The role of the sympathetic system in the rapid circulatory adjustments to acute cardiovascular stresses such as hemorrhage and shock is well recognized. On the other hand, its role in the chronic, steady state circulatory changes that occur in pathophysiologic conditions such as hypertension is not fully appreciated.

Introduction

The purpose of this paper is to highlight the relative importance of the sympathetic system in causing or maintaining an elevated arterial pressure and to review the mechanisms that may be responsible for an exaggerated sympathetic tone.

Dual Theory of Pathogenesis of Hypertension

Increased vascular resistance is the basic hemodynamic abnormality in chronic stable hypertension. Although several factors are involved in its pathogenesis (which investigators have termed the "mosaic theory"), two fundamental mechanisms may underlie the increased vascular resistance in the majority of hypertensive states: a vascular muscle defect, which leads to enhanced vasoconstriction, coupled with a normal or exaggerated sympathetic tone (fig. 1). Either the vascular muscle defect or the excessive sympathetic drive or both may be genetically determined or acquired. A large number of observations in various models of hypertension support this dual theory. Before discussing the sites of abnormal sympathetic control and related mechanisms in hypertensive states, two important questions should be answered: Does increased sympathetic activity cause chronic hypertension? What is the relative importance of the sympathetic nervous system in causing or reversing hypertensive states?

Increased Sympathetic Activity May Cause Chronic Hypertension

Increased sympathetic activity may lead to a sustained increase in vascular resistance through a variety of physiologic and adaptive mechanisms:

**Figure 1. Schematic diagram of dual theory of hypertension.**
1. Increased Vascular Resistance. Sustained arterial constriction may be caused by the released norepinephrine in several vascular beds, e.g., splanchnic, renal, muscular, and cutaneous. Adaptive changes resulting in vascular hypertrophy may maintain a hypertensive state.10

2. Increased Cardiac Output. The sympathetic drive to the heart increases stroke volume, heart rate, and cardiac output. A high cardiac output and the accompanying rise in pressure, such as occur in renal hypertension19 or in hyperkinetic states, may trigger arteriolar hypertension19 or autoregulatory vasoconstriction19 and increase vascular resistance. Venous constriction may contribute to the high cardiac output by increasing central blood volume.14

3. Sodium Retention and Renin Release. Sympathetic drive to the kidney causes sodium and water retention as well as the release of renin-angiotensin and aldosterone.14 These result in increased vascular resistance through arteriolar constriction, increased vascular stiffness, or increased wall-to-lumen ratio which augments the contractile response.15-18

4. Vascular Muscle Defects. Two cellular defects may be the most important mechanisms by which nerves cause a chronic increase in vascular resistance:
   a. Membrane Defect. Sympathetic nerves are necessary for the development of a membrane defect in arteriolar muscle of a strain of spontaneously hypertensive rats (SHR) resulting in an abnormality of electrogenic ion transport and an exaggerated vasoconstrictor response.7
   b. Synthesis of Contractile Protein. Sympathetic nerves increase the rate of synthesis of contractile protein in vascular muscle.14 In hypertensive animals this may lead to greater resistance and enhanced vasoconstriction.19 These and other potential mechanisms are discussed further below.

Relative Importance of the Sympathetic System in Hypertensive States

Three approaches have been used to evaluate the relative importance of the nervous system in hypertension:

1. Production of Hypertension. Hypertension has been produced in animals by surgical or chemical interventions in specific CNS sites, which result in increased sympathetic activity. Lesions of the nucleus tractus solitarius (NTS) of the medulla may cause labile or sustained hypertension.21 Changes in the neurochemical input into the NTS also may cause hypertension, as, for example, by injecting 6-hydroxydopamine (6-OHDA) into the NTS, which destroys adrenergic innervation, or glutamic acid, a putative neurotransmitter.22

2. Sympathetic Abnormalities in Various Models. Sympathoadrenal system abnormalities have been studied in various models of hypertension:
   a. Genetic Models. In the Dahl salt-sensitive strain of hypertensive rats, sympathetic tone is exaggerated and the baroreceptor reflex is impaired even before the onset of hypertension.24 In the SHR, resetting of baroreceptors may occur early and be partially responsible for hypertension.
   b. Renal, DOCA-Salt Hypertension. Recent evidence indicates that nerves may play a dominant role in these models through activation of renal afferents, through a central mechanism, or through facilitation of norepinephrine release at the adrenergic terminal.25-29
   c. Human Hypertension. Abnormalities of arterial baroreflex control of heart rate have been identified in humans with primary labile hypertension in the early stages of the disease before the onset of stable elevations in arterial pressure,30 raising the provocative question of whether this abnormality is causative or secondary. Sympathetic activity was recorded from peripheral nerves in hypertensive humans, and it was found that electrical activity was sustained despite the elevated arterial pressure,31 in contrast to normotensives in whom the activity was suppressed, with a rise in pressure.

3. Reversal of Hypertension. Neurosurgical and chemical interventions that reduce sympathetic activity also reduce or prevent hypertension:
   a. AV3V Lesions in Rats. Lesions of the anter- ventral portion of the third ventricle (AV3V) in rats may correct or prevent hypertension in various models including the renal and DOCA-salt models, suggesting an important role for a CNS mechanism mediated through this particular region of the anterior hypothalamus.23-24
   b. Sodium Depletion. One of the most effective mechanisms for reducing arterial pressure is sodium depletion. The factors that are involved in this beneficial effect include a reduction of sympathoadrenal drive.35-40
   c. Neurochemical Interventions. Interruption of sympathoadrenal influences with drugs such as propranolol,21 guanethidine, prazocin,24 and clonidine44 may reverse hypertension in a variety of hypertensive states including renovascular and essential hypertension in humans. Even in pheochromocytoma, clonidine, which acts primarily by activating central α2 receptors and lowering sympathetic drive, may reduce arterial pressure without changing the levels of circulating catecholamines.47 This finding suggests a role for the sympathetic nervous system in maintaining the elevated pressure in what appears to be primarily a humorally mediated hypertension. Thus, almost regardless of the primary cause, reduction in sympathetic drive with drugs will correct the hypertension in the majority of clinical or experimental situations.
Abnormal Neurogenic Control in Hypertensive States: Sites and Mechanisms

Sympathetic and parasympathetic neurons in the medulla and spinal cord determine the autonomic activity that regulates the circulation through changes in cardiac output and vascular tone. Output from these neurons is constantly modulated by afferent signals from various sensors throughout the body. The influence of efferent autonomic activity is determined by factors operating at the level of the end-organ and the effector cells. Thus neurogenic abnormalities may originate 1) within the central nervous system; 2) at the level of the efferent pathways, the adrenergic terminal, or the effector cells; and 3) at the level of the afferent or sensory endings where the input into the CNS originates.

