Review

Biological Psychiatry

The Impact of Exposure to Cannabinoids in Adolescence: Insights From Animal Models

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ABSTRACT

The regular use of cannabis during adolescence is of particular concern because use by this age group seems to be associated with an increased likelihood of deleterious consequences, as reported by several epidemiologic studies. However, despite their unquestionable value, epidemiologic data are inconclusive. Modeling the adolescent phase in animals appears to be a useful approach to investigate the impact of cannabis use on the adolescent brain. In these models, adolescent cannabinoid exposure has been reported to cause long-term impairment in specific components of learning and memory and to have differential effects on anxiety, social behavior, and depressive-like signs. These findings suggest that it may represent, per se or in association with other hits, a risk factor for developing psychotic-like symptoms in adulthood. The neurobiological bases of this association include the induction of alterations in the maturational events of the endocannabinoid system occurring in the adolescent brain. Alterations in the endocannabinoid system may profoundly dysregulate developmental processes in some neurotransmitter systems, such as gamma-aminobutyric acid and glutamate, mainly in the cortex. The resulting picture strongly resembles the one present in schizophrenic patients, highlighting the translational value of this experimental approach.

Keywords: Adolescence, Cannabinoids, Endocannabinoid system, GABA, Glutamate

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Cannabis use is increasingly pervasive among adolescents, and the evolving policy surrounding the legalization of cannabis reaffirms the need to understand the relationship between cannabis exposure early in life and psychiatric illnesses. Epidemiologic data provide evidence that cannabis exposure in adolescence is an important contributing factor to psychiatric vulnerability; however, the molecular mechanisms underlying this association are poorly understood. Animal models of early cannabis exposure represent a unique tool to characterize the long-lasting behavioral consequences of cannabis use and to clarify the underlying cellular mechanisms. This review highlights the abnormal brain development and behavior present in animals treated with delta9-tetrahydrocannabinol (THC) or synthetic cannabinoids during adolescence.

THE ADOLESCENT BRAIN

The concept that the adolescent brain is still a "work in progress" has emerged over the last 15–20 years (1–4). The development of neuroimaging techniques has fueled this research because it has allowed scientists to study the changes in the adolescent brain directly in living humans. Although a comprehensive review is beyond the scope of this article, the most relevant findings are highlighted.

During adolescence, the brain undergoes dramatic changes in gross morphology characterized by loss of gray matter paralleled by an increase in white matter (5–8). These patterns are regionally and temporally specific, as they occur earlier in more primitive brain regions and later in phylogenetically newer regions, with the most anterior regions of the frontal and temporal lobes being the last to attain adult organization (6,7,9). Animal and human autopsy work suggests that the process of synaptic pruning may play a role in the decrease of gray matter (10,11). From a functional point of view, synaptic pruning represents a developmental advance because it should lead to more efficient patterns of neural communication. The white matter increase, related to increased myelination or axon caliber or both, may indicate that axons become more organized and coherent, creating more efficient neural networks (12). Refinement of circuitry connectivity has been reported to occur mainly among the prefrontal cortex (PFC) and other areas such as the amygdala, striatum, and thalamus (13,14). Moreover, as a result of all these dynamic changes, it is possible that some circuitries in the adolescent brain differ from the adult ones, as has recently been suggested for brain reward circuitry (15). It appears that this circuitry might involve basal ganglia regions that are not classically associated with reward processing in adults (i.e., the dorsal striatum more than the ventral striatum).

Animal models of adolescence have been essential for obtaining information about the neurochemical changes that occur as a function of age. Studies in rodents support the observation that different neurotransmitter systems undergo developmental changes during the adolescent transition period. Dopamine receptor expression peaks during adolescence in cortical and subcortical areas (16,17). A similar

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pattern was demonstrated for dopamine neuron activity (18). The balance of excitatory and inhibitory neurotransmission is vastly different in adolescents compared with adults. The GABAergic system undergoes refinement until the end of adolescence in the neocortex, whereas it reaches mature properties before the onset of puberty in the hippocampus (19–21). Less is known about the glutamatergic system; however, it is accepted that most pruning involves the asymmetric synapses that are excitatory in nature and contain glutamatergic receptors (22). Dynamic changes in the expression of different subunits of glutamate *N*-methyl-D-aspartate (NMDA) and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors have been described in the PFC from adolescence to adulthood (23). Moreover, a sharp decrease in the NMDA/AMPA ratio in the cortical fast-spiking interneurons occurs in adolescence (24).

