Tonic Cardiovascular Effects of Angiotensin II in the Ventrolateral Medulla

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The rostral and caudal parts of the ventrolateral medulla play a major role in the control of blood pressure. Both regions contain a high density of receptor binding sites for angiotensin II, and it has been shown previously that microinjection of angiotensin II into the rostral ventrolateral medulla causes a rise in blood pressure. The aims of this study were to determine the cardiovascular effects of microinjection of angiotensin II and its specific antagonist \([\text{Sar}^1\text{Thr}^8\text{AngII}]\) into the caudal ventrolateral medulla and to characterize the regional vascular effects elicited by both compounds in the rostral ventrolateral medulla. Microinjections of angiotensin II (0.2–20 pmol) into histologically verified sites in the caudal ventrolateral medulla of anesthetized baroreceptor-denervated rabbits produced dose-dependent decreases in blood pressure and renal sympathetic nerve activity, whereas microinjection of \([\text{Sar}^1\text{Thr}^8\text{AngII}]\) (40 pmol) produced increases in these variables. In the rostral ventrolateral medulla, angiotensin II (0.02–20 pmol) elicited a dose-dependent increase in blood pressure, iliac vascular resistance, and renal sympathetic nerve activity, whereas \([\text{Sar}^1\text{Thr}^8\text{AngII}]\) (40 pmol) produced decreases in these variables. The effects on heart rate elicited by either compound in the rostral or caudal ventrolateral medulla were small but were in the same direction as the other cardiovascular variables. In contrast, angiotensin II had no detectable effect on sympathoexcitatory neurons within the rostral dorsomedial medulla, a region that lacks angiotensin II receptor binding sites.

The results indicate that endogenous angiotensin II acts on specific receptors within the rostral and caudal parts of the ventrolateral medulla and has a tonic excitatory action on sympathoexcitatory and sympathoinhibitory neurons within these respective regions. *(Hypertension 1990;15:274–283)*
reflexes do have a powerful modulatory effect on the pressor response elicited by central administration of Ang II. In the present study, therefore, we have determined the cardiovascular effects of microinjection of Ang II and [Sar1Thr8]Ang II into the rostral VLM of rabbits with denervated arterial and cardiopulmonary baroreceptors. In particular, the quantitative relation between different doses of Ang II and evoked changes in blood pressure, heart rate, renal sympathetic activity, and hindlimb vascular resistance was determined.

Although Ang II has been shown to produce cardiovascular effects at sites containing Ang II binding sites, it is not clear whether this is due to a specific action of Ang II on the identified binding sites or whether Ang II has a nonspecific excitatory action on central neurons, including those that lack receptor binding sites as demonstrated by in vitro autoradiography. The final aim of this study was to answer this question by comparison of the physiological response elicited by microinjection of Ang II with that elicited by microinjection of the neuroexcitatory compound L-glutamate into two regions that lack Ang II receptor binding sites, that is, the pressor cell group in the rostral dorsomedial medulla and the hypoglossal nucleus.

Methods

General Procedures

Experiments were performed on 31 rabbits (2.4–3.3 kg body wt). Anesthesia was induced by sodium pentobarbitone (35 mg/kg i.v., followed by continuous infusion at the rate of 7 mg/kg/hr). Body temperature was monitored with a rectal probe and maintained close to 39°C with a thermostatically controlled heating lamp. In all experiments, the trachea was cannulated and catheters placed in a femoral artery and femoral vein. In 23 rabbits, the carotid bifurcations were denervated as previously described, and the vagi and aortic nerves were cut bilaterally in the neck. After these procedures, all rabbits were paralyzed with gallamine triethiodide (4 mg/kg i.v. initially, followed by 7 mg/kg i.m. every 3 hours) and artificially ventilated at a level that maintained end-tidal CO2 close to 4%. The head of the rabbit was placed in a head holder (Narashige Scientific Instr. Lab., Tokyo, Japan) attached to a stereotaxic frame and inclined forward at an angle of 45° to the standard horizontal plane. An occipital craniotomy was performed to expose the dorsal surface of the medulla oblongata.

