AAO Foundation Award Final Report

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Award Type	Biomedical Research
Project Title	Parathyroid Hormone Regulation of the ICER Promoter in Osteoblastic Cells
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Summary/Abstract	We previously showed that parathyroid hormone (PTH) induces inducible cAMP early repressor (ICER) in osteoblastic cells and mouse calvariae. PTH signaling in osteoblastic cells is transduced by PTH receptor 1, which is coupled to cAMP-protein kinase A (PKA), protein kinase C (PKC), and calcium signaling pathways. In the present study, we examined the role of these pathways in mediating PTH-induced ICER mRNA and protein expression in osteoblastic MC3T3-E1 cells. Using RT-PCR, we found that PTH(1-34), forskolin (FSK), and 8-bromo-cAMP (8Br-cAMP) induced ICER expression, while phorbol myristate acetate (PMA), ionomycin, and PTH(3-34) did not. Similar results were found for the induction of ICER protein. PKA inhibition by H89 markedly reduced PTH- and FSK-induced ICER expression, while PKC depletion by PMA had little effect. We also tested ICER induction by other osteotropic signaling agonists. Other cAMP-PKA pathway activators, such as PTH-related protein (PTHrP), induced ICER expression, while agents that signal through other pathways did not. PTHrP maximally induced ICER mRNA at 2-4 h, which then returned to baseline by 10 h. Finally, PTH, FSK, and PTHrP induced ICER in cultured mouse calvariae and osteoblastic ROS 17/2.8, UMR-106, and Pyla cells. We conclude that ICER expression in osteoblasts requires activation of the cAMP-PKA signaling pathway