Haemodynamics of ACTH-induced hypertension in sheep


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Summary

1. Administration of adrenocorticotropic hormone (ACTH) to sheep produced increases in mean arterial pressure within 24 h associated with an increase in cardiac output and cardiac rate. Both cardiac output and blood pressure remained elevated over the 5 days of ACTH treatment.

2. Administration of ACTH during β-adrenoceptor blockade resulted in an increase in blood pressure without changes in cardiac output at 24 h.

3. Administration of a combined steroid infusion over 5 days produced increases in cardiac output identical with the effects of ACTH but with a substantially smaller effect on blood pressure.

4. These data suggest that the observed changes in cardiac output produced by ACTH treatment may be associated with high blood concentrations of adrenocortical steroids rather than being necessary for the development of the hypertension.

Key words: adrenocorticotropic hormone, blood pressure, cardiac output, haemodynamics, sheep.

Abbreviations: ACTH, adrenocorticotropic hormone.

Introduction

Adrenocorticopic hormone (ACTH) administration to sheep produces an adrenally dependent elevation in blood pressure within 24 h which is sustained for the duration of ACTH treatment (Scoggins, Coghlan, Denton, Fan, McDougall, Oddie & Shulkes, 1974). The aim of the present studies was to examine in detail the haemodynamic changes which are associated with the development of ACTH-induced hypertension in sheep. Three separate studies were carried out.

Study 1. Effect of 5 days ACTH treatment on haemodynamics (15 experiments in 12 sheep).

Study 2. Effect of 5 days ACTH treatment on haemodynamics during β-adrenoreceptor blockade (seven experiments in seven sheep). The results in this group were compared with those for ACTH alone in the same animals.

Study 3. Effect of a 5 day combined steroid infusion (which reproduced the metabolic effects but not the blood pressure effects of ACTH) on hemodynamics (Fan, Coghlan, Denton, Oddie, Scoggins & Shulkes, 1975) (six experiments in six sheep).

These studies were designed to determine whether the change in cardiac output was an essential event for development of hypertension in this model or whether it was simply an associated phenomenon.

Methods

All experiments were carried out on adult cross-bred Merino ewes (bodyweight 35–45 kg), which were prepared and maintained as previously described (Scoggins et al., 1974).

The protocols for each of the three studies were similar and included a pretreatment period of 3 days, a 5 day ACTH- or steroid-infusion period and a post-treatment period of 3 days. In the β-adrenoreceptor-blockade experiments, acebutolol (May and Baker Pty. Ltd) was infused intravenously at 10 or 20 mg day⁻¹ kg⁻¹ for 3–5 days before ACTH treatment and for remainder of the experiment. Adequacy of β-receptor blockade was assessed by heart rate response to isoprenaline injection at five different doses.
ACTH (Synacthen, CIBA-GEIGY) was injected intramuscularly, 2 i.u. day\(^{-1}\) kg\(^{-1}\) for 5 days. The combined steroid infusion consisted of: cortisol (5 mg/h); corticosterone (0.5 mg/h); 11-deoxy cortisol (1 mg/h); deoxycorticosterone (25 \(\mu\)g/h); aldosterone (3 \(\mu\)g/h). This infusion produced blood concentrations of these steroids similar to those found after ACTH treatment (Fan et al., 1975).

Blood pressure, cardiac rate and cardiac output were measured daily between 10.00 and 12.00 hours. Water and food intake, urine output and plasma and urine [Na\textsuperscript{+}] and [K\textsuperscript{+}] were also measured daily. Cardiac output was measured by thermodilution either with a pulmonary arterial or with an aortic thermistor. For each determination 10 ml of isotonic sodium chloride solution at 0°C was injected into the right atrium. A total of six thermodilution curves was obtained over a period of 10 min for each cardiac output determination. Stroke volume and total peripheral resistance were calculated. Results were expressed as mean \( \pm \)SEM and analysed by using ANOVA or Student's t-test.

Results

Study 1: haemodynamic effects of ACTH (n = 15)

The mean changes in mean arterial pressure, cardiac output, cardiac rate, stroke volume and total peripheral resistance are shown in Fig. 1.

Increases in blood pressure were seen within 24 h and were associated with an increase in cardiac output from 4.6 \( \pm \) 0.1 to 5.5 \( \pm \) 0.2 litres/min, which was due entirely to an increase in cardiac rate. After 5 days cardiac output had increased to 5.8 \( \pm \) 0.2 litres/min. Over the same period mean arterial pressure rose from 68 \( \pm \) 1 mmHg to 88 \( \pm \) 4 mmHg. Stroke volume was increased on days 4 and 5 of ACTH only. Calculated total peripheral resistance did not change. All haemodynamic parameters had fallen to control values within 48 h of cessation of ACTH. Changes in all other metabolic parameters were similar to those previously reported (Scoggins et al., 1974).

Study 2: effect of ACTH during \( \beta \)-adrenoreceptor blockade (n = 7)

The dose of acebutolol used (10 or 20 mg/day\(^{-1}\) kg\(^{-1}\)) over a 3–5 day period had no effect on basal blood pressure or cardiac output but resulted in a 20-fold reduction in the heart rate response to injections of isoprenaline.