Central Cardiovascular Neurons

The central organization of neurons involved in cardiovascular control has been reviewed by Palkovits. They fall into three groups: 1) afferent neurons with sensory endings in various receptor regions and central projections to the NTS; 2) neurons in the NTS that send axons to the hypothalamus and to the preganglionic vagal and sympathetic efferent neurons; and 3) vagal and sympathetic efferent neurons in the medulla and spinal cord that innervate the heart and blood vessels through postganglionic fibers. Neural imbalance at any or all these sites may contribute to hypertension (fig. 2).

The neurons of the NTS in the medulla are probably the most important in the integration of sensory input from various afferent pathways and in the modulation of reflex autonomic cardiovascular, respiratory, and other functions. Cells of the medial part of the NTS, close to the level of the obex, are involved in blood pressure regulation. Impulses originating in arterial or cardiopulmonary baroreceptors travel in glossopharyngeal and vagal afferent fibers with cell bodies in the petrosal and nodose ganglia, which have central processes that terminate in the NTS. The NTS receives input also from the trigeminal, facial, and vestibular cranial nerves; from hypothalamic nuclei such as the paraventricular and supraoptic nuclei, which may contain vasopressin and neurophysin; and from noradrenergic neurons such as the A group of neurons and the locus ceruleus. The NTS neurons are also rich in catecholamines such as dopamine, norepinephrine (NE), and epinephrine, and receive, in addition to adrenergic terminals, other terminals containing substance P, enkephalin, and other peptides. The origin of these terminals is not yet known.

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**Figure 2.** Schematic diagram of central cardiovascular neurons and their connections with afferent pathways originating in various sensory organs. Hypothalamic nuclei, and vagal and sympathetic efferent neurons, supply various effector sites.
The NTS may also be influenced by humoral factors in blood and CSF because of its close vascular and neural connection with the *area postrema*, which is devoid of a blood-brain barrier and is near the ventricular system.\(^{45}\)

Efferent fibers from the NTS project to three groups of neurons: \(^{50}\) 1) the vagal (nucleus ambiguus, dorsal motor vagal nucleus) and sympathetic preganglionic nuclei (the intermediolateral nucleus in the spinal cord) to modulate the autonomic control of the circulation; 2) the other brain-stem nuclei such as the locus ceruleus, the parabrachial nucleus, and the reticular formation; and 3) the higher centers in the forebrain including the hypothalamus and amygdala.

Reis\(^ {41}\) has emphasized the role of CNS structural or biochemical abnormalities in causing acute as well as chronic hypertension. He proposes that a neural imbalance may cause hypertension either by causing excitation of sympathetic neurons or by suppressing an inhibitory influence on sympathetic neurons.

Several experimental observations support the role of brain stem and forebrain or hypothalamic nuclei in hypertension:

**Brain Stem**

**NTS Lesions.** Chronic labile or sustained hypertension was produced in cats and dogs\(^ {61, 62}\) by electrolytic lesions of the NTS, where fibers from arterial baroreceptors and cardiopulmonary vagal afferents terminate.\(^ {58, 59}\) This hypertension is associated with loss of arterial baroreceptor reflexes and normal renin and aldosterone levels,\(^ {62}\) and is reversed by \(\alpha\)-adrenergic blockers and by clonidine,\(^ {44}\) which suppresses sympathetic efferent activity.

**Modification of Neurochemical Input to the NTS or Brain Stem.** Studies of modification of neurochemical input to cardiovascular neurons point to the involvement of adrenergic neurons, glutamic acid, and \(\gamma\)-aminobutyric acid (GABA).

1. **Adrenergic neurons.** Labile hypertension was caused in rats by destroying the central adrenergic pathways to the NTS with local injections of 6-OHDA or with lesions of the A-2 group of neurons located in the dorsal medulla, where some of the adrenergic innervation of the NTS originates.\(^ {81}\) The effectiveness of clonidine, a central \(\alpha_2\) receptor agonist, in reducing sympathetic drive and arterial pressure in various models of hypertensive animals and in humans raises the possibility that a central defect in \(\alpha_2\) receptors may be involved in the pathogenesis of hypertension.

2. **Glutamic acid.** Several neurotransmitters and neuropeptides have been demonstrated in the cell bodies and nerve terminals in the NTS using biochemical and histochemical techniques. It has been proposed that glutamic acid (1-Glu) may be the mediator of baroreflexes in the NTS.\(^ {28}\) It is densely distributed in this area, can be released by electrical stimulation of the central end of the cut vagi, and when administered in very small amounts into the NTS causes hypotension and bradycardia. Injection of larger doses of 1-Glu or its agonist kainic acid into the NTS causes severe hypertension, inhibits baroreflexes, and is believed to block 1-Glu receptors. This suggests that a defect in 1-Glu receptors in the NTS may contribute to central resetting of baroreceptors and to severe hypertension.

