Effects of Fludrocortisone on Sympathetic Nerve Activity in Humans

Decio Mion, Jr, Robert F. Rea, Erling A. Anderson, Daniel Kahn, Christine A. Sinkey, Allyn L. Mark

Abstract Fludrocortisone reduces plasma norepinephrine in healthy humans, but forearm vascular and pressor responses to norepinephrine are potentiated. The effects of fludrocortisone on sympathetic nerve activity in healthy humans are not known. To investigate these effects we evaluated muscle sympathetic nerve activity, heart rate, and arterial pressure in 11 healthy volunteers during three protocols: (1) before and on day 7 of fludrocortisone (0.4 mg/d) treatment with ad libitum diet (n=6); (2) before and on day 7 of fludrocortisone (0.4 mg/d) or placebo with a 150 mmol/24 h (mEq/24 h) sodium diet (n=7); and (3) before and on day 2 of fludrocortisone (0.4 mg/d) or placebo with a 150 mmol/24 h (mEq/24 h) sodium diet (n=4). Placebo did not alter any parameter. Fludrocortisone produced expected mineralocorticoid effects on hormones and electrolytes: (1) plasma renin activity decreased (P<.05) on the seventh day of fludrocortisone treatment with both diets (1.4±0.3 to 0.8±0.2 ng/mL per hour with ad libitum diet and 3.7±1.2 to 1.3±0.7 ng/mL per hour with 150 mmol/24 h sodium diet); (2) mean 24-hour urinary sodium excretion decreased during treatment (P<.05 day 4 versus day 0) and returned to baseline on day 7 (165±21, 137±31, and 174±30 mmol/24 h [mEq/24 h] with ad libitum diet and 132±18, 82±13, and 113±9 mmol/24 h [mEq/24 h] with 150 mmol/24 h sodium diet on days 0, 4, and 7, respectively); and (3) after 2 days of treatment there was no change in plasma renin activity or 24-hour urinary sodium excretion. With ad libitum diet, fludrocortisone suppressed sympathetic nerve activity (18±4 to 6±3 bursts per minute, P<.05) and increased arterial pressure (90±4 to 96±3 mm Hg, P<.05) and body weight (77±3 to 79±3 kg, P<.05). With the 150 mmol/24 h sodium diet, fludrocortisone also suppressed sympathetic nerve activity on day 2 (19±3 to 11±2 bursts per minute, P<.05) and day 7 (22±3 to 11±3 bursts per minute, P<.05). In contrast to the decrease in sympathetic nerve activity during fludrocortisone, arterial pressure and body weight did not change on either day 2 or 7, and plasma volume was increased only after 7 days of fludrocortisone (41±1 to 45±1 mL/kg, P<.05). This study demonstrates that fludrocortisone suppresses sympathetic nerve activity in humans and that this suppression may be related in part to factors other than increases in arterial pressure or plasma volume. (Hypertension. 1994;23:123-130.)

Key Words • fludrocortisone • sympathetic nervous system • blood pressure • plasma volume

Despite the long-standing interest in the mechanisms involved in the genesis and maintenance of mineralocorticoid hypertension, the role of the sympathetic nervous system is still unclear. In rats, most studies in the deoxycorticosterone acetate (DOCA)-salt model have shown evidence of increased sympathetic activity; (1) increased levels of circulating catecholamines, (2) increased catecholamine synthesis and norepinephrine turnover rate in the heart, and (3) augmented vasodepressor responses to ganglionic blockade. In addition, chemical sympathectomy with centrally administered 6-hydroxydopamine prevents DOCA-salt hypertension. Finally, direct recording of nerve activity has shown increased basal splanchnic sympathetic nerve activity (SNA) and enhanced abdominal sympathetic nerve firing produced by hypothalamic stimulation.

In contrast, humans with primary aldosteronism have shown no increase in plasma catecholamine levels and no detectable changes in blood pressure after combined α- and β-blockade with phentolamine and propranolol. This suggests that increased activity of the sympathetic nervous system does not play an important role in this type of mineralocorticoid hypertension in humans. It has been shown recently that muscle SNA is lower in patients with primary aldosteronism than in normotensive subjects. In addition, patients with 17α-hydroxylase deficiency showed that muscle SNA was suppressed, rose after dexamethasone, and was inhibited by fludrocortisone.

