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Sensitization and ongoing activation in the trigeminal nucleus caudalis

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In the current issue, the article by Boyer et al. [16] titled “General trigemino-spinal central sensitization and impaired descending pain inhibitory controls contribute to migraine progression,” is a study of the electrophysiological properties of neurons in the trigeminal nucleus caudalis (TNC) of rats that received repeated inflammatory soup (IS) infusions on the dura mater. As a model of migraine, the benefit of repeated IS infusions on the dura over single infusions is that repeated nociceptor activation models the multiple attacks of trigeminal pain that migraineurs experience [13]. It is these repeated attacks that induce changes in the neuronal circuits for processing trigeminal pain in the medullary dorsal horn, which is not induced in animal models of migraine that rely upon a single nociceptive event. These changes lead to long-lasting hypersensitivity in trigeminal sensory processing and sensitization. They may also influence the way in which migraineurs react to migraine treatments. Migraine models that use multiple bouts of trigeminal stimulation are essential for understanding how migraine treatments work, and for increasing our understanding of migraine pathophysiology [1].

The transition from episodic to chronic migraine is an important clinical problem because it affects nearly 3% of the total population [3,14]. Each year, approximately 2.5% of patients with episodic migraine transition to chronic migraine [8]. Chronic migraine is defined by more than 15 headache days per month according to the International Headache Society criteria for the diagnosis of headache [6]. In addition to these frequent headaches, many of these chronic migraine patients have a constant baseline headache that is not responsive to acute treatment. The findings in this electrophysiology study suggest that the baseline headache experienced by chronic migraineurs may be due to continuous activation of the secondary sensory neurons in the brainstem and cervical nuclei that process pain from the dura and face. These results also suggest that these patients may be more sensitive to triggers of migraine due to a suppression of the endogenous circuits for descending inhibition of trigeminal pain at the level of the dorsal horn in the brainstem. Continuous activation of neurons in the medullary dorsal horn, hypersensitivity to trigeminal afferent input, and decreased descending inhibition are important potential targets for treating chronic migraine.

Conflict of interest statement

There is no conflict of interest in regard to this work.

Given the long history of the association between pain research and the field of learning and memory, it is surprising that there are not more pain models that rely on repeated nociceptive events to mimic clinical pain conditions. Ronald Melzack's research advisor at McGill University in Montreal (1951–1954) was Donald O. Hebb [10]. Because of Hebb's interest in pain, he led Melzack into a line of study that resulted in the well-known gate theory of pain [11]. Hebb developed a theory of adaptation of neurons in the brain during the learning process that has served as a fundamental concept in our understanding of the brain, from learning and memory to pain [7]. The core of this theory states that repeatedly stimulating a neuron will strengthen the synapse between the stimulated neuron and the neurons that receive excitatory stimulation from that neuron. Multiple inflammatory soup infusions on the dura repeatedly activate pain afferents that innervate the dura and project to the trigeminal nucleus caudalis. In the context of Hebbian plasticity, this repeated activation will strengthen the synapses between the afferents and the secondary sensory neurons, producing profound changes in trigeminal sensory processing, even in the absence of continued infusions of the inflammatory soup onto the dura. Using this model, previous studies have shown changes in von Frey pressure thresholds, central neurotransmitter concentrations, locomotor activity levels, and gene expression after repeated inflammatory soup infusions [9,13,15]. The article by Boyer et al. adds to the previously established changes by demonstrating central sensitization and changes in descending inhibition via electrophysiological recordings and c-FOS expression after repeated IS infusions on the dura.

There are 3 main findings in this article. First, repeated inflammatory soup infusions into the whisker pad do not induce long-term changes in sensory processing of pain in the trigeminal region. Only infusions of the inflammatory soup onto the dura lead to long-lasting referred allodynia on the face of the rat. There is no long-term allodynic state induced by subcutaneous infusion of the inflammatory soup. Second, there is c-Fos expression in the TNC after inflammatory soup that outlasts the acute effects of the last infusion. FOS is an immediate early gene that normally responds within 2 hours of neuronal activation. This long-term c-Fos expression after repeated IS infusions suggests continuous afferent and/or secondary sensory neuron activation that far outlasts the initial nociceptive stimulus in the periphery. The third intriguing aspect of this article is the observation of a decrease in diffuse noxious inhibitory control of trigeminal pain after the repeated stimulation of the dural afferents.

The authors also found extracephalic allodynia in the hindpaws of the rats. The clinical relevance of this lower-extremity allodynia, however, is not clear, as migraineurs do not experience allodynia in their lower extremities. Although 65% of migraineurs experience extracephalic allodynia in the upper extremities, it is often expressed as thermal, not mechanical, allodynia [5]. In the patients who do experience mechanical allodynia, it is manifested as discomfort when wearing jewelry on their wrists or tight-fitting clothing on the upper body. A study from Ashkenazi et al. reported that extracephalic allodynia was not found below the C8 dermatome [2]. As such, it would have been interesting if the authors had tested for allodynia in the forepaws of the rats.

Another significant result in this article is that the authors found ongoing sensitization of neurons in the dorsal horn of the brainstem and even the lumbar region. Recent work on sensitization of neurons in the thalamus suggested that sensitization of neurons in higher brain centers was needed to have spreading allodynia that crosses the dermatomes [4,12]. Boyer et al.'s study clearly shows that repeated inflammatory soup stimulation of the dura causes allodynia outside of the trigeminal region without the need for thalamic sensitization.

This article demonstrates maladaptation of the trigeminal nociceptive system induced by repeated nociceptor activation. Importantly, it is a study of trigeminal pathophysiology after repeated painful stimuli that led to these clinically relevant observations. These studies provide an important bridge for the gap between animal models of trigeminal pain and the clinical manifestation of migraine so that the basic science studies can be used to better understand the pathophysiology of migraine, and for the development of novel treatments.

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