond the reach of the usual messenger.

Binding of the hypothetical neurotransmitter results in the correct induced fit required for receptor activation



Different induced fit resulting from extra binding interaction

We could now design a molecule which would bind to all four of these binding regions. This molecule will bind more strongly than the natural messenger owing to the extra binding interaction.

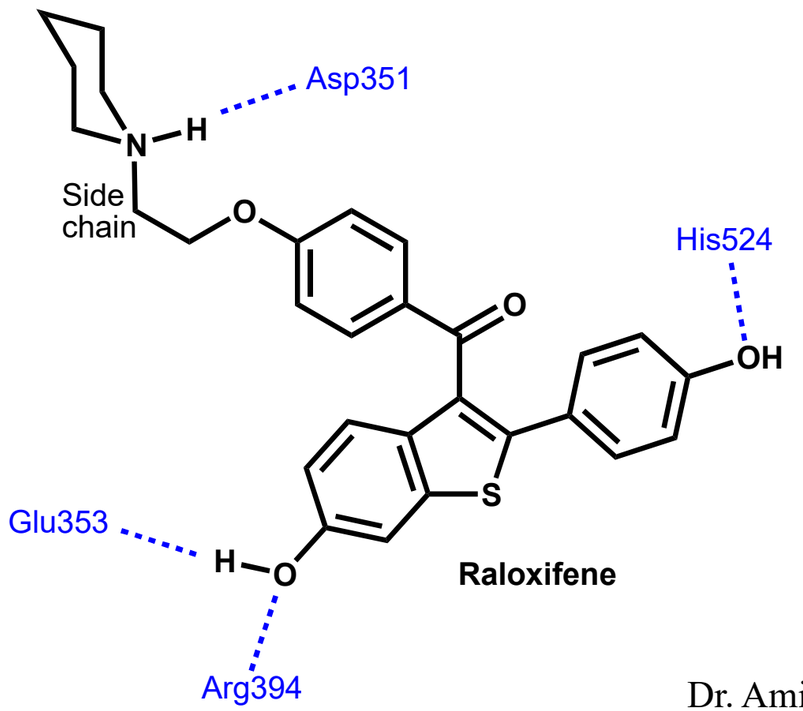


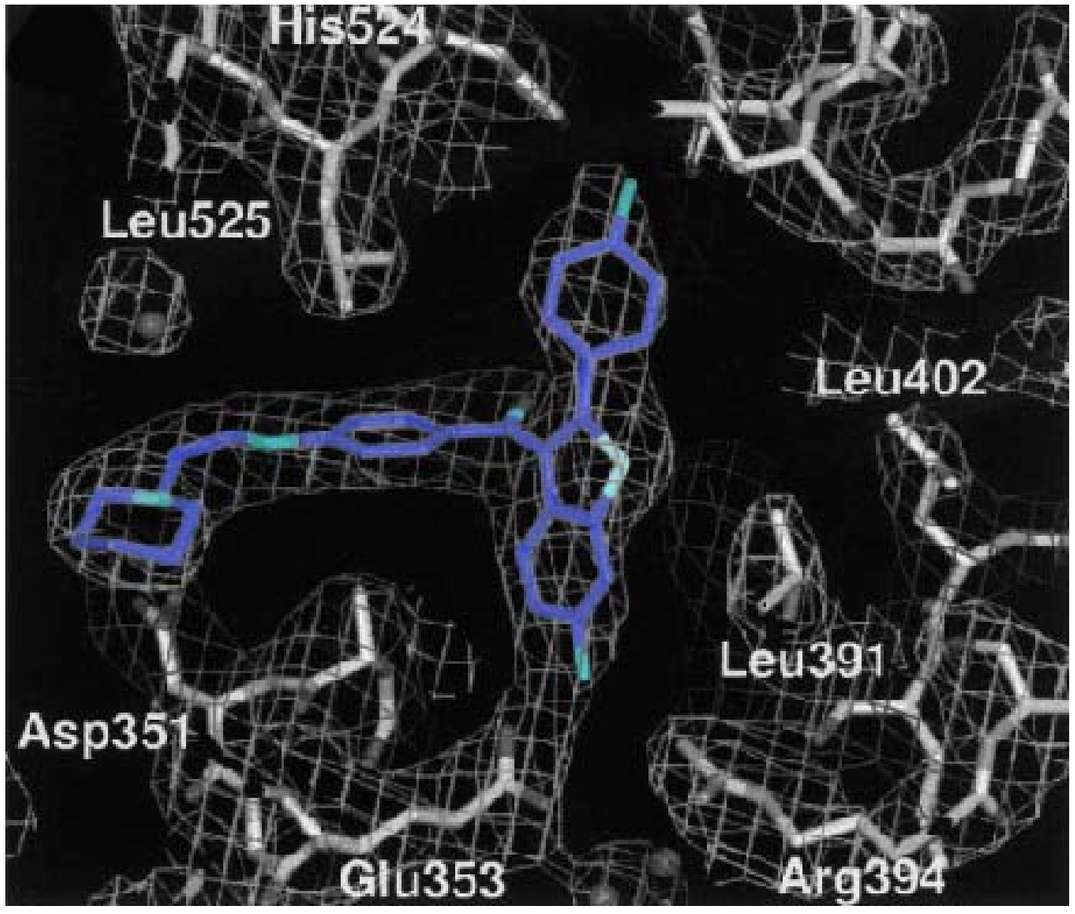
Initial binding

Different induced fit

Case Study: Binding interactions for raloxifene “Antagonists”

