Academic (https://www-cambridge-org.ezp.waldenulibrary.org/academic)

Journals (https://www-cambridge-org.ezp.waldenulibrary.org/core/?site_locale=en_GB&prefCountry=GB)

Cambridge English (https://www-cambridge-org.ezp.waldenulibrary.org/cambridgeenglish)   Education (https://www-cambridge-org.ezp.waldenulibrary.org/education)

Bibles (https://www-cambridge-org.ezp.waldenulibrary.org/bibles)   Digital Products (http://www.cambridge.org.ezp.waldenulibrary.org/digital-products/)

About Us (http://www.cambridge.org.ezp.waldenulibrary.org/about-us)   Careers (http://www.cambridge.org.ezp.waldenulibrary.org/about-us/careers/)

Welcome Guest user

Register

Log In

Chapter 3

Cart (0)

Walden University, Laureate International Univ...   Help

(https://www-cambridge-org.ezp.waldenulibrary.org/academic/subjects/medicine)

Search Stahl Online

Advanced Search
(/common_advanced_search.jsf)

(/common_home.jsf)

(https://www.neiglobal.com/)

Home (/common_home.jsf)   Essential Psychopharmacology 4th ed   The Prescriber's Guide 6th ed (/prescribers_guide.jsf)   Case Studies

Illustrated Guides (/stahl_illustrated.jsf?name=AntiDepressants&srcPage=SI)   Other Titles   Drug Interactions (/drug_interaction.jsf?page=drugDetails)

Stahl's Essential Psychopharmacology

Drug Interactions (/drug_interaction.jsf?page=drugDetails)

4th Edition - 9781107686465

This fully revised edition returns to the essential roots of what it means to become a neurobiologically empowered psychopharmacologist. This remains the essential text for all students and professionals in mental health seeking to understand and utilize current therapeutics.
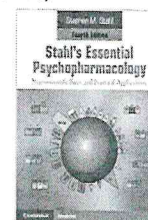
Download   Bookmark   Notes   Cite   Help

My Bookmarks   Disclaimer   TOC   Chapter 3   My Images   Preface to the Fourth Edition   CME Information

Suggested Readings (essential_4th_suggested_readings.jsf?page=further-reading_1.htm&name=Suggested Readings&title=General references: textbooks#c02598-90-1)

Index

- Ligand-gated ion channels as targets of psychopharmacological drug action (essential_4th_chapter.jsf?page=chapter3_introduction.htm...

Ion channels as targets of psychopharmacological drug action

Many important psychopharmacological drugs target ion channels. The roles of ion channels as important regulators of synaptic neurotransmission were covered in Chapter 1 (essential_4th_chapter.jsf?page=chapter1_introduction.htm&name=Chapter 1&title=Anatomical

. Here we discuss how targeting these molecular sites causes alterations in synaptic neurotransmission that are linked in turn to the therapeutic actions of various psychotropic drugs. Specifically, we cover ligand-gated ion channels and voltage-sensitive ion channels as targets of psychopharmacological drug action.
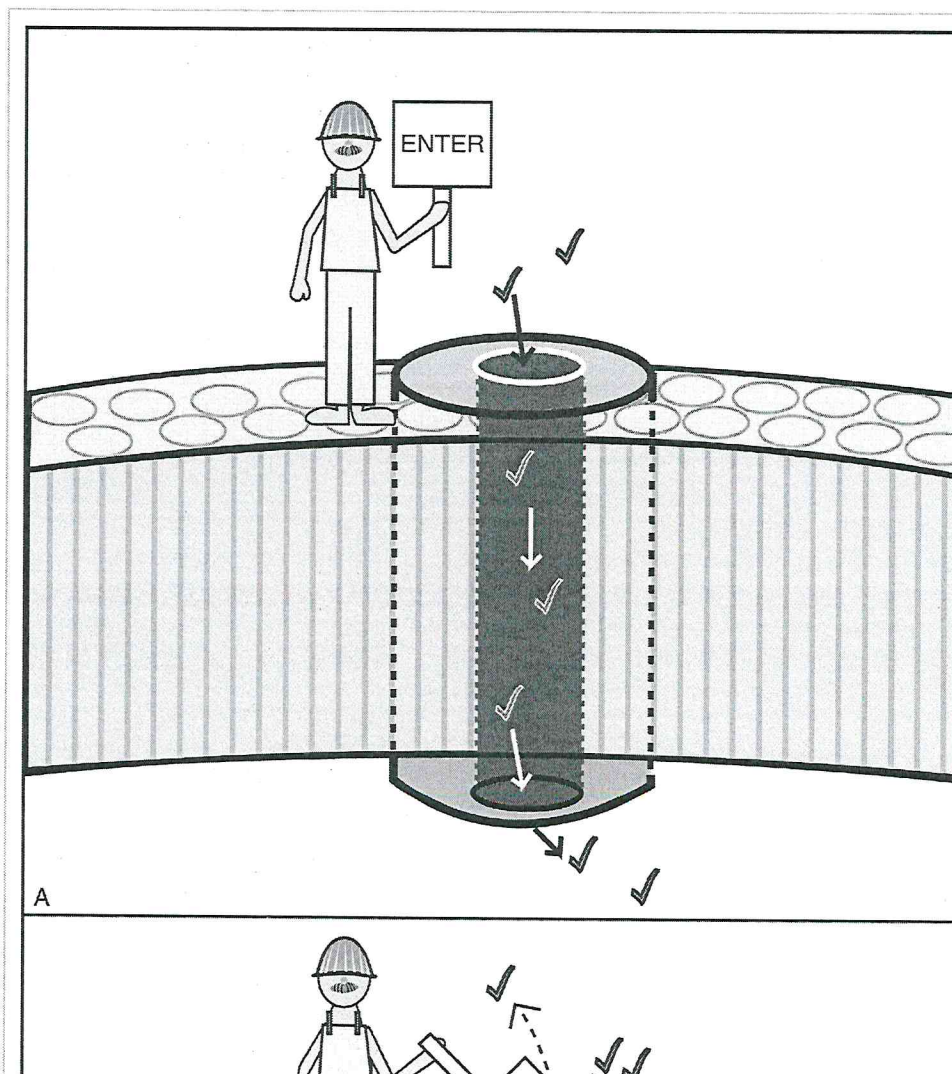
Ligand-gated ion channels as targets of psychopharmacological drug action

Ligand-gated ion channels, ionotropic receptors, and ion-channel-linked receptors: different terms for the same receptor/ion-channel complex

Ions normally cannot penetrate membranes because of their charge. In order to selectively control access of ions into and out of neurons, their membranes are decorated with all sorts of ion channels. The most important ion channels in psychopharmacology regulate calcium, sodium, chloride, and potassium. Many can be modified by various drugs, and this will be discussed throughout this chapter.

There are two major classes of ion channels, and each class has several names. One class of ion channels is opened by neurotransmitters and goes by the names *ligand-gated ion channels*, *ionotropic receptors*, and *ion-channel-linked receptors*. These channels and their associated receptors will be discussed next. The other major class of ion channel is opened by the charge or voltage across the membrane and is called either a *voltage-sensitive* or a *voltage-gated* ion channel; these will be discussed later in this chapter.

Ion channels that are opened and closed by actions of neurotransmitter ligands at receptors acting as gatekeepers are shown conceptually in Figure 3-1. When a neurotransmitter binds to a gatekeeper receptor on an ion channel, that neurotransmitter causes a conformational change in the receptor that opens the ion channel (Figure 3-1A). A neurotransmitter, drug, or hormone that binds to a receptor is sometimes called a *ligand* (literally, "tying"). Thus, ion channels linked to receptors that regulate their opening and closing are often called *ligand-gated ion channels*. Since these ion channels are also receptors, they are sometimes also called *ionotropic receptors* or *ion-channel-linked receptors*.

A

☐ Save image

Figure 3-1. Ligand-gated ion channel gatekeeper. This schematic shows a ligand-gated ion channel. In panel A, a receptor is serving as a molecular gatekeeper that acts on instruction from neurotransmission to open the channel and allow ions to travel into the cell. In panel B, the gatekeeper is keeping the channel closed so that ions cannot get into the cell. Ligand-gated ion channels are a type of receptor that forms an ion channel and are thus also called ion-channel-linked receptors or ionotropic receptors.

These terms will be used interchangeably with ligand-gated ion channels here.

Numerous drugs act at many sites around such receptor/ion-channel complexes, leading to a wide variety of modifications of receptor/ion-channel actions. These modifications not only immediately alter the flow of ions through the channels, but with a delay can also change the downstream events that result from transduction of the signal that begins at these receptors. The downstream actions have been extensively discussed in Chapter 1 (essential_4th_chapter.jsf?
page=chapter1_introduction.htm&name=Chapter 1&title=Anatomical versus chemical basis of neurotransmission#c02598-1-1) and include both activation and inactivation of phosphoproteins, shifting the activity of enzymes, the sensitivity of receptors, and the conductivity of ion channels. Other downstream actions include changes in gene expression and thus changes in which proteins are synthesized and which functions are amplified. Such functions can range from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the ionotropic receptor, and many more. The reader should have a good command of the function of signal transduction pathways described in Chapter 1 (essential_4th_chapter.jsf?
page=chapter1_introduction.htm&name=Chapter 1&title=Anatomical versus chemical basis of neurotransmission#c02598-1-1) in order to understand how drugs acting at ligand-gated ion channels modify the signal transduction that arises from these receptors.

Drug-induced modifications in signal transduction from ionotropic (sometimes called ionotrophic) receptors can have profound actions on psychiatric symptoms. About a fifth of psychotropic drugs currently utilized in clinical practice, including many drugs for the treatment of anxiety and insomnia such as the benzodiazepines, are known to act at these receptors. Because ionotropic receptors immediately change the flow of ions, drugs that act on these receptors can have an almost immediate effect, which is why many anxiolytics and hypnotics that act at these receptors may have immediate clinical onset. This is in contrast to the actions of many drugs at G-protein-linked receptors described in Chapter 2 (essential_4th_chapter.jsf?
page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1), some of which have clinical effects – such as antidepressant actions – that may occur with a delay necessitated by awaiting initiation of changes in cellular functions activated through the signal transduction cascade. Here we will describe how various drugs stimulate or block various molecular sites around the receptor/ion-channel complex. Throughout the textbook we will show how specific drugs acting at specific ionotropic receptors have specific actions on specific

psychiatric disorders.

