

## **Regulation of bone cell function by extracellular pH.**

TIMOTHY R. ARNETT

Department of Anatomy and Developmental Biology, University College London, Gower Street,  
London WC1E 6BT, UK

email: [t.arnett@ucl.ac.uk](mailto:t.arnett@ucl.ac.uk)

Elimination or buffering of the acid produced as a result of metabolism poses a fundamental problem for all multicellular organisms. The most basic function of the vasculature is to deliver nutrients and O<sub>2</sub> to cells and to remove waste products, including H<sup>+</sup> and CO<sub>2</sub>, which, in land vertebrates, are excreted via urine and expired air. The skeletons of land vertebrates contain a massive reserve of base, which is ultimately available as a 'failsafe' mechanism to buffer H<sup>+</sup> if the kidneys and lungs are unable to maintain acid-base balance within narrow limits. The classic cause of chronic, systemic acidosis is kidney disease, and this is associated with bone loss. Mild chronic acidosis often occurs as a result of ageing or menopause or because of dietary acid ingestion. Acute, severe systemic acidosis can be caused by gastroenteritis, where it is associated with increases in bone resorption indices; acute, severe acidosis is also readily induced by vigorous exercise. Acidosis can arise locally (at tissue level) as a result of reduced vascular supply due to inflammation, infection, tumours, wounds, diabetes, ageing, or simply as a result of increased cellular metabolism (and thus H<sup>+</sup> production) due to the stimulatory, mitogenic action of growth factors and cytokines.

The deleterious action of systemic acidosis on the skeleton has long been known but was generally thought to result simply from physico-chemical dissolution of bone mineral - ie, that the skeleton acts as a 'giant ion exchange column' to passively buffer systemic H<sup>+</sup>. However, it is now clear that this net buffering effect is cell-mediated rather than physico-chemical in nature. Bone resorption by cultured osteoclasts from all species studied to date is stimulated directly by H<sup>+</sup> ions. Osteoclasts are particularly sensitive to [H<sup>+</sup>] between pH 7.1-7.3, such that pH reductions of only a few hundredths of a unit cause a doubling of resorption pit formation. Below pH ~7.0, the stimulatory effect plateaus, whereas above pH 7.4, resorption is 'switched off'. Similar responses occur in calvarial bone organ cultures; moreover, H<sup>+</sup>-stimulated Ca<sup>2+</sup> release is almost entirely osteoclast-mediated, with a negligible physico-chemical component. Acidification is the key initial requirement for osteoclasts to be able to excavate resorption pits; once activated, osteoclasts can be further stimulated by a wide range of agents including parathyroid hormone, 1,25(OH)<sub>2</sub> vitamin D, ATP, ADP and RANK ligand. Thus, extracellular H<sup>+</sup> may be regarded as the long-sought 'osteoclast activation factor'. We recently made the surprising observation that osteoclastic resorption can also be activated (at alkaline pH) by low nanomolar concentrations of the alkaloid, capsaicin. The capsaicin receptor (TRPV1 or VR1) is a cation channel that is also activated by low pH and heat, and thus is a candidate receptor that could mediate osteoclast activation.

Acidosis also affects osteoblast function adversely. The mineralisation of bone matrix nodules deposited by osteoblasts in long-term culture is progressively blocked as pH is reduced, with complete inhibition at pH 6.9. This appears to be due not only to a marked increase in bone mineral solubility at low pH but also to strong inhibition of the expression/activity of osteoblast alkaline phosphatase (required for mineralisation); however, osteoblast growth and collagen production are unaltered at pH values as low as 6.9. These results may help explain the osteomalacia that can occur in chronic acidosis.

Considered together, these results indicate that a remarkable reciprocal relationship exists between osteoclast activation and matrix mineralisation by osteoblasts over the pH range ~7.4 to ~6.9. Thus, acidosis exerts a major 'double-negative' action on bone turnover/maintenance. Drugs that block acid-sensing receptors or shift acid-base balance in the alkaline direction may provide novel therapies for bone loss disorders.