Cyclosporin A–Induced Hyperreninemic Hypoaldosteronism
A Model of Adrenal Resistance to Angiotensin II

NAFTALI STERN, SHMARIAHU LUSTIG, DAN PETRASEK, GERARD JENSEN,
PETER EGGENA, DAVID B. N. LEE, AND MICHAEL L. TUCK

SUMMARY We studied the effects of cyclosporin A on the renin-aldosterone axis in Sprague-Dawley rats. Two weeks of intragastric administration of cyclosporin A (5 mg/kg/day or 20 mg/kg/day) resulted in large increases in plasma renin concentration (23 ± 5, 70 ± 12, and 79 ± 11 ng/ml/hr in control rats and rats receiving 5 mg and 20 mg of cyclosporin A, respectively), with no parallel increments in plasma aldosterone. In vitro angiotensin II (ANG II)–stimulated aldosterone secretion by zona glomerulosa cells obtained from cyclosporin A–treated rats was also reduced (4.8 ± 0.5, 1.5 ± 0.2, and 0.2 ± 0.2 ng/10⁵ cells in control rats and rats receiving 5 mg and 20 mg of cyclosporin A, respectively). In contrast, in vitro aldosterone response to graded increments of potassium (3.7–10.7 mmol/L) or adrenocorticotropic hormone (ACTH) (10⁻¹⁰–10⁻⁸ M) was preserved in cyclosporin A–treated rats. When added in vitro to zona glomerulosa cells from untreated rats, cyclosporin A also attenuated ANG II–stimulated aldosterone secretion, but did not affect potassium or ACTH-mediated aldosterone production. Thus, cyclosporin A–induced hyperreninemic hypoaldosteronism in the rat depends on opposing renal and adrenal effects, with a direct or feedback stimulation of renin secretion and a specific blockade of ANG II–mediated aldosterone production.


KEY WORDS • cyclosporin • renin • aldosterone • angiotensin II • adrenocorticotropic hormone

C YCLOSPORIN A (CSA) therapy in humans has been occasionally associated with hyperkalemia, hyperchloremic acidosis, relative hypoaldosteronism, and reduced urinary excretion of potassium.¹⁴ The inappropriately normal aldosterone levels in hyperkalemic CSA-treated humans have been interpreted to reflect the coexisting relative hyporeninemia commonly observed in such patients.¹ In the rat, however, CSA administration appears to stimulate plasma renin activity (PRA).⁵⁻⁷ Yet in a recent study, hyperkalemia with relative hypoaldosteronism was observed in CSA-treated rats fed a high potassium diet.⁸ To date, the mechanism underlying CSA-related hypoaldosteronism has not been investigated.

A large body of evidence suggests that the control of aldosterone secretion is similar in humans and rats.⁹ In particular, the primacy of the renin-angiotensin axis in the physiological control of aldosterone has been demonstrated in both species.¹⁰,¹¹ In the present study, we examined the effect of CSA on the renin-aldosterone axis in vivo as well as its effect on in vitro aldosterone secretion and responsiveness to angiotensin II (ANG II), adrenocorticotropic hormone (ACTH), and potassium in the rat.

Materials and Methods

Rats
Ten-week-old male Sprague-Dawley rats (BK, Fremont, CA, USA) weighing 275 to 350 g were equilibrated in our research animal facility for 7 days before the initiation of any experimental procedures. The rats were allowed free access to tap water and food (Purina Rat Chow,Ralston Purina, St. Louis, MO, USA).
Experimental Protocols

In Vivo Experiments

In two separate experiments, rats received vehicle (pure olive oil, \( n = 15 \)) or CSA (powder) dissolved in olive oil at a dose of 5 mg/kg/day (CSA \( A \), \( n = 18 \)) or 20 mg/kg/day (CSA \( B \), \( n = 18 \)) via an orogastric tube. Following 14 days of vehicle or CSA administration, the rats were decapitated and their blood collected in prechilled tubes. Plasma was separated at 4°C and stored at –20°C until assayed for PRA, plasma renin concentration (PRC), inactive renin (IR), plasma renin substrate (PRS) and aldosterone. For measurement of renin activity (PRA, PRC, and IR), blood collected within the first 3 seconds of bleeding was used.

Immediately following decapitation, the rats' adrenal glands were rapidly removed and placed in ice-cold, 0.9% NaCl solution for subsequent preparation of zona glomerulosa cells.

