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SCIENCE

A Pharmacological Model of TRPA1-Mediated Nociception in Zebrafish for Therapeutic Discovery

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Chronic pain exists in over 50 million American adults, and it can have significant effects on an individual's quality of life. Chronic pain is often inadequately treated with narcotic painkillers such as opioids. The long-term usage of opioids leads to side effects like overdose, tolerance, and dependence, which decreases the number of effective treatments available for chronic pain. A better treatment alternative would be non-narcotic analgesics that target the local transmission of pain (nociception).

Nociception arising from exogenous (environmental) and endogenous (internal) irritants is mediated by the activation of the Transient Receptor Potential, subfamily A1 (TRPA1) channel through calcium influx in sensory neurons. Although the TRPA1 channel is an analgesic target for chronic pain, there are no inhibitors for it that have been approved by the Food and Drug Administration. The TRPA1 channel is present in both humans and zebrafish. In zebrafish, this channel can be activated by chemical irritants (agonists), which would result in an increase in swimming behavior (hyperlocomotion). I hypothesized that this hyperlocomotion can be used to screen novel anti-nociceptive drugs.

A photo of the author in the Leung Lab zebrafish facility at Purdue University.

In my study, I utilized a TRPA1 agonist, ASP7663, to induce hyperlocomotion in 5 days-post-fertilization (dpf) zebrafish larvae, as mentioned in Ganzen, Ko, and colleagues' 2019 article in *Scientific Reports*, "A Critical Evaluation of TRPA1-Mediated Locomotor Behavior in Zebrafish as a Screening Tool for Novel Anti-Nociceptive Drug Discovery." Therefore, the TRPA1-mediated hyperlocomotion modeled chronic neuropathic pain in humans. Chemicals that could block this hyperlocomotion would potentially treat chronic pain. To determine the feasibility of my idea, I pre-treated 5-dpf zebrafish larvae with HC030031, a known TRPA1 antagonist, before challenging them with the ASP7663 agonist. This pre-treatment blocked the ASP7663-induced hyperlocomotion. My results suggest that ASP7663-induced hyperlocomotion in 5-dpf zebrafish larvae is an effective *in vivo* model for screening drugs that act like HC030031. Identifying such compounds can lead to non-narcotic treatment options for chronic pain.

Research advisors Yuk Fai Leung and Logan Ganzen write: "Emre joined this project because of a Collaborative Research Grant from the Purdue Institute for Integrative Neuroscience. His work has contributed to our understanding of how TRPA1 modulates neuropathic pain and has resulted in the development of a zebrafish behavioral assay that can be used to identify novel non-opiate painkillers."

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