Developmental exposure to the Parkinson's disease-associated organochlorine pesticide dieldrin alters dopamine neurotransmission in α-synuclein pre-formed fibril (PFF)-injected mice

College of Osteopathic Medicine
MICHIGAN STATE UNIVERSITY

Sierra L. Boyd, Nathan C. Kuhn, Joseph R. Patterson, Anna C. Stoll, Sydney A. Zimmerman, Mason R. Kolanowski, **Joseph J. Neubecker,** Kelvin C. Luk, Eric S. Ramsson, Caryl E. Sortwell, Alison I. Bernstein

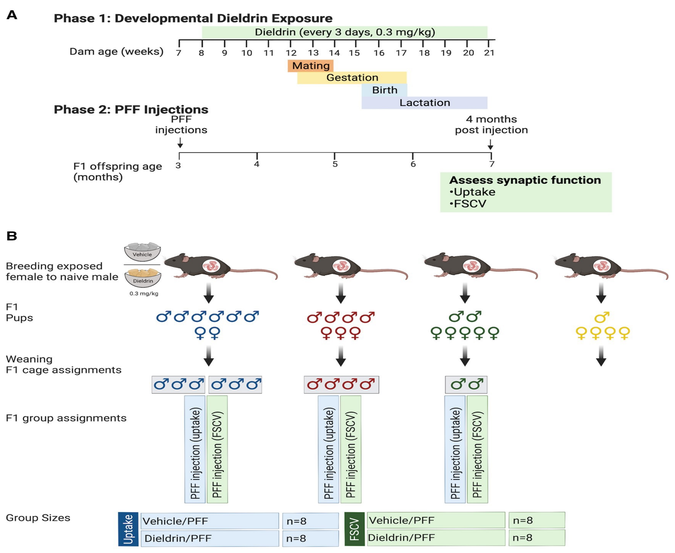
Introduction

- Parkinson's disease (PD) is a growing global health concern characterized by dopaminergic neuron degeneration and α-synuclein-containing Lewy bodies.
- Environmental factors, including exposure to dieldrin, a pesticide associated with PD, have been linked to increased PD risk. Despite dieldrin being phased out, its effects persist due to past exposures during critical neurodevelopmental periods.
- Animal models show dieldrin-induced oxidative stress, dopaminergic cell toxicity, and disrupted dopamine activity, suggesting a potential role in PD.

Objectives

- To investigate the effects of developmental exposure to dieldrin on dopamine neurotransmission in mice.
- To assess how developmental dieldrin exposure influences susceptibility to synucleinopathy induced by α-synuclein pre-formed fibrils (PFFs).
- To explore potential sex-specific differences in the impact of dieldrin exposure on dopamine neurotransmission and synucleinopathy.

Methods



- Dieldrin Exposure Paradigm: Female mice were treated with 0.3 mg/kg dieldrin throughout breeding, gestation, and lactation. Offspring were weaned at 3 weeks of age.
- Preparation of α-synuclein PFFs: Recombinant mouse α-synuclein monomers were converted to PFFs and verified for fibril size.
- Intrastriatal Injection of α-syn PFFs: Male offspring at 12 weeks of age received unilateral intrastriatal injections of PFFs.
- Vesicular Dopamine Uptake: Assessment of vesicular dopamine uptake was conducted using a radioactive assay.
- Fast-scan Cyclic Voltammetry: Dopamine release and uptake were measured using fast-scan cyclic voltammetry in the dorsal striatum.
- Immunohistochemistry: Brain sections were stained and analyzed for α-synuclein pathology using immunohistochemistry.
- Data Analysis and Statistics: Statistical analysis was performed using GraphPad Prism 9 with significance set at $p < 0.05$. Control groups injected with α-synuclein monomers were included for comparison.

Results

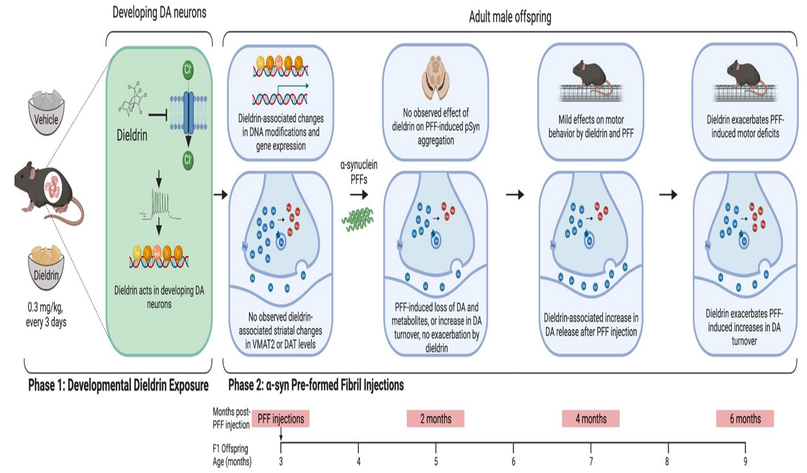


Figure 1: Overview of developmental dieldrin/PFF 2-hit model.

- Quantitative analysis revealed a significant increase in peak dopamine ($p = 0.0394$) and upward velocity ($p = 0.0434$) in the dieldrin/PFF group compared to the vehicle/PFF group.
- There were no significant differences in downward velocity ($p = 0.5303$) or tau ($p = 0.6435$) between the two groups.
- These findings suggest that dieldrin exposure in conjunction with PFFs led to enhanced dopamine release and faster dopamine uptake in the striatum, highlighting the potential role of dieldrin in modulating dopamine neurotransmission in the context of synucleinopathy.

