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neurobehavioral process is likely modulated by multiple interacting neurotransmitter systems, including monoamines. This complexity poses a major challenge to understanding the precise molecular, cellular, and systems level pathways through which various monoamine neurotransmitters affect neuropsychiatric disorders. However, recent advances in

human genetics and genomics, as well as in experimental neuroscience, have shed light on this question. Molecular cloning has identified a large number of genes that regulate monoaminergic neurotransmission, such as the enzymes, receptors, and transporters that mediate the synthesis, cellular actions, and cellular reuptake of these neurotransmitters, respectively. Human genetics studies have provided evidence of tantalizing links between allelic variants in specific monoamine-related genes and psychiatric disorders and trait abnormalities, whereas the ability to modify gene function and cellular activity in experimental animals has clarified the roles of specific genes and neural pathways in mediating behavioral processes. Monoamines act on target cells by binding to specific cell-surface receptors. There are multiple receptor subtypes for each monoamine, which are expressed in diverse regions and subcellular locales and which engage a variety of intracellular signaling pathways. This panoply of receptors thus allows each monoamine neurotransmitter to modulate target cells in many ways; the same molecule may activate some cells while inhibiting others, depending on which receptor subtype is expressed by each cell. The various monoamines are discussed below. Serotonin Although only one in a million CNS neurons produces serotonin, these cells influence virtually all aspects of CNS function. The cell bodies of these serotonergic neurons are clustered in the midline raphe nuclei of the brainstem; the rostral raphe nuclei send ascending axonal projections throughout the brain, whereas the descending caudal raphe nuclei send projections into the medulla, cerebellum, and spinal cord (Fig. 1.4-1). The descending serotonergic fibers that innervate the dorsal horn of the spinal cord have been implicated in the suppression of nociceptive pathways, a finding that may relate to the pain-relieving effects of some antidepressants. The tonic firing of CNS serotonin neurons varies across the sleep–wake cycle, with an absence of activity during rapid eye movement (REM) sleep. Increased serotonergic firing is observed during rhythmic motor behaviors and suggests that serotonin modulates some forms of motor output. FIGURE 1.4-1 Brain serotonergic pathways (in rats). Serotonergic neurons are located in brainstem midline raphe nuclei and project throughout the neuraxis. (There is an approximate similarity between monoamine pathways in rats and in humans.) AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CRN, caudal raphe nuclei; CTX, neocortex; DR, dorsal raphe nucleus; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; MR, median raphe nucleus; NAc, nucleus accumbens; OB, olfactory bulb;

SN, substantia nigra; TE, tectum; TH, thalamus; TM, tuberomammillary nucleus of hypothalamus. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:65.) Most serotonergic innervation of the cortex and limbic system arises from the dorsal and median raphe nuclei in the midbrain; the serotonergic neurons in these areas send projections through the medial forebrain bundle into target forebrain regions. The median raphe provides most of the serotonergic fibers that innervate the limbic system, whereas the dorsal raphe nucleus provides most of the serotonergic fibers that innervate the striatum and thalamus. In addition to the different target fields of these serotonergic nuclei, there are also cellular differences between their constituent neurons. Dorsal raphe serotonergic fibers are fine, with small vesicle-coated swellings called varicosities, whereas median raphe fibers have large spherical or beaded varicosities. It is unclear to what extent serotonin acts

as a true synaptic or “private” neurotransmitter versus action as a local endocrine hormone or “social transmitter,” or whether its roles differ depending on the fiber type from which it is released. These fibers show differential sensitivity to the neurotoxic effects of the amphetamine analog 3,4-methylenedioxy-methamphetamine (MDMA, “ecstasy”), which lesions the fine axons of the dorsal raphe while sparing the thick beaded axons of the median raphe. The significance of these morphological differences is unclear, although recent work has identified functional differences between the serotonergic neurons of the dorsal and median raphe nuclei. Dopamine Dopamine neurons are more widely distributed than those of other monoamines, residing in the midbrain substantia nigra and ventral tegmental area and in the periaqueductal gray, hypothalamus, olfactory bulb, and retina. In the periphery, dopamine is found in the kidney where it functions to produce renal vasodilation, diuresis, and natriuresis. Three dopamine systems are highly relevant to psychiatry: The nigrostriatal, mesocorticolimbic, and tuberohypophyseal system (Fig. 1.4-2). Degeneration of the nigrostriatal system causes Parkinson’s disease and has led to an intense research focus on the development and function of dopamine neurons in the midbrain substantia nigra nuclei. Dopamine cell bodies in the pars compacta division of this region send ascending projections to the dorsal striatum (especially to the caudate and putamen) and thereby modulate motor control. The extrapyramidal effects of antipsychotic drugs are thought to result from the blockade of these striatal dopamine receptors.

FIGURE 1.4-2 Brain dopaminergic pathways (in rats).The three principal dopaminergic pathways: (1) nigrostriatal pathway, (2) mesocorticolimbic pathway, and (3) tuberohypophyseal pathway. AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; NAc, nucleus accumbens; OB, olfactory bulb; PFC, prefrontal cortex; PI, pituitary; SNC, substantia nigra pars compacta; TE, tectum; TH, thalamus; VTA, ventral tegmental area. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:66.) The midbrain ventral tegmental area (VTA) lies medial to the substantia nigra and contains dopaminergic neurons that give rise to the mesocorticolimbic dopamine system. These neurons send ascending projections that innervate limbic structures, such as the nucleus accumbens and amygdala; the mesoaccumbens pathway is a central element in the neural representation of reward, and intense research has been devoted to this area in recent years. All known drugs of abuse activate the mesoaccumbens dopamine pathway, and plastic changes in this pathway are thought to underlie drug addiction. The mesolimbic projection is believed to be a major target for the antipsychotic properties of dopamine receptor antagonist drugs in controlling the positive symptoms of schizophrenia, such as hallucinations and delusions. VTA dopamine neurons also project to cortical structures, such as the prefrontal cortex, and modulate working memory and attention; decreased activity in this pathway is proposed to underlie negative symptoms of schizophrenia. Thus antipsychotic drugs that decrease positive symptoms by blocking dopamine receptors in the mesolimbic pathway may simultaneously worsen these negative symptoms by blocking similar dopamine receptors in the mesocortical pathway. The decreased risk of extrapyramidal side effects seen with clozapine (Clozaril; versus other typical antipsychotic medications) is thought to be due to its relatively selective effects on this mesocortical projection. The tuberohypophyseal system consists of dopamine neurons in the hypothalamic arcuate and paraventricular nuclei that project to the pituitary gland and thereby inhibit prolactin release. Antipsychotic drugs that block dopamine receptors in the pituitary may thus disinhibit prolactin release and cause galactorrhea. Norepinephrine and Epinephrine The postganglionic sympathetic

neurons of the autonomic nervous system release norepinephrine, resulting in widespread peripheral effects including tachycardia and elevated blood pressure. The adrenal medulla releases epinephrine, which produces similar effects; epinephrine-secreting pheochromocytoma tumors produce bursts of sympathetic activation, central arousal, and anxiety. Norepinephrine-producing neurons are found within the brain in the pons and medulla in two major clusterings: The locus ceruleus (LC) and the lateral tegmental noradrenergic nuclei (Fig. 1.4-3). Noradrenergic projections from both of these regions ramify extensively as they project throughout the neuraxis. In humans, the LC is found in the dorsal portion of the caudal pons and contains approximately 12,000 tightly packed neurons on each side of the brain. These cells provide the major noradrenergic projections to the neocortex, hippocampus, thalamus, and midbrain tectum. The activity of LC

neurons varies with the animal's level of wakefulness. Firing rates are responsive to novel and/or stressful stimuli, with largest responses to stimuli that disrupt ongoing behavior and reorient attention. Altogether, physiological studies indicate a role for this structure in the regulation of arousal state, vigilance, and stress response. The projections from lateral tegmental nucleus neurons, which are loosely scattered throughout the ventral pons and medulla, partially overlap those of the LC. Fibers from both cell groups innervate the amygdala, septum, and spinal cord. Other regions, such as the hypothalamus and lower brainstem, receive adrenergic inputs predominantly from the lateral tegmental nucleus. The relatively few neurons that utilize epinephrine as a neurotransmitter are located in the caudal pons and medulla, intermingled with noradrenergic neurons. Projections from these groups ascend to innervate the hypothalamus, LC, and visceral efferent and afferent nuclei of the midbrain. FIGURE 1.4-3 Brain noradrenergic pathways (in rats). Projections of noradrenergic neurons located in the locus ceruleus (LC) and lateral tegmental noradrenergic nuclei (LTN). AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; HY, hypothalamus; OB, olfactory bulb; TE, tectum; TH, thalamus. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:66.) Histamine Histamine is perhaps best known for its role in allergies. It is an inflammatory mediator stored in mast cells and released upon cellular interaction with allergens. Once released, histamine causes vascular leakage and edema and other facial and topical allergy symptoms. In contrast, central histaminergic neural pathways have only more recently been characterized by immunocytochemistry using antibodies to the synthetic enzyme histidine decarboxylase and to histamine. Histaminergic cell bodies are located within a region of the posterior hypothalamus termed the tuberomammillary nucleus. The activity of tuberomammillary neurons is characterized by firing that varies across the sleep–wake cycle, with the highest activity during the waking state, slowed firing during slow-wave sleep, and absence of firing during REM sleep. Histaminergic fibers project diffusely throughout the brain and spinal cord (Fig. 1.4-4). Ventral ascending projections course through the medial forebrain bundle and then innervate the hypothalamus, diagonal band, septum, and olfactory bulb. Dorsal ascending projections

innervate the thalamus, hippocampus, amygdala, and rostral forebrain. Descending projections travel through the midbrain central gray to the dorsal hindbrain and spinal cord. The fibers have varicosities that are seldom associated with classical synapses, and histamine has been proposed to act at a distance from its sites of release, like a local hormone. The hypothalamus receives the densest histaminergic innervation, consistent with a role for this transmitter in the regulation of autonomic and neuroendocrine processes. In addition, strong histaminergic innervation is seen in

monoaminergic and cholinergic nuclei. FIGURE 1.4-4 Brain histaminergic pathways (in rats). Histaminergic neurons are located in the tuberomammillary nucleus of the caudal hypothalamus (TM) and project to the hypothalamus (HY) and more distant brain regions. CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; NAc, nucleus accumbens; OB, olfactory bulb; TE, tectum; TH, thalamus. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:67.) Acetylcholine Within the brain, the axonal processes of cholinergic neurons may either project to distant brain regions (projection neurons) or contact local cells within the same structure (interneurons). Two large clusters of cholinergic projection neurons are found within the brain: The basal forebrain complex and the mesopontine complex (Fig. 1.45). The basal forebrain complex provides most of the cholinergic innervation to the nonstriatal telencephalon. It consists of cholinergic neurons within the nucleus basalis of Meynert, the horizontal and vertical diagonal bands of Broca, and the medial septal nucleus. These neurons project to widespread areas of the cortex and amygdala, to the anterior cingulate gyrus and olfactory bulb, and to the hippocampus, respectively. In Alzheimer's disease there is significant degeneration of neurons in the nucleus basalis, leading to substantial reduction in cortical cholinergic innervation. The extent of neuronal loss correlates with the degree of dementia, and the cholinergic deficit may contribute to the cognitive decline in this disease, consistent with the beneficial effects

of drugs that promote acetylcholine signaling in this disorder. FIGURE 1.4-5 Brain cholinergic projection pathways (in rats). The majority of cholinergic projection neurons are located in the basal forebrain complex (BFC) and the mesopontine complex (MPC). AMG, amygdala; CBM, cerebellum; cc, corpus callosum; CP, caudate putamen; CTX, neocortex; HI, hippocampus; HY, hypothalamus; LC, locus ceruleus; NAc, nucleus accumbens; OB, olfactory bulb; SN, substantia nigra; TE, tectum; TH, thalamus. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:67.) The mesopontine complex consists of cholinergic neurons within the pedunculopontine and laterodorsal tegmental nuclei of the midbrain and pons and provides cholinergic innervation to the thalamus and midbrain areas (including the dopaminergic neurons of the ventral tegmental area and substantia nigra) and descending innervation to other brainstem regions such as the LC, dorsal raphe, and cranial nerve nuclei. In contrast to central serotonergic, noradrenergic, and histaminergic neurons, cholinergic neurons may continue to fire during REM sleep and have been proposed to play a role in REM sleep induction. Acetylcholine is also found within interneurons of several brain regions, including the striatum. The modulation of striatal cholinergic transmission has been implicated in the antiparkinsonian actions of anticholinergic agents. Within the periphery, acetylcholine is a prominent neurotransmitter, located in motoneurons innervating skeletal muscle, preganglionic autonomic neurons, and postganglionic parasympathetic neurons. Peripheral acetylcholine mediates the characteristic postsynaptic effects of the parasympathetic system, including bradycardia and reduced blood pressure, and enhanced digestive function. MONOAMINE SYNTHESIS, STORAGE, AND DEGRADATION In addition to neuroanatomic similarities, monoamines are also synthesized, stored, and degraded in similar ways (Fig. 1.4-6). Monoamines are synthesized within neurons from common amino acid precursors (Fig. 1.4-6, step 1) and taken up into synaptic vesicles by way of a vesicular monoamine transporter (Fig. 1.4-6, step 2). On stimulation, vesicles within nerve terminals fuse with the presynaptic terminal and release the neurotransmitter into the synaptic cleft (Fig. 1.4-6, step 3). Once released, the monoamines interact with postsynaptic receptors to alter the function of postsynaptic cells (Fig. 1.4-6, step 4),

and they may also act on presynaptic autoreceptors on the

nerve terminal to suppress further release (Fig. 1.4-6, step 5). In addition, released monoamines may be taken back up from the synaptic cleft into the nerve terminal by plasma membrane transporter proteins (Fig. 1.4-6, step 6), a process known as reuptake. Reuptake plays an important role in limiting the total magnitude and temporal duration of monoamine signaling. Once monoamines are taken up, they may be subject to enzymatic degradation (Fig. 1.4-6, step 7), or they may be protected from degradation by uptake into vesicles. The processing of acetylcholine differs from this scheme and is described later in this section. FIGURE 1.4-6 Schematic diagram of a monoaminergic synapse. Steps involved in synaptic transmission are described in the text. MAO, monoamine oxidase. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:68.) SEROTONIN The CNS contains less than 2 percent of the serotonin in the body; peripheral serotonin is located in platelets, mast cells, and enterochromaffin cells. More than 80 percent of all the serotonin in the body is found in the gastrointestinal system, where it modulates motility and digestive functions. Platelet serotonin promotes aggregation and clotting through a most unusual mechanism: The covalent linkage of serotonin molecules to small GTP-binding proteins, which can then activate these proteins, is a process termed "serotonylation." Peripheral serotonin cannot cross the blood–brain barrier, so serotonin is synthesized within the brain as well. Serotonin is synthesized from the amino acid tryptophan, which is derived from the diet. The rate-limiting step in serotonin synthesis is the hydroxylation of tryptophan by the enzyme tryptophan hydroxylase to form 5hydroxytryptophan (4-HT) (Fig. 1.4-7). Two isoforms of tryptophan hydroxylase exist— one isoform is found mainly in the periphery, whereas the second isoform is restricted to

the CNS. FIGURE 1.4-7 Synthesis and catabolism of serotonin. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:68.)

