Artemin/GFRα3 signaling axis is involved in the functional plasticity of sensory neurons in osteoarthritis pain

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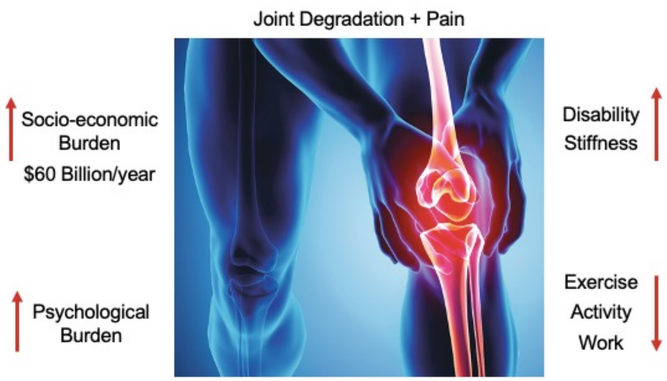
Background: Osteoarthritis (OA) Pain

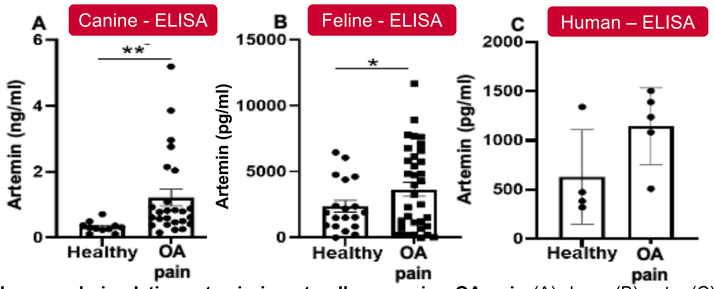
- The disease of OA is a significant contributor to the burden of chronic pain and disability in our society.



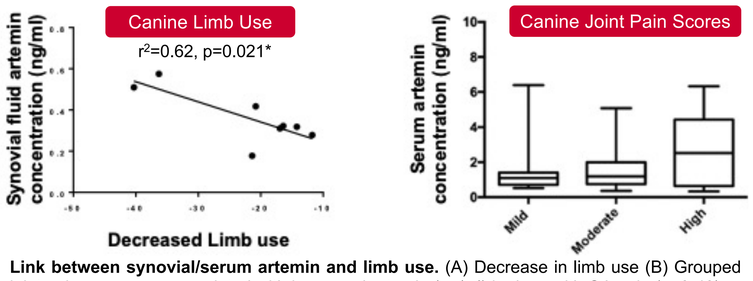
- Clinically efficacious and safe therapeutic options for OA pain management are limited.

Background: Artemin in OA Pain

- **Artemin**, an endogenous ligand is upregulated in OA pain and linked to limb use.



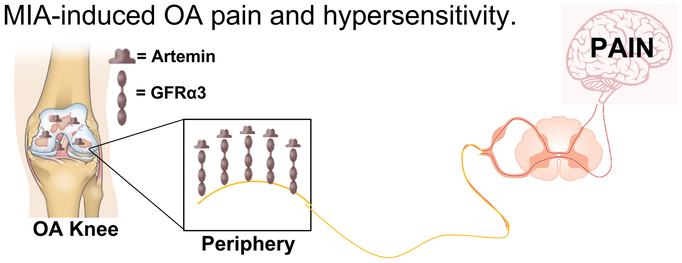
Increased circulating artemin in naturally occurring OA pain (A) dogs, (B) cats, (C) humans. n=4-38. Mean ± SEM. Student's t-test with two-tailed analysis. *p≤0.05, **p≤0.01.



Link between synovial/serum artemin and limb use. (A) Decrease in limb use (B) Grouped joint pain scores are associated with increased artemin (ng/ml) in dogs with OA pain (n=8-43).

Goal and Hypothesis

- **Goal:** Develop new clinically effective therapeutics for OA pain.
- **Hypothesis:** Artemin sequestration systemically reverses MIA-induced OA pain and hypersensitivity.

