Ann. Rev. Pharmacol. Toxicol. 1986. 26:101–16

RENAL CALCIUM METABOLISM AND DIURETICS

Charles T. Stier, Jr. and Harold D. Itskovitz

Departments of Pharmacology and Medicine, New York Medical College, Valhalla, NY 10595

INTRODUCTION

The major purposes of diuretics are to enhance renal excretion of salt and water and to lower blood pressure. However, their effects are not limited to sodium and chloride; they may also influence the renal reabsorption and excretion of calcium, magnesium, potassium, and other ions. It is important to be aware of these effects in order to maintain appropriate body content of essential chemicals. The present review centers on the interactions of diuretic agents with calcium. Knowledge of these interactions may be useful in the appropriate application of diuretic agents for the maintenance of normal blood concentrations and body stores of calcium, especially during the chronic use of diuretic agents. Also, diuretic agents with differing effects on calcium metabolism may be indicated therapeutically in disorders of calcium metabolism. In the present review, we have taken into account the effects of diuretic agents on renal calcium metabolism relative to hormonal and nonhormonal factors and their direct actions within the nephron. Several excellent reviews of diuretics have been published in the past few years (1–3).

CALCIUM HANDLING BY THE KIDNEY

Filtration and Reabsorption

Calcium is present in plasma in three forms: free calcium, calcium anionic complexes, and calcium bound to protein. Filtration of calcium is limited owing to its binding to plasma proteins, and only free calcium and calcium anionic complexes can cross the glomerulus. Measurements of calcium concentrations

0362-1642/86/0415-0101$02.00

in the glomerular fluid of Bowman's space indicate that approximately 60% of plasma calcium may be filtered (4–6). This figure agrees in general with the reported ultrafilterability of calcium across artificial membranes (7). In tubular fluid of the proximal tubule the concentration of calcium is constant and is similar to or slightly exceeds the concentration of ultrafilterable calcium when measured in nondiuretic animals (4, 8–10). In fluid-expanded animals, active proximal tubular reabsorption of calcium has been demonstrated, because concentrations of tubular-fluid calcium lower than ultrafilterable glomerular calcium concentrations have been obtained (5, 8). Active calcium reabsorption in the proximal tubule has been postulated also on the basis of stop-flow microperfusion experiments in rats (11). The tubular basolateral membrane is thought to be the site of active transport of calcium since an appropriate electrochemical gradient for calcium entry into tubular cells exists on the luminal side (12). Two mechanisms of transport have been proposed. The first involves Ca^{2+}-ATPase: This enzyme has been found in the basolateral membrane of rat proximal tubular cells (13, 14). The second mechanism involves a sodium/calcium antiport, in which sodium enters the cell at the basolateral membrane in exchange for calcium. The latter mechanism is driven by the active pumping of intracellular sodium across the basolateral membrane. This explanation is supported by reports that ouabain and perfusion of peritubular capillaries with sodium-free solutions interfere with calcium reabsorption in the proximal tubule (11). Beyond the proximal tubule, reabsorption of calcium occurs in the pars recta and loop of Henle. Reabsorption in these zones accounts for 20–30% of the calcium that enters the tubular fluid at the glomerulus. At the hairpin turn of the loop of Henle, in the juxtamedullary nephron, tubular fluid/plasma concentrations of calcium are lower than those of sodium (15, 16), suggesting a dissociation of transport between these ions in either the pars recta or the descending limb of Henle's loop. This may relate to substantial reabsorption of calcium in segments of the straight proximal tubule (17) or perhaps to greater medullary recycling (entry into the descending limb) of sodium relative to calcium. Reabsorption of calcium has been demonstrated in isolated perfused segments of the thick ascending limb, both in its cortical (18, 19) and medullary (20) segments. Calcium reabsorption here has been found to be passive and is thought to be driven by a lumen-positive transepithelial potential generated in response to active chloride reabsorption (21). In contrast, other studies have reported active calcium reabsorption in perfused segments of cortical thick ascending limbs (20, 22, 23).

The reasons for these different findings are not clear. Studies in the early distal convoluted tubule indicate that the fractions of sodium and calcium reabsorbed are similar, and that they are equal at that point to approximately 85% of calcium filtered at the glomerulus (10, 24).

Hormonal Interactions

VITAMIN D Vitamin D is converted in vivo to 1,25-dihydroxyvitamin D, which is its most active metabolic form. Parathyroid hormone (PTH) stimulates a final hydroxylation that occurs in the kidney. Thus, elevated levels of 1,25-dihydroxyvitamin D have been reported in some patients with hyperparathyroid disease. Vitamin D administration enhances calcium absorption in the intestine and increases plasma calcium concentrations. In parathyroidectomized animals, 1,25-dihydroxyvitamin D will increase urinary excretion of calcium (25). Vitamin D has been used in patients with deficient parathyroid function to raise plasma calcium levels and is usually associated with increased urinary calcium excretion. On the other hand, the renal reabsorption of calcium has been reported to increase after acute vitamin D administration (26). This may or may not be related to its effect of increasing blood calcium levels and secondarily increasing the filtration of calcium across the glomerulus. It has also been reported that administration of vitamin D can increase urinary calcium excretion without altering serum calcium or creatinine clearance (27). Preliminary micropuncture studies suggest possible distal nephron effects (28). The direct renal actions of vitamin D and its metabolites on various nephron segments remain to be fully investigated.

PARATHYROID HORMONE (PTH) PTH plays an important regulatory role in body-calcium metabolism. PTH has extrarenal sites of action to increase bone resorption and intestinal calcium absorption and thus increase plasma calcium concentrations. In the kidney its hypocalciuric action further increases plasma calcium levels. Experimentally and clinically, parathyroidectomy or hypoparathyroidism is accompanied by an increase in urinary calcium excretion, whereas hyperparathyroid states are conversely manifested by reduced renal calcium clearance (29).

