Abstract. Glucocorticoid induced hypertension has been regarded as independent of sodium (Na), in contrast to mineralocorticoid induced hypertension, which is Na+-dependent. These studies compare the effect of Na+ depletion and potassium (K+) loading on glucocorticoid hypertension induced by cortisol in conscious sheep. Cortisol (480 mg/d) for 5 days, in sheep on a normal chaff diet (90–140 mmol/d Na+, 200–250 mmol/d K+) increased mean arterial pressure by 18 mmHg on day 5, increased plasma Na+ concentration, reduced plasma K+ concentration, and did not change urinary Na+ excretion. Following Na+ depletion (Na+ loss 603 ± 49 mmol) cortisol increased mean arterial pressure from 70 ± 1 mmHg to 76 ± 3 mmHg on day 5 (P < 0.001) and the increase in pressure was significantly less than the increase seen on the normal diet (P < 0.05). Plasma Na+ increased and plasma K+ decreased. Urinary Na+ and K+ excretion was unchanged. KCl loading (700–900 mmol/day) for 10 days had no effect on the maximum rise in mean arterial pressure (+18 mmHg with cortisol in K+ loaded sheep). Plasma Na+ and K+ fell, and urinary Na+ excretion increased during the infusion. These studies show that Na+ depletion, but not KCl loading, reduced cortisol induced hypertension in sheep. These data show that glucocorticoid hypertension is not independent of Na+ status.

Administration of steroids with predominantly glucocorticoid actions such as corticosterone and cortisol produce rapid onset hypertension associated with changes in body fluid distribution, but independent of Na+ status (Haack et al. 1977; Knowlton et al. 1952). Glucocorticoid induced hypertension developed in rats on a Na+ restricted diet (Knowlton et al. 1952), whereas mineralocorticoids (such as DOC) do not produce hypertension in rats on a Na+ restricted diet or in Na depleted sheep (Mills et al. 1984a). Although mineralocorticoid hypertension is regarded generally as Na+-dependent, glucocorticoid hypertension is accepted on the other hand as being independent of Na+ status. However, comprehensive studies of Na+ depletion (as distinct from Na+ restriction) are not available to describe the relationship between the magnitude of the hypertension and the degree of Na+ loss.

A relationship between the anti-hypertensive effects of K+ loading and Na+ status has been suggested. An anti-hypertensive effect of KCl loading has been established in several examples of experimental hypertension (Dahl et al. 1972; Meneely & Ball 1958; Goto et al. 1981; Suzuki et al. 1981a). The effect of KCl loading on steroid hypertension is not clear. A high K+ intake has been reported to prevent and reduce the mineralocorticoid hypertension produced by deoxycorticosterone (DOC) (Sato et al. 1982; Suzuki et al. 1981b; Mills et al. 1983, 1984a), but Rosenman et al. (1951) found that a high K+ intake had no effect on DOC hypertension. It has been postulated that K+ loading abolished DOC hypertension by a mechanism involving increased urinary Na+

The present study compared the hypertensive effects of cortisol in sheep on a ‘normal’ Na\(^+\) and K\(^+\) intake, with both K\(^+\) loaded and Na\(^+\) depleted animals.

Materials and Methods

Experiments were carried out in conscious adult cross-bred Merino ewes, body weight 33–40 kg, housed in individual metabolism cages. Each sheep was offered daily 0.8 kg of lucerne-oaten chaff (90–140 mmol/Na\(^+\) kg and 200–250 mmol/K\(^+\) kg) and water ad libitum. All animals had bilateral carotid arterial loops prepared at least 3 months prior to experimentation. Blood pressure (measured via an 18 gauge needle inserted in the carotid artery connected to a Statham pressure transducer), cardiac rate, water intake, urine output and food intake were recorded daily between 09.00 and 11.00 h. Sodium (Na\(^+\)) and potassium (K\(^+\)) analyses in plasma and urine were performed on a Technicon auto analyser. Experiments were carried out in random order, and at least 3 weeks was allowed between experiments in any individual sheep. Data were expressed as mean and standard error of the mean, and the results for each experiment analysed using analysis of variance, and between experiments by 2 way factorial analysis of variance.

Experiment 1. Cortisol infusion

Cortisol (Steraloids Inc) 480 mg/d was infused iv into four sheep for five days. Observations were made on three control days, the five infusion days and three post-infusion days.

Experiment 2. Cortisol infusion following Na\(^+\) depletion

Cortisol, 480 mg/d iv was infused for five days into 11 sheep following 48 h Na\(^+\) depletion produced by parotid duct cannulation and salivary drainage (Abraham et al. 1976). The 2 days of Na\(^+\) depletion followed one control day, and there were three post-infusion observation days.

Experiment 3. Cortisol infusion during KCl loading

Cortisol, 480 mg/d iv for five days, was infused into the same four sheep as in Experiment 1, following 10 days substitution of 2% KCl solution for drinking water. The 2% KCl was continued during the infusion and for a further three post-infusion observation days. Observations were made for the three days prior to and including the infusion and over the three post-infusion days.

