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Ion Channels as Targets of Psychopharmacological Drug Action Ligand-Gated Ion Channels as Targets of Psychopharmacological Drug Action 51 Ligand-Gated Ion Channels, Ionotropic Receptors, and Ion-Channel-Linked Receptors 51 Ligand-Gated Ion Channels: Structure and Function 53 Pentameric Subtypes 53 Tetrameric Subtypes 54 The Agonist Spectrum 56 Different States of Ligand-Gated Ion Channels 63 Allosteric Modulation: PAMs and NAMs 64 Voltage-Sensitive Ion Channels as Targets of Psychopharmacological Drug Action 66 Structure and Function 66 VSSCs (Voltage-Sensitive Sodium Channels) 67 VSCCs (Voltage-Sensitive Calcium Channels) 70 Ion Channels and Neurotransmission 73 Summary 76 Many important psychopharmacological drugs target ion channels. The role of ion channels as important regulators of synaptic neurotransmission has been covered in Chapter 1. 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 will cover ligandgated 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 The terms ligand-gated ion channels, ionotropic receptors, and ion-channel-linked receptors are in fact 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-gated or a voltage-sensitive ion channel, and 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 also sometimes also called ionotropic receptors or ion-channel linked 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 and include both activation and inactivation

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY ENTER NO ENTRY 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. Ligandgated ion channels are a type of receptor that forms an ion channel and are thus also called ion-channel-linked receptors or ionotropic receptors. A B

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 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 drugs for anxiety and for sleep 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, some of which have clinical effects – such as actions on mood – 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 both 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 and ion-channel-linked receptor). These terms try to capture the dual function of these ion channels/receptors and may explain why there is more than one term for this receptor/ion-channel complex. Ligand-gated ion channels are comprised of several long strings of amino acids assembled as subunits around an ion channel. Decorated on these subunits Chapter 3: Ion Channels 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, and 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 GABAA receptors, nicotinic cholinergic receptors, serotonin 5HT3 receptors, and certain glycine receptors (Table 3-1). Drugs that act directly on pentameric ligandgated 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 of the five subunits are chosen for assembly into a fully Table 3-1 Pentameric ligand-gated ion channels Four transmembrane regions Five subunits Neurotransmitter Receptor subtype Acetylcholine Nicotinic receptors (e.g. α7 nicotinic receptors; α4β2 nicotinic receptors) GABA GABAA receptors (e.g. α1 subunits; γ subunits; δ subunits) Glycine Strychnine-sensitive glycine receptors Serotonin 5HT3 receptors 53

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A

B

C 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. 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). Ligand-gated ion channels have receptor binding sites located on all five subunits, both inside and outside the channel. Tetrameric Subtypes Ionotropic glutamate receptors have a different structure from the pentameric ionotropic receptors just discussed. The ligand-gated ion channels for glutamate are comprised of 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

Chapter 3: Ion Channels Table 3-2 Key ligand-gated ion channels directly targeted by psychotropic drugs Neurotransmitter Ligand-gated ion channel receptor subtype directly targeted Pharmacological action Drug class Therapeutic action Acetylcholine Alpha4 Beta2 nicotinic Partial agonist Nicotinic receptor partial agonist (NRPA) (varenicline) Smoking cessation GABA GABAA benzodiazepine receptors Full agonist, phasic inhibition Benzodiazepines Anxiolytic GABAA nonbenzodiazepine PAM sites Full agonist, phasic inhibition “Z DRUGS”/hypnotics (zolpidem, zaleplon, zopiclone, eszopiclone) Improves insomnia GABAA neurosteroid sites (benzodiazepine insensitive) Full agonist, tonic inhibition Neuroactive steroids (allopregnanolone) Postpartum depression Rapid-acting antidepressant Anesthetic Glutamate NMDA NAM channel sites/ Mg++ sites Antagonist NMDA glutamate antagonist (memantine) Pro-cognitive in Alzheimer disease NMDA openchannel sites Antagonist PCP/phencyclidine Ketamine Dextromethorphan Dextromethadone Dissociative hallucinogen Anesthetic Pseudobulbar affect Agitation in Alzheimer disease Rapid-acting antidepressant Treatment-resistant depression Serotonin 5HT3 Antagonist Mirtazapine Vortioxetine Pro-cognitive Antidepressant 5HT3 Antagonist Anti-emetic Reduce chemotherapyinduced emesis PAM, positive allosteric modulator; NAM, negative allosteric modulator; NMDA, N-methyl-D-aspartate; Mg, magnesium. ion channels (Figure 3-3) are analogous to pentameric subtypes of ion channels (Figure 3-2A), but just have 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-3hydroxy-5-methyl-4-isoxazole-propionic acid), kainate, 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.

