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31. Steroids and Hypertension

ADRENOCORTICAL STEROID HORMONES IN PRODUCTION OF HYPERTENSION IN SHEEP

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SUMMARY

In the conscious sheep the contribution of physiological and pharmacological levels of the two major classes of adrenal steroid hormones "glucocorticoids" and "mineralocorticoids" in the production of hypertension have been examined using the model of ACTH induced hypertension, an adrenally dependent steroid hypertension which can be reproduced by infusion over 5 days of a combination of cortisol (5 mg/h), corticosterone (0.5 mg/h), 11-deoxycortisol (1 mg/h), DOC (25 mg/h), aldosterone (3 μg/h), 17α-hydroxyprogesterone (1 mg/h) and 17α,20α-dihydroxyprogesterone (500 μg/h) at rates to produce blood levels seen with ACTH treatment. Hypertension cannot be reproduced by infusion of any of these steroids individually at these rates. Omission of 17α-hydroxyprogesterone and 17α,20α-dihyroxyprogesterone from the infusion results in similar metabolic effects to ACTH but only small increases in blood pressure. These studies together with *in vitro* and *in vivo* assessment of the lack of "mineralocorticoid" and "glucocorticoid" activity of 17α-hydroxyprogesterone and 17α,20α-dihydroxyprogesterone have led us to postulate a new class of steroid action—hypertensinogenic steroids. Infusion of 9α-fluorocortisol (9α-FF) at 0.2 mg/day increases blood pressure without the associated metabolic effects seen at higher dose (0.63 or 2 mg/day). Based on *in vitro* renal receptor affinity of 9α-FF for "mineralocorticoid" and "glucocorticoid" receptors, doses of aldosterone and cortisol approx. equivalent to either 0.63 or 2 mg/day of 9α-FF reproduce the metabolic effects of 9α-FF but have only a small effect on blood pressure. These data suggest that the hypertensive effects of adrenal steroid hormones are not simply related to their "mineralocorticoid" or "glucocorticoid" activity and support our proposal of a further class of steroid hormone action.

Excessive production or administration of adrenal steroid hormones is known to produce hypertension in both clinical and experimental settings. It is generally believed that the hypertension is due to the "mineralocorticoid" and/or "glucocorticoid" activities of these steroid hormones.

Based predominantly on work in the rat, the characteristics of "mineralocorticoid" and "glucocorticoid" hypertension have been defined. The classical characteristics of "mineralocorticoid" hypertension [1–5] are as follows:

(1) Onset is slow. (2) The rise in blood pressure is associated with vol. expansion due to salt and water retention. (3) Hypertension is potentiated by a high sodium intake and does not occur with a sodium poor diet. (4) Plasma potassium concentration is reduced. (5) Plasma renin concentration is reduced. (6) Hypertension is dosage dependent. (7) Hypertension is potentiated by reduced renal mass.

Experimental "glucocorticoid" hypertension [1, 2, 5, 6] is characterized by the following:

(1) Onset is rapid. (2) Hypertension is associated with internal body fluid redistribution. (3) Hypertension is independent of dietary sodium intake. (4) Plasma potassium concentration is rarely low. (5) Plasma renin concentration is variable and may be low, normal or high. (6) Effect may be due to weak "mineralocorticoid" activity if pharmacological dose is used.

The distinction between "glucocorticoid" and "mineralocorticoid" effects is often one of degree and depends predominantly on the dosage of steroid used.

Over the past 35 years a number of experimental models have been used to investigate the role of steroid hormones in production of hypertension [7–11] (Table 1). A variety of other steroids have also been reported to cause hypertension when administered to rats, *e.g.* 18-hydroxy-DOC, aldosterone, estrogen, methylandrostenediol, 9α-fluorocortisone. Similarly, various abnormalities of steroid metabolism have been reported in human essential hypertension, including increased secretion of 18-hydroxy-DOC, 16α,18-dihydroxy-DOC and 16β-hydroxy-DHEA.

