NK1 Receptor Antagonist Blocks Angiotensin II Responses in Renin Transgenic Rat Medulla Oblongata

Debra I. Diz, Brian Westwood, Susan M. Bosch, Detlev Ganten, Carlos Ferrario

Abstract—Angiotensin (Ang) II increases substance P (SP) efflux from perfused slices of medulla oblongata, and a peptide antagonist of SP, [Leu]$^{11}$[CH$_3$NH]-SP, blocks the acute hypotension and bradycardia caused by Ang II injected into the nucleus tractus solitarii (nTS) of Harlan Sprague-Dawley (SD) rats. We investigated whether the same relationships exist in (mRen2)27 renn transgenic (TG) rats, which have chronic elevations of medullary tissue Ang II levels. Ang II increased SP efflux (48% above control, P < 0.01) from slices of medulla prepared from 8- to 12-week old male TG rats. Injections of Ang II (250 fmol in 30 nL) into the nTS of chloralose-urethane anesthetized TG rats produced a significant increase in pressure of 7 ± 2 mm Hg before a 13 ± 3 mm Hg fall in pressure. Ang II induced similar depressor responses in Hannover SD rats but no increase in pressure. After nTS injection of the NK1-selective SP antagonist CP-96,345 (30 pmol in 60 nL), Ang II–induced hypotension was blocked in both groups, as was the pressor component in hypertensive rats. Hypotensive and bradycardic effects of glutamate (0.6 mmol in 30 nL) injected into the nTS were not altered by CP-96,345. In vitro receptor autoradiography showed that the SP antagonist (10 or 100 μM) did not compete for $^{3}$H-Ang II binding in the dorsal medulla, a result suggesting that it did not interact directly with Ang II receptors. Thus, the nTS cardiovascular effects of Ang II are mediated by SP in both normotensive rats and a model of hypertension with altered endogenous levels of Ang II. These findings link Ang II–induced effects on SP release from brain slices of the medulla oblongata to acute cardiovascular actions of the peptide through an NK1 receptor. (Hypertension. 1998;31[part 2]:473-479.)

Key Words: angiotensin II • substance P • NK1 receptor • CP-96,345 • dorsal medulla • (mRen2)27 renn transgenic rat • nucleus tractus solitarii • blood pressure

Our previous work has focused on the cell groups and transmitters involved in the reflex regulation of the cardiovascular system, specifically, the nucleus tractus solitarii (nTS) and dorsal motor nucleus of the vagus (dMNX). These nuclei receive baroreceptor input from the vagus and glossopharyngeal nerves and contain substance P–immunoreactivity.1,2 Several years ago, when first mapping the anatomical distribution of angiotensin II receptors in the dorsal medulla oblongata, nodose ganglion, and vagus nerve,3-7 we observed that the distribution of substance P immunoreactivity had a striking similarity to the distribution of the angiotensin II binding sites.8

As a result of these observations, we investigated the potential functional interactions between these two peptide systems and showed that angiotensin II increases substance P efflux from brain slices.8-10 Moreover, both peptides injected into the nTS cause hypotension/bradycardia at low doses and pressor/tachycardic actions at high doses.11-13 A peptide analogue substance P antagonist, [Leu]$^{11}$CH$_3$NH-11] substance P, blocks the hypotensive/bradycardic actions of angiotensin II in the nTS of normotensive Sprague-Dawley (SD) rats.14 This latter finding firmly linked the anatomical observations to a functional relationship between the two peptide systems with respect to cardiovascular function.

To investigate whether these relationships between angiotensin II and substance P are altered in hypertension, we used the (mRen2)27 renn transgenic (TG) rat, a model for overexpression of tissue angiotensin peptides. This model was developed by Mullins et al.15 and is characterized by extremely high tissue levels of angiotensin II in the medulla oblongata and moderately elevated plasma levels of the peptide.16 Using this model, we observed that the increases in arterial pressure in response to intracerebroventricular injections of angiotensin II were reduced.17 Vasopressin release from the paraventricular nucleus was also markedly attenuated in response to angiotensin II.17 In addition, substance P release from hypothalamic slices was blunted in response to angiotensin peptides in TG compared with normotensive SD rats.10 These reduced responses are also seen in cell cultures derived from the TG rat.18,19 Thus, we formulated the hypothesis that the chronic overexpression of angiotensin II results in downregulation of the response to exogenously administered angiotensins.

