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S.L. Cravo, O.U. Lopes and G.R. Pedrino

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Involvement of catecholaminergic medullary pathways in cardiovascular responses to acute changes in circulating volume

S.L. Cravo[1], O.U. Lopes[1] and G.R. Pedrino[2]

[1]Departamento de Fisiologia, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brasil
[2]Departamento de Ciências Fisiológicas, Universidade Federal de Goiás, Goiânia, GO, Brasil

Abstract

Water deprivation and hypernatremia are major challenges for water and sodium homeostasis. Cellular integrity requires maintenance of water and sodium concentration within narrow limits. This regulation is obtained through engagement of multiple mechanisms and neural pathways that regulate the volume and composition of the extracellular fluid. The purpose of this short review is to summarize the literature on central neural mechanisms underlying cardiovascular, hormonal and autonomic responses to circulating volume changes, and some of the findings obtained in the last 12 years by our laboratory. We review data on neural pathways that start with afferents in the carotid body that project to medullary relays in the nucleus tractus solitarii and caudal ventrolateral medulla, which in turn project to the median preoptic nucleus in the forebrain. We also review data suggesting that noradrenergic A1 cells in the caudal ventrolateral medulla represent an essential link in neural pathways controlling extracellular fluid volume and renal sodium excretion. Finally, recent data from our laboratory suggest that these structures may also be involved in the beneficial effects of intravenous infusion of hypertonic saline on recovery from hemorrhagic shock.

Key words: Baroreceptors; A1 noradrenergic neurons; AV3V; Renal vascular conductance; Blood pressure; Hypertonic saline

Introduction

The maintenance of a stable internal environment is, perhaps, the main objective of all physiological processes (1). Water deprivation and hypernatremia are challenges for the organism. Although daily intake and loss of water and sodium can vary widely, water and sodium concentrations must remain within narrow limits. Therefore, it is no surprise to observe the existence of multiple mechanisms and neural pathways involved in the regulation of the volume and composition of extracellular fluid (ECF). This wide variety of mechanisms ranges from renal mechanisms that alter the handling of sodium up to mechanisms that control ingestive behaviors.

Changes in body fluid osmolality such as those induced by intravenous infusion of small volumes of hypertonic saline (2-7) elicit behavioral, humoral and cardiovascular adjustments. An increase in plasma sodium concentration stimulates the ingestion of water and the release of vasoactive peptides such as vasopressin, atrial natriuretic peptide (ANP) (2) and oxytocin (3), increases lumbar sympathetic activity and reduces renal and splanchnic nerve discharge (4,5), and causes a pattern of cardiovascular adjustments characterized by transient hypertension and marked and sustained increases in renal blood flow and vascular conductance (5-7).

This integrative regulation is represented in several levels of the central nervous system. Similar to what is observed in other regulatory systems, this integrative action is organized in an increasing level of complexity along the neuroaxis.

The medulla oblongata affects several homeostatic systems, including those controlling the volume and composition of the ECF. Within the medulla oblongata, two areas are especially important for the control of ECF volume and composition: the nucleus of the tractus solitarius (NTS) and the ventrolateral medulla (VLM). Since the seminal study of Guertzenstein and colleagues (8-10), the involvement of the

Correspondence: S.L. Cravo, Departamento de Fisiologia, UNIFESP-EPM, Rua Botucatu, 862, 04023-062 São Paulo, SP, Brasil. Fax: +55-11-5573-7820. E-mail: sldcravo@fcr.epm.br

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VLM in ECF regulation has been extensively investigated (11-18). Twelve years ago, our laboratory began a series of studies to identify the participation of the VLM in the cardiovascular responses to acute changes of volume and composition of the ECF. The purpose of this short review is to summarize our findings and the literature concerning the central neural mechanisms underlying cardiovascular, hormonal and autonomic responses to circulating volume changes. We either expanded the ECF by infusion of isotonic solutions, or acutely increased sodium concentration through injection of minute volumes of hypertonic saline (3 M NaCl). The data obtained with these studies allow us to unveil a neural pathway involving carotid body afferents that transmit information to relays in the NTS and VLM, which in turn project to the median preoptic nucleus in the hypothalamus. We also demonstrated a new role of catecholaminergic medullary neurons in the cardiovascular and ingestive responses to sudden changes in ECF composition. Finally, recent data from our laboratory suggest that catecholaminergic neurons may mediate the beneficial effects of intravenous infusion of hypertonic saline on recovery from hemorrhagic shock.