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Table 3-3 Tetrameric ligand-gated ion channels Three transmembrane regions and one re-entrant loop Four 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) AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid; NMDA, N-methyl-D-aspartate.

A

B

C The Agonist Spectrum The concept of an agonist spectrum for G-protein-linked receptors discussed extensively in Chapter 2 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 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 (PAM) as will be shown later. 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). Ligand-gated ion channels have receptor binding sites located on all four subunits, both inside and outside the channel.

The Agonist Spectrum antagonist partial agonist agonist inverse agonist 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 frequency allowed by that binding site (depicted for simplicity's sake with a wider opening), 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 the extremes of agonist and antagonist 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. agonist agonist

channel in its resting state in the absence of agonist

A Chapter 3: Ion Channels Antagonists stabilize the receptor in the resting state (Figure 3-6B), which is the same as the state of the receptor in the absence of agonist (Figure 3-6A). 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 for G-protein-linked receptors. Antagonists 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 like it reverses a full agonist, returning the receptor to its resting state (Figure 3-10). Partial agonists thus produce 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. agonist

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

B 57

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY antagonist antagonist antagonist

channel in its resting state

antagonist binds to the receptor, not affecting the frequency of opening of the channel compared to the resting

A

B state of no agonist antagonist antagonist agonist

the agonist causes the channel to become open more frequently

A 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 ligandgated 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. Figure 3-7 Antagonist acting in the 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. agonist

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

B

Chapter 3: Ion Channels 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.

A

B 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 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; thus, the partial agonist is having 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). agonist partial agonist channel in its resting state the full agonist opens the channel maximally and frequently the partial agonist causes the channel to open more frequently; in this case the partial agonist is having a net agonist action the partial agonist causes the channel to open less frequently; in this case the partial agonist is having a net antagonistic action 1 2

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partial agonist binds to the receptor and causes it to open more frequently than the resting state

A 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, depending upon 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 should 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, a concept that can apply here to ligand-gated ion channels as well. Such 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 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 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. partial agonist

the antagonist causes the channel to return to baseline

B appear as net agonists, or as net antagonists, depending upon the amount of naturally occurring full agonist neurotransmitter which 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 agonist is present, the same partial agonist will become a net antagonist (Figure 3-9). That is, 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 which 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, a partial agonist at ligand-gated ion channels could also theoretically treat states that are mixtures of both

inverse agonist

channel in its resting state

A

B antagonist

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

A excessive and deficient neurotransmitter activity. Partial agonists at ligand-gated ion channels are just beginning to enter into 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 in relationship to G-protein-linked receptors. Inverse Chapter 3: Ion Channels 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. channel closed

channel closed and inactivated

the inverse agonist causes the channel to open very infrequently and eventually stabilizes it in an inactive state Figure 3-12 Antagonist acting in the 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 ligandgated 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. inverse agonist antagonist

the antagonist returns the channel to the resting state

B agonists at ligand-gated ion channels are thought to produce 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 61

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY a silent antagonist is present. Antagonists reverse 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 313). 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 antagonist resting state stabilized by antagonist by inverse agonist inactivated state

possibly reversed immediately by an antagonist 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 the spectrum of 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. Figure 3-13 Inverse agonist actions reversed by antagonist. Antagonists cause conformational change in ligandgated 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). resting state closed state caused

Chapter 3: Ion Channels 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. channel in resting state channel open channel closed channel desensitized channel inactivated 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 from conformational changes 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 since 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 relatively quickly be 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 with 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, 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 back 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

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY receptors described here. Addiction to nicotine and other substances is described in more detail in Chapter 13 on impulsivity and substance abuse. These transitions among various receptor states induced by agonists are shown in Figure 3-15. 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 acetylcholinesterase, and is famous for stimulating nicotinic cholinergic receptors so profoundly and so enduringly that the receptors are not only rapidly desensitized in about the time it takes to smoke a single cigarette, but enduringly inactivated for about the time most smokers take between cigarettes. Ever wonder why cigarettes are the length they are and why most smokers smoke about a pack a day (20 cigarettes) in about 16 waking hours? It all has to do with adjusting the dosing of nicotine to the nature of receptor action of nicotinic 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. agonist agonist resting state open state activated by acute agonist desensitized state activated by prolonged agonist inactivated state not immediately reversed by removal of agonist order of hours order of hours

