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Regulation of Calcium Concentration in Primary and Secondary Hyperparathyroidism

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Abstract

The parathyroid gland is probably the simplest endocrine organ in the body. The only cells of clinical significance are the parathyroid or chief cells. The primary signal that these cells listen to is calcium. Primary hyperparathyroidism is due to a parathyroid adenoma. The most common cause of hypercalcemia in veterinary medicine is hypercalcemia of malignancy associated with variety of neoplasms. Secondary hyperparathyroidism is due to a disease process, most commonly associated with renal and nutritional hyperparathyroidism. Primary and secondary hyperparathyroidism are markedly different in their clinical, laboratory, and pathogenic mechanism.

Introduction

Calcium ion plays key role in many biologic processes including muscle contraction, blood coagulation, enzymatic activity, neural excitability, hormone release, and membrane permeability, in addition to being an essential structural component of the skeleton. To maintain calcium concentration, endocrine control mechanisms have evolved that primarily consist of the interactions of three major hormones, parathyroid hormone, calcitonin, and vitamin D [6]. Other hormones such as adrenal corticosteroids, estrogen, thyroxine, somatotropin and glucagons also contribute to the maintenance of calcium homeostasis [8].

Parathyroid gland in most animal species located in cranial cervical region. The dog and cat have parathyroid gland located within or near the thyroid gland [6]. Other animals have parathyroid glands embedded either in the thymus in young animals or in adipose tissue in adult animals. The parathyroid glands contain a single basic type of secretory cell, the chief cell. The chief cells are in different stages of secretory activity [6]. Inactive chief cells are cuboidal and have uncomplicated interdigitations between contiguous cells. The relatively electron-transparent cytoplasm contains poorly developed electron-dense organelles, and secretory granules are sparse. Chief cells in active stage of the secretory cycle are in the minority in the parathyroid glands of most species. The cytoplasm of active chief cells has an increased electron density due to the close proximity of organelles and secretory granules, increased density of the cytoplasmic matrix, and loss of glycogen particles and lipid bodies. The second cell type in the parathyroid glands of some species is oxyphil cell. These cells are larger than chief cells, and their abundant cytoplasm is filled with numerous large, often bizarre-shaped mitochondria. It has been suggested that oxyphil cells do not have an active role in the biosynthesis of parathyroid hormone. The significance of oxyphil cells in the pathophysiology of the parathyroid gland is not completely understood.

Hormones related to calcium homeostasis

Initial translation product from biosynthesis on ribosomes of the rough endoplasmic reticulum in chief cells is preproparathyroid hormone (prepro PTH) that is rapidly converted to pro PTH by proteolytic cleavage of 25 amino acids from the N-terminal end of the molecule [16]. Enzymes within membranes of the Golgi apparatus cleave a hexapeptide from the N-terminal end of the molecule, forming active parathyroid hormone. Active PTH is packaged into membrane-limited, macromolecular aggregates in the Golgi apparatus for subsequent storage in chief cells. Biologically active PTH secreted by chief cells is a straight chain polypeptide consisting of 84 amino acid residues with a molecular weight 9,500 [18].

Low calcium concentration in serum stimulates the parathyroid cells to undergo hypertrophy and hyperplasia, as well as increasing the production and release of parathyroid hormone [17]. High calcium concentration inhibits the secretion of parathyroid hormone. A change in the total serum calcium concentration of as little as 0.25 mg/dl can stimulate or inhibit the secretion of parathyroid hormone secretion. Concentration of serum calcium does not need to be out of reference range. And elevated blood phosphorus level may lead indirectly to parathyroid stimulation by its ability to lower blood calcium according to the mass-law equation when the serum is saturated with these two ions [5]. Hyperphosphatemia also suppresses the rate of formation of the active form of vitamin D3 (1, 25-dihydroxycholecalciferol) in the kidney, which further contributes to the development of hypocalcemia and parathyroid stimulation [10]. The receptor for the PTH belongs to a family of G protein linked receptors with seven transmembrane spanning domains that activates adenylate cyclase [18].