Ligand-gated ion channels: structure and function

Are ligand-gated ion channels receptors or ion channels? The answer is "yes" – ligand-gated ion channels are a type of receptor and they also form an ion channel. That is why they are called not only a channel (ligand-gated ion channel) but also a receptor (ionotropic receptor or ion-channel-linked receptor). These terms try to capture the dual function of these ion channels/receptors.

Ligand-gated ion channels comprise several long strings of amino acids assembled as subunits around an ion channel. Decorating these subunits are also multiple binding sites for everything from neurotransmitters to ions to drugs. That is, these complex proteins have several sites where some ions travel through a channel and others also bind to the channel; where one neurotransmitter or even two cotransmitters act at separate and distinct binding sites; where numerous allosteric modulators – i.e., natural substances or drugs that bind to a site different than where the neurotransmitter binds – increase or decrease the sensitivity of channel opening.

Pentameric subtypes

Many ligand-gated ion channels are assembled from five protein subunits; that is why they are called pentameric. The subunits for pentameric subtypes of ligand-gated ion channels each have four transmembrane regions (Figure 3-2A). These membrane proteins go in and out of the membrane four times (Figure 3-2A). When five copies of these subunits are selected (Figure 3-2B), they come together in space to form a fully functional pentameric receptor with the ion channel in the middle (Figure 3-2C). The receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel. This pentameric structure is typical for GABA$_A$ receptors, nicotinic cholinergic receptors, serotonin 5HT$_3$ receptors, and glycine receptors (Table 3-1). Drugs that act directly on pentameric ligand-gated ion channels are listed in Table 3-2.

If this structure were not complicated enough, pentameric ionotropic receptors actually have many different subtypes. Subtypes of pentameric ionotropic receptors are defined based upon which forms of each

Table 3-1   Pentameric ligand-gated ion channels

4 transmembrane regions 5 subunits	
Neurotransmitter	**Receptor subtype**
Acetylcholine	Nicotinic receptors (e.g., α_7-nicotinic receptors; $\alpha_4\beta_2$-nicotinic receptors)
GABA	GABA$_A$ receptors (e.g., α_1 subunits)
Glycine	Strychnine-sensitive glycine receptors
Serotonin	5HT$_3$ receptors

of the five subunits are chosen for assembly into a fully constituted receptor. That is, there are several subtypes for each of the four transmembrane subunits, making it possible to piece together several different constellations of fully constituted receptors. Although the natural neurotransmitter binds to every subtype of ionotropic receptor, some drugs used in clinical practice, and many more in clinical trials, are able to bind selectively to one or more of these subtypes, but not to others. This may have functional and clinical consequences. Specific receptor subtypes and the specific drugs

that bind to them selectively are discussed in chapters that cover their specific clinical use.
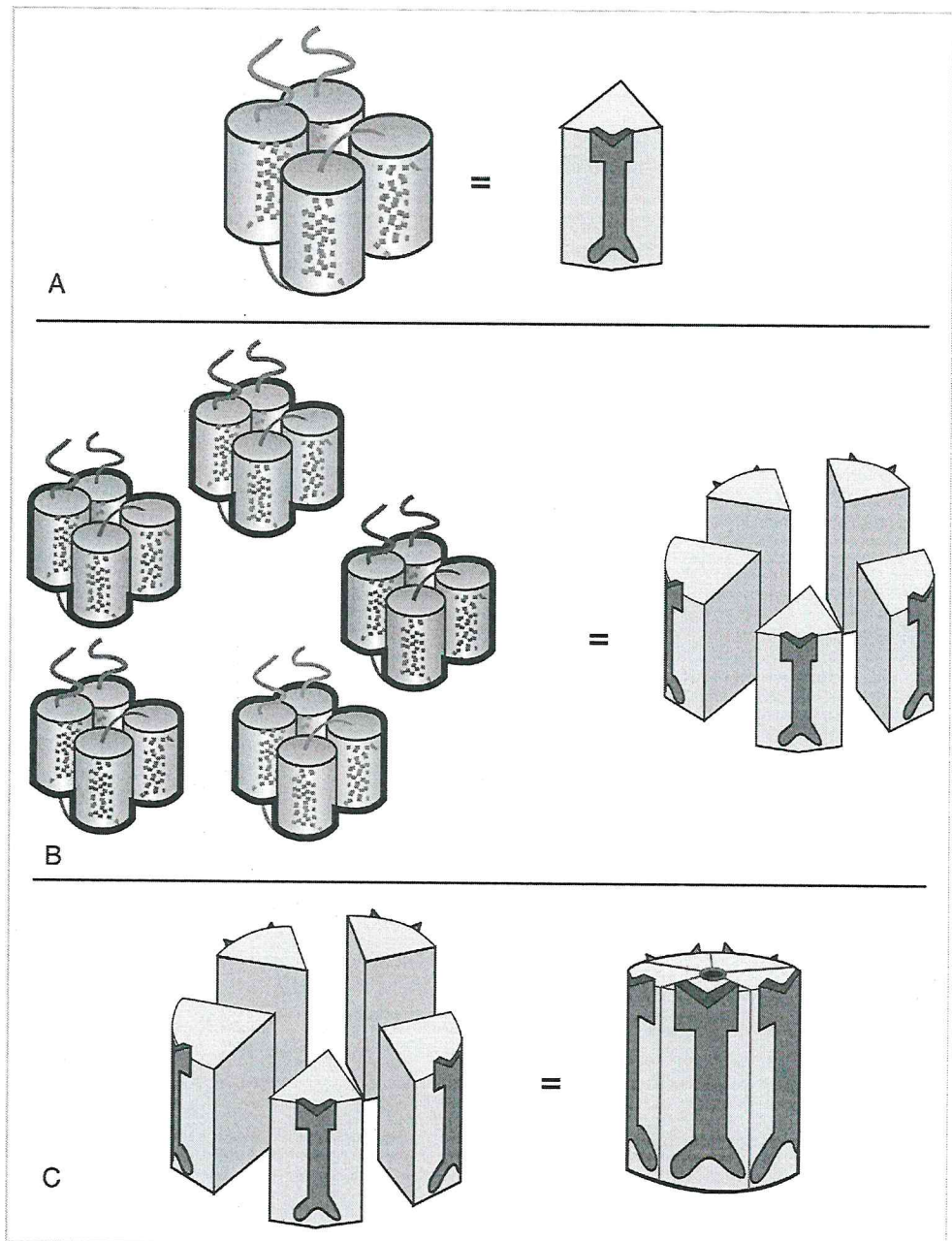
Save image

Figure 3-2. Ligand-gated ion channel structure. The four transmembrane regions of a single subunit of a pentameric ligand-gated ion channel form a cluster, as shown in panel A. An icon for this subunit is shown on the right in panel A. Five copies of the subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Pentameric ligand-gated ion channels have receptor binding sites located on all five subunits, both inside and outside the channel.

Table 3-2   Key ligand-gated ion channels directly targeted by psychotropic drugs

Neurotransmitter	Ligand-gated ion-channel receptor subtype directly targeted	Pharmacologic action	Drug class	Therapeutic action
Acetylcholine	$\alpha_4\beta_2$-nicotinic receptors	Partial agonist	Nicotinic receptor partial agonist (NRPA) (varenicline)	Smoking cessation
GABA	GABA$_A$ benzodiazepine receptors	Full agonist	Benzodiazepines	Anxiolytic
	GABA$_A$ non-benzodiazepine PAM sites	Full agonist	"Z drugs"/hypnotics (zolpidem, zaleplon, zopiclone, eszopiclone)	Improve insomnia
Glutamate	NMDA NAM channel sites/ Mg^{++} sites	Antagonist	NMDA glutamate antagonist (memantine)	Slowing progression in Alzheimer's

Neurotransmitter	Receptor subtype	Agonist/Antagonist	Drug	Use
	NMDA open channel sites	Antagonist	PCP (phencyclidine) Ketamine	disease Hallucinogen anesthetic
Serotonin	5HT$_3$	Antagonist	Antidepressant (mirtazapine)	Unknown; reduce nausea
	5HT$_3$	Antagonist	Antiemetic	Reduce chemotherapy-induced emesis

-aspartate; Mg, magnesium.

PAM, positive allosteric modulator; NAM, negative allosteric modulator; NMDA, *N*-methyl-d-aspartate; Mg, magnesium.

Tetrameric subtypes

Ionotropic glutamate receptors have a different structure from the pentameric ionotropic receptors just discussed. The ligand-gated ion channels for glutamate comprise subunits that have three full transmembrane regions and a fourth re-entrant loop (Figure 3-3A), rather than four full transmembrane regions as shown in Figure 3-2A. When four copies of these subunits are selected (Figure 3-3B), they come together in space to form a fully functional ion channel in the middle with the four re-entrant loops lining the ion channel (Figure 3-3C). Thus, tetrameric subtypes of ion channels (Figure 3-3) are analogous to pentameric subtypes of ion channels (Figure 3-2), but have just four subunits rather than five. Receptor sites are in various locations on each of the subunits; some binding sites are in the channel, but many are present at different locations outside the channel.

This tetrameric structure is typical of the ionotropic glutamate receptors known as AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid) and NMDA (*N*-methyl-d-aspartate) subtypes (Table 3-3). Drugs that act directly at tetrameric ionotropic glutamate receptors are listed in Table 3-2. Receptor subtypes for glutamate according to the selective agonist acting at that receptor, as well as the specific molecular subunits that comprise that subtype, are listed in Table 3-3. Subtype-selective drugs for ionotropic glutamate receptors are under investigation but not currently used in clinical practice.

The agonist spectrum

The concept of an agonist spectrum for G-protein-linked receptors, discussed extensively in Chapter 2 (essential_4th_chapter.jsf?page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1), can also be applied to ligand-gated ion channels (Figure 3-4). Thus, **full agonists** change the conformation of the receptor to open the ion channel the maximal amount and frequency allowed by that binding site (Figure 3-5). This then triggers the maximal amount of downstream signal transduction possible to be mediated by this binding site. The ion channel can open to an even greater extent (i.e., more frequently) than with a full agonist alone, but this requires the help of a second receptor site, that of a positive allosteric modulator, or PAM, as will be shown later.

