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DIFFERENTIAL ACTIVATION OF TRANSCRIPTION FACTORS BY PEROXISOME PROLIFERATOR CIPROFIBRATE IN RAT LIVER AND CULTURED HEPATOCYTES

Jin Tae Hong
KFDA, National Institute of Toxicological Research
5 Nokbun-dong, Eunpyung-gu, Seoul, 122-704, Korea

Peroxisome proliferators induce hepatic peroxisome proliferation and hepatic tumor in rodents. Since they are not genotoxic, biochemical changes or changes in gene expression have been proposed as possible mechanisms. One of mechanism proposed is increasing of hepatic cell proliferation. Peroxisome proliferators increase cell proliferation transiently early after administration *in vivo*, whereas they are wealy mitogenic and are not comitogenic in cultured hepatocytes. In this study, we first compared the activation of transcription factors in rat liver and cultured hepatocytes to see whether the activation is consistant with the cell proliferation pattern. The activation of transcription factor NF-*k*B and AP-1 were increased in rat liver treated ciprofibrate for 2 weeks, but were not increased in cultured hepatocytes treated with 400 μM ciprofibrate. We next test the hypothesis that mitogenic factors might be significant in the cell proliferation of rat hepatocytes which may be lack in cultured hepatocytes. We therefore test the effect of addition of eicosanoids into cultured hepatocytes because eicosanoids have been known to act as a endogeneous hepatic mitogenic factor and previous study show that eicosanoids were decreased by ciprofibrate in cultured rat hepatocytes. The addition of certain concentration of eicosanoids combined with ciprofibrate much greatly increased the activation of transcription factor AP-1. This combination treatment also significantly increased mitogenic activation protein kinase and PKC activities. These result show that change of eicosanoid level(or ratio) may be significant in the activation of transcription factors *in vivo* by peroxisome proliferators.