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LONG LASTING CONSEQUENCES OF CANNABIS EXPOSURE IN ADOLESCENCE

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SUMMARY

Despite the increasing use of cannabis among adolescents, there are little and often contradictory studies on the long-term neurobiological consequences of cannabis consumption in juveniles. Adolescence is a critical phase for cerebral development, where the endocannabinoid system plays an important role influencing the release and action of different neurotransmitters. Therefore, a strong stimulation by the psychoactive component of marijuana, delta-9-tetrahydrocanabinol (THC), might lead to subtle but lasting neurobiological changes that can affect adult brain functions and behaviour.

The literature here summarized by use of experimental animal models, puts forward that heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance, enhanced vulnerability for the use of more harmful drugs of abuse in selected individuals, and may represent a risk factor for developing schizophrenia in adulthood.

Therefore, the potential problems arising in relation to marijuana consumption in adolescence suggest that this developmental phase is a vulnerable period for persistent adverse effects of cannabinoids.

INTRODUCTION

Cannabis is the most commonly used illicit substance among adolescents and young adults. In 2004, 46% of 12th graders in the USA reported having tried cannabis at some point in their lifetime, 34% reported having used within the past month, and 5.6% reported having smoked cannabis daily (Johnston et al., 2004). Initiation into cannabis use typically begins in adolescence, as youths aged 12-17 constitute about two thirds of the new cannabis users (SAMHSA, 2004). Approximately 14% of adolescent-onset cannabis users develops cannabis dependence, a rate roughly twice that reported for adult-onset user (Chen et al., 1997; Chen and Anthony, 2003). Cannabis dependence is defined in the Diagnostic and Statistical Manual of Mental Disorder, (4th edition, text revision, DSM-IVTR) as having at least three out of seven symptoms within one year. Moreover, very recently, record numbers of teenagers were requiring drug treatment as a result of smoking skunk, the highly potent cannabis strain containing 25 times more delta-9-tetrahydrocannabinol (THC, the psychoactive ingredient) than the resin sold a decade ago. Despite the constantly spreading use of cannabis among adolescents, there is little information about its neurobiological long-term consequences. The adolescent brain is particularly sensitive to internal and external variables such as drug exposure, environment and gonadal hormones, since in this period several active neural changes take place (Spear, 2000). In fact, adolescence is characterized by strong neuronal plasticity, with sprouting and pruning of synapses, myelinization of nerve fibers, changes in neurotransmitter concentrations and their receptor levels in brain areas essential for behavioural and cognitive functions (Rice and Barone, 2000). The receptor for cannabinoids (CB1) belongs to the Gi/Go-protein coupled receptor family, and, in mammalian brain, is densely diffused in regions involved in the processing of emotional inputs, rewarding stimuli, habit formation, and higher cognitive functions (Herkenham et

al., 1990). Endogenous cannabinoids modulate neurotransmitter release in many brain regions via CB1 receptors (Morisset and Urban 2001; Wilson and Nicoll 2001, 2002; Wilson et al., 2001). Accumulating evidence indicates that their peculiar mechanism of action as retrograde messengers is able to strongly influence both short-term and long-term forms of synaptic plasticity (Freund et al., 2003; Kreitzer and Regehr, 2002). Moreover, there is evidence for a role of the endocannabinoid system in neural development. Both cannabinoid receptors and endocannabinoid ligands can be detected in the brain during early developmental periods (Romero et al., 1997; Berrendero et al., 1999). The atypical distribution of cannabinoid CB1 receptors during the perinatal period seems to be related to a specific involvement of the endocannabinoid system in brain development. The system constituted by CB1 receptors and their putative endogenous ligands might influence the gene expression of several key genes for neural development as part of the specific function of the endocannabinoid system during this period (Fernandez Ruiz et al., 2004). Moreover, in animal models, cannabinoid receptors have been shown to mature slowly, with maximal levels during adolescence which later drop to adult levels (Rodriguez de Fonseca et al., 1993; McLaughlin et al., 1994; Belue et al., 1995). Like dopamine receptors (Seeman, 1999), cannabinoid receptors may undergo postadolescent pruning. It is, therefore, conceivable that intake of exogenous cannabinoids, especially in vulnerable developmental periods, such as the adolescence, might induce residual effects.