Healthy humans receiving the mineralocorticoid fludrocortisone acetate have a fall in plasma norepinephrine, although forearm vascular and pressor responses to norepinephrine are potentiated. The effects of fludrocortisone on SNA in healthy humans are not known. The purpose of this study was to test the influence of short-term mineralocorticoid treatment on SNA to muscle vascular beds in healthy humans. We also sought to determine if decreases in SNA during fludrocortisone could be accounted for solely by changes in plasma volume, arterial pressure, and hormonal influences. We evaluated muscle SNA in healthy humans before and during fludrocortisone administration using direct recording of the postganglionic nerve activity by microneurography.
Methods

Subjects

Subjects were 11 healthy male volunteers (age, 21±0.4 years, mean±SEM; range, 19 to 23 years). All subjects were free of cardiovascular and other systemic diseases based on a medical history and physical examination. The study was approved by the Institutional Review Committee of the University of Iowa, and all subjects gave informed written consent before participation.

Protocol

Three protocols were performed: (1) 7 days of fludrocortisone with an ad libitum diet, (2) 7 days of fludrocortisone with a 150 mmol/24 h (mEq/24 h) sodium diet, and (3) 2 days of fludrocortisone with a 150 mmol/24 h (mEq/24 h) sodium diet. These protocols are described in detail below.

Protocol 1: Ad Libitum Diet, 7 Days of Fludrocortisone

Six subjects were studied during 12 days (days -4 through 7) while consuming the ad libitum diet. Four subjects were given a synthetic steroid, fludrocortisone acetate tablets (9-a-fluorocortisol, Florinef Acetate, ER Squibb & Sons), as a single daily dose of 0.4 mg/d orally for 7 days (days 1 through 7). Two subjects were given 0.8 mg/d. Experimental sessions were performed twice: before treatment (day 0) and on day 7 of treatment with fludrocortisone.

Protocol 2: 150 mmol/24 h (mEq/24 h) Sodium Diet, 7 Days of Fludrocortisone

Seven subjects (two subjects who participated in protocol 1 and five other subjects) were studied during two 12-day sessions (days -4 through 7) while receiving a diet containing approximately 150 mmol/24 h (mEq/24 h) sodium and 100 mmol/24 h (mEq/24 h) potassium. From days 1 through 7 subjects received either 0.4 mg/d fludrocortisone or placebo orally in a random-order and double-blind design. Subjects underwent experimental sessions before treatment (day 0) and on day 7 of treatment with fludrocortisone and before treatment (day 0) and on day 7 of treatment with placebo.

Protocol 3: 150 mmol/24 h (mEq/24 h) Sodium Diet, 2 Days of Fludrocortisone

Four subjects (two who were studied in protocols 1 and 2 and two who were studied in protocol 2) were studied during two 7-day sessions (days -4 through 2) while fed a diet containing approximately 150 mmol/24 h (mEq/24 h) sodium and 100 mmol/24 h (mEq/24 h) potassium. After 5 days (days -4 through 0) on that diet the subjects were given 0.4 mg/d fludrocortisone or placebo orally for 2 days each (days 1 and 2) in a random-order and double-blind design. Subjects underwent experimental sessions before treatment (day 0) and on day 2 of treatment with fludrocortisone and before treatment (day 0) and on day 2 of treatment with placebo.

Subjects receiving ad libitum diet reported to the Clinical Research Center (CRC) to be weighed and to deliver 24-hour urine collections for sodium, potassium, and creatinine levels on days 0, 4, and 7. The subjects fed the constant sodium and potassium diets reported daily to the CRC to be weighed, to deliver 24-hour urine collections, and to have breakfast, lunch, and dinner. A 24-hour urine collection for sodium, potassium, and creatinine levels was obtained daily. The completeness of collection was assessed by measurement of urinary creatinine. On the morning of days 0, 4, and 7 in protocols 1 and 2 and days 0 and 2 in protocol 3, a catheter was inserted into a peripheral vein. After this procedure subjects remained supine. After 60 minutes rest, blood was drawn for chemical measurements. In the afternoon on days 0 and 7 in protocols 1 and 2 and on days 0 and 2 in protocol 3, the subjects underwent the experimental session.

