SIGNALING PATHWAYS INVOLVED IN THE ACTH AND FGF2 GROWTH-RESPONSES OF PRIMARY RAT ADRENAL CELLS

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In Mattos & Lotfi (Mol Cell Endocrinol, 245, 2005) we reported that p-CREB mediates the anti-mitogenic effect of ACTH (corticotropin) in glomerulosa (G) and fasciculata/reticularis (F/R) culture cells through PKA, but not ERK pathway. Herein we analyzed the involvement of PKC and JNK-pathways in the activation of p-CREB and c-Jun-p proteins in these cells, stimulated with ACTH or FGF2. G and F/R cells were pre-treated with PKC, PKA and JNK inhibitors, and then treated with 10^{-9}M ACTH, using Western Blot assays. We also analyzed the proliferation of these cells with or without 10^{-7}M, 10^{-9}M or 10^{-12}M ACTH for 24-72h through Trypan Blue and MTS assay. We observed that after 72h of 10^{-7}M or 10^{-9}M ACTH treatment, G and F/R cells displayed significant growth inhibition ($P<0,001$) suggesting that, similar to acute treatment, sustained ACTH treatment displays an anti-mitogenic dose-dependent effect in adrenocortical cells *in vitro.* In G and F/R cells, ACTH induces p-CREB in a distinct ratio PKC and PKA-dependent way. In addition, the JNK/c-Jun cascade was activated by FGF2, but not by ACTH. Then, our results showed that, in G and F/R cells, ACTH activates the PKA and PKC pathways converging to CREB-protein, in contrast to activation of JNK/c-Jun protein and ERK pathways by FGF2 treatment. We suggest that PKA and PKC-CREB pathways might be answerable for the ACTH-anti-mitogenic-response of adrenal cells. FAPESP, PRP-USP, CNPq.