Effect of progesterone on renal sodium handling in man: relation to aldosterone excretion and plasma renin activity

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Summary

1. The effect of progesterone on renal haemodynamics and intrarenal sodium handling was evaluated in thirteen normal men on a constant diet. Clearances were measured during maximal water diuresis and again 4–7 days later, this time 3 h after progesterone was given intramuscularly. Seven additional studies were performed 3 days after progesterone administration. Another four tests were performed on volunteers who had manifested renal 'escape' from the sodium-retaining effect of deoxycorticosterone acetate.

2. In acute progesterone studies glomerular filtration rate was unchanged, whereas effective renal plasma flow increased, so that filtration fraction decreased significantly. A similar increase in urinary sodium occurred whether subjects received a low or high sodium diet. Indices which related to the distal delivery of filtrate (fractional urine flow and the sum of fractional free water and sodium clearances) increased significantly in both groups. The progesterone-induced increase in sodium excretion was not related to changes in plasma renin activity, renin substrate or urinary aldosterone. After 3 days of progesterone, the increase of sodium excretion was less than in the acute studies and urinary aldosterone increased two- to four-fold. Progesterone failed to produce an acute increase in urinary sodium in subjects hyperexpanded by administration of exogenous mineralocorticoids.

3. Results suggest that the acute natriuretic action of progesterone is in part independent of aldosterone inhibition and that progesterone may inhibit sodium reabsorption at proximal as well as distal sites in the nephron.

Key words: free water clearance, glomerular filtration, natriuresis, progesterone, renal plasma flow, renin activity, renin substrate.

Introduction

Administration of progesterone to normal man produces a natriuresis (Landau, Bergenstal, Lugibihl & Kascht, 1955). Since the saliuretic effect of the hormone was apparent only in the presence of intact adrenal function or exogenous mineralocorticoid (Loeb, Atchley, Ferrebee & Ragan, 1939; Landau, Lugibihl, Bergenstal & Dimick, 1957; Landau & Lugibihl, 1958), the action of progesterone on the kidney was originally ascribed to competitive inhibition of aldosterone (Landau & Lugibihl, 1958; Sharp & Leaf, 1966). The inhibition of the sodium-retaining effect of infused aldosterone or deoxycorticosterone which has been observed after administration of progesterone to adrenal-deficient patients and to rats is also consistent with this hypothesis (Landau & Lugibihl, 1958; Kagawa, 1958; Landau, 1973). However, progesterone also has vasodilator properties (Kumar, 1963), including renal haemodynamic effects (Chesley & Tepper,
1967), which in themselves may influence renal sodium excretion. Therefore experiments were designed to assess the acute and chronic effect of administered progesterone on glomerular filtration rate, renal plasma flow, renal sodium handling and the renin–angiotensin–aldosterone system in normal man.

Methods

Twenty-eight studies were performed in the Clinical Research Center of the University of Chicago on thirteen normotensive male volunteers, each of whom gave informed consent to participate in the study. Male subjects were chosen to avoid cyclic changes in endogenous oestrogen and progesterone secretion. Their ages ranged from 22 to 44 years, and none had signs or symptoms of cardiac, renal or endocrine disease. Each study began at 06.30 hours after an overnight fast, at which time the subject drank tap water (20 ml/kg body weight) and then assumed a supine posture in bed. When a diuresis occurred, it was maintained by oral replacement in volumes equal to urinary losses. Appropriate priming doses of inulin and sodium p-aminomhippurate were given, and constant infusions of these substances (containing 96 mg/ml inulin and 92–115 mmol/ml PAH\(^{(1)}\) in 150 mmol/l sodium chloride) were started and maintained at a rate of 0-6 ml/min with a Harvard infusion pump. When stable and maximal urine flow was achieved, three to five successive collections of 20–40 min each were made. Each collection was terminated by voluntary voiding. The subject stood, completed voiding in less than 1 min, and remained supine throughout the rest of the study. To minimize postural effects of renin release, blood samples for measurement of inulin, PAH, osmolality, sodium, potassium, renin activity and renin substrate were obtained after the subject had been supine for at least 30 min. Aliquots of urine were analysed for sodium, potassium, osmolality, inulin, PAH and aldosterone.

