The PTH/Vitamin D/FGF23 Axis

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8.1 Calcium and Phosphorus Balance

The skeleton, the gut, and the kidney each play a major role in assuring calcium (Ca^{++}) homeostasis. Overall, in a typical individual if 1,000 mg of Ca^{++} are ingested in the diet per day, approximately 200 mg will be absorbed across the intestinal epithelium and about 200 mg excreted.

The traditional model of transcellular Ca^{++} transport consists of influx through an apical calcium channel (TRPV6), which provides the rate-limiting step, diffusion through the cytosol, and active extrusion at the basolateral membrane by a plasma membrane ATPase (PMCA1b) [1]. Although entry of Ca^{++} has been reported to involve TRPV6, other Ca^{++} channels may also be involved. Ca^{++} binding proteins including calmodulin and calbindin-D9k (CaBP9k) may be important for fine-tuning Ca^{++} channel activity, and in the cytosol, calbindin 9 k may "buffer" and/or mediate the transit of intracellular absorbed Ca^{++} to the basolateral membrane. An additional modulator of transcellular Ca^{++} transport is a Ca ATPase, PMCA1b, encoded by *ATP2B1*, which is important for the extrusion of Ca^{++} at the basolateral membrane to complete the transcellular transport of this ion. Increasing evidence also suggests the importance of paracellular Ca^{++} transport in Ca^{++} absorption via tight junctions.

The skeleton, where approximately 1,000 mg of calcium is stored, is the major Ca^{++} reservoir in the body. Skeletal Ca^{++} is stored mainly in the form of hydroxyapatite crystals, the major inorganic component of the mineralized bone matrix. Ordinarily as a result of normal bone turnover, approximately 500 mg of Ca^{++} is resorbed from the bone per day and the equivalent amount is accreted. Approximately 10 g of Ca^{++} will be filtered daily through the kidney and most will be reabsorbed, with about 200 mg being excreted in the urine. The normal 24-h urine excretion of Ca^{++} may however vary between 100 and 300 mg per day (2.5–7.5 mmoles per day).

The average consumption of phosphorus (Pi) (i.e., about 1,000–1,500 mg) in a Western diet is similar to that of Ca^{++} (about 1,000 mg); however, about 70 % of phosphorus is absorbed daily compared with only about 20–30 % of Ca^{++}. Pi ingested through the diet is absorbed by the small intestine through sodium–phosphate cotransporters, as well as by sodium-independent diffusional absorption across intercellular spaces in the

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lumen. The skeleton also represents the largest reservoir in the body of Pi which is stored in an exact stoichiometry with Ca^{++} as hydroxyapatite crystals. The major control site for Pi homeostasis is the kidney where enhanced reabsorption can occur from the tubular lumen via sodium–phosphate cotransporters, NaPi2s (also known as SLC34As) that are expressed in the renal proximal convoluted tubule [2] (see also Chap. 6).

8.2 Hormones Regulating Ca^{++} and Pi Homeostasis

8.2.1 Parathyroid Hormone (PTH)

PTH secretion from the parathyroid gland and parathyroid cell proliferation are inhibited by serum Ca^{++}acting via a Ca^{++}-sensing receptor (CaSR) [3], and PTH gene transcription [4] and parathyroid cell proliferation [5, 6] may be inhibited by the active form of vitamin D, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], acting via the vitamin D receptor (VDR). Although the major glandular form of PTH is an 84 amino acid peptide, virtually all of the biological activity resides within its amino (NH_2)-terminal domain [7, 8]. Intracellular degradation of PTH(1–84) within the parathyroid cell, which is enhanced by high ambient calcium concentrations, provides a means of modulating the fraction of secreted hormone that is PTH(1–84) (see Chap. 4 for details). The NH_2-terminal domain interacts in target tissues with a classical G protein-coupled receptor (GPCR) termed the PTH/PTHrP receptor type 1, or PTHR1 [9, 10]. PTHR1 couples to several G protein subclasses, including Gs, Gq/11, and G12/13, resulting in the activation of many pathways, although the best studied are the adenylate cyclase (AC) and phospholipase C (PLC) pathways.

