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Cardiovascular adjustments induced by hypertonic saline in hemorrhagic rats: Involvement of carotid body chemoreceptors

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ABSTRACT

The peripheral hyperosmolarity elicited by intravenous infusion of hypertonic saline brings potential benefits to the treatment of hemorrhage. The neural mechanisms involved in these beneficial effects remain unknown. The present study examines the role of carotid chemoreceptors in cardiovascular responses induced by hypertonic saline after hypovolemic hemorrhage in rats. Male Wistar rats (300–400 g) were anesthetized with thiopental, and instrumented for recording of mean arterial pressure. Arterial pressure was reduced to 60 mm Hg by withdrawal of arterial blood over 10 min, and maintained at this level for 60 min by withdrawal or infusion of blood. In control rats (n = 8) with intact chemoreceptors, the subsequent intravenous infusion of hypertonic saline (3 M NaCl, 1.8 ml kg^{-1} body weight, in 2 min) restored blood pressure (pressure increased from 61 ± 4 to 118 ± 5 mm Hg). In experimental rats (n = 8), the carotid body arteries were tied, 30 min after the beginning of the hypotensive phase, leaving the carotid chemoreceptors ischemic. In these rats, hypertonic saline failed to restore blood pressure (pressure increased from 55 ± 1 to 70 ± 6 mm Hg). These findings suggest that the restoration of blood pressure after hypovolemic hemorrhage induced by hypertonic saline depends on intact carotid chemoreceptors.

1. Introduction

Over the past decades, several studies have shown that the hyperosmolarity elicited by infusion of hypertonic saline solution brings potential benefits to the treatment of hypovolemic hemorrhage. Intravenous infusions of hyperosmotic solutions increase blood volume, cardiac output, and regional blood flow, restore arterial pressure, modulate the inflammatory responses, and decrease organ damage (Velasco et al., 1980; Lopes et al., 1981; Rocha e Silva et al., 1986; Rocha e Silva et al., 1987; Vincenzi et al., 2009; Bulger et al., 2007). Collectively, these responses promote cardiovascular stability and restore organ perfusion.

The hemodynamic response to infusion of hypertonic saline in animals submitted to hemorrhage is well established (Velasco et al., 1980; Lopes et al., 1981; Rocha e Silva et al., 1987; for review see Kramer, 2003). However, the neural mechanisms and the afferent pathways involved in this response remain controversial (Lopes et al., 1981; Schertel et al., 1991; Allen et al., 1992; Thrasher and Shifflett, 2001; de Almeida Costa et al., 2009).

Various authors have examined the effect of acute blockade of carotid and aortic afferents on the ability to maintain arterial blood pressure during hemorrhage. The combined removal of both sets of receptors (baroreceptors and chemoreceptors) potentiates the hypotension induced by hemorrhage in anesthetized rabbits (Hosomi et al., 1986) and dogs (Thrasher and Keil, 1998; Thrasher and Shifflett, 2001). Moreover, we recently showed that selective denervation of carotid afferents abolished the restoration of arterial blood pressure induced by infusion of hypertonic saline in rats submitted to hypotensive hemorrhage (de Almeida Costa et al., 2009). However, this denervation eliminates both carotid baroreceptors and chemoreceptors, and it is not yet clear which of the two mediates the response to hypertonic saline.

The present study examines the role of the carotid body chemoreceptors in cardiovascular responses induced by hypertonic saline in rats submitted to controlled hypovolemic hemorrhage. This was done by measuring the cardiovascular responses to hypertonic saline after tying the carotid body arteries of rats subjected to hypovolemic hemorrhage.

