

Abstract

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Potentiating effects of nonactive/active vitamin D analogues and ketoconazole in parathyroid cells.

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BACKGROUND AND OBJECTIVE: 1,25-dihydroxyvitamin D(3)[1alpha,25(OH)(2)D(3), calcitriol], and its less calcaemic synthetic analogues have therapeutic potential in several diseases, including hyperparathyroidism (HPT). We have suggested that non-1alpha-hydroxylated (nonactive) vitamin D analogues may present an alternative in tumour cells expressing 25-hydroxyvitamin D(3) 1alpha-hydroxylase (1alpha-hydroxylase). The aim of this study was to investigate biological effects of a non-1alpha-hydroxylated vitamin D analogue in normal and tumour parathyroid cells.

PATIENTS AND METHODS: Effects of vitamin D analogues and ketoconazole on parathyroid hormone (PTH) secretion (radioimmunoassay) and PTH mRNA expression (reverse transcription-polymerase chain reaction) were studied in primary bovine parathyroid cells. Proliferation of tumour cells isolated from HPT patients was determined by thymidine incorporation.

RESULTS: EB1285, non-1alpha-hydroxylated precursor of the vitamin D analogue EB1089, suppressed PTH secretion and PTH mRNA level as well as increased expression of 25-hydroxyvitamin D(3)-24-hydroxylase (24-hydroxylase) in bovine parathyroid cells. EB1285 also inhibited cell proliferation of parathyroid tumour cells from primary (pHPT) and secondary HPT (sHPT) patients. Combined treatment with the cytochrome P450-dependent enzyme inhibitor ketoconazole and EB1285 or with active vitamin D compounds potentiated the suppressive effect on PTH secretion from bovine parathyroid cells. Ketoconazole alone displayed PTH suppression and increased 24-hydroxylase expression.

CONCLUSION: The results support the idea that a non-1alpha-hydroxylated vitamin D analogue may elicit vitamin D receptor (VDR) effects in 1alpha-hydroxylase expressing parathyroid tumour cells. Further studies are warranted to elucidate whether precursor vitamin D analogues as well as inhibitors of 24-hydroxylase present therapeutic alternatives in patients suffering from HPT.

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