

IHS Fellowship Report



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Calvarial periosteal nociceptors in post-traumatic headache: oxytocin delivery strategy

Fellowship from September 2021 to August 2022

Stanford University, Stanford, USA

Mentor: David Yeomans

Overview

A critical gap exists in our understanding of the pathophysiology of post-traumatic headache (PTH), a common sequela to mild traumatic brain injury (mTBI). A potential strategy to alleviate these headaches may be by targeting the oxytocin receptors expressed on trigeminal nerve branches innervating the damaged calvarial periosteum (CP). Seminal studies suggest that the activation of CP trigeminal (CPT) sensory nerve terminals may play a role in some headaches. Previously, we reported that the binding of oxytocin (OT) to oxytocin receptors (OTR) on trigeminal ganglion (TG) neurons *in vitro* decreased their excitability, and nasal OT delivery reduced headache pain in mTBI-induced rats and chronic migraine patients. In addition, encapsulating OT into microparticles has been shown to have prolonged drug delivery abilities. Here, our objectives are to evaluate if: 1) CPT neurons and CP fibres express OT; 2) CP stimulation leads to activation of the TG neurons, and 3) mTBI induced inflammation increases OTR expression; 4) CP injection of OT following mTBI will reduce PTH-like allodynia; 5) CP injection of OTR antagonist prior to OT injection for PTH-related pain analysis; 6) co-label CPT neurons with OTR+CGRP expression; 7) develop OT loaded microparticles; 8) test OT-loaded microparticles in PTH rodent model to investigate the sustained analgesic effects.

Summary of research

Research till date: 1) CPT neurons and CP fibres expressed OTR: TG sections show abundant retrograde tracer labelling of the CPT neurons that co-express OTR. In CP tissue, OTR staining was significantly increased in the lipopolysaccharide inflammation vs saline; 2) CP stimulation led to rapid activation of the TG neurons: pERK levels (indicating neuronal excitation) were significantly increased in the inflammatory mediators vs synthetic interstitial fluid group; 3) OTR expression in the TG is increased after mTBI; and 4) CP injection of OT following mTBI was anti-allodynic after 30 minutes and 1 hour after injection; 5) CP injection of OTR antagonist prevented the OT analgesic effect on the PTH-related pain in mice model of mTBI up to 1-hour post-injections; 6) we show CPT neurons co-label with OTR and CGRP antibody expression; 7) we developed poly lactic-co-glycolic acid (PGLA) microparticles encapsulated with OT; and 8) we demonstrate that PGLA-OT microparticles injected into the CP produced sustained analgesic effect in mTBI-induced allodynia for up to 24 hours post-injection.

In conclusion, we demonstrate that oxytocin receptor expressed on calvarial periosteal trigeminal afferents can be a potential target for oxytocin delivery for PTH-related pain modulation. This approach may enable the development of novel targeted therapeutic strategies for PTH.

Conclusion

Within the 1-year the fellowship I was able to complete the proposed research aims. I successfully transitioned from Dr Frank Porreca's group at University of Arizona to Dr David Yeomans' laboratory at Stanford University where I gained expertise in novel techniques and concepts that will help me develop my independent career. I gained critical thinking, collaboration, networking and preliminary results to apply for my independence grant.

The IHS fellowship has been highly impactful for my career due to the new avenues and opportunities it opened up. The fellowship has supported my long-term goal by providing a rich environment for success. As an international postdoctoral trainee in the US, the eligibility criteria for many fellowships and grants are largely limited to US citizens. Therefore, gaining the IHS fellowship has been critical to my career development and has helped highlight my research work to the international headache community.

Over the course of the fellowship, I have applied for an early career development NIH grant: K99/RO1 (eligible for international postdocs). To be successful in gaining the grant, a critical component is the preliminary results. With thanks to the IHS fellowship, I was able to collect

the required preliminary data for the NIH K99/RO1 deadline and I am currently in the process of re-submitting my grant application. Obtaining the highly competitive K99/RO1 grant will be exceedingly advantageous for my early career development.

I am continuing to work with Dr Yeomans for the next year and I plan to gain independent funding and transition to a faculty position at a highly regarded US university by mid-2024.

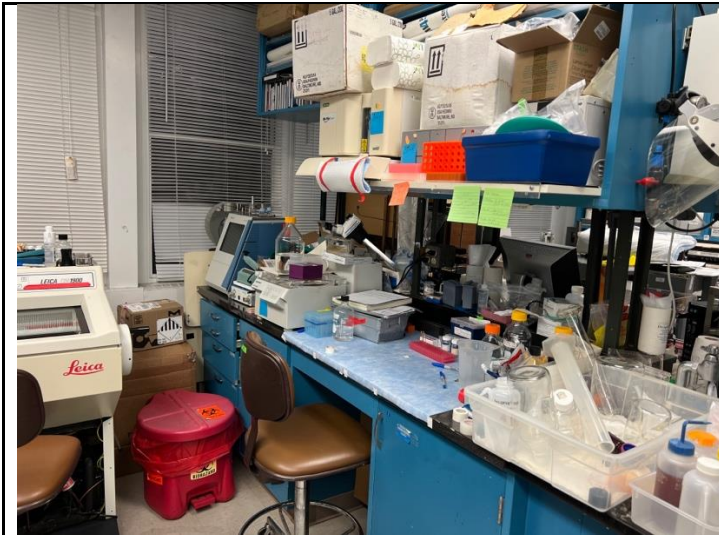
I highly recommend future IHS fellowship applicants be open to explore new avenues. In addition, I would highly recommend reaching out to your mentors for guidance and support. I would not be in this position, if not for all of my mentors' support!



Stanford University, near Oval Garden



Fall colors near my lab.



My work station.



School of medicine – Stanford University



Laboratory of Dr. Yeomans



Customized Lab coat.