Clearance studies

Clearance studies were performed on subjects in four protocols.

I. Low salt–acute progesterone. Eight subjects consumed a constant diet containing between 13 and 40 mmol of sodium and 80–120 mmol of potassium per day. After 7–10 days of the diet the initial clearance test (control, C) was performed. Four to 7 days later, a second study (experimental, E) was performed 3 h after administration intramuscularly of 310 \(\mu\)mol of progesterone in oil (Prolutin, Schering Corp., Bloomfield, N.J., U.S.A.). Three subjects were studied again on several occasions, and in two the order of the studies was reversed. One subject who was studied three times received a standard hospital sodium-restricted diet during the first two studies and a constant metabolic sodium restricted diet during the third. Progesterone was administered 1, 3 and 6 h before each experiment. Results were similar on all three occasions. Another subject who was studied twice received 620 \(\mu\)mol of progesterone during the second test. The natriuresis was similar each time.

II. High salt–acute progesterone. Six studies were performed in five volunteers (including four of the subjects who participated in protocol I), on a constant diet containing 240 mmol of sodium/day. Potassium content remained unchanged.

III. Low and high salt–3 day progesterone. Five subjects who were consuming constant diets completed seven clearance studies after receiving progesterone (155 \(\mu\)mol intramuscularly twice daily for 3 days). Dietary sodium content ranged from 20 to 40 mmol/day during four studies and was 240 mmol/day during the remaining three. Progesterone was not administered until balance conditions prevailed. The clearance procedure was performed the morning of the fourth day. Potassium content was constant as described.

IV. High salt–deoxycorticosterone acetate. Four subjects whose diets contained 240 mmol of sodium and 80–120 mmol of potassium/day received DOCA in oil (Percorten acetate, Ciba), 26 \(\mu\)mol intramuscularly twice daily for 5–8 days, until ‘escape’ was achieved as assessed by stabilization of weight and a return of urinary sodium excretion to values obtained before mineralocorticoid administration. Clearance studies were performed before initiation of treatment and again after DOCA escape had occurred. DOCA administration was continued, and 3 days later a third study was performed 3 h after progesterone (310 \(\mu\)mol) had been administered intramuscularly and 3 h after the last dose of DOCA. Daily weights, blood pressure and 24 h urine collections were obtained throughout protocols III and IV.

\(^{(1)}\) Abbreviations: PAH, sodium p-aminomhippurate; DOCA, deoxycorticosterone acetate; ERPF, effective renal plasma flow; GFR, glomerular filtration rate.
Determinations

Serum and urinary sodium and potassium were measured with an I.L. flame photometer. Osmolality was measured with either an Advanced Instruments or Fiske osmometer. Inulin and PAH were determined by modifications of the anthrone (Davidson & Sackner, 1963) and diazotization (Smith, Finkelstein, Aliminosa, Crawford & Graeber, 1945) methods. Urinary aldosterone was measured by a modification (Ehrlich, 1966) of the double-isotope derivative technique of Kliman & Peterson (1960). Large urine volumes from each clearance period were concentrated in a flash evaporator before hydrolysis and extraction. Plasma renin activity (Haber, Koerner, Page, Kliman & Purnode, 1969) was measured by radioimmunoassay. Renin substrate was determined by measuring the angiotensin I generated by adding exogenous human renin to EDTA-treated plasma (Krakoff, 1973).

Glomerular filtration rate was calculated from the clearance of inulin; effective renal plasma flow from the clearance of PAH. Osmolal (Cosm.), free water (Cw), and sodium (CN) net and fractional clearances were calculated from standard formulae. Distal sodium delivery during water diuresis was calculated from the sum of CN and Cw, and the fractional distal sodium reabsorption was derived from the formula Cw/(CN + Cw). Statistical analyses were performed by comparing results of the experimental and control studies by the paired Student’s t-test. Results for grouped data are presented as mean value ± SEM.

