ABSTRACT
Arterial blood pressure was recorded directly in 11 normotensive subjects, in 11 patients with essential hypertension and in 10 patients with renovascular hypertension. The pressor response to intravenous injections of norepinephrine, tyramine, angiotensin and ephedrine was compared in these three groups. An infusion of angiotensin was then given and the pressor response to injections of norepinephrine, tyramine, and ephedrine was again measured; in some cases, a comparison of the effects of the cold pressor test was made.

In normotensive subjects, angiotensin infusion caused a significant increase in the responses to tyramine and ephedrine but not to norepinephrine; this occurred with subpressor doses and was unrelated to the level of blood pressure. In patients with renovascular hypertension, the mean pressor responses to injections of tyramine and ephedrine and the ratio of response to tyramine to that to norepinephrine were significantly increased, and the infusion of angiotensin failed to cause any further increase in these responses. In contrast, in patients with essential hypertension, the average response to injections of tyramine was not significantly increased, but during angiotensin infusion the response to tyramine increased as in normotensive subjects. It is proposed that increased response to tyramine, and lack of the potentiating effect of angiotensin demonstrated in renovascular hypertension, may be caused by increased formation of endogenous angiotensin due to renin secretion in this disease.

ADDITIONAL KEY WORDS
diagnosis of hypertension
sympathetic nervous system
cold pressor test
hypertension with renal artery stenosis
norepinephrine release
ephrine
renin
essential hypertension

McCubbin and Page (1) recently found in dogs that angiotensin increases their response to tyramine and other agents that cause release of endogenous norepinephrine and they suggested that angiotensin has an indirect effect on the sympathetic nervous system. Subsequently, Page et al. (2) found in dogs that the pressor response to tyramine is augmented in both the acute and chronic phases of experimental renal hypertension. The findings appear to be important in clarifying the mechanism of experimental hypertension. It is not yet known, however, wheth-
er angiotensin causes this action in man and whether it augments the response to tyramine in human hypertensive patients. The present investigation was undertaken to study the effect of angiotensin in man and to compare the response to tyramine among normotensive and hypertensive patients.

**Methods**

Studies were performed on hospitalized normotensive and essential and renovascular hypertensive patients. Normotensive patients (3 females and 8 males, ranging in age from 19 to 53 years) had no evidence of significant cardiovascular disease. Essential hypertension was diagnosed in patients (4 females and 7 males, ranging in age from 23 to 65 years) following thorough examination, including excretory pyelogram, tests for pheochromocytoma, aortography and, in some cases, renal biopsy. Renovascular hypertension was diagnosed in patients who had renovascular hypertension (3 females and 7 males, ranging in age from 19 to 54 years) by demonstration of severe stenotic lesions of one or two main renal arteries by aortography and of ischemic patterns in split renal function studies. Patients with clinical evidence of heart or renal failure were not included in these series.

All medications had been discontinued for a period of at least 2 weeks prior to the study, and the patients were in the fasting state and remained in the supine position throughout the study. After giving local anesthesia, an 18 gauge needle was inserted into a femoral artery and a plastic catheter was introduced through it; arterial pressure was then measured continuously with a strain gauge transducer and recorded on a direct-writing oscillograph. The mean arterial pressure (diastolic plus one third of pulse pressure) was calculated from the record.

When arterial pressure had stabilized, test drugs mixed in physiologic saline (total volume 1 ml) were injected through a three-way stopcock at the end of a fine polyethylene tube with a needle inserted into an arm vein, and then flushed rapidly into the vein with 2 ml of physiologic saline. The drugs were norepinephrine hydrochloride (0.05 to 0.1 μg/kg, as the base), tyramine hydrochloride (0.05 to 0.1 mg/kg, as the salt), ephedrine hydrochloride (0.1 mg/kg, as the salt) and angiotensin (valyl-5 octapeptide, Ciba, 0.02 μg/kg). Test drugs were given in the following order: tyramine, ephedrine, norepinephrine and angiotensin. Usually two responses were recorded with a given dose and successive injections were separated by an interval of at least 3 min. The cold pressor test was performed by immersing one hand to just above the wrist in ice water for 1 min. All pressor responses are expressed as changes in mean arterial pressure in millimeters of mercury.

