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Essential hypertension as a result of neurochemical changes at the rostral ventrolateral medulla

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ABSTRACT

Acute ischemia of the brainstem has been known to produce hypertension. After an initial review of central nervous system mechanisms contributing to systemic hypertension and the impact of the rostral ventrolateral medulla (RVLM) on arterial pressure, the authors propose that essential hypertension involves neurochemical changes at the level of the RVLM which are triggered by cerebral ischemia. Experimental and clinical data are presented to show that there is a link between ischemia of the brainstem and chronic hypertension. Atherosclerosis of the cerebral circulation leads to ischemia of the RVLM and other regions with autonomic function. This ischemic process results in increased availability of angiotensin II in the RVLM, which maintains the chronic hypertensive state via either direct stimulation of the RVLM or exacerbation of brainstem ischemia due to increased vasoconstriction.

1. Introduction

Neural mechanisms, particularly the baroreceptor reflexes, are well recognized to be critical for short-term control of arterial pressure (AP), but their role in chronic maintenance of AP is still undetermined.[1] There is clear experimental and clinical evidence that disturbances of central nervous system (CNS) mechanisms of cardiovascular regulation may produce acute hypertension.[2] However, the evidence for the role of the CNS in the pathogenesis of chronic hypertension, including human essential hypertension, is largely indirect and based primarily on studies on the spontaneously hypertensive rat (SHR), an experimental model of human essential hypertension.

Over the past two decades, extensive experimental evidence has accumulated on the critical role of sympathoexcitatory bulbospinal neurons of the rostral ventrolateral medulla (RVLM) in tonic,[3–5] reflex,[6] and adaptive[7] control of AP. Experimental evidence has indicated that direct activation of neurons of the RVLM is involved in sympathoexcitatory responses to experimental brainstem ischemia[8] and is directly excited by hypoxia.[9] Thus, there is experimental evidence linking cerebral ischemia, hypoxic activation of RVLM neurons, and sympathoexcitation. We propose that neurochemical changes at the RVLM level triggered by hypoxia may result in the development and maintenance of chronic hypertension.

2. RVLM neurons and AP

RVLM neurons are functionally and neurochemically complex. They include the C1 group of epinephrine-synthesizing neurons,[10] and most contain L-glutamate, the amino acid responsible for the direct, tonic excitation of sympathetic preganglionic neurons.[11] Catecholamines, substance P, and neuropeptide Y are present in bulbospinal projections from the RVLM neurons and receive multiple neurochemical influences from descending pathways and local neurons.[12] Sympathoexcitatory neurons of the RVLM send direct projections to the intermediolateral cell column of the spinal cord (Fig. 1). They are functionally organized into target-specific topographic subgroups controlling sympathetic outflow to the blood vessels, heart, and adrenal gland.[13] These sympathoexcitatory neurons also mediate the baroreflex.[6] They receive direct inhibitory input from gamma-aminobutyric acid-ergic (GABA) neurons of the caudal ventrolateral medulla, which relays influences from neurons of the nucleus tractus solitarius receiving baroreceptor information.[14] RVLM neurons also receive input from the paraventricular neurons (PVN) and other hypothalamic regions and are thus involved in homeostasis and stress responses.[15] They also mediate sympathetic responses through their input from somatosensory pathways.[16]

