Metabolic effects of ACTH in the sheep

BRUCE A. SCOGGINS, JOHN P. COGHLAN, DEREK A. DENTON, JAMES S. K. FAN, JOHN G. MCDougALL, CATHERINE J. ODDIE, AND ARTHUR A. SHULKES
Howard Florey Institute of Experimental Physiology and Medicine, University of Melbourne, Parkville, Australia

The effects of systemic administration of adrenocorticotrophic hormone (ACTH) on the renal handling of sodium, potassium, and water and on plasma levels of sodium and potassium have been examined in the dog (11, 12) and in man (4, 14, 23). The studies in man and those of Ganong (12) in the dog have also studied the changes in aldosterone and glucocorticoid secretion and the activity of the renin-angiotensin system. It has been suggested that the effects of ACTH on electrolyte and water status are primarily mediated by the stimulation of corticosteroid secretion from the zona fasciculata rather than by its effects on aldosterone secretion (5), the secretion of the latter hormone being suppressed after an initial period of stimulation (4, 14, 23).

Clinical syndromes such as 17-hydroxylase deficiency, mediating by the stimulation of corticosteroid secretion from the zona fasciculata, and glucocorticoid and deoxycorticosterone levels were significantly increased with ACTH. Aldosterone levels remained unchanged and within the normal Na replete range. ACTH resulted in a significant increase in systolic and diastolic blood pressure within 24 h. This increase was sustained for the duration of ACTH treatment. Changes in blood pressure were not related to changes in external Na status or in body weight. Hypokalemic alkalosis was rapidly produced without change in urinary K excretion. Increases in both urine output and water intake were observed in all animals. Withdrawal of the ACTH stimulus resulted in rapid return of blood pressure and plasma [K] to normotensive levels associated with a naturessis. Water turnover was normal within 7 days. The effects of ACTH in the sheep at doses to give maximal stimulation of adrenal steroid secretion, particularly the effect on blood pressure, are in contrast to those observed in other species. The rapidly induced changes in blood pressure with ACTH in the sheep suggest this may be a useful new model of experimental hypertension.

provide information about the interrelationships between adrenocortical function, electrolyte metabolism, and blood pressure regulation.

MATERIALS AND METHODS

General

Twelve adult crossbred Merino sheep, 10 wethers and 2 ewes, of body weight 40–50 kg were used. Animals were housed in individual metabolism cages allowing separate collection of urine and feces. Each animal was offered daily 0.8 kg of lucerne-oaten chaff and water ad lib. Food and water intake and urine output were recorded daily. Total water intake was measured twice each week in five experiments. Food was sampled weekly and analyzed for sodium and potassium. All animals had bilateral carotid loops prepared at least 6 weeks prior to experimentation (18). Body weight was measured prior to administration of ACTH and on the 5th or 10th day of treatment.

Experimental

Each experiment was divided into three periods: a pre-ACTH control period of 7 days, ACTH for 5 or 10 days, and a post-ACTH period of up to 20 days. During each period diastolic and systolic blood pressure, water, sodium, and potassium intake and output were measured daily. Carotid arterial bleeds were taken for analysis of plasma ions and blood corticosteroids. Blood corticosteroid samples were taken on the morning prior to ACTH administration and on the 5th day of ACTH. In the 5 experiments with 10 days of ACTH administration, samples were taken on both the 5th and 10th days of treatment. Daily recordings and bleeds were taken as close to 1000 h as possible. During experiments with intramuscular ACTH, the animal was bled and blood pressure was recorded prior to the morning injection of ACTH. ACTH (Corticotrophin Zn, Organon) was given by intramuscular injection (40 IU each 12 h) for 5 days in 20 experiments and for 10 days in 5 experiments. ACTH (Synacthen, Ciba) was given by intravenous infusion (4 IU/h) for 5 days in two experiments.

Methods

Diastolic and systolic blood pressure were measured by auscultatory sphygmomanometry using a carotid arterial loop. Sodium and potassium analyses in plasma, urine, feces, and food were done on a Technicon AutoAnalyser. Bicarbonate and chloride were measured on a Technicon
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Peripheral arterial blood aldosterone, cortisol, corticosterone, deoxycortisol, and deoxycorticosterone were measured by double-isotope derivative dilution procedure (24).