Despite the vast literature on experimental steroid hypertension there is a surprising lack of data, except in the rat. In this species blood pressure response depends on a whole host of factors including the strain, age and sex of the animal; the dosage, form, mode and duration of the steroid hormone administration and the electrolyte status and renal mass of the animals. Often the steroid or steroids responsible for the hypertension is not known and the mechanism of increase in blood pressure is frequently unresolved.

ACTH hypertension in sheep [12] is characterized by a significant rise in both systolic and diastolic blood pressure within 24 h after ACTH administration (80–100 I.U. daily intramuscularly in divided

Table 1. Major models of experimental steroid hypertension

DOCA salt ± nephrectomy	Rat	Selye, 1943 [7]
Adrenal regeneration hypertension	Rat	Skelton, 1955 [8]
Metapyrone	Dog	Adlin and Channick, 1966 [9]
Salt-sensitive genetic hypertension	Rat	Dahl, 1962 [10], Rapp and Dahl, 1971 [11]
ACTH hypertension	Sheep	Scoggins *et al.* 1973 [12]

doses). This rise in blood pressure reaches a maximum between the third and fifth day of ACTH administration, of about 20 mm Hg. The hypertension is rapidly reversed on ACTH withdrawal, blood pressure falling to normal limits within 24 h. The rise in blood pressure is associated with hypokalaemia in the absence of any significant change in urinary potassium excretion, hypernatraemia, an increase in both water drinking and urine output, initial urinary sodium retention followed by a natriuresis and a large natriuresis coincident with the fall of blood pressure on ACTH withdrawal [7]. Renin and angiotensin II levels are in the low normal range for sodium replete sheep [13]. The hypertension has been shown to be adrenally dependent and ACTH infusion to adrenalectomized sheep maintained on basal levels of steroid replacement does not produce hypertension.

This model of ACTH hypertension in sheep has a number of advantages over other major models of steroid hypertension. Although the dosage of ACTH is high, the hypertension is dependent on endogenous adrenal steroid production and is thus due to physiological rather than pharmacological concentrations of adrenal steroids. The model has, as a result, potential for understanding the mechanisms of action of steroid hormones, not seen in pharmacological models where massive doses of steroid are given, *e.g.* DOCA salt hypertension in the rat. ACTH hypertension is rapid in onset and offset and does not require dietary modification or reduction in renal mass. Sheep are large placid animals and tolerate a variety of experimental procedures with equanimity. This allows easy examination of haemodynamic parameters and metabolic balance data which is difficult to obtain in smaller animals. ACTH hypertension is reproducible in that firstly, repeated administration of ACTH to the same animal results in similar increments of blood pressure with each experiment (*e.g.* in 1 animal in 5 experiments over 41 months the mean increment in mean arterial pressure was 22 ± 2 mm Hg) and, secondly, hypertension of a similar degree was produced in almost all of the 50 or so sheep we have studied.

ACTH hypertension in the sheep is not associated with an increase in body weight or extracellular fluid vol. but plasma vol. is expanded from day 1–day 5 [14] suggesting an internal body fluid redistribution. In some preliminary studies of cardiac output using the dye dilution method we demonstrated an increase in cardiac output on day 5 of ACTH treatment [15]. Recently we have studied a larger series of animals ($n = 15$) using a thermodilution technique. In this series [16], cardiac output was significantly increased on the first day of ACTH treatment and remained elevated for the duration of ATCH administration (Fig. 1). On ACTH withdrawal cardiac output fell and returned to base-line values within 48 h. Total peripheral resistance was unchanged. Cardiac rate was increased as in previously reported studies [12] and stroke vol. was increased by day 4 of ACTH. However, in adrenally denervated sheep, hypertension occurred following ACTH administration in the absence of any such rise in cardiac output [15], suggesting that the increase in output was not essential for the production of the hypertension. It remains to be established whether the increase in cardiac output has a primary role in production of the hypertension or whether the cardiac output rise is simply associated with steroid, administration.

