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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 μ M ferrous sulfate with 1~100 μ M desferrioxamine or 1~100 μ M 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.