RESULTS

Administration of ACTH for 5 Days

Results for an individual experiment are shown on Fig. 1, and grouped results for all experiments are shown on Fig. 2 and Table 1. The individual experiment (Fig. 1) shows results for intravenous administration of ACTH. Comparison of these results with those for intramuscular injection of ACTH (Fig. 2) shows that there are no significant differences in the observed responses to ACTH arising from the route of administration. Blood corticosteroid levels were also similar in both series of experiments. Although the effect of ACTH administration was examined in 22 experiments, only in 5 studies were results for the immediate post-ACTH period obtained. In the other 17 experiments various stimuli to aldosterone secretion were investigated at this time as part of a series of studies on aldosterone biosynthesis.

Blood pressure. ACTH resulted in a significant elevation in systolic and diastolic blood pressure in all experiments. Systolic blood pressure rose from 93 ± 3 mm Hg (mean ± SE) on the day prior to treatment to 104 ± 3 mm Hg (P < 0.05) within 24 h. A maximum value of 120 ± 5 mm Hg was seen on the 4th day of ACTH. On the 5th day, a value of 117 ± 5 mm Hg was obtained. Diastolic blood pressures were 61 ± 4 for the day prior to ACTH, and 73 ± 4, 82 ± 4, and 81 ± 4 mm Hg for the 1st, 4th, and 5th days of treatment, respectively. On cessation of ACTH administration, arterial pressure returned rapidly to normotensive levels, the values at the end of 24 h being 91 ± 2 mm Hg systolic and 68 ± 3 mm Hg diastolic (Figs. 1 and 2).
ACTH range.

Creatinine rose within 24 h to 4.5 ± 0.2 meq/liter, a value similar to the control level. It then remained within the pre-ACTH range.

Potassium fell rapidly with ACTH administration from a control value of 4.5 ± 0.1 to 3.9 ± 0.1 meq/liter (P < 0.001) on the first post-ACTH day. This value was not different from the pre-ACTH value. Plasma bicarbonate, chloride, and urea. Plasma bicarbonate rose significantly (P < 0.001) from a control level of 24.6 ± 0.9 to 29.6 ± 2 meq/liter on the 5th day of ACTH administration (Table 1). On cessation of ACTH plasma bicarbonate returned to normal levels, 23.7 ± 1 meq/liter, within 24 h. Plasma chloride levels fell with ACTH administration from 107 ± 8 to 102 ± 15 meq/liter on the 5th day of ACTH (P < 0.01, n = 5). There was no significant change in plasma urea, values of 25 ± 1 and 24 ± 1 mg/100 ml (n = 5) being obtained before and after 3 days of ACTH, respectively.

Hematocrit. There was no significant change in hematocrit with ACTH administration.

Sodium and potassium intake. Seasonal changes in the sodium and potassium content of lucerne-oaten chaff mixture resulted in fluctuations in sodium and potassium intake between experiments. Because all animals ate the 0.8 kg of food offered each day, intake over the period of the study was constant for the duration of an individual experiment. The sodium intake varied between experiments. The sodium intake varied between experiments. The sodium intake varied between experiments. The sodium intake varied between experiments. The sodium intake varied between experiments. The sodium intake varied between experiments. The sodium intake varied between experiments.

Cardiac rate. Cardiac rate rose progressively from 62 ± 2 beats/min to 76 ± 2 and 74 ± 3 beats/min on the 4th and 5th days of ACTH, respectively (Table 1). Insufficient animals were observed post-ACTH to follow the return to normal.

Plasma sodium and potassium. Plasma sodium rose from 145 ± 0.4 to 147 ± 0.5 meq/liter (P < 0.001) on the 1st day of ACTH and remained significantly elevated for the next 4 days. On the 5th day plasma sodium was 147 ± 0.6 meq/liter. Following cessation of ACTH administration, plasma sodium fell significantly to a level of 143 ± 0.6 meq/liter (P < 0.001), on the first post-ACTH day. This value was not different from the pre-ACTH value. Plasma potassium fell rapidly with ACTH administration from a control value of 4.5 ± 0.1 to 3.9 ± 0.1 meq/liter (P < 0.01) on the 1st day of ACTH. It continued to fall reaching a minimum level of 3.3 ± 0.1 meq/liter on the 4th and 5th days of ACTH. Following cessation of ACTH, plasma potassium rose within 24 h to 4.5 ± 0.2 meq/liter, a value similar to the control level. It then remained within the pre-ACTH range.

