

Abstract

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Vitamin D modulation of the activity of estrogenic compounds in bone cells in vitro and in vivo.

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BACKGROUND: Vitamin D analogs modulate different organs, including modulation of energy metabolism, through the induction of creatine kinase (CK) activity.

METHODS AND RESULTS: Skeletal organs from vitamin D-depleted rats showed lower constituent CK than those from vitamin D-replete rats. Moreover, estradiol-17beta (E2) or dihydrotestosterone (DHT), which increased CK in organs from intact female or male rats, respectively, stimulated much less CK in vitamin D-depleted rats. Treatment of intact female rats with noncalcemic vitamin D analogs significantly upregulated E2- and DHT-induced CK response. These analogs upregulated the CK response to selective estrogen receptor modulators (SERMs) in organs from intact or ovariectomized (Ovx) female rats but abolished SERMs' inhibitory effect on E2-induced CK. These analogs significantly increased estradiol receptor alpha (ERalpha) protein in skeletal organs as well as histomorphological and biochemical changes due to this treatment followed by E2 or DHT. The analogs alone markedly altered the growth plate and the trabeculae and increased trabecular bone volume (%TB V) and trabecular width. The addition of E2 or DHT to this treatment restored all parameters as well as increased %TBV and cell proliferation. Treatment of Ovx female rats with JK 1624 F2-2 (JKF) decreased growth-plate width and increased %TB V, whereas QW1624 F2-2 (QW) restored growth-plate width and %TB V. Treatment of E2 with JKF restored %TBV and growth-plate width, whereas E2 with QW restored all parameters, including cortical width. There was also upregulation of the response of CK to E2 in both combined treatments. Our human-derived osteoblast (hObs)-like cell cultures respond to estrogenic compounds, and pretreating them with JKF upregulated the CK response to E2, raloxifene (Ral), and some phytoestrogens. ERalpha and ERbeta proteins, as well as mRNA, were modulated by CB 1093 (CB) and JKF. JKF increased specific nuclear E2 binding in female hObs but inhibited specific membranous E2 binding. hObs express 25 hydroxyvitamin D3-1alpha hydroxylase (1-OHase)-mRNA and its biological activity, which are both modulated by parathyroid hormone (PTH) and estrogenic compounds.

CONCLUSION: Our results demonstrate mutual interaction between vitamin D and estrogenic compounds. We therefore conclude that combined treatment with less-calcemic analogs of vitamin D and estrogenic compounds might be superior for treatment of bone damage caused by ovariectomy in female rats, with possible application for postmenopausal osteoporosis.

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