The perfectly orchestrated occurrence of all these dynamic changes is fundamental for attaining a correctly shaped adult brain. Any interference with these developmental processes might represent a risk factor for mental disease.

THE ENDOCANNABINOID SYSTEM IN THE ADOLESCENT BRAIN

The endocannabinoid system is a lipid signaling system consisting of specific cannabinoid receptors (CB_1 and CB_2 receptors), endogenous ligands (mainly anandamide and 2-arachidonoylglycerol), and a battery of enzymes responsible for the synthesis and degradation of the ligands. Despite the important role of the endocannabinoid system in brain development (25,26), little is known about its status during adolescence. The few experimental data highlight the dynamic nature of this system during adolescence, mainly in the mesocorticolimbic structures (e.g., PFC, nucleus accumbens, caudate putamen), areas involved in reward, motivation, and cognition. CB_1 receptor density increases during the transition from adolescence to adulthood (23,27–30), a developmental window when other neuroreceptor systems have already started undergoing pruning. The efficacy of CB_1 receptor coupling with G proteins through adolescence does not show significant alteration, at least in the PFC, implying that CB_1 receptors seem to be more efficient in adolescence (23). Few data are available regarding changes in the level of the two main endocannabinoids, anandamide and 2-arachidonoylglycerol, during adolescence. In male rats, a continuous increase in PFC anandamide levels throughout the adolescent period was reported, anandamide being almost three times higher in later adolescence (29). However, 2-arachidonoylglycerol concentrations in the same brain area were lower in later adolescence, a finding paralleled in the nucleus accumbens. A similar picture was observed in the PFC of female rats, with anandamide levels increasing from mid to late adolescence and then decreasing into adulthood and 2-arachidonoylglycerol levels first decreasing and subsequently increasing (23).

Moreover, despite the dynamic changes observed in endocannabinoid levels, the activity of fatty acid amide hydrolase and of monoacylglycerol lipase did not show any variation throughout the developmental window, suggesting a more likely involvement of the synthetic enzymes in regulating their levels. Finally, Lee *et al.* (31), in a study using male rats, reported that anandamide, oleoylethanolamide, and palmitoylethanolamide increased from preadolescence to early adolescence and then decreased between early and late adolescence in the amygdala, hippocampus, PFC, and hypothalamus. These temporal changes in tissue *N*-acylethanolamine content were coupled with opposite changes in fatty acid amide hydrolase activity, suggesting that they were triggered by a transient alteration in their metabolism. Collectively, these studies emphasize the active and dynamic nature of development of the endocannabinoid system during the adolescent period.

Another important point is the clarification of the physiologic role of the endocannabinoid system in events occurring in the adolescent brain. Rubino *et al.* (23) recently demonstrated that the endocannabinoid tone is fundamental to the occurrence of some maturational processes within the glutamatergic system in the PFC. Administration of the CB_1 receptor antagonist AM251 from early to late adolescence significantly prevented the decrease in postsynaptic density-95, GluN2A, and GluA2, suggesting that the endocannabinoid tone could play a role in the elimination of excitatory synapses and thus in pruning. On this basis, pharmacologic or environmental factors interfering with the physiologic role played by the endocannabinoid system in adolescent neuronal remodeling could lead to altered brain maturation.

LONG-LASTING EFFECTS OF CANNABINOID EXPOSURE DURING ADOLESCENCE

Emotional Reactivity and Social Behavior

Exposure to cannabinoids in adolescent rodents leads to dysregulation of emotional processes in adulthood (Tables 1 and 2). Chronic administration of THC or synthetic cannabinoids (WIN 55,212-2 or CP-55,940) during adolescence was shown to decrease social behavior later in life in both sexes (20,32–36). When general anxiety was assessed using the elevated plus maze or the open field test, contrasting data were reported, again in both sexes. Adult animals that were exposed to cannabinoids during adolescence showed no changes in their behavior (37–42), an anxiolytic-like response (42–44), or even anxiety (45). This lack of consistency regarding anxiety studies might be due to differences in the cannabinoid compound used (synthetic vs. natural), the precise developmental period of exposure, the strain of animals used, or the behavioral test used to measure anxiety as well as the well-known biphasic effect of endocannabinoids on anxiety (46,47).

