Haemodynamic effects of increasing extracellular potassium concentration in ACTH-induced hypertension in sheep


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Summary

1. ACTH administration (20 µg day⁻¹ kg⁻¹) to sheep produces hypertension associated with a raised cardiac output and hypokalaemia.

2. The aim of the present experiments was to detail the haemodynamic changes associated with restoration of the extracellular potassium concentration in sheep with ACTH-induced hypertension.

3. After 7 days of ACTH treatment potassium chloride (10 mmol/h) was infused for 3 days to restore plasma [K⁺] to the pre-ACTH value.

4. ACTH reduced plasma [K⁺] from 4.4±0.1 to 3.2±0.2 mmol/l but 3 days of potassium chloride infusion returned plasma [K⁺] to 4.3±0.2 mmol/l.

5. ACTH increased mean arterial pressure from 67±2 to 88±1 mmHg in the first 7 days and it remained elevated during potassium chloride infusion (91±5 mmHg on day 10).

6. Cardiac output rose with 7 days ACTH treatment from 4.9±0.2 to 6.0±0.6 l/min but fell progressively with potassium chloride infusion to 4.9±0.3 l/min on day 10.

7. These studies suggest that potassium status or extracellular [K⁺] may play a role in determining the haemodynamic profile associated with steroid-induced hypertension.

Key words: ACTH, haemodynamics, hypertension, potassium, sheep.

Introduction

Potassium depletion and/or hypokalaemia are commonly associated with clinical or experimental situations characterized by excessive production of steroid hormones with affinity for the 'mineralocorticoid' receptor. Potassium depletion has also been reported to increase cardiac output without any resulting change in blood pressure in the dog (Galvez, Bay, Roberts & Ferris, 1977; Knochel, Folley & Lipscomb, 1978). In these experiments potassium depletion was initiated by either dialysis (Galvez et al., 1977) or administration of 11-deoxycorticosterone acetate (DOCA) (Knochel et al., 1978) and was maintained by a low potassium diet.

ACTH-induced hypertension in the sheep is a model of steroid-induced hypertension which has characteristics of both 'mineralocorticoid' and 'glucocorticoid' administration but in which the hypertension appears to be due to a 'hypertensigenic' class of steroid action (Scoggins, Butkus, Coghlan, Denton, Fan, Humphery & Whitworth, 1978). Hypokalaemia is produced by ACTH without a significant increase in urinary potassium excretion (Scoggins, Coghlan, Denton, Fan, McDougall, Oddie & Shulkes, 1974). The hypertension produced by ACTH administration in the sheep is associated with a raised cardiac output, due in the first 3 days to a rise in heart rate (Scoggins, Allen, Coghlan, Denton, Graham, Humphery & Whitworth, 1979).

The aim of the present experiments was to examine the haemodynamic effect of restoring the extracellular [K⁺] to normal in animals receiving ACTH who were hypertensive, with a raised cardiac output and hypokalaemia.

Methods

All experiments were carried out on conscious adult cross-bred Merino sheep (40–45 kg), which were prepared and maintained as previously
described (Scoggins et al., 1974). ACTH (Synacthen CIBA-GEIGY) was injected intramuscularly (20 µg day⁻¹ kg⁻¹) for 11 days. Potassium chloride (10 mmol/h) was infused by constant intravenous infusion from days 8–10 of ACTH treatment.

Blood pressure, cardiac rate and cardiac output were measured daily between 10.00 and 12.00 hours. Cardiac output was measured by thermodilution with an aortic thermistor and injections of 10 ml of sodium chloride solution (154 mmol/l) at 0°C into the right atrium (Scoggins et al., 1979). Stroke volume and total peripheral resistance were calculated.

Water and food intake, urine output and plasma and urine [Na⁺] and [K⁺] were measured daily. Results are expressed as the mean ± SEM carried out with the Student’s t-test.

Results

Results for the pre-ACTH period, days 6 and 7 of ACTH treatment and for the 3 days of potassium chloride infusion are shown in Table 1.

Effect of ACTH administration

Seven days of ACTH administration produced a rise in mean arterial blood pressure from 67 ± 1 to 88 ± 1 mmHg associated with a rise in cardiac output from 4.9 ± 0.2 to 6.0 ± 0.6 l/min (P < 0.05). Cardiac rate rose from 63 ± 1 to 76 ± 9 beats/min (P < 0.05). Stroke volume was not changed by ACTH treatment. Calculated total peripheral resistance was slightly increased in three of the six sheep, resulting in an increase in the mean value from 14.0 ± 1 to 16.5 ± 2 units on day 7 of ACTH treatment.