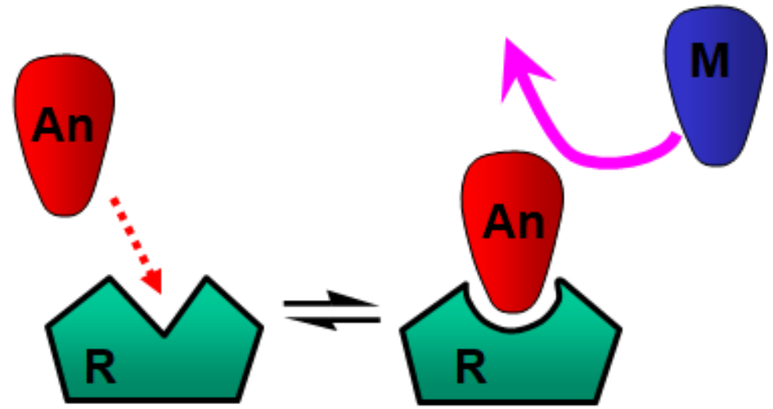
Raloxifene is an antagonist of the estrogen receptor and is used for the treatment of hormone-dependent breast cancer. It is a synthetic agent which binds to the binding site without activating the receptor and prevents estradiol from binding.





Antagonists acting at the binding site

Reversible Antagonists

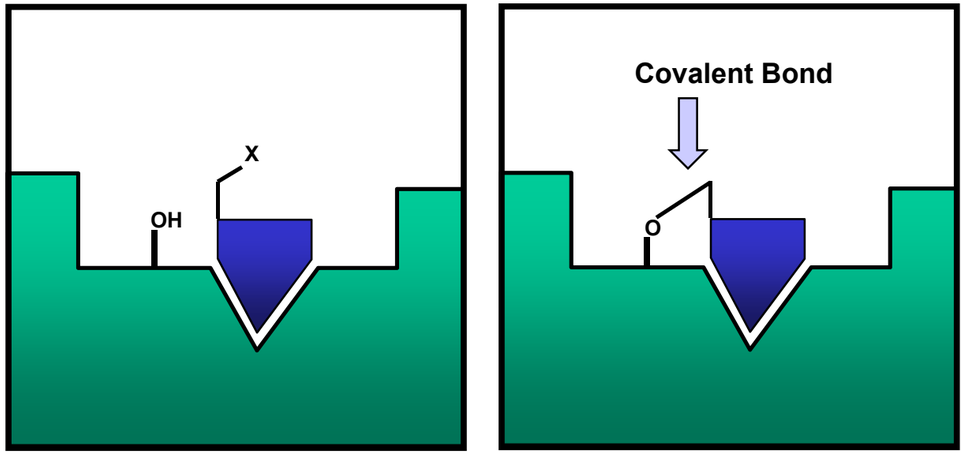


Antagonist binds reversibly to the binding site

- Intermolecular bonds involved in binding
- Different induced fit means receptor is not activated
- The antagonist does not undergo any reaction
- Level of antagonism depends on strength of antagonist binding and concentration
- Messenger is blocked from the binding site
- **<u>Increasing the messenger concentration reverses antagonism</u>**

Irreversible Antagonists

- Antagonist binds irreversibly to the binding site
- Different induced fit means that the receptor is not activated
- Covalent bond is formed between the drug and the receptor
- Messenger is blocked from the binding site
- **<u>Increasing messenger concentration does not reverse antagonism</u>**
- Often used to label receptors