In the kidney, Ca^{++} reabsorption primarily occurs in the distal tubules and collecting ducts [11]. Ca^{++} ions cross the apical membrane from the tubular lumen via TRPV5, a highly selective Ca^{++}channel, and are then transported across the basolateral membrane into the blood system by the sodium/calcium exchanger 1 (NCX1) and a plasma membrane ATPase. PTH regulates the expression of TRPV5 and NCX1 [12] as well as their activity. The PTH regulation of at least TRPV5 appears to occur through protein kinase C (PKC) [13]. TRPV5 is also regulated through the PKC-signaling pathway by the Ca^{++} sensing receptor (CaSR) [14] (see also Chap. 5).

Pi reabsorption across the apical membrane of renal proximal tubules mainly occurs through two sodium-dependent phosphate cotransporters, NaPi-2a and NaPi-2c, that are exclusively expressed in the brush border membrane of the proximal tubules [15] (see also Chap. 6). PTH increases Pi excretion in the proximal tubule mainly by reducing the levels of these transporters. Thus, PTH binding to PTHR1 at either apical or basolateral membrane results in removal of the transporters from the brush border membrane via clathrin-coated pits [16, 17]. PTH activation of apical PTHR1 leads to phospholipase C (PLC)–protein kinase C (PKC) stimulation mediated by sodium–hydrogen exchanger regulatory factor (NHERF), whereas activation of basolateral PTHR1 utilizes the AC/protein kinase A (PKA) pathway [18]. Following endocytosis NaPi-2 is eventually transported to the lysosomes for degradation.

PTH also stimulates the conversion of 25-hydroxyvitamin D [25(OH)D] to 1,25$(OH)_2$D in the kidney by transcriptional activation of the gene encoding the 25-hydroxyvitamin D-1α hydroxylase [1(OH)ase] enzyme (CYP27B1) apparently by the AC/PKA pathway [19] (see also Chap. 11).

The bone undergoes constant remodeling in response to endocrine, autocrine/paracrine, and intracrine signals and bone mineral is maintained through a balance between bone formation and resorption. PTH binds to PTHR1 on cells of the osteoblastic lineage [20] including progenitor cells, osteoblasts, and osteocytes and can stimulate a variety of factors ultimately leading to increased proliferation of mesenchymal stem cells, such that these cells are committed into the osteoblast lineage, to enhance osteoblast differentiation and activity with new bone matrix production [21] and ultimately mineralization of bone tissue. However, osteoblastic cells also produce the TNF-related cytokine, receptor activator

of nuclear factor κ-B (RANK) ligand (RANKL), a critical stimulator of osteoclast production and action, as well as the soluble RANKL decoy receptor, osteoprotegerin (OPG) [22]. PTH enhances production of RANKL and inhibits production of OPG leading to increased osteoclastogenesis and osteoclastic bone resorption [23]. Bone resorption leads to the release of Ca^{++} and Pi as a result of the degradation of hydroxyapatite, and it is the resorptive effect of PTH which plays a major role in mineral and particularly Ca^{++} homeostasis

8.2.2 Vitamin D

8.2.2.1 Metabolism of Vitamin D

Vitamin D can be obtained as vitamin D3 (cholecalciferol), via UV-light irradiation of a skin precursor, 7-dehydrocholesterol [24], or can be ingested from the diet as vitamin D3 or as the plant-derived sterol vitamin D2 (ergocalciferol). Vitamin D is then transported to the liver, bound to a plasma vitamin D binding protein (DBP) [25], where it is hydroxylated at the C-25 position of the side chain to produce 25(OH)D, the most abundant circulating form of vitamin D [26]. The final step in the activation to the hormonal form, $1,25(OH)_2D$, occurs mainly, but not exclusively, in the kidney via a tightly regulated 1α-hydroxylation reaction catalyzed by a mitochondrial enzyme 1(OH)ase, or CYP27B1 [27]. The renal *CYP27B1* gene is stimulated by PTH and hypocalcemia and inhibited by hyperphosphatemia thus sensing the need for mineral homeostasis. The renal *CYP27B1* gene is also product-inhibited by $1,25(OH)_2D$, which acts via a short negative feedback loop to limit its own production [28]. $1,25(OH)_2D$ circulates bound to vitamin D binding protein (DBP), to exert its endocrine actions in various target tissues. Extrarenal 1α-hydroxylation has also been described resulting in the production of $1,25(OH)_2D$, which can act locally in an intracrine mode [29]. The $1,25(OH)_2D$-mediated endocrine or intracrine signal may be terminated in all target cells via the catalytic action of CYP24A1, an enzyme that initiates the process of $1,25(OH)_2D$ catabolism [30]. The *CYP24A1* gene is transcriptionally activated by $1,25(OH)_2D$ [31]. This feed forward induction of $1,25(OH)_2D$ catabolism therefore prevents hypervitaminosis D.