During protocols, subjects continued their normal daily activities but were asked to refrain from strenuous physical exercise.

Diet

CRC dietitians developed a eucaloric diet adjusted to each subject's projected activity level. The diet contained approximately 3500 cal/d (15% protein, 40% fat, and 45% carbohydrate), with a calcium content of 320 mg/1000 cal. The same menu was repeated each day for each subject. Meals were prepared in the CRC and foods were weighed to the nearest gram. A duplicate of each subject's diet was prepared once each study period during protocol 2 for analysis of sodium and potassium. The sodium and potassium contents of the diets were as follows: placebo treatment (n = 7): sodium, 141±9 mmol/24 h (mEq/24 h) and potassium, 95±5 mmol/24 h (mEq/24 h); fludrocortisone treatment (n = 7): sodium, 143±10 mmol/24 h (mEq/24 h) and potassium, 95±2 mmol/24 h (mEq/24 h) (mean±SEM). Subjects were instructed not to ingest anything other than the diet and distilled water supplied by the CRC. Water intake was unrestricted. Subjects were judged to be compliant by observation of meals eaten in the CRC and by daily inquiry about food consumed away from the CRC. At least 3 to 4 weeks of ad libitum diet were allowed between the two dietary periods. Subjects were asked to avoid consumption of alcohol and caffeine and to refrain from any medications, including "over-the-counter" medications.

Chemical Measurements

Creatinine levels were measured by the autoanalyzer method on an AutoAnalyzer II (Technicon Instruments, Tarrytown, NY). Sodium and potassium levels were measured by ion-selective electrodes (E2A Na/K electrode system, Beckman Instruments, Arlington Heights, Ill). Plasma renin activity was measured by radioimmunoassay of angiotensin I (Rianen, Du Pont Co, Billerica, Mass). Serum aldosterone levels were measured by radioimmunoassay (BioScience, Van Nuy, Calif). Corticotropic was measured by radioimmunoassay without extraction, using an antisemum to purified human corticotropin obtained from Immununotrich Corp, Stillwater, Minn. Cortisol was measured by radioimmunoassay using a specific cortisol antiserum obtained from Damon Diagnostics, Needham Heights, Mass. Plasma arginine vasopressin and atrial natriuretic peptide were measured using radioimmunoassay. The interassay and intra-assay coefficients of variation for plasma arginine vasopressin were 15.9% and 7.0%, respectively, and for atrial natriuretic factor were 12.2% and 4.5%, respectively. Plasma catecholamines were determined by high-performance liquid chromatography with electrochemical detection (Bioanalytical Systems, Inc, West Lafayette, Ind). This assay is sensitive to 18 pg of norepinephrine and 22 pg of epinephrine, with coefficients of variation for norepinephrine and epinephrine of 7.7% and 11.5%, respectively.

Experimental Methods and Sessions

All subjects were studied without sedation in the supine position. Heart rate, blood pressure, central venous pressure, respiratory movements, forearm blood flow, and efferent muscle SNA were recorded during the experimental sessions. Heart rate was derived from an electrocardiogram. Blood pressure was measured with an automatic sphygmomanometer (Life Stat 200, Physio Control Corp, Redmond, Wash) during the last half of each minute. Central venous pressure was measured through an 18.5-gauge polyethylene catheter inserted percutaneously into a left median antecubital vein and advanced to an intrathoracic position. The reference point for measurement of central venous pressure in all subjects was defined as the midaxillary position. Respiratory movements were recorded by a pneumotrace. Forearm blood flow was measured with venous occlusion plethysmog-
Fludrocortisone and Sympathetic Activity in Humans

