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Commissural NTS lesions enhance the pressor response to central cholinergic and adrenergic activation

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HIGHLIGHTS

- Lesions of the commNTS enhance the pressor responses to i.c.v. injection of carbachol.
- commNTS inhibitory mechanisms are involved in the modulation of the pressor responses.
- commNTS lesions impair sympathetic activation produced by peripheral chemoreceptor.

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ABSTRACT

Electrolytic lesions of the commissural nucleus of the solitary tract (commNTS) in rats enhance the pressor response to bilateral carotid occlusion or to intravenous infusion of hypertonic NaCl without changing baroreflex responses. In an opposite direction, commNTS lesions abolish the pressor responses to peripheral chemoreflex activation. These opposite effects of commNTS lesions apparently result from an impairment of sympathetic activation in one case and in a facilitation of vasopressin secretion in the others. In the present study, we investigated the effects of the electrolytic lesions of the commNTS in the pressor responses that depend on sympathetic activation and vasopressin secretion produced by central cholinergic or adrenergic activation with intracerebroventricular (i.c.v.) injections of carbachol or noradrenaline, respectively, in unanesthetized rats. Male Holtzman rats (280–320 g, $n = 8$–15/group) with acute (1 day) or chronic (21 days) sham or commNTS lesions (1 mA × 10 s) and a stainless steel cannula implanted in the lateral ventricle were used. Acute commNTS lesions increased the pressor response to i.c.v. injection of carbachol (0.5 nmol/1 μ1) (52 ± 2, vs. sham: 37 ± 2 mmHg) or noradrenaline (80 nmol/1 μl) (45 ± 6, vs. sham: 30 ± 3 mmHg), whereas chronic commNTS lesions did not affect the pressor responses to the same treatments. Lesions of the commNTS impaired chemoreflex responses produced by intravenous KCN, without changing baroreflex responses. The results suggest that commNTS-dependent inhibitory signals are involved in the modulation of the pressor responses to central cholinergic and adrenergic activation, probably limiting vasopressin secretion.

1. Introduction

Signals from peripheral baro and chemoreceptors reach the nucleus of the solitary tract (NTS) before ascending to other central sites that control the autonomic and hormonal responses involved in the cardiovascular regulation [24].

In unanesthetized rats, the electrolytic lesions of the most caudal portion of the NTS, the commissural NTS (commNTS), reduce the pressor and bradycardic responses produced by chemoreflex activation with intravenous (i.v.) injection of potassium cyanide (KCN) and the pressor responses to L-glutamate injected into the lateral portion of the intermediate NTS, without changing the responses to baroreflex activation [13]. Although commNTS lesions do not affect baseline mean arterial pressure (MAP) in normotensive rats, these lesions reduce MAP to normotensive levels, for at least five days, in spontaneously hypertensive rats (SHR) [23,30]. The reduction of baseline MAP in SHR or the pressor responses to i.v. KCN by commNTS lesions suggests that the commNTS is part of the hindbrain mechanisms involved in sympathetic activation.

On the other hand, commNTS lesions enhance the pressor responses to bilateral common carotid occlusion or to intragastric (i.g.) gavage of 2 M NaCl [4,29], suggesting that commNTS inhibitory mechanisms may oppose the action of the pressor mechanisms activated in these conditions. The enhanced pressor responses to bilateral common carotid occlusion or to i.g. gavage of 2 M NaCl was abolished in rats pre-treated with a

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vasopressin antagonist, suggesting that vasopressin secretion induced by hyperosmolarity or by common carotid occlusion is inhibited by commNTS mechanisms [4,29]. Therefore, studies have suggested that commNTS may have opposite roles in the control of sympathetic activation and vasopressin release which results in opposite effects of the commNTS lesions on cardiovascular responses depending on the condition tested [4,13,23,27,30]. The reasons for these differences on cardiovascular regulation are not clear yet.

Except for the pressor responses to glutamate injection into the intermediate NTS, all the other cardiovascular responses tested in the commNTS-lesioned rats were produced by the activation of peripheral mechanisms or a mix of central and peripheral mechanisms almost exclusively integrated in the hindbrain. It was not tested yet the effects of the commNTS lesions in the pressor responses produced by the activation of forebrain mechanisms that increase sympathetic activity and/or vasopressin release like the pressor responses to forebrain cholinergic or adrenergic activation ([1,8,6,17,19,31]). Considering that previous studies have shown that commNTS lesions may affect sympathetic activation and vasopressin secretion in opposite directions, in the present study, we tested the effects of the commNTS lesions in the pressor responses produced by central cholinergic or adrenergic activation with the injection of carbachol or noradrenaline, respectively, into the lateral ventricle (LV).

