Selective Inhibition by des-1-Asp-8-Ile-Angiotensin II of the Steroidogenic Response to Restricted Sodium Intake in the Rat

By Christina A. Sarstedt, E. Darracott Vaughan, Jr., and Michael J. Peach

ABSTRACT

Angiotensin III (des-1-Asp-angiotensin II) is a potent steroidogenic agent in many species. The effects of the heptapeptide in the adrenal zona glomerulosa are resistant to blockade by C-terminally substituted analogues of angiotensin II (1-Sar-8-Ile- or 1-Sar-8-Ala-octapeptides). For this reason, the effects of 7-Ile-angiotensin III, a C-terminally substituted analogue of the heptapeptide, and 1-Sar-8-Ile-angiotensin II on aldosterone biosynthesis in rabbit adrenal cortical cell suspensions and on urinary aldosterone excretion in sodium-deprived rats were studied. In the in vitro studies, 7-Ile-angiotensin III was a better antagonist of angiotensin II- or angiotensin III-induced steroidogenesis than was 1-Sar-8-Ile-angiotensin II. In the rats, subcutaneously administered 1-Sar-8-Ile-angiotensin II (0.9 µmoles/kg) produced prolonged blockade of the pressor responses to exogenous angiotensin II. 7-Ile-angiotensin III (0.9 µmoles/kg) had no effect on resting blood pressure or on blood pressure responses to angiotensin II infusions. At the doses studied, however, 7-Ile-angiotensin III caused a marked decrease (30%) in aldosterone excretion in sodium-deprived rats, but 1-Sar-8-Ile-angiotensin II had no effect on aldosterone excretion. In the sodium-deprived rats, the administration of 7-Ile-angiotensin III was not associated with an acute increase in plasma renin activity, but treatment with 1-Sar-8-Ile-angiotensin II resulted in a sixfold increase in plasma renin activity. These results are consistent with a role for angiotensin III in the control of aldosterone biosynthesis.
7-Ile-AII BLOCKADE OF ALDOSTERONE SYNTHESIS

and output, as determined by the stable levels of urinary sodium that were seen at this time. In each of the experiments to be described, a different group of rats was used. In each study, half of the rats were on the normal-sodium diet and half were on the low-sodium diet.

ASSESSMENT OF THE EFFECTS OF ANGIOTENSIN ANALOGUES ON BLOOD PRESSURE

A group of rats, half on the normal-sodium diet and half on the low-sodium diet, was anesthetized with ether. In each rat an iliac artery and a femoral vein were cannulated with PE-50 intramedic tubing. The cannulas were exteriorized through the dorsal surface of the rat and flushed with a solution of heparin and 5% dextrose in water (D5W). The rats were placed in restraining cages for 1 hour to recover from the anesthesia. Their blood pressure was monitored through the arterial cannula attached to a Statham P23D pressure transducer conected to a Brush Mark 220 recorder. The rats were divided into groups so that six rats on each diet received a subcutaneous injection of one of the angiotensin analogues, 1-Sar-8-Ile-angiotensin II or 7-Ile-angiotensin III, in a vehicle of Wesson oil (18) or of the vehicle alone (the control group). The two peptides were administered in mole-equivalent doses ranging from 0.09 to 0.9 μmoles/kg. The minimally effective dose of subcutaneously administered 1-Sar-8-Ile-angiotensin II that blocked the cardiovascular response to exogenous angiotensin II for an 8-10 hour period was determined. To establish the existence and the duration of blockade, intravenous (10 seconds) infusions of angiotensin II in D5W were administered via the femoral vein cannula every 30 minutes using a Harvard infusion pump. The minimum dose of octapeptide analogue required to block the pressor response to angiotensin II for 8-10 hours was used in the experiments designed to examine the ability of this analogue to reduce aldosterone excretion.

DETERMINATION OF THE EFFECTS OF SODIUM DEPRIVATION ON PLASMA AND URINARY ALDOSTERONE, SODIUM, AND POTASSIUM CONCENTRATION

A group of 12 rats (half on the low-sodium diet) was studied. After equilibration of sodium intake and excretion, urinary levels of aldosterone were determined via the method of Farmer et al. (17), after purification over Sephadex LH-20 (16). Urinary concentrations of sodium and potassium were determined by atomic absorption spectrophotometry. At the end of the 6-hour period, the rats were decapitated, and blood samples were collected. Plasma aldosterone was extracted with dichloromethane and purified by LH-20 Sephadex column chromatography (16); the aldosterone levels were estimated by radioimmunoassay with the aldosterone-18, 21-dihemisuccinate antibody (19). Ion concentrations in the plasma were determined by atomic absorption spectrophotometry.