Finally, adolescent exposure to THC or WIN 55,212-2 also induced passive coping strategy in the forced swim test and anhedonia, measured as sucrose preference or palatable food consumption (20,36,37,39). This finding suggests the presence of dysfunction in motivational processes, especially among female animals (37). Along the same line, Chadwick *et al.* (48) reported that adolescent exposure to CP-55,940 decreased sexual motivation in adult female rats. As a whole, these findings suggest the presence of altered emotional reactivity and hedonic processes after adolescent cannabinoid exposure.

Table 1. Effects of Adolescent Cannabinoid Exposure on Emotional Behavior in Male Animals

Adolescent Treatment	Affected Behavior and Time of Testing	References
WIN 55,212-2, 1.2 mg/kg 0, 1, or 2 injections daily (PND40–65)	PND85: ↓ social behavior	(32)
CP-55,940, .15–.20–.30 mg/kg (PND30–50)	PND86: ↓ social behavior	(33)
THC, 1–5 mg/kg irregularly (PND32–55)	PND70: ↓ social behavior	(35)
THC, 2.5–5–10 mg/kg twice daily (PND35–45)	PND75: No changes in anxiety (EPM, OF); no changes in FST parameters; ↓ sucrose preference	(37)
CP-55,940, .4 mg/kg (PND28–38)	PND100: ↓ time in closed arms in EPM	(38)
WIN 55,212-2, .2 mg/kg or 1 mg/kg (PND30–50)	PND70: No changes in anxiety (EPM, OF); ↑ immobility in FST (low dose); no changes in FST (high dose); ↓ sucrose preference	(39)
CP-55,940, .4 mg/kg (PND28–43)	PND64: No changes in anxiety (EPM)	(40)
WIN 55,212-2, 1 mg/kg twice daily (PND35–48)	PND60–70: No changes in anxiety (EPM)	(41)
THC, 2–4–8 mg/kg (PND43–45)	PND70–80: No changes in anxiety (EPM) in Fisher rats; ↑ open arm time (EPM) in Lewis rats	(42)
CP-55,940, .4 mg/kg (PND35–45)	PND75: ↑ open arm time (EPM); no changes in OF parameters	(43)
WIN 55,212-2, 1.2 mg/kg 0, 1, or 2 injections daily (PND40–65)	PND90: ↑ open arm time and entry (EPM)	(44)
THC, 2.5–5–10 mg/kg (PND28–45)	PND71: ↓ time in the center (OF)	(45)

EPM, elevated plus maze; FST, forced swim test; OF, open field; PND, postnatal day; THC, delta9-tetrahydrocannabinol.

Cognition

Adolescent exposure to synthetic or natural cannabinoid agonists induced impairments in the performance of the classic or spatial version of the novel object recognition test in adulthood in rodents (20,33–36,49–51). Similarly, spatial working memory deficits (tested by the eight-arm radial maze) were described after adolescent THC exposure in adult rats (52,53). A persistent THC effect selective for spatial working memory was also observed under well-controlled experimental conditions in adolescent monkeys (54). Finally, adult animals exposed to WIN 55,212-2 in adolescence showed impairments in the attentional set-shifting task and thus in cognitive flexibility (55). In contrast, no lasting effects of adolescent cannabinoid exposure were observed in pure spatial memory measured in the Morris water maze (38,49,56) or in aversive memory (52,53). These data seem to suggest that adolescent cannabinoid exposure might affect the forms of memory where PFC plays a role.

