The effect of potassium loading and sodium depletion on DOC induced hypertension in sheep


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Abstract. This study examines the physiological effects of 11-deoxy cortisolone (DOC) at 2 rates of continuous iv infusion for 5 days in conscious sheep. DOC treatment, in sheep on Na and K intake 80 and 120 mmol/day respectively, increased mean arterial pressure (MAP) by 12 mmHg at 50 mg/day and by 10 mmHg at 5 mg/day. Both rates of infusion raised plasma [Na] and lowered plasma [K]. Urinary Na excretion fell on the first day of infusion. On cessation of infusion there was a natriuresis. A high K intake of approximately 800 mmol/day for 7 to 10 days prior to and during DOC (5 mg/day) treatment abolished the rise in blood pressure, the rise in plasma [Na], the initial Na retention and the post-DOC natriuresis. Plasma [K] rose with high K intake and fell with DOC. Na depletion prior to DOC infusion (5 mg/day) prevented the rise in MAP. Urinary Na excretion remained low and plasma [K] fell. This study shows that K loading abolishes DOC hypertension in sheep by a mechanism which may involve modification of the Na retaining effects of the steroid.

The hypertensive and ‘mineralocorticoid’ properties of DOC are well established. Grollman et al. (1940) reported that DOC raised blood pressure in the rat, and it is also pressor in dogs (Kuhlman et al. 1939) and pigs (Berecek & Bohr 1978). DOC administration, usually together with reduction in renal mass and a high sodium (Na) intake, has become the most studied model of adrenocortical steroid dependent hypertension. It is considered by many to be the classical example of mineralocorticoid induced hypertension. Although a high physiological rate of DOC infusion (1.2 mg/day) had no effect on blood pressure in sheep (Fan et al. 1975), higher pharmacological rates of infusion have not been studied.

The anti-hypertensive properties of a high K diet were first reported by Meneely & Ball (1958) and Dahl et al. (1972) who showed that it increased the survival time of salt loaded rats and moderated the hypertensive effects of Na loading. The effect of K loading on steroid hypertension remains unclear. Although it appears to prevent and reduce DOC hypertension in rats (Suzuki et al. 1981a; Sato et al. 1982), others found K loading accentuated DOC hypertension in the same species (Rosenman et al. 1951).

In the present study the effects of continuous DOC infusion have been examined in conscious sheep on a normal level of K intake and in animals K loaded for 7—10 days prior to DOC infusion.

Materials and Methods

Nineteen adult crossbred oophorectomized merino ewes (body weight 35—45 kg) with bilateral carotid arterial loops were used in this study. They were housed in individual metabolism cages to allow for separate collections of urine and faeces and were offered daily 0.8 kg of lucerne/oaten chaff containing 90—120 mmol/kg Na and 200—250 mmol/kg K with water ad libitum.

Experiment 1

DOC (Steraloids) was continuously infused iv at 5 mg/day (208 µg/h) for 5 days into 6 sheep and at 50 mg/day (2.08 mg/h) for 5 days into 4 sheep.
**Experiment 2**

The effects of continuous infusion of DOC at 5 mg/day for 5 days were examined in 6 sheep in which drinking water was replaced by a 2% KCl solution commencing 7 to 10 days prior to the DOC infusion.

**Experiment 3**

Acute Na depletion was produced in 4 sheep by 48 h uncompensated parotid salivary drainage following parotid duct cannulation (Abraham et al. 1976). Na depletion produced a Na loss of 580 ± 110 mmol over the 48 h. DOC (5 mg/d) was infused continuously for 5 days during which the animals received <50 mmol Na/day and 200–300 mmol K/day.

Mean arterial blood pressure (MAP) and heart rate (HR) were recorded daily at around 10.00 h via an indwelling needle in the carotid artery connected to a Bentley pressure transducer and Gould-Brush amplifier and recorder. Plasma [Na], [K] and osmolality and fluid and electrolyte balance were measured daily. Blood samples were taken from the carotid artery by needle puncture.

Na and K analyses in plasma and urine were performed on a Technicon auto analyser. Results were expressed as the mean and standard error of the mean and have been analysed by analysis of variance.

