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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 microglia inhibitors (minocycline, propentofylline and fluorocitrate) or microglia toxin (saporin toxin conjugated to macrophage antigen complex-1) or microglial $P2X_4R$-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 protease 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 $P2X_4R$, BDNF and p38 phosphorylation in spinal microglia was also observed in a female rat model of bone cancer pain and spinal injection of $P2X_4R$ siRNA prevent the initial mechanical hypersensitivity of bone cancer pain [12]. In addition, $P2X_4R$ upregulation exclusively occurred in spinal microglia in herpetic pain model of female mice and intrathecal $P2X_4R$ 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 existing evidence for a sex-dependent role of astrocytes in pain processing. For example, Vacca 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]. Nakamoto1 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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References

1. Chen G, Zhang YQ, Qadri YJ, Serhan CN, Ji RR (2018) Microglia in pain: Detrimental and protective roles in pathogenesis and resolution of pain. Neuron 100: 1292-1311.
2. Ji RR, Berta T, Nedergaard M (2013) Glia and pain: Is chronic pain a gliopathy? Pain 154: S10-28.
3. Gao YJ, Ji RR (2010) Targeting astrocyte signaling for chronic pain. Neurotherapeutics 7: 482-493.
4. Sorge RE, Mapplebeck JC, Rosen S, Beggs S, Taves S, et al. (2015) Different immune cells mediate mechanical pain hypersensitivity in male and female mice. Nat Neurosci 18: 1081-1013.
5. Taves S, Berta T, Liu DL, Gan S, Chen G, et al. (2016) Spinal inhibition of p38 MAP kinase reduces inflammatory and neuropathic pain in male but not female mice: Sex-dependent microglial signaling in the spinal cord. Brain Behav Immun 55: 70-81.
6. Paige C, Maruthy GB, Mejia G, Dussor G, Price T (2018) Spinal inhibition of p2xr or p38 signaling disrupts hyperalgesic priming in male, but not female, mice. Neuroscience 385: 133-142.
7. Fernandez-Zafra T, Gao T, Jurczak A, Sandor K, Hore Z, et al. (2019) Exploring the transcriptome of resident spinal microglia after collagen antibody-induced arthritis. Pain 160: 224-236.
8. Berta T, Park CK, Xu ZZ, Xie RG, Liu T, et al. (2014) Extracellular caspase-6 drives murine inflammatory pain via microglial TNF-alpha secretion. J Clin Invest 124: 1173-1186.
9. Berta T, Qadri YJ, Chen G, Ji RR (2016) Microglial signaling in chronic pain with a special focus on caspase 6, p38 map kinase and sex dependence. J Dent Res 9: 1124-1131.
10. Chen G, Luo X, Qadri MY, Berta T, Ji RR (2018) Sex-dependent glial signaling in pathological pain: Distinct roles of spinal microglia and astrocytes. Neurosci Bull 34: 98-108.
11. Yang Y, Li H, Li TT, Luo H, Gu XY, et al. (2015) Delayed activation of spinal microglia contributes to the maintenance of bone cancer pain in female Wistar rats via P2X7 receptor and IL-18. J Neurosci 35: 7950-7963.
12. Jin XH, Wang LN, Zuo JL, Yang JP, Liu SL (2014) P2X4 receptor in the dorsal horn partially contributes to brain-derived neurotrophic factor oversecretion and toll-like receptor-4 receptor activation associated with bone cancer pain. J Neurosci Res 92: 1690-702.
13. Matsumura Y, Yamashita T, Sasaki A, Nakata E, Kohno K, et al. (2016) A novel P2X4 receptor-selective antagonist produces anti-allodynic effect in a mouse model of herpetic pain. Sci Rep 6: 32461.
14. Vacca V, Marinelli S, Pieroni L, Urbani A, Luvisetto S, et al. (2014) Higher pain perception and lack of recovery from neuropathic pain in females: A behavioural, immunohistochemical and proteomic investigation on sex-related differences in mice. Pain 155: 388-402.
15. Nakamoto K, Aizawa F, Kinoshita M, Koyama Y, Tokuyama S (2017) Astrocyte activation in locus coeruleus is involved in neuropathic pain exacerbation mediated by maternal separation and social isolation stress. Front Pharmacol 8: 401.
16. Mika J, Osikowicz M, Rojewska E, Korostynski M, Wawrzczak-Bargiela A, et al. (2009) Differential activation of spinal microglial and astroglial cells in a mouse model of peripheral neuropathic pain. Eur J Pharmacol 623: 65-72.
17. Chen G, Park CK, Xie RG, Berta T, Nedergaard M, et al. (2014) Connexin-43 induces chemokine release from spinal cord astrocytes to maintain late-phase neuropathic pain in mice. Brain 137: 2193-209.
18. Bartley EJ, Fillingim RB (2013) Sex differences in pain: A brief review of clinical and experimental findings. Br J Anaesth 111: 52-58.