The objective of the present work was to determine whether in the TG rat, the responses to exogenous angiotensin II were altered in the dorsal medulla in terms of either magnitude of the response or dependence on substance P. In addition, we used a NK1-selective tachykinin receptor antag-
Methods

Experiments were carried out in a total of 34 Hannover SD rats or 30 hypertensive hemizygous TG rats obtained from the Hypertension Center transgenic breeding colony at Bowman Gray School of Medicine at 9 to 12 weeks of age. If TG and normotensive littersmates born to the same SD mother were used, rats were genotyped by polymerase chain reaction amplification of the mouse renin gene to disqualify those carrying the gene. 20,21 Before surgery rats were housed in group cages and had free access to standard rat chow and water. Housmg was in a temperature- and humidity-controlled room with a 12 hour light/dark cycle. Tail-cuff systolic blood pressure was determined on SD control and TG hypertensive animals in the week preceding the experiment by using a Narco Bios-Systems apparatus (Division of International Biomedical, Inc.). All procedures involving animals adhered to institutional guidelines and were approved by the Institutional Animal Care and Use Committee.

Substance P Release Studies

TG (n=18) or SD (n=18) rats were decapitated, the brain was removed rapidly, and a block of the medulla oblongata was dissected out. Chambers filled with 1 mL of Krebs solution containing 20 μmol/L bacitracin (Sigma Chemical Co.) and 6 μmol/L dithiothreitol (Sigma Chemical Co.) and bubbled with 95% O2, 5% CO2 to a pH of 7.4, as reported previously (11). Tissue was perfused with oxygenated Krebs solution for 16 minutes before two 6-minute collections (~2.5 mL volume each). The first 6-minute collection was used to determine basal efflux, and the second collection included either the angiotensin II stimulus (2 μmol/L, Bachem) or continued perfusion with buffer (control group). At the end of the experiment, the tissue was removed from the chamber, blotted dry, and weighed. One-mL samples were measured for substance P by radioimmunoassay (INCASTAR Corporation) as reported (10). Values below the detection limit were assigned the detection limit of 4 pg/tube. Cross-reactivity of the antibody with other tachykinin peptides (physalaemin, edeosin), as reported by the manufacturer of the assay kit, was less than 0.002%. Interassay variability averaged 15%. Previous studies indicated no interference in the assay of the inhibitors or angiotensin peptides (20).

Microinjection Studies

After induction of anesthesia in 9 TG and 11 SD rats by intraperitoneal injection (35 mg chloralose, 750 mg urethane/kg), catheters were introduced into the femoral artery and vein. Rats were placed in a stereotaxic frame with the head flexed downward at 45° and surgically opened to expose the dorsal medulla by incising the atlanto-occipital membrane. The pipette was placed into the nTS (0.5 mm rostral and 0.5 mm lateral to calamus splenius, i.e., the caudal tip of the area postrema, and 0.5 to 0.6 mm below the dorsal surface) (21). Arterial pressure and heart rate were acquired via strain gauge transducer (Model DTX, Spectramed, Inc.) connected to an amplifier (Grass) using a computerized system based on the DTVEE acquisition system (Data Translation, Inc., Hewlett Packard, Inc.).

Experimental Protocol

Unilateral microinjections of 30 to 60 nL were made with multibarrelled glass micropipettes (80 to 120 μm outer diameter) over a 40- to 60-second interval (11,13). Angiotensin II (250 fmol, Bachem) or glutamate (0.6 nmol, Sigma Chemical Co.) was injected into the nTS in a volume of 30 nL to locate sites for depressor effects. Then angiotensin II and glutamate injections were repeated approximately 10 to 20 minutes after a 60-nL injection of artificial cerebrospinal fluid (aCSF). All data reported on the response to angiotensin II or glutamate for the “before” period indicated the value obtained after the 60-nL aCSF injection to control for any dilutional effect of the volume of the injectate used for the substance P antagonist studies. We and others have previously shown that responses to the low doses of angiotensin II (fin01 range) are reproducible when given 30 minutes apart (11,21,24). Therefore, 30 to 60 minutes later, the substance P NKI receptor selective antagonist CP-96,345 (30 pmol in 60 nL) was injected into the nTS. Arterial blood pressure and heart responses in TG and glutamate microinjections were evaluated again at 10 to 20 minutes after the substance P antagonist. Depth of anesthesia throughout the experiment was monitored by a variety of indices, including corneal reflexes as well as respiratory rhythm, arterial pressure, and heart rate stability. Additional intravenous anesthesia was given as needed, but no series of injections was given within 10 minutes of any additional anesthesia. Histological evaluations of coronal frozen brainstem sections (30 μm) were done at the end of every experiment to exclude any animals in which the pipette tip was not localized within the immediate portion of the medullary nTS within the rostrocaudal level –13.5 to –13.9 according to the atlas of Paxinos and Watson (25).