2. Materials and methods

2.1. Animals

The experiments were performed on 29 male Wistar rats weighing 300–400 g. They were obtained from the central animal house of the Universidade Federal de São Paulo. Rats were housed in a temperature-controlled room (22–23 °C) on a 12:12 h light–dark cycle, and

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had free access to food and tap water throughout the study. All experimental and surgical procedures were approved by the Ethics Committee of the Universidade Federal de São Paulo and were performed in strict accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

2.2. Surgical procedures, hypovolemic hemorrhage, and infusion of hypertonic saline

On the day of experiments, rats were anesthetized with halothane (2% in 100% O_2). The right femoral vein was cannulated for administration of drugs, and the femoral artery was cannulated for measurement of arterial blood pressure (AP). Administration of halothane was terminated, and subsequent procedures were done with sodium thiopental (initial dose of 40 mg kg^{-1} body weight, i.v., with supplemental doses of 10 mg kg^{-1} body weight, i.v., when necessary). A tracheostomy was performed to reduce airway resistance. Body temperature was maintained at 37 ± 0.5 °C with a thermostatically controlled heating pad.

The carotid body chemoreceptors were selectively inactivated using a standard procedure described before (Franchini and Krieger, 1992). The sternocleidomastoid muscles were reflected laterally, exposing the carotid sheath of the cervical fascia. Under a surgical microscope, the carotid body artery (CBA) was visualized where it branches from the external carotid artery, between the occipital and the internal carotid artery. In experimental rats, the left and right CBA were dissected free, and a loose 6–0 silk suture was placed around them. The loose suture was tightened and the CBA were cut just distal of the suture, leaving the carotid bodies ischemic. In control rats, the CBA were visualized, but not dissected free, and no suture was placed around them. All surgeries were done with care by a skilled researcher using appropriate surgical tools. Under these conditions, carotid sinus nerve damage is unlikely.

Hypovolemic hemorrhage was induced by slow withdrawal of blood over 10 min until MAP reached 60 mm Hg. The average volume removed was 27 ml kg^{-1} body weight. Until 1 h after the initiation of hemorrhage, blood was withdrawn or reinfused as needed to maintain MAP. At 30 min after the initiation of hemorrhage, the loose suture around the carotid body arteries was tightened and the carotid body arteries were cut, leaving the carotid bodies ischemic. One hour after the initiation of hemorrhage, hypertonic saline was infused in 2 min through the femoral vein cannula (3 M NaCl, 1.8 ml kg^{-1} body weight; Pedrino et al., 2005; de Almeida Costa et al., 2009).

2.3. Validation of carotid body artery ligation

Functioning of the arterial chemoreceptors is commonly verified with cyanide, but because the responses to cyanide were weak in intact rats anesthetized with barbiturates, we used a separate group of conscious rats to validate ligation technique. Rats previously fitted with cannulas in the femoral artery and vein were anesthetized with