Results

I. Low salt–acute progesterone

Acute effects of progesterone on renal function and intrarenal sodium handling in eleven studies are summarized in Table 1. Changes in GFR varied, resulting in similar mean values in control (136 ± 3.8 ml/min) and progesterone (133 ± 4.8 ml/min) experiments. ERPF increased in nine of eleven studies from a mean value of 600 ± 15.9 ml/min to 689 ± 41.8 ml/min (P < 0.025). Progesterone consistently produced an increase in sodium excretion (mean ± 80.4 ± 15.9 μmol/min; P < 0.001). Mean urinary potassium decreased in seven of eleven experiments, but the changes were not statistically significant. Fractional urine flow (V/GFR) and the percentage of filtered sodium delivered distally (Cw + CN/GFR) increased in ten of eleven experiments. The increments averaged 1.8 ± 0.4 ml/100 ml GFR (P < 0.001) and 2.3 ± 0.7 ml/100 ml GFR (P < 0.005) respectively. Fractional sodium reabsorption decreased in the distal nephron, as indicated by the decrease in Cw/(CN + Cw) which occurred in every study (C = 0.93 ± 0.02; E = 0.89 ± 0.02; P < 0.001).

Table 2 summarizes the response of plasma renin activity, renin substrate concentration and urinary aldosterone excretion to acute progesterone administration in seven studies. Plasma renin activity decreased in six of seven studies from a mean value of 0.99 ± 0.15 pmol h⁻¹ ml⁻¹ to 0.74 ± 0.08 pmol h⁻¹ ml⁻¹ (P < 0.05). Plasma renin substrate concentration did not change (C = 1448 ± 106 pmol/ml; E = 1390 ± 86 pmol/ml) in response to progesterone. Urinary aldosterone excretion increased during each study from a mean value of 18 ± 1.6 pmol/min to 27.5 ± 5.4 pmol/min (P < 0.01).

