GANGLIONIC TRANSMISSION

Transmission through autonomic ganglia is more complex than neurotransmission at the neuromuscular and postganglionic neuroeffector junctions and is subject to numerous pharmacological and physiological influences. In some ganglionic synapses, especially at parasympathetic ganglia, there is a simple presynaptic to postsynaptic cell relationship; in others, the presynaptic to postsynaptic cell relationship may involve neurons interposed between the presynaptic and postsynaptic elements (interneurons).

In a variety of sympathetic and certain parasympathetic ganglion cells (e.g., vagal ganglia in the sinoatrial node), cells exhibiting the characteristic catecholamine fluorescence spectrum have been found. These cells are referred to as small intensely fluorescent (SIF) cells. At some autonomic ganglia, the SIF cell is a true interneuron, receiving afferent innervation from preganglionic cholinergic neurons and forming efferent synapses with postganglionic neurons. At other autonomic ganglia, its function is not completely understood, but the SIF cell is believed to play a role in the modulation of ganglionic transmission. Many SIF cells are thought to contain dopamine or norepinephrine as their neurotransmitter.

Unlike the receptors at postganglionic neuroeffector junctions or at skeletal neuromuscular junctions, both types of cholinergic receptors, that is, nicotinic and muscarinic, are present on the cell bodies of the postganglionic neurons. Stimulation of the preganglionic neuron results in the release of acetylcholine (ACh) from the preganglionic nerve terminal, which in turn activates postganglionic cholinergic receptors and leads ultimately to the formation of a propagated action potential down the postganglionic axon. At the more complicated synapses, the release of ACh from preganglionic neurons results in the appearance of complex postsynaptic potential changes consisting of several temporally arranged components. There is an initial fast excitatory postsynaptic potential (EPSP) followed by a succession of much slower postsynaptic potential changes, including a slow EPSP that lasts for 2 to 5 seconds, a slow inhibitory postsynaptic potential (IPSP) lasting about 10 seconds, and a late slow EPSP lasting for 1 to 2 minutes.

There is considerable diversity among nicotinic acetylcholine receptors, and at least one source of this diversity is the multiplicity of acetylcholine receptor genes. Cholinergic–nicotinic receptors in skeletal muscle are different from those in autonomic ganglia and the central nervous system.

Excitatory and Inhibitory Potentials

The interaction of ACh with the postsynaptic nicotinic receptor results in depolarization of the membrane, an
influx of Na\(^+\) and Ca\(^{2+}\) through a neuronal nicotinic receptor channel, and the generation of the fast EPSP. This change in postsynaptic potential is principally responsible for the generation of the propagated action potential in the postganglionic neuron. Generally, several presynaptic terminals innervate a single ganglion cell, and several preganglionic axon terminals must fire simultaneously for transmission to take place. Ganglionic blocking agents prevent transmission by interfering with the postsynaptic action of ACh. The drugs either interact with the nicotinic–cholinergic receptor itself or with the associated ionic channel complex.

Interaction of ACh with the postsynaptic gangionic cell muscarinic receptor is responsible for slowly developing depolarization, the slow EPSP, which has a longer latency than the fast EPSP and a duration of 30 to 60 seconds. The slow EPSP is due to inhibition of a voltage-dependent \(K^+\) current called the M current, and inhibition of the M current involves activation of G proteins. At least five types of muscarinic receptors (M\(_1\), M\(_2\), M\(_3\), M\(_4\), and M\(_5\)) have been identified using functional studies and at least five subtypes (m\(_1\), m\(_2\), m\(_3\), m\(_4\), and m\(_5\)) identified by molecular cloning techniques. The M\(_1\) receptor, which appears responsible for inhibiting the M current, can be blocked by atropine.

