Renal Osteodystrophy and Vitamin D Derivatives: Cellular Mechanisms of Hyperparathyroidism in Uremia

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I. INTRODUCTION

Renal osteodystrophy (ROD) is one of the most frequent and important complications of uremic patients on long-term dialysis. Secondary hyperparathyroidism (2HPT) is the central feature of ROD (1). Almost all patients on maintenance dialysis may develop 2HPT during their course despite of oral active vitamin D therapy. Thus the control of 2HPT is critical and needs more specific and rational therapeutic approaches. In this paper, we will summarize the recent advance in the pathogenesis of 2HPT in chronic renal failure at cellular level and its clinical implications.

II. PTH SECRETION AND SYNTHESIS IN CHRONIC RENAL FAILURE

Parathyroid hormone (PTH) secretion are mainly controlled by plasma concentration of calcium (Ca) ion and 1,25-dihydroxyvitamin D (1,25(OH)2D). Thus in chronic renal failure, primarily as a consequence of phosphate retention, hypocalcemia directly stimulates PTH secretion and reduced plasma level of 1,25(OH)2D stimulates PTH secretion in part by causing skeletal resistance to PTH and by shifting the set-point of PTH secretion for Ca to the right (2). In addition, it is recently suggested that phosphate retention per se may directly stimulate PTH hypersecretion (3). Thus, phosphate binders and active vitamin D sterols are widely used to prevent phosphate retention and to maintain physiological concentration of Ca and 1,25(OH)2D in dialysis patients. Despite these treatment modalities, 2HPT may develop particularly in long-term dialysis patients. In such patients, only transient, but supraphysiological concentration of 1,25(OH)2D can normalize PTH secretion (4). Thus, it is suggested that resistance of the parathyroid cells to the physiological concentrations of 1,25(OH)2D in circulation may be one of the causes of PTH hypersecretion in chronic renal failure.

Synthesis of PTH is also negatively regulated by plasma calcium and 1,25(OH)2D within a physiologically relevant range. Extracellular Ca ion concentration negatively affects the steady state levels of PTH mRNA as shown in dispersed parathyroid cell preparation (5) and in vivo (6). This negative regulation is mediated by a sequence around -3.5 kilo base pairs (bps) in the 5' flanking region of the human PTH gene as shown by Okazaki and associates (7). 1,25(OH)2D is another factor that regulates PTH synthesis at transcriptional level, as shown in vitro (8) or in vivo (9). For the human PTH gene, the negative regulation of transcription was shown to be mediated by the sequence at -212 to -353 bps in the 5' flanking region of the PTH gene (10). It is assumed that PTH synthesis in advanced chronic renal failure may be enhanced by the decreased concentrations of plasma Ca ion and 1,25(OH)2D. However, it has not been determined until recently what extent both mechanisms are involved especially in the early phase of chronic renal failure. In our chronic renal failure rats made by 7/8 nephrectomy, PTH mRNA levels were elevated without any detectable changes in plasma concentrations of either Ca ion or 1,25(OH)2D (11). When pharmacological doses of 1,25(OH)2D3 were administered, these elevated PTH mRNA levels were promptly returned to normal. These data clearly show that pharmacological, but not physiological concentration of 1,25(OH)2D can suppress PTH mRNA levels in the early phase...
of chronic renal failure. Thus, the resistance of the parathyroid cells to the physiological concentrations of 1,25(OH)2D may be a cause of increased PTH synthesis in chronic renal failure.

III. PARATHYROID CELL PROLIFERATION IN CHRONIC RENAL FAILURE

Marked hyperplasia of parathyroid glands is another feature of 2\textsuperscript{nd}HPT in chronic renal failure. Parathyroid cell proliferation is closely related to enhanced PTH synthesis and secretion, but the mechanism has not been clarified.

Szabo and associates reported that [3H]-thymidine incorporation into parathyroid cells isolated from renal failure animals could be suppressed by the preadministration of 1,25(OH)2D\textsubscript{3} (12). Kremer and associates demonstrated that 1,25(OH)2D\textsubscript{3}, but not higher concentrations of extracellular Ca, could suppress c-myc expression of dispersed parathyroid cells (13). We found that c-myc expression in parathyroid glands was increased in chronic renal failure rats without any detectable changes in serum concentrations of Ca and 1,25(OH)2D. Enhanced expression of c-myc could be suppressed to normal levels by pharmacological doses of 1,25(OH)2D\textsubscript{3}. Thus, enhanced parathyroid cell proliferation in chronic renal failure may also be due to the resistance of the parathyroid cells to the physiological concentration of 1,25(OH)2D.

