Developmental pyrethroid exposure disrupts molecular pathways for circadian rhythms and MAP kinase in mouse brain

Jennifer H. 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 Nawor[2], Brian P. Kistler[2], Gary W. Miller[3], Rammohan Shukla[1], Rob McCullumsmith[1], James Burkett[1]

[1]University of Toledo College of Medicine, Department of Neurosciences; [2]Department of Medicine; [3]Columbia University

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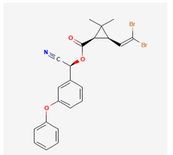
Video Presentation

INTRODUCTION



- Neurodevelopmental disorders (NDDs) are lifelong, incurable brain disorders with few biomarkers and few treatments[1]. The incidence of NDDs is rapidly rising, with 17% of children in the US now affected[2].
- Developmental pyrethroid exposure **(DPE)** results in an increase in dopamine transporter that directly causes an ADHD-like behavioral phenotype in mouse[3].
- **Two recent epidemiological studies** have linked pyrethroid pesticides with autism risk[4,5].

Key experimental question:

- Does developmental exposure to pyrethroids cause **brain-wide molecular changes**

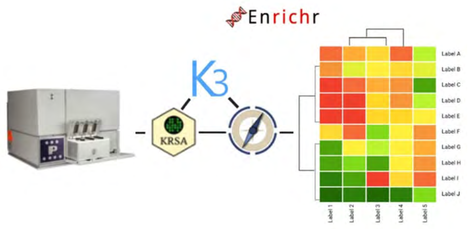
EXPERIMENTAL DESIGN

Pesticide exposure

Transcriptome

24-Hour Mobility

Kinome



Multiomics

RESULTS

FIGURE 1: DPE causes transcriptional changes to clock genes

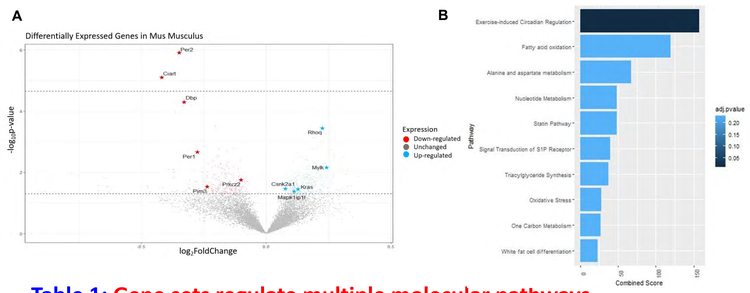


Table 1: Gene sets regulate multiple molecular pathways

A CHEA3 Analyses

Rank	TF	Score
1	SOX18	37.33
2	FOSB	41.67
3	PRRX1	46
4	ZNF524	51.33
5	MYC	57.33
6	ZNF326	67
7	JUN	70.33
8	TWIST1	74
9	NR4A1	79.5
10	ZNF672	83.67

B KEA3 Analyses

Rank	Protein	Mean rank
1	CSNK1D	33.1
2	CSNK1E	33.91
3	PRKDC	35.91
4	MAPK1	44.45
5	EGFR	45.73
6	ATM	47.82
7	SRC	51.18
8	CSNK2A1	55.09
9	CSNK1A1	55.64
10	MASTL	57.75

Key: Regulates
- synaptic plasticity
- adult neurogenesis
- circadian rhythm

FIGURE 2: DPE increases activity in kinases regulating synaptic plasticity

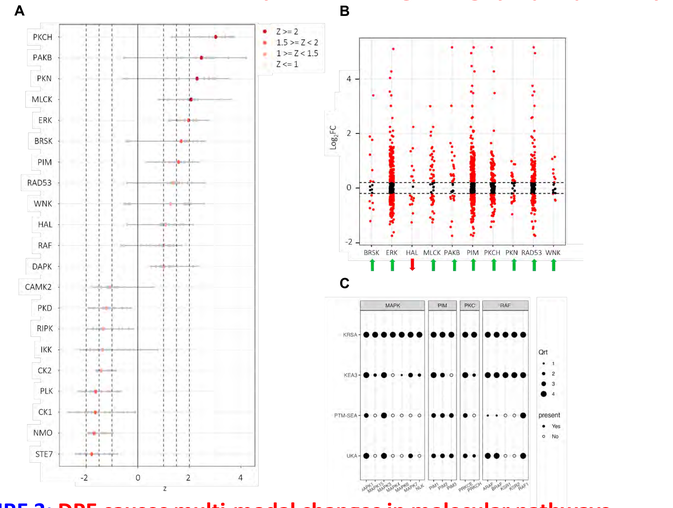


FIGURE 3: DPE causes multi-modal changes in molecular pathways

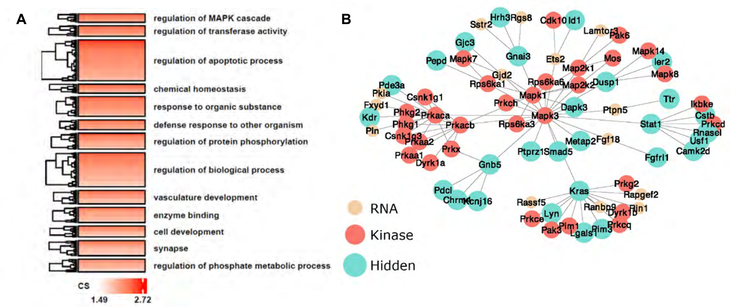
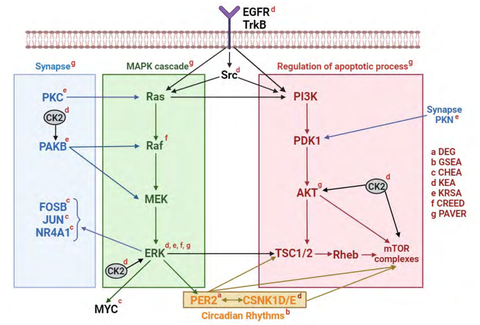


FIGURE 4: Multi-modal changes in circadian rhythms, MAPK, growth/apoptosis, and synapse function



CONCLUSIONS

DPE may alter circadian rhythm

- Genetic results from transcriptome in mouse show significant disruptions in two CLOCK genes and a pattern of changes in genes of interest concentrating in circadian rhythm gene sets.

DPE may alter synaptic plasticity

- Disruptions in synaptic plasticity and changes in dendritic spines have been implicated in the etiology of autism.
- All seven kinases with increased kinase activity in DPE mice have roles in synaptic plasticity, and synapse function was identified as a significant cluster in the multi-omics network.
- This broad increase in kinase activity may reflect a biophenotype of dendritic spine overgrowth and/or decreased synaptic pruning, as is seen in autistic patients and some mouse models.

Multi-modal changes in MAPK and mTOR cascades

- Adult neurogenesis is known to contribute to hippocampal structural and functional plasticity, and is also related to cognition and memory, which are deficient in DPE mice. The largest identified multi-modal gene cluster in our data was for the regulation of apoptotic processes, which directly affects adult neurogenesis, in part through the mTOR pathway.

Remaining to be done

- Multi-omics on 112 vole brains.

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