

SECTION

# IV

## DRUGS AFFECTING THE CENTRAL NERVOUS SYSTEM

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# 24

## Introduction to Central Nervous System Pharmacology

Charles R. Craig

### REVIEW OF BASIC NEUROSCIENCE

The functional unit of the central nervous system (CNS) is the neuron, and most neuropharmacological agents have the neuron as their primary site of action. CNS neurons are capable of transmitting information to and receiving information from other neurons and peripheral end organs, such as muscle cells, glandular cells, and specialized receptors, for example, those involved with proprioception, temperature sensing, and so on.

The depolarization associated with an action potential results in the calcium-facilitated release of a specific chemical substance at the synapse between two neurons (see Chapter 2). This chemical substance or *neurotransmitter* is released, diffuses across the synaptic cleft, and interacts with the membrane of the second neuron to initiate a local change in the ionic composition and a local altered potential difference in the second neuron. This potential difference change is known as a *postsynaptic potential*, and the direction of the potential change may be either *depolarizing* or *hyperpolarizing*. A depolarizing postsynaptic potential is called an *excitatory postsynaptic potential* (EPSP). If the magnitude of depolarization produced by EPSPs in the second neuron is great enough, an action potential produced in the second neuron will be transmitted in an all-or-none fashion through the neuron and its processes. If, on the other hand, a hyperpolarizing potential (known as an *inhibitory postsynaptic potential*, or IPSP) is produced, it will inhibit the formation of depolarizing action potentials.

Most cells normally receive a large excitatory input with a more or less constant generation of action potentials. The net result of generated IPSPs will be to decrease the number of nerve impulses per unit of time. By these mechanisms, neurotransmitters producing ei-

ther an EPSP (*excitatory neurotransmitter*) or an IPSP (*inhibitory transmitter*) directly influence the number of action potentials generated by the neurons with which they interact.

Morphologically, many synapses in the CNS appear to be quite similar to those for the peripheral autonomic nervous system. Electron microscopic studies have verified the similarities and have shown the presence of several types of storage vesicles in the areas of synapses. Neurons may synthesize, store, and release one or more transmitters. Many more synapses exist in the CNS than in the periphery, and many more neurotransmitters appear to be involved.

The several ways in which pharmacological agents can either increase or decrease neurotransmission are illustrated in Fig. 24.1. The agent can increase the amount of transmitter at the synapse and thereby produce an exaggerated effect. This can be accomplished by (1) increasing the rate of transmitter synthesis, (2) increasing the rate of transmitter release, or (3) prolonging the time the transmitter is in the synapse. This last mechanism can be accomplished either by inhibiting enzymatic breakdown or by inhibiting the reuptake of a previously released transmitter.

In contrast, an agent can produce a diminished response by (1) decreasing synthesis of transmitter, (2) increasing transmitter metabolism, (3) promoting an increased neuronal uptake, or (4) blocking access of the transmitter to its receptor. The first three processes tend to diminish the amount of transmitter in the synaptic cleft. Some agents (including several useful drugs) possess most of these capabilities at norepinephrine, dopamine, serotonin, histamine, and acetylcholine (ACh) synapses. Several important drugs interfere with

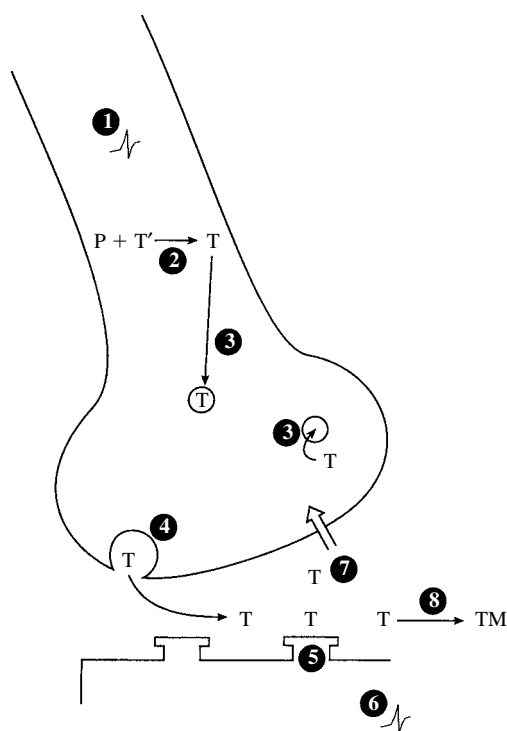


FIGURE 24.1

Sites where drugs may act to alter neurotransmission. The steps are depicted for a typical neurotransmitter (T). Some neurotransmitters do not follow this scheme. Site 1 is an action potential; site 2, synthesis of T from T'; site 3, storage of T in vesicles; site 4, release of T in response to the action potential; site 5, binding of T to receptor; site 6, intracellular response to action of T at site 5; site 7, reuptake of T across neuronal membrane; site 8, metabolism of T to an inactive metabolite, TM.

other CNS transmitter systems, particularly some of the amino acid transmitters, in some of the above-mentioned ways to produce their effects.