2. Materials and methods

2.1. Animals

Male Holtzman rats weighing 280–320 g were used. The animals were housed individually in stainless steel cages in a room with controlled temperature (23 ± 2 °C) and humidity (55 ± 10%). Lights were on from 7:00 am to 7:00 pm. Standard Purina chow and tap water were available ad libitum. The Ethical Committee for Animal Care and Use from Dentistry School of Araraquara-UNESP approved the experimental protocols used in the present study.

2.2. Lesion of the commNTS

Rats anesthetized with halothane were fixed to a stereotaxic frame (model 900, David Kopf Instruments). The dorsal surface of the brain stem was exposed. A tungsten wire electrode (0.2 mm of diameter) was introduced into the brain stem 0.0 and 0.5 mm caudal to calamus scriptorius, in midline and 0.5 mm below the dorsal surface of the brain. Lesions were performed using cathodal current (1 mA × 10 s in each points of the electrode introduction).

2.3. Implant of cannulas into the LV

Rats were anesthetized with ketamine (80 mg/kg of body weight) combined with xylazine (7 mg/kg of body weight) and placed in a stereotaxic frame (model 900, David Kopf Instruments). A stainless steel 23-gauge cannula was implanted into the lateral cerebral ventricle (LV) using the coordinates 0.3 mm caudal to bregma, 1.5 mm lateral to midline and 3.5 mm below to dura mater. The cannulas were fixed to the cranium using dental acrylic resin and jeweler screws. The rats received a prophylactic dose of penicillin (30,000 IU) given intramuscularly post-surgically.

In rats used to test the effects of acute commNTS lesions, the stainless steel cannula was implanted into the LV 5 days before the lesion and in rats used to test the effects of chronic commNTS lesions, the cannula was implanted 15 days after the lesion.

2.4. Arterial pressure and heart rate recording

Mean arterial pressure (MAP) and heart rate (HR) were recorded in unanesthetized rats. One day before recording, the rats were anesthetized with ketamine (80 mg/kg of body weight) + xylazine (7 mg/kg of body weight), a polyethylene tubing (PE-10 connected to a PE-50) was inserted into the abdominal aorta through the femoral artery for arterial pressure recording and a second polyethylene tubing was inserted into the femoral vein for drug administration. Arterial and venous catheters were tunneled subcutaneously and exposed on the back of the rat to allow access in unrestrained, freely moving rats. To record pulsatile arterial pressure, MAP and HR, the arterial catheter was connected to a Stathan Gould (P23 Db) pressure transducer coupled to a pre-amplifier (model ETH-200 Bridge Bio Amplifier) that was connected to a Powerlab computer data acquisition system (model Powerlab 16SP, ADInstruments).

2.5. Injections into the LV

Injections into the LV were performed using a Hamilton syringe connected to an injector needle (2 mm longer than the cannula fixed to the animal's head) by a PE-10 polyethylene tubing.

2.6. Drugs

Carbachol (0.5 nmol/1 μl) or noradrenaline (80 nmol/1 μl) was injected into the LV. Phenylephrine (5 μg/kg of body weight) and sodium nitroprusside (30 μg/kg of body weight) were injected i.v. for testing baroreflex. Potassium cyanide (KCN, 40 μg/0.1 ml/rat) was injected i.v. for chemoreflex test. All drugs were purchased from Sigma Chem. Co., St. Louis, MO, USA. The doses of carbachol and noradrenaline were adapted from the previous studies that tested the effects of noradrenaline and carbachol injected into the LV on arterial pressure [22,10].

2.7. Histology

At the end of the experiments, rats were deeply anesthetized with sodium thiopental (70 mg/kg of body weight, ip). Saline followed by 10% buffered formalin was perfused through the heart. The brains were frozen, cut coronally (50 μm sections), stained with Giemsa stain and analyzed by light microscopy to confirm the site of injection into the LV and the lesions in the commNTS.

2.8. Statistical analysis

The results are reported as means ± standard errors of means (SEM). One way ANOVA combined with a Student Newman Keuls tests were used for comparisons. Differences were considered significant at $p < 0.05$.

