05 - 2 Transporters, Receptors, and Enzymes as Targets

01 - 2 Transporters, Receptors, and Enzymes as Tar

2 Transporters, Receptors, and Enzymes as Targets of Psychopharmacological Drug Action

Transporters, Receptors, and Enzymes as Targets of Psychopharmacological Drug Action Neurotransmitter Transporters as Targets of Drug Action 29 Classification and Structure 29 Monoamine Transporters (SLC6 Gene Family) as Targets of Psychotropic Drugs 31 Other Neurotransmitter Transporters (SLC6 and SLC1 Gene Families) as Targets of Psychotropic Drugs 34 Where Are the Transporters for Histamine and Neuropeptides? 35 Vesicular Transporters: Subtypes and Function 35 Vesicular Transporters (SLC18 Gene Family) as Targets of Psychotropic Drugs 35 G-Protein-Linked Receptors 36 Structure and Function 36 G-Protein-Linked Receptors as Targets of Psychotropic Drugs 36 Enzymes as Sites of Psychopharmacological Drug Action 45 Cytochrome P450 Drug Metabolizing Enzymes as Targets of Psychotropic Drugs 49 Summary 50 Psychotropic drugs have many mechanisms of action, but they all target specific molecular sites that have profound effects upon neurotransmission. It is thus necessary to understand the anatomical infrastructure and chemical substrates of neurotransmission (Chapter 1) in order to grasp how psychotropic drugs work. Although there are over 100 essential psychotropic drugs utilized in clinical practice today (see Stahl’s Essential Psychopharmacology: the Prescriber’s Guide), there are only a few sites of action for all these therapeutic agents (Figure 2-1). Specifically, about a third of psychotropic drugs target one of the transporters for a neurotransmitter; another third target receptors coupled to G proteins; and perhaps only 10% target enzymes. All three of these sites of action will be discussed in this chapter. The balance of psychotropic drugs target various types of

ion channels, which will be discussed in Chapter 3. Thus, mastering how just a few molecular sites regulate neurotransmission allows the psychopharmacologist to understand the theories about the mechanisms of action of virtually all psychopharmacological agents. In fact, these molecular targets form the basis of how psychotropic drugs are now named. That is, there is a modern movement afoot to name psychotropic drugs for their pharmacological mechanism of action (e.g., serotonin transport inhibitor, dopamine D2, and serotonin 5HT2A antagonist) rather than for their therapeutic indication (e.g., antidepressant, antipsychotic, etc.). Naming drugs for therapeutic indication has led to endless confusion, because many drugs are used for indications far beyond their original use (e.g., so-called antipsychotics that are used for depression). Thus, throughout this textbook we will use the new nomenclature for drugs (neuroscience-based nomenclature), which is based upon mechanism of action and not therapeutic indication, wherever possible. This chapter and the next will explain all known mechanisms targeted by psychotropic drugs that form the basis for how they are named. Finally, since there are genetic variants known for many targets of psychotropic drugs, there is an ongoing effort to determine to what extent such genetic variants may increase or decrease the odds that a patient will have a good clinical response or side effects to drugs that engage that target, in a process called pharmacogenomics. The scientific foundation for clinical application of genetic variants of psychotropic drug targets is still evolving, but current insights will be mentioned briefly when the specific target is described throughout this textbook. NEUROTRANSMITTER TRANSPORTERS AS TARGETS OF DRUG ACTION Classification and Structure Neuronal membranes normally serve to keep the internal milieu of the neuron constant by acting as barriers to the intrusion of outside molecules and to the leakage of internal molecules. However, selective permeability

cellular functioning. Good examples of this are neurotransmitters, which are released from neurons during neurotransmission, and in many cases are also transported back into presynaptic neurons as a recapture mechanism following their release. This recapture – or reuptake – is done in order for neurotransmitter to be

reused in a subsequent neurotransmission. Also, once inside the neuron, most neurotransmitters are transported again into synaptic vesicles for storage, protection from metabolism, and immediate use during a volley of future neurotransmission. Both types of neurotransmitter transport – presynaptic reuptake as well as vesicular

storage – utilize a molecular transporter belonging to a “superfamily” of 12-transmembrane-region proteins (Figures 2-1A and 2-2). That is, neurotransmitter transporters have in common the structure of going in and out of the membrane 12 times (Figure 2-1A). These transporters are a type of receptor that binds to the

neurotransmitter prior to transporting that neurotransmitter across the membrane. Recently, details of the structures of neurotransmitter transporters have been determined and this has led to a proposed subclassification of neurotransmitter transporters. That is, there are two major subclasses of

plasma membrane transporters for neurotransmitters (Tables 2-1 and 2-2). Some of these transporters are presynaptic and others are on glial membranes. The first subclass is comprised of sodium/chloride-coupled transporters, called the solute carrier SLC6 gene family, and includes transporters for the

monoamines serotonin, norepinephrine, and dopamine (Table 2-1 and Figure 2-2A) as well as for the neurotransmitter GABA (γ-aminobutyric acid) and the amino acid glycine (Table Figure 2-1 The molecular targets of psychotropic drugs. There are only a few major sites of action for the wide expanse of psychotropic drugs

utilized in clinical practice. Approximately one-third of psychotropic drugs target one of the twelve-transmembraneregion transporters for a neurotransmitter (A), while another third target seven-transmembrane-region receptors coupled to G proteins (B). The sites of action for the remaining third of psychotropic drugs

include enzymes (C), four-transmembrane-region ligand-gated ion channels (D), and six-transmembrane-region voltage-sensitive ion channels (E). 7 transmembrane region G-protein linked ~ 30% of psychotropic drugs The Five Molecular Targets of Psychotropic Drugs 12 transmembrane region transporter ~ 30% of

psychotropic drugs A B C D E 6 transmembrane region voltage-gated ion channel ~ 10% of psychotropic drugs Enzyme ~ 10% of psychotropic drugs 4 transmembrane region ligand-gated ion channel ~ 20% of psychotropic drugs

= 7 E

Chapter 2: Transporters, Receptors, and Enzymes Table 2-1 Presynaptic monamine transporters Transporter Common abbreviation Gene family Endogenous substrate False substrate Serotonin transporter SERT SLC6 Serotonin Ecstasy (MDMA) Norepinephrine transporter NET SLC6 Norepinephrine Dopamine Epinephrine Amphetamine Dopamine transporter DAT SLC6 Dopamine Norepinephrine Epinephrine Amphetamine MDMA = 3.4-methylenedioxymethamphetamine Table 2-2 Neuronal and glial GABA and amino acid transporters Transporter Common abbreviation Gene family Endogenous substrate GABA transporter 1 (neuronal and glial) GAT1 SLC6 GABA GABA transporter 2 (neuronal and glial) GAT2 SLC6 GABA beta-alanine GABA transporter 3 (mostly glial) GAT3 SLC6 GABA beta-alanine GABA transporter 4 also called betaine transporter (neuronal and glial) GAT4 BGT1 SLC6 GABA betaine Glycine transporter 1 (mostly glial) GlyT1 SLC6 Glycine Glycine tranporter 2 (neuronal) GlyT2 SLC6 Glycine Excitatory amino acid transporters 1–5 EAAT1–5 SLC1 L-glutamate L-aspartate 2-2 and Figure 2-2A). The second subclass is comprised of

