RENAL CALCIUM, PHOSPHATE AND MAGNESIUM HANDLING: LEARNING OBJECTIVES

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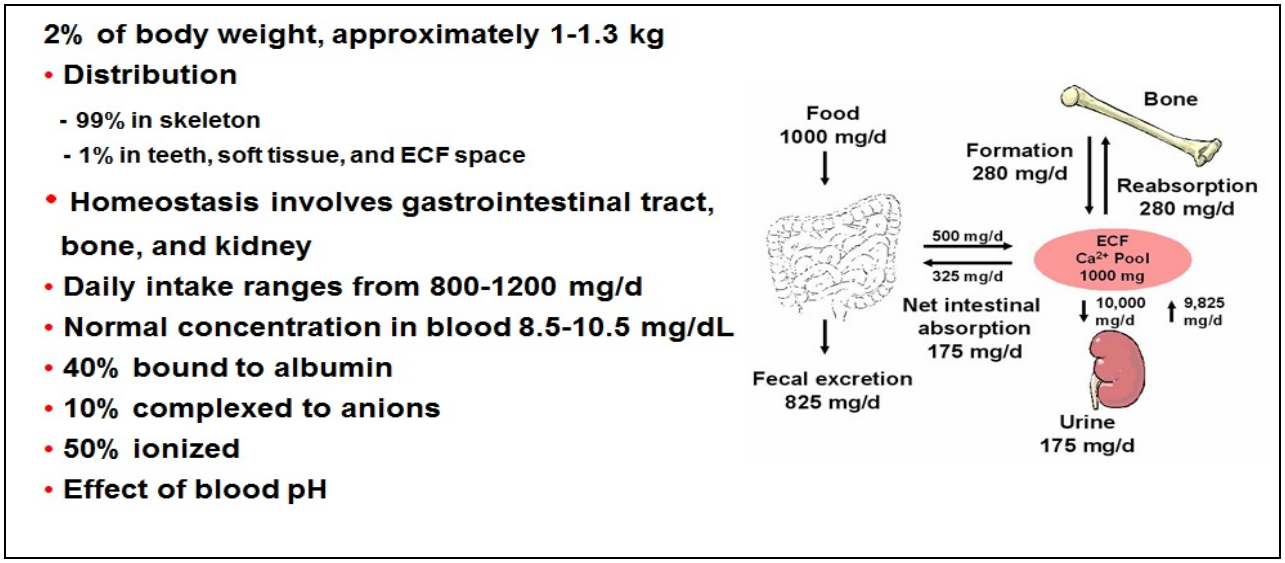
LEARNING OBJECTIVES:

- Diagram the cellular mechanism of Ca^{2+} and Mg^{2+} transport in the proximal tubule, thick ascending limb, and distal convolute tubule.
- List the apical transporters involved in phosphate transport in the proximal tubule.
- Given a patient with an abnormal plasma Ca^{2+}, Mg^{2+}, or phosphate level, identify the regulatory factor that may be responsible for the disorder.
- List the factors responsible for the regulation of Ca^{2+}, Mg^{2+}, and phosphate transport in the kidney.

Tubular Calcium Transport

Introduction

The total amount of calcium in the human body ranges from 1000 to 1300 g. Approximately 99% of body calcium resides in the skeleton; the other 1% is present in the extracellular and intracellular spaces. Although >99% of the total body calcium is located in bone, calcium is a critical cation in both the extracellular and intracellular spaces. Approximately 1% of the calcium in the skeleton is freely exchangeable with calcium in the extracellular fluid compartment. Serum calcium concentration is held in a very narrow range in both spaces.



Total body calcium homeostasis and calcium metabolism in the normal human in neutral calcium balance

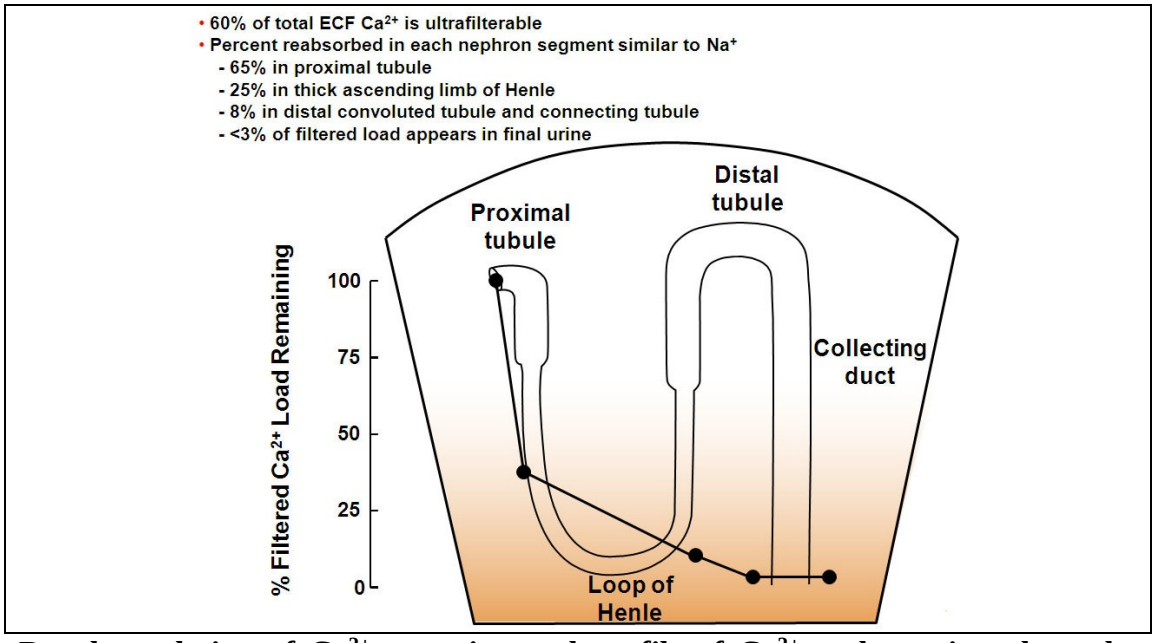
Calcium balance is tightly regulated by the concerted action of calcium absorption in the intestine, reabsorption in the kidney, and exchange from bone, which are all under the control of the calciotropic hormones that are released upon a demand for calcium. When 1 g of calcium is ingested in the diet, approximately 800 mg is excreted in the feces and 200 mg in the urine. Approximately 400 mg of the usual 1000 mg dietary calcium intake is absorbed by the intestine, and calcium loss by way of intestinal secretions is approximately 200 mg/d. Therefore, a net absorption of calcium is approximately 200 mg/d.

Calcium is absorbed almost exclusively within the duodenum, jejunum, and ileum. Each of these intestinal segments has a high absorptive capacity for calcium, with their relative calcium absorption being dependent on the length of each respective intestinal segment and the transit time of the food bolus. There are two routes for the absorption of calcium across the intestinal epithelium: the paracellular pathway (*i.e.*, between the cells) and the transcellular route (*i.e.*, through the cell). The paracellular pathway is passive, and it is the predominant route of calcium absorption when the lumen concentration of calcium is high. The paracellular route is indirectly influenced by calcitriol [1,25$(OH)_2$D] because it is capable of altering the structure of intracellular tight junctions and making the tight junction more permeable to the movement of calcium. However, 1,25$(OH)_2$D mainly controls the active absorption of calcium.