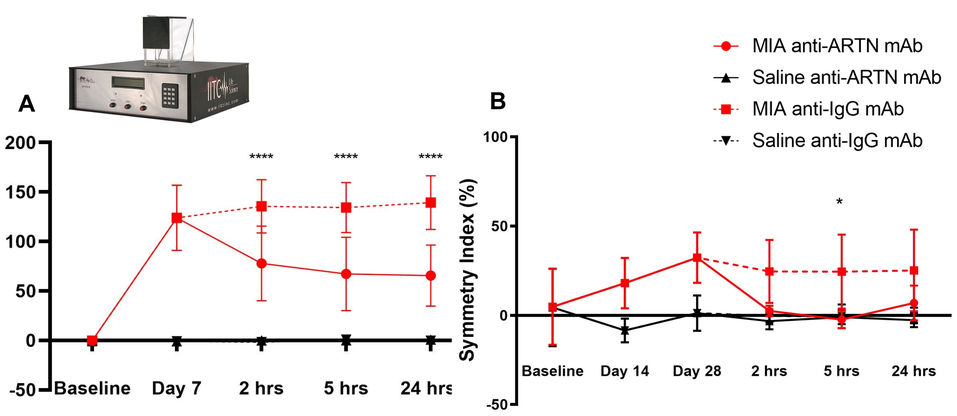


Results

Blocking artemin signaling reverses OA pain at early and late time points

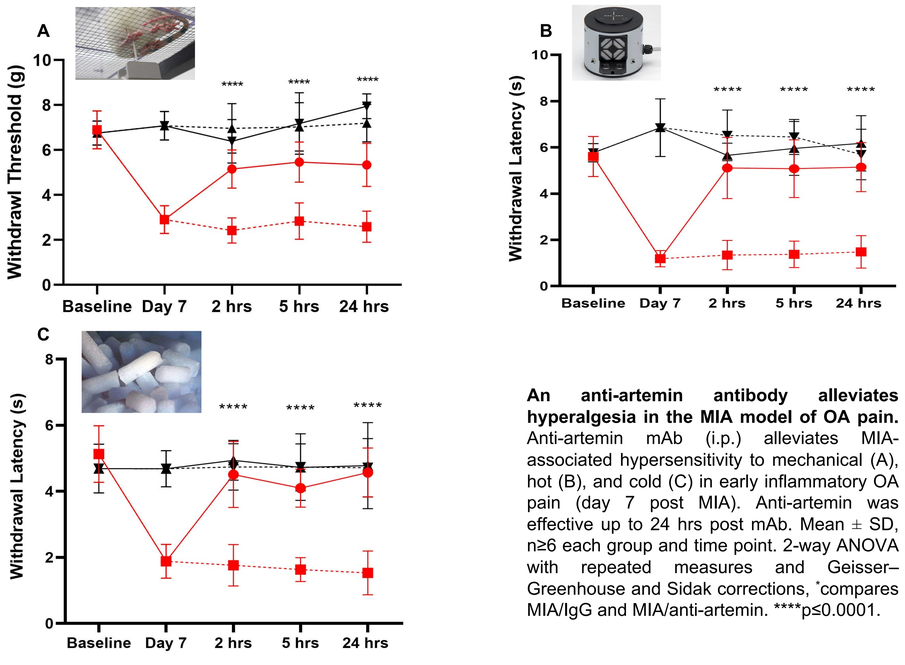
QR Code: Abstract & Additional Results

Anti-artemin antibody rescues MIA-induced limb asymmetry on days 7 and 28



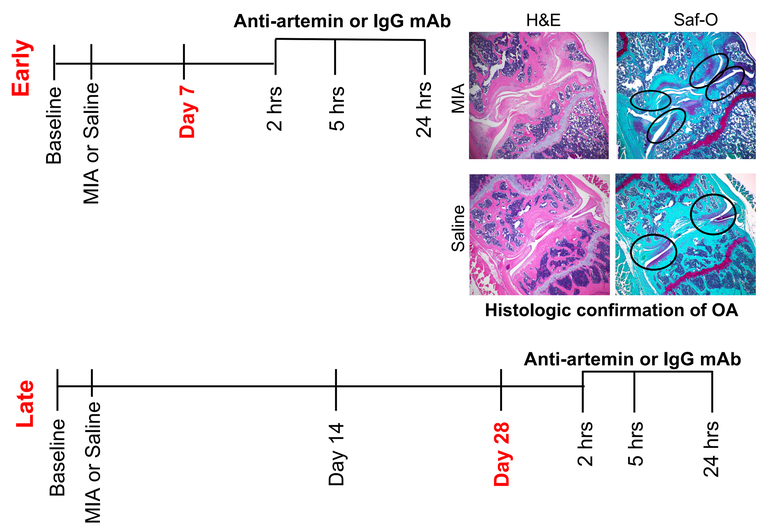
MIA induction causes limb asymmetry and an anti-artemin antibody alleviates limb disuse. Hindlimb Symmetry Index at baseline, days 7 (A), 14, 28 (B) and then 2, 5, and 24 hrs after anti-artemin or anti-IgG antibody administration (i.p.). *compares MIA/IgG and MIA/anti-artemin. Mean ± SD. N ≥6 each group and time point (* = p<0.05; **** = p<0.001). 2-way ANOVA with repeated measures and Holm-Sidak multiple comparisons test.

Anti-artemin antibody rescues MIA-induced hypersensitivity on day 7



An anti-artemin antibody alleviates hyperalgesia in the MIA model of OA pain. Anti-artemin mAb (i.p.) alleviates MIA-associated hypersensitivity to mechanical (A), hot (B), and cold (C) in early inflammatory OA pain (day 7 post MIA). Anti-artemin was effective up to 24 hrs post mAb. Mean ± SD, n≥6 each group and time point. 2-way ANOVA with repeated measures and Geisser–Greenhouse and Sidak corrections, *compares MIA/IgG and MIA/anti-artemin. ****p≤0.0001.

Methods: Timeline

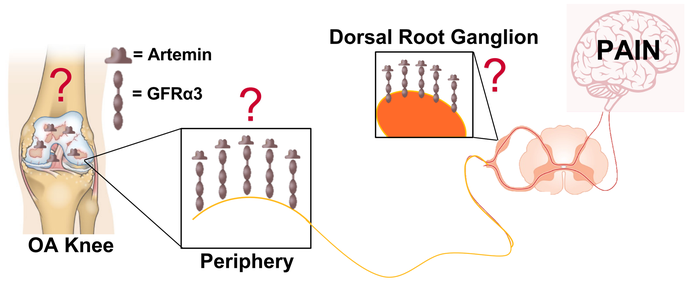


Conclusions

