Magnesium Relations with Parathyroid Hormone, Calcitonin and Bone

By *Frank W. Heaton*

Department of Biological Sciences, University of Lancaster, Lancaster LA1 4YQ, England

Zusammenfassung

Die Parathyreoidhormonsekretion reagiert auf Veränderungen in der Plasma-Magnesium-Konzentration und kann eine Homöostasekontrolle des Magnesiumstoffwechsels hervorrufen durch seine Wirkung auf den Knochen, in dem die Magnesiumreserven des Körpers liegen, die Nieren und den Dünndarm. Diese Kontrolle unterstützt seine Wirkung auf die Kalziumhomöostase. Bei schwerem Magnesiummangel verschwindet diese Beziehung, und es entstehen verschiedene Nebeneffekte auf Kalzium.
Kalzitonin steht wahrscheinlich in keiner direkten Beziehung zum Magnesiumstoffwechsel.

Schlüsselwörter:
Magnesium, Parathyroidea, Kalzitonin, Knochen, Kalziumhomöostasis.

Summary

Parathyroid hormone secretion responds to variations in plasma magnesium and it has the potential to operate a homeostatic control on magnesium metabolism through its actions on bone, which provides the magnesium reserve in the body, kidney and small intestine. Any such control must be subsidiary to its function in calcium homeostasis, but these relations breakdown in severe magnesium deficiency, producing secondary effects on calcium. Calcitonin probably has no direct relation with magnesium metabolism.

Keywords:
Magnesium, Parathyroid hormone, Calcitonin, Bone, Calcium homeostasis.

Résumé

Les sécrétions des hormones du parathyroide sont sensitives aux variations dans le magnésium du plasma, et ils peuvent régler l'homéostasie du magnésium en conséquence de ses actions sur les os, d'où viennent les réserves de magnésium pour tout le corps, sur les reins et sur l'intestin grêle. Un tel contrôle doit être inférieur à la fonction du parathyroidea dans l'homéostasie du calcium, mais ces relations ci s'arrêtent dans le cas d'une insuffisance de magnésium et ils produisent des effets auxilliaires sur le calcium. La calcitonine n'a probablement aucune relation directe au métabolisme du magnésium.

Mots-clefs:
Magnésium, Parathyroidea, Calcitonine, Os, Calcium homéostasie.

Any attempt to understand the regulation of magnesium metabolism requires consideration of the utilization of ingested magnesium, its excretion in the urine, and the distribution of magnesium in the body between extracellular fluid, the intracellular compartment and the skeleton. The magnesium concentration in the plasma of man and higher animals varies slightly between about 0.8 and 1.0 mM in different species, but it normally remains remarkably constant within any one species. The extracellular fluid, however, only contains about 1% of the total body magnesium. About 34% of the total occurs in the cells of the body and the remaining 65% is found within the skeleton.
Thus bone contains the largest compartment of body magnesium but although part of this forms a reserve of the metal, the level in plasma seems to be finely regulated by the balance between intestinal absorption and urinary excretion in the normal individual. An extensive review of metabolic balance measurements in human subjects indicates that intestinal absorption is a linear function of dietary magnesium intake, with a net absorption of 35 —40% of intake under normal conditions [96]. Regulation of urinary excretion is therefore the principal mechanism controlling total body magnesium and there is a close positive correlation between the intestinal absorption and urinary excretion of magnesium over the normal range of human intake [83].

Magnesium in bone

Experimentally induced magnesium deficiency in laboratory animals has shown that part of the skeletal magnesium forms a reserve which can be mobilized during deficiency to help meet the requirements of other tissues. The extent of this labile reserve varies with the age of the animal and falls from about 30% of the total bone magnesium in young rats [23] to 17% in adult animals [54]. More recent studies with specimens from a variety of patients having wide variations in serum magnesium level confirm that the magnesium concentrations in bone and serum rise and fall together, but the magnesium in muscle is independent of these levels [2].
The chemical form of magnesium in bone is still not defined although it is clear that two types of pool occur. The investigations of Alfrey and Miller [1] with human bone indicate that about 30% of the total magnesium is present in a surface limited pool, either dissolved in the hydration shell or adsorbed on the surface of the hydroxyapatite crystals, whereas the remaining 70% forms an integral part of the bone crystal. This surface pool of magnesium exchanges fairly rapidly with the magnesium in plasma, and although its size is now thought to be smaller than the 60 —70% of the total previously estimated from chemical fractionation of bone [39], it is in accord with the proportion of magnesium lost from bone during deficiency in experimental animals. The deeper pool is believed to be deposited at the time of bone formation and it is probably released only on resorption of the bone.