Under normal circumstances, tryptophan concentration is rate limiting in serotonin synthesis. Therefore, much attention has focused on the factors that determine tryptophan availability. Unlike serotonin, tryptophan is taken up into the brain by way of a saturable active carrier mechanism. Because tryptophan competes with other large neutral amino acids for transport, brain uptake of this amino acid is determined both by the amount of circulating tryptophan and by the ratio of tryptophan to other large neutral amino acids. This ratio may be elevated by carbohydrate intake, which induces insulin release and the uptake of many large neutral amino acids into peripheral tissues. Conversely, high-protein foods tend to be relatively low in tryptophan, thus lowering this ratio. Moreover, the administration of specialized low tryptophan diets produces significant declines in brain serotonin levels. After tryptophan hydroxylation, 5-hydroxytryptophan is rapidly decarboxylated by aromatic amino acid decarboxylase (an enzyme also involved in dopamine synthesis) to form serotonin. The first step in the degradation of serotonin is mediated by monoamine oxidase type A (MAOA), which oxidizes the amino group to form an aldehyde. MAOA is located in mitochondrial membranes and is nonspecific in its substrate specificity; in addition to serotonin, it oxidizes norepinephrine. The elevation of serotonin levels by MAO inhibitors (MAOIs) is believed to underlie the antidepressant efficacy of these drugs. After oxidation by MAOA, the resulting aldehyde is further oxidized to 5-hydroxyindoleacetic acid (5-HIAA). Levels of 5-HIAA are often measured as a correlate of serotonergic system activity, although the relationship of these

levels to serotonergic neuronal activity remains unclear. Catecholamines The catecholamines are synthesized from the amino acid tyrosine, which is taken up into the brain via an active transport mechanism (Fig. 1.4-8). Within catecholaminergic neurons, tyrosine hydroxylase catalyzes the addition of a hydroxyl group to the meta position of tyrosine, yielding L-dopa. This rate-limiting step in catecholamine synthesis is subject to inhibition by high levels of catecholamines (end-product inhibition). Because tyrosine hydroxylase is normally saturated with substrate, manipulation of tyrosine levels does not readily affect the rate of catecholamine synthesis. Once formed, L-dopa is rapidly converted to dopamine by dopa decarboxylase, which is located in the cytoplasm. It is now recognized that this enzyme acts not only on L-dopa but also on all naturally occurring aromatic L-amino acids, including tryptophan, and thus it is more properly termed aromatic amino acid decarboxylase. In noradrenergic and adrenergic neurons, dopamine is actively transported into storage vesicles, where it is oxidized by dopamine β-hydroxylase to form norepinephrine. In adrenergic neurons and the adrenal medulla, norepinephrine is converted to epinephrine by phenylethanolamine Nmethyltransferase (PNMT), which is located within the cytoplasmic compartment.

FIGURE 1.4-8 Synthesis of catecholamines. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:69.) Two enzymes that play major roles in the degradation of catecholamines are monoamine oxidase and catechol-Omethyltransferase (COMT). MAO is located on the outer membrane of mitochondria, including those within the terminals of adrenergic fibers, and oxidatively deaminates catecholamines to their corresponding aldehydes. Two MAO isozymes with differing substrate specificities have been identified: MAOA, which preferentially deaminates serotonin and

norepinephrine, and MAO type B (MAOB), which deaminates dopamine, histamine, and a broad spectrum of phenylethylamines. Neurons contain both MAO isoforms. The blockade of monoamine catabolism by MAO inhibitors produces elevations in brain monoamine levels. MAO is also found in peripheral tissues such as the gastrointestinal tract and liver, where it prevents the accumulation of toxic amines. For example, peripheral MAO degrades dietary tyramine, an amine that can displace norepinephrine from sympathetic postganglionic nerve endings, producing hypertension if tyramine is present in sufficient quantities. Thus patients treated with MAO inhibitors are cautioned to avoid pickled and fermented foods that typically have high levels of tyramine. Catechol-O-methyltransferase (COMT) is located in the cytoplasm and is widely distributed throughout the brain and peripheral tissues, although little to none is found in adrenergic neurons. It has a wide substrate specificity, catalyzing the transfer of methyl groups from S-adenosyl methionine to the m-hydroxyl group of most catechol compounds. The catecholamine metabolites produced by these and other enzymes are frequently measured as indicators of the activity of catecholaminergic systems. In humans, the predominant metabolites of dopamine and norepinephrine are homovanillic acid (HVA) and 3-methoxy-4hydroxyphenylglycol (MHPG), respectively. Histamine As is the case for serotonin, the brain contains only a small portion of the histamine found in the body. Histamine is distributed throughout most tissues of the body, predominantly in mast cells. Because it does not readily cross the blood–brain barrier, it is believed that histamine is synthesized within the brain. In the brain, histamine is formed by the decarboxylation of the amino acid histidine by a specific L-histidine decarboxylase. This enzyme is not normally saturated with substrate, so synthesis is sensitive to histidine levels. This is consistent with the observation that the peripheral administration of histidine elevates brain histamine levels. Histamine is metabolized in the brain by

histamine N-methyltransferase, producing methylhistamine. In turn, methylhistamine undergoes oxidative deamination by MAOB. Acetylcholine Acetylcholine is synthesized by the transfer of an acetyl group from acetyl coenzyme A (ACoA) to choline in a reaction mediated by the enzyme choline acetyltransferase (ChAT). The majority of choline within the brain is transported from the blood rather than being synthesized de novo. Choline is taken up into cholinergic neurons by a highaffinity active transport mechanism, and this uptake is the rate-limiting step in acetylcholine synthesis. The rate of choline transport is regulated such that increased cholinergic neural activity is associated with enhanced choline uptake. After synthesis, acetylcholine is stored in synaptic vesicles through the action of a vesicular acetylcholine transporter. After vesicular release, acetylcholine is rapidly broken down by hydrolysis by acetylcholinesterase, located in the synaptic cleft. Much of the choline produced by this hydrolysis is then taken back into the presynaptic terminal via the choline transporter. Of note, although acetylcholinesterase is localized primarily to cholinergic neurons and synapses, a second class of cholinesterase termed butyrylcholinesterase is found primarily in the liver and plasma as well as in glia. In the

treatment of Alzheimer’s disease, strategies aimed at enhancing cholinergic function, primarily through the use of cholinesterase inhibitors to prevent normal degradation of acetylcholine, have shown moderate efficacy in ameliorating cognitive dysfunction as well as behavioral disturbances. Cholinesterase inhibitors are also used in the treatment of myasthenia gravis, a disease characterized by weakness due to blockade of neuromuscular transmission by autoantibodies to acetylcholine receptors. Transporters A great deal of progress has been made in the molecular characterization of the monoamine plasma membrane transporter proteins. These membrane proteins mediate the reuptake of synaptically released monoamines into the presynaptic terminal. This process also involves cotransport of Na^+ and Cl^- ions and is driven by the ion concentration gradient generated by the plasma membrane Na^+/K^+ ATPase. Monoamine reuptake is an important mechanism for limiting the extent and duration of activation of monoaminergic receptors. Reuptake is also a primary mechanism for replenishing terminal monoamine neurotransmitter stores. Moreover, transporters serve as molecular targets for a number of antidepressant drugs, psychostimulants, and monoaminergic neurotoxins. Whereas transporter molecules for serotonin (SERT), dopamine (DAT), and norepinephrine (NET) have been well characterized, transporters selective for histamine and epinephrine have not been demonstrated. Among drugs of abuse, cocaine binds with high affinity to all three known monoamine transporters, although the stimulant properties of the drug have been attributed primarily to its blockade of DAT. This view has been recently supported by the absence of cocaine-induced locomotor stimulation in a strain of mutant mice engineered to lack this molecule. In fact, psychostimulants produce a paradoxical locomotor suppression in these animals that has been attributed to their blockade of the serotonin transporter. The rewarding properties of cocaine have also been attributed primarily to dopamine transporter inhibition, although other targets mediate these effects as well, since cocaine still has rewarding effects in mice lacking the dopamine transporter. It appears that serotonergic as well as dopaminergic mechanisms may be involved. Transporters may also provide routes that allow neurotoxins to enter and damage monoaminergic neurons; examples include the dopaminergic neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and the serotonergic neurotoxin MDMA. Vesicular Monoamine Transporter In addition to the reuptake of monoamines into the presynaptic nerve terminal, a second transport process serves to concentrate and store monoamines within synaptic vesicles. The transport and storage of monoamines in vesicles may serve several purposes: (1) to enable the regulated release of transmitter under

appropriate physiological stimulation, (2) to protect monoamines from degradation by MAO, and (3) to protect neurons from the toxic effects of free radicals produced by the oxidation of cytoplasmic monoamines. In contrast with the plasma membrane transporters, a single type of vesicular monoamine transporter is believed to mediate the uptake of

monoamines into synaptic vesicles within the brain. Consistent with this, blockade of this vesicular monoamine transporter by the antihypertensive drug reserpine (Serpasil) has been found to deplete brain levels of serotonin, norepinephrine, and dopamine and to increase the risk of suicide and affective dysfunction. RECEPTORS Ultimately, the effects of monoamines on CNS function and behavior depend on their interactions with receptor molecules. The binding of monoamines to these plasma membrane proteins initiates a series of intracellular events that modulate neuronal excitability. Unlike the transporters, multiple receptor subtypes exist for each monoamine neurotransmitter (Table 1.4-1). Table 1.4-1 Monoamine Receptors: Overview Serotonin Receptors The 5-hydroxytryptophan type 1 (5-HT1) receptors comprise the largest serotonin receptor subfamily, with human subtypes designated 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, and 5-HT1F. All five 5-HT1 receptor subtypes display intronless gene structures, high affinities for serotonin, and adenylate cyclase inhibition. The most intensively studied of

these has been the 5-HT1A receptor. This subtype is found on postsynaptic membranes of forebrain neurons, primarily in the hippocampus, cortex, and septum and on serotonergic neurons, where it functions as an inhibitory somatodendritic autoreceptor. There is significant interest in the 5-HT1A receptor as a modulator of both anxiety and depression. The downregulation of 5-HT1A autoreceptors by the chronic administration of serotonin reuptake inhibitors has been implicated in their antidepressant effects, and SSRIs may produce some behavioral effects via increases in hippocampal neurogenesis mediated by postsynaptic 5-HT1A receptor activation. In addition, partial 5-HT1A receptor agonists such as buspirone (BuSpar) display both anxiolytic and antidepressant properties. Much recent attention has focused on the contributions of 5-HT2A/C receptors to the actions of atypical antipsychotic drugs such as clozapine (Clozaril), risperidone (Risperdal), and olanzapine (Zyprexa). Analysis of the receptor-binding properties of these drugs has led to the hypothesis that 5-HT2A receptor blockade correlates with the therapeutic effectiveness of atypical antipsychotics. Of interest, the 5-HT2A receptor has also been implicated in the cognitive process of working memory, a function believed to be impaired in schizophrenia. The 5-HT2C receptor is expressed at high levels in many CNS regions, including the hippocampal formation, prefrontal cortex, amygdala, striatum, hypothalamus, and choroid plexus. Stimulation of 5-HT2C receptors has been proposed to produce anxiogenic effects as well as anorectic effects, which may result from interactions with the hypothalamic melanocortin and leptin pathways. 5-HT2C receptors may also play a role in the weight gain and development of type 2 diabetes mellitus associated with atypical antipsychotic treatment. Indeed, a line of mice lacking this receptor subtype exhibits an obesity syndrome associated with overeating and enhanced seizure susceptibility, suggesting that this receptor regulates neuronal network excitability. A variety of antidepressant and antipsychotic drugs antagonize 5-HT2C receptors with high affinity. Conversely, hallucinogens such as lysergic acid diethylamide (LSD) display agonist activity at 5-HT2 (and other) serotonin receptor subtypes. 5-HT2C receptor transcripts also undergo RNA editing, producing isoforms of the receptor with significantly altered basal versus serotonin-induced activity. Alterations in 5-HT2C receptor messenger ribonucleic acid (mRNA) editing have been found in the brains of suicide victims with a history of major depression, and SSRIs have been shown to alter

these editing patterns. Dopamine Receptors In 1979, it was clearly recognized that the actions of dopamine are mediated by more than one receptor subtype. Two dopamine receptors, termed D1 and D2, were

distinguished on the basis of differential binding affinities of a series of agonists and antagonists, distinct effector mechanisms, and distinct distribution patterns within the CNS. It was subsequently found that the therapeutic efficacy of antipsychotic drugs correlated strongly with their affinities for the D2 receptor, implicating this subtype as an important site of antipsychotic drug action. Recent molecular cloning studies have identified three additional dopamine receptor genes encoding the D3, D4, and D5 dopamine receptors. On the basis of their structure, pharmacology, and primary effector mechanisms, the D3 and D4 receptors are considered to be “D2-like,” and the D5 receptor “D1-like.” The functional roles of the recently discovered subtypes remain to be definitively elucidated. The D1 receptor was initially distinguished from the D2 subtype by its high affinity for the antagonist SCH 23390 and relatively low affinity for butyrophenones such as haloperidol (Haldol). Whereas D1 receptor activation stimulates cyclic adenosine monophosphate (cAMP) formation, D2 receptor stimulation produces the opposite effect. Adrenergic Receptors As for the α1 receptors, the functions of α2 receptor subtypes (designated α2A, α2B, and α2C) have been difficult to determine due to a lack of selective agonists and antagonists; α2 receptors display both presynaptic autoreceptor and postsynaptic actions, and all appear to inhibit cAMP formation and to activate potassium channels with resultant membrane hyperpolarization. These receptors regulate neurotransmitter release from peripheral sympathetic nerve endings. Within the brain the stimulation of α2 autoreceptors (likely the α2A subtype) inhibits firing of the noradrenergic neurons of the LC, which have been implicated in arousal states. This mechanism has been proposed to underlie the sedative effects of the α2 receptor agonist clonidine (Catapres). In addition, the stimulation of brainstem α2 receptors has been proposed to reduce sympathetic and to augment parasympathetic nervous system activity. This action may relate to the utility of clonidine in lowering blood pressure and in suppressing the sympathetic hyperactivity associated with opiate withdrawal. Activation of α2 receptors inhibits the activity of serotonin neurons of the dorsal raphe nucleus, whereas activation of local α1 receptors stimulates the activity of these neurons, and this is thought to be a major activating input to the serotonergic system. Histamine Receptors Histaminergic systems have been proposed to modulate arousal, wakefulness, feeding behavior, and neuroendocrine responsiveness. Four histaminergic receptor subtypes have been identified and termed H1, H2, H3, and H4. The H4 receptor was identified

recently and is detected predominantly in the periphery, in regions such as the spleen, bone marrow, and leukocytes. The other three histamine receptors have prominent expression in the CNS. H1 receptors are expressed throughout the body, particularly in smooth muscle of the gastrointestinal tract and bronchial walls as well as on vascular endothelial cells. H1 receptors are widely distributed within the CNS, with particularly high levels in the thalamus, cortex, and cerebellum. H1 receptor activation is associated with Gq activation and stimulation of phosphoinositide turnover and tends to increase excitatory neuronal responses. These receptors are the targets of classical antihistaminergic agents used in the treatment of allergic rhinitis and conjunctivitis. The well-known sedative effects of these compounds have been attributed to their actions in the CNS and have implicated histamine in the regulation of arousal and the sleep–wake cycle. Accordingly, a line of mutant mice lacking histamine displays deficits in waking and attention. In addition, the sedation and weight gain produced by a number of antipsychotic and

