

Basis of Gender Differences in Migraine and Temporomandibular Pain

Robert M. Klein¹ K. Michael A. Welch² Nancy E.J. Berman¹

¹ Department of Anatomy & Cell Biology, University of Kansas Medical Center, Kansas City, Kansas, USA

²Department of Neurology, Rosalind Franklin University of Medicine and Science, The Chicago Medical School, North Chicago, IL, USA

Many more women than men suffer from migraine and temporomandibular pain. Painful episodes are linked to the menstrual cycle. The consistent link between perception of pain (nociception) and female cyclicity strongly suggests that female hormones are involved in causing head and face pain. Our laboratory uses transdisciplinary (e.g. cellular, molecular and behavioral) approaches to study gender differences in pain. The trigeminal ganglion is the primary site of cell bodies for orofacial sensory innervation. Our in vivo studies demonstrate:

- Estrogen receptor (ER) alpha on trigeminal neurons
- ER alpha as well as pain-related neuropeptides, galanin and neuropeptide Y (NPY), are modulated by the estrous cycle.
- Serotonin, a nociceptive neuromodulator, is localized in trigeminal neurons in all subtypes including neurons containing the pain modulator, calcitonin gene-related peptide (CGRP).
- Tryptophan hydroxylase, the rate-limiting enzyme required for serotonin synthesis, is regulated during the cycle.

In vitro studies using microarrays show that estrogen treatment of female trigeminal neurons regulates genes with potential relevance to menstrual migraine, including ERK-1. Protein activity assays demonstrate that exposure of cultured neurons to estrogen leads to activation of ERK, a cytoplasmic/nuclear signaling molecule. ERK activation occurs during nociception, inflammatory, and neuropathic pain in males providing a cross-gender pain marker. Our findings suggest that estrogen receptors in trigeminal neurons modulate nociceptive responses through serotonin and neuropeptides. Variations in estrogen receptor signaling and neuropeptide plasticity in trigeminal neurons across the female cycle may be major contributors to increases in painful episodes at specific phases of the menstrual cycle.