·Special Lectures·

Contribution of interleukin-1beta in neuropathic pain

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Abstract

Interleukin-1beta (IL-1β), a pro-inflammatory cytokine, has been implicated in the development of peripheral and central sensitization that is charactistic of neuropathic pain. Recent studies demonstrated that IL-1β is an important messenger that is interacted with glia and neurons in the central neurous system in the neuropathic pain states. Some new studies showed that IL-1β activation was regulated by several other cytokines such as CCL2, MMP-2 and MMP-9 during the neuropathic pain conditions. This review will briefly describe the key role of IL-1 β and its signaling contributes to the peripheral and central nervous system in the neuropathic pain.

【摘要】 炎性因子白细胞介素-1β(IL-1β)参与神经病理性疼痛的中枢和周围敏化过程,此为其特征性病理变化。IL-1β是介导中枢神经系统胶质细胞与神经元相互作用的重要炎性因子,其活化受到其他炎性因子的调控,如趋化细胞因子配体2(CCL2)和基质金属蛋白酶2、9(MMP-2、9)等。本文简要概述IL-1β在中枢性和周围性神经病理性疼痛中的主要作用机制。

Neuropathic pain is a chronic pain condition that occurs after nerve damage, such as that induced by bone compression in cancer, diabetes, infection, autoimmune disease, or physical injury [1]. Neuropathic pain can manifest as spontaneous pain, allodynia (pain evoked by a normally innocuous stimulus), and hyperalgesia (enhanced pain evoked by a noxious stimulus). Particularly, tactile allodynia is a cardinal symptom of neuropathic pain [2]. Recent studies estimated that more than 1.5 billion people worldwide suffer from chronic pain, and that approximately 3%-4.5% of the global populations are afflicted with neuropathic pain, resulting in concerted efforts by the scientific community to tackle this health problem [3]. Development of effective therapeutic strategies requires a better understanding of molecular and cellular mechanisms underlying the pathogenesis of neuropathic pain. Cytokine is one of the major components involved in the neuropathic pain processing. This review will briefly describe the key role of interleukin-1beta (IL-1β) in the peripheral and central brain activation during the neuropathic pain.

IL-1α and 1β are prototypic proinflammatory cytokines that exert pleiotropic effects on a variety of cells and play key roles in acute and chronic inflammatory and autoimmune disorders. There are two IL-1 receptors: IL-1 receptor type 1 (IL-1RⅠ) and IL-1 receptor type 2 (IL-1RⅡ). IL-1α and IL-1β signal through IL-1RⅠ. Binding to IL-1RⅡ does not lead to cell signaling and it is therefore considered a decoy receptor. Once IL-1 binds with IL-1 receptor, a second receptor termed IL-1 receptor accessory protein (IL-1RAcP) gets recruited at the cell membrane to form a high affinity binding receptor complex leading to intracellular signaling. A third IL-1 family member, IL-1 receptor antagonist (IL-1ra), binds to IL-1 receptors and prevents the interaction of IL-1 with its receptors, acting as a natural IL-1 inhibitor [4-5]. In this review, we will focus on the IL-1β activation in the peripheral and central nervous system during the neuropathic pain.

Several animal models have been used to investigate the neuropathic pain mechanisms. These models include chronic constriction injury (CCI) of sciatic nerve [6], transection of the sciatic nerve [7], partial sciatic nerve ligation (PSNL) [8], spinal nerve ligation (SNL) [9], spared nerve injury (SNI) [10], chronic compression of the dorsal (CCD) root ganglion [11] and chronic constriction injury of infraorbital nerve (CCI-ION) [12]. Neuropathic pain is also induced by infection, inflammation, or demyelination of the sciatic nerve [13],

as well as by chemotherapy (e.g., paclitaxel) [14] and toxin [(e.g., 2'-3' dideoxycytidine (ddC)] [15].

