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Calcium Regulation of Parathyroid Hormone Release

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Background

The parathyroid hormone (PTH) release is mainly regulated by the extracellular calcium concentration and the secretion is inhibited by raised calcium levels. In this respect the parathyroid is a paradox among endocrine cells where the hormone release is triggered by raised intracellular calcium (Ca^{2+}_i) concentrations (9). Hyperparathyroidism (HPT) is characterized by a disturbed regulation of the PTH release from the pathological parathyroid cells due to a relative insensitivity of the secretion to changes in the extracellular calcium concentration (7 12). The present paper summarizes studies of PTH release and Ca^{2+}_i regulation of parathyroid cells, which point to the existence in the parathyroid of a cell membrane-bound receptor mechanism for calcium. This receptor mechanism appears relatively unique for the parathyroid cell, and its reduced expression in the pathological parathyroid tissue may explain the development of hypercalcaemia in HPT.

Hormone regulation in normal parathyroid cells

The PTH release shows an inverse and sigmoidal relationship to the extracellular calcium concentration (2) with a basal, non-suppressible release being maintained even at high ambient calcium concentrations. The mechanisms by which extracellular calcium regulates PTH release have not been completely understood. Although suggested otherwise, several findings indicate that CAMP is not the important mediator in this regulation (1). Instead recent studies have revealed that increases in extracellular calcium are translated into closely related increments in the concentration of Ca^{2+}_i in the parathyroid cell (7,10). Studies of ^{45}Ca fluxes have furthermore suggested that calcium enters the parathyroid cell by means of a receptor-operated gating mechanism, rather than through voltage-dependent calcium channels, present in most other secretory cells (11). Further support for the presence of such a specialized calcium receptor mechanism on parathyroid cells was recently offered by the finding that the trivalent cation Lanthanum despite its restriction to the exterior of these cells, can induce calcium influx and a raised Ca^{2+}_i (3).

Hormone regulation in abnormal parathyroid cells

HPT seems invariably associated with an increased parathyroid cell mass which indicates that there may exist some link between the proliferation of parathyroid cells and their functional dedifferentiation in HPT. However, the hypercalcaemia in HPT appears to be more closely related to the defective regulation of PTH secretion than to the increased parathyroid tissue mass (12). Thus, cells of parathyroid adenomas and hyperplastic glands characteristically display variable degrees of right shifts in the dependency of the secretion on changes in ambient calcium (12). This regulatory defect is correlated to the degree of hypercalcaemia in adenomatous as well as primary and secondary hyperplasias. An important basis for the defective regulation of PTH secretion in HPT is the inability of the abnormal parathyroid cells to adequately regulate the Ca^{2+}_i concentrations. The pathological parathyroid tissue is thus characterized by reduced levels of Ca^{2+}_i and by right shifts in the relationship between Ca^{2+}_i and extracellular calcium (7,12).

Monoclonal antiparathyroid antibodies

With the aim of recognizing specialized cell surface structures of parathyroid cells, monoclonal antiparathyroid antibodies were raised by a hybridoma technique after immunization of mice with intact human parathyroid cells. Four antibodies were produced, which reacted in immunohistochemistry with surface structures of parathyroid cells and proximal tubular cells of the kidney, but not with a large number of other human tissues (4).

Studies of human parathyroid cells revealed that the antibodies competed with calcium and counteracted the rise in Ca^{2+}_i normally obtained when parathyroid cells are exposed to increasing concentrations of extracellular calcium (4,5). Together with the demonstration by immunofluorescence that the antibodies bind to surface structures of parathyroid cells, the results indicate that they recognize the specialized parathyroid receptor mechanism involved in the sensing and gating of calcium (5). Further studies have shown that these antibodies block not only the calcium-induced steady state increase in Ca^{2+}_i but also a transient increase in Ca^{2+}_i, believed to be due to inositol-1,4,5-triphosphate-induced mobilization of intracellular Ca^{2+} (8). It therefore seems likely that the antibodies interact with the calcium receptor itself rather than with a Ca^{2+} channel associated with it (8).

The antiparathyroid antibodies yield an intense and homogeneous immunohistochemical staining of normal human parathyroid tissue. In contrast, adenomatous and hyperplastic parathyroid tissues invariably display a clearly reduced staining intensity (6). In studies of the abnormal cells, the antibodies were found

to interfere not only with the regulation of Ca^{2+}_i but also with the calcium regulation of the PTH release. These findings suggest that the regulatory defect of the pathological parathyroid cells in HPT may be due to a reduced expression of the calcium receptor mechanism, recognized by the presently used antibodies (6).

Conclusion

The studies described herein lend strong support to the idea that the parathyroid cell is equipped with a specialized receptor mechanism for the sensing and gating of calcium. The principal regulatory defect in HPT seems to be associated with a reduced expression of the putative calcium receptor on the pathological parathyroid cells.

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