Parathyroid Hormone without Parathyroid Glands

In mammals, PTH is a component in a complex signaling system involving three structurally related ligands and two G protein-coupled receptors, which share significant amino acid sequence homology (Fig. 1). PTH is a peptide hormone comprising 84 amino acids that is made by the parathyroid glands (and to a much smaller extent by the thymus) and acts through the PTH/PTH-related peptide (PTHrP) receptor to regulate the serum calcium concentration. PTHrP is made in virtually all tissues, but exploration of its biological roles has been best studied in the growth plate and the mammary gland. Due to alternative splicing, there are three different forms of PTHrP in humans comprising 139, 141, and 173 amino acids. PTHrP also acts through the PTH/PTHrP receptor, but instead of functioning as a circulating hormone, it is primarily a paracrine/autocrine factor that regulates cellular growth and differentiation (only during lactation and in patients with the humoral hypercalcemia of malignancy syndrome does it function as a hormone).

PTH also activates a second receptor, the PTH-2 receptor. However, only the human PTH-2 receptor is efficiently activated by PTH, whereas the receptor homologs from other species are activated poorly, if at all. It was therefore not too surprising that the primary ligand for the PTH-2 receptor was determined to be a distinct peptide, tuberoinfundibular peptide (TIP39), which is only distantly related PTH and PTHrP (1). The biological roles of this novel peptide are largely unknown, but it seems to be involved in nociception and perhaps in the regulation of some pituitary hormones (2–4). However, intact TIP39 and amino-terminally truncated TIP39 analogs can bind to the PTH/PTHrP receptor, making it possible that this peptide could also modulate actions mediated by PTH or PTHrP.

Fish do not have anatomical structures corresponding to parathyroid glands, and these animals were therefore thought not to produce PTH. However, there was early evidence that certain fish tissues contain PTH-like immunoreactivity (5, 6), and a partial trout peptide with significant amino acid sequence homology to mammalian PTH had been deduced from trout genomic DNA sequences (7). Furthermore, fish have been shown to produce a PTHrP molecule (8), which was not too surprising given the presence of cartilagenous and/or osseous structures in most fish species. Fish PTHrP signals through a receptor that is homologous to the mammalian PTH/PTHrP receptor as shown in zebrafish (zPTH1R) (9). Zebrafish also express proteins homologous to mammalian TIP39 (10) and the PTH-2 receptor (11), and their expression patterns suggest that both proteins have biological roles which may be related to those in humans. Lastly, zebrafish have a third receptor, the PTH3 receptor (zPTH3R), which appears to be activated less efficiently by human PTH than by human PTHrP, and it thus appeared to be a PTHrP-selective receptor (9).

The recent discovery of PTH molecules in fish has provided further insights into this complex system involving multiple receptors and multiple ligands (12, 13). In contrast to mammals, fish appear to have two distinct PTH molecules, PTH1 and PTH2, and both ligands efficiently activate the zPTH1R and the zPTH3R (12, 13). PTH2 is considerably less potent at the zPTH1R than is PTH1, whereas both ligands have similar potency at the zPTH3R. Phylogenetic analyses suggest that PTH1 and PTH2 evolved from a common precursor in fish, likely through a gene duplication event, and a similar mechanism may have led to the development of two PTH/PTHrP receptors, the zPTH1R and the zPTH3R. The appearance of two PTH ligands (13, 14), and possibly even more PTHrP ligands as suggested by the presence of several homologs in fish genomic databases, appears to have occurred after the development of distinct PTH, PTHrP-, and TIP39 molecules. Although there is some indication to suggest that TIP39 may be the basal group from which PTH and PTHrP were derived (10), sequence analysis of the homologs of these peptides from additional species is required to confirm this prediction. Although cDNA cloning from total fish embryos confirmed that both PTH ligands are indeed expressed, the cellular source of these mRNAs and their biological roles remained elusive.

