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RENAL ELECTROLYTE EXCRETION AND RENIN RELEASE DURING CALCIUM AND PARATHORMONE INFUSIONS IN CONSCIOUS RABBITS

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SUMMARY

1. Following a random block experimental design in each case, three repeated measurement studies were carried out in three different groups of conscious rabbits, to investigate the renal effects of increasing doses of intravenous calcium chloride ($CaCl_2$) and bovine parathyroid hormone (PTH).

2. In the first study, each rabbit received either $CaCl_2$ (0·15, 0·3, 0·5 or 1·0 mg kg^{-1} min^{-1}) or vehicle alone (control) for 160 min. In the second study, rabbits were given either PTH (0·15 μg kg^{-1} min^{-1}), $CaCl_2$ (1·0 mg kg^{-1} min^{-1}), PTH plus $CaCl_2$ (0·15 μg kg^{-1} min^{-1} and 1·0 mg kg^{-1} min^{-1}, respectively) or vehicle alone; PTH was infused for just over 60 min. In the third study, a much smaller dose (0·05 mg kg^{-1} min^{-1}) of $CaCl_2$ was infused for 100 min.

3. $CaCl_2$ infusion produced a striking fall in fractional excretion of sodium of at least 50% ($P < 0·01$), but this was not dose related, being almost maximal at the smaller doses infused. Although this effect was evident in the absence of any changes in total plasma calcium concentration at the lower doses of $CaCl_2$, renal calcium excretion was increased between 2- and 20-fold ($P < 0·01$) at all doses infused. Fractional excretion of chloride doubled at the two higher doses of $CaCl_2$ ($P < 0·01$), but potassium excretion was unchanged. There were no consistent alterations in mean arterial blood pressure, effective renal plasma flow, glomerular filtration rate or plasma renin activity (PRA); total plasma calcium concentration was consistently elevated only during infusion of the high dose by just under 1 mmol l^{-1}.

4. PTH infusion had no measured effect on fractional excretion of sodium or renal calcium excretion, but doubled fractional potassium excretion ($P < 0·05$). Heart rate and PRA increased ($P < 0·01$ and $< 0·05$, respectively), the latter by 50%, but systemic pressure and renal haemodynamics were not significantly affected. By contrast, PTH infused with $CaCl_2$ produced a 4-fold rise in fractional sodium excretion and although renal calcium excretion remained increased, it was reduced by *ca.* 80% when compared with renal calcium excretion during infusion of $CaCl_2$ alone. Infusion of PTH alone increased PRA, but when PTH and $CaCl_2$ were infused together, PRA did not change.

5. These observations are not fully explained, but may involve PTH-related changes in renal tubular and juxtaglomerular cell permeability to calcium, cytosolic calcium concentration and a sodium–calcium exchange process.

INTRODUCTION

Under a variety of experimental conditions, hypercalcaemia (*ca.* 3–4 mmol l^{-1} or more) has been shown to increase water and electrolyte excretion (Levitt, Halpern, Polimeros, Sweet & Gribetz, 1958; Epstein, 1968; Vanherweghem, Ducobu, D'Hollander & Toussaint, 1976; Lins, 1979*a*, *b*). In broad terms, the parallel changes in sodium and calcium clearance have been attributed to the mainly passive (solvent drag and electrochemical differences), and indirectly sodium-related, proximal tubular reabsorption of calcium (Sutton & Dirks, 1978; Dennis, Stead & Myers, 1979; Suki, 1979). Although active reabsorption of calcium via a calcium-dependent ATPase transport system is likely, evidence from micropuncture studies suggests that it is largely confined to the distal nephron where handling of sodium and calcium appear independent (Suki, 1979).