Chapter 3: Ion Channels 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 (γ-aminobutyric acid) at GABAA types of ligand-gated chloride ion channels. GABA binding to GABAA sites increases chloride ion flux by opening the ion channel, and benzodiazepines acting as agonists at benzodiazepine receptors elsewhere on the GABAA 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 reducing anxiety, inducing sleep, blocking convulsions, blocking short-term memory, and relaxing muscles. 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 changes in the ligand-gated ion channel that block or reduce the actions that normally occur when the neurotransmitter can bind to the receptor/ion channel complex at different sites from where 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 in its site, the PAM causes conformational changes in the ligand-gated ion channel that open the channel even further and more frequently Figure 3-16 Positive allosteric modulators. 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. 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. NT1 NT1 NT1 PAM + PAM + binding site within membrane

 When either PCP or ketamine bind to their NAM site, they prevent glutamate/glycine cotransmission from opening the channel.

VOLTAGE-SENSITIVE ION CHANNELS AS TARGETS OF

PSYCHOPHARMACOLOGICAL DRUG ACTION Structure and Function Not all ion channels are regulated by neurotransmitter ligands. Indeed, critical aspects of nerve conduction, action potentials, and neurotransmitter release are all mediated by another class of ion channels, known as voltage-sensitive or voltage-gated ion channels because their opening and closing are regulated by the ionic charge or voltage potential across the membrane in 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 either have 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, also used as a treatment for resistant depression and suicidal thoughts. These agents bind to a site inside the calcium channel, but can get into the channel to block it only when the channel is open. Figure 3-17 Negative allosteric modulators. 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.

NAM

NAM

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. neurotransmitter

Chapter 3: Ion Channels associated with the four subunits, and these appear to have regulatory functions. Let us now build a voltage-sensitive ion channel from scratch, and describe the known

functions for each part of the proteins that make up these channels. The subunit of a pore-forming protein has six transmembrane segments (Figure 3-19). Transmembrane segment 4 can detect the difference in charge across the membrane, and is thus the most electrically sensitive part of the voltage-sensitive channel. Transmembrane segment 4 thus functions like a voltmeter, and when it detects a change in ion charge across the membrane, it can alert the rest of the protein, and begin conformational changes of the ion channel, and either open it or close it. This same general structure exists for both VSSCs (Figure 3-19A) and for VSCCs (Figure 3-19B), but the exact amino acid sequence of the protein subunits are obviously different for VSSCs compared to VSCCs. Each subunit of a voltage-sensitive ion channel has an extracellular amino acid loop between transmembrane segments 5 and 6 (Figure 3-19). This section of amino acids serves as an “ionic filter” and is located in a position so that it can cover the outside opening of the pore. This is illustrated as a colander configured molecularly to allow only sodium ions to filter through the sodium channel on the left and only calcium ions to filter through the calcium channel on the right (Figure 3-19). Four copies of the sodium-channel version of this protein are strung together to form one complete ion channel pore of a VSSC (Figure 3-20A). The cytoplasmic loops of amino acids that tie these four subunits together are sites that regulate various functions of the sodium channel. For example, on the connector loop between the third and fourth subunits of a VSSC, there are amino acids that act as a “plug” to close the channel. Like a ball on an amino acid chain, this “pore inactivator” stops up the channel on the inner membrane surface of the pore which they reside. An electrical impulse in a neuron, also known as the action potential, is triggered by summation of the various neurochemical and electrical events of neurotransmission. These are discussed extensively in Chapter 1, which covers the chemical basis of neurotransmission and signal transduction. Electrically, the action potential is shown in Figure 3-18. The first phase is sodium rushing “downhill” into the sodium deficient, negatively charged internal milieu of the neuron (Figure 3-18A). This is made possible when voltage-gated sodium channels open the gates and let the sodium in. A few milliseconds later, the calcium channels get the same idea, with their voltage-gated ion channels opened by the change in voltage potential caused by the sodium rushing in (Figure 3-18B). Finally, after the action potential is gone, during recovery of the neuron’s baseline internal electrical milieu, potassium makes its way back into the cell through potassium channels as sodium is again pumped out (Figure 3-18C). It is now known or suspected that several psychotropic drugs work on voltage-sensitive sodium channels (VSSCs) and voltage-sensitive calcium channels (VSCCs). These classes of ion channels will be discussed here. Potassium channels are less well known to be targeted by psychotropic drugs and will thus not be emphasized. VSSCs (Voltage-Sensitive Sodium Channels) Many dimensions of ion-channel structure are similar for VSSCs and VSCCs. Both have a “pore” that is the channel itself, allowing ions to travel from one side of the membrane to the other. However, voltage-gated ion channels have a more complicated structure than just a hole or pore in the membrane. These channels are long strings of amino acids, comprising subunits, and four different subunits are connected to form the critical pore, known as an α subunit. In addition, other proteins are Figure 3-18 Ionic components of an action potential. The ionic components of an action potential are shown graphically here. First, voltage-sensitive sodium channels open to allow an influx of “downhill” sodium into the negatively charged internal milieu of the neuron (A). The change of voltage potential caused by the influx of sodium triggers voltage-sensitive calcium channels to open and allow calcium influx (B). Finally, after the action potential is gone, potassium enters the cell while sodium is pumped out, restoring the neuron’s baseline internal electrical milieu (C). K+ Ionic Components of an Action Potential Na+ A B C Ca++

