

Poster presentation

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## Upregulation of Egr-1 biosynthesis in pituitary gonadotropes following activation of GnRH and muscarinic acetylcholine receptors

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Stimulation of pituitary gonadotropes expressing the Gq/11-coupled gonadotropin releasing hormone (GnRH) and muscarinic M3 acetylcholine receptors with GnRH or carbachol upregulates the biosynthesis of the zinc finger transcription factor Egr-1. Receptor stimulation activates phospholipase C, leading to elevated cytosolic Ca<sup>2+</sup> levels following stimulation. Accordingly, GnRH- and carbachol-triggered biosynthesis of Egr-1 was blocked by BAPTA-AM, an intracellular calcium chelator. Ca<sup>2+</sup>-mediated activation of extracellular signal-regulated protein kinase (ERK) was accomplished via activation of protein kinase C and transactivation of the EGF receptor. Calmodulin was also required to connect GnRH and carbachol signaling with the upregulation of Egr-1 gene transcription. Lentiviral-mediated expression of a dominant-negative mutant of Elk-1, a key transcriptional regulator of serum response element-driven gene transcription, impaired GnRH- and carbachol-induced biosynthesis of Egr-1. Thus, Elk-1 connects the GnRH- and carbachol-induced signaling cascades in the nucleus with the Egr-1 gene. Lentiviral-mediated expression of MAP kinase phosphatase-1 (MKP-1), the enzyme that dephosphorylates and inactivates ERK, completely blocked Egr-1 biosynthesis following GnRH or carbachol stimulation, indicating that MKP-1 functions as a nuclear shut-of-device of these signaling pathways. Chromatin immunoprecipitation experiments revealed that Egr-1 bound *in vivo* to the regulatory regions of the basic fibroblast growth factor (bFGF) and transforming growth factor beta (TGFbeta) genes following stimulation of the cells with GnRH or carbachol. As a result, elevated levels of bFGF and TGFbeta mRNA

were detected in GnRH and carbachol stimulated gonadotropes, corroborating the view that Egr-1 transactivates the bFGF and TGFbeta genes following stimulation of the cells with GnRH or carbachol.