PROJECT SUMMARY (See instructions):

Migraine is 2-3 times more prevalent in females than in males. Many studies implicate a role for female hormones in this sex difference but specific mechanisms mediating these effects are not known. Migraine therapeutics are only effective in about 50% of patients. It is now recognized that one of the prevailing reasons for suboptimal management of migraine is related to insufficient consideration of individualized *predictor-based* (e.g. age or sex) pain management. Thus, there is *an urgent need to customize migraine management based on sex-specific pain pharmacology*. Our long-term goal is to define sex-specific migraine mechanisms, and utilize this knowledge to provide more effective migraine management schemes.

Our prior studies show that migraine-like behavior in rats can be generated by stimulating the dura/meninges with agents such as mustard oil (MO), low pH, and the cytokine IL-6. Clinical data indicate that migraine attacks are preceded and accompanied by elevation in the major pituitary hormone prolactin (PRL) in serum. We have also shown that the PRL receptor (Prlr) is dramatically more responsive in female damage-sensing neurons than in males. Our preliminary data indicate that PRL application to female, but not male dura enhances TRPA1-mediated release of a key migraine-related vasodilator, calcitonin gene related peptide (CGRP). The objective of this proposal is to accumulate preliminary data on peripheral (from dura) mechanisms that may contribute to the sex-specific regulation of migraine by the PRL system (i.e. PRL and Prlr). Our central hypothesis is that *PRL contributes to migraine in a female-specific manner via modulation of nociceptive signaling from the dura/meninges*. The rationale for this study is that understanding mechanisms contributing to sex-dependent effects of PRL and Prlr in migraine-relevant mechanisms will 1) greatly expand knowledge of sex differences in pain mechanisms; and 2) provide translational potential by identifying sex-specific pain pharmacology for the development of novel therapeutic strategies specifically tailored for migraine management. Our hypothesis is tested by interconnected yet independent aims. **Aim 1** evaluates PRL and Prlr expression and function in the meninges and in peripheral sensory neurons/ terminals innervating the dura of female and male rats. **Aim 2** defines the contribution of Prlr to migraine-related behavior induced by stimulation of the dura in females and males. The proposed study is innovative since if defines the sex-specific role of the PRL system in regulating nociceptive signaling from the dura/meninges, thus providing a potential explanation for the sex difference in migraine prevalence. The proposed research is also significant as it advances our knowledge of sex differences in peripheral migraine mechanisms, and has substantial translational potential based on novel sex-specific migraine pain pharmacology.

RELEVANCE (See instructions):

The rationale for the study is related to the intent of U.T. BRAIN:

1. This application will form and develop successful new research partnerships between the laboratories of Dr. Dussor (PI) and Dr. Akopian (co-PI).
2. This project opens a novel research line for both laboratories. A role of pituitary hormones in migraine has been proposed on the basis of *correlative* clinical studies, but mechanistic studies on how pituitary hormones contribute to the sex-dependency of migraine are grossly lacking.
3. To our knowledge, there are no NIH funded studies on neuro-endocrine mechanisms involving pituitary hormones and the sex-dependency of migraine. The NIH also has an open Program Announcement for migraine (PA-14-068) until May 2017. This application is focused on collecting preliminary data and early to mid-stage proof of concept data, which will increase competitiveness of this research line for future federal funding opportunities.
4. This proposal will employ a multidisciplinary approach, which is based on expertise of the PI and co-PI. This project will create a convergent BRAIN research team utilizing multi-institutional resources of the UT System, and allow us to build competitive research programs based on pituitary hormones and migraine.

Collaboration contributions and responsibilities:

PI will contribute to this collaboration by providing *expertise in cellular mechanisms of dural afferent activation and a preclinical behavioral model of migraine*. PI's lab responsibility will be related to *Aim 2*: (a) PRL-induced migraine-like pain from females/males; (b) Prlr in migraine-like pain in females/males.

Co-PI will contribute to this collaboration by providing *expertise in sex-dependent mechanisms of pain/nociception; and in pharmacology and physiology of the PRL system in the nervous system*. Co-PI's lab responsibility will be related to *Aim 1*. Specifically, they will (a) investigate functional expression of PRL and Prlr in meninges of females/males; and (b) examine Prlr-mediated responsiveness of sensory neurons innervating dura of female/males.