3. **GABA \((\gamma\)-aminobutyric acid).** GABA is an inhibitory transmitter found in the spinal cord, nucleus ambiguous, and other more rostral brain areas.\(^ {55, 56}\) Bicuculline, a GABA receptor antagonist, and muscimol, a powerful GABA agonist that binds to central GABA receptors, have been used to evaluate the role of GABA in the regulation of arterial pressure.\(^ {56, 57}\) When the agonist muscimol is administered into the cerebral ventricles in very small doses it causes bradycardia, hypotension, and a decrease in renal sympathetic nerve activity.\(^ {57}\) These effects are reversed by bicuculline. The specificity and potency of the effects suggest that GABA receptors in the region of the forebrain play an important role in central regulation of sympathetic drive. The central pressor action of substance P (a pressor neuropeptide), but not that of angiotension, may be blocked by a GABA derivative (baclofen), supporting the specificity of action of this transmitter.\(^ {58}\) On the other hand, recent studies\(^ {59}\) indicate that GABA may also exert a restraint on vagal neurons in the nucleus ambiguous since direct microinjection of bicuculline (GABA blocker) into this nucleus causes bradycardia and hypotension, which are reversed by the GABA agonist muscimol. The action of muscimol is specific since it does not affect the bradycardia and hypotension caused by clonidine, which activates central \(\alpha_2\) receptors.

It thus appears that GABA inhibits sympathetic outflow when it is released in the forebrain and inhibits parasympathetic outflow when released in the brain stem.

**Forebrain**

**Hypothalamic Stimulation.** Central projections from the NTS to the paraventricular (PAH) and supraoptic nuclei (SON) in the hypothalamus have been demonstrated recently.\(^ {60}\) Stimulation of the carotid sinus nerve activates these hypothalamic units with much greater frequency than stimulation of aortic depressor nerves.\(^ {60}\) In turn, stimulation of PAH and SON increases blood pressure, causes tachycardia, and inhibits the reflex vagal bradycardia elicited by carotid sinus nerve stimulation but not aortic nerve stimulation.\(^ {60}\) These experiments indicate that neurons of the NTS may modulate vagal or sympathetic efferent activity through long bulbar or supra-bulbar tracks that relay in hypothalamic or forebrain structures. Various hypothalamic nuclei may therefore play a role in neurogenic hypertension.

**AV3V Lesions.** Lesions of the anteroventral portion of the third ventricle in the anterior hypothalamus

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reverse, prevent, or delay hypertension in several different models. For example, the lesion is effective in renal hypertension, which may be renin-dependent, as well as in DOCA-salt hypertension, where renin levels are suppressed. It is also effective in one genetic model, the Dahl salt-sensitive strain of rats, but not in another, the SHR. The hypertension and increased sympathetic activity caused by baroreceptor denervation or lesions of the NTS may be significantly attenuated by lesions of AV3V. It appears that AV3V plays a permissive role in the activation of sympathetic neurons in a variety of hypertensive states where either humoral factors, such as angiotension, or neural factors, such as baroreceptor or visceral sensory afferent activity (e.g., renal afferents), may be important. The AV3V region is also involved in the control of drinking, the release of vasopressin, and possibly the release of a natriuretic factor. Its electrical stimulation causes vasodilatation in skeletal muscle, vasocstriction in renal and splanchnic beds, and some bradycardia.

Despite the fact that the effectiveness of the lesion may be limited to certain species (primarily the rat) and the mechanisms involved are not clear, the observations by Brody, Johnson, and their colleagues are valuable in demonstrating that a neurogenic pathway localized to a specific CNS site may be involved in maintaining the elevated arterial pressure in different models of hypertension, emphasizing the critical role of the nervous system in a large variety of hypertensive states either genetic or acquired.

Neuropeptides. Angiotensin, leucine enkephalins, and substance P are some of the neuropeptides present in the medulla, pons, hypothalamus, median eminence, and other areas which contribute to the regulation of arterial pressure. They have been localized by biochemical, histochemical, and immunocytochemical techniques. When injected into the cerebral ventricle they cause hypertension and tachycardia, and inhibit baroreflexes. Their hypertensive effect is caused primarily by increased sympathetic activity. The pressor effect of central angiotensin and leucine-enkephalin may also be dependent on the presence of vasopressin and the release of ACTH and corticosterone contribute to the hypertension.

The spontaneously hypertensive rat (SHR) is particularly sensitive to the central pressor effects of these neuropeptides. Angiotensin is the central neuropeptide that has been studied more thoroughly. Various components of the renin-angiotensin system have been localized in brain nuclei. Renin activity was found to be increased in noradrenergic nuclei of SHR including A-1, A-5, and the NTS. Sensitivity to central angiotensin in SHR may be related to increased receptor density or affinity in the area of the anterior hypothalamus near the AV3V containing the organum vasculosum of the lamina terminals. Central injection of saralasin, the angiotensin receptor blocker, or a converting enzyme inhibitor, lowers blood pressure in SHR.

Efferent Mechanisms, Adrenergic Terminal, and Vascular Muscle

The vasoconstrictor response to sympathetic stimulation is exaggerated in several models of hypertension either because of greater release of the neurotransmitter NE or augmented contractile response of arterial muscle. The following mechanisms may be involved:

Vascular Muscle

Membrane Defect. Abnormalities in active and passive sodium transport have been described in red cells or vascular muscle in various animal models of hypertension and in humans with essential hypertension. Although an integrated scheme for these defects is not yet apparent, the following findings support the concept that increased intracellular sodium may contribute to increased vasoconstriction:

1. Increased cation permeability. Tobian and Binion reported in 1952 increased sodium content of the arterial wall in hypertensive subjects, but the evidence of increased permeability of arterial muscle to cations was reported more than 20 years later in DOCA-salt and genetic hypertension. Several investigators concluded that sodium and/or potassium permeability is increased in red cells of patients with essential hypertension or rats with genetic hypertension.

