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Psychosis, Schizophrenia, and the Neurotransmitter Networks Dopamine, Serotonin, and Glutamate Symptoms of Psychosis 77 The Three Major Hypotheses of Psychosis and Their Neurotransmitter Networks 78 The Classic Dopamine Hypothesis of Psychosis and Schizophrenia 79 The Dopamine Neurotransmitter Network 79 The Classic Dopamine Hypothesis of the Positive Symptoms of Psychosis: Mesolimbic HyperDopaminergia 90 Corollary to the Classic Dopamine Hypothesis of Schizophrenia: Mesocortical HypoDopaminergia and the Cognitive, Negative, and Affective Symptoms of Schizophrenia 95 The Glutamate Hypothesis of Psychosis and Schizophrenia 95 The Glutamate Neurotransmitter Network 96 The NMDA Glutamate Hypofunction Hypothesis of Psychosis: Faulty NMDA Neurotransmission at Glutamate Synapses on GABA Interneurons in Prefrontal Cortex 105 The Serotonin Hypothesis of Psychosis and Schizophrenia 111 The Serotonin Neurotransmitter Network 113 The Serotonin Hyperfunction Hypothesis of Psychosis 131 Summary and Conclusions Regarding Dopamine, NMDA, and Serotonin Neurotransmission in Psychosis 141 Schizophrenia as the Prototypical Psychotic Disorder 141 Beyond the Positive and Negative Symptoms of Schizophrenia 143 What Is the Cause of Schizophrenia? 148 Other Psychotic Illnesses 156 Mood-Related Psychosis, Psychotic Depression, Psychotic Mania 157 Parkinson’s Disease Psychosis 157 Dementia-Related Psychosis 157 Summary 158 Psychosis is a difficult term to define and is frequently misused not only in the media, but unfortunately among mental health professionals as well. Stigma and fear surround the concept of psychosis, sometimes using the

pejorative term “crazy.” This chapter gives a general description of psychotic symptoms and explores the major theories of how all forms of psychosis are linked to the neurotransmitter systems dopamine, serotonin, and glutamate. An overview of specific psychotic disorders, with an emphasis on schizophrenia, is presented here but does not list the diagnostic criteria for all the disorders in which psychosis is either a defining feature or an associated feature. The reader is referred to standard reference sources such as the DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) and the ICD (International Classification of Diseases) for that information. Although schizophrenia is emphasized here, we will approach psychosis as a syndrome associated with a variety of disorders that are all targets for the various drugs that treat psychosis and that will be discussed in Chapter 5. SYMPTOMS OF PSYCHOSIS Psychosis is a syndrome – that is, a mixture of symptoms – that can be associated with many different psychiatric disorders, but is not a specific disorder itself in diagnostic schemes such as the DSM or ICD. At a minimum, psychosis means delusions and hallucinations. Delusions are fixed beliefs – often bizarre – that have an inadequate rational basis and can’t be changed by rational arguments or evidence to the contrary. Hallucinations are perceptual experiences of any sensory modality – especially auditory – that occur without a real external stimulus, yet are vivid and clear, just like normal perceptions, but not under voluntary control. Delusions and hallucinations are the hallmarks of psychosis and are often called the “positive symptoms” of psychosis. Psychosis can also include other symptoms such as disorganized speech, disorganized behavior, gross distortions of reality testing, and so-called “negative symptoms” of psychosis, such as diminished emotional expression and decreased motivation.

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Psychosis itself, whether part of schizophrenia or another disorder, can be paranoid, disorganized/excited, or depressive. In addition, perceptual distortions and motor disturbances can be associated with any type of psychosis. Perceptual distortions include being distressed by hallucinatory voices; hearing voices that accuse, blame, or threaten punishment; seeing visions; reporting hallucinations of touch, taste, or odor; or reporting that familiar things and people seem changed. Motor disturbances are peculiar, rigid postures; overt signs of tension; inappropriate grins or giggles; peculiar repetitive gestures; talking, muttering, or mumbling to oneself; or glancing around as if hearing voices. In paranoid psychosis, the patient has paranoid projections, hostile belligerence, and grandiose expansiveness. This type of psychosis often occurs in schizophrenia and in many drug-induced psychoses. Paranoid projection includes preoccupation with delusional beliefs; believing that people are talking about oneself; believing one is being persecuted, or being conspired against; and believing people or external forces control one’s actions. A particular type of paranoid delusion may be seen in Parkinson’s disease psychosis; namely, the belief that one’s spouse is being unfaithful or that one’s spouse or loved ones are stealing from them. Hostile belligerence is verbal expression of feelings of hostility; expressing an attitude of disdain; manifesting a hostile, sullen attitude; manifesting irritability and grouchiness; tending to blame others for problems; expressing feelings of resentment; complaining and finding fault; as well as expressing suspicion of people. This, too may be seen especially in schizophrenia and drug-induced psychoses. Grandiose expansiveness is exhibiting an attitude of superiority; hearing voices that praise and extol; believing one has unusual powers or is a well-known personality, or that one has a divine mission, which is often seen in schizophrenia and in manic psychosis In a disorganized/excited psychosis, there is conceptual disorganization, disorientation, and excitement. Conceptual disorganization can be characterized by giving answers that are irrelevant, or incoherent; drifting off the subject; using neologisms; or

repeating certain words or phrases. Any psychotic disorder may exhibit disorganization. Disorientation is not knowing where one is, the season of the year, the calendar year, or one's own age and is common in psychoses associated with dementias and in drug-induced states. Excitement is expressing feelings without restraint; manifesting speech that is hurried; exhibiting an elevated mood; an attitude of superiority; dramatizing oneself or one's symptoms; manifesting loud and boisterous speech; exhibiting overactivity or restlessness; and exhibiting excess of speech. Excitement can be especially characteristic of mania or schizophrenia. Depressive psychosis is characterized by psychomotor retardation, apathy, and anxious self-punishment and blame. Psychomotor retardation and apathy are manifested by slowed speech; indifference to one's future; fixed facial expression; slowed movements; deficiencies in recent memory; manifesting blocking in speech; apathy toward oneself or one's problems; slovenly appearance; low or whispered speech; and failure to answer questions. It can be hard to distinguish from negative symptoms of psychosis. Anxious self-punishment and blame is the tendency to blame or condemn oneself; anxiety about specific matters; apprehensiveness regarding vague future events; an attitude of self-deprecation, manifesting depressed mood; expressing feelings of guilt and remorse; preoccupation with suicidal thoughts, unwanted ideas, and specific fears; and feeling unworthy or sinful, seen often in psychotic depression In summary, the term "psychosis" can be considered to be a set of symptoms in which a person's mental capacity, affective response, and capacity to recognize reality, communicate, and relate to others is impaired. This brief discussion of clusters of psychotic symptoms does not constitute diagnostic criteria for any psychotic disorder. It is given merely as a description of several types of symptoms that can occur as a part of many different types and causes of psychosis in order to give the reader an overview of the nature of behavioral disturbances associated with the various psychotic illnesses. THE THREE MAJOR HYPOTHESES OF PSYCHOSIS AND THEIR NEUROTRANSMITTER NETWORKS The dopamine (DA) hypothesis of psychosis is well known and has in fact become a classic, and one of the most enduring ideas in psychopharmacology. However, DA is not the only neurotransmitter linked to psychosis. Increasing evidence implicates both glutamate and serotonin neuronal networks as well in the pathophysiology and treatment of some forms of psychosis, not only schizophrenia, but psychoses associated with Parkinson's disease, with various forms of dementia, and with numerous psychotomimetic drugs. Thus, there are

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-1 Neurotransmitter pathways linked to psychosis. Psychosis has been theoretically linked to three major neurotransmitter pathways. The longstanding dopamine theory centers around the concept of hyperactive dopamine 2 (D2) receptors in the mesolimbic pathway. The glutamate theory proposes that N-methyl-D-aspartate (NMDA) receptors are hypoactive at critical synapses in the prefrontal cortex, which could lead to downstream hyperactivity in the mesolimbic dopamine pathway. The serotonin theory posits that there is serotonergic hyperactivity particularly at serotonin 2A (5HT2A) receptors in the cortex, which also could result in hyperactivity in the mesolimbic dopamine pathway. It is likely that one or more of these three pathways is involved in the development of psychosis. Three Neurotransmitter Pathways Linked to Psychosis Dopamine Theory Hyperactive dopamine at D2 receptors in the mesolimbic pathway Glutamate Theory NMDA receptor hypofunction Serotonin Theory 5HT2A receptor hyperfunction in the cortex Table 4-1 Pharmacological models link dopamine and serotonin receptor agonists and NMDA glutamate receptor antagonists to psychosis symptoms Psychostimulants (cocaine, amphetamine) Dissociative anesthetics (PCP, ketamine) Psychedelics (LSD, psilocybin) Proposed mechanism

Dopamine D2 agonist NMDA antagonist Serotonin 5HT2A agonist (and to a lesser extent 5HT2C) Main type of hallucinations Auditory Visual Visual Most frequently associated delusions Paranoid Paranoid Mystical Insightfulness No No Yes D2, dopamine 2; PCP, phencyclidine NMDA, N-methyl-D-aspartate; LSD, lysergic acid diethylamide; 5HT, 5-hydroxytryptamine (serotonin). now three major neurotransmitter systems hypothetically linked to psychosis (Figure 4-1 and Table 4-1). What follows is a discussion of each of these three hypotheses accompanied by an extensive presentation of the neuronal pathways and receptors for the three neurotransmitter networks for DA, glutamate, and serotonin. THE CLASSIC DOPAMINE HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA If one had asked any mental health clinician or researcher over the past 50 years what neurotransmitter was linked to psychosis, the resounding answer would have been DA, and specifically DA hyperactivity at D2 DA receptors in the mesolimbic pathway. This so-called DA hypothesis of psychosis makes sense because release of DA by amphetamine causes a paranoid psychosis similar to the psychosis in schizophrenia (see Table 4-1), and drugs that block DA D2 receptors have been the mainstay of treatment for essentially all forms of psychosis for over 50 years. Furthermore, this DA theory has proven so powerful that some may still assume (wrongly) that all positive symptoms of psychosis are caused by excessive DA in the mesolimbic pathway and that all treatments must therefore block DA D2 receptors in this pathway. As it turns out, however, there is much more to psychosis than mesolimbic DA, and much more to the treatment of psychosis than D2 antagonists, as will be discussed in Chapter 5. Before reviewing the classic and the updated DA hypothesis, not only of psychosis but of drugs that treat psychosis, it is important to understand fully DA neurotransmission, so we will begin with a discussion of DA receptors and brain circuits. The Dopamine Neurotransmitter Network To understand the potential role of DA in schizophrenia, we will first review how DA is synthesized, metabolized, and regulated, then show the functions of DA receptors, and finally show the localization of key DA pathways in the brain. Synthesis and Inactivation of Dopamine in Dopaminergic Neurons Dopaminergic neurons utilize the neurotransmitter DA, which is synthesized in dopaminergic nerve terminals from the amino acid tyrosine after it is taken up into the neuron from the extracellular space and bloodstream by

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-2 Dopamine synthesis. Tyrosine (TYR), a precursor to dopamine, is taken up into dopamine nerve terminals via a tyrosine transporter and converted into DOPA by the enzyme tyrosine hydroxylase (TOH). DOPA is then converted into dopamine by the enzyme DOPA decarboxylase (DDC). After synthesis, dopamine is packaged into synaptic vesicles via the vesicular monoamine transporter (VMAT2) and stored there until its release into the synapse during neurotransmission. TOH DDC TYR DOPA DA (dopamine)

tyrosine transporter Dopamine is Produced VMAT2 E E Figure 4-3 Dopamine’s action is terminated. Dopamine’s action can be terminated through multiple mechanisms. (A) Dopamine can be transported out of the synaptic cleft and back into the presynaptic neuron via the dopamine transporter (DAT), where it may be repackaged for future use. Alternatively, dopamine may be broken down extracellularly via the enzyme catechol-O-methyltransferase (COMT). Other enzymes that break down dopamine are monoamine oxidase A (MAO-A) and monoamine oxidase B (MAO-B), which are present in mitochondria within the presynaptic neuron and in other cells such as glia. (B) In the prefrontal cortex, DATs are relatively sparse; thus, the predominant method of dopamine inactivation is via MAO-A or MAO-B intracellularly, and COMT extracellularly. Dopamine can also diffuse away from the synapses and be taken up by the norepinephrine transporter (NET) at neighboring neurons. Dopamine Action Is Terminated B E E norepinephrine transporter (NET) DA

Cortical dopamine terminal MAO A or B destroys DA COMT destroys DA dopamine transporter (DAT) A E E DA Striatal dopamine terminal MAO A or B destroys DA COMT destroys DA tyrosine hydroxylase (TOH) and then by the enzyme DOPA decarboxylase (DDC) (Figure 4-2). DA is then taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission. Excess DA that escapes storage in synaptic vesicles can be destroyed within the neuron by the enzymes monoamine oxidase A (MAO-A) or monoamine oxidase B (MAO-B) (Figure 4-3A). In the striatum and some other brain regions, DA terminals have a presynaptic transporter (reuptake pump) called DAT (DA transporter), which is unique for DA and which terminates DA's synaptic action by whisking it out of the synapse back into the presynaptic nerve terminal where it can be re-stored in synaptic vesicles for subsequent reuse in another neurotransmission (Figure 4-3A). DATs are the principle pathway of inactivation for DA at synapses where DATs are present, with secondary inactivation extracellularly by catechol-O-methyltransferase (COMT). DATs are not in high density at the axon terminals of all DA neurons (Figure 4-3B). For example, in the prefrontal cortex, DATs are relatively sparse, and thus DA is inactivated in these synapses by other mechanisms, principally COMT (Figure 4-3B). When DATs are not present, DA can also diffuse away from synapses where it is released until it eventually reaches a neighboring norepinephrine (NE) neuron and confronts its NE transporters (NETs) that then inactivate this DA by transporting it into NE neurons as a "false" substrate (Figure 4-3B). a tyrosine pump, or transporter (Figure 4-2). Tyrosine is converted into DA first by the rate-limiting enzyme

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Dopamine Receptors Receptors for DA are the key regulators of dopaminergic neurotransmission (Figure 4-4). We have already mentioned the DA transporter DAT and the vesicular monoamine transporter VMAT2, which are both types of receptors. A plethora of additional DA receptors exist, including at least five pharmacological subtypes and several more molecular isoforms (Figure 4-4). Currently, Figure 4-4 Postsynaptic dopamine receptors. There are two groups of postsynaptic dopamine receptors. D1-like receptors, which include both D1 and D5 receptors, are excitatory and thus stimulate the postsynaptic neuron. D2-like receptors, which include D2, D3, and D4, are inhibitory and thus inhibit the postsynaptic neuron. Postsynaptic Dopamine Receptors D1-Like Receptors DAT Excitatory and stimulate postsynaptic neuron Inhibit postsynaptic neuron D2-Like Receptors D1 D1 D5 D2 D3 D4 D2 D3 D4 D5 Figure 4-5 Presynaptic dopamine receptors. Dopamine 2 and 3 are also located presynaptically, where, due to their inhibitory actions, they act as autoreceptors to inhibit further dopamine release. The D2 autoreceptor is less sensitive to dopamine than the D3 autoreceptor and thus it takes a higher concentration of synaptic dopamine for the D2 autoreceptor to become activated (left) than it does for the D3 autoreceptor to become activated (right). Presynaptic Dopamine Receptors DAT D1 D5 D2 D3 D4 D1 D5 D2 D2 D3 D3 D4 DA receptors are divided into two groups. The first group is the D1-like receptors, including both D1 and D5 receptors. D1-like receptors are excitatory, and positively linked to adenylate cyclase (Figure 4-4, left). The second group is the D2-like receptors, including D2, D3, and D4 receptors. D2-like receptors are inhibitory and negatively linked to adenylate cyclase (Figure 4-4, right). Thus, the neurotransmitter DA can be either excitatory or

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY inhibitory, depending upon which DA receptor subtype it binds. All five DA receptors can be located postsynaptically (Figure 4-4), but D2 and D3 receptors can also both be located presynaptically, where, due to their inhibitory actions, they act

as autoreceptors to inhibit further DA release (Figure 4-5). Note in Figure 4-5 that more DA presynaptic autoreceptor (D2 or D3) “gatekeeper” - open A presynaptic autoreceptor (D2 or D3) “gatekeeper” - closed B has accumulated in the synapse with a D2 presynaptic autoreceptor (on the left) than in the synapse with a D3 presynaptic autoreceptor (on the right). This is because the D3 receptor is more sensitive to DA and thus it takes a lesser concentration of synaptic DA to activate the D3 receptor and turn off further DA release compared to neurons having the D2 presynaptic receptor. Figure 4-6 Presynaptic dopamine autoreceptors. Presynaptic D2 and D3 autoreceptors are “gatekeepers” for dopamine. (A) When dopamine autoreceptors are not bound by dopamine (no dopamine in the gatekeeper’s hand), the molecular gate is open and allows dopamine release. (B) When dopamine binds to the dopamine autoreceptor (now the gatekeeper has dopamine in his hand), the molecular gate closes and prevents dopamine from being released. dopamine

Presynaptic D2/D3 receptors act as “gatekeepers” either allowing DA release when they are not occupied by DA (Figure 4-6A) or inhibiting DA release when DA builds up in the synapse and occupies the gatekeeping presynaptic autoreceptor (Figure 4-6B). Such receptors are located either on the axon terminal (Figure 4-7) or on the other end of the neuron in the somatodendritic area of the DA neuron (Figure 4-8). In both cases, they are considered presynaptic and occupancy of these D2 or D3 autoreceptors provides negative feedback input, or a braking action upon the release of DA from the DA neuron (Figures 4-7B and 4-8B). Thus, DA neurons can be regulated quite differently depending upon which DA receptors are present. This is exemplified not only by synapses with D3 presynaptic autoreceptors having their DA release regulated in a A B Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks different manner than synapses with D2 presynaptic autoreceptors (Figure 4-5), but also when comparing mesocortical DA neurons with mesolimbic and nigrostriatal (mesostriatal) neurons side by side (Figure 4-9). Mesocortical DA neurons arising from the ventral tegmental area (VTA) in the brainstem and projecting to prefrontal cortex have either D2 or D3 autoreceptors on their cell bodies in the VTA, but there are only sparse D2/D3 receptors in the prefrontal cortex pre- or postsynaptically (Figure 4-9A). Without autoreceptors on axon terminals in the prefrontal cortex, DA release is not shut off by this mechanism and thus is freer to diffuse away from the synapse where it is released, as shown by the large blue cloud of DA. Moreover, as already mentioned, mesocortical DA neurons have few if any DATs on their presynaptic nerve terminals in the Figure 4-7 Presynaptic dopamine autoreceptors. Presynaptic D2 and D3 autoreceptors can be located on the axon terminal, as shown here. When dopamine builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits dopamine release (B). DA presynaptic autoreceptor (D2 or D3) 83

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY somatodendritic autoreceptor (D2 or D3) A B prefrontal cortex. Without DATs to whisk synaptic DA back into the presynaptic neuron, or D2/D3 presynaptic autoreceptors to turn off DA release as synaptic DA accumulates, this allows a larger diffusion radius of DA away from presynaptic terminals (Figure 4-9A) compared to terminals that have DATs and D2/D3 autoreceptors present (Figure 4-9B – note the sizes of the blue clouds in these figures). That is a good thing perhaps, since the predominant postsynaptic receptor in the prefrontal cortex is the D1 receptor, and the D1 receptor is the least sensitive to DA and thus requires a higher concentration of DA to be present to be activated compared to D2 or D3 receptors. Greater diffusion of DA also means the possibility of volume neurotransmission (see Chapter 1 and Figures 1-6 and 1-7) so that DA from one presynaptic terminal can communicate

with D1 receptors anywhere within its diffusion radius in the prefrontal cortex and Figure 4-8 Somatodendritic dopamine autoreceptors. D2 and D3 autoreceptors can also be located in the somatodendritic area, as shown here. When dopamine binds to the receptor here, it shuts off neuronal impulse flow in the dopamine neuron (see loss of lightning bolts in the neuron in B), and this stops further dopamine release. thus beyond the synapse from where it was released. On the other hand, mesostriatal DA neurons have either presynaptic D2 or D3 receptors present, not only on the cell bodies in the VTA and substantia nigra, but also on presynaptic nerve terminals and postsynaptic sites in the striatum (Figure 4-9B). Furthermore, DATs are present on presynaptic nerve terminals in the striatum of these DA neurons. As mentioned, neurons with D2 autoreceptors have a wider diffusion radius compared to those with D3 autoreceptors, providing a range of possibilities for regulation of DA release in the striatum (Figure 4-9B). Classic Dopamine Pathways and Key Brain Regions The five classic DA pathways in the brain are shown in Figure 4-10. They include the tuberoinfundibular DA pathway, a thalamic DA pathway, the nigrostriatal DA pathway, and most importantly for the DA hypothesis,