<table>
<thead>
<tr>
<th>Day</th>
<th>Pre-ACTH</th>
<th>ACTH</th>
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<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>91 ± 5</td>
<td>95 ± 3</td>
<td>93 ± 3</td>
</tr>
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<td>Diastolic blood pressure, mm Hg</td>
<td>83 ± 9</td>
<td>87 ± 9</td>
<td>89 ± 3</td>
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<tr>
<td>Cardiac rate, beats/min</td>
<td>62 ± 2</td>
<td>66 ± 7</td>
<td>68 ± 7</td>
</tr>
<tr>
<td>Plasma</td>
<td>145 ± 4.5</td>
<td>145 ± 4.5</td>
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<tr>
<td>Plasma [Na], meq/liter</td>
<td>0.6 ± 0.1</td>
<td>0.5 ± 0.1</td>
<td>0.4 ± 0.1</td>
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<tr>
<td>Plasma [K], meq/liter</td>
<td>22 ± 22</td>
<td>22 ± 22</td>
<td>22 ± 22</td>
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<tr>
<td>Plasma HCO3, meq/liter</td>
<td>24.6 ± 0.4</td>
<td>29.6 ± 23.7</td>
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<td>Urinary K, meq/day</td>
<td>287 ± 262</td>
<td>215 ± 239</td>
<td>219 ± 239</td>
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<tr>
<td>Excretion, meq/day</td>
<td>30 ± 22</td>
<td>22 ± 22</td>
<td>22 ± 22</td>
</tr>
<tr>
<td>Urinary Na, meq/day</td>
<td>63 ± 48</td>
<td>64 ± 36</td>
<td>32 ± 73</td>
</tr>
<tr>
<td>Excretion, meq/day</td>
<td>11 ± 9</td>
<td>9 ± 5</td>
<td>9 ± 5</td>
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<tr>
<td>Urine Vol, liters</td>
<td>0.60 ± 0.75</td>
<td>0.76 ± 0.81</td>
<td>0.81 ± 0.81</td>
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<td>Water Intake, liters</td>
<td>1.50 ± 2.10</td>
<td>2.03 ± 2.43</td>
<td>2.80 ± 3.40</td>
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<td>22 ± 22</td>
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NS = not significant. * P < 0.05. † P < 0.01.
and potassium intake varied from 250 to 400 meq/day (mean 330 ± 40 meq/day).

Urinary sodium and potassium excretion. ACTH administration resulted in a significant reduction in urinary sodium excretion for the first 2 days, excretion falling from 64 ± 9 to 36 ± 5 meq/day on the 1st day and to 32 ± 5 meq/ day after 2 days. By the 4th day urinary sodium excretion had risen to 99 ± 9 meq/day. On the 5th day intake and urinary output (111 ± 12 meq/day) were similar. The mean sodium output of 273 ± 81 meq/day on the 1st day post-ACTH was well in excess of sodium intake. This natriuresis continued for a further day following cessation of ACTH administration. Although the natriuresis occurred in all animals, there was considerable variation between animals on the amount of sodium excreted during this 48-h period. By the 3rd post-ACTH day urinary sodium excretion had fallen to 49 ± 26 meq/day. Although not clear from the grouped experimental data (Fig. 2, Table 1), in each animal significant urinary sodium retention had occurred by the 4th or 5th day after cessation of ACTH. This is shown in the individual experiment on Fig. 1. Urinary potassium excretion showed no significant change throughout the period of ACTH administration. Similarly, there were no changes observed in the post-ACTH period.

Fecal sodium and potassium excretion. Fecal sodium excretion was measured in five experiments. Throughout the period of study fecal sodium excretion varied from 10 to 30 meq/ day. There was no significant reduction in excretion during the period of urinary sodium retention which occurred in the first 2 days following cessation of ACTH. Further, increased fecal sodium loss did not accompany the post-ACTH natriuresis. Fecal potassium excretion varied from 20 to 80 meq/day and was not influenced by ACTH. The calculated external sodium balance on the 4th and 5th days of ACTH indicated that the animals were in a slightly negative sodium status.

