2007

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# Carbachol Regulation of ERK and the Transcription Factor Elk-1 in MCF-7 Breast Cancer Cells

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Abstract

Cancer has numerous molecular, biochemical and physiological hallmarks including uncontrolled cell growth and proliferation. Previous studies on MCF-7 breast cancer cells have shown that both intracellular calcium levels and the extracellular signal-regulated protein kinase (ERK) is activated downstream of the G-protein coupled receptor (GPCR) agonist, carbachol. Calcium/calmodulin regulate the calcium/calmodulin-dependent kinase (CaM Ks) family of proteins that have been proposed to regulate ERK and transcription. Our goal was to determine the mechanism of carbachol activation on ERK and the transcription factor Elk-1 in MCF-7 cells. Our results suggest that 10 μM carbachol treatment of MCF-7 cells triggers ERK1/2 phosphorylation (pERK) and activation within 5 minutes. Interestingly, inhibition of the CaM Kinase family of proteins with the selective inhibitor KN-93 blocked carbachol activation of ERK. Similar to ERK regulation, Elk-1 was phosphorylated in response to carbachol treatment in an ERK- and CaM Kinase-dependent manner. Carbachol treatment of MCF-7 cells triggered nearly a 4-fold increase in cell proliferation by 96 hours, a result that was completely blocked by the muscarinic m3-subtype GPCR inhibitor, 4-DAMP. Consistent with these results, blockade of either CaM Kinase or ERK (with U0126) activities resulted in the inhibition of cell growth. Taken together our results suggest that carbachol treatment of MCF-7 cells activates ERK, the transcription factor Elk-1, and cell growth in a CaM kinase-dependent manner.