antidepressant drugs have been attributed to H1 receptor antagonism. Conversely, H1 receptor agonists stimulate arousal and suppress food intake in animal models. Cholinergic Receptors M1 receptors are the most abundantly expressed muscarinic receptors in the forebrain, including the cortex, hippocampus, and striatum. Pharmacological evidence has suggested their involvement in memory and synaptic plasticity, and recent evaluation of mice lacking the M1 receptor gene revealed deficits in memory tasks believed to require interactions between the cortex and the hippocampus. Nicotinic receptors have been implicated in cognitive function, especially working memory, attention, and processing speed. Cortical and hippocampal nicotinic acetylcholine receptors appear to be significantly decreased in Alzheimer's disease, and nicotine administration improves attention deficits in some patients. The acetylcholinesterase inhibitor galantamine used in the treatment of Alzheimer's disease also acts to positively modulate nicotinic receptor function. The α7 nicotinic acetylcholine receptor subtype has been implicated as one of many possible susceptibility genes for schizophrenia, with lower levels of this receptor being associated with impaired sensory gating. Some rare forms of the familial epilepsy syndrome autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) are associated with mutations in the α4 or β2 subunits of the nicotinic acetylcholine receptor. Finally, the reinforcing properties of tobacco use are proposed to involve the stimulation of nicotinic acetylcholine receptors located in mesolimbic dopaminergic reward pathways. AMINO ACID NEUROTRANSMITTERS For more than 50 years, biogenic amines have dominated thinking about the role of neurotransmitters in the pathophysiology of psychiatric disorders. However, over the last decade, evidence has accumulated from postmortem, brain imaging, and genetic

studies that the amino acid neurotransmitters, in particular glutamic acid and γaminobutyric acid (GABA), play an important, if not central, role in the pathophysiology of a broad range of psychiatric disorders including schizophrenia, bipolar disorder, major depression, Alzheimer's disease, and anxiety disorders. Glutamic Acid Glutamate mediates fast excitatory neurotransmission in the brain and is the transmitter for approximately 80 percent of brain synapses, particularly those associated with dendritic spines. The repolarization of neuronal membranes that have been depolarized by glutamatergic neurotransmission may account for as much as 80 percent of the energy expenditure in the brain. The concentration of glutamate in brain is 10 mM, the highest of all amino acids, of which approximately 20 percent represents the neurotransmitter pool of glutamate. The postsynaptic effects of glutamate are mediated by two families of receptors. The first are the glutamate-gated cation channels that are responsible for fast neurotransmission. The second type of glutamate receptor are the metabotropic glutamate receptors (mGluR), which are G-protein-coupled receptors like α-adrenergic receptors and dopamine receptors. The mGluRs primarily modulate glutamatergic neurotransmission. Major Glutamatergic Pathways in the Brain. All primary sensory afferent systems appear to use glutamate as their neurotransmitter including retinal ganglion cells, cochlear cells, trigeminal nerve, and spinal afferents. The thalamocortical projections that distribute afferent information broadly to the cortex are glutamatergic. The pyramidal neurons of the corticolimbic regions, the major source of intrinsic, associational, and efferent excitatory projections from the cortex, are glutamatergic. A temporal lobe circuit that figures importantly in the development of new memories is a series of four glutamatergic synapses: The perforant path innervates the hippocampal granule cells that innervate CA3 pyramidal cells that innervate CA1 pyramidal cells. The climbing fibers innervating the cerebellar cortex are glutamatergic as well as the corticospinal tracks. Ionotropic Glutamate Receptors. Three families of ionotropic glutamate receptors have been identified on the basis of

selective activation by conformationally restricted or synthetic analogs of glutamate. These include α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainic acid (KA), and N-methyl-D-aspartic acid (NMDA) receptors. Subsequent cloning revealed 16 mammalian genes that encode structurally related proteins, which represent subunits that assemble into functional receptors. Glutamate-gated ion channel receptors appear to be tetramers, and subunit composition affects both the pharmacologic and the biophysical features of the receptor. Metabotropic Glutamate Receptors. These receptors are so designated because their effects are mediated by G proteins. All mGluRs are activated by glutamate, although their sensitivities vary remarkably. To date, eight mGluRs have been cloned. These genes encode for seven membrane-spanning proteins that are members of the superfamily of G-protein-coupled receptors.

The Role of Astrocytes. Specialized end-feet of the astrocyte surround glutamatergic synapses. The astrocyte expresses the two Na+-dependent glutamate transporters that play the primary role in removing glutamate from the synapse, thereby terminating its action: EAAT1 and EAAT2 (excitatory amino acid transporter). The neuronal glutamate transporter, EAAT3, is expressed in upper motor neurons, whereas EAAT4 is expressed primarily in cerebellar Purkinje cells and EAAT5 in retina. Mice homozygous for null mutations of either EAAT1 or EAAT2 exhibit elevated extracellular glutamate and excitotoxic neurodegeneration. Notably, several studies have described the loss of EAAT2 protein and transport activity in the ventral horn in amyotrophic lateral sclerosis. The astrocytes express AMPA receptors so that they can monitor synaptic glutamate release. GlyT1, which maintains subsaturating concentrations of glycine in the synapse, is expressed on the astrocyte plasma membrane. GlyT1 transports three Na+ out for each molecule of glycine transported into the astrocyte. This stoichiometry results in a robust reversal of the direction of transport when glutamate released in the synapse activates the AMPA receptors on the astrocyte, thus depolarizing the astrocyte. Thus glycine release in the synapse by GlyT1 is coordinated with glutamatergic neurotransmission. Similarly, activation of the astrocyte AMPA receptors causes GRIP to dissociate from the AMPA receptor and bind to serine racemase, activating it to synthesize D-serine. D-Serine levels are also determined by D-amino acid oxidase (DAAO) with low D-serine levels in the cerebellum and brainstem where DAAO expression is high, and high D-serine levels are found in corticolimbic brain regions where DAAO expression is quite low. In contrast, the expression of GlyT1 is highest in the cerebellum and brainstem. This distribution suggests that D-serine is the primary modulator of the NMDA receptor in the forebrain, whereas glycine is more prominent in the brainstem and cerebellum. Plasticity in Glutamatergic Neurotransmission. The extinction of conditioned fear has been shown to be an active process mediated by the activation of NMDA receptors in the amygdala. Treatment of rats with NMDA receptor antagonists prevents the extinction of conditioned fear, whereas treatment with the glycine modulatory site partial agonist D-cycloserine facilitates the extinction of conditioned fear. (DCycloserine is an antibiotic used to treat tuberculosis that has 50 percent of the efficacy of glycine at the NMDA receptor.) To determine whether the phenomenon generalizes to humans, patients with acrophobia were administered either placebo or a single dose of D-cycloserine along with cognitive behavioral therapy (CBT). D-Cycloserine plus CBT resulted in a highly significant reduction in acrophobic symptoms that persisted for at least 3 months as compared to placebo plus CBT. Other placebo-controlled clinical trials support the notion that D-cycloserine is a robust enhancer of CBT, suggesting that pharmacologically augmenting neural plasticity may be used to bolster psychological interventions. Fragile X mental retardation protein (FMRP), which is deficient in individuals with fragile X syndrome, appears to be synthesized locally within the spine during

times of NMDA receptor activation and also plays a role in transporting specific mRNAs to the spine for translation. Notably, mice in which the FMRP gene has been inactivated through a null mutation as well as patients with fragile X syndrome have fewer dendritic spines, the preponderance of which have an immature morphology. Loss of FMRP exaggerates responses of mGluR5, which stimulates dendritic protein synthesis, and treatment with an mGluR5 antagonist reverses the fragile-X-like phenotype in mice with the FMRP gene inactivated. Excitotoxicity. In the early 1970s, it was shown that the systemic administration of large amounts of monosodium glutamate to immature animals resulted in the degeneration of neurons in brain regions where the blood–brain barrier was deficient. Excitotoxicity has also been implicated in the proximate cause of neuronal degeneration in Alzheimer's disease. Most evidence points to the toxic consequences of

aggregates of β-amyloid, especially β-amyloid1–42. The β-amyloid fibrils depolarize neurons, resulting in loss of the Mg2+ block and enhanced NMDA receptor sensitivity to glutamate. The fibrils also impair glutamate transport into astrocytes, thereby increasing the extracellular concentration of glutamate. β-Amyloid directly promotes oxidative stress through inflammation that further contributes to neuronal vulnerability to glutamate. Thus, several mechanisms contribute to neuronal vulnerability to NMDAreceptor-mediated excitotoxicity in Alzheimer's disease. Memantine, a recently approved treatment for mild to moderate Alzheimer's disease, is a weak noncompetitive inhibitor of NMDA receptors. It reduces tonic sensitivity of NMDA receptors to excitotoxicity but does not interfere with "phasic" neurotransmission, thereby attenuating neuronal degeneration in Alzheimer's disease. Inhibitory Amino Acids: GABA GABA is the major inhibitory neurotransmitter in the brain, where it is broadly distributed and occurs in millimolar concentrations. In view of its physiological effects and distributions, it is not surprising that the dysfunction of GABAergic neurotransmission has been implicated in a broad range of neuropsychiatric disorders including anxiety disorders, schizophrenia, alcohol dependence, and seizure disorders. Chemically, GABA differs from glutamic acid, the major excitatory neurotransmitter, simply by the removal of a single carboxyl group from the latter. GABA is synthesized from glutamic acid by glutamic acid decarboxylase (GAD), which catalyzes the removal of the α-carboxyl group. In the CNS, the expression of GAD appears to be restricted to GABAergic neurons, although in the periphery it is expressed in pancreatic islet cells. Two distinct but related genes encode GAD. GAD65 is localized to nerve terminals, where it is responsible for synthesizing GABA that is concentrated in the synaptic vesicles. Consistent with its role in fast inhibitory neurotransmission, mice homozygous for a null mutation of GAD65 have an elevated risk for seizures. GAD67 appears to be the primary source for neuronal GABA because mice homozygous for a null mutation of GAD67 die at birth, have a cleft pallet, and exhibit major reductions in brain GABA. GABA is catabolized by GABA transaminase (GABA-T) to yield succinic semialdehyde. Transamination generally occurs when the parent compound, α-ketoglutarate, is present to receive the amino group, thereby regenerating glutamic acid. Succinic semialdehyde is oxidized by succinic semialdehyde dehydrogenase (SSADH) into succinic acid, which re-enters the Krebs cycle. GABA-T is a cell surface, membrane-bound enzyme expressed by neurons and glia, which is oriented toward the extracellular compartment. As would be anticipated, drugs that inhibit the catabolism of GABA have anticonvulsant properties. One of the mechanisms of action of valproic acid is the competitive inhibition of GABA-T. γ-Vinyl-GABA is a suicide substrate inhibitor of GABA-T that is used as an anticonvulsant in Europe (vigabatrin [Sabril]). The synaptic action of GABA is also terminated by high-affinity transport back into the presynaptic terminal as well as into astrocytes. Four genetically distinct GABA high-

affinity transporters have been identified with differing kinetic and pharmacological characteristics. They all share homology with other neurotransmitter transporters with the characteristic of 12 membrane-spanning domains. The active transport is driven by the sodium gradient so that upon depolarization, transportation of GABA out of the neuron is favored. GABA transported into astrocytes is catabolyzed by GABA-T and ultimately converted to glutamic acid and then to glutamine, which is transported back into the presynaptic terminal for GABA synthesis. Tiagabine (Gabitril) is a potent GABA transport inhibitor that is used to treat epilepsy. Preliminary results suggest that it also may be effective in panic disorder. GABAA Receptors. GABAA receptors are distributed throughout the brain. The GABAA complex, when activated, mediates an increase in membrane conductance with an equilibrium potential near the resting membrane potential of –70 mV (Fig. 1.4-9). In the mature neuron, this typically results with an influx of Cl−, causing membrane hyperpolarization. Hyperpolarization is inhibitory because it increases the threshold for generating an action potential. In immature neurons, which have unusually high levels of intracellular Cl−, activating the GABAA receptor can counterintuitively cause depolarization. For this reason, anticonvulsants that act by enhancing GABAA receptor activity may actually exacerbate seizures in the neonatal period. FIGURE 1.4-9 Schematic representation of the GABAA receptor. The receptor-channel complex is a heteropentamer. The GABA binding site is at the interface of the α and β subunits. The benzodiazepine binding site is at the interface between the γ and α subunits. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:81.)

Barbiturates such as phenobarbital and pentobarbital are noted for their sedative and anticonvulsant activities. Barbiturates allosterically increase the affinities of the binding sites for GABA and benzodiazepines at concentrations that are pharmacologically relevant. Barbiturates also affect channel dynamics by markedly increasing the long open state and reducing the short open state, thereby increasing Cl− inhibition. Chemically modified analogs of progesterone and corticosterone have been shown in behavioral studies to have sedative and anxiolytic effects through their interaction with the GABAA receptor complex. They share features with barbiturates, although they act at a distinctly different site. Thus, they allosterically enhance agonist ligand binding to the receptor and increase the duration of chloride channel opening. A variety of behavioral effects associated with steroid administration or fluctuation of endogenous steroids and sex-specific effects of GABAergic drugs have been linked to the action of endogenous neurosteroids. With regard to GABAA receptor antagonists, picrotoxin, like the barbiturates, alters channel dynamics but in the opposite direction by reducing long open states and favoring the briefest open state. The proconvulsant pentylenetetrazol also acts by reducing chloride channel permeability. Penicillin, which at high concentrations is proconvulsant, binds to the positively charged residues in the channel, thereby occluding it. As a general class, anesthetics including barbiturates, steroids, and volatile anesthetics increase chloride conductance, thereby inhibiting neurotransmissions. Amino acids in the membrane-spanning domain of the GABA receptor subunits confer sensitivity to anesthetics. The precise mechanism whereby ethanol enhances GABAA receptor function remains unclear due to inconsistent results, suggesting that subunit composition may be important. However, recent studies suggest that ethanol increases the response of the tonic GABA-activated currents, which contain the δ subunit and exhibit remarkably high affinity to GABA. Recently, recombinant DNA strategies exploiting site-directed mutagenesis have permitted the identification of sites on the specific subunits that mediate the pharmacological action of drugs such as the benzodiazepines. Removal of the binding ability for benzodiazepines has established

that the α1 subunit plays a major role in the sedative and amnestic effects of benzodiazepines, whereas inactivating the benzodiazepine site on the α2 subunit eliminates the anxiolytic effect of benzodiazepines GABAB Receptors. The GABAB receptors are distinguished pharmacologically from GABAA receptors by the fact that they are insensitive to the canonical GABAA receptor antagonist bicuculline and that they are potently activated by baclofen [β-(4chlorophenyl)-γ-aminobutyric acid], which is inactive at GABAA receptors. They are members of the G-protein-coupled superfamily of receptors but are highly unusual, as they are made of a dimer of two seven-transmembrane-spanning subunits. GABAB receptors are widely distributed throughout the nervous system and are localized both presynaptically and postsynaptically. The postsynaptic GABAB receptors cause a longlasting hyperpolarization by activating potassium channels. Presynaptically, they act as autoreceptors and heteroreceptors to inhibit neurotransmitter release.