**Results**

**Effects of Fludrocortisone on Body Weight, Electrolytes, and Hormones**

With ad libitum diet, 24-hour urinary sodium excretion fell from day 0 to day 4 ($P<.05$) and returned to baseline on the seventh day of treatment (Fig 1, Table 1). Plasma sodium tended to increase on the fourth day of fludrocortisone treatment. Fludrocortisone treatment lowered ($P<.05$) plasma aldosterone, potassium, and norepinephrine compared with placebo on the seventh day. Plasma atrial natriuretic peptide tended to increase during fludrocortisone treatment but was not different from placebo. There was no difference ($P>.05$) between placebo and fludrocortisone treatment on days 0, 4, and 7 in plasma epinephrine and vasopressin.

In protocol 3, with constant sodium diet and 2 days of fludrocortisone, 24-hour urinary sodium excretion, body weight, plasma sodium, renin activity, aldosterone, potassium, atrial natriuretic peptide, norepinephrine, epinephrine, and vasopressin showed no difference between fludrocortisone and placebo treatment on day 0 and day 2 (Tables 1 and 2). Plasma aldosterone was significantly lower on the second day of fludrocortisone treatment when compared with placebo values. Body weight tended to increase during fludrocortisone treatment (Fig 2, Table 1). Plasma renin activity, although not different from placebo, was reduced on both evaluations during fludrocortisone treatment. Fludrocortisone treatment lowered ($P<.05$) plasma aldosterone, potassium, and norepinephrine compared with placebo on the seventh day. Plasma atrial natriuretic peptide tended to increase during fludrocortisone treatment but was not different from placebo. There was no difference ($P>.05$) between placebo and fludrocortisone treatment on days 0, 4, and 7 in plasma epinephrine and vasopressin.

**Effects of Fludrocortisone on Hemodynamics and Muscle Sympathetic Nerve Activity**

As shown in Fig 3, with ad libitum diet, 7 days of fludrocortisone treatment resulted in a marked (67%) suppression in muscle SNA, from 18±4 bursts per minute on day 0 to 6±3 bursts per minute on day 7.
TABLE 1. Body Weight, Electrolytes, and Plasma Renin Activity and Aldosterone

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Protocol</th>
<th>Day 0</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight, kg</td>
<td></td>
<td>77.2±3</td>
<td>78.2±3*</td>
<td>78.8±3*</td>
<td></td>
<td>80.9±3</td>
<td>80.8±3</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2</td>
<td>81.7±1</td>
<td>81.8±2</td>
<td>82.4±2</td>
<td>3</td>
<td>80.4±3</td>
<td>80.1±3</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>81.1±1</td>
<td>81.3±1</td>
<td>81.2±2</td>
<td>3</td>
<td>80.4±3</td>
<td>80.1±3</td>
</tr>
<tr>
<td>Urinary sodium excretion, mmol/24 h (mEq/24 h)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>1</td>
<td>165±21</td>
<td>137±21*</td>
<td>174±30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2</td>
<td>132±18</td>
<td>82±13†</td>
<td>113±9</td>
<td>3</td>
<td>119±15</td>
<td>109±25</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>123±17</td>
<td>121±10</td>
<td>126±8</td>
<td>3</td>
<td>119±24</td>
<td>114±11</td>
</tr>
<tr>
<td>Plasma sodium, mmol/L (mEq/L)</td>
<td></td>
<td>142±1</td>
<td>143±1</td>
<td>142±1</td>
<td></td>
<td>140±1</td>
<td>141±1</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>1</td>
<td>142±0</td>
<td>142±0</td>
<td>141±1</td>
<td>3</td>
<td>140±1</td>
<td>141±1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>140±0</td>
<td>141±1</td>
<td>141±1</td>
<td>3</td>
<td>140±1</td>
<td>141±1</td>
</tr>
<tr>
<td>Plasma renin activity, (ng/mL)/h</td>
<td></td>
<td>1.4±0.3</td>
<td>1.2±0.3</td>
<td>0.8±0.2*</td>
<td></td>
<td>0.7±0.1</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2</td>
<td>3.7±1.2</td>
<td>1.2±0.3</td>
<td>1.3±0.7</td>
<td>3</td>
<td>4.3±0.1</td>
<td>4.1±0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>1.9±0.3</td>
<td>2.4±0.7</td>
<td>2.2±0.6</td>
<td>3</td>
<td>0.8±0.4</td>
<td>0.8±0.2</td>
</tr>
<tr>
<td>Plasma potassium, mmol/L (mEq/L)</td>
<td></td>
<td>4.0±0.1</td>
<td>3.8±0.1</td>
<td>3.7±0.1*</td>
<td></td>
<td>4.3±0.1</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>3</td>
<td>4.4±0.1</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>4.3±0.1</td>
<td>3</td>
<td>4.4±0.1</td>
<td>4.2±0.1</td>
</tr>
<tr>
<td>Plasma aldosterone, pg/mL</td>
<td></td>
<td>70±8</td>
<td>40±4</td>
<td>49±7</td>
<td></td>
<td>64±9†</td>
<td>73±5†</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>2</td>
<td>129±53</td>
<td>89±19</td>
<td>64±9†</td>
<td>3</td>
<td>131±23</td>
<td>73±5†</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>112±13</td>
<td>158±44</td>
<td>121±14</td>
<td>3</td>
<td>104±9</td>
<td>129±14</td>
</tr>
</tbody>
</table>