A sodium–calcium exchange mechanism has also been postulated which in addition to participating in active calcium reabsorption by promoting cellular efflux of calcium (Suki, 1979; Costanzo, 1984), may also be involved in the regulation of renal tubular sodium reabsorption through changes in cytosolic calcium concentration linked with active sodium–potassium exchange (Taylor & Windhager, 1979). Originally described in the squid axon (Baker, Blaustein, Hodgkin & Steinhardt, 1969; Blaustein & Hodgkin, 1969), this process has become of particular interest in recent years with the suggestion that it may operate in most epithelia, including renal tubular cells, and might be involved in both proximal and distal tubular reabsorption of calcium (Ullrich, Rumrich & Klöss, 1976; Friedman, Figueiredo, Maack & Windhager, 1981; Frindt, Windhager & Taylor, 1982; Lorenzen, Lee & Windhager, 1984; Costanzo, 1984). However, its significance in over-all tubular reabsorption of sodium and calcium is unknown (Suki, 1979; Taylor & Windhager, 1979; Roland, Rouse & Suki, 1984). As changes in intracellular calcium concentration are an important consequence of altered sodium–calcium exchange and may affect sodium transport and renin release, elevation leading to inhibition in each case (Peart, 1978; Park & Malvin, 1978; Taylor & Windhager, 1979), we have examined the effect of graded calcium chloride infusions and parathormone infusion (the latter considered as a general stimulus to raising cytosolic calcium; Borle, 1973) on renal function in conscious rabbits.

METHODS

The protocol, including the techniques of recording systemic blood pressure, heart rate, renal haemodynamics and electrolyte excretion in conscious rabbits, have already been described in detail in an earlier publication (Dimaline, Peart & Unwin, 1983) and will only be presented in outline, together with any modifications.

The first two studies were performed in two different groups of Sandy Half-lop rabbits, using an identical random block experimental design (Armitage, 1977) in each case. In the first study (5×5), each of five rabbits (3·2–4·0 kg) received in random order at intervals of 5–7 days an intravenous infusion of either calcium chloride ($CaCl_2$: Evans Medical) at 0·15, 0·3, 0·5 or 1·0 mg kg^{-1} min^{-1} or vehicle (0·28 M-glucose: control) alone, over 160 min. In the second study, bovine parathyroid hormone (PTH: NIBSC reagent 77/533; *ca.* 2500 i.u. mg^{-1}) was used in an attempt to alter cellular calcium flux and thereby increase cytosolic calcium concentration. The freeze-dried PTH was initially dissolved in 1 g 100 ml^{-1} sodium acetate, containing 0·1 g 100 ml^{-1} rabbit albumin (adjusted to pH *ca.* 4 with glacial acetic acid) and then diluted in 0·28 M-glucose

vehicle just prior to infusion. In the second study (4 × 4), four rabbits (3·3–4·2 kg) each received either PTH (0·15 μg kg^{-1} min^{-1}), $CaCl_2$ (1·0 mg kg^{-1} min^{-1}), PTH plus $CaCl_2$ (0·15 μg kg^{-1} min^{-1} and 1·0 mg kg^{-1} min^{-1}, respectively) or vehicle alone. In the case of PTH plus $CaCl_2$, PTH was given over the last 60 min of $CaCl_2$ infusion.

Vascular and urethral catheters were inserted under lignocaine local anaesthesia. Each infusion consisted of an initial fluid load (25 ml kg^{-1} 0·28 M-glucose over 20 min) followed by a maintenance infusion (1·1 ml min^{-1}) during which seven 30 min urine collections were made, with intervals of 10 min. Renal clearances of the continuously infused radioactive compounds ^{51}Cr-labelled ethylene diaminetetraacetate (EDTA; 0·74 kBq min^{-1}) and sodium *p*-[^{125}I]aminohippurate (Hippuran; 1·38 kBq min^{-1}) were used to estimate glomerular filtration rate (G.F.R.) and effective renal plasma flow (E.R.P.F.), respectively. Each $CaCl_2$ infusion was begun 5 min before the start of the third urine collection and continued until the end of the sixth urine collection (total *ca.* 160 min). In the second study, PTH was infused during the fifth and sixth urine collections only (*ca.* 60 min). Arterial blood samples were taken, and blood pressure and heart rate recorded at the mid-point of each urine collection.

In both studies, concentrations of sodium, potassium, chloride and calcium in urine and plasma were measured, together with haematocrit and plasma renin activity (PRA; radioimmunoassay). Arterial plasma solids (PS; a measure of plasma protein concentration, corrected for plasma sodium concentration) were determined in the first study ($CaCl_2$ only), and plasma and urine phosphate concentrations estimated in the second study (PTH and $CaCl_2$). The assay methods used have already been described (Dimaline *et al.* 1983).

