Angiotensin II Studies in Hypertension

By Milton Mendelowitz, M.D., Robert L. Wolf, M.D., Stanley E. Gitlow, M.D., and Nosrat E. Naftchi, M.S.

Following the production of experimental hypertension through the alteration of intrarenal hemodynamics by Goldblatt in 1934, investigators have identified, isolated, described, and synthesized the active pressor octapeptide angiotensin II. Others have described the metabolism and distribution of extracted and synthetic angiotensin II and have also suggested that this peptide is implicated in the etiology of primary hypertension. Concomitantly, the reactivity of the vascular bed of the digit to a variety of stimuli, including angiotensin II, was under study. The unique properties of the digital vascular bed made it possible to calculate pressure-flow ratios and radius equivalents from which the work of vasoconstriction per unit of vasoactive substance administered per minute could be determined.

Digital vascular reactivity to intravenously infused norepinephrine, after sympathetic blockade by indirect heat and the administration of a ganglionic blocking drug, was found to be increased in the primary hypertensive patient, compared to the normotensive subject. Vascular reactivity to angiotensin II was then also studied. Fifteen normotensive subjects and 15 patients with primary (untreated) hypertension were tested under 3 sets of conditions: at rest in the supine position, after ganglionic blockade, and after infusing sufficient angiotensin II to bring the blood pressure to approximately the recorded level before ganglionic blockade.

The results are summarized in table 1 and indicate that the patients with primary hypertension were more reactive to angiotensin II than the subjects with normal blood pressure. Furthermore, the reactivity per unit weight of angiotensin II was approximately 10-fold greater than that of norepinephrine in both hypertensive and normotensive subjects. In contrast, vascular reactivity to angiotensin II, as well as to \( l \)-norepinephrine, was normal in patients with secondary renal hypertension (table 2). These reactions are probably not restricted to the digit since similar increases in reactivity to angiotensin II have been reported in forearm muscle blood vessels of patients with primary hypertension. It should be pointed out that the differences between normal and hypertensive reactions are brought out in both instances by prior sympathetic ganglionic blockade.

In addition, the distribution and turnover of angiotensin II was also studied. Methods were developed to label angiotensin II with \( I^{131} \) and to study the distribution and rate of degradation of this substance after its intravenous administration in normotensive and hypertensive subjects.

Angiotensin II was trace-labeled with \( I^{131} \), and the nonpeptide-bound iodide and iodate were removed by passage through resin columns. The thyroidal accumulation of \( I^{131} \) was prevented by the oral administration of large quantities of stable iodide in the form of Lugol’s solution or a saturated solution of potassium iodide. After the intravenous administration of angiotensin II-\( I^{131} \), the \( I^{131} \) released from angiotensin II-\( I^{131} \) by metabolic degradation was therefore not reutilized to any significant degree and was nearly quantitatively excreted in the urine. If the rate of urinary excretion of the \( I^{131} \) released from the degraded angiotensin II-\( I^{131} \) were rapid, compared to the degradation rate of the

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Table 1

A. Reactivity to Infused Angiotensin II (AT) After Vasodilatation

<table>
<thead>
<tr>
<th></th>
<th>Work of vasoconstriction $10^3$ ergs Mean ± S.D.</th>
<th>Rate of AT infusion $\mu g./min.$ Mean ± S.D.</th>
<th>Work $\mu g./min.$ $10^3$ ergs/ $\mu g./min.$ Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive—15 patients</td>
<td>0.62 ± 0.3</td>
<td>1.9 ± 0.7</td>
<td>0.35 ± 0.13</td>
</tr>
<tr>
<td>Hypertensive—15 patients</td>
<td>1.5 ± 0.9</td>
<td>1.1 ± 0.3</td>
<td>1.4 ± 0.68</td>
</tr>
</tbody>
</table>