In contrast to its effects on calcium, PTH increases phosphate excretion by the kidney. Micropuncture and microperfusion studies have localized the principal sites of PTH actions to the distal nephron for increased calcium reabsorption and to the proximal tubule for its phosphaturic effect. After administration of PTH to intact or thyroparathyroidectomized dogs, delivery of calcium and sodium to the late proximal tubule is increased proportionately (30). However, in distal tubular fluid and the final urine the Ca/Na ratio is substantially decreased by PTH, supporting selective enhancement of calcium reabsorption at distal sites. In isolated perfused segments of cortical thick ascending tubules (20, 31–33) and in granular portions of the distal convoluted tubule and collecting duct (18, 32), PTH increases absorption of calcium when added to the bath. These nephron segments have been reported to possess

PTH-sensitive adenylate cyclase activity (32, 34). Analogs of cyclic AMP have been shown to mimic the effects of PTH on these nephron segments (31–33). In contrast, calcium absorption in perfused thick ascending medullary limbs (20) and cortical collecting tubules (18, 32, 33) is not affected by PTH. In these same areas, PTH-sensitive adenylate cyclase activity has been reported to be very low (32, 34).

CALCITONIN Although calcitonin's extrarenal effects generally oppose those of PTH—it inhibits the reabsorption of bone calcium and decreases intestinal calcium absorption—its renal effects are similar to those of PTH in that it causes a hypocalciuric effect. Acute administration of calcitonin has been reported to exert a hypocalciuric action (35, 36) although in some studies calcium excretion was unchanged (37) or increased (38). Microperfusion studies in vivo have shown decreased urinary calcium excretion in association with increased calcium reabsorption in the loop of Henle, whereas calcitonin was observed to exert little effect on either proximal or distal tubular calcium absorption (39). In isolated perfused tubular preparations calcitonin increased calcium absorption and stimulated adenylate cyclase activity (40) in medullary thick ascending loops but had no effect on calcium absorption in cortical thick ascending limbs (41). Thus, calcitonin differs in its nephron sites of action from PTH, which stimulates calcium absorption in the cortical thick ascending limb but has no effect on medullary thick ascending loops. The hypocalciuric effect of calcitonin may depend also upon its ability to diminish plasma-calcium concentrations, since urinary calcium excretion is maintained when hypocalcemia is prevented by intravenous infusions of calcium chloride (39). Thus, the renal excretion of calcium after calcitonin is believed to be reduced relative both to its effects on the plasma calcium concentration and to its effects on the renal tubule.

Nonhormonal Interactions

Alterations in clearance of sodium are generally accompanied by similar alterations in the clearance of ultrafilterable calcium. This has led to the suggestion that the renal reabsorption of sodium and calcium are interdependent (29). Infusions of sodium chloride produce an increase in urinary calcium clearance that parallels the increase in sodium, even when the glomerular filtration of these ions is maintained below control levels (42). Micropuncture studies have shown proportionate reductions in proximal tubular reabsorption of sodium and calcium during saline volume expansion. On the other hand, a dissociation of sodium and calcium excretion occurs when sodium is infused with certain nonreabsorbable anions that complex with calcium. Thus, sodium sulfate infusions have been found to produce significantly greater increases in clearance of calcium than of sodium (29). However, when calcium is infused

with other nonreabsorbable anions such as gluconate or lactate, the excretion of sodium is greater than that of calcium (43). In contrast, calcium chloride infusion markedly increases urinary calcium excretion, with little or no effect on sodium excretion (10). Even with a subsequent infusion of saline under this circumstance the dissociation persists and is believed to be related, in part, to suppression of PTH release (43).

During infusions of magnesium, the clearance of calcium greatly exceeds that of sodium. This dissociation relates in part to decreased PTH release secondary to hypermagnesemia. Magnesium also acts directly to diminish the tubular reabsorption of calcium to a greater extent than sodium reabsorption (44). In contrast to infusions of magnesium, those of phosphate decrease urinary calcium excretion (45) whereas phosphate depletion elevates urinary calcium.

Alterations in acid-base balance also influence the excretion of calcium. Chronic metabolic acidosis increases total urinary calcium excretion and the ratio of calcium-to-sodium clearance (46). The effects of acidosis do not appear to be due to lowering blood pH alone since respiratory acidosis has a delayed effect, increasing urinary calcium excretion only after several weeks when net acid excretion is increased. Alkalosis, resulting from bicarbonate administration, has an opposite effect and increases renal sodium excretion relative to that of calcium (46).

Nonionic substances, such as glucose or protein, which do not increase (but may decrease) sodium excretion, generally increase urinary calcium. The effects of glucose relate in part to increased insulin secretion. Hypercalciuria has also been reported after fasting which, in this case, has been related to the resultant ketoacidosis (43). Alterations in renal hemodynamics by vasodilator agents result in increases in fractional urinary calcium excretion that parallel that of sodium (47).

DIURETICS

By affecting one or another of the physiologic mechanisms that influence the renal handling of calcium, the different diuretics may either increase or decrease calcium excretion. Their final effects will be the result of many interrelated forces: direct renal actions and alterations in hormonal and nonhormonal factors. In the following discussion, we summarize the effects of diuretic agents on urinary calcium describing them in terms of the previously listed mechanisms.

Carbonic Anhydrase Inhibitors

Carbonic anhydrase inhibitors, typified by acetazolamide, exert their diuretic effects by blocking the generation of hydrogen ions. These ions have a major

effect of enhancing the reabsorption of bicarbonate in the proximal tubule. Thus, carbonic anhydrase inhibitors produce a marked increase in urinary bicarbonate and phosphate excretion. Since phosphate anions are poorly reabsorbed beyond the proximal tubule, their excretion leads to an increased excretion of sodium and water. Generally, acetazolamide has been reported to produce an associated increase in calcium excretion (48–50), though it is less than that of sodium. In several studies calcium excretion was unaffected (51–53). The ability of acetazolamide to increase calcium excretion has been observed in thyroparathyroidectomized animals, suggesting that its calciuric effect is not related to changes in circulating PTH levels (50). Although administration both of PTH and of acetazolamide produces qualitatively similar results, no inhibitory effect of PTH or cyclic nucleotides
activity has been reported. In stop-flow microperfusion studies of rat proximal tubules, acetazolamide did not influence active calcium transport, suggesting that its calciuric effect was passive (11). This is consistent with observations that acetazolamide does not inhibit microsomal calcium-activated ATPase from rat kidneys (52) or ATP-dependent calcium uptake by microsomes isolated from rat kidneys (54).

