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Invited Editorial

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ESSENTIAL HYPERTENSION:
IS IT ALL IN THE BRAIN?

After a century of work on high blood pressure, do we understand it? In part, yes. Most of us agree—as a prejudiced observer I would rather say, admit—that essential hypertension mainly derives from the brain. In their Lead Article, Julian Paton and Mohan Raizada concentrate on the rat. Why does an animal model of hypertension created by selective inbreeding seem to have especially involved the brain’s blood supply? The arteries of the brainstem in spontaneous hypertensive rats (SHRs, developed by Aoki and Okamoto) are much smaller than those in the Wistar-Kyoto rats from which SHRs were derived. The arterial endothelium in SHRs appears to be unduly sticky. It encourages dense leukocyte adhesion that may restrict blood flow and compromise oxygen delivery to important nuclei. These include the nuclei of the solitary tracts, which (in humans) lie in the floor of the 4th ventricle at the level of the obex. There, they receive afferent nerve impulses from the arterial baroreceptors and connect with inhibitory caudal medullary nuclei. The latter have connections with rostral ventrolateral medullary nuclei whose activity increases when inhibition is withdrawn. A comparable complicated reciprocal system presumably underlies the human “baroreflex” relating arterial pressure inversely to heart rate.

The invited Discussants of our Dialogue concur that essential hypertension is initiated and sustained by the sympathetic nervous system. Murray Esler and Elisabeth Lambert demonstrate that fat and thin essential hypertensive individuals have different patterns of sympathetic nervous system activity, which need to be taken into account when deciding on treatment. Guido Grassi pays special attention to increased insulin resistance, which may accompany, and perhaps cause, increased sympathetic nervous system activity: or is it the other way around? Vito Campese and his colleagues suggest that in chronic renal failure, afferent nerve impulses from injured kidneys may activate the sympathetic nervous system and raise blood pressure.

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I am delighted that Patrice Guyenet regards as seminal Harvey Cushing’s century-old paper quantifying the relation between brainstem compression and the resultant blood pressure elevation, and that the work has a “considerable following.” Arthur Guyton recognized the “Cushing response” as immensely powerful, but he regarded it only as a “last ditch” protection for an ischemic brain. But Patrice is also the co-author of a chapter in a 1985 book that emphasized the “critical importance of employing conscious unrestrained animals in studies of cardiovascular regulation.” General anesthesia makes all the difference, as Jim McCubbin and I showed in Cleveland 45 years ago. Also, in unanesthetized fetal sheep in utero, blood pressure accurately follows induced elevations of cerebrospinal fluid (CSF) pressure. There have been relevant human observations, eg, a 33-year-old woman unconscious from a subarachnoid hemorrhage in whom each repeated spontaneous elevation in CSF pressure produced an exactly corresponding elevation in blood pressure 20 seconds later.

So do I think that essential hypertensives get cerebral ischemia? Yes I do—but only in a restricted sense. When any of us rest or sleep and our blood pressure falls to a basal level, I have suggested that any further fall is arrested as soon as the brainstem detects the approach of unfavorable perfusion conditions. Basal elevations of blood pressure determine the pattern of blood pressure behavior later in the day, as a superb Japanese community-based study showed.

Kety and his colleagues found that cerebral blood flow was normal in essential hypertension. But a few weeks after one kidney has been removed from a dog and stable hypertension has been established by inducing perinephritis or by using a constricting Goldblatt clamp on the main renal artery, renal blood flow returns to its original level even though the hypertension persists. So the normality of cerebral blood flow in essential hypertension is not a good reason to reject increased proximal cerebral arterial resistance as a cause of raised blood pressure. Unless you have examined the main cerebral arteries in the neck and skull base of nearly 100 human cadavers (as Drew Thomson and I did long ago), you may not appreciate the extent to which these large arteries can be narrowed or even occluded by atheromatous deposits.

Although my interpretation of the etiology of essential hypertension is fiercely disputed, it has two merits. It explains why there is no natural animal model for essential hypertension, apart from models involving the use of selective inbreeding or cholesterol feeding. And invoking a structural etiology also explains why prolonged (6-year) hypotensive drug treatment of essential hypertensives in a large study had no lasting effect on blood pressure, which reverted to its original value soon after the drug treatment was withdrawn. Should we perhaps pay as much attention to preventing or reversing the stenotic atheromatous disease of our patients’ large cerebral arteries as we do to lowering their blood pressure with drugs?
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Hypertension is universally defined as a blood pressure greater than 140/90 mm Hg. It is the world’s biggest “silent killer,” yet in 95% of patients hypertension remains idiopathic (ie, primary or essential hypertension). Primary hypertension now affects around 970 million people worldwide and in many cases it has an underlying neurogenic component. It is well established that primary hypertension increases the risk of stroke, renal failure, endothelial dysfunction, and coronary heart disease. Within the UK and USA, 1 in 3 males and females will develop essential hypertension at some stage of their lives (www.heartstats.org; www.americanheart.org). A remarkable statistic is that 59% of British hypertensive patients taking antihypertensive medication remain hypertensive (www.heartstats.org). A similar figure, of around 50%, was reported for patients in the USA.¹ This suggests unambiguously a major requirement for gaining further insight into the pathophysiological changes that occur with primary hypertension. Indeed, Mann has stated that “… pathologies exist other than with blood volume and peripheral renin angiotensin system” and that “There is a need for further research attention to consider neurogenically mediated hypertension.”¹

With the majority of hypertensive patients on medication remaining hypertensive, new targets and a better understanding of blood pressure control are required. We believe an effective strategy would be to better understand central nervous control of circulation. We highlight progress in our understanding of brain control of cardiovascular autonomic outflows in homeostatic regulation of circulation, and the changes that occur with hypertension. We review evidence that correlates alterations of cardiovascular autonomic activity with the development of hypertension in animal models and humans. We comment on the response of the autonomic nervous system and its reflex control in hypertensives after exposure to antihypertensive agents. We address the possibility of a causative role of the autonomic nervous system in the development of hypertension. We summarize possible central nervous system mechanisms that may underpin the development and maintenance of high blood pressure. As some antihypertensive agents interfere with the renin-angiotensin system, and may cross the blood-brain barrier, our attention focuses on central angiotensin II type 1 receptor–mediated intracellular signaling. Based on recent data, we conclude with a novel hypothesis for the etiology of hypertension that is consistent with the historical viewpoint of Cushing.

Keywords: brainstem; autonomic nervous system; sympathetic; heart rate variability; baroreceptor reflex; set point; endothelial nitric oxide synthase; endothelial dysfunction

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SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tr>
<td>Ang II</td>
<td>angiotensin II</td>
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<td>AT1, R</td>
<td>angiotensin II type 1 receptor</td>
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<td>CVLM</td>
<td>caudal ventrolateral medulla</td>
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<tr>
<td>eNOS</td>
<td>endothelial nitric oxide synthase</td>
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<td>GABA</td>
<td>gamma-aminobutyric acid</td>
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<td>NTS</td>
<td>nucleus of the solitary tract (nucleus tractus solitarius)</td>
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<td>RVLM</td>
<td>rostral ventrolateral medulla</td>
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<tr>
<td>SHR</td>
<td>spontaneously hypertensive rats</td>
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<tr>
<td>THM</td>
<td>Traub-Hering-Mayer (wave)</td>
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Hypertension is universally defined as a blood pressure greater than 140/90 mm Hg. It is the world’s biggest “silent killer,” yet in 95% of patients hypertension remains idiopathic (ie, primary or essential hypertension). Primary hypertension now affects around 970 million people worldwide and in many cases it has an underlying neurogenic component. It is well established that primary hypertension increases the risk of stroke, renal failure, endothelial dysfunction, and coronary heart disease. Within the UK and USA, 1 in 3 males and females will develop essential hypertension at some stage of their lives (www.heartstats.org; www.americanheart.org). A remarkable statistic is that 59% of British hypertensive patients taking antihypertensive medication remain hypertensive (www.heartstats.org). A similar figure, of around 50%, was reported for patients in the USA.¹ This suggests unambiguously a major requirement for gaining further insight into the pathophysiological changes that occur with primary hypertension. Indeed, Mann has stated that “… pathologies exist other than with blood volume and peripheral renin angiotensin system” and that “There is a need for further research attention to consider neurogenically mediated hypertension.”¹
In primary hypertension, but also other diseases (such as diabetes, obesity, and the metabolic syndrome), sympathetic nerve activity is also raised. Therefore, it is necessary to review our current understanding of the central nervous regulation of the cardiovascular system as well as the evidence that indicates its dysfunction in primary hypertension, in both animal models and hypertensive humans.

**THE OVERALL AIM OF CENTRAL NERVOUS CONTROL OF THE CARDIOVASCULAR SYSTEM**

The cardiovascular system has a major role in homeostasis that is achieved by adjusting blood flow to different vascular beds in proportion to the level of their metabolic activity. Not enough emphasis can be given to the importance of the control of blood flow—arterial pressure is simply a means to drive perfusion. The nervous system achieves adequate perfusion of organs by maintaining arterial pressure within relatively fine limits, partly assisted by afferent feedback signals. The net effect is to regulate cardiac output in the face of different behavioral demands through the interplay of reflex inputs and central drives. Parenthetically, breathing is adjusted simultaneously and proportionately, thereby matching minute ventilation with cardiac output; an essential coupling for optimal perfusion efficiency. In order to achieve this regulation of cardiovascular effectors, the autonomic outflows are patterned, and these patterns are highly specific for the different repertoire of behaviors exhibited by the organism.

From studies in humans and animals, much has now been learned of the cardiovascular responses that accompany sleep, exercise, and emotional responses, yet it is only with respect to affective behavior that we have a detailed description of the central structures and neural pathways that are involved in mediating these complex autonomic changes. The classic investigations into the defense reaction, and the “playing-dead” or freezing response, have shed considerable light on the role of the amygdala and hypothalamus in organizing these responses. These two distinct modes of behavior may have provided insight of considerable significance in understanding response profiles to environmental and emotional stress, and subsequently hypertension. However, it is the downstream neuronal machinery within the medulla oblongata and spinal cord that provides the neuronal substrate that plays out these cardiovascular adjustments and maladjustments; it is these mechanisms that we will review here.

**CARDIOVASCULAR AUTONOMIC NEURONS**

The sympathetic and vagal preganglionic neurons are the final common pathway within the central nervous system through which control can be exerted (Figure 1). Sympathetic preganglionic neurons are localized segmentally within the intermediolateral cell column of the thoracic and upper lumbar spinal cord. Vasomotor neurons are distributed throughout the extent of the column. Sympathetic neurons that influence cardiac activity, both chronotropic and inotropic, are restricted to the upper thoracic segments of the cord (T1–T4). The postganglionic neurons are located outside the central nervous system in paravertebral chains. Each preganglionic neuron can innervate up to 10 postganglionic neurons. The vagal preganglionic neurons that affect the heart are located within both the external formation of the nucleus ambiguus located in the ventrolateral medulla and the dorsal vagal nucleus (reviewed in Jänig, 2006). The latter are likely to control coronary blood flow in addition to other cardiac influences. Evidence exists that vagal preganglionic neurons subserving chronotropic and dromotropic function are separated spatially within the nucleus ambiguus and that this organization is reflected by separate cardiac ganglia containing postganglionic neurons capable of altering beat rate, contractility, or conduction speed. This level of organization within both the medulla and the cardiac ganglia suggests a highly organized level of neural control which, as we discuss below, may be represented within the brainstem. Finally, there is an intimate coupling of cardiovascular autonomic activity (cardiomotor and vasomotor) with breathing; it is clear that at some levels the strength of this coupling is altered in hypertension: heart rate variability is depressed, but it is unclear whether the excitatory respiratory modulation of sympathetic vasoconstrictor fibers is altered.

**CONNECTIVITY, PHENOTYPE, AND ORGANIZATION OF SYMPATHETIC NEURONS**

From both the ongoing and reflex-evoked patterns of activity of sympathetic postganglionic nerve fibers established in animals (but also found in humans), sympathetic postganglionic fibers have been classified functionally as, for example, skeletal muscle vasoconstrictors, cutaneous vasoconstrictors, pseudomotor neurons, and piloerector neurons. This suggests the possibility of highly organized patterns of innervation of postganglionic neurons from distinct subsets of preganglionic sympathetic neurons. The question of
whether functionally diverse preganglionic neurons receive distinct descending drives from specific subsets of supraspinal sympathetic premotor neurons remains a possibility. These inputs originate from hypothalamic, midbrain, pontine, and medullary cell groups, but show no obvious neuroanatomical differences. However, the phenotypes of the spinally projecting neurons based on their neurochemical content are distinct and may subserve specific functions. There is a vast array of transmitter substances in the terminals forming close appositions with preganglionic sympathetic neurons—e.g., glutamate, gamma-aminobutyric acid (GABA), glycine, norepinephrine, epinephrine, dopamine, serotonin, substance P, encephalin, oxytocin, vasopressin, and purines—which may be coreleased. The physiological significance of these phenotypically distinct innervations may provide the substrate for activating specific populations of preganglionic neurons allowing differential control of blood flow, as occurs during exercise, such that catecholaminergic innervation might, for example, be essential for activating renal vasoconstrictors but not other vascular beds. We consider the innervation of sympathetic preganglionic neurons that arise from the rostral ventrolateral medulla (RVLM).

**RVLM PREMOTOR SYMPATHETIC NEURONS**

A major source of excitatory input to sympathetic preganglionic nerves originates from the RVLM. Spinally projecting RVLM neurons form a relatively discrete group of cells from the caudal to the facial nucleus, extending caudally toward the obex. They comprise both glutamate (i.e., express vesicular glutamate transporter-2) and epinephrine-containing neurons (e.g., those that are immunopositive for tyrosine hydroxylase or phenyl-ethanolamine-N-methyl-transferase, the C1 group). It has been estimated that between 50% to 70% of RVLM neurons are C1 cells, but that 80% of C1 neurons also express vesicular glutamate transporter 2. There is a wealth of information suggesting that the RVLM region and the spinally projecting neurons contained within it have a sympathoexcitatory function essential for the maintenance of arterial pressure. However, the level of arterial pressure following RVLM lesions can return back to control under certain circumstances, supporting the importance of other descending sympathoexcitatory pathways.

At the single cell level, RVLM spinally projecting neurons have properties consistent with sympathoexcitatory function: (i) they have a strong cardiac rhythm in their ongoing discharge, which originates from an inhibitory input generated by the arterial baroreceptor reflex; (ii) they fire at around 20 Hz in the rat and this discharge rate is directly related to the level of arterial blood pressure; and (iii) spike-triggered averaging shows a strong correlation with postganglionic sympathetic nerve activity. Guyenet’s group has studied the functional role of the C1 neurons using a selective

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**Figure 1.** Location of premotor sympathetic neurons. Descending drives to the sympathetic preganglionic motor neurons (located within the intermediolateral cell column, IML) originate from the lateral hypothalamic nuclei (LH) and paraventricular hypothalamic nuclei (PVH), the A5 noradrenergic cell group in the caudal ventrolateral pons, the rostral ventrolateral medulla (RVLM), the rostral medullary medulla or midline raphe (pallidus, magnus, and obscurus [Rob]), as well as spinal segmental interneurons within the lamina of the dorsal horn at cervical, thoracic, and lumbar levels. See text for discussion.

Other abbreviations: LC, locus coeruleus; LF, lateral funiculus; LPG, lateral paragigantocellular nucleus; PB, parabrachial nucleus; Py, pyramid; 3V and 4V, third and fourth ventricle, respectively.

neurotoxin. This resulted in a slight fall in arterial pressure and reduced evoked pressor responses from the RVLM, underpinning a role for this cell group in maintenance of arterial pressure. Additionally, highly discrete loci could be identified within the RVLM that activated different sympathetic motor outflows and vascular beds in the cat. This was consistent with the idea of a viscerotopographical representation within the RVLM, which was rather analogous to the motor homunculus in the cortex. The idea of RVLM viscerotopography is provocative and begs the question of whether functional specificity exists within other nuclei that connect to the RVLM. We shall return to this when we consider the nucleus of the solitary tract (NTS).

The origin(s) of the activity of RVLM premotor sympathetic neurons is an important question. In an in vitro slice preparation, spinally projecting RVLM cells exhibit tonic beating activity due to an intrinsic pacemaker property (reviewed in Guyenet, 2006), but under what conditions this is expressed in vivo have not been defined. Based on in vivo experiments, Lipski et al could not demonstrate pacemaker activity, rather they proposed that RVLM activity was dependent on excitatory synaptic inputs originating from other autonomic centers. A source comes from the respiratory network that is anatomically juxtaposed to the RVLM. The expiratory Bötzinger cells and inspiratory pre-Bötzinger cells, both also located in the ventrolateral medulla, are like-

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**Figure 2.** Characteristics of a caudal ventrolateral medullary (CVLM) GABAergic neuron. The neuron is activated by baroreceptor stimulation (Panel A) achieved by raising arterial pressure (AP) by tightening a snare around the abdominal aorta. Note concurrent inhibition of sympathetic nerve activity (SNA). CVLM neurons have ongoing activity that is pulse-modulated (Panel B), suggestive of a beat-by-beat baroreceptor input, and inhibited when arterial pressure is lowered either by sodium nitroprusside or activation of cardiopulmonary receptors with phenylbiguanide (Panel C). The phenotype of this cell was gamma-aminobutyric acid (GABA)-ergic (Panel D) as demonstrated by labeling the cell with biotinamide juxtacellularly and revealed with streptavidin Cy3 (white arrow) and subsequent processing for GAD67 mRNA by in situ hybridization (black arrow; same neuron). The location of the cell is shown in (Panel E) and was 1.35 mm caudal to the facial nucleus and 1.9 mm lateral to midline. Not shown here, but discussed in text, is that many CVLM neurons have respiratory modulated discharge and are therefore a potential site at which respiratory modulation of sympathetic activity occurs.