II. High salt–acute progesterone

Table 1 summarizes the acute effects of progesterone on renal function and intrarenal sodium handling in six studies. Changes were similar in direction and magnitude to those seen during sodium restriction. GFR remained unchanged, whereas ERPF increased from a mean value of 669 ± 49.1 ml/min to 762 ± 36.1 ml/min (P < 0.001). Urinary sodium excretion increased in all cases, and the increase was similar to that observed in the subjects ingesting a low salt diet (mean 106 ± 24.3 μmol/min on high salt intake vs. 80.4 ± 15.9 μmol/min on low salt intake; P < 0.7). Both V/GFR and (Cw + CN)/GFR increased consistently by a mean value of 2.4 ± 0.5 ml/100 ml GFR (P < 0.005) and 2.4 ± 0.5 ml/100 ml GFR (P < 0.005) respectively. Cw/(CN + Cw) decreased in five of six studies (C = 0.88 ± 0.04; E = 0.86 ± 0.03; P < 0.02). Alterations in plasma renin activity were variable, with similar mean values in control (0.32 ± 0.07 pmol h⁻¹ ml⁻¹) and experimental (0.42 ± 0.08 pmol h⁻¹ ml⁻¹) studies (Table 2). Base-line values were lower (0.32 ± 0.07 vs. 0.99 ± 0.15 pmol h⁻¹ ml⁻¹) than in the low salt series. Plasma renin substrate concentration did not change (C = 1508 ± 174 pmol/ml; E = 1423 ± 220 pmol/ml) after progesterone. Urinary aldosterone excretion increased in four studies and remained constant in one (C = 10.8 ± 2.7 pmol/min; E = 14.8 ± 4.3 pmol/min; not significant).
<table>
<thead>
<tr>
<th>Protocol</th>
<th>n</th>
<th>GFR (ml/min)</th>
<th>ERPF (µmol/min)</th>
<th>UNa/V (mmol/l)</th>
<th>SNa (mmol/l)</th>
<th>SK (ml/min)</th>
<th>V/GFR (ml/100 ml GFR)</th>
<th>Cwater + CNa (GFR)</th>
<th>Cwater + CNa (GFR)</th>
<th>Cwater + CNa (GFR)</th>
<th>Uosm. (mosmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Control</td>
<td>11</td>
<td>136±3.8</td>
<td>600±15.9</td>
<td>120±21.2</td>
<td>138±0.9</td>
<td>4.1±0.03</td>
<td>11.9±1.0</td>
<td>10.8±1.0</td>
<td>9.1±1.0</td>
<td>0.93±0.02</td>
<td>63.9±5.6</td>
</tr>
<tr>
<td>Experimental</td>
<td>11</td>
<td>133±4.8</td>
<td>689±41.8</td>
<td>200±31.4</td>
<td>138±0.9</td>
<td>4.2±0.09</td>
<td>13.7±1.9</td>
<td>12.6±1.2</td>
<td>11.4±1.3</td>
<td>0.89±0.02</td>
<td>74.2±6.2</td>
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<tr>
<td>P (C vs. E)</td>
<td>N.S.</td>
<td>&lt;0.025</td>
<td>&lt;0.001</td>
<td>N.S.</td>
<td>N.S.</td>
<td>&lt;0.01</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>&lt;0.001</td>
<td>&lt;0.05</td>
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</tr>
<tr>
<td>II. Control</td>
<td>6</td>
<td>136±3.2</td>
<td>669±49.1</td>
<td>248±30.1</td>
<td>137±1.0</td>
<td>4.3±0.2</td>
<td>14.9±1.5</td>
<td>14.1±1.2</td>
<td>12.3±1.1</td>
<td>0.88±0.04</td>
<td>66.2±4.6</td>
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<tr>
<td>Experimental</td>
<td>6</td>
<td>136±2.7</td>
<td>762±36.1</td>
<td>354±30.4</td>
<td>137±0.7</td>
<td>4.2±0.1</td>
<td>17.5±1.6</td>
<td>16.5±1.1</td>
<td>14.7±1.1</td>
<td>0.86±0.03</td>
<td>65.2±4.6</td>
</tr>
<tr>
<td>P (C vs. E)</td>
<td>N.S.</td>
<td>&lt;0.001</td>
<td>&lt;0.005</td>
<td>N.S.</td>
<td>N.S.</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>&lt;0.005</td>
<td>&lt;0.02</td>
<td>N.S.</td>
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<tr>
<td>III. Low salt(1)</td>
<td>4</td>
<td>128±5.4</td>
<td>600±34.6</td>
<td>118±39.6</td>
<td>136±0.4</td>
<td>4.1±0.04</td>
<td>12.3±2.2</td>
<td>12.2±1.7</td>
<td>10.4±1.7</td>
<td>0.93±0.04</td>
<td>62.3±9.3</td>
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<tr>
<td>Control</td>
<td>4</td>
<td>134±7.5</td>
<td>653±47.6</td>
<td>210±57.1</td>
<td>136±6.8</td>
<td>4.3±0.05</td>
<td>15.3±3.0</td>
<td>14.6±2.2</td>
<td>12.6±2.1</td>
<td>0.91±0.03</td>
<td>70.0±8.5</td>
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<tr>
<td>Acute progesterone</td>
<td>4</td>
<td>124±6.5</td>
<td>628±38.0</td>
<td>126±8.6</td>
<td>136±4.8</td>
<td>4.2±0.03</td>
<td>12.9±2.1</td>
<td>13.2±1.2</td>
<td>10.7±1.2</td>
<td>0.92±0.03</td>
<td>71.0±6.5</td>
</tr>
<tr>
<td>3 day progesterone</td>
<td>4</td>
<td>132±5.6</td>
<td>634±30.8</td>
<td>218±25.4</td>
<td>137±1.2</td>
<td>4.4±0.3</td>
<td>12.7±0.67</td>
<td>12.4±0.2</td>
<td>10.6±0.2</td>
<td>0.89±0.01</td>
<td>67.3±8.1</td>
</tr>
<tr>
<td>High salt(1)</td>
<td>3</td>
<td>134±5.6</td>
<td>634±30.8</td>
<td>218±25.4</td>
<td>137±1.2</td>
<td>4.4±0.3</td>
<td>12.7±0.67</td>
<td>12.4±0.2</td>
<td>10.6±0.2</td>
<td>0.89±0.01</td>
<td>67.3±8.1</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>132±1.6</td>
<td>728±21.1</td>
<td>342±40.9</td>
<td>136±1.0</td>
<td>4.3±0.1</td>
<td>15.6±0.98</td>
<td>15.5±0.4</td>
<td>13.6±0.6</td>
<td>0.86±0.06</td>
<td>66.3±7.4</td>
</tr>
<tr>
<td>Acute progesterone</td>
<td>3</td>
<td>132±2.7</td>
<td>738±24.0</td>
<td>285±24.3</td>
<td>135±6.8</td>
<td>4.6±0.1</td>
<td>14.1±2.0</td>
<td>14.3±1.4</td>
<td>12.3±1.6</td>
<td>0.87±0.06</td>
<td>70.7±9.7</td>
</tr>
</tbody>
</table>

