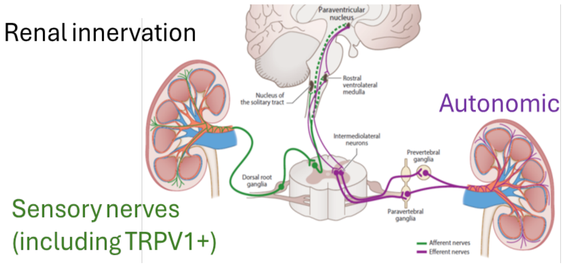
Ablation of TRPV1-Expressing Sensory Neurons Attenuates Cisplatin-Induced Kidney Injury (CIKI) and Inflammation

Gayoung Yang[1,2], Sophie Laumet[1], Joe Folger[1], Geoffroy Laumet[1],
[1]Department of Molecular, Cellular and Integrative Physiology, Michigan State University, East Lansing, MI
[2]Michigan State University College of Osteopathic Medicine, East Lansing, MI

INTRODUCTION

- Cisplatin is a widely used first-line chemotherapeutic agent for treating solid tumors, including those of the bladder, ovaries, testes, lungs, and head and neck[1].
- However, its use in clinical practice is limited due to its severe adverse effects, particularly nephrotoxicity; 20%–35% of patients develop acute kidney injury after cisplatin administration[1,2].
- No effective treatments exist for CIKI, highlighting the urgent need for strategies that reduce nephrotoxicity without compromising cisplatin's anticancer efficacy[1].
- The kidney receives both autonomic and sensory innervation, but the role of sensory innervation in kidney injury remains underexplored[3].
- TRPV1 is a nociceptive ion channel in sensory neurons that, when activated by harmful stimuli (e.g., low pH, heat, injury), releases neuropeptides and chemokines to modulate immune responses[3,4].

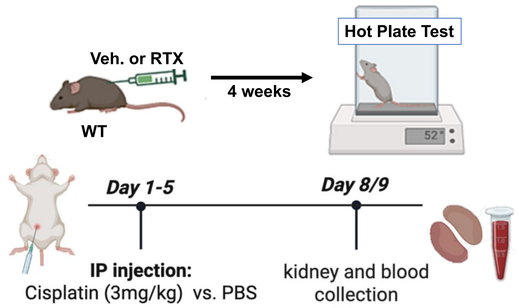


HYPOTHESIS

Targeted ablation of TRPV1+ renal sensory neurons may reduce cisplatin-induced kidney injury, allowing intensified dosing and revealing a neuroimmune mechanism to protect kidney function during chemotherapy.

METHOD

- Resiniferatoxin (RTX) injection selectively targets and ablates TRPV1+ sensory neurons in C57BL/6J mice.
- TRPV1+ neuronal loss was confirmed using the hot plate test 4 weeks post RTX injection and TRPV1+ mRNA levels in the trigeminal nerves.
- CIKI model: Mice were administered daily intraperitoneal (IP) injections of cisplatin (3 mg/kg) or PBS (control) for 5 consecutive days. Blood and kidney tissues were collected 4 days post-injection for analysis.



RESULTS

1. RTX-Induced TRPV1⁺ Neuronal Denervation

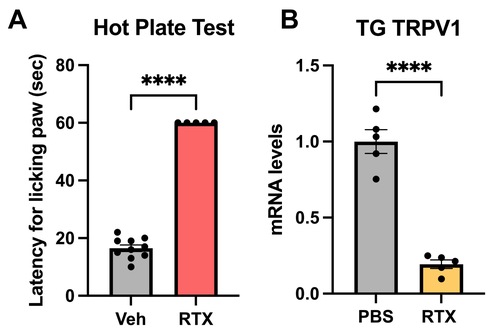


Figure 1. Four weeks post RTX injection, hot plate testing showed increased paw-lick latency in RTX-treated mice, indicating reduced sensitivity to noxious heat (A). TRPV1 mRNA levels in the trigeminal ganglion were significantly reduced, confirming neuronal loss (B).

2. RTX Reduces Renal Injury and Inflammation Following Cisplatin

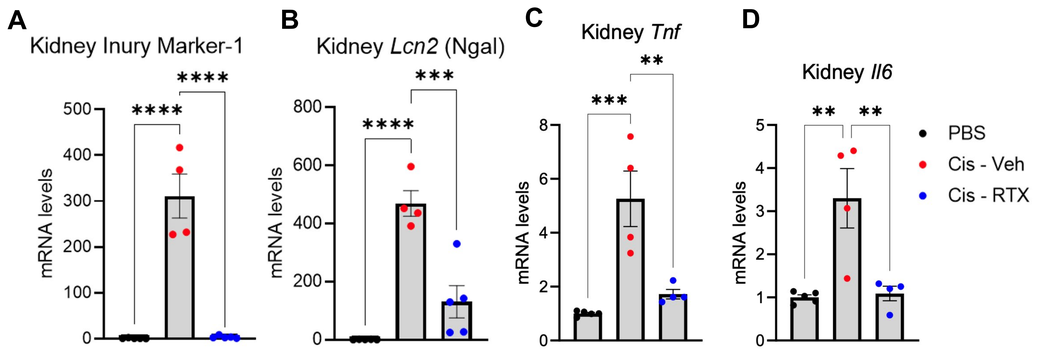


Figure 2. RTX treated mice show significantly reduced cisplatin-induced kidney injury, as evidenced by decreased expression of kidney injury markers KIM-1 and LCN2 (A-B) and reduced levels of inflammatory cytokines IL-6 and TNFα (C-D).

