Metabolic Effects of Progesterone in the Dog[1] (34324)

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Progesterone has been reported to be natriuretic (1–4) and catabolic (4–6) in man. Kagawa *et al.* (7) demonstrated natriuresis in the rat. Progesterone was also shown to elevate peripheral plasma renin activity (PPRA) in the dog (8). Both *in vivo* (3, 4) and *in vitro* (9) studies suggest that the natriuretic effect is through the blocking of aldosterone action. The purpose of the present investigation was to study the metabolic effects of progesterone in the dog and attempt to correlate them with changes in PPRA.

Materials and Methods. Four female mongrel dogs, weighing 16–25 kg, were maintained in metabolic cages; and complete 24-hr urine collections were obtained by daily bladder catheterizations. The dogs were initially placed on a sodium diet containing approximately 35–40 meq (normal sodium diet) for 30 days. On this diet PPRA was assayed on alternate days and daily urinary sodium and urea excretion were measured. After initial stabilization, a synthetic progesterone[4] (200 mg, im/day) was administered for 6 days. The dogs were then allowed to stabilize for another 6 days and an aldosterone antagonist (spironolactone, 300 mg/day, po) was administered in the diet for 5 days. The dogs were then placed on a sodium diet containing 3–6 meq/day (low sodium diet) and were allowed to stabilize for one week. The same studies utilizing progesterone and spironolactone were then repeated on this diet.

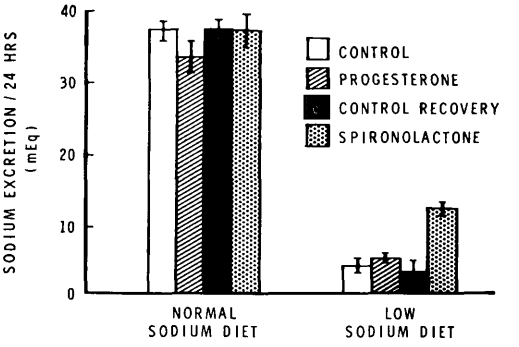

FIG. 1. Effects of progesterone and spironolactone on sodium excretion.

The bloods for PPRA were drawn into heparinized tubes and immediately centrifuged in the cold, and the plasma was separated and frozen. The PPRA was measured by a modification of the method of Helmer (10) as described by Boonshaft *et al.* (11). Renin activities are expressed in terms of nanograms of angiotensin II generated per milliliter of plasma per hour of incubation. Urinary sodium was determined with an IL flame photometer using an internal lithium standard. Urinary urea was measured by the urease method (12).

Results. On the normal sodium diet, the control sodium excretion was 37.4 ± 1.3 meq/24 hr (mean ± SEM) and the control urea excretion was 5.71 ± 0.38 g/24 hr. After progesterone administration, the sodium excretion was 32.2 ± 1.9 meq/24 hr ($p > .05$) and the urea excretion was 5.65 ± 0.29 g/24 hr (Table I) which also was not significant ($p > .05$). After spironolactone administration, the urinary sodium excretion was 37.2 ± 2.3 meq/24 hr (Fig. 1) which was not significant ($p > .05$). The PPRA was

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[4] Obtained from Arcum Pharmaceutical Corporation with certification of chemical analysis.

TABLE I. Effects of Progesterone on PPRA and Urea Excretion on Normal and Low Sodium Diets.

	Normal sodium diet		Low sodium diet	
	Control	Progesterone	Control	Progesterone
PPRA (ng/ml/hr)	0.8 ± 0.2	0.8 ± 0.2	1.9 ± 0.2	1.6 ± 0.1
Urea excretion (g/24 hr)	5.71 ± 0.38	5.65 ± 0.31	4.43 ± 0.32	4.83 ± 0.16

0.8 ± 0.2 ng/m/hr on the control sodium diet and 0.8 ± 0.2 ng/ml/hr after progesterone (Table I) which was not significant ($p > .05$).

On the low sodium diet, the control sodium excretion was 4.9 ± 0.5 meq/24 hr and the control urea excretion was 4.43 ± 0.32 g/24 hr. After progesterone administration, the sodium excretion was 5.7 ± 0.5 meq/24 hr (Fig. 1) and the urea excretion was 4.83 ± 0.16 g/24 hr. These values were not significantly different ($p > .05$). However, the PP RA levels had increased on the low sodium control diet to 1.9 ± 0.2 ng/ml/hr which was significant ($p < .001$) compared to the normal sodium diet, but after the administration of progesterone, the PPRA was 1.6 ± 0.1 ng/ml/hr which was not significant ($p > .05$). Spironolactone administration increased the sodium excretion to 12.7 ± 0.7 meq/24 hr on the low sodium diet which was significant ($p < .001$).

Discussion. Landau *et al* (1–4) have well documented that progesterone in man is both natriuretic and catabolic. They have studied dose–response curves over a range of 6.25 to 300 mgs/day and have shown that the magnitude of the response is dose related. With the lower doses, small negative balances were induced, but with higher doses as much as 300–400 meq of sodium were lost over an 8-day period. The mechanism of the natriuresis was unclear, but data obtained from adrenalectomized subjects in which no effect was demonstrable suggested that the effect might be through blockage of endogenous aldosterone action. The *in vitro* studies of Crabbé (9), which showed that large doses of progesterone can inhibit aldosterone-induced sodium transport by the toad bladder, offered some confirmation for this hypothesis.

Recently Winer (8) has shown that administration of progesterone to dogs results in an increase in PPRA. In order to understand the mechanism for this increase in PPRA, *i.e.*, (a) direct stimulation of progesterone on renal renin release, or (b) stimulation of renin release through induction of negative sodium balance, the present study was performed. In order to demonstrate a maximum effect, a dose of 200 mg of progesterone/day was chosen.

On the normal sodium diet no natriuretic effect or change in PPRA was noted. Since the control PPRA levels were low and may have been depressed by a 35 meq/day sodium diet, a low endogenous aldosterone secretion rate was considered to explain the lack of progesterone effect on this diet. The lack of spironolactone effect on sodium excretion seemed to support this conclusion. In order to study progesterone effect when endogenous aldosterone levels were not depressed, the studies were repeated on a low sodium diet. On this diet, as evidence for the presence of aldosterone, PPRA was significantly increased and spironolactone induced a definite natriuresis. In spite of this, no definite effect of progesterone on PPRA or sodium excretion could be demonstrated.

Progesterone did not cause an increase in urea excretion on either the control or low sodium diet. The difference in the urea excretion on the two diets is explained by differences in their protein content.

Summary. The metabolic effects of progesterone were studied in the dog. In contrast to man, no metabolic effects were demonstrable: (a) PPRA was not altered; (b) urea excretion was not increased; and (c) natriuresis was not induced even in animals which were responsive to an aldosterone antagonist.

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