Total calcium concentration in plasma ranges from 8.5-10.5 mg/dl or about 2.5 mM. Of this, 40% is bound to plasma proteins, mainly albumin. This fraction is non-filterable. The filterable fraction consists of a non-ionized moiety of calcium complexed to several anions such as bicarbonate, citrate, phosphate and sulfate, and a fraction of freely ionized calcium. Protein binding of calcium in plasma is affected by the albumin concentration and pH. For each 1.0-g/dl decrease in serum albumin, total serum calcium decreases by 0.8 mg/dl. Systemic alkalosis decreases ionized calcium. Because both hydrogen ions and calcium are bound to serum albumin, in the presence of metabolic alkalosis, bound hydrogen ions dissociate from albumin, freeing up the albumin to bind with more calcium and thereby decreasing the freely ionized portion of the total serum calcium. Acidosis increases ionized calcium concentration.

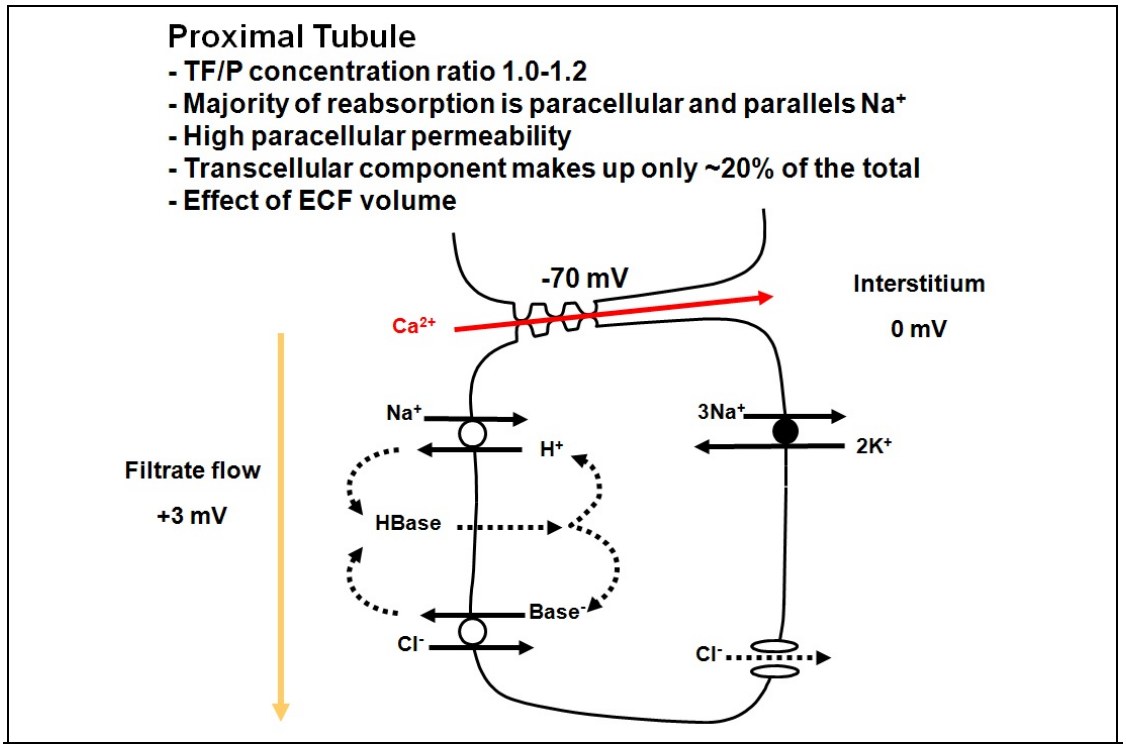
Kidney Handling of Calcium

In humans who have normal renal function roughly 10 g of calcium is filtered per day. The amount of calcium excreted in the urine usually ranges from 100 to 200 mg per 24 hours; hence, 98%–99% of the filtered load of calcium is reabsorbed by the renal tubules. Approximately 60%–70% of the filtered calcium is reabsorbed in the proximal convoluted tubule, 20% in the loop of Henle, and 10% by the distal convoluted tubule. The terminal nephron, although responsible for the reabsorption of only 5%–10% of the filtered calcium load, is the major site for regulation of calcium excretion.



Renal regulation of Ca^{2+} excretion and profile of Ca^{2+} reabsorption along the nephron

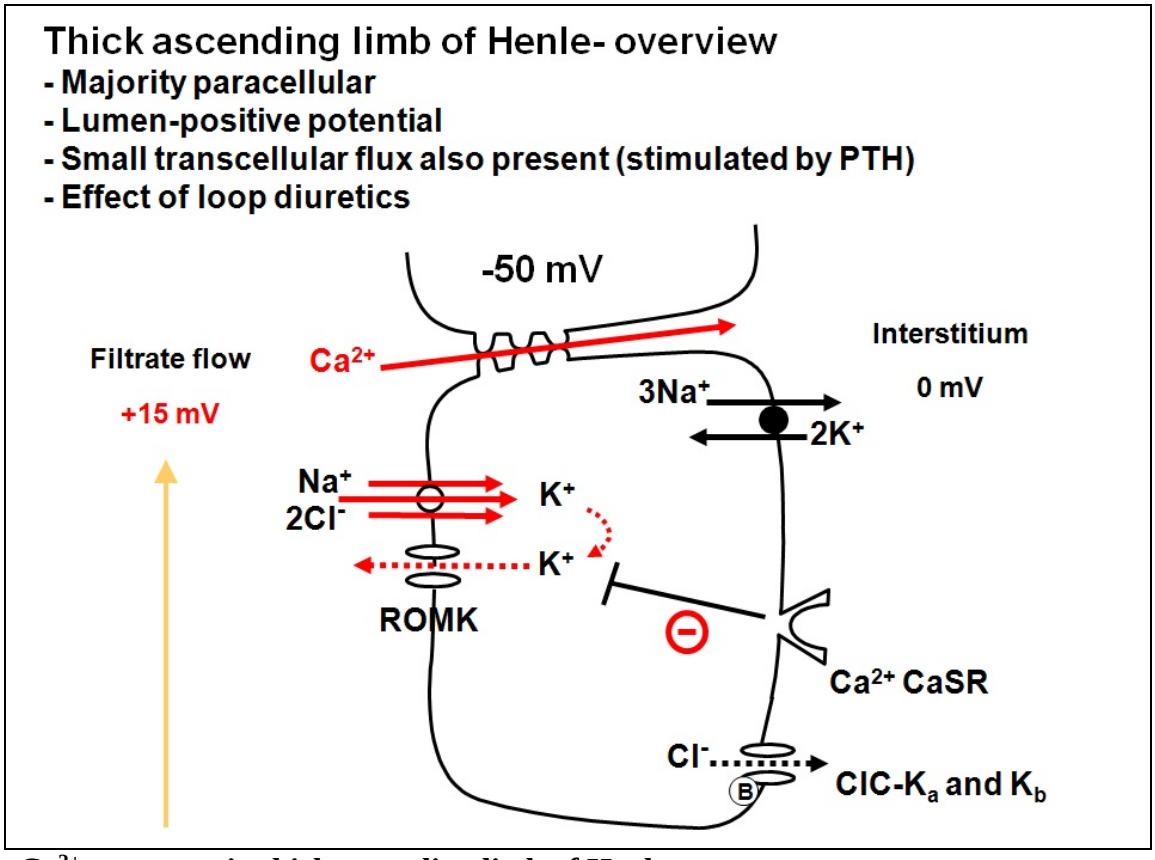
The reabsorption of calcium in the proximal convoluted tubule parallels that of sodium and water. Increases in proximal tubule Na^+ and volume reabsorption increase luminal calcium concentration that leads to more calcium being passively reabsorbed. In addition, some of the ultrafilterable calcium may be reabsorbed by solvent drag. Both of these mechanisms explain the tight coupling between the rates of Na^+ and calcium reabsorption in proximal tubule. In states of ECF volume contraction, proximal tubular sodium and calcium reabsorption are both increased. No reabsorption of calcium occurs within the thin segment of the loop of Henle.



