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Modulation of the CD200/CD200R Axis by IFN-β Treatment in a Mouse Model of Experimental Autoimmune Encephalomyelitis

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ABSTRACT

Background: Interferon-β (IFN-β), a glycoprotein released during viral infections, plays a crucial role in modulating T cells involved in multiple sclerosis (MS). CD200 is an immunomodulatory molecule expressed in many cell types, including neurons. It reduces the progression of MS and experimental autoimmune encephalomyelitis (EAE) by interacting with CD200R, mainly expressed on myeloid lineage cells. This interaction prevents brain damage and slows the progression of the disease.

Objective: This study investigated changes in the expression of CD200 and CD200R genes in the brains of mice induced with EAE.

Methods: Female C57B/L6 mice were divided into three distinct groups: 1) EAE-induced and treated with IFN-β, 2) EAE-induced and treated with phosphate-buffered saline (PBS), and 3) a healthy control group. Two weeks after treatment, the mice were euthanized, and whole-brain tissues were used for mRNA extraction. After cDNA synthesis, the expression of CD200 and CD200R genes was evaluated using Taqman Real-Time PCR. Leukocyte infiltration and demyelination were assessed using Hematoxylin and Eosin staining (H&E) as well as Luxol fast blue (LFB).

Results: IFN-β treatment significantly reduced disease progression and demyelination. Furthermore, mice treated with IFN-β showed improved weight gain. The findings also indicated no notable change in CD200 gene expression across the groups examined. However the expression of CD200R decreased in the IFN-β-treated group, but significantly increased in the untreated group.

Conclusion: Our findings suggest that IFN-β treatment may decrease CD200R expression by reducing inflammation. Additionally, the elevated expression in the untreated group may explain why EAE is self-limiting.

Keywords: CD200, CD200R, Central Nervous System, Experimental Autoimmune Encephalomyelitis, Interferon beta

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INTRODUCTION

Multiple sclerosis (MS) is a complex autoimmune inflammatory disorder with an unclear etiology. However, genetics and environmental variables, such as infections, contribute to its development. Obesity, vitamin D insufficiency, and some viruses, notably the Epstein-Barr virus (EBV), all increase the risk of the disease (1). Affecting over 2 million people worldwide, the disease is most prevalent between ages of 20 and 40with women being more susceptible (2, 3). MS targets the central nervous system (CNS), where immune cells attack and degrade the myelin sheath surrounding nerve axons (4).

Interferon-beta (IFN-β) is a widely used therapy for multiple sclerosis (MS) aimed at symptom management and relapse prevention rather than offering a cure. IFN-β alleviates disease symptoms by suppressing immune cell proliferation and differentiation (5). It regulates T lymphocytes and induces Tregs through unknown processes (6). Additionally, it inhibits T cell activation and proliferation by reducing antigen presentation, costimulatory molecules, and the expression of major histocompatibility complex (MHC)-II (7). This cytokine also induces the expression of B-cell activating factor (BAFF) in B lymphocytes, neutrophils, astrocytes, and fibroblasts (8). However, many aspects of the processes underlying the efficacy of IFN-β in treating MS are still unknown.

CD200 is a glycoprotein found in a variety of cell types, such as activated T cells, B cells, follicular dendritic cells (FDCs), and cells within the CNS (9, 10). The widespread distribution of this molecule on several cell types demonstrates the importance of its biological role. This molecule binds to its receptor, CD200R, which is structurally similar to CD200. Both CD200 and CD200R have two immunoglobulin superfamily (IgSF) domains, but CD200R has more extended cytoplasmic domains, affecting its signaling potential (11). The expression of CD200R is primarily restricted to myeloid cells (12, 13). CD200 binds to CD200R through cell-to-cell contact, triggering the synthesis of inhibitory cytokines by lymphocytes. In the intact CNS, microglia, specialized phagocytes of the nervous system, are suppressed by the local interaction between CD200 and CD200R (14). In humans, reduced expression of CD200 is observed in multiple sclerosis, leading to the disruption of macrophage activation (15, 16). In contrast, heightened levels of CD200 expression on neurons decrease the pathogenesis of experimental autoimmune encephalomyelitis (EAE), which serves as a model for MS (17). Similarly, aging also reduces CD200 expression, leading to the onset of neurodegenerative diseases, which was attenuated in CD200Fc-treated rats (18).

