

MICRO REPORT

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The high-affinity IgG receptor FcγRI modulates peripheral nerve injury-induced neuropathic pain in rats

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Abstract

The Fc gamma receptor I (FcγRI; CD64) is the high-affinity receptor of the immunoglobulin G protein (IgG). It is usually expressed in immune cells and has recently been identified to distribute in the nervous system and play critical roles in various neurological disorders. Presently, the impacts of FcγRI in neuropathic pain was largely unknown. Here, we aimed to investigate the impacts of FcγRI in neuropathic pain through pain-related neurobehavioral studies and underlying mechanisms by biochemical methods in animal and cell models. Specifically, we first utilized the chronic constriction injury (CCI) rat model that displayed neuropathic pain related symptoms and signs, including thermal hyperalgesia and mechanical allodynia. These neurobehavioral defects were significantly attenuated by the anti-FcγRI antibody, which was associated with reduced levels of neuropeptide substance P, C₃, and TNF-α. Furthermore, we validated our animal findings using the embryonically neural crest-originated PC12 cell model. We found that stimulation of the IgG immune complex led to increased levels of FcγRI and inflammatory mediators, which were attenuated by the anti-FcγRI antibody in these cells. Collectively, our results from animal and cell-based studies suggest that FcγRI is a critical player for peripheral nerve injury-induced neuropathic pain by mediating pain-related immunological events, which therefore may provide a new therapeutic target for protection against chronic pain.

Keywords: Neuropathic pain, Fc gamma receptor, Anti-FcγRI antibody, Spinal cord, Peripheral nerve injury, Inflammatory mediators

Main text

Neuropathic pain, resulting from somatosensory nervous system dysfunction, is characterized by allodynia, hyperalgesia and spontaneous pain [1]. Neuropathic pain is closely related to immunological responses [2–5], which commonly displays elevated levels of antigen-specific immunoglobulins, particularly the presence of immune complexes of IgG and/or IgG in serum [6]. Fc-gamma receptors (FcγRs), the receptors of IgG, were typically expressed on immune cells and may trigger effector responses including cytokine production and phagocytosis [7]. Besides immune cells, IgG and FcγRs also were identified and distributed on neurons of the central and peripheral nervous system [8–10]. Moreover, FcγRs were increasingly recognized for their involvement in various neurological

disorders including Alzheimer's diseases, Parkinson's disease, ischemic stroke, and multiple sclerosis [11, 12]. The increased knowledge of FcγRs in the nervous system pathophysiology has led to novel preventative and therapeutic strategies for neurological disorders [13]. FcγRI is the high-affinity IgG receptor of the IgG receptor family proteins [14]. In this study, we investigated the effects of FcγRI on neuropathic pain and inflammatory mediators induced by peripheral nerve injury.

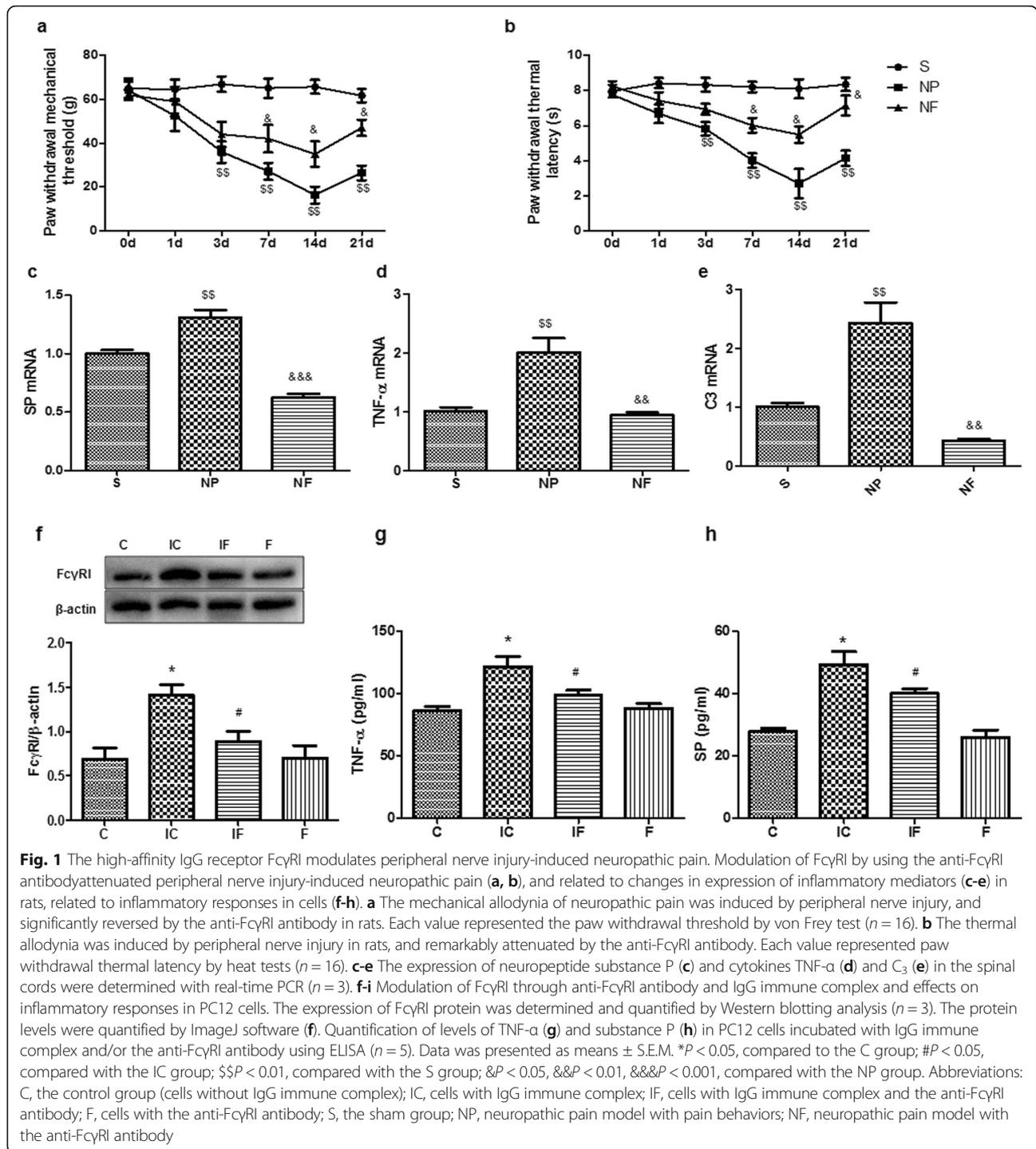
First, we observed that the mechanical and thermal allodynia of neuropathic pain was induced by peripheral nerve injury in rats and lasted for 3 weeks (Fig. 1a). The detailed methods used in this study were described in the Additional file 1. Interestingly, the mechanical hyperalgesia was significantly attenuated after treatment with the anti-FcγRI antibody (4 μg/ml) in neuropathic pain rats on postoperative 3, 7, and 14 d, compared with the NP group (Fig. 1a). In the thermal behavioral tests, the latency was significantly extended by the anti-FcγRI antibody in neuropathic pain rats on postoperative 7, 14 and 21d, compared with that in the

