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Abstract

AKT and its substrate BAD promote prostate cancer cell survival. Agonists, such as carbachol, and hormones that increase intracellular calcium concentration can activate AKT leading to cancer cell survival. LNCaP prostate cancer cells express the carbachol-sensitive M3-subtype of GPCR's that increase intracellular calcium and activate the family of Ca2+/Calmodulin-dependent Protein Kinases (CaM Ks). One type of CaM Kinase, CaM Kinase Kinase (CaM KK), directly phosphorylates AKT on threonine 308. AKT phosphorylation and activation can enhance cell survival through phosphorylation BAD protein and the subsequent blockade of caspase activation. Our goals were to examine the mechanism of carbachol activation of AKT and BAD in LNCaP prostate cancer cells and evaluate whether CaM KK may be mediating carbachol's activation of AKT and cell survival. The results suggest that carbachol triggered phosphorylation of both AKT and BAD in LNCaP cells. AKT and BAD phosphorylation were blocked by the selective CaM KK inhibitor, STO-609, as well as siRNA directed against CaM KK. Taken together this data suggests a role for CaM KK in the pathway. In addition, the bacterial toxin anisomycin triggered caspase activation in LNCaP cells that was blocked by carbachol treatment. Finally, our results suggest that carbachol treatment of LNCaP cells promoted cell survival through CaM KK and its phosphorylation of AKT.