Role of carotid afferents in responses to ECF changes

Several lines of evidence have suggested that, besides their well-known role in arterial blood pressure regulation, aortic and carotid afferents are also involved in cardiovascular adjustments induced by acute changes in volume or composition of the extracellular compartment (2,3,5,19-24). In a previous study, Morris and Alexander (2) showed that the ANP release after hypernatremia is severely reduced after sinoaortic denervation (SAD). Since hypernatremia in this study was induced by intravenous infusion of a small volume of hypertonic saline, ANP release could not be attributed to atrial expansion or activation of cardiopulmonary afferents. Several subsequent studies suggested that SAD also impairs the release of vasopressin, ANP and oxytocin (2,3,19,24). Additional studies indicated that aortic and carotid afferents are involved in the modulation of renal sympathetic nerve activity (5,25) and regulation of regional blood flow (20,23) during changes of circulating volume.

Consistent with these findings, results from our laboratory have shown that carotid and aortic baroreceptor afferents are involved in cardiovascular responses to hypervolemia and hypernatremia (20,23). In these studies, SAD abolished renal vasodilation, an important mechanism for the increase of sodium and water excretion, induced by volume expansion or hypertonic saline infusion, whereas bilateral vagotomy was ineffective in modifying these responses. Noteworthy is the observation that the effect of SAD was restricted to the renal territory, i.e., SAD did not block the hindlimb vasodilation induced by volume expansion. Overall, these results support the idea that integrity of the carotid and aortic afferents is essential for the cardiovascular responses that follow acute changes in ECF composition.

Several studies have shown that acute blockade of carotid and aortic afferents impairs the ability to maintain arterial pressure during hemorrhagic shock. The combined removal of baroreceptors and chemoreceptors potentiates the hypotension induced by hemorrhage in anesthetized rabbits (22) and dogs (24). This finding is predictable, and compatible with the known importance of the baroreceptor reflex in minimizing sudden changes in arterial blood pressure.

Recently, we showed that selective denervation of carotid afferents abolished the recovery of arterial blood pressure induced by infusion of hypertonic saline in rats submitted to hypotensive hemorrhage (21). In that study, carotid afferents were removed after the induction of hemorrhagic shock and mean arterial pressure was lower than 60 mmHg, i.e., below afferent threshold. Therefore, removal of carotid afferents did not modify the establishment of hypotension, but minimized the beneficial effects of hypertonic solution in the recovery phase.

It should be emphasized that the technique used in this study destroyed not only baroreceptor but also chemoreceptor afferents present in the carotid bifurcation. We subsequently examined the role of carotid body chemoreceptors in the effect of hypertonic saline, inactivating the carotid body chemoreceptors by ligation of the carotid body arteries. That study indicated that the nervous organ glomus caroticum has a prominent and determinant role in the effect of hyperosmotic saline (26). When the function of carotid body chemoreceptors was blocked, leaving all nerves in the area functional, hyperosmotic saline failed to restore arterial pressure. Thirty years ago, Gallego et al. (27) demonstrated that hypertonic solutions cause excitation of chemosensory afferents and depolarization of carotid body type I cells. Our recent studies are compatible with this early observation and suggest that the sensitivity of the chemoreceptors to tonicity has functional effects and triggers homeostatic responses.

The caudal ventrolateral medulla

The earliest evidence indicating a role of the VLM in body fluid homeostasis can be traced to the studies of Feldberg, Guertzenstein and Rocha e Silva Jr. (28-30). These investigators demonstrated that topical application of nicotine to the caudal VLM (CVLM) induced release of vasopressin, but not oxytocin, in anesthetized cats. Inhibition of neuronal activity in the CVLM also inhibited the vasopressin release induced by carotid occlusion. Combining the effects of selective blockade of sites in the rostral (RVLM) and CVLM on the cardiovascular and hormonal responses with bilateral carotid occlusion, they postulated that the RVLM is primarily related to pressor responses, whereas

the CVLM is essential for vasopressin release.

Shortly afterward, Blessing et al. (11) demonstrated that CVLM sites similar to those described in cats regulate vasopressin release in rabbits. They also demonstrated that these sites contain catecholaminergic cells belonging to the A1 group as originally described by Dahlstroem and Fuxe (31) in the 1960s. Combining functional and neuroanatomical studies, they demonstrated that A1 cells in the CVLM directly project to the supraoptic (SON) and paraventricular nuclei (PVN) of the hypothalamus, the two main sources of vasopressin (32,33).

At first it was thought that A1 neurons in the CVLM inhibit sympathoexcitatory neurons in the RVLM (34), but it became clear later that the CVLM neurons that mediate sympathoinhibition are GABAergic, and mainly distributed around the periambigual area (dorsally and medially to the A1 neurons). Now it is widely accepted that catecholaminergic A1 cells in the CVLM do not project to the RVLM, and that their main projections are to diencephalic nuclei involved in the control of water and salt balance (4,12-15,17,18).

