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Reproducing the Rotenone Model of Parkinson's Disease in Rats

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INTRODUCTION

- Parkinson's Disease (PD) is a progressive and debilitating neurodegenerative disease, characterized by motor symptoms such as tremors, bradykinesia, impaired posture, and muscle rigidity.
- The underlying pathology involves the degeneration of nigrostriatal dopaminergic neurons.
- The precise triggers for PD are unknown: nonetheless, age, sex, and genetics are among the major risk factors.
- The genetic component of PD risk is estimated at just 30%. Accordingly, 70% of the risk for PD is environmental. While many potential environmental triggers for PD may exist, there is growing evidence that prolonged exposure to certain pesticides and herbicides elevates PD risk.
- The lab is interested in studying the role of environmental exposure to pesticides in neurological disorders. In this regard, we are interested in studying molecular mechanisms for pesticide exposure and PD.
- Rotenone, a chemical compound found in fungicides, is reputable in its application as a pesticide model of PD due to its propensity to induce dopaminergic degeneration, α -synuclein inclusions, motor deficits, and non-motor symptoms in rats.
- The purpose of the study was to establish and validate the rotenone model of PD at the VCU Neurology Research lab.

METHODS

- Animal studies were approved by the VCU Institutional Animal Care and Use Committee.
- Animals: Thirty-six male Lewis rats at 12-14 months (middle-aged) were obtained from Hilltop, Scottsdale, PA. They were randomly divided into control and experimental groups.
- Rotenone administration: Control group received vehicle (VEH, 98% Miglyol 812 N, and 2% DMSO) injections. The experimental groups received rotenone (ROT). ROT was injected at 3 mg/kg, i.p. once daily for nine days. Animals were weighed daily prior to injections (Fig. 1).
- Bar Test: The onset of PD-like signs was assessed using a "bar test". Here, the forepaws of rats were placed on a 3 cm diameter cylindrical bar which was elevated 9 cm from the ground. The time taken by a rat to descend and correct its posture was noted with a cut-off time of 180s.
- Tissue Collection: After the behavioral studies, euthanasia was completed in two approaches: some rats were rapidly decapitated following isoflurane anesthesia and the striatum was dissected while others were fixed using 4% paraformaldehyde for subsequent molecular and staining studies.

REFERENCES

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2. Greenamyre, J. T., Cannon, J. R., Drolet, R., & Mastroberardino, P. G. (2010). Lessons from the rotenone model of Parkinson's disease. *Trends in pharmacological sciences*, 31(4), 141–143. <https://doi.org/10.1016/j.tips.2009.12.006>

ACKNOWLEDGEMENTS

This study was supported by VCU Parkinson's and Movement Disorder Center Pilot Grant Program.

