Role of serum Ca, parathyroid hormone, and NaCl infusion on renal Ca and Na clearances

MASSRY, SHAUL G., JACK W. COBURN, LLOYD W. CHAPMAN, AND CHARLES R. KLEEMAN. Role of serum Ca, parathyroid hormone, and NaCl infusion on renal Ca and Na clearances. Am. J. Physiol. 214(6): 1403-1409. 1968.—The effect of changes in serum calcium and parathyroid hormone (PTH) levels was studied in 15 thyroparathyroidectomized (T-PTX) dogs receiving CaCl₂ and/or NaCl infusion in different sequences and rates and, in some, parathyroid extract (PTE). In T-PTX dogs calcium clearance (Cca) was 4-6 times greater than sodium clearance (CNa) with Cca/CNa of 5.10 ± 0.94 (mean ± se). After PTE, Cca fell and Cca/CNa returned to normal. During CaCl₂ infusion both calcium and sodium excretion increased, but Cca was disproportionately higher than CNa at all levels of serum calcium. During calcium infusion both calcium and sodium excretion increased, but Cca was disproportionately higher than CNa at all levels of serum calcium. During calcium infusion both calcium and sodium excretion increased, but Cca was disproportionately higher than CNa at all levels of serum calcium. During hypercalcemia, the high Cca/CNa was not influenced by saline infusion or PTE administration. The results indicate that: 1) the normal interdependence between Cca and CNa is altered by PTH by its effect on a small fraction of calcium reabsorption, 2) the renal tubular reabsorption of sodium is depressed during calcium infusion, and 3) during hypercalcemia, either increased filtered calcium or high extracellular or tubular fluid calcium concentration may primarily alter the relation between Cca and CNa.

Numerous studies have shown that the renal clearances of sodium and diffusible calcium are closely related (2, 3, 15, 17, 18). The clearance ratios of these two ions remain nearly unity in the normocalcemic dog with intact parathyroid glands when sodium excretion is increased by saline infusion (15, 18). This relationship has been attributed to an intimate association between the tubular mechanisms involved in the reabsorption of these ions.

Kleeman et al. (10) showed that calcium clearance is decreased following the administration of parathyroid extract (PTE). Data from stop-flow experiments suggest that this decrease in calcium clearance is due to enhanced distal reabsorption of calcium (20). The evaluation of the relation between the clearance of sodium and calcium in the absence or presence of parathyroid hormone (PTH) might further characterize the interdependence between the tubular reabsorption of these ions.

During calcium infusion the excretion of both calcium and sodium is augmented; however, the character of this association and the mechanism(s) underlying this sodium diuresis are not clearly defined. Hypercalcemia, increased filtered calcium, and suppression of PTH secretion accompany calcium infusion. Each may independently affect the close interrelationship between the renal excretion of calcium and sodium.

In the present study, the effect of variations in serum calcium and parathyroid hormone levels on the renal handling of calcium and sodium was investigated with and without saline infusion.

The results indicate that: 1) the normal interdependence between calcium and sodium excretion is altered by PTH by its effect on a small fraction of calcium reabsorption, 2) the renal tubular reabsorption of sodium is depressed during calcium infusion, and 3) during hypercalcemia, either the increased filtered calcium or the high extracellular or tubular fluid calcium concentration may primarily alter the relation between the clearances of sodium and calcium.

METHODS

Thyroparathyroidectomy (T-PTX) was performed in 15 female mongrel dogs, weighing 14-20 kg, under pentobarbital anesthesia. The complete removal of the parathyroid glands was confirmed by the appearance of hypocalcemia. Two days after T-PTX, clearance studies were carried out under anesthesia. Respiration was con-
trolled by Harvard respirator pump with ventilation adjusted to maintain pH within normal range. Glomerular filtration rate (GFR) was measured by exogenous creatinine clearance. Urine was collected from a retention catheter, and the bladder was washed with air at the end of each collection. Blood was withdrawn at the midpoint of each period from an indwelling needle in the left femoral vein. To prevent variations in mineralocorticoid activity, aldosterone was infused (60 μg/hr) throughout all experiments, except the chronic PTE administration studies (infra vide), beginning 2 hr before urine was first collected. Water diuresis was induced by the infusion of 600–900 ml of 2.5% dextrose in water over 60–90 min, the rate of the infusion was then adjusted to correspond to the rate of urine flow. After the collection of three control clearance periods of 10–20 min duration, one of several procedures were followed whereby calcium chloride and hypotonic saline were infused at several rates and varying sequences in the absence of PTH or with PTE (Lilly) administration. In some studies, clearance periods of 10–20 min duration were obtained throughout the whole experiment, while in others urine samples were collected only after the stabilization of serum calcium level following any change in the solution infused. The following types of experiments were performed: 