Ca^{2+} reabsorption in the proximal tubule

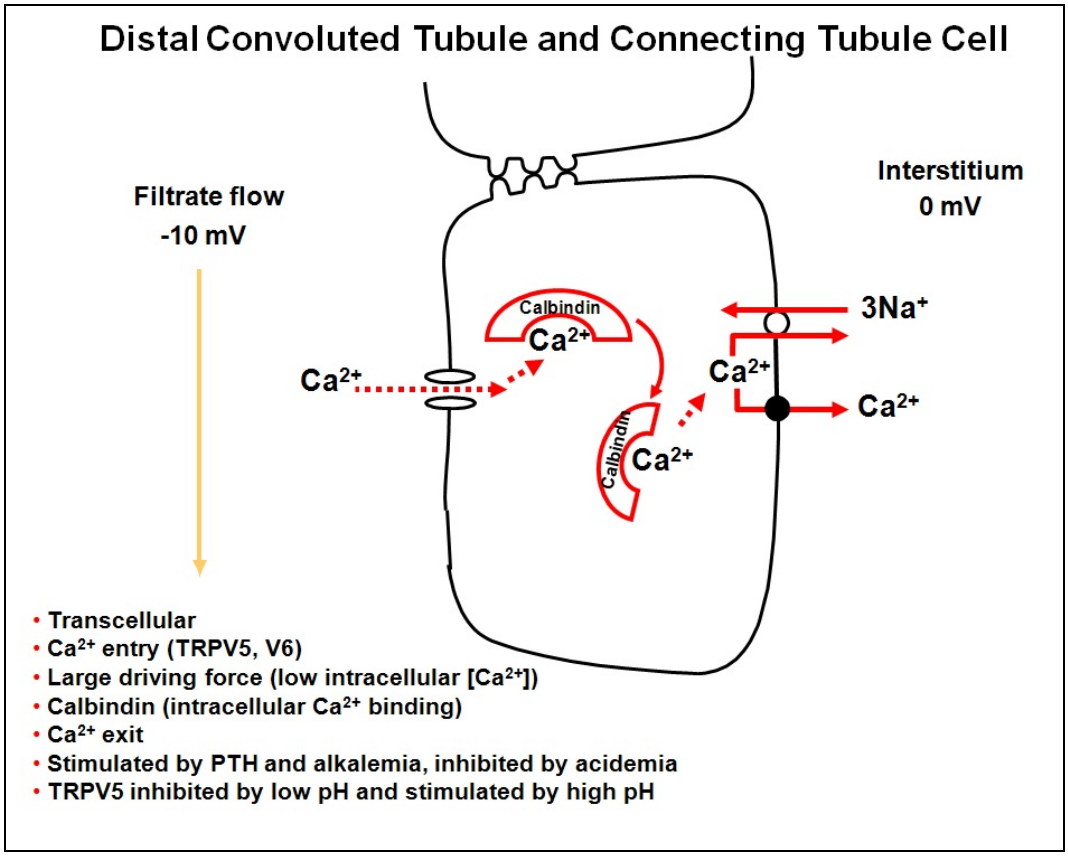
In the thick ascending limb of the loop of Henle, 20% of the filtered calcium is reabsorbed. In this segment, the bulk of calcium reabsorption proceeds through the paracellular pathway and is proportional to the transtubular electrochemical driving force. The apical Na^+-K^+-$2Cl^-$ cotransporter NKCC2 and the renal outer medullary potassium K^+ (ROMK) channel generate the "driving force" for paracellular cation transport. Whereas NaCl reabsorption through NKCC2 is electroneutral (NKCC2 translocates one Na^+, one K^+, and two Cl^- ions from the lumen into the cell), apical potassium represents the rate-limiting step of this process and potassium ions back-diffuse into the lumen through the ROMK channels. Na^+ and Cl^- accumulated inside the cell are then transported into the bloodstream through basolateral Na^+-K^+-ATPase and Cl^- channels, respectively. Overall, these processes yield a net cellular reabsorption of NaCl and the generation of a lumen-positive transepithelial potential difference, which drives nonselective calcium reabsorption through the paracellular route.

Calcium transport in the thick ascending limb of the loop of Henle is also influenced by the calcium-sensing receptor (CaSR), which is localized in the basolateral membrane. The calcium-sensing receptor, expressed on the basolateral surface of the thick ascending limb, plays an important role in regulating urinary calcium excretion. When calcium binds to this receptor, calcium reabsorption is inhibited. Calcium binding to the receptor leads to the generation of an arachidonic acid metabolite (20-hydroxyeicosatetraenoic acid [20-HETE]) that then inhibits the potassium channel (ROMK) in the luminal membrane. Inhibition of potassium recycling via the potassium channel diminishes the generation of the lumen-positive electrical gradient, and therefore, passive calcium and magnesium reabsorption are inhibited. This interaction explains why an increase in blood calcium concentration leads to decreased calcium reabsorption in this segment.



Ca^{2+} transport in thick ascending limb of Henle

Both activating and inactivating mutations of the CaSR have been identified. Inactivating mutations lead to enhanced calcium reabsorption, resulting in hypercalcemia and hypocalciuria. Activating mutations, in which the receptor has increased sensitivity to plasma calcium levels, have the opposite effect, resulting in decreased calcium reabsorption, and thus, hypocalcemia and hypercalciuria. The calcium-sensing receptor binds divalent cations. One such cation is magnesium, which presumably explains why hypermagnesemia can lead to increased urinary calcium excretion.



Ca^{2+} transport in distal convoluted tubule

In contrast with the proximal tubule and the thick ascending limb of the loop of Henle, the distal tubule reabsorbs calcium exclusively *via* the transcellular route. The distal convoluted tubule absorbs 5%–10% of the filtered calcium. This active process can be divided into three steps. The first step requires calcium influx across the apical membrane. The transient receptor potential vanilloid 5 (TRPV5) has been identified as the responsible protein in this process. The second step is the diffusion of calcium through the cytosol. During this process, calbindin-D28k binds intracellular calcium transported *via* TRPV5 and shuttles it through the cytosol toward the basolateral membrane where calcium is extruded *via* sodium-calcium exchanger and the plasma membrane calcium-ATPase, which is the final step in this process. Calcium transport through TRPV5 is stimulated by parathyroid hormone (PTH) and alkalosis while acidosis exerts an inhibitory effect.

Factors Regulating Calcium Handling in the Kidney

Parathyroid hormone (PTH)

PTH is an important factor regulating renal calcium absorption. PTH is a polypeptide secreted from the parathyroid gland in response to a decrease in the plasma concentration of ionized calcium. Therefore, the major physiologic role of the parathyroid gland is to regulate calcium homeostasis. PTH acts to increase the plasma concentration of calcium in three ways: (1) it stimulates bone resorption, (2) it enhances intestinal calcium and phosphate absorption by promoting the formation within the kidney of 1,25(OH)2D, and (3) it augments active renal calcium absorption in the distal nephron. These effects are reversed by small changes in the serum calcium concentration that lower PTH secretion. Changes in serum calcium are sensed by the CaSR, which is localized in the cell membrane of the parathyroid cells. The receptor permits variations in the plasma calcium concentration to be sensed by the parathyroid gland, leading to desired changes in PTH secretion. PTH also promotes phosphorus excretion by decreasing proximal tubular phosphate reabsorption (discussed further in the phosphorus lecture).