When angiotensin was infused, it was dissolved in 5% glucose solution in a concentration of 1 μg/ml and then infused into a vein of the other arm at a rate of 0.30 to 1.0 μg/min.

**Results**

**EFFECT OF ANGIOTENSIN INFUSION ON RESPONSE TO TYRAMINE**

In control observations the pressor response to a given dose of tyramine and of norepinephrine was measured several times; there were no significant differences between the responses. Angiotensin was then infused into 11 normotensive subjects at an average rate of 0.58 μg/min. After 30 to 60 min, when mean arterial pressure had stabilized at an average of 104 mm Hg (average control level, 88 mm Hg), tyramine and norepinephrine were injected again in the same doses. Figure 1

![Figure 1](http://circres.ahajournals.org/)

Effect of angiotensin infusion on arterial pressure responses to tyramine and norepinephrine in a 19-year old normotensive subject. Test drugs injected intravenously. T = tyramine, 0.1 mg/kg; N = norepinephrine, 0.1 μg/kg.

_Circulation Research, Vol. XIX, October 1966_
ANGIOTENSIN AND TYRAMINE IN MAN

The infusion of angiotensin caused a significant increase in response to tyramine in all subjects. The response to norepinephrine was unchanged or increased slightly in some cases. The increase in response to tyramine persisted during the infusion and returned to the control level after stopping the infusion.

In patients with essential hypertension, the response to tyramine was increased in 7 out of 8 patients, while in patients with renovascular hypertension, the response to tyramine was unchanged in all patients tested.

EFFECT OF ANGIOTENSIN ON RESPONSE TO EPHEDRINE AND COLD PRESSOR RESPONSE

Table 1 summarizes the results of the study on the effect of angiotensin on the response to ephedrine and the cold pressor test. The mean arterial pressure (MAP) and rise in MAP were recorded during the infusion of angiotensin and compared with the control period.

MAP = mean arterial pressure; n.s. = not significant.

Table 1: Effect of Angiotensin on Response to Ephedrine and Cold Pressor Response

<table>
<thead>
<tr>
<th></th>
<th>No. of cases</th>
<th>Rate of infusion avg μg/min</th>
<th>MAP Mean ± S.D.</th>
<th>Norepinephrine Responses to Tyramine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systol. and diastr. BP avg. mmHg</td>
<td>Dose avg mg/kg</td>
</tr>
<tr>
<td>Control</td>
<td>11</td>
<td>0.58</td>
<td>110/74, 137/88</td>
<td>88 ± 2.7</td>
</tr>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
<td>104 ± 3.6</td>
<td>n.s.</td>
</tr>
<tr>
<td>Significance of difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essential Hypertension</td>
<td>8</td>
<td>0.46</td>
<td>173/112, 190/122</td>
<td>132 ± 5.5</td>
</tr>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
<td>145 ± 6.1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Significance of difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renovascular Hypertension</td>
<td>7</td>
<td>0.54</td>
<td>126/105, 205/120</td>
<td>129 ± 7.5</td>
</tr>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
<td>148 ± 6.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>Significance of difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The effect of angiotensin infusion on the response to ephedrine and the cold pressor test was observed with subpressor doses of angiotensin.
KANEKO, TAKEDA, NAKAJIMA, UEDA

Angiotensin infusion - 58m.n 0.60/ig/min

FIGURE 2
Effect of angiotensin infusion on arterial pressure responses to tyramine and norepinephrine in a 54-year old patient with renovascular hypertension. T = tyramine, 0.1 mg/kg; N = norepinephrine, 0.1 μg/kg.

FIGURE 3
Relationship between changes of response to tyramine, measured after more than 30 min of infusion of angiotensin and expressed as per cent of the response in the control period, and rise in mean arterial pressure caused by infusion of angiotensin alone. ○ = patients with essential hypertension, ● = normotensive patients, × = patients with renovascular hypertension.

Response was also measured. In 7 normotensive subjects, the response to ephedrine was increased significantly (P < 0.001) by infusion of angiotensin. The cold pressor response was not changed. Table 2 summarizes the results for 7 subjects and Figure 4 shows one example of the response to ephedrine. In 4 patients with renovascular hypertension, infusion of angiotensin did not significantly modify either the response to ephedrine or the cold pressor response (Table 2).

