Local Modulation of Adrenergic Neurotransmission

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SUMMARY The cardiovascular reflexes, by regulating the traffic in the sympathetic nerves, govern the amount of norepinephrine released from the nerve endings. However, the final adjustments in the amount of neurotransmitter available to activate the β receptors in the heart and the α receptors in the blood vessels take place at the sympathetic neuroeffector junction. Thus, a decrease in pH, hyperosmolarity, moderate increases in the concentration of K⁺ ion, adenosine and adenine nucleotides depress the release of norepinephrine at any given level of sympathetic nerve activity. These metabolic changes, which occur in active tissues, and in particular in adenosine, have been proposed as mediators of the accompanying local hyperemia. In addition, they apparently facilitate this local dilatation by disconnecting the blood vessels in the active tissues from sympathetic control. Acetylcholine, histamine and 5-hydroxytryptamine are present in and around certain blood vessels and can activate specific receptors on the prejunctional fibers and cause vasodilatation by reducing the output of neurotransmitter. Some of the norepinephrine released into the synaptic cleft may depress its continued release by activating prejunctional α receptors. In contrast, angiotensin II, by a local action on the nerve endings, can augment the release of transmitter. Decreases in local temperature reduce transmitter release but augment the affinity of the postjunctional α receptors for norepinephrine. The role of these local events at the neuroeffector junction, their physiologic significance and potential clinical importance are discussed in this review.

GEORGE ELGIE BROWN was a pioneer in clinical investigation. After reports were received from Australia that surgical sympathectomy had been performed on patients with spasitic disorders of the skeletal muscles, Brown, recognizing the postoperative warmth of the feet of such patients, persuaded the neurosurgeon, A.W. Adson, to perform sympathectomies on selected patients with peripheral vascular disease. While the heyday of surgical sympathectomy has passed, its extensive use through the 1950s provided a major stimulus for research on the sympathetic nervous system and on the blood vessels of the limbs and their diseases. Brown wrote more than 120 papers, ranging from the diagnosis of Raynaud's disease and the sensitivity of denervated vessels to epinephrine to the role of the sympathetic nervous system in essential hypertension.

Particularly since 1946, with the demonstration by von Euler that norepinephrine is the neurotransmitter at the sympathetic neuroeffector junction, the growth in our knowledge of the complex events that occur at the terminations of the sympathetic nerves in the heart and the blood vessels has been remarkable. The signals that originate in the arterial baro- and chemoreceptors, the cardiopulmonary receptors, the receptors in skeletal muscles, and those that originate from centers within the brain, after translation into changes in sympathetic outflow, end in alterations of the amount of norepinephrine liberated from the nerve terminals into the junctional (synaptic) clefts between the nerves and the cardiac or vascular smooth muscle cells.

The sympathetic nerves end in varicosities that contain vesicles formed in the neuronal cell body. These vesicles descend to the periphery with the axonal flow. They are the storage sites for norepinephrine. The adrenergic nerve endings take tyrosine from the extracellular fluid and transform it in the neuromplasm to dopamine by successive enzymatic reactions. The dopamine is taken up by the storage vesicles, where it is converted to norepinephrine by the enzyme dopamine-β-hydroxylase. The release of norepinephrine is initiated by the action potentials, generated in the ganglionic cell body, and the consequent penetration of Ca⁺⁺ into the neuromplasm. With the increased intraneuronal Ca⁺⁺ concentration, the vesicles migrate to and fuse with the neuronal cell membrane; they empty their contents into the junctional cleft (exocytotic release; fig. 1). The norepinephrine diffuses toward the effector cells to activate β receptors in the heart and α receptors in the blood vessels. This sets in

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motion the complex cellular events that cause the heart to quicken, its contractility to increase and the vascular smooth muscle cells to contract. The released norepinephrine is removed from the junctional cleft by neuronal uptake (amine pump; uptake 1), by overflow to the extracellular fluid and the bloodstream, by binding to connective tissues, and by the active uptake in the muscle cells (extraneuronal uptake; uptake 2) and subsequent metabolism by the enzymes catechol-O-methyl transferase and monoamine oxidase. The relative importance of these pathways varies in different tissues, depending mainly on the density of innervation and the width of the junctional cleft between the nerve varicosities and the muscle cells. In the blood vessel wall, these events at the neuroeffector junction interact with local metabolic changes in the tissues, with certain vasoactive agents present in and around the vessels, and with circulating substances. The outcome of these interactions dictates the responses of the heart, the resistance and capacitance vessels, and hence of the arterial blood pressure to the various stresses that beset the body.