Glycine as a Neurotransmitter. Glycine is an inhibitory neurotransmitter primarily in the brainstem and spinal cord, although the expression of glycine receptor subunits in the thalamus, cortex, and hippocampus suggest a broader role. Glycine is a nonessential amino acid that is synthesized in the brain from L-serine by serine hydroxymethyltransferase. Glycine is concentrated within synaptic vesicles by H+- dependent vesicular inhibitory amino acid transporter (VIAAT or VGAT), which also transports GABA. Termination of the synaptic action of glycine is through reuptake into the presynaptic terminal by the glycine transporter II (GlyT2), which is quite distinct from GlyT1 that is expressed in astrocytes and modulates NMDA receptor function. The inhibitory effects of glycine are mediated by a ligand-gated chloride channel, which can also respond to β-alanine, taurine, L-alanine, L-serine, and proline, but not to GABA. The canonical antagonist for the glycine receptor is the plant alkaloid strychnine. The receptor was first identified through the specific binding of [3H]strychnine. [3H]Glycine binds to two sites: One that is displaceable by strychnine and represents the glycine A receptor and a second that is insensitive to strychnine and is designated the glycine B receptor, representing the glycine modulatory site on the NMDA receptor. Neuropsychiatric Implications of Amino Acid Transmitters Schizophrenia. Evidence accumulating from postmortem, pharmacological, and genetic studies is shifting the focus of the pathophysiology of schizophrenia from dopamine to glutamate and GABA. Indeed, after the use of D2 receptor antagonists as the sole treatment of schizophrenia for the last 50 years, more than two thirds of the treated patients remain substantially disabled. Early postmortem studies indicated a reduction in the activity of GAD in the cortex in patients with schizophrenia as compared to suitable controls. With the advent of immunocytochemistry and gene expression techniques, it has been possible to more precisely define the GABAergic deficit in schizophrenia. It appears that the parvalbumin-positive GABAergic interneurons in the intermediate layers of the cortex bear the brunt of the pathology, which includes reduced expression of GAD67, parvalbumin, and the GABA transporter (GAT). The finding that GABAA receptors are upregulated, as measured by autoradiography or with antibodies, supports the theory that these changes reflect hypofunction of the presynaptic GABAergic neurons. These particular GABAergic interneurons, which include the chandelier cells, play an important role in negative feedback inhibition to the pyramidal cells in the cortex. Despite this highly reproducible neuropathology, genes related to GABAergic function have not figured prominently in genomewide searches, suggesting that GABAergic deficits may be a downstream consequence of some more proximal genetic defects. The theory that hypofunction of NMDA receptors is an etiologic factor in schizophrenia initially arose from the observation that phencyclidine (PCP) and related dissociative anesthetics that block NMDA receptors produce a syndrome that can be indistinguishable from schizophrenia (Fig. 1.4-10). Dissociative anesthetics

are so named because they prevent

the acquisition of new memories while the patient is apparently conscious. In fact under laboratory conditions, low-dose infusion of ketamine can produce the positive symptoms, negative symptoms, and specific cognitive deficits associated with schizophrenia in clear consciousness. Subsequent studies indicated that low-dose ketamine can also cause enhanced amphetamine-induced subcortical dopamine release as is observed in schizophrenia as well as abnormal cortical eventrelated potentials (ERPs) and disruption of prepulse inhibition in experimental animals. FIGURE 1.4-10 Pathological circuit in schizophrenia. The NMDA receptors on the rapidly firing parvalbumin (PV) expressing GABAergic interneurons in the intermediate levels of the cortex are disproportionately sensitive to antagonists or loss of the coagonist, D-serine. NMDA receptor hypofunction causes reduced expression of PV, GAD67, and the GABA transporter and upregulation of GABAA receptors on pyramidal neurons. Disinhibition of the pyramidal neurons causes cognitive dysfunction and negative symptoms and drives excessive subcortical dopamine release resulting in psychosis. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:83.) A number of putative risk genes for schizophrenia are closely associated with NMDA receptor function. DAAO, which encodes a protein that activates D-amino acid oxidase, has been repeatedly linked to the risk of schizophrenia. D-Amino acid oxidase itself has been associated with increased risk. Recently an allelic variant of serine racemase in the promoter region has also been associated with the risk for schizophrenia. Each of these gene variants could reduce the availability of D-serine in the cortex, thereby impairing NMDA receptor function. Notably, cerebrospinal fluid (CSF) and blood levels of D-serine are significantly reduced in patients with schizophrenia. Neuregulin 1 appears to be a convincing risk gene and interacts directly with NMDA receptors. Dysbindin, another risk gene, is expressed in glutamatergic terminals. mGluR3, which downregulates glutamate release, has also been associated with schizophrenia. Recent findings have provided a link between the GABAergic neuropathology and NMDA receptor hypofunction. Chronic treatment of rats with NMDA receptor antagonists causes a downregulation of GAD67, parvalbumin, and GAT. The sensitive subpopulation of GABAergic neurons is the rapidly firing interneurons that provide the perisomatic innervation of the pyramidal cells. Their NMDA receptors appear to be much more sensitive to antagonists than those less active

GABAergic neurons and pyramidal cells. The subtly reduced GABAergic inhibition results in a disinhibition of the glutamatergic pyramidal output. This degradation of the inhibitory feedback could account for the cognitive deficits and negative symptoms in schizophrenia, and the disinhibited output also results in elevated subcortical dopamine release and psychosis. Thus psychosis would be considered a downstream event resulting from a disruption in critical glutamatergic– GABAergic synaptic function in the cerebral cortex. Anxiety and Depression. GABAergic dysfunction has been associated with anxiety disorders, especially panic disorder, as well as with major depressive disorder. Clinically, there is considerable comorbidity between anxiety and affective disorders. Decreased levels of the GABAA receptor modulators, the three α-reduced neuroactive steroids, have been found both in plasma and in CSF in major depressive disorder. Effective treatment with selective serotonin reuptake inhibitors (SSRIs) increases the neurosteroid levels. In contrast, in patients with panic disorder, the plasma neurosteroid levels were significantly elevated, perhaps as a compensatory mechanism. Magnetic resonance spectroscopy (MRS) has disclosed significant reductions in GABA levels in the anterior cingulate

and in the basal ganglia of medicated patients with panic disorder. Positron emission tomography (PET) scanning reveals a highly selective reduction in benzodiazepine receptor sites bilaterally in the insular cortex in panic disorder. A genomewide screen has shown significant linkage at 15q in a region containing GABAA receptor subunit genes and panic disorder. MRS reveals significant reductions in both GABA and glutamate/glutamine (Glx) in the prefrontal cortex in major depressive disorder. Postmortem studies indicate upregulation of the GABAA receptor α1 and β3 subunits in the cerebral cortices of depressed patients who committed suicide, consistent with a reduction in GABAergic neurotransmission. The reduced levels of GABA in the occipital cortex in episodes of major depressive disorder normalized with effective treatment with SSRI or with electroconvulsive therapy. Glutamatergic dysfunction has also been implicated in depression. NMDA receptor antagonists have antidepressant effects in several animal models of depression including forced swim, tail suspension, and learned helplessness. A single injection of ketamine provides protection from the induction of behavioral despair in rats for up to 10 days. Chronic treatment with antidepressants alters the expression of NMDA receptor subunits and decreases glycine receptor B binding. Two placebo-controlled clinical trials have shown that a single dose of ketamine can produce a rapid, substantial, and persistent reduction in symptoms in patients with major depressive disorder. Alcoholism. Ethanol at concentrations associated with intoxication has a dual action of enhancing GABAergic receptor function and attenuating NMDA receptor function. The GABA receptor effects may be associated with the anxiolytic effects of ethanol. Persistent abuse and dependency on ethanol result in a downregulation of GABAA receptors and an upregulation of NMDA receptors such that acute discontinuation of ethanol results in a hyperexcitable state characterized by delirium tremens. Furthermore, supersensitive NMDA receptors in the context of thiamine

deficiency may contribute to the excitotoxic neuron degeneration of Wernicke– Korsakoff's syndrome. Acamprosate is a derivative of homotaurine that was developed as an agent to reduce alcohol consumption, craving, and relapse in alcoholic patients, for which it exhibits moderate efficacy in clinical trials. Because of taurine's resemblance to GABA, it was thought that acamprosate acted via GABAA receptors, but electrophysiological studies found little evidence to support this hypothesis. Subsequent studies demonstrated that it inhibited NMDA receptor responses in cortical slices and recombinant NMDA receptors. The precise mechanism whereby acamprosate alters NMDA receptor function, however, remains unclear. Fetal alcohol syndrome is the most common preventable cause of mental retardation. Convincing evidence has been developed that the microencephaly associated with fetal alcohol exposure results from inhibition of NMDA receptor function, resulting in widespread neuronal apoptosis in the immature cortex. NMDA receptor activation is essential for immature neuronal survival and differentiation. NEUROPEPTIDES Neuropeptides represent the most diverse class of signaling molecules in the CNS. Initially discovered for their role in the hypothalamic regulation of pituitary hormone secretion, the complex role of peptides in brain function has emerged over the last 30 years. Many neuropeptides and their receptors are widely distributed within the CNS where they have an extraordinary array of direct or neuromodulatory effects, ranging from modulating neurotransmitter release and neuronal firing patterns to the regulation of emotionality and complex behaviors. More than 100 unique biologically active neuropeptides have been identified in the brain, a subset of which is presented in Table 1.4-2. Adding to the complexity of neuropeptide systems in the CNS, the actions of many peptides are mediated via multiple receptor subtypes localized in different brain regions. In fact, the discovery of new peptides and receptor subtypes has outpaced our understanding of the roles

of these peptides in normal or aberrant CNS function. Pharmacological, molecular, and genetic approaches are now leading the way in our understanding of the contribution of neuropeptide systems in psychiatric disorders. Table 1.4-2 Selected Neuropeptide Transmitters

Neuropeptides have been implicated in the regulation of a variety of behavioral and physiological processes, including thermoregulation, food and water consumption, sex, sleep, locomotion, learning and memory, responses to stress and pain, emotion, and social cognition. Involvement in such behavioral processes suggests that neuropeptidergic systems may contribute to the symptoms and behaviors exhibited in major psychiatric illnesses such as psychoses, mood disorders, dementias, and autism spectrum disorders. Investigating Neuropeptide Function The roles of neuropeptides in CNS function and behavior have been examined using a multitude of experimental techniques. The levels of analysis include the following:

Molecular structure and biosynthesis of the peptide and its receptor(s), the neuroanatomical localization of the peptide and its receptor(s), the regulation of the expression and release of the peptide, and the behavioral effects of the peptide. Most information on neuropeptide biology is derived from laboratory animal studies; however, there is a growing database on the localization, activity, and potential psychiatric relevance of several neuropeptide systems in humans. Most neuropeptide structures have been identified based on the chemical analysis of purified biologically active peptides, leading ultimately to the cloning and characterization of the genes encoding them. Characterization of the gene structure of peptides and their receptors has provided insight into the molecular regulation of these systems, and their chromosomal localization is useful in genetic studies examining the potential roles of these genes in psychiatric disorders. Structural characterization permits the production of immunological and molecular probes that are useful in determining peptide distribution and regulation in the brain. Quantitative radioimmunoassays on microdissected brain regions or immunocytochemistry on brain sections are typically used to localize the distribution of peptide within the brain. Both techniques use specific antibodies generated against the neuropeptide to detect the presence of the peptide. Immunocytochemistry allows researchers to visualize the precise cellular localization of peptide-synthesizing cells as well as their projections throughout the brain, although the technique is generally not quantitative. With molecular probes homologous to the mRNA encoding the peptides or receptor, in situ hybridization can be used to localize and quantify gene expression in brain sections. This is a powerful technique for examining the molecular regulation of neuropeptide synthesis with precise neuroanatomical resolution, which is impossible for other classes of nonpeptide neurotransmitters that are not derived directly from the translation of mRNAs, such as dopamine, serotonin, and norepinephrine. Generally, the behavioral effects of neuropeptides are initially investigated by infusions of the peptide directly into the brain. Unlike many nonpeptide neurotransmitters, most neuropeptides do not penetrate the blood–brain barrier in amounts sufficient enough to produce CNS effects. Furthermore, serum and tissue enzymes tend to degrade the peptides before they reach their target sites. The degradation is usually the result of the cleavage of specific amino acid sequences targeted by a specific peptidase designed for that purpose. Thus, intracerebroventricular (ICV) or site-specific infusions of peptide in animal models are generally required to probe for behavioral effects of peptides. However, there are some examples of delivery of neuropeptides via intranasal infusions in human subjects, which in some cases has been shown to permit access of the peptide to the brain. One of the greatest impediments for exploring the roles and potential therapeutic values of neuropeptides is the inability of the peptides or their agonists/antagonists to penetrate

the blood–brain barrier. Thus the behavioral effects of most peptides in humans are largely uninvestigated, with the exception of a few studies utilizing intranasal delivery. However, in some instances small-molecule, nonpeptide agonists/antagonists have been developed that can be administered peripherally and permeate the blood–brain barrier in sufficient quantities to affect receptor activation. The use of pretreatment and posttreatment CSF samples or of samples obtained during the active disease state versus when the patient is in remission addresses some of

the serious limitations in study design. For such progressive diseases as schizophrenia or Alzheimer's disease, serial CSF samples may be a valuable indicator of disease progression or response to treatment. Even with these constraints, significant progress has been made in describing the effects of various psychiatric disease states on neuropeptide systems in the CNS. Biosynthesis Unlike other neurotransmitters, the biosynthesis of a neuropeptide involves the transcription of an mRNA from a specific gene, translation of a polypeptide preprohormone encoded by that mRNA, and then posttranslational processing involving proteolytic cleavage of the preprohormone to yield the active neuropeptide. Over the last 25 years the gene structures and biosynthetic pathways of many neuropeptides have been elucidated. The gene structure of selected neuropeptides is illustrated in Figure 1.411. Neuropeptide genes are generally composed of multiple exons that encode a protein preprohormone. The N-terminus of the preprohormone contains a signal peptide sequence, which guides the growing polypeptide to the rough endoplasmic reticulum (RER) membrane. The single preprohormone molecule often contains the sequences of multiple peptides that are subsequently separated by proteolytic cleavage by specific enzymes. For example, translation of the gene encoding NT yields a preprohormone, which upon enzymatic cleavage produces both NT and neuromedin N.