high-affinity glutamate transporters, also called the solute carrier SLC1 gene family (Table 2-2 and Figure 2-2A). In addition, there are three subclasses of intracellular synaptic vesicle transporters for neurotransmitters: the SLC18 gene family comprised both of vesicular monoamine transporters (VMATs) for serotonin, norepinephrine, dopamine, and histamine and the vesicular acetylcholine transporter (VAChT); the SLC32 gene family and their vesicular inhibitory amino acid transporters (VIAATs); and finally the SLC17 gene family and their vesicular glutamate transporters, such as vGluT1–3 (Table 2-3 and Figure 2-2B). Monoamine Transporters (SLC6 Gene Family) as Targets of Psychotropic Drugs Reuptake mechanisms for monoamines utilize unique presynaptic transporters (Figure 2-2A) in each different monoamine neuron but the same vesicular transporter (Figure 2-2B) in the synaptic vesicle membranes of all three monoamine neurons plus histamine neurons. That is, the unique presynaptic transporter for the monoamine serotonin is known as SERT, for norepinephrine is known as NET, and for dopamine, DAT (Table 2-1 and Figure 2-2A). All three of these monoamines are then transported into synaptic vesicles of their respective neurons by the same vesicular transporter, known as VMAT2 (vesicular monoamine transporter 2) (Figure 2-2B and Table 2-3). Although the presynaptic transporters for these three neurotransmitters – SERT, NET, and DAT – are unique in their amino acid sequences and binding affinities for monoamines, each presynaptic monoamine transporter nevertheless has appreciable affinity for amines other than the one matched to its own neuron (Table 2-1). Thus, if other transportable neurotransmitters or drugs are in the vicinity of a given monoamine transporter, they may also be transported into the presynaptic neuron by hitchhiking a ride on certain transporters that can carry them into the neuron. For example, the norepinephrine transporter NET has high affinity for the transport of dopamine as well as for norepinephrine; the dopamine transporter DAT has

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Cl - Na+ Cl - Na+ SERT SERT ATPase SERT SERT K+ K+ SERT GAT serotonin transporter GABA transporter GlyT NET norepinephrine transporter glycine transporter EAAT DAT dopamine transporter excitatory amino acid transporter Figure 2-2A Sodium–potassium ATPase. Transport of many neurotransmitters into the presynaptic neuron is not passive, but rather requires energy. This energy is supplied by sodium– potassium ATPase, an enzyme that is also sometimes referred to as the sodium pump. Sodium–potassium ATPase continuously pumps sodium out of the neuron, creating a downhill gradient. The “downhill” transport of sodium is coupled to the “uphill” transport of the neurotransmitter. In many cases this also involves cotransport of chloride and in some cases countertransport of potassium. Examples of neurotransmitter transporters include the serotonin transporter (SERT), the norepinephrine transporter (NET), the dopamine transporter (DAT), the GABA transporter (GAT), the glycine transporter (GlyT), and the excitatory amino acid transporter (EAAT). VMAT VMAT H proton pump + VMAT VMAT H+ H+ VMAT2 VIAAT vesicular monoamine transporter (5HT, NE, DA, HA) vesicular inhibitory amino acid transporter (GABA) VAChT VGluT vesicular acetylcholine vesicular glutamate transporter (glutamate) transporter (ACh) Figure 2-2B Vesicular transporters. Vesicular transporters package neurotransmitters into synaptic vesicles through the use of a proton ATPase, or proton pump. The proton pump utilizes energy to pump positively charged protons continuously out of the synaptic vesicle. Neurotransmitter can then be transported into the synaptic vesicle, keeping the charge inside the vesicle constant. Examples of vesicular transporters include the vesicular monoamine transporter (VMAT2), which transports serotonin (5HT), norepinephrine (NE), dopamine (DA), and histamine (HA); the vesicular acetylcholine transporter (VAChT), which transports acetylcholine; the vesicular inhibitory amino acid transporter (VIAAT), which transports GABA; and the vesicular glutamate transporter (VGluT), which transports glutamate. high affinity for the

transport of amphetamines as well as for dopamine; the serotonin transporter SERT has high affinity for the transport of “Ecstasy” (the drug of abuse MDMA or 3,4-methylenedioxymethamphetamine) as well as for serotonin (Table 2-1). How are neurotransmitters transported? Monoamines are not passively shuttled into the presynaptic neuron,

Chapter 2: Transporters, Receptors, and Enzymes and in this case, there is binding of neither sodium nor monoamine. An example of this is shown for the serotonin transporter SERT in Figure 2-2A where the transport “wagon” has flat tires indicating no binding of sodium, as well as absence of binding of serotonin to its substrate binding site since the transporter has low affinity for serotonin in the absence of sodium. The allosteric site for a drug that inhibits this transporter is also empty (the front seat in Figure 2-2A). However, in Figure 2-2A in the presence of sodium ions, the tires are now “inflated” by sodium binding and serotonin can now also bind to its substrate site on SERT. The situation is now primed for serotonin transport back into the serotonergic neuron, along with cotransport of sodium and chloride down the gradient and into the neuron and countertransport of potassium out of the neuron (Figure 2-2A). If a drug binds to an inhibitory allosteric site, namely the front seat on the SERT transporter wagon in Figure 2-2A (i.e., drugs such as the selective serotonin reuptake inhibitor fluoxetine [Prozac]), this reduces the affinity of the serotonin transporter SERT for its substrate serotonin, and serotonin binding is prevented. Why does this matter? Blocking the presynaptic monoamine transporter has a huge impact on neurotransmission at any synapse that utilizes that neurotransmitter. The normal recapture of neurotransmitter by the presynaptic neurotransmitter transporter in Figure 2-2A keeps the levels of this neurotransmitter from accumulating in the synapse. Normally, following release from the presynaptic neuron, neurotransmitters only have time for a brief dance on their synaptic receptors, and the party is soon over because the monoamines climb back into the presynaptic neuron on their transporters (Figure 2-2A). If one wants to enhance normal synaptic activity of because it requires energy to concentrate monoamines into a presynaptic neuron. That energy is provided by transporters in the SLC6 gene family coupling the “downhill” transport of sodium (down a concentration gradient) with the “uphill” transport of the monoamine (up a concentration gradient) (Figure 2-2A). Thus, the monoamine transporters are really sodiumdependent cotransporters; in most cases, this involves the additional cotransport of chloride, and in some cases the countertransport of potassium. All of this is made possible by coupling monoamine transport to the activity of a sodium–potassium ATPase (adenosine triphosphatase), an enzyme sometimes called the “sodium pump” that creates the downhill gradient for sodium by continuously pumping sodium out of the neuron (Figure 2-2A). The structure of a monoamine neurotransmitter transporter from the SLC6 family has recently been proposed to have binding sites not only for the monoamine, but also for two sodium ions (Figure 2-2A). In addition, these transporters may exist as dimers, or two copies working together with each other, but the manner in which they cooperate is not yet well understood and is not shown in the figures. There are other binding sites on this transporter – not well defined – for several drugs such as the many selective serotonin reuptake inhibitors (known as SSRIs) and other related agents used to treat unipolar depression. When these drugs bind to the transporter, they inhibit reuptake of monoamines. These drugs do not bind to the substrate site (where the monoamine itself binds to the transporter) and are not transported into the neuron, and thus are said to be allosteric (i.e., “other site”). In the absence of sodium, there is low affinity of the monoamine transporter for its monoamine substrate, Table 2-3 Vesicular neurotransmitter transporters Transporter Common abbreviation Gene family Endogenous substrate Vesicular monoamine transporters 1 and 2 VMAT1 VMAT2 SLC18 Serotonin Dopamine Histamine

