Pathogenesis of secondary hyperparathyroidism and fibroblast growth factor 23: a pharmacological validation of the “trade-off hypothesis”

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TO THE EDITOR: We read with great interest the recent publication in this Journal by Khuituan et al. (9) entitled “Fibroblast growth factor-23 abolished 1,25-dihydroxyvitamin D3-induced enhanced duodenal calcium transport in male mice.” The authors demonstrated that FGF23 abolished 1,25(OH)2D3-induced duodenal calcium absorption whereas FGF23 per se had no effect on calcium absorption. In more detail, they found that FGF23 antagonized the 1,25(OH)2D3-induced upregulation of TRPV5, TRPV6, and calbindin-D9k mediated by MAPK/ERK, p38 MAPK, and PKC via FGF receptor isofoms in duodenal epithelial cells.

Why does impaired renal function cause hyperparathyroidism? More than 40 years ago, Bricker et al. (3, 4) answered the question by applying their “trade-off hypothesis”: a small decrease in glomerular filtration rate (GFR) leads to a transient hyperphosphatemia, and reciprocal hypocalcemia stimulates parathyroid hormone (PTH) secretion in order to increase urinary phosphate excretion and to increase renal calcium reabsorption. This, in turn, permits a restoration of blood phosphate and calcium levels to normal but stabilizes PTH secretion in a higher range. This elegant trade-off hypothesis can be validated pharmacologically. First, sevelamer hydrochloride, a phosphate binder, can decrease blood PTH level in parallel with reduction in phosphate (10), inhibit parathyroid cell proliferation (12), and arrest/reverse parathyroid gland hyperplasia (11,13) in chronic kidney disease (CKD) rats with secondary hyperparathyroidism (2HPT). These results clearly indicate that phosphate retention underlies the pathogenesis of 2HPT. Second, R-568 and cinacalcet hydrochloride (cinacalcet), calcimimetics can restore the parathyroid hyperfunction in CKD rats and patients with 2HPT (14). In other words, these results also indicate that hypocalcemia causes and promotes 2HPT, because calcimimetics input an apparent hypercalcemic stimulation against the calcium receptor on parathyroid gland cell surface (14). Third, cinacalcet administration lowers blood PTH and phosphate levels in dialysis patients (14). Reduction in PTH induced by cinacalcet, however, increases blood phosphate level with decreased urinary phosphate excretion in pre-dialysis patients with CKD stages 3 and 4 (5, 6). Finally, cinacalcet treatment increases urinary calcium excretion and leads to severe hypocalcemia in these patients (5, 6). This set of results shows that PTH should be increased when GFR declines in order to maintain the normal range both in blood phosphate and calcium levels.

However, the above consistent story was applied before the year 2000. FGF23 was discovered as a novel phosphaturic factor in 2000 (1,17,18). FGF23 negatively regulates 1,25(OH)2D3 through 1-αHase downregulation and 24-OHase upregulation (16). In addition, blood FGF23 levels gradually increase associated with the progressive decline of renal function and negatively correlates with blood 1,25(OH)2D3 level in pre-dialysis CKD patients (7, 15). Therefore, we attempted to provide another pharmacological validation for involvement of FGF23 in the pathogenesis of 2HPT. We administered anti-FGF23 neutralizing antibody to CKD rats with high circulating levels of FGF23 and PTH, low 1,25(OH)2D3, and normal blood phosphate level (8). Eliminating the effect of FGF23 with neutralizing antibody markedly increased blood phosphate level accompanied by reduced urinary phosphate excretion. The antibody treatment also normalized blood 1,25(OH)2D3 level with increased 1-αHase and decreased 24-OHase expressions in the kidney. These changes were followed by increased blood calcium levels, leading to decreased PTH. Hence, this study clearly indicates that FGF23 prevents the incidence of hyperphosphatemia and also lowers 1,25(OH)2D3 in early stages of CKD. Thus, FGF23 plays a central role in the pathogenesis of 2HPT through a reduction of 1,25(OH)2D3 and calcium, thereby increasing PTH secretion.

Lastly, we were greatly impressed anew by the description in the footnote of Bricker’s paper (3). “If vitamin D resistance occurs and decreases the net enteric absorption of calcium at any point in the course of chronic renal disease, an additional factor would contribute to the genesis of hyperparathyroidism.” Indeed, Bricker exactly predicted the existence of FGF23 in 1972. In addition to the inhibitory effect of FGF23 (“an additional factor” itself) on the production of 1,25(OH)2D3, as Khuituan et al. have just demonstrated this year (9), FGF23 can inhibit 1,25(OH)2D3-induced intentional calcium absorption and thereby may induce hypocalcemia, leading to increased PTH secretion. Most recently, it has been reported that decreased expression of renal α-Klotho, a coreceptor for FGF23, leads to hypercalciumia (i.e. negative calcium balance and a cause of hypocalcemia) in early diabetic nephropathy (2). Therefore, the reduction in renal α-Klotho, which also might blunt the phosphaturic effect of FGF23 and lead to phosphate retention, may contribute to the early pathogenesis of 2HPT, at least in diabetic nephropathy. We are compelled to admire the clear foresight of Neal Bricker as well as the progress of science: visiting old, learn new.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
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