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Cannabis abuse in adolescence and the risk of psychosis: A brief review of the preclinical evidence

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ABSTRACT

Epidemiological studies suggest that *Cannabis* use during adolescence confers an increased risk for developing psychotic symptoms later in life. However, despite their interest, the epidemiological data are not conclusive, due to their heterogeneity; thus modeling the adolescent phase in animals is useful for investigating the impact of *Cannabis* use on deviations of adolescent brain development that might confer a vulnerability to later psychotic disorders. Although scant, preclinical data seem to support the presence of impaired social behaviors, cognitive and sensorimotor gating deficits as well as psychotic-like signs in adult rodents after adolescent cannabinoid exposure, clearly suggesting that this exposure may trigger a complex behavioral phenotype closely resembling a schizophrenia-like disorder. Similar treatments performed at adulthood were not able to produce such phenotype, thus pointing to a vulnerability of the adolescent brain towards cannabinoid exposure. The neurobiological substrate of the adolescent vulnerability is still largely unknown and experimental studies need to elucidate the cellular and molecular mechanism underlying these effects. However, the few data available seem to suggest that heavy adolescent exposure to cannabinoids is able to modify neuronal connectivity in specific brain areas long after the end of the treatment. This is likely due to disruption of maturational events within the endocannabinoid system during adolescence that in turn impact on the correct neuronal refinement peculiar of the adolescent brain, thus leading to altered adult brain functionality and behavior.

1. Introduction

Schizophrenia is a syndrome where multiple genetic and environmental factors operate together to push individuals over a threshold into expressing the characteristic clinical picture (Paparelli et al., 2011). It has been characterized by the presence of positive, negative and cognitive symptoms. Positive symptoms consist of items indicative of overall hyperactivity such as agitation, delusions, and hallucinations. In contrast, negative symptoms refer to abnormalities in social interaction, lack of motivation, affective flattening, restricted emotional experience and expression, poverty of speech, and reduced hedonic capacity. Cognitive symptoms include deficits in attention and working memory that lead to an inability to organize one's life and to work effectively.

Epidemiological studies suggest that cannabis use during adolescence confers an increased risk for developing psychotic symptoms later in life (D'Souza et al., 2009; Evins et al., 2012). However, epidemiological studies have a correlative nature and studies on human subjects are limited by the associated ethical concerns and experimental difficulties, which can be circumvented by animal models. Using laboratory animals offers two distinct advantages: minimal genetic variation and good control of environmental factors help to minimize sources of variability; in addition, animal models can be subjected to environmental and/or pharmacological manipulations necessary to identify causative links. Although animal studies on the effects of adolescent exposure to cannabinoids are scant, they generally support the human research, providing direct evidence for a causal link between cannabinoid exposure in adolescence and abnormal development and behavior. Indeed, a number of behavioral paradigms have been considered to be valid translational models to assess the three different classes of symptoms present in schizophrenia. The most used and accepted paradigms measure prepulse inhibition of startle (PPI — a measure of sensorimotor gating, or the ability of an organism to attain information and process it correctly), social interaction, latent inhibition (a measure of a reduction in learning of sensory input to which prior exposure has occurred without any consequence), working memory and drug-induced hyperactivity (Lodge and Grace, 2009; Powell and Miyakawa, 2006).

Commonly the experimental paradigms are based on protocols where animals are treated with THC, the psychoactive ingredient of *Cannabis sativa*, or synthetic cannabinoids, during part of their adolescence, that in rodents spans from 28 to 50 even 60 post natal day (PND). Later in life, usually during early adulthood (from 75 PND on), the behavior of treated animals is monitored.

Abbreviations: PND, post natal day; PPI, pre-pulse inhibition; THC, delta9-tetrahydrocannabinol; PCP, phencyclidine; COMT, catechol-O-methyltransferase; CB1, cannabinoid receptor 1; 5-HT2A serotonin 2A receptor, NMDA N-methyl-D-aspartate receptor; mGluR5, metabotropic glutamate receptor 5; MGL, monoacylglycerol lipase; FAAH, fatty acid amide hydrolase; CB2, cannabinoid receptor 2.

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Table 1
Effect of adolescent cannabinoid exposure on adult behaviors relevant to a schizophrenia-like phenotype.

