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RNA N^6-methyladenosine modifications in the mesolimbic dopamine system of subjects with alcohol use disorder

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The rewarding effect of alcohol is mainly mediated by the mesolimbic dopamine system, including the amygdala (AMY), the hippocampus (HIP), the nucleus accumbens (NAc), the prefrontal cortex (PFC), and the ventral tegmental area (VTA). Alcohol consumption may alter the epitranscriptome of these brain regions. Our recent study demonstrated epitranscriptomic changes in postmortem NAc of subjects with alcohol use disorder (AUD). This study further investigated RNA N^6-methyladenosine (m^6A) modifications in postmortem AMY, HIP, PFC, and VTA of 12 European AUD subjects by comparing them to 12 matched control European subjects using the Arraystar m6A Single Nucleotide Array assay, detecting 9,274 m^6ACA sites across the epitranscriptome. In the AMY, 116 m^6ACA sites (103 mRNAs/7 ncRNAs) were differentially methylated (P<0.05&|FC|≥1.5), and the top pathways overrepresented by differentially methylated mRNAs included *Wnt Signaling, TGF-beta Signaling*, and *Axon Guidance*. In the HIP, 147 m^6ACA sites (142 mRNAs/6 ncRNAs) were differentially methylated (P<0.05&|FC|≥1.5), and the top pathways overrepresented by differentially methylated mRNAs included *TGF-beta Signaling, Toll-like receptor Signaling*, *and NF-kappa B Signaling*. In the PFC, 401 m^6ACA sites (365 mRNAs/9 ncRNAs) were differentially methylated (P<0.05&|FC|≥1.5), and the top pathways overrepresented by differentially methylated mRNAs included *Rap1 Signaling, Axon Guidance, and NF-kappa B Signaling*. Finally, in the VTA, 881 m^6ACA sites (722 mRNAs/21 ncRNAs) were differentially methylated (P<0.05&|FC|≥1.5), and the top pathways overrepresented by differentially methylated mRNAs included *MAPK Signaling, NF-kappa B Signaling, and Rap1 signaling*. In summary, alcohol consumption may alter the epitranscriptome of reward-related brain regions, leading altered gene expression and behavioral neuroadaptation to alcohol.