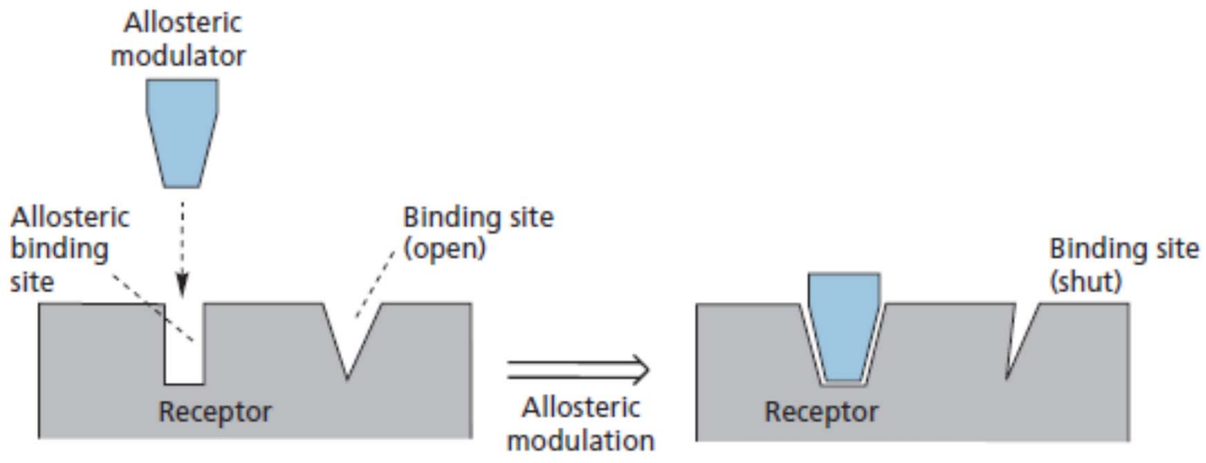


Irreversible antagonism

Antagonists acting out with the binding site

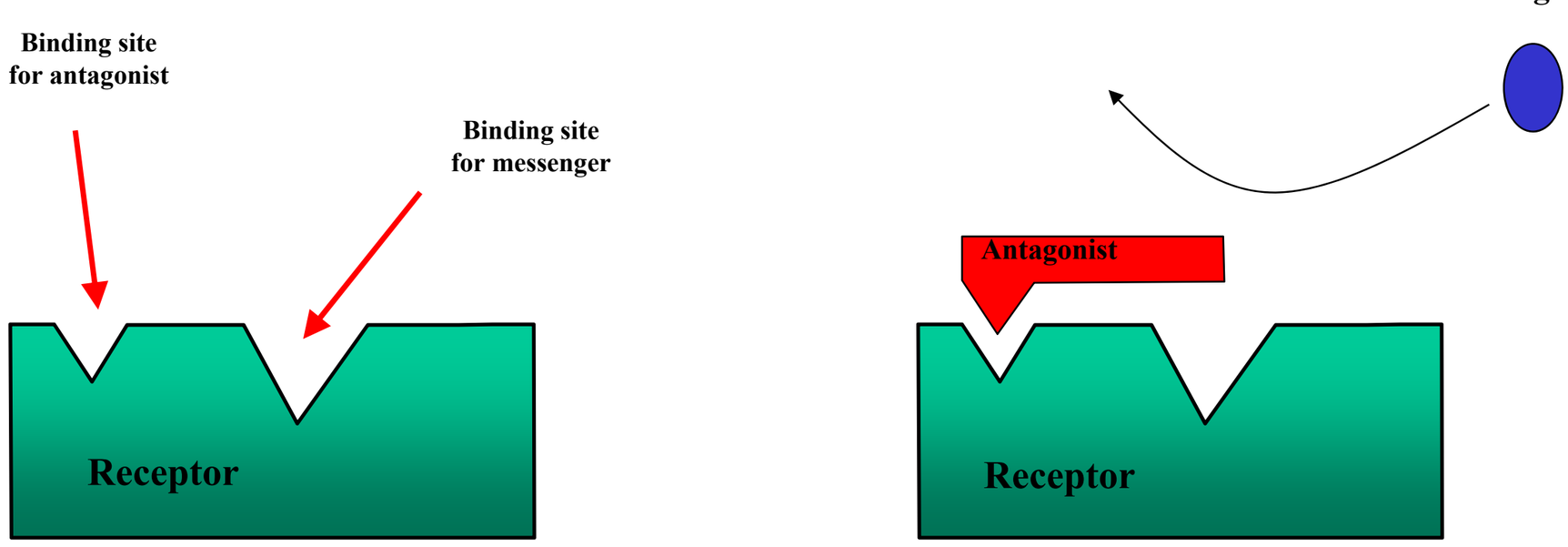
Allosteric Antagonists

The modulator binds to the allosteric binding site and causes it to change shape—an induced fit. This has a ‘knock-on’ effect which alters the shape of the normal binding site. If the site becomes too distorted, then it is no longer able to bind the normal chemical messenger or binds it less effectively. Therefore, it is possible to design an antagonist that will bind to the allosteric binding site rather than to the normal binding site



Antagonists by the Umbrella Effect

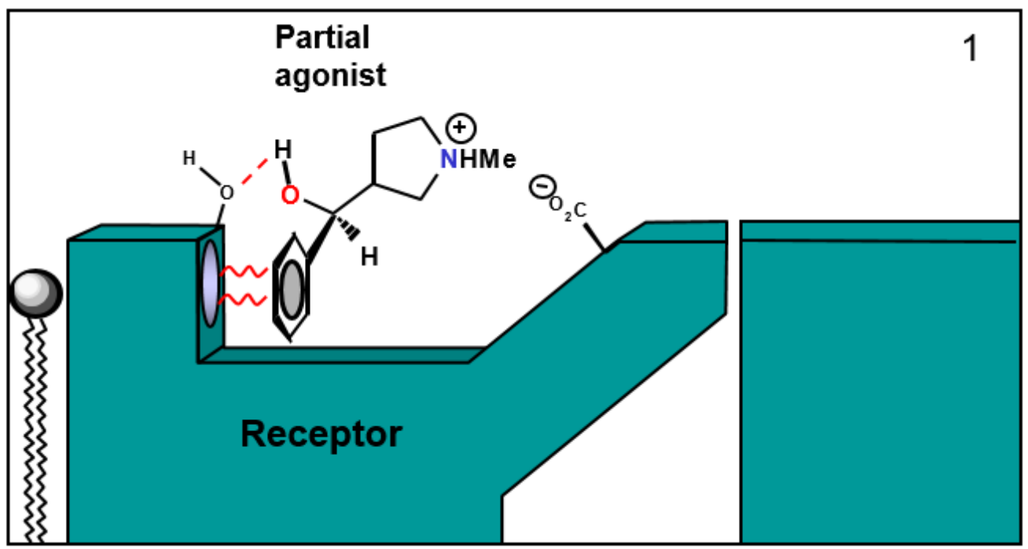
Antagonism by the ‘umbrella’ effect Some antagonists are thought to bind to regions of the receptor which are close to the normal binding site. Although they do not bind directly to the binding site, the molecule acts as a ‘shield’ or as an ‘umbrella’, preventing the normal messenger from accessing the binding site