(1) Statistical assessment was done only on groups involving five or more experiments.
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Table 2. Renin-angiotensin-aldosterone system in protocols I-III

<table>
<thead>
<tr>
<th>Protocol</th>
<th>n</th>
<th>Renin activity (pmol h⁻¹ ml⁻¹)</th>
<th>Renin substrate (pmol/ml)</th>
<th>Aldosterone excretion (pmol/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Control</td>
<td>7</td>
<td>0.99±0.15</td>
<td>1448±106</td>
<td>18.09±1.62</td>
</tr>
<tr>
<td>Experimental</td>
<td>P(C vs. E)</td>
<td>&lt;0.05</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>II. Control</td>
<td>5</td>
<td>0.32±0.070</td>
<td>1508±174</td>
<td>10.8±2.7</td>
</tr>
<tr>
<td>Experimental</td>
<td>P(C vs. E)</td>
<td>N.S.</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>III. Low salt</td>
<td>4</td>
<td>1.26±0.22</td>
<td>1480±153</td>
<td>17.3±2.16</td>
</tr>
<tr>
<td>High salt</td>
<td>3</td>
<td>0.32±0.12</td>
<td>1508±224</td>
<td>10.8±2.7</td>
</tr>
<tr>
<td>Acute progesterone</td>
<td>4</td>
<td>1.13±0.36</td>
<td>1426±111</td>
<td>26.7±6.21</td>
</tr>
<tr>
<td>3 day progesterone</td>
<td>4</td>
<td>5.04±0.84</td>
<td>1600±173</td>
<td>45.4±10.00</td>
</tr>
<tr>
<td>Control</td>
<td>3</td>
<td>0.36±0.14</td>
<td>1569±168</td>
<td>14.3±3.2</td>
</tr>
<tr>
<td>Acute progesterone</td>
<td>3</td>
<td>1.96±0.49</td>
<td>1423±133</td>
<td>29.4±11.6</td>
</tr>
</tbody>
</table>

(1) Statistical assessment was done only on groups involving five or more experiments.

The use of solute excretion and free water generation during these studies as indices of tubular sodium handling is predicated on the assumption that antidiuretic hormone was maximally suppressed during each study. Urinary osmolality averaged 65±6 mosmol/kg during control and 74±6 mosmol/kg during experimental studies (P<0.05) in protocol I and 66±5 mosmol/kg during control and 65±5 mosmol/kg during experimental studies (not significant) in protocol II, demonstrating adequate suppression of antidiuretic hormone. The small increases in Uₜₐₚ during the low sodium–progesterone studies in protocol I can be attributed to fractional decreases in solute reabsorption at the diluting site, rather than to enhanced back diffusion of water secondary to secretion of antidiuretic hormone, which would have caused a decrease in free water clearance.