The role of sodium in this model has been extensively studied [17, 18]. As indicated above, dietary supplementation of sodium is not necessary for production of ACTH hypertension. Normal daily dietary intake for these sheep is 0.8 kg lucerne-oaten chaff, containing 80–120 mmol Na/kg giving a daily intake of 60–100 mmol Na.

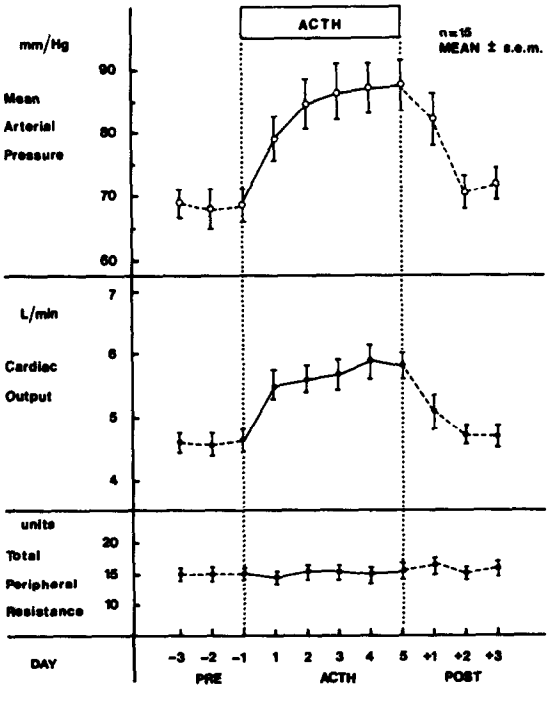

Fig. 1. Changes in mean arterial pressure, cardiac output and calculated total peripheral resistance (mean ± S.E.M.) in ACTH-treated sheep. ($n = 15$).

Studies involving acute sodium depletion (*via* parotid cannulation over 48 h which removes about 20% of total exchangeable sodium) failed to prevent the development of ACTH hypertension, indicating that the blood pressure rise cannot be explained in terms of sodium retention alone. Parotid cannulation during the period of ACTH administration does lower the blood pressure but not to control levels [17]. Chronic sodium depletion, on the other hand, markedly blunts the blood pressure response to ACTH. In a series of sorghum grain fed animals (whose diet contains <5 mmol Na/day) the blood pressure response to ACTH, although significant, was small (a 6 mm Hg rise in mean arterial pressure on day 5, $n = 10$) [18].

ACTH hypertension has also been produced in anephric animals [19]. It is not clear whether or not the kidney plays an important role in the genesis of ACTH hypertension from these studies however, as ACTH is known to produce plasma vol. expansion in the sheep and this mechanism alone may be sufficient in the anephric animal to elevate blood pressure.

Reduction in renal mass has no effect on blood pressure over a 6-month period in sheep on a normal diet. However, reduction of renal mass significantly accentuated ACTH induced hypertension from day 3 of administration onwards (intact sheep ΔMAP + 16 mm Hg on day 5, compared with reduced renal mass +36 mm Hg, day 5, $P < 0.05$, $n = 6$) [20]. Addition of sodium chloride (15 mmol Na/kg/sheep/day) further potentiated the blood pressure rise, ΔMAP in reduced renal mass sheep following ACTH and sodium chloride loading being +66 mm Hg on day 5 ($n = 2$) [20]. The potentiation of ACTH hypertension by reduction in renal mass suggests a vol.-dependent component of the hypertension in relation to reduction in renal excretory capacity for salt and water.

Administration of ACTH to sheep is associated with a highly significant increase in blood levels of cortisol, 11-deoxycortisol, corticosterone and deoxycorticosterone [16]. Plasma aldosterone is elevated on the first day of ACTH administration but by the fifth day is at the lower end of the normal sodium replete range. Infusion of these steroids hormones (at rates appropriate to give blood concentrations similar to conditions of ACTH stimulation) did not reproduce the blood pressure effects of ACTH, although infusion of cortisol, 11-deoxycortisol, deoxycorticosterone, corticosterone and aldosterone together as a combined steroid infusion did reproduce the metabolic effects of ACTH administration [21]. Given that infusion of the major ovine adrenal steroid hormones alone or in combination failed to reproduce the hypertension seen with ACTH, it was postulated that an additional adrenal steroid hormone was responsible for the rise in blood pressure.

