Influence of magnesium on parathyroid hormone secretion and action

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Summary

Although calcium is the major regulator of parathyroid hormone (PTH) secretion magnesium ions effect both the release and action of PTH. Recent studies have shown that an inhibitory effect of magnesium on the release of PTH is dependent on the presence of calcium. The exact mechanisms by which extracellular calcium modifies the magnesium-regulated PTH release are not yet defined but in appears that cytosolic free calcium may act as a second messenger. In vivo studies have described that the renal response to PTH is generally unimpaired by magnesium deficiency and when a blunted response is seen this reflects a resistance to circulating high PTH levels.
Primary hyperparathyroidism (HPT) is seldom associated with magnesium deficiency but both skeletal involvement, psychiatric symptoms and high blood pressure might be related to subtle disturbance of magnesium metabolism in HPT patients.

Résumé

Bien que la secrétion de la parthormone est réglée en général par le calcium, les ions de magnésium affectent la libération et l'action de la PTH. Des études récentes ont montré que l'effet inhibitrice du magnésium sur la libération de la PTH depend de la présence de calcium. Les mécanismes exacts selon lesquels le calcium extracellulaire modifie la libération de la PTH réglée par le magnésium ne sont pas encore definis mais il semble que le calcium libre cytosolique peut agir comme messager secondaire. Des études faites in-vivo ont décrit que l'effet de la PTH sur les reins n'est pas affecté en général par une manque de magnésium; si on observe cependant des réactions modérées, cela reflèt la résistance contre un niveau élevé de circulation de la PTH.

Hyperparathyroidisme primaire (HPT) est rarement lié à une manque de magnésium, mais des altérations squelettiques, des symptômes psychiatriques, et une pression sanguine très haute peuvent être reliés avec des désordres subtiles du métabolisme de magnésium des malades souffrants de HPT.

Zusammenfassung

Obwohl hauptsächlich Calcium die Sekretion von Parathyroid-Hormon (PTH) reguliert, beeinflussen Magnesiumionen sowohl die Freisetzung als auch die Wirkung von PTH. Neuere Studien haben gezeigt, daß ein Hemmeffekt von Mg auf die Freisetzung von PTH die Anwesenheit von Ca erfordert. Die genauen Mechanismen, über die extrazelluläres Ca die Mg-regulierte PTH-Freisetzung modifiziert, sind noch unbekannt, aber es scheint, daß freies zytosolisches Ca als second messenger wirkt. In-vivo-Studien haben gezeigt, daß die Wirkung von PTH auf die Nieren im allgemeinen nicht durch Mg-Mangel beeinträchtigt wird; wenn abgeschwächte Reaktionen beobachtet werden, spiegelt dies eine Resistenz gegenüber hohen zirkulierenden PTH-Spiegeln wider.
Primärer Hyperparathyroidismus ist selten mit Mg-Mangel verbunden, aber Skelettveränderungen, psychische Symptome und erhöhter Blutdruck könnten bei solchen Patienten mit subtilen Störungen des Mg-Metabolismus verknüpft sein.

Introduction

Calcium is the undisputed major regulator of the secretion of parathyroid hormone (PTH) and the major concern for the parathyroid glands is to regulate the plasma calcium levels [23]. However, it is also well recognized that magnesium can affect the secretion and action on PTH but the precise mechanisms for these functions are yet not fully understood.
The recent developments in techniques which enable the study of PTH secretion at the cellular/subcellular level [11, 36, 56, 66] have made it possible to assess directly, without the interference from the plasma factors, the influence of magnesium on the regulation of the secretion of PTH.
This presentation will be divided into three parts. In the first the influence of extracellular magnesium on the synthesis and secretion of parathyroid hormone will be reviewed, thereafter some recent studies on the peripheral actions of magnesium with regard to PTH will be considered. Finally data concerning the possible influence of a disturbed magnesium metabolism on the symptoms in patients with primary hyperparathyroidism is discussed.