Parathyroid hormone (PTH) is involved in the fine regulation of blood calcium concentration in mammals. The target cells of the PTH are primarily located in

bone and kidneys [17]. The hormone also indirectly acts in the intestine to maintain plasma calcium concentration sufficient to ensure body homeostasis [16]. The response of bone to PTH is the result of increasing the activity of osteocytes and (indirectly) osteoclasts in existing bone. Osteoclasts are primarily responsible for the catabolization of PTH on bone [6]. Receptors for PTH are not present on osteoclasts but on osteoblasts. The mechanism for stimulation of osteoclasts by PTH are not completely understood, but increased expression of RANK ligand on osteoblasts by PTH appears to induce maturation of osteoclasts from precursor cells [16]. A long term increase in parathyroid hormone secretion may also result in the formation of greater numbers of osteoblasts with a resultant increase in bone formation as well as resorption. However, resorption is usually greater than formation [6].

The PTH has a rapid (5-10 min) and direct effect on renal tubular function, blocking reabsorption of phosphate in the renal proximal tubule and stimulating phophaturia [8]. The ability of PTH to enhance renal absorption of calcium appears to be due to a direct action on distal convoluted tubule. The PTH also regulates the conversion of 25-hydroxycholecalciferol to biologically active 1,25-dihydroxycholecalciferol and other metabolites of vitamin D [10]. The calcium mobilizing and phosphaturic activities of parathyroid hormone may be mediated through the intracellular accumulation of cyclic 3', 5' adenosine monophosphate (cAMP) and cytosol calcium in target cells [17].

Calcitonin which produced from C-cells of thyroid gland and PTH provide a dual negative feedback control mechanism to maintain concentration of calcium in extracellular fluids [6]. Calcitonin is secreted continuously under conditions of normocalcemia, but the rate of secretion is increased greatly in response to elevations in blood calcium. Hyperplasia of C cells occurs in response to long-term hypercalcemia. Calcitonin exerts its function by interacting with target cells primarily in bone and kidney. The actions of PTH and calcitonin are antagonistic to bone resorption but synergistic with decreasing the renal tubular resorption of phosphorus. The action of calcitonin is not dependent on vitamin D. Vitamin D3 (Cholecalciferol) also involved in regulation of calcium metabolism and stimulates both calcium and phosphorus absorption from the gastrointestinal tracts and Ca and P reabsorption from the bones without a concurrent effect of the kidneys [16].

Primary hyperparathyroidism

Chief cell hyperplasia may be in a distinctly focal or multifocal distribution, which have an increased number of closely packed chief cells, often with an expanded cytoplasmic area. The foci are not encapsulated and are poorly demarcated from adjacent parenchyma [6]. There may be slight compression of adjacent chief cells around larger areas of focal hyperplasia.

Uniform enlargement of all parathyroid glands is due to both hypertrophy and hyperplasia of chief cells and can be induced by chronic renal failure and long-term dietary imbalances. There is not a peripheral rim of compressed atrophic parathyroid parenchyma as around a functional adenoma. The chief cells are packed together often with indistinct cells boundaries. In other hyperplastic parathyroids the chief cells form distinct acinus-like structures.

Primary parathyroid hyperplasia has been described in German shepherd pups associated with hypercalcemia, hypophosphatemia, increased immunoreactivity to parathyroid hormone, and increased clearance of phosphate in the urine [11]. The pups showed stunted growth, muscular weakness, polyuria, polydipsia, and a diffuse reduction in bone density. Lesions included nodular hyperplasia of thyroid C cells and widespread mineralization of lungs, kidney, and gastric mucosa. The disease was inherited as autosomal recessive trait.

Functional adenomas of parathyroid glands are reportedprimarily in older animals, particularly dogs [2, 7]. Tumors of parathyroid chief cells do not appear to be sequelae of long-standing secondary hyperparathyroidism of renal or nutritional origin. Histopathological demonstration of compressed rim of parathyroid parenchyma and a partial to complete fibrous capsule in an enlarged gland lead to diagnosis of adenoma rather than chief cell hyperplasia. Parathyroid carcinomas are larger than adenomas, invade the capsule and adjacent structures, and may metastasize to regional lymph nodes and lung [6]. They are rare in animals.

Initially the excretion of phosphorus and retention of calcium are enhanced. A prolonged increased secretion of parathyroid hormone accelerates osteoclastic bone resorption, and generalized fibrous osteodystrophy results in [6]. Cortical bone is thinned due to increased resorption by osteoclasts stimulated by autonomous secretion of PTH. Fractures of long bone and compression fractures of vertebral bodies may occur [7]. Facial hyperostosis due to extensive osteoblastic proliferation and deposition of poorly mineralized osteoid, and loosening or loss of teeth also has been observed in dogs with primary hyperparathyroidism. Hypercalcemia results in anorexia, vomiting, constipation, depression, polyuria, polydipsia, and generalized muscular weakness due to decreased neuromuscular excitability. Dogs with primary hyperparathyroidism have greatly elevated blood calcium and low blood phosphorus.