A variety of other steroids were identified in ovine adrenal venous blood, as summarized in Table 2. Addition of 17α,20α-dihydroxyprogesterone (500 μg/h) with 17α-hydroxyprogesterone (1 mg/h) to the combined steroid infusion was then shown to reproduce the blood pressure effects of ACTH [17]. We have further shown in 9 sheep, all of whom received ACTH or combined steroid infusion ± 17α,20α-dihydroxyprogesterone ± 17α-hydroxyprogesterone in random order, that blood pressure (day 5) and metabolic effects were identical with ACTH, combined steroid infusion plus 17α,20α-dihydroxyprogesterone or combined steroid infusion plus 17α,20α-dihydroxyprogesterone plus 17α-hydroxyprogesterone (Fig. 2). All three regimes produced blood pressure increments which were significantly greater than those seen with combined steroid infusion alone, in these same 9 animals [18]. This finding of additional hypertensinogenic activity with 17α,20α-dihydroxyprogesterone and 17α-hydroxyprogesterone led us to consider whether steroid hypertension in ACTH-treated sheep could be explained simply in terms of the "mineralocorticoid" or "glucocorticoid" potencies of the relevant adrenal steroid hormones. Accordingly, the ability of 17α,20α-dihydroxyprogesterone and 17α-hydroxyprogesterone to displace either [^{3}H]-dexamethasone or [^{3}H]-aldosterone from renal receptors from adrenalectomized sheep was assessed. Neither of these hormones (at the rates infused together with combined steroids to produce hypertension in sheep) showed significant binding to either "mineralocorticoid" (Type 1) or "glucocorticoid" (Type 2) receptors. Infusion of 17α-hydroxyprogesterone (1 mg/h) or 17α,20α-dihydroxyprogesterone (500 μg/h) alone (rates appropriate for conditions of ACTH stimulation) had no effect on blood pressure in sheep. Similarly, they had no effect on plasma or urine electrolytes, salivary Na/K ratio, water drinking, urine vol., blood glucose

Table 2. Steroids identified in ovine adrenal venous blood

Trivial name	Generic name
Cortisol	4-Pregnen-11β,17α,21-triol-3,20-dione
Corticosterone	4-Pregnen-11β,21-diol-3,20-dione
11-Deoxycortisol	4-Pregnen-17α,21-diol-3,20-dione
Deoxycorticosterone	4-Pregnen-21-ol-3,20-dione
Aldosterone	4-Pregnen-11β,21-diol-3,18,20-trione
17α-Hydroxyprogesterone	4-Pregnen-17α-ol-3,20-dione
17α,20α-Dihydroxyprogesterone	4-Pregnen-17α,20α-diol-3-one
11β,17α-Dihydroxyprogesterone	4-Pregnen-11β,17α-diol-3,20-dione
16α-Hydroxyprogesterone	4-Pregnen-16α-ol-3,20-dione

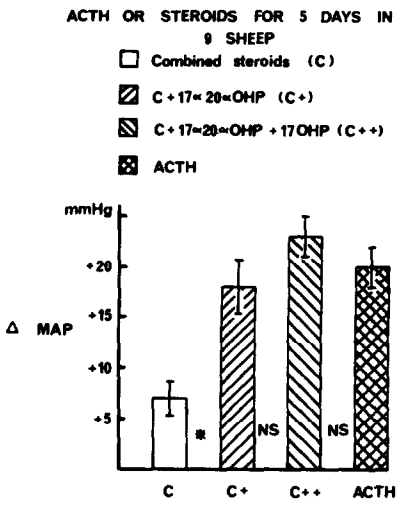

Fig. 2. Change in mean arterial pressure in 9 paired sheep receiving combined steroid infusion, combined steroids plus 17α,20α-dihydroxyprogesterone, combined steroids plus 17α,20α-dihydroxyprogesterone plus 17α-hydroxyprogesterone or ACTH for 5 days.

or blood eosinophil levels. This suggests that in the dosage used they are not producing any demonstrable "mineralocorticoid" or "glucocorticoid" effects.

