19-Nor-deoxycorticosterone Production From Aldosterone-Producing Adenomas

Sami T. Azar and James C. Melby

19-Nor-deoxycorticosterone (19-nor-DOC), a hypertensinogenic mineralocorticoid, equipotent with aldosterone and independent of the renin-angiotensin system, is synthesized in the kidney and excreted in excess in the urine of patients with aldosterone-producing adenomas. This current study evaluated the adrenal and renal venous levels of aldosterone and 19-nor-DOC after adrenal and renal venous catheterization and blood sampling in five patients with aldosterone-producing adenomas. Aldosterone (mean±SEM) in the adrenal vein ipsilateral to the tumor (469±293 ng/dl) was higher than in the contralateral vein (70±59 ng/dl). 19-Nor-DOC (mean±SEM) was also higher in the ipsilateral (548±286 ng/dl) than in the contralateral (51±14 ng/dl) adrenal vein. In the renal veins, ipsilateral aldosterone (2.2±0.8 ng/dl) and 19-nor-DOC (12.2±2.4 ng/dl) were respectively similar to contralateral aldosterone (1.5±0.5 ng/dl) and 19-nor-DOC (14.6±1.3 ng/dl), whereas 19-nor-DOC was higher than aldosterone in each renal vein. The present study demonstrates that 19-nor-DOC is produced, not only from the kidneys, but also from the ipsilateral adrenal of patients with aldosterone-producing adenomas. The ipsilateral adrenal 19-nor-DOC production is comparable to that of aldosterone, suggesting that 19-nor-DOC may be contributing to the hypertension and hypokalemia in this disease. In the contralateral adrenal, aldosterone is suppressed to a greater extent than 19-nor-DOC, suggesting that these two steroids are under the influence of two different regulatory mechanisms.

KEY WORDS • aldosterone • adenoma • hyperaldosteronism • deoxycorticosterone • endocrine hypertension

Excessive aldosterone production is believed to be the underlying cause of primary aldosteronism. However, nonaldosterone mineralocorticoids such as deoxycorticosterone (DOC) and 18-hydroxy-DOC have been reported to be elevated in some patients with primary aldosteronism, which is a disease associated with hypertension, hypokalemia, and suppressed renin. Both DOC and 18-hydroxy-DOC are relatively weak mineralocorticoids and are unlikely to play a significant role in the pathophysiology of this disease. 19-Nor-deoxycorticosterone (19-nor-DOC), a potent mineralocorticoid, was found to be elevated in the urine of these patients at levels proportional to those of aldosterone.1 19-Nor-DOC, which is not normally present in the adrenal gland, is synthesized from DOC by a series of adrenal oxidative reactions at the 19 position to form 19-oxo-DOC and 19-oic-DOC, which serve as precursors for its synthesis in the kidney.2•3 However, the site of 19-nor-DOC production in patients with primary aldosteronism is not known, and it is not clear whether it is solely synthesized in the kidneys. The present study was designed to evaluate the extent of 19-nor-DOC production and the site of its production in patients with primary aldosteronism due to aldosterone-producing adrenal adenomas (APA).

Methods

Five patients, two men and three women, aged 39–52 years, were examined and a diagnosis of APA was formed based on their presentation with hypertension and hypokalemia together with low serum renin, elevated plasma aldosterone, and high urinary tetra-hydroaldosterone. The diagnosis of APA was confirmed by radiologic methods (computed tomography scan or magnetic resonance imaging of adrenals) followed by surgical and pathological findings after adrenalectomy. Two right and three left adrenal tumors were found in the five patients. Before surgery, all patients gave consent for bilateral adrenal vein sampling after venous catheterization as described earlier.4 Blood was collected from the ipsilateral and the contralateral tumor sites, and plasma aldosterone5 and 19-nor-DOC6 were determined. All the procedures were uneventful and without any complications.

Statistics

Data, expressed as mean±SEM, were analyzed by two-way analysis of variance followed by a Scheffe's test. For multiple comparison, p<0.05 was considered significant.

