Topic DAT18-04: Effects of Cannabis Use and Cannabinoids on the Developing Brain **(R01, R03, R21)**

Purpose

To encourage research project applications to study of effects and functional consequences of cannabis and cannabinoid exposure on the developing brain, from pre-, peri-, and post-natal development through young adulthood in animal models and humans.

Background

Cannabis use has been stable, but substantial, in adolescents, and has increased in young adults and pregnant women in recent years. This parallels softening attitudes across all age groups about the perceived risk of harm and relaxed local laws and policies against cannabis use. In addition, various formulations of the cannabis plant, as well as two of its component cannabinoids: delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) have been suggested as treatments for a range of conditions, without a detailed understanding of either their beneficial or adverse effects, especially on the developing (and vulnerable) brain. Growing evidence suggests that exposure to cannabis and cannabinoids during prenatal, perinatal, postnatal, childhood and adolescent development may produce long lasting neurobiological and neurodevelopmental effects that could have wide-ranging impacts extending into adulthood, including reduced cognitive function and heightened vulnerability to multiple drug addictions. In animal models, early exposure to cannabinoids leads to specific neuronal alterations, especially in the nucleus accumbens enkephalin/D2 striatopallidal neurons, as well as dysregulation of repressive epigenetic marks, and impaired synaptic plasticity. These may result in behavioral outcomes, such as increased impulsivity and altered reward sensitivity. It is particularly important to understand how and when the brain is most vulnerable to the insult or injury by these substances, using both animal models as well as human studies.

Research Objectives

Studies in humans and animals have suggested adverse psychiatric, cognitive, and behavioral consequences of cannabis/cannabinoid exposure in both adults and children, often dependent on time of exposure; frequency of use; genetic and genomic factors, and environment. Research is needed on the impact of acute, as well as chronical cannabis/cannabinoid exposure on outcomes such as, molecular, cellular, and neurobiological alterations; structural and function brain imaging and connectivity; and behavior. Research areas of interest for this announcement include, but are not limited to, the following:

- Cellular and molecular mechanisms of cannabis or cannabinoid exposure on known and yet to be discovered receptor signaling in neurogenesis, migration, and neuronal and glial differentiation.
- Effects on chromatin remodeling, gene transcription, post transcriptional RNA processing and protein translation.
- Single nucleotide polymorphisms of cannabinoid receptors, FAAH, co-activators and other molecules, known or to be identified, that affect physiology in the presence of cannabis and cannabinoids.
- Changes in brain structure and activity as a function of cannabis/cannabinoid use, alone or in conjunction with other abused substances (i.e. nicotine, opioids, alcohol).
- Behavioral consequences of genetic, cellular and neuroanatomical changes induced by cannabis/cannabinoid exposure during development, such as:
    - Effects of early cannabis and cannabinoid exposures on critical aspects of cognitive processes (attention, memory, decision-making, impulsivity, etc.) in later life
    - Effects of cannabinoids, especially THC, THC agonists and antagonists, on cognitive, emotional and motivational processes at different stages of development
    - Vulnerability changes produced by early life cannabis/cannabinoid exposure, on subsequent drug sensitivity or the motivation for administering 'other' substances of abuse, and studies on the neurobiological mechanisms for cross-sensitization, potentiation, as well as accelerated transition to compulsive substance use disorders.

Instructions for submitting applications:

- Insert "**DAT**-" (four characters) in the beginning of the Project Title of the application. [Note: NIH limits the Project Title to 200 characters (including spaces and punctuation)].
- Insert the DAT Code (e.g., DAT18-01) before the first sentence of the abstract. (This is for internal NIDA tracking purposes only).

Relevant Funding Opportunities

Funding opportunities that can be used to pursue these and other research activities include, but are not limited to:

R01 NIH Research Project Grant (Parent R01 Clinical Trial Not Allowed) PA-18-484
R01 NIH Research Project Grant (Parent R01 Clinical Trial Required) PA-18-345
R03 NIH Small Research Grant Program (Parent R03 Clinical Trial Not Allowed) PA-18-488
R21 NIH Exploratory/Developmental Research Grant Program (Parent R21 Clinical Trial Not Allowed) PA-18-489
R21 NIH Exploratory/Developmental Research Grant Program (Parent R21 Clinical Trial Required) PA-18-344
Administrative Supplements to Existing NIH Grants and Cooperative Agreements (Parent Admin Supp Clinical Trial Optional) PA-18-591

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AREAS OF EXPERTISE

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- Cell and Molecular Imaging

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AREAS OF EXPERTISE

- Biobehavioral Research
- Developmental Disorders

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