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Comparative analysis of vestibular receptor and baroreceptor inputs to the nucleus tractus solitarius following acute hypotension in conscious rats

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HIGHLIGHTS

- c-Fos protein following acute hypotension was measured in NTS of conscious rats.
- Activation in NTS following acute hypotension is largely due to baroreceptor inputs.
- And moderately due to the signals originating from vestibular receptors.
- And at least partly dependent on the other inputs except vestibular and baroreceptors.
- c-Fos protein expression was localized to caudal portion of NTS in BL and SAD groups.

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ABSTRACT

Blood pressure is maintained by the interaction between the arterial baroreflexes and the vestibulocardiovascular reflexes during postural changes. In this study, the influence of the vestibular receptors on the maintenance of blood pressure following acute hypotension was quantitatively compared with the role of baroreceptors in terms of c-Fos protein expression in the nucleus tractus solitarius (NTS). Expression of c-Fos protein in the NTS was measured in conscious rats that had undergone bilateral labyrinthectomy (BL) and/or sinoaortic denervation (SAD). Expression of c-Fos protein increased significantly in the NTS in the sham group after sodium nitroprusside (SNP) administration. However, the BL, SAD, and SAD + BL groups showed significant decreases in c-Fos protein expression compared to that of the sham group. The SAD group showed relatively more reduction in c-Fos protein expression than the BL group, and the SAD + BL group showed the least expression among the three experimental groups. The c-Fos protein expression in the NTS following acute hypotension was localized to the caudal portions of the nuclei in the BL and SAD groups. These results suggest that the role of vestibular receptors in maintaining blood pressure following acute hypotension is less potent than that of the baroreceptors but more potent than other afferent inputs in conscious rats. In addition, afferent signals for maintaining blood pressure originating from the vestibular receptors and the baroreceptors may converge in the caudal portion of the NTS.

1. Introduction

Peripheral vestibular receptors in the inner ear control autonomic outflow as well as postural equilibrium in response to movements and gravitational forces [28]. Excitation of the vestibular system induces functional changes to the cardiovascular system, including modulation of blood pressure, pulse rate, baroreceptor reflex, and blood flow to the extremities [21]. Electrical or selective natural stimulation of the peripheral vestibular receptors induces an increase in sympathetic nerve activity [12,26]. Hypotension induced by head-up tilting is augmented by vestibular lesions in cats, which indicates that vestibular inputs play an important role in maintaining arterial blood pressure during postural changes [6,10]. Moreover, neurons from the medial and inferior vestibular nuclei project to the nucleus tractus solitarius(NTS), which controls

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autonomic responses including those related to cardiovascular function during head movement [2,27].

The baroreflex is a feedback control system for maintaining arterial blood pressure during hemorrhage, postural changes, and exercise. Signals from the baroreceptors are conveyed by branches of the glossopharyngeal and vagus nerves to the NTS, which is an essential component of the circuitry mediating the baroreceptor reflex [24]. The NTS analyzes the context of input signals and initiates baroreflex responses by virtue of its influence on sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM) [5]. This causes sympathetic preganglionic neuronal activity to decrease, thereby lowering blood pressure [8].

The baroreflex and vestibulosympathetic reflex may coordinate to maintain blood pressure during movement [7]. An additive effect of the baroreflex and vestibulosympathetic reflex on sympathetic nerve activity in muscles during head-down vestibular stimulation and lower body negative pressure was revealed in humans. We also reported that both of the vestibular receptors and baroreceptors cooperate with each other during acute hypotension, and the afferent signals from the vestibular receptors and the baroreceptors may integrate in the RVLM to facilitate the maintenance of blood pressure [16]. Although both vestibular receptors and baroreceptors cooperate to maintain blood pressure, the role of each receptor in the maintenance of blood pressure has not been quantitatively clarified.