Thus, it appears unlikely that the effects on blood pressure of these hormones can be explained simply in terms of their "glucocorticoid" or "mineralocorticoid" potencies.

The possibility (under the short-term conditions of study used in the ACTH model) of producing either typical "glucocorticoid" or "mineralocortocoid" type hypertension in the sheep was then examined. Infusion of aldosterone at 80 μg/h ($n = 5$) to produce blood concentrations of aldosterone some 4–5 times greater than that seen in severely sodium-deficient sheep produced no change in blood pressure or cardiac rate over a 5-day period but did show the classical "mineralocorticoid" effects of hypernatraemia, hypokalaemia, initial urinary sodium retention and a subsequent natriuresis on aldosterone withdrawal. Cortisol at 5 mg/h ($n = 5$) (a rate appropriate to give blood concentrations similar to those seen under conditions of maximal ACTH stimulation) produced an increase in water drinking and urine output but no change in plasma or urinary electrolytes. Mean arterial blood pressure rose by 10 mm Hg on day 5, about half the increment seen with ACTH, but greater than that with combined steroid infusion (+7 mm Hg) (Fig. 2). Cortisol at 20 mg/h ($n = 5$) (a rate producing blood concentrations well outside the physiological range) produced rises in blood pressure from day 1 to day 5 similar to those seen under conditions of ACTH stimulation. At this dose cardiac rate was increased, as seen in ACTH treated animals and significant "mineralocorticoid" effects of hypernatraemia and hypokalaemia were seen, without any initial urinary sodium retention. Urine output was elevated. Dexamethasone (1 mg/h) ($n = 5$) (equivalent to cortisol at 10 mg/h in renal receptor experiments) had minor effects on blood pressure (MAP + 8 mm Hg on day 5) but also produced an increase in heart rate, hypokalaemia, transient urinary sodium retention and an increase in urine output.

Thus, in the short term it is not possible to produce hypertension in sheep with pharmacological levels of the predominantly "mineralocorticoid" hormone aldosterone. However, hypertension can be induced by the administration of pharmacological levels of cortisol, at rates at which cortisol is also demonstrating significant "mineralocorticoid" activity. Whether or not the rise in blood pressure seen with cortisol at 20 mg/h is due to the known glucocorticoid or mineralocorticoid effects exhibited at this dose, or whether it represents an additional hypertensinogenic property distinct from the "glucocorticoid" or "mineralocorticoid" properties is debatable.

The synthetic steroid 9α-fluorocortisol (9αFF) has both "glucocorticoid" and "mineralocorticoid" properties. 9αFF produces hypertension in man, with many of the characteristics of "mineralocorticoid" type hypertension [4] but in the rat 9αFF hypertension is associated predominantly with "glucocorticoid" activity [24]. It was thus of interest to infuse 9αFF in sheep at three different dose levels in an attempt to separate the dose dependent metabolic effects from changes in glood pressure.

Infusion of 9αFF at 0.2 mg/day increased blood pressure without any associated metabolic changes. Blood pressure increased significantly from day 1 through to day 5 of infusion, with a mean arterial pressure rise of 16 mm Hg on day 5 ($n = 6$).

The effects of infusion of 9αFF at 0.63 mg/day ($n = 4$) or 2 mg/day ($n = 6$) were indistinguishable. Blood pressure increased significantly within 24 h with a maximum rise of 33 mm Hg and 29 mm Hg respectively on day 5. Plasma potassium showed a profound fall over the period of 9αFF administration in the absence of any increase in urinary potassium excretion, but rapidly returned to control values on steroid withdrawal. Plasma sodium increased and there was an initial urinary sodium retention with a natriuresis on 9αFF withdrawal. Water intake and urine output did not change.

