News Release

Title

Repeated cold stress, an animal model for fibromyalgia, elicits proprioceptor-induced chronic pain with microglial activation in mice

Key Points

• Researchers have investigated the causative of chronic pain seen in fibromyalgia using a mouse model of fibromyalgia, and found overactivity of proprioception in some muscles and activation and accumulation of microglia in the restricted areas of the spinal cord.
• Researchers developed a mouse that can fluorescently label overactive neurons in nervous systems and examined the fibromyalgia model, and found that neural circuits along the reflex arc were fluorescently labeled. Concomitantly microglia were activated along this reflex arc.
• Removal of microglia suppressed pain behavior in the model. In conclusion, a continuous activation of muscle tension locally activates microglia in the spinal cord via hyperactivation of proprioceptive sensory neurons. As long as the microglial activation continues, the activated microglia function as a memory of the pain in fibromyalgia.

Summary

A research group led by Professor Hiroshi Kiyama, Associate Professor Sumiko Kiryu-Seo, Researcher Wakatsuki in Nagoya University Graduate School of Medicine (Dean: Hiroshi Kimura) and Associate Professor Masaya Yasui in Tokoha University has identified one of the mechanisms underlying abnormal pain seen in human fibromyalgia using a mouse model of fibromyalgia called the repeated (or intermittent) cold stress model. In this experiment, the researchers used a transgenic mouse, which allows tracing of overactivated neurons by GFP. A continuous hyperexcitation of the proprioception activates the reflex arc in the spinal cord, and concomitantly the microglia along the reflex arc are activated in the spinal cord. Because a chemical ablation of microglia dramatically reduced the pain seen in animals, the activated microglia along the reflex arc would be the causative of the chronic pain. These suggest that the reduction of hyperactivated muscle tonus and suppression of microglial activation could be the therapeutic targets.

Research Background

Fibromyalgia is characterized by chronic pain, fatigue, and other somatic symptoms. The researchers have recently revealed the possibility that microglial activation in spinal cord induces chronic pain in a rat model of myalgic encephalomyelitis. However, it remained unclear about the mechanism how microglia were activated in spinal cord. The present study explores the mechanistic link between microglial activation in spinal cord and hyperactivation of proprioception in a mouse model of fibromyalgia.

Research Results

The research group used the repeated-cold stress (RCS) model known as a mouse model of fibromyalgia. When mice were kept for one week in an environment that repeated cold (7˚C) and room temperature during the daytime, they developed chronic pain and reduced activity due to fatigue over a prolonged period of time. Skin, muscle, and blood tests on these mice did not indicate damage or inflammation. These symptoms are similar to those seen in humans with fibromyalgia. The researchers recently developed *Atf3*:BAC transgenic mice, in which a fluorescent protein (GFP) labels mitochondria in hyperactivated neurons under the control of *Atf3* gene regulatory element. ATF3 is a marker of cellular hyperactivity and injury. By using *Atf3*:BAC Tg mouse in RCS model, entire hyperactive neurons were visualized by GFP, because mitochondria are distributed in cell body, axon and dendrite. Thus, the mouse can be used to reveal the neuronal circuit that is overactivated in the brain (Figure 1). The mice revealed the neuronal circuits along the reflex arch in RCS model; from the muscle spindle of the intramuscularis pedis muscle to intrinsic sensory neurons in the dorsal root ganglion, from the dorsal horn of the spinal cord to motor neurons in the anterior horn of the spinal cord, and to the neuromuscular junction in the intramuscularis pedis muscle. Microglia were also activated along this neural pathway in spinal cord. To inhibit the microglial activation, RCS-loaded mice were treated by a drug that inhibits the proliferation and activation of microglia. Researchers did not observe microglial accumulation along this reflex arch and pain behavior in the mice.

Research Summary and Future Perspective

Proprioceptor hyperactivation leads to local microglial activation along the reflex arc (Fig.2); this prolonged microglial activation may be responsible for chronic pain in the present model. Proprioceptor-induced microglial activation might be the common cause of chronic pain in both the fibromyalgia and myalgic encephalomyelitis models, although the experimental models are different.