In the mammalian CNS powerful inhibitory systems function continually to slow the number of action potentials generated. The effects of stimulating an excitatory pathway can appear to be exaggerated if normal inhibitory influences to that region are diminished. Correspondingly, an inhibitory pathway will appear exaggerated if part of the excitatory influence to that system has been removed.

## CENTRAL NERVOUS SYSTEM NEUROTRANSMITTERS

A large number of CNS neurotransmitters have been either tentatively or positively identified. While a detailed discussion of the various central neurotransmitters and the criteria for their identification is beyond the scope of this text, a summary of the most important mammalian central neurotransmitters follows.

### Acetylcholine

The discovery that ACh was a transmitter in the peripheral nervous system formed the basis for the theory of neurotransmission. ACh is also a neurotransmitter in the mammalian brain; however, only a few cholinergic tracts have been clearly delineated. ACh is an excitatory neurotransmitter in the mammalian CNS. There is good evidence that ACh (among other neurotransmitters) is decreased in certain cognitive disorders, such as Alzheimer's disease.

### Dopamine

Quantitatively, dopamine is the most important of the biogenic amine neurotransmitters in the CNS. The three major distinct dopaminergic systems in the mammalian brain are categorized according to the lengths of the neurons. There is a system comprising ultrashort neurons within amacrine cells of the retina and periglomerular cells in the olfactory bulb. Of the several intermediate-length dopaminergic neuronal systems, the best studied are neurons in the tuberobasal ventral hypothalamus that innervate the median eminence and the intermediate lobe of the pituitary. These neurons are important in the regulation of various hypothalamohypophysial functions, including prolactin release from the anterior pituitary. The best-categorized of the dopamine neuronal systems are the long projections from nuclei in the substantia nigra and ventral tegmental areas to the limbic cortex; other limbic structures, including the amygdaloid complex and piriform cortex; and the neostriatum (primarily the caudate and putamen). In Parkinson's disease, the primary biochemical feature is a marked reduction in the concentration of dopamine in this long projection system (see Chapter 31).

Several classes of drugs, notably the antipsychotics, discussed in Chapter 34, interfere with dopaminergic transmission. In general, dopamine appears to be an inhibitory neurotransmitter. Five dopamine receptors have been identified; the most important and best studied are the  $D_1$ - and  $D_2$ -receptor groups. The  $D_1$ -receptor, which increases cyclic adenosine monophosphate (cAMP) by activation of adenylyl cyclase, is located primarily in the region of the putamen, nucleus accumbens, and in the olfactory tubercle. The  $D_2$ -receptor decreases cAMP, blocks certain calcium channels, and opens certain potassium channels.

### Norepinephrine

Most central noradrenergic neurons are located in the nucleus locus ceruleus of the pons and in neurons of the reticular formation. Fibers from these nuclei innervate a large number of cortical, subcortical, and spinal-medullary fields. Many functions have been ascribed to the central noradrenergic neurons, including a role in

affective disorders (see Chapter 33), in learning and memory, and in sleep–wake cycle regulation. The mammalian CNS contains both  $\alpha$ - and  $\beta$ -adrenoceptors.

### Epinephrine

Epinephrine is found only in very low concentrations in the mammalian CNS, and it is unlikely to play a major role as a neurotransmitter.

### Serotonin

Serotonin (5-hydroxytryptamine, or 5HT) is present in the brain as well as in the periphery. In humans, about 90% of the total serotonin in the body is in enterochromaffin cells in the gastrointestinal tract; the remaining 10% occurs primarily in the platelets and brain. The physiological significance of the vast amounts of serotonin constantly synthesized and metabolized in the periphery still remains an enigma. Brain serotonin has been implicated as a potential neurotransmitter in the mediation of a wide variety of phenomena (see Actions).