Table 3-3   Tetrameric ligand-gated ion channels

| 3 transmembrane regions and one re-entrant loop 4 subunits	
Neurotransmitter	**Receptor subtype**
Glutamate	AMPA (e.g., GluR1–4 subunits)
	KAINATE (e.g., GluR5–7, KA1–2 subunits)
	NMDA (e.g., NMDAR1, NMDAR2A–D, NMDAR3A subunits)

-aspartate.

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, *N*-methyl-d-aspartate.

Antagonists stabilize the receptor in the resting state, which is the same as the state of the receptor in the absence of agonist (Figure 3-6). Since there is no difference between the presence and absence of the antagonist, the antagonist is said to be neutral or silent. The resting state is not a fully closed ion channel, so there is some degree of ion flow through the channel even in the absence of agonist (Figure 3-6A) and even in the presence of antagonist (Figure 3-6B). This is due to occasional and infrequent opening of the channel even when an agonist is not present and even when an antagonist is present. This is called constitutive activity and is also discussed in Chapter 2 (essential_4th_chapter.jsf?page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1) for G-protein-linked receptors. Antagonists
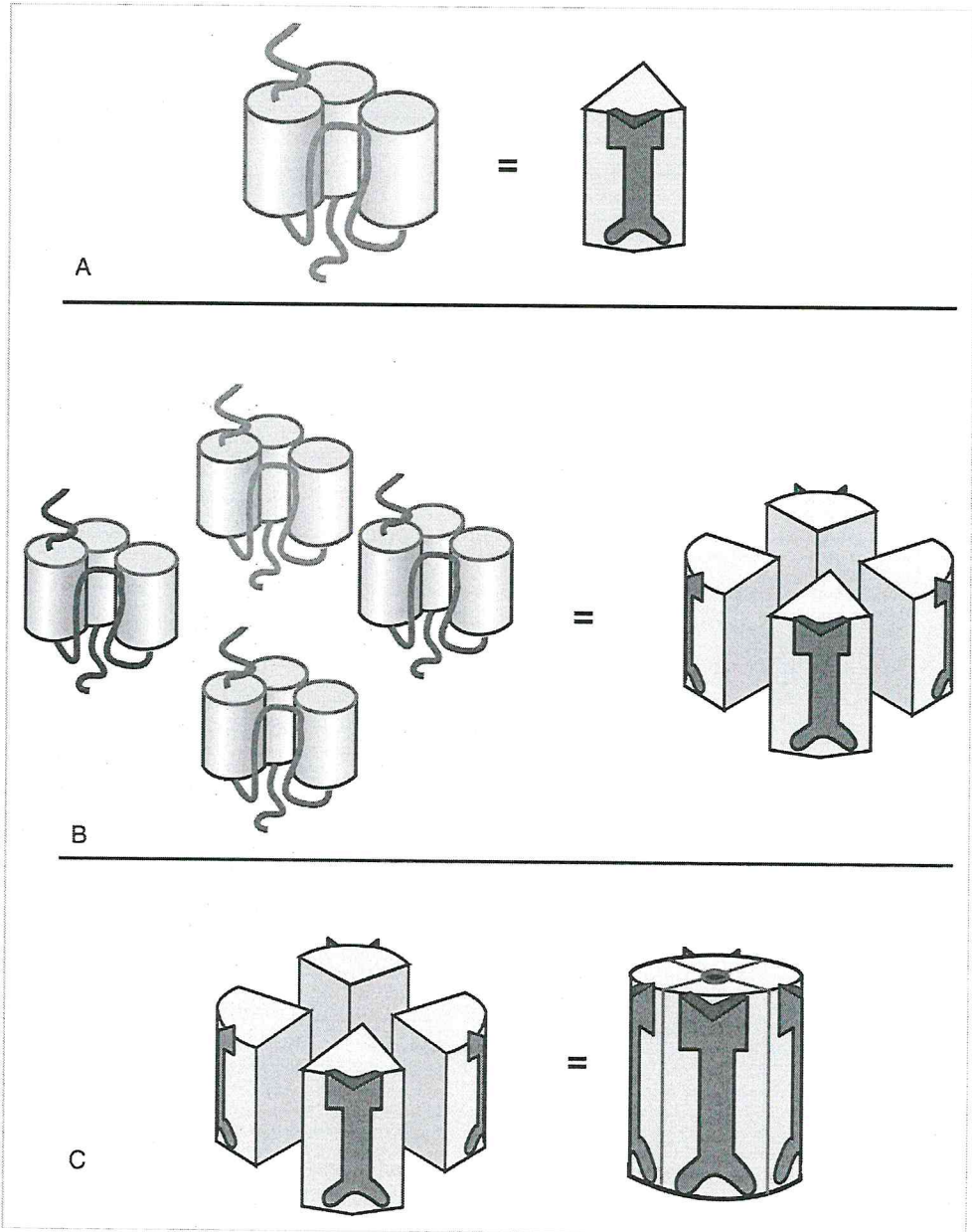
☐ Save image

Figure 3-3. Tetrameric ligand-gated ion channel structure. A single subunit of a tetrameric ligand-gated ion channel is shown to form a cluster in panel A, with an icon for this subunit shown on the right in panel A. Four copies of these subunits come together in space (panel B) to form a functional ion channel in the middle (panel C). Tetrameric ligand-gated ion channels have receptor binding sites located on all four subunits, both inside and outside the channel.
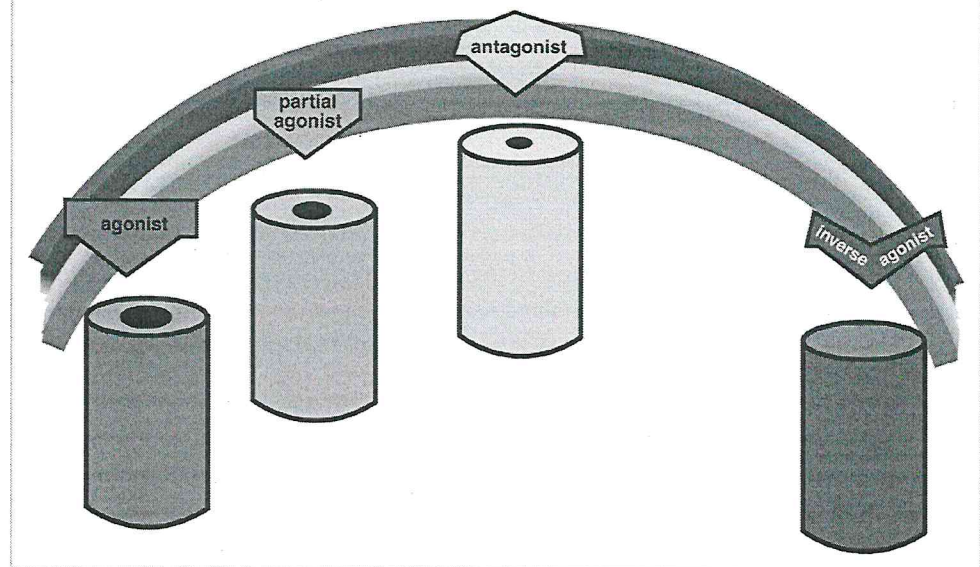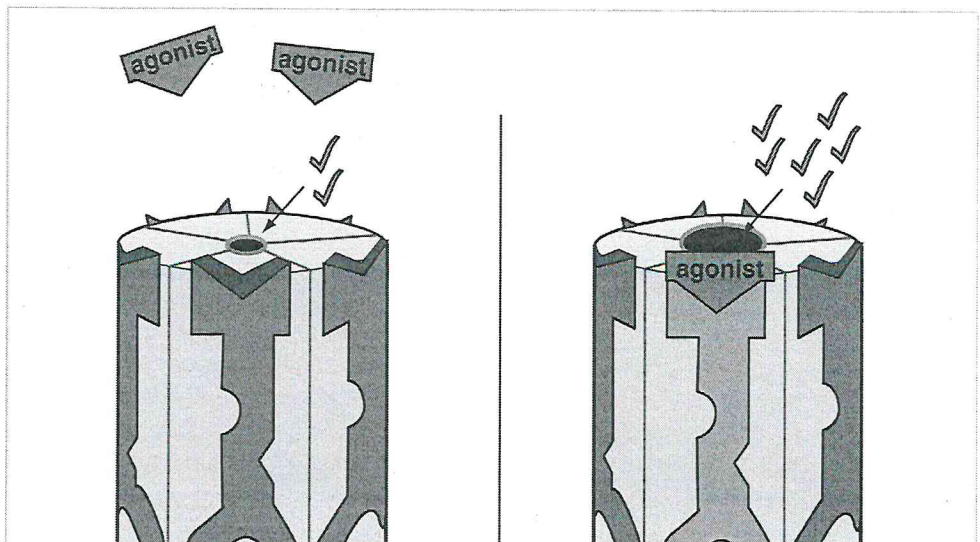
Save image

Figure 3-4. Agonist spectrum. The agonist spectrum and its corresponding effects on the ion channel are shown here. This spectrum ranges from agonists (on the far left), which open the channel the maximal amount and frequency allowed by that binding site, through antagonists (middle of the spectrum), which retain the resting state with infrequent opening of the channel, to inverse agonists (on the far right), which put the ion channel into a closed and inactive state. Between agonists and antagonists are partial agonists, which increase the degree and frequency of ion-channel opening as compared to the resting state, but not as much as a full agonist. Antagonists can block anything in the agonist spectrum, returning the ion channel to the resting state in each instance.
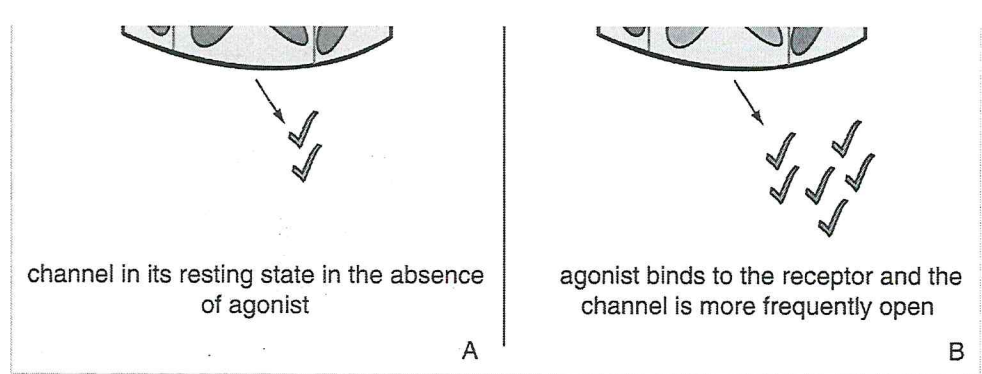
of ion-channel-linked receptors reverse the action of agonists (Figure 3-7) and bring the receptor conformation back to the resting baseline state, but do not block any constitutive activity.