This review aims to examine the existing literature on the long-term consequences of cannabinoid exposure during adolescence, considering its effect on the emotional behaviour, cognitive function, psychotic illness and the "drug gateway" hypothesis.

Adolescent cannabinoid exposure and adult emotional behaviour

There is an increasingly robust body of cross-sectional and prospective data supporting an association between adolescent use of cannabis and subsequent development of

depressive and/or anxiety disorders (Fergusson et al., 2002, Patton et al., 2002; Rey et al., 2002; Hayatbakhsh et al., 2007) but also conflicting data suggesting no association between early cannabis use and later depression (Arsenault et al., 2002). Nevertheless, even in case of such an association it is not possible to differentiate between an effect mediated by cannabis on neurodevelopment, or by other underlying factors such as genetic vulnerability and early adverse experience predisposing to early cannabis use and depressive/anxiety symptoms.

Animal data in the literature are still scarce and conflicting, depending on the period of exposure, the dose and the cannabinoid agonist used. Chronic administration of CP-55,940 in rats during adolescence (from postnatal day PND 35-45) resulted in marked behavioural effects in adulthood such as a decrease in the level of emotionality/anxiety in the open field and in the elevated plus maze (Biscaia et al., 2003). These effects seem sex-related and their nature depends on the specific behavioural test involved, with more marked effects in females than males. In contrast, O'Shea et al. (2004; 2006) reported increased anxiety after adolescent (from PND 30-51) but not adult CP-55,940 treatment in both female (O'Shea et al., 2004) and male rats (O'Shea et al., 2006). Recently, we studied the effect of adolescent exposure to increasing doses of THC for 11 days (35-45 PND) on adult emotional behaviour, considering anxiety and depression in rats of both sexes (Rubino et al., 2008). Neither females nor males showed any changes in anxiety responses (elevated plus maze and open field tests) but females presented significant "behavioural despair" (forced swim test) paralleled by anhedonia (sucrose preference) (fig. 1). In contrast, male rats showed no behavioural despair but did present anhedonia. This different behavioural picture was supported by biochemical parameters of depression, namely CREB alteration. In fact, in the hippocampus and prefrontal cortex CREB appears to be a vital mediator of antidepressant effects since a variety of antidepressant treatments increase CREB activity

in these brain regions (Nibuya et al, 1996; Thome et al, 2000; Sairanen et al, 2007; Tiraboschi et al, 2004). In addition, significant reductions in CREB protein levels have been found in the prefrontal cortex and hippocampus of suicide subjects (Dwivedi et al, 2003). Conversely, elevated CREB activity in the NAc produces various depressive-like effects in rodents (see for review Carlezon et al., 2005) that appear to be partly due to dynorphin, an endogenous ligand of k opioid receptors that is a target gene of CREB (Newton et al, 2002). In our hands, the depressive profile observed in female rats was supported by biochemical data showing that only females had low CREB activity in the hippocampal formation and prefrontal cortex and high activity in the NAc paralleled by increases in dynorphin expression (fig. 1). To support the idea of adolescents being specifically vulnerable to enduring adverse effects of cannabinoids adult female rats were exposed to the same THC treatment paradigm and no significant alterations in depressive-like behaviour were observed (Parolaro and Rubino, unpublished results), supporting the presence of an age-dependent vulnerability of the brain.

Adolescent cannabinoid exposure and adult cognitive function

Although few human studies have specifically addressed this issue, there is some evidence that exposure during adolescence may lead to lasting deficits in attention (Ehrenreich et al., 1999) and working memory (Schwartz et al., 1989).

Experimental data regarding long-term consequences of adolescent cannabinoid exposure on cognitive behaviour is scarce and not always in accordance, depending on the compound administered, the treatment paradigm used and the cognitive task performed. Adolescent exposure to increasing doses of the synthetic cannabinoid agonist CP-55,940 for 21 days (PND 30-50) induced impaired working memory in adult female (O'Shea et al., 2004) and male rats (O'Shea et al., 2006) checked by the object recognition test. A similar impairment in object recognition memory was observed in adult male rats after a