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-9 Mesocortical vs. mesostriatal neurons. (A) Mesocortical neurons project from the ventral tegmental area (VTA) to the prefrontal cortex (PFC). In the VTA, dopamine release is regulated by somatodendritic D2 and D3 autoreceptors. In the PFC, however, there are few D2 or D3 presynaptic autoreceptors to inhibit dopamine release, as well as few dopamine transporters (DATs) to remove dopamine from the synapse. Thus, dopamine is more freely able to diffuse away from the synapse (indicated by the large blue cloud). Postsynaptically, the predominant dopamine receptor is D1, which is excitatory. (B) Dopamine release from mesolimbic neurons (projecting from the VTA to the striatum) is regulated by somatodendritic D3 autoreceptors in the VTA and by presynaptic D3 autoreceptors and DATs in the striatum (left). Dopamine release from nigrostriatal neurons (projecting from the substantia nigra [SN] to the striatum) is regulated by somatodendritic D2 autoreceptors in the SN and by presynaptic D2 autoreceptors and DATs in the striatum (right). D2 autoreceptors are less sensitive to dopamine than D3 autoreceptors, thus allowing for a wider diffusion radius (indicated by the comparative sizes of the blue clouds). Postsynaptically, D1, D2, and D3 receptors are all present in the striatum. mesocortical VTA A B D3 D3 D3 D3 D3 D3 D3 D3 D2 D2 D2 D2 D2 D2 D2 D2 mesostriatal (mesolimbic and nigrostriatal) VTA and SN D3 D3 DAT D1 D3 D2 D1 PFC striatum striatum PFC D2 D2 DAT D2 D2 D D1 D1 D1 D1 D1 D1 D3 D2 the mesocortical and the mesolimbic DA pathways. Advances in neuroscience propose some more recent and sophisticated ways to view these pathways in schizophrenia, but first we will consider the classic approach. Tuberoinfundibular Dopamine Pathway The DA neurons that project from hypothalamus to anterior pituitary gland are known as the tuberoinfundibular DA pathway (Figure 4-11). Normally, these neurons are tonically active and inhibit prolactin release. In the postpartum state, however, the activity of these DA neurons is decreased. Prolactin levels can therefore rise during breast feeding so that lactation will occur. If the functioning of tuberoinfundibular DA neurons is disrupted by lesions or drugs, prolactin levels can also rise. Elevated prolactin levels are associated with galactorrhea (breast secretions), gynecomastia (enlarged breasts especially in men), amenorrhea (loss of ovulation and menstrual periods), and possibly other problems such as sexual dysfunction. Such problems can occur after treatment with many drugs for psychosis that block DA D2 receptors, and will be discussed further in Chapter 5. In untreated schizophrenia, the function of the tuberoinfundibular pathway may be relatively preserved (Figure 4-11). Thalamic Dopamine Pathway Recently, a DA pathway that innervates the thalamus in primates has been described. It arises from multiple sites,

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-10 Five dopamine pathways in the brain. (a) The nigrostriatal dopamine pathway, which projects from the substantia nigra to the basal ganglia or striatum, is part of the extrapyramidal nervous system and controls motor function and movement. (b) The mesolimbic dopamine pathway projects from the midbrain ventral tegmental area (VTA) to the nucleus accumbens, a part of the limbic system of the brain thought to be involved in many behaviors such as pleasurable sensations, the powerful euphoria of drugs of abuse, and delusions and hallucinations of psychosis. (c) The mesocortical dopamine pathway also projects from the midbrain VTA but sends its axons to areas of the prefrontal cortex, where they may have a role in mediating cognitive symptoms (dorsolateral prefrontal cortex or DLPFC) and affective symptoms (ventromedial prefrontal cortex or VMPFC) of schizophrenia. (d) The tuberoinfundibular dopamine pathway projects from the hypothalamus to the anterior pituitary gland and controls prolactin secretion. (e) The fifth dopamine pathway arises from multiple sites, including the periaqueductal gray, ventral mesencephalon, hypothalamic nuclei, and lateral parabrachial nucleus, and projects to the thalamus. Its function is not currently well known. Classic Dopamine Pathways and Key Brain Regions striatum tegmentum substantia nigra hypothalamus VMPFC DLPFC pituitary nucleus accumbens thalamus b a c d e Figure 4-11 Tuberoinfundibular dopamine pathway. The tuberoinfundibular dopamine pathway from the hypothalamus to the anterior pituitary gland regulates prolactin secretion into the circulation. Dopamine inhibits prolactin secretion. In untreated schizophrenia, activation of this pathway is believed to be "normal." normal NORMAL Tuberoinfundibular Pathway

including the periaqueductal gray matter, the ventral mesencephalon, from various hypothalamic nuclei, and from the lateral parabrachial nucleus (Figure 4-10). Its function is still under investigation, but may be involved in sleep and arousal mechanisms by gating information passing through the thalamus to the cortex and other brain areas. There is no evidence at this point for abnormal functioning of this DA pathway in schizophrenia. Nigrostriatal Dopamine Pathway Another key DA pathway is the nigrostriatal DA pathway, which projects from DA cell bodies in the brainstem substantia nigra via axons terminating in the striatum (Figure 4-12). Classically, the nigrostriatal DA pathway has been considered to be part of the extrapyramidal nervous system, and to control motor movements via its connections with the thalamus and cortex in cortico-striato-thalamo-cortical (CSTC) circuits or loops (Figure 4-13A). A more sophisticated anatomical model of how DA regulates CSTC loops and motor movements in the striatum is shown in Figures 4-13B through Figure Nigrostriatal Pathway normal NORMAL Figure 4-12 Nigrostriatal dopamine pathway. The nigrostriatal dopamine pathway projects from the substantia nigra to the basal ganglia or striatum. It is part of the extrapyramidal nervous system and plays a key role in regulating movements. When dopamine is deficient, it can cause parkinsonism with tremor, rigidity, and akinesia/bradykinesia. When dopamine is in excess, it can cause hyperkinetic movements such as tics and dyskinesias. In untreated schizophrenia, activation of this pathway is believed to be "normal." Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks 4-13F as the "direct" and "indirect" DA pathways. The so-called direct pathway (shown in Figure 4-13B on the left and in Figures 4-13C and 4-13E) is populated with D1 dopamine receptors that are excitatory (Figure 4-13E; see also Figure 4-4, left) and projects directly from the striatum to the globus pallidus interna to stimulate movements ("go" pathway) (Figure 4-13C). The so-called indirect pathway (shown in Figure 4-13B on the right and in Figures 4-13D and 4-13F) is populated with D2 dopamine receptors that are inhibitory (Figure 4-13F; see also Figure 4-4, right) and projects

indirectly to the globus pallidus interna via the globus pallidus externa and subthalamic nucleus. Normally, this pathway blocks motor movements (“stop” pathway) (see Figure 4-13D). Dopamine inhibits this action at D2 receptors in the indirect pathway (Figure 4-13F) and this says “don’t stop” to the stop pathway, or “go more.” The bottom line is that dopamine stimulates motor movements in both the direct and indirect motor pathways. Synchronizing the outputs of these pathways is thought to lead to the smooth execution of motor movements. Classic CSTC (Cortico-Striato-Thalamo-Cortical) Loop C T S DA SN C = cortex T = thalamus S = striatum SN = substantia nigra Figure 4-13A Cortico-striato-thalamo-cortical (CSTC) loop. In the most simple terms, the nigrostriatal dopamine pathway is considered to control motor movements via its connections with the thalamus and cortex in a circuit known as the cortico-striatothalamo-cortical loop. 87

 Figure 4-13B Direct and indirect dopamine pathways for motor control. Populated with excitatory D1 receptors, the direct pathway for dopamine regulation of motor movements (left) projects from the striatum to the globus pallidus interna and results in the stimulation of movement. The indirect pathway for dopamine

regulation of motor movements (right) projects to the globus pallidus interna via the globus pallidus externa and subthalamic nuclei. This pathway is populated with inhibitory D2 receptors and normally blocks motor movements. Thalamus Cortex Dopamine Regulation of Direct (D1) and Indirect (D2) Pathways: Stop and Go Signals for Motor Movement GP /SNr r c e i e i GP STN Striatum SNc direct pathway “go” indirect pathway “stop” DA DA GABA GABA GABA GABA glu glu D1 D2 +

motor output STN= subthalamic nucleus SN = substantia nigra reticulata SN = substantia nigra compacta GP = globus pallidus externa GP = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid DA = dopamine D1 = dopamine 1 receptor D2 = dopamine 2 receptor Although there is no evidence at this point for abnormal functioning of this DA pathway in schizophrenia (Figures 4-12 and 4-13), deficiencies of DA in these motor pathways cause movement disorders including Parkinson’s disease, characterized by rigidity, akinesia/bradykinesia (i.e., lack of movement or slowing of movement), and tremor. DA deficiency in the striatum can hypothetically also be involved in the mechanism that produces akathisia (a type of restlessness) and dystonia (twisting movements especially of the face and

Go - Direct Pathway Activated GO glu + Cortex Thalamus GABA BA

STN GP /SNr i activation of direct pathway “GO” GP e STN= subthalamic nucleus SNr = substantia nigra reticulata SNc = substantia nigra compacta GPe = globus pallidus externa GPi = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid Striatum SNc Figure 4-13C

Activation of the direct (go) dopamine pathway. A γ-aminobutyric acid (GABA) neuron projecting from the striatum to the globus pallidus interna is activated. The released GABA inhibits activity of another GABAergic neuron that projects to the thalamus. In the absence of GABA release in the thalamus, a glutamatergic neuron is activated and releases glutamate into the cortex, stimulating movement. neck). These same movement disorders can be replicated by drugs that block D2 DA receptors

in this pathway, causing drug-induced parkinsonism (sometimes called by its better-known but much less accurate name extrapyramidal symptoms or EPS). This will be discussed in more detail in Chapter 5 on drugs for the treatment of psychosis. Not only can too little DA activity cause movement disorders, so can too much. Thus, hyperactivity of DA in the nigrostriatal pathway is thought to underlie various hyperkinetic movement disorders such as chorea, dyskinesias, and tics (in conditions such as

Huntington’s disease, Tourette syndrome, and others). Chronic stimulation of D2 DA receptors in the nigrostriatal pathway by treatment of Parkinson’s disease with levodopa is hypothesized to underlie the emergence of abnormal hyperkinetic and dyskinetic movements (called Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Stop - Indirect Pathway Activated STOP: don’t go Cortex GABA G

Thalamus glu glu + STN GP /SNr i GABA

G

activation of indirect pathway GP e “STOP” “don’t go” Striatum STN= subthalamic nucleus SN = substantia nigra reticulata SN = substantia nigra compacta GP = globus pallidus externa GP = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid r c e i SNc Figure 4-13D Activation of the indirect (stop) dopamine pathway. A γ-aminobutyric acid (GABA) neuron projecting from the striatum to the globus pallidus externa is activated. The released GABA inhibits activity of another GABAergic neuron that projects to the subthalamic nucleus (STN). In the absence of GABA release in the STN, a glutamatergic neuron is activated and releases glutamate into the globus pallidus interna, which in turn stimulates a GABAergic neuron to release GABA into the thalamus. GABA then binds to a glutamatergic neuron, inhibiting it from releasing glutamate into the cortex and thus inhibiting movement. levodopa-induced dyskinesias or LID). Chronic blockade of these same D2 DA receptors in the nigrostriatal pathway is hypothesized to cause another hyperkinetic movement disorder known as tardive dyskinesia. Tardive dyskinesia and its treatment will be discussed further in Chapter 5 on drugs for psychosis. The Mesolimbic Dopamine Pathway The mesolimbic DA pathway projects from DA cell bodies in the VTA of the brainstem (i.e., mesencephalon) to the nucleus accumbens in the ventral striatum, which is part of the limbic system (thus, mesolimbic) (Figures 4-10 and 4-14 A–D). DA release from this pathway is thought to have an important role in several 89

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY D1 Stimulation of Go Pathway GO glu + Cortex Thalamus GABA BA

STN GP /SNr i GP e D1 stimulation of “GO” pathway - “go more” + DA Striatum STN= subthalamic nucleus SN = substantia nigra reticulata SN = substantia nigra compacta GP = globus pallidus externa GP = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid DA = dopamine D1 = dopamine 1 receptor r c e i SNc Figure 4-13E Dopamine-1 receptor stimulation of the go pathway. Dopamine released from the nigrostriatal pathway binds to postsynaptic D1 receptors on a γ-aminobutyric acid (GABA) neuron

projecting to the globus pallidus interna. This causes phasic activation of the direct (go) pathway, essentially telling it to “go more.” normal emotional behaviors, including motivation, pleasure, and reward (Figure 4-14A). Although this may be an oversimplification, the mesolimbic dopamine pathway may in fact be the final common pathway of all reward and reinforcement, including not only normal reward (such as the pleasure of eating good food, orgasm, listening to music) (Figure 4-14A), but also

emotions experienced when rewards are too high (Figures 4-14B and C) or too low (Figure 4-14D). Too much DA in this pathway classically is thought to cause the positive symptoms of psychosis (Figure 4-14C) as well as the artificial reward (drug-induced “high”) of substance abuse (Figure 4-14B) (see also discussion on drugs of abuse in Chapter 13). On the other hand, too little DA in this pathway hypothetically causes the symptoms of anhedonia, apathy, and lack of energy seen in conditions such as unipolar and

bipolar depression and in the negative symptoms of schizophrenia (Figure 4-14D). D2 Inhibition of Stop Pathway Inhibition of stop or “GO” g + glu Cortex Thalamus

GABA G STN GP /SNr i GP e D2 D2

DA STN= subthalamic nucleus SN = substantia nigra reticulata SN = substantia nigra compacta GP = globus pallidus externa GP = globus pallidus interna glu = glutamate GABA = γ-aminobutyric acid DA = dopamine D2 = dopamine 2 receptor r c e i Striatum D2 inhibition of “STOP” pathway - “don’t stop, so go more” SNc Figure 4-13F Dopamine-2 receptor inhibition of the stop pathway. Dopamine released from the nigrostriatal pathway binds to postsynaptic D2 receptors on a γ-aminobutyric acid (GABA) neuron projecting to the globus pallidus externa. This causes inhibition of the indirect (stop) pathway, thus instead telling it to “go.” The Classic Dopamine Hypothesis of the Positive Symptoms of Psychosis: Mesolimbic HyperDopaminergia As mentioned above, hyperactivity of this mesolimbic DA pathway (“hyperdopaminergia”) hypothetically accounts for positive psychotic symptoms (that is, delusions and hallucinations) as a final common pathway for psychosis, whether those symptoms are part of the illness of schizophrenia, of drug-induced psychosis, or whether positive psychotic symptoms accompany mania, depression, Parkinson’s disease, or dementia. Hyperactivity of mesolimbic DA neurons may also play a role in causing impulsive, agitated, aggressive, and hostile symptoms in any of the illnesses associated with positive symptoms of psychosis (Figure 4-15). Although mesolimbic DA hyperactivity can be a direct pharmacological consequence of psychostimulants such as cocaine and methamphetamine, mesolimbic DA hyperactivity in psychosis associated with schizophrenia, mania,

overactivation DA neuron A motivation reward Figure 4-14 Mesolimbic dopamine pathway. (A) The mesolimbic dopamine pathway, which projects from the ventral tegmental area (VTA) in the brainstem to the nucleus accumbens in the ventral striatum, is involved in regulation of motivation and reward. Classically, hyperactivity of this pathway is associated with drug-induced highs (B) and is believed to account for the positive symptoms of psychosis (C), while hypoactivity is associated with symptoms of anhedonia, apathy, and lack of energy as well as with the negative symptoms of

schizophrenia. Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Classic Mesolimbic Pathway normal HIGH B drug-induced high normal HIGH C positive symptoms normal LOW affective symptoms D (SIGH) negative symptoms anhedonia apathy lack of energy 91

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-15 Mesolimbic dopamine hypothesis. Hyperactivity of dopamine neurons in the mesolimbic dopamine pathway theoretically mediates the positive symptoms of psychosis such as delusions and hallucinations. Mesolimbic overactivity may also be associated with impulsivity, agitation, violence/aggression, and hostility. The Classic Mesolimbic Dopamine Hypothesis of Positive Symptoms of Schizophrenia mesolimbic overactivity = positive symptoms of schizophrenia positive symptoms hostility violence/ aggression *#%! agitation impulsivity haircuts depression, Parkinson's disease, or Alzheimer disease and other dementias may be the indirect consequence of dysregulation in prefrontal circuits and their glutamate and serotonin neurons as well as dopamine neurons. These brain circuits are discussed in detail in the following sections on glutamate and serotonin. New Developments in the Dopamine Hypothesis of Positive Symptoms of Psychosis in Schizophrenia Classically, DA projections from the substantia nigra to the dorsal striatum (Figure 4-12) have been considered to regulate motor movements and to be in parallel with pathways from the VTA to the ventral striatum (nucleus accumbens) that regulate emotions (Figure 4-14A). A simplistic notion is that there is a dorsal or "upper" striatum for motor movements (the "neurologists' striatum") and a ventral or "lower" striatum for emotions (the "psychiatrists' striatum") (Figure 4-16A). These concepts have been derived largely from anatomical and pharmacological studies in rodents combined with drug studies in humans. Although heuristically valuable, recent results from human neuroimaging studies show that the idea of separate dedicated pathways where anatomical differences correlate with function (motor vs. emotion) may need to be modified. That is, neuroimaging of DA activity in the striatum of living, unmedicated patients with schizophrenia does not show the expected hyperdopaminergia uniquely in the ventral striatum. Instead, the hyperdopaminergia may be especially present in an intermediate part of the striatum

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks and lateral substantia nigra may also be important in mediating the positive symptoms of schizophrenia (Figure 4-16B). These findings indicate a remarkable development in thinking about the dorsal striatum and nigrostriatal pathways as having emotional as well as motor components. Compulsions and habits are also theoretically localized to the dorsal striatum (discussed called the associative striatum, which receives input from the substantia nigra but not from the VTA (Figure 4-16B). These findings suggest that a more sophisticated formulation of DA pathways may be necessary in order to understand the hyperdopaminergia of schizophrenia. That is, hyperdopaminergia in projections not only from the VTA but perhaps especially from the medial Figure 4-16 Integrative hub mesostriatal hyperdopaminergia. (A) A classic understanding of striatal functioning has been that the dorsal striatum regulates motor movement and the ventral striatum regulates emotions, with overactivity of dopamine in the ventral striatum associated with the positive symptoms of schizophrenia. (B) Neuroimaging data in unmedicated patients with schizophrenia suggest that dopaminergic activity may be unaltered in the ventral striatum, but may instead be overactive in an intermediate part of the striatum called the associative striatum, which receives input from the substantia nigra rather than the ventral tegmental area (VTA). Rather than separate nigrostriatal and mesolimbic projections, a better conception may be that of a mesostriatal pathway. dorsal striatum normal SN VTA ventral striatum sensorimotor associative normal SN(L) SN(L) substantia nigra lateral SN(M)

substantia nigra medial VTA ventral tegmental area VTA ventral SN(M) dorsal striatum schizophrenia Classic Mesolimbic Hyperdopaminergia SN VTA ventral striatum overactivation A B sensorimotor associative schizophrenia SN(L) VTA ventral SN(M) New Concept: Integrative Hub Mesostriatal Hyperdopaminergia

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-17 Mesocortical pathway to the dorsolateral prefrontal cortex (DLPFC). The mesocortical dopamine pathway projects from the ventral tegmental area (VTA) to the prefrontal cortex. Projections specifically to the DLPFC are associated with cognitive and executive functioning (A), with hypoactivity in this pathway classically believed to be involved in the cognitive and some negative symptoms of schizophrenia (B). negative symptoms A B Classic Mesocortical Pathway to DLPFC LOW normal cognitive symptoms (SIGH) Figure 4-18 Mesocortical pathway to the ventromedial prefrontal cortex (VMPFC). The mesocortical dopamine pathway projects from the ventral tegmental area (VTA) to the prefrontal cortex. Projections specifically to the VMPFC are associated with emotions and affect (A), with hypoactivity in this pathway classically believed to be involved in the negative and affective symptoms of schizophrenia (B). negative symptoms A B Classic Mesocortical Pathway to VMPFC LOW normal affective symptoms (SIGH) in Chapter 13). Thus, the dorsal striatum may not be all motor and only the neurologists' striatum! It may also have an important role in emotional regulation. The bottom line is that rather than thinking of the projections from the midbrain to the striatum as parallel pathways with separate and distinct functions (as in Figure

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks dorsolateral prefrontal cortex (Figure 4-17) whereas affective and other negative symptoms of schizophrenia may be due to a deficit of DA activity in mesocortical projections to ventromedial prefrontal cortex (Figure 4-18). The behavioral deficit state suggested by negative symptoms certainly implies underactivity or lack of proper functioning of mesocortical DA projections, and a leading theory is that this is the consequence of neurodevelopmental abnormalities in the N-methyl-Daspartate (NMDA) glutamate system, as described in the following section on glutamate. THE GLUTAMATE HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA The glutamate theory of psychosis proposes that the NMDA (N-methyl-D-aspartate) subtype of glutamate receptor is hypofunctional at critical synapses in the prefrontal cortex (Table 4-1 and Figure 4-1). Disruption of NMDA glutamate functioning can be hypothetically due to the neurodevelopmental abnormalities in schizophrenia, to the neurodegenerative abnormalities in Alzheimer disease and other dementias, and to the NMDA receptor blocking actions of drugs such as the dissociative anesthetics 4-16A), the new notion from neuroimaging is that the VTA–substantia nigra complex is instead an integrative hub and its pathways can be thought of as mesostriatal rather than nigrostriatal/mesolimbic (Figure 4-16B). Hyperdopaminergia of schizophrenia in this sense is mesostriatal rather than purely mesolimbic. Corollary to the Classic Dopamine Hypothesis of Schizophrenia: Mesocortical HypoDopaminergia and the Cognitive, Negative, and Affective Symptoms of Schizophrenia Another DA pathway also arising from cell bodies in the VTA but projecting to areas of the prefrontal cortex is known as the mesocortical DA pathway (Figures 4-17 through 4-19). Branches of this pathway into the dorsolateral prefrontal cortex are hypothesized to regulate cognition and executive functions (Figure 4-17), whereas branches of this pathway into the ventromedial parts of prefrontal cortex are hypothesized to regulate emotions and affect (Figure 4-18). The exact role of the mesocortical DA pathway in mediating symptoms of schizophrenia is still a matter of debate, but many researchers believe that cognitive and some negative symptoms of schizophrenia may be due to a

deficit of DA activity in mesocortical projections to the Figure 4-19 Mesocortical dopamine hypothesis. Hypoactivity of dopamine neurons in the mesocortical dopamine pathway theoretically mediates the cognitive, negative, and affective symptoms of schizophrenia. The Classic Mesocortical Dopamine Hypothesis of Cognitive, Negative, and Affective Symptoms of Schizophrenia negative symptoms affective symptoms (SIGH) cognitive symptoms