2.9. Experimental protocol

One day after the implantation of the arterial and venous catheters, different groups of rats with sham or commNTS lesions (1 and 21 days) had the arterial catheters connected to the pressure transducer. Around 20 min after starting the recordings of MAP and HR, carbachol (0.5 nmol/1 μl) was injected into the LV. In the same rats, three hours after the injection of carbachol, phenylephrine (5 μg/kg of body weight), sodium nitroprusside (30 μg/kg of body weight) and potassium cyanide (KCN, 40 μg/0.1 ml/rat) were injected i.v. The interval between the i.v. injections was 5 min.

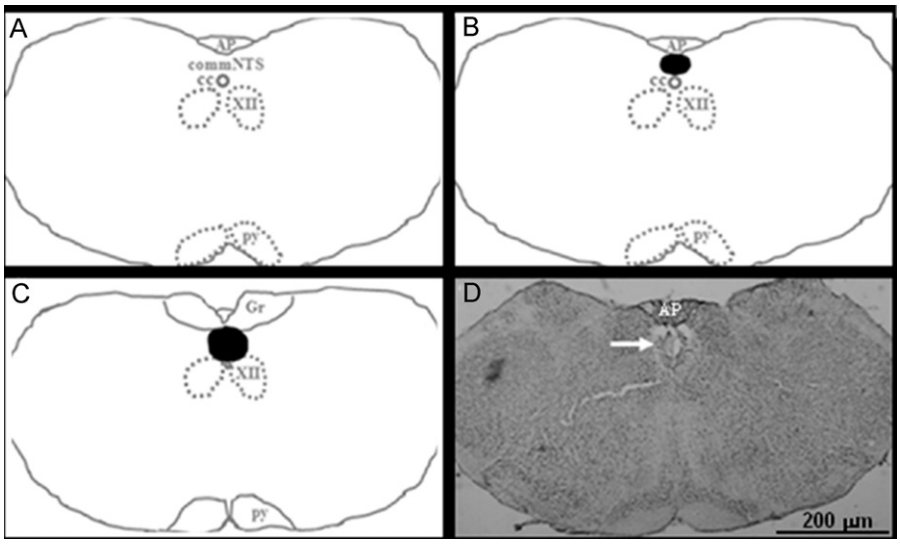

Fig. 1. (A–C) Schematic diagrams and (D) photomicrograph showing (A) the localization of the commNTS within the medulla oblongata and (B–D) the lesion correctly placed in the commNTS (dark in B and C and indicated by the arrow in D). AP, area postrema; cc, central canal; XII, hypoglossal nucleus; Gr, gracile nucleus; py, pyramidal tract.

In other groups of rats with sham or commNTS lesions (1 and 21 days) the same protocol was tested, except that noradrenaline (80 nmol/1 μl) instead of carbachol was injected into the LV.

3. Results

3.1. Histological analysis

Fig. 1 presents schematic diagrams and a photomicrograph showing the site of the lesion correctly placed in the commNTS. The commNTS lesions were located in the midline, above the central canal and extended from the level of the obex to around 1 mm caudal to the obex. Lesions were restricted to the commNTS, and did not involve the lateral portions of the NTS, hypoglossal nucleus or the area postrema, as previously shown [4,13,28,29].

3.2. Pressor responses to i.c.v. carbachol or noradrenaline in commNTS-lesioned rats

Acute (1 day) commNTS lesions enhanced the pressor responses to i.c.v. injection of carbacol (0.5 nmol/1 μl) (52 ± 2 mmHg, vs. sham rats: 37 ± 2 mmHg) [$F(1, 29) = 50.22$; $p < 0.001$] (Fig. 2A) or noradrenaline (80 nmol/1 μl) (45 ± 6 mmHg, vs. sham rats: 30 ± 3 mmHg) [$F(1, 22) = 10.23$; $p < 0.05$] (Fig. 2B). Chronic (21 days) commNTS lesions did not modify the pressor responses to i.c.v. carbachol (43 ± 4 mmHg, vs. sham rats: 39 ± 4 mmHg) (Fig. 2A) or noradrenaline (34 ± 4 mmHg, vs. sham: 32 ± 4 mmHg) (Fig. 2B).