### Synthesis and Fate

Dietary tryptophan is the source of the formation of serotonin. Enzymes and cofactors necessary for serotonin synthesis are present in both the enterochromaffin cells of the gastrointestinal tract and neurons in the brain. Tryptophan is initially hydroxylated to form 5-hydroxytryptophan. Decarboxylation of the latter compound results in the formation of serotonin (Fig. 24.2).

The enzymes responsible for the metabolism of serotonin are present in all of the cells containing this amine and in the liver. Serotonin is initially oxidatively deaminated to form 5-hydroxyindoleacetaldehyde; this compound is subsequently rapidly oxidized to the major metabolite 5-hydroxyindoleacetic acid, which is excreted in the urine. Much of the serotonin released in the brain at synapses is taken back into the initial neuron by an active reuptake mechanism to be released again.

### Actions and Site of Actions

Most of the serotonin in the brain is in the brainstem, specifically in the raphe nuclei; considerable amounts also are present in areas of the hypothalamus, the limbic system, and the pituitary gland. Current evidence indicates that serotonin is involved in the regulation of several aspects of behavior, including sleep, pain perception, depression, sexual activity, and aggressiveness. Some of the most important antidepressant agents are believed to prevent the reuptake of serotonin (see Chapter 33). Serotonin also may be involved in temperature regulation and in the hypothalamic control of the release of pituitary hormones.

In addition to its presumed role as a neurotransmitter within the brain, serotonin is synthesized in the pineal gland, where it is a precursor for the synthesis of melatonin, a hormone that influences endocrine activity, presumably by an action within the hypothalamus.

The mammalian brain appears to have an abundance of sites with which serotonin interacts. Fourteen

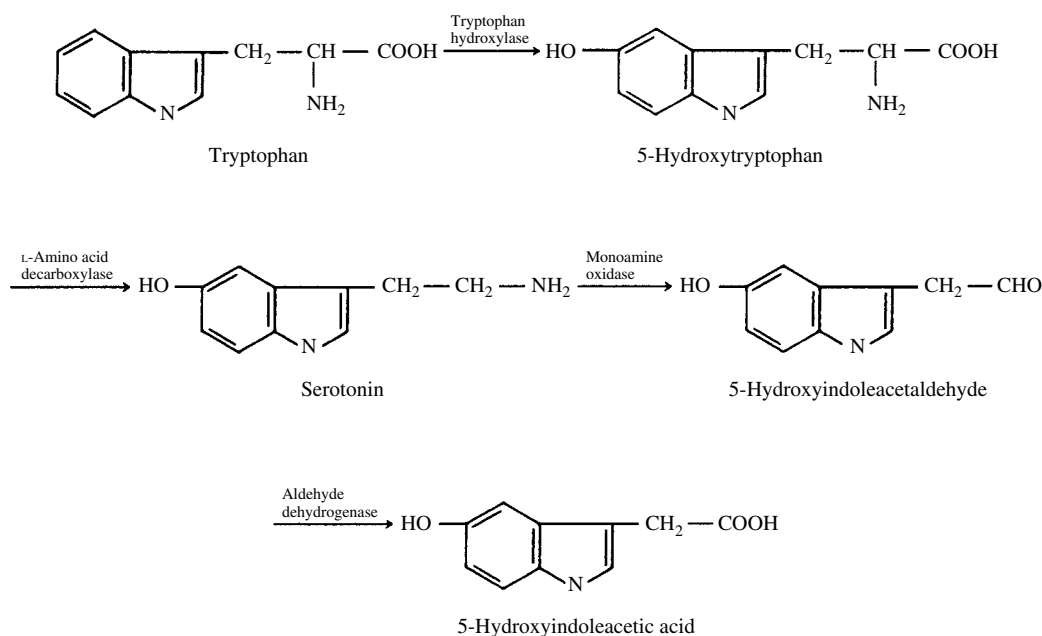


FIGURE 24.2

Steps involved in the synthesis and metabolic degradation of serotonin.

distinct mammalian receptor subtypes for serotonin have been established, not all of which have been identified in the brain. They are characterized as 5-HT<sub>1</sub>, 5-HT<sub>2</sub>, . . . 5-HT<sub>7</sub> subsets. There are at least five subtypes of the 5-HT<sub>1</sub> subset and three receptor subtypes for the 5-HT<sub>2</sub> subset. The interested reader may explore the various subsets and subtypes in the work by Hoyer et al. listed at the end of this chapter.

### Amino Acid Neurotransmitters

A large number of amino acids serve as neurotransmitters in the mammalian CNS.