Behavior	Agonist	Adolescent treatment	Species	Test	Effect	Reference
Cognition	WIN55,212-2	PND 45–60	Rat	NOR	=	Abush and Akirav, 2012
	CP 55,940	PND 30–50	Rat	NOR	↓	O'Shea et al., 2004, 2006
	THC	PND 28–55	Rat	NOR	↓	Quinn et al., 2008
	THC	PND 35–45	Rat	NOR	↓	Realini et al., 2011
	CP 55,940	PND 29–49	Rat	NOR	↓	Renard et al., 2013
	WIN55,212-2	PND 40–65	Rat	NOR	↓	Schneider & Koch, 2003
	THC	PND 35–45	Rat	Radial maze	↓	Rubino et al., 2009a, 2009b
	THC	PND 35–45	Rat	Passive avoidance	=	Rubino et al., 2009a, 2009b
	WIN55,212-2	PND 45–60	Rat	Water maze	=	Abush and Akirav, 2012
	THC	PND 30–50	Rat	Water maze	=	Cha et al., 2007
	CP 55,940	PND 28–38	Rat	Water maze	=	Higuera-Matas et al., 2009
Sensorimotor gating	WIN55,212-2	PND 30–35	Mouse	PPI	↓	Gleason et al., 2012
	CP 55,940	PND 28–42	Rat	PPI	=	Llorente-Berzal et al., 2011
	WIN55,212-2	PND 32–52	Mouse	PPI	=	O'Tuathaigh et al., 2012
	WIN55,212-2	PND 40–65	Rat	PPI	↓	Schneider & Koch, 2003
	WIN55,212-2	PND 40–65	Rat	PPI	↓	Wegener and Koch, 2009
Social behavior	WIN55,212-2	PND 40–65	Rat	Social interaction	↓	Leweke and Schneider, 2011
	CP 55,940	PND 30–50	Rat	Social interaction	↓	O'Shea et al., 2004, 2006
	THC	PND 28–55	Rat	Social interaction	↓	Quinn et al., 2008
	THC	PND 35–45	Rat	Social interaction	↓	Realini et al., 2011
Locomotor activation	WIN55,212-2	PND 40–65	Rat	Open field	↑	Wegener and Koch, 2009
	THC	PND 35–45	Rat	PCP-induced hyperlocomotion	↑	Zamberletti personal communication

= Not altered.
↓ Impaired.
↑ Increased.

In the following sections the more relevant results obtained in different laboratories, our included, are briefly summarized based on the considered effect (Table 1).

2. Cognitive deficits

Consistent data have been obtained regarding cognition. Adolescent exposure to synthetic or natural cannabinoid agonists has been reported to induce impairments in object recognition memory at adulthood in both male and female rats (O'Shea et al., 2004, 2006; Quinn et al., 2008; Realini et al., 2011; Renard et al., 2013; Schneider & Koch, 2003), suggestive of working memory dysfunction (Ennaceur and Delacour, 1988). Similarly, spatial working memory deficits (tested by the 8-arm radial maze) have been observed after adolescent THC exposure in adult male and female rats (Rubino et al., 2009a, 2009b). Curiously enough, Abush and Akirav (2012) did not find long-lasting alteration in the classic version of the novel object recognition test, but only in the spatial version of the task. This discrepancy might be due to the fact that they treated animals in the last part of adolescence (45–60 PND), whereas all the other groups applied an earlier treatment. Since adolescence represents a period of changes and rearrangements for the brain, it is possible that treatments applied during different intervals of time might trigger different consequences. When other forms of memory were considered, no lasting effects were observed. This was the case for aversive memory (Rubino et al., 2009a, 2009b) or "pure" spatial learning in the Morris water maze (Abush and Akirav, 2012; Cha et al., 2007; Higuera-Matas et al., 2009). All these data point towards a task-specific effect of adolescent cannabinoid exposure on cognition, the working memory component being the most affected.

3. Prepulse inhibition

Loss of normal PPI is widely accepted as an endophenotype of schizophrenia with high translational validity, since it can be assessed in both animals and humans. Impairments in PPI were observed long after chronic adolescent treatment with the cannabinoid agonist WIN 55,212-2 in rats and mice (Gleason et al., 2012; Schneider and Koch, 2003; Wegener and Koch, 2009), suggestive of the presence of disrupted sensorimotor gating. However, some groups also reported no alterations in this behavior after adolescent exposure to synthetic cannabinoid agonists (Llorente-Berzal et al., 2011; O'Tuathaigh et al., 2012). The reason for this discrepancy is quite difficult to find: data for both evidence were obtained in mice and rats, using a synthetic cannabinoid agonist. The only speculation we may put forward is that the last two groups performed a long treatment (15 or 21 days) with the same dose of agonist (CP55940 0.4 mg/kg or WIN 55,212-2 1 or 2.5 mg/kg), thus 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.

4. Social interaction

Individuals suffering from schizophrenia often exhibit impaired social interaction (e.g., social withdrawal), which is considered to be a negative symptom of the disorder. Measurements of social behavior in rodents are relatively easy, as they show a well-structured stable degree of social behavior. Chronic treatment with synthetic cannabinoid agonists such as CP-55,940 and WIN 55,212-2 during adolescence induced a significant decrease in social behavior measured in the social interaction test (Leweke and Schneider, 2011; O'Shea et al., 2004, 2006). Similar findings were reported also after adolescent treatment with the natural compound THC (Quinn et al., 2008; Realini et al., 2011).

5. Hyperactivity and stereotypy

Finally, it has been suggested that locomotor hyperactivity may have some face validity for certain components of the positive symptoms of schizophrenia, such as psychotic agitation (van den Buuse, 2010). However, despite its ease of quantification in rodents, very few data are available about the long-term effect of adolescent cannabinoid exposure on this behavioral sign. Adult rats exposed to WIN 55,212-2 during adolescence showed a significant increase in locomotor activity when tested in the open field (Wegener and Koch, 2009). Our group recently observed that adolescent exposure to THC increased the locomotor activating effect of acute PCP, when this was administered acutely in adulthood (Zamberletti et al., personal communication). In fact, the low dose of PCP injected (2.5 mg/kg) did not induced locomotor activation in vehicle-treated animals but significantly increased locomotion in THC-treated rats. Moreover, stereotyped behaviors were observed in