Partial agonists produce a change in receptor conformation such that the ion channel opens to a greater extent and more frequently than in its resting state but less than in the presence of a full agonist (Figures 3-8 and 3-9). An antagonist reverses a partial agonist, just as it reverses a full agonist, returning the receptor to its resting state (Figure 3-10). Partial agonists thus produce ion flow and downstream signal transduction that is something more than the resting state in the absence of agonist, yet something less than a full agonist. Just as is the case for G-protein-linked receptors, how close this partial agonist is to a full agonist or to a silent antagonist on the agonist spectrum will determine the impact of a partial agonist on downstream signal transduction events.

The ideal therapeutic agent in some cases may need to have ion flow and signal transduction that is not too hot, yet not too cold, but just right, called the "Goldilocks" solution in Chapter 2 (essential_4th_chapter.jsf?page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1), a concept that can apply here to ligand-gated ion channels as well. Such

channel in its resting state in the absence of agonist

A

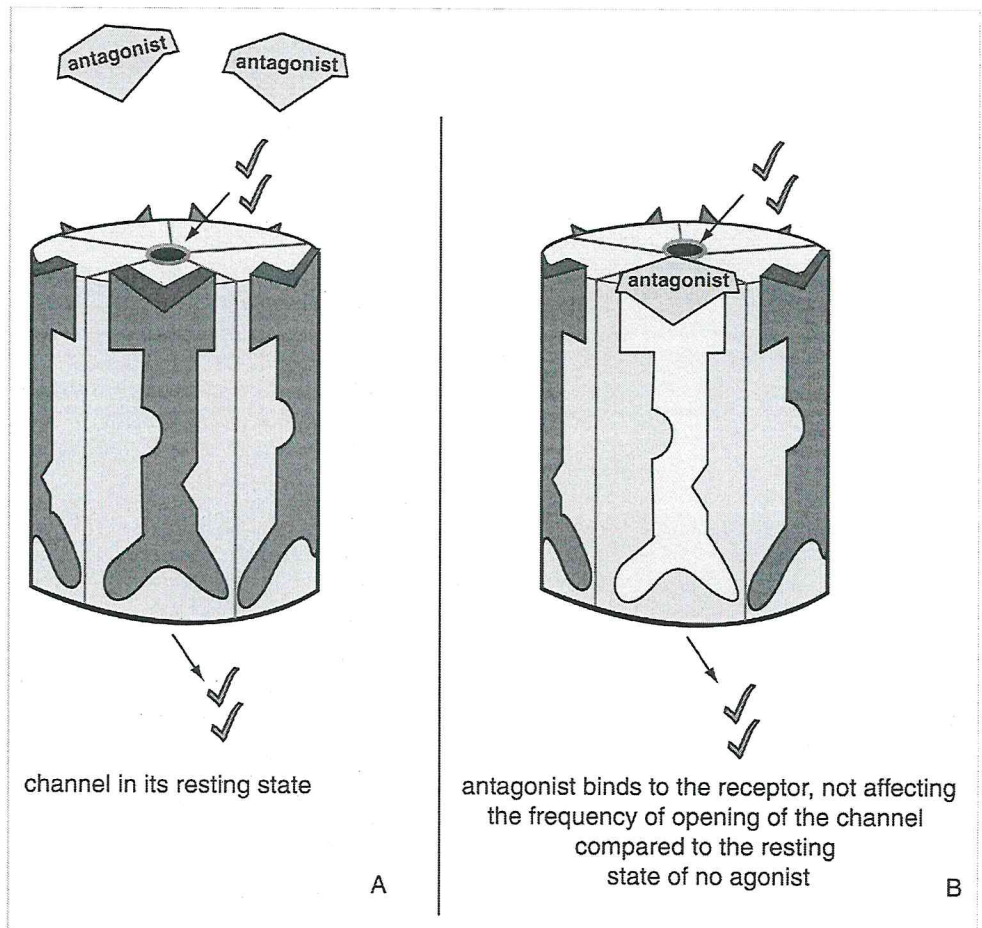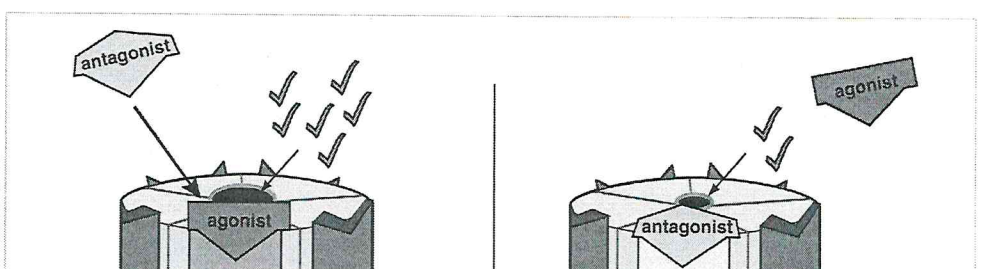agonist binds to the receptor and the channel is more frequently open
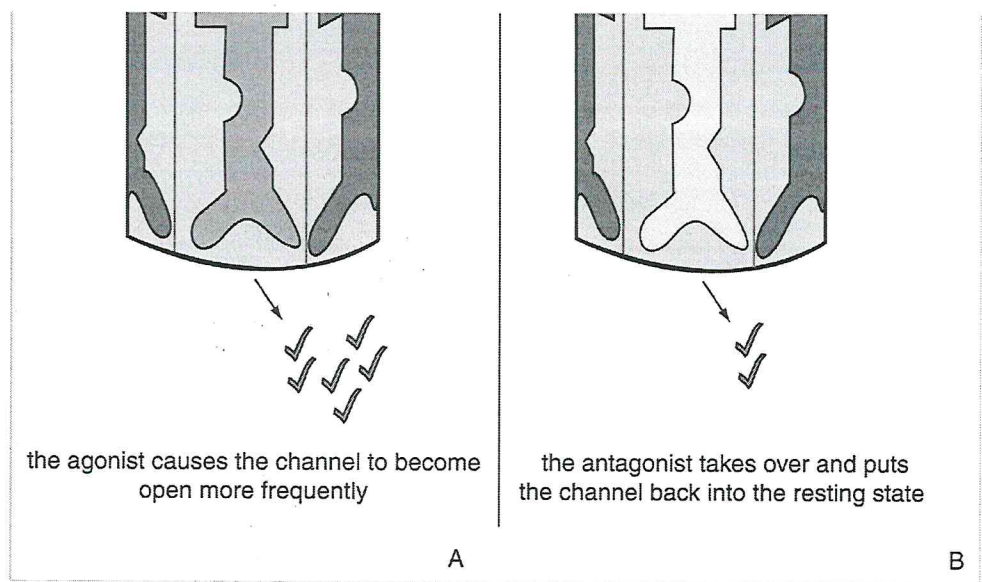
B

Save image

Figure 3-5. Actions of an agonist. In panel A, the ion channel is in its resting state, during which the channel opens infrequently (constitutive activity). In panel B, the agonist occupies its binding site on the ligand-gated ion channel, increasing the frequency at which the channel opens. This is represented as the red agonist turning the receptor red and opening the ion channel.

channel in its resting state

A

antagonist binds to the receptor, not affecting the frequency of opening of the channel compared to the resting state of no agonist

B

Save image

Figure 3-6. Antagonists acting alone. In panel A, the ion channel is in its resting state, during which the channel opens infrequently. In panel B, the antagonist occupies the binding site normally occupied by the agonist on the ligand-gated ion channel. However, there is no consequence to this, and the ion channel does not affect the degree or frequency of opening of the channel compared to the resting state. This is represented as the yellow antagonist docking into the binding site and turning the receptor yellow but not affecting the state of the ion channel.

the agonist causes the channel to become open more frequently

the antagonist takes over and puts the channel back into the resting state

A

B

Save image

Figure 3-7. Antagonist acting in presence of agonist. In panel A, the ion channel is bound by an agonist, which causes it to open at a greater frequency than in the resting state. This is represented as the red agonist turning the receptor red and opening the ion channel as it docks into its binding site. In panel B, the yellow antagonist prevails and shoves the red agonist off the binding site, reversing the agonist's actions and restoring the resting state. Thus, the ion channel has returned to its status before the agonist acted.

partial agonist

partial agonist

partial agonist

channel in its resting state

partial agonist binds to the receptor and causes it to open more frequently than the resting state but less frequently than with a full agonist