DETERMINATIONS OF THE EFFECTS OF THE PEPTIDE ANALOGUES ON ALDOSTERONE EXCRETION

The rats used in these experiments were divided into three equal groups: one group received control injections of vehicle alone, another received subcutaneous injections of 0.9 μmoles/kg of the octapeptide analogue 1-Sar-8-Ile-angiotensin II in oil, and the third received subcutaneous injections of 0.9 μmoles/kg of the heptapeptide analogue 7-Ile-angiotensin III. Half of each of...
these three groups was on the normal diet and half was on the sodium-restricted diet so that there were actually six experimental groups. Control urine samples were collected for 6 hours during the same daytime period beginning 24 hours prior to the experimental injections of the peptide antagonists. The experimental urine samples were collected for 6 hours immediately after the injections. Urinary sodium and potassium values were determined, and the aldosterone-γ-lactone radioimmunoassay procedure (17) was used to estimate urinary aldosterone levels. The data were tested for significance (P < 0.05) using Student's t-test for paired data. All values are expressed as means ± SE.

DETERMINATION OF PLASMA RENIN ACTIVITY

Plasma renin activity was estimated in sodium-deprived rats treated with the analogues 30 minutes prior to decapitation and collection of blood samples. The plasma was separated from the blood cells by centrifugation and then incubated for 1 hour to generate angiotensin I. Angiotensin I concentrations were estimated by radioimmunoassay.

MATERIALS

Recrystallized deoxyribonuclease, bovine serum albumin, lima bean trypsin inhibitor, and ACTH were purchased from Sigma, and crude collagenase was purchased from Worthington Biochemical Corporation. 1-Asp-5-Ile-angiotensin II and des-1-Asp-5-Ile-angiotensin II (hereafter called angiotensin III) were purchased from Schwarz-Mann and supplied by Dr. F. M. Bumpus of the Research Division of the Cleveland Clinic. D-[1, 2-3H]-aldosterone (specific activity 43 c/mmole) was purchased from New England Nuclear Corporation, aldosterone-7-lactone antiserum from Antibodies, Incorporated, aldosterone-18, 21-dihemisuccinate antibody from New England Nuclear Corporation, 5% dextrose in water from Cutler, Incorporated, sodium heparin from Upjohn, and Sephadex LH-20 from Pharmacia Fine Chemicals. The low-sodium rat chow (4 μEq sodium/g chow) was obtained from General Biochemicals. For the plasma renin activity determinations, the plasma renin kit from New England Nuclear Corporation was used.

The peptides 1-Sar-8-Ile-angiotensin II and 7-Ile-angiotensin III were generously supplied by Dr. M. Khosla of the Research Division of the Cleveland Clinic.

<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Antagonist analogue</th>
<th>Concentration (M)</th>
<th>Increase in aldosterone (ng/10^6 cells)</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>None</td>
<td></td>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1-Sar-8-Ile-AII</td>
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<td></td>
</tr>
<tr>
<td>3</td>
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<td>5 x 10^-9</td>
<td>0.00</td>
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</tr>
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<td>1 x 10^-8</td>
<td>0.00</td>
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</tr>
<tr>
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<td>None</td>
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<td>1.25 ± 0.2</td>
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</tr>
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<td>7-Ile-AIII</td>
<td>1 x 10^-8</td>
<td>0.63 ± 0.08</td>
<td>89</td>
</tr>
<tr>
<td>30</td>
<td>None</td>
<td></td>
<td>10.21 ± 1.20</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>1-Sar-8-Ile-AII</td>
<td>3 x 10^-7</td>
<td>1.45 ± 0.3</td>
<td>86</td>
</tr>
<tr>
<td>30</td>
<td>7-Ile-AIII</td>
<td>5 x 10^-9</td>
<td>7.45 ± 0.6</td>
<td>27</td>
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<tr>
<td>30</td>
<td>7-Ile-AIII</td>
<td>1 x 10^-8</td>
<td>1.02 ± 0.2</td>
<td>90</td>
</tr>
</tbody>
</table>

N = 8-10 experimental observations.
Results

IN VITRO EFFECTS OF ANGIOTENSIN ANALOGUES ON ALDOSTERONE BIOSYNTHESIS

The effects of angiotensin II, angiotensin III, 1-Sar-8-Ile-angiotensin II, and 7-Ile-angiotensin III on aldosterone synthesis are presented in Figure 1. Each of the peptides showed agonistic activity. Angiotensin III was more potent than angiotensin II at equimolar doses. The heptapeptide analogue 7-Ile-angiotensin III was less potent than either naturally occurring peptide and more potent than the octapeptide analogue 1-Sar-8-Ile-angiotensin II.