Overall the metabolic effects of the 7 days ACTH administration before potassium chloride infusion were similar to those previously reported for 5 and 10 days ACTH treatment (Scoggins et al., 1974). With the exception of the small increase in peripheral resistance seen only on day 7 of ACTH treatment the haemodynamic effects of ACTH were identical with those found in a larger series of animals (Scoggins et al., 1979).

Effects of potassium chloride infusion during ACTH treatment

Infusion of potassium chloride solution (10 mmol/h) produced a rise in plasma [K⁺] to 4.0 ± 0.2 mmol/l after 24 h and to 4.3 ± 0.2 mmol/l on days 2 and 3 of infusion. Urinary potassium excretion rose from 281 ± 67 to 510 ± 90 mmol/day on day 3 of potassium chloride infusion. Plasma [Na⁺] was unchanged. Urinary sodium excretion was 136 ± 21, 142 ± 43 and 76 ± 14 mmol/day for the 3 days of potassium chloride infusion. Both water intake and urine volume rose within 24 h of potassium chloride infusion and remained elevated for the 72 h of infusion. Water intake rose from 2.41 ± 0.70 to a maximum of 3.88 ± 0.51 litres/day in the first 24 h of infusion. Urine volume was maximal on the second day of potassium chloride infusion (2.97 ± 0.78 litres/day).

Mean arterial pressure was not changed by potassium chloride infusion and it remained

| TABLE 1. Metabolic and haemodynamic effects of potassium chloride infusion during ACTH administration in six sheep |
| Results are means ± SEM. |
| Pre-ACTH | ACTH administration |
| | Day 6 | Day 7 | Day 8 (KCI) | Day 9 (KCI) | Day 10 (KCI) | Day 11 |
| Mean arterial pressure (mmHg) | 67 ± 1 | 88 ± 4 | 88 ± 1 | 92 ± 4 | 84 ± 3 | 91 ± 6 | 86 ± 4 |
| Cardiac output (l/min) | 4.8 ± 0.1 | 5.8 ± 0.4 | 6.0 ± 0.6 | 5.9 ± 0.6 | 5.4 ± 0.6 | 4.9 ± 0.3 | 5.3 ± 0.4 |
| Total peripheral resistance (units) | 14.0 ± 1 | 15.4 ± 1 | 16.5 ± 2 | 16.8 ± 1 | 16.3 ± 1 | 18.6 ± 1 | 17.3 ± 1 |
| Cardiac rate (beats/min) | 63 ± 0.6 | 72 ± 6 | 76 ± 9 | 80 ± 10 | 78 ± 10 | 77 ± 6 | 77 ± 8 |
| Stroke volume (ml/beat) | 79 ± 3 | 80 ± 6 | 76 ± 4 | 76 ± 6 | 72 ± 6 | 66 ± 4 | 66 ± 6 |
| Plasma [K⁺] (mmol/l) | 4.4 ± 0.1 | 3.2 ± 0.1 | 3.3 ± 0.2 | 4.0 ± 0.2 | 4.3 ± 0.3 | 4.3 ± 0.2 | 4.1 ± 0.2 |
| Urinary K excretion (mmol/day) | 193 ± 14 | 235 ± 43 | 281 ± 67 | 376 ± 84 | 426 ± 101 | 510 ± 90 | 284 ± 33 |
| Plasma [Na⁺] (mmol/l) | 145 ± 1 | 147 ± 1 | 146 ± 1 | 145 ± 1 | 145 ± 1 | 145 ± 1 | 147 ± 1 |
| Urinary Na excretion (mmol/day) | 64 ± 11 | 123 ± 34 | 156 ± 35 | 136 ± 21 | 142 ± 43 | 76 ± 14 | 47 ± 34 |
| Urine volume (l/day) | 0.58 ± 0.10 | 1.28 ± 0.30 | 2.48 ± 0.66 | 2.97 ± 0.78 | 2.71 ± 0.74 | 2.25 ± 0.49 | 1.09 ± 0.17 |
| Water intake (l/day) | 1.42 ± 0.20 | 1.60 ± 0.18 | 2.41 ± 0.70 | 3.88 ± 0.51 | 3.15 ± 0.54 | 3.23 ± 0.59 | 2.37 ± 0.34 |
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Elevated compared with the pre-ACTH values. In contrast cardiac output showed a progressive fall during the 3 days of potassium chloride infusion and by day 3 it had reached 4.9 ± 0.3 litres/min, a value which was not significantly different from the pre-ACTH level. These changes were associated with a fall in stroke volume and a rise in total peripheral resistance. Cardiac rate was unchanged.

