Sex Dimorphism in Spinal glial Signaling in Pathological Pain
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Abstract
Following painful stimuli and injuries, activated microglia and astrocytes contribute to the facilitation of pain signaling via glia-neuronal signaling pathway. The purpose of this mini-review is to compare recent progress of the last 5 years on microglia and astrocyte control of pain, especially sex differences in pathological pain.

Keywords: Microglia; Astrocyte; Pain; Sex difference

Introduction
Following painful stimuli and injuries, glial cells exhibit various changes in function and morphology, which are called activation of glial cells. Activated glial cells, including microglia and astrocytes, can modulate neuronal excitability and synaptic function via glia-neuronal signaling pathway and therefore contribute to the facilitation of pain signaling [1-3]. At present, the concept that glial activation is a common mechanism leading to pathological pain has been widely accepted. However, it should be emphasized that microglia and astrocytes have distinct functions in the induction, development and maintenance of pathological pain [2]. In addition, sex differences associated with pathological pain in recent years have received increasing attention. The purpose of this mini-review is to compare recent progress of the last 5 years (2014-2018) on microglia and astrocyte control of pain, especially sex differences in pathological pain.

Sex-related Role of Microglial Signaling in Pathological Pain
In the past five years, the most interesting finding is that spinal inhibition of microglial function reduced peripheral nerve injury-induced mechanical allodynia in male but not in female mice. Sorge et al. found Spared Nerve Injury (SNI) induced not only equivalent microgliosis in the spinal cords of male and female mice, but also similar levels of mechanical allodynia in both sexes [4]. However, intrathecal injection of microglial inhibitors (minocycline, propentofylline and fluorocitrate) or microglia toxin (saporin toxin conjugated to macrophage antigen complex-1) or microglial P2X4R-BDNF signaling inhibitors (TNP-ATP, Y1036 and TrkB-Fc) reduced SNI-induced mechanical allodynia in male but not female mice [4]. Furthermore, this male-specific response is testosterone-dependent because minocycline does not inhibit allodynia in castrated male mice but reduces allodynia in females treated with testosterone. In contrast, female mice have more T lymphocytes (CD4+ and CD8+ lymphocyte) in the blood and exhibit increased T lymphocyte marker (CD3e, CD4 and CD8a) expression in the spinal cord after injury. Briefly, female mice switch from microglia to T lymphocytes for neuropathic pain sensitization [4].

Sex-dependent microglial signaling in neuropathic pain has been confirmed by elsewhere. Taves et al. found there are no sex-difference in microgliosis and expression of the microglial markers CX3CR1 and IBA-1 in the spinal cord dorsal horn of the mouse Chronic Constriction Injury (CCI) model. However, P38 (a member of the mitogen-activated protein kinase family) has more profound activation in the spinal microglia of male mice following nerve injury [5]. Intrathecal injection of the p38 inhibitor skepinone inhibited CCI-induced mechanical allodynia in male mice and rats but not in female mice and rats 7 days after nerve injury. Intriguingly, formalin-induced spontaneous pain behavior was also relieved in male mice but not in females by intrathecal injection of skepinone [5]. Spinal inhibition of p38 signaling has been shown to disrupt IL-6 and PGE2-induced persistent pain in male but not female mice [6]. Recently, in a collagen antibody-induced mouse arthritis pain model, Zafra et al. found that intrathecal injection of the microglial inhibitors minocycline inhibited mechanical allodynia in male but not in female mice during the post-inflammatory phase (day 54-60 after collagen antibody injection) [7]. These reports indicate that there is sex-dependent microglial signaling in inflammatory pain.

Previous reports indicate that p38 plays an important role in the release of TNF-α triggered by caspase 6 [8], a cysteine protesase could modulate synaptic plasticity and contribute to pathological pain. Berta et al. found spinal microglial caspase 6/p38 signaling is male dominant in some inflammatory and neuropathic pain conditions. Intrathecal injection of the caspase 6 inhibitor ZVEID reduced CCI-induced mechanical allodynia in only male but not female mice. Compared to wild-type mice, CCI-induced mechanical allodynia was reduced only in male but not female caspase 6-KO mice [9]. In addition, Chen et al. found that intrathecal injection of recombinant active caspase 6 protein elicited mechanical hypersensitivity only in naive male mice but not in females [10]. In contrast, intrathecal injection of TNF elicited similar levels of mechanical hypersensitivity in both sexes [10]. These results imply that sex-dependent caspase 6 signaling in inflammatory and neuropathic pain may be due to sex dependence release of TNF from microglia.

Notably, sex differences microglia signaling in pain process may be different in different pain models, especially in bone cancer pain models of female rats. For example, Yang et al. found that delayed spinal microglia activation contributes to the maintenance of bone cancer pain in female rats [11]. Upregulation of P2XR, BDNF and p38 phosphorylation in spinal microglia was also observed in a female rat model of bone cancer pain and spinal injection of P2X_R siRNA prevent the initial mechanical hypersensitivity of bone cancer pain [12]. In addition, P2X_R upregulation exclusively occurred in spinal microglia in herpetic pain model of female mice and intrathecal P2X_R antagonist

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NP-1815-PX inhibited mechanical allodynia in herpetic pain [13]. Therefore, it is necessary to conduct a broader and in-depth study of sex-dependent microglial signaling in different pain models.

**Sex-related Role of Astroglial Signaling in Pathological Pain**

Astrocytes are the most abundant cells in the spinal cord and are critical for synaptic transmission and homeostasis maintenance. Unlike rapid activation of microglia, activated astrocytes are usually found a few days or later after painful stimuli and last longer. Activated astrocytes can play an important role in the development and maintenance of chronic pain through a variety of mechanisms. However, whether or not astrocyte signaling is sex-specific in pain regulation remains unclear. Some results support the existence for a sex-dependent role of astrocytes in pain processing. For example, Vacc et al. found that CCI-induced mechanical allodynia is much longer in female mice than in male mice and CCI-induced reactive astrocytes and microglia are also much longer in female mice [14]. Nakamoto et al. et al. found that MSSI stress (maternal separation and social isolation stress) induces increased expression of GFAP protein in locus coeruleus of female but not male mice, which contributes to neuropathic pain exacerbation in female mice [15]. Additionally, Zafra et al. found that intrathecal injection of astrocyte inhibitor pentoxifylline inhibited mechanical allodynia in male but not in female mice at the late stage of collagen antibody-induced arthritis model [7]. It is worth noting that pentoxifylline is believed to not only attenuate the activation of astrocytes, but also inhibit the activation of microglia [16]. However, recent observations from our laboratory suggest that sex-independent astroglial signaling occurs in inflammatory and neuropathic pain. Intrathecal injection of astrocyte cytotoxin L-AA or JNK inhibitors D-JNKI-1 or ERK inhibitors U0126 can equally reduce nerve-injury-induced mechanical hypersensitivity in male and female mice [10]. Furthermore, nerve injury-induced upregulation of connexin-43 exclusively occurred in spinal astrocytes [17] and intrathecal connexin-43 blocker effectively inhibited neuropathic pain in both sexes [10].

**Conclusions and Perspectives**

Clinical data show that men and women not only respond differently to pain but also to responsiveness to both drug and non-drug pain interventions [18]. Given that current unsatisfactory treatment of chronic pain, the study of the mechanism of chronic pain remains the focus of research, in which the sex differences in pain processes are receiving increased attention. From the current findings, the sex differences in glial cell regulation of pain may be different in different pain conditions and different stages of pain process. Future research needs to clarify whether the sex-related roles of glial cells are related to gender differences in clinical pain.

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