While the local metabolic and humoral changes in the tissues affect the muscle cells directly, in recent years evidence has accumulated that many of these changes can alter the amount of transmitter released from the sympathetic nerve terminals in the face of a constant frequency of activation of the postganglionic sympathetic fibers. This may occur with changes in the concentration of some of these substances, which are too small to affect the muscle cells directly. Thus, they may act as the final modulators of the sympathetic control of the organs and tissues of the body. Among the inhibitory modulators are the products of cellular metabolism, acetylcholine and other vasoactive substances such as histamine and 5-hydroxytryptamine. The most important facilitatory modulator is angiotensin II. In addition, and of particular importance for the cutaneous vessels, local changes in temperature have complex actions at the neuroeffector junction.

Factors That Reduce the Output of Transmitter from the Sympathetic Nerve Endings

Metabolic

Acidosis

Metabolic acidosis relaxes myogenically active vascular smooth muscle and depresses the contractile response of isolated blood vessels to sympathomimetic amines and sympathetic nerve stimulation. A moderate degree of acidosis (changing from pH 7.4 to 7.1) does not affect the basal tension or responsiveness of isolated cutaneous veins to increasing concentrations of norepinephrine, but does depress the response to sympathetic nerve stimulation. The acidosis acts by inhibiting the release of norepinephrine, possibly by depressing Ca++ entry into the nerve.
Potassium Ions

An increase in K+ concentration has at least three actions on the adrenergic nerve endings: inhibition of release of norepinephrine by nerve impulses (fig. 2), inhibition of neuronal uptake of norepinephrine and, with higher concentrations, a direct liberation of transmitter. The inhibition of norepinephrine release probably results from a decreased Ca++ influx into the nerve endings.10, 11

Hyperosmolarity

Hyperosmolarity causes vasodilatation of many vascular beds in the intact organism.12 Studies on isolated blood vessels demonstrate that it reduces the release of norepinephrine during activation of the sympathetic nerves (fig. 2). A combination of tissue shrinkage, inhibition of sympathetic nerve activity and of the response to α-adrenergic stimulation, and depression of spontaneous myogenic activity could account for the vasodilator action in vivo.13

Adenosine and Adenine Nucleotides

Adenosine and the adenine nucleotides cause dilatation by a local action on the smooth muscle of the blood vessels.14-18 In addition, when the sympathetic nerves are active, adenosine, ADP and ATP cause additional dilatation of the vessels by inhibition of norepinephrine release17, 18 (figs. 2 and 3). Whether this effect is due to hyperpolarization of the neuronal membrane, to inhibition of Ca++ influx into the endings, which results in inhibition of the exocytotic process.9

Figure 2. A concentration of adenosine (left) and increases in potassium concentration (middle) or in osmolality (right), which do not inhibit contractile responses to norepinephrine, cause relaxation (upper) and a significant depression of the release of 3H-norepinephrine (lower) evoked by nerve stimulation in three groups of five saphenous veins each. ES = electrical stimulation. (Reprinted with permission from McGrath MA, Vanhoutte PM: Vasodilatation caused by peripheral inhibition of adrenergic neurotransmission. In Mechanisms of Vasodilatation, edited by Vanhoutte PM, Leusen I. Basel, S. Karger, 1978, p 248.)

Figure 3. Depression by adenosine of the response of six canine saphenous vein strips to electrical stimulation and norepinephrine. The contraction of the strips caused by electrical stimulation is due to release of norepinephrine from the adrenergic nerve endings. The asterisks indicate that the decrease in tension caused by adenosine is significant. Note that the contractions induced by nerve stimulation are more depressed by adenosine than those caused by exogenous norepinephrine. This indicates that in the veins contracted by nerve stimulation, part of the relaxation caused by adenosine is due to interference with sympathetic neurotransmission. This is confirmed in other studies by the fact that adenosine depresses the output of 3H-norepinephrine evoked by nerve stimulation (see figure 2). A similar inhibition of adrenergic neurotransmission is seen when ADP or ATP is substituted for adenosine. (Reprinted with permission from Verhaeghe RH, Vanhoutte PM, Shepherd JT: Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. Circ Res 40: 208, 1977.)
Muscular Exercise