In Vitro Aldosterone Secretion

In vitro secretion of aldosterone was measured using zona glomerulosa cells prepared from rats that had received either vehicle or CSA as described above. In an additional set of experiments, the effect of CSA added in vitro to prepared zona glomerulosa cells from normal, untreated rats was also examined.

Zona glomerulosa cell suspensions were prepared by the method of Williams et al. 10 In brief, freshly obtained adrenals were first decapsulated, and the capsular portions were preincubated for 50 minutes at 37°C in a modified (buffered) Krebs-Ringer solution containing collagenase (1.85 mg/ml), DNAse (0.025 mg/ml), l-glutamine (0.2 mg/ml), essential and nonessential amino acids (1.25% each, vol/vol) and 4% bovine serum albumin. The potassium concentration was 3.7 mmol/L. After preincubation, cells were filtered through a double layer of gauze and then centrifuged for 10 minutes at 750 g at room temperature. The supernatant was discarded, and the pellet containing the cells was washed twice in the Krebs-Ringer buffer. For the determination of aldosterone secretion rate, cells were resuspended in the same buffer to yield approximately 75,000 to 100,000 cells per milliliter (94 ± 2% of which were zona glomerulosa cells and the rest of which were fasciculata cells).

Two-milliliter aliquots of the cell suspension were incubated in triplicate with graded concentrations of ANG II, ACTH, and potassium. Cells were incubated for 1 hour at 37°C in a shaking-water bath at 50 oscillations per minute under 95% O\(_2\), 5% CO\(_2\). To examine the in vitro effect of CSA, the CSA was first dissolved for 1 hour at 37 °C in a shaking-water bath at 50 oscillations per minute under 95% O\(_2\), 5% CO\(_2\).

Analytical Methods

PRA was measured as described elsewhere 12 by incubation of plasma with a volume (1:10) of 1 M sodium phosphate buffer and angiotensinase inhibitors (pH 7.4) for 1 or 3 hours. Generated angiotensin I (ANG I) was determined by radioimmunoassay. 13 For the measurement of PRC ("active renin"), 50 \( \mu l \) of plasma was incubated for 3 hours at 37°C with 5 \( \mu l \) of 1 M sodium phosphate buffer and 250 \( \mu l \) of 24-hour nephrectomized rat plasma in the presence of angiotensinase inhibitors (pH 7.4). The amount of ANG I generated was determined by radioimmunoassay 12 and expressed as nanograms per milliliter per hour.

In the in vitro effect of CSA, the CSA was first dissolved for 1 hour at 37 °C in a shaking-water bath at 50 oscillations per minute under 95% O\(_2\), 5% CO\(_2\). Generated angiotensin I (ANG I) was determined by radioimmunoassay. 13 For the measurement of PRC ("active renin"), 50 \( \mu l \) of plasma was incubated for 3 hours at 37°C with 5 \( \mu l \) of 1 M sodium phosphate buffer and 250 \( \mu l \) of 24-hour nephrectomized rat plasma in the presence of angiotensinase inhibitors (pH 7.4). The amount of ANG I generated was determined by radioimmunoassay 12 and expressed as nanograms per milliliter per hour.

Results

The Effect of Cyclosporin A on the Renin-Aldosterone Axis in Vivo

The effects of 2 weeks of CSA therapy on the renin-aldosterone system are summarized in Table 1. Overall, PRA, PRC, and IR were higher in CSA-treated rats (\( p < 0.05-0.001 \)) than in the control rats. Although levels were generally higher in the CSA\( A \) rats, the differences between levels in the CSA\( A \) and CSA\( A \) rats reached statistical significance only for IR (\( p < 0.01 \)).

### Table 1: Plasma Renin Activity, Plasma Renin Concentration, Inactive Renin, Plasma Renin Substrate, Plasma Aldosterone, and Plasma Potassium in Control and Cyclosporin A-Treated Sprague-Dawley Rats