Studies on acute hypotension-induced responses of the brainstem are critical to understand the mechanism underlying orthostatic hypotension. Previous studies in our laboratory have found that acute hypotension increases neuronal activity, expression of c-Fos protein, and glutamate release in the vestibular nuclei [15,17,22]. These effects were eliminated by the removal of peripheral vestibular receptors, which indicates that acute hypotension influences the vestibular neuronal activity by augmenting the afferent signals from the peripheral vestibular receptors. These findings suggest that afferent signals from the peripheral vestibular receptors in acute hypotension are transduced to the RVLM through the NTS to maintain blood pressure.

A population of neurons expressing c-Fos protein responds to acute hypotension in the NTS, a primary integrator of baroreceptor afferent input and vestibular afferent input. Therefore, evaluation of c-Fos protein expression would reflect the quantitative role of each receptor in maintaining blood pressure, since c-Fos protein is sensitive, inducible, and is a high-resolution marker of individual cell groups and extended neural systems that are activated by various stimuli [19]. However, the expression of c-Fos protein in the central nervous system could also be greatly affected by physiological stimuli induced by anesthetics. Therefore, to clarify the role of vestibular receptors and baroreceptors and to quantify their relative influence on the regulation of blood pressure during acute hypotension, the expression of c-Fos protein in the NTS was analyzed in conscious rats with bilateral labyrinthectomy and/or baroreceptor unloading.

2. Materials and methods

2.1. Animals

Adult male Sprague-Dawley rats (Changchun, China) weighing 220–250 g were used. All animal protocols and procedures described were approved by the institutional ethical committee on experimental use of animals. The animals had free access to food and water. Efforts were made to minimize the number of animals used and suffering. The rats were divided into four groups for immunohistochemical analysis ($n = 8$ per group): a sham group, in which both the vestibular-end organs and sinoaortic baroreceptors were intact; the bilateral labyrinthectomy (BL) group, in which the sinoaortic baroreceptors were intact, but a bilateral labyrinthectomy was performed; the sinoaortic denervation (SAD) group, in which the sinoaortic baroreceptors were denervated, but the vestibular end organs remained intact; and the BL + SAD group, in which both the bilateral vestibular end organs and sinoaortic baroreceptors were removed.

2.2. Labyrinthectomy

A chemical labyrinthectomy was performed as described previously [9,14]. Briefly, 100 μL of sodium arsanilate (100 mg/mL) was intratympanically injected into the bilateral middle ear of the rats under isoflurane anesthesia (Ilsung Co.; Seoul, Korea), which chemically damaged the membranous labyrinth. The damage to the epithelial cells in peripheral vestibular receptors was confirmed by immunohistochemical staining. As a control, saline, instead of sodium arsanilate solution, was injected intratympanically in the sham and SAD rats. The labyrinthectomies were performed 48 h prior to experimentation.

2.3. Sinoaortic denervation

Under isoflurane anesthesia, the carotid sinus nerve was sectioned bilaterally following a midventral incision in the neck, and the internal, external, and common carotid arteries were stripped of connective tissue at the level of bifurcation and painted with 10% phenolethanol to denervate the carotid sinus. For aortic arch denervation, the aortic arch nerve was severed bilaterally proximal to its junction with the vagus nerve [25]. In the sham and BL groups, the rats received similar cervical incisions while leaving nerves, vessels, and baroreceptors intact. After the surgery, the animals breathed spontaneously without significant changes in respiratory rhythm. SAD was performed 24 h prior to experimentation.

2.4. Acute hypotension

Two heparinized polyethylene tubes were inserted into the femoral artery for recording the blood pressure, and into the femoral vein for sodium nitroprusside (SNP) infusion, under isoflurane anesthesia. The tubes were guided toward the skull percutaneously, fixed into the skull, and connected to the tubes of a cybernation metabolism cage to allow free movement in a conscious state during the experiment. The blood pressure was recorded from the unilateral femoral artery using a pressure transducer and physiography (Grass model 7400; USA). SNP was infused in 3 min at a dose of 15 μg/kg/min, and blood pressure decreased by 30–40 mmHg during this period.