Given the significance of the CD200/CD200R axis in autoimmune diseases, we have focused on the dynamics of changes within this axis to determine if it could be utilized for more efficient treatment of MS. This study uniquely integrates preclinical and molecular assessment to uncover the relationship between IFN-β and the CD200/CD200R axis. Therefore, we induced EAE in mice, and after administering IFN-β, we assessed any changes in this axis by examining variations in disease progression, demyelination, and weight.

MATERIAL AND METHODS

Animals

Eight-week-old female C57BL/6 mice were obtained from the Pasteur Institute in Tehran, Iran. The animals were kept in a pathogen-free environment with 50±5% relative humidity, temperatures of 23±2˚C, and a 12/12 dark/light cycle. All experiments were conducted in accordance with the ethical guidelines of the Kurdistan University of Medical Sciences (ethical approval number: IR.MUK.REC.1395.394).

EAE Induction and IFN-β Treatment

To induce EAE, C57BL/6 mice were given

a subcutaneous (sc) injection on day 0 at the right flank consisting of 250 µg $MOG_{35–55}$ (Myelin Oligodendrocyte $Glycoprotein_{35–55}$; Biobasic, Canada) dissolved in phosphate-buffered saline (PBS) and mixed with Freund's complete adjuvant (Sigma-Aldrich, St. Louis, MO, USA). The adjuvant contained 4 mg/ml of Mycobacterium tuberculosis H37Ra (BD Difco Laboratories, Detroit, MI, USA) in a total volume of 200 µl. After immunization on days 0 and 2, 250 ng Bordetella pertussis toxin (Sigma) was injected intraperitoneally (*i.p*) (19). When symptoms appeared on day 9, the EAE-induced mice were randomly divided into two separate groups: one group received 10,000 IU of IFN-β (Rebif - Merck) intraperitoneally every other day for two weeks, while the other group received PBS as a control. In the present study, we had three groups (n=8): 1) EAE-induced mice with no treatment (PBS – EAE group), 2) EAE-induced mice treated with IFN-β (EAE+IFN-β group), and 3) a healthy control group which received only PBS. The clinical presentation of EAE was evaluated, and the body weight of the mice was recorded daily for up to 25 days following immunization. Disease progression was assessed using a standardized clinical scoring system as follows: 0 indicates no symptoms; 1 signifies incomplete loss of tail tone; 2 denotes complete loss of tail tone; 3 represents limp tail accompanied by atypical gait; 4 – indicates paralysis of the hind limbs; 5 signifies hind limb paralysis with partial paralysis of the trunk; 6 denotes paralysis of both hind and forelimbs; and 7 indicates a moribund state or death (20, 21).

Histological Studies

On Day 25 after EAE induction, mice were anesthetized with ketamine (150 mg/kg) and xylazine (10 mg/kg) before being euthanized. Their brains were then harvested, and 5 µm paraffin-embedded sections were prepared. These sections were stained with Hematoxylin and Eosin (H&E) to assess leukocyte infiltration, and Luxol Fast Blue (LFB) to detect demyelination. An observer unaware of the treatment groups examined all sections under a light microscope.

Inflammation was graded on the following scale: 0 indicates no inflammatory cells; 1 signifies few inflammatory cells; 2 denotes perivascular inflammatory cell aggregates; 3 represents pronounced perivascular cuffing extending into adjacent brain tissue or diffuse parenchymal infiltration without defined cuffing. Demyelination severity was assessed using this scale: 0for intact white matter; 1for isolated demyelinated foci; 2for several regions of demyelination; 3for extensive demyelinated areas (22, 23).