Abbreviations: LRN, lateral reticular nucleus; ION, inferior olivary nucleus; 7, facial nucleus.

likely to contribute to the central respiratory modulation of RVLM neurons and hence provide the substrate for central cardiorespiratory coupling underpinning the matching of cardiac output with minute ventilation. In summary, RVLM neurons play a pivotal role in the command of sympathetic outflow based on both their ongoing activity, the integration of synaptic drives from other central nervous system regions regulating cardiovascular activity, as well as reflex pathways such as baroreceptor, peripheral chemoreceptor, and nociceptive inputs. The transmitter released at the level of the preganglionic neuron may be vascular bed–specific, but is also likely to be state-dependent and undoubtedly susceptible to modulation by transmitter substances released endogenously at the level of the intermedio-lateral cell column. Finally, a major inhibitory input to RVLM neurons originates from the arterial baroreceptors, which provide one of the major restraining controls over cardiovascular sympathetic nerve activity. The caudal ventrolateral medulla (CVLM) is pivotal in relaying this information.

THE CAUDAL VENTROLATERAL MEDULLA

A major source of the inhibitory input to RVLM sympathoexcitatory neurons originates from a group of GABA-containing neurons in the CVLM (Figure 2). In turn, the CVLM is a major target for an efferent projection from baroreceptor-activated glutamatergic neurons within the NTS, which receives the baroreceptor afferent terminals (reviewed in Guyenet, 2006). Chemical stimulation of the CVLM evoked a profound depressor response dependent upon GABAergic transmission in the RVLM. CVLM neuron activity is pulse-modulated, presumably by baroreceptors, tightly coupled to arterial pressure, and inversely coupled to sympathetic discharge (Figure 2). These cells express an enzyme necessary for production of GABA; they contain glutamate decarboxylase 67 mRNA and therefore fulfill the criterion for a sympahtoinhibitory CVLM neuron. Many CVLM neurons also show respiratory modulation, which could explain the respiratory related discharge of RVLM neurons and, as such, provides another access point for coupling of sympathetic and respiratory activity.

VAGAL PREGANGLIONIC CARDIOMOTOR (INHIBITORY) NEURONS

There are two spatially separate pools of cardiac vagal motor neurons. Those motor neurons located in the nucleus ambiguus have B-fiber axons that effect chronotropic. However, there appear to be spatially distinct subgroups of ambiguus neurons with distinct cardiac function (e.g., chronotropism, dromotropism, and inotropism), but whether all these functions are mediated by B fibers is not known. A second group of cardiac vagal motor neurons is located in the dorsal vagal nucleus. These neurons have C-fiber axons in most species (except rabbit). While activation of cardiac vagal motor cells with C fibers produces bradycardia, this effect is smaller than activating B-fiber axons originating from the nucleus ambiguus, and with a different time course and pharmacology of action within the cardiac ganglion. Thus, C-fiber cardiac vagal motor neurons may also control cardiac functions other than chronotropism, which could include coronary blood flow, for example. Unlike B-fiber–type cardiac vagal motor neurons, the majority with C fibers appear not to be modulated by baroreceptor inputs. A particularly powerful source of afferent input to the nucleus ambiguus arises from the caudal NTS, which forms the central reflex arc and is essential for mediating the baroreceptor reflex–mediated vagal slowing. Vagal activity also has negative inotropic and dromotropic influences on the heart. Whether these responses are mediated by fibers producing chronotropic effects or separate pools is not clear.

CENTRAL COUPLING OF CARDIO-VASCULAR AUTONOMIC ACTIVITY WITH BREATHING

It is necessary to describe, briefly, the location and organization of the central respiratory network. The fundamental rhythm generator for respiration resides within a network spanning the pons and medulla, which is modulated by afferent signals originating from stretch receptors located within the bronchioles (pulmonary stretch receptors). The normal pattern of breathing (eupnea) consists of a ramp inspiratory discharge in the phrenic nerve and this is dependent upon an intact pons (medial and lateral parabrachial nuclei, and Kölliker-Fuse nucleus). Indeed, destruction of rostral pontine structures results in apneusis (prolonged inspiration). Parenthetically, normal respiratory-cardiovascular coupling also appears to be dependent on an intact pons. Within the ventrolateral medulla, the respiratory network resides as two bilateral columns running rostrocaudally from the level of the facial nucleus to the lateral reticular nucleus. These medullary regions map precisely on areas critical for cardiovascular control such as the RVLM, CVLM, and nucleus ambiguus cardiac vagal motor neurons, for example. This forms the anatomical substrate allowing functional coupling...
between the two systems. Essential elements for respiratory rhythm generation include the Bötzinger (just caudal to the facial nucleus), and caudal to this, the pre-Bötzinger complex. The latter contains autoactive neurons capable of producing intrinsic bursting that drive inspiration. This intrinsic activity is unlikely to operate in normal breathing, where it has been shown that reciprocating inhibitory synaptic interactions between neurons are essential. It is unclear as to all of the behavioral states in which intrinsic bursting plays a role in breathing, but the pathophysiological condition of gasping is one such state.

The central coupling of respiration and the cardiovascular system has been known for over 70 years. Anrep and his colleagues demonstrated in 1936 that sinus arrhythmia was the consequence of respiratory influences of the vagal outflow to the heart, which were partly of central origin (Figure 3). Cardiac vagal preganglionic motor neurons are actively hyperpolarized during inspiration by a wave of chloride-dependent inhibitory postsynaptic potentials. Hence, any influence that increases inspiratory drive will lead, by this process, to both a suppression of vagal efferent discharge and a reduced sensitivity of these neurons to other excitatory inputs, such as baroreceptor mediated excitatory drive. The outcome is a tachycardia in inspiration—sinus arrhythmia. Both the pattern and phase of firing of the postinspiratory neuron is similar to ambiguous cardiac vagal motoneurons with B-fiber axons, which are also excited by baroreceptor reflex activation, forming the idea of common cardiorespiratory neurons.

Based on unpublished data from D. Baekey, T. Dick, and J. F. R. Paton.

Figure 3. Common cardiorespiratory neurons in the medulla. Simultaneous recordings of arterial pressure (AP), heart rate (HR) in beats per minute (bpm), integrated thoracic sympathetic chain activity (SNAth), integrated phrenic nerve activity (PNA), and two ventrolateral medullary expiratory neurons from the Bötzinger complex together with their corresponding firing rates in steady state conditions and during a baroreceptor reflex. The three phases of breathing are clearly demarked (horizontal lines) as inspiration (I), postinspiration (PI), and expiration (E), based on the firing of PNA and the two respiratory cells. Note the sinus arrhythmia (open arrow) as well as the Traube-Hering-Mayer waves in the arterial pressure trace (solid arrow); the latter are mediated by the respiratory-related increases in sympathetic discharge (coincident with the inspiratory-expiratory transition). During the transient rise in arterial pressure, to stimulate the baroreceptor reflex, both heart rate and SNA are reduced (*). This also activates the postinspiratory neuron (Post-insp) and inhibition of the expiratory augmenting (Exp-aug) neuron, reflecting an inhibitory connection between these cells. Note the accentuated sinus arrhythmia (double open arrows) after the stimulus, which reflects an increased excitability of cardiac vagal motor neurons; the postinspiratory neuron also exhibits heightened excitability reflected by its higher peak discharge frequency (square head arrows). The pattern and phase of firing of the postinspiratory neuron is similar to ambiguous cardiac vagal motoneurons with B-fiber axons, which are also excited by baroreceptor reflex activation, forming the idea of common cardiorespiratory neurons.

**Based on unpublished data from D. Baekey, T. Dick, and J. F. R. Paton.**
rons discharge during the first part of the expiratory phase, a time when heart rate falls, which is an important component of sinus arrhythmia (Figure 3). Such cells could form a common cardiorespiratory neuron, as suggested previously. It should be realized that this central coupling is also geared precisely with control of the larynx, such that the glottis opens during inspiration (abduction), but exhibits adduction in early expiration. Indeed, laryngeal adductor motor neurons show similar discharge profiles to cardiac vagal motor neurons and postinspiratory cells. Parenthetically, this respiratory patterning of cardiac vagal and laryngeal motor outflows is mirrored by similar changes in the excitability of sympathetic pre- and postganglionic motor neurons (Figure 3). Studies in the rat and cat have shown that sympathetic neurons show distinct phases of activity correlating with the central respiratory cycle (Figure 3), which cause respiratory related waves in arterial pressure, Traub-Hering-Mayer (THM) waves (Figure 3). As mentioned earlier, there is evidence that neurons in the CVLM and RVLVM have their activity modulated by respiratory activity, which could account for the respiratory related discharge of postganglionic sympathetic nerves, but it also remains a distinct possibility that a portion of the respiratory discharge of sympathetic preganglionic neurons is mediated by direct connections from spinally projecting respiratory neurons in the medulla and pons.

**THE NTS AND REFLEX CONTROL OF THE CARDIOVASCULAR SYSTEM**

The importance of the NTS in cardiovascular control should not be underestimated. Destruction of the NTS (or a stroke in this region) leads acutely to fulminating hypertension with concomitant pulmonary edema, and chronically to maintained hypertension. The NTS plays a major role in: (i) regulation of baroreceptor reflex gain; and (ii) determination of the set point of arterial pressure. The primary site of termination of baroreceptor afferents is the NTS (Figure 4), and as such this structure provides a most powerful site for modulation. Neurophysiological studies have shown that specific areas of the NTS (dorsolateral and dorsomedial) receive innervation from the arterial baroreceptor reflex arc. Incoming baroreceptor afferents terminate in the nucleus tractus solitarii (NTS). Glutamate is an important transmitter here. Whether these same neurons project out of the NTS directly to the nucleus ambiguus (NA) and caudal ventrolateral medulla (CVLM) is not known. It is likely that there are separate NTS neurons projecting to the NA and CVLM (see Figure 6). Both the latter projections are excitatory and involve glutamate acting on inotropic receptors. The CVLM sends inhibitory gamma-aminobutyric acid (GABA)-ergic projections to the rostral ventrolateral medulla (RVLVM) (see Figure 2), which is a premotor site driving sympathetic preganglionic neurons located in the intermediolateral cell column (IML). From here, projections pass out of the ventral root targeting relevant sympathetic preganglionic nerves that innervate target organs. Increased arterial pressure excites the NTS, causing inhibition of sympathetic activity and excitation of cardiac vagal outflows. This reflexly evoked reciprocal pattern of autonomic activity is unique to the baroreceptor reflex.

**Abbreviations:** AP, area postrema; CC, CE, and CI, common, external, and internal carotid arteries; DLF, dorsolateral funiculus; DMNX, dorsal vagal motor nucleus; PY, pyramid; Rob, raphe obscurus; X, vagus; 4V, fourth ventricle.

baroreceptors (myelinated and unmyelinated fibers). There is compelling evidence that some NTS neurons that are excited by stimulation of the arterial baroreceptors (*Figure 5*) also receive convergent excitatory inputs from other reflex inputs that exert qualitatively similar reflex response patterns. There is compelling evidence that some NTS neurons that are excited by stimulation of the arterial baroreceptors (*Figure 5*) also receive convergent excitatory inputs from other reflex inputs that exert qualitatively similar reflex response patterns. Furthermore, many NTS neurons that are excited by baroreceptor stimulation are inhibited by chemoreceptor afferent inputs. One interpretation of this is a functional organization of NTS neurons based on their projection targets to different types of neurons, e.g., cardiac vagal, CVLM, or RVLM neurons. Indeed, the majority of intracellularly labeled baroresponsive NTS neurons (including those shown to receive direct afferent inputs) project out of the NTS to ventrolateral medullary regions encompassing the nucleus ambiguus and the CVLM. This defined functional output is upheld by the recent demonstration of distinct pressure thresholds for baroreceptor reflex–mediated vagal bradycardia versus sympathoinhibition (*Figure 6*). Again, this supports the idea of separate channels of information leaving the NTS destined for each limb of the autonomic nervous system. This degree of organization is supported by the observation that numerous neuromodulators acting within the NTS affect preferentially the cardiac vagal component of the baroreceptor reflex and not the sympathetic component. Thus, these data lead to the prediction that within the NTS there are dedicated premotor cardiac vagal neurons and pre-CVLM neurons, and that these form completely separate entities, which provide flexibility for independent modulation of baroreceptor control of heart rate versus vascular resistance. This is seen, for example, during exercise. Interestingly, the baroreceptor control of sympathetic nerve activity is better correlated to cardiac output rather than to the absolute level of arterial pressure in humans, suggesting that baroreceptors are designed to detect changes in blood flow. Indeed, it is known that carotid sinus baroreceptors are sensitized under conditions of altered flow and pressure, rather than static pressure changes alone, such that they exhibit lower thresholds for discharge. Ultimately, it is blood

![Figure 5](https://example.com/baroreceptors.png)

**Figure 5.** Baroreceptive neurons in the NTS are under a restraining inhibitory tone. Whole-cell recordings of baroreceptive neurons from rat. **Panel A** depicts a typical “adaptive” response where the peak depolarization and firing response occurs before the maximal stimulus, in this case a rise in carotid sinus pressure (arrowed). Note the afterhyperpolarization that reduces the electrical excitability of the neuron to subsequent baroreceptor inputs. **Panel B** depicts the firing response of another baroreceptive neuron showing an adaptive response in control (i) and after (ii) bicuculline, a gamma-aminobutyric acid A (GABA<sub>A</sub>) receptor antagonist. A mechanism for driving this inhibition is from angiotensin II and nitric oxide (see Figures 7 and 8 and text for discussion.)
flow to organs that really matters and it would now appear that baroreceptor modulation of vascular resistance provides a means to accurately control this.

**A ROLE FOR ARTERIAL BARORECEPTORS IN THE CHRONIC REGULATION OF ARTERIAL PRESSURE**

A most relevant issue, which has significant clinical implications, is the role of baroreceptors in long-term control of arterial pressure. Arterial baroreceptors have long been thought to buffer arterial pressure on a moment by moment basis and to reset at higher pressure levels. However, recent data have shown that baroreceptor unloading causes a persistent reflex-mediated pressor response that is maintained for days. Additionally, electrical stimulation of the carotid sinus region in conscious dogs results in a maintained lower level of arterial pressure that again lasts for days. This study showed that there was no compensatory change in plasma renin levels, which might have been expected to increase in response to lower renal blood flow, suggesting an inhibitory influence on its release, perhaps via a persistent baroreceptor reflex–mediated sympathoinhibition of renal nerve discharge. The latter further demonstrates the persistent and potent ability of baroreceptors to lower arterial pressure if stimulated chronically. The success of this has led the authors to propose clinical trials using this approach for alleviating the symptoms of primary hypertension. Therefore, an assessment of baroreceptor reflex function remains essential in evaluating our understanding of the regulation of arterial pressure in the long term; this now becomes highly pertinent in disease states such as primary hypertension.

**EVIDENCE SUPPORTING CENTRAL AUTONOMIC DYSFUNCTION IN PRIMARY HYPERTENSION**

Both sympathetic and parasympathetic components of the cardiovascular autonomic nervous system and their reflex regulation by the arterial baroreceptors undergo significant change in conditions of essential hypertension. Whether measuring norepinephrine spillover, or making direct neural recordings from func-
tionally defined sympathetic vasoconstrictor fibers destined for skeletal muscle in humans, sympathetic activity is elevated in patients with essential hypertension. This can have two detrimental effects: (i) increased peripheral vascular resistance, which causes elevations in arterial pressure, and (ii) end-organ damage. Grassi has stated that “the sympathetic nervous system has moved towards center stage in cardiovascular medicine” and that “data in both animal and human studies unequivocally show that sympathetic activation characterizes the hypertensive state and participates in the development, maintenance, and progression of elevated blood pressure values.” Consistent with a postulated potential causative role for sympathetic overactivity in hypertension are the findings of raised levels of muscle vasoconstrictor sympathetic nerve activity in both borderline and “white coat” hypertensive patients, making the case that, from its onset (or even before), hypertension is associated with heightened sympathetic activity to the vasculature and heart. Indeed, normotensive offspring with one hypertensive parent have autonomic dysfunction, as exhibited by depressed baroreceptor reflex function, increased reflex activation of sympathetic activity destined for the heart during orthostatic challenges, and reduced cardiac vagal reactivation after isometric hand-grip. In addition, in such subjects, reduced heart rate variability was also expressed. Similarly, heart rate variability is reduced in spontaneously hypertensive rats (SHR), “white coat” hypertensives, and human hypertensives, and can even precede the onset of hypertension in humans. This is highly relevant, as reduced heart rate variability is a prognostic indicator of morbidity and mortality for cardiovascular disease and sudden death. These data all indicate an inhibition of cardiac vagal motor outflow that can precede the onset of hypertension. Finally, both hypertensive humans and the SHR exhibit reduced cardiac baroreceptor reflex gain. As discussed above, since the baroreceptor reflex has the potential to play a role in the chronic regulation of arterial pressure, a reduction in its sensitivity may have long-lasting detrimental consequences for blood pressure homeostasis.

**ELEVATED SYMPATHETIC DISCHARGE: A COMMON PROBLEM OF MULTIPLE DISEASES**

Sympathetic nerve activity is raised in primary hypertension, diabetes, obesity (eg, the metabolic syndrome), and heart failure. A vital question is whether there is a link and, if so, what it is? The issue remains also as to whether the disease occurs before or after the elevation in sympathetic nerve discharge. We would like to consider obesity. Recently, it has become clear that the raphe system plays a role in thermoregulation. Raphe neurons (eg, the raphe magnus and pallidus) project directly, via small myelinated axons, to sympathetic preganglionic neurons to release serotonin (5-hydroxytryptamine), which is known to excite sympathetic preganglionic neurons. Raphe magnus neurons are temperature-sensitive and their inhibition lowers the discharge of sympathetic vasoconstrictor fibers supplying the tail in the rat, a major thermoregulatory organ in this species, but not those in the splanchnic bed or the heart, indicating that these raphe neurons affect a functionally specific subpopulation of sympathetic preganglionic neurons. Dinoprostone administration, which evokes thermogenesis, produced activation of sympathetic nerves innervating both brown adipose fat and the tail, which was mediated via the raphe magnus.

