Baroreceptor reflex regulation in anesthetized transgenic rats with low glia-derived angiotensinogen

Atsushi Sakima,1 David B. Averill,1 Sherry O. Kasper,1 LaRhonda Jackson,1 Detlev Ganten,2 Carlos M. Ferrario,1 Patricia E. Gallagher,1 and Debra I. Diz1

1Hypertension and Vascular Disease Center, Department of General Surgery, and Department of Physiology and Pharmacology, Wake Forest University School of Medicine, Winston-Salem, North Carolina; and 2Charite-University Medicine Berlin, Berlin, Germany

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Sakima A, Averill DB, Kasper SO, Jackson LR, Ganten D, Ferrario CM, Gallagher PE, Diz DL. Baroreceptor reflex regulation in anesthetized transgenic rats with low glia-derived angiotensinogen. Am J Physiol Heart Circ Physiol 292: H1412–H1419, 2007. First published November 3, 2006; doi:10.1152/ajpheart.00984.2006.—Endogenous angiotensin (ANG) II and ANG-(1–7) act at the nucleus tractus solitarius (NTS) to differentially modulate neural control of the circulation. The role of these peptides endogenous to NTS on cardiovascular reflex function was investigated in transgenic rats with low brain angiotensinogen (Aogen) due to glial overexpression of an antisense to Aogen (ASrAOGEN) and in Sprague-Dawley (SD) rats. Arterial baroreceptor reflex sensitivity (BRS) for control of heart rate (HR) in response to increases in mean arterial pressure (MAP) was tested before and after bilateral microinjection of the angiotensin type 1 (AT1) receptor blocker candesartan or the ANG-(1–7) receptor blocker (D-Ala7)-ANG-(1–7) into the NTS of urethane-chloralose-anesthetized ASrAOGEN and SD rats. Baseline MAP was higher in ASrAOGEN than in SD rats under anesthesia (P < 0.01). Injection of candesartan or (D-Ala7)-ANG-(1–7) decreased MAP (P < 0.01) and HR (P < 0.05) in ASrAOGEN, but not SD, rats. The BRS at baseline was similar in ASrAOGEN and SD rats. Candesartan increased BRS by 41% in SD rats (P < 0.01) but was without effect in ASrAOGEN rats. In contrast, the reduction in BRS after (D-Ala7)-ANG-(1–7) administration was comparable in SD (31%) and ASrAOGEN rats (34%). These findings indicate that the absence of glia-derived Aogen is associated with an increase in MAP under anesthesia mediated via AT1 and ANG-(1–7) receptors within the NTS, 2) the absence of an endogenous ANG II contribution to tonic inhibition of BRS, and 3) a continued contribution of endogenous ANG-(1–7) to tonic enhancement of BRS.

baroreceptors; solitary tract nucleus; brain renin-angiotensin system; transgenic rats

ENDOGENOUS ANGIOTENSIN (ANG) II contributes to cardiovascular and autonomic reflex function (1, 8, 17, 21, 52). ANG II receptors have been identified in the nucleus tractus solitarius (NTS), where baroreceptor and chemoreceptor afferents terminate and ANG II, of endogenous or exogenous origin, is known to attenuate baroreflex function (1, 8, 11, 14, 24, 30, 40, 46). ANG-(1–7) is also present in the brain, in the hypothalamus and medulla oblongata, at concentrations equivalent to or greater than ANG II (12). ANG-(1–7), from endogenous or exogenous sources, enhances baroreflex control of heart rate (HR), resulting in actions opposite to those of ANG II (1, 6, 9, 13, 21, 44, 52).