#### $\gamma$ -Aminobutyric Acid

$\gamma$ -Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian CNS. GABA is primarily synthesized (Fig. 24.3) from glutamate by the enzyme L-glutamic acid-*l*-decarboxylase (GAD); it is subsequently transaminated with  $\alpha$ -ketoglutarate by GABA<sub>A</sub>-oxoglutarate transaminase (GABA-T) to yield glutamate and succinic semialdehyde.

Two types of GABA receptors have been identified in mammals, a GABA<sub>A</sub>- and a GABA<sub>B</sub>-receptor. The GABA<sub>A</sub>-receptor (or recognition site), when coupled with GABA, induces a shift in membrane permeability, primarily to chloride ions, causing hyperpolarization of the neuron. This GABA receptor appears to be part of a macromolecule that contains, in addition to the GABA<sub>A</sub>-receptor, benzodiazepine and barbiturate binding sites and the chloride ionophore (chloride channel). See Figure 24.4.

A number of drugs are thought to exert their CNS effect by altering GABA<sub>A</sub>-receptor activity. The 1,4-benzodiazepines,  $\beta$ -carbolines, barbiturates, alcohols, and general anesthetics appear to facilitate GABA transmission by interacting at this macromolecular complex. Vigabatrin, a newly approved anticonvulsant, elevates brain GABA by inhibiting the breakdown enzyme GABA-T. Several CNS convulsants, including bicuculline, picrotoxinin, and pentylenetetrazol, are antagonists at the GABA receptor. Since GABA agonists

have been shown to be anticonvulsants and GABA antagonists are convulsants, there is much interest in the role of GABA in epilepsy (see Chapter 32). The GABA<sub>B</sub>-receptor, in contrast, is not modulated by benzodiazepines, is not linked to chloride movement, and is not nearly as well characterized as is the GABA<sub>A</sub>-receptor. The GABA<sub>B</sub>-receptor is coupled to K<sup>+</sup> channels and is activated by the antispastic agent baclofen.

#### Glycine

Glycine is another inhibitory CNS neurotransmitter. Whereas GABA is located primarily in the brain, glycine is found predominantly in the ventral horn of the spinal cord. Relatively few drugs are known to interact with glycine; the best-known example is the convulsant agent strychnine, which appears to be a relatively specific antagonist of glycine.

#### Glutamic Acid and Aspartic Acid

These two excitatory amino acids (EAAs) are widely distributed throughout the mammalian CNS. Their administration leads to rapid depolarization of neurons and an increase in firing rate. There are two distinct classes of EAA receptors: ionotropic receptors and metabotropic receptors. The ionotropic receptors directly gate ion channels, while the metabotropic receptors are coupled to intracellular G proteins. Receptors are named according to their sensitivity to the action of selective agonists (Table 24.1). The best-characterized receptor is known as the NMDA (*N*-methyl-D-aspartate) receptor, which directly gates a Mg<sup>++</sup> cation channel that is also permeable to Ca<sup>++</sup> and Na<sup>+</sup>. Compounds that block the NMDA receptor complex may attenuate the neuronal damage following anoxia, such as occurs during a stroke; much of the neuronal damage associated with strokes may be related to the release of glutamic acid, aspartic acid, or both. Similarly, neuronal damage may occur as a result of seizures, and this also may be related to excessive EAA release. Antagonists of the NMDA receptor complex are being studied for possible uses in strokes and other types of hypoxia.

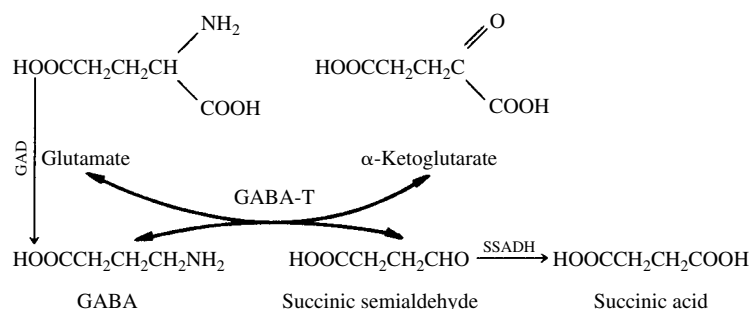


FIGURE 24.3

Steps in the synthesis and metabolism of GABA.

## Histamine

Histamine occurs in the brain, particularly in certain hypothalamic neurons, and evidence is strong that histamine is a neurotransmitter. Distribution of histamine, its synthetic enzyme (histidine decarboxylase), and methyl histamine (the major brain metabolite) is not uniform. Possible roles for histamine in the regulation of food and water intake, thermoregulation, hormone release, and sleep have been suggested. Additional information on histamine can be found in Chapter 38.