A

B
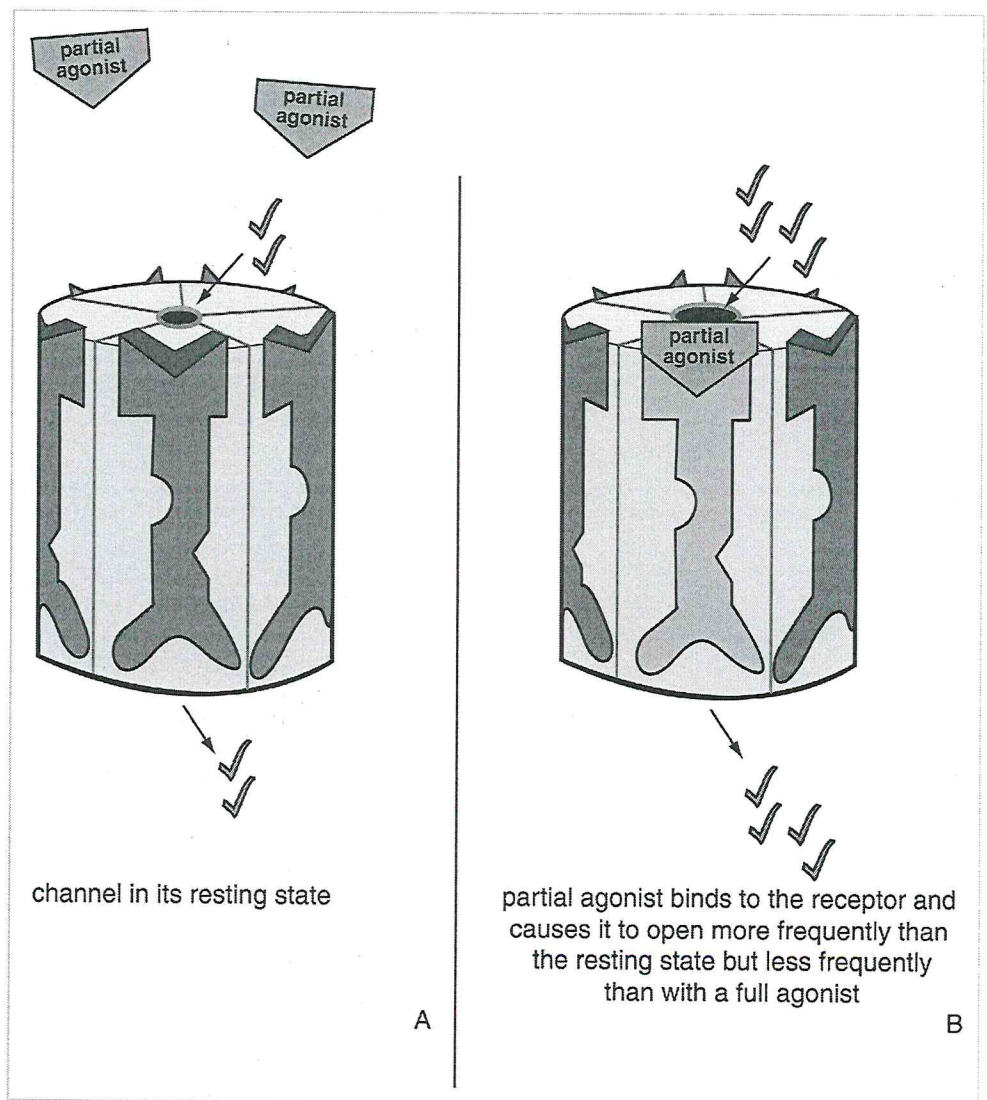
Save image

Figure 3-8. Actions of a partial agonist. In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the partial agonist occupies its binding site on the ligand-gated ion channel and produces a

conformational change such that the ion channel opens to a greater extent and at a greater frequency than in the resting state, though less than in the presence of a full agonist. This is depicted by the orange partial agonist turning the receptor orange and partially but not fully opening the ion channel.
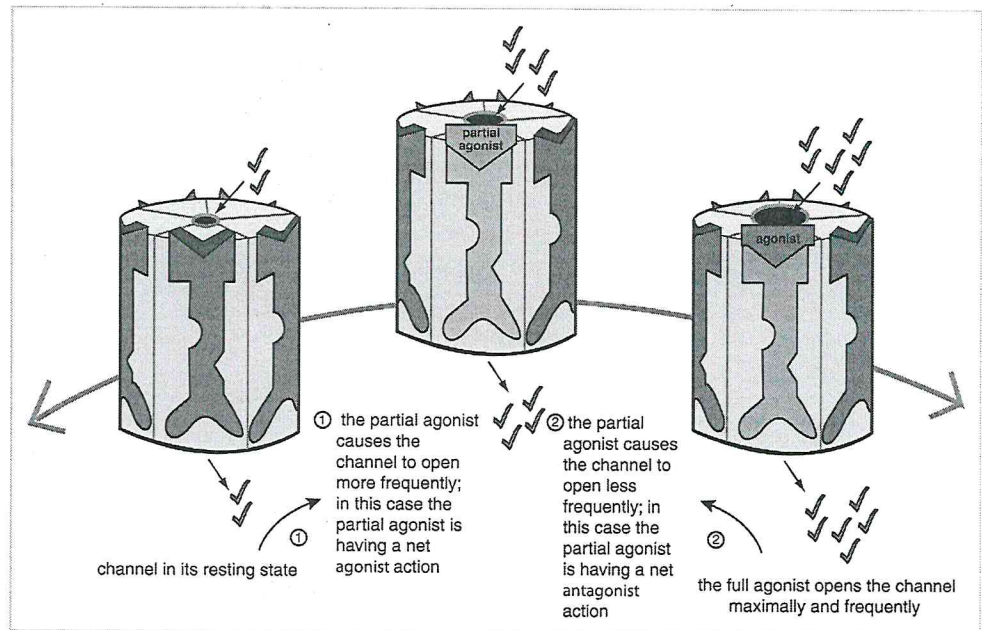
Save image

Figure 3-9. Net effect of partial agonist. Partial agonists act either as net agonists or as net antagonists, depending on the amount of agonist present. When full agonist is absent (on the far left), a partial agonist causes the channel to open more frequently as compared to the resting state and thus has a net agonist action (moving from left to right). However, in the presence of a full agonist (on the far right), a partial agonist decreases the frequency of channel opening in comparison to the full agonist and thus acts as a net antagonist (moving from right to left).
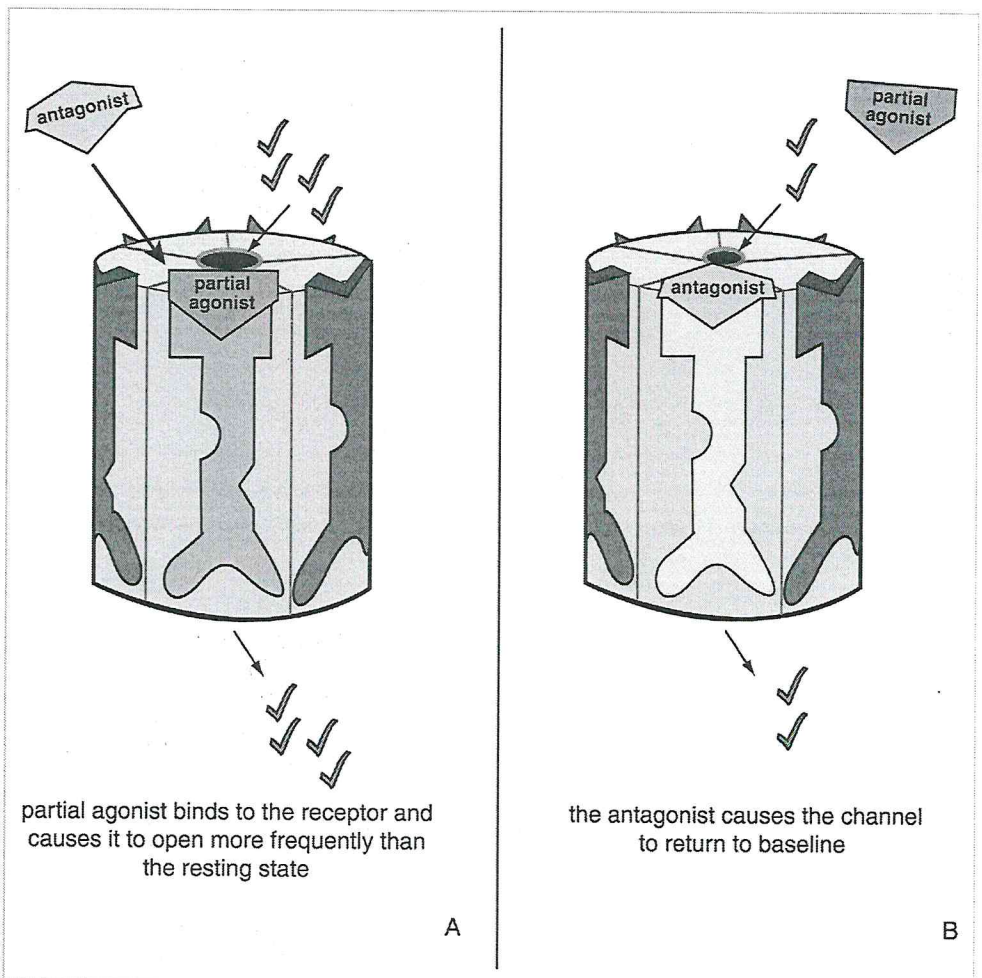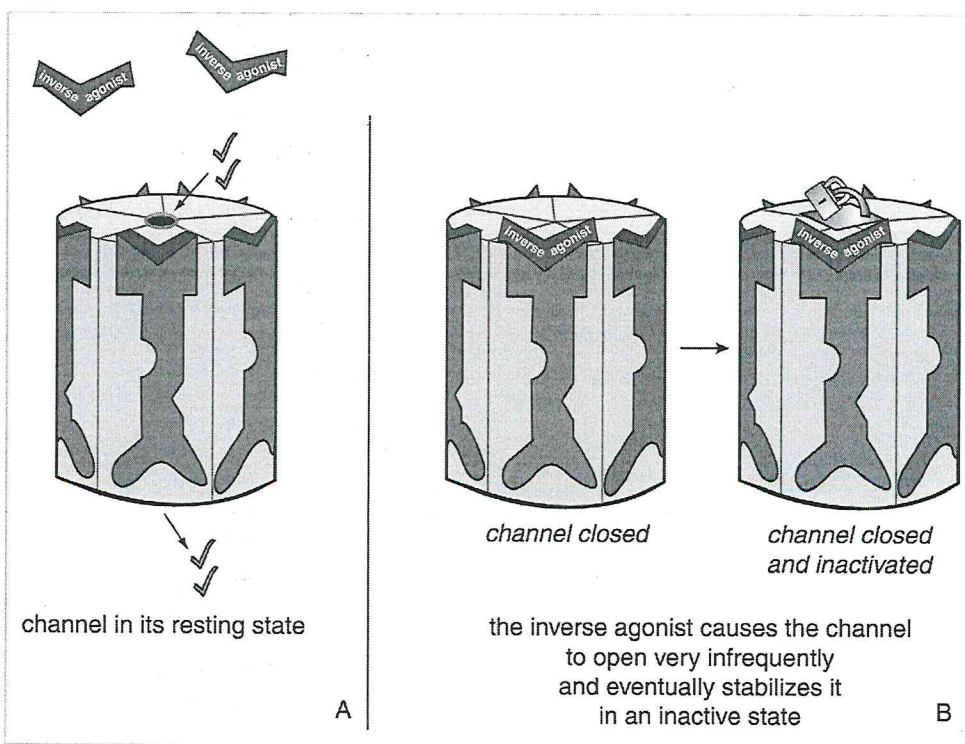
Save image

Figure 3-10. Antagonist acting in presence of partial agonist. In panel A, a partial agonist occupies its binding site and causes the ion channel to open more frequently than in the resting state. This is represented as the orange partial agonist docking to its binding site, turning the receptor orange, and partially opening the ion channel. In panel B, the yellow antagonist prevails and shoves the orange partial agonist off the binding site, reversing the partial agonist's actions. Thus the ion channel is returned to its resting state.

an ideal state may vary from one clinical situation to another, depending upon the balance between full agonism and silent antagonism that is desired. In cases where there is unstable neurotransmission throughout the brain, finding such a balance may stabilize receptor output somewhere between too much and too little downstream action. For this reason, partial agonists are also called "*stabilizers*," since they have the theoretical capacity to find the stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 3-9).