Micropuncture studies indicate that acetazolamide inhibits sodium and calcium reabsorption to parallel degrees in the proximal tubule of intact and parathyroidectomized animals (53). However, by the final urine, sodium excretion but not calcium excretion was increased, which was interpreted as indicating a greater distal reabsorption of calcium than of sodium. Also, during chronic acetazolamide administration the resultant metabolic acidosis may be associated with hypercalciuria. In studies using isolated canine kidneys perfused at constant pressure with autologous blood maintained in a nearly normal physiologic state, we observed significant increases in calcium excretion and comparable sodium clearance relative to calcium clearance following additions of acetazolamide (Figure 1). Our results support a direct action of acetazolamide on renal calcium metabolism, independent of changes in circulating hormones or systemic hemodynamics.

Loop Diuretics

The organomercurials, furosemide, and ethacrynic acid are diuretics that have the thick ascending loop of Henle as their main site of action. These agents act primarily to inhibit the 1 Na^+/1 K^+/2Cl^- cotransporter that is localized to the luminal membrane of the cortical and medullary portions of the thick ascending limb (55). The earliest effect of the loop diuretics (especially furosemide) is to increase urinary calcium excretion to a degree that parallels or most often is greater than their natriuretic effect. Few studies have tracked the long-term effects of loop diuretics on calcium balance. In isolated perfused rabbit cortical thick ascending limbs, furosemide inhibited calcium absorption in association

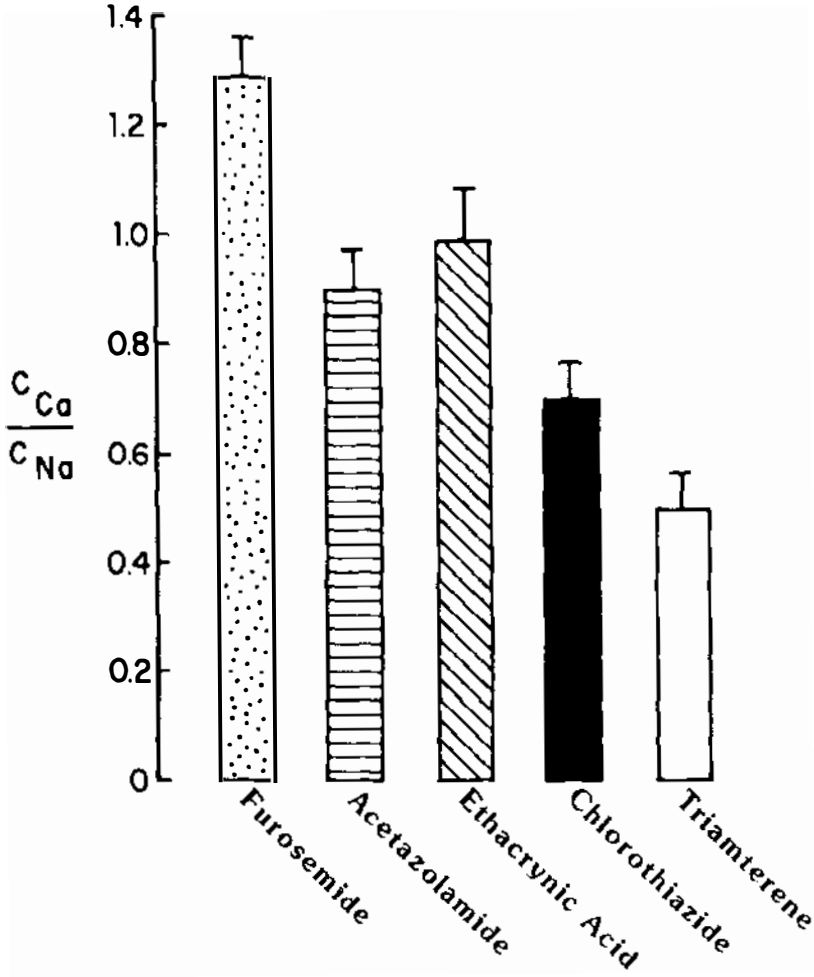

Figure 1 Ratio of calcium clearance to sodium clearance (C_{Ca}/C_{Na}) during peak natriuretic responses in isolated blood-perfused dog kidneys following bolus injections of diuretics. Furosemide ($n \approx 9$) > ethacrynic acid ($n = 5$) = acetazolamide ($n = 8$) ≥ chlorothiazide ($n = 3$) = triamterene ($n = 11$) by ANOVA.

with a reduction in the lumen-positive transepithelial voltage thought to drive passive calcium-ion transport in this segment (56). Furosemide causes slightly more calciuria than natriuresis (49, 50, 57–63). This dissociation appears to reside in the thick ascending limb of the loop of Henle. In vivo microperfusion studies in the rat have demonstrated relatively greater inhibition of calcium absorption than of sodium absorption in Henle's loop on intraluminal adminis-

tration of furosemide, with little or no effect on the transport of these ions in the superficial distal tubule (64). Mercurial diuretics like furosemide have been reported to increase urinary calcium more than they do that of urinary sodium (65, 66). Ethacrynic acid, on the other hand, increases urinary calcium and sodium to similar degrees (48–50, 58, 59, 67). In our own studies using isolated, blood-perfused dog kidneys, we have shown that furosemide increases the clearance of calcium over that of sodium to a degree significantly greater than that caused by ethacrynic acid (Figures 1 and 2). Whereas furosemide consistently increased calcium clearance in excess of sodium clearance, ethacrynic acid affected calcium clearance to a similar (or slightly lesser) degree than sodium clearance on bolus administration (Figure 1) or infusion (Figure 2), respectively. We do not know the reason for this difference between furosemide and ethacrynic acid but have considered the possibility that it may relate to an additional effect ethacrynic acid has of enhancing calcium absorption relative to sodium absorption at an early distal site. This site is not shared by furosemide since other agents that act at distal sites beyond the loop of Henle (such as the thiazides and amiloride), tend to enhance the renal clearance of sodium relative to calcium in our isolated kidney preparation. When amiloride was infused during infusion of either furosemide or ethacrynic acid C_{Ca}/C_{Na} decreased (Figure 2). Chlorothiazide further decreased C_{Ca}/C_{Na} in kidneys infused with furosemide plus amiloride, but did not do so in kidneys that received ethacrynic acid plus amiloride. These results suggest that thiazides and ethacrynic acid share a distal site of action (perhaps the distal convoluted tubule) at which furosemide does not act.