## Other Possible Amino Acid Neurotransmitters

Several additional amino acids are considered to be neurotransmitter candidates. Among these are taurine,  $\alpha$ - and  $\beta$ -alanine, 2-phenylethylamine, and imidazole-4-acetic acid. No available drugs are known to act via these amino acids.

## Peptides as Neurotransmitters

A large number of endogenous peptides are produced by neurons that appear to possess the essential charac-

teristics of neurotransmitters (e.g., their release is  $\text{Ca}^{++}$ -dependent, they are localized in specific neurons, and their release induces changes in postsynaptic neuronal systems).

The names of the agents can be terribly misleading to the beginning student. Many of the peptides have

**TABLE 24.1** Receptors for Excitatory Amino Acids

Receptor Designation	Function
Ionotropic NMDA	Produces excitation by increasing $\text{Ca}^{++}$ conductance; generates slow component of EPSP
AMPA Kainate	Generates fast component of EPSP Specific distribution, similar pharmacologically to AMPA
Metabotropic 1S,3R-ACPD	Linked to $\text{IP}_3$ formation

NMDA, *N*-methyl-D-aspartate; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid; 1S,3R-ACPD, L-amino-cyclopentane-1S,3R-dicarboxylic acid;  $\text{IP}_3$ , inosine triphosphate

been around for many years and were named according to their known effects when they were discovered. Examples are gastrin and cholecystokinin (CCK), compounds that were historically known as gut hormones. It is important, therefore, to realize that the names of the neuroactive peptides may bear no resemblance to their function in the brain. Many of the neuroactive peptides exist as families of chemically related compounds or occur within larger precursor molecules (or propeptides). However, several forms may be “active,” and several slightly different structures may confer subtle changes in selectivity. Many neuroactive peptides appear to co-exist and be released along with one or more of the “traditional” neurotransmitters, such as ACh, dopamine, or serotonin.

More than two dozen peptides are being studied as probable central neurotransmitters, and likely many more compounds remain to be discovered. Therefore, this chapter makes no attempt to cover them all. A few

of the most important peptide transmitters are discussed briefly, with still others listed in Table 24.2. For additional information, see the supplemental reading list at the end of this chapter.

### Substance P

The first neuropeptide to be isolated and characterized is known as substance P. Although this 11–amino acid peptide (undecapeptide) has been known for more than 60 years, its exact physiological role is still not clear. Substance P occurs in high concentrations in neurons projecting into the *substantia gelatinosa* layer of the spinal cord from dorsal root ganglia, among many other areas of the brain. Substance P can directly depolarize motor neurons in a manner analogous to that of other excitatory neurotransmitters. It is probable that substance P is released from small unmyelinated nerve fibers in response to painful stimulation. Levels of sub-

**TABLE 24.2** Known or Suspected Peptide Neurotransmitters

Family (compound)	Number of Amino Acids	Special Characteristics
Vasopressin (antidiuretic hormone)	9	Inhibitory to neurons; may facilitate learning and memory
Oxytocin	9	Inhibitory; very similar to vasopressin
Tachykin peptides		
Substance P	11	Levels of substance P are reduced in Huntington's chorea;
Neurokinin A	10	pain transmission
Neurokinin B	13	
Neurotensin	30	Lowers body temperature; coexists in neurons with dopamine and norepinephrine
Glucagon-related peptides		
Vasoactive intestinal peptide	28	May be involved in pain pathways; concentrated in neocortex; produces vasodilation
Growth hormone releasing hormone	24	high levels in hypothalamus and median eminence
Opioid peptides		
Proopiomelanocortin peptides		
β-Endorphin	30	Most potent of endogenous opioid compounds
Enkephalin pentapeptides		
Met <sup>5</sup> -enkephalin	5	Distributed widely throughout CNS
Leu <sup>5</sup> -enkephalin	5	
Prodynorphin peptides		
Dynorphin A	8	Extended forms of Leu <sup>5</sup> -enkephalin
Dynorphin B	8	
Somatostatin	28	Inhibits basal growth hormone release, causes decreased spontaneous motor activity and sleep disturbances, deficit in cerebrospinal fluid of patients with Alzheimer's disease
Cholecystokinin	8	Coexists with dopamine in nucleus accumbens and with GABA intracortical neurons; may have a role in regulating appetite
Angiotensin II	8	In periphery: induces secretion of aldosterone and modifies blood pressure; centrally: induces drinking behavior
Calcitonin gene-related peptide	37	Causes vasodilation
Corticotropin-releasing factor	41	Regulates corticotropin secretion; produces “anxiogenic” response
Neuropeptide Y	36	One of the most abundant neuropeptides; produces increased feeding, hypothermia; may act at multiple receptors



stance P in the substantia nigra are markedly reduced in the neurological disease Huntington's chorea.