With the worldwide problems of obesity, bodily mechanisms of energy expenditure have driven both clinical and pharmaceutical interest. Normally, leptin, released from adipose tissues, provides a feedback mechanism controlling adiposity. Leptin increases sympathetic activity to brown adipose tissue to initiate thermogenesis and energy expenditure. It is known to act on the arcuate nucleus, which releases α-melanocyte-stimulating hormone that acts on melanocortin-4 receptors; the latter are located within a variety of hypothalamic nuclei known to affect sympathetic activity. Indeed, melanocortin-4 receptor agonist produces the same response as leptin. The precise details of the central pathways involved are as yet unknown, but recent conditional transgenic animals indicate that: (i) an absence of either melanocortin-4 or leptin receptors causes obesity in both mice and humans; and (ii) melanocortin-4 receptors in the para-ventricular hypothalamus and/or amygdala are sufficient to control food intake, but that if located elsewhere, these receptors control energy expenditure, suggesting a functional divergence in the role of these receptors. In conclusion, the central pathways regulating thermogenesis and energy expenditure engage the medullary raphe serotonergic system that selectively drives sympathetic outflows for controlling body heat and energy expenditure. Superimposed onto this serotonergic system is a hypothalamic neuronal circuit that clearly regulates temperature and energy requirements. It is this circuit that requires further interrogation to understand the integrative aspects of obesity, diabetes, hypertension, and heart failure—all contributors to the metabolic syndrome and abnormally elevated sympathetic discharge.
CARDIOVASCULAR AUTONOMIC DYSFUNCTION AND ANTIHYPERTENSIVE TREATMENT

It is now critical to understand the reasons for an elevation in sympathetic activity, and we will restrict this discussion to primary hypertension, which is also associated with decreased vagal tone and subsequent reductions in heart rate variability and cardiac baroreceptor reflex gain. All these variables are prognostic indicators for hypertension and autonomic dysfunction, pinpointing a central nervous malfunction. Current treatments for hypertension including blockers of the renin-angiotensin system, calcium channel antagonists, and exercise, are all associated with reduced arterial pressure, improved heart rate variability, and increased baroreceptor reflex gain, demonstrating that these methods not only affect the autonomic nervous system, but that the detrimental changes in autonomic nervous activity can be reversed (eg, Izdebska et al, 2004).30 This is, of course, essential if new therapeutic treatments are to rely on modifying dysfunctional autonomic circuit activity. The issue of how exercise lowers arterial pressure and restores autonomic cardiovascular function in hypertensives is important, but not well understood, and requires further research.30 However, data from a recent study that used exercise to alleviate cardiovascular autonomic dysfunction again points toward changes in central nervous autonomic cardiovascular circuits controlling premotor sympathetic and cardiac vagal motor neurons by changing the balance of the amount of vasopressin and oxytocin released from central axonal terminals that originate from hypothalamic structures.31

Some treatments for hypertension are known to reduce sympathetic nerve traffic, including pharmacological interventions such as administration of clonidine (an α2-adrenoceptor agonist), and antagonists of β-adrenoceptors. These are known to reduce sympathetic vasoconstrictor activity in hypertensive humans.32 Additionally, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II (Ang II) type 1 receptor (AT1R) antagonists are also prescribed for the treatment of hypertension. However, in contrast, chronic blockade of ACE and AT1R fail to reduce both the bursting frequency of muscle vasoconstrictor nerve activity33 and noradrenaline spillover in hypertensive humans, despite an antihypertensive effect. These findings are surprising given that Ang II has a sympathoexcitatory effect when administered centrally in animals and that inhibitors of AT1R are likely to cross the blood-brain barrier and act on central AT1R. Classically, blood-borne Ang II acts on circumventricular organs (eg, the area postrema and subfornical organ), to activate projections to central nervous circuitry regulating sympathetic activity as well as release of vasopressin, although its plasma level may not rise in hypertensives. However, we now know that Ang II can be synthesized independently within the brain itself and can act as a transmitter or modulator substance.

Evidence from animal models indicates that Ang II has actions on brainstem cardiovascular control circuitry in pathological hypertension. This includes the following findings:

- Ang II heightens the activity of premotor RVLM sympathetic neurons.35 Indeed, antagonizing AT1R in RVLM reduces arterial pressure in the SHR, but not normotensive rats, indicative of a tonic angiotensinergic drive unique to the SHR.35 Moreover, a source of this tonic drive may descend from the hypothalamic paraventricular nucleus.35
- In the SHR, brainstem levels of Ang II are elevated and central administration of captopril normalizes arterial pressure.36
- Central administration of an Ang II type 1 receptor blocker attenuated salt-induced hypertension in rats.37
- In transgenic rats harboring mouse renin gene, Ang II levels were increased within the brain, and animals were hypertensive.38
- Downregulation of astroglial synthesis of brain angiotensinogen decreases blood pressure.39
- Overexpression of angiotensin-converting enzyme 2 (ACE2) lowers arterial pressure in the SHR, but not the normotensive rat.40
- Veerasingham et al (2005), revealed an additional Ang II-mediated signaling pathway involving phosphoinositide 3-kinase (PI3-kinase) in RVLM neurons from SHR, which was not present in neurons from normotensive Wistar-Kyoto rats.41 When PI3-kinase activity was blocked acutely in the RVLM of SHR, but not Wistar-Kyoto rats, arterial blood pressure was reduced.42
- At the level of the NTS, Ang II acting on AT1R depressed the baroreceptor reflex gain. This was mediated by nitric oxide (NO) generated from endothelial nitric oxide synthase (eNOS).43 Therefore, the absence of a reduction in sympathetic bursting in hypertensives when the renin-angiotensin system is blocked requires further discussion.

An issue concerns whether the pattern of sympathetic activity, rather than the absolute number of bursts, changed after blockade of AT1R. This would include its respiratory modulation, (a known excitatory drive, see above), but also intraburst firing frequencies. As the
pattern may affect release of cotransmitter(s), it would be of interest to assess whether the level of neuropeptide Y, a known cotransmitter from sympathetic postganglionic endings that has been associated with hypertension, is altered after blocking the renin-angiotensin system.

Based on the blood pressure–lowering effect after AT1R blockade and the absence of any change in sympathetic activity, alterations in the baroreceptor reflex function curve and its operating point become important. This is particularly important given the recent rejuvenation of the baroreceptors in long-term regulation of arterial pressure. The question is whether there is any change in the baroreceptor reflex function curve, and are they involved in the antihypertensive action of ACE and AT1R inhibitors? Presumably, baroreceptors become unloaded as arterial pressure is lowered. This would normally cause sympathoexcitation if baroreceptor reflex function was unaltered. Since sympathetic activity remained the same rather than increasing, as would have been expected with baroreceptor unloading, the possibility remains that the ACE and AT1R antagonists act on the baroreceptor reflex to prevent this. Interestingly, Struck et al (2002) have shown that in humans an AT1R antagonist is effective in lowering blood pressure and shifts the baroreceptor reflex function curve to the left and returns the sympathetic component of the baroreceptor reflex set point toward normal levels. Thus, it remains to be established as to whether there is a beneficial effect (ie, blood pressure lowering role) of improved baroreceptor reflex function during administration of ACE and AT1R antagonists in hypertensive humans. It also remains unclear as to how these antagonists exert their action on the baroreceptor reflex and whether there is a role for central Ang II in the development of hypertension in humans, as proposed by Krum et al (2006). In this context, recent data from SHR support a beneficial role for improved baroreceptor reflex function in restoring blood pressure and heart rate variability based on Ang II–mediated signaling at the level of the NTS, a structure with one of the highest AT1R-binding sites in the brain. This is discussed below.

A NOVEL MECHANISM WITHIN THE NTS FOR ARTERIAL PRESSURE CONTROL

There is substantial evidence that GABA transmission at the level of the NTS plays a key role in the regulation of arterial pressure control in both health and hypertension (Figure 7). Numerous central and peripheral pathways, as well as endogenous and exogenously applied modulators, act to depress the baroreceptor reflex through enhanced GABA transmission acting on GABAA receptors. This is true for the defense reaction, exercise, and noxiously mediated responses. Here, we consider the importance of the renin-angiotensin system’s effect on GABAergic tone within the NTS, which may have implications for the genesis of neurogenic hypertension. The novel notion of “vascular-neuronal signaling” has been advanced as an important regulatory mechanism for arterial pressure control in both health and hypertension (Figure 7). This mechanism involves acti-

Figure 7. Vascular-neuronal signaling in the NTS regulates cardiovascular function. A differential interference contrast image of living nucleus of the solitary tract (NTS) depicting a capillary full of erythrocytes. Recent findings indicate that angiotensin II (blood-borne or of central origin) acting on angiotensin II type 1 receptors (AT1R) anchored to the endothelium activates endothelial nitric oxide synthase (eNOS) to release nitric oxide (NO) from the endothelium that diffuses into the NTS to enhance release of gamma-aminobutyric acid (GABA), which depresses baroreceptor reflex function. Further, chronic blockade of eNOS in the NTS of conscious rats increases baroreceptor reflex gain and, in the spontaneously hypertensive rat, also lowers arterial pressure. Thus, eNOS activity plays a chronic role in the regulation of baroreceptor reflex gain and the set-point of arterial pressure.
vation of AT1R located on the endothelium of the microvascularule within the NTS and subsequent activation of eNOS to release NO. The NO diffuses across the blood-brain barrier to increase GABA release, via a presynaptic mechanism involving cyclic adenosine diphosphate ribose–triggered calcium release. This results in depressing the excitability of NTS neurons mediating the baroreceptor reflex and reduces reflex gain, which was dependent upon soluble guanylate cyclase. The prediction made was that chronic blockade of eNOS in NTS would improve baroreceptor reflex gain. Using in vivo gene transfer–mediated antagonism of eNOS in the NTS improved baroreceptor reflex gain and reduced arterial pressure in the SHR (Figure 8). The latter was associated with a reduced low frequency component of systolic pressure indicative of a reduction in sympathetic vasomotor tone. In contrast, baroreceptor reflex gain was improved only in the normotensive Wistar-Kyoto rat. In addition, in the SHR, eNOS mRNA was upregulated in NTS compared with normotensive rats (Figure 8). The upregulated eNOS mRNA is intriguing, as this was only found to be the case in adult SHR and not young, prehypertensive SHR. This suggests that the upregulation of eNOS mRNA occurs after the onset of the hypertension. Thus, in the adult SHR, elevated eNOS in the NTS contributed to the maintenance of the pathological state of the cardiovascular system.

It is curious that raised eNOS in the NTS appears to be detrimental to cardiovascular function, whereas plentiful NO in the periphery is seen as a healthy sign. This assumption hinges on whether the raised eNOS is actually producing NO and that NO is responsible for the signaling and detrimental consequences on cardiovascular control. A possibility is that the signaling from eNOS is not mediated by NO, but influenced by superoxide (O2•−). Firstly, O2•− generation in the NTS of the SHR may be raised and this may combine with NO to form peroxynitrite, which acts on NTS neurons, causing sympathoexcitation and depression of baroreceptor reflex function. Secondly, under certain pathophysiological conditions excessive eNOS activity can produce O2•− and this is related to the uncoupling of increased eNOS protein from its cofactor tetrahydrobiopterin. Whether eNOS has uncoupled from tetrahydrobiopterin in the NTS of the SHR is unknown. Extending the idea that the endothelium is altered in the NTS of the SHR and is contributing to the hypertension, it is of interest that another gene important for the expression of junctional adhesion molecule–1, which forms the tight junctions between adjacent endothelial cells, is also upregulated in the SHR. This is also upregulated in prehypertensive SHR indicating a possible causal role in the hypertension. Another known function of junctional adhesion molecule–1 is that it promotes adhesion of leukocytes to the endothelium.
Interestingly, the brainstem of the SHR (including NTS) shows dense leukocyte adhesion. Further, in the NTS of normotensive rats, which are devoid of leukocytes, adenoviral–mediated overexpression of junctional adhesion molecule–1 induced leukocyte adhesion within the microvasculature, and induced hypertension. These observations are important, as leukocytes are a potential source of \( \text{O}_2^- \), which is enhanced in hypertension. This, together with possible eNOS uncoupling (described above), adds further weight to a possible role for \( \text{O}_2^- \) in the NTS of the SHR. If this is the case, then:

(i) NO bio-availability will be low, as it will be readily oxidized—notably, a paucity of NO can contribute to expression of endothelial cell adhesion molecules and leukocyte adhesion, and
(ii) if there is leukocyte adhesion in the microvasculature of the NTS, one might expect high resistance to blood flow in the SHR. This is consistent with the finding that leukocyte adhesion in peripheral vascular beds of the SHR contributes to the raised vascular resistance in this rat strain, and contributes to the hypertension. Moreover, with this increased vascular resistance, blood flow may be restricted, compromising oxygen delivery. It is known that neurovascular compression around the RVLM can itself cause sympathetic-excitation and hypertension, consistent with brainstem ischemia–mediated sympathoexcitation. The intriguing possibility that the SHR brainstem is borderline hypoxic has been proposed. This is reminiscent of the finding of a lower respiratory quotient within the brain of humans with hypertension suggesting a different pattern of oxidative metabolism. Interestingly the internal caliber of brainstem feeder arteries are reduced in prehypertensive, or juvenile, SHR compared with age-and-sex–matched Wistar-Kyoto rats, suggesting a congenital abnormality (Figure 9). This computes to a higher (~15x) resistance to brainstem blood flow in the SHR compared with age-and-sex–matched Wistar-Kyoto rats. A shortage of oxygen in the SHR is consistent with the raised hematocrit in the SHR compared with Wistar-Kyoto rats. The notion of borderline hypoxia in the SHR brainstem is also reminiscent of the Cushing response, in which sympatoexcitation occurs to encourage adequate blood flow into an oxygen-starved brain. With reduced oxygen delivery to brainstem networks regulating arterial pressure, a possibility is that the upregulated eNOS in the NTS in the SHR is a compensatory response to enhance blood flow, perhaps relating to local vasodilatation and/or angiogenesis.

CONCLUSIONS

Based on current drug strategies of ACE inhibitors and angiotensin receptor blockers, Ang II remains a major conspirator for hypertension. While Ang II affects the kidney, peripheral blood vessels, and the heart, there is now ample evidence that it acts centrally at sites within the brain that both command levels of sympathetic discharge and modulate the baroreceptor reflex, which is essential for the chronic homeostatic control of arterial pressure. In endeavoring to provide a relatively contemporary analysis of the central nervous con-
control of the cardiovascular system, we have reviewed the neural pathways by which the excitability of both vagal and sympathetic preganglionic motor neurons are regulated in health and disease. Emphasis has been placed on understanding baroreceptor reflex control and its importance in the chronic control of arterial pressure, something that goes against the current ideology. However, based on accumulating evidence, we must now consider this as a major mechanism affecting long-term control of arterial pressure, and perhaps devise methods to exploit it as an antihypertensive approach. We have discussed some of the central neural mechanisms by which baroreceptor reflex inputs are modulated in physiological and pathophysiological conditions, such as hypertension. A fundamental design principle appears to involve a tight coupling of respiratory and cardiovascular regulation, which provides a neat intrinsic way to elevated cardiac output and respiration that is appropriate to a change in behavioral state. However, it is not inconceivable that an inappropriate change in the strength of coupling between the respiratory rhythm–generating network and sympathetic and cardiac vagal motor neurons could well contribute to excessive sympathetic activity and reduced cardiac vagal excitability, which are both hallmarks of hypertension. We conclude by emphasizing a continuing need to examine central nervous mechanisms underpinning cardiovascular control in hypertension. We believe that we need a better understanding of the genomic and proteomic changes associated with both the neuronal circuitry controlling arterial pressure and the blood vessels perfusing these brain regions during the development of hypertension. Such knowledge should give novel mechanistic data and assist in the design of new therapeutics. We suggest that there are significant changes in the balance of excitatory-versus-inhibitory synaptic transmission, intracellular signaling messengers, and blood-to-brain communication, which can all lead to the generation of excessive sympathetic activity and the depression of baroreceptor reflex gain. Finally, if it is the case that the hypertensive brainstem is borderline hypoxic, and that this is driving excessive sympathetic activity, then antihypertensive drugs that lower blood pressure (and hence blood flow into the brainstem) may only serve to exacerbate the problem. This could account for the high numbers of hypertensive patients that remain hypertensive following drug treatment, as the system fights back to maintain adequate blood flow. We propose that an alternate strategy for consideration in future drug design might do well to consider ways of reducing the resistance of blood flow entering the brain.

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Essential hypertension is commonly “neurogenic,” ie, blood pressure elevation is initiated and sustained by activation of the sympathetic nervous system. Essential hypertension in normal-weight persons is characterized by the activation of sympathetic outflow to the heart, kidneys, and skeletal muscle vasculature, and by increased firing rates in individual sympathetic nerve fibers, with multiple firing salvoes within a cardiac cycle. Obesity-related hypertension differs in two ways: (i) it excludes the cardiac sympathetic outflow; and (ii) it possesses a single-fiber mechanism of sympathetic activation, with recruitment of previously silent fibers, firing at a normal rate. This article looks at the pathophysiological, clinical, therapeutic, and prognostic implications of these variants of essential hypertension.

NEUROGENIC ESSENTIAL HYPERTENSION: HISTORICAL ORIGINS OF THE CONCEPT

There are important historical antecedents to our current understanding that activation of the sympathetic nervous system is a prime mover in the initiation and maintenance of the blood pressure elevation in essential hypertension (Figure 1).

A crucial element in this understanding was the identification of the sympathetic nervous transmitter as norepinephrine, after initial claims for epinephrine and noradrenaline.1 von Euler definitively identified norepinephrine as the transmitter in the 1940s when, using a variety of bioassay systems, he compared the biological properties of transmitter extracted from the sympathetic nerves of a variety of tissues with those of epinephrine and norepinephrine.2 This discovery provided the rationale and impetus for the development of antiadrenergic antihypertensive drugs, and underpinned the development of neurochemical methods for quantifying sympathetic activity in patients with hypertension, taking us into the modern era.

SELECTED ABBREVIATIONS AND ACRONYMS

CNS central nervous system
NGF nerve growth factor
OSA obstrucive sleep apnea

Figure 1. Threads of evidence from times past that suggested an importance for the sympathetic nervous system in the origins of essential hypertension.
METHODS FOR STUDYING THE HUMAN SYMPATHETIC NERVOUS SYSTEM

Measurement of the excretion of the sympathetic transmitter nor-epinephrine in urine is now largely obsolete as a test of human sympathetic nervous activity. Assay of the plasma concentration of nor-epinephrine, while widely used, has two major limitations. The first is that plasma norepinephrine concentrations are dependent on the rate of its removal from plasma, not just sympathetic tone and nor-epinephrine release. The second deficiency is that no information is provided on regional sympathetic nervous function; sympathetic nervous system responses typically show regional differentiation that can only be detected in clinical research by techniques that can assess organ-specific sympathetic function. Clinical microneurography

This technique is a method for studying nerve firing rates in subcutaneous sympathetic nerves distributed throughout skin and skeletal muscle. The technique involves the insertion of fine tungsten electrodes through the skin. The electrode tip is positioned in the sympathetic fibers of, most commonly, the common peroneal nerve near the head of the fibula. One can then generate multifiber recordings of “bursts” of nerve activity synchronous with the heart beat, and more recently, single fiber traces.

