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-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 isoforms 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 hypocalemia 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 generation in fibroblasts (9). The authors demonstrated that FGF23 abolishes 1,25(OH)2D3-induced expression of 24-OHase and decreased 1α-Hydroxylase (1α-HOase) gene expression in the proximal tubule of the kidney in vivo and in cultured proximal tubular cells. This suggested that FGF23 suppresses PTH induction and urinary calcium excretion, 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 hypercalcemia (i.e., negative calcium balance and a cause of hypocalemia) 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

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AUTHOR CONTRIBUTIONS

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