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Research report

SOCS1 regulates neuropathic pain by inhibiting neuronal sensitization and glial activation in mouse spinal cord

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ABSTRACT

Neuropathic pain is still a basic science and clinical challenge now, the neuronal sensitization and glial activation in the spinal cord (SC) level are more far-reaching for contributing to pain hypersensitivity following chronic constriction injury (CCI). Accumulating evidence indicates that astrocytes and microglia are activated in the spinal cord dorsal horn (SCDH) after CCI. Suppressor of cytokine signaling 1 (SOCS1) plays an important role in regulating of neuronal inflammation. Here, we investigated the role of SOCS1 in SC played in neuropathic pain. We find SOCS1 was persistently downregulated in the spinal neurons after CCI in mice. On the contrary, overexpression of SOCS1 in the SC reversed CCI-induced pain behavioral, activation of neurons, astrocytes, microglia, and the expression of proinflammatory cytokines including tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and IL-6. Over all, these results demonstrate that downregulation of SOCS1 contributed to the development and maintenance of neuropathic pain via activating of neurons, astrocytes, microglia, and proinflammatory cytokines. SOCS1 may be developed into a potential target for treating neuropathic pain.

1. Introduction

Neuropathic pain is defined as 'pain initiated or caused by a primary lesion or dysfunction of the nervous system' in contrast to nociceptive pain, neuropathic pain is described as 'burning', 'electric', 'tingling', and 'shooting' in nature (Carlton et al., 2009; Zieglgänsberger et al., 2005). Unfortunately, in marked contrast to inflammatory pain, persistent pain is often difficult to effectively treat with conventional drugs, such as non-steroidal anti-inflammatory drugs and opioids (O'Connor and Dworkin 2009). Therefore, it is necessary to investigate the specific disease stage- and pain type-specific molecular mechanisms. Preclinical and clinical studies have shown that the spinal cord is important for pain perception and modulation underlying physiological and pathological pain status (Miljanich et al., 2013; Moss et al., 2007). Additionally, neuronal sensitization and glial activation in the spinal cord (SC) level are important for contributing to pain hypersensitivity following chronic constriction injury (CCI). Accumulating evidence indicates that astrocytes and microglia are activated in the spinal cord dorsal horn (SCDH) after nerve injury (Bridges and Thompson, 2001; Gao and Ji, 2010; Scholz and Woolf, 2007). These activated glial cells are sufficient to trigger the persistent pain hypersensitivity through forming an integrated network of glial-neuronal and/or glial-glial interaction. In particular, the potent inflammatory mediators including tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and IL-6, which enhance central sensitization and thus evoking pain hypersensitivity (Falk and Dickenson, 2014), mediate functional nerve cellular communication, and thereby contribute to persistent pain processing (Shen et al., 2014).

A family named suppressor of cytokine signaling (SOCS) has emerged as critical regulators of cytokine-mediated signaling in diverse tissues. These proteins are relatively small molecules containing a central src homology2 (SH2) domains and a C-terminal SOCS box (Palmer and Restifo, 2009). SOCS1, a member of SOCS family, act in a negative feedback loop to attenuate signaling via the JAK2/STAT3, NF-κB, TLR4 pathway that is important in the transmission of cytokine signals from the cell surface to the nucleus (Diao et al., 2009; Su et al., 2009). In central nervous system, SOCS1 regulates neuronal damage and neuronal immunity (Baker et al., 2009; Steffensen et al., 2014; Yi et al., 2015). Previous study has demonstrated SOCS1 has a long-lasting decreased in rats spinal cord after CCI and may regulate neuropathic pain through NF-κB and p38 MAPK pathways (Tan et al., 2015). In this study, we set out