Transgenic animals are useful for investigation of the functional role of the brain renin-angiotensin system (RAS) in cardiovascular regulation and fluid homeostasis. In fact, glial and neuronal overexpression of renin and angiotensinogen produces different patterns of alterations in resting arterial pressure and baroreceptor reflex function. Morimoto et al. (42, 43) recently demonstrated that glia- or neuron-specific overexpression of human renin and human angiotensinogen in mouse brain elevated mean arterial pressure (MAP), water intake, and salt appetite. However, only glial overexpression attenuated the baroreceptor reflex sensitivity (BRS), in addition to increasing MAP (51). Transfection of Hannover Sprague-Dawley (SD) rats with the glial fibrillary acidic protein promoter-linked angiotensinogen antisense led to the development of transgenic rats with low brain angiotensinogen [ASr(Aogen)680 (ASrAOGEN rats)] (54). These transgenic rats exhibit a 90% reduction in brain levels of angiotensinogen, a reduction of hypothalamic tissue ANG I, and a tendency for lower hypothalamic ANG II and low plasma vasopressin levels (31, 54). In conscious ASrAOGEN rats, resting MAP is slightly lower and BRS is slightly higher than in SD rats (2, 3, 14, 34, 54, 62). Although astrocytes may be the main source of angiotensinogen in the brain, it is also expressed in neurons, as supported by studies in which renin and angiotensinogen are synthesized by cells in culture and by intact brain (15, 16, 37, 38, 55, 60). We recently found that ANG II and ANG-(1–7) immunoreactivity was similar in neuronal pathways in SD and ASrAOGEN rats (61), suggesting that the neuronal expression of the two peptides might be intact in the face of a depleted glial source of the peptides. In anesthetized ASrAOGEN rats, reports are variable in terms of the resting MAP and depressor responses to microinjection of exogenous ANG II or ANG-(1–7) into the NTS (2, 3, 10, 14, 21), and no data exist on the contribution of endogenous ANG peptides within the NTS to resting blood pressure or baroreflex function in these animals.

The present experiments investigated the hypothesis that the contribution of ANG II and ANG-(1–7) endogenous to the NTS to regulation of baroreceptor reflex function would be diminished in ASrAOGEN rats relative to the control SD rats if the peptides are derived from glial sources, as reported in mice. Thus we determined whether blockade of angiotensin type 1 (AT1) or ANG-(1–7) receptors in the NTS contributed to resting MAP and baroreflex sensitivity control of HR (BRS) in urethane-chloralose-anesthetized SD or ASrAOGEN rats. We
also studied the effects of blockade of AT$_1$ or ANG-(1–7) receptors on the reflex response to activation of cardiopulmonary chemosensitive afferent fibers by phenylbiguanide, since previous studies indicate enhanced responses to this stimulus in ASrAOGEN rats (21).

**METHODS**

*Animals.* Experiments were performed in 3- to 5-mo-old male SD rats [Harlan substrain (Hypertension and Vascular Disease Center Colony, Wake Forest University School of Medicine) or Harlan strain (Harlan Sprague Dawley, Indianapolis, IN)] and age-matched male ASr(Aogen)680 (ASrAOGEN) rats (Hypertension and Vascular Disease Center, Wake Forest University School of Medicine). Previous studies document that, in terms of BRS, Hannover and Harlan SD rats respond similarly to candesartan and (D-Ala$_7$)-ANG-(1–7) (52). Rats were housed in group cages in a temperature- and humidity-controlled room (12:12-h light-dark cycle) with free access to standard rat chow and water.

*Surgical procedures.* The animals were anesthetized intraperitoneally with a combination of urethane and chloralose (750 and 35 mg/kg, respectively); supplemental doses were given intravenously as required on the basis of corneal reflexes, respiratory rate and rhythm, and stability of MAP and HR. Animals spontaneously breathed 70% room air-30% oxygen through a nose cone. Body temperature was maintained at 37.0 ± 1.0°C by a heating pad (model 39 DP, Braintree Scientific, Braintree, MA). Polyethylene catheters (PE-50, Clay Adams, Parsippany, NJ) were inserted into a femoral artery and vein. The venous catheter was positioned near the right atrium. Rats were placed in a stereotaxic frame (David Kopf Instruments) set at a 45° angle, so that the head flexed downward, allowing surgical exposure of the dorsal medulla oblongata after incision of the atlantooccipital membrane (18, 19, 24).

