The author presents a review of the peripheral autonomic nervous system and its sympathetic component with special emphasis given to the neurotransmitter and the adrenergic receptor site. Also discussed are pharmacological interactions and clinical considerations.

The success of anesthesia and the surgical experience is dependent on many factors including an intact autonomic nervous system and the ability of the patient to respond reflexly to stress. Cardiac rate and rhythm, as well as airway resistance, is largely controlled by the antagonistic effects of the sympathetic and parasympathetic nervous systems. Alterations in cardiovascular or pulmonary functions are beacons which warn the anesthetist of imbalances in the involuntary nervous system. Inhibiting or exciting either segment may result in cardiac dysrhythmias, dysfunction or bronchospastic disorders.

Dysrhythmias of vagal predominance have been treated for years with drugs such as the anticholinergics, resulting in competitive antagonism of acetylcholine at the cholinergic muscarinic receptors. The majority of problems that develop during the administration of anesthesia, however, is of sympathetic origin. Appropriate management of these potentially hazardous problems is dependent upon an understanding of the adrenergic system and its effector site, the alpha and beta receptor.

The adrenergic system

The autonomic nervous system plays a major role in maintaining homeostasis. Two major divisions of this system, the sympathetic and parasympathetic, consist of neurons and ganglia which innervate glands, the heart, blood vessels, and visceral smooth muscle. In general, the two divisions have antagonistic effects. The parasympathetic segment functions to conserve or restore the organism while the sympathetic segment prepares the organism for "fight or flight."

Pharmacologically, these systems are classified as cholinergic and adrenergic systems. Cholinergic is a term describing those fibers which release acetylcholine as their neurotransmitter. Acetylcholine is effective on both nicotinic and muscarinic receptors. Adrenergic is a term describing those fibers which release norepinephrine as their neurotransmitter. Norepinephrine is effective on alpha and beta receptors. The systems, their receptors, and the effects of receptor stimulation are summarized in Table 1.1-2

Sympathetic division of the autonomic nervous system originates from cells located in the lateral horns of the spinal cord from T1 to L2-3.3 These preganglionic fibers leave the cord and synapse with postganglionic nerve cells, located in the ganglia on each side of the vertebral column or in the abdominal cavity. Once a synapse has occurred, the impulse is carried by postganglionic fibers to the adrenergic neuroeffector junction.

Anatomically, the postganglionic sympathetic nerve consists of a cell body, long axon, and ex-
Adrenergic nerve terminal

The principal adrenergic neurotransmitter is norepinephrine. The adrenergic neuron synthesizes the catecholamine, stores it in small granules, and finally releases it in response to an appropriate stimulus. The synthesis of norepinephrine is through a series of enzyme-controlled steps, summarized in Table 2.

Phenylethanolamine-N-methyl-transferase is found in the adrenal medulla and is responsible for converting 80% of the medullary norepinephrine to epinephrine. Although the medullary hormones are released and interact with the adrenergic sites during stress, norepinephrine acts as the mediator in homeostasis.

The arrival of an action potential at the postganglionic nerve terminal causes norepinephrine to be released into the synaptic cleft. It then diffuses across the cleft to participate in the neurotransmitter-receptor interaction. Following this interaction, the response is terminated almost entirely by the uptake and return of norepinephrine from the receptor and synaptic cleft back into the nerve terminal. Small amounts may be inactivated in the cytoplasm by monoamineoxidase but most will be returned to the storage vesicle for reuse.

tensively branched terminals. The distal end of this nerve and the adjacent effector cells (which are innervated by this neuron) is known as the neuroeffector junction. The nerve terminal contains the machinery for the synthesis, storage, release, and metabolism of the adrenergic neurotransmitter. The effector cell contains the machinery which receives the transmitter and initiates the alteration of cellular function.
Adrenergic receptor

Since Erhlick proposed that drugs react with specific cellular sites and Langley suggested that the chemical substances which mediate autonomic activity from nerve to effector cells react with specific receptor sites, the concept of receptors has become firmly rooted in pharmacological thought. In 1930, Cannon and Rosenbleuth proposed two hypothetical adrenergic neurotransmitters, an excitatory one (sympathin E) and an inhibitory one (sympathin I), to explain the varied effects.

This concept, however, did not unveil the mysteries of the adrenergic neuroeffector junction. In 1948, Ahlquist published a paper concerning adrenotropic receptors. He suggested that the varied effects of sympathetic activity are due to different receptor types in the effector cell and not to different neurotransmitters. The presence of different adrenergic receptors could be demonstrated by differing orders of potency within a single series of closely related compounds on different physiological systems.

