BMC Neuroscience

Poster presentation

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Up-regulation of tyrosine hydroxylase gene transcription by tetradecanoylphorbol acetate is mediated by the transcription factors Elk-1 and Egr-1

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from Annual Meeting of the Study Group Neurochemistry. International Conference of the Gesellschaft für Biochemie und Molekularbiologie 2006 (GBM 2006): Molecular pathways in health and disease of the nervous system
Witten, Germany. 28–30 September 2006

Published: 23 March 2007

BMC Neuroscience 2007, **8**(Suppl 1):P17 doi:10.1186/1471-2202-8-S1-P17

Tyrosine hydroxylase is the rate-limiting enzyme in the biosynthesis of catecholamines. Expression of the tyrosine hydroxylase gene is regulated at the transcriptional level by extracellular signaling molecules, including EGF, NGF, and glucocorticoids. We have analyzed the stimulation of tyrosine hydroxylase gene transcription by the phorbol ester 12-O-tetradecanoylphorbol-13-acetate (TPA) in noradrenergic locus coeruleus-like CATH.a cells and observed a striking enhancement of the transcriptional activation potential of the ternary complex factor Elk-1, a key transcriptional regulator of serum response element-driven gene transcription. Likewise, TPA strongly upregulated the biosynthesis of the transcription factor Egr-1 via distal serum response elements within the Egr-1 5'-flanking region. Subsequently, Egr-1 responsive transcriptional activation was observed. Overexpression of Egr-1 was sufficient to activate transcription of a tyrosine hydroxylase promoter/reporter gene, corroborating the view that the tyrosine hydroxylase gene is a target gene of Egr-1. Expression of dominant-negative mutants of Elk-1 or Egr-1 impaired TPA-induced stimulation of a tyrosine hydroxylase promoter/reporter gene transcription. In contrast, dominant-negative mutants of the transcription factors ATF2, ATF4, CREB, c-Jun and C/EBP did not change TPA-induced tyrosine hydroxylase promoter activity, indicating that these proteins are not part of the TPA-mediated signaling cascade directed towards the tyrosine hydroxylase gene.