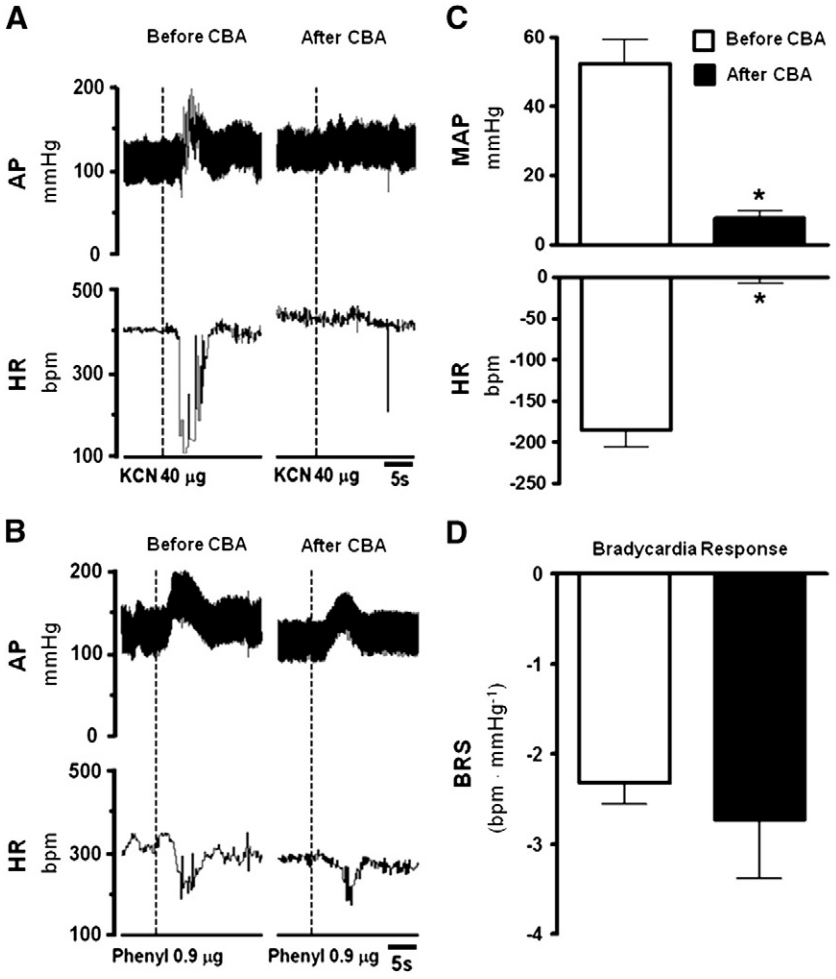

Fig. 1. Effects of bilateral carotid body artery (CBA) ligation in cardiovascular adjustments induced by activation of the arterial chemoreflex (A and C) and the baroreflex (B and D) in conscious rats. A and B) Typical examples. C) Maximal changes of mean arterial pressure and heart rate (HR) induced by KCN administration (40 µg; n = 13). D) Baroreflex sensitivity (BRS) evaluated by bradycardia responses induced by increase of arterial pressure (AP; n = 5). Phenyl = phenylephrine. *$p < 0.05$, paired t test. Responses are similar to those described by other authors (Franchini & Krieger, 1992).

ketamin (100 mg kg^{-1} body weight) and xylazin (20 mg kg^{-1} body weight), and the CBA were tied with 6–0 silk suture and cut. One day before surgery and one day after surgery, 40 μg potassium cyanide (KCN) was injected through the venous cannula while heart rate and blood pressure were recorded.

To confirm the baroreceptors integrity, sequential bolus injections (0.1 ml) of increasing doses of phenylephrine (0.15 to 1.2 μg) were given to induce 5 pressure responses ranging from 4 to 70 mm Hg. Peak increases MAP after phenylephrine injection and the corresponding peak reflex bradycardia were recorded for each dose of the drug. Baroreflex sensibility (BRS) was evaluated by a mean index, calculated as the ratio between changes in HR to the changes in MAP. The mean index was expressed as beats per minute per millimeter of mercury, as described before by Harthmann et al., 2007.

2.4. Recording of arterial pressure and heart rate

The arterial catheter was connected to a pressure transducer. Signals were amplified (ETH200, Iworx, Dover, NH) and digitalized at a frequency of 1000 Hz (PowerLab 8SP; ADInstruments Inc, Colorado Springs, CO). Mean arterial pressure and heart rate were determined from the pulsatile signal with Chart software (v7.1.1; ADInstruments, Inc, Colorado Springs, CO).

2.5. Data analysis and statistics

Results are presented as means ± SEM. The data were analyzed by two-way analysis of variance. When group means differed significantly, the Fisher LSD post hoc test (Statistica 7.0, StatSoft, Inc., Tulsa, OK, USA) was used to detect pair wise differences.

3. Results

3.1. Validation of carotid body artery ligation

The rapid intravenous injection of the mitochondrial respiratory chain blocker, cyanide, is known to induce a pressor response and bradycardia (Franchini and Krieger, 1992). Our cyanide injections in conscious intact rats (n = 13) elicited the same pattern of responses: blood pressure increased by 52 ± 7 mm Hg, and heart rate fell by 185 ± 21 bpm (both 7 s after the beginning of injection of 40 μg KCN, Fig. 1, n = 13). One day after bilateral CBA ligation, cyanide invariably failed to induce bradycardia (−1 ± 7 bpm, 7 s after the beginning of KCN infusion, Fig. 1A and C) or hypertension (8 ± 2 mm Hg, 7 s after the beginning of KCN infusion, Fig. 1A and C).

