Baroreflex modulation by angiotensins at the rat rostral and caudal ventrolateral medulla

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Alzamora, Andréia C., Robson A. S. Santos, and Maria J. Campagnole-Santos. Baroreflex modulation by angiotensins at the rat rostral and caudal ventrolateral medulla. Am J Physiol Regul Integr Comp Physiol 290: R1027–R1034, 2006.—We determined the effect of microinjection of ANG-(1–7) and ANG II into two key regions of the medulla that control the circulation [rostral and caudal ventrolateral medulla (RVLM and CVLM, respectively)] on baroreflex control of heart rate (HR) in anesthetized rats. Reflex bradycardia and tachycardia were induced by increases and decreases in mean arterial pressure produced by intravenous phenylephrine and sodium nitroprusside, respectively. The pressor effects of ANG-(1–7) and ANG II (25 pmol) after RVLM microinjection (11 ± 0.8 and 10 ± 2 mmHg, respectively) were not accompanied by consistent changes in HR. In addition, RVLM microinjection of these angiotensin peptides did not alter the bradycardic or tachycardic component of the baroreflex. CVLM microinjections of ANG-(1–7) and ANG II produced hypotension (−11 ± 1.5 and −11 ± 1.9 mmHg, respectively) that was similarly not accompanied by significant changes in HR. However, CVLM microinjections of angiotensins induced differential changes in the baroreflex control of HR. ANG-(1–7) attenuated the baroreflex bradycardia (0.26 ± 0.06 ms/mmHg vs. 0.42 ± 0.08 ms/mmHg before treatment) and facilitated the baroreflex tachycardia (0.86 ± 0.19 ms/mmHg vs. 0.42 ± 0.10 ms/mmHg before treatment); ANG II produced the opposite effect, attenuating baroreflex tachycardia (0.09 ± 0.06 ms/mmHg vs. 0.31 ± 0.07 ms/mmHg before treatment) and facilitating the baroreflex bradycardia (0.67 ± 0.16 ms/mmHg vs. 0.41 ± 0.05 ms/mmHg before treatment). The modulatory effect of ANG II and ANG-(1–7) on baroreflex sensitivity was completely abolished by peripheral administration of methyalotrine. This result suggests that ANG II and ANG-(1–7) at the CVLM produce a different modulation of the baroreflex control of HR, probably through distinct effects on the parasympathetic drive to the heart.

baroreflex control of heart rate; renin-angiotensin system; arterial pressure

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baroreflex control of HR produced by microinjection of ANG-(1–7) or ANG II into the two key areas that control circulation at the VLM: the RVLM and CVLM.

METHODS

Surgical procedures. Male Wistar rats (260–300 g) were anesthetized with urethane (1.2 g/kg ip) and tracheostomized, and a polyethylene catheter was inserted into the abdominal aorta through the femoral artery for arterial pressure measurement. Another catheter was inserted into the inferior vena cava through the femoral vein for injection of drugs. The animals were placed in a stereotaxic frame (David Kopf Instruments) with the tooth bar 11 mm below the level of the interaural line. The dorsal surface of the brain stem was exposed by a limited occipital craniotomy, and an incision of the atlanto-occipital membrane and meninges was performed, as previously described (3, 41). The animals were kept on a heating pad, and the rectal temperature was checked periodically to maintain a constant body temperature (±37°C). All experiments and surgical procedures were performed in accordance with the guidelines established by the institutional animal welfare committee of the Universidade Federal de Minas Gerais.

Arterial pressure measurements. Pulsatile arterial pressure was continuously monitored by a solid-state strain-gauge transducer (model TP-200T; Nihon Kohden) triggered by the arterial pressure wave. All variables, pulsatile and mean arterial pressure and HR, were recorded continuously on a direct-writing polygraph (model CP-640G; Nihon Kohden).