Variables were measured during fludrocortisone with ad libitum diet (protocol 1) and during 7 days (protocol 2) or 2 days (protocol 3) of fludrocortisone or placebo with 150 mmol/24 h (mEq/24 h) sodium diet.

*P<.05 vs day 0.
†P<.05 vs placebo.

(P<.05). Mean arterial pressure rose significantly (P<.05), from 90±4 to 96±3 mm Hg. Heart rate tended to decrease. There was no change in central venous pressure. The two subjects who received 0.8 mg/d fludrocortisone did not show different responses.

With the constant sodium diet, the suppression in muscle SNA was 50% with 7 days of treatment with fludrocortisone (Fig 2). Muscle SNA on day 7 during fludrocortisone (11±3 bursts per minute) was significantly lower than during placebo (21±3 bursts per minute). There was no significant difference between placebo and fludrocortisone on either day 0 or day 7 in mean arterial pressure, heart rate (61±2 to 59±3 beats per minute with placebo, 60±4 to 58±3 beats per minute with fludrocortisone), or central venous pressure (5±1 to 5±1 mm Hg with placebo, 6±1 to 6±1 mm Hg with fludrocortisone).

With 2 days of fludrocortisone treatment, the suppression of SNA was 42%, and muscle SNA was also significantly lower with fludrocortisone (11±2 bursts per minute) than with placebo (19±3 bursts per minute). Again, there was no significant difference between placebo and fludrocortisone on day 0 and day 2 in mean arterial pressure, heart rate (61±2 to 56±4 beats per minute with placebo, 60±5 to 65±2 beats per minute with fludrocortisone), or central venous pressure (6±1 to 5±1 mm Hg with placebo, 6±1 to 6±1 mm Hg with fludrocortisone).

With placebo treatment, muscle SNA was unaltered in either protocol 2 or protocol 3 (Fig 4). Fig 5 shows representative neurograms of muscle SNA from one subject who participated in protocols 1, 2, and 3.

Effects of Fludrocortisone on Plasma Volume and Hematocrit

Plasma volume in the subjects receiving constant sodium diet was significantly greater on the seventh day of treatment with fludrocortisone (45±1 mL/kg, P<.05) compared with placebo (42±1 mL/kg). On day 0, there was no difference in plasma volume between treatments (41±1 mL/kg with fludrocortisone and 42±1 mL/kg with placebo, P>.05, n=6) (Fig 4). Plasma volume on day 0 and day 2 of fludrocortisone (43±1 and 44±1 mL/kg, respectively, n=4) did not differ significantly from corresponding values during placebo administration (44±1 and 43±1 mL/kg, respectively, n=4) (Fig 4).