Neuroanatomical studies have further extended these original observations demonstrating that A1 noradrenergic cells receive projections from arterial baroreceptors as well as from vagal cardiopulmonary volume receptors (35,36). These neurons are also reciprocally connected with hypothalamic regions known for their involvement in neuroendocrine, hydroelectrolytic, and cardiovascular regulation, including the median preoptic nucleus (MnPO), the subfornical organ (SFO), the PVN, and the SON (32,33).

A functional role of A1 neurons in cardiovascular and humoral responses to acute reductions in central blood volume was also demonstrated in rats (12,13,18). Buller et al. (12) demonstrated that Fos staining induced by hypotensive hemorrhage in neurosecretory vasopressin cells in the SON and PVN was reduced by lesions in the A1 region. Such lesions also reduce the vasopressin secretion induced by decreased circulating volume (13,18).

Despite the abundance of evidence for the role of A1 noradrenergic neurons in response to reductions of blood volume, relatively little is known about their role in response to hypernatremia and volume expansion. Subcutaneous, intraperitoneal and intravenous administration of hypertonic saline increases Fos expression in the A1 group (14,15), indicating neuronal activation.

We have recently demonstrated that A1 noradrenergic neurons are involved in the autonomic and cardiovascular responses induced by increases in plasma sodium concentration (4,17). In those studies, we used anti-dopamine-β-hydroxide-saporin, an immunotoxin that selectively kills dopamine-β-hydroxide (DβH)-containing neurons. Injection of this toxin into the CVLM caused a 62-79% loss of A1 catecholaminergic neurons. The increase of renal blood flow and vascular conduction induced by intravenous hypertonic saline infusion was abolished in rats treated with anti-DβH-saporin (17). Furthermore, lesion of A1 noradrenergic neurons prevented the renal sympathoinhibition induced by hypernatremia (4). Additionally, we have demonstrated that these noradrenergic cells were part of an inhibitory circuit involved in the control of NaCl intake induced by ANG II-dependent mechanisms (37). These studies represent the initial observation that A1 noradrenergic neurons are involved in autonomic, cardiovascular and behavioral adjustments induced by changes in circulating volume.

The anteroventral third ventricle region

The preoptic-periventricular tissue surrounding the anteroventral third ventricle (AV3V) is a forebrain region with a critical role in the maintenance of fluid and electrolyte balance and cardiovascular function (7,38-44). The AV3V received its name because of its location just anteroventral (AV) to the third ventricle (3V). This area encompasses several distinct neural structures including the organum vasculosum laminae terminalis (OVLT), the ventral portion of the MnPO, the preoptic periventricular nucleus (PPO), and the more medial aspects of the medial preoptic nucleus (MPO) (45,46).

The OVLT and SFO are located in regions devoid of a blood brain barrier, and act as sensors of blood composition (47). The MnPO seems to be an integrative and relay station that receives inputs from the SFO and OVLT as well as inputs from high- and low-pressure baroreceptor pathways (48-51). The MnPO connects to regions known to be involved in body fluid homeostasis and cardiovascular regulation, such as the hypothalamic PVN and SON (48,51-53). These connections appear to be important elements of central pathways involved in responses induced by changes in the body fluid volume and composition.

Several lines of evidence have demonstrated the importance of the AV3V in electrolyte balance and cardiovascular homeostasis. Intravenous infusion of hypertonic saline induces c-Fos expression in the AV3V region (54). Functional studies have demonstrated that the dipsogenic and natriuretic effects induced by hypernatremia are markedly reduced in AV3V-lesioned animals (43,55,56). In addition, lesions in this region impair water intake (43) and ANP release (39,57) in response to changes in circulatory volume. Consistent with these findings, our laboratory has demonstrated that electrolytic acute or chronic lesions of the AV3V prevent the renal vasodilation induced by intravenous infusion of hypertonic saline and by volume expansion (7,38).

Neuroanatomical studies have shown that catecholaminergic neurons from the A1 noradrenergic group in the CVLM project strongly to the MnPO (33,58). Microdialysis studies have demonstrated that electrical stimulation of A1 noradrenergic groups stimulates the release of norepinephrine in the MnPO (49,59). Moreover, Tanaka et al. (51) have demonstrated that electrical stimulation of the A1 noradrenergic region in the VLM can increase the discharge

of MnPO neurons that project to the PVN. This excitatory response was blocked by the α-adrenoceptor antagonist phentolamine, but not by the β-adrenoceptor antagonist timolol. These results suggest that the A1 region acts by enhancing the activity of MnPO neurons through an activation of α-adrenoceptors.

