Review

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At the Tip of an Iceberg: Prenatal Marijuana and Its Possible Relation to Neuropsychiatric Outcome in the Offspring

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ABSTRACT

Endocannabinoids regulate brain development via modulating neural proliferation, migration, and the differentiation of lineage-committed cells. In the fetal nervous system, (endo)cannabinoid-sensing receptors and the enzymatic machinery of endocannabinoid metabolism exhibit a cellular distribution map different from that in the adult, implying distinct functions. Notably, cannabinoid receptors serve as molecular targets for the psychotropic plant-derived cannabis constituent Δ^9-tetrahydrocannainol, as well as synthetic derivatives (designer drugs). Over 180 million people use cannabis for recreational or medical purposes globally. Recreational cannabis is recognized as a niche drug for adolescents and young adults. This review combines data from human and experimental studies to show that long-term and heavy cannabis use during pregnancy can impair brain maturation and predispose the offspring to neurodevelopmental disorders. By discussing the mechanisms of cannabinoid receptor-mediated signaling events at critical stages of fetal brain development, we organize histopathologic, biochemical, molecular, and behavioral findings into a logical hypothesis predicting neuronal vulnerability to and attenuated adaptation toward environmental challenges (stress, drug exposure, medication) in children affected by in utero cannabinoid exposure. Conversely, we suggest that endocannabinoid signaling can be an appealing druggable target to dampen neuronal activity if pre-existing pathologies associate with circuit hyperexcitability. Yet, we warn that the lack of critical data from longitudinal follow-up studies precludes valid conclusions on possible delayed and adverse side effects. Overall, our conclusion weighs in on the ongoing public debate on cannabis legalization, particularly in medical contexts.

Keywords: Epilepsy, Marijuana, Psychosis, Schizophrenia, Skunk, Stratification

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The developing central nervous system (CNS) relies on a wide array of signaling mechanisms with their precisely orchestrated cross-talk shaping a combinatorial code for neuronal development. This temporally defined procedure is reflected in the production, differentiation, and migration of neurons and glial cells (1–3). In addition to genetic predisposition, harmful environmental agents can potently impact brain development. These include alcohol and nicotine as unregulated substances and many types of illicit drugs. Marijuana (*Cannabis sativa*), its selectively cultivated subspecies (e.g., skunk), and its synthetic derivatives (designer drugs) are commonly consumed (4,5). According to the US Substance Abuse and Mental Health Services Administration, their use peaks between 15 and 30 years of age with a trend for continued consumption by people aged 30 to 40 years and over (6–8). Due to penal sanctions for cannabis possession and abuse in several European countries (9), potent synthetic cannabinoids, mimicking or amplifying psychoactive effects of Δ^9-tetrahydrocannabinol (THC), are offered as legal alternatives (10). The prevalence of synthetic cannabinoid use by adolescents is significantly higher in the United States (7.4%) than in European countries (e.g., .2% and 1.4% in the United Kingdom and Spain, respectively) without further increases in recent years (10). Alarmingly, cannabinoids are the substance chiefly abused by pregnant women: its prevalence exceeds 10% in the United States (7), while it remains largely unknown yet with predicted socioeconomic variability (1% to 16%) in Europe (9). This generation-driven pattern of cannabis use exposes the brain to THC during at least one critical developmental period: in utero development of fetus, childhood, or teenagehood (11).

A growing body of evidence demonstrates that agents that are generally considered moderately harmful to the mother when consumed at limited quantities (e.g., alcohol, nicotine, morphine, or cannabis) may pose severe threats—unrelated to miscarriage or placental deficits—to the fetus, providing the foundation of neurobehavioral teratology (12). CNS vulnerability is a leading fingerprint of harmful developmental drug effects and predominantly manifests as functional impairments in early childhood or adolescence, much less so by birth (13). These observations fuel the double-hit hypothesis that defines subthreshold stimuli as triggers of severe malfunction of sensitized yet nonsymptomatic neuronal circuits with often considerable delay in postnatal life (14,15). Nevertheless,

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cannabis-induced early prenatal lethality could be underestimated. Rodent and chick experiments show that marijuana embryotoxicity manifests as neural plate aplasia at early intrauterine time points, which, when considering their human equivalents (gestational days 15–19), would likely be clinically misinterpreted as a lack of embryo implantation (16).

In addition to existing sociopolitical, economical, and ethical arguments, recent campaigns aimed to decriminalize cannabis were motivated by current patterns of use and comparisons to alcohol, tobacco, heroin, and methamphetamine citing small-to-moderate adverse public health impact for cannabis (17). This view is particularly prevalent since this "soft drug" (18,19) causes seemingly reversible effects on cognitive abilities after abstinence (20) and leads to psychotic outcomes without relapse in adults (21). Case-control studies in the United Kingdom, however, indicate that high-potency cannabis variants (e.g., skunk) triple the risk (at earlier onset) of psychosis (22). Conversely, cannabidiol, a nonpsychotropic cannabis constituent, is reported as being a potent antipsychotic agent and indicated for disease treatment (23,24) since it appears to reduce the psychotropic action of THC (25). Magnetic resonance imaging showed that neither volumetric nor shape-based measures of brain regions driving conscious behavior are altered by daily marijuana use (26). Moreover, and for human offspring, prenatal marijuana does not induce gross anatomical deformities or deficits in vital functions directly by or after birth (27–29). This lends support to the double-hit hypothesis of THC-induced neuronal sensitization (but see embryotoxicity above), which is favored by THC's efficacious cross-placental transfer and excretion during lactation (30). As such, THC concentration of breast milk in humans may be up to eightfold higher than simultaneously measured maternal plasma concentrations (31). Therefore, it is plausible that continued maternal cannabis use during the first months postpartum could evoke neurological consequences in toddlers by 1 year of age (32) or later.