**Calcium chloride infusion with saline added later (8 dogs).**
Calcium chloride was added to the creatinine sustaining solution to deliver 7–15 mg Ca++/kg per hr for 6–12 hr. The lowest rate (7 mg Ca++/kg per hr) was given first for 3–4 hr. This was followed in some experiments by a higher rate (10 mg Ca++/kg per hr) for additional 3–4 hr, and in still others 15 mg Ca++/kg per hr were given for the same period of time. By this technique serum calcium was raised from hypocalcemic levels of 6 mg/100 ml to normal and hypercalcemic levels as high as 18 mg/100 ml. During the 3rd hr of each rate of calcium infusion the serum calcium level was generally stable. Towards the end of several experiments described above 0.45% saline replaced the 2.5% dextrose in water while the calcium infusion was continued at the same rate. The saline was infused at a rate of 20 ml/min for 60–90 min and then adjusted according to the rate of urine flow for an additional 60–90 min.

**Calcium chloride infusion with acute reduction in glomerular filtration rate (6 dogs).** In six of the above eight dogs, a triple lumen catheter (US Catheter and Instrument) with a balloon attached to its distal end was inserted via the right femoral artery into the aorta to a level above the renal arteries immediately after the induction of anesthesia. Abrupt inflation of the balloon led to cessation of the urine and confirmed its location. Intra-aortic pressure was monitored, both proximal and distal to the balloon, by mercury manometers. Glomerular filtration rate was reduced by the inflation of the balloon during a steady state normocalcemia and/or hypercalcemia before any saline was infused. After each adjustment of the balloon 5 min were allowed for the distal intra aortic pressure to stabilize at 60–70% of its control level. Each inflation period lasted 20–40 min while urine was collected for 3–5 clearance periods of 5–7 min duration.

**Saline infusion with calcium chloride added later (3 dogs).**
After control clearance periods, the 2.5% dextrose in water was discontinued, and 0.45% NaCl was given at a rate of 20 ml/min for 60–90 min and adjusted thereafter to the rate of urine flow. After 3 hr, calcium chloride was added to deliver 7 to 10 mg Ca++/kg per hr for 3–6 hr more while the hypotonic saline infusion was continued.

**Calcium chloride and hypotonic saline infusion with acute PTE administration (2 dogs).**
Calcium chloride, 7–10 mg Ca++/kg per hr, was infused to raise serum calcium to normal levels. Two-hundred units of PTE were then injected intramuscularly every 2 hr for a total of four doses. Two hours after the first PTE injection, the calcium infusion rate was increased to 15 mg Ca++/kg per hr for the rest of the experiment. Hypotonic saline was added during the last 4 hr of the experiment in a manner similar to that described above.

**Chronic PTE administration (2 dogs).** Two days after TPTX, serum calcium was raised from hypocalcemic to normal or hypercalcemic levels by the intramuscular administration of PTE over 3 days. One hundred units of PTE were given at 10 AM and 6 PM on day 1 after the first clearance studies, at 8 AM and 2 PM on day 2, and at 8 AM on day 3. Clearance periods of 15–20 min were obtained between 9–10 AM on the 3 consecutive days.

Blood and urine samples were analyzed for creatinine, sodium and calcium by methods previously reported from this laboratory (15). Water content of serum was determined by refractometry (Goldberg refractometer, American Optical Company, Buffalo, N.Y.). Serum creatinine, sodium, and calcium were measured in each clearance period. Diffusible calcium was determined in ultrafiltrates of serum prepared anaerobically in the Lavietes chambers (12) at room temperature. Ultrafiltrates were prepared from specimens taken during one control period and every 90 min thereafter. Percent diffusibility of calcium was calculated from the follow-
TABLE 1. Relation between calcium and sodium clearances in normal dogs