2.5. Immunohistochemistry

An immunohistochemical analysis of c-Fos protein expression was performed as described previously [13,17]. Deep anesthesia was induced with an overdose of sodium pentobarbital, and the animals were perfused transcardially with 500 mL of 0.9% NaCl at 4 °C and then perfused with 500 mL of 4% paraformaldehyde dissolved in 0.1 M phosphate buffer (pH 7.4) at 4 °C. The brains were dissected and post-fixed with paraformaldehyde fixative solution for 4 h at room temperature. The fixed brains were immersed in 30% sucrose in phosphate-buffered saline (PBS) for 2 days at 4 °C for cryoprotection. Tissue sections of 20-μm thickness were obtained using a freezing microtome (Leica; Nubloch, Germany), incubated for 30 min with 0.3% H_2O_2, rinsed three times for 5 min with 0.01 M PBS, and then incubated with 1% Triton X-100 for 30 min After a brief wash, the tissues were incubated for 30 min with PBS containing 5% bovine serum albumin (PBS + BSA), and then incubated

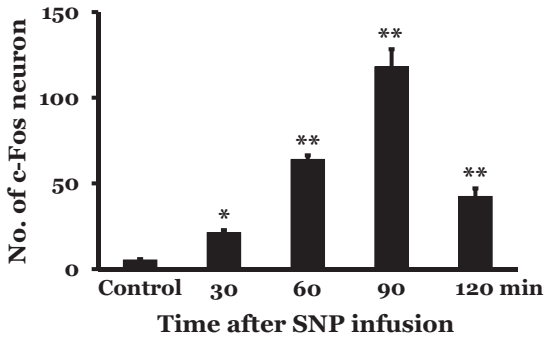

Fig. 1. Temporal changes in c-Fos protein expression in the nucleus tractus solitarius following a 30% reduction in blood pressure that was induced by SNP in conscious rats with intact labyrinths and baroreceptors. Controls received intravenous administration of saline at the same volume as SNP; min indicates the number of minutes after SNP administration. There were 8 rats in each group. * indicates a significant difference from the control group (*$p < 0.05$, **$p < 0.01$).

overnight at 4 °C with rabbit polyclonal anti-c-Fos (1:400; Cell Signaling Technology; Danvers, MA, USA) in PBS + BSA. The following day, tissue sections were incubated with a biotinylated goat anti-rabbit secondary antibody (1:200; Vector Lab; Burlingame, CA, USA) and then with the Elite ABC Kit (Vector Lab) for 2 h at 37 °C. The bound complex was visualized by incubating the tissue with diaminobenzadine. Sections were then dehydrated, cleared in xylene, and mounted with a coverslip using Permount (Fisher Scientific; Pittsburgh, PA, USA). The c-Fos positive neurons in the NTS were counted using a digital image analysis system (Image-Pro; Media Cybernetics; Silver Spring, MD, USA).

2.6. Data analysis

All data are expressed as the mean ± standard error. Differences were identified using multivariate analysis of variance. A $p < 0.05$ was considered significant.

3. Results

3.1. Effect of acute hypotension on c-Fos protein expression

In the control rats with intact labyrinths and baroreceptors, minimal c-Fos protein expression was detected in the NTS following saline infusion. However, acute hypotension induced by SNP significantly increased the expression of c-Fos protein in the NTS. Expression of c-Fos protein was detected at the rostral-caudal portion of the NTS, but mainly increased in the caudal portion of the NTS. The c-Fos protein expression was quantified and was found to be 21.3 ± 1.4, 64 ± 2.4, 118.0 ± 10.3, and 42.4 ± 4.7 at 30, 60, 90, and 120 min after SNP infusion, respectively. The expression peaked at 90 min after SNP infusion and then decreased gradually thereafter (Fig. 1).

