INTRODUCTION

The parathyroid glands first appear during evolution with the movement of animals from an aquatic environment to a terrestrial environment deficient in calcium. Maintenance of normocalcemic state. As discussed later, PTH accomplishes this task by promoting bone resorption and releasing calcium from the skeletal reservoir; by inducing renal conservation of phosphate; and by indirectly enhancing intestinal calcium absorption by increasing the renal proximal tubule secretion of PTH. PTH acts through a G protein-coupled receptor known as the PTH1 receptor (Fig. 1). Teleosts display wide heterogeneity in the sequence of the mature peptides. Mammalian PTHs in the 1-34 sequence of the mature peptides have been detected in teleosts that lack discrete parathyroid glands. However, two forms of PTH have been definitively established, although it has suggested based on sites of expression that PTH may play a role in the development of the teleost neural system, cartilage, and bone. Teleost PTHs display significant amino acid homology to mammalian PTHs in the 1-34 sequence of the mature peptides. Mammalian PTHs in the 1-34 sequence of the mature peptides have been detected in teleosts that lack discrete parathyroid glands. However, two forms of PTH have been definitively established, although it has suggested based on sites of expression that PTH may play a role in the development of the teleost neural system, cartilage, and bone. Teleost PTHs display significant amino acid homology to mammalian PTHs in the 1-34 sequence of the mature peptides.
PTH-related peptide (PTHrP) displays sequence homology with PTH that is limited to the amino-terminal 1-34 region of both peptides. PTHrP was originally identified as the humoral mediator of hypercalcemia of malignancy and is now known to play a number of important physiological roles (e.g., control of endochondral bone development, smooth muscle tone, and morphogenesis of the mammary gland). The PTHrP gene has structural similarity to that of PTH, and the genes are presumed to be derived from a common ancestral gene. This gene duplication event occurred at least five hundred million years ago, as teleosts are known to express homologs of mammalian PTHrP. PTH and PTHrP also display homology to TIP39 (tuberoinfundibular peptide of 39 amino acids), a factor that is expressed in the brain and testes and acts through the G-protein-coupled PTH2 receptor. Recently, TIP39 expression in the testis has been shown to be essential for sperm development. Homology amongst PTH, PTHrP, and TIP39 is reflected in the organization of the genes encoding these polypeptides (Fig. 2).

**FIG. 1.** Phylogenetic analysis of PTH and related polypeptides. Copyright 2004, The Endocrine Society.

**FIG. 2.** Diagrammatic structures of the genes encoding human TIP39, PTH, and PTHrP. Boxed areas represent exons (the 5' end of exon U1 in the TIP39 gene is not known). White boxes denote pre sequences, black boxes are pro sequences, gray stippled boxes are mature protein sequences, and striped boxes are noncoding regions. The small striped boxes preceding the white boxes denote untranslated exonic sequences. The positions of the initiator methionines are also indicated. +1 represents the relative position of the beginning of the secreted protein. Copyright 2002, The Endocrine Society.

**PTH SYNTHESIS AND SECRETION**

There is a single mammalian PTH gene that in humans is present on the short arm of chromosome 11. The primary translation product is the precursor molecule prepro-PTH that includes a 25 amino acid pre sequence, a 6 amino acid pro sequence, and an 84 amino acid mature PTH sequence. The pre sequence functions as a signal sequence that directs the nascent polypeptide to the machinery that transports it across the membrane of the endoplasmic reticulum (ER), where the pre sequence is cleaved. The function of the pro sequence is not as clearly defined, but it seems to be required for efficient ER transport of the polypeptide and may play a role in subsequent events such as protein folding. The pro sequence seems to be cleaved by the protease furin, producing the mature 1-84 PTH polypeptide. Once produced and packaged into secretory vesicles with the parathyroid chief cell, PTH(1-84) is subject to alternative fates. The mature hormone can be secreted through a classical exocytotic mechanism or it may be cleaved by calcium-sensitive proteases present within secretory vesicles, resulting in the production and secretion of fragments of PTH(1-84) that lack the amino-terminal domain and are thus inactive with respect to responses mediated by the PTH1 receptor. Cleavage of circulating PTH(1-84) to carboxyl-terminal fragments can also occur in peripheral tissues such as liver and kidney. Historically, cleavage of PTH(1-84) has been viewed as a mechanism for biological inactivation of the hormone, but there is suggestive evidence that carboxyl-terminal fragments of PTH may display unique biological properties.

**REGULATION OF PTH SECRETION BY EXTRACELLULAR CALCIUM**

The major physiological function of the parathyroid glands is to act as a “calciostat,” sensing the prevailing blood ionized calcium level and adjusting the secretion of PTH accordingly (Fig. 3). The relationship between ionized calcium and PTH secretion is a steep sigmoidal one, allowing significant changes in PTH secretion in response to very small changes in plasma ionized calcium. The midpoint of this curve (“set-point”) is a reflection of the sensitivity of the parathyroid gland to suppression by extracellular calcium.

Alteration in plasma ionized calcium affects the secretion of PTH(1-84) by multiple mechanisms. Short-term increases in extracellular ionized calcium produce increased levels of intracellular free calcium in the parathyroid cell, resulting in activation of calcium-sensitive proteases in secretory vesicles. As a result, there is increased cleavage of PTH(1-84) into carboxyl-
Cells were incubated with indicated levels of calcium, and PTH was determined by radioimmunoassay. [Reproduced with permission from Hormonal Control of Calcium Metabolism, Proceedings of the Seventh International Conference on Calcium Regulating Hormones. Brown EM 1980 Set-point for calcium: Its role in normal and abnormal physiology.]