IV. 1,25(OH)\textsubscript{2}D RECEPTORS IN CHRONIC RENAL FAILURE

What is the nature of this resistance of the parathyroid cells to the physiological concentration of 1,25(OH)2D? Recently, Korkor has shown that the number of 1,25(OH)2D binding sites is decreased in parathyroid glands without any change in the affinity in chronic dialysis patients (14). Such decrease was also demonstrated in parathyroid glands of renal failure animals (15). In our model rats of early phase of chronic renal failure, 1,25(OH)2D receptors detected by Western blot were also decreased. Thus, the decrease of 1,25(OH)2D receptor numbers may be one of the causes of the resistance of the parathyroid cells to the physiological concentrations of 1,25(OH)2D.

What is the cause of this decrease of 1,25(OH)2D receptors? Recently, it has been shown that 1,25(OH)2D up-regulates its receptors in parathyroid glands (16). Thus, up-regulation of 1,25(OH)2D receptors may be disturbed in chronic renal failure. Furthermore, phosphate retention may affect 1,25(OH)2D receptor numbers. However, these possibilities remain to be elucidated.

V. 1,25(OH)\textsubscript{2}D\textsubscript{3} PULSE THERAPY AND NEW VITAMIN D DERIVATIVES

Recent clinical reports demonstrated that the intravenous (4) or oral 1,25(OH)2D\textsubscript{3} pulse therapies could suppress severe 2\textsuperscript{nd}HPT which was uncontrollable with conventional oral active vitamin D therapy. The shift of the set-point of PTH secretion to plasma Ca ion may return to normal by 1,25(OH)2D\textsubscript{3} pulse therapy (17). The inhibiting effect of 1,25(OH)2D\textsubscript{3} pulse therapy may also be brought about through the suppression of PTH mRNA levels. In addition, we have recently demonstrated that 1,25(OH)2D\textsubscript{3} pulse therapy can also induce regression of parathyroid hyperplasia (18). These effects of 1,25(OH)2D\textsubscript{3} pulse therapy are mediated by achieving transient, pharmacological levels of 1,25(OH)2D in circulation, an interpretation consistent with the notion that the resistance of the parathyroid cells to the physiological concentration of 1,25(OH)2D develops in chronic renal failure.

It has also been reported that other vitamin D derivatives, such as 22-oxa-1,25(OH)2D\textsubscript{3} may suppress PTH mRNA in dispersed cell preparations or in normal (19) and uremic animals (11) in vivo (Figure 1): the suppression may not be accompanied by hypercalcemia. Such observations are important because 1,25(OH)2D\textsubscript{3} pulse therapies are often accompanied with marked hypercalcemia, for which the therapy has to be discontinued. Thus, 22-oxa-1,25(OH)2D\textsubscript{3} may be useful in the management of 2\textsuperscript{nd}HPT of chronic uremia. The mechanisms by which these vitamin D derivatives suppress PTH mRNA should be clarified in future.
Fig. 1. Suppression of PTH mRNA by 22-oxa-1,25(OH)₂D₃ in chronic renal failure rats.
Ten μg of total RNA from thyro-parathyroid glands of a single rat were analyzed by Northern blot.
(a). 22-oxa-1,25(OH)₂D₃ (OCT) or vehicle was given i.p. at 24 and 48 hours before sacrifice.
Lane 1: 200 pmol/100g body wt of 1,25(OH)₂D₃, lane 2: vehicle; lane 3: 40 pmol/100g body wt of OCT (This dose of 1,25(OH)₂D₃ can suppress PTH mRNA to normal); lane 4: 200 pmol/100g body wt of OCT.
(b). Effect of OCT, 200 pmol/100g body wt on the PTH mRNA levels in chronic renal failure rats. The ratio of PTH mRNA to actin mRNA ratio of sham-operated rat was taken as 100%.
(Adapted from ref. 11, with permission)

VI. SUMMARY

In the early phase of chronic renal failure, physiological concentrations of 1,25(OH)₂D in circulation may become insufficient to regulate parathyroid cell function normally. As a result, the set-point of PTH secretion to plasma Ca ion concentration shifts to the right, PTH synthesis becomes enhanced at transcriptional level, and parathyroid cells begin to proliferate. This resistance of the parathyroid cells to the physiological concentration of 1,25(OH)₂D may be in part due to the reduction of 1,25(OH)₂D receptor density in parathyroid cells. However, the mechanism by which the number of 1,25(OH)₂D receptors decreases in parathyroid cells in early renal failure remains to be elucidated.

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REFERENCES

[1] Malluche H, Faugere MC (1990): Renal bone disease 1990: An unmet challenge for the nephrologist. Kidney Int. 38: 193-211.

