P 42

The MEK-1 Inhibitor, PD98059 reduces dioxin-induced CYP1A1 expression

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Abstract

We studied whether kinase pathways are involved in TCDD-induced gene expression by treating specific kinase inhibitors including MEK1 inhibitor PD98059, p38 inhibitor SB202190, PI-3 kinase inhibitor Wortmannin or LY294002 or protein tyrosine kinase inhibitor Genestein and then tested the effects of individual inhibitors on TCDD-induced gene expression of cytochrome1A1 gene (CYP1A1). Our results show that PD98059, MEK-1 inhibitor reduces dioxin-inducible transcription of CYP1A1. p44/p42MAPK, that is phosphorylated by Mek-1, are phosphorlylated by treatment of TCDD, peaking at 1nM, 30min treatments. Overexpressions of p44/p42 MAPK dominant negative mutants suppress dioxin dependent transcription of DRE-driven reporter gene in a dose-dependent manner. Our results demonstrate that p44/p42 MAPK is essential for transcriptional activity of AHR/ARNT heterodimer. We found that PD98059 dose-dependently blocks TCDD-induced DRE binding of the AHR/ARNT heterodimer, thereby it reduces TCDD-induced gene expression. Therefore, our results indicate that Mek-1/p44/p42 MAPK pathway is involved in TCDD-induced gene expression. [This study was supported by a grant from Korean Research Foundation Grant (X01529) to H. Park]