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# Carbachol Regulation of AKT in LNCaP Prostate Cancer Cells

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## Abstract

Hormones and agonists that enhance cell survival through binding specific G Protein-Coupled Receptors (GPCRs) are of particular interest in cancer cell survival. LNCaP cells have been shown to express muscarinic cholinergic receptors that are responsive to the agonist, carbachol. In addition, LNCaP cells specifically express the M3-subtype of GPCR's that may couple carbachol to Gq, increases in intracellular calcium, and activation of the intracellular  $Ca^{2+}$ /calmodulin-dependent protein kinases (CaM Ks). The CaM Kinase family of proteins includes CaM KII, CaM Kinase Kinase (CaM KK) and its substrates CaM KIV, CaM KI and the protein kinase AKT. AKT is an anti-apoptotic enzyme that phosphorylates BAD and inhibits caspase activation. Our goals were to examine the mechanism of carbachol activation of AKT in LNCaP prostate cancer cells and evaluate whether CaM Ks may be mediating carbachol's activation of AKT and cell survival in LNCaP cells. The results suggest that AKT phosphorylation was increased in response to a five-minute stimulation with 10 $\mu$ M carbachol in LNCaP cells which was blocked by the CaM K family inhibitor, KN-93 suggesting the involvement of the CaM Kinase proteins in the pathway. In contrast, there was no inhibition by the MEK inhibitor, U0126 suggesting that AKT is activated independently of MEK and ERK. Interestingly, the CaM KK inhibitor, STO-609 potentially inhibited carbachol's activation of AKT. Furthermore, our results indicate that carbachol treatment of LNCaP cells promoted cell survival through CaM Ks. Carbachol's survival effects also appear to be operating through the M3-subtype of GPCRs, CaM KK, and its phosphorylation of AKT.