Thiazide Diuretics

Thiazides and related diuretics, such as chlorthalidone, metolazone, and indapamide, have a primary effect at the early distal tubule diluting site. Agents acting at this site increase sodium excretion to a greater extent than excretion of chloride (in contradistinction to the loop diuretics) and cause a greater osmotic than water diuresis, which prevents the formation of a dilute urine. Acute administration of these agents produces a natriuresis and diuresis with little or no increase in calcium excretion (50, 59, 62, 65, 67). In some studies the clearance of calcium decreased (68, 69), resulting in a marked reduction in the calcium/sodium clearance ratio. Chronic thiazide administration causes an absolute reduction in calcium excretion (70–74) and this forms the basis for its therapeutic role of diminishing idiopathic hypercalciuria and preventing the formation of calcium-containing renal stones (75). Thiazides have also been used for treatment of bone demineralization states, such as osteoporosis. Different studies have suggested several different mechanisms for the hypocalciuric effects of thiazides. These effects include increasing calcium reabsorption by volume depletion and by increased plasma PTH levels as well as potentiation of the actions of PTH (73, 74). However, when administered

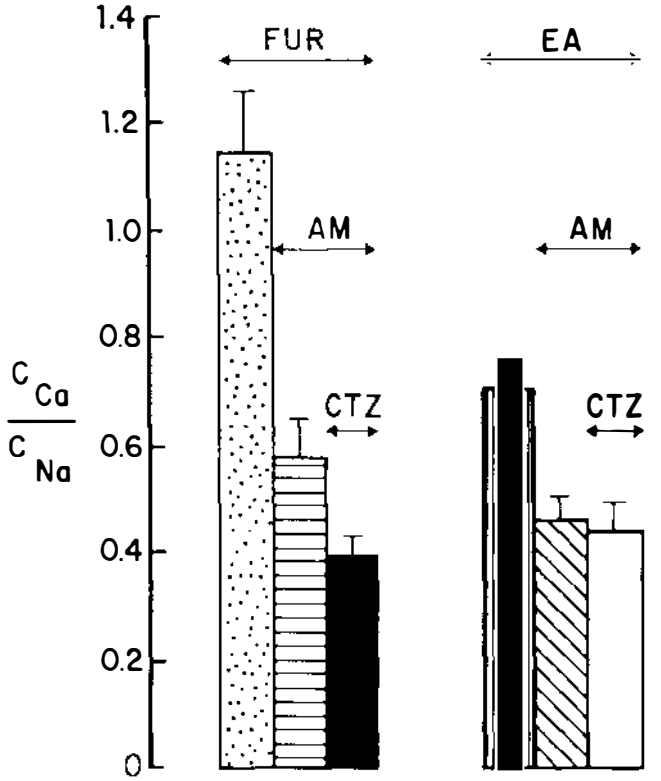

Figure 2 Ratio of calcium clearance to sodium clearance (C_{Ca}/C_{Na}) in isolated blood-perfused dog kidneys following a 1 mg bolus injection and continuous 0.2 mg/min infusion of furosemide (FUR) (n = 8) or ethacrynic acid (EA) (n = 5) and subsequent amiloride (AM) and chlorothiazide (CTZ) (n = 4) administration at the same dose level.

acutely to patients with hypoparathyroidism (76) or to thyroparathyroidectomized dogs (62, 77, 78), chlorothiazide has still been shown to reduce the calcium/sodium in the urine, indicating an effect independent of PTH. In our studies of isolated kidneys, where renal perfusion pressure and perfusate volume are constant, thiazides have been found to exert a direct effect on the kidney to diminish calcium excretion relative to sodium excretion (Figure 1). Microperfusion studies have localized the increase in calcium reabsorption in response to chlorothiazide to the distal convoluted tubule (79), predominantly to its early portion (80).

Potassium-Sparing Diuretics

Agents such as spironolactone (a competitive receptor antagonist of aldosterone) and triamterene or amiloride (which appear to block sodium channels) act at late distal tubular exchange sites to interfere with sodium potassium hydro-

gen ion exchange. As a result, urinary sodium and water excretion is increased while potassium- and hydrogen-ion excretion is diminished. In acute studies, triamterene has been found to cause an early increased urinary calcium excretion, followed by a reduction in urinary calcium after 6 hr (58). In other studies, water-loaded rats that received triamterene were shown to have significantly higher urine-sodium concentrations, while urinary calcium and magnesium were reduced (81). Still other studies in anesthetized dogs demonstrated that triamterene increased the clearance of sodium but had no consistent effect on that of calcium (78). Following administration of triamterene in isolated, blood-perfused dog kidneys, we observed an enhanced excretion of sodium relative to calcium (Figure 1). In a number of cases, calcium excretion was actually reduced. The effect of amiloride on calcium excretion was similar to that of triamterene. Microperfusion studies in rats and isolated segments of the rabbit nephron indicate that amiloride inhibits sodium reabsorption and potassium secretion and reverses the lumen-negative potential in the lumen of cortical collecting tubules, but has no effect in the cortical thick ascending limb (82, 83). Consistent with an action in the distal portion of the nephron, the direct intrarenal infusion of amiloride in clearance studies in dogs has been shown to produce a unilateral hypocalciuric effect (78). Recent microperfusion studies have localized enhancement of calcium absorption to the late segments of the distal tubule with little or no effect on the early distal convoluted tubule (84). Thus, the effects of amiloride on calcium can be observed even after administration of diuretics having earlier nephron sites of action. The hypocalciuric action of amiloride has been found to persist during furosemide diuresis in rats prepared for renal clearance studies (63) and in isolated blood-perfused dog kidneys (Figure 2). Maximally effective doses of amiloride and chlorothiazide have additive effects of reducing the ratio of calcium clearance/sodium clearance (78). That this additivity is the result of different sites of action rather than different mechanisms of action is borne out by microperfusion studies indicating that the principal action of chlorothiazide is on the early distal convoluted tubule and that of amiloride is on the late distal convoluted tubule (80). It is unclear whether the increased calcium absorption of diuretics acting at the distal convoluted tubule and collecting duct is the result of loss of the lumen-negative transmembrane potential or whether it is the result of increased rates of sodium-calcium exchange. Although the increase in calcium absorption with amiloride is highly correlated with the decrease in sodium reabsorption, a similar quantitative relationship using chlorothiazide could not be established (80). Unlike thiazide diuretics, which markedly increase urinary potassium excretion, triamterene lowers urinary potassium, suggesting that the dissociation of sodium and calcium transport is not directly related to potassium in the distal tubule.