Red blood cells from hypertensive humans exhibit increased sodium influx that correlates with arterial pressure. Friedman et al. showed increased passive permeability to sodium and lithium in red cells of SHR. Postnov et al. reported a ouabain-resistant increase in rate constant of sodium efflux from red cells of hypertensive humans and increased permeability of both sodium and potassium from red cells of SHR.

Similar data by Wiley et al. indicate increased permeability to sodium in erythrocytes from SHR but not from a genetically hypertensive New Zealand strain or from renal hypertensive rats.

2. Na-K cotransport system. The Na-K pump regulates Na efflux and K influx so that the ratio Na efflux/K influx equals 1.5. Garay and Meyer have reported that in erythrocytes from healthy donors this ratio is exceeded whereas in essential hypertensive patients this ratio is closer to 1.5. They proposed that a Na-K cotransport system which is not sensitive to ouabain extrudes both internal Na and K and causes the increased ratio of Na efflux/K influx. This pump-independent Na extru-
sion mechanism is similar to that described in human erythrocytes and is inhibited by adding furosemide or by ATP depletion. Garay et al. and DeMendonca et al. demonstrated that this Na⁺-K⁺-cotransport system is suppressed in essential hypertensive patients, in normotensives with a family history of hypertension, and in several varieties of genetically hypertensive rats. If such a defect were present in vascular muscle, it could contribute to increased intracellular sodium and increased vascular resistance.

3. Na-Li countertransport system. Canessa et al. reported that another transport system for sodium that is not sensitive to either ouabain or furosemide is enhanced in red cells of patients with essential hypertension. After loading the cells with lithium, the rate of lithium efflux in exchange for extracellular sodium was significantly increased in cells from hypertensive subjects. In the physiologic milieu, the Na⁺-Li⁺ countertransport system may function as a Na⁺-Na⁺ or a Na⁺-proton exchange system. The relation of this transport system to hypertension is not clear.

4. Na⁺-K⁺ pump activity. The Na⁺-K⁺ ATPase in the cell membrane is responsible for active efflux of Na⁺ and influx of K⁺ resulting in repolarization of the cell. Ouabain, low K⁺, and low temperature suppress the activity of this pump. Ouabain-sensitive rubidium uptake by vascular tissue has been used as an index of Na⁺-K⁺ ATPase pump activity in vascular muscle. Haddy's comprehensive review on the role of this pump in hypertensive humans and animals makes several important points:

a. The pump is electrogenic in vascular muscle and its suppression leads to greater constriction as a result of partial depolarization of the membrane.

b. Suppression of the pump may also lead to greater contraction by virtue of the resulting high intracellular sodium which reduces the electrochemical gradient for sodium, leading to a high intracellular calcium through a Na⁺-Ca²⁺ exchange mechanism.

c. Humoral factors related to renal hypertension or excessive sodium intake, possibly the "natriuretic factor," may suppress the Na⁺-K⁺ pump. It has been demonstrated that in models of renal hypertension with reduced renal mass the Na⁺-K⁺ pump is suppressed.

d. Conversely, in SHR and the Dahl salt-sensitive strain of rats, the activity of the pump may be enhanced but this enhancement may reflect an increase in pump activity in an attempt to compensate for a genetic defect in membrane permeability to sodium and potassium. The increased pump activity may be insufficient to reduce the high intracellular sodium and to increase the transmembrane potential to normal levels.

Sympathetic Nerves and the Genetic Defect in Vascular Permeability to Sodium. The work of Hermosy and Campbell et al. raises the intriguing possibility that the abnormality in membrane permeability of arterial muscle in a genetic type of hypertension (SHR) may be triggered by the nervous system. These investigators noted that membrane permeability of arteor muscle from the caudal artery is reduced in SHR at 16°C (when electrogenesis of the Na⁺-K⁺ pump is suppressed by cold temperature) or with NE, reflecting the greater passive permeability to cations reported by others. When the caudal artery of a 2-week-old control (WKY) or SHR rat was transplanted into the anterior eye chamber of the opposite host, the vascular muscle in the transplant acquired the membrane characteristics of the host as long as innervation of the transplant was not interrupted. Denervation by superior cervical ganglionectomy or transplantation of arteries from older rats prevented the transplant from acquiring the characteristics of the host. Thus, a trophic sympathetic influence exists in the genetically hypertensive rats that triggers a membrane abnormality in vascular muscle leading to hyperactivity, increased permeability, a reduction in membrane potential, exaggerated vasoconstriction, and hypertension.

Sympathetic Nerves and Hypertrophy of Vascular Muscle. Sympathetic denervation reduces the rate of thymidine incorporation in vascular muscle, the rate of growth and hypertrophy with age, and the wall-to-lumen ratio of vessels. Sadoshima et al. and Hart et al. have shown that in stroke-prone hypertensive rats unilateral superior cervical ganglionectomy reduces the wall-to-lumen ratio of vessels on the ipsilateral side of the brain as compared to those of the contralateral side, despite the fact that vessels on both sides of the brain are exposed to equally high arterial pressure (fig. 3). This trophic influence of symp-

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**FIGURE 3.** The wall/lumen ratio of blood vessels in the denervated cerebral hemisphere (SHR-D) is significantly less than in the innervated hemisphere (SHR-I) in spontaneously hypertensive stroke-prone rats. WKY are the normotensive control Wistar Kyoto rats (from Hart et al., ref 20, by permission of authors and publisher).
pathetic nerves may contribute to the high vascular resistance and augmented vasoconstrictor responses. In cerebral vessels, however, the vascular hypertrophy may infer a protective influence against strokes and cerebral edema.14

**cAMP-Protein Kinase in Vascular Muscle.** cAMP-dependent protein kinase is reduced in vascular muscle from the caudal artery of SHR.84 and the affinity of sarcoplasmic reticulum for Ca**++** may also be reduced.85,97 This mechanism could account in part for increased vasoconstrictor responses in SHR.

**Adrenergic Terminal**

Exaggerated responses may be related to pre- or postjunctival receptors.