Hydrogen and potassium ions, hyperosmolarity, adenosine and adenine nucleotides all have been implicated in vasodilatation occurring in metabolically active tissues. In the latter, and in particular in contracting skeletal muscles, the response of the resistance vessels to sympathetic nerve stimulation is reduced.1-21 This can be explained by the inhibition of adrenergic neurotransmission caused by changes in the immediate environment of the metabolically active tissues (fig. 4). The inhibitory effects on the adrenergic nerve terminals occur with lower concentrations of the proposed mediators of hyperemia than the direct effects on the vascular smooth muscle itself.22 During muscular exercise, the cardiac output must increase to provide an adequate blood flow to the active muscles and to the skin for dissipation of heat. The resistance vessels in the other systemic vascular beds and the splanchnic capacitance vessels must constrict to maintain the arterial blood pressure and hence, an appropriate perfusion pressure for the organs and tissues of the body. The increased sympathetic outflow to the cardiovascular system is due primarily to a central command and to reflexes originating in the active muscles.23 The increase in blood flow to the active muscles is achieved predominantly by the local metabolites. The generation of metabolites also restrains the sympathetic activity to the active muscles. During mild exercise, the balance between metabolic and sympathetic activity permits a better ratio of oxygen extraction to blood flow. As the severity of the exercise increases, the excess of metabolites completely inhibit the powerful sympathetic outflow to the working muscles, permitting maximal dilatation of the muscle resistance vessels.24

Neurohumoral

Alpha-adrenergic Receptors

The existence of an inhibitory feedback mechanism, mediated through prejunctional $\alpha$-adrenergic receptors, has been demonstrated in the sympathetic nerve endings to the heart and blood vessels. Thus, when the sympathetic nerves are activated the release of norepinephrine is depressed by certain $\alpha$-adrenergic agonists but is augmented in the presence of certain $\alpha$-adrenergic antagonists. This suggests that these prejunctional receptors exert a negative feedback on

**Figure 4.** The products of cellular activity cause dilatation of the arterioles not only because of their direct inhibitory effect on the smooth muscle cells, but also because they interrupt the vasoconstrictor impulses of the sympathetic nerves. The arteriolar wall is shown as one layer of smooth muscle cells, with an adrenergic nerve ending and one of its varicosities, containing the adrenergic neurotransmitter norepinephrine (NE). $\text{AMP} = \text{adenosine monophosphate}$; $\text{ADP} = \text{adenosine diphosphate}$; $\text{ATP} = \text{adenosine triphosphate}$; $\text{CM} = \text{cell membrane}$; $\text{+} = \text{activation}$; $\text{–} = \text{inhibitory effect}$; $\text{α} = \text{α-adrenergic receptor}$. (Reprinted with permission from Shepherd J, Vanhoutte P: The Human Cardiovascular System: Facts and Concepts. New York, Raven Press, 1979.)
transmitter release. The prejunctional α receptors (α2-adrenergic receptors) have pharmacologic properties different from those of most postjunctional α receptors, at least in the arterial wall; for example, they are activated readily by clonidine, but are insensitive to the antagonist prazosin. The inhibitory effect of norepinephrine on its own release is most easily demonstrated after inhibition of the neuronal uptake mechanism (fig. 5). The role of the prejunctional α-adrenergic receptors in normal circumstances has still to be established. Its importance may be greater in tissues in which the junctional cleft is relatively narrow because this tends to maintain a high concentration of transmitter in the immediate vicinity of the neuronal cell membrane.

It has been suggested that the neuronal amine uptake mechanism operates mainly between nerve impulses and is switched off during depolarization of the nerve varicosities to allow for optimal transmitter diffusion. If the prejunctional α-adrenergic receptor modulation of transmitter release operates optimally when neuronal uptake is inhibited, this might imply that the role of neuronal α-adrenergic receptors is to modulate the junctional concentration of transmitter throughout the excitation-secretion cycle.

