News Release

Title

Hyper-activation of proprioceptor induces microglia-mediated long-lasting pain in a rat model of chronic fatigue syndrome

Key Points

- ○The rat model of myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) exhibits pain behavior and microglial activation in the lumber spinal cord without peripheral tissue damage and/or inflammation. The present study addressed the mechanism underlying the association between microglia-activated pain and the chronic stress using the rat model.
- ○Under the continuous stress of the model, chronic proprioceptor activation occurs and induces the sequential activation of neurons along the spinal reflex arc, and the neuronal activation further activates microglia along the arc. These activated microglia elicit the chronic pain.
- ○ Results indicate that proprioceptor-induced microglial activation may be a key player in the initiation and maintenance of abnormal pain seen in patients with ME/CFS or fibromyalgia (FM).

Summary

The research team led by Prof. Hiroshi Kiyama (Dept. of Functional Anatomy & Neuroscience) of Graduate School of Medicine, Nagoya University (Dean: Prof. Kenji Kadomatsu), and Dr. Masaya Yasui (current position at Department of Anatomy, Aichi Medical University) in collaboration with Prof. Kazuhide Inoue (Kyushu University) found that hyperactivation of proprioceptor induces microglia-activated long-lasting pain in a rat model of myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS).

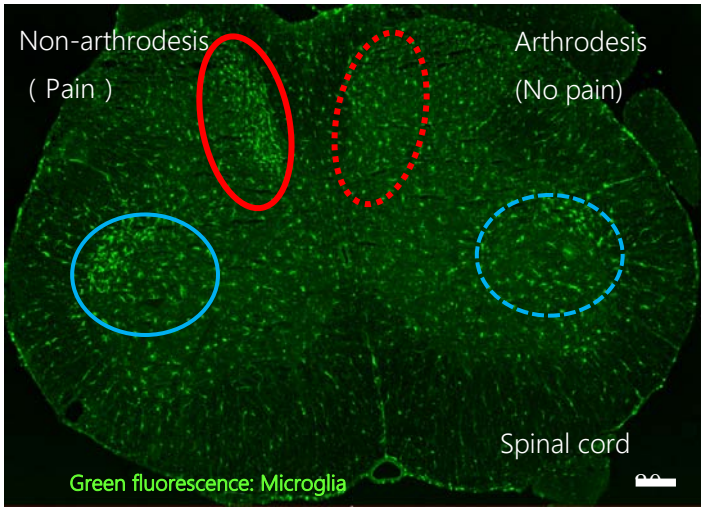
Patients diagnosed with ME/CFS or fibromyalgia (FM) experience chronic pain. However, the mechanisms underlying are still obscure. The present study addressed the mechanism underlying the association between the chronic pain and chronic stress using a rat model of EM/CFS which exhibits microglial activation in the lumber spinal cord and pain behavior without peripheral tissue damage and/or inflammation. The model rats, housed in a cage with a thin level of water (1.5 cm in depth), were used as a chronic stress model for EM/CFS. Under the continuous stress, chronic proprioceptor activation occurs and induces the sequential activation of neurons along the spinal reflex arc, and the neuronal activation further activates microglia along the arc. In this animal model, no evidence for peripheral inflammation and nerve and muscle injuries were observed. These activated microglia are assumed to elicit chronic pain, because the intrathecal application of a microglial inhibitor, minocycline suppressed the pain. The spinal microglial activation by the chronic proprioceptor activation without any inflammation and nerve and muscle injuries in periphery, may play a key role in the initiation and maintenance of abnormal pain in patients with ME/CFS and FM, although significant studies are necessary before extrapolating those findings to patients with ME/CFS and FM.

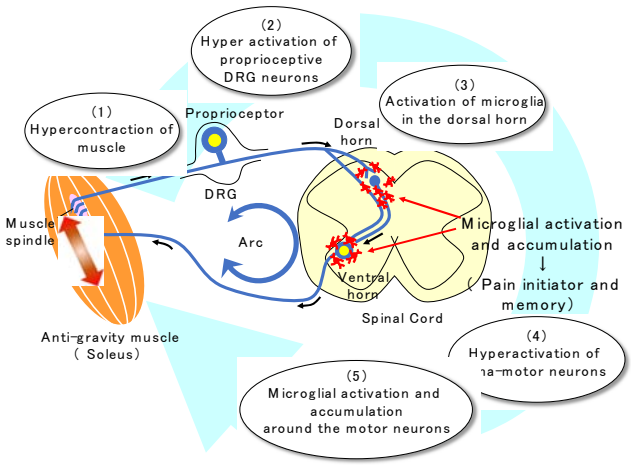
Research Background

Patients diagnosed with myalgic encephalomyelitis / chronic fatigue syndrome (ME/CFS) or fibromyalgia (FM) experience chronic pain. Concomitantly, the rat model of EM/CFS exhibits microglial activation in the lumber spinal cord and pain behavior without peripheral tissue damage and/or inflammation. The present study addressed how the chronic stress activates spinal microglia in the rat model.

Research Results

Chronic or continuous stress-loading (CS) model rats, housed in a cage with a thin level of water (1.5 cm in depth), were used. The neuronal and microglial activations were immunohistochemically demonstrated with antibodies against ATF3 and Iba1. The expression of ATF3, a marker of neuronal hyperactivity or injury, was first observed in the lumbar dorsal root ganglion (DRG) neurons 2 days after CS initiation. More than 50% of ATF3-positive neurons simultaneously expressed the proprioceptor markers. Retrograde labeling using fluorogold showed that ATF3-positive proprioceptive DRG neurons mainly projected to the soleus. Substantial microglial accumulation was observed in the medial part of the dorsal horn on the 5th CS day. Microglial accumulation was subsequently observed around a subset of motor neurons in the dorsal part of the ventral horn on the 6th CS day (Upper Figure). These results suggest that chronic proprioceptor activation induces the sequential activation of neurons along the spinal reflex arc, and the neuronal activation further activates microglia along the arc. Proprioceptor suppression by ankle joint immobilization significantly suppressed the accumulation of microglia in the spinal cord, as well as the pain behavior (Figure below).





Summary Figure

Research Summary and Future Perspective

The present study revealed that CS activates the neuronal pathway along the proprioceptor-mediated spinal reflex arc, and that over-activation of this arc activates microglia along the arc. Such proprioceptor-induced microglial activation may play a key role in the initiation and maintenance of abnormal pain in patients with ME/CF and FM, although significant studies are necessary before extrapolating those findings to patients with ME/CFS and FM.

Publication

Masaya Yasui 1,2, Yuki Menjyo 1, Kyohei Tokizane 1, Akiko Shiozawa 1, Makoto Tsuda 3, Kazuhide Inoue 3, Hiroshi Kiyama 1*

Department of Functional Anatomy and Neuroscience, Nagoya University Graduate School of Medicine, 65 Tsurumaicho, Showa-ku, Nagoya, Aichi 466-8550, Japan

2 Department of Anatomy, Aichi Medical University, 1-1 Yazakokarimata, Nagakute, Aichi 480-1195, Japan

3 Department of Molecular and System Pharmacology, Graduate School of Pharmaceutical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, Fukuoka 812-8582, Japan

Hyperactivation of proprioceptors induces microglia-mediated long-lasting pain in a rat model of chronic fatigue syndrome.

J Neuroinflammation. 2019 Mar 30;16(1):67.

doi: 10.1186/s12974-019-1456-x.

Japanese ver.

https://www.med.nagoya-u.ac.jp/medical_J/research/pdf/Jou_Neu_20190422.pdf