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY ketamine and phencyclidine (PCP) (Figure 4-1 and Table 4-1). In order to understand how glutamate dysfunction could lead to the positive, negative, and cognitive symptoms of psychosis in various disorders, and also how glutamate dysfunction might cause the downstream hyperdopaminergia discussed in the previous section, we will first review glutamate and its receptors and pathways. The Glutamate Neurotransmitter Network Glutamate is the major excitatory neurotransmitter in the central nervous system and is sometimes considered to be the "master switch" of the brain, since it can excite and turn on virtually all central nervous system neurons. In recent years, glutamate has attained a key theoretical role in the hypothesized pathophysiology of schizophrenia, of positive symptoms of psychosis in general, and also in a number of other psychiatric disorders, including depression. It is also now a key target of novel psychopharmacological agents for the treatment of schizophrenia and depression. The synthesis, metabolism, receptor regulation, and key pathways of glutamate are therefore critical to the functioning of the brain and will be reviewed here. Glutamate Synthesis Glutamate, or glutamic acid, is a neurotransmitter that is an amino acid. Its predominant use is not as a Glutamate Is Recycled and Regenerated: Part 1 glutamate 2 EAAT GLU (glutamate) neurotransmitter, but as an amino acid building block for protein biosynthesis. When used as a neurotransmitter, it is synthesized from glutamine in glia, which also assist in the recycling and regeneration of more glutamate following glutamate release during neurotransmission. When glutamate is released from synaptic vesicles of glutamate neurons, it interacts with receptors in the synapse and is then transported into neighboring glia by a reuptake pump known as an excitatory amino acid transporter (EAAT) (Figure 4-20A). The presynaptic glutamate neuron and the postsynaptic site of glutamate neurotransmission may also have EAATs (not shown in the figures) but these EAATs do not appear to play as important a role in glutamate recycling and regeneration as the EAATs in glia (Figure 4-20A). After reuptake into glia, glutamate is converted into glutamine inside the glia by an enzyme known as glutamine synthetase (arrow 3 in Figure 4-20B). It is possible that glutamate is not simply reused but rather converted into glutamine, to keep it in a pool for neurotransmitter use, rather than being lost into the pool for protein synthesis. Glutamine is released from glia by reverse transport via a pump or transporter known as a specific neutral amino acid transporter (SNAT, arrow 4 in Figure 4-20C). Glutamine may also be transported out of glia by a second transporter known as a glial alanine– serine–cysteine transporter or ASC-T (not shown). When Figure 4-20A Glutamate is recycled and regenerated, part 1. After release of glutamate from the presynaptic neuron (1), it is taken up into glial cells via the excitatory amino acid transporter (EAAT) (2). glial cell

Glutamate Is Recycled and Regenerated: Part 2 glial cell glutamine E glutamate Glutamate Is Recycled and Regenerated: Part 3

SNAT glutamine reversed SNAT glial SNATs and ASC-Ts operate in the inward direction, they transport glutamine and other amino acids into glia. Here, they are reversed so that glutamine can get out of the glia and hop a ride into a neuron via a different type of neuronal SNAT, operating

inwardly in a reuptake manner (arrow 5 in Figure 4-20C). Once inside the neuron, glutamine is converted back into glutamate for use as a neurotransmitter by an enzyme in mitochondria called glutaminase (arrow 6 in Figure 4-20D). Glutamate is then transported into synaptic vesicles via a vesicular glutamate transporter (vGluT, arrow 7 in Figure 4-20D), where it is stored Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-20B Glutamate is recycled and regenerated, part 2. Once inside the glial cell, glutamate is converted into glutamine by the enzyme glutamine synthetase (3). glutamine synthetase Figure 4-20C Glutamate is recycled and regenerated, part 3. Glutamine is released from glial cells by a specific glial neutral amino acid transporter (SNAT) through the process of reverse transport (4), and then taken up by SNATs on glutamate neurons (5). glial cell glutamine for subsequent release during neurotransmission. Once released, glutamate's actions are stopped not by enzymatic breakdown, as in other neurotransmitter systems, but by removal by EAATs on neurons or glia, and the whole cycle is started again (Figures 4-20A–D). Synthesis of Glutamate Cotransmitters Glycine and D-Serine Glutamate systems are curious in that one of the key receptors for glutamate requires a cotransmitter in addition to glutamate in order to function. That receptor is the NMDA receptor, described below, and 97

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Glutamate Is Recycled and Regenerated: Part 4 glutamine E glutaminase glutamate vGluT the cotransmitter is either the amino acid glycine (Figure 4-21), or another amino acid, closely related to glycine, known as D-serine (Figure 4-22). Glycine is not known to be synthesized by glutamate neurons, so glutamate neurons must get the glycine they need for their NMDA receptors either from glycine neurons or from glia (Figure 4-21). Glycine neurons contribute only a small amount of glycine to glutamate synapses, since much of the glycine they release is taken back up into those neurons by a type of glycine reuptake pump known as the type 2 glycine transporter (GlyT2) (Figure 4-21). Thus, neighboring glia are thought to be the source of most of the glycine available for glutamate synapses. Glycine itself can be taken up into glia as well as into glutamate neurons from the synapse by a type 1 glycine transporter (GlyT1) (Figure 4-21). Glycine can also be taken up into glia by a glial SNAT (specific neutral amino acid transporter). Glycine is not known to be stored within synaptic vesicles of glia, but as we will learn below, the companion neurotransmitter D-serine is thought possibly to be stored within some type of storage vesicle within glia. Glycine in the cytoplasm of glia is nevertheless somehow available for release into synapses, and it escapes from glial cells by riding outside them and into the glutamate synapse on a reversed GlyT1 transporter (Figure 4-21). Once outside, glycine can get right back into the glia by an inwardly directed GlyT1, which functions as a reuptake pump and is the Figure 4-20D Glutamate is recycled and regenerated, part 4. Glutamine is converted into glutamate within the presynaptic glutamate neuron by the enzyme glutaminase (6) and taken up into synaptic vesicles by the vesicular glutamate transporter (vGluT), where it is stored for future release. glial cell main mechanism responsible for terminating the action of synaptic glycine (Figure 4-21). GlyT1 transporters are probably also located on the glutamate neuron, but any release or storage from the glutamate neuron is not well characterized (Figure 4-21). Glycine can also be synthesized from the amino acid L-serine, derived from the extracellular space, bloodstream, and diet, transported into glia by an L-serine transporter (LSER-T), and converted from L-serine into glycine by the glial enzyme serine hydroxymethyl-transferase (SHMT) (Figure 4-21). This enzyme works in both directions, either converting L-serine into glycine, or glycine into L-serine. How is the cotransmitter D-serine produced? D-serine is unusual in that it is a D-amino acid, whereas the 20 known essential amino acids are all L-amino acids, including D-serine's mirror

image amino acid L-serine. It just so happens that D-serine has high affinity for the glycine site on NMDA receptors, and that glia are equipped with an enzyme that can convert regular Lserine into the neurotransmitting amino acid D-serine by means of an enzyme that can go back and forth between D- and L-serine known as D-serine racemase (Figure 4-22). Thus, D-serine can be derived either from glycine or from L-serine, both of which can be transported into glia by their own transporters, and then glycine converted to L-serine by the enzyme SHMT, and finally L-serine converted into D-serine by the enzyme D-serine racemase (Figure 4-22). Interestingly, the D-serine so

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-21 NMDA receptor cotransmitter glycine is produced. Glutamate's actions at NMDA receptors are dependent in part upon the presence of a cotransmitter, either glycine or D-serine. Glycine can be derived directly from dietary amino acids and transported into glial cells either by a glycine transporter (GlyT1) or by a specific neutral amino acid transporter (SNAT). Glycine can also be produced both in glycine neurons and in glial cells. Glycine neurons provide only a small amount of the glycine at glutamate synapses, because most of the glycine released by glycine neurons is used only at glycine synapses and then taken back up into presynaptic glycine neurons via the glycine 2 transporter (GlyT2) before much glycine can diffuse to glutamate synapses. Glycine produced by glial cells plays a larger role at glutamate synapses. Glycine is produced in glial cells when the amino acid L-serine is taken up into glial cells via the L-serine transporter (L-SER-T), and then converted into glycine by the enzyme serine hydroxymethyl-transferase (SHMT). Glycine from glial cells is released into the glutamate synapse through reverse transport by GlyT1. Extracellular glycine is then transported back into glial cells via GlyT1. glycine GlyT2 glutamate neuron glycine neuron NMDA Receptor Cotransmitter Glycine Is Produced E L-serine L L SHMT SNAT NMDA receptors glial cell GlyT1 (reuptake) GlyT1 L-SER-T reversed GlyT1 (release) produced may be stored in some sort of vesicle in glia for subsequent release on a reversed glial D-serine transporter (D-SER-T) for neurotransmitting purposes at glutamate synapses containing NMDA receptors. D-serine's actions are not only terminated by synaptic reuptake via the inwardly acting glial D-SER-T, but also by an enzyme D-amino acid oxidase (DAO) that converts D-serine into inactive hydroxypyruvate (Figure 4-22). Below, we will discuss how the brain makes an activator of DAO, known not surprisingly as D-amino acid oxidase activator or DAOA. Glutamate Receptors There are several types of glutamate receptors (Figure 4-23 and Table 4-2), including the neuronal presynaptic reuptake pump (EAAT) and the vesicular transporter for glutamate into synaptic vesicles (vGluT), both of which are types of receptors. The general pharmacological

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-22 NMDA receptor cotransmitter D-serine is produced. Glutamate requires the presence of either glycine or D-serine at NMDA receptors in order to exert some of its effects there. In glial cells, the enzyme serine racemase converts L-serine into D-serine, which is then released into the glutamate synapse via reverse transport on the glial D-serine transporter (glial D-SER-T). L-serine's presence in glial cells is a result of either its transport there via the L-serine transporter (L-SER-T) or its conversion into L-serine from glycine via the enzyme serine hydroxymethyl-transferase (SHMT). Once D-serine is released into the synapse, it is taken back up into the glial cell by a reuptake pump called D-SER-T. Excess D-serine within the glial cell can be destroyed by the enzyme D-amino acid oxidase (DAO), which converts D-serine into hydroxypyruvate (OH-pyruvate). glutamate neuron NMDA Receptor Cotransmitter D-Serine Is Produced L L D D D D L SNAT L-SER-T SHMT D-serine racemase DAO OH-pyruvate D glutamate D-

serine L-serine glycine L D glial D-SER-T (reuptake) GlyT1 reversed glial D-SER-T (release) properties of various transporters are discussed in Chapter 2. Shown also on the presynaptic neuron as well as the postsynaptic neuron are metabotropic glutamate receptors (Figure 4-23). Metabotropic glutamate receptors are those glutamate receptors that are linked to G proteins. The general pharmacological properties of G-protein-linked receptors are also discussed in Chapter 2. There are at least eight subtypes of metabotropic glutamate receptors, organized into three separate groups (Table 4-2). Research suggests that Group II and Group III metabotropic receptors can occur presynaptically, where they function as autoreceptors to block glutamate release (Figures 4-23 and 4-24). Drugs that stimulate these presynaptic autoreceptors as agonists may therefore reduce glutamate release. Group I metabotropic glutamate receptors on the other hand may be located predominantly postsynaptically, where they hypothetically interact with other postsynaptic glutamate receptors to facilitate and strengthen responses mediated by ligand-gated ion-channel receptors for glutamate during excitatory glutamatergic neurotransmission (Figure 4-23).

Glutamate Receptors vGluT EAAT NMDA receptor AMPA receptor kainate receptor postsynaptic metabotropic receptor NMDA (N-methyl-D-asparate), AMPA (α-amino3-hydroxy-5-methyl-4-isoxazole-propionic acid), and kainate receptors for glutamate, named after the agonists that selectively bind to them, are all members of the ligand-gated ion-channel family of receptors (Figure 4-23 and Table 4-2). These ligand-gated ion channels are also known as ionotropic receptors and also as ion-channel-linked receptors. The general pharmacological properties of ligand-gated ion channels are discussed in Chapter 3. They tend to be postsynaptic and work together to modulate excitatory postsynaptic neurotransmission triggered by glutamate. Specifically, AMPA and kainate receptors may mediate fast, excitatory neurotransmission, allowing sodium to enter the neuron to depolarize it (Figure 4-25). NMDA receptors in the resting state are normally blocked by magnesium, Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-23 Glutamate receptors. Shown here are receptors for glutamate that regulate its neurotransmission. The excitatory amino acid transporter (EAAT) exists presynaptically and is responsible for clearing excess glutamate out of the synapse. The vesicular transporter for glutamate (vGluT) transports glutamate into synaptic vesicles, where it is stored until used in a future neurotransmission. Metabotropic glutamate receptors (linked to G proteins) can occur either pre- or postsynaptically. Three types of postsynaptic glutamate receptors are linked to ion channels, and are known as ligand-gated ion channels: N-methyl-D-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4isoxazole-propionic acid (AMPA) receptors, and kainate receptors, all named for the agonists that bind to them. presynaptic metabotropic receptor which plugs its calcium channel (Figure 4-26). NMDA receptors are an interesting type of “coincidence detector” that can open to let calcium into the neuron to trigger postsynaptic actions from glutamate neurotransmission only when three things occur at the same time (Figures 4-26 and 4-27): (1) glutamate occupies its binding site on the NMDA receptor (2) glycine or D-serine binds to its site on the NMDA receptor (3) depolarization occurs, allowing the magnesium plug to be removed Some of the many important signals by NMDA receptors that are activated when NMDA calcium channels are opened include long-term potentiation and synaptic plasticity, as will be explained later in this chapter. 101

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Table 4-2 Glutamate receptors Metabotropic Group I mGluR1 mGluR5 Group II mGluR2 mGluR3 Group III mGluR4 mGluR6 mGluR7 mGluR8 Ionotropic

(ligand-gated ion channels; ion-channel-linked receptors) Functional class Gene family Agonists Antagonists AMPA GluR1 Glutamate GluR2 AMPA GluR3 Kainate GluR4 Kainate GluR5 Glutamate GluR6 Kainate GluR7 KA1 KA2 NMDA NR1 Glutamate NR2A Aspartate NR2B NMDA MK801 NR2C Ketamine NR2D PCP (phencyclidine) Key Glutamate Pathways in the Brain Glutamate is a ubiquitous excitatory neurotransmitter that seems to be able to excite nearly any neuron in the brain. That is why it is sometimes called the “master switch.” Nevertheless, there are about a half-dozen specific glutamatergic pathways that are of particular relevance to psychopharmacology and especially to the pathophysiology of schizophrenia (Figure 4-28). They are: (a) Cortico-brainstem (b) Cortico-striatal (c) Hippocampal-striatal (d) Thalamo-cortical (e) Cortico-thalamic (f) Cortico-cortical (direct) (g) Cortico-cortical (indirect) (a) Cortico-brainstem glutamate pathways. A very important descending glutamatergic pathway projects from glutamatergic cortical pyramidal neurons to brainstem neurotransmitter centers, including the raphe for serotonin, the ventral tegmental area (VTA) and substantia nigra for dopamine, and the locus coeruleus for norepinephrine (pathway a in Figure 4-28). This pathway is the corticobrainstem glutamate pathway, and is a key regulator of neurotransmitter release. Direct innervation of monoamine neurons in the brainstem by these excitatory cortico-brainstem glutamate neurons stimulates neurotransmitter release, whereas indirect innervation of monoamine neurons by

A B Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-24 Metabotropic glutamate autoreceptors. Groups II and III metabotropic glutamate receptors can exist presynaptically as autoreceptors to regulate the release of glutamate. When glutamate builds up in the synapse (A), it is available to bind to the autoreceptor, which then inhibits glutamate release (B). mGluR type II/III presynaptic autoreceptor mGluR type II/III presynaptic autoreceptor 103

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-25 Glutamate at AMPA and kainate receptors. When glutamate binds to AMPA and kainate receptors, this leads to fast excitatory neurotransmission and membrane depolarization. Sustained binding of the agonist glutamate will lead to receptor desensitization, causing the channel to close and be transiently unresponsive to agonist. AMPA, kainate receptors desensitized prolonged agonist glutamate agonist resting Na+ K+ open & depolarized fast excitatory neurotransmission closed & desensitized Figure 4-26 Magnesium as a negative allosteric modulator. Magnesium is a negative allosteric modulator at NMDA glutamate receptors. Opening of NMDA glutamate receptors requires the presence of both glutamate and glycine, each of which bind to a different site on the receptor. When magnesium is also bound and the membrane is not depolarized, it prevents the effects of glutamate and glycine and thus does not allow the ion channel to open. In order for the channel to open, depolarization must remove magnesium while both glutamate and glycine are bound to their sites on the ligand-gated ion-channel complex. resting but blocked by Mg++ co-agonists open the channel, but it is blocked by Mg++

- not depolarized glutamate glycine NMDA receptors co-agonists Mg++ open & unblocked depolarization & other mechanisms Na+ Ca++ Mg++ these excitatory cortico-glutamate neurons via γ-aminobutyric acid (GABA) interneurons in the brainstem blocks neurotransmitter release. (b) Cortico-striatal glutamate pathways. A second descending glutamatergic output from cortical pyramidal neurons projects to the striatal complex (pathway b in Figure 4-28). This pathway is known as the cortico-striatal glutamate pathway. This descending glutamate pathway terminates on GABA neurons destined for a

relay station in another part of the striatal complex called the globus pallidus. (c) Hippocampal-accumbens glutamate pathway. Another key glutamate pathway projects from the hippocampus to the nucleus accumbens and is known as the hippocampal-accumbens glutamate pathway (c in Figure 4-28). Specific theories link this particular pathway to schizophrenia (see below). Like the cortico-striatal glutamate pathway (b in Figure 4-28), the hippocampal glutamate projection to the nucleus accumbens (c in Figure 4-28) also terminates on GABA neurons there that in turn project to a relay station in the globus pallidus. (d) Thalamo-cortical glutamate pathway. The thalamocortical glutamate pathway (d in Figure 4-28) brings

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-27 Signal propagation via glutamate receptors. (A) On the left is an AMPA receptor with its sodium channel in the resting state, allowing minimal sodium to enter the cell in exchange for potassium. On the right is an NMDA receptor in the resting state, with magnesium blocking the calcium channel and glycine bound to its site. (B) When glutamate arrives, it binds to the AMPA receptor, causing the sodium channel to open, thus increasing the flow of sodium into the dendrite and potassium out of the dendrite. This causes the membrane to depolarize and triggers a postsynaptic nerve impulse. (C) Depolarization of the membrane removes magnesium from the calcium channel. This, coupled with glutamate binding to the NMDA receptor in the presence of glycine, causes the NMDA receptor to open and allow calcium influx. Calcium influx through NMDA receptors contributes to long-term potentiation, a phenomenon that may be involved in long-term learning, synaptogenesis, and other neuronal functions. resting Na+ K+ Mg++ resting but blocked by Mg++ resting but blocked by Mg++ activated depolarization long-term potentiation glutamate glutamate glycine A B C activated activated Na+ Ca++ information from the thalamus back into the cortex, often to process sensory information. (e) Cortico-thalamic glutamate pathway. A fifth glutamate pathway, known as the cortico-thalamic glutamate pathway, projects directly back to the thalamus, where it may direct the manner in which neurons react to sensory information (pathway e in Figure 4-28). (f) Direct cortico-cortical glutamate pathways. Finally, a complex of many cortico-cortical glutamate pathways is present within the cortex (Figure 4-28, pathways f and g). On the one hand, pyramidal neurons can excite each other within the cerebral cortex via direct synaptic input from their own neurotransmitter glutamate (f in Figure 4-28). (g) Indirect cortico-cortical glutamate pathways. On the other hand, one pyramidal neuron can inhibit another via indirect input, namely via interneurons that release GABA (g in Figure 4-28). The NMDA Glutamate Hypofunction Hypothesis of Psychosis: Faulty NMDA Neurotransmission at Glutamate Synapses on GABA Interneurons in Prefrontal Cortex Although NMDA receptors and synapses are ubiquitous throughout the brain, the NMDA glutamate hypofunction

