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.

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; IP₃, 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
FcyRs: the activating and inhibitory receptors of 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 that mediate a variety of immune functions, including phagocytosis, antibody-dependent cytotoxicity, release of inflammatory mediators and cytokines, and degranulation. Previous studies using FcγRII knockout mice have shown that FcγRII contributes substantially to certain inflammatory and immune responses. 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, systemic lupus erythematosus and the complex regional syndromes. The recombinant soluble human FcγRI has been shown to inhibit the IgG-IC-mediated production of inflammatory cytokines. In addition to the immune cells, recent studies have revealed that FcγRI, but not FcγRII and FcγRIII, is also expressed in a subset of primary sensory neurons. 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. 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.

**FUNCTIONS AND CELLULAR SIGNALING OF FcγRs IN PRIMARY SENSORY NEURONS**

Neuronal FcγRs play an important role in many physiological functions. In the spinal cord, FcγRs participate in IgG uptake into motor neuron terminals and acetylcholine release from motor neuron axons.
The RNA attenuates the IgG-specific knockdown of TRPC3 using small interfering blockade of directly or indirectly. In addition, pharmacological in the same DRG neuron signaling in mast cells vitro receptor po be regulated or sensitized by intracellular calcium. These In contrast with the previous report activated by IgG channel, which is m of FcγRI triggers a Ca$^{2+}$ potential and triggers action potential discharges in DRG neurons. FcγRs expressed on Purkinje cells in the brain terminals. FcγRs expressed on Purkinje cells in the cerebellum contribute to the development and functional establishment in the cerebellum. In DRG neurons, IgG-IC increases the concentration of intracellular Ca$^{2+}$ ([Ca$^{2+}$])$^{17,18}$. 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$^{19}$. 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$^{16,20}$. 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$_c$), 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$_c$ can be regulated or sensitized by intracellular calcium. These features of the I$_c$ 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 FcγRI signaling in mast cells$^{32}$. Thus, it is likely that TRPC channels are a potential downstream transduction channel mediating the I$_c$ 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$_c$. Particularly, specific knockdown of TRPC3 using small interfering RNA attenuates the IgG-IC-induced Ca$^{2+}$ response and the I$_c$[18]. 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$^{18}$. 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$^{16,25,39}$. Crosslinking of neuronal FcγRI by IgG-IC directly excited the primary sensory neurons through 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 FcyRI-mediated 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 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. 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. In addition to the indirect sensitization effects, IgG-IC also directly sensitizes the primary nociceptiveafferents via neuronal FcγRI. 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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REFERENCES


[34] Kiener PA, Rankin BM, Burkhart AL, et al. Cross-linking of Fc gamma receptor I (Fc gamma RI) and receptor II (Fc gamma RII) on mononuclear cells activates a signal transduction pathway common to both Fc receptors that involves the stimulation of p72 Syk protein tyrosine kinase. J Biol Chem. 1993;268:24442-24448.


[36] Liao F, Shin HS, Rhee SG. Tyrosine phosphorylation of phospholipase C-gamma 1 induced by cross-linking of the high-affinity or low-affinity Fc receptor for IgG in U937 cells. Proc Natl Acad Sci U S A. 1992;89:3659-3663.