In vitro studies of PTH release

In an early study it was reported that magnesium and calcium were equally potent in the regulation of PTH secretion in vitro [64] but this was not borne out by subsequent detailed analysis which showed that magnesium was two to three times less effective than calcium in suppressing PTH-secretion [22].
Morrisey and *Cohn* [46], using a preparation of procine parathyroid cells found that in terms of inhibition of secretion calcium and magnesium ions were each more effective in the presence of a minimum concentration of the other, indicating that calcium and magnesium affect separate cellular sites. At all concentrations of magnesium in the extracellular fluid calcium further reduced the secretion of PTH. The higher the concentration of magnesium the more effective was any particular concentration of calcium

in suppressing secretion. This result could thus be attributed to the independent inhibition of secretion by magnesium itself. *Takatsuki* et al. [63] used a perifusion system of bovine parathyroid tissue and could thereby analyze the dynamic changes in hormone secretion during alterations of the ambient concentrations of mineral ions. When magnesium was removed from the medium of glands being perifused with a low calcium concentration there was a rapid fall in PTH release down to a nadir which was less than half of the control rate of secretion. The return of hormone release when magnesium was added was dose-dependent at magnesium concentrations between 0 and 0.8 mM, i.e. up to the physiologic range. At higher concentrations, however, the responses in secretion of PTH were the reverse, i.e. there was a progressive decrease in secretory response with further addition of magnesium.

While both low calcium and adrenergic agonists [8] appear to regulate PTH secretion via the intermediate action of adenylate cyclase and cAMP the effects of magnesium appeared to be more generalized and not related specifically to a single stimulus to hormone secretion. This may imply some more generalized defect in the release mechanism or membrane related to low magnesium rather than impairment of a specific receptor or pool of hormone.

More recently a detailed study was carried out where the relative potencies of extracellular calcium and magnesium in inhibiting PTH release and dopamine-stimulated cAMP accumulation was studied in dispersed bovine parathyroid cells [12]. In this study it was found that at a physiologic concentration of calcium (1.0 mmol/l) the release of PTH was half-maximally suppressed by 1.8 mmol/l magnesium. At lower calcium concentrations, on the other hand, the concentration of magnesium causing half of the maximal inhibition of release of PTH was about twice as high. At calcium concentrations in the subphysiologic range (<100 μmol/l) markedly higher magnesium concentrations (10 to 15 mM) were needed to half-maximally reduce hormonal secretion. On the other hand, when cells were incubated in a medium containing 1 mM magnesium or less, there was little or no change in the sensitivity for calcium. At higher magnesium concentrations, however, the release of PTH was markedly more sensitive to the inhibitory effects of calcium. Thus, half-maximal suppression occurred already at a calcium concentration of 0.2 mM when the magnesium concentration was 5 mM. Extracellular caclium also potentiated markedly the inhibitory effects of extracellular magnesium on dopamine-stimulated accumulation of cyclic AMP.

These findings demonstrated that the inhibition of PTH release by magnesium was critically dependent on the presence of extracellular calcium but not vice versa and suggested that extracellular calcium may play a role in the mechanisms by which extracellular magnesium modulates parathyroid function, perhaps through a magnesium-induced uptake of extracellular calcium. The analysis also indicated that the two cations suppressed PTH independently and additively with calcium having about three times the potency of magnesium on a molar basis. At very low calcium concentrations, however, magnesium was even less potent than explained by such a model, suggesting the presence of calcium was essential for the action of magnesium.

In most endocrine glands regulation of hormone secretion is mediated by the concentration of free, cytoplasmic, calcium so that an increase of this concentration will enhance the secretion of hormone [51]. The parathyroid gland appears to be an exception to this, almost universal, rule since a reduction of the extracellular concentration is a well recognized stimulus to suppression of hormone release [23]. Measurements with the new fluorescent, calcium-sensitive dye Quin-2 [66] have demonstrated that in the dispersed parathyroid cells a reduction of the ambient calcium concentration will cause a reduction of the free intracellular calcium [36] with a close correlation between the free intracellular calcium and the release of PTH to the medium. Thus the parathyroid cell has unique properties. Not only does this cell maintain normal secretory rates at low cytosolic Ca^{2+} concentrations but elevations inhibit and do not stimulate PTH release [36].