Results

In the adrenal vein ipsilateral to the tumor, aldosterone (469±293 ng/dl) was higher than in the contralat-
**TABLE 1.** Aldosterone and 19-Nor-deoxycorticosterone in Adrenal and Renal Veins of Patients With Aldosterone-Producing Adrenal Adenomas

<table>
<thead>
<tr>
<th>Site of venous sampling</th>
<th>Aldosterone (ng/dl)</th>
<th>19-nor-DOC (ng/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>469±293</td>
<td>548±286</td>
</tr>
<tr>
<td>Contralateral</td>
<td>70±59</td>
<td>51±14</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsilateral</td>
<td>2±1</td>
<td>12±2*</td>
</tr>
<tr>
<td>Contralateral</td>
<td>2±0</td>
<td>14±1*</td>
</tr>
</tbody>
</table>

Values given are mean±SEM. Aldosterone and 19-nor-deoxycorticosterone (19-nor-DOC) concentration in the adrenal and renal veins ipsilateral and contralateral to the aldosterone-producing adrenal adenomas (n=5).

*p<0.05 comparing 19-nor-DOC with aldosterone levels.

19-nor-DOC, a potent mineralocorticoid, was first isolated from the urine of rats with adrenal regeneration hypertension. It is hypertensinogenic and has a high affinity to mineralocorticoid receptors. DOC, 19-hydroxy-DOC, 19-oxo-DOC, and 19-oic-DOC serve as precursors for 19-nor-DOC. This steroid is not produced by the adrenal cortex but is synthesized by the kidney. We have previously demonstrated that cultured inner medullary collecting duct cells can synthesize 19-nor-DOC from its adrenal precursors. However, in the present study, we showed that patients with APA secrete 19-nor-DOC not only from the kidneys but also from the APA. This suggests that the tumor cells, in contrast to normal adrenal cells, possess the capacity of converting 19-oxo-DOC and 19-oic-DOC to 19-nor-DOC.

Griffing et al demonstrated that patients with primary aldosteronism have elevated urinary free 19-nor-DOC. They found that the urinary free 19-nor-DOC positively correlated with aldosterone secretion rate. This is consistent with our findings that 19-nor-DOC and aldosterone are secreted in the adrenal veins of APA at comparable levels. Therefore, it can be inferred from the fact that 19-nor-DOC and aldosterone have similar mineralocorticoid activities in vitro and comparable levels in vivo in patients with APA that 19-nor-DOC may have a significant biologic effect in this disorder. Both aldosterone and 19-nor-DOC share DOC as a common precursor, which implies that increased synthesis of DOC in APA may result in high quantities available for 19-nor-DOC production. 19-Nor-DOC synthesis is independent of the renin-angiotensin system and is largely influenced by corticotropin secretion. It was demonstrated that corticotropin enhances the production of 19-nor-DOC, whereas dexamethasone suppresses its production. Moreover, an alteration in sodium balance was found to have a minimal effect on 19-nor-DOC production. The fact that in the contralateral adrenal, aldosterone is suppressed to a greater extent than 19-nor-DOC suggests that these two steroids are under the influence of two different regulatory mechanisms.

19-Nor-DOC, which could never be detected in plasma of normal individuals, was measured in both the ipsilateral and the contralateral veins of the adrenal adenomas. This finding illustrates a unique situation where 19-nor-DOC could be measured in the peripheral blood using radioimmunoassay techniques.

The fact that the 19-nor-DOC level in each renal vein was higher than that of aldosterone suggests that the kidney, in addition to the adrenal adenoma, was producing 19-nor-DOC from its adrenal precursors. In conclusion, the present study demonstrates increased 19-nor-DOC production from adrenals of patients with APA. Since aldosterone and 19-nor-DOC have similar mineralocorticoid activities and are secreted at comparable doses, it is likely that 19-nor-DOC contributes to the hypertension and the hypokalemia in this adrenal disorder.

**References**

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