He found that the order of potency of six sympathomimetic amines in animals was the same for excitatory systems, but differed for several inhibitory systems. Epinephrine and norepinephrine were most active and isoproterenol the least active in terms of vasoconstriction and pupil dilation. Isoproterenol was the most active and norepinephrine the least active as a vasodilator and cardiac stimulant.

Ahlquist therefore proposed the classification of alpha and beta adrenotropic receptors: alpha for the least responsive to isoproterenol and beta for the most responsive to isoproterenol. Approximately 10 years later it was discovered that dichloroisoproterenol selectively antagonized those effects of catecholamines, classified by Ahlquist as beta effects, thus strengthening the argument for two types of adrenoceptors.

The classification of receptors is based on several types of evidence which are all related to the actions of drugs upon tissues or cells. The chemical structure of the transmitter or drug provides a measure of specificity. Although both epinephrine and digitoxin increase the force of myocardial contraction, they are different chemically and their mechanism of action is also different.

Effects which are opposite in character, produced by two different agents, can be presumed to act through different receptor mechanisms. For example, the negative chronotropic effect of acetylcholine on the sinoatrial node is due to an interaction at the cholinergic muscarinic receptor; the positive chronotropic effect of epinephrine is due to an interaction at the adrenergic beta receptor.

In addition, differing orders of potency for a single series of closely related compounds on several biological systems are evidence for different receptor types in the various systems. The degree of vasoconstrictor activities of norepinephrine (NE), epinephrine (E) and isoproterenol (I) from ascending to descending order is:

NE → E → I.

The order of potency for cardiac stimulation is:

I → E → NE.

Finally, selective antagonism of the effects of neurotransmitter provides the strongest basis for receptor classification. The cardiac positive inotropic effect of epinephrine can be blocked by a beta adrenergic receptor blocking drug but the effects of digitalis cannot be blocked by the same drug. The vasoconstrictor effects of norepinephrine can be blocked by an alpha adrenergic receptor blocking drug but not by a beta blocking drug.

Anatomically, adrenergic receptors have not been clearly defined. The concept of receptors is pharmacological; adrenergic receptors can be thought of as hypothetical parts of effector cells that selectively receive molecules with the general structure of norepinephrine. Although alpha and beta receptors recognize and bind the basic catecholamine structure, subtle differences in molecular structure determine distinct pharmacologic specificity. The ability to bind a beta receptor is generally increased by a bulky substitution on the amino N (as seen with isoproterenol).

Affinity for alpha receptors is decreased by such substitutes. A hydroxyl group on the B carbon enhances binding of both alpha and beta receptors. Only molecules that can bind to receptors by virtue of a complementary structure between receptor and drug will be active. Once such binding has occurred, a biologic process may or may not be stimulated, depending on whether a stimulation or blocker has occupied the receptor.

The "second messenger"

Although the exact nature of drug receptor interaction is not known, the link between receptor binding and biologic response seems to be a so-called second messenger such as 3'5' adenosine-monophosphate (AMP). AMP is a cyclic nucleotide formed from adenosinetriphosphate (ATP). The enzyme responsible for synthesizing adenyl cyclase (CAMP) is activated by catecholamines, especially epinephrine and others with strong beta actions. Adenyl cyclase is situated in the cell membrane.
and the pharmacological effects of the catecholamines on the heart and smooth muscle may be due to stimulation of the enzyme through an action on beta receptors. The mechanism of alpha adrenergic stimulation is less clear; it may be associated with increased levels of 3',5'-guanosine monophosphate.\textsuperscript{1}

Regardless of either the exact nature of the receptor or the mechanism of transmitter-receptor interaction, receptor binding of endogenous catecholamines or exogenous sympathomimetic amines activates a biologic response. Alpha receptors are associated with most of the usual adrenergic excitatory functions, such as vasoconstriction or stimulation of uterine or ureteral muscles. Beta receptors are usually associated with inhibitory adrenergic functions such as vasodilation and inhibition of uterine and bronchial muscles.