Mean arterial blood pressure was calculated as two-thirds the diastolic pressure plus one-third the systolic pressure, filtration fraction (f.f.) as the ratio of G.F.R. to E.R.P.F., post-glomerular plasma solids as PS/(1 − f.f.) and percentage fractional electrolyte excretion (FE_x) determined from filtered load (F_x; product of G.F.R. and plasma concentration) and corresponding renal excretion rate (U_xV) thus:

$$FE_x = ((U_xV)/F_x) \times 100.$$

Data were analysed by a two-way analysis of variance (factors: rabbit and treatment) with weight and time as covariates, followed by multiple comparisons with the control if appropriate (Dunnett, 1964); $P < 0.05$ was considered significant. In both studies, the results given are based on the observations made during the fifth and sixth urine collections, i.e. at least 1 h after the start of calcium infusion, when a steady state had been achieved. They are expressed as means and standard error of means (S.E. of means) except if log-normally distributed when presented as geometric means and approximate S.E. of means; all transformed variables are indicated in Tables and Figures.

RESULTS

Systemic blood pressure, heart rate and renal haemodynamics (Table 1)

A small fall in mean heart rate of *ca.* 25 beats min^{-1} was recorded in the first study during infusion of high dose (1·0 mg kg^{-1} min^{-1}) $CaCl_2$, but did not occur at this dose in the second study. PTH alone produced a rise in mean heart rate of almost 40 beats min^{-1}, but not when infused with $CaCl_2$. Neither $CaCl_2$ nor PTH, alone or in combination, altered mean arterial blood pressure. Although not statistically significant when compared with the control value, G.F.R. fell slightly at the low dose (0·15 mg kg^{-1} min^{-1}) of $CaCl_2$ and values of E.R.P.F. relative to G.F.R. were higher during PTH infusion with and without $CaCl_2$, as reflected by reduced f.f. During high dose $CaCl_2$ infusion in both studies, f.f. tended to increase, but only reached statistical significance in the second study.

Urine composition (Table 2).

In the first study, each dose of $CaCl_2$ produced a significant fall in renal and fractional sodium excretion (Fig. 1). This effect was not dose dependent, being almost maximal at the smallest dose (0·15 mg kg^{-1} min^{-1}) infused. Fractional chloride

excretion only increased at the higher doses (0·5 and 1·0 mg kg^{-1} min^{-1}) of $CaCl_2$. Renal calcium excretion rose progressively at each dose of $CaCl_2$ infused (Fig. 1). In the second study, PTH alone produced no significant change in fractional excretion of sodium or renal calcium excretion (Fig. 2), but did increase fractional potassium excretion and was associated with reduced renal phosphate excretion. In contrast PTH plus $CaCl_2$ when infused together, produced a marked increase in fractional