Acetylcholine

In isolated arteries and veins and in intact vascular beds, it has been demonstrated that acetylcholine depresses in a dose-dependent manner the contractile response to sympathetic nerve stimulation by inhibiting the release of norepinephrine (fig. 6). This effect occurs at concentrations that do not affect the basal tension of the smooth muscle cells. This action of acetylcholine is inhibited by muscarinic, but not by nicotinic antagonists; thus, the inhibition of adrenergic neurotransmission results from activation of muscarinic receptors on the adrenergic nerve endings (fig. 7). The cholinergic transmitter also inhibits the release of norepinephrine evoked by high potassium solutions, but not its pharmacologic displacement by indirect sympathomimetic amines, and so acetylcholine must interfere directly with the exocytotic process. In the isolated gastric artery,
transmural field stimulation activates both adrenergic and cholinergic nerve endings; the contractile response to such stimulation is depressed by physostigmine and augmented by atropine, suggesting that the electrical field liberates acetylcholine, which then causes partial inhibition of the release of the adrenergic transmitter. In the blood-perfused stomach of the dog studied in situ, vagal stimulation reduces the vasoconstrictions evoked by sympathetic nerve activation significantly more than those caused by exogenous norepinephrine (fig. 8). Thus, in blood vessels innervated by both adrenergic and cholinergic nerve terminals, acetylcholine liberated from the cholinergic nerve endings causes decreased release of norepinephrine, and prejunctional inhibition of adrenergic neuro-

**Figure 6.** Effect of acetylcholine on tension development and endogenous norepinephrine overflow evoked by nerve stimulation in a superfused canine saphenous vein. Note the inhibitory effect of acetylcholine on the release of norepinephrine from the sympathetic nerve endings. (Reprinted with permission from Vanhoutte PM, Coen EP, De Ridder WJ, Verbeuren TJ: Evoked release of endogenous norepinephrine in the canine saphenous vein. Inhibition by acetylcholine. Circ Res 45: 608, 1979.)

Histamine

The sympathetic nerves and the walls of the blood vessels contain histamine.46, 47 The release of endogenous histamine causes local vasodilatation.48 In man, the infusion of histamine causes a dose-dependent relaxation of resistance vessels in the forearm.49 In isolated arteries and veins, histamine causes marked relaxation and reduces the release of norepinephrine during sympathetic nerve stimulation; this occurs at concentrations which have no direct effects on the vascular smooth muscle cells (fig. 9). Histamine also decreases the overflow of *H*-norepinephrine evoked by sympathetic nerve stimulation; this provides further evidence for the existence of muscarinic receptors on adrenergic fibers. In the heart, the pharmacologic properties of the muscarinic receptors mediating depression of atrial tension, development of ventricular rate and of norepinephrine release from sympathetic nerves are similar.46

**Figure 8.** Comparison of the effects of the same vagal stimulation (VS) (10 Hz) on gastric perfusion pressure in resting conditions and during sympathetic nerve stimulation (right). Left gastric artery perfused at constant flow with autologous blood. (Reprinted with permission from Van Hee RH, Vanhoutte PM: Cholinergic inhibition of adrenergic neurotransmission in the canine gastric artery. Gastroenterology 74: 1266, 1978.)
by high potassium solutions, indicating that it interferes with the exocytic process. The inhibitory effect of histamine is due to activation of prejunctional H2 receptors, since it is blocked by metiamide but not by pyrilamine. This inhibition of adrenergic neurotransmission could explain in part why the vasodilatation caused by the acetylcholine in the intact organism is prolonged, because its direct dilator effect on the vascular smooth muscle cells is unopposed by norepinephrine released from the sympathetic nerve endings.

**5-Hydroxytryptamine**

The inhibitory effect of 5-hydroxytryptamine on adrenergic neurotransmission has been demonstrated in the isolated dog saphenous vein where the monoamine depresses the response to sympathetic stimulation; the relaxation is paralleled by a decreased release of 3H-norepinephrine in preparations previously incubated with 3H-norepinephrine. ES = electrical stimulation. (Reprinted with permission from McGrath MA, Vanhoutte PM: Vasodilatation caused by peripheral inhibition of adrenergic neurotransmission. In Mechanisms of Vasodilatation, edited by Vanhoutte PM, Leusen I. Basel, S. Karger, 1978, p 248.)