Vitamin D

Vitamin D3 (cholecalciferol) is a fat-soluble steroid that is present in the diet and also can be synthesized in the skin from 7-dehydrocholestrol in the presence of ultraviolet light. The hepatic enzyme 25-hydroxylase catalyzes the hydroxylation of vitamin D at the 25 position, resulting in the formation of 25-hydroxyvitamin D or calcidiol. 25-Hydroxyvitamin D produced by the liver enters the circulation and travels to the kidney, bound to vitamin D binding protein. In the kidney, proximal tubular cells contain 1α-hydroxylase that converts 25-Hyroxyvitamin D to 1,25(OH)2D, the most active form of vitamin D. The 1,25(OH)2D enters the circulation and is transported to the small intestine, where it enhances intestinal calcium absorption. The most important endocrine effect of 1,25(OH)2D in the kidney is a tight control of its own homeostasis through simultaneous suppression of 1α-hydroxylase. An intact 1,25(OH)2D–vitamin D receptor system is critical for both basal and PTH-induced osteoclastogenesis. Mature osteoclasts release calcium and phosphorus from the bone, maintaining the appropriate levels of the two minerals in the plasma.

Serum Calcium.

Hypercalcemia is associated with an increase in urinary calcium excretion as a consequence of an increase in the filtered load and a decrease in the tubular reabsorption of calcium. Although hypercalcemia can decrease GFR by renal vasoconstriction, which tends to offset the increase in filtered load, hypercalcemia also causes a decline in tubular reabsorption of calcium by both PTH-dependent and -independent effects. Hypocalcemia decreases renal calcium excretion by decreasing the filtered load and enhancing the tubular reabsorption of calcium.

Extracellular Fluid.

Expansion of the extracellular fluid is associated with an increase in sodium, chloride, and calcium excretion, whereas reciprocal effects are seen with volume contraction. The mechanisms of this effect are interrelated with the effects of sodium reabsorption and compensatory changes that occur as a result of volume expansion.

Metabolic Acidosis.

Acute and chronic metabolic acidosis can be associated with an increase in calcium excretion, independent of PTH changes. The calciuria may, in part, be due to the mobilization of calcium from bone, as the hydrogen ion is buffered in the skeleton; however, direct effects of acidosis on tubular calcium resorption also play a role.

Increases in luminal pH stimulate calcium reabsorption by increasing channel recruitment to the luminal membrane, while decreases in pH have the opposite effect. Decreases in intracellular pH reduce the open probability of the apical membrane calcium channel and reduce calcium reabsorption, while increases in intracellular pH have the opposite effect.

Diuretics.

Loop diuretics decrease calcium absorption as a result of inhibition of the transport of sodium chloride at the NKCC2 transporter in the ascending loop of Henle. The genetic equivalent to the administration of a loop diuretic is Bartter syndrome. These patients are characterized by increased urinary calcium excretion.

Thiazide diuretics, which act in the distal tubule, are associated with hypocalciuria (1,7). Two main mechanisms have been proposed to explain the effect of thiazides on calcium excretion: (1) increased proximal sodium and water reabsorption due to volume depletion, and (2) increased distal calcium reabsorption at the thiazide-sensitive site in the distal convoluted tubule. Thiazide diuretics are commonly used to treat hypertension and to reduce urinary calcium excretion in patients with calcium-containing kidney stones. Gitelman syndrome is a genetic disorder in which NaCl cotransporter activity in the apical membrane of distal convoluted tubule is decreased (an effect similar to thiazide diuretics), and is associated with hypocalciuria.

Based on the above, one can design an effective therapy to treat hypercalcemia. If a patient is treated with a loop diuretic, which would primarily inhibit thick ascending limb NaCl reabsorption and secondarily inhibit calcium reabsorption, the patient would transiently excrete more calcium, but as ECF volume decreased, the increase in proximal tubule calcium reabsorption would limit the amount of calcium excreted. On the other hand, if the patient were volume-expanded, proximal tubule calcium reabsorption would be inhibited, but the thick ascending limb would be able to reabsorb most of the additional calcium delivered out of the proximal tubule, and there would be little effect on calcium excretion. However, if the patient were first volume-expanded and then given a loop diuretic, calcium excretion would increase substantially and plasma calcium levels would fall. The latter approach is used to treat patients with hypercalcemia.

Major Factors Affecting Calcium Reabsorption	
Increased Reabsorption	**Decreased Reabsorption**
PTH (distal) **ECF volume contraction (proximal)** **Metabolic alkalosis (distal)**	**ECF volume expansion (proximal)** **Metabolic acidosis (distal)**

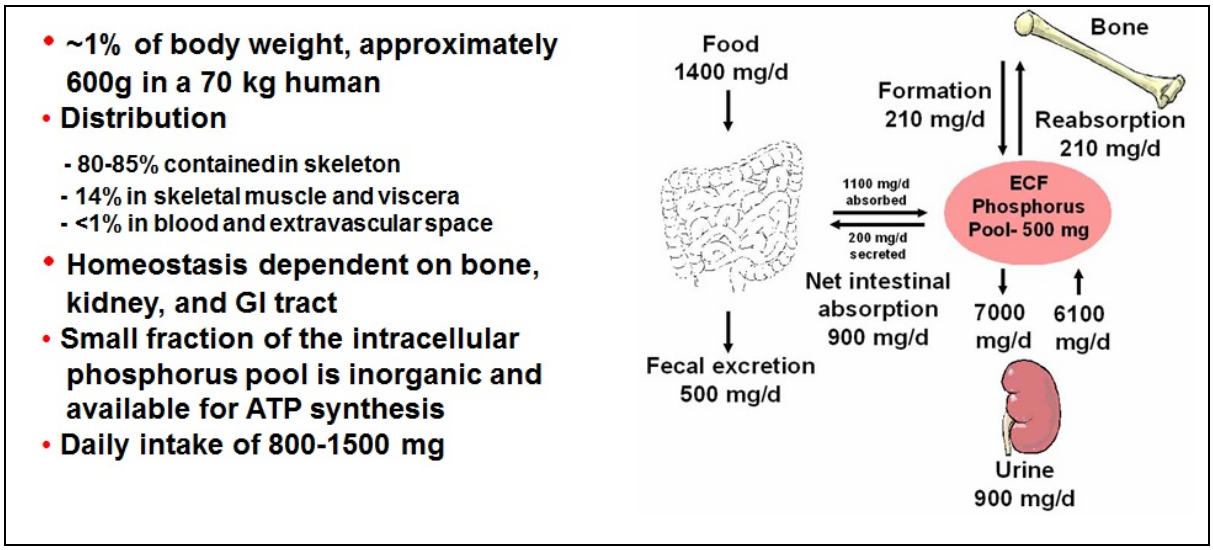
- **PTH increases expression of all proteins involved in distal Ca^{2+} transport**
- **ECF volume contraction- proximal tubular effect**
- **pH effects on luminal Ca^{2+} reabsorption in the distal convoluted tubule and connecting tubule mediated via TRPV5**