Norepinephrine Vesicular acetylcholine transporter VAChT SLC18 Acetylcholine Vesicular inhibitory amino acid transporter VIAAT SLC32 GABA Vesicular glutamate transporters 1–3 vGluT1–3 SLC17 Glutamate

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY these neurotransmitters, or restore their diminished synaptic activity, this can be accomplished by blocking these transporters in Figure 2-2A. Although this might not seem to be a very dramatic thing, the fact is that this alteration in chemical neurotransmission – namely the enhancement of synaptic monoamine action – is thought to underlie the clinical effects of all the agents that block monoamine transporters, including most drugs that treat ADHD (attention deficit hyperactivity disorder). "Stimulants" for ADHD, such as methylphenidate and amphetamine, as well as the drug of abuse cocaine, all act on DAT and NET. Also, most drugs that treat unipolar depression act at SERT, NET, DAT, or some combination of these transporters. However, it is a misnomer to call these agents simply "antidepressants," since they are not firstline treatments for all forms of depression, and they are used for many, many other indications in addition to unipolar depression. Specifically, many drugs that block monoamine transporters are not only effective in the treatment of unipolar depression. They are also used to treat many forms of anxiety, from generalized anxiety disorder to social anxiety disorder to panic disorder; for reducing neuropathic pain in fibromyalgia, postherpetic neuralgia, diabetic peripheral neuropathic pain, and other pain conditions; for improving eating disorders, impulsive–compulsive disorders, obsessive–compulsive disorder, and trauma- and stress-related disorders such as posttraumatic stress disorder. They have additional therapeutic actions as well. Furthermore, some forms of depression, notably bipolar depression and depression with mixed features, are not treated first-line with drugs that block monoamine transporters. No wonder we don't call agents that block monoamine transporters simply "antidepressants" anymore! Given the high prevalence of disorders that inhibitors of monoamine transporters treat, it may come as no surprise that these drugs are among the most frequently prescribed psychotropic drugs. In fact, some estimates are that a monoamine transport inhibitor is prescribed every second of every minute of every hour of every day in the US alone (many millions of prescriptions a year)! Also, about a third of the currently prescribed essential 100 psychotropic drugs act by targeting one or more of the three monoamine transporters. Thus, the reader can see why understanding monoamine transporters and how various drugs act at these transporters is so important to grasping how one of the critical classes of agents in psychopharmacology works. Other Neurotransmitter Transporters (SLC6 and SLC1 Gene Families) as Targets of Psychotropic Drugs In addition to the three transporters for monoamines discussed in detail above, there are several other transporters for various different neurotransmitters or their precursors. Although this includes a dozen additional transporters, there is only one psychotropic drug used clinically that is known to bind to any of these transporters. Thus, there is a presynaptic transporter for choline, the precursor to the neurotransmitter acetylcholine, but no known drugs target this transporter. There are also several transporters for the ubiquitous inhibitory neurotransmitter GABA, known as GAT1–4 (Table 2-2). Although debate continues about the exact localization of these subtypes to presynaptic neurons, neighboring glia, or even postsynaptic neurons, it is clear that a key presynaptic transporter of GABA is the GAT1 transporter, which is selectively blocked by the anticonvulsant tiagabine, thereby increasing synaptic GABA concentrations. In addition to anticonvulsant actions, this increase in synaptic GABA may have therapeutic actions in anxiety, sleep disorders, and pain. No other inhibitors of this transporter are available for clinical use. Finally, there are multiple transporters for two amino acid neurotransmitters, glycine and glutamate (Table 2-2). There are no drugs utilized in clinical

practice that are known to block glycine transporters although new agents are in clinical trials for treating schizophrenia and other disorders. The glycine transporters, along with the choline and GABA transporters, are all members of the SLC6 gene family, the same family to which the monoamine transporters belong and have a similar structure (Figure 2-2A and Tables 2-1 and 2-2). However, the glutamate transporters belong to a unique family, SLC1, and have a somewhat unique structure and somewhat different functions compared to those transporters of the SLC6 family (Table 2-2). Specifically, there are several transporters for glutamate, known as excitatory amino acid transporters 1–5 (EAAT1–5; Table 2-2). The exact localization of these various transporters to presynaptic neurons, postsynaptic neurons, or glia is still under investigation, but the uptake of glutamate into glia is well known to be a key system for recapturing glutamate for re-use once it has been released. Transport into glia results in conversion of glutamate into glutamine, and then glutamine enters the presynaptic neuron for reconversion back into glutamate. No drugs utilized in clinical practice are known to block glutamate transporters.

One difference between transport of neurotransmitters by the SLC6 gene family and transport of glutamate by the SLC1 gene family is that glutamate does not seem to cotransport chloride with sodium when it also cotransports glutamate. Also, glutamate transport is almost always characterized by the countertransport of potassium, whereas this is not always the case with SLC6 gene family transporters. Glutamate transporters may work together as trimers rather than dimers, as the SLC6 transporters seem to do. The functional significance of these differences remains obscure, but may become more apparent if clinically useful psychopharmacological agents that target glutamate transporters are discovered. Since it may often be desirable to diminish rather than enhance glutamate neurotransmission, the future utility of glutamate transporters as therapeutic targets is also unclear. Where Are the Transporters for Histamine and Neuropeptides? It is an interesting observation that apparently not all neurotransmitters are regulated by reuptake transporters. The central neurotransmitter histamine apparently does not have a transporter for it presynaptically (although it is transported into synaptic vesicles by VMAT2, the same transporter used by the monoamines – see Figure 2-2B). Histamine’s inactivation is thus thought to be entirely enzymatic. The same can be said for neuropeptides, since reuptake pumps and presynaptic transporters have not been found for them, and are thus thought to be lacking for this class of neurotransmitter. Inactivation of neuropeptides is apparently by diffusion, sequestration, and enzymatic destruction, but not by presynaptic transport. It is always possible that a transporter will be discovered in the future for some of these neurotransmitters, but at the present time there are no known presynaptic transporters for either histamine or neuropeptides. Vesicular Transporters: Subtypes and Function Vesicular transporters for the monoamines (VMATs) are members of the SLC18 gene family and have already been discussed above. They are shown in Figure 2-2B and listed in Table 2-3. The vesicular transporter for acetylcholine – also a member of the SLC18 gene family but known as VAChT – is shown in Figure 2-2B and listed in Table 2-3. The GABA vesicular transporter is a member of the SLC32 gene family and is called VIAAT (vesicular inhibitory amino acid transporter; shown in Chapter 2: Transporters, Receptors, and Enzymes Figure 2-2B and Table 2-3). Finally, vesicular transporters for glutamate, called vGluT1–3 (vesicular glutamate transporters 1, 2, and 3), are members of the SLC17 gene family and are also shown in Figure 2-2B and listed in Table 2-3. A novel 12-transmembrane-region synaptic vesicle transporter of uncertain mechanism and with unclear substrates, called the SV2A transporter and localized within the synaptic vesicle membrane, binds the anticonvulsant levetiracetam, perhaps interfering with neurotransmitter release and thereby reducing seizures. How do neurotransmitters get inside