peripubertal chronic treatment (PND 40-65) with another synthetic cannabinoid agonist, WIN 55,212, which were not delivered regularly, to mimic the irregular consumption practice in humans (Schneider and Koch, 2003 and 2007). Notably, WIN-55,212 did not lead to long-lasting deficit when administered in adult rats (Schneider and Koch, 2003). When the natural agonist was employed, Cha et al., (2006, 2007) reported no significant lasting effects on spatial learning tested with the Morris water maze in adult male and female rats previously exposed to THC for 21 days (PND 30-50). However, the absence of an effect of chronic THC exposure on subsequent water maze learning does not rule out the possibility that it induced more subtle deficits that could be "unmasked" under certain conditions. It is important to recognize that no behavioural technique can assess all aspects of learning. Therefore, THC could be expected to affect performance on some indices and not others. At this regard, Quinn et al. (2007) reported that adolescent THC exposure of male rats caused lasting memory deficits that were greater than those produced by the same treatment in adult rats. In fact, adolescent THC-pretreated rats spent a decreased percentage of time relative to controls investigating a novel object, suggesting working memory dysfunction (Ennaceur and Delacour, 1988). Overall exploration times were not affected by prior THC treatment, indicating this deficit cannot be attributed to any non-specific impairment or lack of exploration.

Adolescent cannabis exposure and psychosis

Worldwide evidence documents that cannabis use is a modest statistical risk factor for the emergence of psychosis, ranging from psychotic symptoms such as hallucinations and delusions to clinically significant disorders such as schizophrenia. Prospective studies estimate that cannabis use is associated with a twofold increase in later schizophrenia outcomes, and early, adolescent-onset cannabis use is associated with a higher risk (Arseneault et al 2004), possibly because individuals who begin to use cannabis when the

brain is still developing are most vulnerable to its deleterious effects (Ehrenreich et al 1999; Pistis et al 2004; Pope et al 2003; Schneider and Koch 2003). Nonetheless, the vast majority of young people who use cannabis do not develop psychosis, suggesting the hypothesis that, if cannabis is indeed causal, some individuals may be genetically vulnerable to its effects.

Studies on animal models indicated that chronic pubertal -but not adult- treatment (PND 40-65) with the synthetic cannabinoid agonist WIN 55,212-2 leaded to long-lasting disruptions in sensorimotor gating, object recognition, and the performance in a progressive ratio task (Schneider and Koch, 2003). It was suggested that these enduring disturbances might be due to a persistent imbalance in various neurotransmitter systems, including the cannabinoid, the opioid, and the dopaminergic system, induced by chronic cannabinoid stimulation during pubertal development. Since prepulse inhibition (PPI) deficits, object recognition memory impairments, and anhedonia/avolition are among the symptoms of schizophrenia, the authors proposed chronic cannabinoid administration during pubertal development of rats as a new neurodevelopmental animal model for some aspects of the etiology of schizophrenia. This assumption was further supported by the fact that the cannabinoid-induced PPI deficit observed in that study was reversed by a clinically potent antipsychotic drug (Schneider and Koch, 2003). More recently, Schneider and Koch (2007) suggested that pubertal cannabinoid administration in vulnerable individuals acts as a risk factor for inducing enhanced behavioural disturbances related to schizophrenia. They demonstrated that neonatal lesions in the medial prefrontal cortex (mPFC) induced persistent impairments in recognition memory in adult rats and this behavioural deviation in adult rats can be intensified by pubertal chronic cannabinoid treatment compared to shams.

