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Review Article

Hylonome

Parathyroid hormone and plasma calcium control: an editorial

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Abstract

The purpose of this report is to examine the various processes by which parathyroid hormone might control the ionic calcium concentration of plasma and extracellular fluid, and to emphasize the need for study of the maintenance of plasma calcium in the absence of the parathyroid glands. The report discusses mechanisms to explain the control of extracellular calcium and proposes new approaches to the study of calcium homeostasis.

Keywords: Parathyroid Hormone, Blood Calcium, Calcium Homeostasis, Calcium-Phosphates, Lining Cell Complex

Introduction

In 1948 Albright and Reifenstein published a short book entitled "The Parathyroid Glands and Metabolic Bone Disease"[1]. In the Introduction, they made the interesting statement paraphrased as follows: While a lot is yet to be learned about the actions of the hormones of the body, the one whose actions are most clearly understood is parathyroid hormone. They proposed that the hormone controlled blood calcium concentrations by increasing renal phosphate excretion. The basis of their thesis was their contention that plasma, at pH 7.4, was saturated with calcium phosphate ($CaHPO_4$). Since the solubility product of calcium times phosphate is a constant, it would follow that any removal of phosphate from plasma by renal excretion would allow the entrance of additional calcium into plasma. The net result would be an increase in plasma calcium caused by the fall in plasma phosphate. An increase in renal phosphate excretion was the first delineated action of parathyroid hormone and has been recognized as one of its classic actions. This explanation for the control of plasma calcium had to be discarded when it was shown that plasma is not saturated with $CaHPO_4$ and that the parathyroid glands were still functional in nephrectomized rats maintained by peritoneal lavage[2]. In other words, parathyroid hormone maintained blood calcium in the absence of the kidneys, and parathyroidectomy of these animals was followed by a fall in plasma calcium that could be reversed by injection of parathyroid extract[3]. This evidence also negates a later suggestion by Nordin and Peacock[4] that the method by which plasma calcium concentrations were controlled was through parathyroid-induced increases in renal reabsorption of calcium. While the kidneys are not essential for the action of parathyroid hormone, the two actions of parathyroid hormone on the kidney, the classical phosphaturic effect along with the reabsorption of calcium, help decrease the amount of hormone needed to make corrections in plasma calcium concentrations.

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Osteoclastic activity and calcium homeostasis

Over time the explanation of parathyroid control of plasma calcium given in the previous section was replaced by the concept that the hormone controlled blood calcium levels by increasing the rate of bone resorption by osteoclasts. It is well known that parathyroid hormone increases both the number and activity of osteoclasts, despite the fact that these cells do not have parathyroid hormone receptors. Thus, it seemed logical to conclude that the action of these cells provided the calcium to maintain blood calcium concentrations and this explanation of parathyroid hormone action is still widely held. As with the renal phosphate theory, an end organ response was automatically accepted as the basis for a known physiological action. However, it can be readily shown that under physiological conditions the amount of bone resorbed by osteoclasts is

insufficient to provide the calcium required to maintain normal blood levels of calcium[5].

Further evidence to exclude the osteoclast as a primary mediator of blood calcium comes from the absence of hypocalcemia in patients with osteopetrosis and studies on and clinical use of the bisphosphonates to inhibit bone resorption. It has long been known that the bisphosphonates are potent inhibitors of bone resorption[6]. Although clinical use is not associated with extended hypocalcemia[7], bisphosphonates decrease serum calcium in patients with hypercalcemia and transiently decrease serum calcium in normocalcemic patients with osteoporosis[8,9]. In early animal studies with bisphosphonates, no hypocalcemia was observed at any dosage for 9 months of treatment[10]. More recently, Jara et al. elegantly showed that biphosphonates caused significant decreases in bone resorption at a histological level, whereas they found no effect on parathyroid hormone action to normalize plasma calcium[11].

Bronner and Stein[12,13] proposed an alternative model to explain parathyroid hormone action to control blood calcium. They proposed that parathyroid hormone causes shrinkage of osteoblasts thereby exposing low-affinity calcium-binding sites, which results in less calcium bound. They also propose an associated expansion of osteoclasts, which block high affinity calcium-binding sites. Both actions contribute to the increase in calcium in extracellular fluid. Experimental evidence to support their hypothesis is needed. Unfortunately, these investigators have not taken into account the lining cells that cover the majority of bone surfaces[14]. The lining cells are capable of changing shape but are not in physical contact with bone surfaces. These investigators did not take into consideration in this theory the paucity of osteoclasts in normal physiology nor the maintenance of plasma calcium control when osteoclast numbers are reduced to near zero in osteopetrotic patients.