Blood pressure was measured via the femoral arterial catheter, and the mean pressure and heart rate derived from the pulsatile signal by means of a low-pass filter and rate meter, respectively. All signals, including integrated renal sympathetic nerve activity and iliac blood flow (see below) were recorded on a polygraph chart recorder.

Sympathetic nerve activity recording. In experiments in which renal sympathetic nerve activity was recorded, the left kidney was exposed using a retroperitoneal approach. The renal nerve was then dissected free, cut, and immersed in a paraffin pool. Nerve activity was recorded using platinum electrodes, and the signal was amplified, filtered (bandwidth 100–10,000 Hz), rectified, and integrated (reset to zero at 5-second intervals). At the end of each experiment the zero level of sympathetic activity was determined by crushing the nerve.

Blood flow measurement. Left iliac blood flow was measured in some experiments with an electromagnetic flow probe connected to a flowmeter (model RT-510, Narco BioSystems, Houston, Texas). Zero flow was determined by occlusion of the artery just distal to the probe. Mean flow was derived from the pulsatile flow signal by means of a low-pass active filter.

Tongue electromyographic activity. In some experiments the electromyographic (EMG) activity of the tongue was recorded as a means of measuring the degree of activation of hypoglossal neurons after injections of neuroactive compounds into the hypoglossal nucleus. Fine wire electrodes were placed approximately 5 mm apart in the tongue muscle, and the signal was amplified and filtered (band pass 100–10,000 Hz).

Intramedullary Microinjections

Microinjections of various agents were made into a number of medullary sites. In all cases the vehicle solution was physiological saline containing 0.2% bovine serum albumin (pH 7.4), and the total volume injected was 20 nl. In most experiments, a small amount of horseradish peroxidase conjugated with wheat germ agglutinin (WGA-HRP) was added to the vehicle solution (final concentration 0.01%) to permit later visualization of the centers of the injection sites. The agents injected were Ang II (Peninsula Labs., Belmont, California) (from 0.02 to 50 pmol), the Ang II receptor antagonist [Sar1Thr8]Ang II (Sigma Chemical Co., St. Louis, Missouri) (40 pmol), and sodium glutamate (10 pmol).

Microinjections were made from the tip of a glass micropipette held in a micromanipulator and inclined at an angle of 16° from the vertical, with the tip rostral. For each track, the mediolateral and rostrocaudal coordinates of the point of entry of the tip at the dorsal surface of the medulla was determined with respect to the midline and obex, respectively. For each injection site, the depth of the tip was measured with respect to the dorsal surface. Microinjections were made by application of pressure, as previously described. During the injection, the meniscus in the micropipette was observed with a microscope (×25), and the volume injected was determined by measurement of the displacement of the meniscus with respect to a graticule in the eyepiece.

Histology

At the conclusion of experiments in which WGA-HRP had been added to the injectate, the rabbit was
The brainstem was removed and 50 μm thick coronal sections were cut on a freezing microtome. Alternate sections were taken and reacted with 3,3',5,5'-tetramethylbenzidine to identify the sites of WGA-HRP deposition and, hence, injection of Ang II or other compounds. The sections were counterstained with neutral red, examined under a microscope, and the locations of centers of microinjections mapped with respect to anatomic landmarks, with reference to the atlas of Meesen and Olszewski.16

Statistical Analysis

Comparisons between groups were made by using the Wilcoxon rank sum test for unpaired measurements. The correlation between different doses of injected compounds and evoked changes in cardiovascular variables was determined with Spearman's rank correlation coefficient.

Results

Mapping Experiments

In nine baroreceptor-denervated rabbits, microinjections of Ang II (20 pmol) were made into a total of 98 histologically identified sites in the rostral and caudal VLM. Significant pressor responses (>20 mm Hg) were elicited from sites within a highly restricted region, which extended from the caudal pole of the facial nucleus to a level 1.0 mm more caudal (Figure 1). These pressor sites formed a band approximately 1.5 mm in length and aligned imately parallel to the adjacent ventral surface. On the other hand, significant depressor responses (>15 mm Hg) were obtained from sites restricted to the region just ventrolateral to the nucleus ambiguus (NA). LRN, lateral reticular nucleus; N V, trigeminal nucleus; N VII, facial nucleus; Oli, inferior olive; Tr sp V, spinal trigeminal tract.