When the effect of varying the extracellular magnesium concentrations at different calcium concentrations on the concentrations of cytosolic Ca^{2+} and PTH were investigated [58] it was found that when the extracellular calcium concentration was close to zero changes in the extracellular magnesium produced no detectable changes in cytosolic free calcium. At an extracellular calcium concentration of 0.5mM graded increments in extracellular Mg over a wide range led to a stepwise increase of the free cytosolic calcium levels. When the extracellular calcium concentrations were increased to a physiologic level, 1.0 mM, half of the maximal increase of cytosolic calcium (set-point) took place at en extracellular magnesium concentration of around 2 mM whereas the corresponding set-point at the lower calcium concentration occurred at a magnesium concentration which was higher (3.3 mM). Also the corresponding set-points for suppression of PTH release with extracellular magnesium was significantly higher at a low ambient calcium concentration. There were also close correlations between the magnesium-induced inhibition of PTH secretion and the elevation of

the cytosolic calcium. Only for the "calcium-free" medium was the release of PTH not significantly affected by changes of extracellular magnesium.

Thus these two studies together present a picture where magnesium affects the release of PTH through changes of the cytosolic free calcium. Since the effects cannot be mediated in a calcium-free medium some of the response must be the result of magnesium-induced changes of calcium transport across the parathyroid plasma cell membrane. Thus the results suggest that magnesium raises the cytosolic free calcium, at least in part, through uptake of extracellular calcium. These direct observations support previous indirect studies using divalent cation ionophores [10, 24, 44] and agents that modify sodium-calcium exchange [9, 20, 54] which implicated free cytosolic calcium as an intracellular mediator of hormonal secretion in this cell type. The exact mechanisms by which extracellular calcium modifies the magnesium-regulated PTH-release are not yet defined, although it appears that cytosolic free calcium may act as a second messenger.

Magnesium, like calcium, depolarizes parathyroid cells [16]. Moreover, a number of the effects of magnesium on parathyroid function might be understood by changes of the free cytosolic calcium such as the magnesium-induced lowering of basal as well as stimulated cAMP content [13]. Magnesium might also modify parathyroid function through mechanisms other than uptake of extracellular calcium. Hypothetically the presence of extracellular calcium might be essential to promote a magnesium-induced release of intracellular stores of calcium. Magnesium could also affect secretion of PTH through other, yet undefined, mechanisms. However, the recent work by *Brown* et al. elegantly demonstrates the central importance of the free cytosolic calcium concentration in the magnesium-induced changes of PTH secretion.

It is thus quite clear that magnesium can have a modulating, if not regulating, effect on the secretion of PTH. The consequencies for the normal, physiologic, regulation of PTH secretion and the possible role of magnesium in disturbances of parathyroid function are not entirely clarified. However, because the concentration of free magnesium in plasma is only about half of that of calcium and since magnesium is two to three times less potent than calcium on a molar basis any contribution of magnesium to the regulation of PTH secretion is probably small under normal physiological circumstances.

In vivo studies of magnesium and PTH

The effects of hypomagnesaemia on calcium and parathyroid hormone metabolism have been studied quite extensively during the last few decades. Although it is generally agreed that hypomagnesaemia is often associated with a lowering of the serum calcium levels controversy has existed whether this relates to impaired secretion of parathyroid hormone (PTH) or to organ unresponsiveness to PTH. Measurements of the peripheral levels of PTH has thus produced contradictory results. Some investigators have found elevated PTH levels and impaired end-organ (i. e. renal and bone) responsiveness to infusion of exogeneous PTH in magnesium-deficient patients. Others have reported low or inappropriately low levels of PTH but a normal target tissue response in such patients [5, 57, 61].

Calcium is the principal regulator of parathyroid glandular activity. It has been known for many years that the rate of secretion of PTH is inversely dependent on the extracellular concentration of the calcium ion. The studies by *Mayer* et al. in claves [39] showed that a slowly induced decline of calcium concentration from 10.5 to 9.0 mg/100 ml elicited a small and gradual increase in secretory rate. A further decrease with 1 mg/100 ml in total serum calcium induced a marked rise in PTH secretion to a maximal rate whereas below that limit no further stimulation was achieved. Recently similar findings, deduced from measurements in peripheral veins in humans, have been reported from healthy human subjects [7].

