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Sulfatides ameliorate experimental autoimmune neuritis by suppressing Th1/Th17 cells

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ABSTRACT

Sulfatides have immunomodulatory functions, and play protective roles in multiple autoimmune diseases. In the present study, we showed that sulfatides ameliorated experimental autoimmune neuritis in Lewis rats induced with bovine peripheral myelin, which was associated with decreased proportions of Th1 and Th17 cells. Furthermore, compared control group, cells from sulfatide-treated rats exhibited lower potential in proliferation and IL-17 secretion in the presence of BPM or ConA in vitro. Moreover, sulfatides also reduced the proportions of NK and NKT cells. In summary, our study indicated that sulfatides might become a new therapeutic agent in Guillain-Barré syndrome in the future.

1. Introduction

Guillain–Barré syndrome (GBS) is the most common acute peripheral nervous system disorder, characterized by symmetrical limb weakness, limb areflexia, cranial nerve palsy, and respiratory failure. Based on clinical, electrophysiological and pathological characteristics, GBS can be divided into several variants, among which acute inflammatory demyelinating polyradiculoneuropathies (AIDP) is the most common subtype (Dong et al., 2016). Experimental autoimmune neuritis (EAN) mirrors many clinical and immunological aspects of AIDP and serves as an animal model to investigate disease mechanisms and therapy of AIDP (Maurer and Gold, 2002).

Both AIDP and EAN is pathologically characterized by accumulation of autoreactive T cells and macrophages in the peripheral nervous system (PNS), and demyelination. The pathogenesis of AIDP and EAN partially attributes to the augmentation of the T helper 1 (Th1) cells, which is characterized by secreting interferon-γ (IFN-γ) (Zhang et al., 2013). Cytokines produced by Th1 cells contribute to the disease development by recruiting inflammatory cells to the PNS and enhancing the release of other inflammatory products by other cells (Bao et al., 2002). Besides pathogenic effects of Th1 cells, T helper 17 (Th17) cells also contribute to the development of EAN by secreting interleukin 17 (IL-17) (Li et al., 2012; Wang et al., 2014). Regulatory T cells (Tregs) are a subset of T lymphocytes that can negatively regulate the immune response and play a significantly important role in the maintenance of self-tolerance. Studies have demonstrated the protection effects of Treg cells in EAN by reduced infiltration of inflammatory cells in the sciatic nerve (Wang et al., 2018).

Sulfatides, also called 3-O-sulfogalactosylceramides, are abundant in the myelin of the nervous system, pancreatic islet cells, and kidney (Takahashi and Suzuki, 2012). Sulfatides play important roles in myelin function and stability. Mice lacking sulfatides exhibit severe tremoring and develop progressive hindlimb paralysis (Coetzee et al., 1996). Moreover, recent studies illustrated the modulatory function of sulfatides in immune response and autoimmune disease. Sulfatides play preventive roles in the pathogenesis of experimental autoimmune encephalomyelitis (EAE), diabetes, and inflammatory liver disease by suppressing Th17 cells differentiation, type I natural killer T (NKT) cells, dentritic cells (DCs), and IFN-γ and interleukin-4 (IL-4) productions (Buschard et al., 2001; Halder et al., 2007; Jahng et al., 2004; Maricic et al., 2014; Mycko et al., 2014; Rhost et al., 2014; Subramanian et al., 2012). Sulfatides can be presented to type II NKT cells by CD1d molecules expressed by antigen-presenting cells, such as DCs, macrophages, subsets of B cells. Sulfatide-mediated type II NKT cell activation result in inhibition of type I NKT cells, $CD4^+$ and $CD8^+$ T cells (Marrero et al., 2015). It has also been demonstrated that

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sulfatides could directly modulate T cell function (Mycko, Sliwinska, 2014). Thus, sulfatides might be a potent strategy for intervention in autoimmune diseases by targeting type II NKT-mediated inhibition of Th1/Th17 cells or by its direct roles on other immune components than type II NKT cells. However, there has been no study about the effects and mechanisms of sulfatides on EAN.

In the present study, the effects of sulfatides on EAN Lewis rats were exploited. We found that sulfatide administration could ameliorate EAN symptoms by suppressing Th1/Th17 cells. This indicated sulfatides might be a potent strategy for treatment of GBS.