In the 24 h after cessation of the potassium chloride infusion, during which ACTH administration was continued, cardiac output tended to rise (5.3 ± 0.4 litres/min) and total peripheral resistance to fall (17.3 ± 1 units). Other haemodynamic parameters did not change. Plasma [K+] also fell slightly to 4.1 mmol/l, associated with a large fall in urinary excretion of potassium (284 ± 33 mmol/day).

Discussion

The present study shows that restoration of the extracellular [K+] by potassium chloride infusion produces a change in the haemodynamic profile associated with ACTH administration in the sheep. Although blood pressure remained elevated and unchanged the raised cardiac output associated with ACTH treatment was progressively restored to the pre-ACTH level. Calculated total peripheral resistance was raised. These results confirm our hypothesis that changes in extracellular [K+] may play a role in determining the haemodynamic pattern associated with steroid-induced hypertension.

The precise mechanisms involved in the haemodynamic response to potassium chloride infusion in the ACTH-treated sheep are not known. One interpretation of the present results would be that the fall in cardiac output was unrelated to the potassium chloride infusion and would have occurred as a result of 'auto-regulation' of blood flow (Coleman & Guyton, 1969). However, this is unlikely to be the explanation since cessation of the potassium chloride resulted in an increase in cardiac output and ACTH treatment for up to 28 days results in sustained increases in cardiac output in the sheep (unpublished observations).

There have been many reports of the acute effects of changes on plasma [K+] on blood pressure and resistance in various vascular beds (Haddy, Scott, Florio, Daugherty & Huizenga, 1963; Roth, Anderson, Radawski, Scott & Haddy, 1969). From these studies Abbrecht (1972) predicted that potassium deficiency would increase total peripheral resistance and his chronic studies in vivo in the dog supported this conclusion. Others have reported contrary results. In two studies in the normotensive dog potassium depletion produced a fall in plasma [K+] and was associated with an elevation in cardiac output (Galvez et al., 1977; Knochel et al., 1978). Arterial pressure did not change, owing to a fall in total peripheral resistance. Although in other studies there have not been significant increases in cardiac output reported with potassium depletion (Bahler, 1971; Abbrecht, 1972; Lowensohn, Patterson & Olsson, 1978), in only one of these (Abbrecht, 1972) was there no trend towards either a fall in peripheral resistance (Bahler, 1971) or a rise in cardiac output (Lowenstein et al., 1978). In two earlier studies in hypertensive subjects potassium depletion has been reported to cause sodium retention and to reduce blood pressure (Perara, 1953; Fisher & Funcker, 1967). Potassium depletion also reduces blood pressure in the rat (Freed & Friedman, 1951).

A reduction in extracellular [K+] is a feature of 'mineralocorticoid'-induced hypertension in man and experimental animals. In the sheep the fall in plasma [K+] with ACTH or 'mineralocorticoid' administration is unrelated to the changes in urinary potassium excretion which commonly occur in other species. Although the haemodynamic effects of changing potassium status have not been assessed in detail in the normotensive sheep reduction of dietary potassium intake to 15 mmol/day has little effect on plasma [K+] or on basal blood pressure (Humphrey, Coghlan, Denton, Fan, Scoggins & Stewart, 1980). In the present study the infusion of potassium chloride did not result in significant increases in urinary sodium excretion above those seen with ACTH alone. ACTH produces only transient sodium retention in the sheep and after 4 days of ACTH urinary sodium excretion is usually slightly in excess of intake (Scoggins et al., 1974).

The haemodynamic profile in the established phase of primary aldosteronism (Tarazi, Ibrahim, Bravo & Dustan, 1973) resembles that seen with ACTH treatment in the sheep (Scoggins et al., 1979), since both are characterized by raised cardiac output and cardiac rate. The detailed haemodynamic effects of potassium repletion have not been reported in Conn's syndrome. However, correction of the hypokalaemia with spironolactone or amiloride also results in a fall in blood pressure in many patients (Ferris, Beevers, Boddy, Brown, Davies, Fraser, Kremer, Lever & Robertson, 1978). In studies examining the offset of effect of spironolactone the hypokalaemia, hypertension and a raised cardiac
output occur together (Distler, Just & Philipp, 1973).

The significance of the present studies in the sheep to the haemodynamic patterns observed in steroid-induced hypertension in man is not known but they do suggest that potassium status may play a role in the determining whether cardiac output or total peripheral resistance is raised. Haemodynamic studies in man are required to test this hypothesis.

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References


