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

Jennifer Nguyen[1*], Melissa A. Curtis[1], Ali S. Imami[1], William G. Ryan[1], Khaled Alganem[1], Kari L. Neifer[1], Nilanjana Saferin[1], Charlotte N. Nawor[1], Brian P. Kistler[1], Gary W. Miller[2,3], Rammohan Shukla[4], Robert E. McCullumsmith[5], James P. Burkett[6]

[1]College of Medicine and Life Sciences, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[2]Department of Environmental Health, Emory Rollins School of Public Health, Atlanta, GA 30322

[3]Department of Environmental Health Sciences, Mailman School of Public Health, Columbia University, New York, NY 1003

[4]Department of Zoology and Physiology, University of Wyoming, Laramie, WY 82071

[5]Professor, Chair of Department of Neurosciences and Psychiatry, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

[6]Assistant Professor, Department of Neurosciences and Psychiatry, 3000 Arlington Avenue, The University of Toledo, Toledo OH 43615

Email: jennifer.nguyen@rockets.utoledo.edu

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Introduction: Neurodevelopmental disorders (NDDs) are a group of pervasive conditions affecting the developing nervous system, often with few or no identifiable biomarkers. A significant portion of the risk for NDDs, including attention deficit hyperactivity disorder (ADHD), is influenced by environmental factors. One such potential 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 demonstrated that low-dose exposure to the pyrethroid pesticide deltamethrin during development in mice leads to male-biased alterations in ADHD- and NDD-related behaviors, as well as changes in the striatal dopamine system.

Objective: In this study, we employed an integrated multiomics approach to identify the most comprehensive range of biological changes in the mouse brain resulting from developmental pyrethroid exposure (DPE).

Methods: Using a litter-based, split-sample design, we exposed pregnant and lactating mouse dams to deltamethrin (3 mg/kg or vehicle every 3 days) at a dose significantly lower than the EPA's benchmark dose for regulatory guidelines. The male offspring were raised to adulthood, euthanized, and their brains were collected. The whole brain samples were then pulverized and divided for split-sample analysis, including transcriptomics, kinomics, metabolomics, and multiomics integration.

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Results: Transcriptome analysis identified changes in several key clock genes, while kinome analysis showed altered activity in multiple kinases associated with synaptic plasticity. Metabolomics identified changes in folate biosynthesis, critical for preventing neural tube defects. Multiomics integration uncovered a disrupted protein-protein interaction network, highlighting primary clusters related to mitogen-activated protein (MAP) kinase pathways, apoptosis regulation, and synaptic function.

Conclusions: These findings demonstrate that developmental pyrethroid exposure (DPE) induces a multi-modal biophenotype in the brain associated with ADHD, while also revealing novel potential mechanisms of action.

Keywords: Neurodevelopmental Disorders,Autism,Pyrethroids

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