FIGURE 1.4-11 Schematics illustrating the gene structure, preprohormone messenger RNA (mRNA), and processed neuropeptides of thyrotropin-releasing hormone (TRH), corticotropinreleasing factor (CRF), oxytocin (OT), arginine vasopressin (AVP), and neurotensin (NT). Boxed regions indicate the locations of the exons in the respective genes. Shaded or hatched regions indicate coding regions. Each preprohormone begins with a signal

peptide (SP) sequence. Black boxes indicate the locations of the sequences encoding the neuropeptide. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:87.) Distribution and Regulation Although many neuropeptides were originally isolated from pituitary and peripheral tissues, the majority of neuropeptides were subsequently found to be widely distributed throughout the brain. Those peptides involved in regulating pituitary secretion are concentrated in the hypothalamus. Hypothalamic releasing and inhibiting factors are produced in neurosecretory neurons adjacent to the third ventricle that send projections to the median eminence where they contact and release peptide into the hypothalamohypophysial portal circulatory system. Peptides produced in these neurons are often subject to regulation by the peripheral hormones that they regulate. For example, thyrotropin-releasing hormone (TRH) regulates the secretion of thyroid hormones, and thyroid hormones negatively feedback on TRH gene expression. However, neuropeptide-expressing neurons and their projections are found in many other brain regions, including limbic structures, midbrain, hindbrain, and spinal cord. Neuropeptide Signaling Neuropeptides may act as neurotransmitters, neuromodulators, or neurohormones. Neurotransmitters are typically released from axonal terminals into a synapse where they change

the postsynaptic membrane potential, either depolarizing or hyperpolarizing the cell. For classical neurotransmitters, this often involves direct modulation of voltage-gated ion channels. In contrast, neuromodulators and neurohormones do not directly affect the firing of the target cell itself but may alter the response of the cell to other neurotransmitters through the modulation of second messenger pathways. Neuropeptide release is not restricted to synapses or axon terminals but may occur throughout the axon or even from dendrites. The cellular signaling of neuropeptides is mediated by specific neuropeptide receptors. Thus understanding neuropeptide receptor function is essential for understanding neuropeptide biology. Neuropeptide receptors have undergone the same process of discovery and characterization that receptors for other neurotransmitters have enjoyed. Most neuropeptide receptors are G-protein-coupled, seventransmembrane domain receptors belonging to the same family of proteins as the monoamine receptors. Molecular technology has made it possible to clone and characterize neuropeptide receptor genes and complementary DNAs (cDNAs). This is most often accomplished in one of three ways. First, the neuropeptide receptor protein is biochemically purified and partially sequenced, which allows the development of oligonucleotide probes that can be used to isolate the cDNA encoding the protein from a cDNA library. A second approach involves producing expression libraries in which cells containing the receptor cDNA can be isolated based on their ability to bind to a radiolabeled peptide ligand. Finally, many neuropeptide receptors are now isolated based on their sequence homology with other known peptide

receptors. Once the cDNA of the receptor has been isolated, it can be used to produce purified receptor protein for structural and functional studies. By mutation of specific amino acids in the receptor structure and determination of relative binding affinities of peptides with various amino acid substitutions, it is possible to elucidate the nature of the ligand–receptor interaction. This information facilitates the development of drugs that specifically modulate receptor function, including nonpeptide drugs, leading to the ability to manipulate peptide systems in ways that are currently enjoyed by the more classic neurotransmitters. The availability of cDNAs encoding the receptor also permits the neuroanatomical mapping of the receptor-producing cells in the brain, which is critical for understanding the neural circuits modulated by the peptide. Finally, with the cloned receptor in hand, it is possible to use transgenic techniques, such as targeted gene overexpression or gene knockouts, to further elucidate the functions of these receptors. siRNA techniques now allow the targeted synthesis disruption of specific receptor populations, allowing researchers to examine the roles of these receptor populations on physiology and behavior. The following three factors determine the biological roles of a neuropeptide hormone: (1) the temporal–anatomical release of the peptide, (2) functional coupling of the neuropeptide receptor to intracellular signaling pathways, and (3) the cell type and circuits in which the receptor is expressed. Genetic studies have demonstrated that regulatory sequences flanking the receptor coding region determine the expression pattern of the receptor and thus the physiological and behavioral response to the neuropeptide. Peptidases Unlike monoamine neurotransmitters, peptides are not actively taken up by presynaptic nerve terminals. Rather, released peptides are degraded into smaller fragments, and eventually into single amino acids by specific enzymes termed peptidases. The enzymes may be found bound to presynaptic or postsynaptic neural membranes or in solution in the cytoplasm and extracellular fluid, and they are distributed widely in peripheral organs and serum as well as in the CNS. As a result, neuropeptides generally have halflives on the order of minutes once released. Specific Neuropeptides as Prototypes of Neuropeptide Biology Thyrotropin-Releasing Hormone. In 1969, TRH, a

pyroglutamylhistidylprolinamide tripeptide (Table 1.4-3), became the first of the hypothalamic releasing hormones to be isolated and characterized. The discovery of the structure of this hormone led to the conclusive demonstration that peptide hormones secreted from the hypothalamus regulate the secretion of hormones from the anterior pituitary. The gene for TRH in humans resides on chromosome 3q13.3-q21. In the rat it consists of three exons (coding regions) separated by two introns (noncoding sequences) (see Fig. 1.4-11). The first exon contains the 5′ untranslated region of the mRNA encoding the TRH preprohormone, the second exon contains the signal peptide (SP) sequence and much of the remaining N-terminal end of the precursor peptide, and the third contains the remainder of the sequence, including five copies of the TRH precursor sequence, the C-terminal region, and the 3′ untranslated region. The 5′ flanking of the

gene, or promoter, contains sequences homologous to the glucocorticoid receptor and the thyroid hormone receptor DNA binding sites, providing a mechanism for the regulation of this gene by cortisol and negative feedback by thyroid hormone. Enzymatic processing of TRH begins with excision of the progenitor peptides by carboxypeptidases, amidation of the C-terminal proline, and cyclization of the Nterminal glutamine to yield five TRH molecules per prohormone molecule. TRH is widely distributed in the CNS with TRH immunoreactive neurons being located in the olfactory bulbs, entorhinal cortices, hippocampus, extended amygdala, hypothalamus, and midbrain structures. As is the case for most neuropeptides, the TRH receptor is also a member of the seven-transmembrane domain, G-protein-coupled receptor family. Table 1.4-3 Selected Neuropeptide Structures Hypothalamic TRH neurons project nerve terminals to the median eminence; there they release TRH into the hypothalamohypophyseal portal system where it is transported to the adenohypophysis, causing the release of thyroid-stimulating hormone (TSH) into systemic circulation. TSH subsequently stimulates the release of the thyroid hormones triiodothyronine (T3) and thyroxine (T4) from the thyroid gland. TRH neurons in the paraventricular nucleus (PVN) contain thyroid hormone receptors and respond to increases in thyroid hormone secretion with a decrease in TRH gene expression and synthesis. This negative feedback of thyroid hormones on the TRH-synthesizing neurons was first demonstrated by a decrease in TRH content in the median eminence, but not in the PVN of the hypothalamus, after thyroidectomy. This effect can be reversed with exogenous thyroid hormone treatment. The treatment of normal rats with exogenous thyroid hormone decreases TRH concentration in the PVN and the posterior nucleus of the hypothalamus. With a probe against the TRH preprohormone mRNA, in situ hybridization studies have demonstrated that TRH mRNA is increased in the PVN 14 days after thyroidectomy. The ability of thyroid hormones to regulate TRH mRNA can be

superseded by other stimuli that activate the hypothalamic–pituitary–thyroid (HPT) axis. In that regard, repeated exposure to cold (which releases TRH from the median eminence) induces increases in the levels of TRH mRNA in the PVN despite concomitantly elevated concentrations of thyroid hormones. Further evidence of the different levels of communication of the HPT axis are seen in the ability of TRH to regulate the production of mRNA for the pituitary TRH receptor and for TRH concentrations to regulate the mRNA coding for both the α and β subunits of the thyrotropin (TSH) molecule. In addition, TRH-containing synaptic boutons have been observed in contact with TRH-containing cell bodies in the medial and periventricular subdivisions of the paraventricular nucleus, thus providing anatomical evidence for ultrashort feedback regulation of TRH release. Negative feedback by thyroid hormones may be limited to the hypothalamic TRH neurons because negative feedback on TRH synthesis by thyroid hormones has not been found in extrahypothalamic

TRH neurons. The early availability of adequate tools to assess HPT axis function (i.e., radioimmunoassays and synthetic peptides), coupled with observations that primary hypothyroidism is associated with depressive symptomatology, ensured extensive investigation of the involvement of this axis in affective disorders. Early studies established the hypothalamic and extrahypothalamic distribution of TRH. This extrahypothalamic presence of TRH quickly led to speculation that TRH might function as a neurotransmitter or neuromodulator. Indeed, a large body of evidence supports such a role for TRH. Within the CNS, TRH is known to modulate several different neurotransmitters, including dopamine, serotonin, acetylcholine, and the opioids. TRH has been shown to arouse hibernating animals and counteracts the behavioral response and hypothermia produced by a variety of CNS depressants including barbiturates and ethanol. The use of TRH as a provocative agent for the assessment of HPT axis function evolved rapidly after its isolation and synthesis. Clinical use of a standardized TRH stimulation test, which measures negative feedback responses, revealed blunting of the TSH response in approximately 25 percent of euthyroid patients with major depression. These data have been widely confirmed. The observed TSH blunting in depressed patients does not appear to be the result of excessive negative feedback due to hyperthyroidism because thyroid measures such as basal plasma concentrations of TSH and thyroid hormones are generally in the normal range in these patients. It is possible that TSH blunting is a reflection of pituitary TRH receptor downregulation as a result of median eminence hypersecretion of endogenous TRH. Indeed, the observation that CSF TRH concentrations are elevated in depressed patients as compared to those of controls supports the hypothesis of TRH hypersecretion but does not elucidate the regional CNS origin of this tripeptide. In fact, TRH mRNA expression in the PVN of the hypothalamus is decreased in patients with major depression. However, it is not clear whether the altered HPT axis represents a causal mechanism underlying the symptoms of depression or simply a secondary effect of depression-associated alterations in other neural systems. Corticotropin-Releasing Factor (CRF) and Urocortins. There is convincing evidence to support the hypothesis that CRF and the urocortins play a complex role in integrating the endocrine, autonomic, immunological, and behavioral responses of an organism to stress. Although it was originally isolated because of its functions in regulating the hypothalamic–pituitary–adrenal (HPA) axis, CRF is widely distributed throughout the brain. The PVN of the hypothalamus is the major site of CRF-containing cell bodies that influence anterior pituitary hormone secretion. These neurons originate in the

parvocellular region of the PVN and send axon terminals to the median eminence, where CRF is released into the portal system in response to stressful stimuli. A small group of PVN neurons also projects to the brainstem and spinal cord where they regulate autonomic aspects of the stress response. CRF-containing neurons are also found in other hypothalamic nuclei, the neocortex, the extended amygdala, brainstem, and spinal cord. Central CRF infusion into laboratory animals produces physiological changes and behavioral effects similar to those observed following stress, including increased locomotor activity, increased responsiveness to an acoustic startle, and decreased exploratory behavior in an open field. The physiological and behavioral roles of the urocortins are less understood, but several studies suggest that urocortins 2 and 3 are anxiolytic and may dampen the stress response. This has led to the hypothesis that CRF and the urocortins act in opposition, but this is likely an oversimplification. Urocortin 1 is primarily synthesized in the Edinger–Westphal nucleus, lateral olivary nucleus, and supraoptic hypothalamic nucleus. Urocortin 2 is synthesized primarily in the hypothalamus, while urocortin 3 cell bodies are found more broadly in the extended amygdala, perifornical area, and preoptic area. Hyperactivity of the HPA

axis in major depression remains one of the most consistent findings in biological psychiatry. The reported HPA axis alterations in major depression include hypercortisolemia, resistance to dexamethasone suppression of cortisol secretion (a measure of negative feedback), blunted adrenocorticotropic hormone (ACTH) responses to intravenous CRF challenge, increased cortisol responses in the combined dexamethasone/CRF test, and elevated CSF CRF concentrations. The exact pathological mechanism(s) underlying HPA axis dysregulation in major depression and other affective disorders remains to be elucidated. Mechanistically, two hypotheses have been advanced to account for the ACTH blunting following exogenous CRF administration. The first hypothesis suggests that pituitary CRF receptor downregulation occurs as a result of hypothalamic CRF hypersecretion. The second hypothesis postulates altered sensitivity of the pituitary to glucocorticoid negative feedback. Substantial support has accumulated favoring the first hypothesis. However, neuroendocrine studies represent a secondary measure of CNS activity; the pituitary ACTH responses principally reflect the activity of hypothalamic CRF rather than that of the corticolimbic CRF circuits. The latter of the two are more likely to be involved in the pathophysiology of depression. Of particular interest is the demonstration that the elevated CSF CRF concentrations in drug-free depressed patients are significantly decreased after successful treatment with electroconvulsive therapy (ECT), indicating that CSF CRF concentrations, like hypercortisolemia, represent a state rather than a trait marker. Other recent studies have confirmed this normalization of CSF CRF concentrations following successful treatment with fluoxetine. One group demonstrated a significant reduction of elevated CSF CRF concentrations in 15 female patients with major depression who remained depression free for at least 6 months following antidepressant treatment, as compared to little significant treatment effect on CSF CRF concentrations in 9 patients who relapsed in this 6-month period. This suggests that elevated or increasing CSF CRF

concentrations during antidepressant treatment may be the harbinger of a poor response in major depression despite early symptomatic improvement. Of interest, treatment of normal subjects with desipramine or, as noted above, of individuals with depression with fluoxetine is associated with a reduction in CSF CRF concentrations. If CRF hypersecretion is a factor in the pathophysiology of depression, then reducing or interfering with CRF neurotransmission might be an effective strategy to alleviate depressive symptoms. Over the last several years, a number of pharmaceutical companies have committed considerable effort to the development of small-molecule CRF1 receptor antagonists that can effectively penetrate the blood–brain barrier. Several compounds have been produced with reportedly promising characteristics. Oxytocin (OT) and Vasopressin (AVP). The vasopressor effects of posterior pituitary extracts were first described in 1895, and the potent extracts were named AVP. OT and AVP mRNAs are among the most abundant messages in the hypothalamus, being heavily concentrated in the magnocellular neurons of the PVN and the supraoptic nucleus of the hypothalamus, which send axonal projections to the neurohypophysis. These neurons produce all of the OT and AVP that is released into the bloodstream where these peptides act as hormones on peripheral targets. OT and AVP are generally synthesized in separate neurons within the hypothalamus. OT released from the pituitary is most often associated with functions associated with female reproduction, such as regulating uterine contractions during parturition and the milk ejection reflex during lactation. AVP, also known as antidiuretic hormone, regulates water retention in the kidney and vasoconstriction through interactions with vasopressin V2 and V1a receptor subtypes, respectively. AVP is released into the bloodstream from the neurohypophysis following a variety of stimuli including plasma osmolality, hypovolemia,

hypertension, and hypoglycemia. The actions of OT are mediated via a single receptor subtype (oxytocin receptor, OTR), which is distributed in the periphery and within the limbic CNS. In contrast to the OTR there are three vasopressin receptor subtypes, V1a, V1b, and V2 receptors, each of which are G-protein-coupled, seventransmembrane domain receptors. The V2 receptor is localized in the kidney and is not found in the brain. The V1a receptor is distributed widely in the CNS and is thought to mediate most of the behavioral effects of AVP. The V1b receptor is concentrated in the anterior pituitary, and some reports describe V1b receptor mRNA in the brain, although its function is unknown. Neurotensin (NT) Although NT is found in a number of brain regions, it has been most thoroughly investigated in terms of its association with other neurotransmitter systems, particularly the mesolimbic dopamine system, and has gained interest in research on the pathophysiology of schizophrenia. There are several lines of evidence suggesting that NT and its receptors should be considered as potential targets for pharmacological intervention in this disorder. First, the NT system is positioned anatomically to modulate

the neural circuits implicated in schizophrenia. Second, peripheral administration of antipsychotic drugs has been shown to consistently modulate NT systems. Third, there is evidence that central NT systems are altered in patients with schizophrenia. NT was first shown to interact with dopamine systems while undergoing characterization of its potent hypothermicpotentiating and sedative-potentiating activities. Subsequent work indicated that NT possessed many properties that were also shared by antipsychotic drugs, including the ability to inhibit avoidance, but not escape responding in a conditioned active avoidance task; the ability to block the effects of indirect dopamine agonists or endogenous dopamine in the production of locomotor behavior; and the ability to elicit increases in dopamine release and turnover. Perhaps most importantly, both antipsychotic drugs and NT neurotransmission enhance sensorimotor gating. Sensorimotor gating is the ability to screen or filter relevant sensory input, deficits in which may lead to an involuntary flooding of indifferent sensory data. Increasing evidence suggests that deficits in sensorimotor gating are a cardinal feature of schizophrenia. Both dopamine agonists and NT antagonists disrupt performance on tasks designed to gauge sensorimotor gating. Unlike antipsychotic drugs, NT is not able to displace dopamine from its receptor. As noted earlier, NT is colocalized in certain subsets of dopamine neurons and is co-released with dopamine in the mesolimbic and medial prefrontal cortex dopamine terminal regions that are implicated as the sites of dopamine dysregulation in schizophrenia. Antipsychotic drugs that act at D2 and D4 receptors increase the synthesis, concentration, and release of NT in those dopamine terminal regions but not in others. That effect of antipsychotic drugs in increasing NT concentrations persists after months of treatment and is accompanied by the expected increase in NT mRNA concentrations as well as expression of the “immediate early gene” cfos within hours of initial drug treatment. The altered regulation of NT expression by antipsychotic drugs apparently extends to the peptidases that degrade the peptide, because recent reports have revealed decreased NT metabolism in rat brain slices 24 hours after the acute administration of haloperidol. When administered directly into the brain, NT preferentially opposes dopamine transmission in the nucleus accumbens but not the caudate putamen. In the nucleus accumbens, NT receptors are located predominantly on GABAergic neurons, which release GABA on dopamine terminals, thereby inhibiting release. Decreased CSF NT concentrations have been reported in several populations of patients with schizophrenia when compared to those of controls or other psychiatric disorders. Although treatment with antipsychotic drugs has been observed to increase NT concentrations in the CSF, it is not known whether this increase is causal or merely accompanies the decrease in psychotic symptoms seen with successful treatment.