Low concentrations of magnesium clearly block the response of the parathyroid glands to hypocalcaemia but injections of magnesium can rapidly stimulate PTH secretion during these circumstances [57]. There are, however, conflicting reports of the response of the target organs to the administration of PTH during hypomagnesaemia. In many instances normals responses have been found [17, 61] but blunted reactions have also been described [69]. The variance between the different studies are not easily explained by methodological causes alone. Possibly the degree of magnesium depletion or the etiology of the hypomagnesaemia are important [45]. In a recent study [3] of hypomagnesaemic, hypocalcaemic patients it was found that in all patients there was a rapid increase in peripheral PTH levels after injection of magnesium indicating that hypomagnesemia was limiting the secretion of PTH. There was a direct relationship between the serum magnesium concentrations and the circulating levels of aminoterminal (newly released) PTH. Moderate degrees of hypomagnesaemia were associated with raised values for PTH but as magnesium depletion became more profound the N-PTH was lower and even undetectable when the plasma magnesium was as low as

0.2 mmol/l. The effect of the injection of magnesium was rapid but transient and must have been caused by stimulation of hormone release since the time sequence was too short for any new synthesis of hormone [22].

In this study, the renal responsiveness to PTH was studied as increase of plasma cAMP to a single injection of PTH [65]. It was found that when PTH levels were normal or raised, in moderate magnesium deficiency, the renal response was impaired. On the other hand, in severe magnesium deficiency with low or undetectable levels of PTH the renal production of cAMP was normal. Therefore it seems likely that the blunted renal response sometimes reported in patients with moderate magnesium deficiency [47] reflects a resistance to PTH, due to the circulating high concentrations of active PTH, rather than a primary defect causing hypocalcaemia.

Results from in vitro studies and studies in animals show that increases in magnesium above physiologic levels will suppress the secretion of PTH [14, 22, 46, 64, 68] and even, sometimes, lead to hypocalcaemia. In a study of pregnant women with imminent premature labour, who received intravenous magnesium sulphate the serum magnesium concentrations were elevated to a level of around 2 mmol/l during 3 hours [18]. The rapid rise in serum magnesium concentrations was associated with a rapid decline in the PTH levels and also with a reduction of the serum ionized calcium concentrations. During prolonged hypocalcaemia, however, the PTH levels gradually returned towards baseline even though magnesium levels remained elevated. The PTH levels fell before the decrease in serum calcium occurred, however, they remained inappropriately low given the striking degree of hypocalcaemia.

These findings thus extend the concept, previously demonstrated in vitro and in animals that magnesium and calcium have interdependent effects on the secretion of PTH.

Magnesium and primary hyperparathyroidism

Experimental studies in animals [15, 40, 41] indicate uniformly that renal magnesium reabsorption following acute administration of PTH is enhanced. Micropuncture studies have localized the major PTH-induced enhancement of magnesium transport to be pars recta or loop of Henle segments [50]. In contrast many clinical reports have documented chronic renal magnesium wasting in patients with primary hyperparathyroidism (HPT) [25, 27, 34, 62]. However, primary HPT contains several disturbances such as hypercalcaemia, acid-base disorders, phosphate depletion, nephrocalcinosis, which might independently override the direct effects of PTH in the renal magnesium handling.

In one study in humans significant sustained hypercalcaemia was produced in hypoparathyroid patients and a few normal subjects by intramuscular injections of parathyroid extract for as long as ten days [21]. In that experiment no significant alterations in plasma or urinary magnesium concentrations were observed. In a recent study four normal subjects received a continuous intravenous infusion of PTH for 12 days which resulted in a steady state of hypercalcaemia, hypercalciuria and persistent negative calcium balance [29]. In contrast to plasma calcium, plasma magnesium concentrations were not altered by PTH infusion. Significant hypermagnesiuria occurred early but after the initial period it was counteracted by an increased net magnesium intestinal absorption with ensuing net magnesium balance. These findings indicate that hypermagnesuria associated with primary hyperparathyroidism results from either direct or indirect effects of PTH excess per se and does not require the long-term consequencies or complications of the clinical disorder.

