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Developmental pyrethroid exposure disrupts molecular pathways for circadian rhythms and synaptic plasticity in mouse brain

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Introduction: Neurodevelopmental disorders (NDDs) are a group of conditions that impact the developing nervous system, often with few or no clear biomarkers. Environmental factors play a significant role in the risk of NDDs, including attention deficit hyperactivity disorder (ADHD). One such environmental risk is exposure to pyrethroid pesticides during pregnancy, which has been linked to an increased risk of NDDs in the developing fetus. Our recent research showed that low-dose exposure to the pyrethroid pesticide deltamethrin during development in mice results in male-biased changes in ADHD- and NDD-related behaviors, as well as alterations in the striatal dopamine system.

Objective: This study utilized an integrated multiomics approach to comprehensively identify biological changes in the mouse brain caused by developmental pyrethroid exposure (DPE).

Methods: In a litter-based, split-sample design, we exposed pregnant and lactating mice to deltamethrin (3 mg/kg) or a vehicle every three days at a dose significantly lower than the EPA's benchmark for regulatory guidelines. Male offspring were raised to adulthood, euthanized, and their brains collected. Whole brain samples were pulverized and analyzed through split-sample methods, including transcriptomics, kinomics, metabolomics, and multiomics integration.

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Results: Transcriptomic analysis revealed changes in several key clock genes, while kinomic analysis showed altered activity in kinases linked to synaptic plasticity. Metabolomic profiling identified alterations in folate biosynthesis, which is crucial for preventing neural tube defects. Multiomics integration highlighted a disrupted protein-protein interaction network, emphasizing key clusters related to mitogen-activated protein (MAP) kinase pathways, apoptosis regulation, and synaptic function.

Conclusions: These findings indicate that developmental pyrethroid exposure (DPE) leads to a multi-modal biophenotype in the brain associated with ADHD, and suggests new potential mechanisms underlying this effect.

Keywords: Neurodevelopmental Disorders, Autism, Pyrethroids