8.2.2.2 Actions of Vitamin D

The active metabolite, $1,25(OH)_2D$, functions by initially binding to the VDR. The ligand-activated VDR interacts with the retinoid X receptor (RXR) to form a heterodimer that binds to vitamin D responsive elements in the region of genes directly regulated by $1,25(OH)_2D$ [32]. By recruiting complexes of either coactivators or corepressors, ligand-activated VDR–RXR modulates the transcription of genes encoding proteins that carry out the functions of vitamin D.

Under conditions of low dietary Ca^{++}, the $1,25(OH)_2D$/VDR system induces TRPV6 [33] and vitamin D-dependent calcium binding protein 9K (CaBPD9k) [34], to promote transcellular intestinal calcium absorption; the extrusion of calcium at the basolateral membrane is likely constitutive in part and is executed by the Ca ATPases PMCA1b/PMCA2c but could be amplified via induction of these molecules by $1,25(OH)_2D$. $1,25(OH)_2D$ also increases expression of claudins 2 and 12 to possibly promote paracellular Ca^{++} entry [35]. Ca^{++} absorption under normal dietary conditions postnatally does not absolutely require TRPV6 and CaBPD9K.

Pi is predominantly absorbed in the intestine via paracellular mechanisms. Although $1,25(OH)_2D$ may also increase intestinal Pi absorption by increasing expression of NaPi2b [36], because Pi is abundant in the diet, the Pi absorption effect of $1,25(OH)_2D$ may not be as profound as the effect on Ca^{++} transport. The $1,25(OH)_2D$/VDR system can promote bone resorption [37–39], suggesting that at least part of its skeletal action is catabolic. In support of this, the $1,25(OH)_2D$/VDR system enhances the expression of RANKL in osteoblastic cells to stimulate bone resorption through osteoclastogenesis [40]. Furthermore, osteoprotegerin, the soluble decoy receptor for RANKL that tempers its activity, is repressed by the $1,25(OH)_2D$/VDR system, thus amplifying the bioeffect of RANKL.

The action of the $1,25(OH)_2D$/VDR system in the parathyroid gland to suppress PTH synthesis [4] effectively limits PTH-induced bone-resorbing activity and restricts PTH stimulation of renal CYP27B1 thereby preventing hypercalcemia.

8.2.3 Fibroblast Growth Factor 23 (FGF23)

Fibroblast growth factors (FGFs) are a large superfamily of peptides that act mainly as paracrine/autocrine substances to exert a broad range of biological functions in development and organogenesis. They act by binding and activation of FGF receptor (FGFR) tyrosine kinases [41, 42]. The unique FGF19 subfamily consists of FGF19, FGF21, and FGF23 [43] which act as hormones to regulate energy and mineral metabolism (see also Chap. 6).

FGF23 is a phosphaturic hormone produced and secreted by bone cells of the osteoblastic lineage, predominantly late osteoblasts and osteocytes, and was initially identified as the mediator of the human disorder autosomal dominant hypophosphatemic rickets (ADHR) [44]. FGF23 is synthesized as a 32 kDa, 251 amino acid protein, with a signal (leader) sequence of 24 amino acids, an NH_2-terminal FGF homology domain of 155 amino acids, and a unique sequence in its carboxyl (COOH)-domain of 72 amino acids [45]. The molecule can be cleaved between Arg^{179} and Ser^{180} by a subtilisin-like proprotein convertase, yet to be identified, to generate NH_2-terminal and COOH-terminal fragments; the entire sequence of the secreted 25–251 amino acid protein appears to be necessary for its biological action. O-glycosylation within the 162–228 region apparently reduces the susceptibility of the protein to proteolysis [46], and it is possible that the COOH-terminal fragment may compete with intact FGF23 for binding to its receptor complex and function as a competitive inhibitor [47]. ADHR patients carry missense mutations at the proteolytic cleavage site of FGF23 (176RXXR179), which confers resistance to inactivation by proteolytic cleavage [48]. As a result, ADHR patients exhibit increased blood levels of intact FGF23 and Pi-wasting phenotypes.

