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IL-1 β Signaling Initiates Inflammatory Hypernociception

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Acute inflammatory pain associated with tissue injury triggers a wide variety of cellular changes in neurons of the associated sensory ganglia. These responses are frequently accompanied by hyperalgesia (heightened painful response) and allodynia (painful response to non-painful stimuli). Multiple laboratories have proposed that these abnormal sensations following inflammation are due to enhanced excitability or sensitization of nociceptive primary afferent neurons or nociceptors (commonly known as peripheral sensitization). In turn, these pronounced physiologic effects are likely to contribute to spontaneously active or ectopic afferent discharge and activity dependent changes in the response pattern of second order neurons in the spinal cord dorsal horn or trigeminal brainstem nuclei. This causes the once normal inputs to begin to produce abnormal responses or sensations (spinal sensitization). Although it is clear that molecular and possibly anatomical changes in the spinal cord dorsal horn or the trigeminal subnucleus caudalis are responsible for some attributes of this abnormal nociceptive sensation, it remains a mystery as to what molecules and which anatomical site(s) are essential for maintaining the neuronal signals of ongoing tissue inflammation. Several inflammatory mediators (bradykinin, substance P, calcitonin gene-related peptide), cytokines (IL-1 β , TNF α , IL-6), chemokines (MCP-1), growth factors (NGF, NT-3, GDNF), prostaglandin E₂ (PGE₂) and/or complement proteins are thought to play a central role in the inflammatory hypernociception at the site of the inflamed tissue. However, the actions of these inflammatory mediators are not limited to the peripheral site of inflammation and may effectively alter signaling between neurons and glial cells. It is relatively well-accepted that spinal glial activation and the subsequent production of interleukin-1 β (IL-1) play a role in the creation and maintenance of pathological pain states (Watkins et al., 2007). However, as described in this issue of *Brain, Behavior, and Immunity* by the research team of Mamoru Takeda and colleagues (this issue), this pathological effect may not be limited to cells of the CNS. Indeed, the combination of satellite glial cells (SGCs) and IL-1 β may also serve a distinct role in the heightened pain sensitivity. Anatomically, SGCs form a distinct sheath around nearly all individual sensory neurons in DRGs, contribute to the transport and metabolism of molecules such as glutamate, glucose and ascorbate (Hanani, 2005) and maintain ionic homeostasis including the extracellular potassium (K⁺) concentration (Orkand et al., 1966; Newman et al., 1984; Vit et al., 2008). Following inflammation or injury of peripheral tissue, SGC cells begin to exhibit increased expression of glial fibrillary acidic protein (GFAP) and IL-1 β , responses similar to CNS glial cells (Takeda et al., 2007).

Takeda and colleagues (Takeda et al., 2007) also demonstrated that administration of IL-1 β to activated SGCs *in vitro* potentiates neuronal excitability in the trigeminal ganglion. In the experiments now published in this issue of *Brain, Behavior, and Immunity*, the authors significantly extend their *in vitro* observations to *in vivo* conditions by testing the hypothesis that nociceptive trigeminal neurons are selectively sensitized by an IL-1 β paracrine mechanism

and are directly involved in development of tactile hypernociception. Following induction of cutaneous inflammation, extracellular single unit recordings from trigeminal neuronal activity were collected using multibarrel electrodes. Activation of IL-1 β receptors was tested using iontophoretically applied antagonists. The results indicate that inflammation increases the spontaneous activity of small diameter trigeminal neurons through the involvement of IL-1 β receptors. Taken together, these unique *in vivo* results suggest that an interaction between nociceptors and SGCs is essential for sensing ongoing states of peripheral inflammation via IL-1 β . These findings should now be used to better define potential targets for the development of novel analgesics.

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