

Deletion of the intestinal plasma membrane calcium pump, isoform 1, Atp2b1, in mice is associated with decreased bone mineral density and impaired responsiveness to 1, 25-dihydroxyvitamin D3.

KEYWORDS: 1 α ,25-dihydroxyvitamin D(3); Atp2b1; Bone density; Calcium transport; Intestine; Plasma membrane calcium pump; Pmca1

Abstract

The physiological importance of the intestinal plasma membrane calcium pump, isoform 1, (Pmca1, Atp2b1), in calcium absorption and homeostasis has not been previously demonstrated in vivo. Since global germ-line deletion of the Pmca1 in mice is associated with embryonic lethality, we selectively deleted the Pmca1 in intestinal absorptive cells. Mice with loxP sites flanking exon 2 of the Pmca1 gene (Pmca1(fl/fl)) were crossed with mice expressing Cre recombinase in the intestine under control of the villin promoter to give mice in which the Pmca1 had been deleted in the intestine (Pmca1(EKO) mice). Pmca1(EKO) mice were born at a reduced frequency and were small at the time of birth when compared to wild-type (Wt) littermates. At two months of age, Pmca1(EKO) mice fed a 0.81% calcium, 0.34% phosphorus, normal vitamin D diet had reduced whole body bone mineral density ($P < 0.037$), and reduced femoral bone mineral density ($P < 0.015$). There was a trend towards lower serum calcium and higher serum parathyroid hormone (PTH) and 1 α ,25-dihydroxyvitamin D3 (1 α ,25(OH) $_2$ D3) concentrations in Pmca1(EKO) mice compared to Wt mice but the changes were not statistically significant. The urinary phosphorus/creatinine ratio was increased in Pmca1(EKO) mice ($P < 0.004$). Following the administration of 200 ng of 1 α ,25(OH) $_2$ D3 intraperitoneally to Wt mice, active intestinal calcium transport increased ~2-fold, whereas Pmca1(EKO) mice administered an equal amount of 1 α ,25(OH) $_2$ D3 failed to show an increase in active calcium transport. Deletion of the Pmca1 in the intestine is associated with reduced growth and bone mineralization, and a failure to up-regulate calcium absorption in response to 1 α ,25(OH) $_2$ D3.