Major factors affecting Ca^{2+} reabsorption

Tubular Phosphate Transport

Introduction

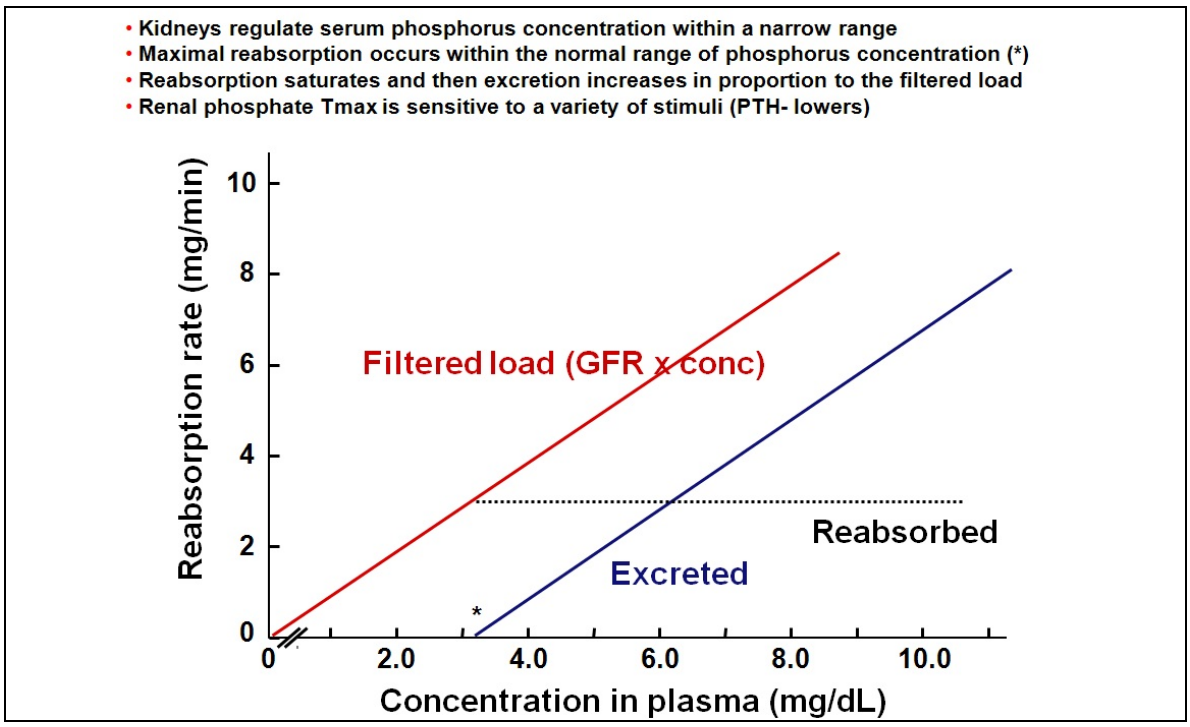
Approximately 80-85% of phosphorus in the body is contained in bone, 14% in cells and soft tissues, and 1% in extracellular fluids (Figure 1). A very small fraction of the intracellular pool is inorganic and available for the synthesis of high energy phosphorus-containing molecules. Neutral phosphate balance is maintained with dietary intakes that range from 800-1500 mg/day. Phosphorus homeostasis is dependent upon the interaction of three organ systems: the gastrointestinal tract; bone; and kidney. A general overview of phosphorus metabolism is shown below.



Total body phosphorus homeostasis and phosphorus metabolism for a normal human in neutral phosphorus balance

The phosphorus concentration that is measured in the clinical laboratory is the inorganic fraction. Plasma phosphate is present primarily in two forms: a monovalent form $H_2PO_4^-$; and a divalent form HPO_4^{2-}. At a normal plasma pH of 7.4, 80% of inorganic phosphate (P_i) is in the divalent form. Normal plasma phosphorus concentration is about 2.5-4.5 mg/dl.

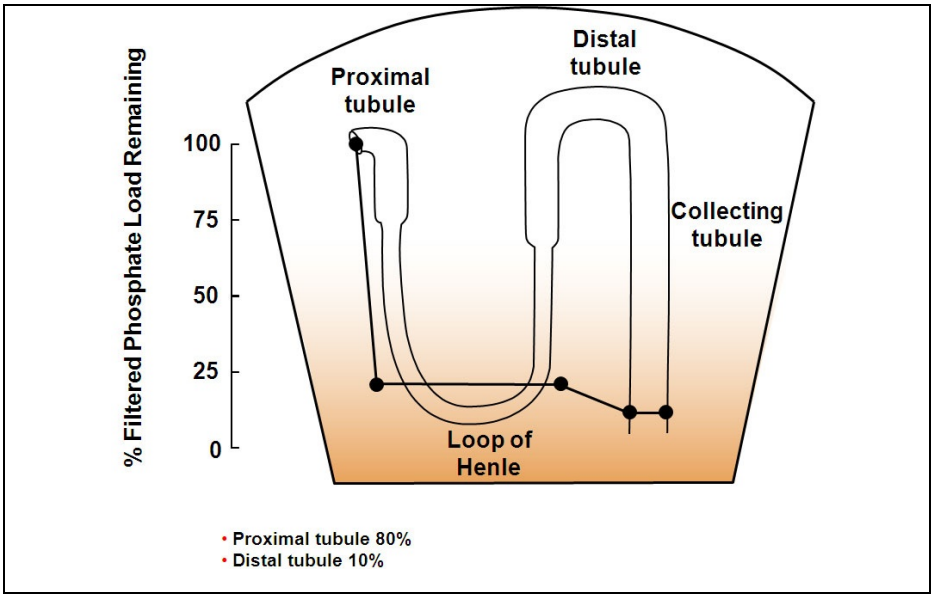
Approximately 85-90% of plasma phosphorus is freely filtered by the glomerulus. The small amount that is nonfilterable is due to protein binding. Normally, the renal tubules reabsorb 80-97% of the filtered load so that only 3-20% of filtered phosphate appears in urine. As plasma phosphorus increases, filtered phosphate and phosphate reabsorption increase. However, the reabsorptive mechanism is quickly saturated and excretion then increases in proportion to the filtered load. The plasma concentration at which maximal phosphate reabsorption occurs lies within the normal range for plasma phosphorus concentration, indicating that the kidneys regulate plasma phosphorus within a narrow range. The $Tmax_{phos}$ refers to the maximal net amount of phosphate that the tubules can transport per unit time. This amount varies under different physiologic conditions. For example, increased circulating levels of parathyroid hormone lowers the $Tmax_{phos}$.



Relationship between urinary phosphate excretion and plasma phosphorus concentration. Typical phosphate titration curve. It demonstrates saturability of net tubular transport. Phosphate can be almost completely retrieved from urine, and the concentration in urine can fall to very low levels.

Within the nephron, approximately 85% of phosphate reabsorption occurs within the proximal tubule. The remainder of the nephron plays a minor role in Pi regulation and the transporters involved have yet to be identified. Within the proximal tubule, Pi transport from the ultrafiltrate across the proximal tubule epithelium is an energy-dependent process that requires sodium. The three renal sodium phosphate cotransporters, Npt2a, Npt2c, and PiT-2, are all positioned in the apical brush border membrane of renal proximal tubule cells and use the energy derived from the transport of sodium down its gradient to move inorganic phosphate from the luminal filtrate into the cell. The amount of phosphate reabsorbed from the filtrate is determined by the abundance of the cotransporters in the apical membrane of proximal tubule cells. Thus, hormones or dietary factors that alter phosphate reabsorption in the kidney do so by changing the abundance of the sodium phosphate cotransporters in the apical membrane of renal proximal tubule cells. An increase in the brush border levels of the sodium phosphate cotransporters abundance results in increased phosphate absorption from the urine, whereas a decrease in cotransporter abundance leads to phosphaturia. Transport of Pi from the renal proximal tubule to the peritubular capillaries occurs via an unknown basolateral transporter.