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-28 Glutamate pathways in the brain. Although glutamate can have actions at virtually all neurons in the brain, there are key glutamate pathways particularly relevant to schizophrenia. (a) The cortico-brainstem glutamate projection is a descending pathway that projects from cortical pyramidal neurons in the prefrontal cortex to brainstem neurotransmitter centers (raphe nucleus, locus coeruleus, ventral tegmental area, substantia nigra) and regulates neurotransmitter release. (b) Another descending glutamatergic pathway projects from the prefrontal cortex to the striatal complex (cortico-striatal glutamate pathway). (c) There is also a glutamatergic projection from the ventral hippocampus to the nucleus accumbens. (d) Thalamo-cortical glutamate pathways ascend from the thalamus and innervate

pyramidal neurons in the cortex. (e) Cortico-thalamic glutamate pathways descend from the prefrontal cortex to the thalamus. (f) Intracortical pyramidal neurons can communicate directly with each other via the neurotransmitter glutamate; these pathways are known as direct cortico-cortical glutamatergic pathways and are excitatory. (g) Intracortical pyramidal neurons can also communicate via GABAergic interneurons; these indirect cortico-cortical glutamate pathways are therefore inhibitory. Key Glutamate Pathways brainstem neurotransmitter centers striatum thalamus nucleus accumbens f b d a c e g theory of psychosis suggests that psychosis may be caused by dysfunction of glutamate synapses at a specific site: namely, at certain GABA interneurons in the prefrontal cortex (see g in Figure 4-28 and Figures 4-29A, 4-29B, and 4-29C). Dysfunction hypothetically can be caused by neurodevelopmental problems in schizophrenia (Figure 4-29B, box 1A), by drug toxicity in ketamine/ phencyclidine abuse (Figure 4-29B, box 1B), or by neurodegenerative problems in dementia (Figure 4-29C). First, interference with normal neurotransmission at these sites between glutamate and GABA neurons could hypothetically be due to neurodevelopmental abnormalities genetically and environmentally programmed in schizophrenia (compare Figure 4-29A, box 1 with Figure 4-29B, box 1A). The loss of function of these inhibitory GABA interneurons (Figure 4-29B, box 2) causes glutamate neurons that they innervate downstream to become “disinhibited” and thus hyperactive (see Figure 4-29B, box 3). Other problems with these GABA neurons in schizophrenia may be that they also have deficits in the enzyme that makes their own neurotransmitter GABA (namely, decreased activity of GAD67 [glutamic acid decarboxylase]), causing a compensatory increase in the postsynaptic amount of the α2 subunit-containing GABAA receptors in the postsynaptic axon initial segment of the pyramidal neurons they innervate (Figure 4-29B, box 2; compare with Figure 4-29A, box 2). Both ketamine and phencyclidine (PCP) can cause psychosis with some of the same clinical characteristics as the psychosis of schizophrenia (Table 4-1). Both agents also block NMDA receptors as antagonists at a site inside the ion channel (Figure 4-30). The mechanism of their psychotomimetic actions is hypothesized to be blocking NMDA receptors at the same sites on GABA interneurons as hypothesized for the neurodevelopmental abnormalities in schizophrenia (compare Figure 4-29B, boxes 1A and 1B). In the case of schizophrenia, the NMDA hypofunction is hypothesized to be caused neurodevelopmentally by genetic and environmental

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-29A Hypothetical site of glutamate dysfunction in psychosis, part 1. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons. (1) Glutamate is released from an intracortical pyramidal neuron and binds to an NMDA receptor on a GABAergic interneuron. (2) GABA is then released from the interneuron and binds to GABA receptors of the α2 subtype that are located on the axon of another glutamate pyramidal neuron. (3) This inhibits the pyramidal neuron, thus reducing the release of cortical glutamate. NMDA receptor Glu 2 GABA R GABA GAD67 GAT1 Glu α

Figure 4-29B Hypothetical site of glutamate dysfunction in psychosis, part 2. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons in the presence of hypofunctional NMDA receptors. (1) Glutamate is released from an intracortical pyramidal neuron. However, the NMDA receptor that it would normally bind to is hypofunctional, preventing glutamate from exerting its effects at the receptor. This could be due to neurodevelopmental abnormalities (1A) or to drug toxicity resulting from ketamine or phencyclidine abuse (1B). (2) This prevents GABA release from the interneuron; thus, stimulation of α2 GABA receptors on the axon of

another glutamate neuron does not occur. (3) When GABA does not bind to the α2 GABA receptors on its axon, the pyramidal neuron is no longer inhibited. Instead, it is disinhibited and overactive, releasing excessive glutamate into the cortex. 1A neurodevelopmental hypofunctional NMDA receptor and synapse in schizophrenia hypofunctional NMDA receptor and synapse after ketamine ketamine Glu Glu 3 GABA R GABA GAD67 GAT1 1B Glu α

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-29C Hypothetical site of glutamate dysfunction in psychosis, part 3. Shown here is a close-up of intracortical pyramidal neurons communicating via GABAergic interneurons in the presence of neurodegeneration associated with dementia. Not all patients with dementia develop symptoms of psychosis. It may be that, in those that do, the neurodegeneration associated with the accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact, at least temporarily. The end result may be excessive glutamate activity in the cortex, as in schizophrenia (see Figure 4-29B, box 1A) or in ketamine abuse (see Figure 4-29B, box 1B). Glu loss of cortical neurons from neurodegeneration stroke Lewy body plaque tangle input (Figure 4-29B, box 1A), whereas in ketamine/PCP psychosis, the NMDA hypofunction is hypothesized to be caused by acute and reversible pharmacological actions directly at NMDA receptors (Figure 4-29B, box 1B). In neurodegenerative disorders that cause Alzheimer disease and other types of dementia, the accumulation of amyloid plaques, tau tangles, Lewy bodies, and/or strokes progressively knocks out neurons as the disease

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY of preserving these particular glutamate neurons is explained further below. Knocking out some neurons while preserving some others could explain why only certain patients develop psychosis as neurodegeneration in dementia progresses. Linking the NMDA Glutamate Hypofunction Hypothesis of Psychosis to the Dopamine Hypothesis of Psychosis What are the consequences to dopamine activity of the hypothetical dysconnectivity of glutamatergic pyramidal neurons with these particular GABAergic interneurons in schizophrenia, ketamine/PCP toxicity, and dementia (Figures 4-29A, 4-29B, and 4-29C)? The short answer is that it theoretically leads to the very same dopamine hyperactivity already discussed above for the dopamine hypothesis of psychosis. Certain glutamate neurons directly innervate VTA/ mesostriatal dopamine neurons, and when they lose their GABA inhibition from any cause they become progresses (Figure 4-29C). Up to half of patients with dementia may at some point in their clinical course experience psychosis (see Chapter 12 for a more extensive discussion on the behavioral symptoms of dementia). Why do some dementia patients experience psychosis and others not? One hypothesis is that in patients with dementia-related psychosis, the neurodegeneration has progressed in such a way as to knock out some glutamatergic pyramidal neurons and GABAergic interneurons in the prefrontal cortex while leaving other glutamatergic pyramidal neurons intact, at least temporarily (Figure 4-29C). This theoretically creates the same dysconnectivity (Figure 4-29C), but by a different mechanism, that occurs in both schizophrenia (Figure 4-29B, box 1A) and in ketamine/ PCP psychosis (Figure 4-29B, box 1B). Hypothetically this occurs in only some patients with dementia and specifically only in those whose pattern of neuronal degeneration leaves glutamate neurons that drive dopamine neurons downstream intact. The significance Figure 4-30 Site of action of PCP and ketamine. The anesthetic ketamine binds as an antagonist to the open channel conformation of the NMDA receptor. Specifically, it binds to a site within the calcium channel of this receptor, which is often termed the PCP site because it is also where phencyclidine

(PCP) binds as an antagonist. A B ketamine or PCP PCP site (in the ion channel) Site of Action of PCP and Ketamine: Bind to Open Channel at PCP Site to Block NMDA Receptor

hyperactive and stimulate too much dopamine release from the mesostriatal projections of those dopamine neurons (Figures 4-31 through 4-34). As discussed in the previous section, neurodevelopmentally deficient NMDA synapses (Figure 4-29B, box 1A) hypothetically cause this downstream glutamate hyperactivity in schizophrenia (Figures 4-31 and 4-32). In PCP/ketamine abuse, the drug acting directly at these synapses (Figure 4-29B, box 1B) causes the downstream glutamate hyperactivity (Figure 4-33), and in dementia, neurodegeneration knocks out cortical neurons (Figure 4-29C) to cause this glutamate hyperactivity (Figure 4-34). In turn, glutamate hyperactivity from any cause (Figures 4-31 through 4-34) theoretically results in dopamine hyperactivity and the positive symptoms of psychosis. Hyperactive glutamate output from the prefrontal cortex can hypothetically not only potentially explain positive symptoms, but also negative symptoms in the case of schizophrenia. When the cascade from NMDA hypofunction to glutamate hyperactivity enhances dopamine release (Figure 4-31), it hypothetically causes positive symptoms of psychosis; however, there is hypothetically a second population of glutamate neurons that project to a different set of VTA neurons, namely, those that are mesocortical rather than mesostriatal/ mesolimbic (Figure 4-35). This circuit actually inhibits dopamine release, due to the presence of a key GABA interneuron in VTA for mesocortical dopamine projections to the prefrontal cortex that is hypothetically lacking for mesostriatal/mesolimbic projection to the striatum (compare Figures 4-31B and 4-35B). Hyperactivity of these specific glutamate neurons innervating mesocortical dopamine neurons in Figure 4-35B would lead to the opposite effects of those discussed for the population of glutamate neurons innervating mesostriatal dopamine neurons: namely, reduced dopamine release, and this hypothetically causes the negative, cognitive, and affective symptoms of psychosis (Figure 4-35B). THE SEROTONIN HYPOTHESIS OF PSYCHOSIS AND SCHIZOPHRENIA The serotonin theory of psychosis proposes that hyperactivity/imbalance of serotonin (5-hydroxytryptamine, 5HT) activity, particularly at serotonin 5HT2A receptors, can result in psychosis (Table 4-1 and Figure 4-1). Disruption of 5HT functioning, leading to positive symptoms of psychosis, can be hypothetically due to the neurodevelopmental abnormalities in schizophrenia, to the neurodegeneration in Parkinson’s Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks disease as well as in Alzheimer disease and other dementias, and to drugs such as LSD, mescaline, and psilocybin (Figure 4-1 and Table 4-1). Interestingly, psychoses associated with serotonin imbalance tend to have more visual DA neuron A Psychosis in Schizophrenia hypofunctional NMDA glutamate synapse in schizophrenia normal HIGH direct innervation so excitatory glu causes DA hyperactivity B positive symptoms overactivation Figure 4-31 NMDA receptor hypofunction and psychosis in schizophrenia, part 1. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If NMDA receptors on cortical GABA interneurons are hypoactive, then GABA release is inhibited and the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens. This is the theoretical biological basis for the mesolimbic dopamine hyperactivity thought to be associated with the positive symptoms of psychosis. 111

Figure 4-32 NMDA receptor hypofunction and psychosis in schizophrenia, part 2. Hypofunctional NMDA receptors at glutamatergic synapses in the ventral hippocampus can also contribute to mesolimbic dopamine hyperactivity. (A) Glutamate released in the ventral hippocampus binds to NMDA receptors on a GABAergic interneuron, stimulating the release of GABA. The GABA binds at receptors on a pyramidal glutamate neuron that projects to the nucleus accumbens; this prevents excessive glutamate release there. The normal release of glutamate in the nucleus accumbens allows for normal activation of a GABAergic neuron projecting to the globus pallidus, which in turn allows for normal activation of a GABAergic neuron projecting to the ventral tegmental area (VTA). This leads to normal activation of the mesolimbic dopamine pathway from the VTA to the nucleus accumbens. (B) If NMDA receptors on ventral hippocampal GABA interneurons are hypoactive, then the glutamatergic pathway to the nucleus accumbens will be overactivated, leading to excessive release of glutamate in the nucleus accumbens. This will lead to excessive stimulation of GABAergic neurons projecting to the globus pallidus, which in turn will inhibit release of GABA from the globus pallidus into the VTA. This will lead to disinhibition of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens. VTA A B striatum globus pallidus nucleus accumbens ventral hippocampus VTA striatum globus pallidus nucleus accumbens ventral hippocampus hypofunctional NMDA glutamate synapse Psychosis in Schizophrenia

DA neuron A Psychosis in Ketamine/PCP NMDA glutamate receptor blocked by ketamine/PCP normal HIGH ketamine direct innervation so excitatory glu causes DA hyperactivity B positive symptoms overactivation Figure 4-33 NMDA receptor blockade and psychosis in ketamine abuse. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If ketamine blocks NMDA receptors on cortical GABA interneurons, then GABA release is inhibited and the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens. hallucinations, whereas those associated principally with dopamine have more auditory hallucinations. In order to understand how hyperactivity of serotonin at 5HT2A receptors could lead to the positive symptoms of psychosis in various disorders, we will first review serotonin and its extensive set of receptors and pathways. Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks DA neuron A Psychosis in Dementia Neurodegeneration of glutamate/GABA connections normal stroke Lewy body plaque tangle HIGH delusions and auditory hallucinations visual hallucinations B positive symptoms overactivation Figure 4-34 Neurodegeneration and psychosis in dementia. (A) The cortical brainstem glutamate projection communicates with the mesolimbic dopamine pathway in the ventral tegmental area (VTA) to regulate dopamine release in the nucleus accumbens. (B) If neurodegeneration leads to the destruction of some glutamatergic neurons and some GABAergic interneurons, but not others, then this could lead to excessive release of glutamate in various brain regions. In the VTA, this could lead to excessive stimulation of the mesolimbic dopamine pathway and thus excessive dopamine release in the nucleus accumbens, resulting in delusions and auditory hallucinations. In the visual cortex, excessive glutamatergic activity could result in visual hallucinations. The Serotonin Neurotransmitter Network Serotonin, better known as 5HT (5-hydroxytryptamine), is a monoamine neurotransmitter which regulates a brain network that is one of the most targeted by psychotropic 113

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Mesocortical Pathway A Negative and Cognitive Symptoms in Schizophrenia hypofunctional NMDA glutamate synapse in schizophrenia normal LOW (SIGH) B glutamate hyperactivity causes key GABA interneurons to inhibit DA release negative symptoms cognitive symptoms affective symptoms Figure 4-35 NMDA receptor hypofunction and negative symptoms of schizophrenia. (A) The cortical brainstem glutamate projection communicates with the mesocortical dopamine pathway in the ventral tegmental area (VTA) via GABAergic interneurons, thus regulating dopamine release in the prefrontal cortex. (B) If NMDA receptors on cortical GABA interneurons are hypoactive, then the cortical brainstem pathway to the VTA will be overactivated, leading to excessive release of glutamate in the VTA. This will lead to excessive stimulation of the brainstem GABA interneurons, which in turn leads to inhibition of mesocortical dopamine neurons. This reduces dopamine release in the prefrontal cortex and is the theoretical biological basis for the negative symptoms of psychosis. drugs. For example, many if not most drugs that treat psychosis and mood target, in one way or another, the serotonin network. Thus, a thorough understanding of serotonin neurotransmission is critical in order to grasp some of the most important principles across the breadth of psychopharmacology, from psychosis to mood and beyond. Serotonin Synthesis and Termination of Action Synthesis of 5HT begins with the amino acid tryptophan, which is transported into the brain from the plasma to serve as the 5HT precursor (Figure 4-36). Two synthetic enzymes then convert tryptophan into serotonin: firstly, tryptophan hydroxylase (TRY-OH) converts tryptophan into 5-hydroxytryptophan (5HTP), and then aromatic amino acid decarboxylase (AAADC) converts 5HTP into 5HT (Figure 4-36). After synthesis, 5HT is taken up into synaptic vesicles by a vesicular monoamine transporter (VMAT2) and stored there until it is used during neurotransmission. 5HT action is terminated when it is enzymatically destroyed by monoamine oxidase (MAO) and converted into an inactive metabolite (Figure 4-37). Serotonergic neurons themselves contain monoamine oxidase B (MAO-B), but it has low affinity for 5HT, so 5HT is only enzymatically degraded when its intracellular concentrations are high. The 5HT neuron also has a presynaptic transport pump for serotonin called the serotonin transporter (SERT) that is unique for 5HT and that terminates serotonin’s actions by pumping it out of the synapse and back into the presynaptic nerve terminal where it can be re-stored in synaptic vesicles for subsequent use in another neurotransmission (Figure 4-37). Unlike dopamine neurons, some of which do not contain their dopamine transporter (DAT), all 5HT neurons are thought to contain SERTs. Also, there are functional polymorphisms in the gene that codes for SERT, which have become of intense interest since they alter the amount of synaptic serotonin and may help predict which patients are less likely to respond as well as more likely to have side effects when given drugs for depression that block SERT. This will be discussed in more detail in Chapter 7 on treatments for mood disorders. 5HT Receptors: Overview Serotonin has more than a dozen receptors, and at least half of them have known clinical relevance (Figure 4-38). Only a few 5HT receptors are located on the serotonin neuron itself (5HT1A, 5HT1B/D, 5HT2B) (Figures 4-38 through 4-41), and their purpose is to regulate the presynaptic serotonin neuron directly, especially its firing and how it releases and stores its own serotonin. Just to be confusing, these same receptors can also be located postsynaptically, as can all known 5HT receptors. First, we describe how those 5HT receptors that are presynaptic

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-36 Serotonin is produced. Serotonin (5-hydroxytryptamine [5HT]) is produced from enzymes after the amino acid precursor tryptophan is transported into the serotonin neuron. Once transported into the serotonin neuron, tryptophan is converted by the enzyme tryptophan hydroxylase (TRY-OH) into 5-

hydroxytryptophan (5HTP), which is then converted into 5HT by the enzyme aromatic amino acid decarboxylase (AAADC). Serotonin is then taken up into synaptic vesicles via the vesicular monoamine transporter (VMAT2), where it stays until released by a neuronal impulse. Serotonin Is Produced 5HT (serotonin) VMAT2 E E

tryptophan transporter 5HTP TRY-OH AAADC tryptophan Figure 4-37 Serotonin's action is terminated. Serotonin's (5HT) action is terminated enzymatically by monoamine oxidase B (MAO-B) within the neuron when it is present in high concentrations. These enzymes convert serotonin into an inactive metabolite. There is also a presynaptic transport pump selective for serotonin, called the serotonin transporter (SERT), which clears serotonin out of the synapse and back into the presynaptic neuron. Serotonin Is Destroyed MAO-B destroys 5HT at high concentrations serotonin transporter (SERT) E Figure 4-38 Serotonin receptors. Presynaptic serotonin (5HT) receptors include 5HT1A, 5HT1B/D, and 5HT2B, all of which act as autoreceptors. There are also numerous postsynaptic serotonin receptors, which regulate other neurotransmitters in downstream circuits. 1A 1A 2A 2B 2B 2C 4 6 1B/D 1B/D + + + + + + + + Serotonin Receptor Subtypes regulate other neurotransmitters in downstream circuits (located on the serotonin neuron itself) regulate serotonin, and then we discuss how postsynaptic 5HT receptors regulate essentially every other neurotransmitter in a network of downstream brain circuits. Presynaptic Receptors: Serotonin Regulating Serotonin As for all monoamine neurons, the serotonin neuron has receptors both on its axon terminals (axon115

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-39 Serotonin (5HT) 1A autoreceptors. (A) Presynaptic 5HT1A receptors are autoreceptors located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors. (B) When serotonin is released somatodendritically, it binds to these 5HT1A receptors and causes a shutdown of 5HT neuronal impulse flow, depicted here as decreased electrical activity and a reduction in the release of 5HT from the synapse on the right. A B 5HT1A somatodendritic autoreceptor 1A 1A terminal autoreceptors) and on its dendrites and soma (somatodendritic autoreceptors), both to help regulate serotonin release (Figures 4-38 through 4-41). Both are considered to be presynaptic. Whereas the dopamine (earlier in this chapter and Figures 4-5 through 4-8) and norepinephrine (Chapter 6 and Figures 6-14

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-40 Serotonin (5HT) 2B autoreceptors. (A) Presynaptic 5HT2B receptors are autoreceptors located on the cell body and dendrites, and are therefore called somatodendritic autoreceptors. (B) When 5HT is released somatodendritically, it binds to these 5HT2B receptors and causes increased 5HT neuronal impulse flow, depicted here as increased electrical activity and increased release of 5HT from the synapse on the right. A B 5HT2B somatodendritic autoreceptor 2B 2B through 6-16) neurons have the same receptors at both ends, for the serotonin neuron, the axon-terminal receptors (with 5HT1B/D pharmacology) (Figures 4-38 and 4-41) are different from the somatodendritic receptors (with 5HT1A and 5HT2B pharmacology) (Figures 4-38 through 4-40).