Characteristics of Angiotensin II–Induced Pressor and Depressor Responses

In 17 baroreceptor-denervated rabbits, the changes in cardiovascular variables produced by different doses of Ang II injected into either the rostral pressor or caudal depressor region were determined. The tip of the micropipette was positioned in each of these regions by using the coordinates as determined in the initial mapping experiments. In 14 of these 17 experiments, the locations of these injection sites were subsequently checked histologically; in all cases, the injection sites were confirmed to be within the rostral pressor or caudal depressor region. In each experiment, no more than two different doses were injected into the pressor or depressor regions, and there was a minimum period of 30 minutes between injections.

Pressor responses. Doses of Ang II ranging from 0.02 to 20 pmol were injected into the rostral pressor region. As shown in Figure 2, Ang II produced dose-dependent increases in mean blood pressure, renal sympathetic nerve activity, and iliac vascular
resistance. The correlation between Ang II dose and each of these three variables was highly statistically significant in all cases (Figure 2). For the highest dose injected (20 pmol), the percentage increases in mean blood pressure, renal sympathetic nerve activity, and iliac vascular resistance, with respect to their preinjection levels, were 32±2% (mean±SEM), 92±11%, and 47±8%, respectively, compared with 7±2%, 16±1%, and 6±2%, respectively, after injection of the vehicle solution. The heart rate also increased with doses of Ang II of 0.2 pmol or greater, but in this case the increase was much smaller (3±1% after injection of 20 pmol). There was no detectable change in heart rate after injection of the vehicle solution.

The time course of the increase in blood pressure after microinjection of 20 pmol Ang II into the rostral pressor region was slow (Figure 3, Table 1). Typically, the pressure began to increase within 5 seconds after the injection, reached a peak within 2 minutes, and remained elevated for 5–10 minutes. For the smallest dose injected (0.02 pmol), the time course of the response was faster but still much slower than the response to injection of the vehicle solution (Table 1).

The time course of the change in renal sympathetic nerve activity after microinjection of 20 pmol was faster than the change in mean blood pressure, both in terms of latency to peak response and duration of the response (Figure 3, Table 1). This was also observed when 0.02 pmol was injected, although the difference in this case was less marked (Table 1).

In five rabbits with intact baroreceptors, microinjections of 20 pmol Ang II were made into the rostral pressor region. The increase in mean blood pressure in these animals was 16±1 mm Hg, which was signif-

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Histograms showing relation between different amounts of angiotensin II (Ang II) injected into pressor sites in rostral ventrolateral medulla and resultant changes in cardiovascular variables. Results are shown as mean±SEM. *p* values represent statistical significance of dose-response relation in each case.

![Figure 3](http://hyper.ahajournals.org/)

**Figure 3.** Tracings showing an example of cardiovascular response elicited by microinjection of angiotensin II (Ang II) into the rostral ventrolateral medulla. Note that mean blood pressure remains elevated after renal nerve activity has returned to control value.
Table 1. Time Course of Responses to Microinjections into the Rostral and Caudal Ventrolateral Medulla

<table>
<thead>
<tr>
<th>Compound injected</th>
<th>Mean blood pressure</th>
<th>Renal sympathetic nerve activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Peak latency (min)</td>
</tr>
<tr>
<td>Rostral VLM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang II (20 pmol)</td>
<td>15</td>
<td>1.6 ± 0.1*</td>
</tr>
<tr>
<td>Ang II (20 fmol)</td>
<td>6</td>
<td>1.1 ± 0.1*</td>
</tr>
<tr>
<td>[Sar&lt;sup&gt;1&lt;/sup&gt;Thr&lt;sup&gt;8&lt;/sup&gt;]Ang II (40 pmol)</td>
<td>6</td>
<td>3.1 ± 0.3*</td>
</tr>
<tr>
<td>Vehicle</td>
<td>11</td>
<td>0.3 ± 0.03</td>
</tr>
<tr>
<td>Caudal VLM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ang II (20 pmol)</td>
<td>8</td>
<td>2.1 ± 0.3†</td>
</tr>
<tr>
<td>[Sar&lt;sup&gt;1&lt;/sup&gt;Thr&lt;sup&gt;8&lt;/sup&gt;]Ang II (40 pmol)</td>
<td>5</td>
<td>2.2 ± 0.3†</td>
</tr>
<tr>
<td>Vehicle</td>
<td>6</td>
<td>0.5 ± 0.1</td>
</tr>
</tbody>
</table>

Results are expressed as mean ± SEM. VLM, ventrolateral medulla; Ang II, angiotensin II.