![Diagram of electrical stimulation](image-url)

**Figure 9.** Concentrations of acetylcholine, histamine and 5-hydroxytryptamine, which do not cause changes in tension in unstimulated preparations or during contraction to exogenous norepinephrine, cause a pronounced relaxation during sympathetic nerve stimulation; the relaxation is due to a decrease in the evoked release of adrenergic neurotransmitter. The experiments were performed on three saphenous vein strips previously incubated with 3H-norepinephrine. ES = electrical stimulation. (Reprinted with permission from McGrath MA, Vanhoutte PM: Vasodilatation caused by peripheral inhibition of adrenergic neurotransmission. In Mechanisms of Vasodilatation, edited by Vanhoutte PM, Leusen I. Basel, S. Karger, 1978, p 248.)

Followed by a dose-dependent increase in resistance.

**Temperature**

When vascular smooth muscle is cooled from 37°C, there is a progressive depression of the contractile process within the cell. The output of norepinephrine from the nerve ending is reduced (fig. 10) and, at

![Diagram of electric stimulation](image-url)

**Figure 10.** Effect of cooling from 37°C to 28°C on contraction and 3H efflux in a helical strip of canine saphenous vein previously incubated with 3H norepinephrine. Cooling augments the contraction but depresses the output of tritiated compounds. (Reprinted with permission from Shepherd JT, Vanhoutte PM: Veins and Their Control. Philadelphia, WB Saunders, 1975, p 269.)
temperatures between 10 and 5°C, the adrenergic transmission is interrupted, although the vascular smooth muscle still contracts when activated by exogenous norepinephrine. Despite these changes, which would be expected to cause the muscle to relax, at temperatures below 37°C but above 10–15°C, the contractile response of the smooth muscle of cutaneous vessels to stimulation of the sympathetic nerves is enhanced (figs. 10 and 11). This is primarily because of an increased affinity for norepinephrine of the α receptors on the vascular smooth muscle cells, and partly because of inhibition by cooling of the neuronal uptake of the transmitter.44-48 These effects are of particular importance for the cutaneous vessels of the extremities, which have a major role in restricting or increasing heat loss from the skin, according to the thermal requirements of the organism. Thus, in a cool environment, the constriction of the skin-resistance vessels mediated by increased sympathetic outflow is reinforced by the local effects of the cold; the resultant reduction in skin blood flow and the accompanying vasoconstriction help to decrease heat loss by decreasing the venous surface area and directing the venous flow through the venae comitantes, where transfer of heat from the accompanying artery takes place. Such a countercurrent exchange creates a thermal short-circuit that carries some of the arterial heat back into the body.4 In rings of vascular smooth muscle stimulated electrically at a low frequency (0.5 Hz), warming from 7° to 9°C, or from 9° to 11°C causes marked increases in tension, presumably because of a combination of resumption of adrenergic neurotransmission and increased responsiveness of the smooth muscle cells to norepinephrine.49 When human extremities are exposed to severe cold, the initial vasoconstriction is followed by alternating periods of vasodilatation and vasoconstriction (the hunting reaction, fig. 12). This may be explained by the combination of increased responsiveness of the cutaneous vascular smooth muscle cells to norepinephrine and alternation between interruption and resumption of adrenergic neurotransmission.

**Factors That Increase the Output of Transmitter from the Sympathetic Nerve Endings**

**Angiotensin II**

Angiotensin II augments vasoconstrictor responses to sympathetic nerve activation, in part because it facilitates the release of adrenergic transmitter.50, 51 The stimulation of adrenergic neurotransmission caused by the octapeptide combines with the activation of central angiotensin receptor sites and the facilitation of transmission at the sympathetic ganglia to augment the amount of norepinephrine present in the vicinity of the cardiac and vascular effector cells.52

**Epinephrine**

There are β2-adrenergic receptors on adrenergic nerve endings which, when activated, facilitate the exocytotic release of norepinephrine. These receptors are insensitive to norepinephrine itself, so can only play a role in the intact organism when enough circulating epinephrine reaches the adrenergic varicosities.53