*Standard error of the difference, $\sigma = 0.18; p < 10^4$. D

B. Reactivity to Infused l-Norepinephrine (NE) After Vasodilatation

<table>
<thead>
<tr>
<th></th>
<th>Work of vasoconstriction $10^3$ ergs Mean ± S.D.</th>
<th>Rate of NE infusion $\mu g./min.$ Mean ± S.D.</th>
<th>Work $\mu g./min.$ $10^3$ ergs/ $\mu g./min.$ Mean ± S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive—16 patients</td>
<td>0.86 ± 0.28</td>
<td>26 ± 8.0</td>
<td>0.031 ± 0.011</td>
</tr>
<tr>
<td>Hypertensive—16 patients</td>
<td>2.4 ± 1.1</td>
<td>18 ± 8.5</td>
<td>0.16 ± 0.10</td>
</tr>
</tbody>
</table>

*Standard error of the difference, $\sigma = 0.026; p < 10^4$. D

Table 2

A. Reactivity to Infused Angiotensin II (AT) After Vasodilatation in Three Individual Subjects with Renal Hypertension

<table>
<thead>
<tr>
<th>Resting brachial blood pressure</th>
<th>Work of vasoconstriction $10^3$ ergs</th>
<th>Rate of AT infusion $\mu g./min.$</th>
<th>Work $\mu g./min.$ $10^3$ ergs/ $\mu g./min.$</th>
</tr>
</thead>
<tbody>
<tr>
<td>160/110</td>
<td>0.53</td>
<td>1.5</td>
<td>0.36</td>
</tr>
<tr>
<td>186/130</td>
<td>0.63</td>
<td>2.5</td>
<td>0.25</td>
</tr>
<tr>
<td>190/136</td>
<td>0.65</td>
<td>2.0</td>
<td>0.33</td>
</tr>
</tbody>
</table>

B. Reactivity to Infused l-Norepinephrine (NE) After Vasodilatation in Seven Individual Subjects with Renal Hypertension

<table>
<thead>
<tr>
<th>Resting brachial blood pressure</th>
<th>Work of vasoconstriction $10^3$ ergs</th>
<th>Rate of NE infusion $\mu g./min.$</th>
<th>Work $\mu g./min.$ $10^3$ ergs/ $\mu g./min.$</th>
</tr>
</thead>
<tbody>
<tr>
<td>160/104</td>
<td>0.63</td>
<td>17</td>
<td>0.036</td>
</tr>
<tr>
<td>126/ 80</td>
<td>0.66</td>
<td>9</td>
<td>0.074</td>
</tr>
<tr>
<td>160/114</td>
<td>0.56</td>
<td>17</td>
<td>0.033</td>
</tr>
<tr>
<td>156/110</td>
<td>0.61</td>
<td>15</td>
<td>0.041</td>
</tr>
<tr>
<td>224/100</td>
<td>0.17</td>
<td>8.2</td>
<td>0.021</td>
</tr>
<tr>
<td>146/ 86</td>
<td>1.7</td>
<td>28</td>
<td>0.061</td>
</tr>
<tr>
<td>136/ 90</td>
<td>2.0</td>
<td>28</td>
<td>0.071</td>
</tr>
</tbody>
</table>

