Lesions of the Commissural Nucleus of the Solitary Tract Reduce Arterial Pressure in Spontaneously Hypertensive Rats

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Abstract—It has been suggested that increased sympathetic activity and arterial chemoreceptors are important for the high blood pressure in spontaneously hypertensive rats (SHR). Electrolytic lesions of the commissural nucleus of the solitary tract (commNTS) abolish (1) the cardiovascular responses to chemoreflex activation with potassium cyanide (KCN) in normotensive rats and (2) the hypertension that follows acute aortic baroreceptor denervation in rats. Therefore, in this study we investigated the effects of electrolytic lesions of the commNTS on basal mean arterial pressure (MAP), baroreflex, and chemoreflex in SHR and in normotensive control Wistar-Kyoto (WKY) and Wistar rats. CommNTS lesions elicited a dramatic fall in MAP to normal levels during the period of study (from the first to fourth day following lesions) in SHR and almost no changes in WKY and Wistar rats. The pressor responses to chemoreflex activation with KCN tested in the days 1 and 4 after commNTS lesions were abolished in SHR and in normotensive strains. The reflex tachycardia induced by sodium nitroprusside was also attenuated in days 1 and 4 after commNTS lesions in SHR, WKY, and Wistar rats. The data suggest that the integrity of commNTS is important for the maintenance of high blood pressure in SHR and for the reflex responses dependent on sympathetic activation either in SHR or in normotensive strains. (Hypertension. 2001;38[part 2]:560-564.)

Key Words: baroreceptors ■ chemoreceptors ■ solitary nucleus ■ rats, spontaneously hypertensive

The arterial pressure in spontaneously hypertensive rats (SHR) starts rising 2 to 3 weeks after birth and reaches hypertensive levels 12 to 14 weeks later. The high blood pressure in SHR seems to be related to increased sympathetic activity. Previous evidence has supported a link between increased chemoreceptor reflex sensitivity and high blood pressure in SHR. Anatomic studies have shown that the carotid body is larger in SHR than in the normotensive control Wistar-Kyoto rats (WKY). Extracellular recordings from carotid sinus afferent nerves have also demonstrated that the sensitivity of arterial chemoreceptors to hypoxia is increased in adult SHR compared with the normotensive control WKY and Wistar rats. Such observations have suggested a possible involvement of arterial chemoreceptors in the hypertensive mechanisms.

The nucleus of the solitary tract (NTS) is the principal site of termination of primary afferent fibers arising from arterial baroreceptors and chemoreceptors. Recent studies have demonstrated that electrolytic lesions of commissural nucleus of the solitary tract (commNTS) abolished the cardiovascular responses induced by chemoreceptor activation with potassium cyanide in normotensive Sprague-Dawley and Wistar rats. A recent study from our laboratory also showed that commNTS-lesioned aortic baroreceptor-denervated rats presented normal arterial pressure, instead of high blood pressure as observed in acute sham-lesioned aortic baroreceptor-denervated rats.

Thus, because the enhanced responses of arterial chemoreceptors have been suggested to be important for hypertension in SHR and because the commNTS lesions reduce the hypertension in aortic baroreceptor-denervated rats and the pressor responses to chemoreceptor activation evoked by KCN, in the present study we sought to investigate (1) the effects of acute commNTS lesions on basal mean arterial pressure (MAP) in SHR and normotensive control WKY and Wistar rats and (2) the baroreceptor and chemoreceptor reflex responses in commNTS-lesioned SHR and normotensive animals.

Methods

Animals

Adult male spontaneously hypertensive rats and normotensive WKY and Wistar rats (250 to 300 g and 14 to 16 weeks old) were used. Standard chow pellets and tap water were available ad libitum. Lighting was maintained on 12-hour/12-hour light/dark cycle. The medical ethics committee of the Universidade Federal de Sao Paulo...
approved all the experiments before they were performed. All experiments were performed in conscious, freely moving rats.

**Cerebral Lesions**

One day before the experiments, rats were anesthetized with 2% halothane mixed with 100% oxygen and placed in a stereotaxic apparatus (Stoelting Laboratory Standard 51600). CommNTS electrolytic lesions were performed as we previously reported.\(^{10–12}\) Sham rats were submitted to the same procedures except the passage of electric current.

**Arterial Pressure Recording and Intravenous Injection**

A Tygon tubing (Microbore Tubing 500°PK) connected to a polyethylene cannula (PE 10) was inserted into the abdominal aorta through the femoral artery for measurement of pulsatile arterial pressure (PAP), MAP, and heart rate (HR). A second polyethylene cannula (PE 50) was inserted into the femoral vein for drug administration. Both tubings were tunneled subcutaneously and exposed on the back of the rat, to allow access when the animal was conscious. PAP and MAP were measured using a strain gauge transducer (Statham P23Db) connected to a low-level DC preamplifier in a polygraph (Grass model). HR was derived by a cardiometer (Grass model 7P4) from arterial pressure waves.