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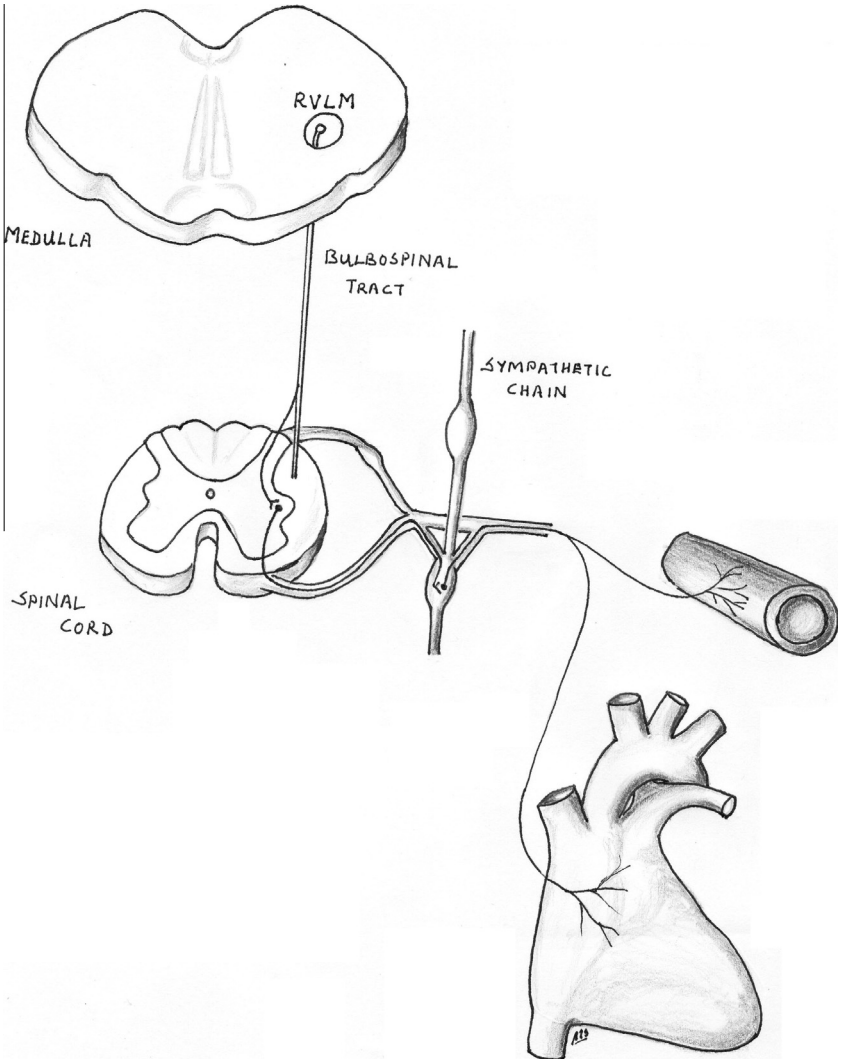

Fig. 1. Sketch showing the sympathoexcitatory output from the rostral ventrolateral medulla (RVLM).

3. RVLM neurons, hypoxic excitation and acute sympathoexcitatory response

The neurons of the RVLM are tonically activated by arterial and cerebrospinal fluid (CSF) blood gas composition and may mediate sympathoexcitatory responses to hypoxia and hypercapnia. The blood flow and capillary density of the RVLM is higher than in surrounding areas. The C1 neurons are rich in mitochondria and send processes that contact the central chemosensitive areas of the ventral medullary surface or are closely apposed to small capillaries.[17] Vasomotor RVLM neurons are excited rapidly by transient brainstem ischemia,[9] local hypoxia[11] and increased CO2/H+ in the CSF.[18] The role of RVLM neurons in mediating central sympathoexcitatory responses to hypoxia has been reviewed by Sun and Reis.[19] Cellular hypoxia directly increases the electrical activity of RVLM neurons. This effect is direct, of short latency, and independent of synaptic glutaminergic inputs or generation of nitric oxide. Neurons of the RVLM appear to act as "chemosensors" much like the peripheral carotid chemoreceptors. To our knowledge the transduction mechanism is still undetermined, but appears to involve an increase in calcium ion conductance. The sympathoexcitatory effects of hypercapnia and CSF acidosis are initiated at "central chemosensitive areas of the ventral medullary surface." Whether RVLM neurons are activated directly or indirectly via local neurons or through a respiratory network is still undetermined.[20]

RVLM neurons are thought to mediate hypertension that occurs during experimental cerebral ischemia.[9] Cerebral ischemia produces a marked increase in blood pressure, and there may be an inverse relationship between cerebral blood flow and systemic arterial pressure.[21] In a dog model, systemic arterial pressure increased significantly (sharply) to 260 mmHg when cerebral perfusion fell to 40–60 mmHg.[21]

Brainstem ischemia or compression produces hypertension, bradycardia, and apnea, known as the Cushing response.[22] There is strong evidence that the Cushing response is initiated when the blood flow to the brainstem falls below a critical level.[23] The cerebral ischemic response is mediated by structures in the ventrolateral medulla.[9,24] Transection of the brainstem at the pontomedullary junction does not alter the reflex; however, transection at C1 or sectioning 3 mm rostral to the obex abolishes the reflex.[23]

Brainstem ischemia in humans has been associated with hypertension. Montgomery observed three patients in whom abrupt increases in arterial blood pressure were closely related to transient symptoms suggestive of vertebrobasilar ischemia.[25] Mass lesions that compress or distort the medulla produce labile hyperten-