Synergistic Effects of Chronic Lead Exposure and Genetic Predisposition on Retinal Degeneration

Anna Avesani[a#]*, **Giorgia Targa**[a], **Michela Di Peco**[a], **Sabina Peluso**[a], **Marco Cambiaghi**[a,b], **Daniele Dell'Orco**[a]

[a] *University of Verona, Department of Neurosciences, Biomedicine and Movement Sciences, Biological Chemistry Section, Strada le Grazie, Verona, Italy*
[b] *Department of Neurology, Hackensack Meridian School of Medicine, Nutley, NJ 07110, USA.*

[#]*corresponding author email: anna.avesani @univr.it*
**presenting poster: Anna Avesani*

1. Abstract

Recent studies suggest a potential link between the accumulation of heavy metals, particularly lead (Pb^{2+}), in the retina and the progression of age-related macular degeneration (AMD) [1] . While the neurotoxic effects of Pb^{2+} are well known [2] [3], its specific impact on retinal health and the potential for a synergistic effect with inherited retinal degeneration remain unclear. This study investigates whether chronic lead exposure has degenerative effects on retinal function and structure and if these effects are amplified by a genetic predisposition to retinal degeneration. We utilize a murine model carrying the p.E111V mutation in the *GUCA1A* gene, which is associated with cone-rod dystrophy [4], and expose both mutant and wild-type mice to prolonged oral Pb^{2+} administration. Our findings will elucidate the complex interplay between genetic and environmental risk factors [5], with significant implications for understanding retinal degeneration pathogenesis and for developing targeted diagnostic and preventive strategies for at-risk populations.

2. Methods and results

This study employs a multidisciplinary approach to investigate the effects of chronic lead exposure in a murine model.

Animal Model: We use both wild-type (C57Bl/6) and mutant mice homozygous for the p.E111V mutation in the *GUCA1A* gene. This model mimics human autosomal dominant cone-rod dystrophy (adCORD).

Experimental Protocol: Starting at postnatal day 30, mice were treated daily via oral gavage for 4 weeks with either lead (II) acetate (PbAc) or sodium acetate (NaAc) [6] [7].

Study Endpoints: We will assess the effects at three critical time points following the final administration: 2 days (acute), 1 month (sub-chronic), and 7 months (chronic).

This project integrates cognitive-behavioural, functional, and morphological characterizations to provide a comprehensive understanding of Pb^{2+} toxicity. In detail, we focused on:

Tissue Pb^{2+} Quantification: the accumulation of Pb^2 in key tissues (brain, retina) and peripheral blood was quantified using Inductively Coupled Plasma Mass Spectrometry (ICP-MS).

Functional and Behavioral Evaluation: Electroretinogram (ERG) and Visual Evoked Potentials (VEP) were used to evaluate retinal and cortical visual function, respectively. Behavioral Tests: Looming and Cliff tests were performed to test the animals' visual perception and defensive behaviors in response to visual stimuli, and the Novel Object Recognition (NOR) test to evaluate short-term memory and visual discrimination.

Morphological and Structural Analysis: retinal health and the degeneration of neuronal layers were analysed through histology and immunofluorescence.

Our preliminary data at the acute time point, confirmed by ICP-MS analysis, show that daily oral administration of PbAc resulted in significant lead accumulation in the brain, retina, and serum. In addition, chronic Pb^{2+} exposure exacerbates visual deficits in genetically predisposed mice to a greater extent than in wild-type controls. These findings support a gene-environment interaction model, suggesting that genetic background amplifies the neurotoxic effects of environmental lead on the retina.

References

[1] Pamphlett, R., Cherepanoff, S., Too, L.K., Kum Jew, S., Doble, P.A., & Bishop, D.P. The distribution of toxic metals in the human retina and optic nerve head: Implications for age-related macular degeneration. PLoS One, 15(10), e0241054. (2020).

[2] Ramírez Ortega, D., González Esquivel, D.F., Blanco Ayala, T., Pineda, B., Gómez Manzo, S., Marcial Quino, J., Carrillo Mora, P., Pérez de la Cruz,V. Cognitive Impairment Induced by Lead Exposure during Lifespan: Mechanisms of Lead Neurotoxicity. Toxics, 9(2), 23. (2021).
[3] Varadarajan KS, Bagga P, Ramesh A, Chugani AN, Patel AB. Chronic lead exposure disrupts neurometabolic activity in mouse brain: An ex vivo ^{1}H-[^{13}C]-NMR study. Neurotoxicology.;94:117-125. (2023).
[4] Marino, V., Dal Cortivo, G., Oppici, E., Maltese, P.E., D'Esposito, F., Manara, E., Ziccardi, L., Falsini, B., Magli, A., Bertelli, M. & Dell'Orco, D. A novel p. (Glu111Val) missense mutation in GUCA1A associated with cone-rod dystrophy leads to impaired calcium sensing and perturbed second messenger homeostasis in photoreceptors. Hum Mol Genet, 27(24), 4204-4217. (2018).
[5] Tchounwou, P.B., Yedjou, C.G., Patlolla, A.K., & Sutton, D.J. Heavy metal toxicity and the environment. Exp Suppl, 101, 133-64. (2012).
[6] Webb AN, Spiers KM, Falkenberg G, Gu H, Dwibhashyam SS, Du Y, Zheng W, Nie LH. Distribution of Pb and Se in mouse brain following subchronic Pb exposure by using synchrotron X-ray fluorescence. Neurotoxicology. 88:106-115. (2022).
[7] Yu Y, Yu L, Zhou X, Qiao N, Qu D, Tian F, Zhao J, Zhang H, Zhai Q, Chen W. Effects of acute oral lead exposure on the levels of essential elements of mice: a metallomics and dose-dependent study. J Trace Elem Med Biol; 62:126624. (2020).