- **MIA OA pain model exhibits limb disuse and hypersensitivity.**
- **Anti-artemin antibody reverses early inflammatory and late chronic pain.**

Future Directions

- Elucidate the role of artemin/GFRα3 signaling in OA pain.
- Identify putative targets for developing safe and effective treatments.



Acknowledgements and References

No conflicts of interest to declare.

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References:

Gupta, A. *et al.* Serum artemin is not correlated with sensitivity within dogs with naturally occurring osteoarthritis pain. *Sci Rep* **11**, 6682, doi:10.1038/s41598-021-85976-y (2021).

2 Minnema, L., Gupta, A., Mishra, S. K. & Lascelles, B. D. X. Investigating the Role of Artemin and Its Cognate Receptor, GFRalpha3, in Osteoarthritis Pain. *Front Neurosci* **16**, 738976, doi:10.3389/fnins.2022.738976 (2022).

3 Minnema, L. *et al.* Correlation of Artemin and GFRalpha3 With Osteoarthritis Pain: Early Evidence From Naturally Occurring Osteoarthritis-Associated Chronic Pain in Dogs. *Front Neurosci* **14**, 77, doi:10.3389/fnins.2020.00077 (2020).

4 Alexander, G. C., Stoller, K. B., Haffajee, R. L. & Saloner, B. An Epidemic in the Midst of a Pandemic: Opioid Use Disorder and COVID-19. *Ann Intern Med* **173**, 57-58, doi:10.7326/M20-1141 (2020).

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