Microinjection procedures. ANG-(1–7), ANG II, or vehicle (sterile 0.9% NaCl) in a volume of 100 nl was injected unilaterally over a 20-s period into the RVLM (2.1 mm anterior, 1.8 mm lateral to the obex, and just above the pia mater in the ventral surface) or CVLM (0.7 mm anterior, 1.8 mm lateral to the obex, and just above the pia mater in the ventral surface) as previously described (3, 41). Microinjections were made with a triple-barreled glass micropipette (90–130 μm OD), fixed to a stereotaxic manipulator, which was inserted into the brain tissue through the dorsal surface. Experiments were carried out only at sites where the micropipette produced a transitory pressor (RVLM) or depressor (CVLM) response (usually 10–20 mmHg). For all experiments, only one site on the medulla (RVLM or CVLM) was tested per animal.

Evaluation of baroreflex sensitivity. Baroreflex control of HR was determined by recording reflex HR changes in response to transient increases or decreases in mean arterial pressure (MAP) produced by repeated bolus injections of graded doses of phenylephrine (0.25–5 μg iv; baroreflex bradycardia) or sodium nitroprusside (0.5–10 μg iv; baroreflex tachycardia) (12, 13). Phenylephrine or sodium nitroprusside doses were injected 1–2 min apart into a femoral vein in 0.1 ml of isotonic NaCl. Blood pressure and HR were allowed to return to basal levels before the next dose was given.

The baroreflex test was performed in a different group of animals before microinjection of the peptides at the RVLM (n = 5–7) or CVLM (n = 5–8). The dose of phenylephrine or sodium nitroprusside that resulted in an intermediate change in MAP (34–45 mmHg) on the basis of the dose-response curve was repeated before and at the peak of the response of the peptide. Peak changes in HR during the initial 5–10 s of the corresponding maximum change in MAP produced with phenylephrine or sodium nitroprusside were recorded. The following formula was used to convert HR to pulse interval (PI, ms): 60,000/HR. The efficiency of the baroreceptor reflex (i.e., the baroreflex sensitivity index) was estimated by the ratio of change in HR (as change in PI) to change in MAP (ΔPI/ΔMAP, ms/mmHg) in each rat before and after microinjections of peptides at the RVLM or CVLM.

Only one microinjection site on the medulla (RVLM or CVLM) was tested in each animal. Two or three microinjections [ANG II, ANG-(1–7), and/or saline in random order] were performed in each animal with ≥30 min between microinjections.

To test the peripheral mechanisms involved in baroreflex changes, the muscarinic receptor antagonist methylatropine (2.5 mg/kg) was initially injected intravenously. After 15 min, the baroreflex control of HR was evaluated before and at the peak of the response induced by unilateral microinjection of ANG-(1–7) (25 pmol, n = 5–6) or ANG II (25 pmol, n = 6 each) into the CVLM. In these experiments, only one peptide or saline was tested in each animal.

The dose of methylatropine was chosen in preliminary experiments in which 2.5 mg/kg iv blocked the cardiovascular effects produced by acetylcholine (30 ng) for ≥60 min after its administration. In addition, the cardiovascular effects of acetylcholine were tested before and at the end of all experiments to verify the effectiveness of the muscarinic blockade.

Drugs. ANG-(1–7) and ANG II were purchased from Bachem (Torrance, CA) or Peninsula Laboratories (Belmont, CA). Methylatropine nitrate, phenylephrine, and sodium nitroprusside were obtained from Sigma (St. Louis, MO).

ANG-(1–7) and ANG II were dissolved in sterile isotonic saline (0.9% NaCl) at 2 mg/ml, and 10-μl aliquots were stored at −20°C. Phenylephrine and sodium nitroprusside were dissolved in sterile saline at 1 mg/ml, and 100-μl aliquots were stored at −20°C. At the time of the experiment, the aliquots were diluted in the desired concentrations and used only once. Methylatropine nitrate was dissolved in sterile saline at the time of the experiment and used only once.

Histological verification of injection sites. At the end of each experiment, 5% alcian blue dye (100 nl) was microinjected into the RVLM or CVLM. The animals were then killed with an excess of anesthetic, and the brain was carefully removed and fixed in 10% phosphate-buffered formalin. Serial coronal sections (40–50 μm) of the medulla oblongata were made and stained with neutral red for later histological examination. Microinjection sites were identified via light microscopy by the deposition of alcian blue dye and referred to standard anatomic structures of the brain stem according to the atlas of Paxinos and Watson (30).