8.2.3.1 Regulation of FGF23 Production

Local Regulators of FGF23 Production

Local regulators produced in osteoblast/osteocytes appear to be important in modulating the release of FGF23. Mutations in the gene encoding the membrane protein PHEX (phosphate-regulating neutral endopeptidase with homology to endopeptidase on the X chromosome) [49–51] and in the gene encoding the SIBLING (small integrin-binding ligand interacting glycoproteins) protein DMP-1 (dentin matrix protein-1) [52, 53] increase FGF23 expression and induce renal Pi wasting in mice and humans. In one apparent mechanism [54], DMP-1 binds to the osteocyte through its integrin-binding domains and to PHEX through its ASARM domain [acidic serine aspartate-rich matrix extracellular phosphoglycoprotein (MEPE)-associated motif]. Binding of DMP-1 to PHEX inhibits production of active FGF-23, while disruption of either DMP-1 or PHEX releases this inhibition, and active FGF23 production is increased. Local relative levels of the mineralization regulators pyrophosphate and phosphate appear to be important modulators [55, 56] and disruption of bone mineralization may release low molecular weight FGFs from the bone matrix which may activate the osteocyte FGFR and stimulate transcription of the *FGF-23* gene [57]. Finally reduced iron and tissue hypoxemia have also been reported to stimulate FGF23 release [58].

Systemic Regulators

Extremely high FGF23 levels are observed in primary deficiency of the Klotho protein (genetic deletion or mutational hypomorph) [59, 60] and the much more common secondary Klotho deficiency in chronic kidney disease (CKD) [61, 62]. However, there are no in vitro data to date to support a direct effect of Klotho, either locally produced or circulating, on FGF23 production.

A critical regulator of FGF23 release is $1,25(OH)_2D$, acting via the VDR [63] in part by directly upregulating gene expression [64] and in part by inhibiting PHEX and by inducing expression of the gene encoding ecto-nucleotide pyrophosphatase/phosphodiesterase (Enpp1), which could alter local levels of pyrophosphate and phosphate [65]. $1,25(OH)_2D$ may also increase the levels of the hypoxia-inducible transcription factor, HIF1A, which might mediate the effects of tissue hypoxemia on FGF23 release [66]. PTH has also been reported to stimulate synthesis and secretion of FGF23 through activation of the PTHR1 on osteocytes/osteoblasts [67, 68].

Increased Pi in the diet and increases in serum Pi can both increase FGF23 release by osteocytic cells; however, the mechanism is still unclear. Nevertheless, this observation has led to the concept that the skeleton therefore serves as a sensor of Pi levels in a manner analogous to the function of the parathyroid glands as a Ca^{++} sensor.

FGF23 is also regulated by serum Ca^{++} [69–71], as initially suggested by several lines of evidence. Thus, serum Ca^{++} levels are independently associated with FGF23 levels in dialysis patients, in transplant recipients, and in patients with primary hyperparathyroidism [3]. In patients with severe secondary and tertiary (persistent) hyperparathyroidism referred for parathyroidectomy, postoperative changes of FGF23 are limited and related to changes of Ca^{++} [72]. In patients with acute untreated hypoparathyroidism occurring after thyroidectomy [73], FGF23 levels are initially reduced when patients are hyperphosphatemic but still hypocalcemic. In contrast, in patients with chronic hypoparathryoidism and hyperphosphatemia who are normocalcemic on calcium and calcitriol treatment, serum FGF-23 levels are elevated [74]. Consequently treatment of hypocalcemia in patients with chronic hypoparathyroidism may raise FGF23 which will promote phosphaturia, but the serum levels of phosphorus concentrations may not completely normalize, possibly because the concerted phosphaturic actions of both PTH and FGF23 may be required.

In vitamin D receptor-null mice, dietary calcium supplementation significantly increases serum calcium levels, FGF23 messenger RNA abundance, and circulating FGF23 levels. In PTH-null mice that are hypocalcemic and hyperphosphatemic, FGF23 levels are reduced [75]. In wild-type mice and PTH-null mice, acute elevation of either serum Ca^{++} or Pi by intraperitoneal injection increased serum FGF23 levels. However, increases in serum Pi by chronic exposure to a high dietary Pi load were accompanied by severe hypocalcemia, which appeared to blunt stimulation of FGF23 release. Calcium-mediated increases in serum FGF23 required a threshold of at least normal serum Pi levels. Similarly, Pi-elicited increases in FGF23 were markedly blunted if serum Ca^{++} was less than normal. The best correlation between Ca^{++} and Pi and serum FGF23 was found between FGF23 and the $Ca^{++} \times Pi$ product.