3.2. Effect of BL or SAD on c-Fos protein expression following acute hypotension

In rats with BL and/or SAD, minimal c-Fos protein expression was detected in the NTS following saline infusion. However, the expression of c-Fos protein in the sham group markedly increased in the NTS 90 min after SNP infusion (114.0 ± 12.3), which was similar to that observed in the control rats with intact labyrinths and baroreceptors. In the BL group, the expression of c-Fos protein increased in the NTS 90 min after SNP infusion (94.5 ± 10.0), but the number of neurons expressing c-Fos protein was reduced by approximately 17% compared to the sham group; c-Fos expression was observed mainly in the caudal portion of the NTS. In the SAD group, increased expression of c-Fos protein was detected in the NTS 90 min after SNP infusion (33.7 ± 7.1), but the number of neurons expressing c-Fos protein was reduced by approximately 70% compared to the sham group; c-Fos expression was mainly localized to the caudal portion of the NTS. In the BL + SAD group, SNP-induced acute hypotension increased the expression of c-Fos protein in the NTS (13.3 ± 9.3); however, the relative level of expression was the lowest among the three experimental groups. The number of neurons that expressed c-Fos protein in the BL + SAD group was reduced by approximately 89% compared to the sham group, but was still significantly greater than that of the control animals. Moreover, the expression of c-Fos protein was observed diffusely at the rostral-caudal portion of the NTS (Figs. 2 and 3).

4. Discussion

The results of this study indicate that in conscious rats, the expression of c-Fos protein is induced in the NTS following acute hypotension, which, in turn, is greatly reduced by SAD and moderately reduced by BL. These observations indicate that the neuronal activation in the NTS induced by acute hypotension is largely due to the signals originating from the baroreceptors and moderately due to the signals originating from the vestibular receptors. Furthermore, in BL + SAD animals, a significant increase in the expression of c-Fos protein was observed compared to that in saline control animals following acute hypotension, which indicates that the neuronal activation in the NTS was at least partly dependent on the alternative inputs originating from regions other than the vestibular receptors and baroreceptors. The c-Fos protein expression in the NTS was localized to the caudal portions of the nuclei in the BL and SAD groups, whereas the BL + SAD group showed diffuse distribution of c-Fos expression at the rostral-caudal portion of the NTS.

The vestibular system modulates blood pressure through the sympathetic nervous system [26]. Animals with BL have reduced blood pressure when their body posture changes from a horizontal to an upright position [6], and patients with bilateral vestibular loss complain of orthostatic hypotension [1]. These reports indicate that the vestibular system plays an important role in maintaining blood pressure during postural changes. In our previous studies, acute hypotension induced by hemorrhage or SNP increased neuronal activity [22] and expression of c-Fos protein in the medial vestibular nuclei [15], and these effects were abolished by the loss of peripheral vestibular receptors. In this study, the reduction of c-Fos protein expression in the NTS following acute hypotension in BL animals suggests the presence of a potential neural pathway from the vestibular nuclei to the NTS [2,27]. It is possible that excitation in the vestibular nucleus results partly from ischemic activation of the hair cells by a reduction in blood flow to the inner ear following acute hypotension [17,22]. Therefore, acute hypotension activates the vestibular receptors, and the afferent signals from the vestibular receptors are relayed to the NTS through the vestibular nuclei.