Release of ACh may activate SIF cells between preganglionic and postganglionic neurons. In this case, activation of a muscarinic receptor on the SIF cells results in the release of a catecholamine; this in turn activates a receptor on the postganglionic cell, leading to the slow IPSP. The catecholamine most frequently released from SIF cells appears to be dopamine. Finally, a late slow EPSP, lasting for 1 to 2 minutes, can be seen at some ganglionic synapses. The mediator is unclear, but it is now well established that there are a large number of peptides in the ganglia, including luteinizing hormone–releasing hormone (LHRH), substance P, angiotensin, calcitonin gene related peptide, vasoactive intestinal polypeptide, neuropeptide Y, and enkephalin.

In addition to the cholinergic and adrenergic receptors on autonomic ganglion cells, there also appear to be receptors for a variety of excitatory and inhibitory substances, including angiotensin, bradykinin, histamine, 5-hydroxytryptamine (serotonin), and substance P. The existence of these receptors provides a wide variety of options to modulate ganglionic transmission. Agonists for these receptors most likely reach the ganglia through the circulation. A composite picture of the status of ganglionic transmission is shown in Figure 14.1. For simplicity, the figure has been divided into a type A synapse, which includes SIF cells, and a type B synapse, which lacks SIF cells. Table 14.1 summarizes the type of ganglionic action potential generated at various synapses, the type of receptor mediating the response, and the primary transmitter or mediator that activates the receptor.

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**GANGLIONIC STIMULANTS**

A variety of agents, including nicotine, lobeline, and dimethylphenylpiperazinium (DMPP), can stimulate ganglionic nicotinic receptors. Although these drugs have little or no therapeutic use, they offer considerable interest for several reasons. First, drugs such as nicotine that both stimulate and block ganglionic receptors have proved valuable as an aid in identifying and localizing postganglionic fibers. Second, nicotine’s use as a potent insecticide and rodenticide and its presence in tobacco smoke have endowed it with considerable toxicological interest.

**Mechanism of Ganglionic Stimulation**

Nicotine, lobeline, trimethylammonium, and DMPP stimulate all autonomic ganglia by simple combination with ganglionic nicotinic receptors on the postsynaptic membrane. This leads to membrane depolarization, an influx of sodium and calcium ions, and the generation of a fast EPSP. These agents produce general stimulation of autonomic ganglia and a complex pattern of mixed sympathetic and parasympathetic responses.

In addition to autonomic ganglia, nicotinic receptors are found in a variety of organs, and their stimulation will produce quite different results in these different tissues. Activation of nicotinic receptors on the plasma membrane of the cells of the adrenal medulla leads to the exocytotic release of epinephrine and norepinephrine; stimulation of nicotinic receptors at the neuromuscular junction results in the contraction of skeletal muscle (see

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**TABLE 14.1** Type of Ganglionic Action Potential per Synapse Type

<table>
<thead>
<tr>
<th>Neurotransmitter/Neuromodulator</th>
<th>Ganglionic Receptor</th>
<th>Ganglionic Action Potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine (from preganglionic neuron)</td>
<td>Nicotinic cholinergic</td>
<td>Fast EPSP</td>
</tr>
<tr>
<td>Acetylcholine (from preganglionic neuron)</td>
<td>Muscarinic cholinergic</td>
<td>Slow EPSP</td>
</tr>
<tr>
<td>Acetylcholine (from preganglionic neuron)</td>
<td>Muscarinic cholinergic or interneuron</td>
<td>Slow IPSP</td>
</tr>
<tr>
<td>Norepinephrine, epinephrine, dopamine (from interneuron)</td>
<td>Adrenergic/dopaminergic</td>
<td>Slow IPSP</td>
</tr>
<tr>
<td>Autacoid (angiotensin, etc.) or peptide (LHRH, etc.)</td>
<td>Autacoid or peptide receptor</td>
<td>Late slow EPSP</td>
</tr>
</tbody>
</table>
Chapter 28). Stimulation of nicotinic receptors in adrenergic nerve terminals leads to the release of norepinephrine; and activation of nicotinic chemoreceptors in the aortic arch and carotid bodies causes nausea and vomiting. Nicotinic receptors in the central nervous system mediate a complex range of excitatory and inhibitory effects.

