Magnesium Deficiency and Parathyroid Function

Common causes of magnesium (Mg) deficiency are small bowel diseases, such as chronic bowel disease, or resection of the small bowel. Chronic alcoholism is also an important cause of Mg deficiency. Clinical features and the degree of Mg deficiency appear to vary depending upon the underlying disorder as well as the portion and extensiveness of the small bowel disease. One of the most prominent manifestations of Mg deficiency is hypocalcemia due to hypoparathyroidism, but there are many uncertainties about the pathophysiology and pathogenic mechanism of hypoparathyroidism caused by Mg deficiency.

Impaired secretion of parathyroid hormone (PTH) has been thought to be a major mechanism of hypocalcemia in Mg deficiency. In many but not all hypomagnesemic patients, the serum PTH levels are either low or within the normal range despite the presence of hypocalcemia. These findings along with the fact that serum PTH levels increase sharply after Mg supplementation indicate that PTH secretion is impaired in these patients. The most important regulator of PTH secretion is serum ionized calcium (Ca); a Ca-sensing receptor has been cloned in parathyroid cells (1). Binding of Ca with this receptor causes an increase in inositol triphosphate production and an elevation in the intracellular Ca concentration (1), and is thought to cause a reduction in PTH secretion. Mg appears to compete with Ca for this receptor, with an affinity two- to three-fold less than that for Ca, causing a rise in the intracellular Ca concentration (2). In addition, an in vitro study using rat parathyroid cells demonstrated that deletion of Mg from the medium reduces PTH release at a constant Ca concentration (3). Thus, Mg acts as a Ca agonist at very high concentrations (4) but may serve as an antagonist at lower concentrations. Based upon these observations, the reduced PTH secretion in hypomagnesemia can be explained by a reduction in the competitive inhibition by Mg of Ca binding to its receptor. Such an alteration in Ca binding to its receptor enables parathyroid cells to respond to serum Ca with higher sensitivity and causes a reduction in PTH secretion at lower serum Ca concentrations. However, the possibility remains that Mg may also affect PTH secretion at other steps in parathyroid cells.

Reduced responsiveness to PTH has also been reported in some patients with hypomagnesemia. One of the postulated sites that causes the disturbance in responsiveness to PTH is adenylate cyclase. There are reports of patients with hypomagnesemia with a reduced urinary cyclic AMP response to PTH (5). Because Mg is required for the catalytic activity of the enzyme, reduction in the intracellular Mg concentration can suppress the enzyme activity. However, many patients with Mg deficiency respond to PTH normally in terms of urinary cyclic AMP excretion, as in the case reported by Mihara et al (6) in this issue of the Journal. In addition, in some of the patients with a blunted response to PTH in urinary cyclic AMP excretion, the increase in plasma cyclic AMP in response to glucagon was normal (5). Although these discrepancies can be explained by a difference in the concentration of Mg required for the catalytic activity of adenylate cyclase in different tissues, little data is available to support such a possibility. In a study using dogs, responsiveness to PTH was found to decline progressively with increasing degree of Mg deficiency (7). Rude et al (5) reported that most of the cases with a reduced urinary cyclic AMP response to PTH have severe hypomagnesemia of 0.6 mg/dl or below; they suggested that only those patients with severe Mg deficiency may develop a blunted renal cyclic AMP response to PTH. However, there are many patients with severe hypomagnesemia with normal cyclic AMP response to PTH.

In the report of Mihara et al (6), they suggested that in their patient, the steps distal to cyclic AMP production in response to PTH may be impaired by Mg deficiency. However, responsiveness to PTH by the Ellsworth-Howard test was normal in terms of renal cyclic AMP and phosphate excretion. Because the test was performed 12 days after admission when serum Mg rose to 1.0 mg/dl and serum phosphate as well as TmP/GFR were normalized, such a possibility could have been better delineated if PTH infusion had been performed prior to the treatment when serum Mg was 0.6 mg/dl and serum phosphate and TmP/GFR were elevated. The examination of the renal responsiveness to dibutyryl cyclic AMP infusion may also provide some insight to the question of whether Mg deficiency can cause resistance to PTH at a step distal to cyclic AMP production.

Serum 1,25-dihydroxyvitamin D is also very low in patients with Mg deficiency. Although serum PTH and nephrogenous cyclic AMP increase rapidly in response to Mg supplementation, 1,25-dihydroxyvitamin D increases much slower (8, 9). In addition, serum osteocalcin, a marker for bone formation, is markedly low in Mg deficiency and increases long after serum PTH is normalized (10). Furthermore, serum Ca increases with a similar time course to that seen in serum osteocalcin (10). These observations suggest that the reduction in responsiveness to PTH by Mg deficiency cannot be fully explained by a reduction in the catalytic activity of adenylate cyclase. Mg is required for many aspects of cellular activity, and the difference in clinical features of Mg deficiency may be due to a variation in the extent and/or the degree of impairment in these multiple steps of cellular functions. Although much has to be clarified to...
understand the pathophysiology and pathogenesis of hypoparathyroidism associated with Mg deficiency, the divergence of the clinical presentation of Mg deficiency points to the importance of this cation.

Toshio MATSUMOTO, MD
The Fourth Department of Internal Medicine,
University of Tokyo School of Medicine,
Mejirodai, Bunkyo-ku, Tokyo 112

References


3) Mahaffee DD, Cooper CW, Ramp WK, Ontjes DA. Magnesium promotes both parathyroid hormone secretion and adenosine 3',5'-monophosphate production in rat parathyroid tissues and reverses the inhibitory effects of calcium on adenylylate cyclase. Endocrinology 110: 487, 1982.


