INTRODUCTION TO CALCIUM HOMEOSTASIS

General aspects

Calcium is the fifth most abundant inorganic element of the body, the principal component of the human skeleton, and a vital participant in normal neuromuscular function, blood coagulation, membrane function, and multiple enzyme reactions. Its transmembrane flux plays a critical role in hormone secretion and metabolic coordination. Exquisitely sensitive homeostatic mechanisms have evolved to monitor and regulate the calcium ion in plasma while allowing an enormous reservoir to exist in bone where it principally serves a mechanical function. The normal adult human has roughly 25 g of total body calcium per kg of lean body mass (about 1-1.5 kg). Ninety-nine percent of it is present in bone as calcium phosphate while only 1% of skeletal calcium is freely exchangeable with the extracellular fluid. Mobilization of extensive amounts of skeletal calcium requires active resorption such as that promoted by vitamin D and parathyroid hormone (PTH). Perhaps the most frequent challenge to calcium homeostasis occurs with dietary calcium deprivation. When this occurs, a triad of efficient systems join to combat any tendency to hypocalcemia (Figure 1). Hormonally-induced bone resorption probably represents the most important mechanism by which sudden deficits in calcium homeostasis are overcome. Reduction in urinary excretion of calcium and increased efficiency of calcium absorption from the gut (in response to calcium deficiency) serve as additional mechanisms for maintaining extracellular fluid calcium; the renal effect is probably more important than previously realized. Renal reabsorption of calcium can rise to essentially 100% but this occurs only if the calcium level drops below 7 mg/dl. If calcium is low but above this level, PTH seems to be the principal effector involved in renal calcium conservation (1-10).

Calcium absorption

Although the dietary intake of calcium varies considerably, it is usually within the range of 0.5 to 1.0 g/day. Somewhere between 25% and 75% of the ingested calcium is absorbed depending on the actual amount ingested (inversely proportional), previous dietary history, and vitamin D status. Fecal calcium consists of both the nonabsorbed fraction and an intestinal secreted fraction. The secreted portion represents a daily loss of between 100 and 200 mg in the stool and this is of importance in chronic dietary calcium deficiency (1).

Absorption of calcium from the small intestine involves both an active process of transport against an electrochemical gradient and a process of simple diffusion (2). Although the precise details of the translocation of calcium is far from understood, it is a process which is exquisitely regulated by vitamin D. Vitamin-D directed synthesis of a high affinity calcium-binding protein is one role the sterol hormone plays in regulating and sequestering cytosolic calcium, although, it probably does not act (as once thought) as the molecule which actually shuttles the ion from the mucosal to serosal cell surface (11). In addition, a calcium dependent ATP-ase and alkaline phosphatase are two other implicated pro-
sorption, like sodium, occurs in the proximal tubule. The action of ultraviolet light on the epidermal lipid 7-dehydro-cholesterol produces cholecalciferol or vitamin D$_3$ (12). Ergocalciferol (vitamin D$_2$), is a similar sterol obtained in the diet. In the liver these sterols are acted upon by the enzyme vitamin D-25-hydroxylase, a general P$_4$500,500 microsomal enzyme which places a hydroxyl group on ring D at the 25th position of the sterol. The product, 25-hydroxyvitamin D (25-(OH)D), is the major circulating form of the vitamin in plasma with normal concentrations ranging from 5 ng/ml to 75 ng/ml depending on the availability of vitamin D substrate (13). This is an important point. The 25-hydroxylase is actually present in virtually every tissue of the body (not just liver), and it is not a tightly regulated enzyme; its activity is not altered by calcium, phosphate, or PTH status. In vitamin D intoxication, for example, the concentration of the 25-(OH)D rises to values greater than 500 ng/ml (14).

This precursor is subsequently converted in the kidney (only site) to the hormonal form of the vitamin, 1,25-dihydroxyvitamin D (1,25-(OH)$_2$D). The enzyme responsible for this hydroxylation in the A-ring is exquisitely regulated by phosphate (directly) and by calcium (via PTH). Also known as calcitriol, this most potent metabolite of vitamin D acts to absorb calcium and phosphate from the gut and resorb these ions from bone. The interrelationships of these homeostatic systems will be discussed after some general comments have been made regarding renal calcium excretion.

