

**Interleukins IL-1B and IL-S Cause Sensitization of Trigeminal Ganglion Neurons
Leading to Changes in the Ganglion and Trigeminal Nucleus Caudalis:
Implications for Understanding their Role in Migraine Pathology**

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Objective: The purpose of this study was to determine whether IL-113 and IL-6 would sensitize trigeminal ganglion neurons to capsaicin by evaluating changes in neurons and glial cells in both trigeminal ganglia and trigeminal nucleus caudalis (TNC).

Background : IL-113 or IL-6 are members of the interleukin family, which are a group of cytokines produced by many diverse cell types (neurons, glial cells, mast cells) that mediate sensitization of sensory neurons and regulate inflammatory and nociceptive responses. The levels of the pro-inflammatory cytokines IL-113 and IL-6, which can be released in response to cortical spreading depression and cortical hyperexcitability, have been reported to be elevated during migraine attacks. However, the role of IL-113 or IL-6 in migraine pathology is not well understood but is likely to involve sensitization of trigeminal nociceptors.

Methods: Male Sprague-Dawley rats were either left untreated (control), injected in the whisker pad with IL -113 or IL -6 alone, or with IL -113 or IL -6 two hrs prior to injection of a subthreshold concentration of capsaicin in the eyebrow region. Both ganglia and the TNC were collected 1 hr after the final injection and sections stained for expression of connexin (Cx) and known pro-inflammatory signaling proteins.

Results : While a subthreshold concentration of capsaicin alone did not cause increased protein expression, injection of IL-113 or IL-6 prior to capsaicin resulted in significant increases in the levels of Cx 26 and 43, PKA, and NF-kB in trigeminal ganglion and levels of c-Fos, GFAP, and GLAST in the TNC. Cx 26 staining was increased in both trigeminal ganglion neurons and satellite glial cells while Cx 43 expression was increased primarily in satellite glia. Similarly, levels of NF-kB, a transcription factor that regulates expression of many pro-inflammatory/nociceptive genes, and the pro-inflammatory signal transduction protein PKA were greatly increased in response to cotreatment. Within the TNC, cotreatment with IL-6 and capsaicin resulted in elevated levels of c-Fos, a marker of neuronal activation, GFAP, a marker of glial activation, and GLAST, a glial protein that functions to remove excess glutamate from the extracellular space. Interestingly, treatment with IL-113 or IL-6 alone resulted in a large increase in GLAST expression in the TNC.

Conclusions: Results from our study provide evidence that IL-113 and IL-6 cause sensitization of trigeminal nociceptors, and therefore, may play a role in the pathogenesis of migraine by lowering the activation threshold to other inflammatory stimuli. Based on our findings, we propose that elevated levels of IL-113 and IL-6 function to facilitate increased expression of signaling proteins in neurons and glia within the ganglia and TNC that contribute to peripheral and central sensitization, respectively, and thus, play important roles in migraine pathology.

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