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FIG. 3. (A) Relationship between PTH secretion and extracellular calcium in normal human parathyroid cells. Dispersed parathyroid cells were incubated with indicated levels of calcium, and PTH was determined by radioimmunoassay. [Reproduced with permission from Brown EM 1980 Set-point for calcium: Its role in normal and abnormal physiology.]

(B) The four parameters describing the inverse sigmoidal relationship between the extracellular calcium concentration and PTH release in vivo and in vitro: maximal secretory rate; slope of the curve at the midpoint; midpoint or set-point of the curve the level of calcium producing 50% of the maximal decrease in secretory rate; minimal secretory rate. Copyright 1983, The Endocrine Society.
others. An important function of CaR in the kidney is to signal the inhibition of calcium reabsorption in the cortical thick ascending limb. This allows plasma calcium to regulate renal calcium excretion independently of PTH, and a reduction in this signaling contributes to the hypercalcemia and hypercalciuria seen in patients with FHH. Although the physiological role of the CaR in other peripheral tissues is not well understood, recent studies with conditional knockout models suggest that the expression of CaR in chondrocytes and osteoblasts is essential for normal endochondral bone development (W. Chang, C. Tu, D. Bikle, and D. Shoback, personal communication).

Several pharmacological agents that interact with CaR have been developed, and these are effective in altering the ability of the CaR to signal. So-called calcimimetic drugs bind to transmembrane regions in the CaR and increase the receptor’s sensitivity to extracellular calcium. This results in an increase in receptor signaling and thus suppression of PTH secretion. Calcimimetic drugs have clinical utility in the medical management of hyperparathyroidism. Calcilytic drugs act as pharmacological antagonists of the CaR, reducing the receptor’s sensitivity to calcium thus increasing the secretion of PTH.

REGULATION OF PTH SECRETION BY 1,25(OH)\(_2\) VITAMIN D

For many years, it has been known that vitamin D deficiency is linked to excessive production of PTH. This is because of reduced suppression of PTH secretion by extracellular calcium and by 1,25(OH)\(_2\) vitamin D. This frequently occurs in the setting of chronic renal failure where 1,25(OH)\(_2\) vitamin D production is diminished, serum calcium is reduced, and phosphate levels are increased. As described below, hyperphosphatemia has an independent effect to increase the secretion of PTH.

The suppression of PTH secretion by 1,25(OH)\(_2\) vitamin D results from the inhibition of transcription of the PTH gene. This seems to involve 1,25(OH)\(_2\) vitamin D–bound interaction of the vitamin D receptor to negative regulatory elements in the PTH gene promoter and 1,25(OH)\(_2\) vitamin D–induced association of the vitamin D receptor with a transcriptional repressor. 1,25(OH)\(_2\) vitamin D and calcium act coordinately to suppress expression of the PTH gene and to inhibit parathyroid cell proliferation.

REGULATION OF PTH SECRETION BY PLASMA PHOSPHATE, α-KLOTHO, AND FIBROBLAST GROWTH FACTOR 23

It has long been known that hyperphosphatemia (as in chronic renal failure) is associated with parathyroid hyperplasia and hyperparathyroidism. This effect of hyperphosphatemia is in part caused by the binding of plasma phosphate to free calcium, which lowers blood ionized calcium, thus stimulating PTH synthesis, secretion, and parathyroid cell number. However, serum phosphate also seems to directly affect the parathyroid gland, increasing PTH synthesis by promoting the stability of PTH mRNA.

In response to hyperphosphatemia, fibroblast growth factor 23 (FGF23) is secreted by osteocytes/osteoblasts and acts on the kidney to inhibit renal phosphate reabsorption. This requires the binding of FGF23 to cognate renal FGF receptors, an interaction that requires a co-factor, namely the transmembrane protein α-Klotho. Interestingly, α-Klotho is also expressed in parathyroid cells, where it may promote PTH secretion through the maintenance of plasma membrane Na\(^{+}/K\(^{-}\) ATPase activity. It has been suggested that α-Klotho serves as a mediator of the effects of plasma phosphate on PTH secretion, although direct evidence is not currently available. Further complicating matters is the observation that FGF23 acts directly on the parathyroid gland to inhibit PTH secretion. The integrated action of phosphate, FGF23, and α-Klotho on the parathyroid gland almost certainly constitutes a new and important physiological mechanism for the control of PTH secretion.

REFERENCES

Chapter 26. Parathyroid Hormone–Related Protein

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INTRODUCTION

In a 1941 case report in the *New England Journal of Medicine*, Fuller Albright first postulated that tumors associated with hypercalcemia might elaborate a PTH-like hormone. (1) Work in the 1980s and 1990s subsequently led to the biochemical characterization of a specific syndrome of humoral hypercalcemia of malignancy (HHM) and the fulfillment of Albright’s predictions by the isolation of PTH-related protein (PTHrP) and the characterization of its gene. (2–6) We now understand that PTHrP and PTH are related molecules that can both stimulate the same type I PTH/PTHrP receptor (PTH1R). (7–9) PTHrP usually serves a local autocrine, paracrine, or intracrine role and normally does not circulate. However, in patients with HHM, PTHrP does reach the circulation and mimics the systemic actions of PTH. Another chapter will discuss malignancy-associated hypercalcemia in detail. This chapter will outline the normal physiology of PTHrP.

Key words: parathyroid hormone–related protein, bone, nuclear transport, carilage, mammary gland, vascular smooth muscle

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