* p<0.001 compared with vehicle alone.
† p<0.01 compared with vehicle alone.
‡ p<0.05 compared with vehicle alone.

Depressor responses. Microinjections of 2 and 20 pmol Ang II into the caudal VLM evoked dose-dependent decreases in mean blood pressure, heart rate, and renal sympathetic nerve activity (Figure 4). Lactic blood flow was not measured in these experiments. An example of the response to an injection of 20 pmol Ang II is shown in Figure 5. The blood pressure began to decrease within 5 seconds after the Ang II injection, reached a minimum level within 1–3 minutes, and then gradually recovered over 5–10 minutes (Table 1). The renal sympathetic nerve activity decreased sharply after the injection (Figure 5) but then tended to remain at a reduced level while the blood pressure gradually increased (Figure 5).

Effects of Microinjection of Angiotensin II Antagonist Into Pressor and Depressor Regions

Microinjection of the Ang II receptor antagonist [Sar<sup>1</sup>Thr<sup>8</sup>]Ang II (40 pmol) into the rostral pressor region in the VLM resulted in decreases in blood pressure, heart rate, and renal sympathetic nerve activity (Figure 6, Table 2). These effects had a slow time course (Figure 6), significantly slower (p<0.01) than the time course of the pressor and sympathoexcitatory effects produced by injection of Ang II.

In contrast, microinjection of [Sar<sup>1</sup>Thr<sup>8</sup>]Ang II into the caudal depressor region produced increases in all the measured variables (Figure 7, Table 2). In this case, the time course of the evoked response was similar to that after injection of Ang II (Table 1).

Effects of Angiotensin II Microinjection Into Other Medullary Sites

Microinjections of Ang II were made into two other medullary regions, the rostral dorsomedial region that contains a pressor cell group and the hypoglossal nucleus. Both of these regions lack Ang II receptor binding sites as revealed by in vitro autoradiography. In four rabbits, microinjections of glutamate (10 pmol) into the rostral dorsomedial region evoked a pressor response of 35 ± 5 mm Hg, in confirmation of previous findings. In contrast, microinjections of Ang II, in doses of either 20 pmol or 50 pmol had no effect on blood pressure (Figure 8A). In two experiments, microinjection of [Sar<sup>1</sup>Thr<sup>8</sup>] Ang II (40 pmol) also had no effect. Similarly, in three experiments glutamate microinjection into the hypoglossal nucleus produced a large increase in tongue EMG activity, whereas microinjection of Ang II (20 pmol) resulted in only a very small and transient increase in EMG activity, similar to that...
produced by microinjection of the same volume of vehicle solution (Figure 8B).

Discussion

This study has demonstrated for the first time that microinjection of Ang II into the caudal VLM produces a decrease in blood pressure and extends previous findings on the pressor effects produced by Ang II in the rostral VLM. Both of these regions in the rabbit contain a high density of Ang II receptor binding sites, as revealed by in vitro autoradiography.8 The first question to consider, therefore, is whether the cardiovascular effects produced by Ang II in the VLM is due to a specific action on these receptor binding sites.

