

It's Never Too Late: The Role of Mast Cells in the Development of Post-Traumatic Headache

Rodent study reveals new insights into the mechanisms of headache after concussion by examining the early and late stage contributions of these innate immune cells

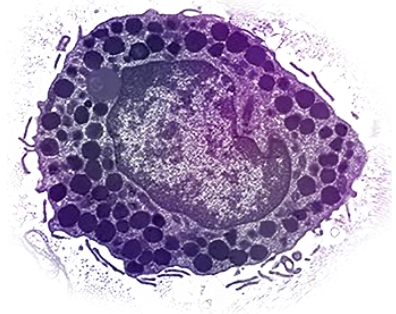


Post-traumatic headache (PTH) is one of the most common and debilitating symptoms following a mild traumatic brain injury such as a concussion. Although the incidence of PTH has been rising in recent years, particularly in military veterans and professional athletes, the causes of PTH remain poorly understood.

A new study published in May of 2019 issue of *PAIN* by researchers Dara Bree and Dan Levy from the Department of Anesthesia at Beth Israel Deaconess Medical Center (BIDMC)

has shed light on the role of a particular type of immune cell known as mast cells in PTH following a mild closed head injury. Bree and Levy demonstrated that mast cells, although not required for the acute generation of PTH, are critical for the development of persistent sensitivity to headache triggers that develop following a concussion. This persistent sensitivity to triggers is thought to be a key factor in the development of persistent PTH.

Mast cells are tightly packed immune cells that contain numerous pro-inflammatory agents, such as histamine, serotonin and prostaglandins. Upon their activation, mast cells release granules containing these inflammatory agents, through a process known as degranulation. Mast cells are found throughout the body, and heavily populate the intracranial dura mater, which is considered a key site for the generation of headaches of intracranial origin. Previous studies from the Levy lab demonstrated that degranulation of dural mast cells can lead to persistent activation of pain neurons that innervate the dura and the headache pain pathway. They also demonstrated that increased degranulation of these cells in the dura mater occurs following a concussive head injury. These findings prompted Bree and Levy to further investigate the role of mast cells in PTH.



The researchers had previously developed a rat model of concussion-evoked PTH, and identified for the first time a role for the neuropeptide calcitonin gene-related peptide (CGRP) in mediating PTH-relevant pain behaviors. While some of the headache-promoting effects of CGRP are thought to involve dural mast cells, the role CGRP plays in mast cell degranulation following a concussive head injury, and the ensuing PTH is unknown and so, the researchers initially set about investigating this question.

Bree and Levy first examined whether blocking CGRP signaling in the dura mater following head injury had any effect on mast cell degranulation. They did so by prophylactically treating rats with a

monoclonal antibody targeting CGRP, a novel treatment approach for migraine, prior to undergoing head injury. They found, however, that levels of mast cell degranulation in animals with head injury that received anti-CGRP antibody treatment were not different from control animals, indicating the blocking CGRP signaling has no effect of mast cell degranulation following head injury.

To further examine the role of mast cells in PTH, the researchers then systemically depleted the inflammatory mediators-containing granules from these cells in rats, so that no intact dural mast cells were present at the time of head injury. Surprisingly the animals with depleted granules developed PTH-like behaviors, including increased sensitivity to touch of the head and facial region (cephalic allodynia) following the injury. This behavior was similar to that observed in control non-mast cell depleted animals, suggesting that mast cells are not required for the initial emergence of PTH post-concussion.

One of the unusual aspects of headaches is that they can be triggered by a variety of factors including stress, dehydration and exposure to certain chemicals such as glyceryl trinitrate (GTN). Persistent sensitivity to triggers following concussion may result in the development of chronic PTH as Bree and Levy demonstrated in their previous work. The researchers wanted to understand what role mast cells may play in the lingering sensitivity to GTN following head injury.

They again systemically depleted mast cell granules in rats, subjected them a mild closed head injury and waited 30 days for the initial PTH symptoms to subside. On day 30 post-injury a low dose of GTN was administered, which in control, non-mast cell depleted animals resulted in the reemergence of pronounced cephalic mechanical pain hypersensitivity, indicating a persistent sensitivity to GTN. Remarkably, in mast cell-depleted animals no cephalic allodynia was observed following GTN treatment, suggesting that an intact population of these cells, *at the time of head injury* is required for the development of long lasting sensitivity to certain headache triggers, a process known as latent pain sensitization.

Intact mast cell content during mild head injury is required for development of latent pain sensitization: implications for mechanisms of post-traumatic headache.

Bree D, Levy D. *Pain*. 2019 May; 160 (5) 1050-1058.