Statistical analysis. Values are means ± SE. Pre- vs. postinjection comparisons in the same animal were evaluated by Student’s t-test for paired observations. Comparisons among different groups were assessed by one-way ANOVA followed by the Newman-Keuls test. These analyses were performed with Graphpad Prism software (version 4.00). The criterion for statistical significance was set at P < 0.05.

RESULTS

Effect of RVLM microinjection of ANG-(1–7) and ANG II on baroreflex sensitivity. As expected, unilateral microinjection of ANG-(1–7) and ANG II at the RVLM produced increases in blood pressure that were not accompanied by significant changes in HR (Table 1). In addition, microinjection of ANG-(1–7) or ANG II into the RVLM did not alter the bradycardic or tachycardic component of the baroreflex (Table 1). The sensitivity of the baroreflex bradycardia after microinjection of ANG-(1–7) (0.57 ± 0.10 ms/mmHg, n = 6) or ANG II (0.49 ± 0.09 ms/mmHg, n = 7) was not statistically different from that observed before the microinjections (0.51 ± 0.12 and 0.44 ± 0.11 ms/mmHg, respectively; Table 1). Similarly, the sensitivity of reflex tachycardia after microinjection of ANG-(1–7) (0.63 ± 0.06 ms/mmHg, n = 6) or ANG II (0.42 ± 0.13 ms/mmHg, n = 6) was similar to that before the microinjections (0.59 ± 0.08 and 0.44 ± 0.05 ms/mmHg, respectively; Table 1). Microinjection of saline into the RVLM did not significantly alter the bradycardic or tachycardic component of baroreflex control (Table 1).
The lack of a modulatory effect of angiotensin peptides on baroreflex control could be related to fact that the microinjections into the RVLM were unilateral. For this reason, in an additional group of animals, we tested the effect of bilateral microinjections of ANG-(1–7) (25 pmol, n = 9) into the RVLM on baroreflex control of HR. Bilateral microinjection of ANG-(1–7) into the RVLM produced a pressor effect (12 ± 1.7 mmHg, baseline MAP = 86 ± 6 mmHg, n = 9; data not shown) similar to that produced by unilateral microinjection (16 ± 1 mmHg, baseline MAP = 94 ± 5 mmHg, n = 6; Table 1). No significant effect on HR was observed (0.3 ± 3.4 beats/min, baseline HR = 298 ± 15 beats/min, n = 9; data not shown), and, as observed with unilateral injection, bilateral microinjection of ANG-(1–7) did not significantly alter the baroreflex bradycardia (0.51 ± 0.09 ms/mmHg vs. 0.53 ± 0.09 ms/mmHg before microinjection, n = 9; data not shown).

Effect of RVLM microinjection of ANG-(1–7) and ANG II on baroreflex sensitivity. Unilateral microinjection of ANG-(1–7) into the RVLM produced a significant decrease in MAP (baseline MAP = 110 ± 6 mmHg, ΔMAP = −11 ± 1.5 mmHg, n = 10) that was similar to the decrease produced by ANG II (baseline MAP = 99 ± 5 mmHg, ΔMAP = −11 ± 1.9 mmHg, n = 13). The changes in blood pressure were statistically different from that produced by saline (baseline MAP = 97 ± 6 mmHg, ΔMAP = −2.5 ± 0.6 mmHg, n = 9). The hypotensive effect of ANG peptides was not accompanied by significant changes in HR (−5 ± 3 and −3 ± 2 beats/min for ANG-(1–7) and ANG II, respectively).

