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THE EFFECT OF DOCA AND 9α-FLUDROCORTISONE ON RENAL RENIN CONTENT AND PRODUCTION

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SUMMARY

1. DOCA and 9α-fludrocortisone were given to rats.
2. Plasma renin fell rapidly with both treatments.
3. Renal renin fell slowly to a low level.
4. Renal renin fell to a lower level with DOCA than with 9α-fludrocortisone.
5. When DOCA and 9α-fludrocortisone were stopped plasma renin levels rose rapidly and the renal renin levels increased.
6. The data suggest that synthesis is altered rapidly but it takes a prolonged time for the kidney to become depleted of renin due to the high tissue stores and the associated inhibition of release.

Key words: angiotensin, DOCA, mineralocorticoids, plasma renin, renal renin, sodium.

INTRODUCTION

Renin is formed in, and released from, the kidney, in response to a number of different stimuli (Monmoto *et al.* 1970; Morgan & Gillies 1975; de Senarclens *et al.* 1977). While the release of renin has been investigated in a large number of experiments (Davis 1971; Davis & Freeman 1976; Vander 1976; Hackenthal & Taugner 1986) there have been relatively few studies into the factors that control the rate at which renin is synthesized (Catanzaro *et al.* 1985; Nakamura *et al.* 1985). The kidney has a large store of renin in comparison to the amount that is released into plasma, which has made it difficult to obtain quantitative data. To determine the rate at which renin is synthesized it would be preferable to have a kidney containing no renin and to then perform various procedures that may alter the synthetic rate. To achieve a kidney with a low renin content rats were given either DOCA or 9α-fludrocortisone and a high sodium intake over a prolonged period. This paper reports the effect on plasma and renal renin.

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METHODS

Sprague-Dawley rats, weighing 250–270 g, were maintained on their normal diet and given normal saline as their drinking fluid. Two groups were studied. One group was given intramuscular deoxycortisone acetate in castor oil (25 mg) on 2 days of each week. The other group was given 9α-fludrocortisone in their drinking water; on their usual fluid intake this gave an intake of approximately 30 μg/rat per day.

Rats were killed at various intervals after mineralocorticoids were started. The rats were killed by decapitation; plasma renin was measured using a radioimmunoassay (Haber *et al.* 1969). The kidneys were removed and homogenized and active and inactive renin content was measured as described previously (Gillies & Morgan 1978).

Calculations were made of the amount of renin produced at various time periods, making the following assumptions. Volume of distribution of renin is 12% of bodyweight (i.e. 30 ml in a 250 g rat), renin half-life ($t_{½}$) in plasma is 0.5 h and renin is only destroyed by being released into plasma and then metabolized.

$$\text{Renin destruction each day} = \frac{\text{PRC} \times \text{VOL} \times \text{time}}{t_{½}}$$

$$= \frac{\text{PRC} \times 30 \times 24}{0.5}$$

From plasma levels and renin levels taken at different times production rates were calculated.

RESULTS

Plasma renin levels fell within 24 h of therapy and remained at a low level throughout treatment. In the DOCA-treated rats renal renin fell to about 10% of its initial value within 2 weeks and to less than 1% of its initial value at 6 weeks. Two weeks after DOCA administration was stopped renal renin had risen to about 10% of its original value (Table 1). In rats treated with 9α-fludrocortisone the fall in plasma renin was similar but renal renin fell more slowly. After 2 weeks of therapy renal renin had fallen to about 50% of its control value and there was a further slow fall to about 25% of its original value. The level did not fall below this. When 9α-fludrocortisone was stopped plasma renin rose rapidly to pretreatment values and within 1 week renal renin levels were near their control values.

In the control situation and assuming renal renin is constant the amount of renin produced each day is that which is capable of producing 8.6 μg angiotensin I/h, while in rats treated with DOCA or 9α-fludrocortisone the production rate of renin is 1.4 μg angiotensin I/h. Thus with a renal renin content of 400 μg/kidney (i.e. 800 μg/rat) it would take 100 days for renal renin to be depleted if the control rate of release continued and 600 days if renin was released and destroyed at the rate found in rats on DOCA. This indicates that a prolonged time may be required to achieve depletion of renal stores but as the level in the DOCA-treated animal fell more rapidly there is probably an intrarenal mechanism of destruction.

DISCUSSION

Extremely low levels of renal renin were obtained after 6 weeks of DOCA administration. 9α-Fludrocortisone did not produce such low values, suggesting that synthesis was not as completely

Table 1. Plasma and renal renin levels in rats that received DOCA on 9α-fludrocortisone

	Plasma renin (ng angiotensin I ml/per h)					
	n	DOCA		*n*	9α-Fludrocortisone	
		Active	Total		Active	Total
Control	7	5.3±0.7	6.0±0.9	8	5.4±0.6	6.1±0.5
2 weeks	6	0.8±0.1	1.0±0.2	3	2.0±0.1	2.3±0.1
4 weeks	3	1.1±0.2	1.4±0.1	4	1.6±0.2	1.8±0.1
4 weeks + 2 weeks off	2	5.7±0.2	6.2±0.2			
6 weeks	13	1.7±0.2	2.4±0.5	4	2.2±0.2	3.1±0.4
6 weeks + 1 week off				4	4.8±0.4	5.2±0.4
	Renal renin (μg angiotensin I/kidney per h)					
Control	10	240±46	356±55			
2 weeks	6	29±6	64±10	4	157±32	312±54
4 weeks	7	3±1	7±2	4	91±16	140±26
4 weeks + 2 weeks off	4	24±8	47±9			
6 weeks	13	0.9±0.1	1.3±0.2	4	65±11	96±12
6 weeks + 1 week off				4	214±13	270±15

Results are mean and standard error of the mean.

inhibited. When 9α-fludrocortisone was stopped renal renin values were close to control values within 1 week, while 2 weeks after stopping DOCA levels were still low. This may reflect a prolonged duration of the action of DOCA.

The calculated values for the rate of renin production and the rate of fall in renal renin in rats on DOCA indicates that in addition to release of renin into the plasma and subsequent destruction, there is likely to be intrarenal destruction of renin; alternatively the half-life in plasma is markedly altered.

Two models are described which deplete the kidney of renin. The DOCA model induces lower levels of renal renin and has a slow return of renin when DOCA is stopped. In the 9α-fludrocortisone model there is less suppression of renal renin and a more rapid return to control levels after the drug is stopped.

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