**Mechanism of Ganglionic Blockade**

Large doses of nicotine produce a prolonged blockade of ganglionic nicotinic receptors. Unlike the blockade of ganglionic transmission produced by most ganglionic blocking agents, that is, a nondepolarizing competitive antagonism, the blockade produced by nicotine consists of two phases. Phase 1 can be described as persistent depolarization of the ganglion cell. The initial application of nicotine to the ganglion cells depolarizes the cell, which initiates an action potential. After a few seconds, however, this discharge stops and transmission is blocked. At this time, antidromic stimuli fail to induce an action potential. In fact, during this phase, the ganglia fail to respond to the administration of any ganglionic blocking drugs and nicotine.
stimulant, regardless of the type of receptor it activates. The main reason for the loss of electrical or receptor-mediated excitability during a period of maintained depolarization is that the voltage-sensitive sodium channel is inactivated and no longer opens in response to a brief depolarizing stimulus. During the latter part of phase 1, all ganglionic stimulants that are not nicotinic, such as histamine, angiotensin, bradykinin, and serotonin, become effective.

Phase 1 is followed by a postdepolarization phase (phase 2) during which only the actions of nicotinic receptor agonists are blocked. This phase takes place after nicotine has acted for several minutes. At this time, the cell partially repolarizes, and its electrical excitability returns. The main factor responsible for phase 2 block appears to be desensitization of the receptor to ACh, which causes transmission failure.

**Pharmacological Actions of Nicotine**

Nicotine is present in varying amounts in all forms of tobacco smoke. Following its absorption from the lungs, the blood nicotine levels are sufficient to cause stimulation but not blockade of nicotinic receptors. In addition to stimulating receptors on autonomic ganglia, all other nicotinic receptors mentioned earlier can be activated. Thus, tobacco smoking stimulates the cardiovascular, respiratory, and nervous systems.

**Cardiovascular System**

The effects of nicotine on the cardiovascular system mimic those seen after activation of the sympathoadrenal system, and they are principally the result of a release of epinephrine and norepinephrine from the adrenal medulla and adrenergic nerve terminals. These effects include a positive inotropic and chronotropic effect on the myocardium as well as an increase in cardiac output. In addition, both systolic and diastolic blood pressures are increased secondary to stimulation of the sympathoadrenal system. These effects are the end result of a summation of adrenergic and cholinergic stimulation.

**Respiratory System**

Low doses of nicotine stimulate respiration through activation of chemoreceptors in the aortic arch and carotid bodies, while high doses directly stimulate the respiratory centers. In toxic doses, nicotine depresses respiration by inhibiting the respiratory centers in the brainstem and by a complex action at the receptors at the neuromuscular junction of the respiratory muscles. At these neuromuscular receptors, nicotine appears to occupy the receptors, and the end plate is depolarized. After this, the muscle accommodates and relaxes. These central and peripheral effects paralyze the respiratory muscles.

**Central Nervous System**

The actions of nicotine on the central nervous system are the result of a composite of stimulatory and depressant effects. These can include tremors, convulsions, respiratory stimulation or depression, and release of antidiuretic hormone from the pituitary. Nausea and emesis are frequently observed after the initial use of nicotine in the form of tobacco smoke. However, tolerance to these effects rapidly develops. This is in contrast to the effects of nicotine on the cardiovascular system, where tolerance develops much more slowly.

**Other Systems**

Additional effects of nicotine include an increase in gastric acid secretion and an increase in the tone and motility of the gastrointestinal tract. These effects are produced because of the predominance of cholinergic input to these effector systems.

**Absorption, Distribution, and Excretion of Nicotine**

Nicotine is well absorbed from the mucous membranes in the oral cavity, gastrointestinal tract, and respiratory system. If tobacco smoke is held in the mouth for 2 seconds, 66 to 77% of the nicotine in the smoke will be absorbed across the oral mucosa. If tobacco smoke is inhaled, approximately 90 to 98% of the nicotine will be absorbed. Nicotine is distributed throughout the body, readily crossing the blood-brain and placental barriers. The liver, kidney, and lung metabolize approximately 80 to 90% of the alkaloid. The kidney rapidly eliminates nicotine and its metabolites.