IL-1β activation has been shown in the peripheral damaged nerves, dorsal root ganglion and spinal cord. Immunohistology showed that the expression of IL-1β immunoactivity was increased after nerve lesion [16]. Using the sciatic nerve injury model, the IL-1β mRNA of sciatic nerve after injury was significantly upregulated [17]. IL-1β expression increased in the spinal cord following peripheral nerve injuries [18]. Immediately after peripheral nerve injury, Schwann cells were activated and macrophages were recruited to the injury site, both secreting IL-1β [19]. In the CCI model in mice, sciatic nerve epineural injections of IL-1R Ⅰ neutralizing antibodies were shown to reduce both thermal hyperalgesia and mechanical allodynia, suggesting a role for the upregulated IL-1β in the induction of neuropathic pain [20-21]. Lysophosphatidic acid (LPA) had been demonstrated as an important initiator for the neuropathic pain. Intrathecal LPA injection increased the expression of IL-1β mRNA in the spinal cord dorsal horn, and IL-1β neutralizing antibody reversed LPA-induced neuropathic pain-like behavior [22].

Some evidence showed that IL-1β is involved in the modulation of nociceptive information in the brain regions [23]. IL-1β is also over-expressed at supraspinal brain regions, particularly in the contralateral side of the hippocampus and prefrontal cortex and in the brainstem, in rat models with neuropathic pain-like behavior [24]. After CCI of the rat infraorbital nerve in the rostral ventromedial medulla (RVM), a major component of brainstem descending pain modulatory circuitry were prolonged elevations of cytokines including tumor necrosis factor-α (TNF-α) and IL-1β [12].

Glia plays an active role in regulation of synaptic transmission in the central nervous system (CNS) [25-27]. After hyperactivation, glia subsequently releases cytokines at the spinal cord [28-32] and spinal trigeminal nucleus [33-34], which may be implicated in central mechanisms of persistent pain [35]. Increasing of IL-1β protein expression depends on glia activation in the rats of CCI model. The IL-1 receptor which localizes in neuron is also increased after infraorbital nerve ligation in rats. Blocking of the glia activation leads to the effect of N-methyl-D-aspartate (NMDA) phosphorylation [12]. IL-1β also directly sensitizes the nociceptors, such as the transient receptor potential cation channel subfamily Ⅴ member 1 (TRP Ⅴ1), a heat and chemical-sensitive cation channel in primary afferent neurons [36].

Recently, there have been several lines of evidence demonstrating that inflammatory chemokines play pivotal roles in the pathogenesis of both classical inflammatory diseases and intractable neuropathic pain. IL-1β, a potent inducer of neuronal CCL2, was also selectively upregulated in RVM reactive astrocytes. Injection of IL-1β (120 fmol) into the RVM induced behavioral hyperalgesia, which was blocked by RS-102895 (10 pmol), a CCR2B chemokine receptor antagonist. However, an IL-1 receptor antagonist (3 pmol) did not prevent CCL2 (3 pmol)-induced hyperalgesia. These results suggest that the effect of CCL2 is downstream to IL-1β signaling [37]. Toll-like receptor 4 (TLR4) expression was associated with both paw withdrawal threshold toward mechanical stimulus and paw withdrawal latency toward thermal stimulus. The protein levels of TNF-α and IL-1β, two downstream proinflammatory cytokines of TLR4 signaling pathway, were also significantly raised and correlated with mechanical/thermal hypersensitivity in diabetic rats [38]. The analgesic effect of siRNA-NFκBp65 might be mediated, at least partly, through the prevention of TNF-α, IL-1β and IL-6 products in the CCI model of rats [39]. The new mechanisms of neuropathic pain have been revealed involving a complex pathway with matrix metallo proteinase (MMP)-9, 2, and IL-1β. Kawasaki et al [40] showed that the CCI model cleavage of IL-1β by MMPs subtypes contributed to different phases of neuropathic pain behavior. After nerve injury, MMP-9 induced neuropathic pain through IL-1β cleavage and microglial activation at early phase, but MMP-2 maintained neuropathic pain through IL-1β cleavage and astrocyte activation at later phase. Therefore, the subsequential activation of microglia followed by activation of astrocytes in the spinal cord during neuropathic pain has been previously documented [19]. Additionally, IL-1β was shown to activate MMPs, suggesting a circular regulation between MMPs and IL-1β [40].

In summary, many recent studies show that IL-1β is not only involved in the inflammatory induced hypersensitivity, but it also contributes to the nerve injury induced neuropathic pain. The involvement of IL-1β is in both the peripheral and central nervous system in the neuropathic pain conditions. IL-1β signaling depends on glia activation circular and modulated by the chemokines activation. The releasing of IL-1β bands to its receptor on neuron leads to synaptic activity and pain transmission contributes to the development of the persistent of neuropathic pain.

Disclosure

No authors report any conflict of interest.

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