2. Materials and methods

2.1. Animals and reagents

Female Lewis rats aged 6–8 weeks, weighing 150–180 g, were purchased from Vital River Corporation (Beijing, China). All rats were housed and fed with standard food and water ad libitum. All the experimental protocols were approved by the institutional ethics committee. The minimum number of animals necessary was used to achieve the scientific objectives, and animal discomfort was kept to the minimum level.

Bovine peripheral myelin (BPM) was obtained from fresh adult bovine cauda equina according to the method previously reported (Norton and Poduslo, 1973). Sulfatides from bovine brain (purity > 97%) were purchased from Sigma-Aldrich. Sulfatides were dissolved in vehicle (0.5% polysorbate-20 [Tween 20] and 0.9% NaCl solution) and diluted in phosphate buffer saline (PBS).

2.2. Induction of EAN and assessment of clinical symptoms

Rat EAN models were induced as previously reported (Zhang et al., 2017). In brief, rats were immunized subcutaneously in the tail base with a total volume of 200 μl emulsion containing 1 mg BPM in saline and an equal volume of complete Freund's adjuvant containing 0.3 mg Mycobacterium tuberculosis (strain H37RA; Difco, Detroit, MI, USA). Clinical scores and body weights were monitored daily from day 0 until day 13 post-immunization (p.i.). Clinical symptoms were scored as follows: 0 = no illness; 1 = paraparesis of the tail; 2 = paraparesis of the hind limbs; 3 = tetra-paresis; 4 = moribund; 5 = death. Intermediate scores of 0.5 increments were given to rats with intermediate signs.

2.3. Treatment with sulfatides

The rats were randomly assigned to two groups: control group, and treatment group, with five or six rats in each group. On days 5, 8, and 11 after EAN induction, rats were administered intraperitoneally (i.p.) with 140 μg sulfatides or vehicle solution (control). The dosage of sulfatides was determined according to previous study (Maricic et al., 2014). Animals were sacrificed on day 13 p.i., just after the symptoms of two groups peaked. Inguinal lymph nodes of each rat were collected for the following experiments.

2.4. Preparation of lymph node mononuclear cells

Lymph nodes were grinded through cell strainers in RPMI 1640 medium (HyClone, Beijing, China). The mononuclear cells (MNCs) were washed twice and re-suspended at the concentration of 2×10^6 cells/ml in RPMI 1640 supplemented with 10% (*v*/v) fetal bovine serum (FBS, Gibco, grand land, NY, USA) and 1% (v/v) penicillin–streptomycin (containing 10,000 IU/ml penicillin and 10,000 μg/ml streptomycin; Hyclone, Logan, UT, USA) for the following experiments.

2.5. Flow cytometric analysis

Th1, Th2, Th17, Treg, NKT, natural killer (NK) cells were identified as $CD4^+IFN\text{-}\gamma^+$, $CD4^+IL4^+$, $CD4^+IL17A^+$, $CD4^+CD25^+Foxp3^+$, $CD3^+CD161a^+$, and $CD3^-CD161a^+$ cells, respectively. For cell surface molecules detection, 1×10^6 MNCs from each rat were stained with the following antibodies: APC anti-CD3(1F4,Biolegend, USA), FITC anti-CD4 (OX35, eBioscience, USA), PE anti-CD4 (W3/25, Biolegend, USA), PE anti-CD161 (10/78, BD Pharmingen™, USA), and PE anti-CD25 (OX39, eBioscience, USA). For Foxp3 detection, cells were first stained with FITC anti-CD4 antibody and PE anti-CD25 antibody, then fixed and permeabilized with Foxp3 staining buffer set (eBioscience, USA) according to the instruction and finally stained with APC anti-Foxp3 antibody (FJK−16S, eBioscience, USA). After staining, cells were analyzed with a flow cytometer.

For intracellular cytokine detection, MNCs were incubated in the presence of Cell Stimulation Cocktail Plus Protein Transport Inhibitors (eBioscience, USA) according to the instruction for 4 h at 37 °C. Then cells were collected, stained for cell surface molecules with the corresponding antibodies and fixed with 2% paraformaldehyde for 20 min at 4 °C. After washes with permeabilization wash buffer (Biolegend, USA) according to the instruction, cells were incubated with PE anti IL-10 (A5–4, BD Pharmingen™, USA), eFluor660 anti-IL-4 (OX81, eBioscience, USA), PE anti-IL-17A (eBio17B7, eBioscience, USA), PE anti-TNF-α (TN3–19.12, Biolegend, USA) or eFluor660 anti-IFN-γ (DB-1, eBioscience, USA) antibody respectively for 30 min at 4 °C. Cells were analyzed with a flow cytometer.