Real-Time PCR

25 days after the induction of EAE, mice were euthanized, and their brains were harvested. The brain tissues were homogenized using a nylon mesh and then centrifuged at 3000 ×g for 10 minutes. Following the manufacturer's protocol, the cell pellets were re-suspended to extract total RNA in TriPure (TriPure Isolation Reagent, Roche, Germany). The purity and concentration of the RNA samples were assessed by measuring absorbance at wavelengths of 230, 260, and 280 nm. Subsequently, complementary DNA (cDNA) was generated using a PrimeScript™ RT reagent Kit (Takara Biotechnology, Otsu, Shiga, Japan), following the manufacturer's guidelines. Real-time quantitative PCR was then conducted using Premix Ex Taq (Probe qPCR) kit and Corbett Research RG-6000 Real-Time PCR Thermocycler (Corbett Life Science, Sydney, Australia). Briefly, for each reaction, 1µl of cDNA, 1µl of forward and reverse primers (both at a concentration of 10 pM), 10 µl of the 2x-PCR master mix, and 7 µl of molecular grade water (Aminsan, Iran) were combined in a 0.2 ml PCR tube. The PCR program was established with the following parameters: an initial denaturation phase at 95°C for 5 minutes; 40 amplification cycles consisting of 20 seconds at 95°C, 20 seconds at 60°C, and 40 seconds at 72°C; and a final extension phase at 72°C for 5 minutes. Gene

expression was evaluated using the ΔΔCT method through LinRegPCR software version 2017.0. The assessments were done in three biological replicates. Primers and probes for CD200 and CD200R can be found in Tables 1 and 2. Mouse glyceraldehyde 3-phosphate dehydrogenase (GAPDH) was used as an endogenous control for normalization.

Statistical Analysis

The progression of clinical symptoms in the IFN-β treated group was statistically compared to two other groups using two-way repeated measures ANOVA. Group comparisons were made using a one-way ANOVA followed by Tukey's multiple comparison tests. Real-Time PCR results were analyzed using LinReg software version 2017. Data normality was assessed using the Shapiro-Wilk test. SPSS 21 was used for data analysis. Results are presented as mean±standard error of the mean (SEM). Statistical significance was established as $p<0.05$ (*), $p<0.01$ (**), $p<0.001$ (***).

RESULTS

IFN-β Administration Reduced the Severity of EAE Complications in C57BL/6 Mice Immunized with MOG

In this study, we investigated the molecular mechanisms of the impact of IFN-β on EAE treatment. The administration of IFN-β significantly reduced disease severity, as evidenced by a marked decrease in disability and paralysis levels compared to the untreated control group.

On day 17, clinical scores reached their peak, measuring 1.3±0.12 in the IFN-β-treated group, which was significantly lower ($p<0.001$) than the untreated group (4.6±0.19) (Fig. 1A and Table 3). Furthermore, IFN-β treatment significantly reduced substantial weight loss with the mean body weight on day 17 being 18±0.2g ($p<0.05$), compared to the untreated group, which had an average weight of 17±0.2g (Fig. 1B). As anticipated, the untreated EAE mice showed progressive clinical symptoms, reaching peak severity on day 17 following EAE induction. Conversely, mice treated with IFN-β showed milder disease manifestations and lower clinical scores.

The Administration of IFN-β Decreased CNS Inflammation and Demyelination

Brain sections were stained with H&E to assess leukocyte infiltration (inflammation) and with LFB to measure demyelination. H&E staining revealed a significant decrease in leukocyte infiltration in the CNS of IFN-β treated mice (1.5±0.2) compared to the untreated control group (2.9±0.1, $p<0.01$) (Fig. 2A).

Table 1. Primers of CD200, CD200R, and GAPDH

Gene	Primer sequence (5' → 3')	Product length
GAPDH F	TGGAGCCAAAAGGGTCATCATC	134
GAPDH R	GGGCTAAGCAGTTGGTGGTG	
CD200 F	CAGAGCAAGGATGGGCAGTC	116
CD200 R	TCACCACTTCCACTTGAGCTG	
CD200R F	AGCTATTGAGGAGGATGAAATG	114
CD200R R	TTGACTTCGCCTTGTGATAC	