Spironolactone, like triamterene and amiloride, increases sodium excretion

but decreases potassium excretion. In this case, the effects are dependent upon aldosterone blockade, since they are not observed in adrenalectomized animals. In intact dogs, adrenalectomy decreases the clearance of calcium relative to sodium. Subsequent administration of aldosterone increases the urinary calcium/sodium primarily by reducing the clearance of sodium (85). In rats on a low-calcium diet, mineralocorticoid administration increases calcium excretion, while sodium excretion is reduced (86). The effect of mineralocorticoids on urinary calcium excretion was thought to be due to extracellular fluid volume expansion subsequent to sodium retention, since an associated study in rats fed a diet low in sodium and calcium revealed no change in urinary calcium. In man, acute administration of aldosterone has resulted in inconsistent changes (87) or no change (88) in calcium excretion whereas spironolactone (Aldactone) has been found to increase both urinary calcium and sodium (89, 90). The latter results with calcium have been questioned subsequently, since substantial quantities of calcium were present in the spironolactone preparation administered (91), and the administration of vehicle alone produced the same degree of calciuria. It is likely that spironolactone may decrease the clearance of calcium relative to sodium clearance, as in the case of adrenalectomy. Taken together, these results indicate that aldosterone and the reversal of its effects exert only a modest influence on urinary calcium reabsorption in the distal nephron. The greater dissociation and hypocalciuria with triamterene and amiloride probably relate to a more complete inhibition of sodium reabsorption in terminal nephron segments by these agents.

CLINICAL USES OF DIURETICS WITH RESPECT TO CALCIUM

The differential actions of diuretic agents on calcium excretion have proved helpful in the clinical management of hypercalcemic and hypercalciuric states. In the former case, administration of furosemide and volume replacement with saline have been used to reduce plasma calcium concentrations acutely (92) and in the latter case of thiazides, to diminish urinary calcium levels. Although hypercalcemia usually does not result from thiazide treatment, an increased prevalence has been reported in patients with underlying disorders, such as primary hyperparathyroidism (93). In such cases hypercalcemia can be reversed by stopping thiazide treatment. Use of carbonic anhydrase inhibitors in the treatment of renal stone formation is limited to alkalinization of the urine. In patients forming calcium calculii, carbonic anhydrase inhibitors may increase urinary calcium excretion and promote calcium stone formation. Renal nephrolithiasis accounts for approximately 2–3% of hospital admissions (94). About 70% of kidney stones are composed of calcium oxalate and/or calcium phosphate. Normocalcemic hypercalciuria appears to predipose to calcium stone

formation. Thiazide diuretics have been shown to reduce both calcium excretion and stone incidence in hypercalciuric patients (95). Combined use of thiazides and amiloride may be therapeutically advantageous since the hypocalciuric effects of these diuretics are additive while the hypokalemia produced by thiazides is prevented by amiloride (96, 97).

SUMMARY AND CONCLUSIONS

Diuretic agents have variable effects on calcium excretion as studied in vivo and in isolated kidneys and nephron segments. Generally, by increasing sodium and water excretion, diuretics will cause a concomitant increase in calcium excretion. As they diminish blood volume and alter renal hemodynamics, diuretics enhance calcium reabsorption in the proximal tubule, modulating their usual effects on calcium excretion. These general effects can be further modulated by additional metabolic actions. For instance, chronic administration of thiazide diuretics may diminish calcium excretion on the basis of altered levels of or responsiveness to PTH. Agents such as acetazolamide, which diminish bicarbonate reabsorption in the proximal tubule, will cause a modest calciuria, if any, because of reabsorption of the increased delivery of calcium, but not sodium, at the distal nephron. Agents acting in the loop of Henle that increase chloride excretion relative to sodium tend to cause greater calcium excretion. Finally, agents that act beyond the loop of Henle, which have their primary effects on cation excretion, tend to cause lesser degrees of calcium excretion, especially relative to sodium. These principles indicate that it may be appropriate to select a specific diuretic agent for different patients, depending upon the state of their calcium balance. It also may be possible to predict alterations in calcium balance, so that these may be anticipated and compensated for with patients on long-term therapy with various diuretic agents.

ACKNOWLEDGMENTS

The excellent secretarial assistance of Gail Price and Pam Blank is gratefully acknowledged. This work was supported in part by National Institute of Health Research Grant HL-28179.

Literature Cited

1. Baglin, A., Prinseau, J. 1981. Diuretiques et calcium. *Nephrologie* 2:189–96
2. Suki, W. N. 1982. Effects of diuretics on calcium metabolism. *Adv. Exp. Med. Biol.* 151:493–500
3. Sutton, R. A. L. 1985. Diuretics in calcium metabolism. *Am. J. Kidney Dis.* 5:4–9
4. Harris, C. A., Baer, P. G., Chirito, E., Dirks, J. H. 1974. Composition of mammalian glomerular filtrate. *Am. J. Physiol.* 227:972–76
5. Lassiter, W. E., Gottschalk, C. W., Mylle, M. 1963. Micropuncture study of renal tubular reabsorption of calcium in normal rodents. *Am. J. Physiol.* 204: 771–75