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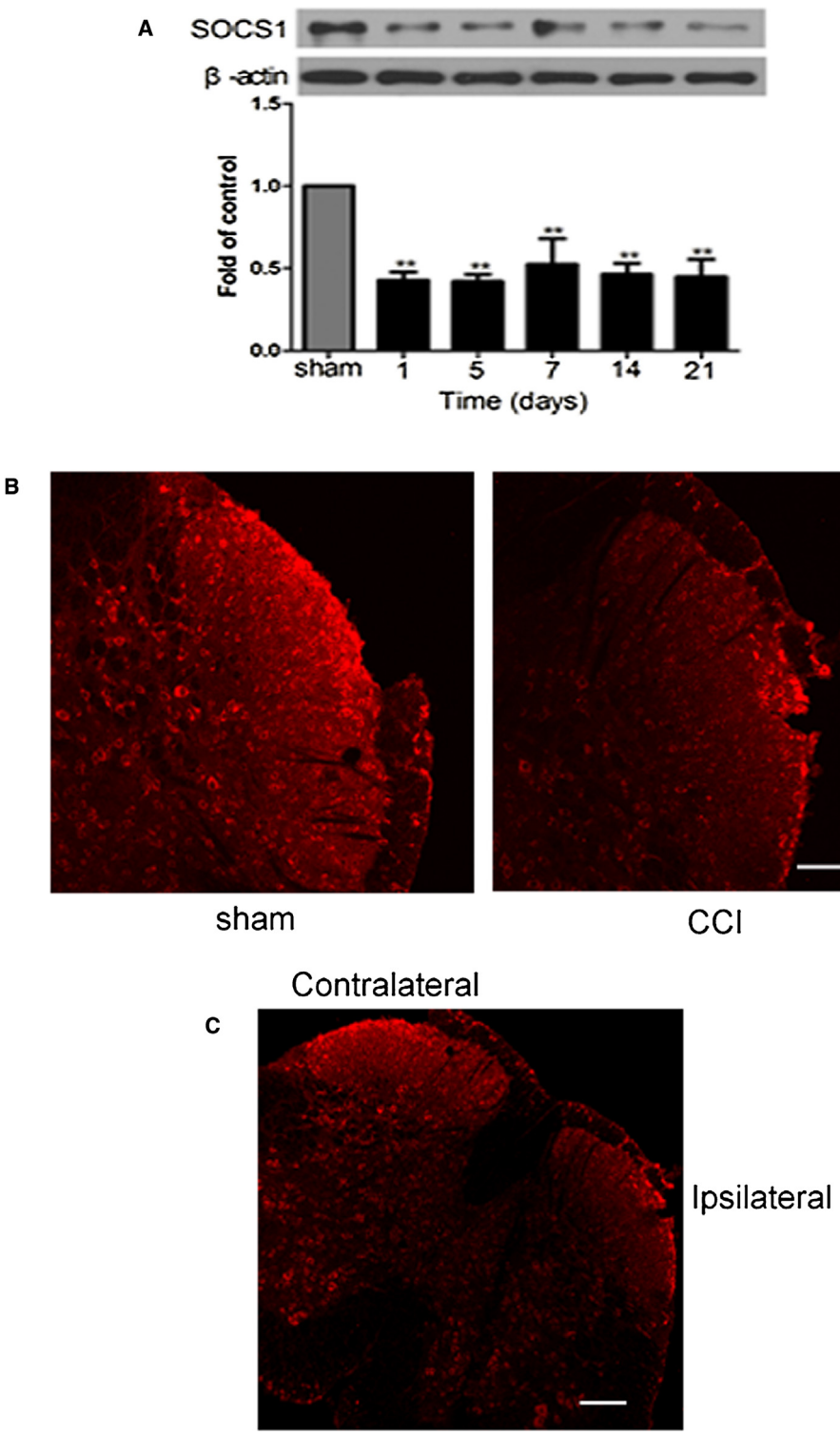

Fig. 1. Expression and distribution of SOCS1 protein in the SC after CCI in mice. (A) Western blot analysis shows time course of SOCS1 expression in sham and CCI mice. Five spinal cord segments were included in each group. **P < 0.01 versus sham control. (B) Confocal images of immunostaining for SOCS1 and its localization in the SC. Tissues were collected at day 14 after CCI. (bar = 100 μm).

to investigate whether SOCS is induced in SCDH and Figs. 1–4 participate in neuropathic pain by using CCI pain model. We find that CCI produces a decrease of SOCS1 in the SC, and that SOCS1 mediated neuronal sensitization and glial activation are crucial for the development and maintenance of neuropathic pain. Furthermore, spinal SOCS1 may be developed into a potential analgesic target for neuropathic pain management.

2. Materials and methods

Animals. Adult male Kunming mice (20–22 g), provided by the Experimental Animal Center of Xuzhou Medical College, were used for these studies. Mice were housed under a 12 h light/dark cycle with food and water ad libitum. All experimental protocols were approved by the Animal Care and Use Committee of Xuzhou