**Histology**

At the end of the experiments, rats were anesthetized with urethane (1.2 g/kg IV), and an intracardiac perfusion with saline followed by 10% formalin was performed. The brains were removed and stored in 10% formalin for \(\approx 48\) hours. Serial coronal sections (40 \(\mu\)m) were prepared and stained by neutral red. Only rats with lesion sites located in the commNTS were used for data analysis. Lesions of the commNTS were located on the midline above the central canal and extended from the level of the obex to \(\approx 1\) mm caudal to the obex. Lesions virtually completely destroyed the commNTS but did not destroy the area postrema or lateral regions of the NTS. The extent of the lesion was defined as the area with total destruction of tissue, as we have reported previously.\(^{10–12}\)

**Statistical Analysis**

All data were expressed as mean±SEM. The results were analyzed by 2-way ANOVA followed by the Newman-Keuls posttest for multiple mean comparisons. Significance level was set at \(P<0.05\).

**Experimental Protocol**

One day before starting the experiments, rats were submitted to the cannulation of the femoral artery and vein. Twenty-four hours later, a control (before commNTS lesion) basal MAP and HR recording was performed in the animals. The chemoreflex evoked by intravenous bolus injection of potassium cyanide (KCN, 40 \(\mu\)g/0.1 mL), and the baroreflex induced by pressor doses of phenylephrine (3 \(\mu\)g/kg IV) and depressor doses of sodium nitroprusside (30 \(\mu\)g/kg IV) were also tested before commNTS lesions. Following these tests, in the same day, the animals underwent commNTS lesions. One, 2, 3, and 4 days after commNTS lesions, basal MAP and HR were recorded in the animals. Chemoreceptor and the baroreceptor reflex were also tested on days 1 and 4 after commNTS lesions. Sham rats underwent the same experimental protocol; however, lesions were not performed.

**Results**

**Effect of commNTS Lesions on Basal MAP and HR**

MAP was reduced in commNTS-lesioned SHR from day 1 to day 4 after lesions compared with those from day 0 (before lesions) and with sham-lesioned SHR in the same period (\(F[1,10]=41.8, P<0.0001\)) (Figure 1).

In contrast, in normotensive control WKY, commNTS lesions produced no changes in MAP (93±3, 97±3, 95±3, and 103±6 mm Hg on days 1, 2, 3, and 4 after commNTS lesions, respectively) compared with the prelesion value (day 0) in the same animals (110±4 mm Hg). The difference between sham- and commNTS-lesioned WKY was not significant (sham WKY had MAP of 110±4 mm Hg before surgery and 113±4, 110±4, 111±4, and 112±7 mm Hg on days 1, 2, 3, and 4 after sham surgery, respectively). In normotensive Wistar rats, commNTS lesions also did not change MAP (108±5, 102±4, 97±4, and 103±3 mm Hg on days 1, 2, 3, and 4 after commNTS lesions, respectively) compared with prelesion value (day 0) in the same animals (108±4 mm Hg). No difference was observed between sham- and commNTS-lesioned Wistar rats (sham Wistar had MAP of 110±3 mm Hg before surgery, and 118±4, 112±3, 107±4, and 106±4 mm Hg on days 1, 2, 3, and 4 after sham surgery, respectively).

In SHR, WKY, or Wistar rats, commNTS lesions produced no changes in HR.

**Chemoreceptor Reflex Test**

In lesioned SHR, chemoreflex activation with intravenous KCN (40 \(\mu\)g/0.1 mL per rat) elicited a depressor response instead of the pressor responses seen in sham-lesioned SHR (\(F[1,10]=77.84, P<0.00001\)) (Figure 2A). However, the bradycardia produced by intravenous KCN was not changed by commNTS lesions in SHR compared with sham-lesioned SHR (\(F[1,10]=3.54, P>0.05\)) (Figure 2B).

In contrast, in WKY (Figure 2C and 2D) and Wistar rats, both the pressor and bradycardic responses evoked by KCN were attenuated on days 1 and 4 after commNTS lesions compared with sham lesions. No difference was observed in the chemoreflex responses between WKY and Wistar rats.