Pseudohyperparathyroidism (Humoral Hypercalcemia of Malignancy)

Humoral hypercalcemia of malignancy (HHM) is a cancer-associated hypercalcemia that is induced by the secretion of humoral factors which have effects distant to the site of the neoplasms [6]. Multiple humoral factors have been associated with HHM, including parathyroid hormone, parathyroid hormone-like proteins, cytokines, steroids such as 1,25 dihydroxycholecalciferol, and prostaglandins. The neoplasms associated with hypercalcemia include lymphoma in several animal species, apocrine gland adenocarcinoma of the anal sac, multiple myeloma and carcinomas (e.g., squamouse cell carcinoma, nasal carcinoma, ovarian stromal tumor, thymoma) [1, 3, 9, 12, 13, 15]. Hypophophatemia may be severe but serum phosphorus concentration may increase after the onset of nephrocalcinosis and renal failure. Concurrent lesions with this are atrophy of the parathyroid gland and hyperplasia of thyroid C cells. Serum PTH concentration is decreased. Lesions are similar to those described in primary hyperparathyroidism but are milder.

Hyperparathyroidism secondary to nutritional imbalance

Nutritional secondary hyperparathyroidism occurs commonly in cats, dogs, some nonhuman primates, horses, domestic and captive birds, and reptiles. The increased secretion of PTH is response to the diets with either a low calcium content or an excessive oxalate or phosphorus content with normal or low calcium content. Inadequate vitamin D3 also causes lesions of hyperparathyroidism in some species, including nonhuman primates and reptiles [6]. These dietary imbalances cause hypocalcemia, which results in parathyroid stimulation. Chief cells undergo hypertrophy and eventually hyperplasia.

Animals with nutritional hyperparathyroidism exhibit normocalcemia and mild to moderate hyperphosphatemia. This condition can be confirmed by increased urinary excretion of phosphorus. Skeletal lesions are similar to described in primary hyperparathyroidism [8].

Hyperparathyroidism secondary to Renal Disease

Secondary hyperparathyroidism as a complicationof chronic renal failure is characterized by excessive production of hormone in response to chronic hypocalcemia [4, 8]. When the renal disease reaches the point at which there is a significant reduction in the glomerular filtration rate, phosphorus is retained and progressive hyperphosphatemia develops, and it may contribute to parathyroid stimulation by its ability to lower blood calcium [16].

Impaired intestinal absorption of calcium due to an acquired defect in vitamin D metabolism may also play a significant role in the development of hypocalcemia in chronic renal insufficiency and uremia. Chronic renal disease impairs the production of 1,25-dihydroxycholecalciferol by the kidney and thereby diminishes intestinal calcium transport and increases mobilization of calcium from the skeleton [14].

Parathyroid glands undergo marked chief cell hyperplasia, and the bones have varying degrees of generalized fibrous osteodystrophy [6]. Chief cells in the parathyroid glands of dogs with chronic renal disease areprimarily in the actively synthesizing stage of the secretory cycle. The animals exhibit hypocalcemina and hyperphosphatemia, marked azotemia, inability to concentrate urine, nonregenerative anemia etc. Younger animals have soft flexible bone "rubber bone" (fibrous osteodystrophy) [6].

Assessment of parathyroid gland

In response to hypocalcemia, chief cells undergo hypertrophy and hyperplasia. The expanded cytoplasmic area is lightly eosinophilic and vacuolated, and perivascular areas are narrow in a hyperplastic parathyroid. In response to hypercalcemia the cytoplasmic area of chief cells is decreased and more densely eosinophilic, often with a widening of intercellular and pericapillary spaces [6].

Parathyroid hormone in the circulations of animals can be measured by sensitive radioimmunoassays (RIA) or immunoradiometric assays (IRMA) [19]. Since the N-terminal end of molecule is highly conserved between human and all mammalian species thus assays directed against this end of PTH are the most sensitive and accurate in assessing parathyroid function.

Conclusion

Parathyroid function is integrated with thyroid C cell function and vitamin D metabolism in the regulation of calcium and phosphorus homeostasis. Altered serum calcium and phosphorus concentrations are often encountered coincidentally during screening with biochemical profiles and in animals with clinical signs of altered calcium metabolism. In animals with hyperparathyroidism, primary and secondary hyperparathyroidism should be differentiated based on history, clinical signs, and biochemical profiles.

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