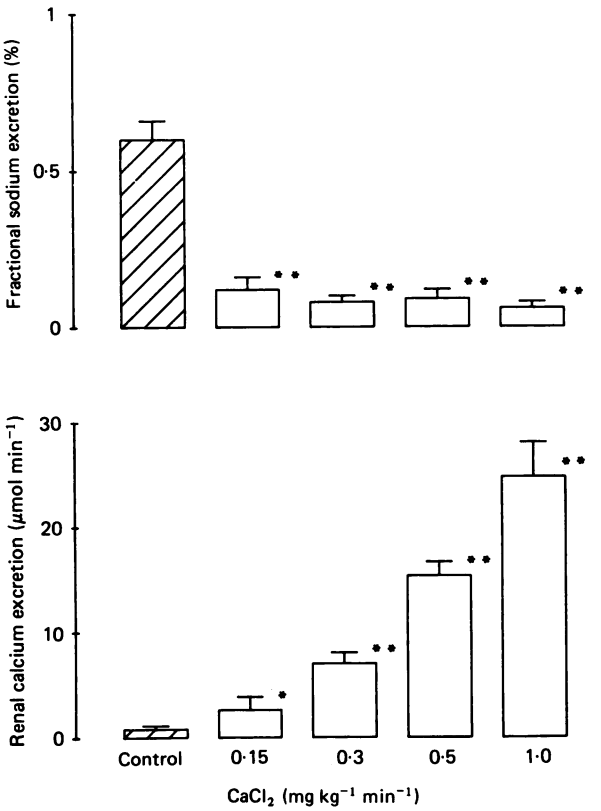

Fig. 1. Effects of increasing doses of $CaCl_2$ on fractional excretion of sodium and renal calcium excretion. These variables were found to be log-normally distributed and therefore results are expressed as geometric means and approximate S.E. of means, $n = 5$ for each group. * and ** indicate significant difference ($P < 0·05$ and 0·01, respectively) from control value as determined by Dunnett's test after analysis of variance.

sodium excretion and the rise in renal calcium excretion was considerably less than during infusion of $CaCl_2$ alone (Fig. 2). Although urine flow rate fell significantly during low dose (0·15 mg kg^{-1} min^{-1}) $CaCl_2$ infusion, the apparent increases observed during higher doses of $CaCl_2$, PTH alone and PTH plus $CaCl_2$ infusions, were not statistically significant.

Plasma composition (Table 3)

Relatively small increments in total plasma calcium concentration were produced during calcium infusion, remaining below 4 mmol l^{-1} and only significantly elevated above control at doses of 0·3 mg kg^{-1} min^{-1} and 1·0 mg kg^{-1} min^{-1}, but not

TABLE 1. Effects of $CaCl_2$ and PTH on systemic and renal haemodynamics

	Control (vehicle only)	$CaCl_2$ (mg kg^{-1} min^{-1}) 0·15	0·3	0·5	1·0	n
B.P. (mmHg)	80±6	86±5	88±4	81±5	83±4	5
H.R. (beats min^{-1})	237±11	239±6	259±10	231±13	213±14	5
E.R.P.F (ml min^{-1})	64·8±5·5	59·7±7·9	62·1±4·3	62·5±3·4	73·0±5·1	5
G.F.R. (ml min^{-1})	16·8±1·5	14·6±1·4	16·0±1·2	16·2±1·0	20·7±1·7	5
F.f. (%)	25·8±0·8	25·9±2·0	25·8±0·8	25·8±0·7	28·3±1·1	5
		PTH (0·15 μg kg^{-1} min^{-1}) and $CaCl_2$ (1·0 mg kg^{-1} min^{-1})				
		PTH	PTH + $CaCl_2$	$CaCl_2$		n
B.P. (mmHg)	88±1	77±5	82±4	80±5		4
H.R. (beats min^{-1})	250±10	*285±9	271±17	251±12		4
E.R.P.F. (ml min^{-1})	66·1±6·1	76·4±4·8	84·5±6·3	63·9±5·1		4
G.F.R. (ml min^{-1})	17·7±2·2	15·7±1·3	16·5±0·8	20·2±1·4		4
F.f. (%)	26·5±1·4	*20·4±1·0	*20·2±1·6	*31·9±0·9		4

Values are expressed as means ± S.E. of means.

n = number of observations.

* signifies $P < 0·01$ when compared with the control value by Dunnett's test after analysis of variance. Abbreviations are as follows: B.P., mean arterial blood pressure; H.R., heart rate; E.R.P.F., effective renal plasma flow; G.F.R., glomerular filtration rate; f.f., filtration fraction.

TABLE 2. Effects of $CaCl_2$ and PTH on fractional electrolyte excretion, urine flow and renal phosphate excretion (PTH study only)

	Control (vehicle only)	$CaCl_2$ (mg kg^{-1} min^{-1}) 0·15	0·3	0·5	1·0	n
†FE_{Cl}(%)	0·55±0·08	0·69±0·23	0·62±0·06	**1·16±0·20	**1·66±0·19	5
†FE_K (%)	16·67±1·84	16·15±4·69	12·50±1·62	11·29±1·77	13·77±1·99	5
†$\dot{V}$ (µl min^{-1})	614·8±160·9	*250·2±127·4	891·2±82·68	994·7±82·6	1000·0±118·9	5