**Ganglionic Blocking Drugs**

Although a number of drugs possessing ganglionic blocking properties have been developed, at the present time they are rarely used clinically. Other drugs, such as curare, are not employed as ganglionic blocking agents, although they block ganglionic nicotinic receptors, especially at high doses. The ganglionic blockers are still important in pharmacological and physiological research because of their ability to block autonomic ganglia.

**Mechanism of Action**

Drugs can block autonomic ganglia by any one of several mechanisms. They may act presynaptically by affecting nerve conduction or neurotransmitter synthesis, release, or reuptake. Acting postjunctionally, drugs may affect the interaction between ACh and its receptor, or they may affect depolarization of the ganglion cell or initiation of a propagated action potential.
Ganglionic nicotinic blockers can be divided into two groups. The first group, characterized by nicotine and related drugs (e.g., lobeline, tetraethylammonium), initially stimulates the ganglia and then blocks them (discussed earlier). These agents are not therapeutically useful. The second group of drugs, which have some therapeutic usefulness but are rarely used, inhibit the postsynaptic action of ACh and do not themselves produce depolarization, thereby blocking transmission without causing initial stimulation.

The site of action of many blocking drugs has been shown to be at the associated ionic channel rather than at the receptor. Prolonged administration of ganglionic blocking drugs leads to the development of tolerance to their pharmacological effects.

**Pharmacological Actions**

In any given tissue, the magnitude of the response produced by ganglionic blocking drugs depends largely on the quantity and relative proportion of the total autonomic input coming from sympathetic and parasympathetic nerves at the time of drug administration (Table 14.2). For example, if cardiac vagal tone is high at the time ganglion blockade is induced, tachycardia results. If heart rate is high, a decrease in rate may be seen.

The extent of the hypotension, especially postural hypotension, produced by a ganglionic blocking agent also depends on the degree of sympathetic tone at the time of drug administration. For instance, patients with normal cardiac function may have their cardiac output diminished after ganglionic blockade, while patients in cardiac failure often respond to ganglionic blockade with an increase in cardiac output. To date, it has not been possible to develop ganglionic blocking drugs that have a high degree of selectivity for either sympathetic or parasympathetic ganglia. However, since these drugs do not affect all of the various ganglia equally, and since the time at which their peak effect occurs will vary among the various types of ganglia, some degree of selectivity of action does in fact exist.

**Clinical Uses**

**Hypertensive Cardiovascular Disease**

Ganglionic blockers were once widely used in the management of essential hypertension, and they constituted an important advance in the treatment of that disease. Unfortunately, the development of tolerance to these drugs and their numerous undesirable side effects resulting from their nonselective ganglion-blocking properties led to a decline in their use. They have now been completely replaced by more effective and less toxic drugs. They do, however, retain some usefulness in the emergency treatment of hypertensive crisis.

**Table 14.2**  

<table>
<thead>
<tr>
<th>Site</th>
<th>Effect of Ganglionic Blockade</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tissues predominantly under parasympathetic (cholinergic) tone</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardium: Atrium; S-A node</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Eye</td>
<td>Mydriasis</td>
</tr>
<tr>
<td>Iris</td>
<td>Cycloplegia</td>
</tr>
<tr>
<td>Ciliary muscle</td>
<td>Decrease in tone and motility; constipation</td>
</tr>
<tr>
<td>GI tract</td>
<td>Urinary retention</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Salivary gland</td>
<td></td>
</tr>
<tr>
<td><strong>Tissues predominantly under sympathetic (adrenergic) tone</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardium: Ventricles</td>
<td>Decrease in contractile force</td>
</tr>
<tr>
<td>Blood vessels: Arterioles</td>
<td>Vasodilation; increase in peripheral blood flow; hypotension</td>
</tr>
<tr>
<td>Veins</td>
<td>Vasodilation; pooling of blood; decrease in venous return; decrease in cardiac output</td>
</tr>
<tr>
<td>Sweat glands*</td>
<td>Decrease in secretion</td>
</tr>
</tbody>
</table>

*Anatomically sympathetic; transmitter is ACh.

