The Effects of Prenatal Cannabis Exposure on the Basolateral Amygdala

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Abstract

Clinical and preclinical studies indicate prenatal cannabis exposure (PCE) pathologically affects fetal brain development and may increase vulnerability to neuropsychiatric disorders, including schizophrenia and mood/anxiety disorders. In review research from our lab suggests that fetal exposure to Δ9-THC sex-selectively impairs mesocorticolimbic (MCL) circuit function. However, there is a distinct lack of focus on PCE models on the BLA. The BLA plays a central role within the MCL where it directly interacts with the VTA, PFC and HIPP. Importantly, our model exhibits significant VTA hyperdopaminergic activity, and sex-specific alterations to PFC/HIPP glutamate firing, alongside region- and sex-specific changes in dopamine (DA), glutamate/GABA molecular markers. These result in outward pathological behavioural manifestations with males exhibiting enhanced anxiety and both sexes exhibiting cognitive deficits. Given the role of the BLA, it is necessary to mechanistically explore the effect of PCE on the BLA. The present study characterized the interconnected pathophenotype of the BLA-MCL circuit using behavioural, electrophysiological, molecular, and mechanistic assays.

Pregnant Wistar rats were assigned to VEH (n=10 dams; n=4 progeny/sex/dam) or 3mg/kg THC (daily, i.p.; n=10 dams; n=4 progeny/sex/dam) from gestational day (GD) 7 to GD22. A subset of progeny (n=8/treatment/sex) were sacrificed on PD21 for molecular assays of the NAc and BLA. Between PD70-85, a subset of progeny (n=20/treatment/sex) were assessed for anxiety, depression, prepulse inhibition, and contextual fear. Between PD90-120, in vivo electrophysiology was used to assess VTA DA-ergic neurons, glutamate, and GABA neurons in the posterior/anterior BLA, and NAc GABA neurons. On PD120, remaining offspring were sacrificed and NAc and BLA punchouts were obtained for molecular assays. A behaviour naïve subset (n=10/sex/treatment) received intra-BLA cannulations for mechanistic assays between PD90-120.

In line with previous results, males exhibit a significant anxiogenic phenotype; however, males also exhibited significantly less freezing, suggesting a deficit in contextual fear learning, consistent with significant increases in GAD67 expression; males also exhibit increases in D1R and GABAARα1. Female progeny did not exhibit any outward pathology but did exhibit significantly greater expression of vGLUT2, GABAARα1, and GABAARɣ2. Disturbances in dopaminergic, glutamatergic, and GABAergic electrophysiological activity were also observed in the male progeny within the VTA-BLA-NAc circuit, but not in the female progeny. These suggest that the anxiogenic deficits observed in males are likely contingent on BLA disruptions, while the female progeny is protected from BLA-dependant etiology. Mechanistic assays are currently ongoing.

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