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Regulation of PTH synthesis and secretion relevant to the management of secondary hyperparathyroidism in chronic kidney disease

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Regulation of PTH synthesis and secretion relevant to the management of secondary hyperparathyroidism in chronic kidney disease. Small decreases in serum Ca^{++} and more prolonged increases in serum phosphate (P) stimulate the parathyroid (PT) to secrete parathyroid hormone (PTH), while 1,25$(OH)_2$-vitamin D_3 decreases PTH synthesis and secretion. A prolonged decrease in serum Ca^{++} and 1,25$(OH)_2D_3$, or increase in serum P, such as in patients with chronic renal failure, leads to the appropriate secondary increase in serum PTH. This secondary hyperparathyroidism involves increases in PTH gene expression, synthesis, and secretion, and, if chronic, to proliferation of the parathyroid cells. A low serum Ca^{++} leads to an increase in PTH secretion, PTH mRNA stability, and parathyroid cell proliferation. Pi also regulates the parathyroid in a similar manner. The effect of Ca^{++} on the parathyroid is mediated by a membrane Ca^{2+} receptor (CaR). 1,25$(OH)_2D_3$ decreases PTH gene transcription. Ca^{2+} and P regulate the PTH gene post-transcriptionally by regulating the binding of parathyroid cytosolic proteins, *trans* factors, to a defined *cis* sequence in the PTH mRNA 3′-untranslated region (UTR), thereby determining the stability of the transcript. The parathyroid *trans* factors and *cis* elements have been defined.

Patients with chronic kidney disease (CKD) have major disturbances in their homeostasis of calcium and phosphate with associated changes in vitamin D metabolism and PTH secretion [1, 2]. The resulting diseases of their parathyroids, bones, and arteries result in a tremendous morbidity and mortality that have become one of the major challenges in the management of patients with CKD before and during their treatment by chronic dialysis. Understanding the pathophysiology of the factors involved has been of major significance to the development of new therapeutic strategies for these patients. However, despite the advances made, there are still large areas where we do not have an in-depth understanding of the mechanisms and consequences of the disturbed mineral metabolism. Central to mineral metabolism is the role of parathyroid hormone (PTH). Most patients with CKD develop secondary hyperparathyroidism, and the mechanisms involved will be reviewed here. The secondary hyperparathyroidism of chronic renal failure comprises increased PTH secretion, increased PTH synthesis, and increased parathyroid cell proliferation. Cellular and molecular studies have yielded insights and highlighted unanswered questions into these changes, particularly related to the regulatory actions of 1,25$(OH)_2$ vitamin D_3, calcium, and phosphate, which have important effects at all three levels of parathyroid dysfunction in CKD.

Vitamin D and the parathyroid

Vitamin D deficiency was known to be associated with secondary hyperparathyroidism, and this was always considered to result from decreased absorption of calcium from the diet with the resultant hypocalcemia stimulating the parathyroid to secrete more PTH [3]. The parathyroid was not considered to be a target organ of vitamin D. With the discovery of 1,25$(OH)_2$-vitamin D_3 as the active metabolite of vitamin D, it became feasible to test this accepted dogma in the laboratory. In vitro, using bovine parathyroid cells in primary culture, 1,25$(OH)_2D_3$ decreased PTH mRNA levels [4]. In vivo studies performed confirmed the physiologic relevance of these in vitro studies [5]. 1,25$(OH)_2D_3$ in physiologically relevant doses dramatically decreased the levels of PTH mRNA in the parathyroids of normal rats without changing the levels of serum calcium. We showed that the effect of 1,25$(OH)_2D_3$ on the PTH gene was transcriptional [5].

We then showed that the 1,25$(OH)_2D_3$ receptor mRNA is expressed at a very high concentration in the rat parathyroid, similar to its concentration in the duodenum, the classic vitamin D target organ [6]. Moreover, the administration of 1,25$(OH)_2D_3$ increased the levels of the 1,25$(OH)_2D_3$ receptor mRNA in the parathyroid, which would then increase the amount of receptor protein in the parathryoid, and thereby amplify the effect of circulating 1,25 $(OH)_2D_3$ on the PTH gene.

Further studies in humans confirmed these findings in patients with CKD [7]. Slatopolsky et al and many other workers then showed the effectiveness of $1,25(OH)_2D_3$ in patients with CKD to decrease PTH secretion and the bone disease due to the high levels of circulating PTH. 1, $25(OH)_2D_3$ also has an action to increase serum calcium, and analogues of $1,25(OH)_2D_3$ were discovered that were less hypercalcemic than the natural compound. In many countries, these compounds are now the mainstay of treatment of patients with CKD.

