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Exploring Immature Neurons in the Adolescent Nucleus Accumbens and Their Connection to Cannabis Use

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Adolescent cannabis use has been linked to an elevated risk of developing substance use disorders and schizophrenia later in life. Despite this, the molecular mechanisms through which its psychoactive component, tetrahydrocannabinol (THC), influences cell type-specific developmental pathways remain unclear. In this study, we explore how adolescent THC exposure affects gene expression networks within different cell types of the nucleus accumbens (NAc) in mice using single nuclei (sn)RNA-seq analysis. Our investigation compared wild-type mice with heterozygous reeler mice, which exhibit reduced expression of Reln, a gene that modulates behavioral changes induced by adolescent THC exposure. While most gene expression networks, termed modules, were associated with either THC treatment or genotype independently across various cell types, we discovered three modules significantly associated with both THC exposure and Reln haploinsufficiency. These modules were linked to pathways involved in addiction, axon guidance, cell junction assembly, and chromatin remodeling. By integrating these findings with human genetic data from GWAS studies on substance use disorders and schizophrenia, we identified a module from a previously undescribed non-neurogenic, immature population of GABAergic neurons, termed GABA-2, that may contribute to the mechanisms linking Reln haploinsufficiency, adolescent cannabis exposure, and increased disease risk. We validated the presence of GABA-2 by RNA-FISH and showed that their abundance declines with age, suggesting a delayed maturation during adolescence. This research provides insight into cell type-specific mechanisms linking neurodevelopmental disruptions and chronic cannabis exposure, offering new directions for future studies.