6. LeGrimellec, C., Poujeol, P., de-Rouffignac, C. 1975. ^{3}H-inulin and electrolyte concentrations in Bowman's capsule in rat kidney. *Pfluegers Arch.* 354:117–31
7. Toribara, T. Y., Terepka, A. R., Dewey, P. A. 1957. The ultrafiltrable calcium in human serum. I. Ultrafiltration methods and normal values. *J. Clin. Invest.* 36:738–48
8. Duarte, C. G., Watson, J. F. 1967. Calcium reabsorption in proximal tubule of the dog nephron. *Am. J. Physiol.* 212:1355–60
9. Agus, Z. S., Gardner, L. B., Beck, L. H., Goldberg, M. 1973. Effects of parathyroid hormone on renal tubular reabsorption of calcium, sodium and phosphate. *Am. J. Physiol.* 224:1143–48
10. Edwards, B. R., Sutton, R. A. L., Dirks, J. H. 1974. Effect of calcium infusion on renal tubular reabsorption in the dog. *Am. J. Physiol.* 227:13–18
11. Ullrich, K. J., Rumrich, G., Kloss, S. 1976. Active Ca^{2+} reabsorption in the proximal tubule of the rat kidney. Dependence on sodium and buffer transport. *Pfluegers Arch.* 364:223–28
12. Suki, W. N. 1979. Calcium transport in the nephron. *Am. J. Physiol.* 237:F1–F6
13. Kinne-Saffran, E., Kinne, R. 1974. Localization of a calcium-stimulated ATPase in the basal-lateral plasma membranes of the proximal tubule of the rat kidney cortex. *J. Membr. Biol.* 17:263–74
14. Doucet, A., Katz, A. I. 1982. High-affinity Ca-Mg-ATPase along the rabbit nephron. *Am. J. Physiol.* 242:F346–52
15. DeRouffignac, C., Morel, F., Moss, N., Roinel, N. 1973. Micropuncture study of water and electrolyte movements along the loop of Henle in *Psammomys* with special reference to magnesium, calcium and phosphorus. *Pfluegers Arch.* 344: 309–26
16. Jamison, R. L., Frey, N. R., Lacy, F. B. 1974. Calcium reabsorption in the thin loop of Henle. *Am. J. Physiol.* 227:745–51
17. Rouse, D., Ng, R. C. K., Suki, W. N. 1980. Calcium transport in the pars recta and thin descending limb of Henle of the rabbit, perfused in vitro. *J. Clin. Invest.* 65:37–42
18. Shareghi, G. R., Stoner, L. C. 1978. Calcium transport across segments of the rabbit distal nephron in vitro. *Am. J. Physiol.* 235:F367–75
19. Bourdeau, J. E., Burg, M. B. 1979. Voltage dependence of calcium transport in the thick ascending limb of Henle's loop. *Am. J. Physiol.* 236:F357–64
20. Suki, W. N., Rouse, D., Ng, R. C. K., Kokko, J. P. 1980. Calcium transport in the thick ascending limb of Henle. Heterogeneity of function in the medullary and cortical segments. *J. Clin. Invest.* 66:1004–9
21. Burg, M. B. 1982. Thick ascending limb of Henle's loop. *Kidney Int.* 22:454–64
22. Rocha, A. S., Magaldi, J. B., Kokko, J. P. 1977. Calcium and phosphate transport in isolated segments of rabbit Henle's loop. *J. Clin. Invest.* 59:975–83
23. Imai, M. 1978. Calcium transport across the rabbit thick ascending limb of Henle's loop perfused in vitro. *Pfluegers Arch.* 374:255–63
24. Agus, Z. S., Chiu, P. J. S., Goldberg, M. 1977. Regulation of urinary calcium excretion in the rat. *Am. J. Physiol.* 232:F545–49
25. Rizzoli, R., Fleisch, H., Bonjour, J.-P. 1977. Effect of thyroparathyroidectomy on calcium metabolism in rats: role of 1,25-dihydroxyvitamin D_3. *Am. J. Physiol.* 233:E160–64
26. Puschett, J. B., Moranz, J., Kurnick, W. S. 1972. Evidence for a direct action of cholecalciferol and 25-hydroxycholecalciferol on the renal transport of phosphate, sodium, and calcium. *J. Clin. Invest.* 51:373–85
27. Alon, U., Wellons, M. D., Chan, J. C. M. 1983. Reversal of vitamin-D2-induced hypercalciuria by chlorothiazide. *Pediatr. Res.* 17:117–19
28. Sutton, R. A. L., Dirks, J. H. 1980. Renal handling of calcium, phosphate, and magnesium. In *The Kidney,* ed. B. M. Brenner, F. C. Rector Jr., pp. 551–618. Philadelphia: Saunders
29. Walser, M. 1961. Calcium clearance as a function of sodium clearance in the dog. *Am. J. Physiol.* 200:1099–1104
30. Sutton, R. A. L., Wong, N. L. M., Dirks, J. H. 1976. Effects of parathyroid hormone on sodium and calcium transport in the dog nephron. *Clin. Sci. Mol. Med.* 51:345–51
31. Bourdeau, J. E., Burg, M. B. 1980. Effect of PTH on calcium transport across the cortical thick ascending limb of Henle's loop. *Am. J. Physiol.* 239: F121–26
32. Imai, M. 1981. Effects of parathyroid hormone and N^6, $O^{2'}$-dibutyrl cyclic AMP on Ca^{2+} transport across the rabbit distal nephron segments perfused in vitro. *Pfluegers Arch.* 390:145–51
33. Shareghi, G. R., Agus, Z. S. 1982. Phosphate transport in the light segment of the