Table 1 shows the effects of the angiotensin analogues 1-Sar-8-Ile-angiotensin II and 7-Ile-angiotensin III on angiotensin II-induced steroidogenesis. The octapeptide analogue (10^{-7}M) reduced the angiotensin II effect to about 14% of the control steroidogenic response, whereas concentrations of 7-Ile-angiotensin III of 5 x 10^{-8}M and 10^{-8}M reduced the angiotensin II effect to 70% and 10% of control, respectively. To achieve a comparable inhibition of angiotensin II-induced aldosterone biosynthesis with 1-Sar-8-Ile-angiotensin II and 7-Ile-angiotensin III, about a tenfold higher concentration of the octapeptide analogue was required.

The effects of equimolar concentrations (10^{-8}M) of 1-Sar-8-Ile-angiotensin II and 7-Ile-angiotensin III on angiotensin III-induced aldosterone biosynthesis are presented in Table 2. This dose of 1-Sar-8-Ile-angiotensin II (10^{-8}M) did not change the steroidogenic response to angiotensin III, but 7-Ile-angiotensin III (10^{-8}M) reduced the effect of angiotensin III on aldosterone biosynthesis to 10% of the control response. To obtain comparable

\[ \text{FIGURE 2} \]

Effects of the antagonists 7-Ile-angiotensin III and 1-Sar-8-Ile-angiotensin II on ACTH- and angiotensin III-induced aldosterone biosynthesis. Each point represents the mean of eight to ten experimental observations 60 minutes in duration. Open squares = ACTH + 7-Ile-angiotensin III (10^{-8}M), open triangles = ACTH + 1-Sar-8-Ile-angiotensin II (10^{-8}M), open circles = angiotensin III + 7-Ile-angiotensin III (10^{-8}M), solid squares = ACTH, solid triangles = angiotensin III + 1-Sar-8-Ile-angiotensin II (3 x 10^{-8}M), and solid circles = angiotensin III.

\[ \text{FIGURE 2} \]

Effects of the antagonists 7-Ile-angiotensin III and 1-Sar-8-Ile-angiotensin II on ACTH- and angiotensin III-induced aldosterone biosynthesis. Each point represents the mean of eight to ten experimental observations 60 minutes in duration. Open squares = ACTH + 7-Ile-angiotensin III (10^{-8}M), open triangles = ACTH + 1-Sar-8-Ile-angiotensin II (10^{-8}M), open circles = angiotensin III + 7-Ile-angiotensin III (10^{-8}M), solid squares = ACTH, solid triangles = angiotensin III + 1-Sar-8-Ile-angiotensin II (3 x 10^{-8}M), and solid circles = angiotensin III.
antagonism of angiotensin III responses with 1-Sar-8-Ile-angiotensin II (3 × 10⁻⁷M), a molar dose ratio of 30:1 was required.

The specificity of 7-Ile-angiotensin III was examined in the rabbit adrenal cortical cell suspension, and the results of this study are represented in Figure 2. 7-Ile-angiotensin III had no significant

![Graph 1](image1)

![Graph 2](image2)

![Graph 3](image3)

**Figure 3**
Tracings of blood pressure in response to angiotensin II infusions (200 ng) with and without subcutaneous injection of the antagonists, 7-Ile-angiotensin III (0.9 μmoles/kg) and 1-Sar-8-Ile-angiotensin II (0.9 μmoles/kg) in normal rats. 1-Sar-8-Ile-angiotensin II blocked the pressor response to angiotensin II infusions. Abbreviations are the same as they are in Figure 1.

![Graph 4](image4)

**Figure 4**
Representative tracings of mean arterial blood pressure in response to subcutaneous injections of 7-Ile-angiotensin III (0.9 μmoles/kg) and 1-Sar-8-Ile-angiotensin II (0.9 μmoles/kg) in sodium-deprived rats. 1-Sar-8-Ile-angiotensin II caused a transient decrease in mean arterial blood pressure. Abbreviations are the same as they are in Figure 1.

