HISTONE H3 PHOSPHORYLATION AND PHOSPHOACETYLATION IN THE LIVER OF RATS TREATED IN VIVO WITH ACUTE ETHANOL

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ABSTRACT

Epigenetic histone modification is emerging as a critical player in the cellular actions of ethanol. In this context, we administered ethanol intraperitoneally to rats, to mimic binge drinking in humans. A dose response and time course experiments revealed that histone H3 phosphorylation and phosphoacetylation increases in vivo in liver. H3 serine 28 phosphorylation was more sensitive than serine-10 to low dose of ethanol, 1.75 g/Kg, but both were not observed at 5 g/Kg. In contrast, phosphoacetylation was observed at 5 g/Kg. There was a biphasic response in phosphorylation of both serines with time while phosphoacetylation increased rapidly at the highest time point (4h). Phosphorylation of JNK, p38, and ERK MAP kinases increased along with liver injury i.e. apoptosis, necrosis, and steatosis. The mRNA expression of genes (i.e. c-Fos, c-Jun, MKP-1, LDL-r, TNFα, and PAI-1) that play role in alcoholic liver injury, were also modulated. ChIP assays revealed differential association of site specific phosphorylation and phosphoacetylation with gene promoters, i.e. serine 10 phosphorylation with c-Fos and c-Jun; serine 28 phosphorylation with c-Jun, and PAI-1; and K9/S10 phosphoacetylation with PAI-1. We demonstrate for the first time that ethanol binge induction of histone H3 phosphorylation and phosphoacetylation in vivo in liver are associated with the promoters of genes. Taken together, these data are relevant to the identification of "early" molecular processes involved in the binge induced liver injury.