

*Neuroscience/ Medicine*  
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*Mechanisms of chronic pain*

*Speaker:*

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### 1. Introduction

Previous basic pain researches revealed that neuronal sensitization and its associated plastic changes of the spinal dorsal horn caused by continuous noxious input from peripheral nervous systems have an extremely important role in development of chronic pain conditions. In clinical cases, however, we often experience that many of chronic pain does not always accompany with continuous noxious input in its background. Especially in musculoskeletal field, these types of chronic severe pains are common in its population. Despite disuse related chronic pain disorders caused by local immobilization therapy are rather common, mechanisms underlying in these chronic pain conditions were not investigated before. According to these previous observations and reports, we hypothesized that appropriate sensory inputs and motor activities (output) are essential for maintaining of normal sensory motor functioning and catastrophes of these neural activities may cause chronic pain disorders. Therefore the aim of this study is to develop animal models of disuse induced chronic pain conditions and investigate underlying neural mechanisms by electrophysiological methods as well as morphological methods.

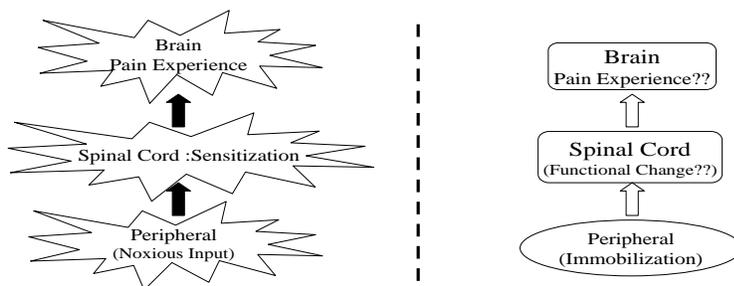


Fig 1

### 2. Development of disuse induced chronic pain model

To develop the rat models of forepaw disuse, a plastic cast was wrapped around the limb from the forearm to the right forepaw and the wrist joint of the rats kept immobilized at 90° of flexion position. After 4 weeks of immobilization, wrist contracture (limited range of motion) and disuse were observed in all treated animals. In the behavior study, there was an increased paw withdrawal frequency shown by responses to application of innocuous mechanical stimuli.

### 3. Electrophysiological testing

In an electrophysiological study, the responses of cervical dorsal horn neurons to mechanical stimuli were examined. In normal (control) animals, the neurons had the following distribution: 63% were low-threshold (LT); 15% were high-threshold (HT); and 22% were

wide-dynamic-range (WDR). In the disuse group, the distribution of the neurons changed to 56% LT, 9% HT, and 35% WDR.

### 3. Immunohistochemistry study

Immunohistochemistry studies were undergone at two time points (24 hours and 7 days after removal of the cast). At 24 hours after cast removal, neuro-peptides (calcitonin gene-related peptide (CGRP) and Substance P) immunofluorescence levels in the ipsilateral spinal dorsal horn were decreased as compared to contralateral side. Although few c-Fos-positive cells were present in both spinal dorsal horn, the ipsilateral layer showed a significant induction of Fos-immunoreactivity after repetitive passive motion stimuli (Fig 2). At 7 days after removal of the cast, passive motion induced significant high CGRP, substance P, and c-Fos expression in the ipsilateral layer, although no differences were observed without motion stimuli.

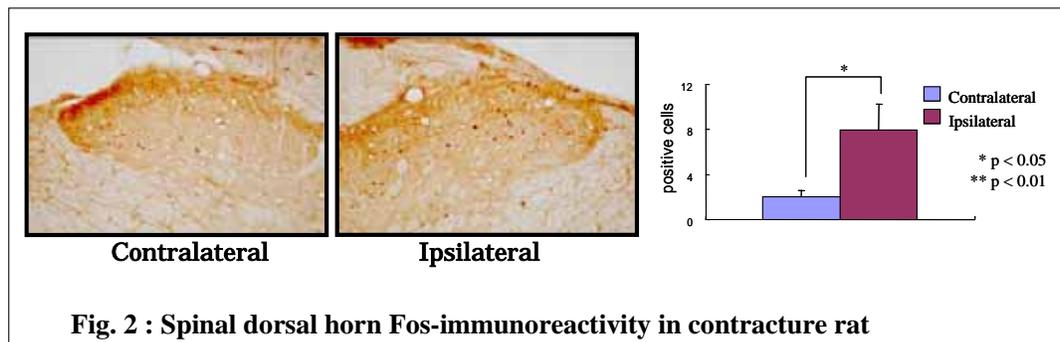


Fig. 2 : Spinal dorsal horn Fos-immunoreactivity in contracture rat

### 4. Discussion

Casting (immobilization) is commonly utilized in musculoskeletal therapy because of its ease, wide application and reasonable outcomes. However, immobilization therapy sometime produces joint contracture and its related pain. The pain in contractured joints is mainly considered to be the result of local changes in the contractured joint itself.

On the other hand, our model of wrist contracture presented electrophysiological and immunohistochemical changes in the spinal dorsal horn, supporting the hypothesis that the changes of peripheral input to the spinal cord may alter the characteristics of dorsal horn neuron during and after immobilization (contracture) .

These spinal neuronal alterations may cause cerebral neuro-functional changes secondarily. Indeed, our recent brain imaging researches revealed that appearance of cerebral plastic changes in patients with chronic pain.

### Conclusion

Our present electrophysiological and immunohistochemical research revealed that neuronal plastic change occurs after experimental animal disuse model. Further investigation of underlying mechanism of contracture and its related pain will contribute the development of future musculoskeletal pain prevention.

### References

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2. Ushida T, Willis WD. Changes in dorsal horn neuronal responses in an experimental wrist contracture model. *J Orthop Sci.* 2001;6(1):46-52.