Water turnover. ACTH resulted in an increase in water drinking and urine output. Water turnover increased on the 3rd day of ACTH and remained elevated for the duration of ACTH administration. A maximum value of water intake, 3.95 ± 0.4 liter/day, was observed on the 5th day. This was significantly (P < 0.001) higher than the control level of 2.03 ± 0.1 liter/day. On the 1st day post-ACTH, urine output (3.55 ± 0.8 liter/day) exceeded water intake (3.34 ± 0.8 liter/day). Water turnover remained elevated in the post-ACTH period for at least 7 days. It was still elevated after all other variables, including urinary sodium excretion, had returned to normal.

Blood corticosteroids. The results of blood steroid analysis for 16 experiments are shown on Fig. 3. ACTH resulted in a significant (P < 0.001) increase in blood cortisol from a pre-ACTH control level of 0.52 ± 0.13 to 9.2 ± 0.9 μg/100 ml on the 5th day. Similarly, blood corticosterone rose from 0.09 ± 0.01 to 0.17 ± 0.02 μg/100 ml (P < 0.001), and blood deoxycorticosterone rose from 2.5 ± 0.7 to 5.6 ± 0.5 ng/100 ml (P < 0.001). Blood aldosterone levels were similar before, 2.1 ± 0.4 ng/100 ml, and after 5 days ACTH, 1.3 ± 0.3 ng/100 ml.

Body weight. Body weight was measured prior to ACTH and on the 5th day of ACTH administration. There was no significant change in body weight, mean values being 42.1 ± 1.6 kg before ACTH and 44.0 ± 2.1 kg on the 5th day of ACTH (n = 11).

Administration of ACTH for 10 Days

The grouped results of ACTH administration to 5 sheep for 10 days are shown on Fig. 4 and Table 2. In these experiments the values obtained for all parameters at the end of 10 days were not significantly different (P > 0.05) than those at 5 days in the same experiments. They also resembled closely the results obtained in the larger series of 5-day experiments previously described. Blood corticosteroid levels were similar at the end of the 5th and 10th days of ACTH in the two experiments in which measurements were made. The important features of the 10-day experiments were: a) the continued increase in water turn over. Although this was not statistically significant, all animals continued to increase their urine output and water intake from 5 to 10 days; however, there was a wide varia-
were seen, and so intramuscular injection was used for the majority of the studies.

ACTH rapidly produced a fall in the plasma potassium level and a metabolic alkalosis. This occurred without significant change in urinary potassium excretion. Hypokalemic alkalosis has been produced experimentally in man and the dog by administration of ACTH and both glucocorticoid and mineralocorticoid hormones (4, 11, 12, 14, 19, 20, 28). Ross (28) showed that in man the effects on urinary potassium excretion were greater if both aldosterone and corticosterone were given together than if aldosterone was given alone. Although the changes in plasma potassium in the sheep were not accompanied by significant changes in urinary potassium excretion, it would seem likely that increased secretion of both mineralocorticoid and glucocorticoid hormones can be responsible for hypokalemia. In other species steroid-induced hypokalemic alkalosis occurs as a result of body potassium depletion due to increased urinary potassium excretion (11, 14, 20, 28). Evidence that a different mechanism may be involved in producing the hypokalemia in the sheep was confirmed 24 h after cessation of ACTH. Plasma potassium returned rapidly to normal, once again, without change in urinary potassium excretion. In contrast, in man, urinary potassium excretion falls to less than intake in the post-ACTH period, and plasma potassium levels remain below normal for at least 3 days (4, 14). Sheep are ruminant herbivores and have a large dietary potassium intake. Also, a large proportion of the extracellular potassium is sequestered in the rumen. It is possible that mineralocorticoid-induced changes in salivary composition result in a shift of potassium into the rumen. The total amount of potassium lost from the extracellular space is small when compared with the daily turnover of this ion, and even if shed into the urine would be difficult to detect. It is also possible that an ACTH-induced increase in extracellular volume could lower plasma potassium without resulting in increased loss of potassium. A 25% increase in the extracellular space would lower plasma potassium by about 1 meq/liter. ACTH may also result in an increase in intracellular potassium, although in other species ACTH-induced glucocorticoid secretion results in a reduction of total intracellular potassium due to tissue catabolism.