Analysis of Data

All data reported on the response to angiotensin II or glutamate for the release studies, responses during the stimulus period were expressed as percent of basal. If basal values and values from the subsequent period were below the detection limit, the data were excluded from the stimulus period analysis, as the percent change from basal could not be determined. Logarithmic transformation of the data was performed to achieve homogeneity of variance for the release studies. Excel (Microsoft Office 95) and InStat and Prism (GraphPad) software were used for these analyses. P < 0.05 was taken to indicate a significant difference among means.

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TABLE 1. Tail-Cuff Systolic Blood Pressure, Body Weight, and Substance P Efflux Data for Transgenic and Sprague-Dawley Rats: Release Studies

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>196±6***</td>
<td>125±6</td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>299±18</td>
<td>345±24</td>
</tr>
<tr>
<td>Basal substance P release (pg/g)</td>
<td>63±7</td>
<td>71±13</td>
</tr>
<tr>
<td>(pg/mL)</td>
<td>10±1</td>
<td>12±2</td>
</tr>
</tbody>
</table>

Expermental period substance P release (percent of basal)

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>79±8 (7)</td>
<td>81±4 (5)</td>
</tr>
<tr>
<td>Ang II</td>
<td>117±12** (10)</td>
<td>102±14 (9)</td>
</tr>
</tbody>
</table>

Systolic blood pressure by tail cuff and body weight were determined in the week preceding the experiment. Basal substance P values indicate the amount of immunoreactive substance P detected in the 6-minute collection period preceding the stimulus period. Values are expressed per gram of wet tissue weight (pg/g) or per milliliter of perfusate collected (pg/mL). Experimental period substance P release is the amount of substance P detected during the second 6-minute collection period expressed as the percent of basal release (first 6-minute collection period). The control treatment consisted of continued perfusion with the Krebs buffer without Ang II (2 μM) during the second collection period. Values are mean±SEM. Numbers in parentheses indicate number of rats.

**P<0.01 compared with control treatment (buffer only) ***P<0.001 when TG rats were compared with SD rats

TABLE 2. Hemodynamic and Body Weight Values in Conscious and Anesthetized Transgenic and Sprague-Dawley Rats: nTS Microinjection

<table>
<thead>
<tr>
<th></th>
<th>TG</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>318±19</td>
<td>339±11</td>
</tr>
<tr>
<td>Conscious</td>
<td>(9)</td>
<td>(11)</td>
</tr>
<tr>
<td>Systolic pressure—tail cuff (mm Hg)</td>
<td>236±10***</td>
<td>129±5</td>
</tr>
<tr>
<td>Anesthesia</td>
<td>(9)</td>
<td>(11)</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>94±3</td>
<td>89±3</td>
</tr>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>130±7**</td>
<td>104±4</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>70±3</td>
<td>73±3</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>349±8</td>
<td>331±6</td>
</tr>
</tbody>
</table>

Body weight and systolic blood pressure by tail cuff were determined in the week preceding the nTS microinjection experiment. The tail-cuff systolic pressure values are from the same rats as those for the arterial pressure and heart rate under anesthesia. Values are mean±SEM. Numbers in parentheses indicate the number of rats.

**P<0.01 and ***P<0.001 when TG rats compared with SD rats

Response to Angiotensin II Injected into the nTS

Figure 1. NK1 antagonist blocks the arterial pressure effects of angiotensin II Mean arterial pressure for a typical experiment in (A) SD and (B) TG rats. The time course of the experiment (in minutes) is given on the x-axis. An injection of artificial cerebrospinal fluid (aCSF, 60 nL) had minimal effects on pressure alone, and there was a significant decrease in pressure in response to injection of angiotensin II (Ang II, 250 fmol in 30 nL) given approximately 10 minutes later. Similarly, the response to glutamate (Glu, 0.6 nmol in 30 nL) was unaltered by the prior 60 nL of aCSF. In contrast, when Ang II was injected 10 minutes after the NK1 receptor antagonist CP-96,345 (CP; 30 pmol in 60 nL), the changes in pressure produced by Ang II were almost totally blocked. The antagonist had no effect on the glutamate response, as shown for the SD rats.