		PTH (0·15 µg kg^{-1} min^{-1}) and $CaCl_2$ (1·0 mg kg^{-1} min^{-1}) PTH	PTH + $CaCl_2$	$CaCl_2$	n
†FE_{Cl} (%)	0·63±0·12	0·91±0·07	**2·16±0·51	**2·06±0·15	4
†FE_K (%)	15·66±1·98	*29·79±3·86	28·84±5·65	15·95±0·84	4
†$\dot{V}$ (µl min^{-1})	653·1±152·2	903·9±155·4	1068·2±212·2	1052·3±196·1	4
†$U_{Pi}V$ (µmol min^{-1})	0·84±0·28	*0·29±0·08	0·97±0·41	0·70±0·58	4

Values are expressed as means±S.E. of means.

† Transformed variable, in which case the geometric mean and approximate S.E. of mean is given.

n = number of observations.

* and ** signify $P < 0·05$ and $< 0·01$ respectively, when compared with the control value by Dunnett's test after analysis of variance.

Abbreviations are as follows: FE, fractional excretion; $U_{Pi}V$, renal phosphate excretion; $\dot{V}$, urine flow.

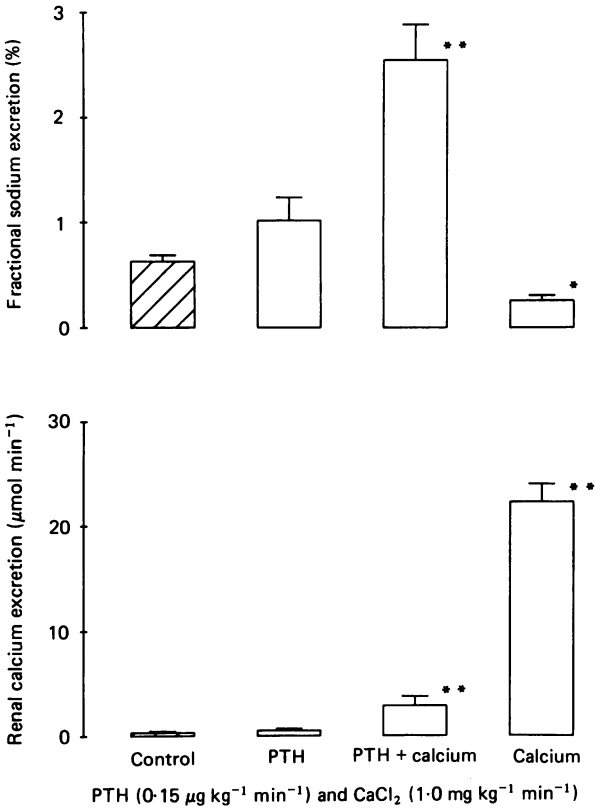

Fig. 2. Effect of PTH, PTH plus $CaCl_2$ and $CaCl_2$ on fractional excretion of sodium and renal calcium excretion. These variables were found to be log-normally distributed and therefore results are expressed as geometric means and approximate S.E. of means, $n = 4$ for each group. * and ** indicate significant difference ($P < 0{\cdot}05$ and 0·01, respectively) from control value as determined by Dunnett's test after analysis of variance.

0·5 mg kg^{-1} min^{-1}. PTH produced no change in total plasma calcium concentration or plasma phosphate concentration, and did not affect the rise in total plasma calcium concentration during $CaCl_2$ infusion. PRA was not influenced by calcium infusion at any dose, but the significant rise during PTH infusion did not occur when $CaCl_2$ was added (Fig. 3). Other measured plasma constituents did not change significantly, including plasma solids and haematocrit.