To specifically demonstrate that CBA ligation did not affect baroreceptor sensitivity, in five rats baroreceptor reflexes also were tested before and after CBA ligation. In these animals, baroreflex sensibility was similar before (−2.32 ± 0.24 bpm mm Hg^{-1}, Fig. 1B and D) and after (−2.73 ± 0.65 bpm mm Hg^{-1}, Fig. 1B and D) CBA ligation. Taken together, these results demonstrated that CBA ligation selectively inactivated the carotid chemoreceptors.

Table 1
Body weight, basal blood pressure and heart rate of control rats and rats to be subjected to bilateral ligation of the carotid body artery (CBA).

	N	MAP (mm Hg)	HR (bpm)	Body weight (g)
Control	8	130 ± 3	395 ± 12	330 ± 12
CBA ligation	8	125 ± 2	380 ± 10	330 ± 12

N = number of animals; MAP = mean arterial pressure, HR = heart rate. Differences between groups were not statistically significant (p > 0.05, t test).

3.2. Effects of ligation of the carotid body arteries on responses to hypertonic saline in rats submitted to hypovolemic hemorrhage

Basal blood pressure and heart rate in control (n = 8) and experimental (n = 8) groups were similar and in the normal range (Table 1). Blood was withdrawn to reduce arterial pressure to 60 mm Hg (61 ± 4 mm Hg in controls, 55 ± 1 mm Hg in rats with CBA ligation) 60 min after the start of hemorrhage (Figs. 2 and 3A). The volume withdrawn was similar in both groups (control 8.1 ± 0.6 ml, CBA ligation 7.8 ± 0.4 ml).

In rats with intact chemoreceptors, infusion of hypertonic saline increased arterial pressure to 118 ± 5 mm Hg (30 min after infusion of hypertonic saline, Figs. 2A and 3A), close to the baseline level. In contrast, pressure failed to return to control values in animals with CBA ligation (70 ± 6 mm Hg, 30 min after infusion of hypertonic saline, Figs. 2B and 3A).

Hemorrhage reduced heart rate both in controls (by 45 ± 16 bpm, 20 min after the beginning of hemorrhage, Figs. 2 and 3B) and in rats with CBA ligation (by 25 ± 11 bpm, 20 min after the beginning of hemorrhage, Figs. 2 and 3B). Infusion of hypertonic saline increased heart rate in controls (by 42 ± 14 bpm, 30 min after infusion), but tachycardia was less pronounced in rats with CBA ligation (11 ± 12 bpm, 30 min after infusion of hypertonic saline, Figs. 2 and 3B).