Norepinephrine spillover rate measurements

The release of neurotransmitters can be clinically studied using radiotracer-derived measurements of the appearance rate of norepinephrine in plasma from individual organs. Microneurographic methods do not give access to the sympathetic nerves of internal organs, a limitation that is overcome by using regional norepinephrine spillover measurements. Neurotransmitter release from the heart and kidneys can be measured by infusion of tritiated norepinephrine, and regional blood sampling from the coronary sinus and renal veins. This allows estimation of cardiac and renal sympathetic activity. These methods have been extensively applied to characterize the sympathetic neural pathophysiology of a range of clinical disorders, including essential hypertension.

THE SYMPATHETIC NEUROBIOLOGY OF ESSENTIAL HYPERTENSION

A neural basis for hypertension exists both in obese and normal-weight persons. Despite the commonality of a shared “neurogenic” basis for hypertension, it is clear that the central nervous system (CNS) mechanisms of sympathetic activation in these two neurogenic “variants” of essential hypertension must differ. This is because of differences in the regional pattern of sympathetic activation, as well as differences in the firing characteristics of individual sympathetic nerve fibers.

Essential hypertension in normal-weight patients

Isotope dilution methodology has demonstrated that the spillover of norepinephrine from the sympathetic nerves of the heart and kidneys is increased two- to threefold in approximately 50% of untreated normal-weight patients with essential hypertension. This finding is key, as it underlies the consensus that essential hypertension is often “neuro-
genic,” and is initiated and sustained by activation of the sympathetic nervous system (Figure 3). The increased rates of norepinephrine spillover from the heart and kidneys are, no doubt, attributable in part to increased sympathetic nerve firing rates in the sympathetic outflow to these organs. This cannot, however, be measured directly. Direct sympathetic nerve recording with clinical microneurography has documented activation of sympathetic efferents in another sympathetic outflow—the outflow to skeletal muscle vasculature.4,8

Obesity-related essential hypertension

At one time, the proposition that obesity-related hypertension is initiated and sustained by neurogenic mechanisms would have been considered to fly in the face of both reason and empirical evidence, since the sympathetic nervous system is thermogenic and promotes negative energy balance and weight loss. Furthermore, early experimental models suggested that sympathetic nervous activity was suppressed in obese people.9

In obesity-related hypertension, as in essential hypertension in normal-weight patients, sympathetic activation is present in the sympathetic outflow to the kidneys and skeletal muscle vasculature.4,7 Paradoxically, sympathetic outflow to the heart is normal or reduced (Figure 3).7

Additionally, single-fiber sympathetic nerve discharge patterns differ from those of normal-weight essential hypertensive patients, in whom there are multiple single-nerve fiber firings within a cardiac cycle (firing salvoes) and increased fiber firing frequencies. In contrast, in obesity-related hypertension, the sympathetic activation involves only an increase in the number of fibers firing, and not their frequency (Figure 4).

CNS ORIGINS OF SYMPATHETIC NERVOUS ACTIVATION IN ESSENTIAL HYPERTENSION

The CNS mechanisms of increased sympathetic outflow from the brain must differ in the normal-weight and obese “variants” of essential hypertension. There are clues as to what
Essential hypertension in normal-weight patients

The hypothalamus and other parts of the limbic system, including the amygdala, receive projections from brainstem noradrenergic neurons. In animal studies, these projections have been shown to be important in stimulating sympathetic nervous system outflow.

To test whether this mechanism applies in human hypertension, we have developed methods to measure brain norepinephrine turnover (or synthesis rate) differentially in the subcortical and cortical brain areas. By measuring the overflow of norepinephrine and its lipophilic metabolites into the internal jugular veins, norepinephrine turnover in subcortical brain regions can be measured (Figure 5). We can identify the internal jugular vein—typically the left vein—which predominantly drains subcortical brain regions using a cerebral venous sinus scan.

In normal-weight patients with essential hypertension, norepinephrine turnover in the brain is only increased in subcortical areas (Figure 5). The increase in brain nor-

Obesity-related essential hypertension

The increase in subcortical forebrain norepinephrine turnover found in normal-weight patients with essential hypertension is absent in obesity-related hypertension. We must search elsewhere for the brain mechanism causing activation of the sympathetic nervous system. There is a long list of possible mechanisms, but as yet, there is no definitive evidence for any of them.

Does the sympathetic activation represent an ongoing response to continued overfeeding, as suggested by the experimental models? Or, perhaps, it is driven by the pathophysiological and clinical changes that accompany obesity once it has developed, such as hyperinsulinemia, high plasma leptin levels, and obstructive sleep apnea?

Hyperinsulinemia

The original hypothesis of Landshberg, which was based on his observation that overfeeding in rats activates the sympathetic nervous system and elevates blood pressure (and originated from his work with James Young), placed insulin center stage in the pathogenesis of obesity-related hypertension. The insulin response to increased dietary energy intake was seen as the prime mover in the following cascade: overfeeding → hyperinsulinemia → sympathetic nervous activation → thermogenesis and hypertension. This has been a highly influential hypothesis, but remains unsubstantiated in human obesity. More recent thinking shifts the emphasis, and attributes the hyperinsulinemia in obesity to the accompanying insulin resistance, rather than specifically to an overfeeding response.

Obstructive sleep apnea

Obstructive sleep apnea (OSA), which is commonly seen in obesity, has been championed as the major, or perhaps even exclusive, cause of the sympathetic activation. Nighttime apneic episodes are accompanied by intense sympathetic nervous activation. It has been suggested that, with time, this episodic nocturnal sympathetic stimulation evolves into ongoing, daytime sympathetic nervous activation. How this might happen, however, remains obscure. It seems probable that OSA is, in fact, one of several causal mechanisms of sympathetic activation in obesity. In support of this idea, an intriguing recent paper describes some elevation of sympathetic tone even in normal-weight men with OSA, allowing a disentangling of the independent, but usually combined, influences of obesity and OSA.

Leptin

It has been proposed that the sympathetic nervous activation of obesity might be driven by high plasma levels of leptin, the “adipocyte hormone.” Leptin, a 16-kDa protein, which is derived principally from adipose tissue, has been implicated in body weight homeostasis. Elevated plasma leptin concentrations are observed in human obesity.
Intravenous infusion of leptin in rats creates activation of the sympathetic outflows to the kidneys and hind-limb vasculature, and is accompanied by the stimulation of epinephrine secretion by the adrenal medulla, and an increase in heart rate—suggesting that the cardiac sympathetic nerves are stimulated. These effects have some parallel, although not particularly close, in the pattern of sympathetic nervous changes observed in human obesity. This suggests that stimulation of the sympathetic nervous system by leptin may be the underlying explanation of sympathetic activation, but it should be emphasized that in human obesity epinephrine secretion rates are normal, and the cardiac sympathetic outflow is not stimulated. Of obesity, in human obesity there is no strong evidence that leptin drives the sympathetic activation.

EVIDENCE THAT CHRONIC MENTAL STRESS IS A CAUSE OF ESSENTIAL HYPERTENSION

In normal-weight patients with essential hypertension, our preliminary research findings suggest the importance of chronic mental stress in both sympathetic activation, and in hypertension pathogenesis.

Rather than using the conventional epidemiological approaches, for example by measuring the blood pressure in people in stressful occupations, such as air traffic controllers, in preliminary studies we tested for the presence of human stress biomarkers. In addition to the changes described above—chronic sympathetic activation in the outflows to the heart and kidneys and activation of brainstem noradrenergic neurons projecting to the hypothalamus and amygdala (Figure 6, page 188)—we have documented that the stress hormone, epinephrine is a cotransmitter in sympathetic nerves. This is not seen in healthy people, but does occur in experimental models of mental stress. It also occurs in patients with panic disorder, who provide a relevant clinical model of recurrent, extreme mental stress responses. Furthermore, we found increased levels of nerve growth factor (NGF), a mental stress reactant, in biopsies of small forearm veins from hypertensive patients (Figure 6).

Although incomplete, this stress biomarker evidence provided the linchpin for the contentious judgment by an Australian Government body, the Specialist Medical Review Council, that mental stress is a proven cause of high blood pressure.
CLINICAL IDENTIFICATION OF NEUROGENIC ESSENTIAL HYPERTENSION

How might neurogenic human hypertension be identified clinically, other than in the obese, where this mechanism is usually operative (Table I)?

- Essential hypertensive patients with an elevated heart rate—which is a common occurrence—do tend to have high sympathetic activity. However, cardiac vagal withdrawal can be a contributing factor, and so a one-to-one relationship of heart-rate-to-sympathetic-activity does not exist.
- The recent diagnostic practice of screening for the presence of primary aldosteronism in hypertensive patients by measuring the plasma aldosterone-renin concentration ratio can uncover patients with high plasma renin activity (Table I). Most of these patients have an increased rate of renin release driven by increased renal sympathetic activity.
- Isolated systolic hypertension in essential hypertension patients under 50 years of age is typically neurogenic, with high sympathetic activity increasing cardiac contractility and left ventricular ejection rates, and reducing arterial distensibility.
- In patients with end-stage renal disease, and often in chronic renal disease of lesser grades, sympathetic nervous activity is increased. In end-stage renal disease, the level of sympathetic activation can be extreme, and reach levels seen in cardiac failure.18

WHAT NEUROGENIC ESSENTIAL HYPERTENSION IS NOT

“White coat” hypertension

In some patients, blood pressure is materially higher at the time of medical consultation than when self-recorded in the home or measured with 24-hour ambulatory monitoring. This is so-called “white coat” hypertension, and is usually due to elevation of blood pressure at the time of the medical consultation. Individuals with “white coat” hypertension do not have neurogenic hypertension, for which hypertension is sustained throughout 24-hour ambulatory blood pressure monitoring.

Table 1. Clinical identification of neurogenic human hypertension.
Recent experience suggests that the “white coat” effect is prominent in shy and rather self-conscious patients, for whom the uncomfortable intimacy of the consultation is a trigger for blood pressure elevation, and is commonly accompanied by blushing. A Japanese study found that “white coat” reactors tended to score low on the Eysenck extroversion scale (and therefore had high introversion scores).\(^\text{19}\) Eysenck argued that highly introverted people find social interactions very aversive. Further support for this hypothesis comes from a study of Italian patients that found that the “white coat” phenomenon was highly correlated with patients’ increase in blood pressure during public speaking—a stereotypical challenge for the introverted.\(^\text{20}\)

**“Labile” Hypertension**

Blood pressure is very changeable in its responses to the internal environment, and to life events. In some patients the day-to-day variability of blood pressure seems to be greater than average. This is used as a diagnostic discriminator to categorize these patients as “labile hypertensives.” To some clinicians, in particular to family physicians and medical generalists, this variant of hypertension is the “signature” of a neurally mediated hypertension. Hypertension specialists, however, are less accepting of the existence of labile hypertension as a discrete entity. Some deny its existence.\(^\text{21}\) Others would suggest that although excess blood pressure lability can be illusory, or artifactual, it is sometimes real and diagnostically important (Table II).

In some patients, eg, those with comorbid panic disorder, labile hypertension is real and is psychogenic. In other patients, such as those with borderline blood pressure elevation, lability of hypertension is **illusory.**\(^\text{21}\) In these patients, blood pressure that is recorded in the clinic, while actually showing the usual degree of variability, creates an illusion of greater fluctuation than normal by oscillating around the cutoff point for the diagnosis of established hypertension.\(^\text{6}\) In other patients, high blood pressure lability is **artifactual,** and is a consequence of the auscultatory gap phenomenon, which can confound the measurement of systolic pressure. The bottom line here is that neurogenic essential hypertension is not a “labile” hypertension. The sympathetic nervous system activation and blood pressure elevation of neurogenic essential hypertension is **sustained,** not reactive and intermittent.

**Pheochromocytoma**

Clearly, neurogenic essential hypertension and pheochromocytoma are separate disorders, so that the clinical issue of concern here is diagnostic difficulties. A persistently elevated heart rate can be present both in neurogenic essential hypertension, and in patients with catecholamine secreting tumors, causing diagnostic uncertainty. The need to identify patients with possible pheochromocytoma, and to confirm the diagnosis by measurement of urinary excretion or plasma concentration of catecholamines and their metabolites, is self-evident. It is unusual for the level of sympathetic activation in neural essential hypertension to be such that plasma and urinary norepinephrine values are so elevated as to suggest pheochromocytoma, but this can sometimes occur, with norepinephrine values elevated as much as three- to four-fold.

**Consequences of Sympathetic Nervous Activation in Hypertension**

While the sympathetic activation present in human hypertension certainly contributes to the elevation in blood pressure—most probably through stimulation of the renal sympathetic nerves, promoting renal tubular sodium reabsorption and renin release—it seems to have additional adverse consequences in hypertensive patients.

**Heart**

High cardiac sympathetic nervous activity in hypertensive patients is probably deleterious. A growth-promoting effect of norepinephrine on cardiac myocytes has been demonstrated in vitro, so a trophic effect of cardiac sympathetic activation in hypertensive patients is probable, and may contribute to the development of left ventricular hypertrophy. We have direct clinical evidence that supports this hypothesis (Figure $7, page 190$).\(^\text{22}\) The general importance of neural mechanisms in arrhythmogenesis is well established and

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**Table II.** “Labile Hypertension”: not a descriptor of neurogenic essential hypertension. Blood pressure is responsive to the internal environment and to life events. In some patients, day-to-day blood pressure variability seems to be greater than usual, providing the basis for their being categorized as “labile” hypertensives. To many doctors, extreme blood pressure lability is the “signature” of a hypertension that is neurally mediated. This is not true. Neurogenic essential hypertension is not typically a “labile” hypertension. The sympathetic nervous system activation and blood pressure elevation of neurogenic essential hypertension is sustained, not reactive and intermittent.
they probably play a role in hypertension as well. Paradoxically, the hypertensive obese may be spared this problem, because they have normal or reduced cardiac sympathetic activity.

**Metabolism**

Glucose utilization by skeletal muscles, through the action of insulin, is influenced by sympathetic nervous outflow to the limbs and skeletal muscle blood flow. It is therefore likely that reduced skeletal muscle blood flow, resulting from neural vasoconstriction, is a primary cause of the insulin resistance and attendant hyperinsulinemia observed in obesity-related hypertension. It is probably also the case for essential hypertension in normal weight patients, in whom insulin resistance is surprisingly common.9,23 Centrally acting imidazoline receptor–binding agents, such as rilmenidine and moxonidine, which inhibit sympathetic outflow, to the skeletal muscle vasculature, reduce insulin resistance. This effect is attributable to the removal of neural vasoconstriction, which is not observed with other antihypertensive drugs.24

There is particular interest in the question of whether prescription of specific antidiureticantihypertensives should become a therapeutic principle in obesity-related hypertension. The preferred drug here should, ideally, target the neural pathophysiology of high sympathetic tone, while also possessing additional attributes: (i) it should not cause further weight gain, by an anti-thermogenic action, and (ii) it should not increase insulin resistance. Large trials have shown that β-adrenergic-blocking drugs increase insulin resistance and also cause an average of 1 to 2 kg weight gain.25 Imidazoline receptor–binding agents, such as rilmenidine and moxonidine, which inhibit sympathetic outflow, might also be expected to increase weight: but surprisingly they do not.25 Weight loss of 1 to 2 kg is typically observed, despite sympathetic inhibition. This is perhaps due to the reduction in neurogenic vasoconstriction in skeletal muscle, producing a favorable effect on insulin resistance and hyperinsulinemia, and consequently favoring weight loss.

Although prescription of the centrally acting sympathetic suppressants in obesity-related hypertension might be preferred on theoretical grounds, at present there is little empirical evidence to support their use. Although one report does describe greater blood pressure reduction in obese than in normal-weight hypertensive patients with combined α- and β-adrenergic blockade,26 the comparative efficacies of all drug classes have not been comprehensively evaluated to date. The limited evidence available does not suggest clear superiority of any particular class of antihypertensive for the treatment of overweight hypertensive patients.

**SHOULD ANTIHYPERTENSIVES TARGET THE NEURAL PATHOPHYSIOLOGY OF ESSENTIAL HYPERTENSION?**

Basing therapy on pathophysiology in heart failure led to a major therapeutic advance—the use of β-adrenergic blockers. By analogy, better delineation of the syndrome of neurogenic essential hypertension might provide a stronger theoretical basis for wider use of antidiureticantihypertensive drugs, centrally acting sympathetic suppressant imidazoline receptor–binding agents such as rilmenidine and moxonidine, or perhaps β-adrenergic blockers, in essential hypertensive patients with high sympathetic tone.
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Sympathetic activation in hypertension: what are the effects on vascular, endothelial, and metabolic function?

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Adrenergic neural function is enhanced in hypertension; it not only influences the development and progression of high blood pressure, but also the occurrence of target organ damage, including cardiac hypertrophy, structural and functional vascular changes, and metabolic abnormalities. This paper will review evidence concerning the importance of sympathetic neural mechanisms in the occurrence of the aforementioned alterations. Particular emphasis will be given to the observed interrelationships in essential hypertension between sympathetic function, arterial stiffness, endothelial function, and insulin resistance. Finally, the therapeutic implications of these findings will be discussed.