The apparent lack of a dose-related fall in renal sodium excretion during $CaCl_2$ infusion, led us to perform the third study in four rabbits (2·6–2·8 kg). A similar protocol was followed using doses of 0·05 and 0·2 mg kg^{-1} min^{-1}, to determine whether such an effect could be shown at a much lower dose of calcium, or whether there might be a critical dose as suggested by the first study. Over-all, the urine, plasma and haemodynamic changes were similar. Fig. 4 illustrates the fall in renal sodium excretion produced by these doses of $CaCl_2$. Renal calcium excretion increased even at the lower dose (from $1{\cdot}4 \pm 0{\cdot}3$ to $2{\cdot}7 \pm 0{\cdot}4$ μmol min^{-1}), but neither dose produced a rise in total plasma calcium concentration. A small reduction in G.F.R. did occur at each dose ($16{\cdot}2 \pm 1{\cdot}0$ *versus* $14{\cdot}2 \pm 0{\cdot}5$ and $14{\cdot}5 \pm 0{\cdot}8$ ml min^{-1}, respectively).

TABLE 3. Effects of $CaCl_2$ and PTH on plasma composition and haematocrit

	Control (vehicle only)	$CaCl_2$ (mg kg^{-1} min^{-1}) 0·15	0·3	0·5	1·0	n
P_{Ca} (mmol l^{-1})	2·99±0·08	3·04±0·08	*3·28±0·07	3·21±0·07	**3·79±0·13	5
P_{Na} (mmol l^{-1})	129·4±1·9	127·0±0·8	130·0±1·5	130·5±1·5	130·5±0·8	5
P_K (mmol l^{-1})	3·77±0·05	*3·55±0·08	3·70±0·11	3·72±0·07	3·82±0·07	5
P_{Cl} (mmol l^{-1})	95·8±1·6	95·7±2·8	99·6±1·5	99·8±1·6	99·4±1·3	5
PS (%)	5·97±0·22	6·44±0·29	6·98±0·24	6·76±0·43	5·59±1·22	5
Hct. (%)	30±2	32±1	32±1	31±1	32±1	5
†PGPS (%)	8·01±0·27	8·63±0·30	9·38±0·32	8·96±0·51	6·18±1·92	5

		PTH (0·15 μg kg^{-1} min^{-1}) and $CaCl_2$ (1·0 mg kg^{-1} min^{-1}) PTH	PTH + $CaCl_2$	$CaCl_2$	n
P_{Ca} (mmol l^{-1})	3·04±0·07	2·86±0·07	**3·71±0·19	**3·86±0·14	4
P_{Na} (mmol l^{-1})	131·3±0·9	130·0±1·4	*134·3±1·2	132·3±1·6	4
P_K (mmol l^{-1})	3·61±0·22	3·37±0·12	3·54±0·24	3·74±0·38	4
P_{Cl} (mmol l^{-1})	96·9±1·7	101·3±1·6	103·3±2·2	102·8±1·7	4
P_{Pi} (mmol l^{-1})	0·77±0·05	0·76±0·06	1·03±0·09	0·84±0·05	4
Hct. (%)	36±2	35±1	33±2	37±2	4

Values are expressed as means±S.E. of means.

† Transformed variable, in which case the geometric mean and approximate S.E. of mean is given.

n = number of observations.

* and ** signify $P < 0·05$ and $< 0·01$ respectively, when compared with the control value by Dunnett's test after analysis of variance.

Abbreviations are as follows: P_{Na}, P_K, etc. plasma concentration; PS, plasma solids; Hct., haematocrit; PGPS, post-glomerular plasma solids.

