

Department of Biological Sciences Seminar Blog

Seminar Date: 3/24/17

Speaker: Dr. Gregory Dussor, University of Texas at Dallas

Title: *“Mechanisms of meningeal pain signaling and the pathophysiology of migraine”*

Mysteries, Models, and Migraines

By: Thomas Kelly

Migraine headaches are the third most common disease on earth, behind tension headaches and dental cavities. They present themselves recurrent severe head pain, typically accompanied by nausea and sensitivity to light and sound. These symptoms can last for hours or even days, and the pain can be debilitating. Migraines affect men and women differently, being 2-3 times more common in women than in men. Because of this, migraines are classified as the 4th most disabling disease in women, while being only the 8th most disabling disease in men. Unfortunately, as common as migraines tend to be, very little is known as to what exactly causes them. This void of knowledge has resulted in a dearth of effective treatments. Available acute treatments for migraines include NSAIDS and Triptans, but these treatments are typically only effective if taken during the early signs of a migraine and have limited efficacy otherwise. Long-term preventative therapies are available for those suffering from chronic, consistently recurring migraines, but these are only effective in about 30% of patients. Worst of all, patients can suffer debilitating migraines brought about by over-using these medications, negating their usefulness in the long run.

Dr. Greg Dussor is an Associate Professor at the University of Texas at Dallas whose research focuses on uncovering the mechanisms behind migraines and discovering potential therapeutic targets within the brain. More specifically, he looks to simulate migraines in rodent models. One main model by which Dr. Dussor analyses migraines is by stimulating the meninges within the dura of rats and looking for peripheral sensitization, a common symptom of migraines. One such study determined that applying pH 6.0 fluid and mast cell mediators to the dura caused peripheral sensitization in the face and hind paws of rats, which is consistent with the sensitization present during migraines (Yan et al., 2013). Mast cells are immune cells located within the dura, the outermost layer of the meninges, and are known to modulate other inflammatory diseases. These applications were therefore chosen for the fact that migraine triggers like stress can cause the degranulation of mast cells within the dura, releasing inflammatory mediators and the acidic contents of the granules. A similar study which was presented during his talk showed sensitization of face and paws when IL-6, a pro-inflammatory interleukin which is elevated in migraine patients, was applied to the dura of rats (Yan et al., 2013). Dr. Dussor further explained of a study in which a possible cause for the increased prevalence of migraines in women was investigated. Prolactin, a hormone released by the pituitary and related to estrogen, has a higher expression in the nerve fibers of the female rat dura than in the male rat dura. Stress also increases blood levels of prolactin in females, but not in males. Prolactin was found to increase the release of CGRP (a neuropeptide linked with many other pain-related pathways) in the female dura, but not in the male dura. Finally, CGRP applied directly to rat dura results in similar hypersensitivity as seen in the previously mentioned studies, but only in female mice. This unique pathway for females that appears

to result in migraine-like symptoms in rats could explain the sexual differences in migraine occurrence.

Meeting with Dr. Dussor over lunch with several other interested grad students, I was struck by the novelty of his research. As a first-year graduate student nearing the end of my lab rotation period and on the verge of picking a lab, the intellectual creativity that drove me to seek my PhD shone through in the pioneering spirit of his chosen focus. As I enjoyed my meal, Dr. Dussor regaled us with the story of his early years as a graduate student choosing a lab within a neuroscience department. He chose to study pain mostly by chance: the lab was heavily recruiting, and he decided that “pain” was relatable. Everyone experiences pain, and therefore pain is a solid, relevant field. Later in his career, he was presented with the opportunity to study migraine. Although not personally experiencing migraines himself, the novelty of it dragged him in.

Migraines, he explained, are unlike any other pain state. Migraines have a pre-state in which the sufferer is aware that a migraine is about to begin. In many cases, this pre-state presents with an “aura”, which makes migraines more closely resemble seizures than other pain states. Unfortunately, this uniqueness also lent itself to the challenge of the puzzle: when migraines are unlike other pain states, how does one model a migraine? The experiments that he sought to accomplish couldn't be done in human subjects, but how do you tell if a rat is experiencing an aura? This challenge required him to build entirely new models for his research, and resulted in reviewers challenging the validity of the models more than the validity of the results. Regardless of the inherent challenge in such an undertaking, I found myself bewitched by the concept of tackling something so unknown that the models themselves had to be built from the ground-up. The intellectual creativity required for

such an undertaking is something that all scientists should envy, and will strongly influence my choice in lab once my rotations end.

Works Cited

Yan, J., Wei, X.m Bischoff, C. Edelmayer, R.M., Dussor, G. 2013. pH-evoked dural afferent signaling is mediated by ASIC3 and is sensitized by mast cell mediators. *American Headache Society* 53(8): 1250-12.

Yan, J., Melemedjian, O.K., Price, T.J., Dussor, G. 2012. Sensitization of dural afferents underlies migraine-related behavior following meningeal application of interleukin-6 (IL-6). *Molecular Pain* 8:6.