**Arterial pressure and HR measurements.** Pulsatile arterial pressure was monitored by a strain gauge transducer connected to the femoral arterial catheter using a BIOPAC (Santa Barbara, CA) data acquisition system, and HR was determined from the arterial pressure wave. Arterial pressure and HR were digitized and recorded with Acknowledge software (version 3.7.2, BIOPAC) as previously reported (52).

**Microinjection and reflex study.** The multibarreled glass pipettes (30–50 μM OD) were made from calibrated capillary glass tubing (Kimble Glass, Vineland, NJ) and coated with silicone (Sigma-Aldrich, St. Louis, MO). The angiotensin type 1 (AT$_1$) receptor antagonist candesartan (CV-11974, 24 pmol) (40) and the ANG-(1–7) receptor antagonist (D-Ala$_7$)-ANG-(1–7) (52) were microinjected bilaterally into the NTS, and after 10 min CVA and BRs were assessed again, so that each animal was used as its own control.

At the end of each experiment, the brain was removed and frozen. Location of the microinjection pipette placement was established by histological evaluations of serial frozen brain sections (30 μm). Only experiments in which the pipette tip could be visualized within the intermediate portion of the medial NTS within the rostrocaudal level −12.5 to −19.5 mm caudal to bregma (47) were included in this study.

**Quantification of mas receptor mRNA.** Total RNA was isolated from the medulla of each rat, quantified by UV spectroscopy, and then incubated with RQ1 DNase (Promega) to eliminate residual DNA before PCR. Approximately 1 μg of total RNA was reverse transcribed as previously described using mas receptor-specific primers (411 bp) and primers for elongation factor 1α sequence (347 bp) (29, 52). Amplification products were separated on 6% polyacrylamide gels, visualized using a PhosphorImager, and quantified by computed densitometry, with the mRNA concentration expressed as the ratio of mas receptor mRNA to control elongation factor 1α.

**Analysis of data.** Values are means ± SE. Baseline values of MAP, HR, BRs, CVA, and mas receptor mRNA in SD and ASrAOGEN rats were compared by Student’s unpaired t-test on data pooled from all animals in each group. Baseline values were compared with the changes in MAP and HR elicited by graded doses of phenylephrine in SD and ASrAOGEN rats by analysis of variance (ANOVA) for repeated measures with Newman-Keuls post hoc multiple comparisons. One-way ANOVA with Newman-Keuls post hoc multiple comparisons was used to compare the baseline (before microinjections) values of the MAP and HR for each antagonist treatment subgroup. Student’s paired t-test was used to evaluate the BRs, CVA, prevailing values of MAP and HR, and changes in MAP and HR before and after microinjections in each antagonist treatment subgroup. The criterion for statistical significance was P < 0.05, and all tests were performed using Prism (GraphPad Software, San Diego, CA) or StatView-J5.0 (SAS Institute, Cary, NC).

**RESULTS**

Baseline MAP, HR, α$_1$-adrenergic cardiovascular responsiveness, and reflex function. The pooled baseline MAP of all anesthetized ASrAOGEN rats (n = 23) was significantly higher than the pooled value from anesthetized SD rats (n = 24; Fig. 1A). In contrast, the pooled data for baseline HR of SD and ASrAOGEN rats did not differ (Fig. 1B). The changes in blood pressure and HR in response to phenylephrine injections are shown in Fig. 2, A and B. The phenylephrine-induced increases in MAP and PI were not different between the two groups of rats. Thus the baseline BRs of the anesthetized ASrAOGEN and SD rats did not differ (Fig. 2, C and D). Typical records of MAP and HR before and after phenylbiguanide injection in an anesthetized SD rat and an ASrAOGEN rat are shown in Fig. 3, A and B, respectively. Phenylbiguanide infusion rapidly and significantly decreased MAP and HR. The depressor response of anesthetized ASrAOGEN rats was significantly greater than that of SD rats (P < 0.01), whereas the bradycardic response of ASrAOGEN rats was only modestly larger than that of SD rats (P < 0.1; Fig. 3D).