synaptic vesicles? In the case of vesicular transporters, storage of neurotransmitters is facilitated by a proton ATPase, known as the “proton pump” that utilizes energy to pump positively charged protons continuously out of the synaptic vesicle (Figure 2-2B). The neurotransmitters can then be concentrated against a gradient by substituting their own positive charge inside the vesicle for the positive charge of the proton being pumped out. Thus, neurotransmitters are not so much transported as they are “antiported” – i.e., they go in while the protons are actively transported out, keeping charge inside the vesicle constant. This concept is shown in Figure 2-2B for the VMAT transporting dopamine, in exchange for protons. Contrast this with Figure 2-2A where a monoamine transporter on the presynaptic membrane is cotransporting a monoamine along with sodium and chloride, but with the help of a sodium–potassium ATPase (sodium pump) rather than a proton pump. Vesicular Transporters (SLC18 Gene Family) as Targets of Psychotropic Drugs Vesicular transporters for acetylcholine (SLC18 gene family), GABA (SLC32 gene family), and glutamate (SLC17 gene family) are not known to be targeted by any drug utilized by humans. However, vesicular transporters for monoamines in the SLC18 gene family (VMATs), particularly those in dopamine neurons, are targeted by several drugs, including amphetamine (as a transported substrate) and tetrabenazine and its derivatives deutetrabenazine and valbenazine (as inhibitors, see Chapter 5) . Amphetamine thus has two targets: monoamine transporters discussed above as well as VMATs discussed here. In contrast, other drugs for ADHD, such as methylphenidate, and the so-called “stimulant” drug of abuse cocaine, target only the monoamine transporters, and in much the same manner as described for SSRIs at the serotonin transporter. 35

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY function of G-protein-linked receptors and their role in signal transduction from specific neurotransmitters as described in Chapter 1 in order to understand how drugs acting at G-protein-linked receptors modify the signal transduction that arises from these receptors. This is important to understand because such druginduced modifications in signal transduction from G-protein-linked receptors can have profound actions on psychiatric symptoms. In fact, the single most common action of psychotropic drugs utilized in clinical practice is to modify the actions of one or more G-protein-linked receptors, resulting in either therapeutic actions or side effects. More than a dozen G-protein-linked receptors as targets of various drugs are discussed in the various clinical chapters that follow. Here we will describe how various drugs stimulate or block these receptors in general, and throughout the textbook we will show how particular drugs acting at specific G-protein-linked receptors have unique actions on improving distinct psychiatric symptoms as well as causing characteristic side effects. G-Protein-Linked Receptors as Targets of Psychotropic Drugs G-protein-linked receptors are a large superfamily of receptors that interact with many neurotransmitters and with many psychotropic drugs (Figure 2-1B). There are many ways to subtype these receptors, but pharmacological subtypes are perhaps the most important to understand for clinicians who wish to target specific receptors with psychotropic drugs utilized in G-PROTEIN-LINKED RECEPTORS Structure and Function Another major target of psychotropic drugs is the class of receptors linked to G proteins. These receptors all have the structure of seven-transmembrane regions, meaning that they span the membrane seven times (Figure 2-1). Each of the transmembrane regions clusters around a central core that contains a binding site for a neurotransmitter. Drugs can interact at this neurotransmitter binding site or at other sites (allosteric sites) on the receptor. This can lead to a wide range of modifications of receptor actions due to mimicking or blocking, partially or fully, the neurotransmitter function that normally occurs at this receptor. Drug actions at G-protein-linked receptors can thus change downstream molecular events – e.g., determining which

phosphoproteins are activated or inactivated and therefore which enzymes, receptors, or ion channels are modified by neurotransmission. Drug actions at G-protein-linked receptors can also determine whether a downstream gene is expressed or silenced, and thus which proteins are synthesized and which neuronal functions are amplified, from synaptogenesis, to receptor and enzyme synthesis, to communication with downstream neurons innervated by the neuron with the G-protein-linked receptor. These actions on neurotransmission at G-proteinlinked receptors are described in detail in Chapter 1 on signal transduction and chemical neurotransmission. The reader should have a good command of the Figure 2-3 Agonist spectrum. Shown here is the agonist spectrum. Naturally occurring neurotransmitters stimulate receptors and are thus agonists. Some drugs also stimulate receptors and are therefore agonists as well. It is possible for drugs to stimulate receptors to a lesser degree than the natural neurotransmitter; these are called partial agonists or stabilizers. It is a common misconception that antagonists are the opposite of agonists because they block the actions of agonists. However, although antagonists prevent the actions of agonists, they have no activity of their own in the absence of the agonist. For this reason, antagonists are sometimes called “silent.” Inverse agonists, on the other hand, do have opposite actions compared to agonists. That is, they not only block agonists but can also reduce activity below the baseline level when no agonist is present. Thus, the agonist spectrum reaches from full agonists to partial agonists through to “silent” antagonists and finally inverse agonists. antagonist The Agonist Spectrum agonist partial agonist inverse agonist

No Agonist: Constitutive Activity E P clinical practice. That is, the natural neurotransmitter interacts at all of its receptor subtypes, but many drugs are more selective than the neurotransmitter itself for just certain receptor subtypes and thus define a pharmacological subtype of receptor at which they specifically interact. This is not unlike the concept of the neurotransmitter being a master key that opens all the doors, and selective drugs that interact at pharmacologically specific receptor subtypes functioning as a specific key opening only one door. Here we will develop the concept that drugs have many ways of interacting at pharmacological subtypes of G-proteinlinked receptors, across what is called an “agonist spectrum” (Figure 2-3). No Agonist An important concept for the “agonist spectrum” is that the absence of agonist does not necessarily mean that nothing at all is happening with signal transduction at G-protein-linked receptors. Agonists are thought to produce a conformational change in G-protein-linked receptors that leads to full receptor activation, and thus full signal transduction. In the absence of agonist, this same conformational change may still be occurring at some receptor systems, but only at very low frequency. This is referred to as constitutive activity, which may be present especially in receptor systems and brain areas where there is a high density of receptors. Thus, when something occurs at very low frequency but among a high Chapter 2: Transporters, Receptors, and Enzymes Figure 2-4 Constitutive activity. The absence of agonist does not mean that there is no activity related to G-proteinlinked receptors. Rather, in the absence of agonist, the receptor’s conformation is such that it leads to a low level of activity, or constitutive activity. Thus, signal transduction still occurs, but at a low frequency. Whether this constitutive activity leads to detectable signal transduction is affected by the receptor density in that brain region. P P P P number of receptors, it can still produce detectable signal transduction output. This is represented as a small – but not absent – amount of signal transduction in Figure 2-4. Agonists An agonist produces a conformational change in the G-protein-linked receptor that turns on the synthesis of second messenger to the greatest extent possible (i.e., the action of a full agonist) (Figure 2-5). The full agonist is generally represented by the naturally occurring neurotransmitter itself, although some drugs can also act in

as full a manner as the natural neurotransmitter itself. What this means from the perspective of chemical neurotransmission is that the full array of downstream signal transduction is triggered by a full agonist (Figure 2-5). Thus, downstream proteins are maximally phosphorylated, and genes are maximally impacted. Loss of the agonist actions of a neurotransmitter at G-proteinlinked receptors, due to deficient neurotransmission of any cause, would lead to the loss of this rich downstream chemical tour de force. Thus, agonists that restore this natural action would be potentially useful in states where reduced signal transduction leads to undesirable symptoms. There are two major ways to stimulate G-proteinlinked receptors with full agonist action. Firstly, several drugs directly bind to the neurotransmitter site on the G-protein-linked receptor itself and can produce the same full array of signal transduction effects as a full agonist (see Table 2-4). These are called direct-acting 37