A close positive correlation between the magnesium concentrations in serum and bone has been established in calves [91], rats [54], pigs [60] and humans [2]. Studies with young chick bone incubated in vitro show that the magnesium concentration in bone depends only on the magnesium concentration in the surrounding medium, irrespective of whether the bone is living or dead [11, 77]. This suggests that the blood-bone equilibrium for magnesium is largely physico-chemical in nature. However the release of magnesium from bone treated with parathyroid hormone is inhibited in a magnesium-free medium [77] and this is consistent with the effects of parathyroidectomy in vivo which are considered in the next section. Parathyroid hormone probably influences the blood-bone exchange of magnesium in the living animal and the hormone presumably acts by influencing the metabolic activity of bone cells.

Relation with parathyroid hormone

Many observations indicate that parathyroid hormone affects magnesium metabolism. Injection of different parathyroid preparations has been found to raise the plasma concentrations of both calcium and magnesium in dogs [24, 32], rats [18, 52] and hamsters [37], a much more sensitive response always being obtained with parathyroidectomized rather than intact animals. Conversely parathyroidectomy significantly lowers the plasma magnesium concentration in rats, irrespective of whether they are on a diet of normal or low-magnesium content [19, 38, 58]. The changes in magnesium are much smaller than the accompanying changes in calcium concentration and this probably explains why disturbances in blood magnesium are not observed in most patients with parathyroid disorders. Serum magnesium is usually normal in primary hyperparathyroidism [41, 45] and a marked fall after partial parathyroidectomy is observed only in patients with extensive bone disease [36, 40], which is attributed to remineralization of the skeleton.

Detailed investigations of renal physiology show that infusion of parathyroid hormone into parathyroidectomized animals increases the tubular reabsorption of magnesium as well as calcium in rats [48, 75] and hamsters [37]. Conversely thyroparathyroidectomy reduces the fractional tubular reabsorption of both metals [14]. These findings appear to conflict with the observation that many patients with primary hyperparathyroidism tend to excrete increased amounts of magnesium in the urine [36, 40] and that the urinary excretion usually falls after partial parathyroidectomy [45], but the explanation lies in the distinction between the primary and secondary effects of the hormone. Its direct action on the renal tubules is clearly to increase the reabsorption of magnesium and calcium, but the parallel action of the hormone on bone causes hypercalcaemia. The increased filtered load of calcium in hyperparathyroidism outweighs the direct action on the kidney and causes a secondary increase in the urinary excretion of both calcium and magnesium, the magnesium excretion being increased by competition with calcium for at least some of the tubular reabsorptive sites.

Parathyroid hormone seems to enhance the transport of magnesium as well as calcium in the small intestine, similar to its action on kidney. Experimental studies with ligated loops of rat intestine show that magnesium absorption is increased by previous injection of the hormone [49] and the faecal excretion of magnesium tends to increase after partial parathyroidectomy in patients with hyperparathyroidism [40].

The close positive correlation between the magnesium concentrations in plasma and bone has been discussed above, and there is good evidence that parathyroid hormone influences this relationship in vivo. Parathyroidectomy lowers the magnesium concentration in plasma and raises the concentration in bone compared with intact control animals when both are receiving magnesium-deficient diet [38, 58]. With animals on a normal magnesium intake parathyroidectomy also raises the magnesium concentration in bone but has no significant effect on the plasma level [43, 44], and it is well established that injection of parathyroid preparations causes resorption of bone with the release of both calcium and magnesium to the plasma [18].

Parathyroid hormone therefore raises the magnesium concentration in plasma by accelerating bone resorption, increasing renal tubular reabsorption of magnesium and enhancing its intestinal absorption, in precisely the same way as it acts on calcium metabolism. This raises the question of whether the hormone exerts a homeostatic control on magnesium as well as calcium, which would require a response by the parathyroid gland to variations in the level of circulating magnesium.

The first evidence that magnesium deficiency stimulates parathyroid gland activity was circumstantial in nature and depended on the demonstration that parathyroidectomy prevents some of the disturbances in calcium metabolism that occur in magnesium-deficient rats [30, 38, 61]. Application of the radioimmunoassay for parathyroid hormone has now provided direct evidence of an inverse relationship between the magnesium concentration in plasma and the secretion of the hormone. Acute studies initially showed that perfusing goat and sheep parathyroid glands with blood of low-magnesium content increases the concentration of hormone in the plasma of blood leaving the gland and conversely perfusing with blood of high-magnesium content lowers its concentration in the venous outflow from the gland [13]. The relationship has been confirmed in longer term studies with patients receiving haemodialysis for chronic renal failure. Raising the dialysate magnesium level for a period of two months lowers the parathyroid hormone concentration in serum and lowering the dialysate magnesium increases the hormone concentration [73, 74].