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TABLE 3
Effect of Restricted Sodium Intake in Rats on Urinary Excretion of Aldosterone, Sodium, and Potassium

<table>
<thead>
<tr>
<th></th>
<th>Normal-sodium diet</th>
<th>Low-sodium diet</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary aldosterone (ng excreted/6 hours)</td>
<td>23.3 ± 11.8</td>
<td>153 ± 76.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Urinary Na⁺ (mEq excreted/6 hours)</td>
<td>0.44 ± 0.12</td>
<td>0.02 ± 0.01</td>
<td>2.71 ± 0.57</td>
</tr>
<tr>
<td>Urinary K⁺ (mEq excreted/6 hours)</td>
<td>2.71 ± 0.57</td>
<td>2.36 ± 0.50</td>
<td>NS</td>
</tr>
</tbody>
</table>

The low-sodium diet contained 4 μEq sodium/g chow. N = 6 for each experimental diet. NS = not significant.

effect on ACTH-induced aldosterone biosynthesis. This figure also depicts the competitive antagonism of angiotensin III exhibited by 7-Ile-angiotensin III.

IN VIVO EFFECTS OF ANGIOTENSIN ANALOGUES ON THE CARDIOVASCULAR SYSTEM

Figure 3 depicts three representative blood pressure tracings of the cardiovascular responses to angiotensin II infusions in rats with and without prior treatment with either of the antagonists. We had previously determined the dose of 1-Sar-8-Ile-angiotensin II (0.9 μmoles/kg) necessary to produce prolonged (8-10 hours) inhibition of the pressor response to angiotensin II. An equimolar dose of the heptapeptide was employed to test its effects on the cardiovascular responses of the rat to administration of exogenous angiotensin II. At this dose, only 1-Sar-8-Ile-angiotensin II blocked the pressor response to angiotensin II infusions. Rats on the low-sodium diet responded to 1-Sar-8-Ile-angiotensin II in a similar manner. 7-Ile-angiotensin III had no effect on the pressor response to angiotensin II infusions in either model.

The effects of mole-equivalent doses of the antagonists on basal mean arterial blood pressure in sodium-deprived rats are presented in Figure 4. 1-Sar-8-Ile-angiotensin II caused a transient decrease of 15 mm Hg in basal arterial blood pressure in these rats. 7-Ile-angiotensin III had no effect on the pressor response to angiotensin II infusions in either model.

The effects of sodium deprivation on the urinary excretion of aldosterone, sodium, and potassium are indicated in Table 3. Urinary aldosterone levels increased sixfold and urinary sodium levels were markedly decreased during restriction of dietary sodium. Plasma aldosterone, sodium, and potassium concentrations after the reduction of sodium intake are presented in Table 4. The concentration of plasma aldosterone was increased fourfold after 5 days of sodium deprivation. At the same time, the plasma ion concentrations were essentially the same as those of rats on the normal-sodium diet. This finding demonstrates that in this rat model it is, indeed, possible to induce aldosterone secretion by reducing sodium intake.

The effects of the antagonists on urinary excretion of aldosterone in normal rats and in sodium-deprived rats are demonstrated in Figure 5. 7-Ile-angiotensin III, in sodium-deprived rats, caused a significant (P < 0.05) decrease of 50% in the urinary excretion of aldosterone. The heptapeptide analogue had no effect on aldosterone excretion in rats on the normal-sodium diet. In a dose that blocked the pressor response to angiotensin II infusions, 1-Sar-8-Ile-angiotensin II had no effect on the low-sodium diet. In the rats maintained on 0.5% saline, neither antagonist had a significant effect on basal arterial blood pressure.

TABLE 4
Effect of Restricted Sodium Intake in Rats on Plasma Concentrations of Aldosterone, Sodium, and Potassium

<table>
<thead>
<tr>
<th></th>
<th>Plasma aldosterone (pg/ml)</th>
<th>Plasma Na⁺ (mM)</th>
<th>Plasma K⁺ (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal-sodium diet</td>
<td>53.5 ± 17.3</td>
<td>125.8 ± 1.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Low-sodium diet</td>
<td>228.1 ± 9.3</td>
<td>128.9 ± 8.7</td>
<td>4.8</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.05</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

The low-sodium diet contained 4 μEq sodium/g chow. N = 6 for each experimental diet. NS = not significant.

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on the urinary excretion of aldosterone in normal or sodium-restricted rats.

**In vivo Effects of the Angiotensin Analogues on Plasma Renin Activity**

In Table 5, the effect of the analogues on plasma renin activity is depicted. Treatment with 1-Sar-8-Ile-angiotensin II caused a significant increase in plasma renin activity, but 7-Ile-angiotensin III had no significant effect on plasma renin activity.