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NP group (Fig. 1b). Because peripheral nervous injury leads to an increase of inflammatory mediators, linked to hyperalgesia and other pain behavioral changes [2], we anticipated that modulation of Fc γ RI will result in mediators changes in our pain model animals. We therefore investigated the influences of Fc γ RI on inflammatory mediators in the spinal cord of our neuropathic pain model animals.

Indeed, we found that the levels of substance P, C $_3$, and TNF- α were significantly higher in the NP group animals than those in the sham animals, as expected and supported by previous studies [15]. The anti-Fc γ RI antibody remarkably decreased the expression of these inflammatory mediators and neuropeptide in the neuropathic pain animals (Fig. 1c-e).

We next carried out cell-based studies to further investigate our animal-based findings. Specifically, the embryonically rat neural crest-originated PC12 cells were utilized and subjected to experiments of the following four groups: the control group (C); the IgG immune complex alone (IC, 0.1 µg/ml); and the group combined with IgG immune complex and anti-FcγRI antibody (IF, IgG immune complex 0.1 µg/ml and the anti-FcγRI antibody 0.2 µg/ml) and anti-FcγRI antibody alone (F, 0.2 µg/ml). We showed that the IgG immune complex significantly up-regulated FcγRI protein level compared to the control by Western blotting analysis (Fig. 1f). Additionally, the group combined with IgG immune complex and anti-FcγRI antibody significantly decreased FcγRI protein levels compared to the IgG immune complex alone (Fig. 1f). There were no significant changes comparing the anti-FcγRI antibody alone to the control. In addition, the IgG immune complex increased the expression of substance P and TNF-α compared to the control, which was attenuated by the addition of anti-FcγRI antibody (Fig. 1g-h). Our results from the animals and PC12 cells suggested that other various cell and animal models should be used in future studies to elucidate the mechanisms by which FcγRI modulates neuropathic pain. Collectively, these results suggested that FcγRI was involved in the IgG immune complex-induced inflammatory responses in cell-based studies, supporting our animal-based results.

Despite increased understanding of FcγRI underlying the pathophysiology of the neuroimmune system, its effects in neuropathic pain began to be elucidated. We utilized both animal and cell models in this study and showed that FcγRI is a critical player for the peripheral nerve injury-induced neuropathic pain. Importantly, the anti-FcγRI antibody attenuated pain-related neurobehavioral defects, and normalized changes of inflammatory cytokines. In summary, our studies showed that FcγRI modulates peripheral nerve injury-induced neuropathic pain in animals through regulating inflammatory mediators. Our finding may provide both novel knowledge of the pathogenesis underlying the neuropathic pain and may suggest new therapeutic strategies to alleviate pain.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13041-019-0499-3>.

Additional file 1: Materials and Methods, Supplementary Figures and Tables

Abbreviations

g: gram; NP: Neuropathic pain; SP: Substance P

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Not applicable.

Authors' contributions

YL, ZZ, and RZ performed most experiments, collected and analyzed data. YL, ZJ and CZ participated in the design of the study. Manuscript was written by YL, ZJ, and critically reviewed by CZ. All authors read and approved the final manuscript.

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Availability of data and materials

Available by contacting the corresponding author for reasonable request.

Ethics approval and consent to participate

All the animal procedures were performed in compliance with the National Institutes of Health Animal Care Guidelines. The experiment protocol used for rats in this study was approved by the Animal Ethical Committee of Weifang Medical University.

Consent for publication

Agreed by all authors.

Competing interests

The authors declare that they have no competing interests.

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