During the past two decades, several studies have shown, conclusively, that neuro-adrenergic cardiovascular influences are markedly potentiated in hypertension, playing a role in the genesis and progression of the disease itself, as well as the related increase in cardiovascular risk. The underlying evidence is based on the following findings: (i) in the early hypertensive stages, heart rate is increased, suggesting the occurrence of a hyper-adrenergic state even in the initial phases of the disease.1 Of note, an increased heart rate caused by sympathetic activation can lead to an increased mortality risk in hypertensive patients;2 (ii) in established hypertension, circulating plasma levels of the adrenergic neurotransmitter are elevated, and this is usually combined with an increase in muscle sympathetic nerve firing rate—this has been directly recorded in conscious humans, using microneurographic measurement;3 (iii) norepinephrine spillover, which is another sensitive marker of sympathetic drive, has been shown to be augmented in hypertension—this indicates that the “net” release of the adrenergic neurotransmitter from sympathetic nerve endings is enhanced when blood pressure is increased;4 (iv) the magnitude of the adrenergic overdrive characteristic of essential hypertension parallels the severity of the high blood pressure, and appears to be peculiar to essential hypertension, as no sympathetic overactivity is detectable in secondary hypertension; and (v) these alterations of sympathetic function appear to be potentiated when hypertension is superimposed upon other diseases that are characterized by an adrenergic overdrive, such as obesity, the metabolic syndrome, diabetes, and heart failure.1,5

Overwhelming evidence has established the adverse cardiovascular and noncardiovascular effects of adrenergic overdrive in hypertension. As schematically depicted in Figure 1, in essential hypertension, a number of manifestations of target organ damage, such as cardiac hypertrophy, vascular remodeling and hypertrophy, atherogenic vascular lesions, and insulin resistance, are strictly dependent in their development and progression on the neuradrenergic dysfunction that frequently accompanies hypertension.1

The present paper will provide an in-depth analysis of the relationships between sympathetic neural function, and hypertension-related vascular and metabolic abnormalities. This will be carried out by separately addressing the effects of adrenergic overdrive on the aforementioned components, ie, the fa-

Keywords: sympathetic activity; vascular remodeling; vascular hypertrophy; endothelial function; insulin sensitivity; insulin resistance; hypertension

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voring of the incidence of vascular structural changes, endothelial dysfunction, and insulin resistance. The clinical and therapeutic implications of these findings will also be highlighted.

**SYMPATHETIC ACTIVITY AND ARTERIAL DISTENSIBILITY**

Studies in both animals and humans have shown that the sympathetic nervous system exerts a powerful influence on vasomotor tone, by selectively and differentially increasing peripheral vascular resistance, thereby allowing blood pressure to be maintained. Thus, organs can be adequately perfused in a variety of behavioral circumstances in which perfusion requirements change profoundly.

Whether, and to what extent, adrenergic influences also modify large artery distensibility was not investigated for many years. This was because of the difficulties involved in performing dynamic research into the behavior of large arteries. However, recent technical advances in the assessment of vascular function have allowed us to define the central role exerted by the sympathetic nervous system in modulating arterial distensibility. For example, it has been shown that an acute increase in sympathetic neural drive is accompanied by an immediate reduction in arterial distensibility. Three different studies support this conclusion: (i) some years ago, we found that in healthy volunteers, intra-arterial infusion of phenylephrine (a drug with similar vascular properties to norepinephrine) was associated with a prompt reduction in arterial distensibility, as assessed by beat-to-beat changes in vessel diameter; (ii) arterial distensibility is also markedly reduced in response to the cold pressor test, a maneuver triggering a consistent and widespread increase in sympathetic drive; and (iii) a reduction in radial, as well as carotid, artery distensibility has been reported during cigarette smoking, a condition that also elicits a marked and long-lasting increase in blood pressure and heart rate, because of the peripheral (and possibly central) sympathoexcitatory effects of nicotine and other tobacco derivatives.

A question of primary importance is whether the relationship between arterial distensibility and sympathetic nerve activity has a phasic or a tonic nature. That is, whether: (i) arterial distensibility is reduced only when sympathetic activity is increased, or (ii) the existing sympathetic drive exerts a continuous stiffening effect on large artery vessels, and its influence is both episodic and tonic. Several studies performed in either animals or humans have addressed this question. In one study, radial artery distensibility was assessed both before and after ipsilateral anesthesia of the brachial plexus in healthy patients preparing for surgical correction of Dupuytren disease. As shown in Figure 2, page 194 (left panel), the arterial distensibility values were markedly higher after the anesthetic. This was the case in all subjects studied, with little concomitant effect on blood pressure, heart rate, or radial artery blood flow. In another study, arterial distensibility was assessed in the femoral artery by determining the relationship between echocardiography-determined, systolic-diastolic changes in vessel diameter and pulse pressure values in the brachial artery. Measurements were taken both before and after ipsilateral subarachnoid anesthesia in healthy subjects undergoing arthroscopic removal of meniscal lesions. As shown in Figure 2 (right panel), subarachnoid anesthesia was followed by a significant increase in femoral artery dis-
SNS activation in hypertension: what are the effects on vascular, endothelial, and metabolic function? - Grassi

tensibility, again with little change in blood pressure or heart rate, as well as nonsignificant changes in contralateral vessel blood flow. Similar findings were observed in 5 patients in whom femoral artery distensibility was assessed both before, and 1 month after, surgical ablation of the ipsilateral lumbar sympathetic chain due to peripheral vascular disease. Thus, removal of sympathetic activity is accompanied by an increase in arterial distensibility, indicating that ongoing sympathetic activity exerts an influence on this arterial function. This is the case in both midsize arteries, such as the radial artery, and relatively large arteries, such as the femoral artery. It is also the case in healthy subjects, as well as in patients with altered vessel anatomy such as those with peripheral artery disease.

An increase in sympathetic neural drive may reduce arterial distensibility through a variety of mechanisms. First, when its increase is accompanied by a rise in blood pressure, distensibility may be reduced because the resulting increase in vessel diameter stretches the most undistensible component of the vessel wall, collagen, making an inverse relationship throughout the blood pressure range from diastole to systole. Second, distensibility can also be reduced by a sympathetic-dependent acute increase in heart rate—assuming that the increase is associated with a stiffening of midsize and large elastic arteries, such as the femoral artery. It is also the case in healthy subjects, as well as in patients with altered vessel anatomy such as those with peripheral artery disease.

The above findings have clear-cut pathophysiological implications that suggest that in diseases characterized by heightened sympathetic activity, arterial distensibility is reduced. This is the case in a variety of pathological conditions, such as heart failure, renal failure, and the metabolic syndrome. This has also been shown to be the case in hypertension, during which both large artery and overall arterial distensibility is reduced, while sympathetic activity is increased. This is particularly the case in elderly individuals with isolated systolic hypertension, in whom alterations in arterial stiffness are particularly pronounced.7

Taken together, these findings strongly support the notion that the therapeutic intervention for the aforementioned clinical conditions should not only be aimed at correcting the main pathophysiological alteration, but also at improving (and possibly reversing) the sympathetic abnormality—and thus the impairment of arterial distensibility.

**SYMPATHETIC ACTIVATION AND VASCULAR HYPERTROPHY**

Several mechanisms have been proposed to explain the vascular structural alterations that characterize essential hypertension. They include the extent and duration of the disease itself, as well as the role of genetic, trophic, and anti-trophic factors. Because among trophic factors a leading role is played by adrenerg-
gic neurotransmitters, the sympathetic nervous system has become a key mechanism in this context. This is also because sympathetic denervation has been shown to trigger a reduction in the arterial wall-to-lumen ratio, and in the rate of thymidine incorporation in vascular smooth muscle cells. Furthermore, cervical gangliectomy reduces the wall-to-lumen ratio of ipsilateral cerebral arteries in stroke–prone hypertensive rats. Also, chemical sympathectomy augments arterial distensibility in carotid and femoral vascular districts in Wistar-Kyoto rats.

It has been unequivocally demonstrated that adrenergic influences also exert provascular hypertrophic effects in hypertensive humans. For example, while studies show that β-adrenergic receptors play a major role in the regulation of human muscle cell growth, it has also been documented that β-blocking agents are unable to exert any beneficial effects on hypertension-related structural alterations in the small artery districts. It is well established, however, that sympathetic alterations can favor the development of the “vascular remodeling” phenomenon, ie, the changes in the media-to-lumen ratio that have been reported in essential and secondary hypertension. Recent studies performed in patients with pheochromocytoma or renovascular hypertension suggest that while hypertrophic “inward” remodeling (the vascular condition characterized by an increased wall thickness associated with a reduced lumen) is triggered by angiotensin II (and thus by the renin-angiotensin-aldosterone system), eutrophic inward remodeling (the vascular condition characterized by a reduced vessel lumen with a normal, or near normal, wall thickness) depends on elevated plasma catecholamine levels. Independent of the type of vascular remodeling, however, it should be remembered that these structural abnormalities may favor the occurrence of vascular atherosclerosis, with obvious adverse impacts on cardiovascular health. This is particularly the case if structural abnormalities are combined with other changes, such as a reduction in arterial distensibility.

**SYMPATHETIC ACTIVATION AND ENDOTHELIAL DYSFUNCTION**

In recent years, the endothelium has become recognized as an organ of great importance in the pathophysiology of cardiovascular disease. Endothelial cells can produce different relaxants, including nitric oxide, which is derived from the transformation of L-arginine into citrulline by the activity of the constitutive endothelial enzyme, nitric oxide synthase. Nitric oxide plays a major role in the regulation of vascular homeostasis, and its availability is crucial for maintaining vessels in a constant state of relaxation, for inhibiting platelet aggregation, for vascular smooth muscle cell proliferation and migration, for monocyte adhesion, and for adhesion molecule expression. Altogether, these effects protect vascular walls from the development of atherosclerosis and vascular thrombosis. Major risk factors such as aging, hypertension, and hypercholesterolemia can also alter endothelial cell function and morphology. One of the peculiar features of an altered endothelium is endothelial dysfunction, which is characterized by impaired nitric oxide availability. This is the leading mechanism in the promotion of atherosclerosis and, therefore, cardiovascular events.

Increasing evidence indicates that, similarly to the angiotensin-sympathetic interactions, there is reciprocal feedback between endothelial function (and nitric oxide synthase), and adrenergic cardiovascular drive. Data collected from studies of rabbits have documented that the atherogenic effects of sympathetic activation may be mediated by the endothelium. This is because chloralose anesthesia (which markedly

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**Figure 3.** Effects of chloralose anesthesia (a maneuver eliciting a marked increase in sympathetic activity) on endothelial cells in rabbit thoracic aorta. Note that the endothelial cell death caused by chloralose was almost completely prevented by β-blockade.

activates sympathetic function) has been shown both at low shear stress and high shear stress status to cause endothelial cell death. This effect appears to be almost completely prevented by β-blockade. This finding indicates the participation of adrenergic factors in the phenomenon (Figure 3, page 195). Evidence also exists, however, that the opposite influence—an effect of the endothelium on sympathetic function—also occurs. Again, experimental studies using different animal models have shown that nitric oxide may attenuate the degree of vasoconstriction mediated by the sympathetic nervous system.

SYMPATHETIC ACTIVATION AND INSULIN RESISTANCE

A relatively large number of diseases including obesity, the metabolic syndrome, and diabetes, are characterized by a marked increase in sympathetic drive and a profound decrease in insulin resistance. This raises the possibility that the two phenomena have a cause-effect relationship (Table I). This is confirmed, indirectly, by the close correlation between the homeostasis model assessment index and the sympathetic nerve firing rate found in patients with visceral obesity, a condition characterized by adrenergic activation and insulin resistance (Figure 4). Recent studies, however, have shown that similar to that described for endothelium function, sympathetic-insulin interactions are reciprocal. That is, sympathetic influences can be regarded as causes of insulin resistance, and insulin resistance (and the related hyperinsulinemia), can be viewed as a sympathoexcitatory factor. These two hypotheses will be discussed separately below.

**Sympathetic influences as a cause of insulin resistance**

In a study of normotensive subjects some years ago, it was shown that a reduction in venous return to the heart unloaded cardiopulmonary stretch receptors, and reduced their restraint on sympathetic activity, which triggered marked vasoconstriction in the forearm. This reflex response was accompanied by decreased glucose uptake in skeletal muscle tissue, which indicated an acute reduction in insulin sensitivity. This was also observed in another study, in which venous return to the heart and cardiopulmonary receptor activity was obtained by applying negative pressure to the lower body. The maneuver caused a marked increase in the forearm release of norepinephrine, and a marked reduction in forearm blood flow. In the absence of any changes in blood pressure, this indicated that the sympathetic activation caused arteriolar vasoconstriction.

### Table I. Relationships between sympathetic activity and insulin sensitivity in cardiovascular and non-cardiovascular disease.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Sympathetic activity</th>
<th>Insulin resistance</th>
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<tbody>
<tr>
<td>Essential hypertension</td>
<td>↑</td>
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<tr>
<td>Pregnancy-induced hypertension</td>
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<tr>
<td>Secondary hypertension</td>
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<tr>
<td>Congestive heart failure</td>
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<td>↑</td>
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<td>Acute myocardial infarction</td>
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<td>Liver cirrhosis</td>
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<tr>
<td>Chronic renal failure</td>
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**Figure 4. Direct relationship between muscle sympathetic nerve activity (MSNA), and waist-to-hip ratio (WHR) or homeostasis model assessment index (HOMA) values in patients with central (closed circles) or peripheral (open circles) obesity.**, bx/100 hb, bursts number corrected for heart rate.

markedly reduced, confirming the adverse effects of sympathetic activation on the cells’ ability to transport glucose across the cell membrane—a hallmark of insulin resistance. This is probably the result of vasoconstriction, which reduces the number of open capillaries, and increases the distance that insulin must travel from the intravascular compartment to reach the cell membrane. It may also be influenced by the fact that in insulin-resistant states, the ability of insulin to increase muscle perfusion is reduced by approximately 30%. Evidence demonstrates that: (i) the rate of diffusion of a substance decreases with the square of the distance to its target; (ii) there is a direct relationship between the number of sympathetic neural bursts to skeletal muscle tissue and the homeostasis model assessment index—a measure of insulin resistance; and (iii) insulin resistance is inversely related to the number of open capillaries, as assessed by the extent of microcirculation that is patent to blood flow. This fits the hypothesis that the sympathetic nervous system makes important modulations to insulin sensitivity through alterations in regional hemodynamics. Hemodynamically independent effects on the transport of glucose across cells may also be involved. Sympathetic activation increases adipose tissue lipolysis, which releases free fatty acids into the circulation, thereby engaging a mechanism that directly inhibits glucose transport across the cell membrane (see above).

**Insulin resistance as a cause of sympathetic activation**

Systemic infusion of insulin in individuals in whom a constant plasma glucose concentration is maintained (the glucose clamp technique) causes a marked increase in sympathetic neural outflow to the skeletal muscle circulation. The ability of sympathetic activation to determine, or worsen, insulin resistance is thus associated, by the resultant increase in plasma insulin levels, with further sympathetic activation. This leads to a “chicken-and-egg” question, ie, which abnormality comes first and starts the vicious circle that maintains both high insulin resistance and high sympathetic activity. In this context, a Japanese study showed that whereas at the time of the development of hypertension a group of nonobese subjects showed an increase in both plasma norepinephrine and insulin levels, 10 years earlier they showed only an increase in plasma norepinephrine. This suggests that there are conditions in which sympathetic activation may precede—and possibly determine—inulin resistance. It is of crucial importance to know whether this is also the case for diseases such as obesity, diabetes, and the metabolic syndrome, in order to implement the most effective preventative measures.

One further point needs to be made concerning mechanisms by which insulin stimulates sympathetic nerve activity. Evidence shows that insulin may increase the release of norepinephrine from sympathetic nerve terminals. It has also been shown, however, that the sympathetic stimulation induced by acutely increasing plasma insulin levels is abolished by a dose of dexamethasone that prevents the secretion of adrenocorticotropic hormone from the hypophysis. Furthermore, prolonged administration of dexamethasone at adrenocorticotropic hormone-blocking doses has been shown to significantly reduce the sympathetic nerve traffic values in obese individuals. By contrast, it has a nonsignificant effect in lean individuals. The sympatho-stimulating effect of insulin may thus depend, at least partly, on the action of insulin in the central nervous system. A potential site could be the hypophysis, or the anterior hypothalamic areas, which are responsible for the release of stimulating factors for hypophysial secretion.

**CONCLUSION**

The findings discussed in this paper have important therapeutic implications. Regression of vascular hypertrophy, improved endothelial function, and amelioration of insulin sensitivity represent important goals of antihypertensive treatment. Because all of these conditions are linked by cause-effect relationships to sympathetic activation, it can thus be recommended that drugs interfering with the sympathetic nervous system should be preferred in the therapeutic approach to hypertension that is aimed at achieving these goals.

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Hypertension and chronic renal failure is a highly prevalent combination, which greatly increases cardiovascular morbidity and mortality. Substantial evidence indicates that sympathetic nervous system (SNS) overactivity may play an important role. In rats with 5/6 nephrectomy, norepinephrine turnover rate increases in brain nuclei involved in noradrenergic blood pressure control, whereas dorsal rhizotomy prevents hypertension. In humans, increased peripheral SNS activity, with normalization of SNS activity after nephrectomy has been documented. Renal injuries may activate renal afferent pathways that connect with integrative brain structures involved in SNS activity and blood pressure regulation. Local increased cerebral production of angiotensin II and subsequent activation of oxidative stress may lead to decreased production of nitric oxide and mediate SNS activation.