### Vasopressin and Oxytocin

Historically vasopressin and oxytocin, two nonapeptides, were the first peptide "neurohormones" to be considered; they are stored in the neurohypophysis and released into the bloodstream upon an appropriate stimulus. In the periphery, oxytocin stimulates the contraction of epididymal and uterine smooth muscle (see Chapter 62) and vasopressin (antidiuretic hormone) facilitates the reabsorption of water from the kidney tubules. In addition to these well-accepted roles as neurohormones, there is convincing evidence that these compounds function as neurotransmitters; they both possess potent inhibitory actions on neurohypophyseal neurons. The significance of their neurotransmitter function is not yet clear.

### Endogenous Opioid Peptides

A seminal discovery during the 1960s and 1970s was the presence of endogenous substances in mammalian brain that appeared to possess the pharmacological qualities of morphine and other opioid analgesics. It had been known for quite awhile that most "drug receptors" were in fact receptors for endogenous transmitters. It was surprising, therefore, when tissue from mouse brain was shown to avidly bind opioids, such as morphine and heroin, in a stereoselective manner. As Avram Goldstein, one of the pharmacologists involved in discovering the endogenous opioids, noted, "It seemed unlikely, *a priori*, that such highly stereospecific receptors should have been developed by nature to interact with alkaloids from the opium poppy."<sup>1</sup>

A series of peptides, occurring naturally in brain and possessing pharmacological properties similar to those of morphine, have been described. At least three separate families of peptides have opioid properties (Table 24.2), and the different classes of peptides reside in separate distinct neurons. It is likely that the endogenous opioid peptides coexist in neurons with other nonopioid neurotransmitters. The initial hope that these endogenous agents or synthetic derivatives of them would be found to retain the analgesic activity of the opioids but be devoid of respiratory depression and/or addictive properties has now somewhat abated.

<sup>1</sup>Goldstein A. Opioid peptides (endorphins) in pituitary and brain. Science 1976; 193:1081–1086.

## BLOOD-BRAIN BARRIER

Not all substances in the bloodstream can readily gain entry into the brain. This apparent barrier to drugs and other chemicals is relative rather than absolute, and in fact there are several barriers to substances entering the brain from the systemic circulation. The term *blood-brain barrier* is usually applied to the lack of passage of certain drugs or other exogenously administered chemicals into the brain.

One important property that determines entry to the brain from the systemic circulation is molecular weight. Compounds with molecular weights of about 60,000 and above tend to remain within the circulatory system. Furthermore, the portion of an administered drug that is bound to plasma proteins is unavailable for distribution to the brain (as well as to other tissues and organs), in part because of the high molecular weight of the plasma protein–drug complex.

There are two physicochemical factors particularly important in allowing a drug to enter the CNS. First, for compounds that are mainly un-ionized at plasma pH ( $pK_a$  7.4 or higher), the drug's *solubility in lipids is an important determinant*. A lipid-soluble agent can more easily penetrate lipid membranes, such as those found in the CNS. The proportion of drug that is un-ionized is another important determinant. These two properties cannot be completely separated, since un-ionized drugs are generally more lipid soluble than ionized ones.

### Location of the Blood-Brain Barrier

The capillaries of the brain are the most likely location of the blood-brain barrier. Brain capillaries differ in several important respects from capillaries in other body locations (Fig. 24.5). For example, the endothelial cells of brain capillaries are so closely joined to each other that passage of substances cannot readily occur through the intercellular clefts between adjacent cells; furthermore, brain capillaries do not contain fenestrae (pores). Fenestrae are prominent in many capillaries, especially those in renal glomeruli and in the choroid plexus. The ability of a drug to leave a capillary by diffusion appears to be directly related to the number of capillary pores. Compared with capillaries at other sites, brain capillaries also appear to possess very few pinocytotic vesicles, which are believed to play a role in the transport of large molecules through capillary walls.

