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Male Acss2 KO Mice Exhibit Decreased Voluntary Alcohol Intake and Blunted Ventral Striatal Chromatin and Gene Expression Changes After Drinking

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Metabolic-epigenetic interactions in the brain are emerging as key gene regulatory pathways that govern responses to environmental insults, including exposure to alcohol and other substances. Recently, we have outlined the critical role of metabolic enzyme Acetyl-CoA Synthase 2 (Acss2), which is nuclear and chromatin-bound in neurons. We found that Acss2 mediates the direct deposition of alcohol-derived acetate onto histones in the brain and is required for conditioned place preference for ethanol reward. Here, we further explored the role of this mechanism in a translational model of voluntary alcohol intake. We found that Acss2 KO mice, particularly males, consume significantly less alcohol during drinking in the dark. Genome-wide transcriptional profiling of key brain regions linked to substance use disorders revealed that Acss2 KO mice exhibit blunted gene expression changes in the ventral striatum following drinking. In line with the observed behavioral differences, the effect of Acss2 KO on transcription was more robust in male mice. Gene expression changes were also associated with depletion of ventral striatal histone acetylation (H3K27ac) in Acss2 KO mice compared to WT controls. Overall, our data outline the important role of Acss2 in orchestrating ventral striatal epigenetic and transcriptional changes during voluntary alcohol drinking, especially in males. Consequently, targeting this key metabolic-epigenetic pathway could be a promising new therapeutic avenue.