8.2.3.2 Actions of FGF23

In addition to being regulated by serum Ca^{++} and Pi levels, FGF23 in turn acts to modulates serum Ca^{++} and Pi levels, thus ensuring that the $Ca^{++} \times Pi$ product remains within a physiological range. FGF23 is therefore not only a phosphoregulatory hormone but a dual calciophosphoregulatory hormone (Figs. 8.1 and 8.2).

FGF23 combines with an FGFR, as well as with Klotho, an obligate coreceptor, in order to transmit the signal of FGF23 to target organs [76]. Thus, Klotho protein forms constitutive binary complexes with FGFR1c, FGFR3c, and FGFR4 which increase the affinity of these FGFRs selectively to FGF23 [77] and produce a heterotrimeric complex which is required for FGF23 to activate downstream signaling molecules, including FGFR substrate-2α and mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinases (ERK1/2). Klotho is a type I membrane protein but may also be expressed, due to alternative RNA splicing, as a secreted form that lacks the transmembrane and intracellular domains; it may therefore also act as a humoral factor [78] and may also have β-glucuronidase activity [79]. A unique structural feature of the endocrine FGFs, including FGF23, is their lack of a heparin-binding domain that is conserved in all paracrine/autocrine FGFs [80].

This heparin-binding domain binds to heparan sulfate (HS) in the extracellular matrix, thereby imposing some restriction to the secretion of non-endocrine FGFs and increasing their local concentration to support their paracrine/autocrine mode of action; in addition, the HS-binding domain is essential for FGFR activation, forming a complex of HS, FGF, and FGFR [81]. Absence of the heparin-binding domain in endocrine FGFs may facilitate their release from sites of production and Klotho proteins substitute for HS in enhancing receptor binding by endocrine FGFs. Although FGFRs are quite ubiquitous, Klotho expression is relatively restricted and may confer tissue specificity for FGF23 action [42].

The major target for FGF23 is the kidney, where it acts to promote phosphate excretion and to decrease production and increase clearance of $1,25(OH)_2D$. FGF23 suppresses Pi reabsorption [28] by inhibiting NaPi2a and NaPi2c on the apical brush border membrane of proximal tubular cells [82]. Although all the FGF23 actions seem to occur in the proximal tubule, Klotho expression is higher in the distal tubules [83]. Because proximal tubules also express Klotho, albeit in lower quantities [84], FGF23 may signal directly in proximal tubules to regulate their function with a small number of FGFR–Klotho complexes. Alternatively FGF23 may act on distal convoluted tubules where Klotho is most abundantly expressed and initiate release of a paracrine factor(s) that acts on adjacent proximal tubules. It is currently unclear but unlikely that circulating Klotho can serve as a coreceptor for FGFR.

FGF23 also lowers blood levels of $1,25(OH)_2D$ by downregulating the expression of the *CYP27B1* gene [31] and by upregulating gene expression of 24-hydroxylase (CYP24A1), which converts $1,25(OH)_2D$ to inactive metabolites [85]. Thus, FGF23 suppresses synthesis and promotes degradation of the active hormonal form of vitamin D. By diminishing circulating $1,25(OH)_2D$ levels, FGF23 can therefore also indirectly reduce vitamin D-stimulated Pi (and Ca^{++}) absorption in the intestine (Figs. 8.1 and 8.2).

In addition, FGF23 acts directly on the parathyroid gland FGFRs (likely via FGFR1 and FGFR3) and Klotho [26, 27] in an ERK1/2-dependent manner [86, 87] to suppress PTH synthesis and secretion [86, 87]; FGF23 may also increase the levels of parathyroid CaSR and VDR to indirectly inhibit PTH gene expression, secretion, and cell proliferation via Ca^{++} and $1,25(OH)_2D$ respectively [88]. However, in most clinical and pathological situations associated with chronically increased circulating FGF23 concentrations,