Microinjection of ANG-(1–7) or ANG II into the CVLM induced a differential effect on the bradycardic and tachycardic component of the baroreflex. Effects of different doses of phenylephrine or sodium nitroprusside before and after CVLM microinjection of ANG II are shown in Fig. 1. Microinjection of ANG II into the CVLM (ΔMAP = −11 ± 2.5 mmHg, baseline MAP = 93 ± 5 mmHg and HR = 297 ± 16 beats/min, n = 8) significantly increased the sensitivity of the baroreflex bradycardia (0.67 ± 0.16 ms/mmHg vs. 0.41 ± 0.05 ms/mmHg before treatment, n = 8; Fig. 2A). In contrast, after microinjection of ANG-(1–7) into the CVLM (ΔMAP = −12 ± 3 mmHg, baseline MAP = 104 ± 5 mmHg and HR =

Table 1. Baseline MAP and HR, changes in MAP and HR, and sensitivity index of baroreflex bradycardia and tachycardia before and after RVLM microinjection of ANG-(1–7), ANG II, or saline

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<th>Baseline</th>
<th>Cardiovacular Changes</th>
<th>Baroreflex Tachycardia</th>
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<tr>
<td></td>
<td>MAP, mmHg n</td>
<td>HR, beats/min</td>
<td>ΔMAP, mmHg</td>
</tr>
<tr>
<td>Saline (100 nl)</td>
<td>5 92±9 284±12 3±1 0.6±2</td>
<td>0.47±0.08 0.48±0.06</td>
<td>4 98±14 325±18 3±1.3 3±1.5 0.55±0.10 0.66±0.05</td>
</tr>
<tr>
<td>ANG-(1–7) 25 pmol</td>
<td>6 94±5 304±11 16±1* 6±6</td>
<td>0.51±0.12 0.57±0.10</td>
<td>6 112±3 321±17 10±1.8* 1±5.0 0.59±0.08 0.63±0.06</td>
</tr>
<tr>
<td>ANG II 25 pmol</td>
<td>7 104±5 300±14 15±3* 0.4±3</td>
<td>0.44±0.11 0.49±0.09</td>
<td>6 104±12 347±13 12±3.0* −4±6.5 0.44±0.05 0.42±0.13</td>
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Values are mean ± SE, MAP, mean arterial pressure; HR, heart rate; PI, pulse interval; RVLM, rostral ventrolateral medulla. *P < 0.05 vs. saline (ANOVA followed by Newman-Keuls test).

Fig. 1. Blood pressure and heart rate (HR) traces illustrating reflex changes in HR induced by mean arterial pressure (MAP) changes produced by bolus intravenous injection of phenylephrine (Phe; 1–5 μg; A) or sodium nitroprusside (NP; 2.5–7.5 μg; B) before and after microinjection of ANG II (25 pmol) into the caudal ventrolateral medulla (CVLM).
treatment with the muscarinic receptor antagonist methylatropine produced the expected increase in baseline HR (average of all animals = 378 ± 10 beats/min vs. 315 ± 11 beats/min before treatment, n = 19) without significant change in baseline MAP (90 ± 4 vs. 95 ± 5 mmHg, n = 19). As previously described (3), the hypotensive effect of ANG-(1–7) was significantly attenuated after peripheral treatment with methylatropine (−3 ± 1 mmHg vs. −12 ± 4 mmHg before treatment, n = 10; Table 2). In contrast, the hypotensive effect of ANG II at the CVLM after methylatropine was not statistically different from that observed before the antagonist (−9 ± 2 mmHg vs. −13 ± 3 mmHg before treatment, n = 9; Table 2). No significant changes in HR were induced by microinjection of angiotensins into the CVLM before or after methylatropine treatment (Table 2). In addition, methylatropine abolished the hypotensive effect produced by intravenous injection of ace- tycloline at the end of the experiments (−2 ± 1 mmHg vs. −22 ± 2 mmHg before treatment, n = 19; data not shown), confirming the effectiveness of the muscarinic blockade.