**Baroreceptor Reflex Test**

Intravenous phenylephrine induced an increased pressor response on day 1 after commNTS lesions in SHR compared
with sham-lesioned SHR (F[1,10]=9.07, P<0.05) but not in commNTS-lesioned WKY (Figure 3A and 3C). Reflex bradycardia was not altered by commNTS lesions in WKY compared to sham lesions in SHR (F[1,10]=1.38, P>0.05) or WKY rats (Figure 3B and 3D). Intravenous sodium nitroprusside produced similar hypotension in sham- and commNTS-lesioned SHR (F[1,10]=1.40, P>0.05) and WKY rats (Figure 4A and 4C), but the reflex tachycardia was reduced after commNTS lesions compared with sham lesions in SHR (days 1 and 4 after lesions) (F[1,10]=22.22, P<0.001) and in WKY rats (day 1 after lesions) (Figure 4B and 4D).
In commNTS-lesioned Wistar rats, the pressor responses to intravenous phenylephrine on days 1 and 4 after lesions (48±2 mm Hg and 54±4 mm Hg, respectively) and the reflex bradycardia (−120±23 bpm and −137±10 bpm) were not different from sham-lesioned Wistar rats in the same period (pressor responses, 49±3 and 51±2 mm Hg; bradycardia, −113±20 and −127±19 bpm, respectively). The hypotensive responses to intravenous sodium nitroprusside were also not altered on days 1 and 4 after commNTS lesions in Wistar rats (−51±5 and −49±3 mm Hg, respectively, versus sham-lesioned Wistar rats [−39±2 and −41±2 mm Hg]). However, the reflex tachycardia evoked by sodium nitroprusside was attenuated on days 1 and 4 after commNTS lesions in Wistar rats (82±14 and 92±14 bpm, respectively, versus sham-lesioned Wistar rats [123±9 and 115±17 bpm]).

**Discussion**

Our data showed that acute (1 to 4 days) electrolytic lesions of commNTS reduced basal MAP in SHR, with stabilization in normal levels during the 4 days of recording, but not basal MAP in normotensive strains. CommNTS lesions in SHR also abolished the pressor response to chemoreceptor reflex activation with KCN, reduced the reflex tachycardia induced by intravenous sodium nitroprusside, and increased the pressor response to intravenous phenylephrine. Similar lesions in normotensive animals attenuated the pressor and bradycardic responses evoked by KCN and also reduced the reflex tachycardia elicited by sodium nitroprusside.

Many studies have suggested a possible role of arterial chemoreceptors in hypertensive mechanisms. Evidence indicates that arterial chemoreceptors have an increased sensitivity to hypoxia in SHR. Our data demonstrated that the electrolytic lesions of commNTS of SHR abolished only the pressor response to chemoreceptor reflex activation with KCN, whereas in normotensive rats, the pressor and bradycardic responses evoked by KCN were attenuated. These data suggest that a different subpopulation of neurons in the NTS might be triggering the pressor and bradycardic responses induced by chemoreceptor activation in SHR, whereas in normotensive rats, the same population of neurons in the commNTS could be involved in both responses. Thus, commNTS lesions affected the high blood pressure of SHR and also abolished the pressor response to chemoreceptor activation. Considering the studies suggesting the correlation between increased arterial chemoreceptor sensitivity and hypertension in SHR, the effects of commNTS lesions on chemoreceptor reflex responses might explain the reduction on SHR basal MAP after commNTS lesions.

One day following commNTS lesions, intravenous phenylephrine produced increased pressor responses in SHR. An explanation for this effect may lie in the fact that commNTS lesions might interfere in the vascular reactivity to intravenous phenylephrine because of changes in the sympathetic activity. We observed an increased pressor response to intravenous phenylephrine in commNTS-lesioned SHR. Indeed, we would expect an enhanced reflex bradycardia, but no differences were observed in reflex bradycardia compared with sham. Previous studies have shown a reduction in the vagal responses to changes in arterial pressure and in baroreceptor sensitivity to reflex control of heart rate in SHR, which could explain the unaltered bradycardia in commNTS-lesioned SHR in the presence of increased pressor response to phenylephrine.
Recent study\textsuperscript{16} has demonstrated that the blockade of excitatory amino acid (EAA) receptors in the rostral ventrolateral medulla (RVLM) decreased arterial pressure of SHR. Those results suggested that tonically active EAA-mediated inputs to RVLM excite RVLM vasomotor neurons. Electrophysiological evidence\textsuperscript{17} has indicated the existence of direct projections from commNTS to RVLM neurons. In addition, we have also demonstrated that inhibition of commNTS neurons in SHR elicited a marked fall in arterial pressure and splanchnic sympathetic nerve activity.\textsuperscript{18} Thus, because our data showed that commNTS lesions reduced arterial pressure in SHR, it is possible that the commNTS might be a source of tonic excitation of RVLM neurons.

In conclusion, our data suggest that the integrity of commNTS is important for the maintenance of high blood pressure in SHR and reflex responses dependent on sympathetic activation.

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