Psychosis

Experimental studies focused on long-lasting effects of adolescent cannabinoid exposure on psychotic-related behaviors in adult rodents are still very scarce, but represent a key point for determining whether cannabis abuse in adolescence represents a risk factor for developing psychosis (schizophrenia) later in life. Positive symptoms of schizophrenia, such as auditory hallucinations and delusions, are uniquely human, so the literature on animal models of these symptoms has focused on two main categories of behaviors: locomotor hyperactivity and disruptions of prepulse inhibition (PPI). The cross-species nature of startle and PPI makes it easy to use animal models of gating deficits, and so measurements of sensorimotor gating are among the most widely used physiologic markers in experimental studies of schizophrenia (57). Impairments in PPI in rats and mice were observed long after chronic treatment with the cannabinoid agonist WIN 55,212-2 in adolescence, suggesting the presence of disrupted sensorimotor gating (44,51,58). In contrast, other groups reported no alterations in this behavior (59–61). The reason for this discrepancy is unclear: all groups used synthetic cannabinoid agonists, but the last three groups performed a longer treatment (15 or 21 days) with the same dose of agonist (CP-55,940 or WIN 55,212-2), triggering a deep state of tolerance in animals. The former groups instead performed a shorter treatment (10 days) or used an irregular protocol of injections (none, one, or two daily injections for 25 days), and this could have led to a less profound tolerance.

Rodent locomotor hyperactivity, either at baseline or after treatment with psychoactive drugs, such as amphetamine or phencyclidine (PCP), has become widely used as a behavioral tool to investigate agitation present in human psychosis. Few authors have investigated basal locomotor activity extensively in adult animals with pre-exposure to cannabinoids during adolescence, and they reported discrepant results. No significant alterations in the open field recordings after CP-55,940

Table 2. Effects of Adolescent Cannabinoid Exposure on Emotional Behavior in Female Animals

Adolescent Treatment	Affected Behavior and Time of Testing	References
THC, 2.5–5–10 mg/kg twice daily (PND35–45)	PND75: ↓ social behavior; no changes in anxiety (EPM, OF); ↑ immobility in FST; ↓ sucrose preference; ↓ high palatable food intake	(20,36,37)
CP-55,940, .15–.20–.30 mg/kg (PND30–50)	PND73: ↓ social behavior	(34)
CP-55,940, .4 mg/kg (PND28–38)	PND100: ↓ time in closed arms in EPM	(38)
CP-55,940, .4 mg/kg (PND28–43)	PND64: No changes in anxiety (EPM)	(40)
CP-55,940, .4 mg/kg (PND35–45)	PND75: ↑ open arm time in EPM; no changes in OF parameters	(43)
THC, 2.5–5–10 mg/kg (PND28–45)	PND71: ↓ time in the center (OF)	(45)
CP-55,940, .4 mg/kg (PND35–45)	PND75: ↓ sexual motivation	(48)

EPM, elevated plus maze; FST, forced swim test; OF, open field; PND, postnatal day; THC, delta9-tetrahydrocannabinol.

Table 3. Interactions Between Exposure to Cannabinoids During Adolescence and Specific Gene Variants

Genetic Modification	Adolescent Treatment	THC Effect[a]	References
COMT KO		Mainly in males: ↑ exploratory activity; ↑ impairment in spatial working memory; ↓ anxiety	(68)
		↑ PPI disruption; ↑ impairment in social behavior; ↑ impairment in social novelty preference	(60)
Nrg1 TM HET	Acute THC	↓ anxiety; ↓ impairment in social behavior	(73)
BDNF HET	CP55,940	↔ learning and memory; ↑ PPI disruption (males only)	(61)

BDNF HET, brain-derived neurotrophic factor heterozygous mutation; COMT KO, catechol-*O*-methyltransferase knockout; Nrg1 TM HET, neuroregulin transmembrane domain heterozygous mutation; PPI, prepulse inhibition; THC, delta9-tetrahydrocannabinol.

[a]THC effect in genetically modified mice vs. THC effect in wild-type mice.

(43) and THC (37), the presence of locomotor hyperactivity after WIN 55,212-2 (44), and reduced baseline locomotor activity after CP-55,940 (61) were reported. Our group observed more recently that adolescent exposure to THC increased the locomotor activating effect of acute PCP in adulthood (20). Similarly, PCP-induced stereotyped behavior was significantly enhanced in THC-treated rats.