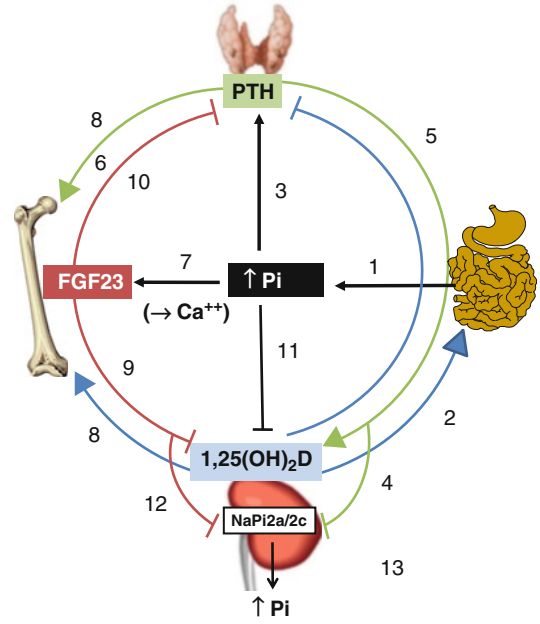

Fig. 8.1 Model of hormonal regulation of Pi (and Ca^{++}) homeostasis. In the presence of normal renal function, increased dietary phosphorus (Pi) (*1*) facilitated by $1,25(OH)_2D$ action on the intestine (*2*) may increase serum Pi levels. Increased Pi levels can directly or indirectly increase PTH secretion (*3*) leading to increased renal Pi excretion (*4*), but also to increased renal Ca^{++} retention, increased $1,25(OH)_2D$ production (*5*), and increased release of Ca^{++} and Pi from the bone (*6*). The increased serum Pi in the presence of a threshold level of serum Ca^{++} can now increase FGF23 secretion from the bone (*7*), as well as PTH (*8*), and $1,25(OH)_2D$ (*8*) which may also each increase FGF23 production. Secreted FGF23 can decrease $1,25(OH)_2D$ (*9*) thus reducing its capacity to further enhance intestinal Pi absorption and can also inhibit PTH (*10*) thus reducing stimulation of renal production of $1,25(OH)_2D$, Pi mobilization from the bone, and enhancement of Pi excretion. Serum Pi per se may also reduce $1,25(OH)_2D$ production (*11*). FGF23 can inhibit proximal tubular NaPi2a and 2c (*12*) and produce phosphaturia (*13*) in place of the suppressed PTH, thereby reducing the Pi (and $Ca^{++} \times$ Pi product). With prolonged elevation of FGF23 and suppression of $1,25(OH)_2D$, secondary hyperparathyroidism may occur to prevent significant hypocalcemia

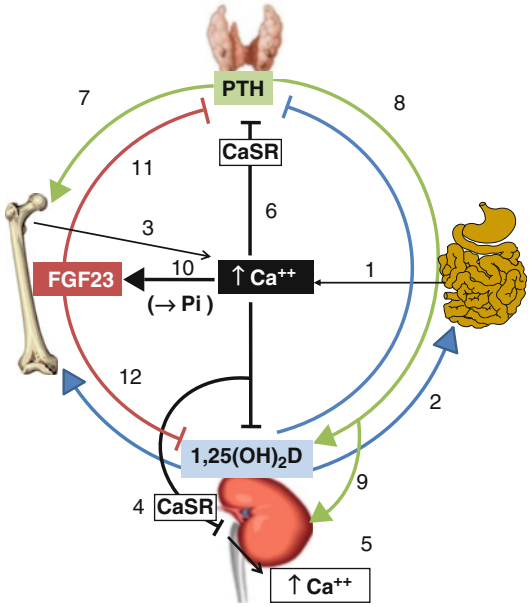

Fig. 8.2 Model of hormonal regulation of Ca^{++} (and Pi) homeostasis. Increased intestinal absorption of Ca^{++} (*1*) facilitated by increased $1,25(OH)_2D$ (*2*) or increased bone resorption (*3*) or both may result in increased serum calcium (Ca^{++}) (and Pi). Serum Ca^{++}, by stimulating the renal CaSR (*4*), can enhance Ca^{++} excretion (*5*). Serum Ca^{++}, acting via the CaSR in the parathyroid gland, can inhibit PTH secretion (*6*). Decreased PTH results in reduced mobilization of skeletal Ca^{++} (and Pi) (*7*), reduced renal production of $1,25(OH)_2D$ (*8*), and reduced renal Ca^{++} retention (*9*) but also in reduced renal Pi clearance. Elevated serum Ca^{++} in the presence of high normal or elevated serum Pi can then increase FGF23 secretion (*10*) which can further inhibit PTH secretion (*11*) and kidney-derived $1,25(OH)_2D$ (*12*) and normalize the $Ca^{++} \times$Pi product