Effects of microinjection of candesartan, (D-Ala$_7$)-ANG-(1–7), or aCSF into the NTS on resting MAP, HR, and reflex function. The effects of bilateral injection of candesartan, (D-Ala$_7$)-ANG-(1–7), or aCSF into the NTS on resting MAP and HR are shown in Fig. 4. Candesartan injected bilaterally...
into the NTS of anesthetized ASrAOGEN rats significantly 
(P < 0.01) and transiently decreased MAP and HR (Fig. 4). 
The onset of depressor responses occurred within 30 s and 
peaked at 3.4 ± 0.7 min. Bilateral injection of (D-Ala7)-ANG-(1–7) 
into the NTS of anesthetized ASrAOGEN rats significantly 
decreased MAP and HR (Fig. 4). The onset of depressor 
responses occurred within 30 s and peaked at 4.5 ± 0.7 min. 
Injection of aCSF did not affect the resting values of MAP and 
HR in the ASrAOGEN animals (Fig. 4). In anesthetized SD rats, 
bilateral injection of candesartan, (D-Ala7)-ANG-(1–7), or aCSF 
into the NTS had no effect on resting MAP and HR (Fig. 4).

The MAP and HR values 5–10 min after injection of the 
receptor antagonists or aCSF into the NTS, which was imme-
diately before the retesting of the reflexes, is shown in Table 1 
for each of the subgroups compared with the initial baseline 
values. Although candesartan and (D-Ala7)-ANG-(1–7) low-
ered MAP and HR of the ASrAOGEN rats immediately after 
injection into the NTS (see above), these values partially 
recovered by the time the reflexes were tested 10–30 min later. 
At the time of reflex testing in ASrAOGEN rats, MAP was 
only modestly lower after than before candesartan injection 
(P = 0.054; Table 1), whereas HR was significantly lower after 
than before candesartan injection (P < 0.05). MAP and HR did 
not differ from the prior baseline values after (D-Ala7)-ANG-(1–7) 
injection into the NTS at the time of the reflex testing 
(Table 1). When the BRS control of HR was retested in the 
presence of candesartan, the BRS was enhanced significantly 
(P < 0.01) in SD, but not in ASrAOGEN, rats (Fig. 5A). In 
contrast, after bilateral injection of (D-Ala7)-ANG-(1–7) into 
the NTS, BRS was significantly attenuated in SD and ASrAOGEN 
rats (Fig. 5B). aCSF injection did not alter BRS or resting MAP 
and HR in SD or ASrAOGEN rats (Fig. 5C, Table 1). Bilateral 
injection of candesartan, (D-Ala7)-ANG-(1–7), or aCSF into 
the NTS had no effect on the magnitude of the pressor 
responses to phenylephrine injection in any of the six groups of 
rats (data not shown).

The reflex reductions in MAP and HR evoked by CVA 
(phenylbiguanide injections) before and 5–10 min after injec-
tion of the receptor antagonists or aCSF are shown in Table 2. 
Intravenous injection of phenylbiguanide elicited significantly 
larger depressor responses at baseline in the ASrAOGEN than 
SD rats at baseline (before NTS microinjections) for the 
subgroups that would receive candesartan or aCSF; the trend 
was similar for animals that would receive (D-Ala7)-ANG-(1–7).
There were no significant differences in the responses to 
CVA before vs. after candesartan or aCSF injection into the
NTS in the SD or the ASrAOGEN animals. On the other hand, after (n-Ala²)-ANG-(1–7) injections into the NTS in ASrAOGEN rats, CVA responses did not differ from those in the SD rats.