Hematocrit was significantly reduced on the seventh day of fludrocortisone treatment compared with pla-
Table 2. Plasma Norepinephrine, Epinephrine, Arginine Vasopressin, and Atrial Natriuretic Peptide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Protocol</th>
<th>Day 0</th>
<th>Day 4</th>
<th>Day 7</th>
<th>Protocol</th>
<th>Day 0</th>
<th>Day 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma norepinephrine, pg/mL</td>
<td>Fludrocortisone</td>
<td>168±9</td>
<td>144±14</td>
<td>130±14</td>
<td>Fludrocortisone</td>
<td>161±20</td>
<td>186±22</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>172±32</td>
<td>157±20</td>
<td>165±23</td>
<td>Fludrocortisone</td>
<td>3</td>
<td>140±4</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>3</td>
<td>132±20</td>
<td>163±21</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma epinephrine, pg/mL</td>
<td>Fludrocortisone</td>
<td>50±14</td>
<td>54±8</td>
<td>44±12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>27±4</td>
<td>30±3</td>
<td>31±2</td>
<td>Placebo</td>
<td>3</td>
<td>37±11</td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>40±11</td>
<td>31±5</td>
<td>26±4</td>
<td>Placebo</td>
<td>3</td>
<td>33±8</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2</td>
<td></td>
<td></td>
<td>Placebo</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Plasma arginine vasopressin, pg/mL</td>
<td>Fludrocortisone</td>
<td>2.4±0.5</td>
<td>3.4±0.8</td>
<td>2.9±0.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2.5±0.5</td>
<td>4.4±0.7</td>
<td>5.5±1.0</td>
<td>Placebo</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fludrocortisone</td>
<td>3.0±0.5</td>
<td>3.0±0.2</td>
<td>3.1±0.5</td>
<td>Placebo</td>
<td>3</td>
<td>2.6±0.8</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>2</td>
<td>3</td>
<td>3.2±0.4</td>
<td>Placebo</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Atrial natriuretic peptide, pg/mL</td>
<td>Fludrocortisone</td>
<td>78±16</td>
<td>87±16</td>
<td>102±11</td>
<td>Placebo</td>
<td>60±7</td>
<td>90±9</td>
</tr>
<tr>
<td></td>
<td>Placebo</td>
<td>65±13</td>
<td>75±16</td>
<td>77±18</td>
<td>Placebo</td>
<td>55±12</td>
<td>59±6</td>
</tr>
</tbody>
</table>

Variables were measured during fludrocortisone with ad libitum diet (protocol 1) and during 7 days (protocol 2) or 2 days (protocol 3) of fludrocortisone or placebo with 150 mmol/24 h (mEq/24 h) sodium diet.

*P<.05 vs placebo.

cebo (0.38±0.01 versus 0.42±0.01 [38±1% versus 42±1%], respectively, P<.05) in protocol 2. However, there was no difference in hematocrit on the second day of protocol 3 (0.41±0.01 [41±1%] with fludrocortisone and 0.41±0.01 [41±1%] with placebo on day 2, P>.05).

Placebo did not change plasma volume from day 0 (42±1 mL/kg) to day 7 (42±1 mL/kg) in protocol 2 and from day 0 (44±1 mL/kg) to day 2 (43±1 mL/kg) in protocol 3.

Effects of Fludrocortisone on Forearm Blood Flow and Vascular Resistance

Forearm blood flow on the seventh day of fludrocortisone was not different from placebo (4±1 and 4±1 mL/min per 100 mL forearm volume). In addition, forearm blood flow was unchanged from day 0 to day 7 (4±1 to 4±1 mL/min per 100 mL forearm volume) of treatment with fludrocortisone and also from day 0 to day 7 (4±0 to 4±1 mL/min per 100 mL forearm volume) of treatment with placebo.

Vascular resistance tended to decrease from 29±4 U on day 0 of fludrocortisone to 26±4 U on day 7; with placebo treatment, vascular resistance was 25±3 and 27±7 on days 0 and 7, respectively (P>.05). There was no difference between vascular resistance with fludrocortisone and placebo treatment on day 0 and day 7.