Adolescent cannabis exposure and the gateway hypothesis

Epidemiological studies showed that the adolescent stage is a developmental period with increased risk of drug abuse (Fried et al., 2001; Martin et al., 2002; Patton et al., 2004; Trad, 1994). Marijuana is widely consumed at this phase of life (Gruber and Pope, 2002) and there is evidence that using the drug at this stage could facilitate later drug abuse, a phenomenon that has been termed as "gateway hypothesis" (Kandel et al., 2006). Literature regarding the cannabis gateway hypothesis based on animal models is scarce and not always in accordance. Ellgren et al., (2004), for example, did not support the gateway hypothesis as no sensitization to the effects of amphetamine on dopamine levels or behaviour was observed in male rats pretreated with WIN 55,212-2 during adolescence. Pistis et al (2004) demonstrated in male rats a long-lasting tolerance to acute cannabinoids as well as the development of long-lasting cross-tolerance to morphine, cocaine, and amphetamine in VTA dopamine (DA) neurons after administration of WIN 55,212-2 during adolescence. They speculated that cannabinoid-induced lacking, or blunted, responses of DA neurons to pharmacologic stimuli might reverberate into reduced responses to natural rewarding and motivational stimuli that might ultimately lead to enhanced vulnerability in selected individuals for the use of more harmful drugs of abuse. In a more recent work, Ellgren et al. (2007) demonstrated that adolescent exposure to THC in male rats increased opiate self-administration in adulthood and that this was associated with discrete alterations of the endogenous opioid system in limbic-related neuronal populations known to mediate reward behaviour. Higuera-Matas et al., (2007) reported that chronic exposure to CP-55,940 during adolescence increased the susceptibility to acquire cocaine self-administration in female but not male rats. This altered susceptibility could be related to changes in female brain metabolic activity

induced by cannabinoids during adolescence, specifically, a hyper-activation of the frontal cortex and a hypo-activation of the amygdalo-entorhinal cortex.

Conclusion

The intrinsic limitation of human epidemiological studies due to the great variability in the cultural, social, and economic background, as well as in the education level of the subjects, makes difficult to establish causal links between adolescent marijuana consumption and development of psychiatric illnesses, altered affective outcomes and drug dependence in adulthood. The strategy to evaluate directly the relationship between prior cannabis experience and adult altered responses independent of cultural, social, and moral factors, is represented by the use of experimental animal models.

In this context, the literature here summarized suggests that heavy cannabis consumption in adolescence may induce subtle changes in the adult brain circuits ending in altered emotional and cognitive performance. In vulnerable individuals, pubertal cannabinoid administration may even act as a risk factor for inducing enhanced behavioural disturbances related to schizophrenia. Moreover, in a specific time window like the adolescence, cannabis use might ultimately lead to enhanced vulnerability in selected individuals for the use of more harmful drugs of abuse.

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Table 1. Effect of adolescent exposure to cannabinoids on adult rat behaviour

	drug	period of treatment	sex	test	effect at adult age	reference
emotional behaviour	CP-55,940	PND 35-45	m, f	open field elevated plus maze	anxiolytic anxiolytic	Biscaia et al., 2003
	CP-55,940	PND 30-51	f	social interaction	reduced	O'Shea et al., 2004
	CP-55,940	PND 30-51	m	social interaction	reduced	O'Shea et al., 2006
	THC	PND 35-45	m, f	open field elevated plus maze	no change no change	Rubino et al., 2008
	THC	PND 35-45	m, f	forced swim test	depressive-like in f no change in m	Rubino et al., 2008
cognition	CP-55,940	PND 30-51	f	novel object recognition	reduced	O'Shea et al., 2004
	CP-55,940	PND 30-51	m	novel object recognition	reduced	O'Shea et al., 2006
	WIN 55,212-2	PND 40-65	m	novel object recognition	reduced	Schneider and Koch, 2003; 2007
	THC	PND 30-51	m	Morris water maze	no change	Cha et al., 2006
	THC	PND 30-51	m, f	Morris water maze	no change	Cha et al., 2007
	THC	PND 32-51	m	novel object recognition	reduced	Quinn et al., 2007
psychosis	WIN 55,212-2	PND 40-65	m	Progressive ratio performance prepulse inhibition	reduced disrupted	Schneider and Koch, 2003
gateway hypothesis	THC	PND 28-32	m	Amphetamine-induced locomotor activity	no change	Ellgren et al., 2004
	WIN 55,212-2	PND 37-39	m	dopamine neurons firing	cross-tolerance to morphine, cocaine and amphetamine	Pistis et al., 2004
	THC	PND 28-49	m	heroin self-administration	increased	Ellgren et al., 2007
	CP-55,940	PND 28-38	m, f	cocaine self-administration	increased in f no change in m	Higuera-Matas et al., 2007

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Figure 1. Effect of adolescent exposure to THC in female rats suggestive of the

depressive-like profile. Top: behavioural data. Bottom: biochemical data. Percentage of

CREB activation in different cerebral areas and dynorphin levels in the nucleus accumbens.

Hippo=hippocampus; PfCtx=prefrontal cortex; NAc=nucleus accumbens