The NTS receives primary inputs from cardiovascular, gastrointestinal, and pulmonary afferents and key components of the central pathway regulating the sympathetic vasomotor activity [11]. Activation of baroreceptors facilitated the expression of c-Fos protein in the dorsal aspect of the commissural part of the NTS and extended rostrally into the confined regions of the dorsal subnucleus [3], which was similar to the pattern of the central projections of the carotid sinus nerve and aortic depressor nerve. The distribution of the vestibular projections has been reported in the NTS. The caudal and intermediate portions of the NTS receive projections from the medial and inferior vestibular nuclei in rabbits [2], and the middle and lateral region of the NTS receives inputs from the

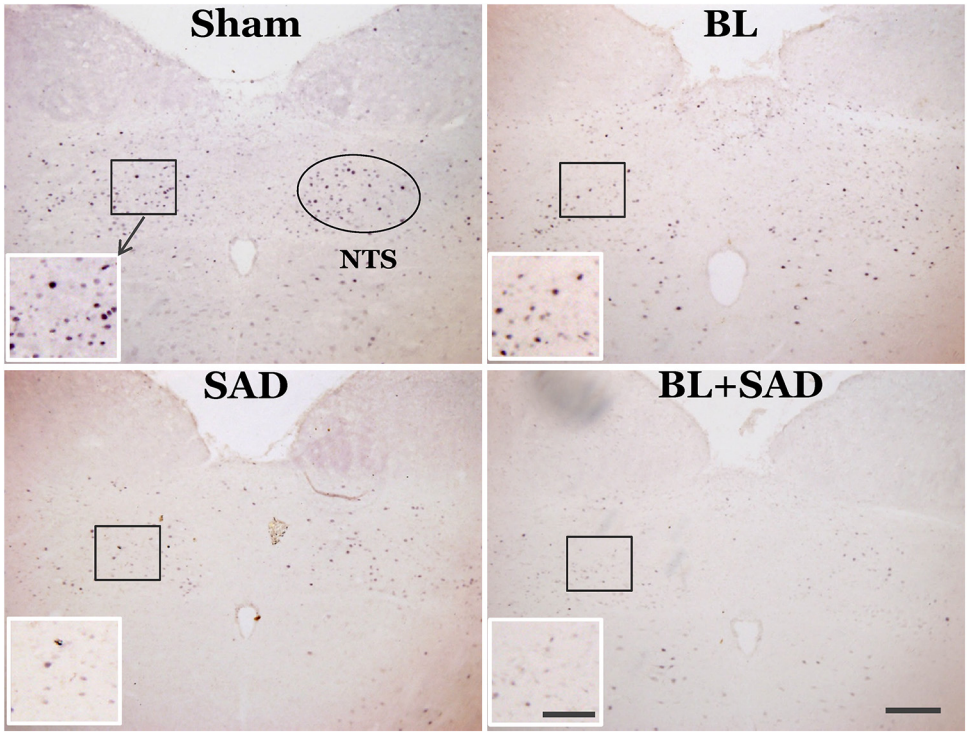

Fig. 2. Photomicrographs showing the effect of acute hypotension on c-Fos protein expression in the nucleus tractus solitarius following a 30% reduction in blood pressure that was induced by SNP infusion in conscious rats with bilateral labyrinthectomy (BL), sinoaortic denervation (SAD), or both bilateral labyrinthectomy and sinoaortic denervation (BL + SAD). Expression of c-Fos protein was measured 90 min after SNP administration. Sham, sham treated. NTS, nucleus tractus solitarius (the coordinate: 0.2 mm rostral to the obex). Scale bar = 200 μm. Rectangle represents higher magnification of the NTS (Scale bar = 100 μm).

medial and inferior vestibular nuclei in cats [27]. Thus, some neurons with vestibular inputs in the NTS receive convergent signals from the baroreceptors.

The immediate early gene protein c-Fos is useful for mapping the functional activity of the brain. Several studies have demonstrated that hypotension elicits c-Fos protein expression in the forebrain and the brain stem nuclei, which affect cardiovascular function [15]. Previous studies in our laboratories have found that SNP-induced acute hypotension increases c-Fos and ERK protein expression in the medial vestibular nuclei [15–17]. SNP decreases the blood pressure by inducing the release of nitric oxide [20]. Several studies have reported that SNP-induced hypotension increases c-Fos protein expression in the supraoptic nucleus, paraventricular nucleus, rostral ventrolateral medullary nucleus, NTS, and vestibular nucleus [15,18].