Postmortem studies have shown an increase in NT concentrations in the dopamine-rich Brodmann's area 32 of the frontal cortex, but that result may have been confounded by premortem antipsychotic treatment. Other researchers have found no postmortem alterations in NT concentrations of a wide sampling of subcortical regions. Decreases in NT receptor densities in the entorhinal cortex have been reported in entorhinal cortices of schizophrenic postmortem samples. A critical test of the hypothesis that NT may act as an endogenous antipsychotic-like substance awaits the development of an NT receptor agonist that can penetrate the blood–brain barrier. Other Neuropeptides A number of other neuropeptides have been implicated in the pathophysiology of psychiatric disorders. These include,

but are not limited to, cholecystokinin (CCK), substance P, and neuropeptide Y. CCK, originally discovered in the gastrointestinal tract, and its receptor are found in areas of the brain associated with emotion, motivation, and sensory processing (e.g., cortex, striatum, hypothalamus, hippocampus, and amygdala). CCK is often colocalized with dopamine in the VTA neurons that comprise the mesolimbic and mesocortical dopamine circuits. Like NT, CCK decreases dopamine release. Infusions of a CCK fragment have been reported to induce panic in healthy individuals, and patients with panic disorder exhibit increased sensitivity to the CCK fragment compared to that of normal controls. Pentagastrin, a synthetic CCK agonist, dose-dependently produced increased blood pressure, pulse, HPA activation, and physical symptoms of panic. Recently, a CCK receptor gene polymorphism has been associated with panic disorder. The undecapeptide substance P is localized in the amygdala, hypothalamus, periaqueductal gray, LC, and parabrachial nucleus and is colocalized with norepinephrine and serotonin. Substance P serves as a pain neurotransmitter, and administration to animals elicits behavioral and cardiovascular effects resembling the stress response. More recent data suggest a role for substance P in major depression and PTSD. Both depressed and PTSD patients had elevated CSF substance P concentrations. Furthermore, in PTSD patients, marked increases in CSF substance P concentrations were detected following precipitation of PTSD symptoms. One study has indicated that a substance P receptor (termed the neurokinin 1 [NK1] receptor) antagonist capable of passing the BBB is more effective than placebo and as effective as paroxetine in patients with major depression with moderate to severe symptom severity, although subsequent studies have been unable to confirm these findings. Neuropeptide Y (NPY) is a 36 amino acid peptide found in the hypothalamus, brainstem, spinal cord, and several limbic structures and is involved in the regulation of appetite, reward, anxiety, and energy balance. NPY is colocalized with serotonergic and noradrenergic neurons and is thought to facilitate the containment of negative effects following exposure to stress. Suicide victims with a diagnosis of major depression are reported to have a pronounced reduction in NPY levels in the frontal cortex and caudate nucleus. Furthermore, CSF NPY levels are decreased in depressed patients. Chronic administration of antidepressant drugs increases neuropeptide Y concentrations in the neocortex and hippocampus in rats. Plasma NPY levels were found to be elevated in soldiers subjected to the "uncontrollable stress" of interrogation, and NPY levels were correlated with the feelings of dominance and confidence during the stress. In addition, low NPY response to stress has been associated with increased vulnerability to depression and PTSD. NOVEL NEUROTRANSMITTERS Nitric Oxide The discovery that gases could function as neurotransmitters revealed that highly atypical modes of signaling existed between neurons. In the early 1990s, nitric oxide was the first gas to be ascribed a neurotransmitter function and proved to be an atypical neurotransmitter for several reasons. First, it was not stored in or released from synaptic vesicles, as it was a small gas it could freely diffuse into the target neuron. Second, its target was not a specific receptor on the

surface of a target neuron, but intracellular proteins whose activity could directly be modulated by nitric oxide, leading to neurotransmission. Nitric oxide also lacks a reuptake mechanism to remove it from the synapse. Although enzymatic inactivation of it is postulated to exist, nitric oxide appears to have a very short half-life of a few seconds. Nitric oxide was initially discovered as a bactericidal compound released from macrophages, and as an endothelial cell it derived relaxation factor allowing for the

dilation of blood vessels. A role for nitric oxide in the brain followed, revealing a role for the gas in neurotransmission, learning and memory processes, neurogenesis, and neurodegenerative disease. Nitric Oxide and Behavior Nitric oxide neurotransmission can play a role in behavior, as neuronal nitric oxide synthase (nNOS)–deficient male mice display exaggerated aggressive tendencies and increased sexual activity. In female mice the contrary is true, as they have reduced aggression. As manic bipolar patients may show both hypersexuality and aggression, the nitric oxide pathway may participate in the psychopathology of affective states. In the periphery, nNOS localizes to neurons that innervate blood vessels of the penis, including the corpus cavernosa. Stimulation of these nerves releases nitric oxide, leading to cyclic guanosine monophosphate (cGMP) formation, blood vessel wall relaxation and vasodilation, penile engorgement, and initial erection. The sustained phase of erection also depends on nitric oxide; turbulent blood flow leads to phosphorylation of eNOS and sustained nitric oxide production. Drugs used in treatment of erectile dysfunction—sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra)—act to inhibit phosphodiesterase type 5 (PDE5), an enzyme that degrades cGMP in the penis (Fig. 1.4-12), thereby potentiating nitric oxide neurotransmission and penile erection.

FIGURE 1.4-12 Neurotransmitter and signaling functions of nitric oxide (NO) via production of cyclic guanosine monophosphate (cGMP). Gaseous nitric oxide is enzymatically generated and freely diffuses into an adjacent neuron (upper right). In comparison to traditional neurotransmitters (upper left), nitric oxide (NO) does not act via a specific neurotransmitter receptor on the surface membrane of a neuron. In contrast, NO freely diffuses across the neuronal membrane and activates the enzyme, guanylyl cyclase, which converts guanosine 5’-triphosphate (GTP) into the second messenger, cGMP. Nitric oxide effects are mediated, in part, by cGMP activation of neuronal protein kinases, new gene expression, and effects on neuronal long-term potentiation (LTP) and long-term depression (LTD). ATP, adenosine triphosphate. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:104.) Numerous lines of evidence have suggested a role for nitric oxide in the regulation of sleep–wake cycles. nNOS expressing neurons occur in several areas that initiate REM sleep, including the pons, dorsal raphe nucleus, laterodorsal tegmentum, and pedunculopontine tegmentum. In animal models, microinjection of compounds that release nitric oxide

result in decreased wakefulness and increased slow wave sleep. Consistent with this, NOS inhibitors show a trend toward decreasing slow wave and REM sleep. Studies of NOS-deficient mice suggest that nitric oxide may serve a more complex role than merely promoting sleep. nNOS-deficient animals also show reduced REM sleep; however, inducible nitric oxide synthase (iNOS)–deficient mice demonstrate the reverse, suggesting a complex interplay between NOS enzymatic isoforms. Nitric Oxide and Mood Disorders. NOS-expressing neurons are well represented in areas implicated in depression, including the dorsal raphe nucleus and prefrontal cortex. A role for nitric oxide has been suggested in antidepressant response, as SSRI

antidepressants can directly inhibit NOS activity. Moreover, in animal studies such as the forced swim test, NOS and soluble guanylyl cyclase inhibitors can achieve antidepressant-like effects. Plasma nitric oxide levels were elevated in patients with bipolar disorder compared to healthy controls. However, in depressed subjects, studies have found decreased nitric oxide levels and increased plasma nitrite, a byproduct of nitric oxide. Reduced NOS has also been described in the paraventricular nucleus of patients with schizophrenia and depression compared to controls. Nitric oxide has been questioned as to its ability to regulate neurotransmission at serotonin, norepinephrine, and dopamine nerve termini. However, there has been no clear consensus, and nitric oxide appears to be able to increase or decrease activity at these neurons depending on the timing of its activation and the region of the brain studied. Nitric Oxide and Schizophrenia. Nitric oxide has been investigated as a candidate molecule contributing to symptoms of schizophrenia. Two genetic studies have identified schizophrenia-associated single nucleotide polymorphisms (SNPs) in CAPON, a protein that associates with nNOS. SNPs in nNOS itself have been associated with schizophrenia, although others have not been able to reproduce such findings. Changes in NOS levels have been reported in postmortem brain samples of individuals with schizophrenia. Abnormalities have been noted in the cortex, cerebellum, hypothalamus, and brainstem, although no specific trend can be discerned. Elevated NOS activity has been noted in platelets from drug-naive and drug-treated individuals with schizophrenia. Some investigators find increased nitric oxide activity and others the reverse. In autopsy samples, schizophrenic patients were found to have abnormally localized NOS expressing neurons in the prefrontal cortex, hippocampus, and lateral temporal lobe, consistent with abnormal migration of these neuronal types during development. In a rat model, prenatal stress led to reduced NOS expressing neurons in the fascia dentate and hippocampus. Neuropathological Roles of Nitric Oxide. Abundant evidence exists that nitric oxide is a direct participant in a variety of neuropathic events. Superoxide, a byproduct of cellular metabolism, can react with nitric oxide to form peroxynitrite (chemical formula $ONOO^-$). This labile and toxic compound forms chemical adducts with protein tyrosine residues, a process termed protein nitration, and deoxyribonucleic acid (DNA),

leading to cellular dysfunction. Cell loss resulting from ischemic stroke is mediated in part by overstimulation of the glutamate NMDA receptor, a process termed excitotoxicity. Nitric oxide produced by NMDA activation appears to mediate a significant portion of this excitotoxic neuronal death, and stroke damage is reduced in mice with a genetic deletion of nNOS. S-Nitrosylation has also been implicated in pathologic processes in the brain. Mutations in the Parkin protein are associated with early onset Parkinson’s disease. Parkin is an E3 ubiquitin ligase, adding ubiquitin molecules to proteins and targeting them for destruction in the cell proteasome. In sporadic Parkinson’s disease (i.e., without the early onset mutation), nitric oxide can nitrosylate the Parkin protein and inhibit its protective E3 ubiquitin ligase function. An overabundance of nitric oxide signaling may thus predispose to the dysfunction and cell death of dopaminergic neurons in Parkinson’s disease by interfering with proteins essential for cell functioning. In Alzheimer’s disease excess oxidation of brain protein, lipids, and carbohydrates has long been appreciated, but nitrosative stress from excess nitric oxide also appears to participate in the disease. Protein disulfide isomerase (PDI) is a cellular protective protein that may help combat the accumulation of misfolded proteins such as the amyloid fibrils occurring in the disease. In both Alzheimer’s and Parkinson’s disease brains, PDI appears to be S-nitrosylated in a harmful way that impedes its cellular protective function. The discovery that nitric oxide participates in neurodegenerative processes raises the possibility for improved diagnostic processes, such as detecting damage to

cellular components produced by nitric oxide prior to the onset of fullblown symptoms. In addition, drugs may be designed to attenuate the damage to crucial neuronal proteins that protect against disease onset. However, completely and nonspecifically inhibiting or stimulating NOS is likely to produce significant side effects because of its wide-ranging activities throughout the body. Carbon Monoxide Although carbon monoxide (CO) is most well known as an air pollutant derived from combustion reactions, it is produced physiologically in a great variety of organisms ranging from human to bacterium. Once thought to be a toxic byproduct of metabolic reactions, carbon monoxide is increasingly recognized to play an important role in regulating a variety of physiological processes in the brain and other organs. These varied effects include regulation of olfactory neurotransmission, blood vessel relaxation, smooth muscle cell proliferation, and platelet aggregation. Carbon monoxide is far better known for its toxic effects than its activities at physiologic concentrations. It binds tightly to heme molecules within hemoglobin, forming carboxyhemoglobin, which can no longer transport oxygen to tissues. One- to two-pack per day smokers typically have 3 to 8 percent of their hemoglobin as carboxyhemoglobin, with nonsmokers having less than 2 percent. Following acute carbon monoxide poisoning, 5 to 10 percent carboxyhemoglobin is associated with impaired alertness and cognition, and 30 to 50 percent carboxyhemoglobin leads to significant drops in oxygen transport to tissues. Carbon Monoxide and Neurotransmission. Carbon monoxide appears to participate in the neurotransmission of odorant perception. Odorants lead to carbon

monoxide production and subsequent cGMP synthesis that promotes long-term adaptation to odor stimuli. Carbon monoxide has the potential to regulate a variety of perceptual and cognitive processes that are yet untested. Similarly, in the rat retina, long periods of light exposure led to increased HO1 expression, carbon monoxide production, and cGMP signaling. Carbon monoxide may also participate in adaptation to chronic pain. HO2-deficient animals manifest reduced hyperalgesia and allodynia after exposure to chronic pain stimuli. Carbon monoxide may thus set the threshold for pain perception, although it is unclear whether the effect occurs in the central or peripheral nervous system. Aside from its role in promoting cGMP production, carbon monoxide may also directly bind to and open the calcium-activated big potassium (BKCa) channel, leading to as yet uncharacterized effects on neurotransmission. In the gastrointestinal (GI) nervous system, carbon monoxide serves as a neurotransmitter to relax the internal anal sphincter in response to nonadrenergic noncholinergic (NANC) nerve stimulation and vasoactive intestinal peptide (VIP). Carbon monoxide has been implicated in the development of hippocampal LTP, although lines of evidence are contradictory. Carbon monoxide and tetanic stimulation of nerves leads to increased excitatory postsynaptic potentials (EPSPs). HO inhibitors that block carbon monoxide production lead to impaired induction of LTP and reduced calcium-dependent release of glutamate neurotransmitter. However, HO2-deficient animals fail to manifest any differences in LTP. These disparate findings may be explained by a role for HO1 in LTP, or an ability of HO inhibitors to nonspecifically block some other processes important to LTP induction. At toxic levels, carbon monoxide is well known to impair oxygen transport by binding to hemoglobin with a higher affinity than oxygen. Amazingly, carbon monoxide itself plays a physiological role in the mechanism by which the carotid body senses oxygen. HO, expressed in glomus cells of the carotid body, uses oxygen as a substrate in the production of carbon monoxide (Fig. 1.4-13). When oxygen levels drop, so does carbon monoxide production, leading to a resetting of the threshold in which the carotid body senses oxygen. The molecular mechanism may occur via carbon monoxide regulation of the carotid body BK ion channel.

FIGURE 1.4-13 Synthesis of carbon monoxide (CO), an unexpected neurotransmitter. Gaseous carbon monoxide is enzymatically synthesized in neurons by way of the enzyme heme oxygenase, also converting heme into the molecule biliverdin and liberating free iron (Fe). Similar to nitric oxide, CO is not stored in neuronal vesicles and can freely diffuse across neuronal membranes. CO also similarly activates soluble guanylyl cyclase, and leads to activation of multiple intracellular signaling molecules such as p38 MAP kinase. CO exerts its neurotransmitter and signaling functions at concentrations far below that at which classical CO toxicity occurs. The significance of this pathway in neurons is underlined by the existence of two distinct heme oxygenase enzymes, one of which is predominantly expressed in the brain. Biliverdin is converted to bilirubin via the enzyme biliverdin reductase. Similar to CO, bilirubin is no longer relegated to the status of toxic byproduct and may be an important antioxidant. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:107.) Endocannabinoids: From Marijuana to Neurotransmission Whether known as cannabis, hemp, hashish, ma-fen, or a variety of slang terms, marijuana has been cultivated and utilized by human populations for thousands of years. Despite long debate as to whether its risks and benefits are evenly matched, it has only been in recent decades that some of the mystery has been revealed by which marijuana exerts its effects on the brain. The "high" users experience, euphoria and tranquility, relates to cannabis acting on a neural pathway involving cannabinoids endogenous to the human brain, or endocannabinoids.