Brain capillaries contain many more mitochondria than do other capillaries, and it is probable that the mitochondria supply energy for active transport of water-soluble nutrient substances into the brain. A large number of lipid-insoluble endogenous substances are known to be transported into the brain. These

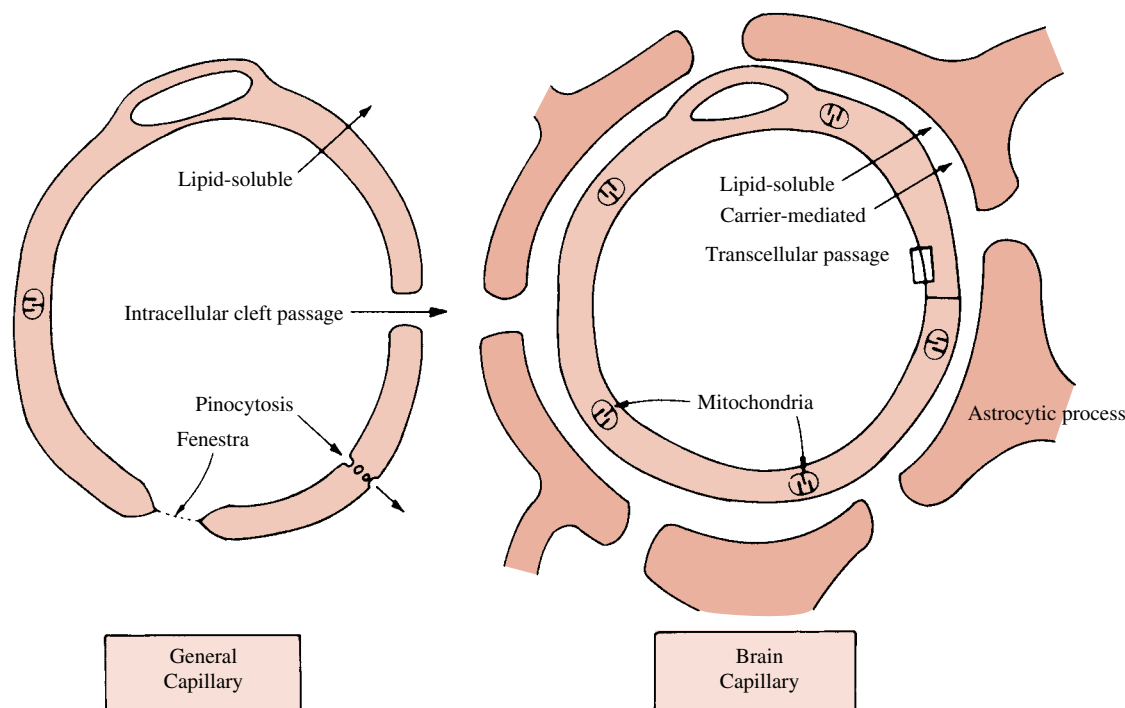


FIGURE 24.5

Major differences between a general (nonneural) and brain capillary. In the brain capillary, the intercellular clefts are sealed shut by tight junctions. There are also reduced pinocytosis and no fenestrae. Exchange of compounds between the circulation and the brain must take place in the cells of the capillary wall, the major barriers of which are the inner and outer plasma membranes of the capillary endothelial cells. (Reprinted with permission from Oldendorf WA. Permeability of the blood-brain barrier. In Tower DB [ed.]. *The Nervous System*. Vol. 1 New York: Raven, 1975.)

substances include glucose, amino acids, simple carboxylic acids, and purines.

### Significance of the Blood-Brain Barrier

It is likely that the blood-brain barrier serves primarily to preserve the internal environment of the brain and prevent sudden increases in concentration of a variety of water-soluble ionized substances, including many circulating neurotransmitters, such as norepinephrine, epinephrine, ACh, serotonin, and dopamine. The concentration in the brain of these bioactive substances appears to be carefully regulated. On the other hand, the biochemical precursors of these transmitters can pass relatively easily, although usually by active transport, from the blood to the brain, and this ensures an adequate supply of locally synthesized transmitters. By and large, the precursors are inactive biologically or have only minimal biological activity. The amino acid transmitters GABA, glycine, glutamic acid, and aspartic acid are actively taken up by the brain capillaries, but ordinarily the transport system for these amino acids is close to saturation. Therefore, a sudden increase in

blood concentration of these substances would have little effect on brain levels. Peptide transmitters will not readily penetrate the brain from the circulation, and they are synthesized in the brain.