**Decreased Presynaptic** α<sub>2</sub> **Receptors.** These are activated by the neuronally released neurotransmitter, and their activation suppresses further release, thus serving a negative feed-back mechanism (fig. 4). Reduction in the number of these receptors results in augmented release of NE upon nerve stimulation. In SHR as well as in the Dahl salt-sensitive rats fed high salt,85 the ratio of the vasoconstrictor response to electrical nerve stimulation to the response caused by intraarterial NE is greater than the ratio observed in control WKY or Dahl S rats on low salt. The exaggerated neurogenic responses may represent facilitated release of the neurotransmitter compatible with the notion of reduced presynaptic α<sub>2</sub> receptors. There are data that indicate that dehydroergocryptine (an α<sub>2</sub> antagonist) binding is reduced in the myocardium of renal hypertensive rats.90

**Decreased Parasympathetic Inhibition of Nor-epinephrine Release.** Activation of presynaptic muscarinic receptors may inhibit the release of NE upon stimulation of sympathetic nerves. The increased circulating levels of NE in human essential hypertension101,100 may therefore be related to decreased parasympathetic activity.101,102 In a recent study, de Champlain et al.100 demonstrated that muscarinic blockade with atropine enhanced the NE response to postural change in those hypertensives who had a normal NE response but did not alter the response in those who had exaggerated NE levels with standing.

**Effect of the Na<sup>+</sup>-K<sup>+</sup> Pump on Norepinephrine Release.** Suppression of the Na<sup>+</sup>-K<sup>+</sup> pump in the adrenergic terminal by ouabain or possibly by excessive sodium intake facilitates the release of NE from nerve terminals.104 Conversely, sodium depletion may suppress the release of neuronal NE.10,94 We have observed in normal subjects that infusion of high sodium, isoosmotic solutions into the brachial artery caused the release of K<sup>+</sup> from the forearm and caused a relatively greater augmentation of the vasoconstrictor response to lower body negative pressure (reflex neurogenic vasoconstriction) than to intraarterial NE, suggesting greater release of NE from nerve terminals.10,94 In some hypertensive individuals, the increased circulating levels of NE may be related to a suppressed Na<sup>+</sup>-K<sup>+</sup> pump.104 Furthermore, excessive sodium intake may facilitate neurogenic vasoconstriction in animals or humans who have a genetic predisposition to hypertension.14,10,97 Possibly through inhibition of the Na<sup>+</sup>-K<sup>+</sup> pump in adrenergic terminals,104

**Increased Postjunctional** α<sub>1</sub> **Receptors.** Increased vascular reactivity to adrenergic stimuli at the adrenergic terminal may be caused by increased number of α<sub>1</sub> or α<sub>2</sub> postjunctival receptors. It is proposed that the α<sub>1</sub> receptors mediate neurogenic responses, whereas both the α<sub>1</sub> and α<sub>2</sub> postjunctival receptors mediate humoral responses.106 The intraarterial injection of prazocin (a specific α<sub>1</sub> blocker) into the brachial artery of patients with essential hypertension causes greater vasodilatation of forearm vessels than in normotensive subjects (fig. 5).48 The vasodilator response to nitroglycerin was equivalent in both groups. The results suggest that α<sub>1</sub>-mediated vasoconstrictor tone is increased in hypertension.

**Afferent or Sensory Input into the Central Nervous System**

The activity of neurons in the NTS is modulated by peripheral impulses arising from sensory receptors in the cardiovascular system, such as the arterial baroreceptors, the cardiopulmonary receptors and the chemoreceptors; in skeletal muscle and skin, such as the somatic or ergoreceptors; and in viscerae, such as liver and kidney. These impulses regulate arterial pressure, blood gases, and blood flow to various organs. The extent to which they cause or sustain hypertension is not clear.

Three aspects of these afferent impulses are reviewed here: 1) the mechanisms involved in arterial baroreflex control of heart rate and peripheral
vascular resistance in hypertensives; 2) the protective role of cardiopulmonary baroreceptors that may cause a decrease in vascular resistance in the early phases of hypertension; and 3) the role of afferent renal nerve activity that may contribute a neurogenic element to renal hypertension.

Arterial Baroreceptors

Decreased sensory input from the carotid sinus and aortic depressor nerves increases sympathetic drive and causes labile or sustained hypertension. The unanswered question, however, is whether impaired input from baroreceptors is a causative factor, i.e., important for the initiation rather than simply the maintenance of elevated pressure. An excellent brief review on the subject of receptors under pressure has recently been published by Brown.8

Early Impairment or Resetting of Baroreceptors. Arterial baroreceptors are reset in hypertension; they have higher pressure threshold and reduced sensitivity to increases in pressure. This resetting is caused, at least in part, by changes in arterial distensibility secondary to the elevated arterial pressure. Krieger8 demonstrated that resetting occurs also acutely, within hours after elevation of arterial pressure, and is reversible.

There is a possibility that resetting might occur before the onset of hypertension. Data from four separate experiments suggest that an abnormal baroreflex may precede or coincide with the onset of mild hypertension. In the early stages of hypertension, in SHR at 10 weeks of age, the strain-sensitivity of aortic baroreceptors is significantly reduced compared to normotensive rats. The Dahl salt-sensitive rats have impaired baroreflexes on low sodium intake in the absence of hypertension (fig. 6). Partial resetting of baroreceptors may occur in the absence of structural vascular changes, and a significant impairment of baroreflexes may occur in the very early stages of labile essential human hypertension.

Change in Strain-Sensitivity of Baroreceptors. In the absence of changes in distensibility, several mechanisms may be involved in the decreased strain-sensitivity of baroreceptors that could cause a reflex increase in vascular resistance.