In tissues that possess both types of receptors such as blood vessels of the skeletal muscles, alpha receptor stimulation is usually excitatory; beta receptor stimulation is usually inhibitory. Heart muscle and lung tissue contain only beta receptors. However, stimulation of beta receptors in the heart is excitatory and results in a positive chronotropic and inotropic effect. Stimulation of beta receptors of the lung is only inhibitory and results in relaxation of bronchial muscle.\textsuperscript{18}

Recently, beta receptors have been separated into beta\textsubscript{1} (cardiac) and beta\textsubscript{2} (bronchial and peripheral vascular receptors). Stimulation of beta\textsubscript{1} receptors increases heart rate and contractility. Stimulation of beta\textsubscript{2} receptors results in dilatation of the bronchioles and arterioles. By knowing the usual response to alpha and beta stimulation and the anatomic distribution of these receptors, it is possible to predict pharmacologic responses to either natural neurotransmitters or synthetic adrenergic drugs. Table 3 represents a partial listing of the organ, its adrenergic receptor, and the physiological response of stimulation.\textsuperscript{14}

Although the anesthetist is concerned with all adrenergic responses, adrenergic receptors in the circulatory system are of great significance in the anesthetized patient. Stimulation of beta receptors in the heart results in an increased rate of pacemaker discharge, increased contractility, increased

\begin{table}[h]
\centering
\caption{Responses to Adrenergic Stimulation}
\begin{tabular}{lll}
\hline
Tissue & Receptor & Responses \\
\hline
Heart & & \\
 sino-atrial node & beta\textsubscript{1} & increased rate \\
 atria & beta\textsubscript{1} & increased contractility \\
 atrioventricular node & beta\textsubscript{1} & increased conduction \\
 ventricle & beta\textsubscript{1} & increased contractility \\
 coronary blood vessels & alpha & vasoconstriction \\
 cardiac metabolism & beta & vasodilatation \\
 Blood vessels & & \\
 skin & alpha & vasoconstriction \\
 skeletal muscle & beta\textsubscript{2} & vasodilatation \\
 veins & alpha, beta & vasoconstriction \\
 renal & alpha, beta & vasoconstriction or vasodilatation \\
 arterioles & dopaminergic & vasoconstriction or vasodilatation \\
 Lung & & \\
 bronchial smooth muscle & beta\textsubscript{2} & relaxation \\
 Gastrointestinal tract & & \\
 stomach & beta & decreased motility; tone \\
 intestine & alpha, beta & contraction of sphincter \\
 Liver & & \\
 glycogen stores & alpha, beta\textsubscript{2} & glycogenolysis \\
 Other smooth muscle & & \\
 spleen & alpha & contraction \\
 uterus (pregnant) & alpha & contraction \\
 uterus (nonpregnant) & beta\textsubscript{2} & relaxation \\
\hline
\end{tabular}
\end{table}

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metabolic activity, and increased oxygen consumption. These effects can be antagonized with beta adrenergic blocking drugs but not with alpha blocking drugs.

The vascular system has both alpha and beta receptors. Systemic arterial and arteriolar vasoconstriction is clearly an alpha receptor function. Alpha adrenergic blocking drugs antagonize the effect but beta blocking drugs do not. Vasodilator responses are considered to be a function of beta receptors since this response is blocked by beta blocking drugs and not by alpha.

The coronary circulation is poorly understood. There is evidence that the epicardial coronaries have an abundance of alpha receptors, whereas, the intramuscular arteries have an abundance of beta receptors. The overall effect of sympathetic stimulation, however, is moderate dilatation of the coronary vasculature and increase in blood flow. Sympathetic activity increases cardiac rate, rhythm, and myocardial oxygen consumption. Metabolic factors are probably the major controllers of myocardial blood flow.16

The renal vascular bed is primarily an alpha receptor system that responds to most catecholamines by constriction. Recent work has shown that dopamine increases renal blood flow by acting on dopaminergic receptors in the renal and mesenteric beds. This response is not altered by either alpha or beta blockade.

Pharmacological considerations of adrenergic receptors

There are a number of pharmacological maneuvers that alter sympathetic function by preventing norepinephrine from interacting with adrenergic receptors. In addition, a number of drugs are available today which augment or suppress sympathetic function by stimulating or blocking alpha and beta receptors.

Drugs which interact with a receptor and elicit a response are termed agonists; compounds which interact with receptors and prevent the action of agonists, are referred to as antagonists.16 Endogenous catecholamines and exogenous sympathomimetic amines are adrenergic agonists. These drugs are classified as catecholamines (epinephrine, norepinephrine, dopamine, isoproterenol and dobutamine) and noncatecholamines (methoxamine, phentolamine, ephedrine and metaraminol).

They produce their effect either through a direct action on adrenergic receptors, through the release of catecholamines from adrenergic nerve terminals (indirect effect), or a combination of both. These drugs may stimulate only alpha receptors, beta receptors, or both. Isoproterenol is the prototype for beta adrenergic stimulators; methoxamine is the prototype for alpha stimulators. The site and mechanism of action of commonly used sympathomimetic amines are summarized in Table 4.