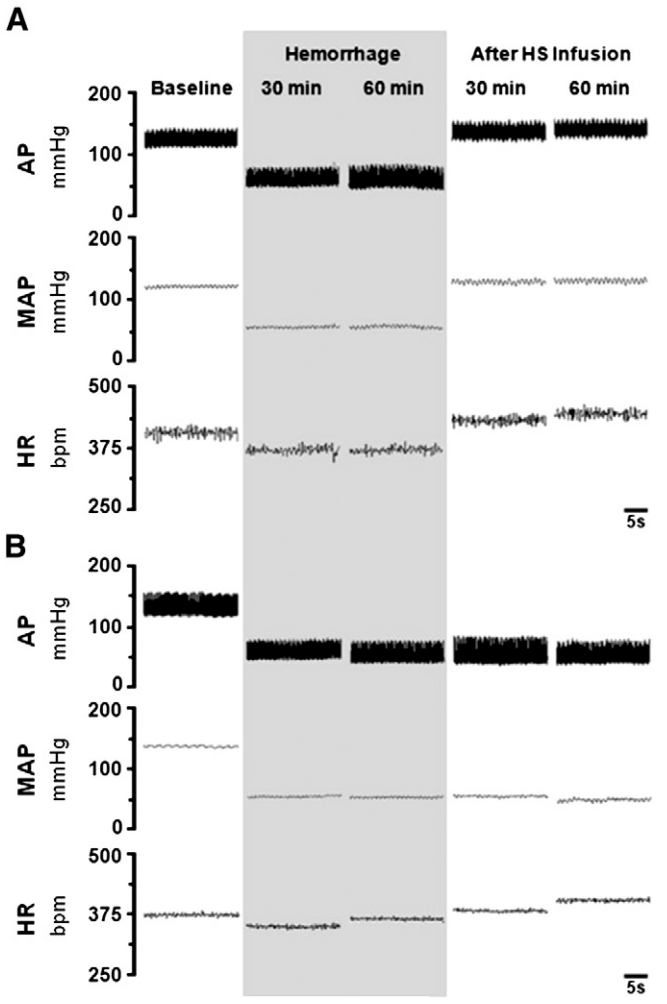

Fig. 2. Typical examples of cardiovascular effects of hemorrhage and hypertonic saline infusion in rats with intact (A) and tied carotid body arteries (B). AP = arterial pressure, MAP = mean arterial pressure, HR = heart rate. Shaded area indicates the period of hemorrhage.

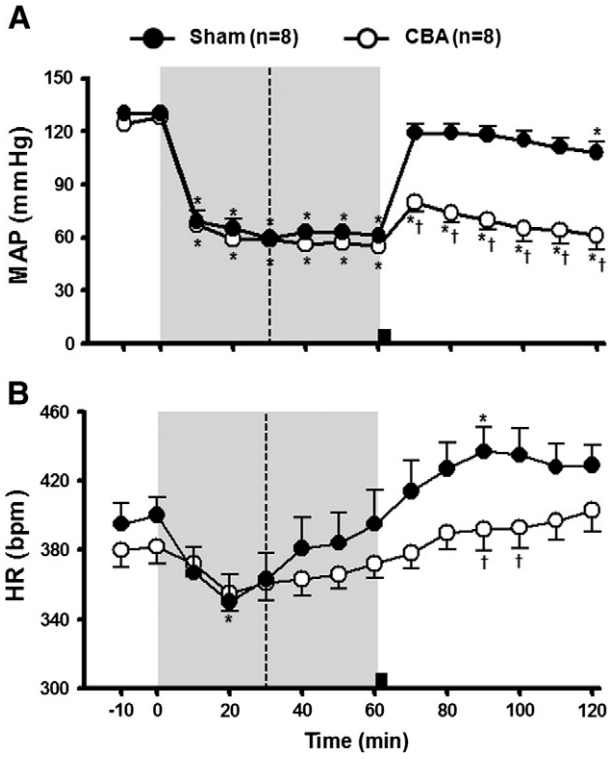

Fig. 3. Effects of bilateral ligation of the carotid body artery (CBA) on cardiovascular adjustments induced by hypertonic saline in rats subjected to hypovolemic hemorrhage. A) Mean arterial pressure (MAP). B) Heart rate (HR). Shaded area indicates the period of hemorrhage. Dashed line at t = 30 min indicates bilateral ligation of the CBA or control treatment (no ligation). Blocks at t = 60 min indicate the infusion of hypertonic saline. *Different from t = − 10 min; †different from time controls, both at $p<0.05$.

4. Discussion

The first reference on the use of hypertonic saline in hemorrhage goes back more than 90 years (Penfield, 1919). We know for sure that systemic administration of prostaglandin synthesis inhibitors, antihistaminergic agents, beta-adrenergic blockers, and serotonin antagonists does not interfere with hyperosmotic saline effects in experimental hemorrhagic shock (Lopes et al., 1981). We also know that alpha-adrenergic, angiotensin and vasopressin antagonists reduce the beneficial effects of hypertonic solutions in hemorrhagic shock (Kosoglou et al., 1986; Velasco et al., 1990; Giusti-Paiva et al., 2007). It seems there is no single pattern that explains the responses to hypertonic saline infusion in hemorrhagic shock. Instead, the relationship between hypertonic solutions and hemorrhage may be a multifunctional mosaic with multiple entrances, in this sense similar to the mechanisms for hypertension (Page, 1949).