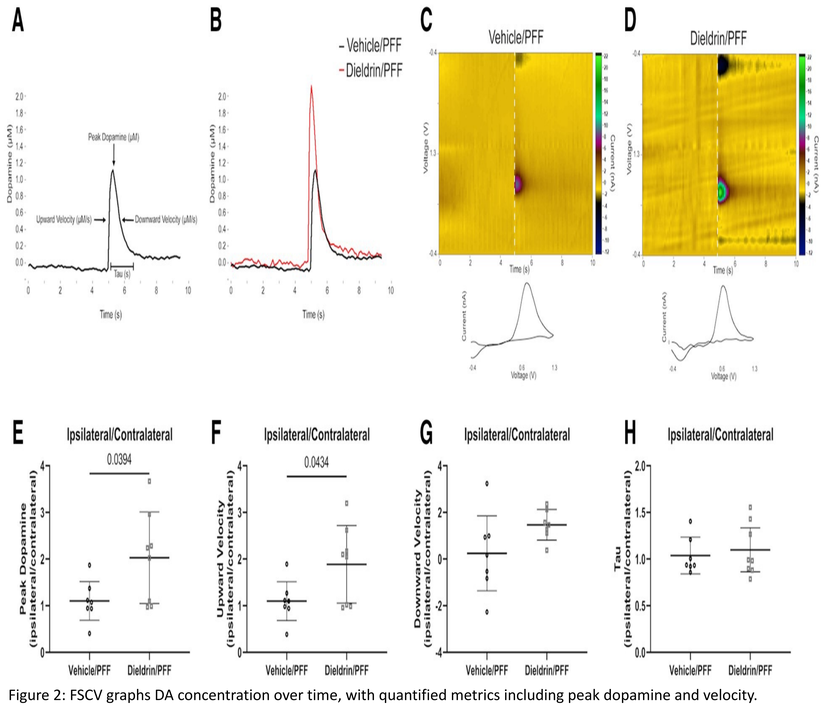


Figure 2: FSCV graphs DA concentration over time, with quantified metrics including peak dopamine and velocity.

Discussion

- Developmental exposure to dieldrin affects dopamine (DA) neurons, making them more susceptible to synucleinopathy-induced deficits in motor behavior. This is attributed to persistent changes in gene regulation and neuroinflammation.
- Dieldrin-exposed animals show enhanced DA release after synucleinopathy induction, preceding changes in DA turnover and motor behavior.
- While no significant effect on VMAT2 uptake was observed, potential alterations in DAT function may contribute to these findings.
- Synucleinopathy induction alone did not reduce DA release, suggesting that remaining neurons can maintain sufficient DA levels despite significant DA loss.
- These results emphasize the importance of studying environmental exposures across the lifespan and shed light on the mechanisms underlying increased susceptibility to Parkinson's disease.

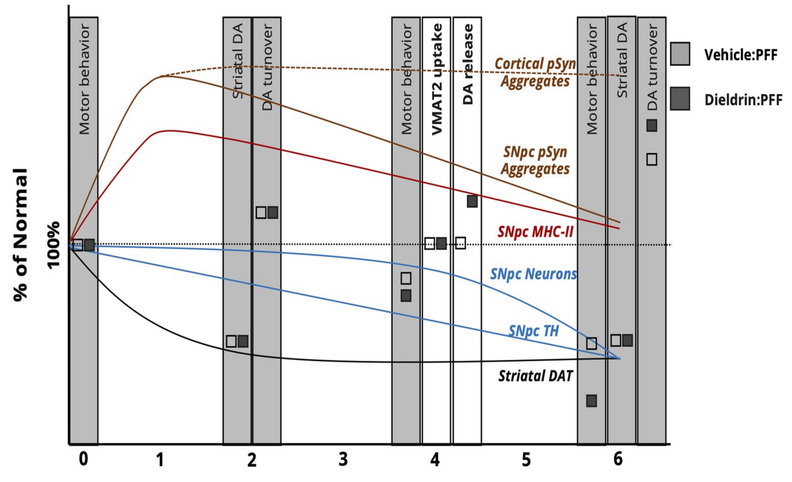


Figure 3. Summary of observed changes in the dieldrin PFF 2-hit model. Timelines show representative changes synuclein pathology, microglial activation, striatal loss, and nigral degeneration in the PFF model based on published literature, shown as the percent change in these markers compared to a saline/monomer injected mouse. Grey boxes indicate previous results from our lab in the dieldrin PFF 2-hit model. White boxes indicate FSCV and uptake results reported here at 4 months post-PFF injection. Light grey and dark grey squares represent results from vehicle: PFF and dieldrin: PFF animals, respectively.

Conclusion

- Developmental exposure to dieldrin exacerbates DA neuron loss in a mouse model of Parkinson's disease.
- Dieldrin exposure during development alters DA neurotransmission, including changes in dopamine release and reuptake dynamics, in mice injected with α-synuclein pre-formed fibrils.

References

Boyd, S., Kuhn, N. C., Patterson, J. R., Stoll, A., Zimmerman, S., Kolanowski, M. R., Neubecker, J. J., Luk, K. C., Ramsson, E. S., Sortwell, C. E., & Bernstein, A. I. (2023b). Developmental exposure to the Parkinson's disease-associated organochlorine pesticide dieldrin alters dopamine neurotransmission in α-synuclein pre-formed fibril (PFF)-injected mice. *Toxicological Sciences*, *196*(1), 99–111. https://doi.org/10.1093/toxsci/kfad086