Two previous publications, VanderWiel and Talmage, 1979; and Talmage, 1995 [15,16], present further evidence against osteoclastic activity controlling plasma calcium concentrations. Their proposal that osteoclastic stimulation by parathyroid hormone should be separated from its ability to control plasma calcium concentrations does in no way diminish the importance of parathyroid stimulation of osteoclast numbers and activity in bone remodeling. In fact, from a clinical point of view, this action may easily be considered an equally important action of the hormone.

The important contributions of Harold Frost have stimulated research on the relation of osteoclasts to osteoblasts and the overall importance of osteoclasts in bone remodeling and renewal[17]. In the adult mammal, particularly in the human, essentially all osteoclastic activity is linked to osteoblastic activity in the same region. Under ideal conditions old bone resorbed by osteoclasts is subsequently replaced by new bone laid down by osteoblasts, with no net change in total bone content. However, frequently the two systems do not work at the same efficiency. There appear to be situations under minimal parathyroid hormone stimulation in which more bone is laid down than resorbed by osteoclasts. This has led to the concept of the anabolic activity of the hormone, an action that has been examined over the years[18]. However, with increased parathyroid activity, the balance is most often in the other direction; namely more bone is resorbed than laid down. Often, in bone remodeling, the osteoblasts are unable to keep up with the osteoclasts. Such situations lead to the bone pathological problems associated with disorders such as hyperparathyroidism, the gradual loss of bone in post-menopausal women, and the bone destruction in Paget's disease. Only in extreme hyperparathyroidism does this imbalance affect plasma calcium control[19].

Parathyroid action on bone surfaces

Over the last fifteen to twenty years most of the emphasis in parathyroid research has centered on the connection between osteoblast and osteoclast function and the function of parathyroid hormone and parathyroid hormone related peptide[20-23]. Only a few reports have involved studies on parathyroid control of plasma calcium concentrations. Two groups, one headed by Neuman and the other by Talmage, were early advocates for the action of parathyroid hormone on bone surfaces in control of blood calcium concentrations. Among Neuman's many studies were experiments to determine if a bone fluid compartment existed, separated from the general extracellular fluid compartment[24], and experiments to ascertain if the pH of bone fluid was different from that of plasma[25]. These results established that bone fluid was a part of the extracellular fluid and not a separate compartment. They also found that the pH of this fluid was neutral (pH=7.4). Because of the large difference between the solubility of tertiary calcium phosphate [$Ca_3(PO_4)_2$] and that of secondary calcium phosphate, Neuman also studied the solubility and forms of calcium in the hydration layer of bone mineral[26]. He hoped to identify intermediate calcium phosphate compounds with varying solubilities. The presence of these intermediaries would explain the ability of plasma to contain calcium in quantities so much greater than the solubility of bone hydroxyapatite. Unfortunately, his untimely death terminated these incomplete studies.

Talmage's efforts dealt primarily with a search for an intracellular calcium transport system that parathyroid hormone could stimulate to increase the return of calcium from bone surfaces to plasma[27]. These studies utilized radioisotopes of calcium and phosphate so that the movement of these ions both at the surface and interior of bone could be measured. The results of these studies were inconclusive because of the tremendous gradient of calcium movement into bone (in humans over 6 g per day). Talmage and Meyer concluded that the metabolic energy needed for active movement of sufficient calcium from bone cells to plasma was too great for a cell-mediated process to be a viable mechanism to maintain calcium homeostasis[27]. In more recent years, Parfitt has emphasized in various reports that all bone surfaces are involved in the control of blood calcium, but concluded that osteoclasts still played an

important secondary role in this function[28,29].

While the precise mechanism of parathyroid action on bone surfaces is still unknown, considerable data have been reported demonstrating that parathyroid hormone acts on bone surfaces. These studies were initiated by Matthews and colleagues[30]. Matthews was one of the pioneers in developing the technique to study non-decalcified bone at the ultrastructural level. From his studies and those of his colleagues, particularly Norimatsu et al.[31] and VanderWiel[32], it was shown that both parathyroid hormone and calcitonin were able to produce specific changes in the structures of the lining cell-osteocyte complex. Lining cells (and osteoblasts) responded rapidly to small doses of parathyroid hormone. In addition, parathyroid hormone as well as calcitonin also produced changes in the extracellular environment at bone surfaces. Their studies also confirmed that lining cells, which may include active osteoblasts, do not form a tight membrane covering bone surfaces. These cells were separated by relatively open channels. Such channels allowed ready interactions between extracellular fluid and the bone surfaces.

In summary, it has been clearly demonstrated that both parathyroid hormone and calcitonin affect intracellular and extracellular aspects of the environment at bone surfaces. How these actions relate to the control of plasma calcium levels is yet to be precisely described.

