EXPERIMENTAL STUDIES ON THE MECHANISM OF ADRENOCORTICOTROPHIC HORMONE-INDUCED HYPERTENSION IN THE SHEEP


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SUMMARY

1. The mechanism of adrenocorticotrophic hormone (ACTH)-induced hypertension in the sheep has been examined.
2. Hypertension was dependent on the presence of the adrenal gland.
3. ACTH-hypertension was not reproduced by administration of cortisol, corticosterone, deoxycorticosterone or deoxycortisol, alone or in combination.
4. Intact adrenal nerves were not necessary for the hypertension.
5. It is postulated that an adrenal factor other than those studied may be responsible for the hypertension.

Key words: adrenocorticotrophic hormone, hypertension.

The metabolic effects of adrenocorticotrophic hormone (ACTH) in the sheep have been examined in detail (Coghlan, Cran, Denton, Fan, McDougall, Oddie, Scoggins & Simpson, 1972). Intramuscular administration of ACTH (zinc hydroxide, Organon) at 1.5–2.0 units kg⁻¹ day⁻¹ to sheep for 5 days resulted in an increase in systemic arterial pressure (mean±SEM, n = 16) from 97±3/67±6 to 123±6/85±4 mmHg. A significant elevation of blood pressure occurred within 24 h. Cardiac output measured on the fifth day of ACTH administration had risen from 3·8±0·2 to 4·5±0·2 l/min (mean±SEM, n = 8). Cardiac rate also rose. ACTH lowered plasma [K⁺] (mean±SEM, n = 22) from 4·5±0·05 to 3·3±0·07 mmol/l and caused an increase in plasma [Na⁺] and [HCO₃⁻]. Water turnover was increased but there was no significant change in urinary potassium excretion. Urinary sodium retention occurred during the first 2–3 days and this was followed by a natriuresis. At the end of ACTH administration the sodium status of the animals was either unchanged or negative. Body weight was not increased. Blood levels of corticosteroids measured by double-isotope dilution derivative analysis (Oddie, Coghlan & Scoggins, 1972) before and on day 5 of ACTH administration were as follows: cortisol (mean±SEM, n = 16) rose from 0·52±0·13 to 9·2±0·9 µg/100 ml;
corticosterone rose from 0.09 ± 0.01 to 0.17 ± 0.02 µg/100 ml; deoxycortisol rose from 0.05 ± 0.01 to 0.45 ± 0.04 µg/100 ml; deoxycorticosterone (DOC) rose from 2.5 ± 0.7 to 5.6 ± 0.5 ng/100 ml. Aldosterone levels remained within the normal range: control 2.1 ± 0.4, and fifth day ACTH 1.3 ± 0.3 ng/100 ml. Blood angiotensin II and plasma renin concentration remained within the normal range for the sheep (Blair-West, Cain, Catt, Coghlan, Denton, Funder, Scoggins & Wright, 1971).

The aim of the present studies was to examine the mechanism of this ACTH-induced hypertension.

METHODS AND RESULTS

Administration of ACTH to four adrenalectomized sheep on intravenous steroid infusion at the basal rate of the undisturbed sodium replete animal (cortisol 100 µg/h, corticosterone 10 µg/h and aldosterone 3 µg/h) with a similar protocol to the experiments outlined above had no effect on blood pressure. This indicated that the hypertension was dependent on the presence of the adrenal gland.

Infusion of individual steroid hormones intravenously for 5 days at rates to give blood levels similar to those observed with ACTH treatment was also without effect on blood pressure. Cortisol (5 mg/h) infused into three animals caused an increase in water turnover. Neither corticosterone (500 µg/h) in one animal nor DOC (50 µg/h) in three animals had any effect on water or electrolyte balance. Deoxycortisol (1 mg/h) infused into two animals caused a small decrease of plasma [K] and caused urinary sodium retention followed by a return to the pre-ACTH level. Aldosterone was not infused since it had previously been shown that blood levels were not elevated with ACTH.

Since it was possible that the individual steroids may have a synergistic effect on blood pressure and electrolyte status if infused together, cortisol, corticosterone, DOC (25 µg/h) and deoxycortisol were infused at the rates indicated above together with aldosterone (3 µg/h) for 5 days into four sheep. There was a small, but not significant, increase in blood pressure 98/72 to 105/81 mmHg. The changes in plasma electrolytes resembled closely those found with ACTH. Plasma [K+] fell from 4.4 to 2.9 mmol/l and plasma [Na+] rose from 145 to 150 mmol/l. Changes in water turnover and urinary electrolyte output were similar to, but not as great as, those observed with ACTH.

Wurtman & Pohorecky (1971) demonstrated that with ACTH administration high adrenal cortical levels of glucocorticoid may activate phenylethanolamine N-methyltransferase (PNMT), the enzyme responsible for conversion of noradrenaline into adrenaline in the adrenal medulla. To examine whether altered adrenal catecholamine production could possibly be responsible for the hypertension, three sheep were subjected to surgical bilateral denervation of the adrenal glands. ACTH administration 2 weeks after denervation resulted in an elevation of blood pressure from 93/67 to 120/88 mmHg, an increase similar to that seen before denervation. The validity of surgical denervation was tested under anaesthesia by electrical stimulation of the splanchnic nerves in the lower thorax. There was no pressor response to stimulation compared with the clear-cut effect in control animals. Histochemical examination of the adrenal medulla for acetylcholinesterase activity by using the technique of Kasa & Csillik (1966) was consistent with an effective denervation.
DISCUSSION

The effects of ACTH on blood pressure and plasma electrolytes in the sheep are much greater than those reported for man (Newton & Laragh, 1968; Biglieri, Shambelan & Slaton, 1969; Gordon, Thomas, Thomas, Pawsey, Mortimer & Harrison, 1972). Further, unlike the results in man, the rise in blood pressure with ACTH in the sheep does not appear to be associated with net sodium retention or weight gain. The fall in plasma [K⁺] in the sheep was not associated with an increase in urinary potassium excretion as occurs in man. The changes in steroid secretion, and the response of the renin-angiotensin system, are similar in both species.

The present studies have shown that ACTH-induced hypertension is adrenally dependent, but not due to increased secretion of cortisol, DOC, corticosterone or deoxycorticisol. Only the changes in plasma and urinary electrolytes and in water turnover were reproduced with infusion of these steroids. Intact adrenal nerves were not necessary for the hypertension. Clinical studies (Melby, Dale & Wilson, 1972) and experimental studies (Rapp & Dahl, 1971) have suggested that 18-hydroxydeoxycorticosterone could be involved in some forms of hypertension. It remains to be determined whether this steroid hormone has a role in this ACTH-induced hypertension in sheep.

ACTH-induced hypertension in the sheep may be a useful and eventually an important experimental model for studies of the role of the adrenal in hypertension.

REFERENCES