As mentioned before, we have recently demonstrated that the renal sympathoinhibition and vasodilation induced by hypernatremia were abolished after lesions of the A1 noradrenergic neurons in the CVLM induced with the selective toxin anti-DβH-saporin (4,17). Consistent with these findings, nanoinjection of norepinephine into the MnPO, the major source of AV3V efferents, increased renal sodium excretion (60) and ANP release, whereas acute pharmacological blockade of α1-adrenoceptors in the AV3V reduced the ANP release induced by blood volume expansion (40). Therefore, we hypothesized that noradrenergic neurotransmission from the A1 noradrenergic group to the MnPO may be involved in the cardiovascular responses to hypernatremia. To confirm this hypothesis, we studied the effects of nanoinjection of adrenergic antagonists into the MnPO and observed that blockade of α1- and α2-adrenoceptors in the MnPO prevented the renal vasodilation induced by intravenous infusion of hypertonic saline (44). Moreover, α1-adrenoceptors seem to be important not only in the initiation, but also in the maintenance of this hypernatremia-induced response (44).

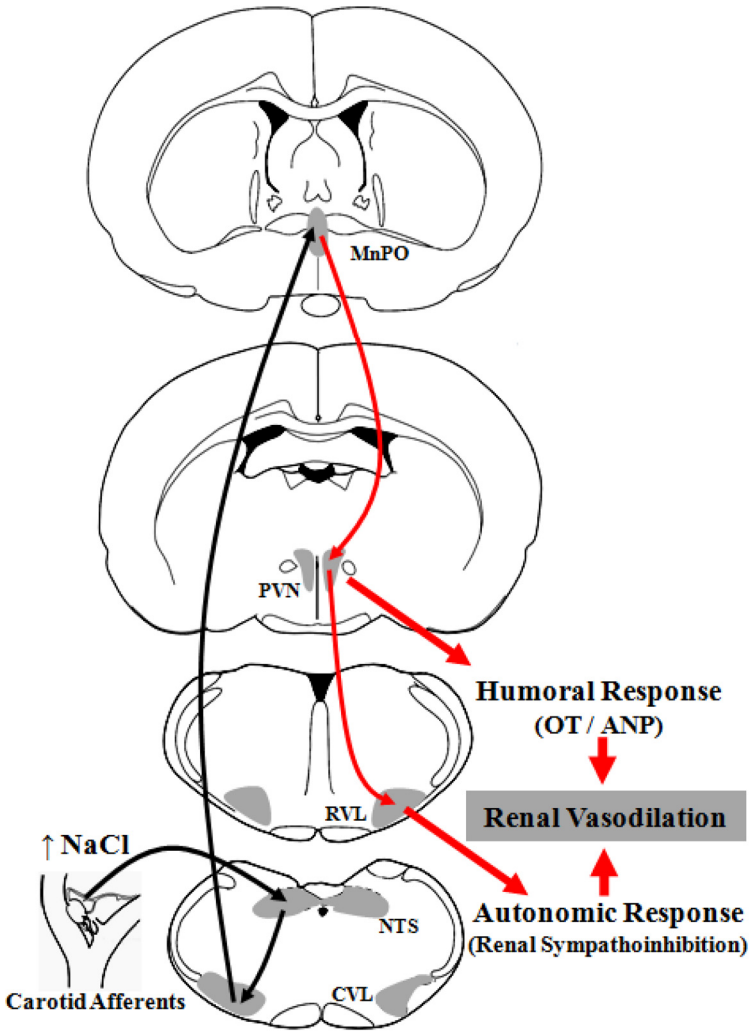

Figure 1. Schematic representation of the neural pathways involved in the control of autonomic, humoral and cardiovascular adjustments induced by peripheral hypernatremia. MnPO = median preoptic nucleus; PVN = paraventricular nucleus; RVL = rostral ventrolateral medulla; CVL = caudal ventrolateral medulla; NTS = nucleus of the solitary tract; OT = oxytocin; ANP = atrial natriuretic peptide.

Overall, these recent lines of evidence support the view that A1 neurons in the CVLM are activated upon stimulation of peripheral carotid afferents (baroreceptor and chemoreceptors), engaging efferent pathways to hypothalamic regions, such as the MnPO, that regulate the endocrine, autonomic, behavioral, and cardiovascular responses that maintain body fluid homeostasis (Figure 1). Since this pathway is important for sympathetic responses to changes of circulating volume, dysfunction of these neurons may result in inadequate function of the renal sympathetic nerves, and this may contribute to the pathophysiology of hypertension, congestive heart failure and cirrhosis.

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