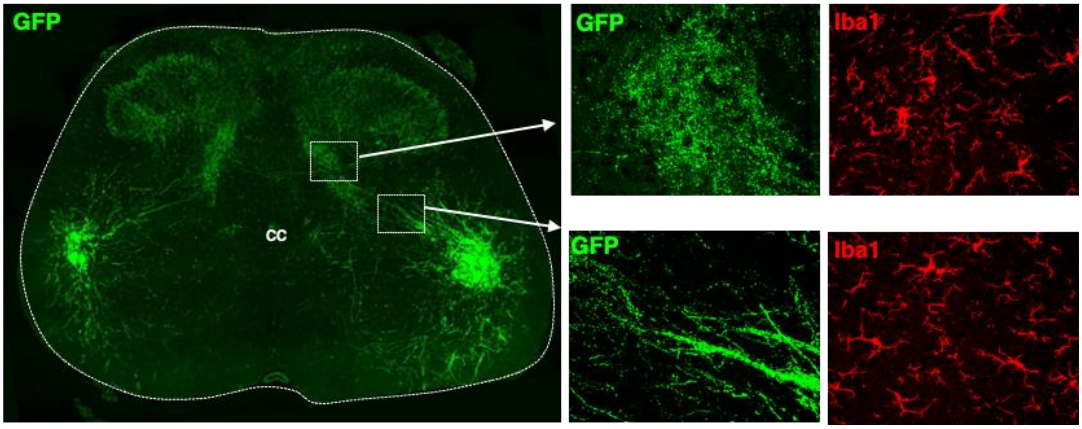

Fig.1 *Atf3*:BAC transgenic mic traced the hyperactivated neuronal circuits along the reflex arc in the spinal cord (GFP staining in green) after RCS loading. Concomitantly, microglial activation was observed along the reflex arc (Iba1: microglia marker, red) was observed. cc: central canal

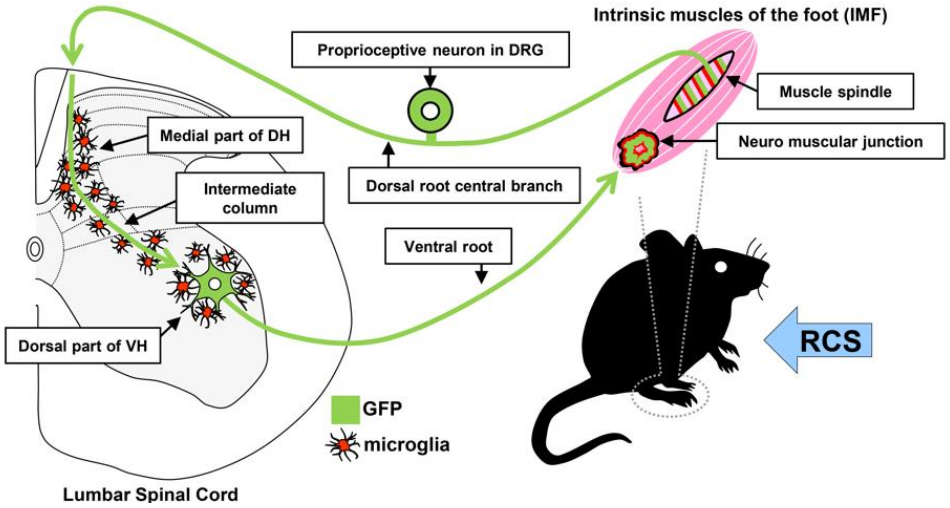

Fig.2 Schematic diagram of the pathway from the spinal cord to the peripheral nerves of the muscle in RCS

Publication

Koji Wakatsuki[1], Sumiko Kiryu-Seo[1*], Masaya Yasui[1,2], Hiroki Yokota[3], Haruku Kida[1], Hiroyuki Konishi[1], Hiroshi Kiyama[1*], Repeated cold stress, an animal model for fibromyalgia, elicits proprioceptor-induced chronic pain with microglial activation in mice, ***J Neuroinflammation***, 21:25 (2024). DOI: 10.1186/s12974-024-03018-6

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