Npt2a mediates the majority of Na /phosphate cotransport in the proximal tubule and is electrogenic transporting three Na^+ ions for each divalent phosphate molecule (HPO_4^{2-}). Npt2c is electroneutral (2 Na^+ ions transported per divalent phosphate molecule). PiT-2, on the other hand, although electrogenic like Npt2a, preferentially transports monovalent phosphate. Npt2b is expressed in intestine and not the kidney. Intestinal Npt2b is regulated by dietary phosphate intake as well as 1,25(OH)2D. As mentioned, Npt2a is responsible for the majority (approximately 70%) of the renal regulation of phosphate transport.



Profile of phosphate reabsorption along the nephron

Regulation of Kidney Phosphate Transport

Renal control of phosphate reabsorption is regulated by a number of hormonal and metabolic factors that are discussed below in more detail. These factors change phosphate reabsorption from the ultrafiltrate by changing the abundance of the three sodium phosphate cotransporters in the brush border membrane of the proximal tubule.

Diet

In the setting of normal renal function, ingestion of phosphorus-containing foods leads to removal of Npt2a, Npt2c, and PiT-2 from the proximal tubule brush border membrane, thereby decreasing phosphate reabsorption from the ultrafiltrate. By contrast, dietary Pi restriction leads to insertion of the sodium phosphate cotransporters in the proximal tubule brush border membrane, increasing phosphate reabsorption.

PTH

PTH causes decreased renal reabsorption of phosphate and phosphaturia by decreasing the abundance of Npt2a, Npt2c, and PiT-2 in the renal proximal tubule brush border membrane. In response to PTH, Npt2a is removed rapidly (within minutes), whereas the decrease in apical membrane abundance of Npt2c and PiT-2 takes hours.

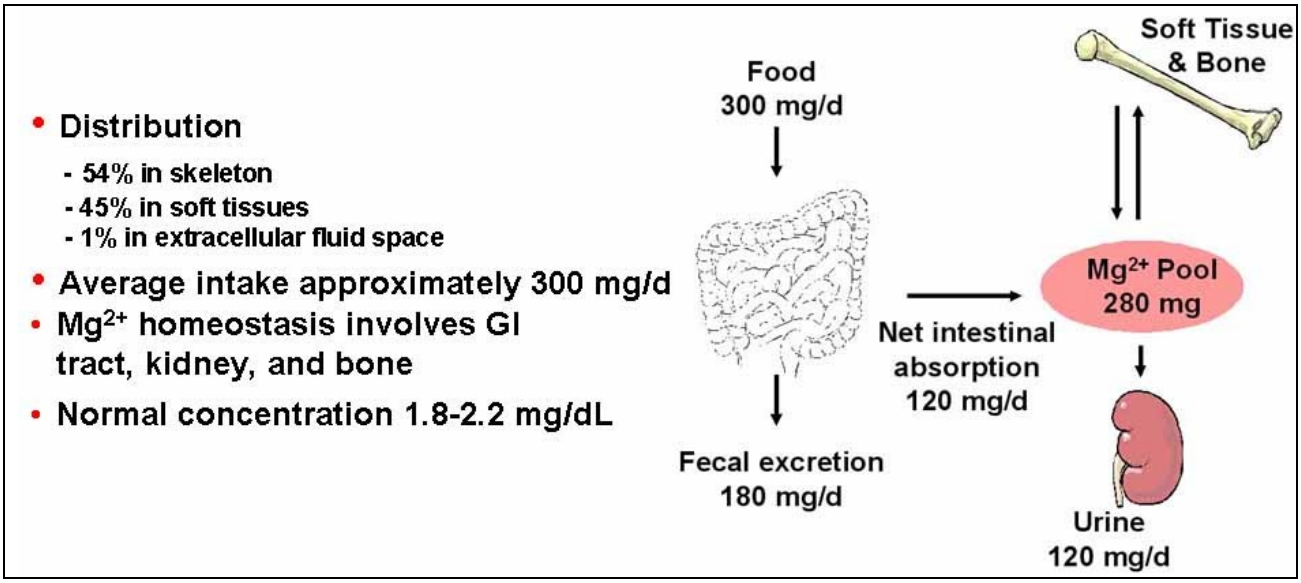
Fibroblast Growth Factor-23

Fibroblast growth factor-23 (FGF23) is produced in osteoblasts in response to increases in serum Pi. To exert its physiologic effects on the proximal tubule, FGF23 requires the presence of a cofactor, Klotho, which is produced in the kidney and activates FGF receptor 1. FGF23 reduces the expression and activity of the sodium phosphate cotransporters in the renal proximal tubule and is also thought to decrease the activity of the intestinal sodium phosphate cotransporter. FGF23 also reduces serum levels of calcitriol by decreasing the renal expression of 1α-hydroxylase, which is the rate-limiting step in calcitriol synthesis. FGF-23 is overproduced by mesenchymal tumors in a rare disorder known as oncogenic hypophosphatemic osteomalacia. Patients present with hypophosphatemia, osteomalacia, renal phosphate wasting, and low $1,25(OH)_2$ vitamin D_3 levels due to suppression of 1α-hydroxylase.

Tubular Magnesium Transport

Introduction

As with calcium and phosphorus, maintenance of normal magnesium balance involves the coordinated actions of the gastrointestinal tract, bone and kidneys. Approximately 54% of total body Mg^{2+} is in the skeleton, 45% in the intracellular compartment (muscle and soft tissues), and 1% in the extracellular space. Total magnesium concentration in plasma in man is maintained within narrow limits, between 1.8-2.2 mg/dl. Sixty percent of serum magnesium exists in the ionized, free, physiologically active form, which is important for its physiologic functions. Ten percent of serum magnesium exists complexed to serum anions. Thirty percent of serum magnesium is albumin-bound