To test this, microinjections of Ang II were made into the rostral dorsomedial medulla, a region that contains pressor neurons12 but lacks Ang II binding sites.9 The absence of any response to Ang II, even in doses higher than those injected into the VLM, in comparison with the pressor responses readily evoked by the neuroexcitatory compound L-glutamate, indicates that Ang II does not have a nonspecific excitatory effect on central neurons. This was further demonstrated by the lack of any excitatory action of Ang II on neurons within the hypoglossal nucleus, another region that lacks Ang II receptor binding sites.8 It thus seems likely that Ang II produces its effects via actions on Ang II receptor binding sites as revealed by in vitro autoradiography.
TABLE 2. Effects of Microinjection of [Sar1Thr8]Angiotensin II (40 pmol) into the Rostral and Caudal Ventrolateral Medulla

<table>
<thead>
<tr>
<th>Variable</th>
<th>Vehicle</th>
<th>[Sar1Thr8]Ang II</th>
<th>Vehicle</th>
<th>[Sar1Thr8]Ang II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ Mean blood pressure (mm Hg)</td>
<td>7±1</td>
<td>-20±2*</td>
<td>-10±1</td>
<td>18±1*</td>
</tr>
<tr>
<td>(mm Hg)</td>
<td>(11)</td>
<td>(6)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Δ Heart rate (beats/min)</td>
<td>1±1</td>
<td>-3±1†</td>
<td>-3±1</td>
<td>3±1†</td>
</tr>
<tr>
<td>(beats/min)</td>
<td>(10)</td>
<td>(6)</td>
<td>(5)</td>
<td></td>
</tr>
<tr>
<td>Δ Renal nerve activity (% control)</td>
<td>16±1</td>
<td>-42±3*</td>
<td>-22±3</td>
<td>48±7*</td>
</tr>
<tr>
<td>(5)</td>
<td>(5)</td>
<td>(4)</td>
<td>(4)</td>
<td></td>
</tr>
</tbody>
</table>

Results are expressed as mean±SEM. Number of experiments in each group is shown in parentheses. VLM, ventrolateral medulla; Ang II, angiotensin II.

*p<0.001 compared with vehicle alone.

The sites within the caudal VLM of the rabbit at which Ang II produced the largest depressor effects were ventrolateral to the nucleus ambiguus and close to the dorsal edge of the lateral reticular nucleus. As mentioned previously, this region contains a high density of Ang II receptor binding sites. It also corresponds to the region containing norepinephrine-synthesizing cells of the A1 group. It has been shown that intracerebroventricular injection of Ang II produces an increase in norepinephrine turnover in the A1 area, which raises the possibility that the depressor effects of Ang II could be mediated by an increase in the activity of A1 cells. On the other hand, a recent study in the rat indicated that excitation of A1 cells does not produce a depressor response. Thus, despite the evidence that there is an interaction between central Ang II and brain catecholamine systems, the depressor effect produced by Ang II in the caudal VLM may be due to an action on non-A1 cells.

Apart from the identity of the caudal VLM cells that mediate the depressor response to Ang II injection, there is the question of the mechanism of this action. The simplest possibility is that Ang II is an excitatory neurotransmitter that acts directly on receptors on depressor neurons. Alternatively, Ang II may be a neuromodulator, acting on presynaptic receptors on the terminals of afferent fibers synapsing with the depressor neurons. By analogy, there is evidence that Ang II may act as a neuromodulator within the nucleus of the solitary tract. Ang II receptors in the nucleus of the solitary tract are situated on the terminals of vagal afferent fibers, and microinjections of Ang II into this nucleus attenuate the baroreceptor reflex. Whatever the mode and site of action of Ang II, however, the results indicate that it is tonically released in the caudal VLM because blockade of Ang II receptors produced sympathoexcitation and a rise in blood pressure.

With regard to the rostral VLM, the results support previous findings in the cat that microinjection of Ang II into rostral VLM or its topical application to the nearby ventral surface produces pressor effects. Unlike these previous studies, however, in the present experiments the carotid sinus bifurcation...
tions were denervated, and the aortic and vagal nerves were cut. It was thus possible to determine the cardiovascular effects of Ang II microinjection without interference from secondary effects arising from stimulation of arterial and cardiopulmonary baroreceptors. In baroreceptor-denervated rabbits, the pressor response to microinjection into the rostral VLM of 20 pmol Ang II was twice as large as that elicited by the same dose in intact rabbits. Our findings are therefore consistent with the results of a previous study, which showed that the pressor effects of intracisternally injected Ang II are greatly potentiated in baroreceptor-denervated animals as compared with intact animals.9