Control of plasma calcium in the absence of parathyroid glands

In 1933 Hastings and Huggins[33] reported the following study. Quantities of blood were removed from both control and parathyroidectomized dogs. Calcium was removed from the blood by precipitation with lead phosphate. Re-infusion of this calcium-free blood resulted in an immediate, significant lowering of serum calcium concentrations in both groups. However, serum calcium rapidly returned to original levels (10 mg/100 ml and 7.5 mg/100 ml, respectively) in both groups of dogs. In other words, there was a degree of control of serum calcium concentrations in parathyroidectomized as well as parathyroid intact animals. This ability of animals, in the absence of parathyroid hormone, to maintain set serum calcium concentrations has been confirmed by numerous investigators, including reports by Copp[34] with EDTA infusion and by Talmage et al.[3] with continuous peritoneal lavage.

The magnitude of the difference in serum calcium concentrations (which is in the range of $1x10^{-3}$ M) compared to the solubility of hydroxyapatite crystals ($1x10^{-4}$ M), the form of tertiary calcium phosphate found in bone, is very striking. Even in the parathyroidectomized state, there is a ten-fold increase in the serum level of calcium above the solubility of tertiary calcium phosphate. The difference in the serum calcium level between parathyroidectomized animals ($1x10^{-3}$ M) and parathyroid intact controls ($1.5x10^{-3}$ M) is merely 50%. Thus, it seems obvious that the major mechanism controlling serum calcium occurs in the absence of parathyroid hormone.

To gain further insight into the problems mammals face in the absence of parathyroid glands, Talmage's group extended (ref. 2 and unpublished data) the studies of Hastings and Huggins. They examined the capacity of tertiary calcium phosphate (including commercial hydroxyapatite) and finely cut, devitalized bone chips to lower serum calcium. Serum samples taken from a variety of mammals including humans were tested. All agents removed calcium and phosphate from the serum samples[33]. In contrast, when secondary calcium phosphate was added to rat serum, both calcium and phosphate contents were increased[2]. Interesting results were obtained when living bone slices were incubated in serum taken from the same group of mammals. Bone samples from parathyroid intact animals were incubated both in normal and decalcified serum and maintained under controlled pH and temperature. The calcium concentration of normal serum fell slightly over the first four hours while that of decalcified serum rose over the same period. By the end of a four-hour incubation period, the calcium concentrations were approximately the same in all samples. If the bone used was taken from a parathyroidectomized animal, the net results were similar but with slightly lower ending calcium levels[35]. These results show that if mammalian blood were to come into direct contact with any form of tertiary calcium phosphate, most of the calcium would be rapidly removed. However, with or without the parathyroid glands, living bone is able to resist this withdrawal and allows blood calcium concentrations to be maintained well above the solubility of tertiary calcium phosphate. It certainly can be concluded that, while parathyroid hormone is essential for elevation of serum calcium concentrations from low to normal levels, the primary process for retaining calcium in serum does not require the presence of the parathyroid glands. However, these observations do not deny the possibility that minute amounts of parathyroid-like hormone may be secreted by other glands[36], or that other hormones such as adrenal cortical hormones may affect the setting of the basic serum calcium concentration[37].

Have possible physical chemical processes been overlooked?

In the preceding discussion, the assumption is that what has been overlooked is a possible primary role of physical chemical processes in setting plasma calcium levels. Such processes would require minimal expenditures of metabolic energy. To examine this possibility, it is necessary to review two unique properties of ionic calcium. The first property concerns the varying forms and solubilities of calcium phosphate compounds; and the second, the striking ability of calcium to complex reversibly with proteins. Could these two characteristics work together in the unique environment of bone surfaces and their adjoining cells to provide control of the concentrations of calcium in extracellular fluids?

The solubility characteristics of secondary and tertiary

calcium phosphate were discussed above. Hydroxyapatite, the major inorganic component of bone, is the crystallized form of tertiary calcium phosphate and has the same solubility. Neuman and Neuman[38] stressed the attachment of water to bone mineral, which he called the hydration shell. There are several forms of hydroxyapatite in which each molecule contains from 2 to 5 molecules of water. This hydration layer is the interface between the crystalline stage and the surrounding fluid. Common cations such as Na^+ and K^+ as well as heavy metals are associated with bone through this hydration layer.

The complexing of calcium to proteins is very important both intra- and extracellularly. The best example intracellularly is its role in muscle contraction. The rapidly reversible complexing of calcium to troponin changes the conformation of this protein permitting contraction. These changes occur by increasing the intracellular calcium ion concentration from $1x10^{-7}$ M to $1x10^{-6}$ M and back in microseconds. In addition, calcium complexed to intracellular proteins is a prominent control mechanism for intracellular signaling. Calcium is also well known as an intracellular second messenger itself.

