

A Comparison of the Effects of Divalent and Trivalent Cations on Parathyroid Hormone Release, 3',5'-Cyclic-Adenosine Monophosphate Accumulation, and the Levels of Inositol Phosphates in Bovine Parathyroid Cells

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Abstract

We compared the effects of a series of di- and trivalent cations on various aspects of parathyroid function to investigate whether these polyvalent cations act on the parathyroid cell through a similar mechanism. Like high extracellular concentrations of Ca^{2+} , high levels of barium (Ba^{2+}), strontium (Sr^{2+}), gadolinium (Gd^{3+}), europium (Eu^{3+}), terbium (Tb^{3+}), and yttrium (Yt^{3+}) each inhibited low calcium-stimulated PTH release and showed IC_{50} values (the concentration producing half of the maximal inhibitory effect) of 1.12 mM, 1.18 mM, 2.2 μM , 2.5 μM , 0.89 μM , and 15 μM , respectively. The inhibitory effects of both divalent (Ca^{2+} and Ba^{2+}) and trivalent (Gd^{3+}) cations were reversible by 76–100% after removal of the cation, suggesting that the polyvalent cation-mediated reduction in PTH release was not due to nonspecific toxicity. The same di- and trivalent cations produced an 80–90% decrease in agonist-stimulated cAMP accumulation with a similar order of potency as for their effects on PTH release. Preincubation overnight with pertussis toxin totally prevented the inhibitory effects of the trivalent cations on cAMP accumulation. The same di- and trivalent cations also increased the accumulation of inositol monophosphate, inositol bisphosphate, and inositol trisphosphate. Their effects on this parameter differed from those on PTH release and cAMP accumulation in several respects. First, Ba^{2+} and Sr^{2+} , rather than being equipotent with Ca^{2+} , were about 2-fold less potent in increasing the levels of inositol phosphates. Second, the trivalent cations were 5–50-fold less potent in raising inositol phosphates than in modulating PTH release and cAMP accumulation, and all were nearly equipotent. These results show that trivalent cations of the lanthanide series mimic the actions of divalent cations on several aspects of parathyroid function, and likely do so by interacting with the cell surface " Ca^{2+} -receptor-like mechanism" through which extracellular Ca^{2+} has been postulated to act. The

pharmacology of the effects of these polyvalent cations on cAMP and PTH release are similar and differ from that for their actions on inositol phosphate metabolism, raising the possibility that there might be more than one form of the putative Ca²⁺ receptor. (*Endocrinology* **127**: 1064–1071, 1990)

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