The selection of the proper sympathomimetic for patients with cardiovascular dysfunction is de-

<table>
<thead>
<tr>
<th>Drug</th>
<th>Site of Action</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Epinephrine</td>
<td>+++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Adrenalin®)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>2. Norepinephrine</td>
<td>+++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Levarterenol®)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>3. Isoproterenol</td>
<td>+++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Isuprel®)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>4. Dopamine</td>
<td>++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Intropin®)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>5. Dobutamine</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>(Inotrex®)</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>6. Methoxamine</td>
<td>+++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Vasoxyl®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Phentolamine</td>
<td>+++</td>
<td>Direct</td>
</tr>
<tr>
<td>(Noasynphrine®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Ephedrine</td>
<td>+</td>
<td>Direct and Indirect</td>
</tr>
<tr>
<td>(Aramine®)</td>
<td>++</td>
<td></td>
</tr>
<tr>
<td>9. Metaraminol</td>
<td>+++</td>
<td>Direct and Indirect</td>
</tr>
<tr>
<td>(Aramine®)</td>
<td>+</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Classification of Adrenergic Receptor Stimulants
dependent upon identification of the pathophysiological process, and the understanding of the receptor and the site of action of the drug.

Alpha adrenergic agonists are useful in modifying circulatory function primarily by their vasoconstrictor action. They elicit reflex vagal bradycardia and may be useful in the treatment of paroxysmal atrial tachycardia. Pure alpha agonists, such as vasoxyl, lack direct cardiac effects but may induce cardiac dilatation and decompensation by increasing afterload or the resistance against which the heart must work. The selection of this type of drug for a patient in cardiogenic shock is inappropriate and hazardous.

Pure beta agonists, such as isoproterenol, have been used effectively in the acute management of complete heart block. Due to its positive inotropic and chronotropic effects as well as vascular dilatation, it also has been used for cardiogenic shock. More recently, dopamine (which has less potential for tachyarrhythmias and good potential for improved renal blood flow) and dobutamine (which demonstrates beta1 selectively with mild chronotropic and arrhythmogenic effects) have replaced isoproterenol.17

The response of adrenergic receptor agonists that stimulate both alpha and beta receptors is dose dependent. Infusions of epinephrine at a rate of 1-2 µg/min primarily affect beta receptors; 2-10 µg/min affect alpha and beta receptors; 10-16 µg/min primarily affect alpha receptors.18 In large doses (greater than 20 µg/kg/min), dopamine's affect on alpha receptors overshadows its action on dopaminergic receptors and results in renal vasoconstriction similar to that produced by norepinephrine.

Excessive activity of the sympathetic nervous system can have a deleterious effect on cardiovascular function. At times it is necessary to block the effector organ response to sympathetic impulses in order to control hemodynamics. The administration of chlorpromazine, droperidol and mephenesin results in mild alpha adrenergic blockade on vascular smooth muscle. Hypotension may occur in the volume depleted patient.

Phenoxybenzamine (Dibenzyline®) is a long acting alpha antagonist used for peripheral vascular diseases such as Raynaud's disease and in the preoperative preparation of a patient for the removal of a pheochromocytoma. It is administered in doses of 20-100 mg. Adverse effects include orthostatic hypotension and tachycardia.

Phentolamine (Regitine®) is an alpha adrenergic blocker with a rapid onset of action. It can be given as a single bolus injection of 1-3 mg or as a continuous infusion of 0.1-0.5 mg/min, titrated to the desired response. Reflex tachycardia and arrhythmias may be associated with its use.

Propranolol (Inderal®) is a beta receptor antagonist which competitively reduces the effect of a beta agonist at the adrenergic beta receptor.10 Because of its ability to decrease heart rate, contractility, and cardiac output, it leads to a reduction in myocardial oxygen consumption and therefore is widely used in the medical management of angina pectoris. It is also useful in the preoperative management of hypertension, thyrotoxicosis, and migraine headache. Its value in the management of preoperative or perioperative dysrhythmias, especially those that are catecholamine induced, is unquestioned. Perioperatively, an intravenous dose of 0.25 to 0.5 mg is given initially, followed by additional doses up to a cumulative total dose of 3 to 5 mg given over a five to ten minute period.20

In the early 1970's, it was popular practice to discontinue propranolol two weeks preoperatively. In 1975, Miller reported the development of untoward myocardial ischemic events in a significant number of patients who were abruptly withdrawn from this antagonist.21

Since then, the pharmacokinetics of propranolol have been studied extensively. The half-life of this drug is 3.4 to 6 hours after discontinuation of chronic oral administration. It disappears from the plasma and atria within 24 to 48 hours and the chronotropic and inotropic responses return to normal within 24 to 48 hours after discontinuing doses of 30 to 240 mg/day.22 Other authors have demonstrated no unusual hemodynamic function during surgery in patients with coronary artery disease receiving moderate doses of oral propranolol.23

The decision to either continue, taper or discontinue the drug is dependent upon the reason the patient is receiving the drug. For the patient with coronary artery disease, abrupt withdrawal of propranolol in the preoperative period may be dangerous. If deemed advisable, it is recommended that it be slowly tapered in a monitored environment.