Parathyroid tissue cultured in vitro responds in a similar way to changes in magnesium concentration within the incubation medium over the physiological range. Lowering the concentration of magnesium or calcium increases the rate of hormone release and raising the concentration of either metal decreases it [12, 62, 94]. However it is worth noting that with very low levels of magnesium in the medium the response is reversed and the release of hormone reduced [94]. Attempts to distinguish between the possible effects of the two metals on the synthesis and secretion of parathyroid hormone, by measuring the incorporation of labelled amino acids from the medium, indicate that calcium influences the rates of both synthesis and secretion, whereas magnesium only appears to influence the secretion process [33, 35].

The relation between magnesium and parathyroid hormone therefore fulfils all the criteria of a negative feedback process, which is necessary for homeostatic control, but two reservations have to be expressed. The relations reviewed so far apply under normal conditions but there is a considerable amount of evidence, to be considered in the last section, that these breakdown during severe magnesium deficiency, and it is therefore important to distinguish between physiological and pathological states. The second point is that even though the potential for homeostatic control exists this does not prove that it is of practical significance even under physiological conditions.

Although the effects of magnesium and calcium on parathyroid hormone secretion are qualitatively similar, the response to calcium is quantitatively much greater than to magnesium. Variations in plasma magnesium produce only 30—50% of the effect resulting from a similar change in calcium concentration in vivo [56] and in vitro the effect of magnesium is about 40% of that produced by an equimolar change in calcium concentration [33]. Similarly it is well established that the effects of parathyroid hormone are much greater on calcium than on magnesium metabolism, as mentioned previously. Any regulatory role of parathyroid hormone on magnesium must therefore be subsidiary to its involvement with calcium homeostasis. Parfitt [70] has critically re-examined earlier work on the renal handling of magnesium in patients with moderate degrees of hypo- or hyperparathyroidism and come to the conclusion that changes in parathyroid hormone secretion are probably not involved in normal magnesium homeostasis. The rapid changes in urinary magnesium excretion that occur can certainly be explained as a direct result of small changes in plasma magnesium concentration.

Relation with calcitonin

The results of attempts to test for a relation between calcitonin and magnesium are very contradictory and care is necessary to distinguish between a direct action and a slower response that may be secondary to a change in calcium metabolism. Calcitonin injected into rats has been observed to lower the magnesium concentration in plasma [67, 69] and to increase its urinary excretion [95, 97]. These changes are similar to the effects of calcitonin on calcium, but it is not clear whether they are independent or related changes. Other studies have, however, reported no effect of calcitonin on plasma magnesium levels in humans, monkeys and rats [9, 29, 65], and Rasmusson [78] found no correlation between serum calcitonin and magnesium concentrations in a series of patients with thyroid carcinoma.

Injection of magnesium salts consistently raises the calcitonin concentration in the venous plasma of pigs, irrespective of whether the magnesium is given by generalised infusion [47, 72] or introduced directly into the thyroid artery [15, 22]. Conflicting evidence is available in humans where injection of magnesium salts in patients with medullary carcinoma lowers the calcitonin concentration in serum [3] although this could be secondary to a fall in serum calcium. Thyroid carcinoma cells in culture are unaffected by the magnesium concentration in the medium but respond to a rise in calcium level by a greatly increased secretion of calcitonin [86]. No change in plasma calcitonin was observed during the development of magnesium deficiency in calves [80].

The variability of these results raises the possibility that the significance of calcitonin may vary between different species. However even in the studies with pigs, which gave a consistent response to magnesium, administration of equivalent amounts of calcium produced a much greater increase in calcitonin secretion and strontium also produced a greater response than magnesium salts [22, 72], so it seems that the increase after giving large amounts of magnesium is a pharmacological rather than a physiological response. There is therefore no evidence of a homeostatic relationship between calcitonin and magnesium metabolism, and it appears unlikely that there is any direct connection of physiological significance.

Hypocalcaemia in magnesium deficiency

The breakdown in calcium homeostasis and development of hypocalcaemia is well established during naturally occurring magnesium deficiency in human subjects and farm animals, as well as in laboratory studies with experimental animals of many species [55, 90]. Many investigations have shown that the rat is atypical in developing hypercalcaemia, but if the dietary intake of calcium is reduced it responds in the same way as other animals and develops hypocalcaemia during magnesium deficiency [50, 92].

Studies with bone cultured in vitro show that magnesium increases calcium release partly by displacing it from the hydration shell by physico-chemical exchange, and partly by stimulating the metabolism and resorption of living bone [51, 68]. Conversely reducing

the magnesium concentration in the surrounding medium reduces the rate of calcium release from living bone [66, 76]. This will tend to reduce the calcium concentration in plasma, but it is inadequate to explain the development of hypocalcaemia in intact animals because the physiological response to both hypocalcaemia and hypomagnesaemia is to increase the secretion of parathyroid hormone and maintain homeostasis. The two hypotheses that have been advanced to explain why this does not occur involve [10] an impaired target organ response to circulating parathyroid hormone and [20] failure of the parathyroid gland during magnesium deficiency.