Table 2. Probes of CD200, CD200R, and GAPDH

Gene	Probe sequence (5' → 3')	Probe length
GAPDH	CCGCCCCTTCTGCCGATGCCC	21
CD200	CGCTACTGCTGCCATGCCCCAAAT	24
CD200R	TGCCTCCACCTTAGTCA	17

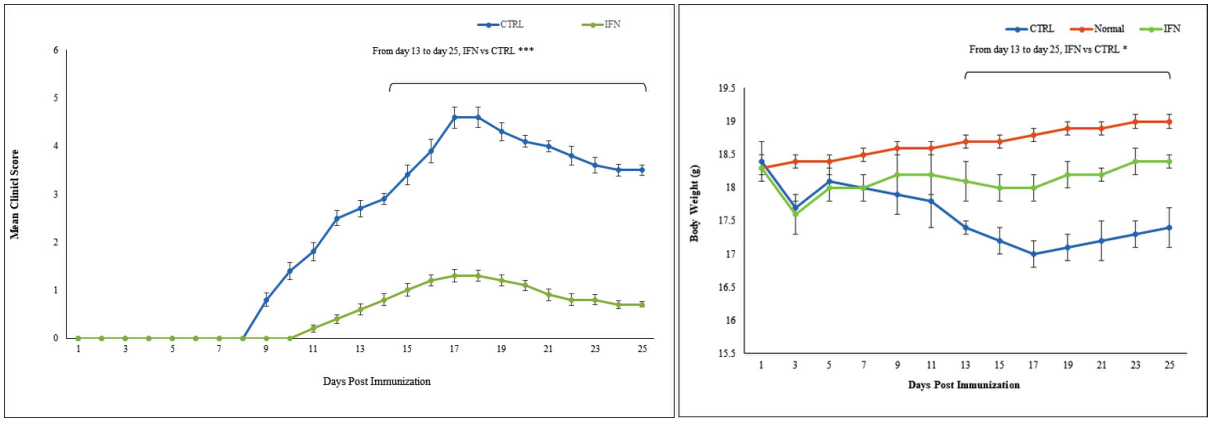

Fig. 1. IFN-β inhibited the development of EAE in MOG-immunized C57BL/6 mice. Female C57BL/6 mice were treated with 10,000 IU of IFN-β in the treated group simultaneously with EAE induction. The mice were monitored for signs of EAE, and the results for all mice were presented as (A) mean clinical score and (B) body weight. Results were expressed as mean±SEM. *p<0.05, **p<0.01, ***p<0.001, compared with the control group. The mice were divided into three groups: 1) untreated control group with EAE (CTRL), 2) IFN-β treated group (IFN) and 3) healthy control group (normal). EAE: experimental autoimmune encephalomyelitis, MOG: myelin oligodendrocyte glycoprotein

Table 3. Clinical features of EAE in mice treated with IFN-β

Group	Day of onset	Maximal score (Score at peak)	Mean score (Last Day)	Cumulative Disease Index (CDI)
CTRL[1]	9.1±0.3	4.6±0.22	3.5±0.11	55.4±0.77
IFN-β[2]	10.7±0.4*	1.3±0.13***	0.7±0.06***	13±0.74***

[1]CTRL: Control group EAE induced received soybean oil; [2]IFN-β : Treatment group with 10,000 IU IFN-β; Data were expressed as mean±SEM. All experiment groups compared with CTRL group. *p<0.05, **p<0.01, ***p<0.001

Similarly, LFB staining demonstrated a significant decrease in demyelination in the treated mice (1.3±0.15) compared to the untreated control group (2.7±0.25, p<0.01) (Fig. 2B), indicating the protective effects of IFN-β during disease progression.

