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RANK ligand and TNF-alpha mediate acid-induced bone calcium efflux in vitro.

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Abstract

Chronic metabolic acidosis stimulates net calcium efflux from bone due to increased osteoclastic bone resorption and decreased osteoblastic collagen synthesis. Previously, we determined that incubation of neonatal mouse calvariae in medium simulating physiological metabolic acidosis leads to a significant, cyclooxygenase-dependent, increase in RNA for bone cell receptor activator of NF-kappaB ligand (RANKL) compared with incubation in neutral pH medium. In this study, we tested the hypothesis that the acid-mediated increase in RANKL expression is a primary mechanism for the stimulated osteoclastic resorption. Acid medium increased the medium concentration of sRANKL without altering the concentration of the decoy receptor osteoprotegerin (OPG). Inhibition of the RANKL pathway with concentrations of OPG up to 25 ng/ml, far greater than physiological, did not significantly decrease the robust acid-induced Ca efflux from bone nor did incubation of the calvariae with a different inhibitor, RANK/Fc (up to 50 ng/ml). Thus acid-induced net Ca efflux appears to involve mechanisms in addition to the RANK/RANKL pathway. Osteoblasts also produce TNF-alpha, another cytokine that stimulates the maturation and activity of osteoclasts. Incubation of calvariae in acid medium caused a significant increase in TNF-alpha levels. Incubation of calvariae with anti-TNF (up to 250 ng/ml) did not significantly decrease acid-induced net Ca efflux. However, the combination of RANK/Fc plus anti-TNF caused a significant but subtotal reduction in acid-induced Ca efflux, whereas the combination of RANK/Fc plus an isotype-matched control for the anti-TNF had no effect on Ca release. Thus simultaneous inhibition of RANKL and TNF-alpha is necessary to reduce acid-induced, cell-mediated net Ca efflux from bone; however, additional osteoblast-produced factors must also be involved in acid-induced, cell-mediated bone resorption.