The effect of angiotensin infusion on the response to 1, 1-dimethyl-4-phenyl piperazinium iodide (DMPP, 10 μg/kg), an autonomic ganglion-stimulating agent, was also observed. The observations were limited because DMPP produced some unpleasant sensations due to parasympathetic stimulation, but it appeared that infusion of angiotensin did not modify the response to DMPP.

RESPONSIVENESS TO TYRAMINE

Because the effect of angiotensin infusion was different in patients with renovascular hypertension, we compared the responses of normotensive subjects, patients with essential hypertension and patients with renovascular hypertension to the doses of tyramine, norepinephrine and angiotensin that were injected in the control period (Table 3).

The average response to 0.1 μg/kg of norepinephrine was significantly greater in the patients with essential hypertension than that in the normotensive group, but there was considerable overlap in responses among the three groups; responses ranged from 22 to 35 mm Hg in the normotensive group, from 19 to 48 mm Hg in the essential hypertensive group, and from 13 to 51 mm Hg in the renovascular hypertensive group.

The mean response to tyramine was found to be significantly enhanced in the renovascular hypertensive group, as compared to...
Effect of angiotensin infusion on arterial pressure responses to tyramine and ephedrine in a 35-year-old normotensive subject. T = tyramine, 0.1 mg/kg; E = ephedrine, 0.1 mg/kg.

that in the normotensive group ($P < 0.001$, Table 3) and to that in the essential hypertensive group ($P < 0.05$). However, there were 3 patients with renovascular hypertension who did not have an increased response to tyramine and there was some overlap in response to tyramine between the renovascular hypertensive group and the essential hypertensive group. Figure 2 shows an enhanced response to tyramine in a patient with renovascular hypertension. The mean response to 0.1 mg/kg of ephedrine was also significantly ($P < 0.01$) augmented in 4 renovascular hypertensive patients when compared with that in 7 normotensive subjects.

There was no significant difference in the pressor responses to single injection of 0.02 μg/kg of angiotensin among the three groups.

Since the response to tyramine is considered to be related in part to responsiveness to norepinephrine, the ratio of response to 0.1 mg/kg of tyramine to that to 0.1 μg/kg of norepinephrine was calculated in each subject as a means of evaluating responsiveness to tyramine. The ratio was increased in 2 of 11 patients with essential hypertension and in 8 of 10 patients with renovascular hypertension as compared to that in the normotensive subjects; the average ratio in the renovascular hypertensive group was significantly greater as compared to that in the normotensive group ($P < 0.001$, Table 3) and to that in the essential hypertensive group ($P < 0.025$), while the average ratio in the essential hypertensive group was not significantly different from that in the normotensive group.

**Discussion**

The present results are in accord with those McCubbin and Page (1) obtained in dogs

**TABLE 2**

Effect of Angiotensin Infusion on the Response to Ephedrine and the Cold Pressor Test

<table>
<thead>
<tr>
<th></th>
<th>Response to ephedrine</th>
<th>Response to cold pressor test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>Rate of infusion avg μg/min</td>
</tr>
<tr>
<td><strong>Normotensive</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>7</td>
<td>0.55</td>
</tr>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significance of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renovascular Hypertension</strong></td>
<td>4</td>
<td>0.64</td>
</tr>
<tr>
<td>Control</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During infusion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significance of</td>
<td></td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; n.s. = not significant.
Responses to Norepinephrine, Angiotensin and Tyramine in Normotensive Subjects and Patients with Essential Hypertension and with Renovascular Hypertension

<table>
<thead>
<tr>
<th></th>
<th>Normotensive subjects</th>
<th>Patients with essential hypertension</th>
<th>Patients with renovascular hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of cases</td>
<td>10</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Sysol. and dist. BP</td>
<td>119/75</td>
<td>172/107</td>
<td>179/105</td>
</tr>
<tr>
<td>avg mmHg</td>
<td>89 ± 2.3</td>
<td>129 ± 3.5</td>
<td>130 ± 6.3</td>
</tr>
<tr>
<td>MAP Mean ± SEM mmHg</td>
<td>26 ± 1.2</td>
<td>35 ± 3.4 P &lt; 0.05</td>
<td>31 ± 3.6 n.s.</td>
</tr>
<tr>
<td>Norepinephrine 0.1 μg/kg</td>
<td>20 ± 1.8</td>
<td>27 ± 4.0 n.s.</td>
<td>24 ± 4.5 n.s.</td>
</tr>
<tr>
<td>Mean ± SEM mmHg</td>
<td>13 ± 0.9</td>
<td>18 ± 2.3 n.s.</td>
<td>26 ± 2.8 P &lt; 0.001</td>
</tr>
<tr>
<td>Angiotensin 5.0 μg/kg Mean ± SEM mmHg</td>
<td>0.49 ± 0.01</td>
<td>0.54 ± 0.05 n.s.</td>
<td>0.90 ± 0.12 P &lt; 0.001</td>
</tr>
<tr>
<td>Tyramine 5.1 mg/kg Mean ± SEM mmHg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MAP = mean arterial pressure; n.s. = not significant.