A target organ refractoriness was first suggested by the observation of a reduced calcaemic response to the injection of parathyroid extract in patients with hypomagnesaemia and hypocalcaemia that returned to normal after correction of the magnesium deficiency [21, 25, 63]. This was confirmed under controlled conditions in thyroparathyroidectomized rats and bones from magnesium-deficient rats incubated in vitro were found to respond to parathyroid hormone by releasing less calcium and phosphate to the medium than bones from control animals [52]. Since then a refractory response to exogenous parathyroid hormone has also been observed in magnesium-deficient chicks [10, 82] and dogs [46]. However, normal calcaemic and phosphaturic responses to injected parathyroid hormone have been reported in several patients with hypomagnesaemia and hypocalcaemia [5, 17, 93], and the reasons for the discrepancy are not fully understood although they may be related to the severity of magnesium depletion.

The action of parathyroid hormone on bone and renal cortex is mediated by the formation of cyclic AMP [8, 64], which acts as an intracellular second messenger and produces the physiological response to the hormone. Magnesium activates adenylate cyclase from both these tissues in vitro [16, 27, 53], as well as preparations from many other organs [85], and this suggests a mechanism by which the response to parathyroid hormone could be impaired in magnesium deficiency. A smaller than normal increase in urinary cyclic AMP excretion has been reported after administering parathyroid hormone to magnesium-deficient patients [88, 89] and rats [26]. Detailed studies of renal cyclic AMP in magnesium-deficient rats, however, indicate no impairment in its formation in response to the hormone either in vitro [26, 34] or in vivo [6], implying that there is no defect in the renal adenylate cyclase system.

A second primary action of parathyroid hormone is to cause a rapid and transient shift of calcium from plasma into bone [71, 84] but this also appears to be unaffected by magnesium deficiency [7]. Another theoretical possibility is that the deficiency might inhibit formation of 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D_3. The formation of this metabolite is controlled by the 1-hydroxylase in kidney mitochondria, which requires magnesium for activity in vitro [31], but again the evidence is that magnesium deficiency in vivo does not affect vitamin D metabolism in either the chick [20] or rat [81]. There is, therefore, no convincing metabolic explanation of the mechanism by which magnesium deficiency impairs the response of target organs to parathyroid hormone.

Magnesium deficiency is known to produce histological changes in bone, including an increase in the amount of unmineralized osteoid tissue [42, 82], and tibia from magnesium-deficient dogs take up parathyroid hormone from the perfusing medium much less readily than bones from control animals [28]. The deficiency also reduces the calcaemic response to injection of 1,25-dihydroxycholecalciferol [79], and it is possible that both this and the impaired response to parathyroid hormone are caused by the changed physical nature of the bone rather than by a biochemical abnormality.

Application of the immunoassay for parathyroid hormone to patients with hypomagnesaemia and hypocalcaemia has produced variable evidence about the state of parathyroid gland activity. In a few cases the serum concentration of the hormone is elevated [21, 87], but in many it is either within the normal range or low [4, 57, 59]. Any parathyroid hormone concentration that is not clearly elevated is inappropriately low for a patient with severe hypocalcaemia and hypomagnesaemia, and the invariable observation that the hormone concentration in serum rises after magnesium therapy confirms that magnesium deficiency inhibits its release from the gland. Moreover the speed of response to the intravenous administration of magnesium salts, when the hormone concentration in serum rises within one minute [5, 87], suggests that the deficiency inhibits the secretion process itself rather than the synthesis of hormone.

These conclusions about parathyroid function in magnesium deficiency are consistent with the findings during culture of normal parathyroid tissue in vitro, which were considered previously. It was shown that magnesium only influences secretion of the hormone, and although the usual response to lowering the magnesium concentration is an increased release of hormone, at very low levels it is reduced [94], thus emphasizing the need to distinguish between physiological and pathological relationships.

The development of hypocalcaemia during magnesium deficiency is therefore a matter of complex origin. The direct effect of the deficiency on heterionic exchange with bone and the metabolism of bone cells acts as a conditioning factor, but is inadequate by itself to produce hypocalcaemia. It may be supported either by a failure of the parathyroid gland to secrete appropriate amounts of hormone or by an inadequate response of target organs to the circulating hormone. A carefully controlled parallel study of both responses during the development of magnesium deficiency is necessary for

clarification because the individual variation between patients is too great to permit conclusions about the relationship between them. Calcitonin certainly does not seem to be involved, because it is pharmacological doses of magnesium that increas calcitonin secretion, whereas magnesium deficiency would have to produce this effect if it were to contribute to the development of hypocalcaemia.

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