

# Hypertension: Cross-Talk Between the Brain and Other Organs

## Summaries of Ten Seminal Papers

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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  $pO_2$ , 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  $pO_2$  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  $pO_2$  directly influence the discharge of VLM sympathoexcitatory neurons. Surely, a mechanism designed for homeostatic regulation of brain  $pO_2$  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.

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1901

Louis Armstrong, the American jazz musician is born; Pablo Picasso begins his blue period; and Nigeria becomes a British protectorate



## Lowering of hypertension by central saralasin in the absence of plasma renin

M. I. Phillips, J. F. Mann, H. Hideyuki, W. E. Hoffman, R. Dietz, P. Schelling, D. Ganten

*Nature*. 1977;270:445-447

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.

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1977

Jean-Bédél 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

M. P. Schlaich, E. Lambert, D. M. Kaye, Z. Krozowski, D. J. Campbell, G. Lambert, J. Hastings, A. Aggarwal, M. D. Esler

*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  $\alpha$ - or  $\beta$ -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 spillover 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. This defect probably also contributes to the elevation in circulating catecholamines. It could not be attributed to a known mutation in the high-affinity norepinephrine transporter, and remains unexplained. Finally, the authors also failed to find any difference in plasma angiotensin concentration between normotensive and hyper-

tensive 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?

2004

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.

2007

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

*Am J Physiol.* 2002;282:R1044-R1053

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.

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2002

Ruth Handler, developer of the Barbie doll dies; floods ravage Central Europe; and a new insect order, Mantophasmatodea, is announced



## 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.

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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 graciously 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 Ang1-7, 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.

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### 1990

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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  $\alpha$ -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 func-

tion 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.

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1973

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.

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### 1974

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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



## Baroreceptor inputs to the nucleus tractus solitarius in the cat: modulation by the hypothalamus

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This 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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1988

Ernst Ruska, the German physicist and developer of the electron microscope, dies;  
François Mitterrand is elected President of France;  
and Jackson Pollock's “Search” is sold  
at auction for \$4 800 000