**Beta adrenergic blockers**

The major side effects encountered with the intraoperative administration of propranolol include bronchoconstriction and excessive cardiac depression. If severe hypotension develops, the anesthetist must understand the pharmacology of beta receptor blockade. Beta blocking drugs are competitive antagonists and there is always a dose
of the agonist (isoproterenol) that will overcome the antagonist.

In the face of beta blockade however, the usual dose of isoproterenol (1-6 µg/min) may have to be increased to 20 µg/min. Sympathomimetics with both alpha and beta effects should be used with caution. With significant beta blockade, the alpha effects of the drug will be pronounced. With cardiac depression, this vasoconstriction and increase in afterload may be hazardous.

If the treatment of myocardial depression with isoproterenol is not effective, the anesthetist can consider the use of glucagon, calcium chloride or digitalis. Glucagon has a separate receptor site on the cell wall and releases adenyl cyclase to convert ATP to CAMP. This results in a positive inotropic effect which is independent of the beta receptors. Calcium chloride and digitalis work intracellulary at the level of the contractile proteins to improve myocardial contractility.

If propranolol is to be continued until the time of surgery, other potential problems must be anticipated. A number of studies of anesthetic drug interactions with propranolol have been done. Methoxyflurane and enflurane have a synergistic effect with the drug; halothane and morphine have additive hemodynamic effects with the beta-blocker. Since parasympathetic effects may predominate with the combination of anesthesia and beta blockade, these patients should receive ample preanesthetic anticholinergic medication. The quaternary ammonium compound glycopyrrolate is a good choice since it produces an effect three to five times the duration of atropine.

Since the patient may not be able to respond to hypovolemia by increasing the heart rate, volume replacement must be adequate. Finally, because of the theoretical possibility of hypoglycemia, these patients should receive parenteral glucose.

Until recently, propranolol was the only beta adrenergic blocker approved for use in this country. In the United Kingdom and other countries, there are at least seven more beta blockers in current use. Ahlquist recently stated that he found it difficult to understand the attitude of the U.S. Federal Drug Administration (FDA) concerning this class of drugs; and he hoped science and common sense would prevail over bureaucratic indecision.

However, metoprolol tartrate (Lopressor®), a synthetic selective beta₁ blocking agent, has recently been approved by the FDA for use as an antihypertensive. The usual initial dose is 50 mg twice daily. Maintenance dosage is approximately 100 mg twice a day with a range of 100 to 450 mg per day. Although it has a preferential effect on beta₁ receptors in cardiac muscle, this effect is not absolute. In higher doses, the beta₂ receptors of bronchial and vascular musculature are also blocked and the anesthetic considerations are similar to those of propranolol.

Finally, one should remember that some adrenergic antagonists produce their effect with blockade sympathetic nervous system activity (reducing the amount of norepinephrine released from the nerve terminal). They do not block receptors; therefore, the circulatory system is responsive to sympathomimetic amines which act directly on adrenergic receptors, but not necessarily to those which act indirectly. The mechanical actions of these drugs include either depletion of the nerve endings of norepinephrine, inhibition of norepinephrine synthesis, or block of release without depletion.

Reserpine (Serpasil®) depletes the nerve endings of norepinephrine. Guanethidine (Ismelin®) initially prevents the release of norepinephrine from the storage area but it later displaces the transmitter and prevents its re-uptake.

The antiarrhythmic bretylum tosylate (Bretylol®) alters adrenergic stimulation of the heart by three mechanisms. High concentrations release norepinephrine from adrenergic neurons. Lower concentrations inhibit the release. Finally, it may block the uptake of norepinephrine into adrenergic nerves and potentiate the action of this agonist on adrenergic receptors. In doses of 5-10 mg/kg, bretylum can be useful in the treatment of life-threatening ventricular arrhythmias that are unresponsive to lidocaine. Serious side effects such as hypotension preclude its routine use.

Conclusion

The patient scheduled for anesthesia is dependent upon an intact autonomic nervous system for stability. Imbalances can threat the patient's survival and, therefore, must be promptly recognized and treated. Proper preoperative and intraoperative management of the surgical patient is dependent upon an understanding of the peripheral adrenergic system, its effector site and drugs that augment or suppress sympathetic function.

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