Pain and central cytokines in two animal models of chronic neuropathic pain

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Introduction

Recent results suggest that *de novo* synthesis of cytokines, including Interleukin-1β (IL-1β), by CNS glial cells may be secondary to inflammatory states, it may also be related to increased neuronal excitability and synaptic potentiation.

In this project we monitor the effect of two neuropathic pain rat models: Chronic Constriction nerve Injury (CCI), and Spared Nerve Injury (SNI) on the evolution of the cytokine Interleukin-1β (IL-1β) gene expression in three brain regions: Right Thalamus, Left Thalamus, and Brain Stem, as well as mechanical allodynia thresholds.

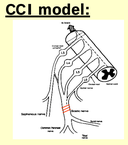
Methods

• **Animals & surgery**: Two sets of Wistar-Kyoto rats were followed: Set 1 was euthanized one week after the chronic pain induction, and Set 2 three weeks after. Both sets had four groups: Control, Sham, CCI, and SNI. Four rats per group.

• **Cytokines expression:** Brain tissue samples from anesthetized rats were dissected using RNA free protocol. RNA was extracted from the samples using standard protocol and reverse transcribed (using Superscript II RT kit, GIBCO/BRL), amplified at least 3 times (Pitossi et al. J. Neuroscience Res. 48:287,1997). Expression is quantified as cycles of amplification to reach gene expression plateau, relative to the house-keeping gene.

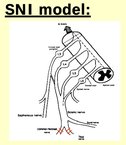
•**Mechanical allodynia**: Thresholds were assessed using Von Frey filaments at various points after the surgery.

CCI model:



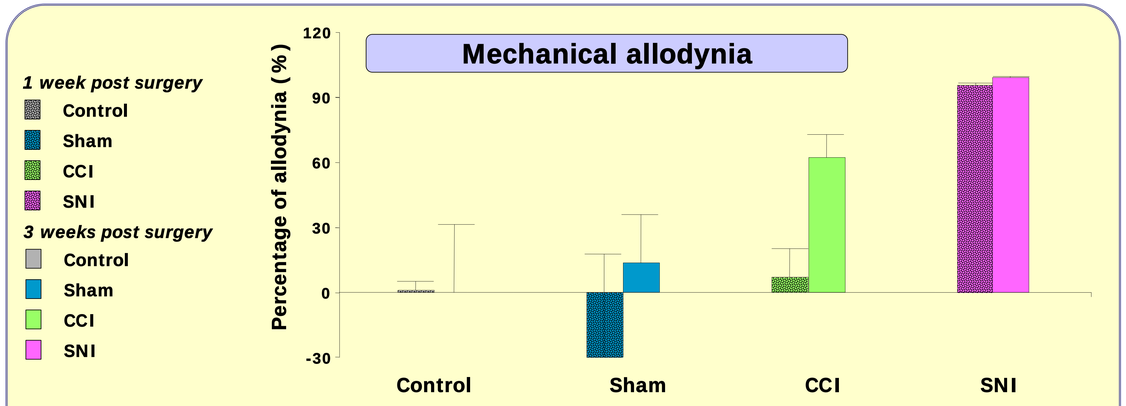
Bennett and Xie (Pain 33:87, 1998)

SNI model:



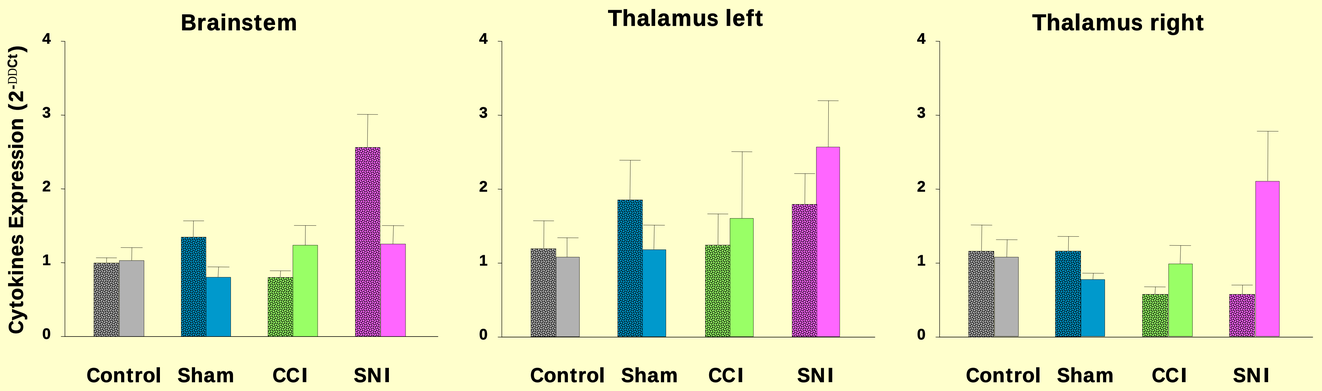
Decosterd and Woolf (Pain 33:149, 2000)

Results



• Allodynia, expressed as ratio of injured paw to uninjured paw thresholds, is increased for CCI only at 3 weeks, and at 1 & 3 weeks for SNI.

Cytokines Expression



• Expression of IL-1β is increased only in SNI rats, at 1 week in the brainstem; and at 3 weeks in the left and right thalami.

Conclusions

1. In CCI rats there is allodynia but no change in IL-1β expression. This implies that the expression is not directly related to the pain behavior.
2. In SNI rats allodynia is maintained but brainstem IL-1β expression is transient. Moreover, thalamic IL-1β expression occurs late (3 weeks) even though allodynia is fully expressed early (1 week). Again these results imply dissociation between IL-1β gene expression and pain behavior.
3. Although the amount of IL-1β RNA is small compared to inflammatory conditions, it should be noted that the expression of interest in this project is for a chronic condition which may have dramatic effects on neuronal signaling in the brain.

Perspectives

• These results imply the involvement of central cytokines in neuropathic pain states.

• Their specific role remains to be determined.

• We suspect a spino-cephalad temporal progression of cytokine signal, which may be critical in central re-organization associated with chronic neuropathic pain.

• We will analyze IL-1β gene expression in other brain structures in these neuropathic pain models.

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