**Differences in mas receptor mRNA in ASrAOGEN and SD rats.** Since ANG-(1–7), but not ANG II, provided a tonic contribution to the baroreceptor reflex in the ASrAOGEN animals, we assessed the expression of the mas receptor mRNA in medullary tissue from animals of the two strains. Relative gene expression of mas receptor mRNA averaged 1.19 ± 0.07 and 1.48 ± 0.09 in SD (n = 9) and ASrAOGEN (n = 7) rats, respectively (P = 0.02).

**DISCUSSION**

These studies demonstrate that different sources contribute to the ANG II and ANG-(1–7) endogenous to the NTS, which modulate reflex function under anesthesia. AT1 receptor blockade in the NTS enhanced BRS in SD, but not in ASrAOGEN, rats. ANG-(1–7) receptor blockade significantly attenuated BRS control of HR in SD and ASrAOGEN rats. Thus glia appear to be an important source of ANG II, but ANG-(1–7) may be derived from nonglial source(s) for modulation of this aspect of BRS, which represents primarily the vagal contribution to control of HR. Interestingly, our experiments also...
Table 1. MAP and HR immediately before reflex testing in SD and ASrAOGEN rats

<table>
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<tr>
<th>Treatment</th>
<th>SD</th>
<th>ASrAOGEN</th>
<th>SD</th>
<th>ASrAOGEN</th>
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<tbody>
<tr>
<td>Candesartan injection</td>
<td>8 95±3 319±8</td>
<td>7 116±14</td>
<td>8 97±2 318±12</td>
<td>7 109±3 *</td>
</tr>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-Ala7-ANG-(1–7) injection</td>
<td>8 92±3 323±11</td>
<td>7 113±3 323±14</td>
<td>8 92±3 316±10</td>
<td>7 109±4 *</td>
</tr>
<tr>
<td>aCSF injection</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>8 97±3 313±9</td>
<td>9 114±3 312±9</td>
<td>8 92±3 323±9</td>
<td>9 112±3 296±6 *</td>
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<td>aCSF</td>
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Values are means ± SE; n, number of rats. Data were obtained in the minute preceding each series of reflex testing. MAP, mean arterial pressure; HR, heart rate; aCSF, artificial cerebrospinal fluid; SD, Sprague-Dawley rats; ASrAOGEN, rats. D-Ala7-ANG-(1–7) significantly attenuated BRS in SD and ASrAOGEN rats to levels not different from those in SD rats. Therefore, even though glia-derived ANG peptides may be reduced, other sources of endogenous ANG II and ANG-(1–7) acting within the NTS contribute to the increase in MAP in response to anesthesia in ASrAOGEN rats.

The two endogenous ANG peptides have opposite actions on the BRS, as revealed using selective antagonists administered directly into the NTS of SD rats, consistent with a number of earlier studies contrasting their effects on reflex function (1, 3, 8, 17, 21, 52). The persistence of a tonic effect of endogenous ANG-(1–7), but not ANG II, on BRS in the ASrAOGEN rats is new evidence in support of the view that these peptides act via independent mechanisms. Previous anatomic, electrophysiological, and functional studies illustrate that the response to ANG II and ANG-(1–7) in the NTS depends on different afferent projections to the nucleus (7), different populations of neurons (5, 27, 63, 64), and different neurotransmitters (4, 19, 23, 25, 33). The present data further imply that ANG II derived from a glial source of angiotensinogen provides tonic suppression of the BRS for control of HR. This is consistent with recent studies in transgenic mice demonstrating that increases in components of the RAS in glia attenuated the BRS, whereas manipulation of the RAS targeted to neurons did not (42, 43, 51). The present observations extend these findings by revealing that effects of ANG-(1–7) on the BRS are not dependent on a glial source of the peptide.