The effect of $1,25(OH)_2D_3$ continued to interest the scientific community, and other interesting findings have come to light. For instance, $1,25(OH)_2D_3$ up-regulates the transcription of the gene coding for the calcium receptor (CaR) in the parathyroid [8], which would make the CaR more sensitive to the ambient serum calcium, and thereby more avidly decrease PTH secretion at a particular serum calcium. In addition, in the setting of hypocalcemia, even though serum levels of $1,25(OH)_2D_3$ increase markedly, there is a paradoxic increase in PTH mRNA and serum PTH levels. This paradox was shown to be due to increased concentration of a protein, calreticulin, in the nuclei of the parathyroids of hypocalcemic rats, which prevented the binding of $1,25(OH)_2D_3$ to its receptor resulting in persistent PTH gene transcription despite markedly elevated $1,25(OH)_2D_3$ [9]. Of particular interest is the finding that the secondary hyperparathyroidism of mice with genetic deletion of the vitamin D receptor can be corrected by a high calcium diet [10]. This result emphasizes the dominant role of serum calcium to regulate the parathyroid.

Another relevant observation with regard to our understanding of the role of vitamin D and the parathyroid is the finding that in nodular hyperplastic glands there is a decrease in the concentration of the $1,25(OH)_2D_3$ receptor protein. The lack of $1,25(OH)_2D_3$ receptor in such cases is of interest because $1,25(OH)_2D_3$ also acts on the parathyroid to decrease parathyroid cell proliferation. In any event, the unraveling of the mechanism of action of $1,25(OH)_2D_3$ on the parathyroid, and its role in the management of patients with CKD, is a classic example of rapid translation of basic science research into clinical applications that benefit patients. There are many open questions in this fascinating saga that await the investigative skills of the alert clinician-scientist.

Calcium and the parathyroid

The parathyroid is geared to respond to a small decrease in serum Ca^{++} concentration by increasing PTH secretion. It recognizes the changes in serum Ca^{++} concentration by a cell membrane G-protein coupled receptor, the calcium receptor (CaR) [11]. Under normal physiologic conditions, serum Ca^{++} acting at the CaR exerts a natural braking action on PTH secretion, helping to limit tonic release by parathyroid cells. The secreted PTH then acts on its target organs, bone and kidney, to correct the serum Ca^{++}. The effect of a low Ca^{++} to stimulate PTH secretion is quite rapid. Low Ca^{++} has another effect on the parathyroid gland to markedly increase PTH gene expression and subsequent PTH synthesis; however, this effect occurs over a time frame of hours and longer [2]. Over an even longer time interval, low Ca^{++} leads to an increase in parathyroid cell proliferation, which initially is polyclonal but, with a prolonged stimulus, may become monoclonal [12]. In patients with CKD there is not only a decrease in serum Ca^{++}, but also a persistent increase in serum phosphate, which markedly amplifies PTH secretion, PTH gene expression, and parathyroid cell proliferation.

Phosphate and the parathyroid

A high serum phosphorus (P) concentration has been known for many decades to be associated with an increase in PTH secretion. However, given uncertainty regarding the direct effect of phosphorus on the parathyroid cell function, this association was always considered to be secondary to decreases in serum Ca^{++} and a decrease in serum $1,25(OH)_2D_3$ levels [13]. It was shown clinically in CKD patients and in laboratory animals with experimental uremia that correction of the serum P with no changes in serum Ca^{++} or $1,25(OH)_2D_3$ levels was able to correct the serum PTH levels. Kilav et al showed in careful studies in rats with normal renal function that serum P regulated PTH mRNA and serum PTH levels independently of changes in either serum Ca^{++} or $1,25(OH)_2D_3$ levels [14]. In vitro studies from a number of laboratories have shown a direct effect of P on the parathyroid to regulate PTH secretion [15, 16] by a mechanism involving inhibition of cytosolic phospholipase A_2 ($cPLA_2$) [17].

Regulation of parathyroid hormone gene expression by serum calcium and phosphate

In uremic secondary hyperparathyroidism, PTH mRNA levels are increased [18]. Research into the regulation of PTH gene expression has been crucial to understanding the pathogenesis of secondary hyperparathyroidism. Because the amount of preformed, mature PTH is limited and degradation of the hormone is rapid, much of the regulatory control of PTH occurs at the level of gene expression [19].

Like $1,25(OH)_2D_3$, the concentrations of Ca^{++} and P regulate the abundance of PTH mRNA. Low serum Ca^{++} and high serum P increase PTH mRNA levels in the rat, and dietary manipulation of these minerals is sufficient to trigger the change [14, 20, 21]. However, unlike $1,25(OH)_2D_3$, the regulatory actions of serum Ca^{++} and P are at the post-transcriptional level [14, 20].