Two-Hit Hypothesis of Schizophrenia and Adolescent Cannabinoid Exposure

It is accepted that the development of schizophrenia cannot be ascribed to single gene mutations or to a single environmental factor. Instead, multiple factors (e.g., gene polymorphisms that enhance risk, environmental events such as stress or drug abuse) can synergize to trigger disease onset, a model commonly known as the "two-hit" hypothesis of schizophrenia (62–64). Cannabis abuse may precipitate psychosis in vulnerable individuals, similar to a two-hit effect (65–67) (Table 3). The catechol-*O*-methyltransferase (COMT) gene encodes the COMT enzyme, which is involved in the degradation of dopamine, particularly in the PFC (68). It was demonstrated in humans that the relationship between cannabis use during adolescence and subsequent psychosis is influenced by the COMT genotype (69). In adult COMT knockout mice, adolescent THC administration induced a larger increase in exploratory activity, greater impairment in spatial working memory, and a stronger antianxiety effect than in wild-type mice. This effect was primarily seen in male animals (68). In addition, COMT knockout mice were more vulnerable to the disruptive effects of adolescent THC treatment on PPI as well as on sociability and social novelty preference (60).

Another gene relevant for schizophrenia is the one encoding for neuroregulin (Nrg1), a neurotrophic factor involved in axonal guidance, myelination, and GABAergic and glutamatergic neurotransmission (70). Nrg1 variants have been associated with dysfunction in numerous schizophrenia-relevant endophenotypes (71,72).

Acute THC exposure in adolescent transgenic mice containing a heterozygous mutation in the neuroregulin transmembrane domain (Nrg1 TM HET) was less anxiogenic than in wild-type animals (73). Similarly, chronic THC exposure induced a lower reduction in investigative sniffing in the social interaction test. It seems that this mutation might exert some protection toward THC effects. This behavioral picture in Nrg1 TM HET mice was paralleled by different alterations in CB_1, 5-hydroxytryptamine 2A, and NMDA receptor binding density in brain regions relevant to schizophrenia. Moreover, Nrg1 TM HET mice, 2 days after the last THC exposure, expressed a different protein profile in the hippocampus compared with wild-type mice (74). Proteins selectively altered included those that affect synapse formation and the dynamics of dendritic spines.

Finally, some studies focused on the brain-derived neurotrophic factor (BDNF) gene, which is involved in brain development and neuroplasticity (61). In female psychotic patients carrying the val66met BDNF polymorphism, cannabis use was associated with onset of the disease 7 years earlier (75). Adolescent CP-55,940 exposure in BDNF heterozygous mice did not modify learning and memory later in life (61). In contrast, male two-hit mice, but not female mice, were hypersensitive to the effect of acute CP-55,940 on sensorimotor gating. This effect may be related to the upregulation of CB_1 receptor density found in the nucleus accumbens.

Besides a gene × environment relationship, an environment × environment interaction might occur. For example, Schneider and Koch (76) demonstrated that neonatal rodents subjected to prefrontal cortex lesioning showed greater impairment in various forms of social behavior and in object recognition memory after WIN 55,212-2 exposure in adolescence. Similarly, exposure to THC in adolescence produced a greater cognitive impairment in rats with chronic PCP treatment (77) and a larger disruption of PPI in rats reared in social isolation (78). In animal models of stressful events early in life (maternal deprivation/separation), animals with adolescent exposure to THC or CP-55,940 had different behavioral outcomes compared with nonstressed control animals. No effect, increased cannabinoid-induced effect, or even decreased cannabinoid-induced effect may arise depending on the sex of the animals and the considered behavior (59,79,80). As further evidence of the existence of a complex interaction between adolescent cannabinoid exposure and animal models of schizophrenia, WIN 55212-2 administration in adolescence did not exacerbate the behavioral and electrophysiologic changes (increased locomotor response to amphetamine administration and increased number of spontaneously active dopamine neurons in the ventral tegmental area) present in the methylazoxymethanol acetate developmental disruption model of schizophrenia (55). WIN 55212-2 treatment attenuated the locomotor response to amphetamine in methylazoxymethanol acetate rats without affecting dopamine neuron activity. As a whole, the interaction between a previous hit (genetic or environmental) and cannabinoid exposure in adolescence might result in a "protective" or detrimental effect depending on the considered genetic profile, sex, and stress level.