Keywords: chronic renal disease; hypertension; sympathetic nervous system hyperactivity; oxidative stress

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Hypertension is commonly associated with renal disease, and it undoubtedly accelerates the decline in kidney function and contributes to the progression of the disease. As patients progress toward end-stage renal disease, hypertension becomes more prevalent. As a result, approximately 85% of renal patients are hypertensive by the time they require renal replacement therapy. When such therapy is initiated, hypertension often persists despite an adequate dialysis regimen and multiple antihypertensive medications, and it contributes to the high prevalence of cardiovascular events and deaths in these patients. Hypertension is the single most important predictor of coronary artery disease in uremic patients, even more than cigarette smoking or hypertriglyceridemia, and treatment of hypertension in these patients is difficult and often inadequate. The pathogenesis of hypertension in patients with renal disease is multifactorial, and may vary depending on factors underlying the disease (Table I, page 200). Traditionally, activation of the renin-angiotensin-aldosterone system and volume expansion secondary to sodium retention have been recognized as the most important factors. However, clinical experience indicates that volume depletion and inhibition of the renin-angiotensin-aldosterone system do not result in normalization of blood pressure in a large number of patients. Many patients remain hypertensive despite reaching dry weight and receiving maximal angiotensin II blockade. This suggests

SELECTED ABBREVIATIONS AND ACRONYMS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>GFR</td>
<td>glomerular filtration rate</td>
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<tr>
<td>IL-1β</td>
<td>interleukin 1β</td>
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<tr>
<td>LC</td>
<td>locus coeruleus</td>
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<tr>
<td>LNAME</td>
<td>Nω-nitro-L-arginine-methyl ester</td>
</tr>
<tr>
<td>NADPH</td>
<td>nicotinamide adenine dinucleotide phosphate</td>
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<td>NE</td>
<td>norepinephrine</td>
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<tr>
<td>nNOS</td>
<td>neuronal isoform of nitric oxide synthase</td>
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<tr>
<td>NO</td>
<td>nitric oxide</td>
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<tr>
<td>PHN</td>
<td>posterior hypothalamic nuclei</td>
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<tr>
<td>PVN</td>
<td>paraventricular nuclei</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>SNS</td>
<td>sympathetic nervous system</td>
</tr>
<tr>
<td>SNX</td>
<td>subtotally nephrectomized (rats)</td>
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Hypertension, SNS overactivity, and the kidney: adverse consequences and therapeutic outlook - Campese and others

Table 1. Factors implicated in the pathogenesis of hypertension in end-stage renal disease

- Sodium and volume excess
- The renin-angiotensin-aldosterone system
- The adrenergic system and baroreceptor activity
- Endothelium-derived vasodepressor substances
- Endothelium-derived vasoconstrictor substances
- Erythropoietin use
- Divalent ions and parathyroid hormone
- Atrial natriuretic peptide
- Structural changes of the arteries
- Pre-existent essential hypertension
- Miscellaneous: anemia, arteriovenous fistula, vasopressin, serotonin, thyroid dysfunction, calcitonin gene–related peptide, hypercalcemia

that other factors must play a role in hypertension associated with renal disease. One such factor involves sympathetic nervous system (SNS) overactivity, and understanding the mechanisms that lead to chronic activation of the SNS in renal disease may help to more adequately treat hypertension in affected patients.

EVIDENCE FOR INCREASED SYMPATHETIC NERVOUS SYSTEM ACTIVITY IN CHRONIC RENAL DISEASE

Our studies on 5/6 nephrectomized rats have provided the most convincing evidence yet for a role of the SNS in the pathogenesis of hypertension associated with chronic renal disease. The turnover rate and secretion of norepinephrine (NE) from the posterior hypotalamic nuclei (PHN) were greater in rats with chronic renal disease than in control rats. However, bilateral dorsal rhizotomy at the level of T-10 to L-3 prevented an increase in blood pressure and PHN NE turnover in chronic renal failure rats, and retarded the progression of renal disease. These studies led us to postulate that increased renal sensory impulses generated in the affected kidney and transmitted to the central nervous system, activate brain regions involved in the noradrenergic control of blood pressure, resulting in hypertension.

Animal studies have shown that the kidney is a sensory organ richly innervated with baroreceptors and chemoreceptors. Renal afferent nerves are connected directly or indirectly to a number of areas in the central nervous system that contribute to blood pressure regulation. Stimulation of renal receptors by adenosine, urea, or electrical impulses, evokes reflex increases in SNS activity and blood pressure. Activation of renal afferents also appears to be the primary mechanism for calcineurin inhibitor-induced hypertension in rats.

Studies in human subjects also support the notion that renal sensory impulses arising within the affected kidney, which are transmitted to the central nervous system, may activate noradrenergic pathways and result in hypertension. Both direct and indirect evidence implicates increased SNS activity in the pathogenesis of hypertension in patients with chronic renal failure. Plasma NE levels are usually increased in hemodialysis patients. In addition, Converse et al. showed that muscle sympathetic nerve activity directly recorded from postganglionic sympathetic nerve fibers in the peroneal nerves was significantly higher in dialysis patients when compared with normal controls; however, bilateral nephrectomy in dialysis patients normalized blood pressure and SNS activity to the level of that in controls. This suggests that the normalization of blood pressure that follows bilateral nephrectomy may be largely due to elimination of afferent impulses from diseased kidneys, rather than the removal of the major source of renin, as originally thought. In another study, the SNS overactivity in end-stage renal disease persisted despite successful restoration of a normal glomerular filtration rate (GFR) with renal transplantation; however, SNS activity decreased significantly in those renal transplant recipients who underwent native kidney nephrectomy. Patients with chronic renal disease but not yet on dialysis also exhibited heightened SNS activity, and this overactivation was independent of volume status.

Ligtenberg et al reported an increase in muscle sympathetic nerve discharge in patients with chronic renal failure and renin-dependent hypertension, compared with age- and weight-matched controls. Klein et al. observed an increased muscle sympathetic nerve activity in hypertensive patients with polycystic kidney disease, regardless of kidney function.

THE PHENOL–RENAL INJURY MODEL

Because of extensive scarring and the presence of renal insufficiency, in the 5/6 nephrectomized rat model, one cannot rule out a contribution of reduced renal function to the genesis of hypertension. To eliminate this factor, one would need a model of hypertension caused by renal injury, but without an alteration of kidney function. We have developed such a model: in the model, hypertension is caused by injecting 50 μL of 10% phenol into the lower pole of one kidney. This leads to an immediate elevation of NE secretion from the PHN (a marker of increased noradrenergic traf-
ficking in the brain), and a rise in renal SNS activity (a marker of peripheral SNS activity) and in blood pressure. Renal denervation prevents the rise in blood pressure and NE secretion from the PHN caused by the phenol injection. These changes occur without any appreciable alteration in kidney function, and thus isolate renal injury from a reduced GFR as the causative element for high blood pressure. The effects of the phenol-induced renal injury are long-lasting.

These studies have demonstrated for the first time that minimal renal injury (1×2 mm wide) can cause hypertension and a permanent activation of the SNS in the rat, even in the absence of any perturbation in GFR.

**THE ROLE OF NITRIC OXIDE AND CYTOKINES**

Recent studies have provided convincing evidence that the neuronal isoform of nitric oxide synthase (NOS; nNOS) and nitric oxide (NO) are present in specific areas of the brain, and modulate central SNS activity. nNOS is an important component of transduction pathways that tonically inhibit sympathetic outflow from the brainstem. In normal rats, the basal activity of the central SNS is regulated by local NO production. Administration of Nω-nitro-L-arginine methyl ester (LNAME) to male Wistar rats has been shown to increase muscle sympathetic nerve activity and blood pressure. We found that LNAME increased the NE turnover rate in the brain, and increased blood pressure in controls as well as in 5/6 nephrectomized Sprague-Dawley rats.

We have shown that following intrarenal injection of phenol in rats, the abundance of nNOS in the PHN, paraventricular nuclei (PVN), and locus coeruleus (LC) was lower than that in control rats receiving an intrarenal injection of saline. This suggests that the stimulatory action of phenol on the SNS could be mediated by downregulation of nNOS in the brain.

Complex relationships exist between the SNS, NO, and cytokines. Cytokines such as interleukin 1β (IL-1β) appear to function as an intermediate modulator for nNOS induction and SNS activity. We have shown that the administration of IL-1β in the lateral ventricle of control and chronic renal failure rats causes a dose-dependent decrease in blood pressure and in NE secretion from the PHN, and an increase in nNOS mRNA abundance in the brain. Moreover, infusion of a specific anti-rat IL-1β antibody in the lateral ventricle led to a rise in secretion of NE from the PHN and in blood pressure in control rats, and to an even further rise in NE secretion from the PHN and in blood pressure in chronic renal failure rats.

Finally, the administration of an anti-rat IL-1β antibody decreased nNOS mRNA expression in several brain nuclei (PHN, LC, and PVN) of both control and chronic renal failure rats. In all, these findings suggest that IL-1β modulates central SNS activity via activation of nNOS.

**OXIDATIVE STRESS AND SYMPATHETIC NERVE ACTIVITY**

Considerable attention has been given to the effects of short-lived reactive oxygen species (ROS) and reactive nitrogen species on blood pressure and cardiovascular toxicity. ROS, or oxygen free radicals, are O₂⁻, hydrogen peroxide (H₂O₂), and the hydroxyl ion (OH⁻). These molecules are chemically unstable and highly reactive, and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and NOS enzymes regulate their concentration. NADPH oxidase is a multimeric enzyme and is responsible for the reduction of oxygen, electron transport, and superoxide production at the cell surface.

ROS production is increased in several experimental models of hypertension and in human hypertension. A causative role for ROS is supported by evidence that scavengers of ROS, such as dimercapto-succinic acid, lазаroidz, cicletanine, tempol (as a superoxide dismutase mimic), and vitamins C and E ameliorate or abrogate hypertension in animal models. Conversely, depletion of glutathione, an endogenous scavenger of ROS, by means of the glutathione synthase inhibitor butahionine sulfoximine, causes a marked elevation of nitrotyrosine—the footprint of peroxynitrite—and marked elevation of blood pressure in rats. The exact mechanisms through which oxidative stress may raise blood pressure have not been fully elucidated, but reduced availability of NO is the prevailing hypothesis. NO actively reacts with O₂⁻ and other ROS to produce peroxynitrite (ONOO⁻), a highly cytotoxic reactive nitrogen species. Increased production of ROS could enhance oxidation/inactivation of NO and result in activation of the SNS.

We tested the hypothesis that the increase in SNS activity in the phenol–renal injury model is due to activation of ROS. To this end, we examined the abundance of several components of NADPH oxidase, including gp91phox/Nox2, p22phox, p47phox, and Nox3 in the PHN, PVN, and LC.
PVN, and LC using real-time polymerase chain reaction. We observed that the intrarenal injection of phenol caused a significant increase in the abundance of several components of NADPH in a variety of brain nuclei involved in the noradrenergic control of blood pressure. Secondly, we evaluated the effects of two superoxide dismutase mimetics, tempol (4-hydroxy-2,2,6,6-tetramethyl piperidinoxyl) and superoxide dismutase-polyethylene glycol, on central and peripheral SNS activation caused by intrarenal phenol injection. Tempol and superoxide dismutase-polyethylene glycol abolished the effects of intrarenal phenol injection on blood pressure, NE secretion from the PHN, renal SNS activity, and nNOS and IL-1β. The data support the hypothesis that ROS may modulate the central and peripheral SNS activation that follows intrarenal phenol injection.

**IMPLICATIONS OF INCREASED SYMPATHETIC NERVOUS SYSTEM ACTIVITY**

**Effects on progression of chronic renal disease**

The potential role of the SNS in the progression of renal failure has received little attention. Amman et al examined whether nonhypotensive doses (1.5 mg/kg body weight per day) of moxonidine, an agent that reduces sympathetic activity, affects glomerulosclerosis, urine albumin excretion, and indices of renal handling of NE in subtotally nephrectomized (SNX) rats. The glomerulosclerosis index was significantly lower in moxonidine-treated rats compared with untreated SNX rats, as was the index of vascular damage. The number of proliferating cells and nuclear antigen–positive glomerular and tubular cells per area was significantly higher in untreated SNX rats than in controls and moxonidine-treated SNX rats. The same was true for the urine albumin excretion rate.

Cilnidipine, an L-/N-type dihydropyridine calcium channel blocker, has been shown to inhibit SNS activity and to reduce the progression of renal disease in several types of hypertensive animal models.56,57

**Effects on cardiovascular diseases**

Increased SNS activity raises arterial pressure, triggers arterial damage, and represents a major player in the pathogenesis of left ventricular hypertrophy. There is consistent evidence that in chronic renal disease patients, high sympathetic tone, as measured by plasma NE, predicts mortality and the development of cardiovascular diseases, such as asymptomatic left ventricular dysfunction and chronic congestive heart failure.58,59 Zoccali et al observed an association between SNS activation, measured by plasma catecholamine levels, and cardiovascular events and mortality in a cohort of 228 patients undergoing chronic hemodialysis who did not have congestive heart failure at baseline and who had a left ventricular ejection fraction >35%. Those patients with plasma NE concentrations above the 75th percentile had an adjusted relative risk for cardiovascular complications that was 1.92 (95% CI 1.20 to 3.07) times higher than in those below this threshold (P=0.006).60 In patients with chronic renal disease, muscle sympathetic nerve activity correlates with blood pressure49 and left ventricular hypertrophy.62—an independent predictor of poor cardiovascular outcomes.61,62 Collectively, these findings suggest that in patients with renal failure, SNS overactivity contributes to the pathogenesis of left ventricular hypertrophy and increases the risk of cardiovascular events.

**Therapeutic implications**

Evidence indicates that drugs that inhibit the SNS should effectively reduce blood pressure, progression of renal disease, and perhaps cardiovascular events in patients with chronic renal disease. It is of interest that both antiadrenergic drugs and agents that inhibit the renin-angiotensin system effectively reduce SNS activity. In the phenol–renal injury model, rats treated with the angiotensin II AT1 receptor antagonist losartan had significantly lower blood pressure and SNS activity.41 Furthermore, in humans with chronic renal disease, muscle sympathetic nerve activity was significantly higher than in control individuals.
and it was dramatically reduced by both an AT1 receptor antagonist (losartan) and an angiotensin-converting enzyme inhibitor (enalapril). These data suggest that locally produced Ang II in the brain as a result of renal afferent impulses, may lead to SNS activation. Inhibition of Ang II with AT1 receptor antagonists may reduce SNS activity and blood pressure in animals as well as human subjects.

Clonidine is a centrally-acting sympatholytic agent known to reduce neural sympathetic outflow. We have shown that administration of clonidine in drinking water (0.027 mg/Kg/day) for 3 weeks prevented the chronic rise in blood pressure and SNS activity otherwise seen in rats with renal injury caused by intra-renal phenol injection. Dihydropyridine-derivative calcium channel blockers have usually been shown to raise SNS activity. However, N-type calcium channel blockers, such as cilnidipine, inhibit SNS activity. Cilnidipine inhibits the increase in blood pressure and plasma NE levels in response to cold stress and electrical sympathetic neurotransmission in pithed spontaneously hypertensive rats. Cilnidipine also attenuates the decrease in renal blood flow and urinary sodium excretion caused by renal nerve stimulation in anesthetized dogs. Cilnidipine was found to be effective in reducing proteinuria in patients with chronic renal disease already treated with renin-angiotensin system inhibitors.

**CONCLUSION**

Several factors have been implicated in the pathogenesis of hypertension associated with renal disease and/or renal failure. While the roles of sodium retention, total body volume expansion, and increased activity of the renin-angiotensin system are well recognized, increasing evidence suggests that afferent impulses from injured kidneys may activate areas of the brain involved in the noradrenergic regulation of blood pressure and contribute importantly to the development and maintenance of hypertension associated with renal diseases. Our studies also provide evidence that locally produced angiotensin II in the brain in response to renal afferent stimuli leads to activation of oxidative stress, downregulation of NO and IL-1β, and an increase in SNS activity and blood pressure (Figure 1).

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The writer of this column has been addicted to the pursuit of music and medicine throughout his life. Medicine has been his master, music his mistress.

Why are many physicians and scientists devoted to music? What have music and medicine in common? Music is art, medicine is both art and science. It is not surprising, therefore, that physicians are attracted to the art of music, especially if there is a traditional and familiar background. Many physicians are attracted to music. Physicians play chamber music or they even are composers. The Russian physician/chemist/composer Alexander Porphyrevich Borodin is an example.

But medicine and music have much more in common: there is the medical interest in the ailment of composers. What, we must ask ourselves, is the basis for the interest in the diseases of composers? What makes Beethoven’s deafness, Chopin’s and Weber’s tuberculosis, Mahler’s bacterial endocarditis so interesting? We all die of some disease and we daily see many ailments in our clinic. I suppose it is the belief, not always justified, that illness is reflected in the creativity of the artist. Thomas Mann, in his book, Dr Faustus, has as his leitmotiv the willful, morbid flight of his hero Adrian Leverkühn into disease, syphilis, which is akin to selling his soul to the devil. There are some instances of close connection between disease and music compositions. The connection is particularly strong and obvious in the work of romantic composers, whose trademark it is to express their “Angst” in their art. Examples certainly are numerous: works of Beethoven, such as the Appassionata or the Fifth Symphony. Gustav Mahler’s symphonies are examples of reflections of personal anxiety. There was the suicide of his brother, the death of his first child, Putzi, and his close proximity to his own death because of his bacterial infection.


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endocarditis, diagnosed by Dr Libman in New York, the first diagnosis ever based on a positive blood culture. We also have to add the stormy relationship with his very unstable and immature wife, Alma. On the score of his last works we find words such as “purgatory,” or “the devil dances with me.” As he wrote, “at one blow I have lost all that I have ever attained of clarity and equanimity.” There are also composers who were psychotic such as Robert Schumann or Jesualdo, the brilliant Renaissance composer, who slaughtered both his wife, her lover, and his child.

Yet we have also examples of sunny compositions written by composers while in the depth of illness such as the Clarinet Concerto of Weber or Schumann’s Rhenish Symphony. Apparently, in the romantic, creative personality, there is no filter between mood and creation.

There is more to the relationship of music to medicine: the neurological basis of musical perception and performance. There are two ways to study this connection: (1) by means of the time-honored observations of neurological deficit, and (2) by techniques that modern physics has given us. Examples are PET scanning and functional magnetic resonance imaging.

A typical example of the diagnosis by neurological deficit is the brain disorder of the French composer Ravel, as related by his neurologist Alajouanine. Ravel was struck down by Wernicke’s aphasia. He developed difficulties in reading notes and in piano playing. On the other hand, recognition of musi-
Imagery tone was excellent. His therefore
was a case of aphasia that left his per-
sonality untouched. His “Art” was lost,
because Art without expression ceases
to be Art.

The conclusions arrived at by neuro-
logical deficit have been greatly ampli-
fied by modern methods of imaging,
primarily PET scan and by functional
magnetic resonance imaging, which en-
ables us to visualize regional changes
in blood flow as a result of changes in
regional neuronal activity. Justine Ser-
gent (see reference) in Montreal has
extensively published in this field, cut
short by her untimely tragic death by
suicide. She has shown, for example,
that sight-reading of music reflects
cooperations by which musical repre-
sentations are transformed by one
modality into another, engaging many
portions of the brain, such as various
parts of the cortex and cerebellum.
Music demands multimodal operations.

