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Neuronal Fc gamma receptor I as a novel mediator for IgG immune complex-induced peripheral sensitization☆

Lintao Qu

Department of Anesthesiology, Yale University School of Medicine, New Haven, CT 06510, USA

Abstract

Chronic pain often accompanies immune-related diseases with an elevated level of IgG immune complex (IgG-IC) in the serum and/or the affected tissues though the underlying mechanisms are largely unknown. Fc gamma receptors (FcγRs), known as the receptors for the Fc domain of immunoglobulin G (IgG), are typically expressed on immune cells. A general consensus is that the activation of FcγRs by IgG-IC in such immune cells induces the release of proinflammatory cytokines from the immune cells, which may contribute to the IgG-IC-mediated peripheral sensitization. In addition to the immune cells, recent studies have revealed that FcγRI, but not FcγRII and FcγRIII, is also expressed in a subpopulation of primary sensory neurons. Moreover, IgG-IC directly excites the primary sensory neurons through neuronal FcγRI. These findings indicate that neuronal FcγRI provides a novel direct linkage between immunoglobulin and primary sensory neurons, which may be a novel target for the treatment of pain in the immune-related disorders. In this review, we summarize the expression pattern, functions, and the associated cellular signaling of FcγRs in the primary sensory neurons.

Lintao Qu☆, M.D., Ph.D., Associate research scientist, Department of Anesthesiology, Yale University School of New Haven 06510, CT, USA

Corresponding author: Lintao Qu, Department of Anesthesiology, Yale University School of Medicine, 333 Cedar Street, New Haven 06510, CT, USA
lintao.qu@yale.edu

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Key Words

immunoglobulin G; calcium, immune complex; Fc gamma receptor; primary sensory afferents; pain; transient receptor potential canonical 3; dorsal root ganglion; nonselective cation channel; voltage-gated calcium channel

Research Highlights

(1) This study reveals a novel immune mechanism of pain that is IgG immune complex directly sensitizes primary sensory neurons through neuronal Fc gamma receptor I.
(2) These findings may suggest new therapeutic strategies for the treatment of pain related to antigen-specific immune diseases.

Abbreviations

IgG-IC, IgG immune complex; FcγRs, Fc gamma receptors; IgG, immunoglobulin G; DRG: dorsal root ganglion; TRPC3, transient receptor potential canonical 3; Syk, spleen tyrosine kinase; PLC, phospholipase C; IP_3, inositol trisphosphate receptor

INTRODUCTION

Pain is a major health problem that often accompanies numerous antigen-specific immune-related disorders. These diseases include autoimmune diseases such as Guillain-Barre Syndrome[1] and rheumatoid arthritis[2], allergic diseases such as atopic and allergic contact dermatitis[3-4], and infectious diseases such as herpes zoster[5]. A common feature of these diseases is an

elevated level of antigen-specific immunoglobulins (Ig), especially IgG in the serum and/or the presence of IgG immune complexes (ICs) in the affected tissue. A traditional immune-cell-centric view for such pain is that IgG-IC induces the release of proinflammatory cytokines from immune cells, which in turn leads to the sensitization of primary sensory neurons[6-8]. Moreover, Fc gamma receptors (FcγRs), expressed on immune cells, appear to play an important role in this process[9-10]. In addition to the indirect effects of IgG-IC on primary sensory neurons, it is not clear whether and/or how IgG-IC directly induces peripheral sensitization.

FcγRs, the receptors binding to the Fc domain of IgG, are widely expressed in the immune cells to regulate the immunity. There are two functionally different classes of FcγRs: the activating and inhibitory receptors[9-10]. Among them, FcγRII functions as inhibitory receptors whereas the remaining three types of FcγRs (FcγRI, FcγRIII, and FcγIV) positively regulate the immune response. Furthermore, FcγRI is the only high affinity receptor for IgG-IC. These receptors mediate a variety of immune functions, including phagocytosis, antibody-dependent cytotoxicity, release of inflammatory mediators and cytokines, and degranulation[10]. Previous studies using FcγRI-knockout mice have shown that FcγRI contributes substantially to certain inflammatory and immune responses[11-12]. Treatments such as intravenous immunoglobulin that potentially block FcγRI or reduce the level of IgG IC have beneficial effects to the painful symptoms in multiple sclerosis[13], systemic lupus erythematosus[14] and the complex regional syndromes[15]. The recombinant soluble human FcγRI has been shown to inhibit the IgG-IC-mediated production of inflammatory cytokines[16]. In addition to the immune cells, recent studies have revealed that FcγRI, but not FcγRII and FcγRII, is also expressed in a subset of primary sensory neurons[17-18]. Moreover, cross-linking of FcγRI by IgG-IC directly activates primary sensory neurons. More importantly, our recent study has identified that transient receptor potential canonical 3 (TRPC3) is a novel downstream transduction channel involved in FcγRI-triggered signaling in primary sensory neurons[19]. These findings provide a potential novel therapeutic strategy for the treatment of pain in the immune-related diseases. In this review, we will discuss the expression pattern, functions, and the associated cellular signaling of FcγRs in primary sensory neurons.