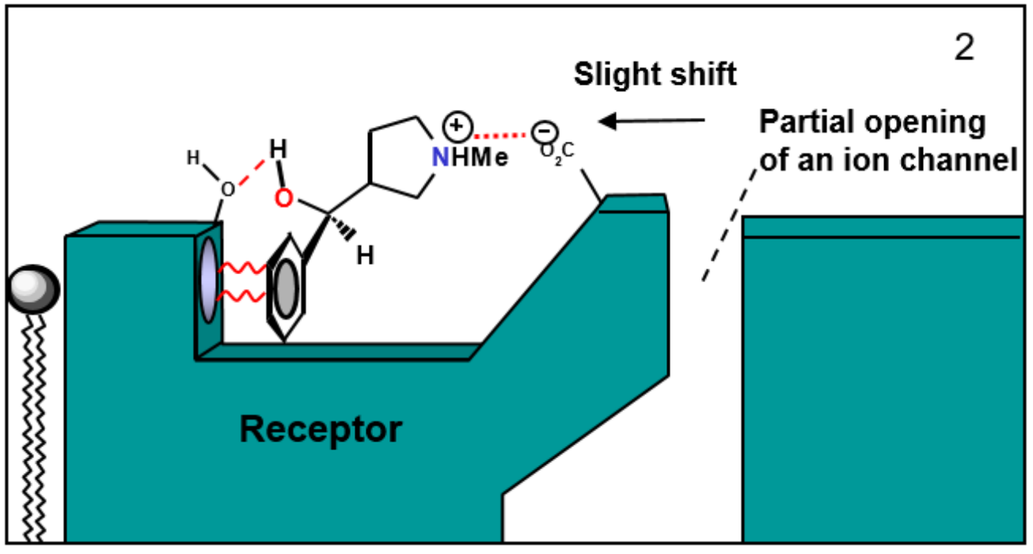


Partial Agonists

The compound acts as an agonist and produces a biological effect, but that effect is not as great as one would get with a full agonist.

a receptor may be responsible for the opening of an ion channel. The normal chemical messenger causes an induced fit that results in the ion channel fully opening up. A partial agonist, however, binds to the receptor and causes a less significant induced fit which results in only a slight distortion of the receptor. As a result, the ion channel is only partially opened





Desensitization and Sensitization

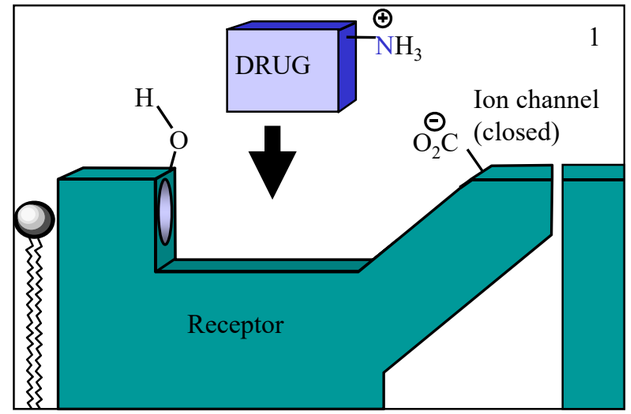
1. Some drugs bind relatively strongly to a receptor and switch it on,
2. but then subsequently block the receptor after a certain period of time.

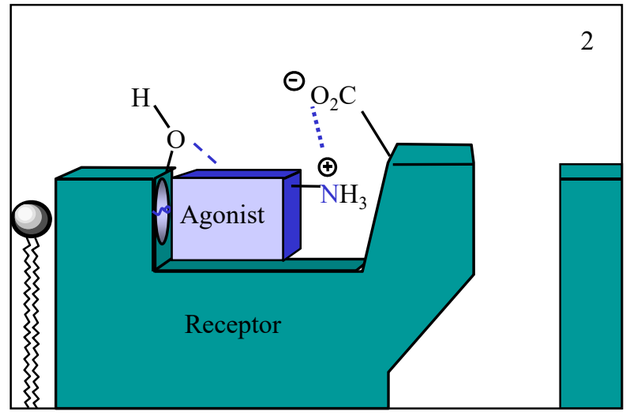
Thus, they are acting as agonists, then antagonists.

As agonists: but it is believed that prolonged binding of the agonist to the receptor results in phosphorylation of hydroxyl or phenolic groups in the receptor.

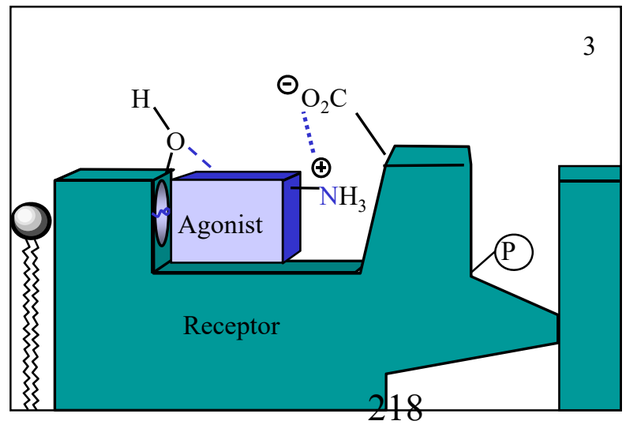
This causes the receptor to alter shape to an inactive conformation despite the binding site being occupied. As antagonists

In the case of an ion channel, this would mean that the channel is closed: 1,2 & 3