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-41 Serotonin (5HT) 1B/D autoreceptors. Presynaptic 5HT1B/D receptors are autoreceptors located on the presynaptic axon terminal. They act by detecting the presence of 5HT in the synapse and causing a shutdown of further 5HT release. When 5HT builds up in the synapse (A), it is available to bind to the autoreceptor, which

then inhibits serotonin release (B). 5HT1B/D axon terminal autoreceptor 5HT1B/D axon terminal autoreceptor A B Presynaptic 5HT1A Receptors Located on the dendrites and cell bodies of serotonin neurons in the midbrain raphe (Figure 4-39A), these presynaptic somatodendritic 5HT1A receptors detect serotonin released from dendrites. How serotonin is released at the opposite end of the neuron from where its classic presynaptic nerve terminals are located is still not yet fully understood, but this appears to be an important process for how the serotonin neuron regulates release at the presynaptic end. When 5HT is released somatodendritically, it activates these 5HT1A autoreceptors and this causes a slowing of neuronal impulse flow through the serotonin neuron and a reduction of serotonin release from its axon terminal

(Figure 4-39B). Downregulation and desensitization of these presynaptic 5HT1A somatodendritic autoreceptors are thought to be critical to the antidepressant actions of drugs that block serotonin reuptake (discussed in Chapter 7 on treatments for mood disorders). Presynaptic 5HT2B receptors Recently, it has been discovered that the somatodendritic area of 5HT neurons is regulated by a second receptor, the 5HT2B receptor (Figure 4-40), which acts in opposition to the 5HT1A receptor. That is, 5HT2B receptors activate the serotonin neuron to cause more impulse flow and increased serotonin release from presynaptic nerve terminals. Thus, it appears at this point in time that the 5HT2B receptors are “feed forward” receptors whereas 5HT1A receptors are “negative feedback” receptors. It is not yet clear which 5HT neurons in the midbrain raphe contain 5HT1A receptors, which contain 5HT2B receptors, and which contain both. Clearly, much more is yet to be learned about 5HT2B receptors and the drugs that act upon them. However, it already appears likely that the balance between actions at presynaptic somatodendritic 5HT1A versus 5HT2B receptors is important in regulating how much serotonin activity and serotonin release is occurring at serotonin presynaptic nerve terminals throughout the brain. Presynaptic 5HT1B/D Receptors Presynaptic 5HT receptors on the axon terminal have the 5HT1B/D subtype and act as negative-feedback autoreceptors to detect the presence of 5HT, causing a shutdown of further 5HT release and 5HT neuronal impulse flow (Figure 4-41). When 5HT is detected in the synapse by presynaptic 5HT receptors on axon terminals, it occurs via a 5HT1B/D receptor, which is also called a terminal autoreceptor (Figure 4-41). In the case of the 5HT1B/D terminal autoreceptor, 5HT occupancy of this receptor causes a blockade of 5HT release (Figure 4-41B). Postsynaptic Serotonin Regulates Other Neurotransmitters in Downstream Brain Circuits It turns out that each neurotransmitter not only controls its own synthesis and release from presynaptic sites; each neurotransmitter also controls the actions of the other neurotransmitters via postsynaptic actions and networks of brain circuits. So, if every neurotransmitter regulates every other neurotransmitter, it’s complicated! No longer can we think of a neurotransmitter acting only synaptically; neurotransmitters also act trans-synaptically in brain circuits that both control other neurotransmitters and are controlled by other neurotransmitters. So, how Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks are we supposed to figure out what is the net effect of a drug acting at a receptor if these receptors are all over the place and if they do different things at different sites? Furthermore, how can we possibly understand psychiatric illnesses involving serotonin if this same neurotransmitter does quite different things in different circuits and in different synapses? The answer in part is to step back and appreciate the wonderful complexity of the brain’s neurotransmitter systems, and that we are only beginning to scratch the surface of how these neurotransmitter systems theoretically work as the substrates of normal feelings and emotions as well as the symptoms of mental illnesses. Here we will hazard a mere glimpse of how neurotransmitters regulate each

other’s neurotransmission by acting through networks of neurons communicating with each other, not only with different neurotransmitters at different nodes in the various neuronal networks, but with different receptor subtypes for the same neurotransmitters at nodes or connecting points within these neuronal networks. Hypothetically, when neural networks are experiencing inefficient information processing (i.e., one could say they are “out of tune”), this in part mediates the symptoms of mental illnesses. A corollary to this notion is that when our drugs “tune” these neuronal networks by their actions at specific receptor subtypes, they have the potential for improving the efficiency of information processing in these neuronal networks, thereby reducing the symptoms of mental illnesses. Although oversimplified and perhaps a bit naïvely reductionistic in presentation, this discussion is the next step past the now dated notion that mental illnesses and drugs that treat them are simply “chemical imbalances” at synapses. In considering the modern neurobiology of mental illnesses and their treatments, one would be well advised to remain humble about what we know and perhaps recall how The Devil’s Dictionary (by Ambrose Bierce) defined the mind in the nineteenth century: MIND, n. A mysterious form of matter secreted by the brain. Its chief activity consists in the endeavor to ascertain its own nature, the futility of the attempt being due to the fact that it has nothing but itself to know itself with. Constructing the 5HT Network Serotonin, as do all neurotransmitters, interacts downstream with other neurons and the neurotransmitters these neurons release (Figures 4-42 and 4-43). Thus, what happens after serotonin is released 119

 serotonin receptor subtype where it is interacting, and upon whether the postsynaptic neuron itself releases the excitatory neurotransmitter glutamate or the inhibitory neurotransmitter GABA. When

serotonin has neurotransmission simultaneously in both excitatory and inhibitory situations, which predominates? The short answer is that it seems to depend upon whether a specific receptor is expressed in a specific location; the density of that receptor, with response more likely with densely depends not only upon what receptor it interacts with (see nine different serotonin receptors in Figure 4-42), but also very much upon what neuron it is communicating with and the neurotransmitter that neuron

releases (see interactions with glutamate and GABA neurons in Figure 4-42 and with glutamate, GABA, norepinephrine (NE), dopamine (DA), histamine (HA), and acetylcholine (ACh) in Figure 4-43). Note all the options that serotonin has for control: it can excite or inhibit depending upon the Figure 4-42 Serotonin (5HT) regulates glutamate release directly and indirectly. Most 5HT receptor subtypes are postsynaptic heteroreceptors and reside on the neurons that release any of a number of neurotransmitters; thus,

serotonin (like all neurotransmitters) can regulate downstream release of numerous neurotransmitters. Left: 5HT’s direct influence on glutamate pyramidal neurons can be both excitatory (e.g., at 5HT2A, 5HT2C, 5HT4, 5HT6, and 5HT7 receptors) and inhibitory (at 5HT1A, 5HT5, and possibly postsynaptic 5HT1B heteroreceptors). Glutamate neurons, in turn, synapse with the neurons of most other neurotransmitters to regulate their downstream release. Right: Glutamate output can also be

controlled indirectly by 5HT receptors on inhibitory GABAergic interneurons. With so many ways to stimulate and to inhibit the glutamate neurons, and with some 5HT receptors having opposing actions on glutamate release due to their presence on both glutamate neurons and GABA interneurons (e.g., 5HT2A), it seems that the coordinated actions of 5HT at its various receptors may serve to “tune” glutamate output and keep it in balance. The net effects of 5HT upon glutamate release depend on

the regional and cellular expression patterns of 5HT receptor subtypes, the density of 5HT receptors, and the local concentration of 5HT.

Raphe GABA GABA 5HT Glu Regulation of downstream release of DA, NE, ACh, HA, 5HT SERT SERT SERT 1A 2A 2A 1A 1B non-parvalbumin positive, regular-spiking, latespiking, or bursting GABA interneurons parvalbumin positive, fast-spiking GABA interneurons excitatory inhibitory :

PFC PFC Raphe 5HT Glu 5HT Receptors Regulate Glutamate Release Directly and Indirectly Through GABA Regulation of downstream release of DA, NE, ACh, HA, 5HT 5 7 1B 1A 2C 2A

-
-
-
-
-

G

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2A 1 1B R

5HT Interacts in a Neuronal Network to Regulate All Major Neurotransmitter Systems = GABA Glu 5HT ACh versus sparsely populated receptors; the sensitivity of a receptor to serotonin; and the amount of release and the firing rate of the serotonin neuron, with some receptors more sensitive to low levels of serotonin than others. Finally, it depends upon whether the interaction is direct (e.g., serotonin directly acting at a glutamate neuron – Figure 4-42, left – or a GABA neuron – Figure 4-42, right) or indirect (e.g., serotonin indirectly acting at glutamate neurons via a GABA neuron that itself innervates a glutamate neuron – Figure 4-42, right). Norepinephrine, dopamine, histamine, and acetylcholine can also receive input directly from serotonin neurons, especially at their cell bodies, or indirectly via glutamate and/or GABA neurons as intermediaries (Figure 4-43). Thus, it can readily be seen that a drug acting directly on serotonin neurons and their receptors not only can affect serotonin itself, but can have profound downstream effects on all the other neurotransmitters. Which ones are affected, in what priority, and at which sites are currently the subject of intense investigation. However, these networks and how they are organized can explain why a drug that acts Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-43 Serotonin (5HT) interacts in a neuronal network to regulate all major neurotransmitter systems. 5HT circuits arise from discrete brainstem nuclei, including the dorsal and median raphe nuclei.

These circuits project to a wide range of cortical and subcortical brain areas, including the prefrontal cortex (PFC) and the loci for the cell bodies of neurons of other neurotransmitters, such as the locus coeruleus (LC) for norepinephrine, the ventral tegmental area (VTA) for dopamine, the tuberomammillary nucleus of the hypothalamus (TMN) for histamine, and the basal forebrain (BF) for acetylcholine. Through these connections, the 5HT network may both modulate itself and directly and indirectly influence virtually all other neurotransmitter networks. Thus, it is not surprising that the 5HT network is thought to regulate a variety of behaviors, including mood, sleep, and appetite, or that dysregulation of the 5HT network has been implicated in many psychiatric disorders. PFC BF HA TMN DA VTA NE LC first and directly at a particular receptor of a particular neurotransmitter can have profound net effects on all sorts of neurotransmitters. Understanding a bit about neural networks can also be the foundation for beginning to grasp why the frequent practice of giving drugs with two or more mechanisms of action (or two different agents with two or more different actions) can have either additive/synergistic effects or canceling/antagonistic effects. This is reflected in the corresponding effects on drug efficacy and side effects. 5HT1A Receptors 5HT1A receptors can promote the release of other neurotransmitters (Figure 4-44). 5HT1A receptors are always inhibitory, but they are very frequently localized upon postsynaptic GABA neurons, which means that the net downstream effect in this case is actually excitatory (Figure 4-44). For example, 5HT1A receptors are located on GABA interneurons in the prefrontal cortex and these GABA interneurons in turn act to inhibit neurotransmitter release from glutamate neurons (see Figure 4-42B). 5HT1A 121

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY GABA Inhibiting Norepinephrine, Dopamine, and Acetylcholine Release Prefrontal Cortex 1A GABA GABA 5HT Raphe 1A NE GABA GABA 1A DA GABA GABA ACh ACh BF DA VTA A 5HT1A Stimulation Increases Release of Norepinephrine, Dopamine, and Acetylcholine Prefrontal Cortex 1A 1A GABA 5HT 5HT Raphe 1A A 1A 1A NE GABA 5HT 1A 1A 1A 5HT DA GABA ACh ACh DA BF BF = Basal Forebrain VTA = Ventral Tegmental Area LC = Locus Coeruleus VTA B Figure 4-44 Serotonin (5HT) 1A stimulation indirectly increases release of other neurotransmitters. (A) 5HT1A heteroreceptors on GABA interneurons in the prefrontal cortex can indirectly regulate the release of norepinephrine (NE), dopamine (DA), and acetylcholine (ACh). (B) Stimulation of 5HT1A receptors is inhibitory; thus, serotonin binding at these receptors could reduce GABA output and in turn disinhibit norepinephrine, dopamine, and acetylcholine release. NE LC NE LC

5HT1B Presynaptic Regulation of NE, DA, HA, and ACh in Prefrontal Cortex Baseline Neurotransmitter Release 5HT 1B Raphe NE 1B DA 1B HA 1B ACh A ACh HA BF TMN 5HT1B Inhibits Neurotransmitter Release 5HT 5HT 1B 1B Raphe 5HT 1B 1B 5HT 1B 1B 1B 5HT 1B 1B 1B BF = Basal Forebrain TMN = Tuberomammillary Nucleus VTA = Ventral Tegmental Area LC = Locus Coeruleus ACh HA BF TMN B Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-45 Serotonin (5HT) 1B stimulation decreases release of other neurotransmitters. (A) 5HT1B receptors on the presynaptic nerve terminals of norepinephrine (NE), dopamine (DA), acetylcholine (ACh), and histamine (HA) neurons can theoretically regulate the release of these neurotransmitters. (B) Stimulation of 5HT1B heteroreceptors on ACh, HA, DA, and NE neurons is inhibitory; thus, serotonin binding at these receptors could potentially decrease the release of these neurotransmitters. Prefrontal Cortex DA VTA NE LC Prefrontal Cortex DA VTA NE LC 123

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY 5HT2A Receptors Regulate Glutamate Release – But It's Complicated GABA 2A + 2A 2A 5HT Glu Raphe Regulation of downstream release of DA, NE, ACh, HA A GABA 2A

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2A 2A 5HT Glu Raphe non-parvalbumin positive, regular-spiking, latespiking, or bursting GABA interneurons Opposite effect on downstream release of DA, NE, ACh, HA B receptors located on other GABA interneurons also inhibit neurotransmitter release from presynaptic terminals of norepinephrine, dopamine, and acetylcholine neurons. Figure 4-46 Serotonin (5HT) 2A stimulation both promotes and inhibits glutamate release. 5HT2A receptors are always excitatory, but depending on their localization can either stimulate or inhibit glutamate release. (A) 5HT2A receptors are located on glutamate pyramidal neurons, and through the stimulation of these receptors can increase glutamate release. (B) However, 5HT2A receptors are also present on GABA interneurons and when stimulated cause GABAergic inhibition of glutamate. Thus, the net effects of 5HT2A stimulation – or of 5HT2A antagonism – on glutamate neurotransmission will depend on multiple factors, including the density of the receptors and the local concentration of 5HT. Prefrontal Cortex Prefrontal Cortex Shown in Figure 4-44A is the baseline condition where a low tonic GABA release allows only a correspondingly low baseline of norepinephrine, dopamine, and

acetylcholine release. However, when serotonin is released at 5HT1A receptors localized on GABA interneurons (Figure 4-44B), this receptor action inhibits the GABA interneurons, reducing their inhibitory GABA release and allowing an increase in the release of downstream norepinephrine, dopamine, and acetylcholine. Thus, serotonin action at these 5HT1A receptors facilitates downstream norepinephrine, dopamine, and acetylcholine release. As will be explained in subsequent chapters, many psychotropic drugs that treat psychosis, mood, and anxiety are 5HT1A agonists or partial agonists. 5HT1B Receptors 5HT1B receptors are inhibitory and can specifically inhibit neurotransmitter release from norepinephrine, dopamine, histamine, and acetylcholine neurons when these receptors are localized upon presynaptic nerve terminals of these neurons

(Figure 4-45). When a receptor for a neurotransmitter other than the one the neuron uses as its own neurotransmitter is present, it is called a “heteroreceptor” (literally, other receptor). In the case of 5HT1B receptors present on non-serotonin presynaptic nerve terminals, they are inhibitory and act to prevent release of those other neurotransmitters (Figure 4-45A). At baseline, some amount of neurotransmitter is shown being released from four different neurons in the prefrontal cortex: norepinephrine, dopamine, histamine, and acetylcholine (Figure 4-45A). However, when serotonin is released upon their presynaptic inhibitory 5HT1B heteroreceptors, this reduces the release of these four neurotransmitters (Figure 4-45B). Thus, serotonin inhibits norepinephrine, dopamine, histamine, and acetylcholine release at 5HT1B receptors. A few agents known to be 5HT1B antagonists that may thus enhance the release of these four neurotransmitters are used to treat depression and are discussed in Chapter 7 on drug treatments for mood disorders. 5HT2A Receptors 5HT2A receptors can both promote and inhibit the release of other neurotransmitters. That is, although 5HT2A receptors are always excitatory, the variability of their location in the brain means that these receptors can both facilitate and inhibit the release of various downstream neurotransmitters. For example, when 5HT2A receptors are localized on glutamate neurons, generally upon the apical dendrites of glutamate neurons, they are excitatory, leading to excitatory glutamate release on downstream targets (Figure 4-46A). On the other hand, when 5HT2A receptors are localized on GABA interneurons that innervate glutamate neurons, excitatory 5HT2A input to Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks the GABA interneuron leads to GABA release, and this GABA is inhibitory to the glutamate neuron it innervates, with opposite effects on neurons downstream to glutamate neurons (Figure 4-46B). Many drugs that treat psychosis and mood have 5HT2A antagonist properties and will be discussed extensively in Chapter 5 on drugs for psychosis and in Chapter 7 on drugs for mood disorders. Additionally, most hallucinogens have 5HT2A agonist properties and this will be discussed in Chapter 13 on drug abuse. 5HT2C Receptors 5HT2C receptors generally inhibit the release of downstream neurotransmitters. 5HT2C receptors are excitatory, postsynaptic, and are mostly present upon GABA interneurons (Figures 4-47A and 4-47B). This means that 5HT2C receptors have net inhibitory effects wherever their GABA interneurons go. For example, when those GABA interneurons with 5HT2C receptors on them innervate downstream norepinephrine or dopamine neurons, the net effect of 5HT is to inhibit norepinephrine and dopamine release (compare baseline levels of norepinephrine and dopamine in the prefrontal cortex in Figure 4-47A with the levels of norepinephrine and dopamine after serotonin release at 5HT2C receptors in Figure 4-47B). Agonists of 5HT2C receptors can treat obesity and antagonists of 5HT2C receptors treat psychosis and mood disorders. 5HT3 Receptors 5HT3 receptors located in the brainstem chemoreceptor trigger zone outside of the blood–brain barrier are well known for their role in centrally mediated nausea and vomiting. However, elsewhere in the central nervous system, especially in the prefrontal cortex, 5HT3 receptors are localized on a particular type of GABA interneuron (specifically that with the properties of not binding to a calcium dye called parvalbumin, and also having a characteristic GABA interneuron firing pattern that is regular-spiking, late-spiking, or bursting, see Figure 4-42, right). Just like 5HT2C receptors, 5HT3 receptors are excitatory upon the GABA neurons they innervate, meaning 5HT3 receptors also exert net inhibitory effects wherever their GABA interneurons go. 5HT3 receptors specifically inhibit the release of acetylcholine and norepinephrine at the cortical level (Figure 4-48). That is, interneurons containing 5HT3 receptors terminate upon the nerve endings of presynaptic acetylcholine and norepinephrine neurons to inhibit them (see baseline state with a low level of GABA release allowing a low level of acetylcholine and norepinephrine release in Figure 4-48A). Acetylcholine and norepinephrine release are reduced 125

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-47A Serotonin (5HT) 2C stimulation, part 1. Excitatory 5HT2C receptors are mostly present on GABA interneurons. When serotonin is absent, the GABA receptors are not stimulated, and thus downstream neurons, in this case norepinephrine (NE) and dopamine (DA) neurons projecting to the prefrontal cortex, are active. prefrontal cortex A brainstem neurotransmitter centers raphe VTA locus coeruleus DA release NE release 5HT neuron NE neuron DA neuron GABA interneurons overactivation 5HT2C receptors when GABA release is increased by serotonin exciting the interneuron at excitatory 5HT3 receptors (Figure 4-48B). Thus, serotonin acting at 5HT3 receptors inhibits both acetylcholine and norepinephrine release. 5HT3 antagonists, including some drugs that treat depression, would be expected to have the opposite effect, namely enhancing the release of acetylcholine and norepinephrine (discussed further in Chapter 7). One of the more important regulatory controls upon excitatory glutamate output from the prefrontal cortex is tonic inhibition by GABA interneurons receiving 5HT input upon their 5HT3 receptors (Figure 4-49A). When 5HT input onto these 5HT3 receptors is increased, the firing rate of the glutamatergic pyramidal neuron is diminished (Figure 4-49B). Not only does this reduce the excitatory effects of glutamate on a plethora of

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks glutamate reciprocally regulates serotonin (i.e., in a feedback loop that normally excites serotonin release from glutamate actions on serotonin cell bodies in the raphe, but now is diminished due to the inhibition of glutamate release by serotonin). This is but one simple example of reciprocal regulations of neurotransmitters by each other. downstream sites it innervates, it also specifically reduces the excitatory feedback loop of glutamate upon serotonin neurons at the level of the midbrain raphe (Figure 4-49B). So, not only does this circuit show serotonin regulating glutamate (i.e., reducing glutamate release by 5HT3 receptor actions at GABA interneurons), it demonstrates one way in which Figure 4-47B Serotonin (5HT) 2C stimulation, part 2. Serotonin binding at 5HT2C receptors on GABA interneurons inhibits norepinephrine (NE) and dopamine (DA) release in the prefrontal cortex. prefrontal cortex brainstem neurotransmitter centers raphe VTA locus coeruleus 5HT neuron NE neuron DA neuron GABA interneurons 5HT2C receptors B 5HT 5HT overactivation

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Baseline Neurotransmitter Release 5HT + GABA GABA 5HT

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5HT Raphe NE GABA ACh A 5HT3 Receptors Inhibit Norepinephrine and Acetylcholine Release 5HT 3+ GA GA + GABA GABA 5HT

-

5HT Raphe 3 + + GABA

-

non-parvalbumin positive, regular-spiking, latespiking, or bursting GABA interneurons 5HT3 receptor stimulated B Figure 4-48 Serotonin (5HT) 3 stimulation inhibits norepinephrine and acetylcholine release. Excitatory 5HT3 receptors located on the terminals of GABA interneurons in the prefrontal cortex can regulate the release of norepinephrine (NE) and acetylcholine (ACh). (A) At baseline, tonic GABA release allows for a low level of NE and ACh release. (B) When 5HT is released, it binds to 5HT3 receptors on GABAergic neurons, causing phasic release of GABA onto noradrenergic and cholinergic neurons, thus reducing the release of NE and ACh, respectively. Prefrontal Cortex GABA Basal Forebrain ACh NE Locus Coeruleus Prefrontal Cortex GABA Basal Forebrain ACh NE Locus Coeruleus

Serotonin and Glutamate Regulate Each Other GABA

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5HT Glu + + Raphe non-parvalbumin positive, regular-spiking, latespiking, or bursting

GABA interneurons Regulation of downstream release of DA, NE, ACh, HA A Serotonin Actions at 5HT3 Receptors Reduces Its Own Release GABA

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-

3 + 5HT Glu + Raphe 5HT3 receptor stimulated Regulation of downstream release of DA, NE, ACh, HA B Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-49 Serotonin (5HT) 3 stimulation inhibits serotonin release. Excitatory 5HT3 receptors located on the terminals of GABA interneurons in the prefrontal cortex can regulate the release of glutamate, and glutamate in turn can regulate release of serotonin. (A) At baseline, low-level serotonin release stimulates 5HT3 receptors on GABA interneurons, which synapse with pyramidal glutamate neurons. Glutamate release downstream regulates release of downstream dopamine (DA), norepinephrine (NE), acetylcholine (ACh), and histamine (HA). Glutamate also regulates 5HT release in the raphe. (B) When concentrations of 5HT are higher, the stimulation at 5HT3 receptors on GABA interneurons increases GABA release. GABA, in turn, inhibits glutamate pyramidal neurons, reducing glutamate output. Decreased release of excitatory glutamate means that there may be a resultant decrease in downstream release of neurotransmitters, including 5HT. Prefrontal Cortex Prefrontal Cortex 129