The blood-brain barrier is not found in all parts of the brain. Certain small areas, including the *area postrema* beneath the floor of the fourth ventricle, an area in the *preoptic recess*, and portions of the floor of the third ventricle surrounding the stalk of the pituitary, appear to be devoid of this barrier.

The ability of the blood-brain barrier to exclude entry of a number of drugs into the brain has several therapeutic implications. Many drugs, most notably certain antibiotics, are relatively excluded from the brain. In the treatment of infectious diseases of the CNS, the physician must, in addition to establishing the organism's drug sensitivity, either select an agent that can get to the site of the infection or use a route (intrathecal) that bypasses the barrier. In the human fetus and newborn, the barrier is not as well developed as it is in later life. This fact also must be taken into consideration when one is prescribing drugs during pregnancy and for neonates (see Chapter 6).

## Study Questions

- The neurotransmitter serotonin is derived from which precursor amino acid?
  - Dopamine
  - Tyrosine
  - Tryptophan
  - Dopa
  - Glutamine
- The major inhibitory neurotransmitter in the mammalian CNS is
  - Acetylcholine
  - Norepinephrine
  - Glycine
  - $\gamma$ -Aminobutyric acid
  - Glutamic acid
- The location of the blood-brain barrier is considered to be
  - At the level of the brain capillaries
  - At the level of glia
  - At the level of neurons
  - At the level of dendrites
- Identify the major excitatory neurotransmitter system in the mammalian CNS.
  - $\gamma$ -Aminobutyric acid
  - Histamine
  - Substance P
  - Glutamate/aspartate
  - Serotonin
- Agents that potentiate the actions of GABA in the brain will likely have which of the following effects?
  - Elevate blood pressure
  - Provide sedation
  - Cause seizures
  - Relieve pain
- What is the number of neurotransmitters in the mammalian CNS?
  - 3
  - 6
  - 15
  - more than 20
- The neurotransmitter in the spinal cord but not the rest of the CNS. Glutamic acid is a major excitatory neurotransmitter in the mammalian CNS.
  - The site of the blood-brain barrier was hotly debated for many years until electron micrographs clearly showed that endothelial cells lining brain capillaries are so closely joined to each other that passages of substances cannot readily occur through the intercellular clefts located between adjacent cells and that this constitutes a barrier to the passage of many substances from the blood to the parenchyma of the brain.
  - GABA is the major inhibitory neurotransmitter in the mammalian CNS. Histamine is a CNS neurotransmitter, but has limited distribution. This is also true for serotonin. Substance P is an excitatory neurotransmitter in the spinal cord.
  - Since GABA is an inhibitory neurotransmitter, agents that potentiate its action are likely to be CNS depressants with sedative activity. GABA has no significant effect on blood pressure and will decrease the incidence of seizures. It has no direct ability to relieve pain.
  - The exact number of agents identified as neurotransmitters in the mammalian CNS is not established, but it is certainly more than 20. More and more compounds are being established as neurotransmitters as scientists who concentrate on this area.

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### ANSWERS

- C.** Dopamine is a precursor for norepinephrine and a neurotransmitter. Tyrosine is a precursor of dopamine and norepinephrine. Dopa (dihydroxyphenylalanine) is a precursor of dopamine and subsequently also of norepinephrine. Glutamine can be converted to the neurotransmitter glutamic acid.
- D.** Acetylcholine and norepinephrine are important neurotransmitters in the peripheral autonomic nervous system but are not nearly as prominent in the CNS. Glycine is a major inhibitory neurotransmitter in the spinal cord but not the rest of the CNS. Glutamic acid is a major excitatory neurotransmitter in the mammalian CNS.

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### Case Study Drugs and the Newborn

**A** mother calls to tell you that her week-old baby is having convulsions. She says the baby exhibited signs of a serious ear infection soon after birth. A physician prescribed penicillin G that apparently was well tolerated. The signs and symptoms of the ear infection appeared to be greatly reduced, but the baby began to have convulsions about an hour after receiving the last injection of penicillin. What would you advise the mother to do?

**ANSWER:** Penicillin G is a potent antagonist of the inhibitory neurotransmitter  $\gamma$ -GABA. Since peni-

cillin G normally does not penetrate the blood-brain barrier to any extent, this is not usually a problem. However, the blood-brain barrier is not fully developed at birth, and substances that normally are excluded from entering the CNS may enter the immature brain of the newborn. Seizures are a manifestation of several GABA antagonists, including penicillin G. Since the mother indicates that the seizures have almost ceased, you instruct her not to administer any more penicillin and to bring her child to your office as soon as she can.