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control rats (( n = 7 ))</th>
<th>CSA( A ) rats (( n = 10 ))</th>
<th>CSA( B ) rats (( n = 11 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>5.5 ± 1.2</td>
<td>12.8 ± 3.4*</td>
<td>29.5 ± 8.5†</td>
</tr>
<tr>
<td>IR (ng/ml/hr)</td>
<td>23.4 ± 5.4</td>
<td>70.3 ± 12†</td>
<td>79.1 ± 10.8†</td>
</tr>
<tr>
<td>PRC (ng/ml/hr)</td>
<td>48.6 ± 6.6</td>
<td>77.0 ± 7.3†</td>
<td>101.4 ± 9.1†§</td>
</tr>
<tr>
<td>PRS (ng/ml)</td>
<td>1689 ± 278</td>
<td>1364 ± 170</td>
<td>1734 ± 126</td>
</tr>
<tr>
<td>PA (ng/dl)</td>
<td>8.0 ± 3.7</td>
<td>6.5 ± 1.6</td>
<td>7.4 ± 2.0</td>
</tr>
<tr>
<td>Plasma potassium</td>
<td>4.5 ± 0.3</td>
<td>4.5 ± 0.2</td>
<td>4.7 ± 0.3</td>
</tr>
</tbody>
</table>

Values are means ± SEM.

CSA\( A \) and CSA\( B \) = cyclosporin A (5 and 20 mg/kg/day, respectively); PRA = plasma renin activity; PRC = plasma renin concentration; IR = inactive renin; PRS = plasma renin substrate; PA = plasma aldosterone.

\*\( p < 0.05 \), \( \dagger p < 0.01 \), \( \S p < 0.001 \) compared to the control group, \( \& p < 0.05 \) compared to the CSA\( A \) group.
Considerable inter-rat variability existed with regard to PRS levels, but the mean values of control, CSA5, and CSA20 rats did not differ significantly. In contrast to the markedly elevated levels of PRA, PRC, and IR in CSA-treated rats, plasma aldosterone levels of the three experimental groups were not significantly different. Neither did plasma potassium levels for the three experimental groups differ significantly (see Table 1).

Effect of Cyclosporin A Therapy on Aldosterone Production by Zona Glomerulosa Cells in Vitro

Basal aldosterone secretion of zona glomerulosa cells obtained from the three experimental groups was comparable (4.9 ± 0.5, 5.4 ± 0.6, and 5.1 ± 0.3 ng/10^6 cells for control, CSA5, and CSA20 rats, respectively). However, ANG II–stimulated aldosterone secretion was reduced in zona glomerulosa cells obtained from CSA5 rats and completely blunted in cells from CSA20 rats (Figure 1). While potassium-mediated aldosterone secretion by zona glomerulosa cells from CSA-treated rats was also somewhat lower than that of control rats, the differences were small and did not attain statistical significance (Table 2). In addition, the aldosterone response to an incremental concentration of ACTH (10^{-11}–10^{-8} M) was not affected by CSA therapy (see Table 2).

Effect of Cyclosporin A Added in Vitro on Aldosterone Secretion from Zona Glomerulosa Cells

The effect of CSA on the dose-dependent aldosterone response to ANG II is depicted in Figure 2. Cyclosporin A (10^{-6} M) did not affect basal aldosterone secretion. In five experiments, mean basal aldosterone production was 9.3 ± 1.7 ng/10^6 cells and 10.4 ± 1.8 ng/10^6 cells in the absence and presence of CSA (10^{-6} M), respectively. ANG II elicited a significant increase in aldosterone production at the lowest concentration used (10^{-10} M), with the peak increment (12.9 ± 2.7 ng/10^6 cells; p < 0.01) observed at 10^{-9} M of ANG II. In the presence of CSA, however, the aldosterone response to ANG II at concentrations of 10^{-10} M was completely inhibited, and the peak increment was observed with 10^{-8} M of ANG II.

In contrast to the inhibitory effect of CSA on ANG II–mediated aldosterone secretion, CSA had no effect on potassium-stimulated aldosterone production (Table 3). The slopes of the potassium-aldosterone dose-response curves and the peak responses were not different in the absence or presence of CSA (10^{-6} M). Similarly, the aldosterone response to ACTH (see Table 3) was not affected by coincubation with CSA (10^{-6} M): neither the apparent threshold dose of ACTH nor the peak response was significantly

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**TABLE 2. The Effect of Cyclosporin A Treatment on the in Vitro Aldosterone Response to Potassium and ACTH**