CD200 and CD200R Expression

PCR products were sent to Macrogen (South Korea) to ensure the functional accuracy of primers and confirm the amplification of the target genes. The sequencing results were aligned using ChromasPro and clustalw add-ons, confirming that the PCR products belonged to the target genes of interest. Taqman Real-Time was then used to evaluate the expression of both CD200 and CD200R in the brains of mice. Our findings indicated that following EAE induction and a two-week treatment with IFN-β (treated group) or PBS (untreated group), CD200 expression was slightly enhanced in the untreated group but modestly reduced in the treated group compared to the healthy control group (Fig. 3). Conversely, CD200R expression increased significantly in the untreated group (p<0.001) compared to both the treated and healthy control groups. However, a slight decrease was observed in the treated group, aligning more closely with the healthy control group (Fig. 4). Furthermore, Spearman's correlation demonstrated a significant association (p=0.027) between the expression levels of CD200 and CD200R in the brain tissues (Fig. 5).

DISCUSSION

CD200 is a widely expressed transmembrane protein, whereas its receptor, CD200Ris predominantly expressed on myeloid cells and activated T lymphocytes (12).

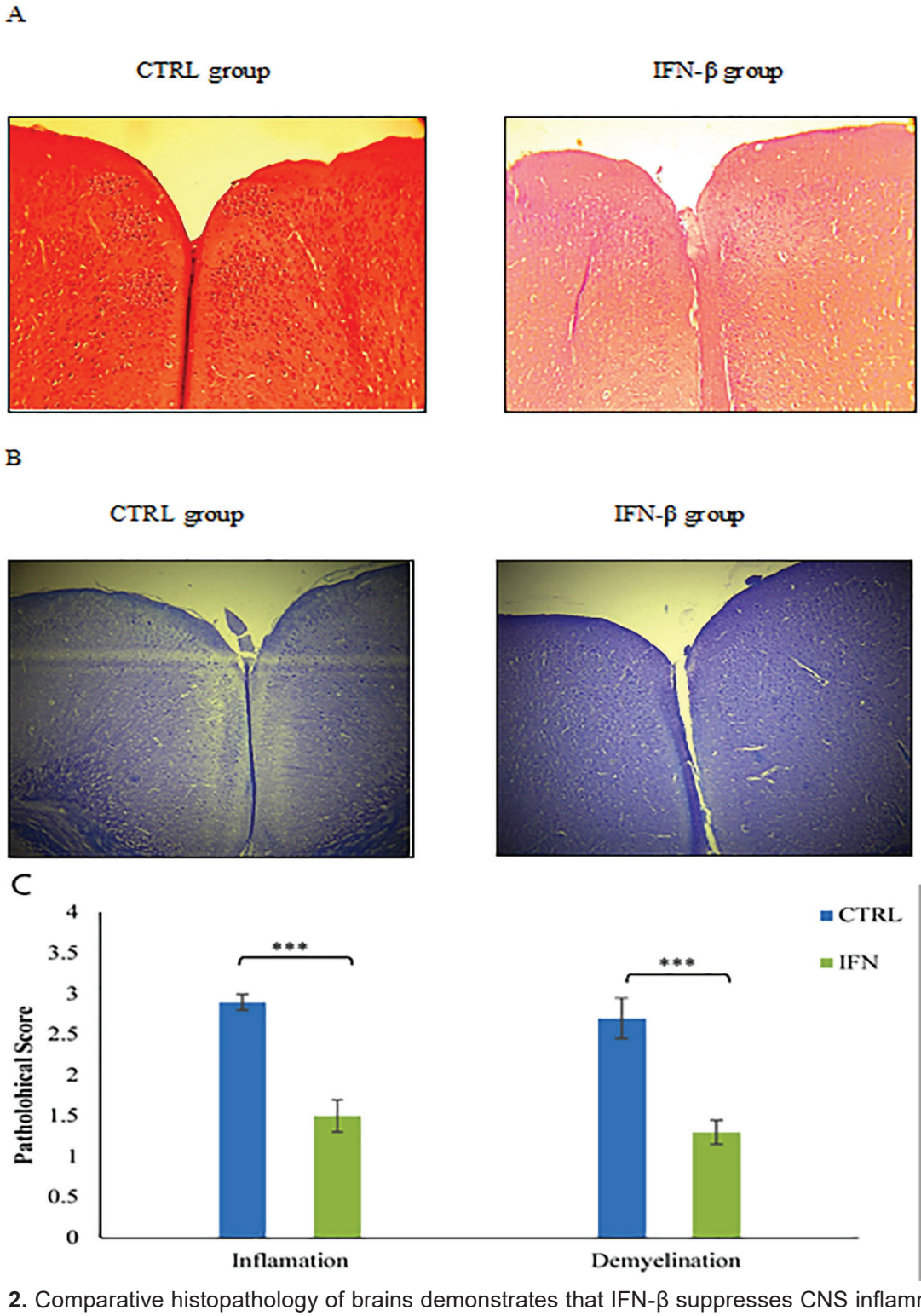