angiotensin II-$^{131}$, then the angiotensin II degradation rate would be rate-limiting for the urinary excretion of $^{131}$ which, under these conditions, would serve as a measure of angiotensin II turnover. This measurement was not possible, however, since both of these rates were relatively rapid. The rate of degradation of angiotensin II, however, could be determined from the decline in plasma angiotensin II-$^{131}$ radioactivity after mechanical mixing in the plasma and erythrocytes and equalization between intra- and extravascular angiotensin II pools were completed.15, 16
Table 3
Rate of Degradation and Space of Distribution of Angiotensin II-I\textsuperscript{131} in Various Subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>Number</th>
<th>Mean</th>
<th>Range</th>
<th>T 1/2 (hr.) Mean</th>
<th>Range</th>
<th>Per cent/hr. Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive (control)</td>
<td>11</td>
<td>33</td>
<td>25-40</td>
<td>10.3</td>
<td>8.0-12.0</td>
<td>6.92</td>
<td>5.77-8.66</td>
</tr>
<tr>
<td>Primary hypertensive (untreated)</td>
<td>7</td>
<td>38</td>
<td>36-45</td>
<td>15.8</td>
<td>12.0-19.0</td>
<td>4.50</td>
<td>3.46-5.77</td>
</tr>
<tr>
<td>Secondary renal hypertensive</td>
<td>1</td>
<td>32</td>
<td></td>
<td>18.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accelerated hypertensive</td>
<td>1</td>
<td>42</td>
<td></td>
<td>37.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normotensive (had acute glomerulonephritis)</td>
<td>1</td>
<td>55</td>
<td></td>
<td>10.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary hypertensive (treated)</td>
<td>1</td>
<td>33</td>
<td></td>
<td>15.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma (before surgery)</td>
<td>1</td>
<td>25</td>
<td></td>
<td>19.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pheochromocytoma (after surgery)</td>
<td>1</td>
<td>52</td>
<td></td>
<td>15.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Following the intravenous administration of angiotensin II-I\textsuperscript{131} to human subjects, approximately two-thirds of the total blood radioactivity was in the plasma, and the remaining one-third was in the erythrocytes. A radiochromato-electrophoretogram of normal human serum to which angiotensin II-I\textsuperscript{131} was added in vitro illustrates the homogeneity of the iodinated preparation and demonstrates that the mobility of the angiotensin II-I\textsuperscript{131} is more rapid than that of the human serum proteins (fig. 1). Paper radiochromato-electro-
phoresis is effected by applying the material to be analyzed at the cathode end of a strip of filter paper stretched across the vertical supports of the buffer vessels of the electrophoretic apparatus and, with the top of the apparatus left open, running the voltage supply at 600 volts. Under these conditions, evaporation of water from the center of the paper strips produces hydrodynamic forces which result in a movement of fluid from the buffer vessels toward the center of the paper strip, and the material to be analyzed, therefore, migrates toward the anode.

The plasma concentration of angiotensin II-I\textsuperscript{131} falls, after intravenous injection,\textsuperscript{*} with a gradually decreasing slope on semi-logarithmic paper until a terminal straight line is observed (fig. 2). The rate of degradation of angiotensin II is represented by this final straight line. An estimate of the apparent space of distribution may be obtained from the zero time extrapolation of the metabolic straight line portion of the curve. Table 3 summarizes the values obtained for the apparent spaces of distribution and the degradation ranges in 11 normotensive (control) subjects, 7 primary hypertensive (untreated) patients, and 6 additional miscellaneous subjects.\textsuperscript{16} The mean half-times of degradation were 10.3 hours and 15.8 hours, respectively, in the normotensive and primary (untreated) hypertensive subjects. The corresponding mean values for the apparent space of distribution were 23 and 26 L., respectively. The total exchangeable

\textsuperscript{*}Plasma radioactivity is established by radiochromato-electrophoresis to be identical with that of angiotensin II-I\textsuperscript{131}.  

\textsuperscript{16}MENDLOWITZ, WOLF, GITLOW, NAFTCHI

![Figure 2](image-url)
angiotensin II may be calculated to approximate 0.41 μg. in the normotensive subjects, 0.99 μg. in the subjects with primary (untreated) hypertension, and 9.3 μg. in the patient with accelerated (malignant) hypertension. The findings indicate that the slow degradation rate of angiotensin II in primary and accelerated hypertension, rather than increased production of angiotensin II, may be the cause of the increased angiotensin II blood levels observed in these patients.

It is of interest that similar slow degradation rates were observed in a patient with renal hypertension and in 1 patient with pheochromocytoma. Since digital vascular reactivity to angiotensin II is usually normal in renal hypertension, it is clear that the slow turnover of angiotensin is not necessarily determined by the same factors that cause increased vascular reactivity.

Summary

1. In primary hypertension, the digital blood vessels are more reactive than normal to angiotensin II as well as to l-norepinephrine.
2. In terms of weight, the potency of angiotensin II in constricting digital blood vessels is 10 times that of norepinephrine in both normotensive and hypertensive subjects.
3. The turnover of angiotensin II-131 is slower than normal in patients with primary hypertension.
4. Digital vascular reactivity to both l-norepinephrine and angiotensin II is normal in "pure" renal hypertension.
5. Angiotensin II-131 turnover, in contrast, in the case of renal hypertension studied, was slower than in the normal group and was similar to that in the case of primary hypertension.

References


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