**Controlled Hypotension**

Ganglionic blocking agents have been used to achieve controlled hypotension in plastic, neurological, and ophthalmological surgery. They are most commonly used in surgical procedures involving extensive skin dissection.

**Adverse Effects**

All of the responses summarized in Table 14.2 can be produced by administration of ganglionic blocking agents. Many of these responses are undesirable effects that limit the therapeutic usefulness of these agents. Mild untoward responses include mydriasis, difficulty in vision accommodation, dry mouth, urinary hesitancy, constipation, diarrhea, abdominal discomfort, anorexia, and syncope. More serious but less frequent disturbances include marked hypotension, constipation, paralytic ileus, urinary retention, and anginal pain.

**INDIVIDUAL AGENTS**

**Trimethaphan**

Trimethaphan camsylate (Arfonad) is an extremely short-acting agent whose major therapeutic use is in the production of controlled hypotension in certain surgical
procedures and in the emergency treatment of hypertensive crisis. Continuous infusion may be employed to maintain its antihypertensive effect, especially in patients with an acute dissecting aortic aneurysm. Much of the decrease in blood pressure following trimethaphan administration is thought to be due to its direct vasodilating properties.

Trimethaphan can produce prolonged neuromuscular blockade in some patients, and therefore, it should be used with caution as a hypotensive agent during surgery. It also has been reported to potentiate the neuromuscular blocking action of tubocurarine, and because of its histamine-releasing properties, trimethaphan should be used with caution in patients with allergies.

**Mecamylamine**

Mecamylamine hydrochloride (Inversine) is a secondary amine and can therefore easily penetrate cell membranes. Its absorption from the gastrointestinal tract is more complete than that of the quaternary ammonium compounds. Mecamylamine is well absorbed orally and crosses both the blood-brain and placental barriers; its distribution is not confined to the extracellular space. High concentrations of the drug accumulate in the liver and kidney, and it is excreted unchanged by the kidney. In contrast to most of the highly ionized ganglionic blocking agents, mecamylamine can produce central nervous system effects, including tremors, mental confusion, seizures, mania, and depression. The mechanism by which these central effects are produced is unclear. Mecamylamine is rarely used today as an antihypertensive drug because it blocks both parasympathetic and sympathetic ganglia.

**Study Questions**

During a laboratory demonstration to depict the complexity of neurotransmission in autonomic ganglia, Professor Smith sets up an anesthetized mammalian preparation in which she is recording postsynaptic events following the electrical stimulation of preganglionic sympathetic nerves. This demonstrates a complex action potential that consists of a fast EPSP followed by a slow IPSP followed by a slow EPSP and finally by a late very slow EPSP.

1. In Professor Smith’s demonstration, the mediator of the fast EPSP is
   (A) Dopamine
   (B) Neuropeptide Y
   (C) Serotonin
   (D) Angiotensin
   (E) Acetylcholine

2. In Professor Smith’s demonstration, the slow EPSP and slow IPSP can both be blocked by prior administration of
   (A) Prazosin
   (B) Sumatriptan
   (C) Atropine
   (D) Losartan
   (E) Chlorpromazine

3. In Professor Smith’s demonstration, the receptor most likely mediating the slow EPSP is
   (A) Nicotinic cholinergic
   (B) Muscarinic cholinergic
   (C) α-Adrenergic
   (D) P2X Purinergic
   (E) β-Adrenergic

4. A patient you are treating in the hospital has a hypertensive emergency, with blood pressure of 210/140 mm Hg. Of the following drugs, which would be most effective intravenously?
   (A) Hydralazine
   (B) Hydrochlorothiazide
   (C) Trimethaphan
   (D) Methyldopa
   (E) Spironolactone

5. Ganglionic blocking agents are rarely used because of the numerous side effects they may produce. One such side effect is
   (A) Increased stimulation of the genital tract
   (B) Urinary hesitation or urgency
   (C) Vasoconstriction
   (D) Increased cardiac output
   (E) Mydriasis

**Answers**

1. E. The principal neurotransmitter released from preganglionic nerve terminals in all autonomic ganglia is acetylcholine. It acts on the postganglionic cell body to activate a nicotinic–cholinergic receptor resulting in a fast EPSP. Dopamine or norepinephrine or both are the mediators released from SIF cells or interneurons. Neuropeptide Y is a peptide neurotransmitter. Angiotensin and serotonin are modulatory mediators. These last three contribute to the late very slow EPSP.