1. Membrane defect. The phase of postexcitatory depression of the baroreceptor discharge following a step input of pressure may be ascribed to increased Na⁺-K⁺ ATPase in membranes of the stretch receptors. We have discussed earlier the fact that a membrane defect is present in vascular muscle and red cells of SHR and of hypertensive humans whereby the permeability to Na⁺ and K⁺ increases, intracellular sodium content rises, and electrogenic Na⁺ pump activity increases. Such a membrane defect could decrease the rate of firing of baroreceptors by enhancing the postexcitatory depression. It is known, for example, that ouabain, which inhibits Na⁺-K⁺ ATPase, increases the sensitivity of baroreceptors causing reflex vasodilation and bradycardia.

2. Sensitivity to cations. Reduction in [Na⁺] or increase in [Ca²⁺] elevates the threshold and decreases the sensitivity of baroreceptors. Conversely, increase in [K⁺] may reduce the threshold. The ionic sensitivity of baroreceptors may be altered in hypertensive animals.

3. Myelinated vs unmyelinated fibers. Although there are more unmyelinated fibers in baroreceptors, they have a higher threshold, discharge irregularly, and contribute less input into the CNS than the myelinated. In hypertension, however, the unmyelinated bundles provide a relatively larger share of the input, as the myelinated fibers are reset more readily.
4. Sympathetic modulation. There is evidence that NE or sympathetic stimulation may increase baroreceptor sensitivity (fig. 7). Additional work is necessary, however, because of the complexity and technical difficulties of such studies.\textsuperscript{131, 132}

Central Resetting. Baroreflexes may be impaired because of a change in the input from various neuronal groups to the NTS or to other CNS nuclei and pathways because of variations in neuropeptides or neurotransmitters. For example, angiotensin, leucine enkephalin, and substance P, which cause hypertension, also suppress baroreflexes.\textsuperscript{87} Lesions of the A-2 group of adrenergic neurons that supply the NTS cause labile hypertension and also selectively inhibit

**Figure 6.** Baroreflex control of heart rate is reduced in Dahl salt-sensitive rats (S Rats) compared to salt-resistant rats (R Rats), even when they are kept on a low sodium diet and in the absence of hypertension (left panel) as compared to a high sodium diet (right panel) (from Gordon et al., ref 25, by permission of author and publisher).

**Figure 7.** Left carotid sinus nerve activity decreases despite a constant distending volume and pressure in the carotid sinus (Left CSP) during distension of the right carotid sinus. Decreased sympathetic activity to the left carotid sinus region is probably the cause of the reduced sensitivity (from Felder RB, Thames MD, Fed Proc 41: 1514, by permission of the authors).
the reflex bradycardia during activation of the arterial baroreceptors. Stimulation of the paraventricular and supraoptic nuclei in the hypothalamus causes hypertension and tachycardia, and inhibits reflex bradycardia caused by carotid nerve stimulation, but not by aortic nerve stimulation.16, 40

Propranolol and clonidine may lower arterial pressure through a central nervous system action. Propranolol, which blocks receptors and clonidine, which activates adrenergic α receptors, inhibit sympathetic drive and may restore baroreceptor sensitivity in hypertension (fig. 8).41 Similarly, during low sodium intake, CNS concentrations of NE increase, and this may contribute to central inhibition of sympathetic activity and discharge.40

**Differential Control of Heart Rate and Resistance in Hypertension.** Most of the information available in the literature concerning baroreflex control of the circulation has been based on studies of reflex changes in heart rate in response to increases or decreases in arterial pressure with intravenous phenylephrine or nitroglycerin. In some studies in humans, responses to changes in transmural pressure of the neck (neck suction or neck pressure) to activate or unload the carotid sinus baroreceptors indicate that changes in peripheral resistance as well as cardiac output may play a significant role.42-44 The results are not consistent, however. Some studies indicate that changes in cardiac output are predominant44 while in others changes in total resistance are more evident.128, 129

In a series of recent studies, we contrasted systematically baroreflex control of heart rate and vascular resistance in normotensive and hypertensive rabbits. The data indicate that in hypertensive rabbits baroreflex control of heart rate is impaired whereas baroreflex control of vascular resistance is preserved or augmented. These findings require reassessment of the role of arterial baroreceptors in the pathogenesis of hypertension and other pathological states where conclusions are based on changes in heart rate exclusively.

1. **Experimental preparation and results.** The reason why baroreflex control of rate is reported much more frequently than baroreflex control of resistance is the simplicity of the measurement, particularly in awake animals and humans. Phenylephrine or nitroglycerin are given intravenously and the reflex change in rate corresponding to a change in pressure is described. Because these drugs have direct vascular effects one cannot examine reflex changes in resistance simultaneously.

We examined reflex changes in vascular resistance in rabbits by perfusing the hindlimb with a pump that maintains blood flow at a constant rate. We interposed along the pump a delay coil to prevent the arrival of phenylephrine or nitroglycerin to the hindlimb vessels until the peak reflex response had been noted (fig. 9). When a bolus of phenylephrine is given intravenously, blood pressure goes up and reflex vasodilatation can be seen before the drug reaches the hindlimb. Reflex responses were studied in renal hypertensive rabbits (unilateral nephrectomy and cellophane wrap of the remaining kidney). Since changes in vascular resistance in hypertensive and normotensive rabbits are difficult to compare because of the high baseline vascular resistance in the hypertensives, we also measured reflex changes in lumbar sympathetic nerve activity.

In hypertensives, baroreflex control of heart rate was impaired both in the awake and in the anesthetized state, whereas baroreflex control of vascular resistance was not only preserved but was enhanced (fig. 10). After normalization of the change in resistance based on the higher baseline resistance in hypertensives, the responses were similar in both groups. Furthermore, the changes in lumbar sympathetic activity were also similar in both groups.

There are many studies that show resetting of arterial baroreceptors in renal hypertension after a few weeks of elevated blood pressure. Why does this resetting affect the control of heart rate but not the control of vascular resistance or lumbar sympathetic activity?