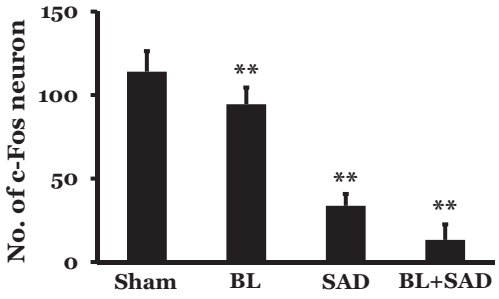

Fig. 3. Effect of acute hypotension on c-Fos protein expression in the nucleus tractus solitarius following a 30% reduction in blood pressure that was induced by SNP infusion in conscious rats with bilateral labyrinthectomy (BL), sinoaortic denervation (SAD), or both bilateral labyrinthectomy and sinoaortic denervation (BL + SAD). Expression of c-Fos protein was measured 90 min after SNP infusion. Sham, sham treated. There were 8 rats in each group. * indicates a significant difference from the sham group (**$p < 0.01$).

A minimal expression of c-Fos protein in the NTS was observed in the saline control group, indicating that the NTS did not receive any significant afferent signals in the conscious animals. Great care was taken to minimize non-specific factors such as stress that may have contributed to the c-Fos protein expression in this study. Hypotension-induced c-Fos protein expression in the NTS was reduced by approximately 17% in BL animals, and by 70% in SAD animals. These results suggest that 17% of the neurons that expressed c-Fos protein in the NTS received projections from the vestibular receptors, while 70% of the neurons that expressed c-Fos protein received projections from the baroreceptors. Therefore, activation of NTS neurons by acute hypotension in conscious animals is largely a consequence of the activation of baroreceptors. The c-Fos protein expression in the NTS following acute hypotension in BL + SAD animals was reduced by approximately 89%, which, however, was still slightly greater than that observed in the saline control animals, indicating that some residual activation of neurons in the NTS occurred even in the absence of vestibular receptor and baroreceptor inputs. These residual effects could be explained as a consequence of the unloading of vagus-innervated cardiopulmonary receptors in response to the hypotensive stimuli [4]. Eventually, the number of neurons in the NTS activated by the vestibular receptor inputs following acute hypotension was greater than that activated by some residual inputs originating from regions other than the vestibular receptor and baroreceptor in conscious animals. For this reason, the vestibular system is considered to play a key role in compensating for orthostatic hypotension.

The distribution of the vestibular receptor and baroreceptor inputs in the NTS is not well defined. Potts et al. [23] reported that 90% of the c-Fos protein expression induced by hypotension in the NTS was reduced by SAD in rabbits, and the remaining 10% originated from other factors, including cardiopulmonary receptors. Considering the significance of the vestibular receptors on maintaining blood pressure, this result is not consistent with those of

the present study. These differences may have resulted from the disparate role of vestibular inputs to the NTS in different species or different experimental methods employed. Expression of c-Fos protein in the NTS following acute hypotension was observed at the caudal portion in BL and SAD animals, and diffusely at the rostral-caudal portion in BL + SAD animals. These results indicate that the main convergence area of the afferent inputs from the vestibular receptor and the baroreceptor following acute hypotension might be the caudal portion of the NTS.

In summary, the neuronal activation in the NTS induced by acute hypotension is largely due to the signals originating from the baroreceptors and moderately due to the signals from the vestibular receptors in conscious rats. Furthermore, the neuronal activation in the NTS was at least partly dependent on the inputs originating from regions other than the vestibular receptors and baroreceptors. The c-Fos protein expression in the NTS was localized to the caudal portion of the nuclei in the BL and SAD groups, but the BL + SAD group indicated diffuse distribution of c-Fos expression at the rostral-caudal portion of the NTS.

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