Hogan et al. (14) have now shown interesting expression patterns for PTH1 and PTH2 in zebrafish. For their detailed study, both PTH ligands were cloned from cDNA, expression was verified by in situ hybridization, and the presence of the PTH1 protein product was verified by immunohistochemical studies. Although both ligands were found to be expressed transiently early in development along the forming lateral line, only PTH1 was expressed in brain and neuronal tissue. The lateral line in fish is histologically closely related to the mammalian vestibular apparatus and inner ear, with hair cells embedded in a gelatinous mass (cupula) (15, 16). Expression of the zebrafish homologs of the calcium-sensing receptor and of the transcription factor glial cells missing 2 (gcm-2) (17), important in mammals for the regulation of PTH secretion and for parathyroid gland development, respectively, was not investigated. It is therefore not certain whether the PTH-expressing cells of the lateral line and the identified neuronal structures may represent parathyroid cell equivalents. However, based on their anatomical locations, it would seem unlikely that these sources for fish PTH expression would be related to the regulation of calcium homeostasis. At least for the lateral line, where PTH1 and PTH2 are expressed only transiently, it is more likely that both peptides have as yet unknown developmental roles,

Abbreviations: PTHrP, PTH-related peptide; TIP39, tuberoinfundibular peptide; zPTH1R, zebrafish PTH/PTHrP receptor; zPTH3R, zebrafish PTH3 receptor.

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and PTH1 may serve similar functions in brain and other neuronal tissues.

For example, it is possible that the transient expression of the PTHs is essential for proper orientation of the lateral line. Orientation of the lateral line is critical for its biological function; the sensitive detection of pressure differences along the lateral line allows the fish to determine its orientation in space. PTHs may have regulatory roles in determining this orientation, similar to the role PTHrP assumes in synchronizing proliferation and in forming the columnar arrangement of mammalian growth plate chondrocytes (18, 19). These possibilities could be investigated further by determining whether the zPTH1R or the zPTH3R are also expressed in the same or adjacent cells of the lateral line. Alternatively, both fish PTH molecules may be involved in hormonal signaling from the lateral line to a more distant tissue(s) expressing zPTH1R and/or zPTH3R, in which case PTH peptides should be detectable in the circulation of fish.

Studies in fish that are similar to those presented by Hogan et al. (14) may help elucidate some of the many nonclassical functions that have been ascribed to PTH in mammals, including a role in development of the mammalian vestibular apparatus and inner ear. This structure is related to the lateral line in fish (15, 16) and at least hearing seems to be impaired in some patients with hypoparathyroidism or pseudohypoparathyroidism (20, 21), and in patients with a syndrome comprising hypoparathyroidism, sensorineural deafness, and renal anomalies (22). The finding that PTH1 is expressed in brain and other neural tissues furthermore suggests other biological roles of this peptide in fish, which may provide additional hints to nonclassical functions of PTH in humans.

Further study of the hormonal system in fish, which involves multiple ligands, multiple receptors, and spatially and temporally distinct expression patterns, is clearly needed. Ultimately, these studies may yield further insights into PTH-dependent processes in fish. Such investigations may also help exploring further the role(s) of PTH in mammals that are unrelated to the regulation of mineral ion homeostasis. Because PTH is now being used for the treatment of osteoporosis (23), it may prove important to further define these nonclassical PTH actions. In addition, insights from studies in fish could direct us to human disorders caused by PTH mutations. Mutations in the mature secreted PTH peptide have not yet been identified in humans with hypoparathyroidism; only very few such cases have been associated with mutations in the pre-pro sequence of PTH (24–26). Ablation of PTH in mice has not been noted to cause abnormalities other than those affecting the regulation of calcium and bone metabolism (27). However, subtle changes affecting hearing, balance, or certain brain functions could have been missed in these animals. Experimental animals like fish, which do not appear to require PTH for regulating extracellular calcium concentration, could thus help in identifying disorders related to mutations in the 1–84 region of PTH.

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References

9. Rubin DA, Jüppner H 1999 Zebrafish express the common parathyroid hormone/parathyroid hormone-related peptide receptor (PTHrP) and a novel receptor (PTH3R) that is preferentially activated by mammalian and fugu parathyroid hormone-related peptide. J Biol Chem 274:28185–28190
Duplicate zebrafish pth genes are expressed along the lateral line and in the central nervous system during embryogenesis. Endocrinology 146:547–551


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