Forearm blood flows on day 0 and day 2 of fludrocortisone treatment (3±0 and 3±1 mL/min per 100 mL.
FIG 3. Bar graphs show effects of fludrocortisone (0.4 mg/d) on mean arterial pressure (MAP), central venous pressure (CVP), heart rate (HR), and sympathetic nerve activity (SNA) in healthy subjects (n=5) with ad libitum diet. *P<0.05 vs day 0. Data are mean±SEM. bpm indicates beats per minute.

forearm volume, respectively) were not different from day 0 and day 2 with placebo treatment (3±0 and 3±1 mL/min per 100 mL forearm volume, respectively). Vascular resistance also was not different (P>.05) on days 0 and 2 of treatment with both treatments (24±2 and 28±9 U, respectively, with fludrocortisone; 27±1 and 32±5 U, respectively, with placebo).

Discussion

The main finding of this study is that fludrocortisone treatment suppresses muscle SNA in healthy humans. The data suggest that this suppression is related in part to factors other than increased arterial pressure or plasma volume.

Fludrocortisone is a steroid with glucocorticoid and mineralocorticoid actions. However, in humans, fludrocortisone exerts its effects as a mineralocorticoid. In fact, in our study, 7 days of fludrocortisone (0.4 mg/d) treatment with ad libitum or constant sodium diet induced electrolytic and humoral changes consistent with expected findings from mineralocorticoid activity.

Previous hemodynamic studies showed that after 1 week of fludrocortisone (0.8 mg/d) administration in healthy subjects the rise in arterial pressure is a consequence of an increase in stroke volume and cardiac output. Also, patients with orthostatic hypotension who received fludrocortisone (0.3 to 1.0 mg/d) showed an increase in arterial pressure associated with transient sodium retention and plasma volume expansion. Patients with primary aldosteronism treated with spironolactone to normalize blood pressure and studied after the cessation of spironolactone showed an increase in cardiac output and normal peripheral resistance, whereas total peripheral resistance was elevated in the chronic phase. The period after the cessation of spironolactone is a condition comparable to the early stage of aldosterone-induced hypertension.

Muscle SNA suppression by fludrocortisone is consistent with reports of decreased SNA found in patients with primary aldosteronism.

To exclude the possibility that the suppressed nerve activity observed in our study is an effect of time or repeated measurements, we included placebo studies in protocols 2 and 3. These studies showed that muscle SNA did not change over time. Our placebo studies confirmed that resting SNA expressed as burst frequency is reproducible across experimental sessions spanning several months. Burst frequency was used to analyze the muscle SNA because it is the only reproducible microneurographic measure of SNA for between-sessions comparisons.

Several potential mechanisms are involved in the suppression of muscle SNA during fludrocortisone. Mineralocorticoid activity typically induces sodium retention, with increases in plasma volume and arterial pressure that stimulate cardiopulmonary and arterial baroreceptors.

In protocol 1 with the ad libitum diet and in protocol 2 with a constant sodium diet, subjects retained sodium. In protocol 2 we demonstrated an increase in plasma volume after 7 days of fludrocortisone. Despite increased plasma volume, our subjects did not show increases in central venous pressure. We used the same

FIG 4. Bar graphs show effects of fludrocortisone (0.4 mg/d) and placebo on sympathetic nerve activity (SNA) and plasma volume (PV) in healthy subjects with 150 mmol/24 h (mEq/24 h) sodium diet before and on the seventh day of treatment (left, protocol 2, n=7) and before and on the second day of treatment (right, protocol 3, n=4). *P<.05 vs placebo. Data are mean±SEM.
reference point for measurement of central venous pressure in each subject for all studies. We suggest that central venous pressure may not reflect adequately plasma volume changes in these conditions because of other factors such as increased venous compliance. Distler et al also failed to find a significant increase in central venous pressure after 1 week of fludrocortisone despite an increase in body weight.