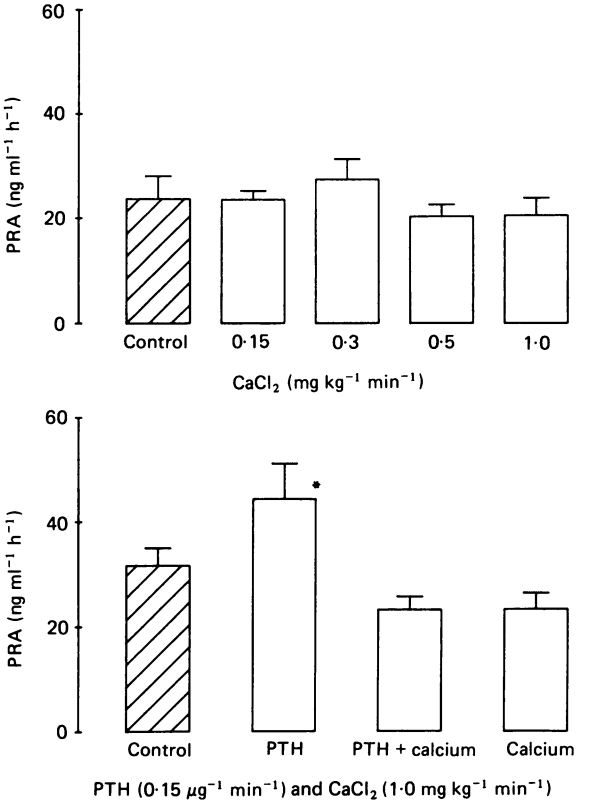

Fig. 3. Effect of $CaCl_2$ and PTH on PRA. This variable was found to be log-normally distributed and therefore results are expressed as geometric means and approximate S.E. of means, $n = 5$ and 4 for each treatment group of calcium and PTH studies, respectively. * Indicates significant difference ($P < 0{\cdot}05$) from control value as determined by Dunnett's test after analysis of variance.

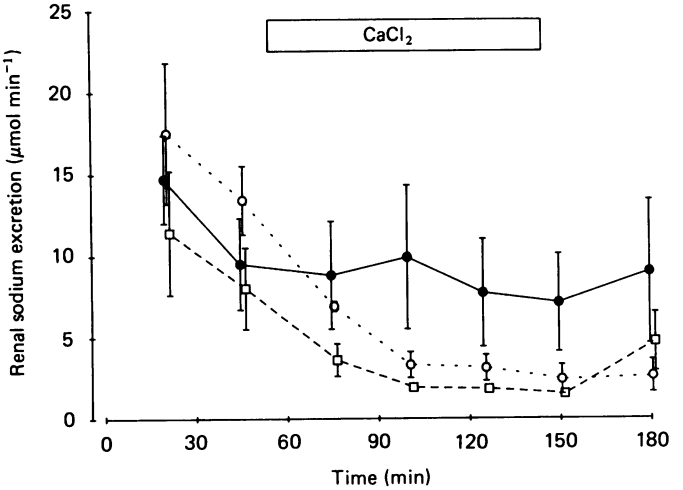

Fig. 4. Changes in renal sodium excretion with time during infusion of vehicle (control; ●) and two low doses of $CaCl_2$ (0·05 (○) and 0·2 (□) mg kg^{-1} min^{-1}). Values are given as means and S.E. of means, $n = 4$.

DISCUSSION

The most striking observation was the consistent reduction in renal sodium excretion during $CaCl_2$ infusion and its apparent 'reversal' by the addition of PTH. Levels of PTH in blood were not measured, but biological activity of infused PTH is suggested by the marked fall in calcium excretion during PTH plus $CaCl_2$ infusion, compared with calcium alone (Dennis *et al.* 1979). Although phosphaturia, the more usual index of PTH action was not observed, the rabbit is unusual in being relatively resistant to this effect of PTH (Berndt, Marchand, Sell, Haas, Dousa & Knox, 1978; Berndt & Knox, 1980) and is comparable with at least one form of pseudohypoparathyroidism in man (Dennis *et al.* 1979).

The fall in sodium excretion was not dose dependent over the wide range of calcium infusions studied, and appeared unrelated to changes in total plasma calcium concentration, but at each dose was associated with increased renal calcium excretion; this may reflect a more direct relationship with both plasma and tubular lumen ionized calcium concentration (Chomdej, Bell & Navar, 1977). This finding contrasts with much previously published work in other species, reporting a natriuresis during calcium infusion (Epstein, 1968; Vanherweghem *et al.* 1976; Lins, 1979*a*, *b*; Sejersted, Steen & Kiil, 1984). Although variations in sodium excretion have been attributed to calcium-induced falls in G.F.R. (Chomdej *et al.* 1977; Lins, 1979*a*), the changes we recorded do not appear consistent enough at each dose to fully explain the observed pattern of renal sodium excretion. It is conceivable that the lack of dose dependence may reflect a varying contribution to alterations in renal sodium excretion by peritubular physical (Gordon, Nashat & Wilcox, 1981) and other factors, and may also explain the apparent critical dose effect at 0·15–0·2 mg kg^{-1} min^{-1} $CaCl_2$. Aldosterone release seems an unlikely explanation for this antinatriuretic response, although Kotchen, Galla & Luke (1977) have reported aldosterone stimulation independent of renin release during dietary calcium loading in rats, but ascribed this to associated positive potassium balance. Even if aldosterone did increase more acutely during calcium infusion, its onset of action is far too slow (Lennane, Stockigt & Peart, 1976). Differing experimental conditions including anaesthesia, species variation, duration of infusion (Wolf & Ball, 1949), saline loading, higher doses of calcium and different associated anions (gluconate or chloride; Bomsztyk, George & Wright, 1984), may all be factors which contribute to this difference.