III. Low and high salt–3 day progesterone

The four volunteers who received progesterone for 3 days while ingesting a low sodium diet lost an average of 1.2 kg; the three on a high sodium diet lost an average of 0.9 kg. Blood pressure did not change.

Table 1 summarizes the effects of 3 days of progesterone administration on renal clearances of subjects receiving either low or high sodium intake. In both groups, changes in urinary sodium excretion were absent or considerably smaller than those observed when the hormone was administered acutely. In several instances the changes in renal haemodynamics and the fractional excretion of solutes and water were also less marked. The changes in the renin–angiotensin–aldosterone system of the same subjects in response to 3 days of progesterone administration are presented in Fig. 1 and Table 2. Plasma renin activity increased from a mean of 1.26±0.22 pmol h⁻¹ ml⁻¹ to 5.04±0.84 pmol h⁻¹ ml⁻¹ (P<0.01) in the four sodium-restricted subjects and from 0.32±0.12 pmol h⁻¹ ml⁻¹ to 1.96±0.49 pmol h⁻¹ ml⁻¹ (P<0.02) in the three volunteers receiving a high sodium intake. Plasma renin substrate concentration (mean C=1480±153 pmol/ml; E=1600±173 pmol/ml on low sodium and C=1508±224 pmol/ml; E=1423±133 pmol/ml on high sodium) did not change. Urinary aldosterone excretion increased from a mean of 17.3±2.16 pmol/min to 45.4±10.00 pmol/min (P<0.01) in the sodium-restricted subjects and from 11.1±2.7 pmol/min to 29.4±11.6 pmol/min (P<0.05) in subjects on high sodium intake.

IV. High salt–DOCA

Results of studies in which progesterone was given to four volunteers who had ‘escaped’ from the renal
subject, while \( \frac{C_{\text{water}}}{C_{\text{water}} + C_{\text{Na}}} \) decreased in every instance. Renal function after DOCA escape was quite variable and steady-state conditions were difficult to achieve. Still, progesterone administration to subjects in whom sodium retention was a consequence of exogenous mineralocorticoid treatment failed to increase sodium excretion. Since the volunteers ingested high sodium diets, plasma renin activity and urinary aldosterone were suppressed during all phases of the study. Plasma sodium and potassium concentrations were similar during each stage, and blood pressure did not change after DOCA administration.

### Discussion

In the present study, sodium excretion increased 3 h after the administration of progesterone to normal subjects on either low or high sodium intake. These observations confirm previous reports demonstrating the natriuretic effect of progesterone in man (Landau et al., 1955; Landau & Lugibihl, 1958) and the clearance data extend the work of others by providing evidence that progesterone inhibits sodium reabsorption in the proximal tubule. In addition, the results suggest that the saluretic effect of progesterone may occur through mechanisms other than its known competitive inhibition of aldosterone.

During maximal water diuresis, changes in the excretion of solutes and free water may be used as indices of sodium handling in specific areas of the nephron. Alterations in fractional urine flow or in the sum of the clearances of sodium and free water per unit of GFR relate reciprocally to changes in fractional sodium reabsorption in the proximal tubule. Similarly, the net reabsorption of filtered solute at diluting sites determines absolute free

### Table 3. Renal function and sodium handling in protocol IV

DOCA = experiment performed after 'escape' occurred; DOCA + progesterone = progesterone after 'escape' occurred. Abbreviations used are defined in Table 1.

