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Review article

Sex and age specific effects of delta-9-tetrahydrocannabinol during the periadolescent period in the rat: The unique susceptibility of the prepubescent animal

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ABSTRACT

Adolescents who use marijuana are more likely to exhibit anxiety, depression, and other mood disorders, including psychotic-like symptoms. Additionally, the age at onset of use and the stress history of the individual can affect responses to cannabis. To examine the effect of early life experience on adolescent Δ-9-tetrahydrocannabinol (THC) exposure, we exposed adolescent (postnatal day (P) 29–38) male and female rats, either shipped from a supplier or born in our vivarium, to once daily injections of 3 mg/kg THC. Our findings suggest that males are more sensitive to the anxiolytic and antidepressant effects of THC, as measured by the elevated plus maze (EPM) and forced swim test (FST), respectively, than females. Exposure to the FST increased plasma corticosterone levels, regardless of drug treatment or origin and females had higher levels than males overall. Shipping increased THC responses in females (acoustic startle habituation) and in males (latency to immobility in FST). No significant effects of THC or shipping on pre-pulse inhibition were observed. Due to differences in timing of puberty in males and females during the P29–38 period of THC treatment, we also dosed female rats between P21–30 (pre-puberty) and male rats between P39–48 (puberty). Pre-pubertal animals showed reductions in anxiety on the EPM, an effect that was not seen in animals treated during puberty. These results suggest that both sexes are more susceptible to changes in emotional behavior when THC exposure occurs just prior to the onset of puberty. Within the animals dosed from P29–38, THC increased cannabinoid receptor 1 (CB1R) mRNA expression and tended to decrease CP55,940 stimulated [^{35}S]GTPγS binding in the central amygdala only of females. Therefore, early stress enhances THC responses in males (in FST) and females (ASR habituation), THC alters CB1R expression and function in females only and prepubescent rats are generally more responsive to THC than pubertal rats. In summary, THC and stress interact with the developing endocannabinoid system in a sex specific manner during the peri-pubertal period.

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1. Introduction

Understanding the effects of marijuana use is increasingly important, as society appears to be moving toward widespread legalization of marijuana, not only for medical purposes but for recreational use as well. It is especially critical to gain an understanding of the effects of marijuana in an adolescent population as nearly 60% of all new marijuana users were under the age of 18 at the initiation of use (SAMHSA, 2014).

Delta-9-tetrahydrocannabinol (THC), the primary psychoactive substance in marijuana, mainly produces its effects through activation of the CB1 receptor, a G-protein coupled receptor located on presynaptic axon terminals throughout the central nervous system. CB1 receptors are present early during development in both humans (Glass et al., 1997; Wang et al., 2003) and rats (Rodriguez de Fonseca et al., 1993; Berrendero et al., 1999) and play a critical role in neural development through the modulation of neurotransmitter release (for review, see Gaffuri et al., 2012). Additionally, many studies have shown the importance of the endocannabinoid system in modulating hypothalamic-pituitary-adrenal (HPA) axis activity throughout development (for review, Lee and Gorzalka, 2012). Activation of the HPA axis by stress exposure during the early postnatal period has been shown to have long lasting effects on stress and response to cannabinoids (Brake et al., 2004; Charil et al., 2010; Llorente-Berzal et al., 2011).

Adolescence is a time of dynamic brain development and therefore also represents a critical time during which substance use has the potential to elicit long-term effects (for review, Schneider, 2008; Renard et al., 2014). Indeed, cannabis use in adolescents is associated with a higher risk for developing depression and anxiety disorders later in life (Patton et al., 2002). However, human studies are limited in their ability to investigate underlying biochemical changes making rodent models of drug use valuable. Animal studies of adolescent cannabinoid exposure have yielded inconsistent results, possibly due to differences in agonist (natural vs synthetic), dosing paradigm, age of testing, time between dosing and testing, and the specific behavioral task used (eg elevated plus maze (EPM) or social interaction)(for review, Rubino et al., 2012). A contributing factor to these disparate findings that should be considered is the previous stress history of the subject as early stress has been shown to affect later subjective responses to drug exposure (Hall and Degenhardt, 2009; McLaughlin and Gobbi, 2012). Although typically not experimentally considered as stressors, transport and shipping increase both behavioral and endocrine measures of stress in mice and rats (Tuli et al., 1995; van Ruiven et al., 1998). Shipping during the peripubertal period produces alterations in response to gonadal hormones into adulthood (Laroche et al., 2009) and sex-specific alterations in CB1 receptor expression (Dow-Edwards et al., 2013) and behavioral response to THC (Wiley and Evans, 2009). Previous work in our lab using shipped animals has shown sex and dose specific differences in anxious-like and locomotor behavior in the early abstinence period (24 h after final THC injection) following adolescent (P35–41) THC exposure (Harte-Hargrove and Dow-Edwards, 2012). Therefore, we wanted to determine whether the stress history (shipping or not) of the animal could interact with the adolescent THC treatment and