2. C. The slow EPSP results from activation of muscarinic–cholinergic receptors on SIF cells or in-
terneurons, which release norepinephrine or dopamine from their terminals. These catecholamines then cause a slow IPSP in the ganglionic cell body. Therefore, both the slow EPSP and subsequent slow IPSP would be prevented by the muscarinic antagonist atropine. Prazosin is an α1-adrenergic antagonist; sumatriptan is a serotonin 5HT1D agonist; losartan is an angiotensin receptor antagonist; and chlorpromazine is a dopamine antagonist. Only atropine would block both the slow EPSP and the slow IPSP.

3. B. The receptor contributing to the slow EPSP is a muscarinic–cholinergic receptor and is activated by ACh. The nicotinic–cholinergic receptor mediates the fast EPSP; an α-receptor may mediate the slow IPSP, and a P2X receptor and a β-adrenergic receptor do not appear to be involved in the complex action potentials seen at autonomic ganglia.

4. C. Trimethaphan is a ganglionic blocking agent that will lower blood pressure very rapidly. Hydralazine is a vasodilator; hydrochlorothiazide and spironolactone are diuretics; and methyldopa is a sympatholytic acting in the central nervous system. All of these drugs are used clinically as antihypertensive agents. None work as rapidly as trimethaphan. Clinically, however, either nitroprusside or clonidine is used much more commonly than trimethaphan in this situation.

5. E. The effect of ganglionic blockade depends upon the predominant autonomic tone exerted within various organ systems. Since the activity of the parasympathetic nervous system predominates in the eye, the effect of ganglionic blockade is mydriasis, not miosis. Similarly, stimulation of the genital tract and urinary retention would be decreased. Since sympathetic nervous system activity predominates in blood vessels and the ventricles, vasodilatation and a decreased cardiac output would follow ganglionic blockade.

SUPPLEMENTAL READING

CASE STUDY Smoking Cessation

A patient who has been a heavy smoker (2 packs of cigarettes per day for 30 years) comes to you for advice to quit smoking. You inform your patient that sudden cessation of smoking will result in withdrawal symptoms that may include restlessness, irritability, anxiety, tension, stress, intolerance, drowsiness, frequent awakenings from sleep, fatigue, depression, impotence, confusion, impaired concentration, gastrointestinal disturbances, decreased heart rate, and impaired reaction times. You advise your patient that successful cessation of tobacco use requires attention to both the positive and negative (withdrawal) reinforcement properties of nicotine and tobacco use. You plan, therefore, to combine both psychological and pharmacological treatment. What are some therapeutic approaches you can suggest?

ANSWER: Several options are available for the pharmacological approach, including nicotine replacement and antidepressant drugs (e.g., bupropion). You explain that nicotine replacement can be carried out with chewing gum (nicotine polacrilex), transdermal patches (e.g., Nicoderm, Habitrol), nasal spray (Nicotrol NS), or vapor inhaler (Nicotrol Inhaler). The objective of the nicotine replacement is to obtain a sustained plasma nicotine concentration that is lower than the venous blood concentrations after smoking. It is known that arterial blood concentrations immediately following cigarette smoke inhalation can be as much as 10 times the venous concentration. You decide on a nicotine patch and combine this strategy with counseling and motivational therapy from a professional trained in such methods. It is quite likely that the combination of the patch plus counseling will ultimately result in a successful cessation of smoking in your patient after a couple of relapses. During a second relapse period, you may wish to consider combining the antidepressant drug bupropion with the other forms of treatment.