**Clinical Implications**

**Inhibition of Exocytotic Release**

In the course of circulatory shock, the accumulation of vasodilator metabolites in the hypoxic tissues probably causes a progressive escape of precapillary resistance vessels from sympathetic control, and the resulting vasodilatation contributes to the irreversibility of the shock condition:54, 55 in the case of endotoxin shock, the release of histamine evoked by the bacterial toxin should amplify the depression of exocytotic release caused by the tissue hypoxia. Drugs such as the general anesthetic agent halothane and local anesthetic agents depress the response of isolated blood vessels to sympathetic nerve stimulation in concentrations that do not affect that to exogenous norepinephrine (fig. 13); local anesthetic agents reduce the release of 3H-norepinephrine evoked by nerve stimulation.56, 57 Thus, prejunctional inhibition of norepinephrine release helps explain the potent
dilator properties of halothane and local anesthetic agents. In halothane, the prejunctional inhibitory effect is of particular importance at the venous side of the circulation because of the tight control exerted by the sympathetic nervous system on the capacitance vessels; the venodilatation resulting from prejunc-
tional inhibition probably plays a major role in the decrease in cardiac output and blood pressure seen during halothane anesthesia. In the case of local anesthetic agents, the inhibitory effect on adrenergic neurotransmission is counteracted, in several commercial preparations, by the addition of α-adrenergic agonists.

Facilitation of Exocytotic Release

In the early stages of experimental hypertension, the release of norepinephrine in the blood vessel wall is greater than normal during sympathetic nerve stimulation, and this phenomenon could play a role in the etiology of the disease. The greater-than-normal release could be due to an inherent defect of the adrenergic neuron, although modulatory influences from circulating substances such as angiotensin II, epinephrine or endogenous inhibition of Na+, K+ ATPase could contribute; if so, the efficacy of β-blocking drugs, angiotensin antagonists and converting-enzyme inhibitors as antihypertensive agents must rest in part on their potential to curtail the facilitatory effect of these hormones on adrenergic neurotransmission. Conversely, the strong vasoconstrictor properties that cardenolides have during sympathetic nerve stimulation (fig. 14) are explained by the profound alterations of the adrenergic neuroeffector interaction they provoke. The cardenolides cause an increase in the output of norepinephrine from the sympathetic nerve endings. This, rather than a direct effect of these drugs on the vascular smooth muscle, is the major cause of the contraction of the blood vessels. The ways in which the cardenolides cause this increased output is complex and involves displacement of norepinephrine from neuronal stores, a reduction of the activity of neuronal monoamine oxidase, a facilitation of the Ca++-dependent exocytotic release of norepinephrine and a partial inhibition of the neuronal amine carrier mechanism.

Figure 12. The heat loss from the right index finger of a normal subject to water at 0-6°C. This heat comes from the blood circulating through the finger and thus represents the finger blood flow. When the finger is placed in the ice-cold water, the blood vessels constrict and the blood flow decreases nearly to zero. This initial constriction is followed by a pronounced vasodilatation, which alternates with episodes of intense constriction, the so-called hunting reaction. (Reprinted with permission from Greenfield ADM, Shepherd JT, Whelan RF: Cold vasoconstriction and vasodilatation. Irish J Med Sci 309: 415, 1951.)

Figure 13. Both the general anesthetic agent halothane and the local anesthetic drug etidocaine depress the response of canine saphenous veins to sympathetic nerve stimulation significantly more than that to exogenous norepinephrine (NE). This demonstrates the inhibitory effect that both agents have on adrenergic neurotransmission. ES = electrical stimulation. (Reprinted with permission from McGrath MA, Vanhoutte PM: Vasodilatation caused by peripheral inhibition of adrenergic neurotransmission. In Mechanisms of Vasodilatation, edited by Vanhoutte PM, Leusen I, Basel, S. Karger, 1978, p 248.)

Figure 14. Effect of acetylstrophanthidin on tension response of canine saphenous vein strips before and during electrical stimulation of the sympathetic nerves. Note the return of tension to prestimulation levels when the electrical stimulus was switched off. (From Breder D, Vanhoutte PM, Shepherd JT: Potentiation of adrenergic venomotor responses in dogs by cardiac glycosides. Circ Res 25: 397, 1969.)