 Indeed, the α unit itself may also be a phosphoprotein, with the possibility that its own phosphorylation state could be regulated by signal transduction cascades and thus increase or decrease the sensitivity of the ion channel to changes in the ionic environment. This is discussed in Chapter 1 as part of the signal transduction cascade, and ion channels in some cases may act as third, fourth, or subsequent messengers triggered by neurotransmission. Both β subunits and the α subunit itself may have various sites where various psychotropic drugs act, especially anticonvulsants, some of which are also useful as mood stabilizers or as treatments for chronic pain. Specific drugs will be discussed in further detail in the chapters on mood stabilizers and pain. Three different states of a VSSC are shown in Figure 3-21. The channel can be open and active, a state allowing maximum ion flow through the α unit (Figure 3-21A). When a sodium channel needs to stop ion flow, it has two states that can do this. One state acts very quickly to flip the pore inactivator into place, stopping ion flow so fast that the channel has not yet even closed (Figure 3-21B). Another state of inactivation actually closes the channel with conformational changes in the ion channel’s shape (Figure 3-21C). The pore inactivation mechanism may be for fast inactivation, and the channel closing mechanism may be for a more stable state of inactivation, but it is not entirely clear. There are many subtypes of sodium channels, but the details of how they are differentiated from each other by differential location in the brain, by differential functions, and by differential drug actions are only beginning to (Figure 3-20A and B). This is a physical blocking of the hole in the pore, and reminiscent of an old-fashioned bathtub plug stopping up the drain in a bathtub. The pore-forming unit of the VSSC is also shown as an icon in Figure 3-20B with a hole in the middle of the pore, and a pore inactivator ready to plug the hole from the inside. Many figures in textbooks represent voltage-gated ion channels with the outside of the cell on the top of a figure and this is the way the ion channel is shown in Figure 3-20A and B. Here, we also show what the channel looks like when the inside of the cell is at the top of the figure, since throughout this book these channels will often be shown on presynaptic membranes where the inside of the neuron is up and the outside of the neuron, namely its synapse, is down, like that orientation represented in Figure 3-20C). In either case, the sodium is kept out of the neuron when the channel is closed or inactivated, and the direction of sodium flow is into the neuron when the channel is open, activated, and the pore is not plugged up with the pore-inactivating amino acid loops. Voltage-sensitive sodium channels may have one or more regulatory proteins, some called β units, located in the transmembrane area and flanking the α pore forming unit (Figure 3-20C). The function of these β subunits is not clearly established, but they may modify the actions of the α unit and thereby indirectly influence the opening and closing of the channel. It is possible that β units may be phosphoproteins, and that their state of phosphorylation or dephosphorylation could regulate how much influence they exert on ion-channel regulation. Figure 3-19 Ionic filter of voltage-sensitive sodium and calcium channels. The extracellular loop between transmembrane segments 5 and 6 of an α pore unit acts as an ionic filter (illustrated here as a colander). (A) Shown here is an α pore unit of a voltage-sensitive sodium channel, with the ionic filter allowing only sodium ions to enter the cell. (B) Shown here is an α pore unit of a voltage-sensitive calcium channel, with the ionic filter allowing only calcium ions to enter the cell. outside the cell voltage-sensitive sodium channel (VSSC) A B 2 4 6 2 4 6 voltage-sensitive calcium channel (VSCC) inside the cell Na+ Ca++