What does all this information teach us
about the secret of musical percep-
tion and the deep emotional reward
we get from listening to great music?
In music we enter a realm, which al-
though dependent on the soma, is in-
tangible. Music, that is, the music I am
speaking of, takes wings from its phys-
cical perch. It passes from something
that is measurable to something that
is immeasurable, only definable by its
impact on our emotion or intellect.
In its final sense, music connects us
with the unattainable and the eternal.

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Summaries of Ten Seminal Papers

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Dialogues Cardiovasc Med. 2007;12:211-221

Concerning a definitive regulatory mechanism of the vaso-motor centre which controls blood pressure during cerebral compression


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Selection of seminal papers by Patrice G. Guyenet, PhD
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Highlights of the years by Ian Mudway, MD
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Concerning a definitive regulatory mechanism of the vaso-motor centre which controls blood pressure during cerebral compression

H. Cushing

Bull Johns Hopk Hosp. 1901;12:290-292

In this classic 1901 paper, Cushing demonstrates that an increase in intracranial tension occasions a rise of blood pressure which tends to find a level slightly above that exerted against the medulla. He concludes with proud satisfaction that he has established a “simple and definite law.”

In the experiments, a cannula was tightly screwed into the skull of dogs. The underlying dura mater was opened allowing free communication between the cerebrospinal fluid and the inside of the cannula, which was then connected to a reservoir of warm saline that could be raised to apply pressure to the brain. Intracranial and femoral blood pressures were recorded with mercury manometers connected to a writing cylinder. Another skull opening was fitted with a glass window through which the exposed convolution and the vascularity of the pial vessels could be beautifully seen during the subsequent experiment.

When intracranial pressure rose above the arterial blood pressure, Cushing observed through the glass window that intracranial blood circulation initially ceased. However, soon after, arterial blood pressure began to rise above the intracranial pressure, and brain blood flow was re-established. Regular cycles of brain ischemia and reperfusion generally ensued (Traub-Hering waves). The rise in arterial pressure caused by intracranial pressure was correctly attributed to the activation of the medullary “vasomotor center” because of the following observations: the rise in systemic pressure was associated with a constriction of splanchnic blood vessels, it was unaltered by vagotomy, it was reversibly eliminated by injection of the local anesthetic cocaine into the brainstem, and it was irreversibly eliminated by cervical cord transection.

After 100 years, we still do not know whether Cushing’s “law” is an important physiological reflex for blood pressure regulation or just an acute pathological response to brain ischemia. Following the work of R. Dampney, D. J. Reis, P. G. Guyenet, and M. K. Sun (1979-1996), we now know that the Cushing response is mostly due to a massive activation of the sympathoexcitatory neurons of the ventrolateral medulla (VLM) and that this activation is intrinsic rather than synaptic. In the 1980s, D. J. Reis and others viewed the response of the sympathoexcitatory neurons to hypoxia as a physiological regulator of brain pO₂, and they proposed that these cells operate as oxygen sensors. Hypoperfusion of the VLM would activate these neurons, causing a rise in systemic pressure and restoration of the oxygen level throughout the brain. The concept is attractive and not especially far-fetched. Metabolic imbalance in exercising skeletal muscles causes a reflex increase in blood pressure (the exercise pressor response) well accepted to be a homeostatic regulation of muscle blood flow. Why wouldn’t the all-important brain be endowed with a similar homeostatic mechanism? Such a mechanism would, in effect, regulate brain pO₂ at the expense of systemic blood pressure, and one could even postulate that herein lies the explanation of essential hypertension: a vascular or inflammatory disease that reduces oxygen delivery to the medulla and causes a chronic increase in sympathetic tone. Unfortunately, these speculations still rest on marginal evidence. Although vascular compression of the ventral surface of the medulla has been reported to cause neurogenic hypertension, the claim is hotly disputed. There is little or no evidence that normal, or even slightly below normal, levels of tissue pO₂ directly influence the discharge of VLM sympathoexcitatory neurons. Surely, a mechanism designed for homeostatic regulation of brain pO₂ should also produce a robust activation of breathing: there is little evidence for that either. So, seminal the Cushing paper? Surely, in as much as it has had a considerable following. Important? We may know in another 100 years’ time.

1901

Louis Armstrong, the American jazz musician is born; Pablo Picasso begins his blue period; and Nigeria becomes a British protectorate
For many years, angiotensin II had been considered a blood-borne hormone that targets the blood vessels, the kidneys, and the adrenal cortex. The circulating hormone was known to be produced by a two-step hydrolysis of angiotensinogen, a plasma protein secreted by the liver. The key regulated step, the conversion of angiotensinogen to angiotensin I, was attributed to renin, an enzyme released by the juxtaglomerular cells of the kidney under the influence of renal artery stretch, intratubular sodium concentration, and the sympathetic nervous system. The second hydrolytic step, the conversion of angiotensin I to angiotensin II, had been shown to be due to angiotensin-converting enzyme (ACE) and to occur in a nonregulated manner within the blood vessels. Yet, soon came the realization that angiotensin I and/or II could also be made by various tissues in the absence of renin of renal origin, and the concept of a tissue renin-angiotensin system (RAS) gradually developed. Evidence that the brain contains an RAS and that injection of angiotensin II into the cerebral ventricles could raise the blood pressure of experimental animals, led soon after to the speculation that the brain RAS could play a role in neurogenic hypertension, ie, in hypertension presumed to be caused by a chronic increase in sympathoadrenal activity.

The present study is an important landmark in the hypertension literature, because it provided the first convincing evidence that neurogenic hypertension might be sustained, at least in part, by an elevated level of brain angiotensin II. The selected experimental model was the stroke-prone spontaneously hypertensive (SP-SH) rat, then—and now—considered to be a model of neurogenic hypertension. This strain was compared with a reasonably close genetic match called the Wistar-Kyoto (WKY) rat. The experimental approach was pharmacological and consisted of testing the effect of intracerebral administration of saralasin, a synthetic peptide with already known angiotensin receptor antagonist properties. The key observation was that saralasin reduced the blood pressure of the SP-SH rats, whereas this drug had no effect in the WKY rats. Moreover, intracerebroventricular injection of saralasin was also capable of lowering the blood pressure of nephrectomized SP-SH rats. This important control experiment indicated that circulating renin had no role in generating the angiotensin responsible for activating the receptors that were blocked by saralasin. The blood pressure-lowering effect of saralasin was relatively small, however, (12 mm Hg) and, consequently, the drug did not normalize the blood pressure of the SP-SH rats.

Later work has confirmed that the brain RAS is upregulated under many pathological conditions characterized by a chronic elevation of the sympathetic system, notably heart failure and various animal models of neurogenic hypertension. Angiotensin II is now believed to alter central nervous system networks largely by elevating the level of radical oxygen species. However, the proximal cause of the pathological upregulation of the brain RAS, elevation that occurs predominantly in the hypothalamus and brainstem, remains highly speculative despite considerable past and ongoing research efforts. Also, the long-standing puzzle regarding how angiotensin II is formed in the brain and how its release is regulated has never been fully solved.

Jean-Bédel Bokassa, President of the Central African Republic, crowns himself Emperor; “Saturday Night Fever,” starring John Travolta, premieres in New York; and Amir Sheikh Jabir al-Ahmad al-Jabir Al Sabah becomes leader of Kuwait
Sympathetic augmentation in hypertension: role of nerve firing, norepinephrine reuptake, and angiotensin neuromodulation


Hypertension. 2004;43:169-175

Is essential hypertension a neurological disease? This is the fundamental question that this remarkable paper addresses. The work stands out in the field because of the uncommon diversity of the methods that were used to address the question of whether essential hypertension has a neurogenic component, ie, whether this disease is caused or maintained by an increased sympathetic vasomotor tone. Given the clinical efficacy of sympatholytic drugs (ganglionic blockers in earlier years and α- or β-blockers and central sympatholytics nowadays), the notion that sympathetic hyperactivity might contribute to hypertension could appear intuitively obvious. Yet, the concept has proven exceedingly difficult to establish. Also, for a long time, this notion was strenuously resisted by cardiovascular physiologists who were armed with considerable skill and were also intent on proving that, in hypertension, the brain was out of the loop and the kidney and/or blood vessels were solely to blame.

In this paper, Schlaich et al begin by showing with direct electrophysiological recordings (microneurography) that the sympathetic tone to muscle arteries is elevated in patients with essential hypertension. This elevation is remarkable, because the authors also show that the baroreflex control of muscle sympathetic tone is not altered in hypertensive patients. Elevated sympathetic tone in the face of elevated systemic pressure and a normal baroreflex strongly suggests that the central nervous system network responsible for sympathetic tone generation is upregulated. Microneurography has its drawbacks, however. Catecholamine spill-over by the heart and kidney was therefore also measured. This index of transmitter release was found to be elevated, as predicted, from a rise in sympathetic tone. Yet, the relationship between norepinephrine release and nerve activity appears to be more complex, since the authors also found that catecholamine reuptake was less efficient in hypertensive patients, and they therefore proposed that circulating angiotensin is probably not a key player in the sympathetic hyperactivity and increase in norepinephrine spillover present in essential hypertension.

Does this paper demonstrate that essential hypertension is a neurological disease? Not really. An association between hypertension and elevated sympathetic tone is demonstrated, but the pesky issue of causality remains. In addition, both microneurography and norepinephrine spillover measure the activity of ganglionic neurons, not preganglionic neurons, therefore these indexes do not directly measure the brain output. Transmission between the two components of the sympathetic system (pre- and postganglionic neurons) is not invariant. It can be modified by circulating factors, including angiotensin II. Furthermore, the study was limited to a small number of subjects, and the authors were careful not to generalize their results to excess. Yet, this paper must also be considered in the context of recent experimental evidence in laboratory animals that demonstrate quite clearly that the master gland (the brain) is capable of regulating blood pressure not just for minutes or hours, but for a week or more. The recently obtained proof of principle that the brain can regulate the long-term level of blood pressure provides the impetus necessary to vigorously pursue clinical research designed to further explore the neurological basis of hypertension. A whole generation of industrial scientists has been searching for antihypertensive drugs that target the kidneys and blood vessels rather than the brain. Could the limitations of current antihypertensive treatment be the result?

Tabaré Vázquez is elected President of Uruguay; a hajj stampede in Mina, Saudi Arabia, results in the death of 251 pilgrims; and Brazil launches its first rocket into space
Junctional adhesion molecule-1 is upregulated in spontaneously hypertensive rats: evidence for a prohypertensive role within the brain stem

H. Waki, B. Liu, M. Miyake, K. Katahira, D. Murphy, S. Kasparov, J. F. Paton
Hypertension. 2007;49:1321-1327

It is perhaps a little early to characterize the Waki paper as seminal, given that the term implies a high impact on subsequent research, which only a seer could predict. However, this creative paper has undoubtedly great potential.

Its main interest and originality is in the promotion of the relatively new concept that a vascular defect in the brain might contribute to hypertension. Junctional adhesion molecule, JAM-1, is a component of endothelial tight junctions that characterize capillaries growing in close association with brain tissue. These tight junctions are an essential component of the blood-brain barrier, but JAM-1 has other and perhaps more important properties, namely, the promotion of leukocyte-endothelial adhesion and subsequent inflammation.

In this paper, the authors begin by demonstrating that the level of expression of JAM-1—especially one of its splice variants—is elevated in the brain of spontaneously hypertensive rats (SHRs) relative to their genetic control, the Wistar-Kyoto (WKY) rats. The difference in the expression level was identified at the mRNA and protein levels. The difference was already present during the prehypertensive period, and therefore cannot be a consequence of the hypertension. The obvious question was whether JAM-1 overexpression actually contributes to the hypertensive process or whether it is simply unrelated. Many differences have been noted before between SHRs and WKY rats relative to gene expression, transmitter level or behavior, and the finding of one more genetic difference would normally probably be of only passing interest. What distinguishes the present study from a very large number of similar observations in other studies on SHRs, are the next experiments that were designed to test whether overexpression of JAM-1 in the WKY rat is capable of producing a rise in blood pressure. JAM-1 overexpression was accomplished by adenoviral transfer. The technique consists of using the adenovirus to deliver a protein of interest continuously to cells. JAM-1-expressing virus (Ade-CMV-JAM-1) was injected into the nucleus of the solitary tract (NTS) in a group of WKY rats, while another group of WKY rats received a control virus (Ade-CMV-JAM-1) to verify that the changes in blood pressure were not due to viral infection per se, but to JAM-1 overexpression. The adenovirus is not specifically neurotropic and, as expected, the virus also infected large numbers of glial and vascular cells. Adenovirus-mediated JAM-1 overexpression was confirmed by immunohistochemistry. The WKY rats subjected to injection of Ade-CMV-JAM-1 developed mild hypertension that was sustained for 2 weeks. The cardiac portion of the baroreflex was measured and found to be unchanged, leading the authors to speculate that JAM-1 targeted NTS mechanisms that control mean blood pressure rather than just the baroreflex, a distinction that remains somewhat vague at present, one must admit. It is also clear that Ade-CMV-JAM-1 does not nearly raise the blood pressure level of the WKY rats to that of their SHR colleagues. The reason could simply be that vascular inflammation promoted by JAM-1 overexpression elsewhere in the brain, also contributes to the hypertensive process in the SHR. Increases in radical oxygen species triggered in the hypothalamus and the brainstem by excess production of brain angiotensin, is strongly suspected to contribute to sympathetic hyperactivity, as for example, in heart failure. A related mechanism could hypothetically account for the adverse effects of JAM-1 overexpression or, as suggested, cytokines released by leukocytes adhering to capillaries could influence NTS neurons by transendothelial release of mediators. Experimental tests of these interesting, but still very theoretical possibilities, will be eagerly awaited.

Apple’s iPhone is released in the United States; Greece suffers its worst heat wave in a century; and Tony Blair resigns as Prime Minister of the United Kingdom
Unloading arterial baroreceptors causes neurogenic hypertension

T. N. Thrasher


This study strongly suggested that, contrary to the prevailing dogma, arterial baroreceptors may have a profound influence on the blood pressure set-point (24-hour mean blood pressure level). This paper is seminal because of its iconoclastic nature: it severely dented a well-entrenched concept developed 30 years earlier, according to which arterial baroreceptors buffer behavior-related changes in blood pressure, but have no effect on the long-term level of blood pressure. The traditional concept was based primarily on the following two observations: baroreceptor denervation produces pressure lability but does not change the mean 24-hour level of blood pressure, and arterial baroreceptors reset quickly and perhaps fully in hypertension.

What Thrasher suggests in this paper is that total baroreceptor denervation is probably a fundamentally flawed experimental approach to determining the role of these mechanoreceptor afferents in blood pressure control. His approach was to leave one buffer nerve intact (carotid sinus nerve), to cut the other three, and to lower blood pressure in the normally innervated carotid sinus in order to "unload" the surviving baroreceptors. This procedure caused an increase in arterial blood pressure of more than 20 mm Hg that persisted unabated for a whole week. This time scale is critical, because according to the proponents of the kidney theory of blood pressure control, 7 days should be many times longer than necessary for the kidney to normalize blood pressure by volume control. When Thrasher lowered the blood pressure in the carotid sinus of control dogs with denervated carotid sinuses, arterial blood pressure did not change. The body weight, plasma electrolytes, and plasma osmolality of experimental and control dogs were identical. A compromised brain circulation could not explain the rise in blood pressure, because dogs with a denervated carotid sinus did not respond to carotid artery occlusion. Carotid chemoreceptor stimulation did not account for the hypertension either, because selective denervation of the carotid sinus made no difference to the outcome. Thrasher speculates that complete denervation of arterial baroreceptors does not cause lasting effects on mean blood pressure because of neuronal plasticity within the nucleus of the solitary tract (NTS). This concept is highly plausible and already supported by compelling evidence. Acute NTS lesions produce fulminating hypertension (see Doba and Reis paper) but, as shown in 1992 by Schreihofer and Sved, no such hypertension is produced in animals in which baroreceptors have been denervated days before the lesion. This observation provides strong evidence that the NTS circuitry becomes reorganized after complete baroreceptor denervation. The ability of the NTS to undergo plasticity changes is further highlighted by recent evidence that the subpostremal zone is one of the few brain regions where neurons are continually born throughout life.

The time scale of Thrasher's experiment remains limited, and it would be an over interpretation to conclude from these experiments that baroreceptors have the ability to cause lifelong hypertension. However, the observation may lead to more practical application in the field of hypertension. Subsequent studies in normotensive and hypertensive dogs by Lohmeier and colleagues have shown that chronic stimulation of baroreceptors causes a long-term and sustained reduction in sympathetic nerve activity and blood pressure. Interestingly, the drop in blood pressure is independent of the renal nerves and is not mediated by increased sodium loss. It is therefore almost certainly mediated by a chronic drop in arteriolar resistance. These observations suggest that buffer nerve stimulation could become an effective therapy in patients with resistant hypertension. If successful, such therapy would owe a great debt to the Thrasher study.
Sympathoexcitatory neurons of rostral ventrolateral medulla exhibit pacemaker properties in the presence of a glutamate–receptor antagonist

M. K. Sun, J. T. Hackett, P. G. Guyenet

Brain Res. 1988;438:23-40

This study is seminal, because it proposed a major alternative to prior theories of sympathetic tone generation that were based on network properties (oscillators). Under anesthesia, blood pressure is maintained within physiological limits by high sympathetic tone to resistance vessels and the heart. In the mid 1980s, the sympathetic vasomotor tone of anesthetized animals had been shown to be dependent on the activity of neurons located in the rostral ventrolateral medulla (RVL). These neurons (RVL sympathoexcitatory neurons) were also known to innervate sympathetic preganglionic neurons and were presumed, correctly, to be both glutamatergic and catecholaminergic. The present paper simply asked why RVL sympathoexcitatory neurons are so active at rest. Conceptually, the possible explanations were, and remain, few. Neurons can be active by virtue of their intrinsic properties (ionic conductances), they can be driven by synaptic inputs, or they can be activated by local factors of non-neuronal origin (hypoxia, pH, factors from glia, blood, blood vessels, etc). By the early 1980s, many types of catecholaminergic neurons (dopaminergic in the substantia nigra, noradrenergic in the locus coeruleus) had been found to possess intrinsic beating properties, ie, the ability to generate action potentials autonomously. Since RVL sympathoexcitatory neurons were suspected to be adrenergic, the possibility that they were also endowed with intrinsic beating properties (the “pacemaker” hypothesis) was simple reasoning by analogy.

