

News Release

Title

A chronic fatigue syndrome model demonstrates mechanical allodynia and muscular hyperalgesia via spinal microglial activation

Key Points

- A chronic stress elicited allodynia and muscular hyperalgesia without peripheral inflammation and nerve injury.
- Microglial activation and accumulation is observed in the spinal dorsal horn of the model animal.
- Minocycline treatment suppressed the microglial activation in dorsal horn and the pain behaviors.

Summary

The research team of Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi MD PhD) led by Professor Hiroshi Kiyama (Department of Functional Anatomy & Neuroscience) revealed that using an animal model for chronic fatigue syndrome (CFS) the abnormal pain seen in patients suffering from CFS may be due to an increased activation of microglia in spinal dorsal horn after chronic stress loading.

Patients with chronic fatigue syndrome (CFS) display multiple symptoms, such as chronic widespread pain, fatigue, sleep disturbance, and cognitive dysfunction. Abnormal pain sensation may be the most serious of these symptoms; however, its pathophysiology remains unknown. To provide insights into the molecular basis underlying abnormal pain in CFS, the research group used a multiple continuous stress (CS) model in rats. Results showed that mechanical allodynia at plantar skin and mechanical hyperalgesia at the anterior tibialis (i.e. muscle pain) were induced by CS loading. Moreover, no signs of inflammation and injury incidents were observed in both the plantar skin and leg muscles. However, microglial accumulation and activation were observed in L4-L6 dorsal horn of CS rats. To evaluate an implication of microglia in pain, minocycline was intrathecally administrated. Minocycline significantly attenuated CS-induced mechanical hyperalgesia and allodynia. These results indicated that activated microglia were involved in the development of abnormal pain in CS animals, suggesting that the pain observed in CFS patients may be partly caused by a mechanism in which microglial activation is involved.

This study was done in collaboration with the group of Professor Kazuhide Inoue (Kyushu University), and the paper presenting above results was published online in an international scientific journal *Glia* on May 23, 2014. This study was supported by grants from a CREST program entitled "Chronic inflammation" led by Prof. Masayuki Miyasaka, JST, Japan and from the MEXT Japan.

Research Background

Patients with chronic fatigue syndrome (CFS) display multiple symptoms, such as chronic widespread pain, fatigue, sleep disturbance, and cognitive dysfunction. Abnormal pain sensation may be the most serious of these symptoms; however, its pathophysiology remains unknown. To provide insights into the molecular basis underlying abnormal pain in CFS, the research group used a multiple continuous stress (CS) model in rats, which were housed in a cage with a low level of water (1.5 cm in depth). Although they have previously revealed several characteristic alterations in the CS animal model, it remains unclear whether this model displays abnormal pain. Here they examined whether CS rats show abnormal (muscle) pain, such as mechanical allodynia and hyperalgesia. In addition, the group investigated the pathophysiology of the pain associated with this animal model, and microglia in spinal cord has merged as a pathogenesis of the abnormal pain.

Research Results

Results showed that mechanical allodynia at plantar skin and mechanical hyperalgesia at the anterior tibialis (i.e. muscle pain) were induced by CS loading. Moreover, no signs of inflammation and injury incidents were observed in both the plantar skin and leg muscles. However, microglial accumulation and activation were observed in L4-L6 dorsal horn of CS rats (Figure). To evaluate an implication of microglia in pain, minocycline was intrathecally administrated. Minocycline significantly attenuated CS-induced mechanical hyperalgesia and allodynia.

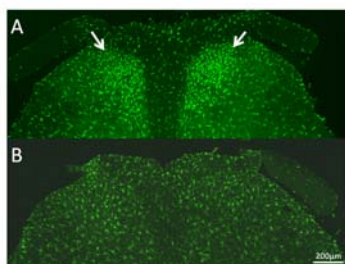


Figure: An accumulation of microglial cells (green fluorescence) is observed in the dorsal horn of spinal cord from a chronic stress loaded rat (A). B shows the microglial localization in the same area from the control animal. Arrows in A indicate the accumulation of microglia in the medial part of the dorsal horn.

Research Summary and Future Perspective

The present study demonstrated that continuous stress elicited mechanical allodynia and muscular hyperalgesia (myalgia) accompanied by microglial activation in the dorsal horn of the spinal cord. Strikingly, suppression of microglial activation by minocycline attenuated the allodynia and hyperalgesia, suggesting that microglial activation may be a cause of the pain, which occurs under chronic stress. Establishing animal models with the full list of symptoms of CFS is actually impossible. However, the model used in the present study demonstrated some symptoms, such as sleep and endocrine system disorders as well as abnormal pain (in this study). Interestingly, all these disorders have been shown to originate from CNS dysfunctions. Therefore the present study together with the previous studies may be providing evidences that the etiology for CFS is

originated from some disorders of CNS function under chronic stress.

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