Elevations in arterial pressure cause baroreceptor reflex-mediated decreases in muscle SNA and could play a role in muscle SNA suppression observed with fludrocortisone. Arterial pressure was increased in protocol 1 but did not change in protocols 2 or 3 with constant sodium intake. Contrasting arterial pressure responses to fludrocortisone have been shown with different doses of steroid and different levels of sodium intake. Therefore, in protocol 1 muscle SNA inhibition could be explained by an increase in plasma volume and arterial pressure.

In protocol 2, with 7 days of fludrocortisone and a constant sodium diet, there was no increase in arterial pressure, but the suppression of SNA could have been due to the increase in plasma volume.

In protocol 3 we tested the short-term effects of fludrocortisone with a constant diet. There was no significant increase in plasma volume, body weight, urinary sodium excretion, or arterial pressure. However, muscle SNA was suppressed even under these conditions. This suppression in muscle SNA could not be explained by increases in arterial pressure or plasma volume with baroreceptor reflex (cardiopulmonary or arterial) inhibition of SNA.

Besides baroreceptor reflex mechanisms, humoral factors that could inhibit muscle SNA were investigated. It is well known that elevated vasopressin levels play an important role in DOCA-salt hypertension in rats. Furthermore, Floras et al showed that vasopressin infusion in healthy subjects causes inhibition of muscle SNA. Haller et al observed elevated plasma concentrations of vasopressin after 7 days of fludrocortisone in a higher dose (0.8 mg/d) without an increase in plasma osmolality. In contrast, patients with primary aldosteronism show vasopressin levels lower than control subjects probably because of an expanded plasma volume and increase in arterial pressure.

In our study vasopressin levels also were not elevated. Thus, the inhibition of SNA cannot be attributed to changes in circulating vasopressin.

Fludrocortisone administration is usually followed by an increase in plasma atrial natriuretic peptide. Weidmann et al showed that atrial natriuretic peptide is increased on the second day of fludrocortisone treatment (0.6 mg/d), with further increases on days 4 and 9. The increase on day 2 occurs without an increase in body weight or arterial pressure and a decrease in urinary sodium excretion. In addition, it has been shown that atrial natriuretic peptide has a sympathoinhibitory action in humans. Therefore, an increased atrial natriuretic peptide level could contribute to muscle SNA suppression by fludrocortisone. In this study, atrial natriuretic peptide showed a tendency to increase on day 2 (protocol 3) and day 7 (protocol 2). However, atrial natriuretic peptide values with fludrocortisone were not different from placebo in either protocol.

Angiotensin II increases peripheral SNA. Fludrocortisone administration induces suppression of the renin-angiotensin system that could be a mechanism of SNA inhibition. In our study, plasma renin activity was suppressed in protocol 1 and tended to decrease in protocol 2; it did not change in protocol 3.

Forearm blood flow did not increase with fludrocortisone as would be expected in the presence of a decrease in sympathetic neural vasoconstrictor activity. Vascular resistance showed only a tendency to decrease. These responses could be explained by increased vascular orpressor responsiveness to norepinephrine observed with fludrocortisone in healthy subjects and patients with autonomic insufficiency. Hypokalemia also has been reported to produce enhanced vascular reactivity. An increased vascular reactivity also could be related to an elevated intracellular free calcium concentration, as shown by Haller et al in platelets of healthy subjects during fludrocortisone treatment. Therefore, these reports suggest that increased vascular reactivity may offset a vasodilator influence of decreased muscle SNA.

In conclusion, fludrocortisone treatment induces marked muscle SNA suppression in healthy humans. This suppression may be related in part to factors other than increases in plasma volume or arterial pressure.

Acknowledgments
Decio Mion, Jr, was a Visiting Research Scientist in the Cardiovascular Center and Department of Internal Medicine,
References


Effects of fludrocortisone on sympathetic nerve activity in humans.
D Mion, Jr, R F Rea, E A Anderson, D Kahn, C A Sinkey and A L Mark

Hypertension. 1994;23:123-130
doi: 10.1161/01.HYP.23.1.123

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1994 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://hyper.ahajournals.org/content/23/1/123

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in
Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial
Office. Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/