Role of DNA methylation in intermittent ethanol exposure-induced changes in neuropeptide Y expression and anxiety-like behaviors

Binge alcohol drinking during adolescence causes molecular changes in the developing brain resulting in substance abuse and alcoholism in adulthood. DNA methylation is an important epigenetic mechanism that regulates neuronal gene expression leading to specific phenotypes. We have modeled the binge pattern of drinking by eight intraperitoneal injections of ethanol (2g/kg) or n-saline to adolescent rats during post-natal days (PND) 28-41 with a 2-day on/off paradigm. We have studied the effects of adolescent intermittent ethanol/n-saline (AIE/AIS) exposure on DNA methylation/demethylation and neuropeptide Y (NPY) expression in the amygdala and the resultant anxiety-like behaviors during adolescence and at adulthood (PND 92). AIE-exposed animals displayed anxiety-like behaviors after 24 hrs of last ethanol injection (ethanol withdrawal), which persisted until adulthood. Concomitantly, DNA methyltransferase (DNMT) activity, DNMT3b mRNA and DNA demethylating factors, i.e., GADD45a, b and g were found to be altered in the amygdala of AIE-exposed rats during adolescence and some of these changes persist in adulthood. To understand the down-stream molecular mechanisms by which DNA methylation may be regulating the anxiety-like and alcohol-drinking behaviors, we examined the DNA methylation specific to the NPY gene promoter and NPY protein levels in the amygdala. NPY protein levels were down-regulated in the central and medial amygdaloid structures of AIE-exposed rats at 24 hrs, with a persistent decrease in adulthood. Reciprocally, DNA methylation at the NPY gene promoter was increased in the amygdala of AIE adult rats, which is consistent with the increase in DNMT function and decrease in the GADD45g levels. To test if DNMT inhibition could reverse AIE-induced anxiety-like and alcohol-drinking behaviors, we treated AIS- and AIE-treated adult rats with 5'-azacytidine, a DNMT inhibitor. Treatment with 5'-azacytidine attenuated AIE exposure-induced anxiety-like behaviors and alcohol intake in adulthood. These results suggest that AIE-induced neuroadaptations alter the homeostasis between DNA methylation/demethylation pathways in the amygdala during adolescence with long-lasting changes persistent at adulthood causing anxiety-like and alcohol-drinking behaviors most likely via NPY gene expression. The novel results of the study raises the possibility of DNMT inhibitors as a promising therapeutic option to treat alcohol-abuse and co-morbid disorders (supported by NADIA grant from NIH-NIAAA to SCP).

Biography

Amul J Sakharkar completed his PhD in Biochemistry from Department of Pharmaceutical Sciences, Nagpur University, India. Subsequently, he received a postdoctoral fellowship at Pennington Biomedical Research Center in Baton Rouge, Louisiana studying the effects of brain trauma on blood brain barrier integrity. He attained additional postdoctoral training at the University of Illinois at Chicago (UIC) examining the role of epigenetics in alcoholism. He is currently a Research Assistant Professor at (UIC) in the Department of Psychiatry studying the impact of adolescent alcohol exposure on drinking behaviors at adulthood and its underlying molecular substrates.

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