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**Results**

**Experiment 1 (Fig. 1).**

DOC treatment at 5 mg/day raised MAP from 70 ± 1 to 80 ± 3 mmHg (P < 0.01) on day 5 of infusion. Cardiac rate did not change. Plasma [Na] increased from 145 ± 1 to a maximum of 148 ± 1 mmol/l (P < 0.01) on day 4. Plasma osmolality was increased from 290 ± 1 to 294 ± 3 mOsm/kg (P < 0.05) on day 2 only. Plasma [K] fell from 4.3 ± 0.1 to 2.6 ± 0.2 mmol/l (P < 0.001) by day 5. Urine volume decreased on the first day of infusion from 0.45 ± 0.01 to 0.22 ± 0.05 l/day (P < 0.05). Water intake did not change. There was significant urinary Na retention on the first infusion day (70 ± 10 pre-infusion to 35 ± 25 mmol/day, P < 0.05) followed by a post-DOC natriuresis, 160 ± 20 mmol/day (P < 0.01) on the first post-infusion day. Urinary K excretion decreased significantly on the first infusion day from 120 ± 10 to 45 ± 20 mmol/day (P < 0.01). Hæmatocrit did not change, 23 ± 1% control and 22 ± 1% day 5.

DOC treatment at 50 mg/day raised MAP from 63 ± 2 to 75 ± 2 mmHg (P < 0.001) on day 5, plasma [Na] from 144 ± 1 to 149 ± 2 mmol/l (P < 0.001) on day 5, and plasma osmolality from 292 ± 1 to a maximum of 298 ± 3 mOsm/kg (P < 0.001) on day 4. Plasma [K] fell from 4.3 ± 0.1 to 2.2 ± 0.2 mmol/l (P < 0.001) on day 5. Cardiac rate did not change. Water intake did not change during the infusion but was decreased on the first day following DOC withdrawal (from 1.80 ± 0.10 pre-infusion to 0.90 ± 0.40 l/day, P < 0.01). Urine volume did not change during the infusion but there was a post-infusion diuresis (1.3 ± 0.04 l/day compared with 0.50 ± 0.01 con-
There was initial Na retention with urinary Na excretion falling from 80 ± 10 to 18 ± 5 mmol/day \((P < 0.05)\) on day 1. There was a first post-infusion day natriuresis of 190 ± 20 mmol/day \((P < 0.001)\). Urinary K excretion decreased on the first infusion day from 145 ± 20 to 81 ± 30 mmol/day \((P < 0.05)\) and was also reduced on day 5 of infusion \((80 ± 30 \text{ mmol/day}, P < 0.05)\).

A comparison of the effects of DOC infusion at 5 and 50 mg/day compared with those obtained in previous studies at 1.2 mg/day (Fan et al. 1975) are shown on Fig. 2.

**Fig. 2.**
The effect of 3 rates of infusion of DOC on MAP, plasma [Na], plasma [K] and urinary Na excretion. Statistics compare the change on the 1st and 5th day of infusion with the pre-infusion value \((*P < 0.05, **P < 0.01, ***P < 0.001)\).

**Experiment 2 (Fig. 3)**
In sheep drinking 2% KCl, DOC treatment at 5 mg/day had no significant effect on MAP \((71 ± 1 \text{ pre-infusion}, 75 ± 5 \text{ mmHg on day 5})\) or plasma [Na]. Plasma [K] rose pre-infusion with the K loading and then fell, from 4.9 ± 0.1 to 4.2 ± 0.2 mmol/l on day 5 of DOC \((P < 0.01)\). Urine volume, also raised by K loading, increased from 1.1 ± 0.1 l/day pre-infusion to 1.5 ± 0.2 l/day \((P < 0.05)\) on day 5. Urinary Na excretion did not change during the DOC infusion. Urinary K excretion was increased 3–4-fold by the K loading procedure but did not change with DOC infusion.
**Experiment 3 (Fig. 4)**

DOC (5 mg/day) administration in Na depleted sheep had no effect on MAP (Fig. 4). Cardiac rate 68 ± 3 beats/min prior to DOC was also unchanged except for a fall to 59 ± 1 beats/min (P < 0.05) on day 3. Plasma [Na] increased from 140 ± 1 to 144 ± 2 mmol/l (P < 0.01) with DOC and plasma [K] fell from 4.5 ± 0.1 to 4.1 ± 0.3 mmol/l (P < 0.01). Urinary Na excretion (which was low due to Na depletion) was unchanged by DOC but there was an increase in Na excretion on the third post-infusion day. Changes in K excretion, urine volume and water intake during DOC infusion were small but there was an increase in both urine output and K excretion in the first 24 h post-infusion.

**Discussion**

DOC at a pharmacological rate of infusion on a normal Na and K intake produced an increase in MAP and plasma [Na] associated with a fall in plasma [K] and a transient period of urinary Na retention. The increase in blood pressure was maximal at 5 mg/day even though the hypokalaemia was more pronounced at the higher rate of infusion.