Despite the fact that proximal tubular reabsorption of sodium and calcium appear interdependent, the lack of change in renal potassium excretion in the present study does suggest a proximal site of increased sodium reabsorption and thus dissociation from calcium. Significant tubular backflux of calcium and dissociation of sodium and calcium reabsorption have been described in the proximal tubule (Shirley, Poujeol & Le Grimellec, 1976; Bomsztyk *et al.* 1984), although the mechanisms are unclear. A clue may lie in the reversal of calcium-induced antinatriuresis by PTH and the absence of PTH-induced renin release during $CaCl_2$ infusion. PTH itself produces a variable natriuresis through inhibition of proximal tubular reabsorption of sodium, increased distal delivery, and increased distal reabsorption (Sutton, Wong & Dirks, 1976). This may explain the lack of natriuresis observed during PTH infusion alone, and the raised potassium excretion reflecting increased distal sodium–potassium

exchange. However, the mechanism of PTH-induced renin release is unknown (Smith, Mouw & Vander, 1979).

As suggested earlier, changes in cytosolic calcium concentration may be involved in the control of both renin release and renal tubular sodium reabsorption. Epithelial (luminal) cell membrane permeability to sodium is thought to fall as cytosolic calcium rises, perhaps through a direct effect of calcium on the cell membrane (Manery, 1966; Ellory, Flatman & Stewart, 1983). On this basis, PTH-induced increases in cell permeability to calcium (Borle, 1973; Borle & Uchikawa, 1978), might be expected to raise cytosolic calcium and thereby inhibit tubular reabsorption of sodium. Sodium–calcium exchange across the contraluminal cell membrane, a largely passive process dependent upon active sodium–potassium exchange, may be a major regulator of cytosolic calcium (Taylor & Windhager, 1979). There is now mounting micropuncture evidence for sodium–calcium counter transport throughout the nephron (Ullrich *et al.* 1976; Friedman *et al.* 1981; Frindt *et al.* 1982; Lorenzen *et al.* 1984; Costanzo, 1984) and recent evidence from *in vitro* experiments with renal basolateral (contraluminal) membrane vesicles, largely from the proximal tubule, that PTH may stimulate sodium–calcium exchange activity (Jayakumar, Cheng, Liang & Sacktor, 1984). Thus hypercalcaemia should reduce endogenous PTH secretion (Habener, Rosenblatt & Potts, 1984) and perhaps decrease or even reverse sodium–calcium exchange. An increase in cytosolic calcium would also be anticipated to inhibit renin release from the juxtaglomerular cells (Peart, 1978; Park & Malvin, 1978), but clearly this did not occur, for it was only in the presence of hypercalcaemia that PTH failed to stimulate renin release. It is possible that PTH increased ionized calcium, which then led to increased calcium influx and thereby inhibited renin release. Unlike Kotchen, Kimball, Luke, Rees & Flamenbaum (1974), who infused 0·3 mg kg^{-1} min^{-1} $CaCl_2$ into the renal artery of the anaesthetized dog, we did not observe any inhibitory action of intravenous $CaCl_2$ infusion on renin release, but this may simply indicate a failure to alter juxtaglomerular cell calcium concentration.

Although there is no complete explanation for these observations, the changes in relation to calcium and PTH seem to indicate a more general ability of the rabbit kidney to handle sodium and calcium independently, perhaps involving some sort of sodium–calcium exchange process.

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