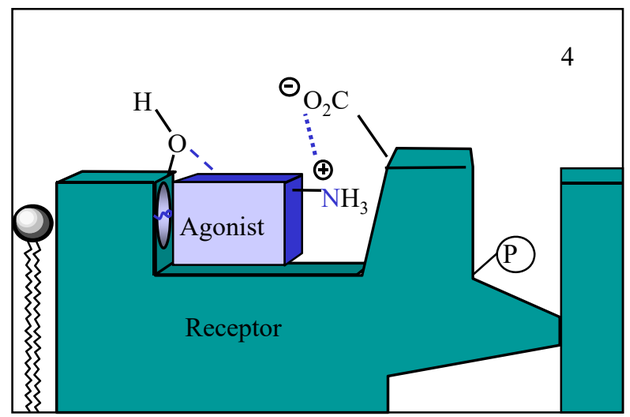


- **Induced fit alters protein shape**
- **Opens ion channel**

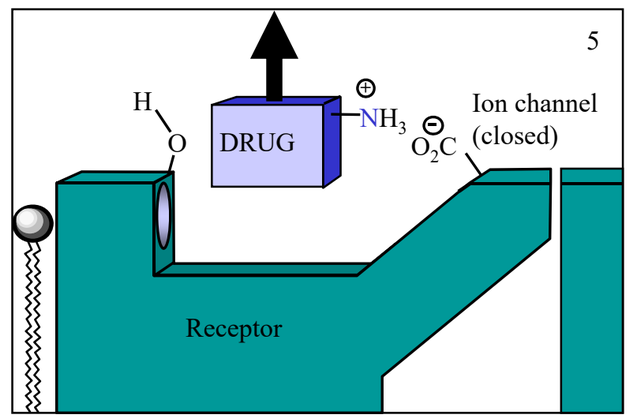


- **Phosphorylation alters shape**
- **Ion channel closes**
- **Desensitization**

This altered tertiary structure is then maintained as long as the binding site is occupied by the agonist. 4



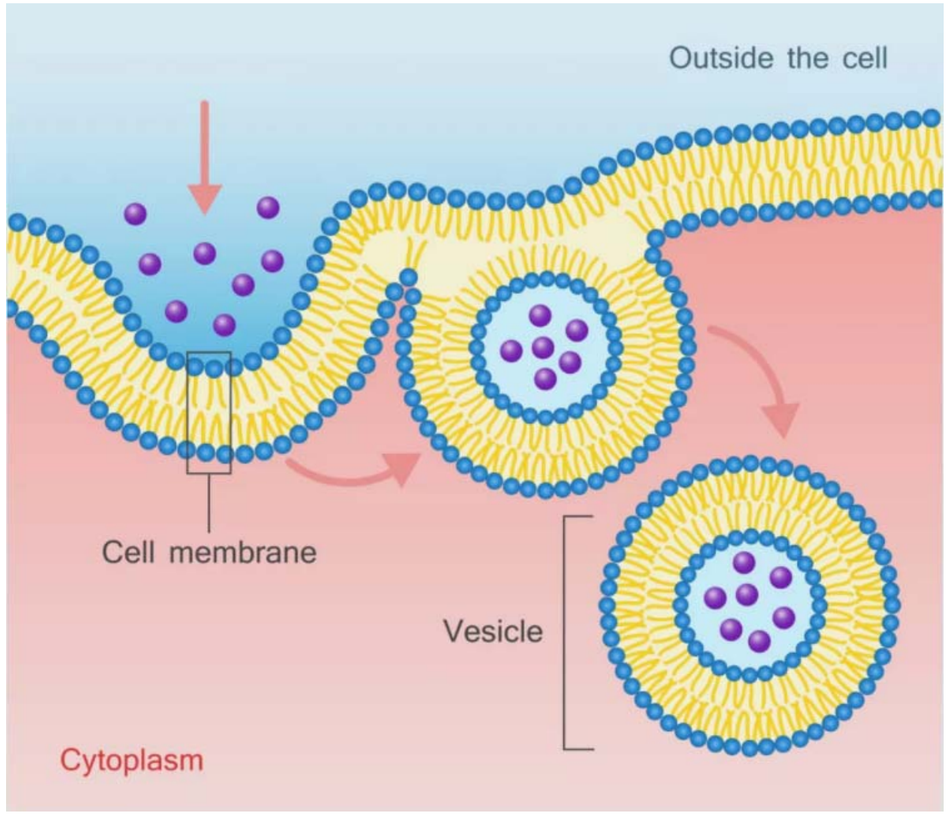
When the drug eventually leaves, the receptor is dephosphorylated and returns to its original resting shape. 5



On even longer exposure to a drug, the receptor/drug complex may be removed completely from the cell membrane by a process called endocytosis .

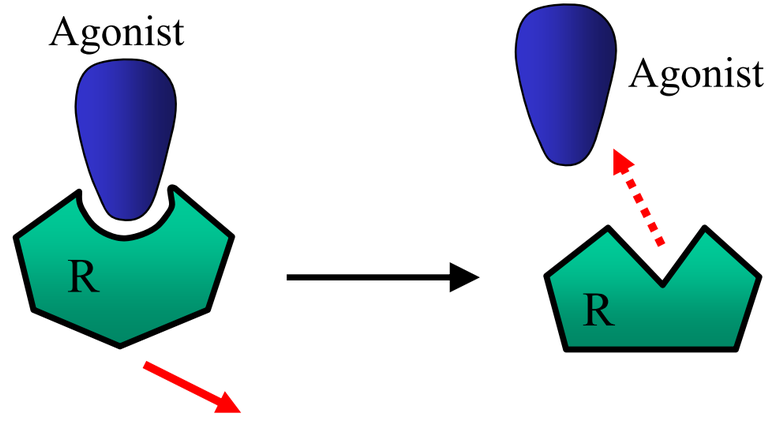
Here, the relevant portion of the membrane is ‘nipped out’, absorbed into the cell, and metabolized.