Just as is the case for G-protein-linked receptors, partial agonists at ligand-gated ion channels can appear as net agonists, or as net antagonists, depending upon the amount of naturally occurring full agonist neurotransmitter that is present. Thus, when a full agonist neurotransmitter is absent, a partial agonist will be a net agonist (Figure 3-9). That is, from the resting state, a partial agonist initiates somewhat of an increase in the ion flow and downstream signal transduction cascade from the ion-channel-linked receptor. However, when full agonist neurotransmitter is present, the same partial agonist will become a net antagonist (Figure 3-9): it will decrease the level of full signal output to a lesser level, but not to zero. Thus, a partial agonist can simultaneously *boost* deficient neurotransmitter activity yet *block* excessive neurotransmitter activity, another reason that partial agonists are called stabilizers. An agonist and an antagonist in the same molecule acting at ligand-gated ion channels is quite an interesting new dimension to therapeutics. This concept has led to proposals that partial agonists could treat not only states that are theoretically deficient in full agonist, but also states that are theoretically in excess of full agonist. As mentioned in the discussion of G-protein-linked receptors in Chapter 2 (essential_4th_chapter.jsf? page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1), a partial agonist at ligand-gated ion channels could also theoretically treat states that are mixtures of both excessive and deficient neurotransmitter activity. Partial agonists at ligand-gated ion channels are just beginning to enter use in clinical practice (Table 3-2), and several more are in clinical development.
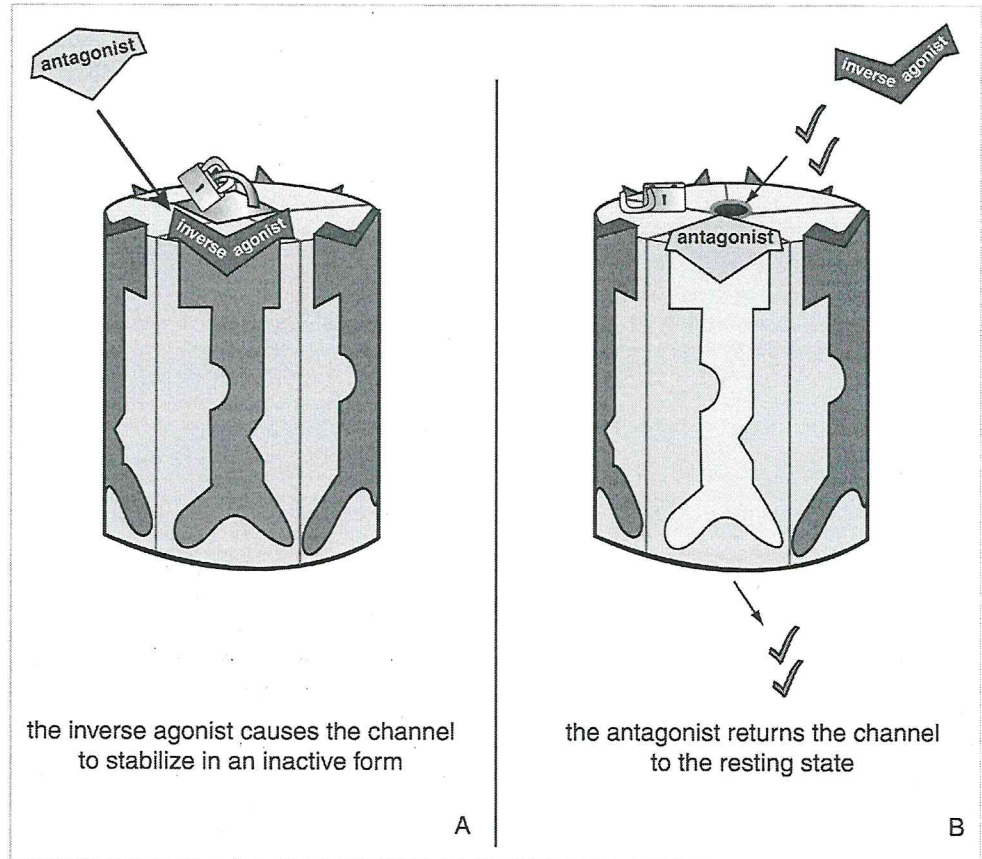
Inverse agonists at ligand-gated ion channels are different from simple antagonists, and are neither neutral nor silent. Inverse agonists are explained in Chapter 2 (essential_4th_chapter.jsf? page=chapter2_introduction.htm&name=Chapter 2&title=Neurotransmitter transporters as targets of drug action#c02598-2-1) in relation to G-protein-linked receptors. Inverse agonists at ligand-gated ion channels are thought to produce

channel in its resting state

channel closed

channel closed and inactivated

the inverse agonist causes the channel to open very infrequently and eventually stabilizes it in an inactive state
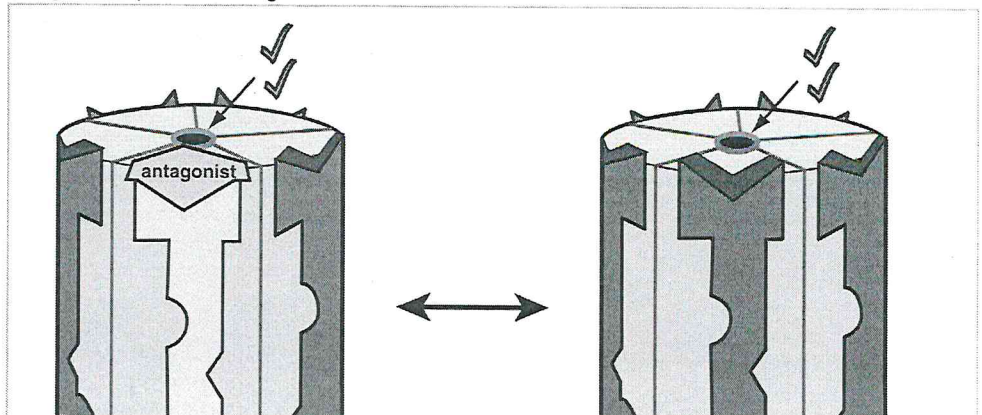
A

B

Figure 3-11. Actions of an inverse agonist. In panel A, the ion channel is in its resting state and opens infrequently. In panel B, the inverse agonist occupies the binding site on the ligand-gated ion channel and causes it to close. This is the opposite of what an agonist does and is represented by the purple inverse agonist turning the receptor purple and closing the ion channel. Eventually, the inverse agonist stabilizes the ion channel in an inactive state, represented by the padlock on the channel itself.
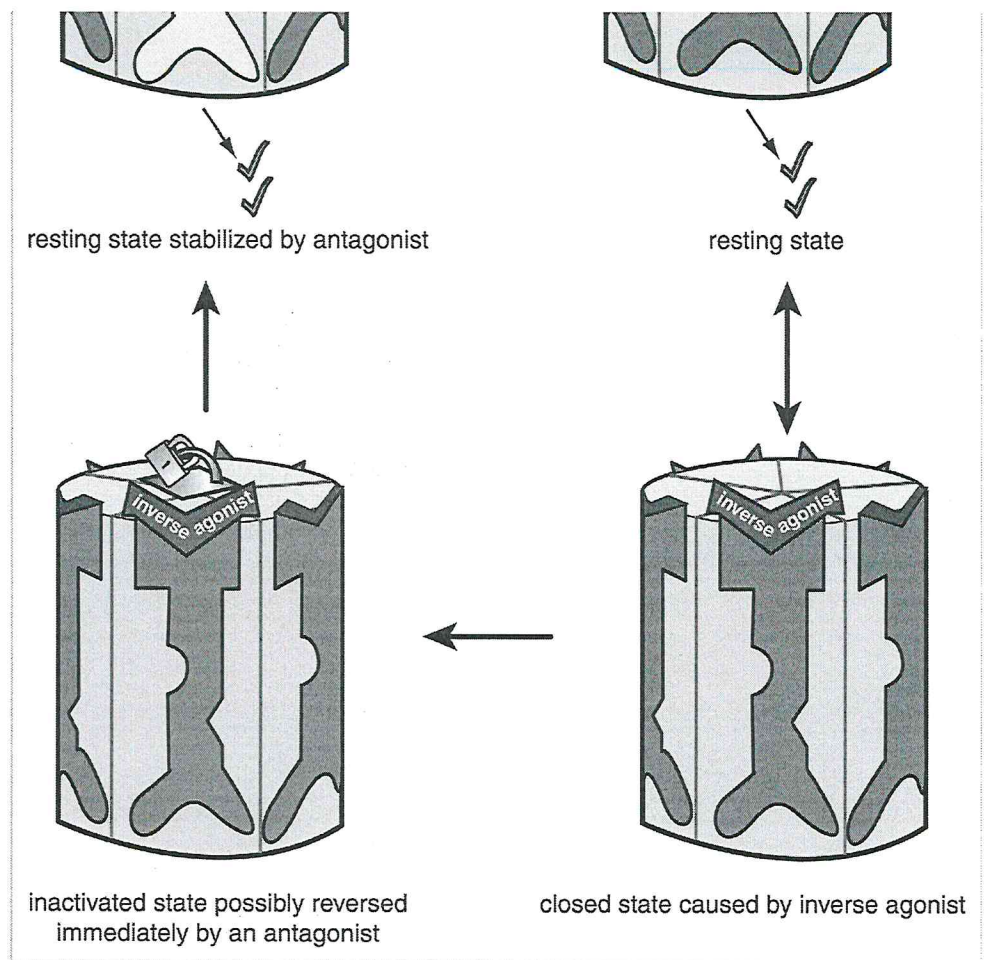