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 2-5 Full agonist: maximum signal transduction. When a full agonist binds to G-protein-linked receptors, it causes conformational changes that lead to maximum signal transduction. Thus, all the downstream effects of signal transduction, such as phosphorylation of proteins and gene activation, are maximized. E 3 P 3 P 3 P 3 P Full Agonist: Maximum Signal Transduction agonist P P P P P P P P P P P P P P P

Chapter 2: Transporters, Receptors, and Enzymes Table 2-4 Key G-protein-linked receptors directly targeted by psychotropic drugs Neurotransmitter G-protein receptor and pharmacological subtype directly targeted Pharmacological action Therapeutic action Dopamine D2 Antagonist or partial agonist Antipsychotic; antimanic Serotonin 5HT2A Antagonist or inverse agonist Antipsychotic actions in Parkinson's disease psychosis Antipsychotic actions in dementia-related psychosis Reduced drug-induced parkinsonism Possible reduction of negative symptoms in schizophrenia Possible mood stabilizing and antidepressant actions in bipolar disorder Improve insomnia and anxiety Agonist Psychotomimetic actions Experimental treatment of refractory depression and other disorders, especially accompanying psychotherapy 5HT1B/1D Antagonist or partial agonist Possible pro-cognitive and antidepressant actions 5HT2C Antagonist Antidepressant 5HT6 ? ? 5HT7 Antagonist Possible pro-cognitive and antidepressant actions 5HT1A Partial agonist Reduced drug-induced parkinsonism Anxiolytic Booster of antidepressant actions of SSRIs/SNRIs Norepinephrine Alpha 2 Antagonist Antidepressant actions Agonist Improved cognition and behavioral disturbance in ADHD Alpha 1 Antagonist Improved sleep (nightmares) Improved agitation in Alzheimer disease Side effects of orthostatic hypotension and possibly sedation GABA GABA-B Agonist Cataplexy Sleepiness in narcolepsy Possible enhanced slow-wave sleep Pain reduction in chronic pain and fibromyalgia Possible utility for alcohol use disorder and alcohol withdrawal Melatonin MT1 Agonist Improvement of insomnia and circadian rhythms MT2 Agonist Improvement of insomnia and circadian rhythms

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Table 2-4 (cont.) Table 2-5 Key G-protein-linked receptors indirectly targeted by psychotropic drugs Neurotransmitter G-protein receptor and pharmacological subtype indirectly targeted Pharmacological action Therapeutic action Dopamine D1,2,3,4,5 agonist actions Dopamine reuptake inhibition/release by methylphenidate/ amphetamine Improvement of ADHD, depression, wakefulness Serotonin 5HT1A agonist (presynaptic somatodendritic autoreceptors) Serotonin reuptake inhibition by SSRIs/SNRIs Antidepressant, anxiolytic 5HT2A agonist (postsynaptic receptors; possibly 5HT1A, 5HT2C, 5HT6, 5HT7 postsynaptic receptors) 5HT2A/2C agonist Serotonin release by MDMA "Empathogen"

experimental treatment of PTSD especially with psychotherapy Norepinephrine All norepinephrine receptors agonist Norepinephrine reuptake inhibition Antidepressant; neuropathic pain; ADHD Acetylcholine M1 (possibly M2–M5) Agonist via increasing acetylcholine itself at all acetylcholine receptors via acetylcholinesterase inhibition Cognition in Alzheimer disease ADHD, attention deficit hyperactivity disorder; SSRIs, selective serotonin reuptake inhibitors; SNRIs, serotonin norepinephrine reuptake inhibitors; PTSD, posttraumatic stress disorder; MDMA, 3.4-methylenedioxymethamphetamine. Neurotransmitter G-protein receptor and pharmacological subtype directly targeted Pharmacological action Therapeutic action Histamine H1 Antagonist Therapeutic effect for anxiety and insomnia Side effect of sedation and weight gain H3 Antagonist/ inverse agonist Improvement of daytime sleepiness Acetylcholine M1 Agonist Procognitive and antipsychotic Antagonist Side effect of sedation and memory disturbance M4 Agonist Antipsychotic M2/3 Antagonist Dry mouth, blurred vision, constipation, urinary retention May contribute to metabolic dysregulation (dyslipidemia and diabetes) M5 ? ? Orexin A, B Ox1,2 Antagonist Hypnotic for insomnia

agonists. Secondly, many drugs can indirectly act to boost the levels of the natural full agonist neurotransmitter itself (Table 2-5) and then this increased amount of natural agonist binds to the neurotransmitter site on the G-protein-linked receptor. Enhanced amounts of full agonist happen when neurotransmitter inactivation mechanisms are blocked. The most prominent examples of indirect full agonist actions have already been discussed above, namely inhibition of the monoamine transporters SERT, NET, and DAT and the GABA transporter GAT1. Another way to accomplish indirect full agonist action is to block the enzymatic destruction of neurotransmitters (Table 2-5). Two examples of this are inhibition of the enzymes monoamine oxidase (MAO) and acetylcholinesterase which will be explained in more detail in later chapters. Antagonists On the other hand, it also is possible that full agonist action can be too much of a good thing and that maximal activation of the signal transduction cascade may not always be desirable, as in states of overstimulation by neurotransmitters. In such cases, blocking the action of the natural neurotransmitter agonist may be desirable. This is the property of an antagonist. Antagonists “Silent” Antagonist: Back to Baseline, Constitutive Activity Only, Same as No Agonist antagonist GE P Chapter 2: Transporters, Receptors, and Enzymes produce a conformational change in the G-protein-linked receptor that causes no change in signal transduction – including no change in whatever amount of any “constitutive” activity that may have been present in the absence of agonist (compare Figure 2-4 with Figure 2-6). Thus, true antagonists are “neutral” and, since they have no actions of their own, are also called “silent.” There are many more examples of important antagonists of G-protein-linked receptors than there are of direct-acting full agonists in clinical practice (see Table 2-4). Antagonists are well known both as the mediators of therapeutic actions in psychiatric disorders and as the cause of undesirable side effects (Table 2-4). Some of these may prove to be inverse agonists (see below), but most antagonists utilized in clinical practice are characterized simply as “antagonists.” Antagonists block the actions of everything in the agonist spectrum (Figure 2-3). In the presence of an agonist, an antagonist will block the actions of that agonist but do nothing itself (Figure 2-6). The antagonist simply returns the receptor conformation back to the same state as exists when no agonist is present (Figure 2-4). Interestingly, an antagonist will also block the actions of a partial agonist (explained below in more detail). Partial agonists are thought to produce a conformational change in the G-proteinFigure 2-6 “Silent” antagonist. An antagonist blocks agonists (both full and partial) from binding to G-proteinlinked receptors, thus preventing agonists from causing maximum signal transduction and instead

changing the receptor's conformation back to the same state as exists when no agonist is present. Antagonists also reverse the effects of inverse agonists, again by blocking the inverse agonists from binding and then returning the receptor conformation to the baseline state. Antagonists do not have any impact on signal transduction in the absence of an agonist. P P P P 41