3. RTX reduces Histopathology score and BUN in CIKI

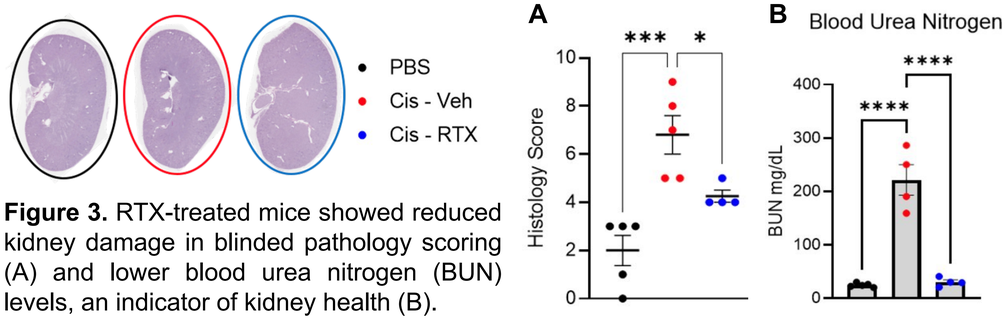


Figure 3. RTX-treated mice showed reduced kidney damage in blinded pathology scoring (A) and lower blood urea nitrogen (BUN) levels, an indicator of kidney health (B).

4. Potential Sex Differences in CIKI

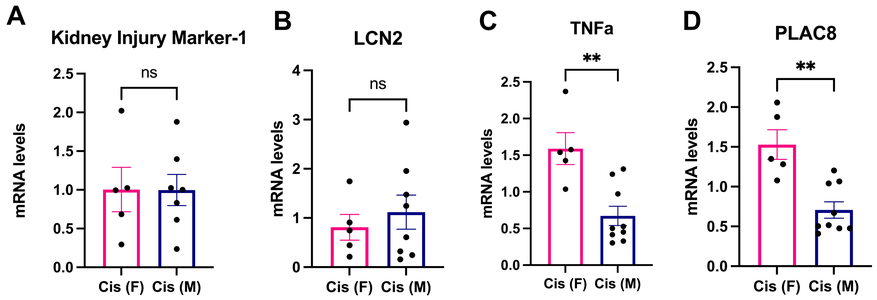


Figure 4. While no sex differences were observed in kidney injury markers KIM-1 and LCN2 (A-B), females showed greater TNFα and PLAC8 expression—both associated with inflammatory responses—following cisplatin treatment compared to males (C-D).

RESULTS

5. Increased immune cell Infiltration Following Cisplatin

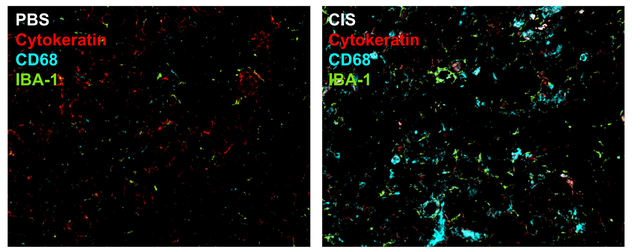


Figure 5. Cisplatin increased CD68 and Iba-1 staining in kidney tissue (10x), indicating elevated macrophage infiltration. Cytokeratin stains epithelial cells.

DISCUSSION

Conclusion

- Ablating TRPV1⁺ sensory neurons protects against CIKI by improving renal function, preserving tissue integrity, and lowering injury markers. This may enable higher cisplatin dosing, enhancing anticancer efficacy without treatment-limiting nephrotoxicity.
- Findings support neuron-targeted nephroprotection, refined biomarker selection, and investigation of sex-specific mechanisms in CIKI and cancer treatment.

Future Directions

- Investigate TRPV1⁺ neuron ablation in tumor-bearing mice and test approved TRPV1⁺ blockers as potential therapies to mitigate CIKI.
- Explore the roles of immune cells in CIKI by depleting neutrophils, monocytes, mast cells, and perivascular macrophages in a mouse model.

OSTEOPATHIC RELEVANCE

These findings demonstrate that TRPV1⁺ sensory neurons play a key role in kidney injury, supporting the **osteopathic principle that body systems are interconnected**. The study emphasizes the need for a **whole-body approach**.

Ablation of these neurons reduced injury, suggesting neural modulation enhances **organ resilience.** This supports **osteopathic principles of self-healing** and highlights OMT's potential to influence neuroimmune function during chemotherapy.

REFERENCES

1. Fang, Cy., Lou, Dy., Zhou, Lq. *et al.* Natural products: potential treatments for cisplatin-induced nephrotoxicity. *Acta Pharmacol Sin* 42, 1951–1969 (2021). https://doi.org/10.1038/s41401-021-00620-9
2. Oh G-S, Kim H-J, Shen A, Lee SB, Khadka D, Pandit A, So H-S. Cisplatin-induced Kidney Dysfunction and Perspectives on Improving Treatment Strategies. Electrolyte Blood Press E BP 2014;12:55–65
3. Osborn JW, Tyshynsky R, Vulchanova L. Function of Renal Nerves in Kidney Physiology and Pathophysiology. Annu Rev Physiol 2021;83:429–450.
4. Laumet G. Peripheral somatosensory neurons listen and orchestrate the immune response. J Allergy Clin Immunol 2024;153:977–97

Lab QR code!

ACKNOWLEDGEMENTS

1. Members of the Neuroimmunology of Pain Lab
2. Funding: NIH R01 NS121259, R01 AI177305
3. MSUCOM DO/PhD program