It is interesting that, in normotensive rabbits, a differential control of rate and resistance may be demonstrated after partial denervation of the arterial baroreceptors (either by section of the carotid sinus nerves or the aortic depressor nerves) (fig. 11). The parasympathetic control of heart rate is impaired by partial denervation of baroreceptor afferents whereas the sympathetic control of resistance is preserved. A careful analysis of these responses in normotensives after partial baroreceptor denervation and vagotomy allowed us to conclude that there is no "redundancy" or "overlap" in the control of vagal neurons by aortic and carotid baroreceptors whereas there is significant

![Figure 8](https://example.com/fig8.png)
"redundancy" or "overlap" in the control of sympathetic neurons (fig. 12).137 Because of these findings, the suppression of reflex control of rate but not of resistance in hypertensives may be explained on the basis of the decline in sensitivity of arterial baroreceptors.

2. Central control in hypertensives. We also examined the possibility of a central dissociation between the control of rate and lumbar sympathetic activity in hypertensives by stimulating electrically the central end of one aortic depressor nerve in rabbits that had both vagi cut, the carotid sinuses denervated, and both aortic depressor nerves cut. Reflex responses were equivalent in the normotensive and hypertensive groups. Thus, there was no evidence of an abnormality in the central control of heart rate or lumbar sympathetic activity in response to stimulation of the inhibitory aortic depressor nerve in hypertensive animals. It is possible, however, that a difference

![Figure 9](image_url)

**Figure 9.** Baroreflex = mean vascular resistance. Schematic diagram of perfusion system and reflex responses to intravenous phenylephrine. The vertical lines indicate the period during which the response of the hindlimb is of reflex origin. Delay circuit is approximately 45 seconds (from Guo et al., ref 127, by permission of publisher).

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![Figure 10](image_url)

**Figure 10.** Panel A. Baroreflex control of heart rate is impaired in hypertensive rabbits (HT) as compared to normotensives (NT). Panels B and C. Baroreflex control of vascular resistance is preserved in HT. Asterisks indicate a significant difference in slopes (p < 0.05).
Sympathetic System in Hypertension

Normotensive rabbits after partial denervation behave like hypertensive rabbits before denervation. Solid line = before denervation; dashed line = after denervation.

The most important finding, in these studies, is that there is preservation of reflex control of vascular resistance in hypertensive animals at a time when reflex control of heart rate is impaired. Thus, on the basis of an evaluation of reflex control of heart rate alone, one cannot predict what is happening to the baroreceptor control of the total circulation. Furthermore, preservation of reflex control of vascular resistance minimizes the role of arterial baroreceptors in maintaining a high vascular resistance in hypertensive animals, assuming, of course, that the baroreflex control of other vascular beds besides the hindlimb is preserved in this model of hypertension as well as in others. This assumption should be tested experimentally. It is of interest, however, that in a study of the carotid baroreflex in hypertensive humans the baroreflex control of total peripheral resistance appeared preserved or even augmented.

Cardiac Sensory Receptors in Hypertension

Whereas the role of arterial baroreceptors in the control of the circulation has been examined for decades, that of the sensory endings in the heart has not been appreciated fully, either in physiologic or pathologic states. These endings may modulate sympathetic tone and neurohumoral drive to the circulation in important ways. They may be activated chemically or mechanically with veratridine or nicotine, during coronary ischemia or volume expansion, and during vigorous cardiac contractions. Their activation not only suppresses sympathetic drive but also changes the gain of the arterial baroreceptors such that, during carotid hypotension for example, the anticipated increase in sympathetic activity is suppressed when cardiac afferent activity is increased and vice versa.

Interaction Between Cardiac Sensory Receptors and Arterial Baroreceptors. We isolated the carotid sinuses and connected them to a pressure reservoir containing Krebs solution. This allowed us to maintain carotid pressure at the desired level. The effect of changes in carotid sinus pressure on renal nerve activity was examined. Input from the cardiac afferents was either increased (by occluding the circumflex artery or with volume expansion) or decreased (by cooling or sectioning the vagi), and the baroreflex was studied under each condition. The results indicate that the gain of the arterial baroreflex is inversely related to the vagal afferent input from cardiac or cardiopulmonary receptors (fig. 13).

Between responses of normotensive and hypertensive animals might be seen if more than one inhibitory afferent input is stimulated since the pattern of summation of afferent impulses may vary in normotensives and hypertensives. This is currently being examined.

Figure 11. Diagram showing the effect of partial denervation of baroreceptors on baroreflex control of heart rate and vascular resistance in normotensive and hypertensive rabbits (based on results obtained in our laboratories: Guo, Thames, and Abboud). Note that normotensive rabbits after partial denervation behave like hypertensive rabbits before denervation. Solid line = before denervation; dashed line = after denervation.

Figure 12. Schematic representation of lack of “redundancy” in control of vagal neurons by carotid and aortic afferents and “redundancy” in the control of sympathetic neurons. This might explain the differential control of rate and resistance in hypertensives with intact afferents and in normotensives with partial denervation.
Protective Effect of Increased Cardiac Afferent Activity in Early Human Hypertension. To study the role of cardiac afferents in humans, we pooled blood in the lower extremities with a "lower body negative pressure box." This unloaded the cardiac receptors and decreased their sensory input, resulting in reflex vasoconstriction. At -10 mm Hg pressure in the box, central venous pressure declined without a change in arterial pressure; the reflex vasoconstriction may be attributed to unloading of cardiac and not arterial baroreceptors. Conversely, the release of negative pressure from the box distended the heart abruptly and increased the sensory input, resulting in reflex vasodilatation. If the resting cardiac sensory afferent activity is increased, one would expect that lower body negative pressure would cause a greater vasoconstriction.