<table>
<thead>
<tr>
<th>Protocol</th>
<th>( n )</th>
<th>GFR (ml/min)</th>
<th>( U_{\text{Na}} ) (( \mu \text{mol} )/min)</th>
<th>( C_{\text{water}} ) (ml/min)</th>
<th>( V/GFR ) (ml/100 ml GFR)</th>
<th>( \frac{C_{\text{water}} + C_{\text{Na}}}{GFR} )</th>
<th>( C_{\text{water}} + C_{\text{Na}} ) (ml/min)</th>
<th>( U_{\text{osm}} ) (mosmol/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>4</td>
<td>130 ± 10-4</td>
<td>213 ± 17-8</td>
<td>11-2 ± 0-8</td>
<td>12-4 ± 0-7</td>
<td>10-5 ± 0-7</td>
<td>0-89 ± 0-06</td>
<td>74-3 ± 5-4</td>
</tr>
<tr>
<td>DOCA</td>
<td>4</td>
<td>147 ± 10-8</td>
<td>410 ± 93-7</td>
<td>19-2 ± 1-20</td>
<td>15-1 ± 0-7</td>
<td>14-3 ± 0-7</td>
<td>0-85 ± 0-09</td>
<td>69-3 ± 8-0</td>
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<tr>
<td>DOCA + progesterone</td>
<td>4</td>
<td>156 ± 10-8</td>
<td>397 ± 19-1</td>
<td>19-0 ± 1-94</td>
<td>15-5 ± 0-7</td>
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<td>0-87 ± 0-06</td>
<td>62-3 ± 4-3</td>
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</tbody>
</table>
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water excretion, while the ratio of free water generation to the sum of sodium and free water clearance represents fractional sodium reabsorption in distal areas of the nephron (Eknoyan, Suki, Rector & Seldin, 1967; Barton, Lockner, Rector & Seldin, 1972; Seldin & Rector, 1973). The basis for the use of such indices is detailed elsewhere (Eknoyan et al., 1967; Barton et al., 1972; Seldin & Rector, 1973; Buckalew, Walker, Puschett & Goldberg, 1970; Levinsky & Levy, 1973) and is beyond the scope of this discussion. It should be stressed, however, that use of variations in osmolar and free water clearances as evidence of alterations in filtrate reabsorption at various nephron sites is inferential, and more direct supportive evidence is derived from animal studies. Still, it is generally accepted that these clearance techniques provide remarkably reproducible and accurate information on the localization of the site of action of diuretics or adrenal cortical hormones in the nephron (Seldin & Rector, 1973).

Acute administration of progesterone to normal men on either low or high sodium diets caused increases in V/GFR, (Cwater + CNa)/GFR and Cwater and decreased Cwater/(Cwater + CNa). These data suggested that after progesterone was administered, fractional sodium reabsorption decreased proximally and distally delivered filtrate increased, accompanied by an absolute increase in sodium reabsorption at the diluting sites (Cwater increased). The increase in reabsorption was less than the increase in delivery so that fractional distal sodium reabsorption decreased and urinary sodium rose.

There are two alternative explanations for the increase in free water excretion other than an increase in distal delivery of sodium. First, the increased renal blood flow could have decreased hypotonicity in the medulla (the 'wash-out' phenomenon). Since some filtered water back-diffuses into the more concentrated medullary interstitium even in the absence of antidiuretic hormone, decreased interstitial solute concentration could reduce back-diffusion so that free water generation appears greater. In the present studies, however, fractional distal delivery increased even in those instances where ERPF remained the same or decreased. However, our clearance studies cannot detect distributional changes within the kidney. For example, total ERPF may remain unchanged whereas the proportion of blood flow to the medulla increases. The second possibility relates to the inhibition by pro-}


gerosterone of distal sodium reabsorption demonstrated in most studies. This led to a small increment in urinary (and presumably intratubular) osmolality, which might in turn have retarded the non-antidiuretic hormone-dependent back-flux of water. The failure of Uosm to increase after progesterone administration is against this alternative. Taken together, the evidence suggests that the best explanation for the increase in Cwater + CNa seen in virtually every study is that distal delivery did in fact increase.