Renal calcium excretion

The physical state of calcium in the urine is complex. Urinary calcium is bound, in part, by anions which are present at much higher concentrations than in plasma because of high rates of renal clearance. Even after correction for the extent of complex formation, it is evident that the concentration of calcium and phosphate greatly exceeds the solubility product of the free ions. Hence, it is thought that specific metabolites may play an important role in inhibiting precipitation of calcium salts which would otherwise occur. The content of calcium in the urine responds in an exponential fashion to dietary calcium intake; that is, calcium excretion increases only a small amount despite rather large increases in dietary calcium. One of the important factors controlling renal excretion of calcium is the quantity of filtered calcium. Protein bound serum calcium is not filtered by the glomerulus, and of the remaining free calcium about 7 to 10 gm per 24 h is normally filtered. Since urinary calcium excretion normally ranges between 135 and 400 mg per 24 h, it is obvious that at least 98% of the filtered calcium is normally reabsorbed. If the blood calcium concentration falls to hypocalcemic levels, this efficiency of reabsorption can rise to essentially 100%. The urinary calcium falls to almost zero. Several lines of evidence indicate that about two-thirds of calcium reabsorption, like sodium, occurs in the proximal tubule. It appears that calcium and sodium ions may share a common pathway; as we will see, therapeutic approaches to both hypo- and hypercalcemia use this principle. Rapid infusion of saline increases the excretion of calcium as well as sodium. In conditions in which sodium excretion is high, calcium excretion is also elevated. Increased oral phosphate has a direct effect to reduce renal calcium clearance. Conversely, hypercalcemia is seen in severe phosphate depletion (4, 15).

High dose corticosteroids have a dramatic effect to increase urinary calcium excretion but the mechanism is not via a direct effect of the steroid on the renal tubule, but rather, it reflects the catabolic effects of steroids on skeletal calcium.

Another major stimulus to the renal handling of calcium is PTH. It is true that a considerable proportion of calcium reabsorption occurs in the proximal tubule and that there are numerous hormonal, nutritional, and metabolic factors which affect this excretion. Nevertheless, the action of PTH on the distal tubule is perhaps the single most important homeostatic influence on urinary calcium excretion. Even mild hypocalcemia will dramatically trigger an increase in circulating PTH secretion which will reduce urinary calcium clearance at the distal tubule and loop of Henle, while increasing that of phosphate at the proximal tubule. The net effect is a return to normocalcemia. Conversely, hypercalcemia results in a reduced secretion of PTH, an increased urinary calcium clearance, and a tendency toward normocalcemia (5, 8, 15). In addition, PTH causes bone breakdown by increasing both the number and the activity of osteoclasts (5).

Calculated homeostasis

The normal homeostatic response to hypocalcemia is most easily viewed as a dual feedback control mechanism involving two hormones, two minerals, and four target tissues (Figure 2) (13). Two signals, namely low plasma calcium and low plasma phosphate, are the primary regulators of this hormonal system; the fulcrum is the renal mitochondrial 1-hydroxylase which converts 25-OHD to 1,25-(OH)$_2$D. The latter then acts at its three major target tissues-bone, intestine, and parathyroid. The ultimate mission of the sterol at these organs is to maintain a critical blood concentration of calcium and phosphate for the proper functioning of such fundamental processes as muscle contraction, skeletal integrity, nerve conduction etc. (see above). What is the sequence of events which ensue if plasma calcium falls below the critical concentration required to carry out these functions? Low extracellular calcium (Figure 2) stimulates the parathyroid glands to biosynthesize and secrete PTH. There is a direct correlation between the extent of hypocalcemia and the magnitude of PTH release. The assumption is that an intracellular calcium pool is changed when plasma calcium falls (or rises), and that the changes in calcium concentration within this pool regulate hormone synthesis and secretion. PTH, in turn, stimulates the 1-hydroxylase by some unknown mechanism. Since it is a peptide hormone it may func-