I. OVERVIEW

Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine (ACh), whereas the adrenergic drugs (Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs act by either stimulating or blocking receptors of the ANS.

II. THE CHOLINERGIC NEURON

The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (Figure 4.2). The postganglionic sympathetic division of sweat glands also uses acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and also play an important role in the central nervous system (CNS).

**Neurotransmission at cholinergic neurons**

Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis, 2) storage, 3) release, 4) binding of ACh to a receptor, 5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and 6) recycling of choline and acetate (Figure 4.3).

1. **Synthesis of acetylcholine:** Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug hemicholinium. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge and, thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol.

2. **Storage of acetylcholine in vesicles:** ACh is packaged and stored into presynaptic vesicles by an active transport process coupled to the efflux of protons. The mature vesicle contains not only ACh but also adenosine triphosphate and proteoglycan. Cotransmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles contain the primary neurotransmitter (here, ACh) as well as a cotransmitter that increases or decreases the effect of the primary neurotransmitter.

3. **Release of acetylcholine:** When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap.
4. **Binding to the receptor:** ACh released from the synaptic vesicles diffuses across the synaptic space and binds to postsynaptic receptors on the target cell, to presynaptic receptors on the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (Figure 4.2). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second messenger molecules.

5. **Degradation of acetylcholine:** The signal at the postjunctional effector site is rapidly terminated, because acetylcholinesterase (AChE) cleaves ACh to choline and acetate in the synaptic cleft (Figure 4.3). [Note: Butyrylcholinesterase, sometimes called pseudocholinesterase, is found in the plasma, but does not play a significant role in the termination of the effect of ACh in the synapse.]

6. **Recycling of choline:** Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential.
Figure 4.3
Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A.
I. OVERVIEW

The adrenergic drugs affect receptors that are stimulated by norepi-nephrine (noradrenaline) or epinephrine (adrenaline). These receptors are known as adrenergic receptors or adrenoceptors. Adrenergic drugs that activate adrenergic receptors are termed sympathomimetics, and drugs that block the activation of adrenergic receptors are termed sympatholytics. Some sympathomimetics directly activate adrenergic receptors (direct-acting agonists), while others act indirectly by enhancing release or blocking reuptake of norepinephrine (indirect-acting agonists). This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1). Sympatholytic drugs are discussed in Chapter 7.

II. THE ADRENERGIC NEURON

Adrenergic neurons release norepinephrine as the primary neurotransmitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. Adrenergic drugs act on adrenergic receptors, located either presynaptically on the neuron or postsynaptically on the effector organ (Figure 6.2).

**Neurotransmission at adrenergic neurons**

Neurotransmission in adrenergic neurons closely resembles that described for the cholinergic neurons (see Chapter 4), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission involves the following steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3).

1. **Synthesis of norepinephrine:** Tyrosine is transported by a carrier into the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase. This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme aromatic l-amino acid decarboxylase to form dopamine in the presynaptic neuron.

2. **Storage of norepinephrine in vesicles:** Dopamine is then transported into synaptic vesicles by an amine transporter system. This carrier system is blocked by reserpine (see Chapter 7). Dopamine is next hydroxylated to form norepinephrine by the enzyme dopa-mine β-hydroxylase.

3. **Release of norepinephrine:** An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes synaptic vesicles to fuse with the cell membrane and to undergo exocytosis to expel their contents into the synapse. Drugs such as guanethidine block this release.

4. **Binding to receptors:** Norepinephrine released from the synaptic vesicles diffuses into the synaptic space and binds to postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. Binding of norepinephrine to receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) second messenger system and the phosphatidylinositol cycle to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors (mainly α2 subtype) that modulate the release of the neurotransmitter.
5. **Removal of norepinephrine**: Norepinephrine may 1) diffuse out of the synaptic space and enter the systemic circulation; 2) be metabolized to inactive metabolites by catechol-O-methyltransferase (COMT) in the synaptic space; or 3) undergo reuptake back into the neuron. The reuptake by the neuronal membrane involves a sodium-chloride (Na+/Cl-) dependent norepinephrine transporter (NET) that can be inhibited by tricyclic antidepressants (TCAs), such as imipramine, by serotonin–norepinephrine reuptake inhibitors such as duloxetine, or by cocaine (Figure 6.3). Reuptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of its effects.

6. **Potential fates of recaptured norepinephrine**: Once norepinephrine reenters the adrenergic neuron, it may be taken up into synaptic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria.
Figure 6.3
Synthesis and release of norepinephrine from the adrenergic neuron. MAO = monoamine oxidase, SNRI = serotonin-norepinephrine reuptake inhibitor.