Further unravelling of the causes of ACTH-induced hypertension in the sheep

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Summary

1. Acute severe sodium subtraction (20–25% of total exchangeable sodium) before or during treatment with adrenocorticotropic hormone (ACTH) does little to modify the increase in blood pressure induced by ACTH.

2. Chronic low salt diet, less than 5 mmol/day, abolishes the blood pressure increase, but the response can be restored by increasing the sodium intake to as little as 10 mmol/day.

3. 17α,20α-Dihydroxyprogesterone infused concurrently with other adrenal steroids will mimic ACTH hypertension and perhaps represents a new class of steroid capable of influencing blood pressure.

Key words: adrenocorticotrophic hormone, 17α,20α-dihydroxyprogesterone, hypertension, steroids.

Introduction

Administration of adrenocorticotrophic hormone at 80 i.u./day to intact trained sheep results in a significant elevation of arterial blood pressure within 24 h and this is sustained over a 5–10 day period of ACTH treatment. Hypokalaemia, an increase in plasma sodium, an increased water intake and urine output are also observed. The increases in blood pressure are not, however, related to changes in the external sodium status or in body weight. This ACTH-induced increase in blood pressure is dependent on the presence of adrenal glands but not on intact adrenal innervation. It is associated with an increase in cardiac output and an increase in plasma volume although not in extracellular space. Intravenous infusion of cortisol, deoxycortisol, corticosterone, deoxycorticosterone and aldosterone at rates to give blood levels similar to those measured during ACTH administration fails to reproduce the elevation in blood pressure. This combined steroid infusion does, however, reproduce all the other metabolic responses found to be characteristic of ACTH treatment (Scoggins, Coghlan, Denton, Fan, McDougall, Oddie & Shulkes, 1974; Shulkes, Coghlan, Denton, Fan, Robinson & Scoggins, 1974; Fan, Coghlan, Denton, Oddie, Scoggins & Shulkes, 1975; Scoggins, Coghlan, Denton, Fan, McDougall, Oddie & Shulkes, 1975). Two major areas of enquiry with this model of hypertension in the sheep will be reported here. First, what is the role of sodium? Secondly, allowing that the hypertension is dependent upon adrenal secretion, can a particular steroid be identified as having a contribution different from other steroids?

Methods

The methods used are detailed in the references given above.

Results

Role of sodium

This has been examined in three situations. First, by severe sodium subtraction after parotid duct cannulation before 5 days ACTH treatment; secondly, by severe sodium subtraction during ACTH treatment; thirdly, by ACTH treatment after chronic low salt intake.

Sodium depletion before ACTH treatment. (a) In a sodium-depletion period of 48 h before ACTH, the mean urinary and salivary sodium loss was 476
mmol (SEM 46, n = 6). There was no significant fall in blood pressure.

(b) ACTH treatment period. ACTH resulted in an increase in systolic blood pressure from 88 (SEM 4) to 97 (SEM 4) mmHg within 24 h (P < 0.05, n = 6). Diastolic pressure had also risen from 63 (SEM 3) to 66 (SEM 2) mmHg (P < 0.01, n = 6). By the fifth day of ACTH treatment blood pressure had risen to 106/78 mmHg.

Sodium depletion during ACTH treatment. (a) ACTH treatment period. This period was extended from 5 to 7 days to accommodate the 2 days sodium depletion. The effects of ACTH on blood pressure, plasma sodium potassium, urinary sodium and potassium excretion are similar to those previously reported by Scoggins et al. (1974).

(b) Sodium depletion period. With ACTH administration continuing, sodium depletion of 473 (SEM 43, n = 7) mmol over a 48 h period resulted in a fall of systolic blood pressure from 120 (SEM 4) to 109 (SEM 5) mmHg (P < 0.05, n = 7). This value is still markedly elevated when compared with the pre-treatment level of 92 (SEM 5) mmHg (P < 0.01, n = 7). Similarly, for diastolic pressure, sodium depletion resulted in a drop from 87 (SEM 3) to 76 (SEM 3) mmHg (P < 0.01, n = 7), but this was still greater than the pre-ACTH value of 66 (SEM 2) mmHg (P < 0.05, n = 7).

