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Distinct role of tumor necrosis factor receptor subtypes 1 and 2 in the red nucleus in the development of neuropathic pain

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HIGHLIGHTS

- Spared nerve injury (SNI) up-regulates TNFR1 and TNFR2 in the red nucleus (RN).
- The up-regulation of TNFR2 in the RN of rats with SNI is earlier than that of TNFR1.
- TNFR1 in the RN plays crucial role in the early and later stages of neuropathic pain.
- TNFR2 in the RN plays an important role in the early stage of neuropathic pain.

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ABSTRACT

Previous studies have demonstrated that tumor necrosis factor-alpha (TNF-α) in the red nucleus (RN) plays a facilitated role in the development of neuropathic pain. Here, the protein levels and roles of two different TNF receptors, p55 type 1 (TNFR1) and p75 type 2 (TNFR2), in the RN of rats with spared nerve injury (SNI) were investigated. Immunohistochemistry demonstrated that both TNFR1 and TNFR2 were significantly increased in the RN of rats with SNI compared with sham-operated and normal rats. The up-regulation of TNFR1 occurred at two weeks after SNI, while TNFR2 had markedly increased already at one week and began to decrease at two weeks after SNI. Microinjection of different doses (500, 250 and 100 ng) of anti-TNFR1 antibody (anti-TNFR1-Ab) or anti-TNFR2-Ab into the RN contralateral to the nerve injury side dose-dependently increased the paw withdrawal threshold of rats, as assessed using von Frey filaments. The analgesic effects produced by anti-TNFR1-Ab at one week and two weeks after SNI did not show significant difference. However, the analgesic effect produced by anti-TNFR2-Ab at two weeks after SNI was significantly lower and shorter than that produced at one week after SNI. Combined injection of anti-TNFR1-Ab and anti-TNFR2-Ab (500 ng for each antibody) into the RN generated a relatively faster and longer analgesic effect compared with single using of anti-TNFR1-Ab or anti-TNFR2-Ab. These results support that TNF-α in the RN plays a crucial role in regulating neuropathic pain, and suggest that the algesic effect of TNF-α is transmitted through both TNFR1 and TNFR2. TNFR1 has equally important role in the early development and later maintenance of neuropathic pain, while TNFR2 is more inclined to play a role in the early development of neuropathic pain.

1. Introduction

Tumor necrosis factor-alpha (TNF-α), one of the major pro-inflammatory cytokines released in response to injury and inflammation, has been associated with the immediate and ongoing stages of chronic neuropathic pain [1,11]. After nerve injury, increased expression of TNF-α is observed in the affected peripheral nerve, dorsal root ganglia (DRG) and spinal cord [14,15]. Intraplantar, endoneurial or intrathecal administration of TNF-α in normal animals reproduces pain hypersensitivity that is similar to that of neuropathic pain in humans [13,22,26]. The up-regulation of TNF-α is also found in different supraspinal regions, such as the hippocampus, locus coeruleus and rostral ventromedial medulla (RVM) in rats following nerve injury. Microinjection of TNF-α into the lateral cerebral ventricle or RVM produces behavioral hyperalgesia and allodynia in normal rats, and exacerbates hyperalgesia in rats with chronic constriction injury (CCI) [6,8,25]. However, animals with neuropathic pain treated with antagonistic agents to

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TNF-α show a marked reduction of pain behaviors [8,19,20]. Our recent study indicates that TNF-α is up-regulated in the red nucleus (RN) after spared nerve injury (SNI), and microinjection of antibody against TNF-α into the RN alleviates mechanical allodynia induced by SNI [12]. These findings reveal an important role of TNF-α in the development of neuropathic pain.

TNF-α exerts its effects through two distinct receptor subtypes, constitutively expressed p55 type 1 (TNFR1) and inducible p75 type 2 (TNFR2). Similar to the up-regulation of TNF-α, increased expression of TNFR1 and/or TNFR2 is also observed in the peripheral nerve, DRG and spinal cord in animal models of neuropathic pain [2,7,16]. Selective stimulation of either TNFR1 or TNFR2 enhances the discharge rate of Aδ fibers in the DRG of rats following spinal nerve ligation (SNL) [17]. In contrast, epineurial or intrathecal injection of neutralizing antibodies against TNFRs alleviates pain behaviors of rats with CCI [9,18]. Mice lacking TNFR1 show an absence of thermal hyperalgesia and a reduction of mechanical and cold allodynia after nerve injury, while mice lacking TNFR2 only show a reduction of mechanical and cold allodynia compared with wild-type mice [21]. Deficiency of TNFR1 or TNFR2, especially TNFR2, results in a delayed onset of heat hyperalgesia in a mouse model of cancer [5]. In summary, TNFR1 and TNFR2 may play different roles in the development of different types of neuropathic pain.