POSSIBLE CELLULAR MECHANISMS

The first target of exogenous cannabinoids is the endocannabinoid system, and alterations in components of this system are expected after exposure to these compounds. A profound CB_1 receptor downregulation and desensitization has been described after chronic THC treatment during adolescence in different cerebral areas (23,37,81). This effect was greater in female than in male rats, probably as a result of the recently described different THC metabolism in the sexes (82) and the alleged presence of more efficient receptors in adolescent female rats (83). Moreover, in adult female rats, adolescent exposure to THC significantly reduced CB_1 receptor density in different brain areas, whereas the downregulation was less marked in male rats (79). Finally, in the PFC of THC-exposed female animals, the significant decrease of CB_1 receptor binding described immediately after the last THC injection and still present in adulthood was paralleled by a significant decrease of anandamide levels (23). This finding suggests that adolescent cannabinoid exposure modifies the dynamic changes present in the endocannabinoid system during adolescence, and this could have implications for the neurodevelopmental processes in which this system might play a role. The different impact of adolescent cannabinoid exposure in males and females, together with the already known sex-specific differences in endocannabinoid system functionality (84,85), could also account for the different phenotype observed in adulthood in the two sexes.

In rodent models of chronic adolescent cannabinoid exposure, one of the most relevant events is the long-lasting negative impact on working memory and decision making, which are refined during adolescence and are mainly dependent on the functional maturation of the PFC. On these bases, articles on the developmental impairment of the GABAergic and glutamatergic system following chronic cannabinoid exposure in adolescence are mainly focused on the PFC. The endocannabinoid tone seems to play a fundamental role for the occurrence of some maturational processes within the glutamatergic system in the PFC (23). However, to date, only two studies have tested the hypothesis that excessive stimulation of CB_1 receptors during adolescence might affect the functional maturation of the glutamatergic system. In female animals, adolescent CP-55,940 or THC exposure induced a significant decrease in K^+-evoked glutamate release in the adult hippocampus (86) as well as alterations in the maturational fluctuations of NMDA and AMPA subunits in the PFC, leading to larger amounts of GluN2B and GluA1 in adulthood (23). Because NMDA receptors play a critical role in regulating the periadolescent maturation of GABAergic networks in the PFC (87), it might be alleged that the GABAergic system also could be affected by adolescent cannabinoid exposure. Cass *et al.* (88) showed that WIN 55,212-2 exposure during early adolescence or midadolescence, but not in late adolescence or adulthood, caused a functional downregulation of GABAergic transmission in the PFC. Similarly, Zamberletti *et al.* (20) demonstrated that adolescent THC exposure resulted in reduced glutamic acid decarboxylase 67 and basal GABA levels in the same brain area.

These findings indicate that adolescent cannabinoid exposure seems to affect not only the endocannabinoid system but also the glutamatergic and GABAergic systems. These three systems are important in shaping cortical oscillations, a neural network activity in the neocortex (89) that is implicated in cognitive and sensory processing (90,91). Cortical oscillations are abnormal in patients with schizophrenia, in which cognitive and sensory functions are also altered (92,93). Chronic exposure to WIN 55,212-2 or THC during adolescence, but not adulthood, permanently suppresses pharmacologically evoked cortical oscillations (94), and this effect seems to be mediated partly by CB_1 receptors; however, there is also evidence of the involvement of CB_2 and noncannabinoid receptors (95).

Because the adolescent brain is characterized by a high rate of synaptic pruning, especially in regions that govern higher cognitive function such as the PFC (96), and it has been suggested that the endocannabinoid system might be involved in the process of synaptic pruning (23), another event that might play a part in the brain alterations triggered by adolescent cannabinoid exposure should include changes in dendritic spines. In male rats, adolescent exposure to WIN 55,212-2 significantly decreased spine density in the nucleus accumbens immediately after treatment (97). Similarly, adolescent THC reduced spine density in the dentate gyrus of the hippocampus in adulthood, paralleled by a significant decrease in dendrite length and number (53). Instead, a significant decrease in the number of spines present on PFC pyramidal neurons was observed in adult female rats exposed to THC in adolescence (23).