Fig. 1 Schematic of the experimental design for PD studies

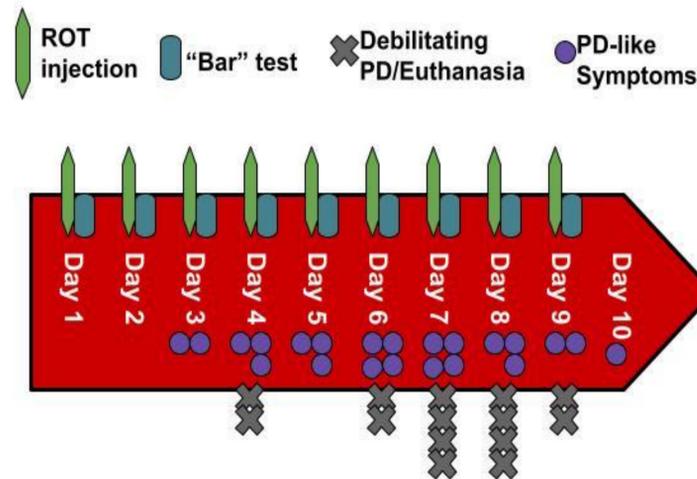


Fig. 2 Mean body weight after daily ROT injections

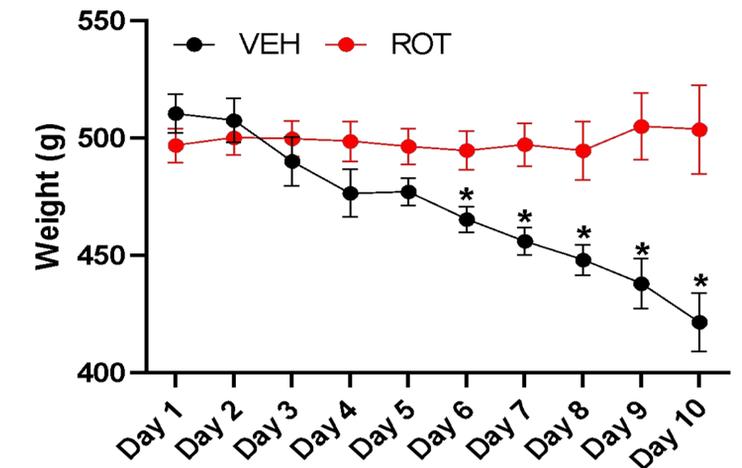


Fig. 3 Increased descend latency after daily ROT injections

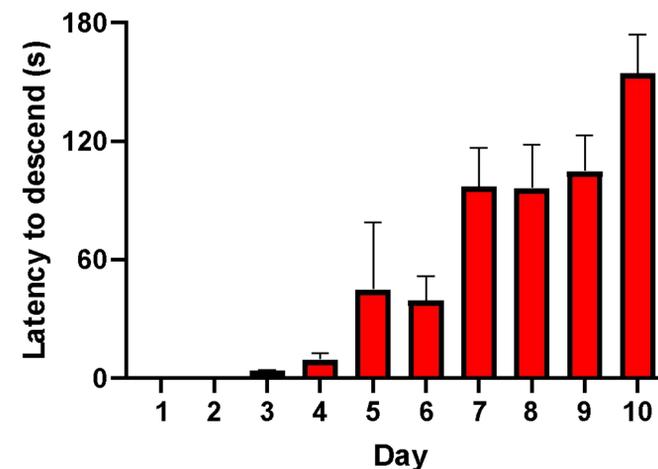
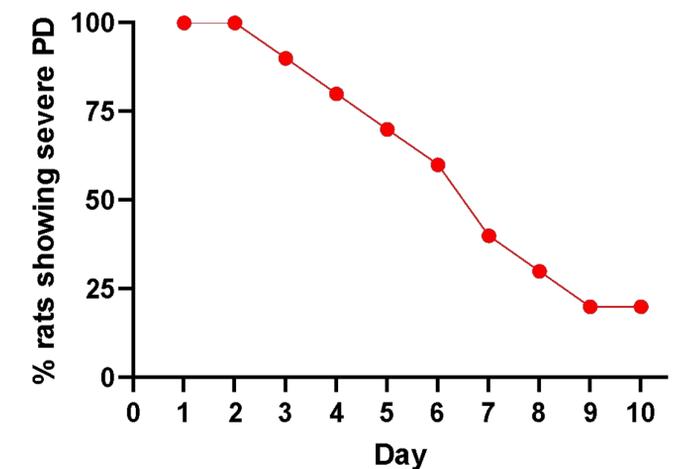


Fig. 4 Increase in percentage of rats expressing severe PD signs during ROT injection regimen



RESULTS

- Beginning day 5, daily intraperitoneal rotenone elicited weight loss of statistical significance in differentiation from the VEH-treated group ($n = 8-12/\text{group}$, $*p < 0.05$, t-test, Fig. 2).
- Daily intraperitoneal rotenone produced progressive behavioral deficits. Rotenone-treated animals exhibited postural instability characterized by increased descent latency in the bar test (Fig. 3). The latency time increased over time following daily ROT injections. Vehicle-treated rats did not exhibit any postural rigidity and scored < 2 s on the bar test.
- Daily ROT injections increased the percent of rats that exhibited severe PD signs and at the end of ROT injection regimen over 80% of rats had developed severe PD while the remainder of rats at the end exhibited mild PD signs on the bar test (Fig. 4).

CONCLUSIONS

- Chronic intraperitoneal rotenone produces behavioral PD-like signs. This study has successfully reproduced a well-known model of PD in rats in our lab.
- This lab will next conduct neurochemical, and histological characterization of the neurological effects of chronic intraperitoneal rotenone to further validate the rotenone model of PD.
- The lab will utilize this model to study the role of epigenetic mechanisms in the development of PD following rotenone exposure.