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT6 Receptors 5HT6 receptors are postsynaptic and may be key regulators of the release of acetylcholine release and of control of cognitive processes. Blocking this receptor improves learning and memory in experimental animals, so 5HT6 antagonists have been proposed as novel pro-cognitive agents for the cognitive symptoms of schizophrenia, Alzheimer disease, and other disorders. 5HT7 Receptors 5HT7 receptors are postsynaptic, excitatory, and frequently localized on inhibitory GABA interneurons, same as discussed above for the 5HT1A, 5HT2C, and 5HT3 receptors. Just like these other receptors localized on Baseline Glutamate Release pyramidal neuron GABA neuron 5HT7 receptor PFC overactivation 5HT neuron raphe A GABA interneurons, 5HT7 receptors generally inhibit the release of downstream neurotransmitters. 5HT7 receptors specifically inhibit the release of glutamate at the cortical level (Figure 4-50B). That is, cortical interneurons containing 5HT7 receptors terminate on apical dendrites of glutamatergic pyramidal neurons (see baseline state with a normal level of glutamate release in the absence of 5HT7 receptor activation in Figure 4-50A). When serotonin binds to 5HT7 receptors on these cortical GABA interneurons, this inhibits glutamate output (Figure 4-50B). 5HT7 receptors also regulate serotonin release at the level of the brainstem raphe

(Figures 4-51A and 4-51B). That is, a recurrent collateral from the serotonin neuron loops backwards to innervate a GABA neuron that Figure 4-50A Serotonin (5HT) 7 stimulation inhibits glutamate release, part 1. 5HT7 receptors are located on GABA interneurons that synapse with glutamate pyramidal neurons. In the absence of serotonin, tonic GABA release results in normal glutamate release downstream. baseline glutamate release

5HT7 Inhibits Glutamate Release pyramidal neuron GABA neuron 5HT7 receptor PFC 5HT neuron raphe B innervates the serotonin cell body. At baseline, serotonin release is not affected by this inhibitory feedback system (Figure 4-51A). However, when serotonin release gets high, this activates serotonin release from the recurrent collateral, stimulating the 5HT7 receptor there (Figure 4-51B). This activates GABA release, which in turn inhibits further serotonin release by its inhibitory actions at the cell body of the serotonin neuron (Figure 4-51B). 5HT7 antagonists are used for the treatment of psychosis and mood and are discussed in more detail in Chapter 7. The Serotonin Hyperfunction Hypothesis of Psychosis If the glare of the dopamine hypothesis blinded some of us to the possibility of alternate explanations for psychosis, it created a dilemma for patients with Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-50B Serotonin (5HT) 7 stimulation inhibits glutamate release, part 2. When serotonin binds to 5HT7 receptors on GABA interneurons, the phasic GABA release leads to inhibition of glutamate release. reduced glutamate release overactivation psychosis secondary to Parkinson’s disease or Alzheimer disease, since treatment with D2 blockers causes harm to these patients, worsening movements in Parkinson’s disease and increasing the risk of stroke and death in Alzheimer disease. Until recently, dogma dictated that all psychoses were due to excessive mesolimbic dopamine and all treatments needed to block D2 receptors there. While this characterization worked well for patients with schizophrenia, it obviously was not ideal for patients with psychosis in Parkinson’s disease or in dementia, since it meant that the only available drugs for psychosis were relatively contraindicated for them. Although serotonin receptors and synapses are ubiquitous throughout the brain, the serotonin hyperfunction hypothesis of psychosis suggests that 131

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Baseline Serotonin Release baseline 5HT release PFC 5HT7 receptor GABA neuron 5HT neuron raphe A psychosis may be caused by an imbalance in excitatory 5HT2A receptor stimulation of those glutamate pyramidal neurons discussed above, which directly innervate VTA/ mesostriatal integrated hub dopamine neurons and visual cortex neurons (Figures 4-52A–D and Figures 4-53 through 4-55). The hallucinogens LSD, mescaline, and psilocybin, which are all powerful 5HT2A agonists, Figure 4-51A Serotonin (5HT) 7 stimulation inhibits serotonin release, part 1. Excitatory 5HT7 receptors located on the terminals of GABA interneurons in the raphe can regulate serotonin release. When 5HT7 receptors are not occupied, serotonin is released into the prefrontal cortex (PFC). overactivation have long been known to induce psychosis, dissociative experiences, and especially visual hallucinations by overstimulating prefrontal and visual cortex 5HT2A receptors (compare Figure 4-52A and 4-52B; see also Figure 4-53). These symptoms can be blocked by 5HT2A antagonists, demonstrating that hallucinogens cause psychosis by 5HT2A stimulation.

5HT7 Inhibits Serotonin Release reduced 5HT release PFC 5HT7 receptor Stimulation of 5HT7 Receptors in the Raphe Reduces Serotonin Release GABA neuron 5HT neuron raphe B The next link in the serotonin hyperfunction hypothesis of 5HT2A overstimulation causing psychosis comes from work in Parkinson’s disease psychosis (PDP), affecting up to half of Parkinson’s patients, especially

later in the disease. Postmortem examinations as well as neuroimaging in living patients with PDP have demonstrated not only loss of dopamine nerve terminals in the motor striatum of the nigrostriatal pathway that causes the classic motor symptoms of Parkinson's disease, but also loss of serotonin nerve terminals in the prefrontal and visual cortex (Figure 4-52C). This Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-51B Serotonin (5HT) 7 stimulation inhibits serotonin release, part 2. When serotonin binds to 5HT7 receptors that innervate GABA neurons in the raphe nucleus, this causes the release of inhibitory GABA, which then turns off further serotonin release. overactivation loss of serotonin and serotonin nerve terminals leads to upregulation and too many 5HT2A receptors in the cortex, perhaps a futile attempt to overcome serotonin loss (Figure 4-52C). The overabundance of 5HT2A receptors leads to an imbalance in their excitatory actions on glutamate dendrites from the remaining serotonin in the cortex, and consequently, the symptoms of psychosis (Figures 4-52C and 4-54). Drugs with 5HT2A antagonist actions can block these symptoms of PDP, as will be explained in further detail in Chapter 5 on drugs for psychosis. These observations support the serotonin 133

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-52A Serotonin (5HT) 2A receptors and psychosis, baseline. Glutamatergic pyramidal neurons in the prefrontal cortex (PFC) project to the ventral tegmental area (VTA) and to the visual cortex. Activity of the glutamatergic pyramidal neurons is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the PFC. At baseline, when excitatory 5HT2A receptors are not stimulated and GABA neurotransmission is tonic, the glutamatergic neurons are not active. PFC Striatum SN VTA Raphe Visual cortex 5HT2A Baseline 5HT2A 5HT2A hyperfunction hypothesis of psychosis by demonstrating that PDP is related to serotonin hyperfunction at 5HT2A receptors that results from the malfunctioning and upregulation of 5HT2A receptors by the disease process of Parkinson's disease. Psychosis in dementia and its link to serotonin hyperfunction at 5HT2A receptors appears to be different from what is happening with hallucinogen psychosis or PDP, where there is postulated overstimulation of 5HT2A receptors. In dementia134

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-52B Serotonin (5HT) 2A receptors and psychosis, hallucinogens. Hallucinogens such as LSD, psilocybin, and mescaline are 5HT2A agonists. (1) When these agents stimulate 5HT2A receptors on glutamatergic pyramidal neurons in the prefrontal cortex (PFC), this causes overactivation of the glutamate neuron. (2) The resultant release of glutamate into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations. PFC SN VTA Raphe Visual cortex visual hallucinations delusions and auditory hallucinations Striatum 5HT2A 5HT2A 5HT2A overactivation hallucinogen (LSD, psilocybin, mescaline) stimulate 5HT2A receptors and excitate glutamate receptors Hallucinogen Psychosis 5HT2A excitation of glutamate by hallucinogens causes mesolimbic DA hyperactivity and psychosis 2 related psychosis there is no consistent evidence for upregulation of 5HT2A receptors like there is in PDP. Instead, in dementia, the accumulation of plaques, tangles, and Lewy bodies, as well as the damage from strokes, hypothetically knocks out cortical neurons and leads to a lack of inhibition of

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-52C Serotonin (5HT) 2A receptors and psychosis, Parkinson's disease psychosis. (1) Loss of nigrostriatal dopamine neurons causes the motor symptoms of Parkinson's disease, such as akinesia, rigidity, and tremor. (2) Parkinson's

disease also causes loss of serotonergic neurons that project from the raphe to the prefrontal cortex (PFC). (3) This leads to upregulation of 5HT2A receptors, in which case normal or even low serotonin release can overstimulate these receptors, causing overactivation of the glutamatergic pyramidal neuron. (4) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations. PFC SN VTA Raphe Visual cortex Loss of raphe 5HT causes upregulated 5HT2A receptors in PFC Normal or even low 5HT release now overstimulates upregulated 5HT2A receptors Upregulated 5HT2A receptors cause glutamate excitation, mesolimbic DA hyperactivity, and psychosis Loss of nigrostriatal DA causes motor symptoms visual hallucinations delusions and auditory hallucinations 2 4 akinesia rigidity tremor Striatum 5HT2A 5HT2A 5HT2A 5HT2A 5HT2A 5HT2A A A Parkinson's Disease Psychosis the surviving glutamate neurons (Figure 4-29C and Figure 4-52D). If there is not enough GABA inhibition to counter the normal 5HT2A stimulation coming to surviving glutamate neurons projecting to the VTA/ mesostriatum integrated hub and to the visual cortex, this enhanced output theoretically causes psychosis in these dementia patients (Figure 4-52D and 4-55). It is now known that selective 5HT2A antagonism reduces

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-52D Serotonin (5HT) 2A receptors and psychosis, dementia. (1) Accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABAergic interneurons while leaving others intact. The loss of GABA inhibition upsets the balance of control over glutamatergic pyramidal neurons. (2) When the effects of stimulation of excitatory 5HT2A receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. (3) Excessive glutamate release into the ventral tegmental area (VTA) causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations. PFC SN VTA Raphe Visual cortex visual hallucinations delusions and auditory hallucinations Striatum 5HT2A 5HT2A 5HT2A stroke Lewy body plaque tangle Psychosis in Dementia sustained 5HT2A excitation no longer balanced by GABA inhibition imbalance between 5HT2A excitation and GABA inhibition causes glutamate excitation, mesolimbic DA hyperactivity, and psychosis loss of normal GABA inhibition by neurodegeneration 137

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY 5HT2A receptors mesolimbic DA neuron A Hallucinogen Psychosis stimulated 5HT2A receptors by hallucinogen delusions and auditory hallucinations visual hallucinations B overactivation Figure 4-53 Serotonin (5HT) 2A receptors and psychosis, hallucinogens. (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory 5HT2A receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Hallucinogens such as LSD, psilocybin, and mescaline are 5HT2A agonists. When these agents stimulate 5HT2A receptors on glutamatergic pyramidal neurons in the prefrontal cortex, this causes overactivation of the glutamate neurons. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex

can cause visual hallucinations. normal HIGH

4 Figure 4-54 Serotonin (5HT) 2A receptors and psychosis, Parkinson’s disease psychosis. (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory 5HT2A receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Loss of nigrostriatal dopamine neurons causes the motor symptoms of Parkinson’s disease, such as akinesia, rigidity, and tremor. Parkinson’s disease also causes loss of serotonergic neurons that project from the raphe to the prefrontal cortex and to the visual cortex. This leads to upregulation of 5HT2A receptors on glutamatergic pyramidal neurons in the prefrontal cortex, in which case normal or even low serotonin release can overstimulate these receptors. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine (DA) pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations. A nigrostriatal DA neuron degeneration of nigrostriatal DA neuron degeneration of raphe 5HT neuron mesolimbic DA neuron 5HT2A receptor visual hallucinations B HIGH normal overactivation upregulated 5HT2A receptors 5HT2A receptor Psychosis in Parkinson’s Disease delusions and auditory hallucinations akinesia rigidity tremor

Figure 4-55 Serotonin (5HT) 2A receptors and psychosis, dementia. (A) Shown here is a cortico-brainstem glutamatergic pathway projecting from the prefrontal cortex to the ventral tegmental area (VTA), and an indirect cortico-cortical glutamatergic pathway in the visual cortex. Activity of both pathways is regulated by serotonergic neurons that project from the raphe nucleus as well as by GABA interneurons in the prefrontal cortex. At baseline, normal stimulation of excitatory 5HT2A receptors on the glutamate neurons is balanced by tonic stimulation of GABA receptors on the same neurons; the net effect is thus normal activation of the glutamatergic neurons. (B) Accumulation of amyloid plaques, tau tangles, and/or Lewy bodies, as well as the damage caused by strokes, may destroy some glutamatergic pyramidal neurons and GABA interneurons while leaving others intact. When the effects of stimulation of excitatory 5HT2A receptors are not countered by GABA inhibition, there is a net increase in glutamatergic neurotransmission. Excessive glutamate release into the VTA causes hyperactivity of the mesolimbic dopamine pathway, resulting in delusions and auditory hallucinations. Excessive glutamate release in the visual cortex can cause visual hallucinations. A mesolimbic DA neuron 5HT2A receptor visual hallucinations B HIGH normal overactivation loss of GABA inhibition normal 5HT2A excitation now out of balance Psychosis in Dementia delusions and auditory hallucinations stroke Lewy body plaque tangle

the psychosis associated with dementia. Presumably this is due to lowering the normal 5HT2A stimulation to surviving glutamate neurons that have lost their GABA inhibition by neurodegeneration. This hypothetically could rebalance the output of the surviving glutamate neurons so that 5HT2A antagonism and its reduction of neuronal stimulation compensates for the loss of GABA inhibition. 5HT2A antagonist treatment of dementiarelated psychosis will be discussed in further detail in Chapter 5 and in Chapter 12 on the treatment of the behavioral symptoms of dementia. Linking the Psychosis Hypothesis of Serotonin Hyperfunction at 5HT2A Receptors to the

Dopamine Hypothesis of Psychosis What are the consequences to dopamine activity of the hypothetical excessive or imbalanced 5HT2A stimulation at glutamatergic pyramidal neurons? The short answer is that it theoretically leads to the very same dopamine hyperactivity already discussed above for the dopamine hypothesis of psychosis and for the NMDA hypofunction hypothesis of psychosis (Figures 4-52 through 4-55). That is, when those glutamate neurons that directly innervate VTA dopamine neurons lose either their serotonin input due to neurodegeneration of serotonin neurons in Parkinson's disease or their GABA inhibition from neurodegeneration of any cause, they become hyperactive and stimulate too much dopamine release from the mesostriatal projections of those dopamine neurons (Figure 4-52 through 4-55), just as happens in schizophrenia. Summary and Conclusions Regarding Dopamine, NMDA, and Serotonin Neurotransmission in Psychosis In summary, there are three interconnected pathways theoretically linked to hallucinations and delusions: (1) Dopamine hyperactivity at D2 receptors in the mesolimbic/mesostriatal pathway, which extends from the VTA/mesostriatum integrated hub to the ventral striatum (2) NMDA receptor hypoactivity at GABAergic interneurons with loss of GABAergic inhibition in the prefrontal cortex (3) Serotonin hyperactivity/imbalance at 5HT2A receptors on glutamate neurons in the cerebral cortex All three neuronal networks and neurotransmitters are linked together, and both 5HT2A and NMDA receptor actions can hypothetically result in hyperactivity of the downstream mesolimbic dopamine pathway. Targeting Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks at any node in this dysfunctional psychosis circuit could theoretically be therapeutic for psychosis of many causes. SCHIZOPHRENIA AS THE PROTOTYPICAL PSYCHOTIC DISORDER Schizophrenia is the prototypical psychotic disorder since it is the most common and best known and expresses prototypical psychotic symptoms. Schizophrenia affects about 1% of the population anywhere in the world and is one of the most devastating illnesses in medicine. Its onset during adolescence and early adulthood coincides with the years of life that should be the most dynamic and formative. Instead, this illness has a chronic course, with marked and lifelong functional disability, decreased lifespan of 25 to 30 years, and an alarming mortality rate that is three to four times that of the general population. On top of all of this misfortune is the fact that 5% of patients with schizophrenia complete suicide. Although the treatments described in this book do improve symptoms, they do not return most patients to normal functioning, nor do they necessarily adequately reduce the anguish that patients and their families feel from the ravages of this illness. Schizophrenia by definition is a disturbance that must last for 6 months or longer, including at least one month of positive symptoms (i.e., delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior) or negative symptoms. Positive symptoms are listed in Table 4-3 and shown in Figure 4-56. These symptoms of schizophrenia are often emphasized since they can be dramatic, can erupt suddenly when a patient decompensates into a psychotic episode (often called a psychotic "break," as in break from reality), and are the symptoms most effectively treated by medications. Delusions are one type of positive symptom, and these usually involve a misinterpretation of perceptions or experiences. The most common content of a delusion in schizophrenia is persecutory, but may include a variety of other themes including referential (i.e., erroneously thinking that something refers to oneself), somatic, religious, or grandiose. Hallucinations are also a type of positive symptom (Table 4-3) and may occur in any sensory modality (e.g., auditory, visual, olfactory, gustatory, and tactile) but auditory hallucinations are by far the most common and characteristic hallucinations in schizophrenia. Positive symptoms generally reflect an excess of normal functions, and in addition to delusions and hallucinations may

 also include distortions or exaggerations in language and communication (disorganized speech) as well as in behavioral monitoring (grossly disorganized or catatonic or agitated behavior). Positive symptoms are well known because they are dramatic, are often the cause of bringing a patient to the attention of medical professionals and law enforcement, and are the major target of drug treatments for schizophrenia. Negative symptoms of schizophrenia are listed in Tables 4-4 and 4-5 and shown in Figure 4-56. Classically, there are at least five types of negative symptoms all starting with the letter A (Table 4-5): alogia – dysfunction of communication; restrictions in the fluency and productivity of thought and speech affective blunting or flattening – restrictions in the range and intensity of emotional expression asociality – reduced social drive and interaction anhedonia – reduced ability to experience pleasure avolition – reduced desire, motivation, or persistence; restrictions in the initiation of goal-directed behavior Negative symptoms in schizophrenia commonly are considered a reduction in normal functions, such as blunted affect, emotional withdrawal, poor rapport, passivity and apathetic social withdrawal, difficulty in abstract thinking, stereotyped thinking, and lack of spontaneity. Negative symptoms in schizophrenia are associated with long periods of hospitalization and poor social functioning. As will be discussed below, it can be Schizophrenia: The Phenotype schizophrenia deconstruct the syndrome... positive symptoms -delusions -hallucinations ...into symptoms Table 4-3 Positive symptoms of psychosis and schizophrenia Delusions Hallucinations Distortions or exaggerations in language and communication Disorganized speech Disorganized behavior Catatonic behavior Agitation Table 4-4 Negative symptoms of schizophrenia Blunted affect Emotional withdrawal Poor rapport Passivity Apathetic social withdrawal Difficulty in abstract thinking Lack of spontaneity Stereotyped thinking Alogia: restrictions in fluency and productivity of thought and speech Avolition: restrictions in initiation of goal-directed behavior Anhedonia: lack of pleasure Attentional impairment Figure 4-56 Positive and negative symptoms. The syndrome of schizophrenia consists of a mixture of symptoms that are commonly divided into two major categories, positive and negative. Positive symptoms, such as delusions and hallucinations, reflect the development of the symptoms of psychosis; they can be dramatic and may reflect loss of touch with reality. Negative symptoms reflect the loss of normal functions and feelings, such as losing interest in things and not being able to experience pleasure. negative symptoms -apathy -anhedonia -cognitive blunting -neuroleptic dysphoria

 Table 4-5 What are negative symptoms? Domain Descriptive term Translation Dysfunction of communication Alogia Poverty of speech; e.g., talks little, uses few words Dysfunction of affect Blunted affect Reduced range of emotions (perception, experience, and expression); e.g., feels numb or empty inside, recalls few emotional experiences, good or bad Dysfunction of socialization Asociality Reduced social drive and interaction; e.g., little sexual interest, few friends, little interest in spending time with (or little time spent with) friends Dysfunction of capacity for pleasure Anhedonia Reduced ability to experience pleasure; e.g., finds previous hobbies or interests unpleasurable Dysfunction of motivation Avolition Reduced desire, motivation, persistence; e.g., reduced ability to undertake and complete everyday tasks; may have poor personal hygiene quite difficult to tell the difference between the negative symptoms of schizophrenia, the cognitive symptoms of schizophrenia, the affective/mood symptoms of schizophrenia, particularly depression, and the side effects of drugs that treat psychosis (discussed in Chapter 5). Although formal rating scales can be used to measure negative symptoms versus cognitive symptoms versus affective symptoms for research studies, in clinical practice it may be more practical to identify and monitor mostly negative symptoms and to do this

quickly by observation alone (Figure 4-57) or by some simple questioning (Figure 4-58). Negative symptoms are not just part of the syndrome of schizophrenia; they can also be part of a “prodrome” that begins with subsyndromal symptoms that do not meet the full Figure 4-57 Negative symptoms identified by observation. Some negative symptoms of schizophrenia – such as reduced speech, poor grooming, and limited eye contact – can be identified solely by observing the patient. Reduced speech: Patient has restricted speech quantity, uses few words and nonverbal responses. May also have impoverished content of speech, when words convey little meaning* Key Negative Symptoms Identified Solely on Observation Poor grooming: Patient has poor grooming and hygiene, clothes are dirty or stained, or subject has an odor* Limited eye contact: Patient rarely makes eye contact with the interviewer* *symptoms are described for patients at the more severe end of the spectrum A B C diagnostic criteria of schizophrenia and occur before the onset of the full syndrome of schizophrenia. Prodromal negative symptoms are important to detect and monitor over time in high-risk patients so that treatment can be initiated at the first signs of psychosis. Negative symptoms can also persist between psychotic episodes once schizophrenia has begun and reduce social and occupational functioning in the absence of positive symptoms. Beyond the Positive and Negative Symptoms of Schizophrenia Although not recognized formally as part of the diagnostic criteria for schizophrenia, numerous studies subcategorize the symptoms of this illness into five