Besides the effects on neuronal populations, treatment with WIN 55,212-2 in adolescence may also induce an increase in the survival of oligodendroglia precursors in the striatum and PFC immediately after treatment (41). In general, the role of glia in cannabinoid-induced effects is still unknown, but because of the increasing importance for brain function of the interaction between glial cells and neurons, future studies are needed to decipher it.

CONCLUSIONS

Preclinical data summarized here support the hypothesis that adolescent exposure to cannabinoids might alter dynamic changes in the endocannabinoid system, leading to impaired brain maturation. This impaired brain maturation provokes the appearance of an altered phenotype later in life characterized by traits similar to psychotic/depressive-like behaviors. Despite the debate over a specific age range for the adolescent period in rodents and the influence of sex-dependent hormones, data indicate that heavy cannabis abuse per se during this developmental window may represent a risk factor for the development of psychiatric disorders. Of utmost importance are the recent articles that have tried to clarify the cellular alterations involved in the altered phenotypes (Figure 1). Their findings indicate that alterations in the endocannabinoid system affect GABAergic and glutamatergic transmission mainly in the cortex, profoundly affecting the functional role of this region. The picture present in patients with schizophrenia characterized by reduction in GABAergic transmission and cortical oscillation as well as altered glutamatergic receptor distribution also has been observed in the PFC of adult animals exposed to cannabinoids in

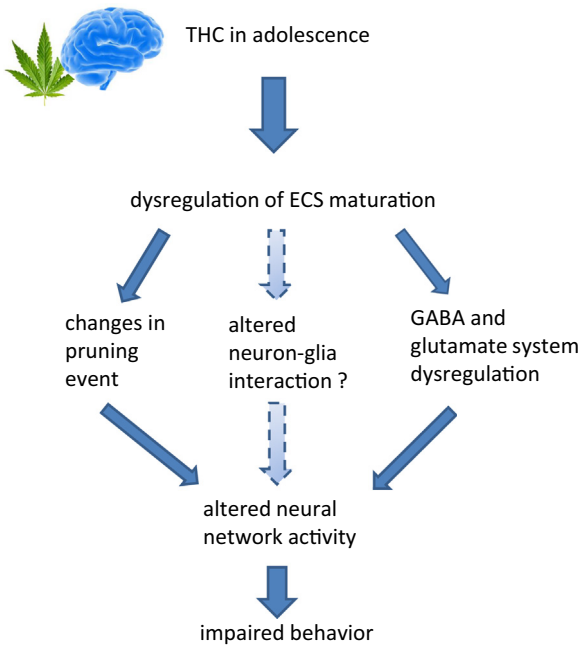

Figure 1. Diagram representing the most important events altered by adolescent cannabinoid exposure leading to impaired behavior in adulthood. ECS, endocannabinoid system; GABA, gamma-aminobutyric acid; THC, delta9-tetrahydrocannabinol.

adolescence, highlighting the translational value of this approach. Finally, because of emerging evidence for the multifaceted role of glial cells in schizophrenia, further studies are needed to understand better the role of glia and mainly of the glia-neuron interaction in the phenotype triggered by adolescent cannabinoid exposure because it may represent another fundamental step in regulating synaptic plasticity. Similarly, the possible role of CB_2 receptors in these events should also be investigated.

Less conclusive are the data on cannabis abuse in adolescence as a "second hit" for schizophrenia because protective or detrimental effects have been observed depending on the nature of the "first hit," suggesting that cannabis exposure can affect behavior differently depending on its interaction with the personal history or genotype of the individual. However, the two-hit hypothesis involving cannabis as a second hit warrants further attention and should be thoroughly studied because it can represent a tool to suggest withdrawal from cannabis for populations with genetic risk.

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ARTICLE INFORMATION

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