Results

Experiment 1. Cortisol infusion (Fig. 1)

Cortisol (480 mg/d) increased MAP from 64 ± 1 mmHg control to a maximum of 86 ± 2 mmHg on day 1 (P < 0.001) and to 82 ± 5 mmHg day 5 (P < 0.001). Heart rate increased from 60 ± 2 beats/min control to 83 ± 8 beats/min day 5 (P < 0.001) and was significantly raised during the 3 post-infusion days. Plasma Na\(^+\) concentration increased from 144 ± 1 mmol/l control to 149
± 1 mmol/l day 5 (P < 0.001), and fell to 141 ± 1 mmol/l on the first post-infusion day (P < 0.01). Plasma K⁺ concentration fell from 4.3 ± 0.1 mmol/l control to 2.1 ± 0.3 mmol/l day 5 (P < 0.001).

Water intake 1.99 ± 0.13 l/d control and 1.59 ± 0.67 l/d on day 5 and urine volume (0.56 ± 0.06 l/d control, 0.64 ± 0.13 l/d on day 5), did not change during the infusion. Urinary Na⁺ excretion was unchanged during the infusion, 81 ± 8 mmol/d control, 47 ± 23 mmol/d on day 1 and 43 ± 12 mmol/d day 5, but there was a natriuresis, 259 ± 73 mmol/d on the first post-infusion day (P < 0.001). Urinary K⁺ excretion decreased, 227 ± 7 mmol/d control, to 108 ± 29 mmol/d on day 5 (P < 0.05).

Experiment 2. Cortisol infusion following Na⁺ depletion (Fig. 2)

In 11 sodium depleted sheep with Na⁺ loss 603 ± 49 mmol, cortisol (480 mg/d iv) increased MAP from 70 ± 1 mmHg to 76 ± 3 mmHg on day 5 (P < 0.001). Heart rate increased from 67 ± 2 beats/min to 77 ± 5 beats/min on day 5 (P < 0.001). Plasma Na⁺ increased on day 4 only, from 143 ± 1 mmol/l to 145 ± 1 mmol/l (P < 0.05), and plasma K⁺ decreased from 4.3 ± 0.1 mmol/l to 3.8 ± 0.2 mmol/l on day 5 (P < 0.001).

Water intake did not change with cortisol infusion, 2.05 ± 0.01 l/d to 2.46 ± 0.27 l/d on day 5. Urine volume increased from 0.35 ± 0.04 l/d to 0.92 ± 0.23 l/d on day 5 (P < 0.001), and there was a post-infusion diuresis, 1.20 ± 0.22 l/d (P < 0.001). Urinary Na⁺ excretion was unchanged, 17 ± 9 mmol/d control, 26 ± 19 mmol/d on day 5, and there was a post-infusion natriuresis, 63 ± 12 mmol/d post-infusion d (P < 0.001). Urinary K⁺ excretion was unchanged, 135 ± 12 mmol/d control to 198 ± 21 mmol/d on day 5.
The Na⁺ depleted animals could be arbitrarily divided into two groups. Moderate Na⁺ depletion with Na loss 300–500 mmol (441 ± 34 mmol, n = 4), with average increase in MAP over five days of 7 mmHg. Severe Na⁺ depletion with a loss in the range of 500–900 mmol (603 ± 49 mmol, n = 7) and an average increase in MAP of 4 mmHg.

Experiment 3. Cortisol infusion during KCl loading (Fig. 3)

Cortisol infusion (480 mg/d) during K⁺ loading increased MAP from 70 ± 2 mmHg control to a maximum of 88 ± 2 mmHg day 1 (P < 0.001), and MAP remained elevated until day 5, 83 ± 3 mmHg (P < 0.001).

Heart rate increased from 66 ± 2 beats/min control to a maximum of 95 < 2 beats/min on day 4 (P < 0.001). Plasma Na⁺ concentration fell from 143 ± 1 mmol/l control to 139 ± 1 mmol/l day 5 (P < 0.01). Plasma K⁺ concentration was raised by 7–10 days K⁺ loading (P < 0.05) but fell from 4.8 ± 0.1 mmol/l to 3.8 ± 0.2 mmol/l day 1 (P < 0.01) during cortisol infusion.

Fluid intake (increased by 10 days K⁺ loading (P < 0.05)) rose from 3.7 ± 0.12 l/d control to 3.73 ± 0.11 l/d day 4 only (P < 0.05). Urine volume increased from 1.38 ± 0.12 l/d control to 2.10 ± 0.18 l/d day 5 (P < 0.01). Urinary Na⁺ excretion increased from 72 ± 14 mmol/d control to 177 ± 62 mmol/d day 4 only (P < 0.01). Urinary K⁺ excretion did not change.

