2008

M3-Muscarinic Receptor Activation of ERK and Cell Growth Requires Calcium/Calmodulin-dependent Protein Kinases in MCF-7 Cells

John M. Schmitt
George Fox University, jschmitt@georgefox.edu

ellen Abell
George Fox University

Andrea Wagner
George Fox University

M3-Muscarinic Receptor Activation of ERK and Cell Growth Requires Calcium/Calmodulin-dependent Protein Kinases in MCF-7 Cells

Ellen Abell, Andrea Wagner and John Michael Schmitt

Biology, George Fox University, Newberg, OR

Abstract

The extracellular signal-regulated protein kinase (ERK) signaling pathway is found in diverse cells throughout the human body. ERK activation has been implicated in breast cancer cell growth and proliferation. Studies have shown that ERK is activated by carbachol, a G Protein-Coupled Receptor (GPCR) agonist, which increases intracellular calcium in MCF-7 cells. The calcium/calmodulin-dependent protein kinase (CaM K) family of proteins including CaM KK, CaM KI, and CaM KII can be activated by increased intracellular calcium. Our goal was to determine whether CaM Ks may be responsible for ERK activation and cell proliferation in carbachol-treated MCF-7 cells and evaluate which GPCR was responsible for these events. Carbachol treatment of MCF-7 cells triggered ERK 1/2 phosphorylation within 5 minutes. Treatment with KN-93, a general CaM Kinase inhibitor and the MEK inhibitor U0126 blocked ERK activation. Carbachol increased MCF-7 cell growth nearly 4-fold, an effect that was also dependent upon CaM Ks and MEK. Interestingly, CaM KK was responsible for ERK activation and cell growth. Pretreatment of MCF-7 cells with 4-DAMP, a selective M3 receptor antagonist, completely blocked carbachol's activation of ERK and cell growth. Taken together these results suggest that carbachol stimulated ERK phosphorylation and MCF-7 cell growth by the M3 subtype GPCR receptor perhaps through CaM KK.