**Discussion**

7-Ile-angiotensin III is a competitive blocker of the adrenal cortical receptor for angiotensin. The heptapeptide analogue blocks angiotensin III activity at a molar dose ratio of 1:1 and angiotensin II activity at a molar dose ratio of about 1:10. In contrast, 1-Sar-8-Ile-angiotensin II blocks angiotensin III at a molar dose ratio of 30:1 and angiotensin II at a molar dose ratio of 3:1. These findings are in agreement with the work of Chiu and Peach (11) showing that 1-Sar-8-Ile-angiotensin II blocks angiotensin III at a molar dose ratio of 50:1 and angiotensin II at a molar dose ratio of 2:1. We found that, at the doses studied, 7-Ile-angiotensin III was ineffective in blocking the pressor responses to angiotensin II infusions. The administration of molar-equivalent doses of 1-Sar-8-Ile-angiotensin II inhibited the cardiovascular responses to angiotensin II. The decrease in mean arterial blood pressure caused by 1-Sar-8-Ile-angiotensin II in sodium-deprived rats is consistent with the effects reported for another 8-substituted angiotensin II analogue by Gavras et al. (20). 7-Ile-angiotensin III had no effect on basal levels of mean arterial blood pressure. This fact suggests that blood pressure in the sodium-deprived rat is partially dependent on angiotensin II (20). These results also suggest that different receptors for the angiotensins exist in vascular smooth muscle and in the adrenal zona glomerulosa.

The sodium-deprived rat has a stimulated renin-angiotensin system (8, 9) as judged by plasma renin activity and aldosterone secretion and excretion. We found that 7-Ile-angiotensin III, the heptapeptide analogue, decreased aldosterone excretion in sodium-deprived rats but that 1-Sar-8-Ile-angiotensin II had no observable effect on aldosterone excretion. Although the dose of 7-Ile-angiotensin III studied produced a 50% decrease in urinary aldosterone excretion in 6 hours.
aldosterone excretion, we did not attempt to maximize this effect; rather, we employed a dose of 7-Ile-angiotensin III equivalent to that of 1-Sar-8-Ile-angiotensin II producing vascular blockade. This dose of 1-Sar-8-Ile-angiotensin II did not affect urinary aldosterone excretion, although it is most probable that higher doses of 1-Sar-8-Ile-angiotensin II would. This finding confirms the report by Bravo et al. (12) demonstrating the inability of 1-Sar-8-Ile-angiotensin II to block effectively aldosterone secretion in dogs. Our results also support the evidence demonstrating the inability of 1-Sar-8-Ile-angiotensin II to block aldosterone secretion in sodium-depleted rats (13) and rabbits (14). The converting enzyme inhibitor (CEI), Bothrops jararaca nonapeptide, in hypophysectomized, sodium-depleted rats causes a significant fall in aldosterone secretion (13). This peptide blocks the conversion of angiotensin I to angiotensin II, which is in turn converted to angiotensin III by aminopeptidases. The present study and data obtained in the presence of CEI (13) indicate that a peptide in the renin-angiotensin cascade beyond angiotensin I is responsible for the stimulation of the adrenal zona glomerulosa. Lowenstein et al. (21) have shown that, in rabbits on a sodium-restricted diet that have been immunized against angiotensin II, plasma aldosterone concentrations are higher than they are in normal rabbits and comparable to those in nonimmunized, sodium-depleted rabbits. Immunization against angiotensin II should not alter angiotensin III titers, allowing the heptapeptide to maintain plasma aldosterone concentration. Studies with 1-Sar-angiotensin II have shown that this peptide is resistant to degradation by plasma angiotensinases (22). One would expect that 1-Sar-8-Ile-angiotensin II would be resistant to N-terminal degradation to 7-Ile-angiotensin III and therefore would be a less effective adrenal cortical antagonist. Hence, 8-Ile-angiotensin II might be an effective blocker of angiotensin III, since this analogue could be degraded more readily to 7-Ile-angiotensin III. The binding of 3H-angiotensin II to the adrenal cortex is reduced by angiotensin III, 1-Sar-8-Ile-angiotensin II, 1-Sar-8-Ala-angiotensin II, and angiotensin II in that order of potency (23). The 1-Sar-substituted analogue of angiotensin II has been reported to have less steroidogenic activity in the adrenal cortex than does angiotensin II (15). These in vitro structure-activity studies suggest that the octapeptides possess less affinity for the adrenal zona glomerulosa receptors than do the heptapeptides angiotensin III and 7-Ile-angiotensin III.

The reactive increase in plasma renin activity observed during treatment with 1-Sar-8-Ile-angiotensin II should result in elevated concentrations of angiotensins. Blockade of the adrenal cortical receptor with 1-Sar-8-Ile-angiotensin II might require continuous incremental doses of antagonist to maintain the blockade.

In summary, we have presented evidence that the angiotensins play a role in the control of aldosterone secretion in the sodium-deprived rat and that 7-Ile-angiotensin III is a selective blocker of the angiotensins in the adrenal zona glomerulosa.

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