Total body magnesium homeostasis

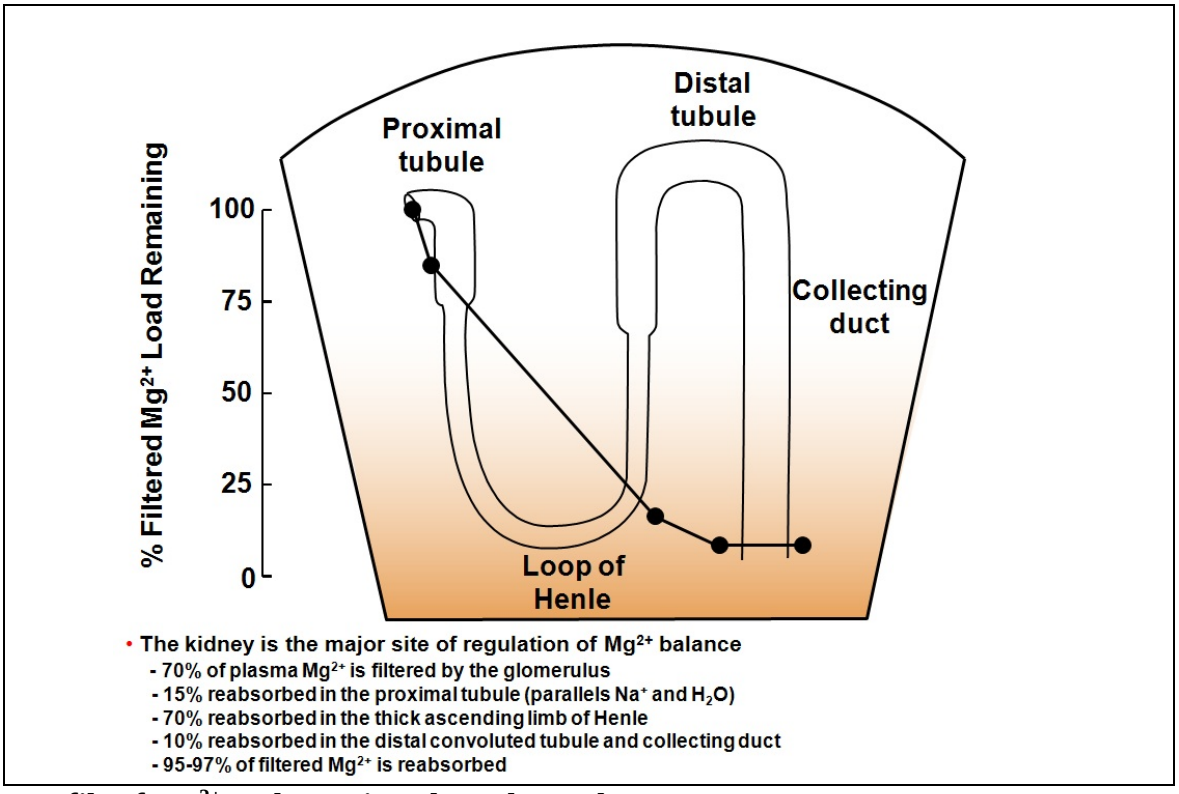
Intestinal magnesium absorption occurs *via* a saturable transcellular pathway and a nonsaturable paracellular passive pathway. The majority of magnesium is absorbed by the small intestine and, to a lesser extent, by the colon. Transcellular magnesium absorption is permitted by the transient receptor potential melastatin (TRPM) cationic channels TRPM6 and TRPM7. Proton pump inhibitors, especially after long-term use, have been associated with hypomagnesemia. Impaired intestinal magnesium absorption, rather than renal absorption, seems to mediate the effect of proton pump inhibitors. Potential mediators include increased intestinal magnesium secretion, decreased active transcellular magnesium absorption due to decreased TRPM6 activity secondary to decreased intestinal acidity, or decreased paracellular magnesium absorption.

Regulation of Magnesium by the Kidney

Assuming a normal GFR, the kidney filters approximately 2000–2400 mg of magnesium per day. This takes into account the fact that only 70% of total serum magnesium (30% is protein-bound) is available for glomerular filtration. Under normal conditions, 96% of filtered magnesium is reabsorbed in the renal tubules by several coordinated transport processes and magnesium transporters detailed below.

Proximal Tubule

Approximately 10-30% of the filtered magnesium is absorbed in the proximal tubule. Similar to calcium, Mg^{2+} reabsorption in this segment parallels Na^{+} and water reabsorption. As a result, Mg^{2+} reabsorption is increased in volume contraction and decreased in volume expansion.



Profile of Mg^{2+} reabsorption along the nephron

Thick Ascending Limb

The main site of Mg^{2+} reabsorption is the thick ascending limb of the loop of Henle where 70% of filtered Mg^{2+} is reabsorbed. The lumen-positive potential in the thick limb provides the major driving force for passive reabsorption through the paracellular pathway. As previously discussed the NKCC2 cotransporter mediates apical absorption of Na, K, and Cl. The apical ROMK mediates apical recycling of K back to the tubular lumen and generation of lumen-positive voltage. The Cl channel ClC-Kb mediates Cl exit through the basolateral membrane. Na-K-ATPase also mediates Na exit through the basolateral membrane and generates the Na gradient for Na absorption. Mg^{2+} reabsorption in thick ascending limb is increased in states of Mg^{2+} deficiency and inhibited with hypermagnesemia. Mg^{2+} can bind to the basolateral Ca^{2+}-sensing receptor. Hypermagnesemia activates the receptor and decreases activity of the ROMK channel, dissipating the lumen-positive potential. As a result, Mg^{2+} reabsorption is decreased. The opposite effect is seen with hypomagnesemia. Loop diuretics inhibit Mg^{2+} reabsorption in this segment by inhibiting the lumen-positive voltage, thus, inhibiting paracellular Mg^{2+} reabsorption.

Claudin-16 (also known as paracellin-1) is a tight-junction protein that is important in conducting or regulating paracellular cation transport in the thick ascending limb. Impaired function of claudin-16 leads specifically to urinary magnesium and calcium losses. An inherited defect in this protein gives rise to the disease called familial hypomagnesemia with hypercalciuria and nephrocalcinosis (calcium deposits in the kidney).

Mutations in claudin-19 also can cause the same clinical syndrome. Both proteins are expressed in the tight junctions of the thick ascending limb of the loop of Henle.