secondary hyperparathyroidism is present. In mice overexpressing FGF23 [89], secondary hyperparathyroidism also tends to occur, suggesting that the effects of FGF23 on Pi, Ca^{++}, and 1,25(OH)D metabolism, which act to stimulate PTH production, may overcome any direct inhibitory effects of FGF23 on PTH release. Downregulation of FGFRs and Klotho in the parathyroids that reduces sensitivity to FGF23 signaling has been reported as the underlying cause of FGF23 resistance in some [90, 91], but not all studies [92] of secondary hyperparathyroidism in uremia. In *Hyp* mice which have a loss of Phex function with resultant increased FGF23 and which are phenocopies of X-linked hypophosphatemic rickets (XLH) in man, secondary hyperparathyroidism occurs and deletion of the gene encoding PTH results in early lethality due to hypocalcemia [93]. Hyperparathyroidism, therefore, is an integral component in the pathophysiology of Hyp, and likely XLH, despite excess circulating FGF23 and may serve as a compensatory mechanism to prevent severe hypocalcemia in mice and perhaps in patients afflicted with the disorder.

8.3 Endocrine Regulation of Pi and Ca^{++} Metabolism

When renal function is normal, in the presence of an increased dietary load of Pi, serum Pi levels may increase, enhanced by $1,25(OH)_2D$ action on the intestine. This increased serum Pi may directly [94] or indirectly (by reducing serum Ca^{++} levels) increase PTH secretion and facilitate renal Pi excretion. However, PTH may also mobilize Pi (and Ca^{++}) from the bone and enhance $1,25(OH)_2D$ production with resultant increased intestinal absorption of Pi (and Ca^{++}). In the presence of a threshold level of serum Ca^{++}, Pi can then increase FGF23 secretion from the bone. $1,25(OH)_2D$ per se and PTH may also increase skeletal production of FGF23. Secreted FGF23 can then inhibit $1,25(OH)_2D$ production, thus reducing its capacity to further enhance intestinal Pi absorption, and can also inhibit PTH thus reducing its capacity to mobilize Pi from the bone, as well as to stimulate renal production of $1,25(OH)_2D$ and to promote Pi excretion. Pi per se may also inhibit $1,25(OH)_2D$ production. FGF23 can inhibit proximal tubular NaPi2a and 2c in the kidney and can produce phosphaturia in place of the suppressed PTH, restoring the serum Pi (and Ca^{++} x Pi product) to normal. With prolonged elevation of FGF23 and prolonged suppression of $1,25(OH)_2D$, secondary hyperparathyroidism may occur to prevent significant hypocalcemia (Fig. 8.1).

Increased serum Ca^{++} may arise from increased intestinal absorption of Ca^{++}, (with Pi) or from increased bone resorption (with Pi) or from both mechanisms. The increased serum Ca^{++} per se by stimulating the renal CaSR can enhance renal

Ca^{++} excretion. The increased serum Ca^{++} acting via the CaSR in the parathyroid gland can inhibit PTH secretion. Decreased PTH results in reduced bone resorption and concomitant mobilization of skeletal Ca^{++} (and Pi), decreased renal Ca^{++} retention, and reduced production of $1,25(OH)_2D$ in the kidney, but also in increased Pi retention. Elevated serum Ca^{++} in the presence of high normal or elevated serum Pi can also increase FGF23 secretion which can further inhibit PTH secretion, can inhibit kidney-derived $1,25(OH)_2D$, and replace the action of PTH in promoting phosphaturia (Fig. 8.2), thereby normalizing the $Ca^{++} \times Pi$ product.

These complex interrelationships underlie the exquisite controls that have evolved to maintain serum Pi and Ca^{++} levels within a defined range when one of these ions is dysregulated but also to ensure an appropriate ratio by maintaining a normal $Ca^{++} \times Pi$ product.

Conclusion

Initial studies on mineral ion regulation focussed on the Ca^{++}-regulating hormones PTH and $1,25(OH)_2D$, but these were also known to have profound effects on renal and intestinal handling of Pi. Analysis of genetic diseases of renal Pi wasting identified FGF23, as a primary hormonal regulator of Pi homeostasis. Subsequently FGF23 was found to participate in complex feedback loops with the classic Ca^{++}-regulating hormones, and all three hormones are now known to share interacting functions on regulating both Ca^{++} and Pi homeostasis.

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