Receptor endocytosis may also occur after short exposures to a ligand, but, in this situation, the receptor is often recycled back to the cell membrane in a re-sensitization process.



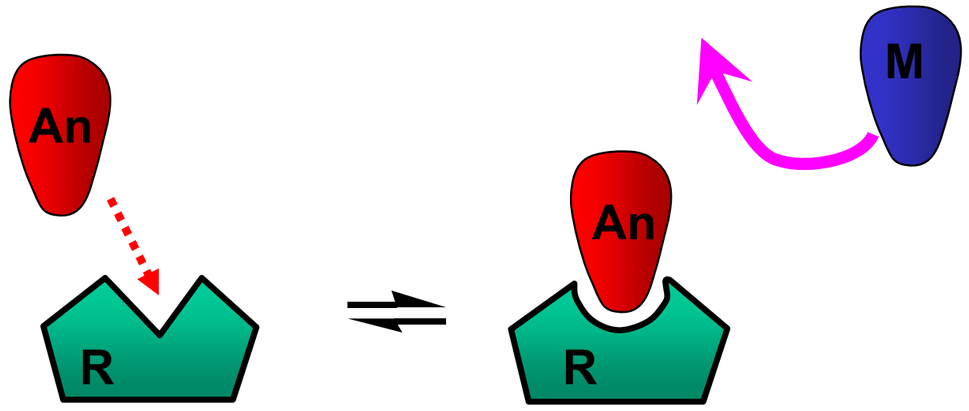
Desensitization

"prolonged activation of a receptor may result in the cell reducing its synthesis of the receptor protein“, so the best agonists bind swiftly to the receptor, pass on their message, and then leave quickly.