Our experiments also suggest that a component of the acute saliuretic response to progesterone is independent of its ability to inhibit mineralocorticoid action. If the natriuretic effect of progesterone were mediated solely by its aldosterone inhibitory capacity, one might expect a greater natriuresis after administration of large doses of the hormone to subjects in whom endogenous aldosterone was increased. In these experiments, however, the progesterone-induced saliuresis was the same or greater in subjects receiving high sodium diets in whom base-line values for plasma renin activity and aldosterone excretion were lower than in volunteers ingesting salt-restricted diets. Further, a large dose of progesterone failed to induce a natriuresis acutely in normal subjects chronically expanded by the administration of exogenous mineralocorticoids. The absence of an acute natriuretic response to progesterone in DOCA-treated normal subjects is consistent with our earlier demonstration of minimal changes in 24 h urinary sodium excretion when normal volunteers who had escaped from the sodium-retaining effects of administered DOCA were treated with progesterone (Ehrlich & Lindheimer, 1972). The observations that progesterone administered to volunteers chronically expanded with DOCA does not produce a substantial natriuresis, either acutely or during a 24 h period (Ehrlich & Lindheimer, 1972), are surprising since the phenomenon of progesterone-induced natriuresis was first described in adrenal-deficient subjects receiving DOCA (Landau et al., 1955). Taken together, our data suggest that the saliuretic effect of progesterone is at least in part independent of mineralocorticoid inhibition.

The natriuresis observed in our acute experiments could not be explained by changes in other components of the renin–angiotensin–aldosterone system. Acute progesterone administration was associated with a small decrease in plasma renin activity, no
change in renin substrate or concentration, and an increase in urinary aldosterone excretion. The change in urinary aldosterone was in a direction which would be expected to decrease and not to enhance sodium excretion. Thus the acute natriuretic effect of progesterone appears to be independent of changes in circulating amounts of renin and renin substrate, as well as in excretion of aldosterone.

After chronic progesterone administration, the increase in sodium excretion was less than that observed in the acute studies. Chronic progesterone administration resulted in a negative sodium balance, which was reflected in a mean weight loss of approximately 1 kg in subjects on both low and high sodium diets. Renin and aldosterone concentrations increased. These results are similar to those of others who have administered progesterone for several days to normal volunteers (Laidlaw, Ruse & Gornall, 1962; Crane & Harris, 1974). Our data presumably reflect compensatory changes to the sodium loss. The finding of decreased exchangeable sodium after progesterone administration supports this interpretation (Crane & Harris, 1974). Blunting of the renal effects of progesterone when the hormone was administered over a period is difficult to explain by any single mechanism. In our studies, by the third day aldosterone excretion had increased at least twofold and the subjects had lost several pounds. The sodium loss per se might be a potent stimulus to sodium reabsorption in the proximal tubule, which is one of the areas in the nephron that progesterone seems to affect acutely.

A number of independently modulated factors influence the renal handling of sodium (Schrier & DeWardener, 1971; Klahr & Slatopolsky, 1973). Increases in GFR after chronic progesterone administration have been reported in man (Chesley & Tepper, 1967), but do not explain the present results, since GFR did not rise in response to the acute administration of progesterone. Renal vasodilatation may enhance sodium excretion. L. E. Earley and coworkers (Martino & Earley, 1967; Earley, 1966; Earley & Schrier, 1973) have suggested that vasodilatation in certain critical areas of the nephron increases interstitial pressure and consequently the back-flux of sodium into the renal tubule. Progesterone, by its ability to relax vascular smooth muscle, might cause vasodilatation in such critical regions, but our data do not permit direct evaluation of this possibility. If maximal regional vasodilatation occurred in response to DOCA-induced expansion, this mechanism could explain the failure of progesterone to increase sodium excretion further after DOCA administration. Another way in which renal vasodilatation could affect sodium excretion is by altering the filtration fraction. Changes in this fraction alter postglomerular albumin concentration, and the subsequent change in peritubular oncotic pressure affects proximal tubular sodium and water handling in the manner consistent with Starling's law (Earley & Schrier, 1973; Brenner & Troy, 1971).

In the present experiments, renal plasma flow increased consistently whereas glomerular filtration rate changed little, resulting in a significant decrease in filtration fraction ($P < 0.02$). Thus it is possible that part of the natriuresis produced by progesterone may be mediated by its effect on the filtration fraction.

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