Figure 3-20 Alpha pore of voltage-sensitive sodium channel. The α pore of a voltage-sensitive sodium channel comprises four subunits (A). Amino acids in the intracellular loop between the third and fourth subunits act as a pore inactivator, “plugging” the channel. An iconic version of the α unit is shown here,

with the extracellular portion on top (B) and with the intracellular portion on top (C). outside the cell Four Subunits Combine to Form the Alpha Pore Subunit, or Channel, for Sodium of a VSSC (Voltage-Sensitive Sodium Channel) I II III IV

= inside the cell outside the cell inside the cell outside the cell inside the cell pore inactivation pore inactivation A B C Na+ pore inactivation Na+ ß ß Figure 3-21 States of voltage-sensitive sodium channel. Such channels can be in the open state, in which the ion channel is open and active and ions flow through the α unit (A). Voltage-sensitive sodium channels may also be in an inactivated state, in which the channel is not yet closed but has been “plugged” by the pore inactivator, preventing ion flow (B). Finally, conformational changes in the ion channel can cause it to close, the third state (C). Three States of a Voltage-Sensitive Sodium Channel (VSSC) open A B C inactivated closed and inactivated

extracellular amino acids connecting segments 5 and 6 acting as an ionic filter (Figure 3-19) – only this time as a colander allowing calcium to come into the cell, not sodium (see Figure 3-19B). Obviously, the exact sequence of amino acids differs between a sodium channel and a calcium

channel, but they have a very similar overall organization and structure. Just like voltage-gated sodium channels, VSCCs also string together four of their subunits to form a pore, called in the case of a calcium channel, an α1 unit (Figure 3-22A and B). The connecting string of amino acids also has functional activities that can regulate

calcium-channel functioning, but in this case the functions are different from that for sodium channels. That is, there is no pore inactivator working as a plug for be clarified. For the psychopharmacologist, what is now of interest is the fact that various sodium channels may be the sites of action of several anticonvulsants, some of

which have mood-stabilizing and pain-reducing properties. Most currently available anticonvulsants probably have multiple sites of action, including multiple sites of action at multiple types of ion channels. The specific actions of specific drugs will be discussed in the chapters that cover specific disorders. VSCCs (Voltage-Sensitive Calcium

Channels) Many aspects of VSCCs and VSSCs are similar – not just their names. Like their sodium-channel cousins, the VSCCs also have subunits with six transmembrane segments, with segment 4 a voltmeter, and with the Figure 3-22 Alpha1 pore of voltage-sensitive calcium channel. The α pore of a voltage-sensitive calcium channel,

termed an α1 unit, comprises four subunits (A). Amino acids in the cytoplasmic loop between the second and third subunits act as a snare to connect with synaptic vesicles, thereby controlling neurotransmitter release (A). An iconic version of the α1 unit is shown here, with the extracellular portion on top (B) and with the intracellular

portion on top (C). Four Subunits Combine to Form the Alpha1 Pore Subunit, or Channel, for Calcium of a VSCC (Voltage-Sensitive Calcium Channel)

outside the cell inside the cell outside the cell inside the cell B C Ca++

outside the cell I II III IV inside the cell A ß snare

Chapter 3: Ion Channels As would be expected, there are several subtypes of VSCCs (Table 3-4). The vast array of VSCCs indicates that the term “calcium channel” is much too general, and in fact can be confusing. For example, calcium channels associated with the ligand-gated ion channels discussed in the previous section, especially those associated with glutamate and nicotinic cholinergic ionotropic receptors, are members of an entirely different class of ion channels from the VSCCs under discussion here. As we have mentioned, calcium channels associated with this previously discussed class of ion channels are called ligand-gated ion channels, ionotropic receptors, or ionchannel-linked receptors, to distinguish them from VSCCs. The specific subtypes of VSCCs of most interest to psychopharmacology are those that are presynaptic, that regulate neurotransmitter release, and that are targeted by certain psychotropic drugs. This subtype designation of VSCC is shown in Table 3-4 and such channels are known as N or P/Q channels.