Methylatropine significantly attenuated the baseline baroreflex sensitivity for the baroreflex bradycardia (0.14 ± 0.02 ms/mmHg vs. 0.33 ± 0.10 ms/mmHg before treatment, n = 10; data not shown) and baroreflex tachycardia (0.18 ± 0.02 ms/mmHg vs. 0.31 ± 0.04 ms/mmHg before treatment, n = 9; data not shown). Furthermore, methylatropine prevented the modulatory effect of ANG-(1–7) and ANG II on baroreflex control of HR. ANG-(1–7) microinjection after methylatropine did not change the baroreflex bradycardia (0.12 ± 0.03 ms/mmHg vs. 0.13 ± 0.04 ms/mmHg before treatment, n = 4; Fig. 3A) or baroreflex tachycardia (0.23 ± 0.01 ms/mmHg vs. 0.22 ± 0.02 ms/mmHg before treatment, n = 5; Fig. 3B). Similarly, ANG II microinjection after muscarinic blockade did not change the baroreflex bradycardia (0.09 ± 0.02 ms/mmHg vs. 0.10 ± 0.02 ms/mmHg before treatment, n = 5; Fig. 3A) or baroreflex tachycardia (0.18 ± 0.05 ms/mmHg vs. 0.27 ± 0.06 ms/mmHg before treatment, n = 4; Fig. 3B).

**Histological examination.** Localization of the microinjections into the RVLM and CVLM in frontal sections of the medulla according to the atlas of Paxinos and Watson (30) is shown in Fig. 4. As shown by dispersion of the dye in all animals, the microinjections into the RVLM were located in the ventral portion of the rostroventrolateral reticular and lateral paragigantocellular nuclei (Fig. 4A). The microinjec-

286 ± 11 beats/min, n = 5), there was a significant decrease in the baroreflex bradycardia (0.26 ± 0.06 ms/mmHg vs. 0.42 ± 0.08 ms/mmHg before treatment, n = 5; Fig. 2A). On the other hand, microinjection of ANG-(1–7) into the CVLM (ΔMAP = −10 ± 1.8 mmHg, baseline MAP = 102 ± 9 mmHg and HR = 335 ± 23 beats/min, n = 5) significantly increased the sensitivity of reflex tachycardia (0.86 ± 0.19 ms/mmHg vs. 0.42 ± 0.10 ms/mmHg before treatment, n = 5; Fig. 2B), whereas microinjection of ANG II (ΔMAP = −11 ± 3 mmHg, baseline MAP = 108 ± 7 mmHg and HR = 304 ± 19 beats/min, n = 5) significantly decreased the sensitivity of reflex tachycardia (0.09 ± 0.06 ms/mmHg vs. 0.31 ± 0.07 ms/mmHg before treatment, n = 5; Fig. 2B). Microinjection of saline into the CVLM did not significantly alter the bradycardic (0.53 ± 0.17 ms/mmHg vs. 0.53 ± 0.13 ms/mmHg before treatment, n = 5) or tachycardic (0.35 ± 0.09 ms/mmHg vs. 0.39 ± 0.15 ms/mmHg before treatment, n = 5) component of the baroreflex (Fig. 2).

Peripheral mechanism involved in the baroreflex modulationary effects induced by microinjection of ANG-(1–7) or ANG II into the CVLM. We next evaluated the contribution of the parasympathetic tonus to the modulatory effect of the ANG peptides at the CVLM on the baroreflex control of HR. Pre-

### Table 2. Baseline MAP and HR and changes in MAP and HR induced by microinjection of ANG-(1–7), ANG II, or saline into CVLM before and after methylatropine

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<th>Baseline</th>
<th>ANG at CVLM</th>
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<tr>
<td>n</td>
<td>MAP, mmHg</td>
<td>HR, beats/min</td>
</tr>
<tr>
<td>ANG-(1–7) Before MA</td>
<td>10</td>
<td>94 ± 7</td>
</tr>
<tr>
<td>After MA (2.5 mg/kg iv)</td>
<td>89 ± 7</td>
<td>388 ± 11*</td>
</tr>
<tr>
<td>ANG II Before MA</td>
<td>9</td>
<td>100 ± 7</td>
</tr>
<tr>
<td>After MA (2.5 mg/kg iv)</td>
<td>91 ± 6</td>
<td>362 ± 16*</td>
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Values are means ± SE. CVLM, caudal ventrolateral medulla; MA, methylatropine. *P < 0.05 vs. before (Student’s t-test for paired observations).
barosensitive neurons are GABAergic (15, 32, 44); however, some neurons are catecholaminergic or cholinergic (39, 43, 46). Although these CVLM neurons are often depicted as a simple relay to the RVLM, GABAergic cells, and possibly others, are likely to innervate multiple sites to provide a more widespread baroreceptor-mediated inhibition of other regions of the central nervous system. Using the microinjection of anterograde tracings into the CVLM, Stocker et al. (42) showed a dense concentration of labeled axons throughout the lateral medullary reticular formation, including the retrofacial nucleus, NA, RVLM, hypoglossal nucleus, intercalated nucleus, and facial nucleus. These data suggest that a functional interaction between medullary sites can exist in the control of the parasympathetic and sympathetic nervous system.