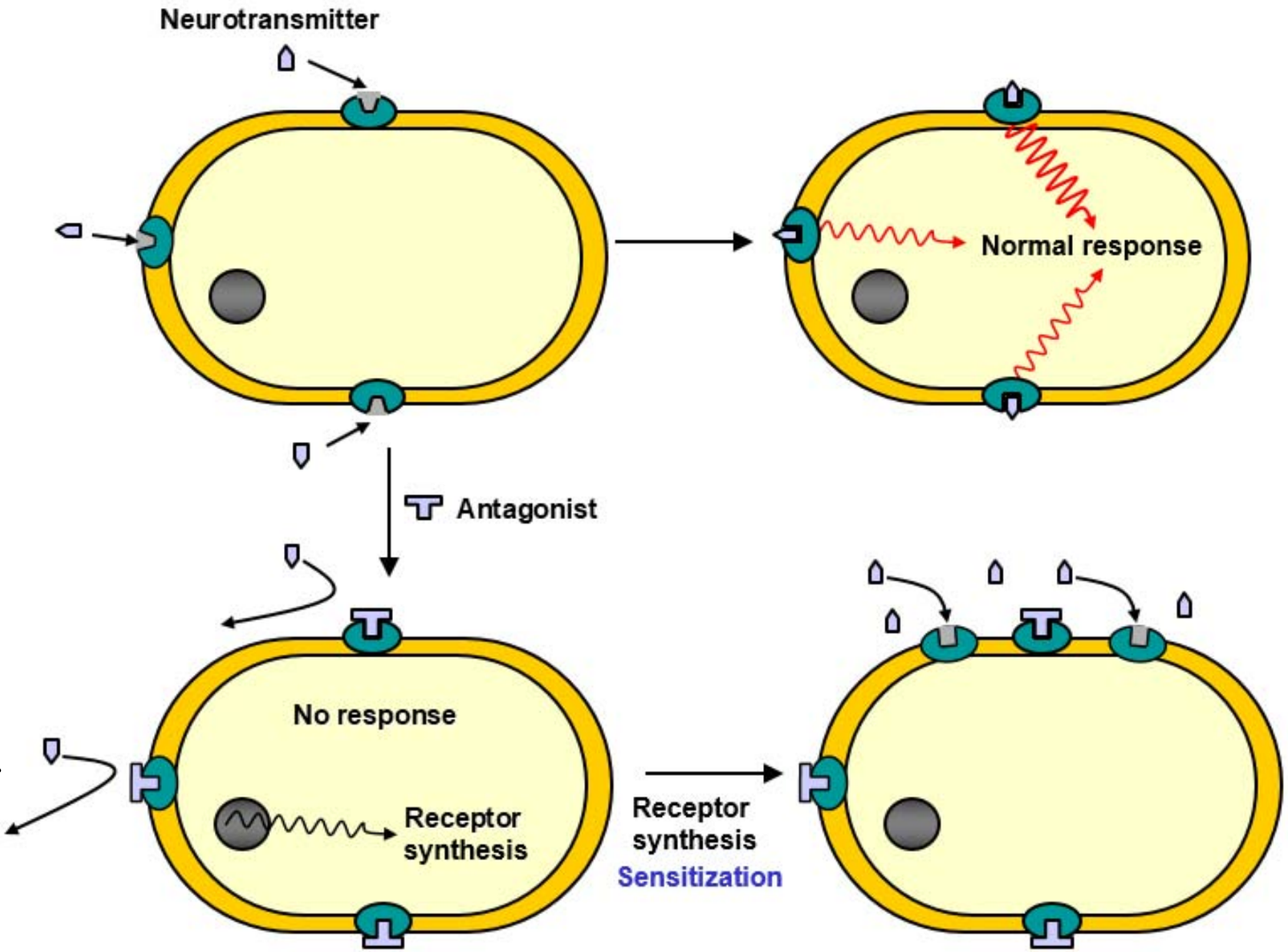
Sensitization

“prolonged exposure of a target receptor to an antagonist may lead to the opposite of desensitization (i.e. sensitization)”. This is where the cell synthesizes more receptors to compensate for the receptors that are blocked.



Tolerance and dependence

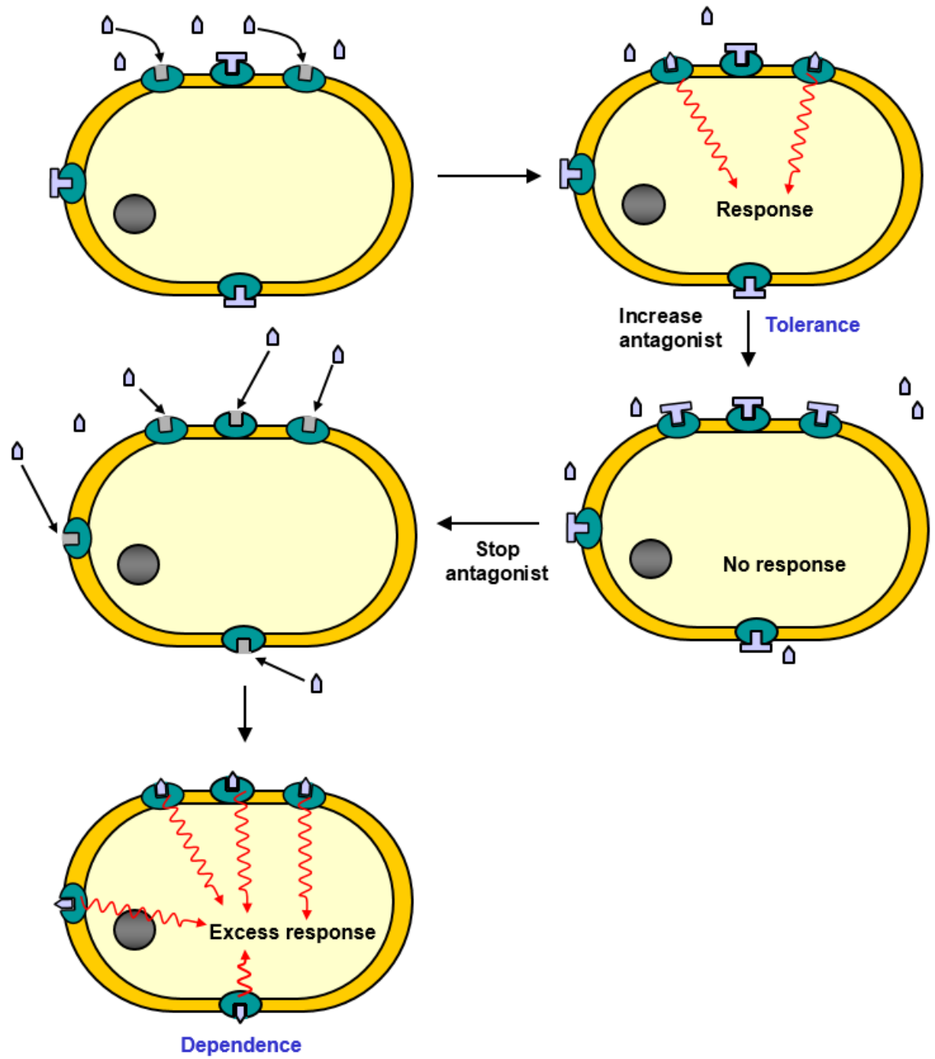
- Depriving a target receptor of its natural ligand by administering an antagonist may induce that cell to synthesize more receptors. By doing so, the cell gains a greater sensitivity for what little ligand is left.
- If a drug is acting to suppress the binding of a chemical messenger, then the cell may respond by increasing the number of receptors.



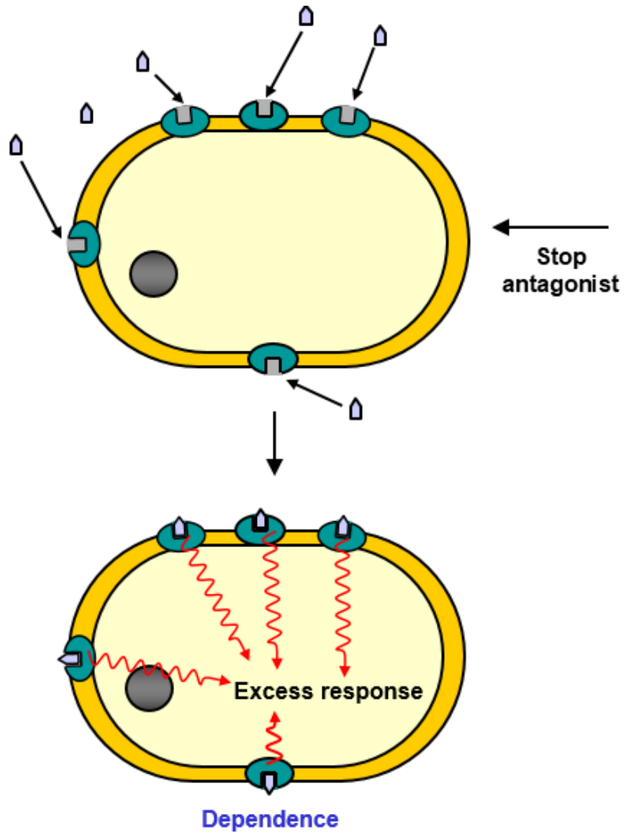
- Can result in tolerance and dependence

