P-76

CYP1A1 GENE EXPRESSION IS DOWN REGULATED BY HYPOXIC AGENTS

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Since hypoxia-inducible factor-1alpha (HIF-1alpha) and the arylhydrocarbon receptor (AhR) shared the AhR nuclear translocator (Arnt) for hypoxia- and AhR-mediated signaling, respectively, it was possible to establish the hypothesis that hypoxia could regulate *Cyp1a1* expression. In order to understand the mechanism of *Cyp1a1* gene expression, we demonstrated here that hypoxic agents such as cobalt chloride, desferrioxamine, and picolinic acid reduced the TCDD induced *Cyp1a1* promoter activity based on the determination of luciferase activity in Hepa I cells transfected with pm*Cyp1a1*-Luc. Also cobalt chloride inhibited the TCDD stimulated Cyp1a1 mRNA level as well as EROD activities in both Hepa I and MCF-7 cells. Hypoxic agents such as cobalt chloride, picolinic acid, and desferrioxamine showed inhibition of luciferase activity that was induced by 1nM TCDD treatment with dose dependent manner. Concomitant treatment of 150 μM ferrous sulfate with 1~100 μM desferrioxamine or 1~100 μM picolinic acid recovered from the hypoxic agents-inhibited luciferase activity that was stimulated by TCDD. Reciprocally, the hypoxic agents down regulated TCDD induced Cyp1a1 mRNA level and CYP1A1 enzyme activity in Hepa I cells.