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Review

Long-term consequences of perinatal and adolescent cannabinoid exposure on neural and psychological processes

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ABSTRACT

Marihuana is the most widely consumed illicit drug, even among adolescents and pregnant women. Given the critical developmental processes that occur in the central nervous system in these populations, their marihuana consumption may have permanent consequences on several brain functions in later adult life. Here, we review what is currently known about the long-term consequences of prenatal and adolescent cannabinoid exposure. The most consistent findings point to long-term impairments in cognitive function that are associated with structural alterations and disturbed synaptic plasticity. In addition, several neurochemical modifications are also evident after prenatal or adolescent cannabinoid exposure, especially in the endocannabinoid, glutamatergic, dopaminergic and opioidergic systems. Important sexual dimorphisms are also evident in terms of the long-lasting effects of cannabinoid consumption during pregnancy and adolescence, and cannabinoids possibly have a protective effect in adolescents who have suffered traumatic life challenges, such as maternal separation or intense stress. Finally, we suggest some future research directions that may encourage further advances in this exciting field.

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1. Introduction

Cannabis remains the most widely used illicit substance worldwide, with an estimated annual prevalence of 3.9% of the adult population in 2013 (around 180 million users aged 15–64 years), yet with marked regional differences (1.9% prevalence in Asia and 10.9% in Oceania for example: United Nations Office on Drugs and Crime, 2013). The debate surrounding the possible legalization of cannabis has become quite lively, and with a growing number of countries and states in the USA having taken this step or contemplating doing so, it is crucial that such a decision is made based on firm scientific grounds.

Prenatal stages and adolescence are two crucial periods when exposure to drugs of abuse affects the ongoing development of the central nervous system (CNS), altering the normal psychological function of the individual. In this review, we will mainly focus on the long-term effects of exposure to "cannabinoid agents" during pregnancy and adolescence (see Table 1 for a list of the cannabinoid agents cited in this review and their binding properties), while we will not deal with acute effects of cannabinoids or those alterations studied immediately after chronic or repeated exposure. Sexual dimorphism in the effects reported will be highlighted whenever studies were carried out on both sexes. Unless otherwise specified, the sex of the animals tested is always masculine.

Although human studies provide the most relevant information regarding the long-term influences of prenatal marihuana exposure on later cognitive development and neural plasticity, several confounding factors might limit the conclusions that can be obtained from such studies, such as a possible malnutrition derived from the maternal consumption of cannabis, different Δ^9-tetrahydrocannabinol (THC) consumption over time and between studies, or differences in educational background or socioeconomic status. For this reason, animal studies are an invaluable tool when it comes to draw causal conclusions regarding the long-term effects of perinatal cannabinoid exposure. There are excellent reviews on the behavioral consequences of prenatal THC and cannabinoid intake during pregnancy and lactation, summarizing our current understanding of this field (Calvigioni et al., 2014; Campolongo et al., 2011; Morris et al., 2011; Trezza et al., 2012; Wu et al., 2011). As such, we will only briefly review their most significant findings. Along with these behavioral effects, prenatal exposure to cannabinoids has consistently been associated with dysregulated neurotransmission in the brain. Thus, we will also describe what is currently known about the neurochemical alterations induced by *in utero* cannabis (see Table 4).

As for prenatal studies, human cohort designs of adolescent cannabis users and abusers might again include confounding factors that affect the reliability of the results obtained. For this reason, the animal studies addressing this issue are crucial research contributions into the long-lasting consequences of cannabinoid exposure during adolescence. As for prenatal intake, there are also excellent reviews on cannabinoid exposure during adolescence and the ensuing adult behavioral alterations (Chadwick et al., 2013; Hurd et al., 2014; Realini et al., 2009; Renard et al., 2014; Rubino and Parolaro, 2008; Schneider, 2009, 2008; Trezza et al., 2012; Viveros et al., 2011a,b), leading us to focus mainly on the most consistent or interesting findings. We will first review the studies on long-term cognitive alterations induced by adolescent cannabinoid exposure (see Table 5), before focusing on the emotional changes (including anxiety or depressive-like behavior: Table 6), thereafter assessing the data available on the altered sensitivity to drugs of abuse found in cannabinoid-exposed individuals. Subsequently, we will review the most important alterations found in the main neurotransmitter systems (see Table 7), as well as focusing on the alterations in morphological and synaptic plasticity induced by adolescent cannabinoid exposure, and on some of the possible underlying molecular mechanisms. Special attention will be paid to possible protective actions of early cannabinoid exposure after traumatic life events, such as chronic stress or maternal deprivation.

We believe that updating our knowledge of the long-term effects of cannabis exposure during these two periods should help to clarify how to cut the Gordian knot of marihuana legalization.

2. Epidemiology of marihuana use during critical developmental periods: pregnancy and adolescence

Marihuana is the illicit drug most widely consumed during pregnancy (Brown and Graves, 2013; Calvigioni et al., 2014; Jaques et al., 2014), its consumption being strongly associated to cigarette smoking (Gaalema et al., 2013) and to a lesser extent, to opioids, stimulants and alcohol (Burns et al., 2006). In the United States, approximately 4.6% of pregnant women reported having consumed marihuana in the past month during the first trimester of pregnancy. This percentage went down to 2.9% during the second trimester and subsequently decreased to 1.4% in the third trimester (Substance Abuse and Mental Health Services Administration, 2009). In Brazil this percentage is similar, around 4.0% in the first trimester (Mitsuhiro et al., 2007), as is the prevalence of its consumption in the general population of pregnant women in Europe. For example, the prevalence of marihuana use during pregnancy in the UK was reported to be around 5% (Fergusson et al., 2002), with a similar prevalence in Spain, where THC was detected in 5.3% of newborns by meconium analysis (Lozano et al., 2007: although this percentage rises to 10.3% in Ibiza, in the Balearic Islands Friguls et al., 2012). In France, 1.2% of women reported having used cannabis during pregnancy, a percentage that rose among younger women, women living alone, or women who had a low level of education or low income (Saurel-Cubizolles et al., 2014). Notably,

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