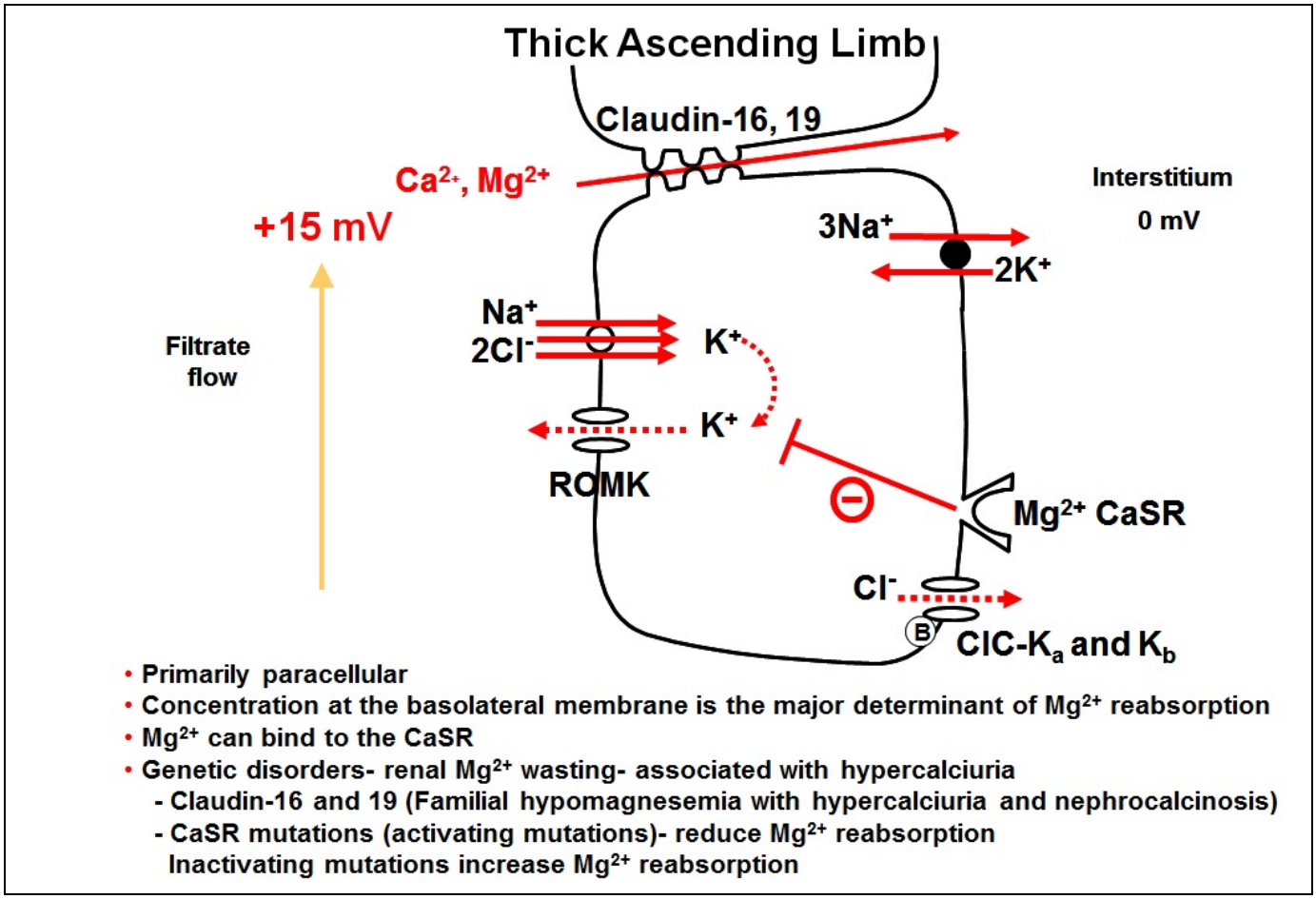


Figure 13. Mg^{2+} transport in thick ascending limb of the loop of Henle

Distal Convoluted Tubule

The remaining 5%–10% of magnesium is reabsorbed in the distal convoluted tubule mainly by active transcellular transport mediated by TRPM6. The absorbed magnesium is then extruded *via* a magnesium/sodium exchanger across the basolateral membrane.

Gitelman syndrome results in renal magnesium wasting due to decreased expression of TRPM6 in the distal convoluted tubule. How a defect in the NaCl cotransporter results in reduced expression of TRPM6 is unclear.

Epidermal growth factor (EGF) acts in a paracrine fashion in the distal nephron to increases magnesium transport through TRPM6. Isolated recessive hypomagnesemia is caused by a mutation in the pro-EGF gene. As a result, EGF is not secreted into the basolateral space of the distal convoluted tubule and renal magnesium wasting develops. Cetuximab and panitumumab are monoclonal antibodies that bind to and block the EGF receptor and are utilized for treatment of EGF responsive cancers such as colorectal and head and neck cancers. These drugs can cause renal magnesium wasting and hypomagnesemia by interfering with magnesium transport in the kidney.

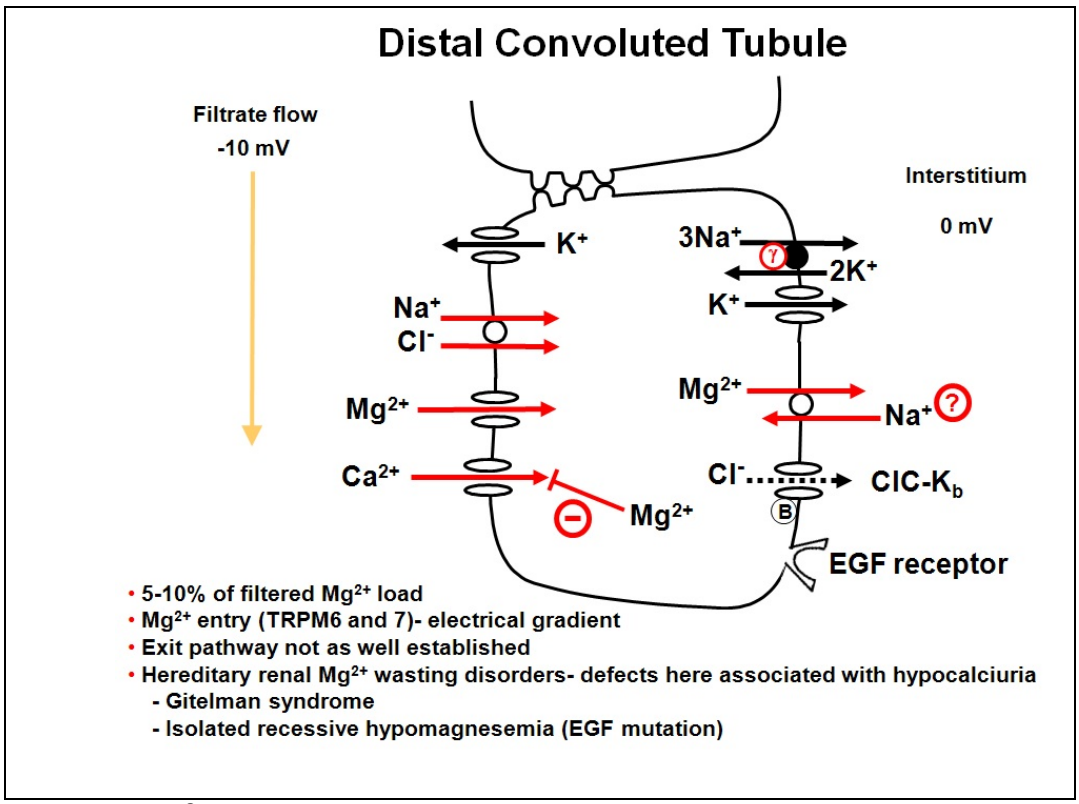


Figure 15. Mg^{2+} transport in distal convoluted tubule

There are several conditions that either increase or decrease urinary magnesium excretion. Extracellular fluid volume expansion inhibits Mg^{2+} reabsorption in proximal tubule. The opposite occurs under conditions of volume depletion. However, ECF volume is not a major regulator of Mg^{2+} reabsorption, given that only 15% of Mg^{2+} is reabsorbed in the proximal convoluted tubule. Loop diuretics inhibit Mg^{2+} reabsorption in thick ascending limb by inhibiting the $Na^+/K^+/2Cl^-$ cotransporter, resulting in a loss of the lumen-positive potential.

Hypermagnesemia is associated with increased Mg^{2+} excretion secondary to an increase in the filtered load, and decreased tubular reabsorption primarily in the thick ascending limb of the loop of Henle. Mg^{2+} interacts with the basolateral Ca^{2+}/Mg^{2+}-sensing receptor leading to decreased activity of the apical membrane potassium channel (ROMK) and dissipation of the lumen-positive voltage. A similar mechanism explains the increase in urinary Mg^{2+} excretion that occurs with hypercalcemia. By contrast, hypomagnesemia and hypocalcemia are associated with increased Mg^{2+} reabsorption in the thick ascending limb of the loop of Henle resulting in decreased Mg^{2+} excretion.

Hypomagnesemia can be secondary to impaired intestinal magnesium absorption or increased urinary magnesium excretion secondary to various hormones or drugs that inhibit magnesium reabsorption. At the clinical level, the assessment of magnesium stores and cause of magnesium deficiency continues to be a real challenge. Simultaneous measurements of serum and urine magnesium may help differentiate the cause of hypomagnesemia.

Although proton pump inhibitors most likely cause impaired intestinal magnesium absorption, most of the other drugs associated with hypomagnesemia impair renal tubular magnesium reabsorption by direct or indirect inhibition of magnesium reabsorption in the thick ascending limb or the distal convoluted tubule.

Hypomagnesemia is associated with hypokalemia, which is mediated by stimulation of the ROMK channel resulting in increased potassium excretion. Hypomagnesemia is also associated with hypocalcemia secondary to impaired PTH release and PTH resistance. Clinical manifestations of hypomagnesemia include weakness and fatigue, muscle cramps, tetany, numbness, seizures, and arrhythmias.

Major Factors Affecting Magnesium Excretion	
Increased Excretion	**Decreased Excretion**
Volume expansion Hypermagnesemia Hypercalcemia Loop diuretics	Volume contraction Hypomagnesemia Hypocalcemia

Major factors affecting Mg^{2+} excretion