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY linked receptor that is intermediate between a full agonist and the baseline conformation of the receptor in the absence of agonist (Figures 2-7 and 2-8). An antagonist reverses the action of a partial agonist by returning the G-protein-linked receptor to that same conformation as exists when no agonist is present (Figure 2-4). Finally, an antagonist reverses an inverse agonist (also explained below in more detail). Inverse agonists are thought to produce a conformational state of the receptor that totally inactivates it and even removes the baseline constitutive activity (Figure 2-9). An antagonist reverses this back to the baseline state that allows constitutive activity (Figure 2-6), the same as exists for the receptor in the absence of the neurotransmitter agonist (Figure 2-4). By themselves, therefore, it is easy to see that true antagonists have no activity and why they are sometimes referred to as "silent." Silent antagonists return the entire spectrum of drug-induced conformational changes in the G-protein-linked receptor (Figures 2-3 and 2-10) to Figure 2-7 Partial agonist. Partial agonists stimulate G-protein-linked receptors to enhance signal transduction but do not lead to maximum signal transduction the way full agonists do. Thus, in the absence of a full agonist, partial agonists increase signal transduction. However, in the presence of a full agonist, the partial agonist will actually turn down the strength of various downstream signals. For this reason, partial agonists are sometimes referred to as stabilizers. GE 3 P 3 P Partial Agonist: Partially Enhanced Signal Transduction partial agonist P P P P P P P P

Chapter 2: Transporters, Receptors, and Enzymes the same place (Figure 2-6) – i.e., the conformation that exists in the absence of agonist (Figure 2-4). Partial Agonists It is possible to produce signal transduction that is something more than an antagonist yet something less than a full agonist. Turning down the gain a bit from full agonist actions, but not all the way to zero, is the property of a partial agonist (Figure 2-7). This action can also be seen as turning up the gain a bit from silent antagonist actions, but not all the way to a full agonist. 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 amount of "partiality" that is desired between agonist and antagonist – that is, where a partial agonist should sit on the agonist spectrum – is both a matter of debate as well as trial and error. The ideal therapeutic agent may have signal transduction through G-proteinlinked receptors that is not too "hot," yet not too "cold," but "just right," sometimes called the "Goldilocks" solution (Figure 2-7). 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, such as when "out-of-tune" neurons are theoretically mediating psychiatric symptoms, it may be desirable to find a state of signal transduction that stabilizes G-protein-linked 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 a stable solution between the extremes of too much full agonist action and no agonist action at all (Figure 2-7). Since partial agonists exert an effect less than that of a full agonist, they are also sometimes called "weak," with the implication that partial agonism means partial clinical efficacy. That is certainly possible in some cases, but it is more sophisticated

to understand the potential stabilizing and “tuning” actions of this class of therapeutic agents, and not to use terms that imply clinical actions for the entire class of drugs that may only apply to some individual agents. Several partial agonists are utilized in clinical practice (Table 2-4) and more are in clinical development. Light and Dark as an Analogy for Partial Agonists It was originally conceived that a neurotransmitter could only act at receptors like a light switch, turning things on when the neurotransmitter is present and turning things off when the neurotransmitter is absent. We now know that many receptors, including the G-protein-linked receptor family, can function rather more like a rheostat. That is, a full agonist will turn the lights all the way on (Figure 2-8A), but a partial agonist will only turn the light on partially (Figure 2-8B). If neither full agonist nor partial agonist is present, the room is dark (Figure 2-8C). Figure 2-8 Agonist spectrum: rheostat. A useful analogy for the agonist spectrum is a light controlled by a rheostat. The light will be brightest after a full agonist turns the light switch fully on (left panel). A partial agonist will also act as a net agonist and turn the light on, but only partially, according to the level preset in the partial agonist’s rheostat (middle panel). If the light is already on, a partial agonist will “dim” the lights, thus acting as a net antagonist. When no full or partial agonist is present, the situation is analogous to the light being switched off (right panel). NO AGONIST -- light is off PARTIAL AGONIST -- light is dimmed but still shining FULL AGONIST -- light is at its brightest A B C

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Each partial agonist has its own set point engineered into the molecule, such that it cannot turn the lights on brighter even with a higher dose. No matter how much partial agonist is given, only a certain degree of brightness will result. A series of partial agonists will differ one from the other in the degree of partiality, so that theoretically all degrees of brightness can be covered within the range from “off” to “on,” but each partial agonist has its own unique degree of brightness associated with it. What is so interesting about partial agonists is that they can appear as a net agonist, or as a net antagonist, 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. That is, from the resting state, a partial agonist initiates somewhat of an increase in the signal transduction cascade from the G-protein-linked second-messenger system. However, when full agonist neurotransmitter is present, the same partial agonist will become a net antagonist. 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. Returning to the light-switch analogy, a room will be dark when agonist is missing and the light switch is off (Figure 2-8C). A room will be brightly lit when it is full of natural full agonist and the light switch is fully on (Figure 2-8A). Adding partial agonist to the dark room where there is no natural full agonist neurotransmitter will turn the lights up, but only as far as the partial agonist works on the rheostat (Figure 2-8B). Relative to the dark room as a starting point, a partial agonist acts therefore as a net agonist. On the other hand, adding a partial agonist to the fully lit room will have the effect of turning the lights down to the intermediate level of lower brightness on the rheostat (Figure 2-8B). This is a net antagonistic effect relative to the fully lit room. Thus, after adding partial agonist to the dark room and to the brightly lit room, both rooms will be equally lit. The degree of brightness is that of being partially turned on as dictated by the properties of the partial agonist. However, in the dark room, the partial agonist has acted as a net agonist, whereas in the brightly lit room, the partial agonist has acted as a net antagonist. Having an agonist and an antagonist in the same molecule is quite an interesting 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 with an excess of full agonist. An agent such as a partial agonist may even be able to treat simultaneously states which are mixtures of both excess and deficiency in neurotransmitter activity. Inverse Agonists Inverse agonists are more than simple antagonists, and are neither neutral nor silent. These agents have an action that is thought to produce a conformational change in the G-protein-linked receptor that stabilizes it in a totally inactive form (Figure 2-9). Thus, this conformation produces a functional reduction in signal transduction (Figure 2-9) that is even less than that produced when there is either no agonist present (Figure 2-4), or a silent antagonist present (Figure 2-6). The result of an inverse agonist is to shut down even the constitutive activity of the G-protein-linked receptor system. Of course, if a given receptor system has no constitutive activity, perhaps in cases when receptors are present in low density, there will be no reduction in activity and the inverse agonist will look like an antagonist. In many ways, therefore, inverse agonists do the opposite of agonists. If an agonist increases signal transduction from baseline, an inverse agonist decreases it, even below baseline levels. In contrast to agonists and antagonists, therefore, an inverse agonist neither increases signal transduction like an agonist (Figure 2-5) nor merely blocks the agonist from increasing signal transduction like an antagonist (Figure 2-6); rather, an inverse agonist binds the receptor in a fashion so as to provoke an action opposite to that of the agonist, namely causing the receptor to decrease its baseline signal transduction level (Figure 2-9). It is unclear from Inverse Agonist: Beyond Antagonism; Even the Constitutive Activity Is Blocked inverse agonist E Figure 2-9 Inverse agonist. Inverse agonists produce conformational change in the G-protein-linked receptor that renders it inactive. This leads to reduced signal transduction as compared not only to that associated with agonists but also that associated with antagonists or the absence of an agonist. The impact of an inverse agonist is dependent on the receptor density in that brain region. That is, if the receptor density is so low that constitutive activity does not lead to detectable signal transduction, then reducing the constitutive activity would not have any appreciable effect.

