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Press information

Prenatal exposure to cannabis impacts sociability of male rats

In a study performed in rats, researchers from Inserm and Aix-Marseille University reveal that prenatal exposure to cannabinoids has sex-specific effects on adult offspring. According to this study published in *eLife*, consuming cannabis during pregnancy can lead to behavioral and neuronal deficits in male descendants. The findings also point towards a potential pharmacological strategy to help reverse these effects in humans.

A study performed in rats by researchers from Inserm and Aix-Marseille University at the Mediterranean Institute of Neurobiology suggests that using cannabis during pregnancy can lead to less sociability and increased neuronal excitability in males.

According to Olivier Manzoni, Inserm Research Director in charge of the study at the Mediterranean Institute of Neurobiology and Director of the Inserm-Indiana University International Associated Laboratory CannaLab, says: "*As cannabinoids can cross the placenta, they may interfere with fetal endocannabinoid signaling during neurodevelopment, which is involved in regulating a variety of processes (synaptic plasticity, appetite, pain sensation), and mediating the pharmacological effects of cannabis. This could in turn lead to some serious long-term deficits. But despite increasing reports of cannabis consumption during pregnancy, the long-term consequences of prenatal cannabinoid exposure remain incompletely understood.*"

To fill this knowledge gap, the researchers in Marseille together with their counterparts from the University of Rome (Italy) and Indiana University (USA) examined how prenatal cannabinoid exposure influences the synaptic and behavioral functions of the medial prefrontal cortex – a brain region often implicated in neuropsychiatric disorders – in adult male and female rats.

Their results revealed that males exposed to cannabinoids while in the uterus were less sociable than normal animals, and spent less time interacting with others. Their social behaviors (interactions and play) were impaired, while the number of attacks among males remained unchanged. Additionally, the researchers saw that the exposed males had a heightened excitability of pyramidal neurons in the prefrontal cortex and a loss of the synaptic plasticity normally mediated by the endocannabinoid system. None of these effects were seen in females.

"*The deleterious effects of prenatal exposure to cannabinoids on social behavior were specific to male offspring only*," explains co-first author and doctoral student Anissa Bara. "*But while social interaction was specifically impaired in males, locomotion, anxiety and cognition remained unaffected in both sexes, suggesting sex-specific behavioral consequences*."

The results also revealed that expression of the mGlu5 gene – an effector of the endocannabinoid system in the prefrontal cortex – was reduced in the males exposed to cannabinoids *in utero*. The team discovered that amplifying mGlu5 signaling could normalize the synaptic and behavioral deficits induced by prenatal exposure to cannabinoids partly by activating the cannabinoid type 1 receptor (CB1R). Similarly, later tests also revealed that enhancing levels of anandamide (a type of endocannabinoid) in exposed males helped to restore normal social behaviors via the CB1R receptor.

However, prenatal exposure to cannabis does not leave females entirely unscathed. The researchers observed major modifications in the expression of synaptic protein genes in females exposed to cannabinoids *in utero*. The functional and behavioral consequences of these modifications remain to be identified.

“Altogether, these results provide compelling evidence for sex-specific effects of prenatal cannabinoid exposure,” concludes co-first author Antonia Manduca, also an Inserm Postdoctoral Researcher at the Mediterranean Institute of Neurobiology. “The fact that increasing mGlu5 signaling and enhancing anandamide levels helped to reverse the negative effects of early exposure in rats also hints at a new pharmacological strategy that could one day be trialled in humans.”

Sources

Sex-dependent effects of in utero cannabinoid exposure on cortical function
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