Fig. 2. Comparative histopathology of brains demonstrates that IFN-β suppresses CNS inflammation and demyelination. Histopathological evaluation of brains from the treated group (IFN-β) and control groups were performed. Brains from each group, collected on day 25 post-immunization, were fixed in paraformaldehyde, and embedded in paraffin. Five μm sections from different regions of the brains from each groups were stained with (A) H&E to enumerate infiltrating leukocytes and with (B) Luxol fast blue to assess demyelination. (C) CNS inflammatory foci and infiltrating inflammatory cells were quantified. Pathological scores including inflammation and demyelination were analyzed and shown with bar graphs as mean scores of pathological inflammation or demyelination±SEM. *p<0.05, **p<0.01, ***p<0.001 compared with the control group. Mice were divided into three groups: 1) untreated control group (CTRL), 2) IFN-β treated group (IFN) and 3) healthy normal group.

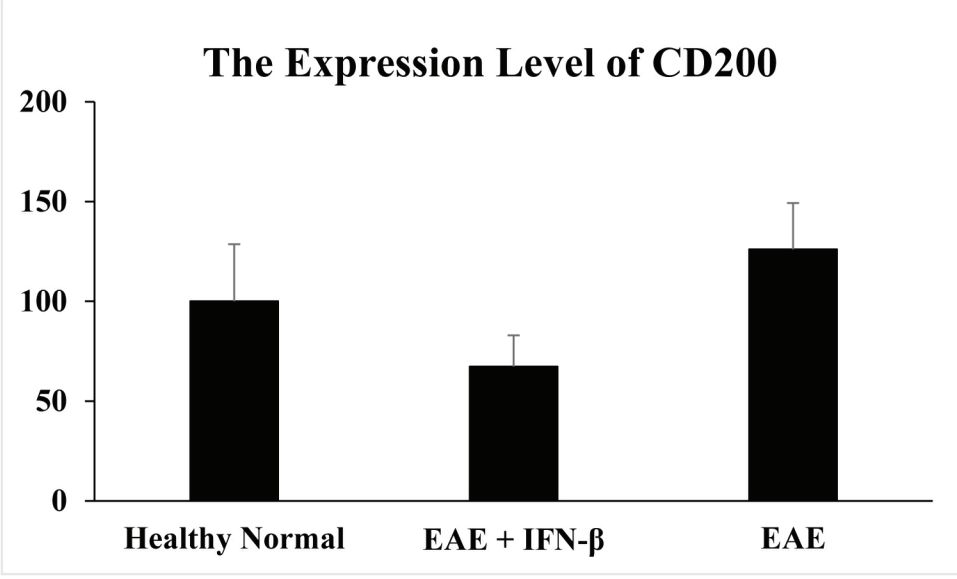

Fig. 3. The comparison of the expression level of CD200 among the experimental groups (n=5). Female C57BL/6 mice were treated with 10,000 IU IFN-β every two days after symptoms appeared on the 9th day of EAE induction using MOG and Freund's complete adjuvant along with Bordetella pertussis toxins. The treatment continued for 14 days. Two control groups, one healthy and the other EAE-induced, received only PBS. Whole brains were used for RNA extraction and cDNA synthesis. Taqman Real-time PCR was applied to evaluate the expression levels of CD200. Data are presented as mean±standard error of the mean. No significant difference was observed among the experimental groups. EAE: experimental autoimmune encephalomyelitis