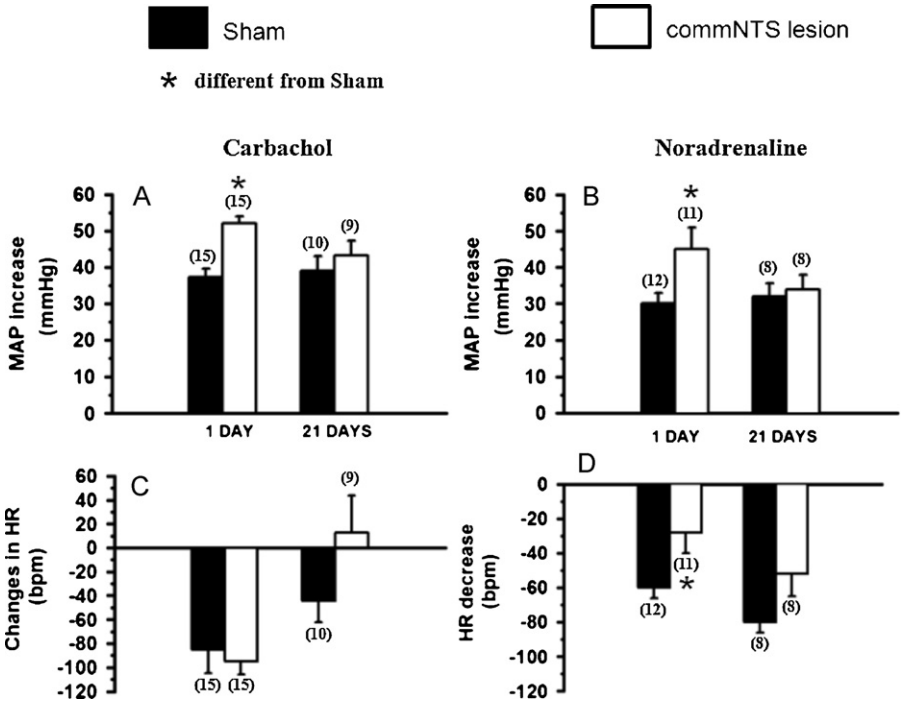

Fig. 2. Changes in (A and B) MAP and (C and D) HR produced by i.c.v. injection of (A and C) carbachol (0.5 nmol/1 μl) or (B and D) noradrenaline (80 nmol/1 μl) in rats with sham or commNTS lesions (1 and 21 days). The results are represented by means ± SEM. The number of rats is indicated in parenthesis above each bar.

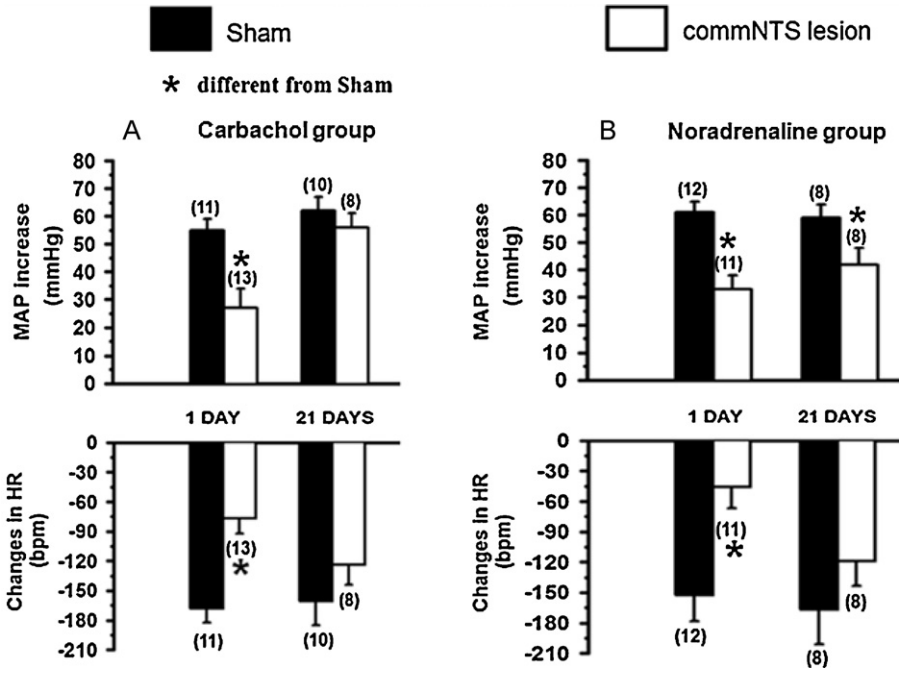

Fig. 3. Increases in MAP and reductions in HR produced by i.v. injections of KCN (40 μg/0.1 ml/rat) in sham or commNTS-lesioned rats (1 or 21 days) of the groups of rats that received (A) carbachol or (B) noradrenaline i.c.v. The results are represented by means ± SEM. The number of rats is indicated in parenthesis above or below each bar.