the inverse agonist causes the channel
to stabilize in an inactive form

A

the antagonist returns the channel
to the resting state

B

Figure 3-12. Antagonist acting in presence of inverse agonist. In panel A, the ion channel has been stabilized in an inactive form by the inverse agonist occupying its binding site on the ligand-gated ion channel. This is represented as the purple inverse agonist turning the receptor purple and closing and padlocking the ion channel. In panel B, the yellow antagonist prevails and shoves the purple inverse agonist off the binding site, returning the ion channel to its resting state. In this way, the antagonist's effects on an inverse agonist's actions are similar to its effects on an agonist's actions; namely, it returns the ion channel to its resting state. However, in the presence of an inverse agonist, the antagonist increases the frequency of channel opening, whereas in the presence of an agonist, the antagonist decreases the frequency of channel opening. Thus an antagonist can reverse the actions of either an agonist or an inverse agonist despite the fact that it does nothing on its own.

a conformational change in these receptors that first closes the channel and then stabilizes it in an inactive form (Figure 3-11). Thus, this inactive conformation (Figure 3-11B) produces a functional reduction in ion flow and in consequent signal transduction compared to the resting state (Figure 3-11A) that is even less than that produced when there is either no agonist present or when a silent antagonist is present. Antagonists reverse

resting state stabilized by antagonist   resting state

inactivated state possibly reversed   closed state caused by inverse agonist
immediately by an antagonist

Save image

Figure 3-13. Inverse agonist actions reversed by antagonist. Antagonists cause conformational change in ligand-gated ion channels that stabilizes the receptors in the resting state (top left), the same state they are in when no agonist or inverse agonist is present (top right). Inverse agonists cause conformational change that closes the ion channel (bottom right). When an inverse agonist is bound over time, it may eventually stabilize the ion channel in an inactive conformation (bottom left). This stabilized conformation of an inactive ion channel can be quickly reversed by an antagonist, which restabilizes it in the resting state (top left).

this inactive state caused by inverse agonists, returning the channel to the resting state (Figure 3-12).

In many ways, therefore, an inverse agonist does the *opposite* of an agonist. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. Also, in contrast to antagonists, which stabilize the resting state, inverse agonists stabilize an inactivated state (Figures 3-11 and 3-13). It is not yet clear if the inactivated state of the inverse agonist can be distinguished clinically from the resting state of the silent antagonist at ionotropic receptors. In the meantime, inverse agonists remain an interesting pharmacological concept.

In summary, ion-channel-linked receptors act along an agonist spectrum, and drugs have been described that can produce conformational changes in these receptors to create any state from full agonist, to partial agonist, to silent antagonist, to inverse agonist (Figure 3-4). When one considers signal transduction along this spectrum, it is easy to understand why agents at each point along the agonist spectrum differ so much from each other, and why their clinical actions are so different.
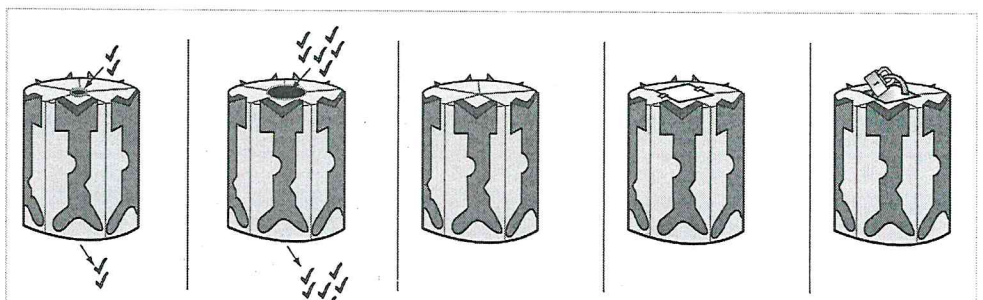
☐ Save image

Figure 3-14. Five states of ligand-gated ion channels. Summarized here are five well-known states of ligand-gated ion channels. In the resting state, ligand-gated ion channels open infrequently, with consequent constitutive activity that may or may not lead to detectable signal transduction. In the open state, ligand-gated ion channels open to allow ion conductance through the channel, leading to signal transduction. In the closed state, ligand-gated ion channels are closed, allowing no ion flow to occur and thus reducing signal transduction to even less than is produced in the resting state. Channel desensitization is an adaptive state in which the receptor stops responding to agonist even if it is still bound. Channel inactivation is a state in which a closed ion channel over time becomes stabilized in an inactive conformation.
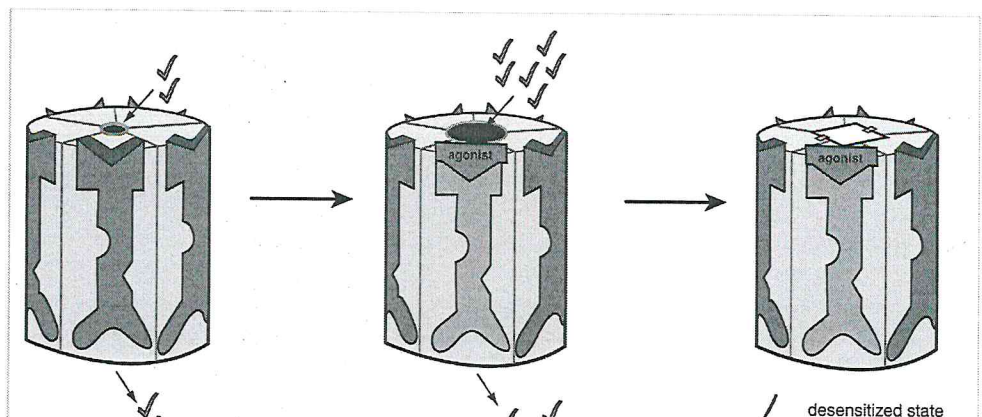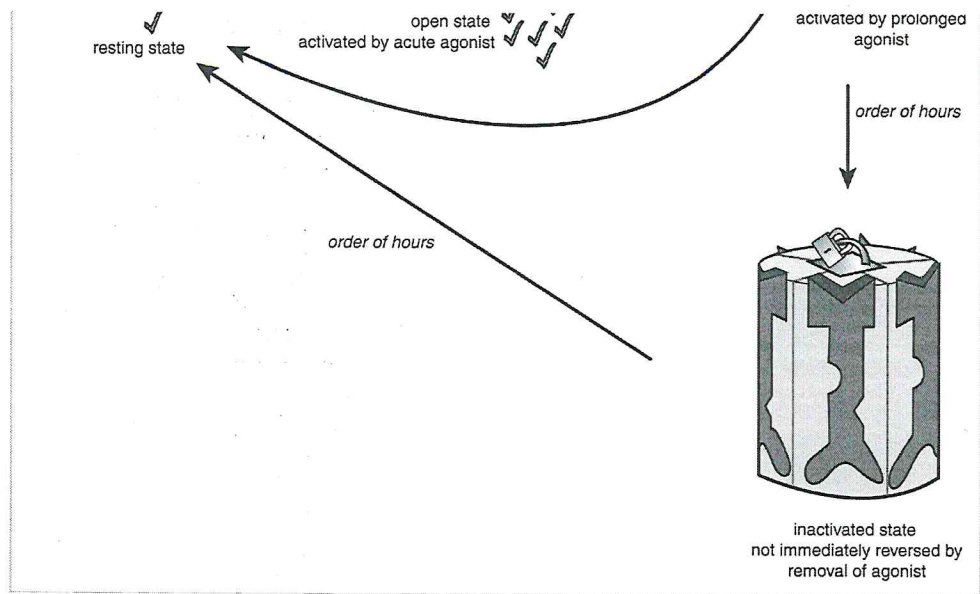
Different states of ligand-gated ion channels

There are even more states of ligand-gated ion channels than those determined by the agonist spectrum discussed above and shown in Figures 3-4 through 3-13. The states discussed so far are those that occur predominantly with acute administration of agents that work across the agonist spectrum. These range from the maximal opening of the ion channel caused by a full agonist to the maximal closing of the ion channel caused by an inverse agonist. Such changes in conformation caused by the acute action of agents across this spectrum are subject to change over time, because these receptors have the capacity to adapt, particularly when there is chronic or excessive exposure to such agents.

We have already discussed the resting state, the open state, and the closed state shown in Figure 3-14. The best-known adaptive states are those of desensitization and inactivation, also shown in Figure 3-14. We have also briefly discussed inactivation as a state that can be caused by acute administration of an inverse agonist, beginning with a rapid conformational change in the ion channel that first closes it, but over time stabilizes the channel in an inactive conformation that can be relatively quickly reversed by an antagonist, which then restabilizes the ion channel in the resting state (Figures 3-11 through 3-13).

Desensitization is yet another state of the ligand-gated ion channel shown in Figure 3-14. Ion-channel-linked receptor desensitization can be caused by prolonged exposure to agonists, and may be a way for receptors to protect themselves from overstimulation. An agonist acting at a ligand-gated ion channel first induces a change in receptor conformation that opens the channel, but the continuous presence of the agonist over time leads to another conformational change where the receptor essentially stops responding to the agonist even though the agonist is still present. This receptor is then considered to be desensitized (Figures 3-14 and 3-15). This state of desensitization can at first be reversed relatively quickly by removal of the agonist (Figure 3-15). However, if the agonist stays much longer, on the order of hours, then the receptor converts from a state of simple desensitization to one of inactivation (Figure 3-15). This state does not reverse simply upon removal of the agonist, since it also takes hours in the absence of agonist to revert to the resting state where the receptor is again sensitive to new exposure to agonist (Figure 3-15).