It is our hypothesis that angiotensin peptides modulate the activity of neurons in the CVLM that may also be involved in controlling baroreceptor modulation of the parasympathetic outflow. Figure 5 presents a simplified schematic model to illustrate our hypothesis. Inasmuch as the baroreflex circuit is activated by the pressor response produced by phenylephrine, an increase in the activity of the parasympathetic preganglionic neurons in the NA is expected on the basis of the well-recognized NTS-NA pathway. ANG II acting on CVLM neurons would increase the activity of cardiac vagal neurons in the NA, through a direct or an indirect pathway that is yet to be identified. On the other hand, ANG-(1–7) would produce an opposite effect, decreasing the activity of these vagal efferents. One of the possible overall changes in the baroreflex control of the HR curve induced by angiotensin peptides at the CVLM is also illustrated in Fig. 5.

Several studies have shown depressor responses to microinjections of excitatory amino acids or peptides into the medial and ventral portions of the lateral reticular nucleus (8, 26, 47). The depressor effects evoked by the microinjections of neuro-active drugs into these sites are consistent but small in magnitude compared with those elicited from the periambigual area, which are also accompanied by large alterations in HR (26, 47). Future studies are necessary to verify the existence of such a pathway, which connects the ventral part of the CVLM to the parasympathetic neurons on the NA or other medullary sites.

The fact that ANG II and ANG-(1–7) presented distinct modulatory effects on the baroreflex is not surprising. In previous studies, we showed opposite effects for these peptides on baroreflex modulation: intracerebroventricular infusion (10) or NTS microinjection (12) of ANG-(1–7) produces significant facilitation of the baroreflex bradycardia, whereas ANG II at these same sites induces attenuation (9–11, 25). It is also not unusual that ANG II exerts an excitatory action upon microinjection into a specific area and, at the same site, results in attenuation of the baroreflex. For example, at the NTS, ANG II induces hypertensive effects that mimic stimulation of the baroreflex; however, upon its microinjection, an attenuation of the baroreflex bradycardia is observed (9, 11). At the CVLM, the hypotensive effect of angiotensin peptides is not accompanied by consistent changes in HR or cardiac output (3, 38), thus suggesting that both peptides induced stimulatory effects on GABAergic CVLM neurons probably projecting to the RVLM. In fact, the hypotensive effect of ANG II at the CVLM is associated with a decrease in renal sympathetic activity (48) and is blocked by application of muscimol, a GABA agonist,

![Image](http://ajpregu.physiology.org/)

**Fig. 3.** Baroreflex bradycardia sensitivity index (A) and baroreflex tachycardia sensitivity index (B) before and after CVLM microinjection of ANG-(1–7) (25 pmol, n = 5 each) or ANG II (25 pmol, n = 4–5) in animals treated with methylatropine (2.5 mg/kg iv). None of the indexes of baroreflex sensitivity after CVLM microinjection were statistically different from those before CVLM microinjection.
Even though the hypotensive effect of ANG-(1–7) at the CVLM is similar, previous results indicate that it involves a sympathoinhibitory peripheral mechanism (3). Taken together, these data suggest that differential effects can result from the interaction of angiotensin peptides with barosensitive neurons, which present phasic activity, or with nonbarosensitive neurons, which are tonically involved in the control of blood pressure, at least in the CVLM and NTS. Consistent with this hypothesis, using the whole cell patch-clamp technique, Kasparov and Paton (24) showed that, in a