Although previous study has proved that TNF-α in the RN plays a facilitated role in the development of neuropathic pain [12], but the receptor mechanisms of TNF-α in mediating neuropathic pain are still unknown. Thus, the purpose of the current study was to examine the protein levels of TNFR1 and TNFR2 in the RN of rats with SNI, and to clarify the roles of these receptors in the development of neuropathic pain.

2. Materials and methods

2.1. Animals

Male Sprague-Dawley rats weighing 200–230 g were used in experimental procedures approved by the Institutional Animal Care Committee of Xi'an Jiaotong University, China. All experiments conformed to the ethical guidelines of the International Association for the Study of Pain [27].

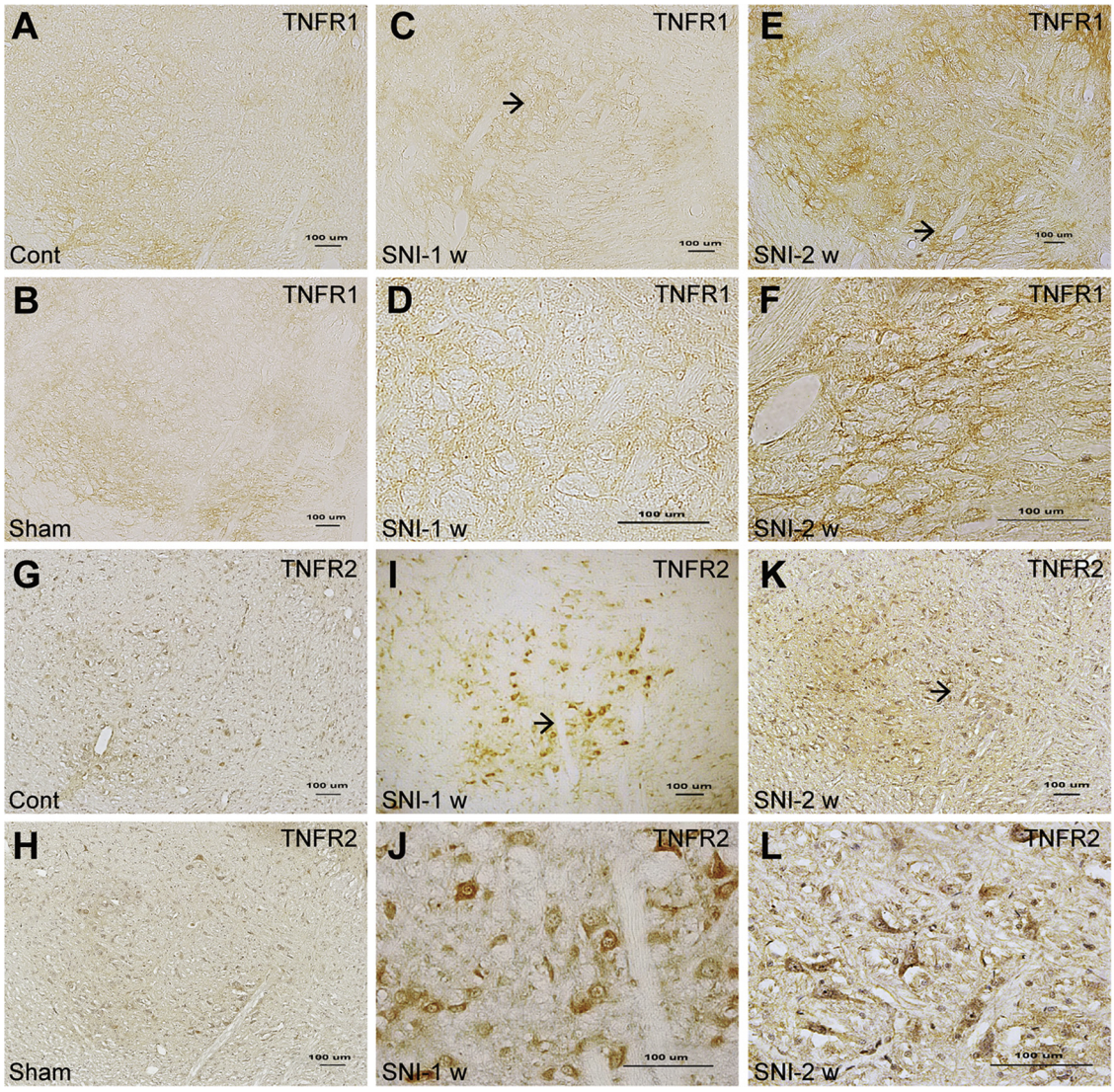

Fig. 1. Protein levels of TNFR1 and TNFR2 in the RN of rats with SNI. TNFR1 immunoreactivity was increased in the RN at two weeks (E and F) but not one week (C and D) after SNI compared with sham-operated (B) and normal rats (A), while TNFR2 immunoreactivity was markedly increased at one week (I and J) and began to decrease at two weeks (K and L) after SNI compared with sham-operated (H) and normal rats (G). Sham-operated rats did not show significant up-regulation of TNFR1 or TNFR2 immunoreactivity. Scale bar = 100 μm.