Acute or chronic commNTS lesions did not affect the changes in HR produced by i.c.v. injection of carbachol (Fig. 2C). Acute commNTS lesions reduced the bradycardia to i.c.v. injection of noradrenaline (−28 ± 12 bpm, vs. sham rats: −60 ± 6 bpm) [$F(1, 22) = 10.13$; $p < 0.05$], whereas chronic commNTS lesion did not modify the bradycardia to i.c.v. injection of noradrenaline (−52 ± 13 bpm, vs. sham rats: −80 ± 6 bpm) (Fig. 2D).

Acute or chronic commNTS lesions did not affect the baseline MAP (104 ± 3 and 108 ± 3 mmHg, respectively) or HR (340 ± 11 and 356 ± 13 mmHg, respectively) compared to the baseline MAP (110 ± 3 and 116 ± 1 mmHg, respectively) and HR (387 ± 15 and 386 ± 17 mmHg, respectively) of sham rats.

3.3. Baroreflex and chemoreflex responses in commNTS-lesioned rats

In the rats tested for the effects of i.c.v. carbachol, acute (1 day) commNTS lesions reduced the pressor [$F(1, 23) = 10.05$; $p < 0.05$] and bradycardic responses [$F(1, 23) = 19.66$; $p < 0.001$] to i.v. injection of KCN (40 μg/0.1 ml/rat), whereas chronic (21 days) commNTS lesions did not reduce the pressor [$F(1, 17) = 0.79$; $p > 0.05$] or bradycardic [$F(1, 17) = 1.34$; $p > 0.05$] responses to i.v. KCN (Fig. 3A). Acute or chronic commNTS lesions did not modify the pressor and bradycardic response to i.v. injection of phenylephrine or the hypotension to i.v. infusion of sodium nitroprusside, however, acute commNTS lesions reduced the tachycardic responses to i.v. sodium nitroprusside (60 ± 6 bpm, vs. sham rats: 91 ± 7 bpm) [$F(1, 23) = 12.67$; $p < 0.005$].

In the rats tested for the effects of i.c.v. noradrenaline, acute [$F(1, 22) = 17.87$; $p < 0.001$] or chronic [$F(1, 15) = 4.75$; $p < 0.05$] commNTS lesions reduced the pressor response to i.v. injection of KCN (40 μg/0.1 ml/rat) (Fig. 3B). Acute commNTS lesions also reduced the bradycardic responses [$F(1, 22) = 10.07$; $p < 0.05$] produced by i.v. injection of KCN (40 μg/0.1 ml/rat). Acute or chronic commNTS lesions did not modify the pressor and bradycardic responses to i.v. injection of phenylephrine or the depressor and tachycardic responses to i.v. sodium nitroprusside.

4. Discussion

The present results show that acute (1 day) electrolytic lesions of the commNTS enhance the pressor responses to i.c.v. injection of carbachol or noradrenaline, suggesting that commNTS inhibitory mechanisms are involved in the modulation of the pressor responses to central cholinergic or adrenergic activation. The bradycardia to i.c.v. injection of carbachol was not modified by the commNTS lesions, however, the bradycardia to i.c.v. injection of noradrenaline was reduced in commNTS-lesioned rats, which may also facilitate the pressor responses. The same commNTS lesions that facilitated the pressor responses to i.c.v. carbachol or noradrenaline reduced the pressor and bradycardic responses to peripheral chemoreflex activation with i.v. KCN and did not affect the changes in HR produced by baroreflex activation. These results suggest that the inhibitory mechanisms deactivated by commNTS lesions are not the same involved in the baroreflex modulation of autonomic responses involved in cardiovascular regulation. The facilitation of the pressor responses to i.c.v. injection of carbachol or noradrenaline by commNTS lesions is similar to the results of previous studies that showed enhanced pressor responses to bilateral common carotid occlusion or to i.g. gavage of 2 M NaCl in commNTS-lesioned rats [4,29]. Therefore, the present results extend the conclusion of the previous studies suggesting that the commNTS inhibitory mechanisms also modulate the pressor responses to forebrain cholinergic or adrenergic activation.