DOC is a classical 'mineralocorticoid' and Na dependency is a characteristic of this type of hypertension. Many studies have demonstrated an absence of DOC hypertension in animals on a low Na diet (Grekin et al. 1982; Selve et al. 1943). In the sheep Na depletion prior to administration of DOC also prevented the development of hypertension. In the rat sensitisation procedures such as substitution of drinking water with saline and/or reduction in renal mass which accentuate the Na retention are nearly always used to produce DOC hypertension although DOC hypertension has been reported in rats on a normal Na intake (Hall & Hall 1969).

In the rat and pig, like the sheep, pharmacological amounts of DOC have to be used to produce hypertension. Given a blood clearance rate of 90 l/h, blood DOC concentration would be 230 ng/100 ml at an infusion rate of 5 mg/day and 2300 ng/100 ml at 50 mg/day. These concentrations are very much higher than those found in ACTH treated sheep (Scoggins et al. 1974) (5.6 ± 0.5 ng/100 ml), under conditions of maximal adrenal stimulation. At 1.2 mg/day, a rate of infusion which had no physiological effect (Fan et al. 1975), the calculated blood DOC concentration of 55 ng/100 ml is still ten times that found with ACTH stimulation. Recently Bohr & Mitchell (1982) have reported that sheep receiving 100 mg/kg body weight DOCA develop hypertension. Similar doses of DOCA also raise blood pressure in pigs (Berecek & Bohr 1978). In the pig DOC can produce hypertension without prior reduction in renal mass or increase in Na intake. However, the Na intake of the pigs is much higher on a body weight basis than that of the sheep used in the present study.

The increase in blood pressure found with DOC in the present study is less than that seen with ACTH (Scoggins et al. 1974) or with some other steroids (Whitworth et al. 1979; Scoggins et al. 1983). Infusions of cortisol at 480 mg/day—a pharmacological rate of infusion—raise MAP by 25 mmHg associated with evidence of in vivo...
'mineralocorticoid' activity (Whitworth et al. 1979). 9α-fluorocortisol - a steroid with affinity for both the type 1 'mineralocorticoid' ovine renal receptor and type 2 'glucocorticoid' receptor also produces much greater effects on blood pressure at rates of infusion which reduce Na excretion and lower plasma [K] (Coghlan et al. 1979). In contrast, a pharmacological rate of infusion of aldosterone has no effect on blood pressure even though Na excretion and plasma [K] fell (Whitworth et al. 1979). Taken together these data suggest that there is no simple relation between the ability of a steroid to retain Na - a 'mineralocorticoid' effect - and its ability to raise blood pressure.

A large number of studies in a wide range of species has failed to characterise the physiological mechanisms by which 'mineralocorticoid' hormones such as DOC raise blood pressure (Scoggins et al. 1982; Mitchell & Bohr 1983; Schalekamp et al. 1981). Although many different mechanisms have been proposed these cannot individually explain DOC hypertension under all circumstances.

In the K loaded sheep DOC administration failed to raise blood pressure. Similar findings have been reported in K loaded rats. In the K loaded animals there was no fall in urinary Na excretion with DOC infusion. The diuretic and natriuretic effects of K loading together with changes in renal sympathetic tone have been proposed as being responsible for the anti-hypertensive effect of K loading (Sato et al. 1982; Suzuki et al. 1981b). In sheep K loading does not produce a sustained natriuresis, within 3-4 days Na excretion returns to normal. However, K loading for 7-10 days did block the Na retaining effects of DOC administration. Failure to retain Na has been proposed as an explanation for the absence of hypertension (Suzuki et al. 1981a,b). However, although the renal 'mineralocorticoid' effects of DOC were blocked there was a fall in plasma [K] from the high level associated with K loading back to the normal range. Sheep have the ability to rapidly shift K from the extracellular to the intracellular space and this occurs without change in urinary K excretion (Scoggins et al. 1973). Pigs are also able to redistribute K under the influence of DOC (Grekin et al. 1982).

In ACTH induced hypertension, another type of steroid dependent hypertension, K loading has little effect on the rise in blood pressure (Mills et al. in press). However, this type of hypertension is not dependent on Na status (Humphrey et al. 1983) and can not simply be explained by the 'glucocorticoid' and 'mineralocorticoid' activities of the major ovine corticosteroids (Scoggins et al. 1982, 1983).

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References


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