Another well-known subtype of VSCC is the L channel. This channel exists not only in the central nervous system, where its functions are still being clarified, but also on vascular smooth muscle where it regulates blood pressure and where a group of drugs known as dihydropyridine “calcium channel blockers” interact as therapeutic antihypertensives to lower blood pressure. R and T the VSCC, as was described above for the VSSC; instead, the amino acids connecting the second and third subunits of the VSCC work as a “snare” to hook up with synaptic vesicles and regulate the release of neurotransmitter into the synapse during synaptic neurotransmission (Figure 3-22A and Figure 3-23). The orientation of the calcium channel in Figure 3-22B is with the outside of the cell at the top of the page, and this is switched in Figure 3-22C so that the inside of the cell is now at the top of the page, so the reader can see how these channels might look in various configurations in space. In all cases, the direction of ion flow is from outside the cell to the inside when that channel opens to allow ion flow to occur. Several proteins flank the α1 pore-forming unit of a VSCC, called γ, β, and α2δ (Figure 3-22C). Shown here are γ units that span the membrane, cytoplasmic β units, and a curious protein called α2δ, because it has two parts: a δ part that is transmembrane, and an α2 part that is extracellular (Figure 3-22C). The functions of all these proteins associated with the α1 pore-forming unit of a VSCC are just beginning to be understood, but already it is known that the α2δ protein is the target of certain psychotropic drugs, such as the anticonvulsants pregabalin and gabapentin, and that this α2δ protein may be involved in regulating conformational changes of the ion channel to change the way the ion channel opens and closes. Figure 3-23 N and P/Q voltage-sensitive calcium channels. Voltage-sensitive calcium channels that are most relevant to psychopharmacology are termed N and P/Q channels. These ion channels are presynaptic and involved in the regulation of neurotransmitter release. The intracellular amino acids linking the second and third subunits of the α1 unit form a snare that hooks onto synaptic vesicles (A). When a nerve impulse arrives, the snare “fires,” leading to neurotransmitter release (B). N P/Q glutamate Ca++ snare A B vesicle N P/Q Opening a Presynaptic Voltage-Sensitive N or P/Q Calcium Channel: Triggers Neurotransmitter Release ß ß

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 3-24 Snare proteins. Proteins that link the voltage-sensitive calcium channel to the synaptic vesicle, called snare proteins, are shown here; they include SNAP 25 (synaptosomal-associated protein 25), synaptobrevin, syntaxin, and synaptotagmin. A VMAT (vesicular monoamine transporter) is shown on the left. Another transporter, SV2A, is shown on the right. The mechanism of this transporter is not yet clear, but the anticonvulsant levetiracetam is known to bind to this site. N P/Q Docking of Synaptic Vesicle with Presynaptic Membrane, VSCC (Voltage-Sensitive Calcium Channel), and Snare Proteins presynaptic membrane synaptic vesicle membrane synaptobrevin SNAP 25 syntaxin synaptotagmin VMAT SV2A Ca++ ß Table 3-4 Subtypes of voltage-sensitive calcium channels (VSCCs) Type Pore-forming Location Function L Cav1.2, 1.3 Cell bodies, dendrites Gene expression, synaptic integration N Cav 2.2 Nerve terminals Dendrites, cell bodies Transmitter release Synaptic integration P/Q Cav, 2.1 Nerve terminals Transmitter release Dendrites, cell bodies Synaptic integration R Cav, 2.3 Nerve terminals Cell bodies, dendrites Transmitter release Repetitive firing, synaptic integration T Cav, 3.1, 3.2, 3.3 Cell bodies, dendrites Pacemaking, repetitive firing, synaptic integration

channels are also of interest, and some anticonvulsants and psychotropic drugs may also interact there, but the exact roles of these channels are still being clarified. Presynaptic N and P/Q VSCCs have a specialized role in regulating neurotransmitter release because they are linked by molecular “snares” to synaptic vesicles (Figure 3-23). That is, these channels are literally hooked to synaptic