<table>
<thead>
<tr>
<th>Secretagogue</th>
<th>Control rats</th>
<th>CSA20 rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.7 mmol/L</td>
<td>7.0 ± 1.3</td>
<td>5.8 ± 0.5</td>
</tr>
<tr>
<td>8.7 mmol/L</td>
<td>9.5 ± 1.6</td>
<td>9.5 ± 0.2</td>
</tr>
<tr>
<td>10.7 mmol/L</td>
<td>12.9 ± 3.0</td>
<td>9.8 ± 0.2</td>
</tr>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-11} M</td>
<td>17.2 ± 3.9</td>
<td>17.4 ± 2.8</td>
</tr>
<tr>
<td>10^{-10} M</td>
<td>17.8 ± 1.6</td>
<td>17.7 ± 3.8</td>
</tr>
<tr>
<td>10^{-9} M</td>
<td>19.3 ± 2.1</td>
<td>25.2 ± 1.4</td>
</tr>
<tr>
<td>10^{-8} M</td>
<td>33.9 ± 7.2</td>
<td>26.5 ± 0.5</td>
</tr>
</tbody>
</table>

Results are expressed as mean increments in aldosterone secretion rate ± SEM (ng/10^6 cells/hr). CSA20 = cyclosporin A (20 mg/kg/day).

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**TABLE 3. The Effect of Cyclosporin A Treatment on the in Vitro Aldosterone Response to Potassium and ACTH**

<table>
<thead>
<tr>
<th>Secretagogue</th>
<th>Control rats</th>
<th>CSA20 rats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.7 mmol/L</td>
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<td>5.8 ± 0.5</td>
</tr>
<tr>
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<td>9.5 ± 1.6</td>
<td>9.5 ± 0.2</td>
</tr>
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<tr>
<td>ACTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-11} M</td>
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</tr>
</tbody>
</table>

Results are expressed as mean increments in aldosterone secretion rate ± SEM (ng/10^6 cells/hr). CSA20 = cyclosporin A (20 mg/kg/day).
adrenal zona glomerulosa to ANG II and augment basal aldosterone secretion as well as aldosterone responsiveness.\(^5\) States of hyperreninemic hypoaldosteronism in which the elevation in renin secretion does not invoke an appropriate aldosterone response are encountered in cases of structural adrenal abnormality or with enzymatic deficiencies in the mineralocorticoid biosynthetic pathway.\(^21\) These conditions, however, entail generalized hyporesponsiveness of aldosterone secretion (e.g., to ANG II, ACTH, and potassium) rather than stimulus-specific refractoriness.\(^2\) Thus, observations in this study that CSA administration renders the zona glomerulosa resistant to ANG II but not to ACTH or potassium offer a unique model of hyperreninemic hypoaldosteronism. The hyperreninemia in CSA-treated rats may reflect, in part, adrenal hyporesponsivity to ANG II.

The evidence for CSA-related insensitivity to ANG II is threefold. First, the state of hyperreninemic hypoaldosteronism per se implies hyporesponsiveness to ANG II that cannot be accounted for by changes in serum potassium. Some evidence suggests that CSA stimulates ACTH secretion, thereby leading to elevated plasma corticosterone.\(^23\) Although chronic exposure to high levels of ACTH may cause a decrease in aldosterone secretion, this effect appears to depend on suppression of the renin-angiotensin axis.\(^24\) In the face of the marked stimulation of renin in CSA-treated rats, the possibility that hyperstimulation of ACTH by CSA precipitates relative hypoaldosteronism seems unlikely, but may not be excluded entirely.

Second, that hyperreninemic hypoaldosteronism in CSA-treated rats is induced by decreased adrenal sensitivity to ANG II is further supported by the observation that zona glomerulosa cells obtained from these rats show a blunted aldosterone response to graded increments of ANG II in vitro. Collectively, this finding and the apparent preservation of aldosterone responsivity to stimulation with potassium and ACTH suggest that CSA caused a specific reduction in ANG II–mediated responsiveness rather than a generalized hypofunction of the zona glomerulosa.

Third, the similarity between the stimulus-response profile of zona glomerulosa cells from CSA-treated rats and cells from untreated rats to which CSA has been added ex vivo suggests that CSA attenuates ANG II–stimulated aldosterone secretion directly rather than via extraadrenal mediators. In view of this information, stimulation of renin secretion (and, by inference, ANG II secretion) in CSA-treated rats may be necessary to maintain "normal" aldosterone levels.