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>$C_{cr}$</th>
<th>$C_{ca}$</th>
<th>$C_{ca}$/ $C_{cr}$</th>
<th>$S_{ca}$</th>
<th>$S_{Na}$</th>
<th>$C_{Na}$</th>
<th>$C_{Na}$/ $C_{Na}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal dogs, receiving aldosterone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38.6</td>
<td>8.47</td>
<td>1.38</td>
<td>140</td>
<td>0.99</td>
<td>1.39</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>50.1</td>
<td>9.60</td>
<td>0.33</td>
<td>137</td>
<td>0.29</td>
<td>1.15</td>
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</tr>
<tr>
<td>3</td>
<td>85.1</td>
<td>9.29</td>
<td>0.31</td>
<td>152</td>
<td>0.30</td>
<td>1.01</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>45.8</td>
<td>9.21</td>
<td>0.29</td>
<td>135</td>
<td>0.32</td>
<td>0.91</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>43.3</td>
<td>8.76</td>
<td>0.70</td>
<td>122</td>
<td>1.26</td>
<td>0.56</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>61.5</td>
<td>8.50</td>
<td>0.39</td>
<td>147</td>
<td>0.83</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>39.2</td>
<td>9.37</td>
<td>0.43</td>
<td>131</td>
<td>0.85</td>
<td>0.31</td>
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</tr>
<tr>
<td>8</td>
<td>80.0</td>
<td>9.23</td>
<td>1.06</td>
<td>130</td>
<td>0.97</td>
<td>1.08</td>
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<tr>
<td>9</td>
<td>72.2</td>
<td>9.60</td>
<td>0.63</td>
<td>143</td>
<td>0.59</td>
<td>1.07</td>
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<tr>
<td>10</td>
<td>53.8</td>
<td>10.32</td>
<td>0.18</td>
<td>143</td>
<td>0.25</td>
<td>0.72</td>
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<tr>
<td>11</td>
<td>84.2</td>
<td>9.79</td>
<td>0.27</td>
<td>139</td>
<td>0.28</td>
<td>0.97</td>
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<tr>
<td>12</td>
<td>90.6</td>
<td>9.84</td>
<td>0.33</td>
<td>135</td>
<td>0.50</td>
<td>1.06</td>
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</tbody>
</table>

Normal dogs, receiving aldosterone, 60 µg/hr

<table>
<thead>
<tr>
<th>Dog No.</th>
<th>$C_{cr}$</th>
<th>$C_{ca}$</th>
<th>$C_{ca}$/ $C_{cr}$</th>
<th>$S_{ca}$</th>
<th>$S_{Na}$</th>
<th>$C_{Na}$</th>
<th>$C_{Na}$/ $C_{Na}$</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>31.2</td>
<td>8.83</td>
<td>0.13</td>
<td>131</td>
<td>0.12</td>
<td>1.09</td>
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<tr>
<td>2</td>
<td>47.6</td>
<td>9.21</td>
<td>0.61</td>
<td>131</td>
<td>0.34</td>
<td>1.79</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td>10.80</td>
<td>0.66</td>
<td>133</td>
<td>0.42</td>
<td>1.57</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>104.0</td>
<td>10.47</td>
<td>1.23</td>
<td>142</td>
<td>1.01</td>
<td>1.21</td>
<td></td>
</tr>
<tr>
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<td>61.3</td>
<td>9.17</td>
<td>0.44</td>
<td>149</td>
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<td>1.91</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>57.9</td>
<td>9.33</td>
<td>0.25</td>
<td>147</td>
<td>0.20</td>
<td>1.25</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: $C_{cr}$ = creatinine clearance; $S_{ca}$ = serum calcium; $C_{ca}$ = clearance of diffusible calcium; $S_{Na}$ = serum sodium; and $C_{Na}$ = sodium clearance.

The percent diffusibility of calcium evidenced no appreciable change in any given experiment or in the total group with the various manipulations described above (Fig. 1). Therefore the mean percent diffusibility of calcium in each experiment was used to calculate the diffusible calcium for those clearance periods where direct measurements were not made. The following formula was used:

\[
\text{percent diffusibility} = \frac{\text{diffusible calcium mg/100 ml serum}}{\text{total calcium/100 ml serum}} \times 100
\]

All clearances of calcium are expressed in terms of the diffusible fractions.

RESULTS

In the control clearance periods in 15 T-PTX dogs (3 clearance periods each), calcium clearance ($C_{ca}$) was 4-6 times greater than sodium clearance ($C_{Na}$) with a $C_{Ca}/C_{Na}$ ratio of 5.10 ± 0.94 (mean ± se). This value is considerably higher than that observed in nonoperated normal dogs, whether receiving a similar small quantity of aldosterone ($N = 6, C_{Ca}/C_{Na} = 1.47 ± 0.14$) or not.

Although larger quantities of aldosterone administered to adrenalectomized dogs markedly altered the interrelationship between $C_{Ca}$ and $C_{Na}$ (14), the small amount used in the present study produced an effect which would not change the interpretation of the results.
The data from the studies when 0.45% saline was infused from the beginning to the end of the experiment are presented in Fig. 3. Both calcium and sodium clearances increased and the relation between them gradually approached that observed in intact dogs receiving saline infusion (15). With hypocalcemia and sodium excretion rates below 250 μEq/min, $C_{Ca}$ exceeded $C_{Na}$ and the data fell beyond the 95% confidence limits observed in the normals. When sodium excretion exceeded 300 μEq/min, and serum calcium was low or normal, the $C_{Ca}/C_{Na}$ ratio was similar to that noted in normal dogs during saline infusion. With hypercalcemia induced by additional calcium infusion $C_{Ca}$ exceeded $C_{Na}$ despite continued saline infusion.