Disturbances of magnesium metabolism are well recognized features of primary hyperparathyroidism (HPT) and a number of reports have described various indices of magnesium deficiency in patients with primary HPT [27, 34, 70]. These earlier reports however stem from a time when most patients who were recognized to have primary HPT had marked hypercalcaemia and often severe symptoms of bone and stone disease. The picture of primary HPT has changed considerably over the last few decades [26, 49]. Nowadays most patients appear largely asymptomatic and their serum calcium values are only moderately elevated, i.e. values above 3.0 mmol/l are only encountered in a minority of patients.

When we, previously, investigated magnesium metabolism in some detail among consecutive patients with primary HPT we could not detect any deviations regarding serum and magnesium concentrations compared with healthy subjects [33]. Nor were there any differences for the content of magnesium in muscle biopsies, the retention of intravenous magnesium, or the gastrointestinal magnesium absorption [19]. Consequently there was no evidence that the mild-to-moderate state of HPT caused magnesium deficiency.

However, also in this largely asymptomatic patient group, none of whom had any evidence of overt hyperparathyroid bone disease, there was a significant correlation between the pre- and postoperative ratios of serum magnesium compared with that for the alkaline phosphatases. Further, there was a direct correlation between the serum alkaline phosphatase levels and the retention of the intravenous magnesium load. Thus also in

patients with mild-to-moderate HPT, bone involvement, as reflected by the enzymatic activity, appears to be common and, following parathyroidectomy, there seems to be an increased need for magnesium.

During recent years we have evaluated patients with primary HPT in some detail regarding the occurrence of possible psychiatric symptoms. In a prospective study it was then found that the majority of HPT patients had psychiatric symptoms of such magnitude that their everyday life was affected [32]. Symptoms of a depressive character were the most commonly encountered. When measurements of biogenic amines in the cerebrospinal fluid were performed it turned out that these levels were markedly lowered in the HPT patients. Furthermore there were significant correlations between the serum magnesium levels and the CSF concentrations of HVA (the metabolite of dopamine) as well as with some of the depressive symptoms. Magnesium may affect catecholaminergic and cholinergic neurotransmission [2] and the serum magnesium levels have been found to be low in patients with depression [4] as well as in alcohol withdrawal and delirium [59, 67]. The CSF magnesium concentrations have recently been demonstrated to be lower in both depression and adjustment disorders [6]. Our premilinary findings suggest that a moderate disturbance of magnesium metabolism in primary HPT is associated with a disturbance of the function of the central nervous system and provide a basis for further speculations and studies.

HPT is often associated with a raised blood pressure and there is an overrepresentation of hypertension in this disorder [35]. Long-term follow-up of patients with HPT has shown that there is an increased risk of death from cardiovascular causes in unattended HPT which also, to some extent, persists after successful parathyroid surgery [48, 53]. The cause of the raised blood pressure is not quite clear.

Recent studies have elucidated that within the reference range for blood pressure, in healthy subjects, there is an inverse correlation between the plasma ionized calcium concentrations and the mean blood pressure [30]. It has also been demonstrated that patients with essential hypertension have lower levels of ionized calcium plasma than normotensive individuals [31, 42, 43, 52, 60]. A relationship between blood pressure and serum magnesium concentrations has also been proposed [52]. In a recent study we found, however, that in patients with mild HPT there was an inverse relationship between the systolic blood pressure and the serum magnesium levels [37, 38]. These findings suggest that the disturbances of magnesium metabolism could affect the symptomatology of the HPT patients.

Magnesium is not the dominating regulator of parathyroid function and action and in the well-nourished inhabitant of the industrialized countries nutritional magnesium deficiency is probably rare. However, the potential influence of magnesium on calcium and parathyroid hormone metabolism, also in physiological situations, should serve as a stimulus to further investigations.

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