A previous study from our laboratory has shown that the pressor response to Ang II microinjected into the rostral VLM is due to an increase in peripheral sympathetic activity as the pressor response was abolished by ganglionic blockade with hexamethonium.2 The present results indicate that Ang II in the rostral VLM produces a widespread activation of sympathetic vasomotor and cardiac nerves, as the increase in blood pressure was accompanied by an increase in all other cardiovascular variables measured (i.e., renal sympathetic nerve activity, iliac vascular resistance, and heart rate). It was also observed, however, that the time course of the increase in renal sympathetic activity was different from that of the pressor response. Typically, the renal nerve activity reached a peak level and then decreased back to the control level while the blood pressure remained elevated. The longer duration of the pressor response could be due to the release of circulating hormones such as adrenomedullary catecholamines or vasopressin.

As described in Results, the region within the rostral VLM of the rabbit from which Ang II produced significant pressor responses extended from the caudal pole of the facial nucleus to the level 1.0 mm more caudal, and in the mediolateral direction formed a band approximately 1.5 mm in length and aligned parallel to the adjacent ventrolateral surface. This region corresponds very closely to the location of both Ang II receptor binding sites8 and to a dense group of bulbospinal cells17 in the rostral VLM of the rabbit, both of which also form bands aligned parallel to the ventrolateral surface. Similarly, in the rostral VLM of the cat, there is a remarkable correlation between the location of Ang II pressor sites, receptor binding sites, and bulbospinal neurons,2-4 which in this species are all restricted to the discrete region referred to as the subretrofacial nucleus.4 Furthermore, the bulbospinal cells in the subretrofacial nucleus project directly to sympathetic preganglionic nuclei in the spinal cord26 and are known to have a sympathoexcitatory function.27,28 It is not known, however, whether the Ang II receptors are located on the bulbospinal cells themselves or on the terminals of afferent fibers that synapse with the bulbospinal cells.

There is evidence that there are two groups of sympathoexcitatory neurons within the rostral VLM that can be distinguished by their chemical and functional properties. One group is part of the Cl group of catecholamine-synthesizing neurons,29 and the other group consists of non-catecholamine cells.
that have an intrinsic pacemaker activity. Recently, it has been shown that cells of the latter group are not excited by Ang II applied in vitro. This raises the possibility that Ang II may excite only catecholamine cells within the rostral VLM, many of which project to the spinal cord. In support of this, the location of catecholamine cells within the rostral VLM in both the rabbit and cat corresponds closely with the location of Ang II binding sites and also, as pointed out previously, with Ang II pressor sites. An alternative explanation, however, for the lack of effect of Ang II on rostral VLM cells in vitro is that Ang II acts presynaptically by modulating the release of transmitter from terminals synapsing with sympathoexcitatory neurons.

Andreotta and coworkers recently reported that application of the Ang II antagonist [Sar1Thr8]Ang II to the ventral surface of the rostral medulla of the cat produced a fall in blood pressure. The site of action of this compound could not be defined precisely, however, as it spread over a considerable distance in both the rostrocaudal and mediolateral directions. The present study demonstrated that this antagonist produces its depressor effect when microinjected directly into that part of the rostral VLM containing a high density of Ang II receptor binding sites. It therefore follows that Ang II is tonically released into the rostral VLM, possibly from the terminals of fibers, as Ang II-immunoreactive terminals have been described in this region, at least in the rat. The origin of such fibers is unknown at present, although it may be speculated that it is either the nucleus of the solitary tract or the hypothalamic paraventricular nucleus, both of which have been shown to contain Ang II-immunoreactive neurons.

In conclusion, the results demonstrate that endogenous Ang II can modulate the ongoing activity of sympathetic nerves innervating the cardiovascular system via actions on both sympathoexcitatory and sympathoinhibitory neurons within the rostral and caudal parts of the VLM, respectively. Both groups of neurons may therefore be important sites at which brain Ang II can influence blood pressure.

Acknowledgments

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**KEY WORDS** • brain angiotensin system • ventrolateral medulla • angiotensin II receptor • baroreceptor reflex • sympathetic nerve activity
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