EXPRESSION PATTERN OF FcγRs IN PRIMARYSENSORY NEURONS

FcγRs are typically expressed on immune cells to regulate the immunity, including monocytes, macrophages, and polymorphonuclear leukocytes[10, 20]. Surprisingly, several studies have revealed that FcγRs are also observed in some types of neurons, including motor neurons in the spinal cord[21], Purkinje cells in the cerebellum[22], and dorsal root ganglion (DRG) neurons[17-18]. Andoh and Kuraishi[17] first provided direct evidence that the high affinity IgG receptor FcγRI, but not the low affinity receptors FcγRII and FcγRIII, is expressed in cultured mouse lumbar DRG neurons, especially small- or medium-diameter neurons. A more recent study has detected the mRNA expression of all types of FcγR (FcγRI, II, III, and IV) in mouse superior cervical ganglion neurons. Moreover, the mRNA expression level of FcγRI observed in superior cervical ganglion neurons is higher than in the bone marrow derived mouse mast cells[23]. Consistent with previous studies[17, 24], our recent study has indicated FcγRI, but not FcγRII and FcγRIII, is also expressed in a subset of rat DRG neurons[18, 25]. In addition, FcγRI is present on both the somata and axons of DRG neurons, suggesting that IC might activate the FcγRI on the somata and/or the axons of DRG neurons including nerve terminals in the peripheral tissue[18]. In contrast with Andoh and Kuraishi's study[17], no FcγRI expression has been detected in satellite glia in our recent study[18]. This discrepancy between two studies is likely due to different biomarkers used in two studies. In our study[18], glutamine synthetase is used as a marker for satellite glial cells whereas the lack of a general neuronal marker, Protein Gene Product 9.5 (PGP9.5), is used as a criterion for satellite glial cells in the study by Andoh and Kuraishi[17]. Since PGP9.5 is absent in both glial cells and other non-neuronal cells such as immune cells, the PGP9.5- negative cells that display immunostaining for FcγRI might actually be the immune cells such as macrophages. In addition, we have shown that FcγRI is expressed on rat DRG neurons across all size categories, especially abundant in large-sized DRG neurons[18], inconsistent with the findings observed in the cultured mouse DRG neurons[17, 24]. Importantly, we provide direct evidence for the first time that FcγRI is co-expressed with nociceptive neuronal markers isolectin B4, transient receptor potential vanilloid 1, substance P and calcitonin gene-related peptide in DRG neurons, suggesting a potential role of FcγRI in the pathogenesis of pain[18].

FUNCTIONS AND CELLULAR SIGNALING OF FcγRs IN PRIMARY SENSORY NEURONS

Neuronal FcγRs play an important role in many physiological functions[26]. In the spinal cord, FcγRs participate in IgG uptake into motor neuron terminals and acetylcholine release from motor neuron axon

terminals[21]. FcγRs expressed on Purkinje cells in the cerebellum contribute to the development and functional establishment in the cerebellum[22]. In DRG neurons, IgG-IC increases the concentration of intracellular Ca^{2+} ($[Ca^{2+}]_i$)[17-18]. Moreover, replacement of the intact IgG with F(ab′)2 fragments lacking the Fc portion or pretreatment with FcγRI antibody prevents the IgG-IC-induced $[Ca^{2+}]_i$ increase, suggesting that an interaction between Fc portion of IgG and neuronal FcγRI is essential for the IgG-IC-induced calcium response[18]. By contrast, individual components (antigen or antibody alone) of IgG-IC fail to trigger $[Ca^{2+}]_i$ increase, indicating that only the intact IgG-IC might have the conformation capable of activating FcγRI on primary sensory neurons[18]. In addition, both calcium entry from extracellular space and calcium release from internal stores contribute to FcγRI-induced calcium response in DRG neurons[18]. Furthermore, Ca^{2+} influx through L- or N-type voltage-gated calcium channels is partly involved in this process[17].