Prejunctional Modulation

The relative specificity of prejunctional \( \alpha_2 \)-adrenergic receptors for agonists and antagonists has important therapeutic consequences. Thus, clonidine has a great affinity for prejunctional \( \alpha_2 \)-adrenergic receptors and reduces the release of norepinephrine in the periphery during sympathetic nerve stimulation.\(^{23, 24}\) By contrast, \( \alpha_1 \)-adrenolytic agents, such as phenoxybenzamine and phentolamine, interrupt the \( \alpha_1 \)-adrenergic negative feedback, and hence considerably augment the evoked release of adrenergic neurotransmitter; in the blood vessel wall, this is masked by their \( \alpha_1 \)-adrenolytic properties on the vascular smooth muscle cells, while in the heart the greater release of norepinephrine results in a \( \beta \)-adrenergically-mediated increase in heart rate. This is not seen with \( \alpha_1 \)-selective \( \alpha_2 \)-adrenolytic drugs like prazosin.\(^{45}\) Inhibition of prejunctional \( \alpha_2 \)-adrenergic receptors is also seen with antidepressant drugs such as dexamiso and amitryptiline;\(^{59, 70}\) in the case of amitryptiline, this may help explain the tachycardia and arrhythmias that it can cause.

With regard to the muscarinic prejunctional receptors, it is likely that prejunctional inhibition of norepinephrine release helps explain the diffuse bleeding which can occur in the gastrointestinal wall when the vagal tone is abnormally high.\(^{45}\) Also it seems logical to assume that during episodes of vasovagal syncope both the heart and the cholinergically innervated blood vessels escape very rapidly from sympathetic adrenergic control because the liberated acetylcholine switches off the release of norepinephrine at the prejunctional level. Conversely, when drugs with muscarinic blocking properties are given on a background of cholinergic nerve activity, the resulting augmentation of the release of adrenergic transmitter explains the cardiovascular acceleration and the increases in plasma catecholamine concentration they sometimes cause; this is especially so with drugs such

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**Figure 15.** (left) In control conditions, gallamine does not affect the contractile response and the evoked release of \( ^3 \)H-norepinephrine to nerve stimulation in five saphenous veins of the dog. (right) If the preparations are exposed throughout the experiment to acetylcholine, the release of norepinephrine, and hence the contractile response to electrical stimulation, are smaller than in control solution; in the presence of acetylcholine, gallamine causes a large increase in the evoked release of norepinephrine because it inhibits the prejunctional muscarinic receptors. This experiment illustrates how, in conditions in which there is a background cholinergic activity, drugs with muscarinic blocking properties can cause cardiovascular acceleration because they withdraw the inhibitory effect of the cholinergic transmitter on the exocytotic release of norepinephrine. (Reprinted with permission from Vercruysse P, Bossuyt P, Hanegraefs G, Verbeuren TJ, Vanhoutte PM: Gallamine and pancuronium inhibit pre- and postjunctional muscarinic receptors in canine saphenous veins. J Pharmacol Exp Ther 209: 225, 1979.)
as atropine, amitryptiline, gallamine (fig. 15) and pancuronium bromide.42, 70-72

Postjunctional Modulation

Only recently has it become obvious that pharmacologic characteristics of the \( \alpha \)-adrenergic receptors of vascular smooth muscle are not uniform, and that different subtypes (e.g., \( \alpha_1 \) and \( \alpha_2 \)) may coexist in a given blood vessel.1, 28, 73 Differences in the distribution of subtypes of \( \alpha \)-adrenergic receptors will probably explain variations in sensitivity to hypotensive effects of drugs such as clonidine and prazosin among different speceies, or among hypertensions of different origin.

The adrenergic sensitivity of vascular smooth muscle cells, and the way it is modulated by local temperature changes, may well explain the vasospastic episodes seen in primary Raynaud’s disease on exposure of the peripheral vessels to cold. Indeed, in normal people, the instantaneous increase in \( \beta \)-adrenergic responsiveness caused by moderate cooling is probably tempered by a simultaneous increase in \( \beta \)-adrenergic sensitivity of the vascular smooth muscle cells. The relative absence of \( \beta \)-receptor sensitivity, whether idiopathic, due to hypothyroidism or caused by \( \beta \)-adrenergic blocking agents, exaggerates the vasoconstriction due to the increased affinity of the postjunctional \( \alpha \)-adrenergic receptors caused by local cold, and thus precipitates the vasospasm.82, 76

Acknowledgment


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