Thus, at low dose, 0.2 mg/day, 9αFF increased blood pressure but did not produce any demonstrable metabolic effects. At both 0.63 and 2 mg/day, however, the rise in mean arterial pressure was associated with urinary sodium retention, hypokalaemia and hypernatraemia.

Studies in the ovine renal cystosol receptor system indicate that 9αFF is approx. equipotent with aldosterone in displacement of [^{3}H]-aldosterone from Type 1 "mineralocorticoid" receptors, and approx. equipotent with dexamethasone in displacement of [^{3}H]-dexamethasone from Type 2 "glucocorticoid" receptors. On the basis of this receptor data we calculated approx. "mineralocorticoid" and "glucocorti-

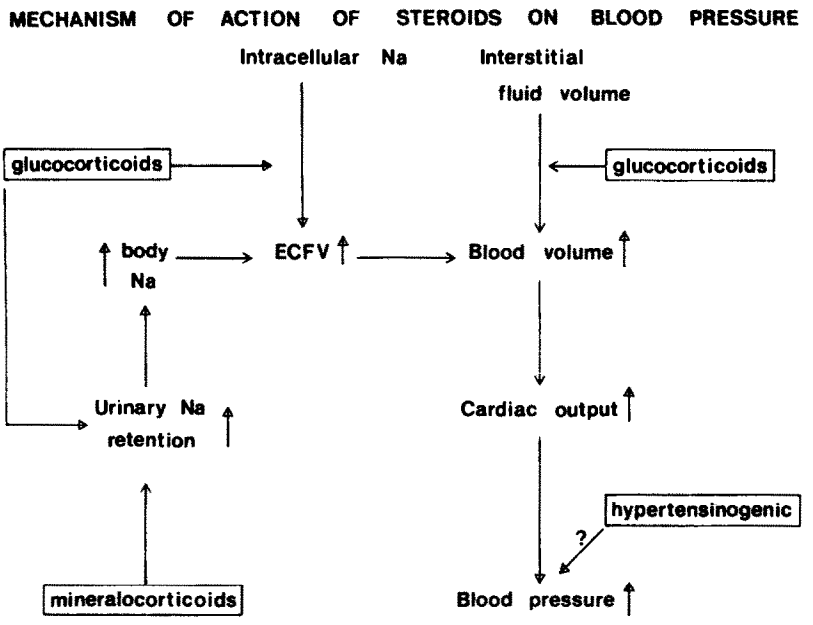

Fig. 3. Proposed mechanism of action of adrenocortical steroids on blood pressure.

coid" equivalents for 9αFF at both 0.63 and 2 mg/day. Infusion of cortisol 6.3 mg and aldosterone 0.63 mg/day (roughly equivalent to 9αFF at 0.63 mg/day) produced metabolic effects of initial urinary sodium retention and hypokalaemia indistinguishable from those of 9αFF but no increase in blood pressure. Similarly, cortisol at 24 mg/day and aldosterone 2 mg/day (roughly equivalent to 9αFF at 2 mg/day) produced initial urinary sodium retention and hypokalaemia indistinguishable from those of 9αFF but increased blood pressure by only 10 mm Hg on day 5.

Thus it appears that the blood pressure raising effect of 9αFF may not be explicable simply in terms of its "mineralocorticoid" or "glucocorticoid" properties. This supports our contention that steroid hormones can raise blood pressure by mechanisms distinct from classical "glucocorticoid" and "mineralocorticoid" actions.

A working hypothesis (Fig. 3) for the action of adrenal steroids on blood pressure can be summarized as follows: glucocorticoid activity increases blood pressure by expansion of blood volume at the expense of interstitial fluid vol. or a shift of intracellular sodium into the extracellular fluid vol. compartment. Mineralocorticoid activity causes urinary sodium retention expansion of extracellular fluid vol. and blood vol., an increased cardiac output and hence an increase in blood pressure. There appears to be a third class of adrenal steroid action which we have provisionally labelled "hypertensinogenic" which raises blood pressure *via* a mechanism yet to be determined. The evidence for a new class of steroid action in production of hypertension in sheep suggests the need for a reclassification of adrenal steroid hormones.

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