TOX 7

Cytochrome P-450 3A4 proximal promoter activity by histone deacetylase inhibitor in HepG2 cell.

Kim JaYoungo, Ahn MeeRyung[1], Sheen YhunYhong
Ewha Womans University, College of Pharmacy, National Institute of Toxicological Research, Korea Food & Drug Administration[1]

Cytochrome P-450 3A4 (CYP3A4) is major enzyme in human liver, the role of this is detoxification and metabolizing more than 50% clinical drugs in use. Expression of CYP3A4 is transciptionally regulated by the Pregnenolone X receptor (PXR), of which human form is Steroid and Xenobiotics receptor (SXR). SXR is activated by wide range of endogenous and exogenous compounds, and then induces CYP3A4 gene expression. In the previous study, it has been known that proximal promoter (-864 to +64) does not response to chemical inducers such as pregnenolone 16a-carbonitrile (PCN), Rifampicin, Estrogen in terms of transcription of CYP 3A4 in cultured cells. Here, we developed luciferase reporter gene assay system to detect SXR-based CYP 3A4 transcriptional activity. We have used CYP3A4-Luc plasmid that contains proximal promoter of human CYP3A4 gene upstream of the luciferase gene. We did transient transfection of 3A4-luciferase gene and SXR. In the HepG2 cells transfected with CYP3A4-Luc, when rifampicin treatment was combined with histone deacetylase inhibitor (HDAC Inhibitor), such as Trichostatin A, Hc-toxin and IN 2001 of the luciferase activity was induced 10-20 fold over control.