In contrast to the findings with glial overexpression of the RAS to alter the BRS, neuronal overexpression had a greater impact on resting arterial pressure and the set point for the reflex in mice (42, 43). Neither ANG II nor ANG-(1–7) in neuronal pathways originating from the paraventricular nucleus (PVN) appears to be different in ASrAOGEN vs. SD rats (61). Descending pathways from the PVN to the NTS and rostral ventrolateral medulla are thought to participate in the acute pressor responses to behavioral stress and elevated circulating ANG II via activation of central angiotensinergic pathways (2, 28, 36, 48, 49, 58). Reports indicate that, for the rostral ventrolateral medulla, both peptides contribute to activation of the sympathetic nervous system (2, 28, 48, 49, 58).

The finding that peptides and their receptors may be involved in activation of sympathetic outflow and support of resting arterial pressure at sites in the dorsal medulla is new with respect to ANG-(1–7). The elevated AT1 receptor levels in the PVN of ASrAOGEN rats (see below) would provide a mechanism for the exaggerated activation of descending pressor responses to stress and anesthesia in ASrAOGEN rats relative to SD rats under the same circumstances. Whether these receptors are responding to locally generated ANG peptides or circulating ANG II is not known. However, elevated circulating ANG II is a feature of the response to anesthesia.

One potential concern in the present study is the slight residual effect of the significant fall in MAP and HR as a result of ANG II or ANG-(1–7) receptor blockade in the ASrAOGEN rats at the time the response to CVA and BRS was tested. However, candesartan and (D-Ala7)–ANG-(1–7) resulted in similar reductions in MAP and HR, and although candesartan had no effect on the BRS in the ASrAOGEN rats, the effect of (D-Ala7)–ANG-(1–7) on the BRS was similar in SD and ASrAOGEN rats. Moreover, a lower pressure in the ASrAOGEN rats would be more consistent with values in the SD rats, where we consistently observe a candesartan-induced enhancement of the BRS. Certainly, any greater anesthetic-induced increase in...
ANGIOTENSINS, BAROREFLEX, AND GLIAL ANGIOTENSINOGEN

Table 2. Effects of Candesartan or d-Ala²-ANG-(1–7) on the response to CVA activation in SD and ASrAOGEN rats

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<tr>
<th>Treatment</th>
<th>SD</th>
<th>ASrAOGEN</th>
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<tbody>
<tr>
<td>Candesartan injection</td>
<td>n</td>
<td>ΔMAP, mmHg</td>
</tr>
<tr>
<td>Baseline</td>
<td>8</td>
<td>-55±6</td>
</tr>
<tr>
<td>Candesartan</td>
<td>8</td>
<td>-61±4</td>
</tr>
<tr>
<td>d-Ala²-ANG-(1–7) injection</td>
<td>Baseline</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>aCSF injection</td>
<td>Baseline</td>
<td>8</td>
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</table>

Values are means ± SE; n, number of rats. Data obtained at the maximum change (Δ) after phenylbiguanide injection. CVA, cardiopulmonary vagal afferent. *P < 0.01 vs. baseline MAP in SD. †P < 0.055 vs. corresponding MAP in SD.

AsrAOGEn compared with older SD rats (22), in studies in which the methods used to test the reflex were the same as those used in the present study. As with most studies utilizing injections into the NTS, anesthesia may yield results at odds with those in conscious animals. However, in conscious animals and animals anesthetized with the urethane-chloralose mixture in our experiments, the magnitude of attenuation of the reflex by ANG II is similar to that described by Michelini and Bonagamba (41) in normal control rats. In a recent study in a separate group of ASrAOGEn rats, ganglionic, β-adrenergic, and muscarinic receptor blockade was used to further evaluate the contribution of the sympathetic activation to the elevation in pressure and the resting HR in the ASrAOGEn vs. SD rats (53). MAP was again higher in the ASrAOGEn than in the SD control rats, and evidence of increased sympathetic outflow contributing to the increase in resting pressure under anesthesia was obtained. Therefore, differences in anesthetics, the way the baroreflex responses were determined, and, potentially, the age of the animals may contribute to different BRs and resting MAP (10, 14, 21). However, ours is the only study that used receptor blockers to assess directly the role of endogenous peptides in resting MAP, HR, or BRs.