"Tolerance is a situation where higher levels of a drug are required to get the same biological response"

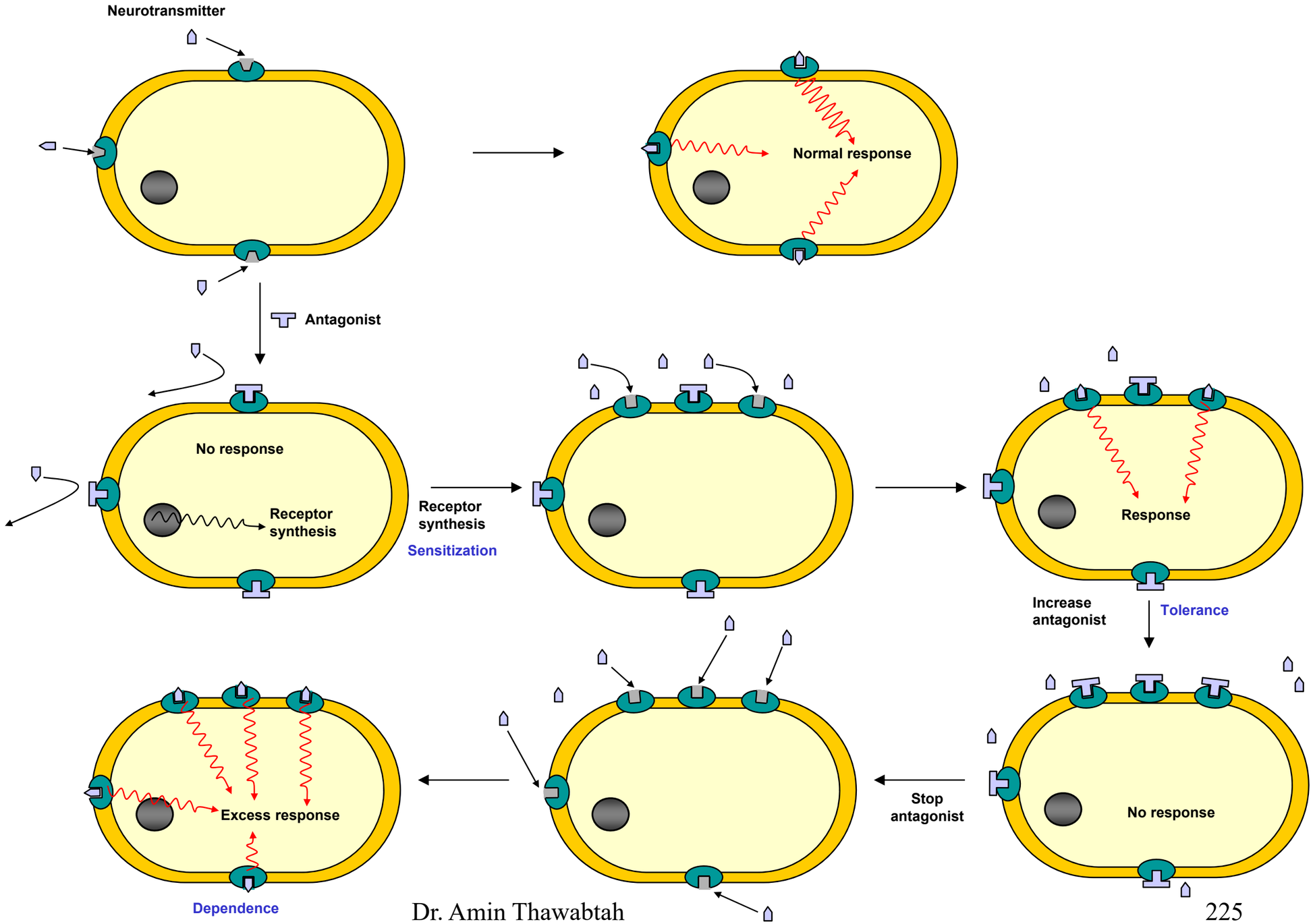
- Increased doses of antagonist are required to achieve same effect (tolerance)
- If the drug is suddenly stopped, then all the receptors suddenly become available. There is now an excess of receptors, which makes the cell supersensitive to normal levels of messenger



- The supersensitive to normal levels of messenger, causes withdrawal symptoms when antagonist withdrawn.
- These withdrawal symptoms would continue until the number of receptors returned to their original level. During this period, the patient may be tempted to take the drug again in order to ‘return to normal’ and will have then acquired a dependence on the drug.



Sensitization, Tolerance and dependence



Homework: Q 1,2,7
The deadline 3\11\2020