Statistical analyses

Cortisol treatment in the 11 Na⁺ depleted sheep increased MAP from 70 ± 6 mmHg (mean ± SD) to an average of 75 ± 9 mmHg (mean MAP for the five days of cortisol infusion in Na⁺ depleted sheep). Two way factorial analysis showed the increase in MAP in Na⁺ depleted sheep was significantly less than that in Na⁺ replete sheep (64 ± 3 mmHg control, 83 ± 6 mmHg average for cortisol infusion, P < 0.05).

For each of the 11 Na⁺ deplete sheep, a regression analysis comparing the degree of Na⁺ loss over the two days of acute Na depletion, with the average increase in MAP over the five days of cortisol infusion, showed a correlation between the parameters of r = −0.54, P = 0.08 (Fig. 49).

The average increase in MAP with cortisol treatment in the moderate Na⁺ depleted sheep was significantly less than the replete sheep (P < 0.01). Similarly, the severe Na⁺ depleted sheep also had a smaller rise in MAP (P < 0.001).

A comparison between K⁺ loaded sheep and sheep on a chaff diet showed K⁺ loading did not modify the increase in MAP with cortisol treatment (70 ± 7 mmHg control, 86 ± 5 mmHg average MAP for the five days of cortisol infusion in K⁺ loaded sheep). The MAP rise during K⁺ loading was significantly greater than that found in Na⁺ depletion (P < 0.001).
Fig. 4. Shows the average increase in blood pressure (MAP) over the 5 days of cortisol (480 mg/day) infusion compared with the degree of Na⁺ loss for each of the 11 Na⁺ depleted sheep. The average increase in MAP for the 4 sheep on a 'normal' diet is also shown.

Discussion

Cortisol is the major naturally occurring glucocorticoid in sheep. It produced increased water intake and urine volume at an infusion rate (120 mg/d iv) which is close to the upper physiological range and additional mineralocorticoid-like effects, (hypernatraemia and hypokalaemia) at higher rates of infusion (480 mg/d iv) (Whitworth et al. 1979). Cortisol administration in the present study produced hypertension and hypokalaemia without urinary Na⁺ retention, confirming our previous studies (Whitworth et al. 1979). Cortisol raised blood pressure in the rat (Friedman et al. 1952) and in man at 6–8 mg/h (Whitworth et al. 1984) but reduced blood pressure in the dog (45 mg/day) (Lohmeier & Kastner 1982). Acute Na⁺ depletion blunted the rise in blood pressure seen with cortisol administration in the present study, but the hypertension was unaffected by K⁺ loading.

The rise in heart rate (rather than reflex bradycardia) seen in association with the rise in pressure raises the possibility of increased sympathetic nervous activity, as in DOC hypertension (Chalmers 1978).

Cortisol infusion increased MAP in the 11 Na⁺ depleted animals, +6 mmHg on day 5, but average increase in pressure was less than on the normal chaff diet. The sheep depleted of 300–500 Na⁺ mmol were analysed separately, and this degree of depletion also reduced cortisol hypertension. Acute Na⁺ depletion blocked DOC hypertension in the sheep (Na⁺ loss 580 ± 110 mmol) (Mills et al. 1984a), but not ACTH hypertension (Na⁺ loss 476 ± 46 mmol) (Coghlan et al. 1976). However, with profound Na⁺ loss (500–900 mmol) hypertension of all types may be blocked because of fluid volume contraction.

K⁺ loading caused a dose-related decrease in deoxycorticosterone (DOC) saline hypertension in the rat, thought to involve the natriuretic effects of K⁺ (Suzuki et al. 1981b; Fujita & Sato 1983, 1984). If K⁺ acts through increased Na⁺ excretion, then the physiological effects of K⁺ should be similar to Na⁺ depletion. In the sheep, K⁺ loading alone produced negative Na⁺ status, an increase in cardiac output and extracellular fluid volume, a fall in peripheral resistance, but had no effect on the pressor responsiveness to angiotensin II, AVP, noradrenaline or tyramine (Mills et al. 1985). In contrast, uncompensated acute Na⁺ depletion increased peripheral resistance, reduced cardiac output and extracellular fluid volume and plasma volume, and reduced pressor responsiveness to angiotensin II (Coghlan et al. 1977; McDougall et al. 1978; Mason et al. 1984). K⁺ loading was effective in blocking DOC hypertension in sheep (Mills et al. 1984a), but did not reduce 9α-fluorocortisol (2 mg/day) hypertension in the sheep, whereas Na⁺ depletion was effective in reducing both DOC and 9α-fluorocortisol hypertension (Mills et al. 1984a,b; Whitworth et al. 1986). These results suggested that in the
sheep K+ may not be acting through mechanisms involving Na+. Cortisol (at 480 mg/day) hypertension was reduced by Na+ depletion but unaffected by K+ loading, which increased urinary Na+ excretion but did not block the hypertension. These results are not consistent with the proposal that the anti-hypertensive effects of K+ loading work via mechanism(s) involving modified Na+ handling.

In summary, cortisol induced hypertension in sheep is blunted by Na+ depletion, but KCl loading has no effect on the hypertensinogenic action of cortisol.

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References


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