

**A novel mechanism of TNF- $\alpha$  in inflammatory hyperalgesia: Nociceptor priming via p38 modulation of TTX-R Na<sup>+</sup> channel**

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Inflammatory pain is characterized by hyperalgesia due to the sensitization of primary sensory nociceptive neurons. In experimental animal, following tissue injury or immunologic recognition of non-self stimulus, direct-sensitizing mediators such as eicosanoids and sympathetic amines are released. These mediators acting on neuronal membrane receptors trigger metabotropic events starting with the activation of second messenger pathways and ending with the lowering of the nociceptor threshold and facilitating neuronal membrane excitability, i.e. nociceptor sensitization. In fact, application of PGE<sub>2</sub> causes an increase in excitability of cultured primary nociceptive neurons as well as hyperalgesia *in vivo*. This phenomenon is associated with the facilitated activation of the tetrodotoxin-resistant (TTX-R) Nav1.8 currents. The TTX-R Nav1.8 channels are mainly expressed in nociceptive afferents neurons and accounts for almost all TTX-R current during the action potentials in those neurons (1).

Beside the direct-sensitizing mediators such as PGE<sub>2</sub>, cytokines have also been demonstrated to be important in the genesis of inflammatory hyperalgesia. Since the first experimental demonstration of the participation of cytokines in such phenomenon many efforts have been made to elucidate their role in inflammatory hyperalgesia. In the inflammatory scene, it seems that TNF- $\alpha$  plays an important role in the induction of an inflammatory hyperalgesic cytokine cascade, which is responsible for the release of direct-sensitizing mediators. It is likely that cytokines constitutes a link between the injuries and the release of hyperalgesic direct-acting mediators (2).

Despite the evidences that TNF- $\alpha$  does not act direct on nociceptors to induce hyperalgesia, it has been described that sensory neurons express TNF- $\alpha$  receptors (TNFR1 and TNFR2). This data suggests that TNF- $\alpha$  might also directly sensitize the nociceptors during inflammation. In fact, it was demonstrated that the topical application of TNF- $\alpha$  evokes a rapid action potential in the nociceptive neurons *in vivo*, and increases the sensitivity to mechanical and chemical stimuli.

In an attempt to elucidate the mechanism by which TNF provoke such effect, Jin & Gereau (3), in a recent study published in *The Journal of Neuroscience*, investigate the influence of this cytokine on the TTX-R Na<sup>+</sup> activity. It was demonstrated that TNF- $\alpha$  enhances TTX-R Na<sup>+</sup> currents in primary afferent nociceptive neurons by activating MAPkinase (p38) intracellular pathway. It was suggested that TNF- $\alpha$  directly acting on TNFR1 sensitizes the nociceptive neurons.

However, other possibilities concerning this effect should be considered: 1) direct action of TNF on sensory neurons but with secondary induction of the production of another mediator, such as prostanoids. Actually, Nicol et al. (4), demonstrated that the enhanced sensitivity of nociceptive neurons induced by TNF- $\alpha$  is mediated by cyclooxygenase products since the inhibition of such enzyme blocked this effect, 2) action on cells other than sensory neurons, such as satellite cells, that in turn produce another direct sensitizing mediator.

In an attempt to clarify these questions, the importance of direct effect of TNF- $\alpha$  on sensory neurons to the development of inflammatory hyperalgesia was tested. Parada et al. (5), showed that the effective attenuation of TNFR1 expression in sensory neurons by intrathecal treatment with antisense oligodeoxynucleotides to TNFR1 did not alter either TNF- $\alpha$ - or Cg-induced acute mechanical hyperalgesia. These results suggest that the TNF- $\alpha$  direct effects on TNFR1 on sensory neurons via are not relevant for acute inflammatory hyperalgesia. However, the treatment with antisense oligodeoxynucleotides to TNFR1 blocks the increased susceptibility of the sensory neurons to PGE<sub>2</sub> induced by Cg or TNF- $\alpha$ , which was referred as chronic priming (6)

Therefore, it seems that TNF- $\alpha$  acting on TNFR1 on sensory neurons membrane is not involved in the direct induction of acute inflammatory hyperalgesia, but might be responsible for priming of the nociceptors and for inducing PGE<sub>2</sub> production in the inflammatory site.

Moreover, it is likely that TNF- $\alpha$  directly acting on nociceptors modulates TTX-R Na<sup>+</sup> currents via p38 activation, and thus, amplifying the latter effect of PGE<sub>2</sub> on this channel activity. These different mechanisms of TNF- $\alpha$  suggest its role in acute and priming to chronic inflammatory hyperalgesia.

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