Phosphate as Another Major Regulator of Parathyroid Function

**Key words:** PTH, parathyroid hyperplasia, phosphate sensor

The parathyroid gland is the key organ for the maintenance of calcium homeostasis. The parathyroid senses minute changes of the extracellular calcium ion concentration and secretes parathyroid hormone (PTH) to maintain calcium ion concentration within a narrow physiological range (1). Secretion of PTH is negatively regulated by calcium ion and by 1,25-dihydroxyvitamin D (calcitriol). Thus, sustained decrease of these two major parameters leads to secondary hyperparathyroidism, i.e., PTH hypersecretion, hypoparathyroidism, and enhanced parathyroid cell proliferation, as seen in uncontrolled uremic patients (2).

The role of phosphate in the pathogenesis of secondary hyperparathyroidism has long been recognized as indirect effects mediated by hypocalcemia (3, 4) or by suppression of calcitriol production. In addition to such mechanisms, several groups suggested possible direct effects of phosphate on parathyroid function independent of calcium or calcitriol (5, 6). Recent data with organ culture of parathyroid fragments clearly showed that a high phosphate concentration per se stimulates PTH secretion (7, 8). Interestingly enough, such an effect was more evident in parathyroid tissue from diffuse hyperplasia than that from nodular hyperplasia (9). In other words, parathyroid cells lose sensitivity to phosphate as hyperplasia progresses (10).

Several mechanisms have been suggested for this direct effect of phosphate. Since a decrease of calcium-sensing receptor was as recently shown to be prevented by dietary phosphate restriction (11), the modulation of calcium-sensing receptor by phosphate may be responsible. Modulation of calcitriol receptor by phosphate may be also possible as already demonstrated in the intestine (12). In addition, the existence of a phosphate sensor on parathyroid cell membrane has long been speculated. Recently, the phosphate transporter of parathyroid cell, that is regulated by calcitriol and phosphate, has been cloned (13). However, its roles in phosphate sensing remain to be elucidated.

In yeast, extracellular phosphate, which is one of the main nutrients, deliberately regulates phosphatase gene transcription (14). The mechanism of this regulation has been elucidated at molecular levels and most of the molecules included in this system have been already identified. They include presumed phosphate sensor, transporter, transcription factors and so on. Possible binding sites for these transcription factors have been identified in human gene promoter sequences, and binding proteins to these elements have also been cloned. It was also shown that molecules that regulate the activity of these transcription factors are homologues of cyclin and cyclin-dependent kinase (15). Thus, phosphate may directly regulate parathyroid cell function and proliferation through mammalian analogues of these molecules, which should be examined more extensively in the future.

In contrast to the control of PTH secretion by phosphate, the control of PTH synthesis by phosphate has been more clearly investigated. According to the studies by Moallem et al (16), the 3'-untranslated sequence of PTH gene is a very important determinant of PTH mRNA stability. This sequence is protected from endonuclease by protective factors. They clearly showed that a low phosphate diet decreases the amount of these protective factors in parathyroid cells, resulting in the suppression of PTH synthesis (16).

In addition to a high serum phosphate concentration, dietary phosphate load itself may modify parathyroid function. In our previous study with renal failure rats, mild dietary phosphate restriction completely prevented hyperparathyroidism and phosphate load induced hyperparathyroidism without any detectable change in the serum phosphate concentration or that of calcium or calcitriol (6). In the case of X-linked hypophosphatemic rickets reported in this issue (17), long-term oral phosphate load was suspected to be responsible for the development of severe hyperparathyroidism.

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Phosphate reabsorption at proximal tubule is disturbed in this disease due to PHEX mutation (18), which results in sustained activity of phosphatonin, a phosphaturic factor. Thus, in this case with low dose of active vitamin D sterol, severe hyperphosphatemia was not observed despite large doses of oral phosphate at least during the last 8 years.

These observations suggest that there may be a sensing mechanism of phosphate load, in addition to that of serum phosphate concentration. Candidate organs for such a mechanism are intestine and kidney, which are the entrance and exit of dietary phosphate load. Regulation of phosphate-responsive genes in the proximal tubule cells of the kidney, such as 25 (OH)-vitamin D-1α-hydroxylase and sodium-phosphate cotransporter genes (19), has recently been extensively studied. However, to date little information is available on the sensing mechanism of phosphate load in the intestine (20). In addition to the sensing mechanism of phosphate load, there should be a system to deliver this information to parathyroid cells. Elucidation of this new 'entero-parathyroid axis' is very exciting and may lead to the development of new categories of drugs.
for disorders of phosphate metabolism.

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References