[2] Coburn JW, Llach F (1987): Renal osteodystrophy, In Clinical Disorders of Fluid and Electrolyte Metabolism., edited by Maxwell MH, Kleeman CR, Narins RG, Fourth edition, New York, McGraw-Hill Book Company, p985.

[3] Lopez-Hilker S, Dusso AS, Rapp NS, Martin KJ, Slatopolsky E (1990): Phosphorus restriction reverses hyperparathyroidism in uremia independent of changes in calcium and calcitriol. Am. J. Physiol. 259: F432-F437.

[4] Slatopolsky EA, Weerts C, Thielan J, Horst R, Harter H, and Martin KJ (1984): Marked suppression of secondary hyperparathyroidism by intravenous administration of 1,25-dihydroxycholecalciferol in uremic patients. J. Clin. Invest. 74: 2136-2143.

[5] Heinrich G, Kronenberg HM, and Potts Jr. JT (1983): Parathyroid hormone messenger ribonucleic acid: effect of calcium on cellular regulation in vitro. Endocrinology 112: 449-458.

[6] Yamamoto M, Igarashi T, Muramatsu M, Fukagawa M, Motokura T, Ogata E (1989): Hypocalcemia increases and hypercalcemia decreases the steady state level of parathyroid hormone messenger ribonucleic acid in the rat. J. Clin. Invest. 83: 1053-1056.

[7] Okazaki T, Igarashi T, and Ogata E: Calcium-responsive DNA element in the human parathyroid hormone gene. (abstract) J Bone Mineral Research 5: S141

[8] Silver J, Russell J, and Sherwood LM (1985): Regulation by vitamin D metabolites of messenger ribonucleic acid for preproparathyroid hormone in isolated bovine parathyroid cells. Proc. Natl. Acad. Sci. USA 82: 4270-4273.

[9] Silver J, Naveh-Many T, Mayer H, Schmelzer HJ, Popovtzer MM (1986): Regulation by vitamin D metabolites of parathyroid hormone gene transcription in vivo in the rat. J. Clin. Invest. 78: 1296-1301.

[10] Okazaki T, Igarashi T, and Kronenberg HM (1988): 5'-Flanking region of parathyroid hormone gene mediates negative regulation by 1,25(OH)2 vitaminD3. J. Biol. Chem. 263: 2203-2208.

[11] Fukagawa M, Kaname S, Igarashi T, Ogata E, Kurokawa K (1991): Regulation of parathyroid hormone synthesis in chronic renal failure in rats. Kidney Int. 39: 874-881.

[12] Szabo A, Merke J, Beier E, Mall G, and Ritz E (1989): 1,25(OH)2 vitamin D3 inhibits parathyroid cell proliferation in experimental uremia. Kidney Int. 35: 1049-1056.

[13] Kremer R, Bolivar I, Goltzman D, Hendy GN (1989): Influence of calcium and 1,25-dihydroxyxcholecalciferol on proliferation and proto-oncogene expression in primary cultures of bovine parathyroid cells. Endocrinology 125: 935-941.

[14] Korkor, AB (1987): Reduced binding of [3H]1,25-dihydroxyvitamin D3 in the parathyroid glands of patients with renal failure. N. Engl. J. Med. 316: 1573-1577.

[15] Merke J, Hugel U, Zlotowski A, Szabo A, Bommer J, Mall G, Ritz E (1987): Diminished parathyroid 1,25(OH)2D3 receptors in experimental uremia. Kidney Int. 32: 350-353.

[16] Naveh-Many T, Marx R, Keshet E, Pike JW, Silver J (1990): Regulation of 1,25-dihydroxyvitamin D3 receptor gene expression by 1,25-dihydroxyvitamin D3 in the parathyroid in vivo. J Clin Invest 86: 1968-1975

[17] Delmez JA, Tindira C, Grooms P, Dusso A, Windus DW, Slatopolsky E (1989): Parathyroid hormone suppression by intravenous 1,25-dihydroxyvitamin D. A role for increased sensitivity to calcium. J. Clin. Invest. 83: 1349-1355.

[18] Fukagawa M, Kitaoka M, Okazaki R, Harada S, Takano K, Sekine N, Kaname S, Matsumoto T, Ogata E, and Kurokawa K (1990): Regression of parathyroid hyperplasia by calcitriol pulse therapy in chronic dialysis patients. N. Engl. J. Med. 323: 421-422

[19] Brown A, Ritter C, Finch J, Morrissey J, Martin K, Murayama E, Nishii Y, Slatopolsky E (1989): The noncalcemic analogue of vitamin D, 22-oxacalciferol, suppresses parathyroid hormone synthesis and secretion. J. Clin. Invest. 84: 728-732.