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Key Negative Symptoms Identified with Some Questioning Reduced emotional responsiveness: Patient exhibits few emotions or changes in facial expression, and when questioned can recall few occasions of emotional experience* A (SIGH) Reduced interest: Reduced interests and hobbies, little or nothing stimulates interest, limited life goals and inability to proceed with them* B Reduced social drive: Patient has reduced desire to initiate social contacts and may have few or no friends or close relationships* C *symptoms are described for patients at the more severe end of the spectrum Match Each Symptom to Hypothetically Malfunctioning Brain Circuits mesocortical/ prefrontal cortex mesolimbic positive symptoms negative symptoms aggressive symptoms affective symptoms cognitive symptoms dorsolateral prefrontal cortex ventromedial prefrontal cortex orbitofrontal amygdala cortex dimensions: not just positive and negative symptoms, but also cognitive symptoms, affective symptoms, and aggressive symptoms (Figure 4-59). This is perhaps a more sophisticated if complicated manner of describing the symptoms of schizophrenia. Cognitive symptoms of schizophrenia include impaired attention and information processing, manifesting as difficulties with verbal fluency (i.e., the ability to produce spontaneous speech), problems with serial learning (of a list of items or a sequence of events), and impairment in vigilance for executive functioning (i.e., problems with sustaining and focusing attention, concentrating, Figure 4-58 Negative symptoms identified by questioning. Other negative symptoms of schizophrenia can be identified by simple questioning. For example, brief questioning can reveal the degree of emotional responsiveness, interest level in hobbies or pursuing life goals, and desire to initiate and maintain social contacts. Figure 4-59 Localization of symptom domains. The different symptom domains of schizophrenia may best be subcategorized into five dimensions: positive, negative, cognitive, affective, and aggressive. Each of these symptom domains may hypothetically be mediated by unique brain regions. nucleus accumbens reward circuits prioritizing, and modulating behavior based upon social cues). Important cognitive symptoms of schizophrenia are listed in Table 4-6. Cognitive symptoms begin before the onset of the first psychotic illness and manifest as lower than expected IQ scores. IQ and cognition then worsen during the prodrome before the onset of full-

blown psychosis, and then progressively worsen throughout the course of schizophrenia. Cognitive symptoms in schizophrenia do not include the same symptoms commonly seen in dementia, such as shortterm memory disturbance; instead, cognitive symptoms of schizophrenia emphasize “executive dysfunction,”

Table 4-6 Cognitive symptoms of schizophrenia Problems representing and maintaining goals Problems allocating attentional resources Problems focusing attention Problems sustaining attention Problems evaluating functions Problems monitoring performance Problems prioritizing Problems modulating behavior based upon social cues Problems with serial learning Impaired verbal fluency Difficulty with problem solving which includes problems representing and maintaining goals, allocating attentional resources, evaluating and monitoring performance, and utilizing these skills to solve problems. Affective symptoms are frequently associated with schizophrenia, but this does not necessarily mean that they fulfill the full diagnostic criteria for a comorbid anxiety or affective disorder. Nevertheless, depressed mood, anxious mood, guilt, tension, irritability, and worry frequently accompany schizophrenia. These various symptoms are also prominent features of major depressive disorder, numerous anxiety disorders, psychotic depression, bipolar disorder, schizoaffective disorder, organic dementias, childhood psychotic disorders, and treatment-resistant cases of depression, bipolar disorder, and schizophrenia, among many others. Affective symptoms of schizophrenia, particularly symptoms of depressed mood, anhedonia, lack of motivation, and lack of pleasure, can also be quite difficult to distinguish from the negative symptoms of schizophrenia and from a comorbid mood or anxiety disorder. Wherever encountered, affective symptoms need to be treated. In the case of schizophrenia, when affective symptoms are not sufficiently improved by traditional drugs for the positive symptoms of psychosis, consideration can be given to adding drugs used to treat anxiety and/or depression (e.g., selective serotonin reuptake inhibitors, SSRIs), not only to relieve the current affective symptoms, but also to prevent suicide, which is unfortunately very common in patients with schizophrenia. There is no drug treatment for the disorder of schizophrenia itself, only for the symptoms of Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks schizophrenia. Thus, whenever possible, consideration should be given to treat the affective symptoms of schizophrenia even if they do not reach full criteria for a comorbid mood or anxiety disorder. Even though affective symptoms in a patient with schizophrenia may very well respond to drug treatments for depression or anxiety, these same treatments are not very effective if at all for true negative symptoms. Aggressive symptoms, such as overt hostility, assaultiveness and physical abuse, frank violence, verbally abusive behaviors, sexually acting-out behaviors, selfinjurious behaviors including suicide, and arson and other property damage can all occur in schizophrenia. Aggression is different from agitation in that aggression tends to refer to intentional harm, while agitation is a more nonspecific and often nondirected state of heightened psychomotor or verbal activity, accompanied by an unpleasant state of tension and irritability. In schizophrenia, both can occur alongside positive symptoms, particularly when positive symptoms are out of control, and both agitation and aggression often improve when positive symptoms are reduced by drugs that treat psychosis. Both agitation and aggression can also occur in patients with dementia but must be distinguished from positive psychotic symptoms, since new treatments are evolving for agitation in dementia that differ from treatments for psychosis in dementia and these also differ from treatments for psychosis in schizophrenia. Treatments of agitation and aggression are discussed in more detail in Chapter 5 on treatments for psychosis and in Chapter 12 on treatments for the behavioral symptoms of dementia. Aggressive symptoms can also occur in numerous other

disorders that exhibit problems with impulse control such as bipolar disorder, childhood psychosis, borderline personality disorder, antisocial personality disorder, drug abuse, attention deficit hyperactivity disorder, conduct disorders in children, and many others. For schizophrenia, the topic of violence – a type of aggression – is controversial. The stereotype of schizophrenia patients as frequent violent perpetrators of mass shootings is an unfortunate exaggeration contributing to the stigma of this illness. Most patients with schizophrenia in fact are not violent, and patients are more likely to be a victim of violence than a perpetrator. However, some studies do suggest that schizophrenia patients commit violence more often than the general population, although the increased rate is 145

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY not large, and the violence is often linked to a lack of adequate medication treatment as well as to concomitant substance abuse. Not surprisingly, schizophrenia patients who commit violence often become involved in the criminal justice system. This may be a sorry reflection of the lack of adequate outpatient treatment as well as the lack of short-term crisis and inpatient beds in the community for treating patients with schizophrenia. It is a shocking fact that in the United States we have "criminalized" serious mental illnesses such as schizophrenia, since our largest "mental health institutions" are now jails and prisons. For example, the twin towers of the Los Angeles County Jail, the New York City jail at Rikers Island, and the Cook County Chicago jail are the largest mental health facilities in the country. Up to a quarter of the 2 million inmates in jails and prisons throughout the country have serious mental illnesses. Although patients with schizophrenia do get treatment in jail and prison, this treatment is widely acknowledged to be substandard in correctional environments and the correctional environment itself is inherently countertherapeutic. Furthermore, when released, patients often do not take medication, are homeless, and eventually are re-arrested for another violent offense. In California, the numbers of patients with serious mental illnesses who are arrested for a felony and found incompetent to stand trial because of their illness and who have had 15 or more prior arrests have been increasing; half of them have not accessed reimbursable mental health services including medication for the six months prior to their arrest and half are in an unsheltered homeless condition. Fortunately, innovative treatment programs modeled on a successful program in Miami, Florida seek to decriminalize the treatment of schizophrenia by diversion programs sending patients to treatment with housing rather than to jail and prison. Nevertheless, once sent to jail, prison, or state forensic hospitals, patients with schizophrenia can frequently experience and cause violence. Some of this is due to the fact that institutions have violent environments and some of this is due to the fact that those with serious mental illnesses who find themselves in institutions are a small subset of all patients, specifically those most likely to commit violence. If schizophrenia is roughly 1% of the population, there are an estimated 400,000 patients with this illness in the State of California, whose population is about 40 million. If up to 200,000 individuals are incarcerated in California and perhaps 25% of them (or approximately 40,000 of them) have a serious mental illness requiring treatment with drugs for psychosis, this would mean that perhaps 10% of all patients with schizophrenia in California are in prison or jail – again probably those who are the most likely to engage in violence when unmedicated and/or abusing drugs. An even smaller subpopulation of patients with schizophrenia are those who commit a violent felony and are judged either incompetent to stand trial or insane, and sent to one of the five state forensic hospitals in California. This population is only a few thousand patients, or perhaps only 1% of all patients with schizophrenia in California. Unfortunately, they are the most violent subset of schizophrenia patients: not surprising, as a violent felony put them in the state forensic hospital in the first place.

Studies show that violence in this setting is actually associated with criminogenic risk, suggesting that it is the process of criminalization from living in an institutional setting, and not the positive symptoms of psychosis, that are driving a lot of this violence. Once in the state forensic hospitals they often continue to commit violent acts, even when treated and medicated. But not all patients with schizophrenia even in state forensic hospitals are violent; only about a third of them commit a violent act during hospitalization, usually a single event within the first 120 days. Actually, about 3% of state forensic patients (a few hundred at most or fewer than 1 per 100,000 patients with schizophrenia in California) commit about 40% of the violence within the state forensic hospital, about half against staff and about half against other patients. Thus, only a tiny fraction of patients with schizophrenia commit a lot of violence, and the number of patients with violence is frequently exaggerated by media. Nevertheless, working in a state forensic hospital can be very dangerous, as can living as a patient in these settings. Treating violence in patients with schizophrenia can be very important in state forensic hospitals, jails, and prisons, as can preventing violence in these patients when they leave these settings. Rather than lumping all forms of violence together, experts parse violence in institutionalized patients with schizophrenia into three types: impulsive, predatory, and psychotic (Figure 4-60). Psychotic violence, associated with positive symptoms of psychosis, which typically command hallucinations and/or delusions, is actually the least common type of violence in institutional settings, despite the fact that these patients have a psychotic illness (Figure 4-60). This is presumably

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-60 Three types of violence. There are at least three different types of violence: psychotic, impulsive, and organized/psychopathic. Psychotic violence is associated with positive symptoms of psychosis. The most common form of violence is impulsive; it is associated with autonomic arousal and often precipitated by stress, anger, or fear. Organized or psychopathic violence is planned and is not accompanied by autonomic arousal. Psychotic - 17% Associated with positive symptoms of psychosis – typically command hallucinations and/or delusions Organized - 29% Planned behavior not typically associated with frustration or response to immediate threat Might not be accompanied by autonomic arousal Planned with clear goals in mind Also called predatory, instrumental, proactive, or premeditated aggression Impulsive - 54% Characterized by high levels of autonomic arousal Precipitated by provocation Associated with negative emotions, such as anger or fear Usually represents response to perceived stress Also called reactive, affective, or hostile aggression because treatment in institutional settings is often effective for positive symptoms. However, treating positive symptoms does not quell all violence, since the most common form of violence in institutional settings is actually impulsive violence – often precipitated by provocation as a response to stress and associated with negative emotions such as anger or fear (Figure 4-60). For these reasons, impulsive violence is also called reactive, affective, or hostile aggression. The third form of violence, also more common than psychotic violence, is psychopathic or organized and is planned behavior not typically associated with frustration or response to immediate threat (Figure 4-60). If psychotic violence and impulsive violence are “hot-blooded” with emotional arousal, organized violence is “coldblooded” and not accompanied by autonomic arousal as it is planned with clear goals in mind (Figure 4-60). Organized violence is what is commonly seen in patients with psychopathic or antisocial personalities and is associated with criminogenic behaviors more than with psychotic symptoms. Nevertheless, psychotic patients in institutional settings can also have psychopathic tendencies and commit organized violence, which may require forms of confinement rather than drugs in order to manage. Certain treatments, such as clozapine or high

doses of standard drugs for schizophrenia, may also be useful for psychotic or impulsive violence in patients with underlying psychotic disorders, but behavioral interventions may be particularly helpful to prevent violence linked to poor impulsivity associated with violence (i.e., by reducing provocations from the environment). Impulsive and organized violence in schizophrenia are not as clearly related to dopamine D2 overactivity as psychotic violence when positive symptoms of schizophrenia are out of control, especially in the small population of frequent aggressors. In California state forensic hospitals, these frequent aggressors that can be so difficult to manage have an underlying psychotic illness, exhibit psychotic or impulsive violence rather than organized violence, and

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY have a cognitive deficiency beyond that usually associated with schizophrenia. Aggression and violence are discussed in further detail in Chapter 13 on impulsivity and compulsivity and are also differentiated from agitation and from positive symptoms or psychosis in dementia in Chapter 12. What is the Cause of Schizophrenia? What causes schizophrenia: nature (i.e., genetics) or nurture (i.e., the environment or epigenetics)? Is schizophrenia neurodevelopmental or neurodegenerative? The modern answer indeed may be "yes" in part to all of these. Genetics and Schizophrenia Modern theories of mental illness have long abandoned the notion that single genes cause any of the major Classic Theory: Genes Cause Mental Illness hypothetical mental illness gene abnormal gene product causes neuronal malfunction mental illness mental illnesses (Figure 4-61). Genes do not code directly for mental illnesses or for psychiatric symptoms, behaviors, personalities, or temperaments. Instead, genes code directly for proteins and epigenetic regulators (see Figures 1-31 and 1-32). It is thought that the actions of genes must "conspire" amongst themselves (Figure 4-62, upper left) and amongst environmental stressors (Figure 4-62, upper right) in order to produce a mental illness (Figure 4-62, bottom). Thus, current theories state that inheriting many risk genes for a mental illness sets the stage for a mental illness, but does not cause a mental illness per se. More properly, individuals inherit risk for mental illness, but they do not inherit mental illness. Whether this risk evolves into a manifest mental disorder is hypothesized to be dependent upon what happens in the environment to an individual who has risk genes. Figure 4-61 Classic theory of inherited disease. According to the classic theory of inherited disease, a single abnormal gene can also cause a mental illness. That is, an abnormal gene would produce an abnormal gene product, which, in turn, would lead to neuronal malfunction that directly causes a mental illness. However, no such gene has been identified, and there is no longer any expectation that such a discovery might be made. This is indicated by the red cross-out sign over this theory.

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-62 The nature and nurture of schizophrenia. Schizophrenia may occur as the result of both genetic (nature) and epigenetic (nurture) factors. That is, an individual with multiple genetic risk factors, combined with multiple stressors causing epigenetic changes, may have abnormal information processing in the form of dysconnectivity, abnormal long-term potentiation (LTP), reduced synaptic plasticity, inadequate synapse strength, dysregulated neurotransmission, and abnormal competitive elimination of synapses. The result may be psychiatric symptoms such as hallucinations, delusions, and thought disorder. abnormal LTP dysconnectivity abnormal competitive elimination of synapses abnormal synaptic plasticity and connectivity inadequate synaptic strength dysregulation of glutamate, dopamine, serotonin delusions thought disorder hallucinations schizophrenia multiple life events a few hundred risk genes Nature Nurture abusive childhood neuroplasticity

synaptogenesis neurotransmitter systems cognition neurotoxicity of psychosis stress vulnerability polygenic risk score cumulative environmental stress factors obstetric events traumatic experience (e.g., combat) bullying virus or toxin marijuana !!

@

!! @ Recent evidence suggests that a portfolio of a few hundred specific genes – each with a small contribution of less than 1% – may together confer risk for schizophrenia (Table 4-7). The function of all of these risk genes is not fully known, but may be to regulate such key aspects of the brain as neurotransmitter systems, synaptogenesis, neuroplasticity, neurodevelopment, cognition, the neurotoxicity of psychosis, and stress vulnerability, amongst other functions (Figure 4-62, upper left). One way to deal with this complexity is to add up all the abnormal genes any individual has amongst the known few hundred risk genes, and compute what is

STAHL'S ESSENTIAL PSYCHOPHARMACOLOGY synaptogenesis (Figure 4-62, bottom). How can that be? Normal genes causing mental illness? Hypothetically, yes, when environmental stressors (Figure 4-62, upper right) cause various critical normal genes to be expressed when they should be silenced, or silenced when they should be expressed, in a process called epigenetics (Figure 1-30). Some of the best evidence that environmental stressors and normal genes are also involved with abnormal genes in the causation of schizophrenia is that only half of identical twins of patients with schizophrenia also have schizophrenia. Having identical genes is thus not enough to cause schizophrenia and instead epigenetics is also in play, such that the affected twin not only expresses some abnormal genes that the unaffected co-twin might not express, but also expresses some normal genes at the wrong time or silences other normal genes at the wrong time; together these factors may cause schizophrenia in one co-twin but not the other. In summary, mental illnesses such as schizophrenia are now thought to be due not only to the summed biological action of abnormal genes with flawed DNA causing flaws in the structure and function of the proteins and regulators they code (Figure 4–62, upper left), but are also due to the environment, which plays upon both abnormal genes and normal genes that make normal functioning proteins and regulators but are activated or silenced at the wrong times (Figure 4-62, upper right). In other words, schizophrenia results from both nature and nurture (Figure 4-62, bottom). called a "polygenic risk score" suggesting how much risk there might be for developing schizophrenia. Even with this simplification, the known contribution of all risk genes added together only confers a portion of the risk for schizophrenia. What comprises the remaining risk? In schizophrenia, it is various environmental stressors, specifically, cannabis use, emotionally traumatic experiences such as early childhood adversity, bullying, obstetric events, sleep deprivation, being a migrant, and others (Figure 4-62, upper right). For example, the incidence of psychosis has been shown to be higher in cities with a lot of migrants; in one such city, London, the incidence of psychosis falls by one-third if migrants and their children are excluded from the population studied. Other studies show that there is a high correlation between the frequency of cannabis use and the rate of psychosis across European cities, and that if nobody smoked high-potency cannabis, 12% of all cases of firstepisode psychosis across Europe would be prevented. In particular cities, the estimated reduction in

firstepisode psychosis would be 32% in London and 50% in Amsterdam. How does the environment unmask schizophrenia in those who have genetic risk for it? The answer is that the environment hypothetically puts a load on the neural circuits where the risk genes are expressed and causes these circuits to malfunction under pressure (Figure 4-62, bottom). Furthermore, these same stressors can even cause normal genes to malfunction and together all of this causes aberrant neuroplasticity and Table 4-7 Some candidate susceptibility risk genes involved in biological functions implicated in schizophrenia Genes Description Glutamate neurotransmission and synaptic plasticity GRIA1 Ionotropic glutamate receptor mediating fast synaptic neurotransmission GRIN2A Glutamate gated-ion-channel protein and key mediator of synaptic plasticity GRM3 Encodes glutamate metabotropic receptor 3, one of the major excitatory neurotransmitter receptors, extensively explored as a potential drug target in schizophrenia Calcium channel and signaling CACNA1C Encodes an α1 subunit of voltage-sensitive calcium channels CACNB2 One of the voltage-sensitive calcium channels Neurogenesis SOX2 Transcription factor essential for neurogenesis SATB2 Essential for cognitive development and involved in long-term plasticity

Schizophrenia: Problems with Neurodevelopment, Neurodegeneration, or Both? In the case of schizophrenia, two major questions always arise: (1) How does the scheming of nature and nurture lead to the full onset of this illness around the time of adolescence? (2) What kind of neurobiological processes underlie this disorder such that the results of nature and nurture can appear to be neurodevelopmental at the onset of schizophrenia yet neurodegenerative over the lifetime course of this illness? Both the neurodevelopmental and the neurodegenerative theories of schizophrenia are discussed next. Neurodevelopment and Schizophrenia Modern research findings strongly suggest that something is amiss in the way the brain makes, retains, and revises its synaptic connections in schizophrenia, starting from birth. Telltale signs of this include the cognitive deficits, lowering of IQ, oddness, and social deficits of patients before the overt onset of a psychotic break that signals the full diagnostic criteria of schizophrenia. In order to grasp what might be going wrong with neurodevelopment in schizophrenia, it is important to first have an understanding of normal neurodevelopment. An overview of normal neurodevelopment is shown in Figure 4-63. After conception, stem cells differentiate into immature neurons. Only a minority of neurons that are formed are selected for inclusion in the developing brain. The others die off naturally in a process called apoptosis. It remains a mystery why the brain makes so many more neurons than it needs, and how it decides which neurons to select for inclusion in the developing brain, but it is certainly feasible that abnormalities in the process of neuronal selection could be a factor in neurodevelopmental disorders, from autism to intellectual disability (formerly known as mental retardation) to schizophrenia on the severe end of the spectrum, and ADHD (attention deficit hyperactivity disorder) and dyslexia on the mild to moderate end of the spectrum. At any rate, those neurons that are selected migrate and then differentiate into different types of neurons, after which synaptogenesis (making of synaptic connections) occurs (Figure 4-63). Most neurogenesis (i.e., birth of new neurons), neuronal selection, and neuronal migration occur before birth, although new neurons continue to form in some brain Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks areas throughout life. After birth, differentiation and myelination of neurons as well as synaptogenesis also continue throughout a lifetime. All along the way, not just prenatally or even just in childhood but throughout adult life, disruption of this neurodevelopmental process (Figure 4-63) can hypothetically result in various psychiatric symptoms and illnesses. In the case of schizophrenia, the suspicion is that the neurodevelopmental process of synaptogenesis and brain restructuring has gone awry. Synapses are normally formed at a furious rate between

birth and age 6 (Figure 4-64). Although brain restructuring occurs throughout life, it is most active during late childhood and adolescence in a process known as competitive elimination (Figures 4-63 and 4-64). Competitive elimination and restructuring of synapses peak during pubescence and adolescence, normally leaving only about half to two-thirds of the synapses that were present in childhood to survive into adulthood (Figures 4-63 and 4-64). Since the onset of positive symptoms of psychosis (psychotic “breaks”) follows this critical neurodevelopmental period of peak competitive elimination and restructuring of synapses, it has thrown suspicion on possible abnormalities in these processes as underlying in part the onset of schizophrenia. In order to understand how aberrant competitive elimination could contribute to the onset and worsening of schizophrenia, it is important to consider how the brain decides which synapses to keep and which ones to eliminate. Normally, when glutamate synapses are active, their N-methyl-D-aspartate (NMDA) receptors trigger an electrical phenomenon known as long-term potentiation (LTP) (shown in Figure 4-65). With the help of gene products that converge upon glutamate synapses and receptors, ion channels, and the processes of neuroplasticity and synaptogenesis, LTP normally leads to structural and functional changes of the synapse that make neurotransmission more efficient, sometimes called “strengthening” of synapses (Figure 4-65, top). This includes changes in synaptic structure such as an increase in the number of AMPA (α-amino-3-hydroxy5-methyl-4-isoxazole-propionic acid) receptors for glutamate. AMPA receptors are important for mediating excitatory neurotransmission and depolarization at glutamate synapses. Thus, more AMPA receptors can mean a “strengthened” synapse. Synaptic connections that are frequently used develop frequent LTP and consequential robust neuroplastic influences, thus strengthening them according to the old saying “nerves 151