The first described medicinal use of cannabis dates to approximately 2700 BC in the pharmacopeia of Chinese Emperor Shen Nung, who recommended its use for a variety of ailments. At this time, adverse properties were also apparent, and large amounts of the fruits of hemp could lead to "seeing devils," or a user might "communicate with spirits and lightens one's body." For centuries, cannabis was employed in India as an appetite stimulant; habitual marijuana users remain well acquainted with "the munchies." For many years the mechanisms by which the active components of marijuana, cannabinoids, exerted their psychoactive effects remained a mystery. Chemists sought to isolate the psychoactive components of cannabis from the many components of the plant oil (Table 1.4-4). Table 1.4-4 Selected Discoveries in Cannabinoid Research Discovery of the Brain Endocannabinoid System. Estimates suggest that 20 to 80 µg of tetrahydrocannabinol (THC) reaches the brain after one smokes a marijuana cigarette (i.e., "joint"). This is comparable to the 100 to 200 µg of norepinephrine

neurotransmitter present in the entire human brain. Thus the effects of THC might be explained by the effects on neurotransmitter systems. In the 1960s, there were at least two schools of thought on how THC exerted its psychoactive effects. One held that THC worked in a manner similar to that of the inhaled volatile anesthetics (i.e., no specific receptor existed), and it might have a generalized effect on neuronal membranes or widespread actions on neurotransmitter receptors. A competing school of thought speculated that specific receptors for cannabinoids existed in the brain, but they were difficult to identify due to the lipophilic nature of these chemicals. Novel cannabinoids were synthesized that were more water soluble, and in the late 1980s, this allowed for the discovery of a specific cannabinoid receptor, CB1. Several additional endocannabinoids were soon discovered, 2-arachidonylglycerol (2-AG), N-arachidonyldopamine (NADA), 2-arachidonoylglycerol ether (noladin ether), and virodhamine (Fig. 1.4-14). The reason for having several different endocannabinoids may lie with their differing affinities for the cannabinoid receptors, CB1 and CB2. Anandamide appears to have the greatest selectivity for the CB1 receptor,

followed by NADA and noladin ether. In contrast, virodhamine prefers CB2 receptors and has only partial agonist activity at CB1. 2-AG appears not to discriminate between CB1 and CB2.

FIGURE 1.4-14 Endogenous cannabinoids. At least five endocannabinoids exist in the mammalian brain, each differing in affinity for CB1 and CB2 cannabinoid receptors. All are derived from the essential omega-6 fatty acid, arachidonic acid, which is also a substrate in the

formation of prostaglandins and leukotrienes. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:111.) Biosynthesis of Endocannabinoids. Arachidonic acid is utilized as a building block for biosynthesis of endocannabinoids, prostaglandins, and leukotrienes and is found within cellular phospholipids of the plasma membrane and other intracellular membranes. Synthesis of anandamide requires the sequential action of two enzymes (Fig. 1.4-15). In the first reaction the enzyme N-acetyltransferase (NAT) transfers an arachidonic acid side chain from a phospholipid to phosphatidylethanolamine (PE), generating NAPE (N-arachidonyl-phosphatidylethanolamine). In the second reaction the enzyme N-arachidonyl-phosphatidylethanolamine phospholipase (NAPD-PLD) converts NAPE to anandamide. Because NAPE is already a natural component of mammalian membranes, it is the second step that generates anandamide, which is most crucial to neurotransmission.

FIGURE 1.4-15 Retrograde neurotransmission of the endocannabinoids, anandamide, and 2arachidonylglycerol (2-AG). Anandamide is synthesized on demand for

neurotransmission via a two-step process. The enzyme NAT transfers the arachidonic acid chain from a phospholipid (APL) to phosphatidylethanolamine (PE), thereby producing NAPE. A second enzyme, NAPE-PLD, generates anandamide. 2-AG is similarly synthesized in two steps by the enzymes PLC and DAGL. The endocannabinoids made in a postsynaptic neuron cross the synapse and activate presynaptic CB1 receptors, and suppress neurotransmission of the presynaptic neuron (although activation of the presynaptic neuron occurs in some cases). Enzymes involved in endocannabinoid synthesis are yellow, those that break them down in red. 2-AG is predominantly inactivated in the presynaptic neuron by MAGL, whereas anandamide is destroyed in the postsynaptic neuron by FAAH. PE, phosphatidylethanolamine; APL, arachidonyl phospholipids; NAT, N-acyltransferase; NAPE, N-arachidonyl-phosphatidylethanolamine; NAPE-PLD, N-arachidonyl-phosphatidylethanolamine phospholipase D; FAAH, fatty acid amide hydrolase; MAGL, monoacylglycerol lipase; PLC, phospholipase C; DAG, diacylglycerol; DAGL, diacylglycerol lipase; R1-R3, various acyl or akyl side chains of phospholipids; R', side chain of phospholipid head group. (From Sadock BJ, Sadock VA, Ruiz P. Kaplan & Sadock's Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009:112.) Endocannabinoids are not stored in synaptic vesicles for later use, but are synthesized on demand as is done for the gaseous neurotransmitters. An important criterion for a signaling molecule to be considered a neurotransmitter is that neuronal depolarization should lead to its release. Depolarization leads to increases in cellular calcium, which in turn promotes synthesis of the endocannabinoids and their release. The mechanism is explained in part by calcium activation of NAPE-PLD and DAGL, leading to augmented biosynthesis of anandamide and 2-AG, respectively. Endocannabinoids generated in a neuron must cross the synaptic cleft to act on cannabinoid receptors. Similar to THC, endocannabinoids are highly lipophilic and thus poorly soluble in CSF. It is hypothesized that a

specific endocannabinoid transporter exists to allow endocannabinoids to cross the synaptic cleft and allow entry into the target neuron. Inactivation of Endocannabinoids. Neurotransmitters are typically inactivated either by reuptake from the neurons that release them or by degradation by highly specific enzymes, such as the example of acetylcholine being hydrolyzed by acetylcholinesterase. At least two enzymes exist to target the destruction of endocannabinoids and attenuate their neurotransmission. Fatty acid amide hydrolase (FAAH) converts anandamide to arachidonic acid and ethanolamine (Fig. 1.4-15). FAAH is found in regions of the brain where CB1 receptors are predominant and localizes to postsynaptic neurons where anandamide is made. Rapid degradation of anandamide in part explains its relatively low potency compared to THC. Confirming a role of FAAH in anandamide inactivation, knockout mice without FAAH exhibit a 15-fold increase of anandamide, but not 2-AG. These mice have greater behavioral responses to exogenous anandamide, owing to its decreased degradation. The endocannabinoid 2-AG is inactivated by FAAH, but also by a monoacylglycerol lipase (MAGL) located in presynaptic neurons. Pharmacologic inhibitors of FAAH have analgesic effects and reduce anxiety in animal

models, but do not have the undesirable effects of THC such as immobility, lowered body temperature, or greater appetite. Such a pharmacological strategy would be analogous to MAOIs and COMT inhibitors (COMTIs). MAOIs, used to treat depression, slow the breakdown of serotonin and other monoamines, thereby increasing serotonin, whereas COMTIs serve an analogous role in blocking destruction of dopamine and other catecholamines. Cannabinoid Receptors. Underscoring their importance in neural functions, CB1 receptors are possibly the most abundant G-protein-coupled receptors in the brain. They occur at highest density in the basal ganglia, cerebellum, hippocampus, hypothalamus, anterior cingulate cortex, and cerebral cortex, particularly the frontal cortex. Humans or animals that receive large doses of THC develop catalepsy, a reduction of spontaneous movement, and freeze in bizarre and unnatural postures. The action of cannabinoids in the basal ganglia and cerebellum may be associated with these behaviors, which may prove relevant in understanding catatonic symptoms in schizophrenia. CB1 receptors are predominantly found on axons and nerve termini, with little present on neuronal dendrites and the cell body. CB1 receptors tend to be localized to the presynaptic rather than postsynaptic side of the neuronal cleft, suggesting a role in regulation of neurotransmission. A second cannabinoid receptor, CB2, is predominantly expressed on the surface of white blood cells of the immune system, but small amounts appear to be present in the brainstem. EFFECTS ON NEUROTRANSMISSION. The cannabinoid CB1 receptor is associated with G proteins that mediate its intracellular signaling, in part, through inhibition of adenylyl cyclase. This leads to a decrease in levels of the important second messenger, cyclic adenosine monophosphate. Activation of the CB1 receptor also leads to activation of potassium channels and inhibition of N-type calcium channels. Because calcium is integral to neurotransmitter release, cannabinoids can block neurotransmission through this mechanism. Cannabinoid receptors also activate mitogen-activated protein kinases. With the use of cell culture models and slices of brain, cannabinoids have been shown to block the release of a variety of neurotransmitters, including GABA, norepinephrine, and acetylcholine. Norepinephrine and acetylcholine tend to be excitatory neurotransmitters, and cannabinoid inhibition of their release would be expected to have an overall inhibitory effect. However, GABA is an inhibitory neurotransmitter, and cannabinoid inhibition of it would lead to overall excitatory effects, demonstrating that cannabinoids can have complex effects on neurotransmission depending on the specific context. Cannabinoids also appear to increase the release of brain endorphin neurotransmitters and increase dopamine release in the nucleus accumbens, a “reward center”

relevant to addiction and learning. The endocannabinoids have been implicated in a variety of forms of synaptic plasticity, including LTP and long-term depression (LTD). Endocannabinoids in Anxiety and Mood. Endocannabinoid

neurotransmission may be an important regulator of anxiety, and cannabis users regularly describe a tranquilizing effect of THC. Loss of signaling by the endocannabinoid system appears to promote anxiety-like states in animal studies. CB1 receptor–deficient animals exhibit more pronounced anxiety behavior when exposed to stress or new environs. The endocannabinoid pathway may represent an attractive target in understanding posttraumatic stress responses and phobias. Although one cannot yet safely measure endocannabinoid levels in human subjects, this model is supported by clinical trials of the cannabinoid receptor blocker, rimonabant (Acomplia), which may offer promise as a strategy for weight loss (see below). A frequent adverse reaction to the drug is increased anxiety and depression. ADDICTION. The endocannabinoid system may be an attractive target for understanding addiction. Mice deficient in CB1 receptors are unsurprisingly resistant to the behavioral effects of cannabinoids; they also appear to have reduced addiction to and withdrawal from opiates. Further interaction has also been found between the opioid and cannabinoid systems, as cannabinoids appear to increase the release of dopamine in the nucleus accumbens, a key reward area of the brain implicated in addiction. This dopamine release appears to require μ-opioid receptors, as pharmacological inhibition of these receptors blocks the ability of cannabinoids to increase dopamine release. Rats with a preference for alcohol have decreased FAAH activity, suggestive of greater cannabinoid signaling. CB1 receptor antagonists dampen their alcohol consumption, whereas inhibiting FAAH increases their alcohol consumption. Furthermore, CB1deficient animals also appear to have reduced alcohol intake. A single amino acid mutation in human FAAH has been found to be associated with drug abuse, and this abnormal enzyme appears to be less stable than its wild-type counterpart. Endocannabinoids in Psychosis. Heavy use of cannabis can produce psychotic symptoms in individuals with no prior history of psychiatric disorder, although it is unclear whether this is solely due to the drug or to an underlying vulnerability to psychosis in such persons. Cannabis use often worsens psychosis in schizophrenia, and heavy use has been associated with developing schizophrenia, although some suggest that this association is an accelerated development of symptoms in those who would eventually manifest schizophrenia. Nonetheless, the endocannabinoid system has implications for the pathophysiology of schizophrenia, as cannabinoid signaling appears to increase the release of dopamine. Medications that act as antagonists of D2 receptors will likely remain a component of schizophrenia treatment for some time. FEEDING. Following drug ingestion, THC users develop an increased appetite (“the munchies”), and cannabis has been utilized as an appetite stimulant for centuries. This effect may depend on CB1 receptors present in the hypothalamus. Endocannabinoid levels increase in the hypothalamus and limbic system when animals are deprived of food. Mice genetically deficient in CB1 receptors become resistant to developing obesity

after being given a high-fat diet. Similarly, the CB1 receptor antagonist, rimonabant, appears to facilitate weight loss by blocking cannabinoid signaling. In a clinical trial of more than 3,000 obese patients, those treated with 20 mg per day of rimonabant lost 6.3 kg at 1 year, compared to 1.6 kg in the placebo group. Nausea was the most common side effect reported. A 2007 meta-analysis of clinical trials reported an overall 4.7 kg weight loss with rimonabant treatment, besting the weight-loss drugs orlistat (Xenical; 2.9 kg) and sibutramine (Meridia; 4.2 kg). Effects on Brain Injury and Pain. In mouse models of traumatic brain injury, 2AG appears neuroprotective, reducing brain

edema, infarct size, and cell death, while improving functional outcomes. Anandamide also protected against brain injury in a model of multiple sclerosis (MS), and human patients with the disease have increased production of anandamide. A study of cannabinoid agonist, HU-211, led to more rapid clinical improvement following head trauma. FAAH inhibitors improved motor symptoms in a mouse model of Parkinson's disease, likely via cannabinoids increasing dopamine neurotransmission. There is increasing evidence that neurotransmission via the endocannabinoid pathway regulates pain perception. THC and cannabinoid agonists have proven effective in animal models of acute and chronic pain, ranging from burn injury to nerve damage and inflammation. The CB1 receptor plays an important role in these effects, as the analgesic effects of cannabinoid drugs are lost when CB1 antagonist rimonabant is given. Similarly, the analgesic effect of THC is lost in mice that are genetically deficient in the CB1 receptor. Stress has long been associated with diminished pain perception, such as in cases of injured military personnel who demonstrate remarkable pain tolerance, a phenomenon known as stress-induced analgesia. The endocannabinoid system may mediate these effects. Animal models reveal anandamide and 2-AG production after stress, and stressinduced analgesia is blocked by the CB1 blocker, rimonabant, in these animals. Endocannabinoid regulation of pain perception appears to be distinct from that of the endogenous opiate system, but the two pathways may share overlapping neural pathways. Evidence for this has been provided using CB1 blocker, rimonabant, and naloxone (Narcan), which blocks opiate receptors. Rimonabant attenuates analgesia provided by THC and cannabinoids, but only partly blocks the response to morphine. However, the opposite is true for opiates: Naloxone blocks morphine-induced analgesia but also partially blocks the analgesia of THC and cannabinoid drugs. Combinations of cannabinoid and opiate drugs evince synergistic analgesic effects in animal models. Although it was initially assumed that cannabinoids exert their analgesic effects via the CNS, in animal models it has been shown that localized administration of cannabinoids may also be effective, including drugs selective for the CB2 receptor, whose expression is minimal in the CNS. Endocannabinoids may also influence pain sensitivity by mechanisms that do not involve the CB1 and CB2 receptors. Both anandamide and NADA can also activate a calcium channel known as the vanilloid receptor (also known as transient receptor potential vanilloid type 1 [TRPV-1]) that is found on sensory nerves. This same receptor is also famous for being