vesicles. Some experts think of this as a cocked gun – loaded with neurotransmitters packed in a synaptic vesicle bullet (Figure 3-23A) ready to be fired at the postsynaptic neuron as soon as a nerve impulse arrives (Figure 3-23B). Some of the structural details of the molecular links – namely, with snare proteins – that connect the N, P/Q VSCC with the synaptic vesicle are shown in Figure 3-24. If a drug interferes with the ability of the channel to open and let in calcium, the synaptic vesicle stays tethered to the voltage-gated calcium channel. Neurotransmission can thus be prevented, and this may be desirable in states of excessive neurotransmission, such as pain, seizures, mania, or anxiety. This may explain the action of certain anticonvulsants. Indeed, it is neurotransmitter release that is the raison d'etre for presynaptic voltage-sensitive N and P/Q channels. When a nerve impulse invades the presynaptic area, this causes the charge across the membrane to change, in turn opening the VSCC, allowing calcium to enter, and this makes the synaptic vesicle dock into and merge with the presynaptic membrane, spewing its neurotransmitter contents into the synapse to effect neurotransmission (Figures 3-25 and 3-26). This conversion of an electrical impulse into a chemical message is triggered by calcium and sometimes called excitation–secretion coupling. Anticonvulsants are thought to act at various VSSCs and VSCCs and will be discussed in further detail in the relevant clinical chapters. Many of these anticonvulsants have several uses in psychopharmacology, from chronic pain to migraine, from bipolar mania to bipolar depression to bipolar maintenance, and possibly as agents for anxiety and sleep aids. These specific applications and more details about hypothetical mechanisms of action are explored in depth in the clinical chapters dealing with the various psychiatric disorders. ION CHANNELS AND NEUROTRANSMISSION Although the various subtypes of ligand-gated ion channels and voltage-gated ion channels are presented separately, the reality is that they work cooperatively during neurotransmission. When the actions of all these Chapter 3: Ion Channels ion channels are well orchestrated, brain communication becomes a magical mix of electrical and chemical messages made possible by ion channels. The coordinated acts of ion channels during neurotransmission are illustrated in the Figures 3-25 and 3-26. The initiation of chemical neurotransmission by a neuron's ability to integrate all of its inputs, and then translate them into an electrical impulse is presented in Chapter 1. We now show how ion channels are involved in this process (Figure 3-26). After a neuron receives and integrates its inputs from other neurons, it then encodes them into an action potential, and that nerve impulse is next sent along the axon via VSSCs that line the axon (Figure 3-25). The action potential could be described as lighting a fuse, with the fuse burning from the initial segment of the axon to the axon terminal. Movement of the burning edge of the fuse is carried out by a sequence of VSSCs that open one after the other, allowing sodium to pass into the neuron, and then carrying the electrical impulse so generated along to the next VSSC in line (Figure 3-25). When the electrical impulse reaches the axon terminal, it meets VSCCs in the presynaptic neuronal membrane, already loaded with synaptic vesicles and ready to fire (see axon terminal of neuron A in Figure 3-25). When the electrical impulse is detected by the voltmeter in the VSCC, it opens the calcium channel, allowing calcium to enter, and bang!, the neurotransmitter is released in a cloud of synaptic chemicals from the presynaptic axon terminal via excitation–secretion coupling (see axon terminal of neuron A in Figure 3-25 and enlarged illustrations of this in Figure 3-26). Details of this process of excitation–secretion coupling are shown in Figure 3-26, beginning with the action potential about to invade the presynaptic terminal, and with a closed VSSC sitting next to a closed but poised VSCC snared to its synaptic vesicle (Figure 3-26A). As the nerve impulse arrives in the axon terminal, it first hits the VSSC as a wave of positive sodium charges delivered by the openings of upstream sodium channels, which are detected by the sodium channel's voltmeter (Figure 3-26B). This opens the last sodium channel

shown, allowing sodium to enter (Figure 3-26C). The consequence of this sodium entry is to change the electrical charge nearby the calcium channel, and then this is detected by the VSCC's voltmeter (Figure 3-26D). Next, the calcium channel opens (Figure 3-26E). At this point, chemical neurotransmission has now been irreversibly triggered, 73

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY and the translation of an electrical message into a chemical message has begun. Calcium entry from the VSCC now increases the local concentrations of this ion in the vicinity of the VSCC, the synaptic vesicle, and the neurotransmitter release machinery (Figure 3-26F). This causes the synaptic vesicle to dock into the inside of the presynaptic membrane, then merge with it, spewing its neurotransmitter contents out of the membrane and into the synapse (Figure 3-26G). This amazing process occurs almost instantaneously and simultaneously from many VSCCs releasing neurotransmitter from many synaptic vesicles. Summary: From Presynaptic to Postsynaptic Signal Propagation reception integration chemical encoding electrical encoding signal propagation presynaptic signal transduction A B glutamate postsynaptic signal transduction reception integration chemical encoding electrical encoding signal propagation presynaptic signal transduction Figure 3-25 Signal propagation. Summary of signal propagation from presynaptic to postsynaptic neuron. A nerve impulse is generated in neuron A, and the action potential is sent along the axon via voltage-sensitive sodium channels until it reaches voltagesensitive calcium channels linked to synaptic vesicles full of neurotransmitters in the axon terminal. Opening of the voltage-sensitive calcium channel and consequent calcium influx causes neurotransmitter release into the synapse. Arrival of neurotransmitter at postsynaptic receptors on the dendrite of neuron B triggers depolarization of the membrane in that neuron and, consequently, postsynaptic signal propagation.