STAHL’S ESSENTIAL PSYCHOPHARMACOLOGY Figure 4-63 Overview of neurodevelopment. The process of brain development is shown here. After conception, stem cells differentiate into immature neurons. Those that are selected migrate and then differentiate into different types of neurons, after which synaptogenesis occurs. Most neurogenesis, neuronal selection, and neuronal migration occur before birth, although new neurons can form in some brain areas even in adults. After birth, differentiation and myelination of neurons as well as synaptogenesis continue throughout a lifetime. Brain restructuring also occurs throughout life, but is most active during childhood and adolescence in a process known as competitive elimination. Key genes involved in the process of neurodevelopment include DISC1 (disrupted in schizophrenia-1), ErbB4, neuregulin (NRG), dysbindin, regulator of G-protein signaling 4 (RGS4), D-amino acid oxidase activator (DAOA), and genes for α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA). stem cell immature neurons eliminated Overview of Neurodevelopment eliminated

conception birth death conception birth neurogenesis selection migration differentiation and myelination Synaptogenesis (presynaptic; axonal growth & connections) Synaptogenesis (postsynaptic; dendritic arborization) Competitive elimination of synapses (loss of dendritic arborization) conception birth death conception birth years years death DISC1 DISC1 ErbB4 NRG ErbB4 NRG NRG dysbinden DISC1 NRG dysbinden DISC1 RGS4 DAOA NRG AMPA Figure 4-64 Synapse formation by age. Synapses are formed at a furious rate between birth and age 6. Competitive elimination and restructuring of synapses peaks during pubescence and adolescence, leaving about half to two-thirds of the synapses present in childhood to survive into adulthood. Birth Age 6 Age 14-60

 to ineffective LTP and fewer AMPA receptors trafficking into the postsynaptic neuron (Figure 4-65, bottom). Such a synapse would be “weak,” theoretically causing inefficient information processing in its circuit and possibly also causing symptoms of schizophrenia. that fire together wire together” (Figure 4-65, top). However, if something is wrong with the genes that regulate synaptic strengthening, it is possible that this causes less effective use of these synapses, makes the NMDA receptors hypoactive (Figure 4-29B), and leads Figure 4-65 Neurodevelopmental hypothesis of schizophrenia. Dysbindin, DISC1 (disrupted in schizophrenia-1), and neuregulin are all involved in “strengthening” of glutamate synapses. Under normal circumstances, N-methyl-D-aspartate (NMDA) receptors in active glutamate synapses trigger long-term potentiation (LTP), which leads to structural and functional changes of the synapse to make it more efficient, or “strengthened.” In particular, this process leads to an increased number of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, which are important for mediating glutamatergic neurotransmission. Normal synaptic strengthening means that the synapse will survive during competitive elimination. If the genes that regulate strengthening of glutamate synapses are abnormal, combined with environmental insults, then this could cause hypofunctioning of NMDA receptors, with a resultant decrease in LTP and fewer AMPA receptors. This abnormal synaptic strengthening and dysconnectivity would lead to weak synapses that would not survive competitive elimination. This would theoretically lead to increased risk of developing schizophrenia, and these abnormal synapses could mediate the symptoms of schizophrenia. normal synaptic strengthening multiple flawed genes epigenetics/flawed environment NMDA receptor LTP NMDA receptor glutamate AMPA receptors abnormal synaptic strengthening and dysconnectivity synapse survives competitive elimination weak synapse competitively eliminated NMDA receptor AMPA receptor Neurodevelopmental Hypothesis of Schizophrenia: Key Susceptibility Genes Causing Abnormal Synaptogenesis dysbindin DISC1 neuregulin

 Another important aspect of synaptic strength is that this likely determines whether a given synapse is eliminated or maintained. Specifically, “strong” synapses with efficient NMDA neurotransmission and many AMPA receptors survive, whereas “weak” synapses with few AMPA receptors may be targets for elimination (Figure 4-65). This normally shapes the brain’s circuits so that the most critical synapses are not only strengthened but also survive the ongoing selection process, keeping the most efficient and most frequently utilized synapses while eliminating inefficient and rarely utilized synapses. However, if critical synapses are not adequately strengthened in schizophrenia, it could lead to their wrongful elimination, causing dysconnectivity that disrupts information flow from circuits now deprived of synaptic connections where communication needs to be efficient (Figure 4-65). Sudden and catastrophic competitive elimination of “weak” but critical synapses during adolescence could even explain why schizophrenia has onset at this time. If abnormalities in genes converging upon the processes of neuroplasticity and synaptogenesis lead to the lack of critical synapses being strengthened, these critical synapses may be mistakenly eliminated during adolescence, with disastrous consequences, namely the onset of symptoms of schizophrenia. This could explain why genetically programmed dysconnectivity present from birth is masked by the presence of many additional weak connections prior to adolescence, acting with exuberance to compensate for defective connectivity, and when that compensation is destroyed by the normal competitive elimination of synapses in adolescence, schizophrenia emerges. Thus, aberrant neurodevelopment of both not forming adequate synapses and competitively and erroneously removing critical

synapses during adolescence may provide partial answers both to why schizophrenia has its full catastrophic onset at this critical stage of neurodevelopment, and why schizophrenia has aspects of a neurodevelopmental disorder, especially around the time of full onset of the disorder. Neurodegeneration and Schizophrenia Many patients with schizophrenia have a progressive, downhill course, especially when available treatments are not used consistently and there are long durations of untreated psychosis (Figure 4-66). Such observations have led to the notion that this illness may thus be neurodegenerative in nature. If schizophrenia looks as though it begins as aberrant neurodevelopment, it can seemingly appear that as it progresses, it is neurodegenerative. In other words, if the manner in which synapses are made and revised dramatically during adolescence potentially explains how the full onset of schizophrenia can be conceptualized as neurodevelopmental, then the manner in which synapses are made and revised in a more methodical manner throughout adult life could potentially explain how the long-term course of schizophrenia can be conceptualized as neurodegenerative. As stated earlier, normally, almost half of the brain's synapses are eliminated in adolescence (Figure 4-64). However, what is often not appreciated as well is that, in adulthood, you may lose (and replace elsewhere) about 7% of the synapses in your cortex every week! You can imagine if this process in adulthood runs amok over a long period of time that this could have pervasive cumulative consequences on adult brain development – or lack thereof – and be manifest as a progressively declining clinical course and even brain atrophy (Figure 4-66). That is, the strengthening or weakening of synapses occurs not only when these synapses first form, but continues throughout life as a sort of ongoing remodeling in response to what experiences the individual has, and thus how often that synapse is used or neglected. The strengthening or weakening of glutamate synapses in particular is an example of "activity dependent" or "use dependent" or "experience dependent" regulation of NMDA receptors and functionality at glutamate synapses. The old saying is, "use it or lose it." In schizophrenia, it is possible that abnormal synaptogenesis prevents normal synapses from strengthening even if the patient is "using" that synapse. It is also possible that the "wrong" synapses are "used" and strengthened, while the critical synapses for full functioning are not used and therefore lost along with the function those connections would have provided, yielding a progressive downhill course. Evidence is accumulating that allowing the positive symptoms of psychosis to persist unabated hastens the progressive loss of brain tissue associated with recurrent episodes of psychotic breaks (usually with repeated hospitalizations) in schizophrenia (Figure 4-66). Abnormalities in these continuing dynamics at NMDA receptors and glutamate synapses in particular may explain why the course of schizophrenia is progressive and changes over time for most patients; namely, from an asymptomatic period to a prodrome (maybe due to laying down deficient synapses initially in the

Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks Figure 4-66 Course of illness in schizophrenia. Although schizophrenia may begin as a neurodevelopmental disorder, its progressive nature suggests that it may also be a neurodegenerative disorder. Strengthening and weakening of synapses occurs throughout the lifetime. In schizophrenia, it is possible that abnormal synaptogenesis prevents normal synapses from strengthening even if they are being "used," and/or allows the "wrong" synapses to strengthen and be retained. There is evidence that recurrent episodes of psychotic breaks are associated with progressive loss of brain tissue in schizophrenia and loss of treatment responsiveness. 0 20 40 60 80 100 22 24 26 28 30 32 34 36 38 40 Response Prodrome Course of Illness in Schizophrenia First episode Level of functioning (%) Age (years) Chronic relapsing/residual symptoms Progressive brain tissue loss First episode Second episode Third episode Fourth episode Treatment resistance young brain) to a first-break psychosis

(when synaptic remodeling dramatically accelerates and perhaps the wrong synapses are eliminated) (Figure 4-66). One powerful indication of a downhill course in schizophrenia is what happens over time to treatment responsiveness and to the brain's structure. At the time of a first-break psychosis, there is often robust treatment responsiveness to medicines for psychosis, and the brain can appear grossly normal (see first episode brain in Figure 4-66). However, as the number of psychotic episodes mounts, often due to medication discontinuation, this can often be accompanied by declining treatment responsiveness to medications for psychosis and progressive loss of brain tissue observable on structural neuroimaging (see second, third, and fourth episodes and accompanying brain scans in Figure 4-66). Finally, the patient too often can progress to a state of pervasive negative and cognitive symptoms without recovery and with relative resistance to treatment with drugs for psychosis and with even more dramatic signs of brain degeneration observed with neuroimaging. The good news is that there is evidence that reducing the period of untreated psychosis may slow the progression of schizophrenia, and there is even hope that presymptomatic or prodromal treatments prior to the onset of full psychotic symptoms in schizophrenia may some day prevent or slow the onset of the illness altogether. In fact, there is an emerging concept in psychopharmacology in general that treatments that reduce symptoms can also be disease modifying. Whether or not the same agents that treat the symptoms of schizophrenia could also prevent the emergence of schizophrenia when given to high-risk individuals who are either presymptomatic or in a state with only mild prodromal symptoms remains speculative. However, it already seems quite clear that continuous treatment of patients with schizophrenia once it has begun is now the standard of care in treatment of schizophrenia in order to maximize the chances of preventing or slowing a deteriorating course, brain-tissue loss, a tripling of suicide attempts, and treatment resistance with repetitive relapses after the first episode. Is the neurodevelopmental onset and neurodegenerative progression of schizophrenia the case for any psychotic illness? Fortunately not. As will be briefly discussed in the following section of this chapter, although schizophrenia is the commonest and best known psychotic illness, it is not synonymous with psychosis, but is just one of many causes of psychosis and each has its own unique onset and course of illness. The natural history and course of illness for schizophrenia are not generally the same for every other psychotic illness, although severe forms of bipolar psychosis are sometimes lumped together with severe forms of

 schizophrenia and referred to together as "serious mental illness" or SMI. These forms of psychosis can all have a dismal functional outcome, including homelessness, premature death, and even confinement in the criminal justice system. Schizophrenia affects approximately 1% of the population, and in the United States there are over 300,000 acute schizophrenic episodes annually. Between 25% and 50% of schizophrenia patients attempt suicide, and up to 10% eventually succeed, contributing to a mortality rate eight times greater than that of the general population. Life expectancy of a schizophrenia patient may be 20 to 30 years shorter than the general population, not only due to suicide, but also due to premature cardiovascular disease. Accelerated mortality from premature cardiovascular disease in schizophrenia patients is caused by genetic and lifestyle factors, such as smoking, unhealthy diet, and lack of exercise, leading to obesity and diabetes, but also – sorrily – from treatment with some antipsychotic drugs that themselves cause an increased incidence of obesity and diabetes and thus increased cardiac risk. In the United States, over 20% of all social security benefit days are used for the care of

schizophrenia patients. The direct and indirect costs of schizophrenia in the US alone are estimated to be in the tens of billions of dollars every year. Many of these costs in the US are borne by the criminal justice system of courts, jails, prisons, and state and forensic hospitals that provide housing and treatment for patients with schizophrenia due to the lack of adequate outpatient treatment or long-term hospitals, as has already been discussed. This may be changing due to innovative outpatient diversion programs that are beginning to divert patients from the criminal justice system to community housing and treatment, which is far less expensive and possibly more humane and effective than alternating homelessness and no treatment with incarceration in a revolving-door fashion. OTHER PSYCHOTIC ILLNESSES Psychotic disorders have psychotic symptoms as their defining features, but there are several other disorders in which psychotic symptoms may be present but are not necessary for the diagnosis. Those disorders that require the presence of psychosis as a defining feature of the diagnosis include schizophrenia, substance/ medication-induced (i.e., drug-induced) psychotic disorder, schizophreniform disorder, schizoaffective disorder, delusional disorder, brief psychotic disorder, shared psychotic disorder, psychotic disorder due to Table 4-8 Disorders in which psychosis is a defining feature Schizophrenia Substance/medication-induced psychotic disorders Schizophreniform disorder Schizoaffective disorder Delusional disorder Brief psychotic disorder Shared psychotic disorder Psychotic disorder due to another medical condition Childhood psychotic disorder Table 4-9 Disorders in which psychosis is an associated feature Mania Depression Cognitive disorders Alzheimer disease and other dementias Parkinson’s disease another medical condition, and childhood psychotic disorder (Table 4-8). Disorders that may or may not have psychotic symptoms as an associated feature include mood disorders (both bipolar mania and many types of depression), Parkinson’s disease (known as Parkinson’s disease psychosis or PDP), and several cognitive disorders such as Alzheimer disease and other forms of dementia (Table 4-9). Symptoms of schizophrenia are not necessarily unique to schizophrenia. It is important to recognize that several illnesses other than schizophrenia can share some of the same five symptom dimensions described here for schizophrenia and shown in Figure 4-59. Thus, numerous disorders in addition to schizophrenia can have positive symptoms (delusions and hallucinations), including Parkinson’s disease, bipolar disorder, schizoaffective disorder, psychotic depression, Alzheimer disease and other organic dementias, childhood psychotic illnesses, drug-induced psychoses, and others. Negative symptoms can also occur in disorders other than schizophrenia, especially mood disorders and dementias where it can be difficult to distinguish between negative symptoms such as reduced speech, poor eye contact, diminished emotional responsiveness, reduction of interest, and reduced social drive and the cognitive and affective symptoms that occur in these other disorders.

Schizophrenia is certainly not the only disorder with cognitive symptoms. Autism, post-stroke (vascular or multi-infarct) dementia, Alzheimer disease, and many other organic dementias (Parkinsonian/Lewy body dementia; frontotemporal/Pick’s dementia, etc.), and mood disorders including major depression and bipolar depression can also be associated with various forms of cognitive dysfunction. Mood-Related Psychosis, Psychotic Depression, Psychotic Mania Mood disorders, from unipolar depression to bipolar disorder, can have symptoms of psychosis that accompany their mood symptoms. We have already discussed how schizophrenia can have symptoms of depressed mood, anxious mood, guilt, tension, irritability, and worry. Thus, schizophrenia can have affective symptoms and mood disorders can have psychotic symptoms. The point is, whenever psychotic symptoms are encountered, they need to be treated, and

whenever affective symptoms are encountered, they too need to be treated, not only to relieve the current affective symptoms, but to prevent suicide, which is unfortunately common in patients with schizophrenia. Parkinson’s Disease Psychosis Parkinson’s disease begins of course with prominent motor symptoms. Motor symptoms are believed to be caused by deposition of Lewy bodies containing α-synuclein in the substantia nigra. However, Parkinson’s disease progresses in over half the cases, especially in those with concomitant dementia, to psychosis with delusions and hallucinations, called Parkinson’s disease psychosis (PDP). Several causes are proposed for PDP, the most prominent theory being the accumulation of Lewy bodies in the cerebral cortex as well as in serotonin cell bodies in the midbrain raphe (Figures 4-52C and 4-54). Psychosis in Parkinson’s disease is a big risk factor for hospital admissions, for nursing-home placement, and for mortality, with mortality after 3 years of about 40% for Parkinson’s patients after onset of psychosis. PDP is not simply schizophrenia in a Parkinson’s patient. First, the hallucinations in PDP tend to be visual rather than auditory (e.g., seeing people, animals). Second, the delusions tend to be a particular type of persecutory belief (e.g., the impression that someone, particularly a loved one, is trying to harm, steal from, or deceive), or jealousy (e.g., the impression that your partner is cheating on you). Third, insight into the false nature of these hallucinations and delusions is initially Chapter 4: Psychosis, Schizophrenia, and Neurotransmitter Networks retained, which is not characteristic of psychosis in psychiatric disorders. PDP is conceptualized as an imbalance in serotonin and dopamine with upregulation of 5HT2A receptors and treatable with 5HT2A antagonists (Figure 4-52C and Figure 4-54). Dementia-Related Psychosis As the world’s population ages, and without a known disease-modifying target to prevent the relentless march of dementia, the behavioral symptoms of dementia are attaining more and more attention, as dementia patients are surviving longer and as their dementia progresses. Agitation and psychosis are particularly important, common, and disabling behavioral symptoms of dementia and can be difficult to distinguish from each other in dementia. However, it is important to do so whenever possible, as the neuronal pathways for these different behaviors are also different, and so are their evolving treatments. Agitation in dementia is discussed in detail in Chapter 12 on dementia. In this chapter we have only briefly covered psychosis in dementia. Although we have discussed how psychosis is generally defined as the presence of delusions and/or hallucinations, it is delusions that are often more common in many dementias, especially Alzheimer disease, where there is a 5-year-period prevalence of delusions of over 50%. However, in Lewy body dementia, patients often have the same visual hallucinations and delusions characteristic of PDP, not surprising since Lewy body deposition in the cerebral cortex is thought to be a contributing cause of psychosis in both conditions. From a pharmacological point of view, it may matter little what causes the disruption of brain pathways that brings on the symptoms of psychosis. It may matter far more where the pathways are disrupted and which pathways are disrupted. That is, whether an amyloid plaque, a tau tangle, a small stroke, or a Lewy body disrupts the glutamate–GABA connections or the serotonin–glutamate connections in the cerebral cortex, it may not matter as long as the disruption leads to downstream dopamine hyperactivity and the symptoms of delusions and hallucinations (Figure 4-52D and 4-55). When those same pathological conditions occur in other pathways, presumably those patients do not experience psychosis, but perhaps the other symptoms of dementia, such as memory disturbances and agitation. Alzheimer disease dementia patients may have a serotonin component to their psychosis, since serotonin in presubiculum of the cerebral cortex is reported 157

 to be low in patients with psychotic compared with nonpsychotic dementia. Furthermore, the C102 allele of the 5HT2A receptor gene may also be

associated with psychosis in Alzheimer disease. In addition, Alzheimer patients with psychosis have significantly more plaques and tangles in the medial temporal-presubicular area and middle frontal cortex and five times higher levels of abnormal paired helical filament-tau protein in entorhinal and temporal cortices. If these lesions disrupt regulation of glutamate–GABA–serotonin–dopamine circuits, they would be expected to be the cause of psychosis (Figure 4-52D and 4-55). SUMMARY This chapter has provided a brief description of psychosis and an extensive explanation of the three principal theories of psychosis, namely those linked to dopamine, glutamate, and serotonin (5HT). The major dopamine, glutamate, and serotonin pathways in the brain have all been described. Overactivity of the mesolimbic dopamine system may mediate the positive symptoms of psychosis and may be linked to hypofunctioning NMDA glutamate receptors in parvalbumin-containing GABA interneurons in the prefrontal cortex and hippocampus in some psychotic disorders such as schizophrenia. Underactivity of the mesocortical dopamine system may mediate the negative, cognitive, and affective symptoms of schizophrenia and could also be linked to hypofunctioning NMDA receptors at different GABA interneurons. Imbalance in serotonin neurotransmission, particularly excessive activity at 5HT2A receptors in the cortex, may explain psychosis in Parkinson’s disease. Imbalance between serotonin and GABA neurotransmission at glutamate neurons in the cerebral cortex due to neurodegenerative processes knocking out GABA inhibition may lead to excessive excitation of glutamate neurons by serotonin acting at 5HT2A receptors and that can be relieved by 5HT2A antagonists. The synthesis, metabolism, reuptake, and receptors for dopamine, glutamate, and serotonin are all described in this chapter. D2 receptors are targets for drugs that treat psychosis, as are 5HT2A receptors specifically for the psychosis associated with Parkinson’s disease and with dementias. NMDA glutamate receptors require interaction not only with the neurotransmitter glutamate, but also with the cotransmitters glycine or D-serine. Dysconnectivity of NMDA-receptor-containing synapses caused by genetic and environmental/ epigenetic influences is a major hypothesis for the cause of schizophrenia, including its upstream glutamate hyperactivity and NMDA receptor hypofunction, as well as its downstream increases in mesolimbic dopamine but decreases in mesocortical dopamine. A whole host of susceptibility genes that regulate neuronal connectivity and synapse formation may represent a hypothetical central biological flaw in schizophrenia.