2.6. Cell proliferation assay

MNCs of lymph nodes (2×10^6 cells/ml) were labeled for 15 min at 37 °C with the 2 μM fluorescent dye carboxyfluorescein diacetate, succinimidyl ester (CFSE) (CFDA-SE, Molecular probes), washed, and cultured in triplicates in the presence of Con A (final concentration 5 μg/ml), BPM (final concentration 10 μg/ml) for 72 h at 37 °C in the incubator. Cells proliferation were analyzed with a flow cytometer.

2.7. ELISA analysis of IL-17 concentration in MNCs culture supernatants

MNCs of lymph nodes (2×10^6 cells/ml) were cultured in triplicates in the presence of Con A (final concentration 5 μg/ml), BPM (final concentration 10 μg/ml) for 72 h at 37 °C in the incubator. Then the supernatants were collected and stored at −20 °C for further IL-17 detection. The IL-17 levels were measured with rat IL-17 ELISA kit (eBioscience, USA) according to the instruction. The results were expressed as mean ± SEM ($n = 5$).

2.8. Histopathology and immunohistochemistry of sciatic nerve

To evaluate the inflammatory cell infiltration in peripheral nerve system, sciatic nerves were collected and fixed with 4% paraformaldehyde. After dehydration, the nerves were embedded in paraffin and sliced into sections (3 μm). The sections were stained with hematoxylin and eosin (HE) to evaluate total inflammatory cell infiltration. To detect macrophage infiltration, deparaffinized and rehydrated sections were exposed to citrate in a pressure cooker for antigen retrieval followed by blocking endogenous peroxidase activity with 0.3% hydrogen peroxide for 15 min. Then the sections were exposed to 1:200 dilution of mouse anti-rat CD68 antibody (1:200, Abcam, USA). Further, the sections was incubated with HRP-conjugated goat anti-mouse secondary antibodies (Zhongshan Goldenbridge Biotechnology, Beijing, China), followed by incubation with diaminobenzidine (DAB) substrate (Zhongshan Goldenbridge Biotechnology, Beijing, China). The sections were observed under a microscope.

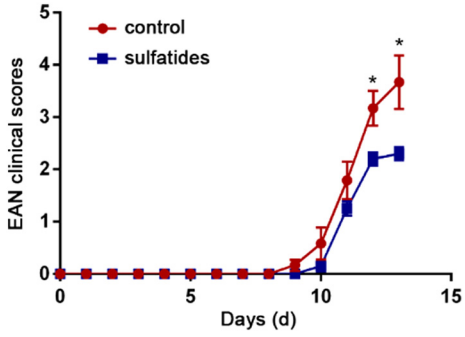

Fig. 1. Effects of sulfatides on experimental autoimmune neuritis (EAN).
EAN was induced in Lewis rats by immunization with BPM (1 mg/rat). On days 5, 8, and 11 after EAN induction, rats were administered i.p. with 140 μg sulfatides or vehicle solution (control). These data come from two independent experiments. Results are expressed as mean ± SEM (*$p < .05$, **$p < .01$).

2.9. Statistical analysis

Statistical analysis of the data was performed using SPSS 22 and Prism 6 software. Differences between two groups were analyzed using student's *t*-test. Results were expressed as mean ± SEM, and a level of $p < .05$ was considered to be significant.

3. Results

3.1. Sulfatides inhibit the development of EAN

To explore the effect of sulfatides on EAN, the rats were administered i.p. with 140 μg sulfatides or vehicle solution on days 5, 8, and 11 after EAN induction. The dosage of sulfatides was determined according to previous study and considering the differences between mice and rats (Maricic et al., 2014). Rats in control group showed clinical symptoms on day 9 p.i., while rats injected with sulfatides showed neurological deficits on day 10 p.i.. The symptoms progressed rapidly and peaked around day 12 p.i.. Clinical scores were lower in the sulfatides treatment group than those in control group on days 12 and 13p.i. ($p < .05$) (Fig. 1). Clinical scores were 2.20 ± 0.27 and 2.30 ± 0.27 in the sulfatide treated group on days 12 and 13 p.i., while clinical scores were 3.17 ± 0.82 and 3.67 ± 1.25 respectively in control group. These data indicate that sulfatide intervention ameliorates the illness of the EAN rats.