rabbit cortical collecting tubule. *Am. J. Physiol.* 242:F379–84
34. Chabardes, D., Imbert, M., Clique, A., Montegut, M., Morel, F. 1975. PTH sensitive adenyl cyclase activity in different segments of the rabbit nephron. *Pfluegers Arch.* 354:229–39
35. Sorensen, O. H., Hindberg, I. 1972. The acute and prolonged effect of porcine calcitonin on urine electrolyte excretion in intact and parathyroidectomized rats. *Acta Endocrinol.* 70:295–307
36. Rasmussen, H., Anast, C., Arnaud, C. 1967. Thyrocalcitonin, EGTA, and urinary electrolyte excretion. *J. Clin. Invest.* 46:746–52
37. Clark, J. D., Kenny, A. D. 1969. Hog thyrocalcitonin in the dog: urinary calcium, phosphorus, magnesium and sodium responses. *Endocrinology* 84:1199–1205
38. Aldred, J. P., Kleszynski, R. R., Bastian, J. W. 1970. Effects of acute administration of porcine and salmon calcitonin on urine electrolyte excretion in rats. *Proc. Soc. Exp. Biol. Med.* 134: 1175–80
39. Quamme, G. A. 1980. Effect of calcitonin on calcium and magnesium transport in rat nephron. *Am. J. Physiol.* 238: E573–78
40. Chabardes, D., Imbert-Teboul, M., Montegut, M., Clique, A., Morel, F. 1976. Distribution of calcitonin-sensitive adenylate cyclase activity along the rabbit kidney tubule. *Proc. Natl. Acad. Sci. USA* 73:3608–12
41. Suki, W. N., Rouse, D. 1981. Hormonal regulation of calcium transport in thick ascending limb renal tubules. *Am. J. Physiol.* 241:F171–74
42. Blythe, W. B., Gitelman, H. J., Welt, L. G. 1968. Effect of expansion of the extracellular space on the rate of urinary excretion of calcium. *Am. J. Physiol.* 214:52–57
43. Goldberg, M., Agus, Z. S., Goldfarb, S. 1976. Renal handling of phosphate, calcium and magnesium. See Ref. 28, pp. 340–90
44. Massry, S. G., Ahumada, J. J., Coburn, J. W., Kleeman, C. R. 1970. Effect of $MgCl_2$ infusion on urinary Ca and Na during reduction in their filtered loads. *Am. J. Physiol.* 219:881–85
45. Lau, K., Goldfarb, S., Goldberg, M., Agus, Z. S. 1982. Effects of phosphate administration on tubular calcium transport. *J. Lab. Clin. Med.* 99:317–24
46. Sutton, R. A. L., Wong, N. L. M., Dirks, J. H. 1979. Effects of metabolic acidosis and alkalosis on sodium and calcium transport in the dog kidney. *Kidney Int.* 15:520–33
47. Gonda, A., Wong, N., Seely, J. F., Dirks, J. H. 1969. The role of hemodynamic factors on urinary calcium and magnesium excretion. *Can. J. Physiol. Pharmacol.* 47:619–26
48. Barker, E. S., Elkinton, J. R., Clark, J. K. 1959. Studies of the renal excretion of magnesium in man. *J. Clin. Invest.* 38:1733–45
49. Sotornik, I., Schuck, O., Stribrna, J. 1969. Influence of diuretics on renal calcium excretion. *Experientia* 25:591–92
50. Eknoyan, G., Suki, W. N., Martinez-Maldonado, M. 1970. Effect of diuretics on urinary excretion of phosphate, calcium, and magnesium in thyroparathyroidectomized dogs. *J. Lab. Clin. Med.* 76:257–66
51. Besarab, A., Pomerantz, P., Swanson, J. W. 1982. Effect of exogenous adenosine 3':5'-cyclic monophosphate, parathyroid hormone and acetazolamide on electrolyte excretion by the isolated perfused rat kidney. *Renal Physiol.* 5:124–35
52. Gemba, M., Nishimura, K. 1977. Effects of diuretics on calcium excretion and Ca^{++}-activated ATPase in rat kidney. *Jpn. J. Pharmacol.* 27:205–11
53. Beck, L. H., Goldberg, M. 1973. Effects of acetazolamide and parathyroidectomy on renal transport of sodium, calcium, and phosphate. *Am. J. Physiol.* 224: 1136–42
54. Dan, T., Gemba, M. 1980. Effects of diuretics on calcium uptake and release in renal microsomes. *Biochem. Pharmacol.* 29:2339–43
55. Steinmetz, P. R., Koeppen, B. M. 1984. Cellular mechanisms of diuretic action along the nephron. *Hosp. Prac.* 19:125–34
56. Bourdeau, J. E., Buss, S. L., Vurek, G. G. 1982. Inhibition of calcium absorption in the cortical thick ascending limb of Henle's loop by furosemide. *J. Pharmacol. Exp. Ther.* 221:815–19
57. Antoniou, L. D., Eisner, G. M., Slotkoff, L. M., Lilienfield, L. S. 1967. Sodium and calcium transport in the kidney. *Clin. Res.* 15:476 (Abstr.)
58. Hanze, S., Seyberth, H. 1967. Effects of the diuretics furosemide and ethacrynic acid and triamterene on renal magnesium and calcium excretion. *Klin. Wochenschr.* 45:313–14
59. Duarte, C. G. 1968. Effects of ethacrynic acid and furosemide on urinary calcium, phosphate and magnesium. *Metabolism* 17:867–76
60. Antoniou, L. D., Eisner, G. M., Slot-