Chapter 3: Ion Channels Figure 3-26 Excitation–secretion coupling. Details of excitation–secretion coupling are shown here. An action potential is encoded by the neuron and sent to the axon terminal via voltage-sensitive sodium channels along the axon (A). The sodium released by those channels triggers a voltage-sensitive sodium channel at the axon terminal to open (B), allowing sodium influx into the presynaptic neuron (C). Sodium influx changes the electrical charge of the voltage-sensitive calcium channel (D), causing it to open and allow calcium influx (E). As the intraneuronal concentration of calcium increases (F), the synaptic vesicle is caused to dock and merge with the presynaptic membrane, leading to neurotransmitter release (G). neurotransmitter vesicle Action Potential VSSC VSCC A B C D E F G VSSC VSCC VSSC VSCC VSSC VSCC VSSC VSCC VSSC VSCC VSSC VSCC VSSC VSCC Na+ Ca++ Ca++ Ca++

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY By now, only about half of the sequential phenomena of chemical neurotransmission have been described. The other half occurs on the other side of the synapse. That is, reception of the released neurotransmitter now occurs in neuron B (Figure 3-25), which can set up another nerve impulse in neuron B. This whole process, from nerve impulse generation and propagation of it along neuron A to its nerve terminal, then sending chemical neurotransmission to neuron B, and finally propagating this second nerve impulse along neuron B, is summarized in Figure 3-25. VSSCs in presynaptic neuron A propagate the impulse there, and then VSCCs in presynaptic neuron A release the neurotransmitter glutamate. Ligand-gated ion channels on dendrites in postsynaptic neuron B next receive this chemical input, and translate this chemical message back into a nerve impulse propagated in neuron B by VSSCs in that neuron. Also, ligand-gated ion channels in postsynaptic neuron B translate the glutamate chemical signal into another type of electrical phenomenon called long-term potentiation, to cause changes in the

function of neuron B. SUMMARY Ion channels are key targets of many psychotropic drugs. This is not surprising because these targets are key regulators of chemical neurotransmission and the signal transduction cascade. There are two major classes of ion channels: ligandgated ion channels and voltage-sensitive ion channels. The opening of ligand-gated ion channels is regulated by neurotransmitters whereas the opening of voltagegated ion channels is regulated by the charge across the membrane in which they reside. Ligand-gated ion channels are both ion channels and receptors. They are also commonly called ionotropic receptors as well as ion-channel-linked receptors. One subclass of ligand-gated ion channels has a pentameric structure, and includes GABAA receptors, nicotinic cholinergic receptors, 5HT3 receptors, and certain glycine receptors. The other subclass of ligand-gated ion channels has a tetrameric structure, and includes many glutamate receptors, including the AMPA, kainate, and NMDA subtypes. Ligands act at ligand-gated ion channels across an agonist spectrum, from full agonist, to partial agonist, to antagonist, to inverse agonist. Ligand-gated ion channels can be regulated not only by neurotransmitters acting as agonists, but also by molecules interacting at other sites on the receptor, either boosting the action of neurotransmitter agonists as positive allosteric modulators (PAMs), or diminishing the action of neurotransmitter agonists as negative allosteric modulators (NAMs). In addition, these receptors exist in several states, from open, to resting, to closed, to inactivated, to desensitized. The second major class of ion channels is called either voltage-sensitive ion channels or voltage-gated ion channels, since they are opened and closed by the voltage charge across the membrane. The major channels from this class of interest to psychopharmacologists are the voltage-sensitive sodium channels (VSSCs) and the voltage-sensitive calcium channels (VSCCs). Numerous anticonvulsants bind to various sites on these channels, and may exert their anticonvulsant actions by this mechanism, as well as their actions as mood stabilizers, treatments for chronic pain, drugs for anxiety, and sleep effects.