activated by capsaicin, which causes the hot sensation after eating chili peppers. Thus endocannabinoids can exert opposing functions: Promoting analgesia through the CB1 and CB2 receptors, but potentially increasing pain via TRP channels. Although CB2 receptors are largely expressed in the periphery, postmortem analyses reveal an upregulation in brain from those with Alzheimer's disease. The rapid development of novel cannabinoid drugs may allow for targeting of specific symptoms, rather than elicit all of the typical effects of THC. For instance, ajulemic acid demonstrates analgesic and anti-inflammatory properties, but may offer a benefit of limited psychoactive side effects. In a randomized clinical trial of this compound, Mathias Karst and colleagues found efficacy in reducing chronic neuropathic pain. Effects in the Periphery. Cannabinoids lead to direct relaxation of vascular smooth muscle by local CB1 receptors. This vasodilation extends to the conjunctiva, leading to a "bloodshot" appearance in some cannabis users. Relaxation of ocular arteries by cannabinoids may offer utility as a treatment for glaucoma, a condition of high intraocular pressure, and activation of CB1 receptors in the kidney can improve renal blood flow. A role in generalized blood pressure regulation is unproven, and blood pressure is unaltered in persons treated with rimonabant or animals deficient in CB1 receptors. Cannabinoid signaling may also be relevant to ectopic pregnancy, as CB1deficient mice retain many embryos in

the oviduct. Nonpsychoactive Cannabinoids Although THC is the principal psychoactive component of cannabis, the many nonpsychoactive cannabinoids also have intriguing properties and may regulate neurotransmission. Cannabidiol may offer potential therapeutic effects and appears to stimulate TRPV-1 receptors and influence endocannabinoid degradation. In addition, cannabidiol demonstrated a protective effect in a mouse model of inflammatory arthritis. Although results have been mixed, purified cannabidiol may also exert antipsychotic activity, although the net effect of plant cannabis use typically exacerbates schizophrenia symptoms owing to THC. Tetrahydrocannabivarin is a plant cannabinoid that antagonizes CB1 receptors. It is a candidate marker to distinguish whether a patient has been using plant-derived cannabis or prescription THC, which contains no tetrahydrocannabivarin. Eicosanoids Overview. Clinical findings suggest that the dietary supplements omega-3 fatty acids, eicosapentaenoic acid (EPA), its ester ethyl-eicosapentaenoic (E-EPA), and docosahexaenoic acid (DHA), help relieve symptoms of depression, bipolar illness, schizophrenia, and cognitive impairment. DHA and EPA may help reduce behavioral outbursts and improve attention in children. Chemistry. Essential fatty acids are a group of polyunsaturated fats that contain a carbon–carbon double bond in the third position from the methyl end group in the fatty

acid chain. They are essential because unlike monosaturated and saturated fatty acids, polyunsaturated fatty acids cannot be synthesized de novo and can be acquired only through diet from natural fats and oils. Linoleic acid (LA) is the parent compound of omega-6 fatty acids, and α-linolenic acid (ALA) is the parent compound of omega-3 fatty acids. Both omega-3 and omega-6 groups use the same enzymes for desaturation and chain elongation. Omega-3 fatty acids are synthesized by algae and plankton. Fish such as herring, salmon, mackerel, and anchovy feed on these aquatic species and become a rich dietary source of omega-3. EPA and DHA are highly unsaturated omega-3 fatty acids that contain 6 and 5 double bonds on their long structural chain, respectively. They are positioned in the cell membrane by phospholipids and play a crucial role in cell membrane signaling. Effects on Specific Organs and Systems. The strongest scientific evidence for treatment with fatty acid supplements comes from the cardiovascular literature. Several human trials have demonstrated that omega-3 fatty acids lower blood pressure, reduce the rate of recurrent myocardial infarction, and lower triglyceride levels. In the nervous system, fatty acids are essential components of neurons, immune cells, and glial phospholipid membrane structures. They increase cerebral blood flow, decrease platelet aggregation, and delay progression of atherosclerosis in the cardiovascular system. Omega-6 fatty acids appear to reduce inflammation and neuronal apoptosis and decrease phosphatidylinositol second messenger activity. Omega-3 fatty acids have been suggested to alter gene expression. In the CNS, fatty acids are selectively concentrated in neuronal membranes and involved in cell membrane structure. Omega-6 arachidonic acid has been shown to enhance glutamate neurotransmission, stimulate stress hormone secretion, and trigger glial cell activation in the setting of oxidative toxicity and neurodegeneration. The omega-3 fatty acids DHA and EPA appear to protect neurons from inflammatory and oxidative toxicities. Increases in serotonin, enhancement of dopamine, and regulation of CRF have been demonstrated in cell culture models. In rodent models of depression, chronic EPA treatment normalized behavior in open field tests. Serotonin and norepinephrine were also increased in the limbic regions. Mice fed omega-3 poor diets had reduced memory, altered learning patterns, and more behavioral problems. Therapeutic Indications. Clinical research with the use of fish oil for mood disorders was based on epidemiology studies where there appears to be negative correlation between fish consumption and depressive symptoms. Countries with lower per

capita fish consumption had up to 60 times increased rates of major depression, bipolar disorder, and postpartum depression. Observational studies concluded that the lower incidence of seasonal affective disorder in Iceland and Japan, rather than latitude predicted, is related to the amount of fatty acid these populations consume in their diet. A study in Norway showed that use of cod liver oil decreased depressive symptoms. Depression after a myocardial infarction shows higher arachidonic acid to EPA ratio.

Postmortem studies in brains of patients diagnosed with major depressive disorder show reduced DHA in the orbitofrontal cortex. The first randomized, controlled pilot study of omega-3 fatty acids focused on adjunctive treatment in both bipolar and unipolar patients with depression in addition to their standard lithium (Eskalith) or valproic acid (Depakene) treatment. The omega-3 fatty acid group had significant improvement on the Hamilton Depression scale and a longer period of remission than the placebo group. A subsequent larger study supported a benefit from treatment with E-EPA for bipolar illness. However, a study of a group of patients with either bipolar disorder or rapid cycling treated with E-EPA showed no significant difference on any outcome measure between the EPA and placebo groups. Bleeding time was also increased in the treatment group. There are no current data on monotherapy in bipolar illness or depression. The most convincing evidence comes from early brain development and learning studies. Pregnant mothers who consumed foods rich in DHA gave birth to infants who had improved problem-solving skills, but not necessarily improved memory. Visual acuity and eye development are also associated with DHA supplementation during pregnancy. Reports of behavioral studies of prisoners in England who consumed higher amounts of seafood containing omega-3 fatty acids showed a decrease in assault rates. A Finnish study of violent criminals identified lower levels of omega-3 fatty acids in their system compared to the nonviolent offenders. The negative and psychotic symptoms of schizophrenia may be improved with supplementation with omega-3 fatty acids. Antipsychotic medications like haloperidol (Haldol) appear to have fewer extrapyramidal side effects when combined with antioxidants and omega-3 fatty acids. EPA and DHA have been associated with decreased dementia incidence. After reviewing the Rotterdam study of a longitudinal cohort of more than 5,300 patients, fish consumption appeared to be inversely related to development of new cases of dementia. A later analysis of the study after 6 years demonstrated that low intake of omega-3 fatty acids was not associated with increased risk of dementia. In contrast, the Zutphen study, also in the Netherlands, concluded that high fish consumption was inversely related with cognitive decline at 3-year follow-up and after 5 years. Well-designed clinical trials are needed before omega-3 fatty acids can be recommended for prevention of cognitive impairment. Precautions and Adverse Reactions. The most adverse complication of eicosanoid use is increased risk for bleeding. Dietary sources can contain heavy metals, and there is no standard preparation for capsule formulations. Treatment studies have yielded a variety of different doses, but evidence for the therapeutic dose and clinical guidelines are almost nonexistent. The length of treatment still needs to be determined. Neurosteroids

Background. Although steroids are critical for the maintenance of body homeostasis, neurosteroids are synthesized from cholesterol in the brain and independent of peripheral formation in the adrenals and gonads. Neurosteroids are produced by a sequence of enzymatic processes governed by cytochrome P450 (CYP) and non-CYP enzymes, either within or outside the mitochondria of several types of CNS and peripheral nervous system (PNS) cells. Recent work has shown that neurosteroids can operate through a nongenomic pathway to regulate neuronal excitability through

their effects on neurotransmittergated ion channels. Receptors are generally located in the nucleus, membrane, or microtubules of the CNS and PNS. Although steroids and neurosteroids can act on the same nuclear receptors, neurosteroids differ from steroids in their topological distribution and regional synthesis. The most well-known effect of neurosteroids is on the GABA receptor, particularly the GABAA receptor. Neurosteroids acting primarily at this site include allopregnanolone (3α,5α-tetrahydroprogesterone), pregnanolone (PREG), and tetrahydrodeoxycorticosterone (THDOC). Dehydroepiandrosterone sulfate (DHEA-S), the most prevalent neurosteroid, acts as a noncompetitive modulator of GABA, and its precursor dehydroepiandrosterone (DHEA) has also been shown to exert inhibitory effects at the GABA receptor. Some neurosteroids may also act at the NMDA, α-amino-3-hydroxy-5-methyl-4-isoxazole-propanoic acid (AMPA), kainate, glycine, serotonin, sigma type-1, and nicotinic acetylcholine receptors. Progesterone is also considered a neurosteroid and has the ability to regulate gene expression at progesterone receptors. Neurosteroids in Neurodevelopment and Neuroprotection. In general, neurosteroids stimulate axonal growth and promote synaptic transmission. Specific neuroprotective effects are unique to each neurosteroid. DHEA acts to regulate brain serotonin and dopamine levels, suppress cortisol, increase hippocampal primed burst potentiation and cholinergic function, decrease amyloid-β protein, inhibit the production of proinflammatory cytokines, and prevent free radical scavenging. DHEA and DHEA-S have both been shown to have a role in glial development and neuronal growth and to promote their survival in animals; the injection of these substances into the brains of mice promoted long-term memory while reversing amnesia. Progesterone is linked to myelinating processes like aiding in the repair of damaged neural myelination (Color Plate 1.4-16). Allopregnanolone contributes to the reduction of contacts during axonal regression. Role of Neurosteroids in Mental Illness. Neurosteroids have distinct implications for the maintenance of normal neurologic function and also may contribute to neuropathology. Neurosteroids are differentially regulated in males and females and may affect the manifestation of psychological disorders in these two populations. Specifically, they play a distinct role in depression and anxiety disorders and may be targeted by psychiatric medications in the near future.

DEPRESSION. When compared with nondepressed controls, studies show that depressed patients have lower plasma and CSF concentrations of allopregnanolone. In addition, this research has elucidated an inverse relationship between allopregnanolone concentrations and severity of depressive illness. However, there are no allopregnanolone-based therapies available for humans, so its direct efficacy is unsubstantiated. Antidepressant drugs, specifically fluoxetine (Prozac), have been shown in multiple studies to increase the levels of certain neurosteroids. Nonetheless, there is debate over the therapeutic properties of neurosteroids, prompting the investigation of neurosteroid concentrations in patients undergoing nonpharmacological therapies. Preliminary results indicate that the lack of modifications in neurosteroid levels during nonpharmacological treatments supports the validity of the pharmacological properties of antidepressants, not their therapeutic action, in the elevation of neurosteroid levels in medicated populations. ANXIETY DISORDERS. In patients with anxiety disorders, the major mechanism of action is on the GABA receptor. Homeostasis characterized by normal GABAergic activity is restored after panic attacks as neurosteroids are released in response to stress. Allopregnanolone stimulates GABAergic activity with 20 times the strength of benzodiazepines and 200 times the potency of barbiturates. Both positive and negative regulation of the GABAA receptor are correlated with anxiolytic and anxiogenic action, respectively. PSYCHOTIC DISORDERS. In addition to their primary relevance to the pharmacological treatment of mood and anxiety disorders, neurosteroids contribute to

psychotic, childhood, substance abuse, eating, and postpartum disorders. The effect of neurosteroids on psychotic disorders such as schizophrenia is mediated by DHEA and DHEA-S. DHEA has been dispensed to decrease anxiety in patients with schizophrenia, as DHEA and DHEA-S suppress GABA inhibition and heighten the neuronal response at the NMDA and sigma receptors. DHEA and DHEA-S levels are typically elevated in the initial episode of a patient with schizophrenia, indicating neurosteroids are upregulated by the onset of psychosis. Because neurosteroid levels are studied across various illness stages, some questions still exist regarding the role of neurosteroids in psychosis. CHILDHOOD MENTAL ILLNESS. In children, the clinical symptomology of ADHD is inversely correlated with DHEA and pregnenolone levels. SUBSTANCE ABUSE. Alcohol is theorized to regulate the GABA receptor and induce de novo steroid synthesis in the brain; specifically, pregnenolone, allopregnanolone, and allotetrahydrodeoxycorticosterone levels are increased in the brain and periphery in response to increases in peripheral alcohol levels. It is hypothesized that sharp increases in ethanol concentration may mimic the acute stress response and elevate neurosteroid concentrations by the HPA axis. To prevent ethanol dependence, researchers are investigating fluctuations in neurosteroid levels and in vivo neurosteroid responsiveness. Neurosteroids (increased allopregnanolone levels in particular) are

associated with drug abuse. However, DHEA-S may actually check the acquisition of morphine tolerance. Past research has shown that DHEA-S levels were also increased in patients who abstained from cocaine use in a treatment program, and as patients relapsed DHEA-S concentrations decreased accordingly. EATING DISORDERS. With regard to eating disorders, DHEA has been shown to diminish food intake, temper obesity, moderate insulin resistance, and lower lipids in rats with a model of youth-onset, hyperphagic, and genetic obesity. By regulating the serotonergic system, DHEA is hypothesized to promote a reduced caloric load. Although hypothetical, low levels of DHEA and DHEA-S are recorded in young women with anorexia nervosa, and 3 months of oral DHEA supplementation increased bone density and tempered the emotional problems associated with the disorder. POSTPARTUM AND GYNECOLOGICAL DISORDERS. Because estrogen and progesterone levels fluctuate during the course of pregnancy and drop markedly after delivery, neurosteroids are thought to contribute to postpartum disorders. Low postpartum DHEA concentrations have been linked to mood instability. In addition, allopregnanolone levels correlated with mood disorders during pregnancy and in premenstrual syndrome (PMS). It has been noted that women with premenstrual dysphoric disorder have higher allopregnanolone/progesterone ratios than normal controls; women treated for this disorder reported improvement as allopregnanolone levels decreased. NEUROSTEROIDS, MEMORY DISORDERS, AND AGING. Neurosteroid levels may be irregular in neurodegenerative disorders and aging conditions such as Alzheimer’s disease and Parkinson’s disease. DHEA levels at age 70 are only about 20 percent of their maximum value recorded in the late 20s, and some researchers believe DHEA supplementation can prevent or slow the cognitive declines associated with the aging process. However, conflicting studies have indicated that DHEA administration does not improve cognitive measures in patients. In addition, in patients with Alzheimer’s disease, DHEA concentrations have been found to be markedly decreased. REFERENCES Abi-Dargham A. The neurochemistry of schizophrenia: A focus on dopamine and glutamate. In: Charney DS, Nestler E, eds. Neurobiology of Mental Illness. 3rd ed. New York: Oxford University Press; 2009:321. Berger M, Honig G, Wade JM, Tecott LH. Monoamine neurotransmitters. In: Sadock BJ, Sadock VA, Ruiz P, eds. Kaplan & Sadock’s Comprehensive Textbook of Psychiatry. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. Butler JS, Foxe JJ, Fiebelkorn IC, Mercier MR, Molholm S. Multisensory representation of frequency across audition and touch: High density electrical mapping reveals

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