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Effect of HDAC inhibitors on the Ah Receptor mediated CYP1A1 transcription

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Acetylation of histone in chromatin is one mechanism involved in the regulation of gene transcription and is tightly controlled by the balance of acetyltransferase and deacetylase (HDAC) activities. In this study, we have investigated the effect of HDAC inhibitors on the promoter activity of AhR responsive gene, CYP1A1 using recombinant cell lines. Recombinant cell lines were prepared by transient or stable transfection with pCYP1A1-Luc under transcriptional control of the XRE. Here we tested various HDAC inhibitors, such as trichostatin A (TSA), suberoylanilide hydroxamic acid (SAHA), HC-toxin and a novel HDAC inhibitor, IN 2001. In the human breast cancer cell line, MCF-7 cells, HDAC inhibitors increased both basal and 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) stimulated CYP1A1 promoter activity. And also, in mouse Hepa 1c1c7 cells, HDAC inhibitors showed similar effect on the CYP1A1 promoter activity to that of MCF-7 cells. Our studies showed that TCDD plus HDAC inhibitor increased not only promoter activity of CYP1A1 but also induced CYP1A1 mRNA level in Hepa 1c1c7 cells. Furthermore, we have examined the effect of HDAC inhibitors using mcyp1a1-luc stably-transfected Hepa 1c1c7 cell. In this stable cell line, HDAC inhibitors increased only the basal promoter activity and did not increase the TCDD stimulated promoter activity. Thus, our results suggest histone acetylation is important in the AhR responsiveness. And AhR responsiveness can be potentiated by the inhibition of histone deacetylation, i.e. hyperacetylation of histone, which results in activation of *CYP1A1*gene expression.

Keyword : CYP1A1, HDAC inhibitor