Fig. 4. Drawings of frontal sections of the medulla oblongata from the atlas of Paxinos and Watson (30) showing the location of microinjections in the rostral ventrolateral medulla (RVLM, A) and CVLM (B) obtained from histological examination of alcian blue dye deposition in frontal sections of the medulla of rats. Numbers below each drawing refer to distance from bregma. AP, area postrema; Amb, nucleus ambiguus; IO, inferior olive; LR, lateral reticular nucleus; LPGi, lateral paragigantocellular nucleus; py, pyramidal tract; RVL, rostroventrolateral reticular nucleus; Sol, nucleus of solitary tract; XII, hypoglossal nucleus.

Fig. 5. A: simplified schematic representation of medullary pathway of baroreflex control of HR. Baroreceptor afferents make their first synapse at the nucleus of the solitary tract (NTS). Neurons at the NTS drive baroreceptor information mainly to 2 areas/nuclei: 1) the nucleus ambiguous (NA) and the dorsal motor nucleus of the vagus (not shown), which contain preganglionic cells of the parasympathetic system, and 2) the CVLM, which, in turn, modulates premotor neurons of the RVLM that control activity of preganglionic cells of the sympathetic system in the intermediolateral column of the spinal cord. +, Excitatory effect; −, inhibitory effect. B: correlation between reflex changes in HR expected for MAP changes induced by vasoactive drugs before and after ANG II or ANG-(1–7) microinjection at the CVLM. ANG II and ANG-(1–7) acting at the CVLM can differentially modulate parasympathetic output of the baroreflex. Whether this effect involves a direct or indirect pathway is yet to be explored.
subpopulation of NTS neurons that tended to exhibit ongoing activity, ANG II potentiated NTS-evoked excitatory postsynaptic potentials. In a different subpopulation of neurons, characterized as silent cells, ANG II enhances inhibitory postsynaptic potentials. This latter effect could potentially account for the ANG II-mediated depression of the baroreceptor reflex. In addition, these authors showed that both effects were blocked by losartan and that the potentiation of excitatory, but not inhibitory, synaptic transmission involves the release of substance P. Thus other possible mechanisms, yet to be explored, may involve the release of other neurotransmitters, the activation of other interneurons, or the participation of other receptor subtypes in the effect induced by angiotensin peptides in the baseline and baroreflex control of blood pressure in different medullary sites such as the CVLM and NTS.

Only a few studies have evaluated the effect of angiotensins in the RVLM or CVLM on the baroreflex control of arterial pressure. In the rat, Sesoko et al. (40) showed that bilateral microinjection of the ANG II antagonist sarthran into the CVLM increased the sensitivity for reflex activation of RSNA but did not alter the sensitivity for reflex suppression of RSNA, suggesting that ANG II attenuates baroreflex control of RSNA only for a fall in arterial pressure. These data are in agreement with our results showing that ANG II at the CVLM attenuates baroreflex-mediated tachycardia. The studies addressing baroreflex control of sympathetic activity were performed with nonselective angiotensin antagonists, sarthran and saralasin, which may interfere with AT\(_1\) and AT\(_2\) and the ANG-(1–7) nonselective angiotensin antagonists, CV-11974, into the RVLM of transgenic rats with low angiotensin levels in the brain did not significantly alter arterial pressure (5). Taken together, these data suggest that, in addition to its well-known excitatory central action, ANG II may induce an inhibitory effect depending on the endogenous level of the angiotensins peptides, at least at the RVLM.

In conclusion, the data presented in this study show that microinjection of ANG II or ANG-(1–7) into the RVLM does not affect the baroreflex control of HR, microinjection of ANG II or ANG-(1–7) into the CVLM produces differential effects that lead to changes in the parasympathetic drive to the heart. Furthermore, our data indicate that the non-RVLM CVLM connections, possibly with the NA, may be an additional pathway for the modulatory influence of angiotensin peptides on the baroreflex control of HR.

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