Extracellularly, calcium complexes to cell membranes in equilibrium with the ionic concentration in body fluids. Here, for the most part, equilibration is slow. However, rapid equilibration does occur between soluble plasma proteins and ionic calcium. The amount of calcium attached to proteins in plasma is in direct proportion to the ionic concentration of calcium. The speed of equilibration is so rapid that measurement of changes in total calcium in plasma are used as accurate estimates of small changes in ionic calcium.

The intriguing question is, "Could a situation exist where the reverse occurs? In other words, could the amount of calcium complexed to proteins determine the ionic concentration of the fluid with which it is in contact?" The most likely site for this interaction to occur in mammals is the bone surface.

A new approach to the study of calcium homeostasis

As a basis of this study, the unique properties of the bone surface are important. There are four major components: 1) Hydroxyapatite is embedded in and surrounded by collagenous matrix. The properties of hydroxyapatite have been discussed above. 2) A layer of cells on the surface of bone that communicate with interior cells (osteocytes) by protoplasmic extensions. According to VanderWiel,[32] all bone surfaces of non-decalcified sections examined under high magnification were covered by lining cells. Recently, Miller and Jee have provided an excellent review of the morphology and function of the lining cells[14]. Also, Chow and Chambers[39] reaffirmed that bone surfaces were covered by an "organic" layer of cells and protein. These cells appear to have the same origin as osteoblasts and may or may not have the ability to synthesize collagen. They are responsive to both parathyroid hormone and calcitonin[31]. 3) The fluid component of bone is part of the extracellular fluid compartment that constantly equilibrates with plasma. This component is responsible for bringing calcium to bone mineral and calcium from bone mineral to extracellular fluid. According to Neuman and Neuman[25], the pH of this fluid is 7.4. 4) A component not mentioned earlier is the layer of non-collagenous proteins found on bone surfaces. These proteins are believed to play an important role in matrix and mineral organization. While relatively large amounts of these proteins are present, their precise functions are still unclear even after years of study[40]. Of the dozen or more proteins that have been identified, many have a high affinity for calcium, especially when it is in the form of hydroxyapatite. They also contain regions with specific binding sequences and numerous sites for phosphorylation. Two of these proteins, osteonectin and osteocalcin are recognized as calcium binding proteins[41]. Stimulation of bone in vitro with parathyroid hormone, vitamin D, or mechanical force induces changes in synthesis and turnover of these proteins[42-44]. Clearly, there are potential roles for one or more surface proteins in the regulation of ion movements from bone to extracellular fluid. This possibility is discussed below.

It can be assumed that the functions of these four components are interrelated. But what is the specific relationship of bone surface proteins to the hydration layer of hydroxyapatite? Is it possible that all or some of these proteins are kept saturated with calcium by their communication with bone mineral through the hydration shell? If so, they could be the proteins continuously complexed with calcium. This complexed calcium would rapidly equilibrate with that in the extracellular fluid which bathes bone surfaces. If this were the case, the amount of exchangeable calcium on these proteins could determine the ionic calcium content of plasma. Bronner and Stein[12, 13] suggested that changes in the Km of the bone calcium binding sites alter the levels of exchangeable calcium in extracellular fluid. They propose that these changes can be explained in one of two ways: a single class of binding sites whose Km is altered simultaneously and rapidly; or two classes of binding sites that have different Km's, e.g., high or low. They have opted for the second possibility, discussed earlier, as the more likely model to explain hormonal activity.

We believe that the exchangeable calcium to maintain extracellular calcium requires continuous movement of calcium from fluid to bone mineral, from bone mineral to protein, and from protein to fluid. Such a mechanism could account for the movement of a large amount of calcium (estimated to be 6 g per day in humans) transferred daily in and out of bone in the living mammal. Further, this type of process would explain why the concentration of calcium present in plasma in the absence of the parathyroid glands is higher than that due purely to the solubility of hydroxyapatite.

Our current hypothesis is that parathyroid hormone acts through the extensive lining cell network. Thus, these cells

activate a process that increases the exchangeable calcium complexed to surface proteins. Rapid equilibration leads to elevation of the calcium ion concentration of extracellular fluids. These effects could be mediated by the movement of phosphate in a manner similar to the action of parathyroid hormone on the kidney. In this regard, Norimatsu et al.[31] have reported that parathyroid hormone decreased the amount of phosphate on bone surfaces. Also, Jara et al.[11] reported that marked hypercalcemia and a reduced response to parathyroid hormone were produced in rats maintained on a phosphate deficient diet. Clearly, the results of these experiments suggest a unique role for phosphate in calcium homeostasis.

While the role of parathyroid hormone in such a process is still in the conjecture stage, the hypothesis put forth here provides a reasonable mechanism for the control of calcium homeostasis. For proof of this hypothesis the unique relationship of bone surface proteins to underlying hydroxyapatite must be established. It is hoped that this editorial will stimulate investigators to further examine the mechanisms of maintenance of blood calcium.

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