The mechanism by which CSA affects zona glomerulosa function cannot be determined from our study. CSA is an extremely hydrophobic compound that readily penetrates cell membranes\(^25\) and may thus interfere with either membrane-receptor-related or postreceptor events. In human T cells, CSA blocks the in vitro expression of the interleukin-2 gene after the initial plasma-membrane-associated events of activation.\(^26\) It is noteworthy that, by current models, the in vitro requirements for both activation of the ANG II pathway in zona glomerulosa cells\(^27\) and stimulation of

### Table 3. The In Vitro Effect of Cyclosporin A (10^{-6} M) on Potassium- and ACTH-Stimulated Aldosterone Production by Zona Glomerulosa Cells

<table>
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<tr>
<th>Secretagogue</th>
<th>Control rats</th>
<th>CSA, 10^{-6} M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.7 mmol/L</td>
<td>15.4 ± 6.6</td>
<td>9.6 ± 2.6</td>
</tr>
<tr>
<td>8.7 mmol/L</td>
<td>29.0 ± 8.1</td>
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<td>10.7 mmol/L</td>
<td>24.1 ± 5.3</td>
<td>19.4 ± 6.2</td>
</tr>
<tr>
<td>ACTH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10^{-10} M</td>
<td>23.2 ± 4.2</td>
<td>23.5 ± 5.1</td>
</tr>
<tr>
<td>10^{-9} M</td>
<td>47.1 ± 2.2</td>
<td>40.8 ± 10.1</td>
</tr>
<tr>
<td>10^{-8} M</td>
<td>35.7 ± 4.0</td>
<td>41.1 ± 7.4</td>
</tr>
</tbody>
</table>

Results are expressed as the mean increments from baseline aldosterone secretion rate ± SEM (ng aldosterone/10^6 cells/hr).

CSA = cyclosporin A.

Discussion

This study provides evidence that CSA administration had a dichotomous effect on renin and aldosterone secretion in the rat. The disproportional increase of PRA in CSA-treated rats in the absence of a parallel rise in plasma aldosterone levels resulted in relative hyperreninemic hypoaldosteronism. Since the increased PRA levels were not accompanied by changes in plasma angiotensinogen (i.e., PRS), the higher PRA in CSA-treated rats can be taken to reflect stimulation of renin secretion rather than substrate-dependent kinetic alteration in the renin reaction. The concomitant rise in PRC, which represents renin activity in the presence of excess substrate, further supports the notion of stimulated renin secretion in rats given CSA. Also, the parallel rise in trypsin-activatable renin (IR), PRC, and/or PRA is compatible with chronic stimulation of the renin-angiotensin system such as is seen during sodium restriction or mineralocorticoid deficiency.\(^16\) However, the possibility that the enhanced renin secretion reflects feedback stimulation in response to CSA-induced inhibition of converting enzyme activity and, consequently, low ANG II levels, cannot be excluded from our data. Overall, our findings are in agreement with previous reports that CSA therapy is associated with increased PRA in the rat\(^3\) and dog,\(^7\) and that CSA directly enhances the secretion of renin in vitro.\(^18\) The effect of CSA treatment on PRA is at variance with reports in humans.\(^1-4\) where PRA levels are low- to high-normal. However, the simultaneous effects of hypervolemia, glucocorticoids, β-blockers, and CSA on the renin-aldosterone axis in many CSA-treated patients complicates the interpretation of any comparisons to our study. Possible interspecies differences may also be involved.

The renin-angiotensin system is the major physiological regulator of aldosterone secretion. Increased circulatory levels of ANG II normally sensitize the adrenal zona glomerulosa to ANG II and augment basal aldosterone secretion as well as aldosterone responsiveness.\(^5\) States of hyperreninemic hypoaldosteronism in which the elevation in renin secretion does not invoke an appropriate aldosterone response are encountered in cases of structural adrenal abnormality or with enzymatic deficiencies in the mineralocorticoid biosynthetic pathway.\(^21\) These conditions, however, entail generalized hyporesponsiveness of aldosterone secretion (e.g., to ANG II, ACTH, and potassium) rather than stimulus-specific refractoriness.\(^2\) Thus, observations in this study that CSA administration renders the zona glomerulosa resistant to ANG II but not to ACTH or potassium offer a unique model of hyperreninemic hypoaldosteronism. The hyperreninemia in CSA-treated rats may reflect, in part, adrenal hyporesponsivity to ANG II.

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interleukin-2 production by human T cells can be fulfilled by the combination of a rise in intracellular calcium and the presence of phorbol myristate acetate. Therefore, the possibility that CSA inhibits the aldosterone response to ANG II by interfering with signalling events in zona glomerulosa cell activation, as has been demonstrated in human T cells, merits direct investigation. Because of its selective effect on ANG II–mediated activation, CSA may serve as a useful probe in the study of regulatory steps involved in aldosterone secretion.

Acknowledgments

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