ACTH caused a marked increase in water turnover in the sheep. The relationship between the adrenal cortex and water metabolism has been reviewed in detail (13, 16, 35). In man, water turnover is not influenced by ACTH (32). However, polyuria and polydipsia have been produced experimentally in both the dog (1) and rat (26) following administration of ACTH and adrenocortical hormones. The precise mechanism of the observed increases in water turnover is not known, but may be due to hypokalemic nephropathic polyuria (27), glucocorticoid-induced changes in filtration rate (19), a direct anti-ADH action of mineralocorticoids on the renal tubule (37), or a primary increase in thirst as a result of osmolar imbalance (15). Hypervolemia has also been shown to inhibit proximal tubular sodium and water reabsorption (17).

Administration of ACTH in the sheep resulted in a significant increase in both diastolic and systolic blood pressure within 24 h. Blood pressure was elevated by at least
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<td>6 7 8 9 10</td>
<td>11 12 13 14 15</td>
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<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>98 91 98 98 106 110</td>
<td>110 111 113 114 115 112</td>
<td>112 113 114 115 116</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>62 64 62 74</td>
<td>74 81 81 78 82</td>
<td>72 62 58 58 58</td>
</tr>
<tr>
<td>Cardiac rate, beats/min</td>
<td>56 59 63 69</td>
<td>75 76 74 74 76</td>
<td>77 76 71 69 69</td>
</tr>
<tr>
<td>Plasma [Na], meq/liter</td>
<td>147 146 146 148 140</td>
<td>140 148 150 147 140 144 144 143 145 144</td>
<td></td>
</tr>
<tr>
<td>Plasma [K], meq/liter</td>
<td>4.5 4.2 4.5 4.1 3.7</td>
<td>3.5 3.4 3.5 3.3 3.1 3.6 4.6 4.3 4.3 4.5 4.1</td>
<td></td>
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<tr>
<td>Urinary K excretion, meq/day</td>
<td>100 204 204 104 157</td>
<td>208 147 168 177 165 171 216 135 194 239 174 145 186</td>
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</tr>
<tr>
<td>Urinary Na excretion, meq/day</td>
<td>34 18 25</td>
<td>22 25 21</td>
<td>26 16 23 16 15 37 21 37 56 23 32 32</td>
</tr>
<tr>
<td>Urine vol, liters</td>
<td>4.5 4.2 4.5 4.1 3.7</td>
<td>3.5 3.4 3.5 3.3 3.1 3.6 4.6 4.3 4.3 4.5 4.1</td>
<td></td>
</tr>
<tr>
<td>Water intake, liters</td>
<td>1.88 2.16 1.66 1.90 2.45</td>
<td>2.33 1.75 2.88 3.03 3.2 4.3 5.5 4.9 3.9 3.2 2.4 2.9 2.5</td>
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NS = not significant. *P < 0.05. **P < 0.01.

20 mm Hg within 4 days, and it remained at this level for the duration of ACTH treatment. There have been many clinical studies on ACTH administration, and the earliest of these (25) demonstrated that ACTH could cause an increase in blood pressure in man. Hypertension is also a common side effect of long-term corticotrophin therapy (29) and a feature of syndromes characterized by increased endogenous ACTH secretion (3, 34). Studies in man where similar doses of ACTH (1-2 IU/d per kg) have been used for a similar time period to those reported in this study have produced conflicting results (4, 14, 23). However, in two of these studies in which little or no response in blood pressure was obtained, the number of subjects was small. In the most comprehensive study, Gordon and colleagues (14) found a small but significant increase in blood pressure on the 4th day. This accompanied the increase in body weight which was observed from the 1st day of ACTH treatment. In the sheep, blood pressure was increased after 5 or 10 days of ACTH without any consistent changes in body weight and without any evidence of an increase in total body sodium status. However, as is noted in the results, a small urinary sodium retention occurred during the first 2 days. In man, all studies in which ACTH has been given for 5-10 days, sodium retention and an increase in body weight have been observed (4, 14, 23). It is not clear from experiments in the dog whether ACTH causes a rise in blood pressure. Davis and Howell (11) reported no effect and Ganong (12) did not report blood pressures in his most recent studies. Sodium retention for the first 5 days of treatment also occurred in the dog (12).

The mechanism of the hypertension induced by ACTH is not clearly understood. A number of possibilities require examination. These are i) redistribution of sodium within the body arising in part from changes in salivary electrolyte composition, ii) the role of the renin angiotensin system, iii) the importance of known adrenal glucocorticoid and mineralocorticoid hormones, iv) whether an as yet unidentified adrenal steroid is involved, and v) do adrenal catecholamines play an important role? Some of these possibilities will be discussed here, but specific answers relevant to ACTH-induced hypertension in the sheep require further experimentation.