Substance P Efflux in Response to Angiotensin Peptides in TG and SD Rats

There were no differences in basal release of substance P from medullary slices between the hypertensive and normotensive animals when expressed on the basis of tissue weight or concentration in the perfusate (Table 1). Values for substance P in the perfusate tended to decline with time to ~80% of basal as seen for the control group of either TG or SD rats perfused with buffer only throughout the experiment, as was reported previously. In contrast, in the presence of angiotensin II, substance P efflux increased above the time control group to a similar extent in both groups rats. The increase was statistically significant for the TG rats (P<0.01) with a similar trend in the SD rats (P=0.09).
Effects of Substance P Antagonist CP-96,345 Injected into the nTS on Angiotensin Peptide Responses in TG and SD Rats

As indicated above, baseline mean arterial pressure and heart rate under anesthesia in these experiments did not differ between the hypertensive and normotensive rats for all rats studied (Table 2) or for any individual group (Figures 1 and 2). The fall in blood pressure in response to angiotensin II was also similar in the two groups of rats. In both TG (n=7) and SD (n=9) rats, angiotensin II decreased mean arterial pressure approximately -13 mm Hg (Figs 1 and 2) after a prior aCSF injection of 60 nL. In only the TG rats was the depressor response preceded by a significant increase in pressure of 7±4 mm Hg (P<0.05 versus zero). When the angiotensin II injections were given approximately 10 min after 60 nL of 30 pmol CP-96,345, the angiotensin II depressor responses were blocked (P<0.05; Figures 1A, 1B, and 2). The angiotensin II-induced pressor effect was reduced by approximately 50% and no longer represented a significant increase in pressure (4±4 mm Hg, not significantly different from zero). In a limited number of SD rats (n=6), we injected angiotensin II into the nTS 40 to 60 minutes after the NK1 antagonist. There was only partial recovery of the depressor response at this time (-6±2 mm Hg). This is similar to what we observed with the modified peptide antagonist in previous studies in which the magnitude of the hypotensive and bradycardic responses to glutamate (comparison of values indicated as “before” CP-96,345; n=5) or TG rats (-20±2 mm Hg before versus -21±7 mm Hg after CP-96,345; n=5) There was also no effect of the antagonist on the fall in heart rate with glutamate in these same SD (-41±1 beats/min before versus -40±1 beats/min after CP-96,345) or TG rats (-24±1 beats/min before versus -34±1 beats/min after CP-96,345). There was no significant difference between SD and TG rats in terms of the magnitude of the hypotensive and bradycardic responses to glutamate (comparison of values indicated as “before” CP-96,345 in the above; n=5, each; P>0.05).

The NK1 antagonist CP-96,345 was also evaluated for its ability to interact directly with Ang II receptors in the dorsal medulla of SD rats. There are reported interactions between losartan, an angiotensin II AT1 receptor blocker, and NK3 receptors in the hypothalamus. The nonpeptide substance P antagonist CP-96,345 did not compete for '*'1-angiotensin II binding in sections of medulla oblongata from two SD rats. Angiotensin II binding was unaltered by the CP-96,345 at either 10 µM (6±6% competition) or 100 µM (0±0% competition).

Discussion

The present study has four major findings. First, we showed that basal and angiotensin II-stimulated substance P release was similar in medullary slices from TG and SD rats. Second, the depressor effect of angiotensin II in the nTS of TG rats was similar to that seen in SD rats, and an NK1-selective substance P antagonist blocked the cardiovascular effects in both groups of animals. Third, there was an initial pressor component to the responses in the TG rat, consistent with actions seen in response to higher doses of angiotensin II. Finally, under chloralose-urethane anesthesia, the mean arterial pressure was
normalized in the TG rats. Given that this anesthetic agent maintains pressure at conscious levels in normotensive rats, one interpretation is that the level of pressure in the TG rat is largely supported by centrally mediated sympathetic outflow. This interpretation is supported by the fact that urethane anesthesia is known to inhibit an overactive sympathetic nervous system at both central and peripheral sites of action. In addition, urethane anesthesia normally activates the renal renin-angiotensin system to maintain pressure. Since the TG rat has suppressed renal renin, the failure to activate this system could also contribute to the exaggerated fall in pressure that is seen in these animals.

We recently reported that the acute depressor and bradycardic effects of angiotensin II in Harlan Sprague-Dawley rats were blocked by prior administration of a peptide substance P antagonist. This confirmed a functional relationship between these transmitter systems that was postulated on the basis of anatomical, electrophysiological, and pharmacological data. Importantly, the previous findings revealed a mechanism to account for the similar cardiovascular effects of angiotensin II and substance P in this brain region. Moreover, the pressor component of the response in TG rats is similar to what is seen with higher (pmol as opposed to fmol range) doses of either angiotensin II or substance P, and the CP-96,345 antagonist blocked both the pressor and depressor responses. The current studies also extend the previous findings by demonstrating that substance P acts at an NK1 receptor. This consistent with data indicating that substance P is the major tachykinin present in the dorsal medulla and that the majority of the peptide's actions are mediated by the NK1 receptor subtype.