Chapter 2: Transporters, Receptors, and Enzymes Figure 2-10 Agonist spectrum. This figure summarizes the implications of the agonist spectrum. Full agonists cause maximum signal transduction, while partial agonists increase signal transduction compared to no agonist but decrease it compared to full agonist. Antagonists lead to constitutive activity and thus, in the absence of an agonist, have no effects; in the presence of an agonist, they lead to reduced signal transduction. Inverse agonists are the functional opposites of agonists and actually reduce signal transduction beyond that produced in the absence of an agonist. agonist no agonist or silent antagonist Agonist Spectrum partial agonist GE 3 P 3 P 3 P 3 P 2 P 3 P 3 P 3 P inverse agonist GE GE G GE a clinical point of view what the relevant differences are between an inverse agonist and a silent antagonist. In fact, some drugs that have long been considered to be silent antagonists, such as serotonin 2A antagonists and histamine 1 antagonists/antihistamines, may turn out in some areas of the brain actually to be inverse agonists. Thus, the concept of an inverse agonist as clinically distinguishable from a silent antagonist is still evolving and the clinical differentiation between antagonist and inverse agonist remains to be clarified. In summary, G-protein-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 2-10). When one considers the spectrum of signal transduction along this spectrum (Figure 2-10), 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. ENZYMES AS SITES OF PSYCHOPHARMACOLOGICAL DRUG ACTION Enzymes are involved in multiple aspects of chemical neurotransmission, as discussed extensively in Chapter 1 on signal transduction. Every enzyme is the theoretical target for a drug acting as an enzyme inhibitor. However, in practice, only a minority of currently known drugs utilized in the clinical practice of psychopharmacology are enzyme inhibitors. Enzyme activity is the conversion of one molecule into another, namely a substrate into a product (Figure 2-11). The substrates for each enzyme are very unique and selective, as are the products. A substrate (Figure 2-11A) comes to the enzyme to bind at the enzyme's active site (Figure 2-11B), and departs as a changed molecular entity called the product (Figure 2-11C). The inhibitors of an enzyme are also very unique and selective for one enzyme compared to another. In the

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY by the substrate (Figure 2-12B). The irreversible type of enzyme inhibitor is sometimes called a "suicide inhibitor" because it covalently and irreversibly binds to the enzyme protein, permanently inhibiting it and therefore essentially "killing" it by thus making the enzyme nonfunctional forever (Figure 2-12). Enzyme activity in this case is only restored when new enzyme molecules are synthesized. presence of an enzyme inhibitor, the enzyme cannot bind to its substrates. The binding of inhibitors can be either irreversible (Figure 2-12) or reversible (Figure 2-13). When an irreversible inhibitor binds to the enzyme, it cannot be displaced by the substrate; thus, that inhibitor binds irreversibly (Figure 2-12). This is depicted as binding with chains (Figure 2-12A) that cannot be cut with scissors Figure 2-11 Enzyme activity. Enzyme activity is conversion of one molecule into another. Thus, a substrate is said to be turned into a product by enzymatic modification of the substrate molecule. The enzyme has an active site at which the substrate can bind specifically (A). The substrate then finds the active site of the enzyme and binds to it (B) so that a molecular transformation can occur, changing the substrate into the product (C). After a Substrate Binds to an Enzyme, It Is Turned into a Product Which is Then Released from the Enzyme. A B C E E E Figure 2-12 Irreversible enzyme inhibitors. Some drugs are inhibitors of enzymes. Shown here is an irreversible inhibitor of an enzyme, depicted as binding to the enzyme with chains (A). A competing substrate cannot remove an irreversible inhibitor from the enzyme, depicted as scissors unsuccessfully attempting to cut the chains off the inhibitor (B). The binding is locked so permanently that such irreversible enzyme inhibition is sometimes called the work of a "suicide inhibitor," since the enzyme essentially commits suicide by binding to the irreversible inhibitor. Enzyme activity cannot be restored unless another molecule of enzyme is synthesized by the cell's DNA. Irreversible inhibitor Irreversible inhibitor A B E Substrate

Chapter 2: Transporters, Receptors, and Enzymes However, in the case of reversible enzyme inhibitors, an enzyme's substrate is able to compete with that reversible inhibitor for binding to the enzyme, and literally shove it off the enzyme (Figure 2-13). Whether the substrate or the inhibitor "wins" or predominates depends upon which one has the greater affinity for the enzyme and/or is present in the greater concentration. Such binding is called "reversible." Reversible enzyme Figure 2-13 Reversible enzyme inhibitors. Other drugs are reversible enzyme inhibitors, depicted as binding to the enzyme with a string (A). A reversible inhibitor can be challenged by a competing substrate for the same enzyme. In the case of a reversible inhibitor, the molecular properties of the substrate are such that it can get rid of the reversible inhibitor, depicted as scissors cutting the string that binds the reversible inhibitor to the enzyme (B). The consequence of a substrate competing successfully for reversal of enzyme inhibition is that the substrate displaces the inhibitor and shoves it off (C). Because the substrate has this capability, the inhibition is said to be

reversible. Reversible inhibitor Reversible inhibitor A B C E Substrate Reversible inhibitor Substrate

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY important enzyme in the signal transduction pathway of neurotrophic factors (Figure 2-14). That is, some neurotrophins, growth factors, and other signaling pathways act through a specific downstream phosphoprotein, an enzyme called GSK-3 (glycogen synthase kinase), to promote cell death (so-called proapoptotic actions). Lithium has the capacity to inhibit this enzyme (Figure 2-14B). It is possible that inhibition of GSK-3 is physiologically relevant, because this action could lead to neuroprotective actions, long-term plasticity, and may contribute to the antimanic and mood-stabilizing actions known to be associated with lithium. It is also possible that the antimanic agent valproate and the neurostimulatory treatment for depression ECT (electroconvulsive therapy) may have actions on GSK-3 as well (Figure 2-14B). The development of novel GSK-3 inhibitors is in progress. inhibition is depicted as binding with strings (Figure 2-13A), such that the substrate can cut them with scissors (Figure 2-13B) and displace the enzyme inhibitor, and bind the enzyme itself with its own strings (Figure 2-13C). These concepts can be applied potentially to any enzyme system. Several enzymes are involved in neurotransmission, including in the synthesis and destruction of neurotransmitters, as well as in signal transduction. Only a few enzymes are known to be targeted by psychotropic drugs currently used in clinical practice, namely monoamine oxidase (MAO), acetylcholinesterase, and glycogen synthase kinase (GSK). MAO inhibitors are discussed in more detail in Chapter 7 on treatments for mood disorders and acetylcholinesterase inhibitors are discussed in more detail in Chapter 12 on dementia. Briefly, regarding GSK, the antimanic agent lithium may target this Figure 2-14 Receptor tyrosine kinases. Receptor tyrosine kinases are potential targets for novel psychotropic drugs. Left: Some neurotrophins, growth factors, and other signaling pathways act through a downstream phosphoprotein, an enzyme called GSK-3 (glycogen synthase kinase), to promote cell death (proapoptotic actions). Right: Lithium and possibly some other mood stabilizers may inhibit this enzyme, which could lead to neuroprotective actions and long-term plasticity as well as possibly contribute to moodstabilizing actions. P P membrane neurotrophin insulin IGF-1 Wnt glycoproteins GSK-3 (Glycogen Synthase Kinase): Possible Target for Lithium and Other Mood Stabilizers lithium ? valproate ? ECT neuroprotective long-term plasticity antimanic / mood stabilizer proapoptotic GSK-3 GSK-3 neurotrophin insulin IGF-1 Wnt glycoproteins