An important question is: In hypertensive humans, is the activity of cardiac afferents increased, thus suppressing sympathetic tone, or decreased, thus contributing to a high sympathetic drive and resistance? The results indicate that lower body negative pressure caused greater vasoconstriction in patients with borderline hypertension than in the normotensive subjects (fig. 14). This effect could not be ascribed to increased vascular reactivity. Thus, in the supine position, cardiac afferent activity is increased in borderline hypertension, suppressing in part the sympathetic drive and providing a "protective" compensatory effect, which may offset the influence of impaired arterial baroreceptor activity on vascular resistance. In the upright position, on the other hand, just as during lower body negative pressure, the sympathoadrenal drive may be excessive. As a corollary, renin levels are reported to increase markedly in the upright position in patients with borderline hypertension in contrast to normotensives.

Decreased Cardiac Afferent Activity in Animal Models of Hypertension. What happens in late stages of hypertension after cardiac hypertrophy may be different. The sensitivity of cardiac sensory afferents may decrease, causing a high level of sympathetic drive. Kezdi and Thoren et al. have shown that, in renal as well as genetic (SHR) models of hypertension, activity of sensory cardiac C fibers is decreased during either transient aortic occlusion or volume expansion. This results in lesser inhibition of renal sympathetic activity and lesser natriuresis and diuresis for equivalent increases in left atrial pressure. On the other hand, volume expansion may cause a greater rise in left atrial pressure in SHR than WKY because of decreased compliance of capacitance vessels. The greater rise in left atrial pressure may cause greater activation of cardiac afferents despite their higher threshold, resulting in greater reflex inhibition of sympathetic efferents.

Sodium Restriction and Increased Cardiac Afferent Activity. The hypertensive effect of sodium depletion has been recently ascribed in part to an increase in cardiac sensory activity. This is based on a study of the baroreflex control of renal nerve activity during changes in arterial pressure with phenylephrine or nitroprusside in dogs that had been treated with a low sodium diet for a period of 3 weeks, in contrast to normal dogs. In the dogs with restricted sodium intake, there is greater suppression of renal nerve activity when arterial pressure increases, and lesser increase in renal nerve activity when arterial pressure falls.

![Figure 13](https://example.com/figure13.png)

**Figure 13.** Carotid baroreflex control of renal nerve activity decreased during transient occlusion of the circumflex coronary artery and increased markedly following bilateral vagotomy. This establishes the importance of cardiac sensory input in the modulation of the arterial baroreflex (see ref 135).

![Figure 14](https://example.com/figure14.png)

**Figure 14.** Withdrawal of the inhibitory influence of cardiac afferents with lower body negative pressure (LBNP) causes a greater augmentation of forearm vascular resistance in borderline hypertensives than in normotensives (see refs 137 and 138; adapted from Mark and Kerber, ref 138, by permission of author and publisher).
Following section of both vagi, reflex changes in renal nerve activity are equivalent in both groups of animals. The suppression of renal nerve activity with sodium deprivation was thus ascribed to increased vagal sensory afferent activity during low sodium intake. This may have been related to a relative increase in central blood volume despite a decline in total blood volume during sodium restriction.141

To summarize, the cardiac afferents may play an important role in inhibiting neurohumoral drive when patients with borderline hypertension are placed in the supine position (fig. 15). The supine position causes cardiac distension and activation of these nerve endings. Similarly, a low sodium diet may increase their activity. During the late stages of hypertension and left ventricular hypertrophy, decreased activity of these sensory endings may contribute to the high sympathetic tone, increased vascular resistance, and greater sodium retention.

Responses to electrical stimulation of renal afferents and to the activation of these afferents by changes in renal perfusion pressure, oxygen tension, and sodium handling144 suggest that the kidney is a sensory organ capable of transmitting neural signals to the central nervous system. Activation of these nerves give hemodynamic effects that are similar to those seen during stimulation of the AV3V region,146 i.e., renal and mesenteric vasoconstriction and dilatation of the hindlimb. Central projection of renal afferents may be to the hypothalamus.146

Thus, an important trigger mechanism for the development of renal hypertension or the maintenance of other types of hypertension may be the activation of sensory neural signals projecting to the brain from the kidney.

**Summary**

One may postulate a genetic defect in membrane permeability, in the transport of sodium, or in the sodium pump in vascular muscle which could account for increased intracellular sodium and enhanced vascular contractility. If the electrogenic sodium pump is overactive, as in SHR, its inhibition may lead to significant depolarization and greater contraction. Sympathetic innervation may be essential for the development of membrane abnormality as well as for the development of hypertrophic vascular changes, both of which augment contraction and vascular tone.

**Role of Renal Afferents in Hypertension**

An increase in renal afferent activity has been implicated in the maintenance of high sympathetic tone in certain types of renal hypertension and even in SHR. The work of Katholi et al.146 in both renal and DOCA salt hypertension and of Winternitz et al.148 in SHR suggests that renal denervation may reduce arterial blood pressure because of interruption of the afferent neural influence on sympathetic tone, rather than through a direct effect on sodium and water handling by the kidney.147
A similar membrane defect at the sensory endings of arterial stretch receptors may account for impaired arterial baroreceptor reflexes seen in very early phases of hypertension or, in some genetic models, before hypertension develops. This defect may be related to the sodium pump or sodium transport in the receptor region and cause a decrease in baroreceptor discharge and in the strain-sensitivity of the baroreceptors, resulting in exaggerated sympathetic drive. Further information is needed on the baroreflex control of various efferent in hypertension. Another membrane defect at the adrenergic nerve terminals may facilitate release of endogenous NE. Excessive salt intake may unmask or exaggerate the membrane defects. In the central nervous system a defect in glutamine, NE, or GABA receptors may contribute to a high central sympathetic drive. Greater receptor affinity to various pressor neuropeptides such as angiotensin and leucine enkephalin or greater release of these peptides may also account for the excessive CNS sympathetic activation or impairment of baroreflexes at a central level. Cardiac receptors may have a variable influence on sympathetic drive in the various stages of hypertension, depending on the degree of cardiac hypertrophy or cardiac size. Finally, increased renal afferent nerve activity may provoke an increase in sympathetic activity and provide a link between natriuretic factors and the sympathetic nervous system in hypertension.

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