Gestational cannabinoid exposure influences extracellular kynurenic acid and glutamate levels in the medial prefrontal cortex of adolescent offspring.

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Cannabis is the illicit drug most commonly abused by pregnant women. The main psychoactive component of marijuana, delta9–tetrahydrocannabinol (Δ9-THC), can reach the fetus through the placenta and the blood-brain barrier. Several longitudinal studies of children and adolescents prenatally exposed to marijuana reported a significant impairment of higher cognitive functions (Smith et al., 2006; El Marroun et al., 2011; Huizink, 2013), as well as a link to psychiatric disorders (Jutras-Aswad et al., 2009; Mathews et al., 2014). Preclinical studies indicate that prenatal exposure to cannabinoids induces cognitive deficits in rat offspring (Ferraro et al., 2009). Moreover, these impairments are associated with alterations of aminoacidergic neurotransmission in the hippocampus and the prefrontal cortex (PFC) (Mereu et al., 2003; Antonelli et al., 2005). In particular, some of the deleterious effects on cognitive functions resemble those observed in adult rats, which had been prenatally exposed to the tryptophan metabolite (L-) kynurenine, the direct bioprecursor of the neuroactive compound kynurenic acid (KYNA) (Pocivavsek et al., 2014). We therefore investigated whether alterations in KYNA levels in the rat brain might play a role in the short- and long-term consequences of prenatal cannabinoid exposure.Pregnant Wistar rats were treated daily with 9-THC [5 mg/kg or vehicle (sesame oil) by oral gavage] from gestational day (GD) 5 through GD 20. Three vehicle-treated and five 9-THC-treated dams were euthanized at GD 20, and the levels of kynurenine and KYNA were determined in maternal and fetal plasma and brain. The remaining dams (n=4 per group) gave birth, and one adolescent [postnatal day (PD) 35–45] male rat per litter was used to determine the extracellular levels of KYNA and glutamate by in vivo microdialysis in the medial PFC (mPFC).

No changes were found in kynurenine and KYNA levels in the fetal and maternal plasma or in the fetal and maternal brain. However, extracellular basal KYNA levels in the mPFC were significantly higher in prenatally 9-THC-exposed adolescent rats ($p<0.01$) compared to the vehicle group. In addition, following gestational 9-THC treatment, adolescent rats had significantly lower extracellular glutamate levels than the vehicle group ($p<0.05$). The present data demonstrate that prenatal cannabinoid exposure leads to long-term alterations of KYNA and glutamate levels in the mPFC in adolescence. As an increase in KYNA levels has been associated with cognitive dysfunction and psychiatric disorders, the possibility that this mechanism could underlie the detrimental effects of prenatal marijuana exposure is hypothesized.