Administration of ACTH during acebutolol infusion produced increases in mean arterial pressure identical with those seen with ACTH alone in the same sheep. The increase in blood pressure over the first 24 h of ACTH treatment (64.5 \( \pm \) 2 to 77 \( \pm \) 3 mmHg) occurred without change in cardiac output in acebutolol-treated sheep (4.6 \( \pm \) 0.15 litres/min control, 4.7 \( \pm \) 0.15 litres/min on day 1 ACTH). However, cardiac output did not remain at these control values and had risen to 5.5 \( \pm \) 0.3 litres/min on day 5 of ACTH administration. Changes in heart rate and stroke volume were similar to those obtained with ACTH alone. Total peripheral resistance was significantly higher on both days 1 and 5 of ACTH treatment during \( \beta \)-adrenoreceptor blockade when compared with ACTH alone. Metabolic effects of ACTH in animals receiving acebutolol were similar to those seen with ACTH alone.
The combined steroid infusion reproduced all the metabolic features of ACTH treatment but had substantially less effect on blood pressure. After 5 days mean arterial pressure had risen from $66 \pm 2$ to $75 \pm 1$ mmHg ($\Delta = +9$ mmHg) compared with an increase of from $68 \pm 1$ to $88 \pm 4$ mmHg ($\Delta = +20$ mmHg) after ACTH treatment. Despite these substantial differences in blood pressure response, changes in cardiac output were identical in the two groups. With combined steroid infusion cardiac output rose from $4 6 \pm 0.2$ to $5 6 \pm 0.4$ litres/min on day 5, a value similar to that seen with ACTH ($5.8 \pm 0.2$ litres/min). The combined steroid infusion also produced a small increase in cardiac rate ($62 \pm 4$ to $67 \pm 3$ beats/min on day 5 of infusion).

**Discussion**

In the present study, ACTH-induced hypertension in the sheep was associated from onset with significant elevations of both cardiac output and cardiac rate. Calculated total peripheral resistance did not change over the 5 days of ACTH treatment.

The haemodynamic changes reported with steroid-induced hypertension are as conflicting as those in other models of hypertension. Studies in man after either administration of 9α-fluorocortisol to normal subjects (Distler & Philipp, 1976) or withdrawal of spironolactone in patients with primary aldosteronism (Distler, Just & Philipp, 1973) show an initial increase in cardiac output followed by a gradual rise in resistance and a return of cardiac output to control values. Studies of steroid-induced hypertension involving DOCA and salt administration in the pig (Terris, Berecek, Cohen, Stanley, Whitehouse & Bohr, 1976) or dog (Conway & Hatton, 1978) suggest that changes in cardiac output play a minor role.

The present studies provide comprehensive documentation of haemodynamic changes in a model of steroid-induced hypertension. Measurements were made daily in conscious animals and the haemodynamic profile was similar in all animals.

This is in contrast to the studies by Bravo, Tarazi & Dustan (1978) in which only 5 of 11 dogs showed an increase in cardiac output when first measured after 14 days of metapyrone treatment. In the study by Conway & Hatton (1978) cardiac output was not measured until the third experimental day, when the dogs already had a significant rise in arterial pressure.

The mechanisms involved in the increase in cardiac output in ACTH-treated sheep are not clear. Although a redistribution of extracellular fluid from the interstitial space to the vascular compartment occurs within 24 h of ACTH treatment (Scoggins, Coghlan, Denton, Fan, McDougall, Oddie & Shulkes, 1975) this increase in plasma volume was not accompanied by an increase in stroke volume. Rather, a rise in heart rate was associated with the increase in cardiac output. The rapid return of cardiac output to pre-ACTH values on cessation of ACTH is associated with a marked diuresis and natriuresis and a fall in both plasma volume and extracellular fluid volume (Scoggins et al., 1975).

To determine whether the increase in cardiac output is essential for development of ACTH hypertension, ACTH was administered to animals during β-adrenoreceptor blockade. Blood pressure rose without any increase in cardiac output at 24 h similar to findings in the dog by Bravo et al. (1978), and Conway & Hatton (1978) for 'mineralocorticoid' models of hypertension. Although cardiac output then rose progressively over the next 4 days in these β-adrenoreceptor-blocked animals the hypertension was associated with increases in total peripheral resistance not seen without ACTH alone. These results in the sheep also confirm an earlier study in which bilateral surgical denervation of the adrenals failed to prevent either the tachycardia or the rise in blood pressure seen with ACTH treatment (Shulkes, Coghlan, Denton, Fan, Robinson & Scoggins, 1974). Cardiac output measured after 5 days in the denervated animals was not significantly different from the pre-ACTH value.

The combined steroid-infusion experiments suggest that at least part of the change in cardiac output seen in ACTH hypertension may simply be associated with the effects of high circulating concentrations of steroids and not primarily related to development of the hypertension. After 5 days of combined steroid infusion changes in cardiac output were identical with those seen with ACTH although the effects on blood pressure were much less.

Hypokalaemia is a feature of ACTH administration in the sheep and 'mineralocorticoid' models of hypertension in other species. As potassium depletion alone will produce increases in cardiac output without changes in blood pressure (Knochel, Foley & Lipscomb, 1978; Galvez, Bay,
Roberts & Ferris, 1977) hypokalaemia might play an important role in the ACTH hypertension model.

Studies of this model of ACTH hypertension have led to the concept of 'hypertensinogenic' class of steroid hormone action rather than 'mineralocorticoid' or 'glucocorticoid' activities being solely responsible for the hypertension in steroid-induced models of hypertension (Coghlan, Denton, Fan, McDougall & Scoggins, 1976). Further studies to elucidate the relationships between the various classes of steroid hormone activity and the observed haemodynamic changes they produce will be required to fully understand the physiological mechanisms involved in ACTH hypertension.

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References