and show that angiotensin potentiates the pressor response to agents that cause release of endogenous norepinephrine in man. An-giotensin infusion clearly potentiated responses to tyramine and ephedrine without significantly affecting response to norepinephrine in man. Angiotensin infusion, however, potentiated responses to both tyramine and sympathetic nerve stimulation.

TABLE 3
nerve stimulation was enhanced, although there was no increased output of norepinephrine and no impaired inactivation of norepinephrine; this suggests that the site of the enhancing effect of angiotensin may be at the level of the excitation-contraction mechanism of the smooth muscle cells.

It is noteworthy that response to tyramine alone and the effect of infusion of angiotensin on the tyramine response were different in patients with essential hypertension than in those with renovascular hypertension. In the essential hypertensive group, most patients did not show increased response to tyramine alone compared to the normotensive group, but after angiotensin infusion there was a significant increase in response to tyramine as in the normotensive group.

In the renovascular hypertensive group, most patients showed increased response to tyramine alone; the mean responses to tyramine and ephedrine and the ratio of response to tyramine to that to norepinephrine were all significantly increased. After infusion of angiotensin, however, the response to tyramine or ephedrine did not increase. Human renovascular hypertension is comparable to the acute phase of experimental renal hypertension in dogs in this respect. Page et al. (2) showed that in the acute phase of renal hypertension in dogs, angiotensin fails to cause further increase in the already augmented response to tyramine. The increased response to tyramine in renovascular hypertensive patients and the failure of exogenous angiotensin to increase the response further, may be caused by increased formation of endogenous angiotensin due to increased renin secretion in this disease. In one patient with renovascular hypertension, the response to tyramine was re-examined after successful repair of the renal artery stenosis; response to tyramine decreased from 22 to 11 mm Hg when arterial pressure had decreased from 195/116 (142) to 135/94 (108) mm Hg.

Varying response to tyramine in patients with renovascular hypertension might be related to the varying levels of circulating renin reported to occur in this disease (9). The lack of increased response to tyramine and the presence of a potentiating effect of angiotensin observed in most essential hypertensive patients suggest that this disease is usually not dependent upon increased levels of circulating renin, in accord with the observations of Helmer (10). There still exists a possibility that the renal pressor system might be involved in some essential hypertensive patients who had increased response to tyramine.

It is conceivable that in renovascular hypertension, increased renin secretion could have dual and opposing effects on neural tone: a tendency to decrease sympathetic discharge through the baroreceptors on one hand and a tendency to increase sympathetic tone by peripheral sensitization on the other hand. The net effects, then, should be variable. In the present study, the effect of intravenous administration of 5 mg/kg of tetraethylammonium bromide (TEAB), a ganglion-blocking agent, on arterial pressure was measured at the end of the experiments in 7 patients with renovascular hypertension. Two patients showed a rise in pressure (+35 and +16 mm Hg in mean arterial pressure) and in 5 patients there was a decrease in pressure ranging from −16 to −58 mm Hg. The findings support the hypothesis.

We considered that measurement of the response to tyramine could be helpful in diagnosis of renovascular hypertension. However, there is overlap in responses to tyramine in patients with essential and renovascular hypertension, and patients with pheochromocytoma also show increased response to tyramine (11).

Acknowledgment

The authors wish to thank Dr. James W. McCubbin for his valuable suggestions and encouragement during the performance of this research.

References

Effect of Angiotensin on the Pressor Response to Tyramine in Normotensive Subjects and Hypertensive Patients

YOSHIHIRO KANEKO, TADANAO TAKEDA, KOUJI NAKAJIMA and HIDEO UEDA

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