Chapter 2: Transporters, Receptors, and Enzymes CYTOCHROME P450 DRUG METABOLIZING ENZYMES AS TARGETS OF PSYCHOTROPIC DRUGS Pharmacokinetic actions are mediated through the hepatic and gut drug metabolizing system known as the cytochrome P450 (CYP450) enzyme system. Pharmacokinetics is the study of how the body acts upon drugs, especially to absorb, distribute, metabolize, and excrete them. The CYP450 enzymes and the pharmacokinetic actions they represent must be contrasted with the pharmacodynamic actions of drugs, the latter being the major emphasis of this book. Pharmacodynamic actions at the specific drug targets discussed earlier in this chapter and also in Chapter 3 are known as the mechanism of action of psychotropic drugs, and account for the therapeutic effects and side effects of drugs. However, most psychotropic drugs also target the CYP450 drug metabolizing enzymes either as a substrate, inhibitor, and/or inducer, and a brief overview of these enzymes and their interactions with psychotropic drugs is in order. CYP450 enzymes follow the same principles of enzymes transforming substrates into products as illustrated in Figures 2-11 through 2-13. Figure 2-15 depicts the concept of a psychotropic drug being absorbed through the gut wall on the left and then sent to the big blue enzyme in the liver to be biotransformed so that the drug can be sent

back into the bloodstream to be excreted from the body via the kidney. Specifically, CYP450 enzymes in the gut wall or liver convert the drug substrate into a biotransformed product in the bloodstream. After passing through the gut wall and liver, the drug will exist partially as unchanged drug and partially as biotransformed product in the bloodstream (Figure 2-15). There are several known CYP450 systems. Six of the most important enzymes for psychotropic drug metabolism are shown in Figure 2-16. There are over 30 known CYP450 enzymes, and probably many more awaiting discovery and classification. Not all individuals have all the same genetic form of the CYP450 enzymes and types of enzyme for any individual can now be readily determined with pharmacogenetic testing. These enzymes are collectively responsible for the degradation of a large number of psychotropic drugs, and variations in the genes encoding for the different CYP450 enzymes can alter the activity of these enzymes, resulting in alterations of drug levels at standard doses. Most individuals have “normal” rates of drug metabolism from the major CYP450 enzymes and are said to be “extensive metabolizers”; most drug doses are set for these individuals. However, some individuals have genetic variants of these enzymes and may be either intermediate metabolizers or poor metabolizers, with reduced enzyme activity that can result in increased risk for elevated drug levels, drug–drug interactions, and Figure 2-15 CYP450. The cytochrome P450 (CYP450) enzyme system mediates how the body metabolizes many drugs, including antipsychotics. The CYP450 enzyme in the gut wall or liver converts the drug into a biotransformed product in the bloodstream. After passing through the gut wall and liver (left), the drug will exist partly as unchanged drug and partly as biotransformed drug (right). gut bloodstream CYP450 drug unchanged drug biotransformed drug Figure 2-16 Six CYP450 enzymes. There are many cytochrome P450 (CYP450) systems; these are classified according to family, subtype, and gene product. Five of the most important are shown here, and include CYP450 1A2, 2B6, 2D6, 2C9, 2C19, and 3A4. 2B6 1A2 2D6 2C19 2C9 3A4 1 = family A = subtype 1 = gene product

 reduced amounts of active metabolites. Such patients may require less than standard doses of drugs metabolized by their variant CYP450 enzymes. On the other hand, some patients can also be ultra-rapid metabolizers, with elevated enzyme activity, subtherapeutic drug levels, and poor efficacy with standard doses. When genetic variations are unknown, it can lead to altered efficacy and side effects of psychotropic drugs. Since the genes for these CYP450 enzymes can now be readily measured and used to predict which patients might need to have dosage adjustments of certain drugs up or down, the practice of psychopharmacology is increasingly moving to the measurement of genes for drug metabolism, especially in patients who do not respond or do not tolerate standard doses of psychotropic drugs. This is called genotyping the patient for pharmacogenomic use. Sometimes it is useful to couple genotyping with therapeutic drug monitoring that can detect the actual levels of drug in the blood and thus confirm the predictions from genetic testing of which CYP450 enzyme type has been shown to be present. The use of pharmacogenomic testing in combination with therapeutic drug monitoring (sometimes also called phenotyping) can help in the management particularly of treatment-resistant patients. Drug interactions mediated by CYP450 enzymes and their genetic variants are constantly being discovered, and the active clinician who combines drugs must be alert to these, and thus be continually updated on what drug interactions are important. Here we present only the general concepts of drug interactions at CYP450 enzyme systems, but the specifics should be found in a comprehensive and up-to-date comprehensive reference source (such as Stahl’s Essential Psychopharmacology: the Prescriber’s Guide, a companion to this textbook) before prescribing. SUMMARY Nearly a third of psychotropic drugs in clinical practice bind to a neurotransmitter transporter, and another third of psychotropic drugs bind to G-protein-

linked receptors. These two molecular sites of action, their impact upon neurotransmission, and various specific drugs that act at these sites have all been reviewed in this chapter. Specifically, there are two subclasses of plasma membrane transporters for neurotransmitters and three subclasses of intracellular synaptic vesicle transporters for neurotransmitters. The monoamine transporters (SERT for serotonin, NET for norepinephrine, and DAT for dopamine) are key targets for most of the known drugs that treat unipolar depression, ADHD, and numerous other disorders ranging from anxiety to pain. The vesicular transporter for all three of these monoamines is known as VMAT2 (vesicular monoamine transporter 2), which not only stores monoamines and histamine in synaptic vesicles, but is also inhibited by drugs recently introduced to treat movement disorders such as tardive dyskinesia. G-protein receptors are the most common targets of psychotropic drugs, and their actions can lead to both therapeutic effects and side effects. Drug actions at these receptors occur in a spectrum, from full agonist actions, to partial agonist actions, to antagonism, and even to inverse agonism. Natural neurotransmitters are full agonists, and so are some drugs used in clinical practice. However, most drugs that act directly on G-protein-linked receptors act as antagonists. A few act as partial agonists, and some as inverse agonists. Each drug interacting at a G-protein-linked receptor causes a conformational change in that receptor that defines where on the agonist spectrum it will act. Thus, a full agonist produces a conformational change that turns on signal transduction and second-messenger formation to the maximum extent. One novel concept is that of a partial agonist, which acts somewhat like an agonist, but to a lesser extent. An antagonist causes a conformational change that stabilizes the receptor in the baseline state and thus is “silent.” In the presence of agonists or partial agonists, an antagonist causes the receptor to return to this baseline state as well, and thus reverses their actions. A novel receptor action is that of an inverse agonist, which leads to a conformation of the receptor that stops all activity, even baseline actions. Understanding the agonist spectrum can lead to prediction of downstream consequences on signal transduction, including clinical actions. Finally, a minority of psychotropic drugs target enyzmes for their therapeutic effects. Several enzymes are involved in neurotransmission, including in the synthesis and destruction of neurotransmitters as well as in signal transduction, but in practice only three are known to be targeted by psychotropic drugs. A larger portion of psychotropic drugs target the cytochrome P450 drug metabolizing enzymes, which is relevant to their pharmacokinetic profiles but not their pharmacodynamic profiles.