The mechanism(s) that may explain the elevated resting MAP of the anesthetized ASrAOGEn rats is likely related to activation of the sympathetic nervous system (53). In fact, urethane or chloralose enhances sympathetic outflow in cats or rats (39, 57). It would appear that anesthesia with both agents would activate angiotensinergic neural pathways at the level of the NTS, leading to increased blood pressure. Recent evidence showed that, in the rat model of chronic nitric oxide synthase inhibition (Nω-nitro-L-arginine methyl ester-hypertensive rats) or the rat model of heart failure (rats with aortocaval shunt), ANG II endogenous to the NTS contributed to resting arterial pressure via sympathetic activation (26, 56). In contrast, although mRNA levels of AT1 receptor subtypes were significantly higher in brain stem areas of spontaneously hypertensive than Wistar-Kyoto rats, microinjection of CV-11974 into the NTS did not decrease blood pressure in spontaneously hypertensive or Wistar-Kyoto rats (50). Fontes et al. (28) showed that the AT1 antagonist CV-11974 injected into the RVLM elicited an increase in MAP in conscious normotensive rats and a decrease in MAP in conscious mRen2 rats, with no significant change in MAP in conscious ASrAOGEn rats (2). Taken together, these results suggest that the cardiovascular role of ANG peptides endogenous to the NTS or RVLM depends on their local levels as well as their source: glia, neural pathways, or the systemic circulation.

In the present study, there was a larger blood pressure response to CVA in anesthetized ASrAOGEn rats, consistent with our previous data (21). We hypothesized that blockade of AT1 receptors would enhance the responses to CVA by phenylbiguanide in the SD rats. This was based on a reduced response to CVA in (mRen2)27 rats with long-term elevations in endogenous ANG II in the medulla oblongata (21). However, the present data show that AT1 receptor blockade in the NTS had no effect on the CVA response in ASrAOGEn or SD rats, consistent with findings in young and old SD rats (52). We cannot rule out the possibility that we did not detect an enhancement of the MAP response to CVA as a result of a floor effect, given that MAP fell to approximately the same level (35–40 mmHg) in ASrAOGEn and SD rats. On the other hand, sys-
temic captopril treatment augments the initial bradycardia and hypotension caused by activation of cardiac chemosensitive fibers (45), which may suggest an inhibitory influence of endogenous ANG II on this reflex response. Converting enzyme inhibition is associated with elevated ANG-(1–7) levels, and (n-Ala²)-ANG-(1–7) injected into the NTS appeared to normalize the exaggerated response to CVA by phenylbiguanide in the ASrAOGEN rats, although the baseline response was not as robust in this group of rats as in the other subgroups studied. ANG-(1–7), but not ANG II, facilitates potassium-stimulated release of serotonin from medullary slice preparations, as indicated by an increase in the metabolite 5-hydroxyindoleacetic acid (23). The potential for differential actions of ANG II and ANG-(1–7) on CVA might be explained by many of the same mechanisms suggested for different actions of the two peptides on the BRS, including different transmitter mechanisms (23) or different sites of action within the NTS (7, 20), as well as differences in the source (glia, neurons, or plasma) of the two peptides.

In conclusion, AT₁ and ANG-(1–7) receptors within the NTS responding to peptides derived from nonglial sources, likely released from descending neural pathways from the subfornical organ and PVN activated in response to elevated peptides, contribute to elevated MAP in urethane-chloralose-anesthetized ASrAOGEN rats. In contrast, ANG-(1–7), but not ANG II, endogenous to the NTS contributes to resting BRS for control of HR of ASrAOGEN rats. In contrast, subfornical organ and PVN activated in response to elevated likely released from descending neural pathways from the NTS responding to peptides derived from nonglial sources, as well as differences in the source (glia, neurons, or plasma) of the two peptides.

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