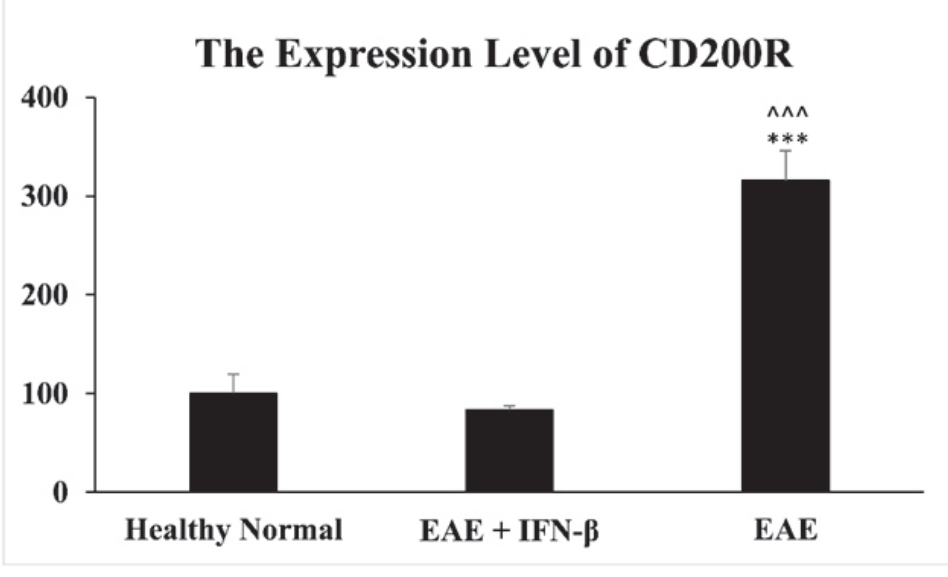

Fig. 4. The comparison of the expression level of CD200R among the experimental groups. EAE induced in female C57BL/6 mice using MOG and Freund's complete adjuvant along with Bordetella pertussis toxins. Nine days after EAE induction, the mice were treated with 10,000 IU of IFN-β (every two days) for 14 days. Control groups, one healthy and the other EAE-induced, received only PBS. Whole brains were used for RNA extraction and cDNA synthesis. Taqman Real-time PCR was used to assess the CD200R expression levels. Data are presented as mean±SE of the mean. ****p*-value at <0.001 represents a significant difference compared to the healthy normal group. ^^^ *p*-value at <0.001 represents a significant difference compared to the EAE+IFN-β group. CD200R: CD200 receptor, EAE: experimental autoimmune encephalomyelitis, MOG: myelin oligodendrocyte glycoprotein

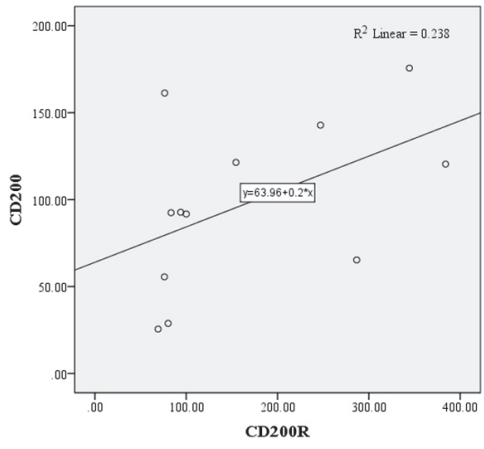

Fig. 5. Scatter plots representing the correlation between CD200 and CD200R expression levels in brain tissue. The CD200 expression level had a significant direct correlation with CD200R expression level, as indicated by Spearman's test (p=0.027).