In addition to calcium response, IgG-IC increases the release of substance P from the cultured DRG neurons through neuronal FcγRI, which suggests a potential role of neuronal FcγRI in pain sensation[17]. Our recent study provides novel evidence for a role of neuronal FcγRI in the excitability of DRG neurons[18, 25]. Binding of IgG-IC to neuronal FcγRI directly depolarizes the membrane potential and triggers action potential discharges in DRG neurons. In macrophages and monocytes, the activation of FcγRI triggers a Ca^{2+}-dependent, nonselective cation channel, which is mainly permeable to Na^+[27-29]. In DRG neurons, a nonselective cation channel can be also activated by IgG-IC (I_{IC}), which contributes to the IgG-IC-induced membrane potential depolarization[19, 30]. In contrast with the previous report[27], this current is selective for Ca^{2+} and Na^+ as well. In addition, the I_{IC} can be regulated or sensitized by intracellular calcium. These features of the I_{IC} are similar to those of transient receptor potential canonical 3 (TRPC3) channels *in vitro*[31]. Accordingly, a recent study revealed that TRPC3/6/7 channel subtypes are involved in FcεRI signaling in mast cells[32]. Thus, it is likely that TRPC channels are a potential downstream transduction channel mediating the I_{IC} in the DRG neurons. Using single-cell RT-PCR, we have revealed that TRPC3 mRNA is always coexpressed with FcγRI (CD64) mRNA in the same DRG neuron[19]. This result suggests that FcγRI is more likely associated with the TRPC3, either directly or indirectly. In addition, pharmacological blockade of the TRPC3 inhibits the I_{IC}. Particularly, specific knockdown of TRPC3 using small interfering RNA attenuates the IgG-IC-induced Ca^{2+} response and the I_{IC}[19].

The signaling pathways of FcγRI in immune cells have been widely described[10]. Activation of FcγRI by IgG-IC results in phosphorylation of spleen tyrosine kinase (Syk), a non-receptor tyrosine kinase[33-34]. Activated Syk stimulates phospholipase C (PLC), which hydrolyzes the membrane phospholipids phosphatidylinositol 4,5-bisphosphate to produce inositol trisphosphate receptor (IP_3) and diacylglycerol (DAG)[20, 34-37]. IP_3 binds to IP_3 receptors in endoplasmic reticulum and evokes Ca^{2+} release from the internal Ca^{2+} stores. Our recent study reveals the similar signaling pathways of FcγRI in DRG neurons[19]. Moreover, the Syk-PLC-IP_3 signaling pathway is involved in the functional coupling of FcγRI to TRPC3 in DRG neurons[19].

FUNCTIONAL IMPLICATIONS

Excitation of primary nociceptive neurons is one of major factors for pain sensation, and a sustained increase in excitability leading to peripheral and central sensitization could contribute to the development and maintenance of chronic pain[38]. Recent studies suggest a potential role of neuronal FcγRI in pain sensation and the development of chronic pain[18, 25, 39]. Crosslinking of neuronal FcγRI by IgG-IC directly excited the primary sensory neurons though neuronal FcγRI[17-18], which may cause pain sensation. In addition, activation of neuronal FcγRI triggered the release of certain proinflammatory neurotransmitters from DRG neurons, such as substances P[17]. These mediators may further induce neurogenic inflammation, and in turn excite DRG neurons via their own receptors expressed on DRG neurons through a paracrine or autocrine pathway[40-41]. Our recent study has shown that neuronal FcγRI triggers a nonselective cation channel, which may contribute to the IgG-IC-induced excitation of DRG neurons[19, 30]. Moreover, TRPC3 acts as a novel and crucial downstream transduction channel mediating the depolarizing effects of IgG-IC on DRG neurons[19]. Meanwhile, the Syk-PLC-IP_3 signaling pathway contributes to the functional coupling of FcγRI to TRPC3 in DRG neurons[19]. These findings may provide novel therapeutic strategies to treat the pain in immune-related diseases.

It should be noted that the FcγRI-meidated neuropathic mechanisms become critical only under certain pathological conditions. The surface of a primary sensory neuron is normally protected against the large molecules, such as IgG-IC or IgG, due to the presence of blood-nerve/brain-barriers and the surrounding glial cells. By contrast, under pathological conditions that disrupt these barriers and demyelinate the peripheral and central neurons[42-44], the neuronal surface is more readily exposed to IgG-IC present in the serum or surrounding

tissues. Binding of IgG-IC to neuronal FcγRI directly activates the primary sensory neurons, therefore may induce pain, hyperalgesia and allodynia. Interestingly, FcγRI is also expressed in the large diameter DRG neurons. The possible IgG-IC-induced activation of medium- and large-diameter neurons may contribute to paresthesias, allodynia and hyperalgesia[45-47] in the immune-related diseases. The expression of FcγRI in the axons might suggest a potential role of neuronal FcγRI in axonal degeneration and regeneration following nerve injury[48]. However, no information is available about the role of neuronal FcγRI in the pathogenesis of pain *in vivo*. Generating neuronal FcγRI knockout mice is required for the future *in vivo* studies.

CONCLUSION

Chronic pain is often resistant to the established drug therapies, and the new therapeutic strategies are welcome. Recent evidence suggests that peripheral immune activation is necessary and sufficient to sustain chronic pain. IgG-IC appears to be a critical factor for the pathogenesis of pain by inducing the release of proinflammatory cytokines from the immune cells[6-8]. In addition to the indirect sensitization effects, IgG-IC also directly sensitizes the primary nociceptive afferents *via* neuronal FcγRI[17-19, 25, 39]. Better understanding of the FcγRI signaling in the peripheral nervous system will provide new potential therapeutic strategies in the treatment of chronic pain in the IgG-IC-mediated diseases.

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