Although there was no evidence on the basis of external sodium balance and body weight changes, the sodium retention and the elevation in blood pressure obtained with ACTH in sheep may well be associated with internal redistribution of sodium within the body. It is well documented that adrenal hormones may influence the distribution of fluid between cells and the extracellular com-
partment (19, 20, 36). Similar changes on electrolytes can also be produced with ACTH in the nephrectomized animal, suggesting extrarenal sites of action of adrenal steroids (38). ACTH has been shown to cause increases in the extra-cellular space not associated with comparable changes in either plasma volume or body weight (19) and also to cause increased blood pressure in man independently of significant sodium retention (8).

The pronounced natriuresis which occurs in the 24- to 48-h period immediately following cessation of ACTH treatment is suggestive of shedding a sodium load. However, this natriuresis has also been observed following the cessation of either ACTH or administration of various glucocorticoid hormones in man (4, 23) in studies in which no change in blood pressure was observed.

Changes in urinary sodium excretion during the administration of ACTH resemble closely those seen in other species (11, 12, 14). Retention of sodium occurs for 2 days, and this is followed by renal “escape,” sodium excretion being close to or greater than pre-ACTH levels for the remainder of the treatment period. Plasma sodium levels remained slightly elevated throughout the ACTH period but fell rapidly during the natriuresis.

The hypertension does not appear to be due to increased activity of the renin-angiotensin system. Preliminary studies in the sheep (30) have shown that both plasma renin concentration and blood angiotensin II levels to be within the normal range following ACTH. Similarly in the dog (12) and man (2, 14) ACTH causes inhibition of plasma renin activity. Plasma renin levels are normal or suppressed in clinical syndromes characterized by excessive endogenous ACTH production (3, 7).

A role for both mineralocorticoid and glucocorticoid hormones in causing blood pressure elevation has been proposed, since ACTH produces large increases in the rate of secretion of steroid hormones of both types. Aldosterone would be the exception, since only a transient rise in the secretion of this hormone occurs with ACTH (4, 14, 23). There have been numerous studies examining the hypertensive effects of adrenocortical hormones, however, although it is clear that they can produce elevations in blood pressure, the species of animal, dietary salt intake, and prior preparation of the animal and the dose of hormone used are very important. Of the species examined, only the rat responds to steroid administration with sustained elevations in blood pressure. A syndrome similar to that observed in the sheep with ACTH has been produced experimentally in the dog with metyrapone (2-methyl-1, 2-di-3-pyridyl-1-propanone) (1, 21). It has been suggested that excess production of DOC due to metyrapone-induced inhibition of adrenal 11β-hydroxylase is the cause of the hypertension and that the levels of blood DOC obtained in these animals are much greater than those found in dogs receiving parenteral doses of DOCA which in the absence of salt does not cause hypertension (36).

Of the steroids measured in this study, cortisol, corticosterone, DOC, deoxycortisol, and aldosterone, all except the latter showed significant increases with ACTH. Although the metabolic effects of cortisol and corticosterone have been examined (9, 10, 19, 25, 28), there is no clear-cut evidence that either of these steroids can raise blood pressure at physiological concentrations. A role for these glucocorticoid hormones and in particular for corticosterone, a steroid which has mineralocorticoid activity, has been invoked in Cushing's syndrome and other hypertensive adrenal disorders (5).

Clinical evidence in essential hypertension for an as yet unidentified adrenocortical factor(s) has been well documented (22, 31). Recently 18-hydroxydeoxycorticosterone has been proposed as an additional factor which may play a role in hypertension (22). Whether this steroid or an unidentified factor is responsible for the raised blood pressure seen with ACTH in the sheep remains to be determined.

These findings suggest that ACTH-induced hypertension in the sheep may be a useful new model for the study of adrenally dependent experimental hypertension.

ACTH (Synacthen) was gratefully received from Ciba-Geigy Ltd. (Australia) and ACTH (Corticotrophin) was received from Organon Pty. Ltd. (Australia).

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REFERENCES


10. Conn, J. W., L. H. Louis, and S. S. Fajans. The probability...
that Compound F (17-hydroxycorticosterone) is the hormone produced by the normal human adrenal cortex. Science 113: 713–714, 1951.


