TEXAS TECH UNIVERSITY HEALTH SCIENCES CENTER™

Graduate School *of* Biomedical Sciences

Dissertation Defense

Role of amygdala neurons in the modulation of pain with particular focus on CRF neurons

Presented by:

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ABSTRACT: Pain is a clinically relevant health care issue that affects millions of people worldwide. Only limited therapeutic options are available, and they are frequently associated with severe side effects, resulting in a desperate need for new and effective analgesic strategies.

The mutual interactions of multiple components such as sensory, cognitive and emotional-affective, form the highly complex and unpleasant experience of pain. The amygdala, a limbic brain region, plays a key role in emotional behaviors and in (negative) averse-affective aspects of pain and pain modulation. Abnormally increased amygdala output activity correlates with pain states. Therefore, reducing uncontrolled amygdala activity is a desirable strategy to mitigate pain.

The corticotropin releasing factor (CRF) system in the amygdala has been linked to pain behaviors and pain-related amygdala plasticity, but little is known about the role of amygdala CRF neurons in pain. A major type of amygdala output neurons, CRF neurons in the central nucleus of the amygdala (CeA) project to various other brain regions to regulate behaviors. One way to modulate neuronal activity selectively is optogenetics, which is based on the expression of excitatory or inhibitory light sensitive molecules in specific cell types and their activation by light of appropriate wavelengths. Optogenetic modulation of amygdala neurons could mitigate pain. Pharmacological modulation of neurotransmitter function is also a promising strategy to mitigate pain. Glutamate, a ubiquitous neurotransmitter in the central nervous system (CNS), acts not only on ligand gated ion channels but also on G protein-coupled metabotropic glutamate receptors (mGluRs) to modulate neuronal excitability and synaptic transmission. Group II mGluRs, which consists of mGluR2 and mGluR3 subtypes, couple to Gi/o to decrease neurotransmitter release, are expressed throughout the nervous system, and they have emerged as effective therapeutic targets in several diseases, including pain. Amygdala group II mGluRs have been linked to pain modulation, but the roles of individual subtypes and their contributions to systemically acting group II mGluR activators are not yet known.

The results of this research project showed that optogenetic activation of amygdala CRF neurons generated sensory and emotional-affective pain-like behaviors and spinal nociceptive processing under normal conditions in the absence of tissue injury, whereas optogenetic inhibition of CRF neurons in an arthritis pain model mitigated affective, but not sensory, pain behaviors and inhibited spinal nociceptive processing. While activation of either mGluR2 or mGluR3 subtype inhibited emotional responses in an arthritis pain model, mGluR2 also inhibited sensory pain behaviors and mGluR3 also anxiety-like behaviors. This work identified amygdala CRF neurons as an important target for optogenetic and pharmacological interventions to mitigate pain.

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