The “pacemaker” hypothesis was explored both in vivo and in vitro. The key experiment in vivo was the injection into the hindbrain of a high dose of kynurenate, a blocker of glutamatergic transmission. This treatment clearly attenuated synaptic transmission, because it blocked a series of sympathetic reflexes mediated via inhibition or excitation of RVL sympathoexcitatory neurons. Yet RVL sympathoexcitatory neurons remained highly active. Furthermore, their discharge became remarkably regular (pacemaker-like) and, using tricks of the trade, the possibility that an upstream oscillating network could be responsible for the regularity of their discharge was eliminated. The next experiments extended these observations in vitro. First, a preparation of brainstem and cervical spinal cord from the juvenile rat was set up. This preparation—the first of its kind in fact—was perfused through the basilar artery and kept alive at the reasonably high temperature of 30°C. Recordings performed in the RVL revealed highly active neurons that had very similar properties to the sympathoexcitatory neurons recorded in vivo, namely spinal projections and a regular discharge rate that was impervious to glutamate transmission blockade. Finally, cells with regular discharges were also found in the same region in brain slices. It was concluded that RVL sympathoexcitatory neurons could indeed be endowed with intrinsic beating properties.

The pacemaker theory has received additional support since that time, but its validity has still not been totally proven. In its favor, adrenergic neurons clearly have the ability to generate action potentials independently of conventional synaptic transmission in slices. Partially characterized subthreshold ionic conductances (sodium and calcium currents) are responsible for this activity, but local factors including pH and oxygen could also be involved. The pacemaker theory has been objected to because these neurons are silent when totally isolated, but isolation also deprives them of their dendrites in which conductances required for their autoactivity could very well reside. In the end, the pacemaker theory only accounts for the driving force behind the resting sympathetic tone. The infinitely subtle regulation of this neural outflow is due to a neuronal network of astounding complexity in which RVL sympathoexcitatory neurons are a mere nodal point.

1988

The Soviet Union begins its program of economic reform (perestroika); Baron Philippe de Rothschild, one of the most successful wine growers in the world dies; and Egyptian author Naguib Mahfouz is awarded the Nobel Prize for Literature.
Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene

J. J. Mullins, J. Peters, D. Ganten

Nature. 1990;344:541-544

This paper is famous because it was the first to suggest that an increase in the level of angiotensin produced locally in certain tissues, rather than in the blood, could cause hypertension. The paper is also remarkable on technical grounds, because of the use of transgenic rats, a difficult technology that has somehow never taken hold. Finally, proponents of the brain as the master regulator of blood pressure have a particular fondness for this paper, because it emerges that the brain plays a key role in the hypertension of the transgenic rats produced by Ganten and colleagues.

The rats were produced by microinjecting a linear DNA fragment encoding the entire mouse ren-2 gene including more than 5 and 9 kilobases of 3' and 5' flanking region, respectively, into fertilized eggs. Three of five founders carried the gene. They were successfully bred, and passed the gene to their offspring, leading to stable transgenic lines. These animals had very elevated levels of blood pressure. The hypertension could be reduced by more than half by chronic oral treatment of the rats with captopril, the prototypical angiotensin-converting enzyme inhibitor. This compelling pharmacological evidence demonstrated that the transgene did cause hypertension by elevating the level of angiotensin II somewhere in the body. Yet, the hypertension was clearly not due to an increase in circulating renin or angiotensin. In fact, both of these components of the circulating renin-angiotensin system (RAS) were lower in the transgenic rats than in the controls. This downregulation was attributed to a secondary effect of the hypertension, consistent with the well-known inhibitory effect of elevated blood pressure on the secretion of renin by juxtaglomerular cells. The rest of the experiments describe the tissue distribution of the transgene. High levels were found in the adrenal glands, leading the authors to speculate that the hypertension might be due, at least in part, to elevated secretion of mineralocorticoids by the adrenal cortex.

The investigators did not report having tested the brain for renin overexpression in these rats, and did not appear to have at first considered that the hypertension might have been due to overproduction of angiotensin in the brain. Strong evidence that this was the case was obtained later, when one of the transgenic lines (mRen-2) 27 obtained its Green Card and gracially agreed to be subjected to further diagnostic tests in the US. This work revealed that the hypertension was exacerbated by salt, and that the brain of the rats had extremely elevated levels of angiotensin II and of a related peptide called Angl-7, whose role is still not entirely clear. More importantly, these authors (Carlos Ferrario and colleagues) were able to show that the intracerebral administration of a neutralizing antibody directed against angiotensin II could produce a massive decrease in the blood pressure of the (mRen-2) 27 rats, whereas it had virtually no effect in control rats. This experiment suggested very strongly that an increase in brain angiotensin II made a major contribution to the hypertension in (mRen-2) 27 rats, and these rats therefore represented, at least in part, a neurogenic model of hypertension. Ganten and his collaborators also found subsequently that selective downregulation of brain angiotensinogen by expression of antisense RNA, reduces the blood pressure of the (mRen-2) 27 rat, further demonstrating the importance of the brain RAS in the long-term control of blood pressure. Multiple brain regions are probably implicated, including the hypothalamus and the rostral ventrolateral medulla.

1990

Violeta Chamorro is elected President of Nicaragua, becoming the first female president in Latin America; the “Scandinavian Star,” a Bahamas-registered ferry, catches fire en route from Norway to Denmark, resulting in 158 deaths; and wrecking cranes begin tearing down the Berlin Wall at Brandenburg Gate.
Acute fulminating neurogenic hypertension produced by brainstem lesions in the rat

N. Doba, D. J. Reis

Circ Res. 1973;32:54-53

In this study, the authors demonstrated that bilateral lesions of the nucleus of the solitary tract (NTS) produce fulminating hypertension in rats, leading to pulmonary edema, heart failure, and death. This paper is seminal because it provides the most complete demonstration that severe hypertension can be neurogenic, namely, that it can occur via activation of the sympathetic nervous system and consequent increases in arterial resistance. This paper was highly influential in starting the perennial debate on the role of a hyperactive sympathetic nervous system in hypertension.

The contribution of arterial baroreceptors to short-term blood pressure stability had been demonstrated well before the Doba and Reis paper, and these afferents were already known to innervate the NTS. More importantly, E. M. Krieger in Brazil had already demonstrated that acute hypertension could be produced by sectioning the peripheral nerves that contain arterial baroreceptors. Despite this precedent, Doba and Reis’s study is seminal because of the extreme nature of the hypertension that was observed and because of the thoroughness of their investigation. The authors proved that the hypertension was caused by catecholamine release, as it was blocked by an α-adrenergic receptor antagonist. They proved that neither the kidneys nor the adrenal glands were involved in the rise in blood pressure, since the ablation of these organs did not prevent it. They ruled out a role of tissue hypoxia by measuring blood gases. They also determined that the hypertension was caused by an extreme rise in arteriolar resistance, and they identified the cause of death as heart failure with pulmonary edema. Finally, they suggested that the hypertension was not simply due to the withdrawal of a lower brainstem reflex, but that it required the integrity of the brain area rostral to the pons. The notion that baroreceptors influence the autonomic network at many levels of the brain in addition to the medulla oblongata is very sensible, but the underlying circuitry remains rather poorly understood.

The Doba and Reis paper has spawned numerous studies designed to test whether baroreceptor denervation in animals and, more importantly, a deficit in baroreceptor function in man, can produce chronic hypertension and whether such hypertension is caused by increased sympathetic tone. At the other end of the spectrum, an entire school of cardiovascular physiologists led by A. Guyton in Mississippi was endeavoring with considerable success to demonstrate that the kidney is responsible for the long-term regulation of blood pressure via its regulation of blood volume, and that the sympathetic system was merely involved in short-term adjustments of blood pressure related to behavior. Tests performed in many species in subsequent years appeared to support this interpretation, because presumably, total and selective baroreceptor denervation was found to increase the lability of blood pressure, but not its average 24-hour level. To this day, there is no definitive explanation as to why NTS lesions are capable of causing a hypertension of such magnitude and why chronic barodenervation produces such minimal effect on mean blood pressure. Most speculations revolve around the completeness of the elimination of baroreceptors, and the emergence of countervailing mechanisms that adjust sympathetic tone downward. The P-word (plasticity) is mentioned in hushed tones, but no significant inroad into its cellular mechanisms has been achieved yet. In the final analysis, the discrepancy between the effects of baroreceptor denervation and NTS lesions is probably related to two simple facts: the NTS is indeed essential for blood pressure control, but its role in this context goes well beyond the simple processing of arterial baroreceptor inputs.

The Sears Tower in Chicago is completed, becoming the world’s tallest building; ethernet, the standard for connecting computers over short distances is invented by Robert Metcalfe; and Michael Tippett’s 3rd Piano Sonata, premieres.
Fall in blood pressure produced from discrete regions of the ventral surface of the medulla by glycine and lesions

P. G. Guertzenstein, A. Silver

J Physiol. 1974;242:489-503

This study left its mark in the scientific literature, because it identified with unprecedented accuracy a region of the medulla oblongata that is now regarded as a critical nodal point in the central nervous system circuitry responsible for blood pressure control. What Guertzenstein and Silver discovered was that inhibition of neurons located somewhere above the ventral medullary surface about 2 mm caudal to the trapezoid body, causes a massive drop in the blood pressure of anesthetized cats. This observation inspired a vast amount of follow-up research designed to identify the responsible neurons and their connections, an effort that is still underway several decades later.

Late 19th century investigators had already demonstrated that an intact medulla oblongata is necessary for anesthetized animals to maintain their blood pressure within normal physiological limits, and that regions located rostral to this part of the brain were not essential. In the late 1960s and early 1970s, attempts were made to locate the areas of the medulla oblongata that were most important for blood pressure control, in the hope that a single critical region, a “vasomotor center,” would be found. No such region had been clearly identified by the time Guertzenstein and Silver started their work. Guertzenstein and Silver’s success can be attributed to several factors besides scientific flair. Their main technical innovation was the use of glycine to silence neurons without affecting fibers of passage. They also made use of the “cup technique,” which involves the gentle application of a small plastic tube to the surface of the brain that allows chemicals to be applied over a restricted area of the brain. Last but not least, Guertzenstein and Silver were well aware of prior studies on the ventral medullary surface by respiratory physiologists such as H. H. Loeschke in Germany and R. A. Mitchell in San Francisco. These authors had already pioneered the required surgical techniques. They had introduced the use of cooling probes to inhibit brain activity and cotton wicks to apply chemicals over a restricted region of the ventral medullary surface. With these simple methods, they had defined several so-called chemosensitive regions believed to contain neurons that mediate the stimulatory effect of carbon dioxide on breathing. These authors had also reported that considerable blood pressure changes could be elicited by cooling the ventral medullary surface. Guertzenstein and Silver had the intelligence to put everything together in the manner most convincing for the time. Their paper is an excellent example of integrative neurobiology. It is especially notable for its use of several convergent physiological approaches (electrical stimulation, lesions, the effect of glycine) and for the precision of its histology.

At present, we know that the region of the medulla oblongata that Guertzenstein and Silver pinpointed in their 1974 paper contains a bilateral cluster of excitatory neurons that innervate sympathetic preganglionic neurons. For reasons that are still debated (see commentary on the Sun et al paper), these neurons are highly active under anesthesia. Their destruction or inhibition eliminates sympathetic tone to the heart and resistance arteries, causing the massive drop in blood pressure originally described by Guertzenstein and Silver. Finally, we also know that baroreflex compensation through the intact contralateral side is the reason why Guertzenstein and Silver found that unilateral application of glycine to the ventral surface produces little effect on blood pressure.

1974

Muhammad Ali knocks out George Foreman in the eight round of the “Rumble in the Jungle” fight in Kinshasa, Zaire to regain the Heavyweight Boxing Title; Israel formally signs the Sinai accord with Egypt; and American television host Ed Sullivan dies, aged 73 years
his paper is a shining example of 1980s electrophysiological wizardry. By performing truly heroic experiments, the authors elucidated a cellular mechanism that is presumably responsible for baroreflex modulation by the hypothalamus. A little background information is necessary to appreciate the work: the context of the study concerns how blood pressure rises during emotional behavior or, perhaps, exercise. Electrical stimulation of the hypothalamus produces what was coined by Hilton as the “defense reaction,” an integrated behavioral response associated with strong autonomic signs that include increased blood pressure and respiration. The blood pressure increase is associated with, and probably partly due to, a downregulation of the vagal component of the cardiac baroreflex. Others have postulated that the same, or closely-related, areas of the hypothalamus might be engaged in the production of the autonomic signs associated with exercise, and refer to the process as “central command.” In any event, these autonomic manifestations persist to some degree under anesthesia, and under these conditions, it is also possible to observe a reduction in both components of the baroreflex. The present study examines how hypothalamic stimulation biases the baroreflex at the cellular level.

The authors postulated that hypothalamic stimulation might downregulate the baroreflex by reducing the response of neurons in the nucleus of the solitary tract (NTS) to baroreceptor afferents, and they proceeded to test the hypothesis using electrophysiological methods. With extracellular recordings, they showed first that hypothalamic stimulation reduced the activation of NTS neurons by baroreceptor inputs. This effect was only produced when the region of the hypothalamus that triggers the defense reaction was being stimulated. This region was identified histologically as residing in, or close to, the fornix. The cellular mechanism responsible for attenuating the baroreceptor input to NTS cells was revealed using intracellular recordings. This approach is extremely difficult in such a mechanically unstable portion of the brain as the NTS. Yet, the authors were able to clearly show that the NTS neurons were hyperpolarized by hypothalamic stimulation. This and other evidence described in the paper suggested that the activation of NTS neurons by baroreceptor inputs was reduced by a postsynaptic mechanism consisting of hyperpolarization and reduced neuronal resistance (shunting). Both effects are most probably due to the release of gamma-aminobutyric acid (GABA). Hyperpolarization would cause the membrane potential of the NTS neurons to move away from their action potential threshold, and a reduced neuronal resistance would attenuate the magnitude of the depolarization caused by baroreceptor inputs.

The study is important because it demonstrated that transmission between baroreceptor afferents and their target neurons in the NTS is not an invariant process, but one that can be regulated by inputs from other brain regions with important consequences on heart rate and sympathetic tone, and hence blood pressure. Since then, this principle has been generalized by evidence that the baroreflex can be modulated at the level of the NTS by many other inputs besides the hypothalamus, for example by inputs from nociceptors and muscle afferents. The relative importance of these NTS mechanisms to the autonomic adjustments to pain and exercise is more difficult to assess. Blood pressure is controlled by a vast network of neurons. Baroreflex biasing at the NTS level is only one of many mechanisms by which blood pressure is adjusted during various behaviors. Direct regulation of preganglionic activity, sympathetic tone-generating neurons in the ventrolateral medulla, and many other regions are also known to contribute.
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Instructions for authors

GENERAL INSTRUCTIONS

- Manuscripts should be provided on word-processor disks (3 5-in, for IBM, IBM-compatible, or Apple computers) with three hard copies (text and figures) printed on one side of standard-sized white bond paper, double-spaced, with 2.5-cm margins. Pages must be numbered. Standard typed page = 25 lines of 75 characters (including spaces) double-spaced, 2.5-cm margins = a total of 275 words per page.

- All texts should be submitted in English. In the case of translations, the text in the original language should be included.

- On the title page, provide title of manuscript (title should be concise, not exceeding 120 characters, including spaces), short running title, keywords, and acknowledgments, as well as full names (first name, middle name(s), and last name) with highest academic degrees (in country-of-origin language), affiliations/address, telephone No., fax No., and E-mail address.

- Illustrations (photographs, tables, graphs, figures--high-quality printouts, glossy prints, and/or high-quality scans as jpg files) should be of good quality or professionally prepared, numbered according to their order, with proper orientation indicated (eg, “top,” or “left”), and SHORT legends provided, not repetitive of text. As figures and graphs may need to be reduced or enlarged, all absolute values and statistics should be provided. All illustrations should be cited in the text, with distinct numbering for figures and tables. Illustrations will be reproduced in full color only when clearly necessary, eg, images from nuclear medicine or histology.

- Include HEADINGS using a consistent style for the various levels of headings, to highlight key points and facilitate comprehension of the text. The Publisher reserves the right to add or delete headings when necessary.

- Abbreviations should be used sparingly and expanded at first mention.

- Use Système International (SI) units.

- Use generic names of drugs.

- All references should be cited in the text and numbered consecutively using superscript arabic numerals. The author-date system of citation is NOT acceptable. “In press” references are to be avoided. In the bibliography, titles of journals should be abbreviated according to the Index Medicus. All authors should be listed up to six; if there are more, only the first three should be listed, followed by “et al.” (Uniform requirements for manuscripts submitted to biomedical journals: see www.icmje.org.) Where necessary, references will be styled to Dialogues in Cardiovascular Medicine copyediting requirements.

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The lead article should not exceed 30 standard typed pages (7000 to 8000 words), including an abstract of no more than 200 words, no more than 50 references, and a minimum of 5 - maximum of 10 illustrations (figures and/ or tables). A maximum of 5-10 keywords should be included. The 3 questions for the respondents should be introduced in or after the conclusion. A separate list of “10 references of seminal papers” as well as a separate list of “100 Key References” should be provided.

RESPONDENT ARTICLES

Respondent articles should not exceed 15 standard typed pages (3000 to 4000 words), including an abstract of no more than 125 words, no more than 10 references, and a minimum of 3 - maximum of 5 illustrations (figures and tables). A maximum of 5-10 keywords should be included.

SEMINAL PAPER SUMMARIES

Seminal paper summaries take up one page of Dialogues in Cardiovascular Medicine: the length of each summary should IM-PERATIVELY be comprised between 500 and 600 words, i.e, not exceed 3000 characters. Summaries that are too short or too long will be returned to the author or edited by the Publisher. No figures, tables or references should be included in seminal paper summaries.

FASCINOMA CARDIOLOGICA ARTICLES

Fascinoma Cardiologica articles (A Lexicon of the Heart; Icons of Cardiology; Plants and the Heart; Traits of Discovery, etc) should not exceed 2000 words (8 standard typed pages), should include 3 to 5 illustrations (figures and tables), and cite no more than 15 references. A maximum of 5-10 keywords should be included. No abstract.