Differently from acute commNTS lesions, chronic (21 days) commNTS lesions did not affect the pressor responses to i.c.v. carbachol or noradrenaline, results similar to those of the previous study [28] that showed no difference in the pressor response produced by bilateral carotid occlusion in chronic commNTS-lesioned rats. The recovery of the inhibitory function in chronic commNTS-lesioned rats is probably related to the neural plasticity, a mechanism that allows areas not damaged by the lesion, like remaining portions of the NTS, to replace the function impaired by the commNTS lesions. Although the electrolytic lesions may also damage the fibers of passage, a previous study showed that the effects of electrolytic lesions or neurotoxic lesions of

dopamine-beta-hydroxylase-containing neurons in the commNTS are similar, suggesting that the effects of the commNTS lesions were not due to the destruction of the fibers of passage [14].

Lesions of the commNTS increase osmotic-induced activation of the paraventricular and supraoptic hypothalamic nuclei and plasma vasopressin levels ([5] and unpublished results from our laboratory). The enhanced pressor response to an i.g. gavage of 2 M NaCl or to common carotid occlusion in commNTS-lesioned rats was abolished by the pre-treatment with vasopressin antagonist [4,29]. Therefore, the suggestion is that the commNTS is part of a central circuitry that inhibits vasopressin secretion. The pressor response to forebrain cholinergic or adrenergic activation are mediated by increases in sympathetic activity and vasopressin release [1,8,6,17,19,31]. Therefore, similar to the increase of i.g. 2 M NaCl- or carotid occlusion-induced pressor responses [4,29], the increased pressor response to central cholinergic or adrenergic activation in commNTS-lesioned rats might be due to an increase in vasopressin secretion. Although it is not possible to completely discard an increased sympathetic activation to i.c.v. carbachol or noradrenaline in commNTS-lesioned rats, the evidence of previous studies [13] suggesting that commNTS lesions impair sympathetic activation produced by peripheral chemoreceptor activation or by glutamate injected into the intermediate NTS signals in an opposite direction.

The intermediate and commNTS are anatomically connected to the lateral parabrachial nucleus (LPBN), the region surrounding the anteroventral part of third ventricle (AV3V region), the paraventricular (PVN) and the supraoptic nuclei (SON) of the hypothalamus [16,25,26,32]. These connections may convey signals from the peripheral cardiovascular receptors that ascend to forebrain areas involved in the control of fluid-electrolyte balance and cardiovascular regulation like those involved in the inhibitory control of vasopressin secretion. Without excluding other receptors, arterial baroreceptors are the main source of inhibitory signals that limit the pressor responses by facilitating parasympathetic activity and inhibiting sympathetic activity and vasopressin secretion. The commNTS receives mainly the primary afferent projections from the peripheral chemoreceptors, whereas more rostral parts of the NTS, like the intermediate NTS receives mainly the primary afferent projections from arterial baroreceptors [24]. Although commNTS is not the main site of the first synapse of baroreceptor afferents, it might receive baroreceptor signals from the intermediate NTS, before they could reach forebrain areas involved in the control of vasopressin secretion. However, differently from the control of vasopressin secretion, the autonomic control of the cardiovascular system by baroreceptor signals seems to be independent from the commNTS. This might explain why commNTS lesions strongly affect the baroreceptor modulation of vasopressin secretion and only slightly influence autonomic responses mediated by sympathetic and parasympathetic mechanisms. On the other hand, an increase in vasopressin secretion to central cholinergic or adrenergic activation by commNTS lesions is supported by previous studies that proposed the importance of chemoreceptor reflex in the control of fluid-electrolyte balance [18]. The exposition of mammals to low oxygen pressure (moderate high-altitude hypoxia) results in diuresis, which might be a consequence of reduced vasopressin secretion due to an inhibitory action of peripheral chemoreceptor. The lesions of the commNTS may remove the inhibitory mechanisms activated by peripheral chemoreflex increasing vasopressin secretion by stimuli like central cholinergic or adrenergic activation. Therefore, the present and previous results suggest that the control of neural/autonomic and/or humoral responses to peripheral baroreceptor or chemoreceptor activation may involve opposite mechanisms in the commNTS and the result can be opposite cardiovascular responses depending on which is the predominant mechanism activated.

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