The state of inactivation may be best characterized for nicotinic cholinergic receptors, ligand-gated ion channels that are normally responsive to the endogenous neurotransmitter acetylcholine. Acetylcholine is quickly hydrolyzed by an abundance of the enzyme acetylcholinesterase, so it rarely gets the chance to desensitize and inactivate its nicotinic receptors. However, the drug nicotine is not hydrolyzed by acetylcholinesterase, and is famous for stimulating nicotinic cholinergic receptors so profoundly and so
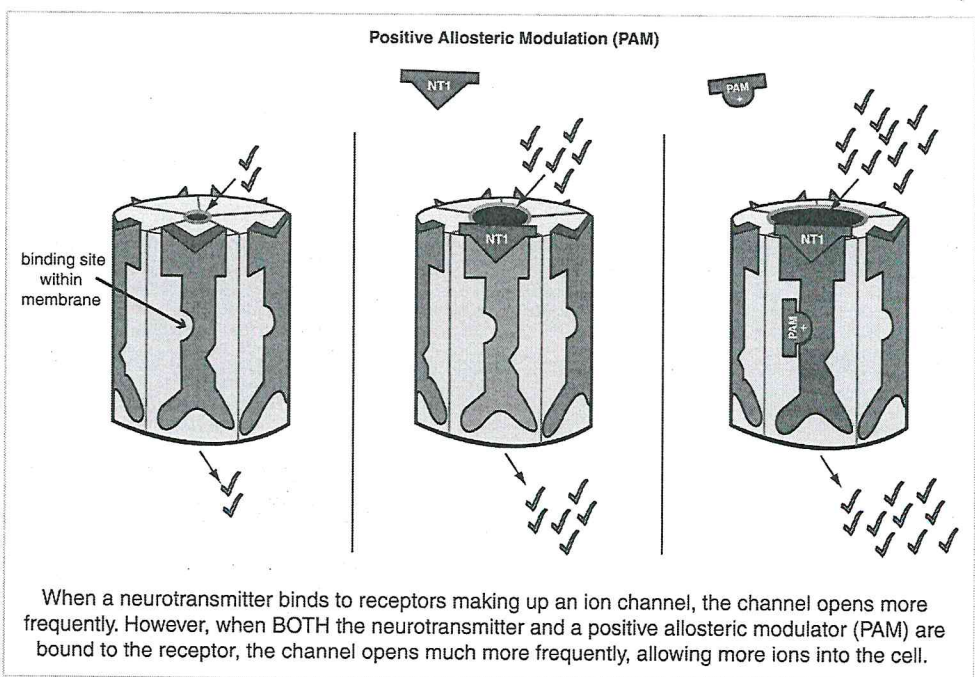

desensitized state

resting state

open state
activated by acute agonist

activated by prolonged agonist

order of hours

order of hours

inactivated state
not immediately reversed by
removal of agonist

☐ Save image

Figure 3-15. Opening, desensitizing, and inactivating by agonists. Agonists cause ligand-gated ion channels to open more frequently, increasing ion conductance in comparison to the resting state. Prolonged exposure to agonists can cause a ligand-gated ion channel to enter a desensitized state in which it no longer responds to the agonist even if it is still bound. Prompt removal of the agonist can reverse this state fairly quickly. However, if the agonist stays longer, it can cause a conformational change that leads to inactivation of the ion channel. This state is not immediately reversed when the agonist is removed.

enduringly that the receptors are not only rapidly desensitized, but enduringly inactivated, requiring hours in the absence of agonist to get back to the resting state. These transitions among various receptor states induced by agonists are shown in Figure 3-15. Desensitization of nicotinic receptors is discussed in further detail in Chapter 14 (essential_4th_chapter.jsf? page=chapter14_introduction.htm&name=Chapter 14&title=Overview of impulsive-compulsive disorders#c02598-14-1).

Allosteric modulation: PAMs and NAMs

Ligand-gated ion channels are regulated by more than the neurotransmitter(s) that bind to them. That is, there are other molecules that are not neurotransmitters but that can bind to the receptor/ion-channel complex at different sites from where

Positive Allosteric Modulation (PAM)

binding site within membrane

When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a positive allosteric modulator (PAM) are bound to the receptor, the channel opens much more frequently, allowing more ions into the cell.

☐ Save image

Figure 3-16. Positive allosteric modulators (PAMs). Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their
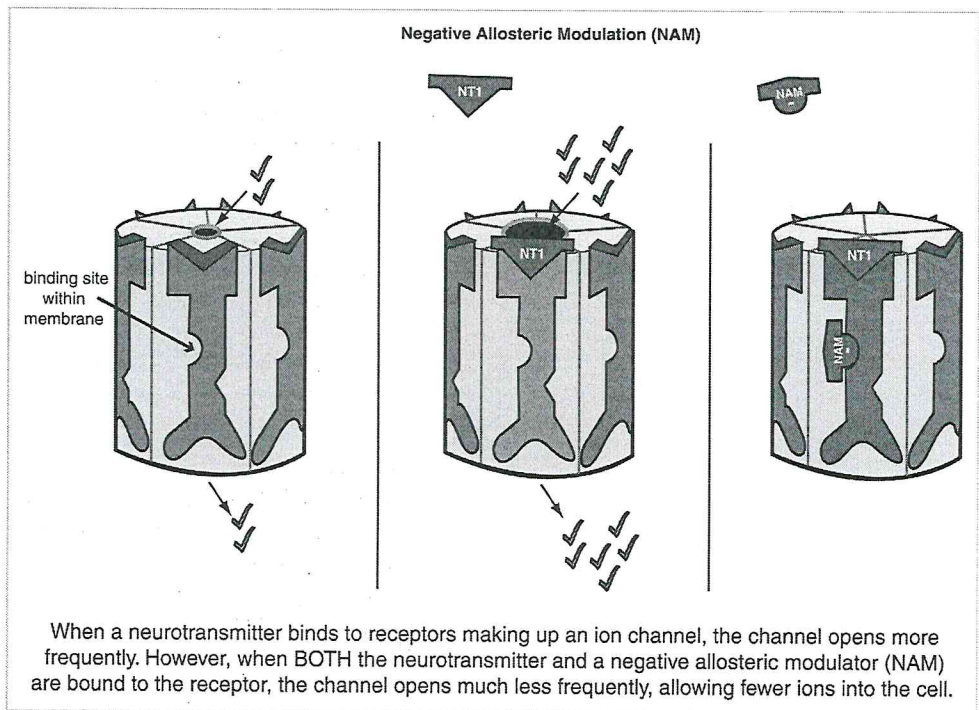
own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a PAM binds to its site while an agonist is also bound, the channel opens more frequently than when only the agonist is bound, therefore allowing more ions into the cell.

neurotransmitter(s) bind. These sites are called *allosteric* (literally, "other site") and ligands that bind there are called allosteric modulators. These ligands are modulators rather than neurotransmitters because they have little or no activity on their own in the absence of the neurotransmitter. Allosteric modulators thus only work in the presence of the neurotransmitter.

There are two forms of allosteric modulators – those that boost what the neurotransmitter does and are thus called positive allosteric modulators (PAMs), and those that block what the neurotransmitter does and are thus called negative allosteric modulators (NAMs).

Specifically, when PAMs or NAMs bind to their allosteric sites while the neurotransmitter is *not* binding to its site, the PAM and the NAM do nothing. However, when a PAM binds to its allosteric site while the neurotransmitter is sitting at its site, the PAM causes conformational changes in the ligand-gated ion channel that open the channel even further and more frequently than happens with a full agonist by itself (Figure 3-16). That is why the PAM is called "positive." Good examples of PAMs are benzodiazepines. These ligands boost the action of GABA at $GABA_A$ types of ligand-gated chloride ion channels. GABA binding to $GABA_A$ sites increases chloride ion flux by opening the ion channel, and benzodiazepines acting as agonists at benzodiazepine receptors elsewhere on the $GABA_A$ receptor complex cause the effect of GABA to be amplified in terms of chloride ion flux by opening the ion channel to a greater degree or more frequently. Clinically, this is exhibited as anxiolytic, hypnotic, anticonvulsant, amnestic, and muscle relaxant actions. In this example, benzodiazepines are acting as full agonists at the PAM site.

On the other hand, when a NAM binds to its allosteric site while the neurotransmitter resides at its agonist binding site, the NAM causes conformational

When a neurotransmitter binds to receptors making up an ion channel, the channel opens more frequently. However, when BOTH the neurotransmitter and a negative allosteric modulator (NAM) are bound to the receptor, the channel opens much less frequently, allowing fewer ions into the cell.

☐ Save image

Figure 3-17. Negative allosteric modulators (NAMs). Allosteric modulators are ligands that bind to sites other than the neurotransmitter site on an ion-channel-linked receptor. Allosteric modulators have no activity of their own but rather enhance (positive allosteric modulators, or PAMs) or block (negative allosteric modulators, or NAMs) the actions of neurotransmitters. When a NAM binds to its site while an agonist is also bound, the channel opens less frequently than when only the agonist is bound, therefore allowing fewer ions into the cell.

changes in the ligand-gated ion channel that block or reduce the actions that normally occur when the neurotransmitter acts alone (Figure 3-17). That is why the NAM is called "negative." One example of a NAM is a benzodiazepine inverse agonist. Although these are only experimental, as expected, they have the opposite actions of benzodiazepine full agonists and thus diminish chloride

conductance through the ion channel so much that they cause panic attacks, seizures, and some improvement in memory – the opposite clinical effects of a benzodiazepine full agonist. Thus, the same allosteric site can have either NAM or PAM actions, depending upon whether the ligand is a full agonist or an inverse agonist. NAMs for NMDA receptors include phencyclidine (PCP, also called "angel dust") and its structurally related anesthetic agent ketamine. These agents bind to a site in the calcium channel, but can get into the channel to block it only when the channel is open. When either PCP or ketamine bind to their NAM site, they prevent glutamate/glycine cotransmission from opening the channel.