A more indirect way of cannabinoids to compromise pregnancy outcome and fetoplacental development is through their effect on maternal and placental hormone signaling. In animal models, endocannabinoid release in the magnocellular hypothalamus modulates glutamatergic and gamma-aminobutyric acid (GABA)ergic inputs to oxytocin neurons that tune their burst firing during parturition and lactation (33). At the periphery, endocannabinoid signaling was placed as a key node of placental autonomy and a trigger for trophoblast invasion (34). Likewise, the suckling reflex, one of the first perinatal functions to ensure the individual's survival, is shaped by type 1 cannabinoid receptor (CB_1R)-dependent signaling pathways (35), and its disruption experimentally by CB_1R antagonists provokes death.

Neuropsychiatric disorders represent a significant section of human illnesses in Western societies. The longitudinal Ottawa Prenatal Prospective Study and the Maternal Health Practices and Child Development Study showed that children of both low-risk (Ottawa Prenatal Prospective Study) and high-risk (Maternal Health Practices and Child Development Study) pregnant women exhibit signs of neuropsychiatric disturbances at later ages. In this review, we collected scientifically substantiated information showing that prenatal, perinatal, or adolescent cannabis exposure can interfere with brain ontogeny, inducing subtle and long-lasting neurofunctional impairments.

ENDOCANNABINOID SIGNALING IS A SUBSTRATE OF CANNABIS IN FETAL CNS

Initial understanding about how cannabinoid ligands exert their cellular actions was based on observations in the adult nervous system. This cross-correlational landscape has changed recently, with mechanistic analysis in embryonic brains and peripheral tissues dissecting the mode of action for THC and other CB_1R receptor ligands (36–38). In fact, by consensus, CB_1R is the major neuronal target of THC in both the adult and embryonic brain (27,36,39,40). Yet, signaling via type 2 cannabinoid receptors (CB_2R) (41), G-protein coupled receptor 55 (42), peroxisome proliferator-activated receptors (43), and transient receptor potential ion and cation channels (TRPM8, TRPA1, TRPV2, and probably also TRPV1) (44) has also been described (42,45). In particular, CB_2R (46) and TRPV1 (47) signaling may be relevant for neuronal development for their involvement in the control of neural progenitor proliferation (40) and neurite outgrowth and directional guidance (Figure 1).

The molecular identification of cannabinoid-sensing receptors prompted the exploration of endogenous ligands, which are lipophilic derivatives of arachidonic acid: N-arachidonoylethanolamide (anandamide [AEA]) (48) and 2-arachidonoylglycerol (2-AG) (49,50). In the adult brain, presynaptic CB_1Rs (51–54) produce state-dependent, bidirectional modulation of synaptic neurotransmission at both inhibitory and excitatory synapses (55). Significantly, endocannabinoids affect both short-term and long-term synaptic plasticity, and as a general rule, attenuate presynaptic neurotransmitter release. Disturbance of CB_1R-mediated control of synaptic plasticity is typically seen upon drug exposure and likely leads to neuronal circuit failures (56–59). Besides, CB_1Rs might also be found along the somatodendritic plasma membrane of neurons (60). Yet, the study of their trafficking, particularly endocytosis, suggests vastly different constitutive cycling and limited ligand binding.

Cannabis is clearly not THC alone. Instead, the large majority of plant components, whose relative composition depends on the plant variety (e.g., selectively cultivated subspecies), do not directly interact with CB_1Rs. Such CB_1R-independent, or more generally receptor independent, actions underpin the importance of distinguishing between different varieties of cannabis when describing their psychotropic and medicinal actions. Most plant cannabinoids investigated so far interact with TRPV1, TRPV2, TRPM8, and TRPA1 channels (61). The propyl analogue of THC, Δ^9-tetrahydrocannabivarin, a minor cannabinoid, is a neutral antagonist for CB_1R (62) and/or can weakly inhibit 2-AG biosynthesis (61). Similarly, the other most abundant cannabinoid, cannabidiol, has several non-CB_1R targets (63), including its inhibition of endocannabinoid inactivation (64). This, though indirectly, can augment CB_1R activity.

Understanding the role of endocannabinoid signaling in CNS ontogeny reached a critical advance when not only cannabinoid receptors (65) but also key nodes of the enzymatic machinery that controls endocannabinoid bioavailability were explored in the developing brain (66–68). Accordingly, α and β isoforms of *sn*-1-diacylglycerol lipases and *N*-acyl-phosphatidylethanolamine-selective phospholipase D generate 2-AG and AEA, respectively