koff, L. M., Lilienfield, L. S. 1969. Relationship between sodium and calcium transport in the kidney. *J. Lab. Clin. Med.* 74:410–20
61. Tambyah, J. A., Lim, M. K. L. 1969. Effect of furosemide on calcium excretion. *Br. Med. J.* 1:751–52
62. Edwards, B. R., Baer, P. G., Sutton, R. A. L., Dirks, J. H. 1973. Micropuncture study of diuretic effects on sodium and calcium reabsorption in the dog nephron. *J. Clin. Invest.* 52:2418–27
63. Devane, J., Ryan, M. P. 1983. Dose-dependent reduction in renal magnesium clearance by amiloride during furosemide-induced diuresis in rats. *Br. J. Pharmacol.* 80:421–28
64. Quamme, G. A. 1981. Effect of furosemide on calcium and magnesium transport in the rat nephron. *Am. J. Physiol.* 241:F340–47
65. Parfitt, A. M. 1969. The acute effects of mersalyl, chlorothiazide and mannitol on the renal excretion of calcium and other ions in man. *Clin. Sci.* 36:267–82
66. Walser, M. 1971. Calcium-sodium interdependence in renal transport. In *Renal Pharmacology*, ed. J. W. Fischer, E. J. Cafruny, pp. 21–41. New York: Appleton-Century-Crofts.
67. Demartini, F. E., Briscoe, A. M., Ragan, C. 1967. Effect of ethacrynic acid on calcium and magnesium excretion. *Proc. Soc. Exp. Biol. Med.* 124:320–24
68. Duarte, C. G., Bland, J. H. 1965. Calcium, phosphorus and uric acid clearances after intravenous administration of chlorothiazide. *Metabolism* 14:211–19
69. Costanzo, L. S., Weiner, I. M. 1974. On the hypocalciuric action of chlorothiazide. *J. Clin. Invest.* 54:628–37
70. Lamberg, B. A., Kuhlback, B. 1959. Effect of chlorothiazide and hydrochlorothiazide on the excretion of calcium in urine. *Scand. J. Clin. Lab. Invest.* 11: 351–57
71. Higgins, B. A., Nassim, J. R., Collins, J., Hilb, A. 1964. The effect of bendrofluazide on urine calcium excretion. *Clin. Sci.* 27:457–62
72. Seitz, H. Jaworski, Z. F. 1964. Effect of hydrochlorothiazide on serum and urinary calcium and urinary citrate. *Can. Med. Assoc. J.* 90:414–20
73. Brickman, A. S., Massry, S. C., Coburn, J. W. 1972. Changes in serum and urinary calcium during treatment with hydrochlorothiazide: Studies on mechanisms. *J. Clin. Invest.* 51:945–54
74. Parfitt, A. M. 1972. The interactions of thiazide diuretics with parathyroid hormone and vitamin D. Studies in patients with hypoparathyroidism. *J. Clin. Invest.* 51:1879–88
75. Yendt, E. R., Cohanim, M. 1978. Prevention of calcium stones with thiazides. *Kidney Int.* 13:397–409
76. Costanzo, L. S., Moses, A. M., Rao, K. J., Weiner, I. M. 1975. Dissociation of calcium and sodium clearances in patients with hypoparathyroidism by infusion of chlorothiazide. *Metabolism* 24:1367–73
77. Quamme, G. A., Wong, N. L. M., Sutton, R. A. L., Dirks, J. H. 1975. Interrelationship of chlorothiazide and parathyroid hormone: a micropuncture study. *Am. J. Physiol.* 229:200–5
78. Costanzo, L. S., Weiner, I. M. 1976. Relationship between clearances of Ca and Na: effect of distal diuretics and PTH. *Am. J. Physiol.* 230:67–73
79. Costanzo, L. S., Windhager, E. E. 1978. Calcium and sodium transport by the distal convoluted tubule of the rat. *Am. J. Physiol.* 235:F492–F506
80. Costanzo, L. S. 1985. Localization of diuretic action in microperfused rat distal tubules: Ca and Na transport. *Am. J. Physiol.* 248:F527–35
81. Ryan, M. P., Phillips, O. 1977. Diuretic-induced calcium and magnesium excretion in the rat. *Irish J. Med. Sci.* 146:303
82. Duarte, C. G., Chomety, F., Giebisch, G. 1971. Effect of amiloride, ouabain, and furosemide on distal tubular function in the rat. *Am. J. Physiol.* 221:632–39
83. Stoner, L. C., Burg, M. B., Orloff, J. 1974. Ion transport in cortical collecting tubule; effect of amiloride. *Am. J. Physiol.* 227:453–59
84. Costanzo, L. S. 1984. Comparison of calcium and sodium transport in early and late rat distal tubules; effect of amiloride. *Am. J. Physiol.* 246:F937–45
85. Massry, S. G., Coburn, J. W., Chapman, L. W., Kleeman, C. R. 1967. The acute effect of adrenal steroids on the interrelationship between the renal excretion of sodium, calcium and magnesium. *J. Lab. Clin. Med.* 70:563–70
86. Suki, W. N., Schwettmann, R. S., Rector, F. C., Seldin, D. W. 1968. Effect of chronic mineralocorticoid administration on calcium excretion in the rat. *Am. J. Physiol.* 215:71–74
87. Lamberg, B. A., Paloheimo, J., Torsti, P. 1964. Changes in the urinary excretion of calcium after intravenous injection of aldosterone. *Acta Med. Scand.* 179: (Suppl. 412):205–13
88. Lemann, J. Jr., Piering, W. F., Lennon, E. J. 1970. Studies of the acute effects of aldosterone and cortisol on the in-

terrelationship between renal sodium, calcium and magnesium excretion in normal man. *Nephron* 7:117–30
89. Wills, M. R., Gill, J. R., Bartter, F. C. 1969. The interrelationships of calcium and sodium excretions. *Clin. Sci.* 37:621–30
90. Ben-Ishai, D., Viskoper, R. J., Menczel, J. 1972. Effect of spironolactone on urinary calcium excretion. *Israel J. Med. Sci.* 8:495–501
91. Prati, R. C., Alfrey, A. C., Hull, A. R. 1972. Spironolactone-induced hypercalciuria. *J. Lab. Clin. Med.* 80:224–30
92. Suki, W. N., Yium, J. J., Von Minden, M., Saller-Hebert, C., Eknoyan, G., Martinez-Maldonado, M. 1970. Acute treatment of hypercalcemia with furosemide. *N. Engl. J. Med.* 283:836–40
93. Christensson, T., Hellstrom, K., Wengle, B. 1977. Hypercalcemia and primary hyperparathyroidism. *Arch. Int. Med.* 137:1138–42
94. Nordin, B. E. C., Hodgkinson, A., Peacock, M., Robertson, W. G. 1979. Urinary tract calculi. In *Nephrology*, ed. J. Hamburger, J. Crosnier, J. P. Grunsfeld, pp. 1090–1128. New York: Wiley
95. Cunningham, E., Oliveros, F. H., Nascimento, L. 1982. Metolazone therapy of active calcium nephrolithiasis. *Clin. Pharmacol. Ther.* 32:642–45
96. Leppla, D., Browne, R., Hill, K., Pak, C. Y. C. 1983. Effect of amiloride with or without hydrochlorothiazide on urinary calcium and saturation of calcium salts. *J. Clin. Endocrinol. Metab.* 57:920–24
97. Alon, U., Costanzo, L. S., Chan, J. C. M. 1984. Additive hypocalciuric effects of amiloride and hydrochlorothiazide in patients treated with calcitriol. *Min. Elec. Metab.* 10:379–86