The results obtained with hypercalcemia during 1) calcium infusion alone, 2) calcium infusion and PTE administration, 3) calcium and saline infusion, and 4) calcium and saline infusion with PTE injection are presented in Fig. 4. There is a direct and significant relationship between calcium and sodium clearance ($C_{Ca} = 1.4$ $C_{Na} + 2.6$, $r = 0.96$, $P < 0.001$). However, the regression line is above that observed during saline infusion to intact or to hypo- or normocalcemic T-PTX dogs. It is clear that hypercalcemia is associated with a greater calcium clearance for any given level of sodium clearance irrespective of parathyroid hormone administration or saline infusion.

In order to clarify the mechanisms underlying the saluresis induced by calcium infusion, sodium excretion was measured during acute reduction in glomerular filtration rate and filtered sodium. Despite the decrease in GFR (10-35%), and the concurrent reduction in filtered sodium (14-40%), the excretion of sodium exceeded control rate (+67 to 488%) when urinary calcium surpassed the control values (+231 to 2,740%). A representative experiment is presented in Table 3 and a summary of all such experiments is given in Table 4.

**DISCUSSION**

These studies demonstrate that the interdependence between the renal clearances of sodium and calcium is...
altered in the absence of PTH. Despite the hypocalcemia and the consequent decrease in filtered calcium, its clearance was greater than that of sodium. Since PTE administration restored the Cca/Cna ratio to normal by decreasing Cca without changes in sodium excretion, it appears that PTH alters the clearance relationship between these ions mainly through its influence on calcium reabsorption.

In the proximal tubule, where the major part of calcium is reabsorbed (11), Frick and co-workers (7) reported no effect of PTE on calcium reabsorption. Widrow and Levinsky (20) concluded from the stop-flow studies that PTH enhances calcium reabsorption in the distal nephron, where 10% or less of filtered calcium is transported (11). It seems, therefore, that this hormone may influence only a small fraction of calcium transport in the kidney. When calcium delivery to the distal segment of the nephron is greatly augmented, the effect of PTH on calcium excretion may become less evident or even totally masked. The data obtained during saline infusion to T-PTX dogs support this postulate (Fig. 3). Saline infusion leads to decreased proximal reabsorption and enhanced distal delivery of calcium and sodium (3, 5, 6, 15). Although less calcium might be reabsorbed in the distal nephron in the absence of PTH, this amount may constitute such a small portion of the calcium cleared that the calcium and sodium clearance relationship may not differ from that noted during saline infusion to intact dogs. The absence of an effect of PTE administration on calcium reabsorption during hypercalcemia is also consistent with this concept; augmented distal calcium delivery is most likely present and the PTH effect may also be obscured.

An increase in urinary sodium occurs during calcium infusion (1, 13, 21). Although the mechanisms involved have not been clearly defined, it was suggested that the augmented sodium excretion might be due to a competition between calcium and sodium ion for a common reabsorptive site (8). This postulate implies a decrease in sodium reabsorption as renal tubular reabsorption of
It is possible that a high calcium concentration may impair sodium reabsorption by altering the membrane permeability to this ion. Curran, Herrera, and Flanigan (4) reported a decrease in the permeability of frog skin to sodium when the mucosal calcium concentration was increased from zero to 1.5 mM. In the present study, sodium reabsorption decreased as the concentration of the diffusible calcium in blood was increased from 1.5 to 3.0 mM. Whether such a concentration change may affect tubular permeability to sodium is unknown.

During calcium infusion in the T-PTX animals there was a disproportionate increase in calcium clearance above the rise in sodium clearance. This was particularly apparent as serum calcium increased from low to normal levels. The following speculations provide a possible explanation. With the increase in serum and filtered calcium from low levels towards normal, both absolute proximal reabsorption and distal delivery of calcium probably increase. A slight decrease in sodium reabsorption may result from the increased calcium reabsorption. In addition, less calcium might be reabsorbed in the distal nephron since the PTH-dependent mechanism for calcium reabsorption, which does not affect sodium transport, is inactive. The result might then be an increase in calcium clearance. With hypercalcemia, the increment in sodium excretion was more marked (Fig. 2). Either greater competitive inhibition of sodium transport, or a more pronounced effect on membrane permeability could be responsible.

The failure of saline infusion to alter the clearance relationship noted between these two ions during hypercalcemia, suggests that calcium reabsorption may be inhibited to a greater degree than that of sodium. However, this inhibition could be proportional. Hypercalcemia probably leads to an absolute increase in calcium reabsorption and reduction in that of sodium. Therefore, the same fractional inhibition of proximal reabsorption of these ions by saline infusion could result in the observed progressive increase in the difference between calcium and sodium clearance.

We thank Mr. Herb Hansen and Mrs. Miriam Bick for their technical assistance.

**REFERENCES**


