

Developmental Cannabis Exposure and the Protracted Effects On Brain and Behavior

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The developing brain is particularly sensitive to drug exposure which is of concern especially for marijuana (*cannabis sativa*) since it is the most abused illicit substance by teens and pregnant women, two vulnerable populations relevant for neurodevelopmental health. Despite the recent perceived low health risk of cannabis use by the general public, there is emergent clinical awareness about the spectrum of behavioral and neurobiological disturbances associated with developmental cannabis exposure such as anxiety, depression, psychosis, social impairments and drug addiction. Δ^9 -tetrahydrocannabinol (THC) is the phytocannabinoid in cannabis most linked to such psychopathologies and its concentration has increased in the cannabis plants commonly consumed today. Scientific questions central to our neurodevelopmental research relate to understanding the potential long-term consequences of THC on adult brain and behavior. Disturbances of the epigenome (chemical changes to the DNA and histone proteins that regulate gene transcription) have generally been hypothesized as the molecular machinery that underlies persistent, often tissue-specific transcriptional and behavioral effects observed within one's lifetime and even into subsequent generations. This presentation will highlight our molecular studies used to gain knowledge about transcriptional and epigenetic mechanisms associated with prenatal and adolescent THC exposure.

Our laboratory has utilized multidisciplinary strategies to investigate the developmental effects of cannabis through examination of postmortem human fetal brain specimens and rodent models that allow us to obtain direct mechanistic insights about specific long-term behavioral and neurobiological impact of THC. Gene transcription, epigenetic mechanisms and morphological parameters are studied in mesocorticolimbic brain regions such as the nucleus accumbens and medial prefrontal cortex highly implicated in addiction and psychiatric vulnerability. Moreover, *in vivo* gene manipulations are conducted to provide causal relationships with behaviors observed long after the developmental exposure to THC.

Our findings to date suggest significant impact of cannabis exposure during *in utero* or adolescent development on mesocorticolimbic neuronal systems relevant to features of reward, motivation, negative affect and goal-directed behaviors in adulthood. It is clear that cannabinoid exposure alters the normal epigenetic landscape and related neurobiological systems. Discussion of recent findings will also be placed in the framework of understanding cell-specific alterations. Additional evidence will be discussed regarding the potential for cross-generational effects of THC exposure that can influence the epigenome and behavior of future generations.

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