It is unlikely that the substance P mechanisms contributing to the acute depressor and bradycardic effects or the pressor effects of angiotensin II in the dorsal medulla are the same as those mediating the baroreceptor reflex actions of angiotensin II in this brain area. This is because substance P reportedly facilitates the baroreceptor reflex, whereas angiotensin II inhibits it. However, in the present study, the substance P antagonist did not produce any significant change in pressure or heart rate. There was a tendency for lower heart rate immediately after the antagonist in this study in the SD rats, which was similar in magnitude to a significant drop in heart rate observed in our previous study using a modified peptide analogue substance P antagonist. Interestingly, this modest decrease in heart rate is also similar to the effects of the angiotensin II antagonist Sarthran injected into the nTS. A lower heart rate without an accompanying change in pressure has been interpreted as a possible facilitation of the baroreceptor reflex, which would support a role for endogenous angiotensin II and substance P to inhibit the reflex control of heart rate. In addition, the bidirectional actions (pressor at high doses and depressor at low doses) of both substance P and angiotensin II would be consistent with dose-dependent effects that might account for inhibition of the reflex by either peptide at high doses.

Another possible explanation for the different acute versus baroreceptor reflex effects of angiotensin II is that angiotensin II may actually inhibit substance P release when the afferent fibers and/or intrinsic neurons of the nTS are activated. This idea is based on our finding that there is no facilitation of substance P release by angiotensin II in the presence of high potassium in the brain slices from the medulla. This latter point is important for interpretation of the present findings in light of the normalization of pressure under anesthesia. When blood pressure decreased with the anesthetic in the TG rats, the subsequent alterations in activity of the baroreceptor reflex nerves might have contributed to the equivalent depressor responses observed in the two groups of rats.

In these studies, we used several controls to verify the specificity of the effects of the NK1 receptor antagonist. First, we showed that the cardiovascular responses to nTS injections of glutamate were not blocked by the NK1-selective substance P antagonist. In addition, we ruled out a direct interaction of the substance P antagonist with the angiotensin II receptor by showing that CP-96,345 did not compete for 125I-angiotensin II labeled receptors in the dorsal medulla. Moreover, the doses of the antagonist used are below those shown previously to be specific. To confirm the spread of the injectate to the nTS, we used 30-nL injections of angiotensin II and 60-nL injections of the substance P antagonist to ensure that the antagonist spread to at least the same area as the peptide. This was considered necessary, given the overall size of the multibarreled pipettes. Thus, while we are confident that the peptide acted within the medial nTS, we cannot rule out the possibility that the antagonist spread to the adjacent dmX. However, this would still provide an action of substance P within the dorsal medulla where substance P-containing nTS interneurons may synapse on dmX vagal motor neurons to mediate the effects of nTS angiotensin II.

A major interest in the present work was to determine whether the responses to angiotensin II were attenuated in a model of hypertension with chronic overexpression of tissue angiotensin II levels. We hypothesized that the responses would be suppressed, since we previously found that exogenously administered angiotensin peptides in the hypothalamus of TG rats evoked smaller pressor responses and attenuated release of vasopressin and substance P. In addition, there are reports of alterations in substance P content and receptors in sympathetic ganglia and brain of other rat models of hypertension. Therefore, we predicted that substance P release, both basal and angiotensin II-induced, might be suppressed in the TG rat, leading to reduced depressor responses elicited by angiotensin II injections into the nTS. In fact, we did not observe any loss of responsiveness in the TG rats with respect to either the substance P release or the cardiovascular actions. A number of observations may provide insights for these findings and the difference between the responses mediated by hypothalamic versus medullary pathways. First, hypothalamic tissue levels of angiotensin II are tenfold higher in TG rats than in SD control rats, whereas in the medulla oblongata, the elevation is only threefold. Second, angiotensin-(1-7) levels are elevated in the hypothalamic tissue of TG rats but suppressed in the medulla oblongata. These tissue levels, the balance between the angiotensin II and the opposing actions of angiotensin-(1-7), may play a role in the regulation of the responses. In fact, another interesting parallel should be noted between the angiotensin and substance P peptide systems. The substance P heptapep-
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