Chronic low salt diet. (a) Sodium intake less than 5 mmol/day. Sheep on all-grain rations of this low sodium content, after 5 days ACTH treatment, did not become hypertensive. Control blood pressure was 85/61; day 1, 90/68; day 5, 90/67 mmHg (n = 4).

(b) Sodium intake of 10 mmol/day. This group, where as yet n = 3, by day 5 the blood pressure had risen from 80/58 to 101/75 mmHg.

Conclusions. (1) Acute sodium depletion before ACTH does not modify the hypertension. (2) Acute sodium depletion (20-25% of exchangeable sodium) during ACTH does not return blood pressure to normal. (3) It appears likely that further chronic studies on low salt intake will demonstrate a permissive role for sodium in development of the hypertension.

Adrenal steroids

Of the many steroids recently identified in sheep adrenal vein blood during ACTH treatment, two compounds will increase blood pressure: 17α-hydroxyprogesterone and 17α,20β-dihydroxyprogesterone. However, these had a hypertensive effect only if they were infused concurrently with an infusion of classical adrenal steroids, which, as noted above, of itself was not hypertensive (Fan et al., 1975). The combined steroid infusion together with 18-hydroxy-deoxycorticosterone (300 mmol/h, which is probably not physiological) did increase blood pressure on the fifth day.

17α-Hydroxyprogesterone. The five sheep in the first group were given a combined steroid infusion together with 17α-hydroxyprogesterone at 3 μmol/h intravenously for 5 days. This rate approximated to adrenal secretion measured after ACTH treatment. Systolic blood pressure increased from 82 (SEM 1) to 94 (SEM 2) mmHg and 102 (SEM 2) mmHg on the fourth and fifth days respectively (P < 0.05 and P < 0.005, n = 5). Diastolic pressure showed a significant increase from 56 (SEM 1) to 61 (SEM 1) mmHg on day 2 (P < 0.005). Neither systolic nor diastolic blood pressure was elevated within 24 h.

17α,20β-Dihydroxyprogesterone. Sheep in the second group (n = 6) were given a combined steroid infusion together with 17α,20β-dihydroxyprogesterone at 1.5 μmol/h, approximating the measured values during ACTH treatment. Systolic blood pressure was significantly elevated within 24 h, rising from a control value of 85 (SEM 2) to 92 (SEM 3) mmHg (P < 0.01). On day 5 of infusion, systolic blood pressure was 100 (SEM 3) mmHg (P < 0.01). Diastolic blood pressure was also significantly elevated within the first 24 h, rising from a control value of 60 (SEM 3) to 68 (SEM 3) mmHg (P < 0.01) and was further elevated on the fifth day of infusion to 70 (SEM 2) mmHg (P < 0.005). This increased blood pressure and other metabolic changes are virtually indistinguishable from those observed after ACTH treatment.

Discussion

At the present time the mechanism by which ACTH and in particular 17α,20β-dihydroxyprogesterone influence blood pressure is obscure. From these studies, the fact that these steroids on their own are incapable of increasing blood pressure, and the fact that they did not reduce the salivary Na/K ratio upon ipsilateral carotid artery infusion in the sodium-deficient and adrenalectomized sheep, would not suggest a classical mineralocorticoid action. It is unlikely that they act as glucocorticoids because doubling the cortisol infusion rate of the combined
steroid infusion will not mimic ACTH. If 17α,20α-dihydroxyprogesterone is not a glucocorticoid then recognition of the class of steroids which increase blood pressure acting in concert with other steroids and sodium availability, but not as classical mineralocorticoids, has important implications for future clinical research and in other experimental models of hypertension.

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References