CD200-CD200R axis plays a key role in regulating myeloid cell function by modulating costimulatory signals with CD200 deficient mice displaying more activated myeloid cells, including microglia in the brain (24). Moreover, these mice exhibited increased susceptibility to experimental autoimmune encephalomyelitis and collagen-induced arthritis (CIA) (25). Additionally, in Alzheimer's disease, reduced expression of CD200 by nerve cells and CD200R by microglial cells contribute to chronic neuroinflammation (26). Beyond its critical role in CNS immune regulation, the CD200/CD200R axis is exploited by several viruses, including rat Cytomegalovirus (27), Kaposi's sarcoma-associated herpesvirus (KSHV) (28). These pathogens encode CD200-like proteins, termed viral CD200 (vCD200) or viral orexin receptor 2 (vOX2) to subvert host immune responses. The viral protein shares structural homology with host CD200 (11, 30) and engages the same receptor (31). vCD200 represents one of several viral immune evasion strategies that dampen host defenses to promote viral persistence. During the lytic phase of the viral cycle, when viral proteins are exposed and the pathogen is most vulnerable to immune, detection KSHV dramatically upregulate vCD200 expression (~100-fold) (32). This induction highlights the critical role of the CD200/CD200R axis in suppressing antiviral immunity during active infection.

Given the critical roleof CD200 and its receptor in maintaining immune tolerance, this study aimed to assess the effect of IFN-β treatment on the expression of CD200 and CD200R in EAE-induced mice. Following EAE induction, mice received IFN-β treatment which significantly reduced both CNS inflammatory cell infiltration and demyelination compared to untreated controls These findings demonstrate that IFN-β administration effectively decreased inflammatory cell infiltration and demyelination, offering substantial protection for EAE-induced mice. Furthermore, this study sought to determine whether the therapeutic effects of IFN-β were mediated through modulation of the CD200/CD200R pathway. Our findings showed that CD200 expression changed slightly in the untreated and IFN-β-treated mice compared to healthy mice. Moreover, CD200R expression significantly increased in EAE-induced mice. However, in IFN-β treated mice, it decreased to a level comparable to healthy control mice. These findings were consistent with previous reports by Valente T *et al.* (33), who showed that CD200 expression slightly decreased and CD200R expression increased before the onset of EAE. Our data showed that two weeks after the onset of the disease condition (23rd day post-EAE induction) there were differences between IFN-β treated and untreated mice. Additionally, assessments were conducted to confirm the induction of the disease and the efficacy of the treatment. These assessments included external symptoms, disease progression rate, demyelination of the CNS, and weight of the mice. The results confirmed the successful induction of the disease and the effectiveness of the beta interferon treatment.

Minimal CD200 changes but significant CD200R upregulation, suggests that myeloid cells (particularly microglia) are the primary

responders within the neuroinflammatory microenvironment. I CD200R elevation likely represents a compensatory mechanism whereby myeloid cells attempt to mitigate CNS inflammation and prevent neural damage. However, the relatively stable CD200 expression implies limited neuronal responsiveness to these inflammatory challenges, highlighting the predominant role of the myeloid compartment in neuroimmune regulation.

According to the results of this study, it is unclear whether IFN-β directly reduces CD200R expression or indirectly decreases the expression of this anti-inflammatory protein by attenuating neuroinflammation. Additionally, the induction of CD200R expression may be involved in reducing inflammation and alleviating disease symptoms. It appears that inducing CD200R expression could enhance the responsiveness of myeloid cells to CD200, suggesting that this molecule could be a suitable target for treating EAE. In this regard, treating rats with the recombinant secretory form of CD200 (CD200:Fc) reduced microglial cell activation in their brains (34). Considering the findings of the present study and the high levels of CD200R in myeloid cells, in addition to its importance in maintaining tolerance in the CNS, it can be hypothesized that blocking CD200R might be associated with severe tissue damage. This was confirmed in another *in vivo* study where inhibition of CD200R by antibody led to CNS injury and intensified EAE, which was accompanied by a remarkable increase in cell infiltration, composed of T lymphocytes and activated inducible nitric oxide synthase^{+} (iNOS) macrophages within spinal cord inflammatory lesions (35).

CONCLUSIONS

Altogether, the findings of the current study demonstrate that the expression of CD200R is elevated in the inflammatory microenvironment of the brains of mice suffering from EAE. This suggests that the impact of CD200 on the disease is intensified by signaling through the CD200/CD200R axis. It highlights the importance of evaluating the effect of CD200 as a new treatment for the EAE process. Additionally, IFN-β treatment may have shifted the brain microenvironment towards an anti-inflammatory condition which warrants further investigation.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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