

Multimodal Characterization of the Impact of Prenatal THC Exposure on Primate Brain Development

Cannabis legalization has been accompanied by increased use during pregnancy. Human epidemiologic studies associate prenatal cannabis exposure (PCE) with cognitive and psychiatric vulnerabilities in offspring; however, causal inference remains limited by confounding factors. Rodent models, while informative, fail to capture key features of primate cortical development, including prolonged neurogenesis, expanded association cortex, and neural stem cell (NSC) programs. Notably, we previously found that endocannabinoid signaling (ECS) genes are expressed in primate NSCs early in telencephalic development, whereas in rodents their expression emerges later in neurons. Thus, early PCE may exert effects on brain patterning and NSC function in primates that cannot adequately be modeled in rodents, underscoring the need for mechanistic studies in translational nonhuman primate models.

Here, we expose pregnant rhesus macaques to Δ^9 -tetrahydrocannabinol (THC), the principal psychoactive constituent of cannabis, from early to mid-gestation, corresponding to the first–second trimester in humans. Using a multimodal fetal-to-postnatal approach, we show that disruption of early corticogenesis during the NSC-to-neuron transition leads to lasting brain dysfunction. We observe that THC exposure reduces fetal intracranial volume and alters cortical synaptic density, as assessed by longitudinal in utero and postnatal structural MRI and SV2A PET imaging, respectively. Single-nucleus multiomics of fetal and infant macaque brains reveals region- and cell type–specific disruption of transcriptional and epigenetic programs regulating synaptogenesis and axon guidance. Complementary experiments in human induced pluripotent stem cell (iPSC)-derived brain organoids show reduced radial glial stem cell proliferation and premature neurogenesis following THC exposure.

This study provides a mechanistic framework linking prenatal cannabinoid exposure to altered molecular programs that shape neurodevelopmental trajectories and increase vulnerability to psychiatric and substance-use disorders in primates, with direct implications for public health policy and clinical guidance on cannabis use during pregnancy.

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