The effects of hyperosmolar solutions on cardiovascular structures have been extensively analyzed in animals (for review see Kramer, 2003). Studies have shown that infusion of hypertonic saline is accompanied by increased cardiac contractility (Wildenthal et al., 1969; Velasco et al., 1980; Kien and Kramer, 1989), arterial blood pressure (Velasco et al., 1980; Lopes et al., 1981; Pedrino et al., 2005, 2006; de Almeida Costa et al., 2009) and perfusion of coronary, renal and muscular tissues (Gazitua et al., 1971; Pedrino et al., 2005). These effects of hypertonic solutions contribute to restoration of organ perfusion and reduce subsequent organ injury in hemorrhagic rats.

Although hypertonic solutions can directly affect the cardiac and vascular function, various lines of evidences suggest that hypernatremia also activates reflexes that involve the central nervous system (for review see McCann et al., 2003; Bourque, 2008; Toney and Stocker, 2010). Over the past years, our laboratory has investigated the involvement of neuronal structures on the cardiovascular responses to hypernatremia (Pedrino et al., 2005, 2006, 2008). In these studies, we have demonstrated that lesions of medullary (Pedrino et al., 2006, 2008) and hypothalamic regions (Pedrino et al., 2005) abolished the renal vasodilatation and sympathoinhibition induced by hypernatremia. Overall, these results support the idea that integrity of the central nervous system is essential for the cardiovascular responses that follow acute changes in extracellular fluid compartment composition.

The crucial question remains the same: does or doesn't the nervous system participate in hypertonic saline effects through a reflex. Till the present results, no clear and definitive answer to this question has been presented. Although 30 years ago the lung innervation was proposed to mediate the beneficial effects of hypertonic saline after hemorrhagic shock in dogs (Lopes et al., 1981), this was challenged many times and became controversial. Unfortunately, the exact role of arterial chemoreceptors in these responses is not easily evaluated in dogs because both thoracic and carotid chemoreceptors are functional in these animals (Comroe and Mortimer, 1964). In contrast, in the rat, thoracic chemoreceptors, although present, are not functional (Sapru and Krieger, 1977).

We recently showed that the recovery of blood pressure by hypertonic saline in rats subjected to hemorrhage depends on carotid receptors, because it is blocked by selective denervation of the carotid sinus, and not by selective aortic denervation (de Almeida Costa et al., 2009). Furthermore, several studies have reported an important role of baroreceptors in the responses induced by increases in plasma sodium concentration (Kenney and Bealer, 1993; Weiss et al., 1996). However, it should be emphasized that the technique used in these studies destroyed not only baroreceptor but also chemoreceptor afferents. The present report provides a new key observation: the beneficial cardiovascular effects of hypertonic saline infusion in hypovolemic hemorrhage specifically depend on integrity of carotid body chemoreceptor. To the best of our knowledge, no other study has yet demonstrated that carotid body chemoreceptors participate in arterial blood pressure recovery induced by increases in plasma sodium concentration in hemorrhagic rats.

Despite the abundance of evidence that supports an important role carotid body chemoreceptors in the detection of variation in the arterial PO_2, PCO_2 and pH (for review see Gonzalez et al., 1994; Milsom and Burleson, 2007), relatively little is known regarding the role of these receptors during changes in plasma sodium concentration. Gallego et al. (1979) demonstrated that hypertonic solutions cause excitation of chemosensory afferents and depolarization of carotid body type I cells. Consistent with these findings, the current study indicates that the nervous organ glomus caroticum has a prominent and determinant role in the hyperosmotic effects. When the function of carotid body chemoreceptors was blocked, leaving all nerves in the area functional, no recovery of arterial blood pressure induced by hyperosmotic saline was observed in hemorrhagic rats. Taken together, these results suggest that hypertonicity acts on the glomus caroticum to trigger homeostatic responses.

Our results are compatible with the hypothesis that hypertonic solutions activate several reflex mechanisms that restore internal homeostasis in hemorrhagic rats. Animals lacking carotid body chemoreceptors would lack these adjusting mechanisms. How the carotid body chemoreceptors structures are affected by hypertonic saline remains to be clarified.

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