3.2. Sulfatide treatment suppresses Th1 and Th17 cells

Imbalance of $CD4^+$ T cell subtypes plays critical role in the

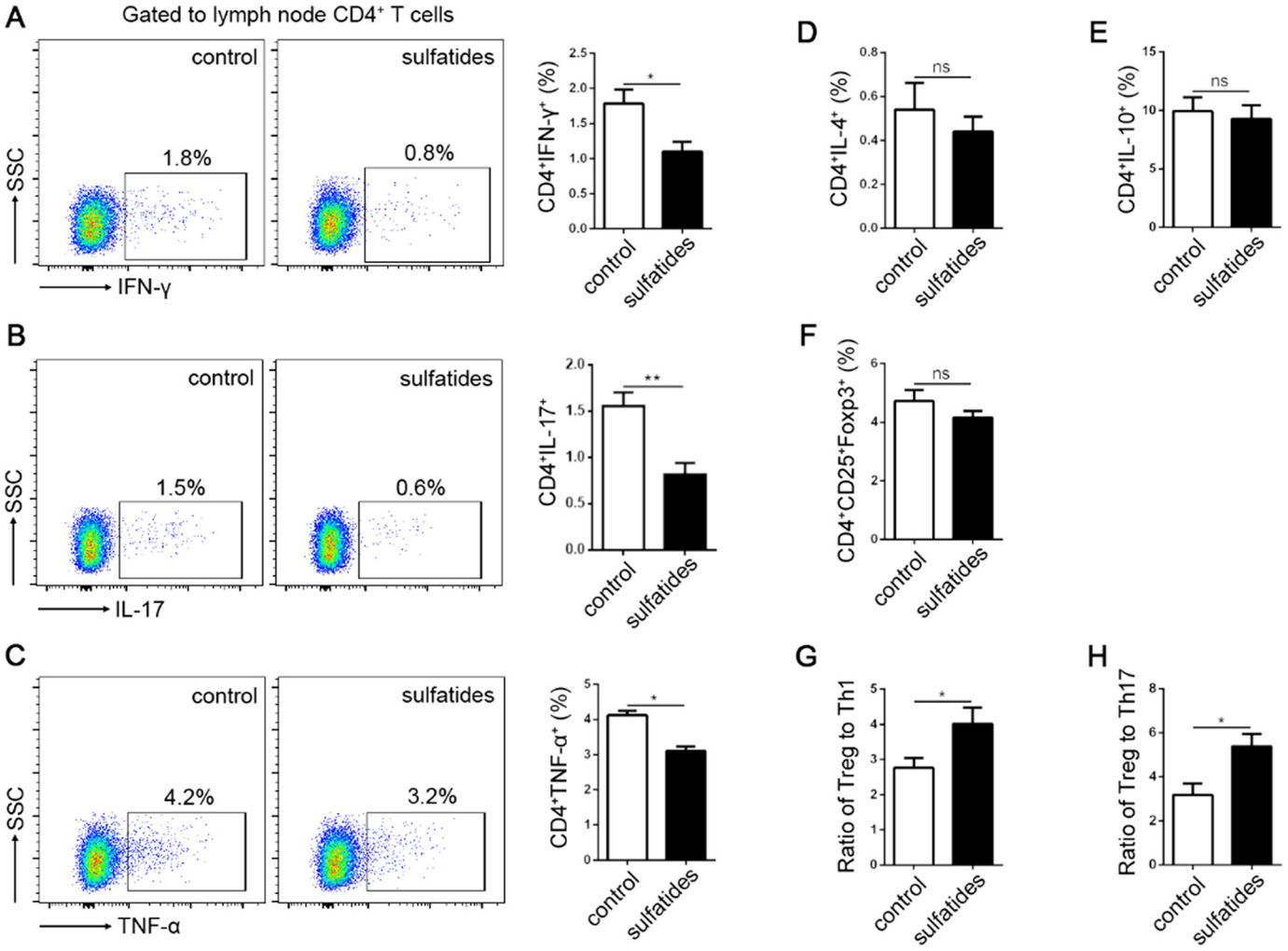

Fig. 2. Sulfatide treatment reduced the percentages of IFN-γ, TNF-α and IL-17 positive cells among $CD4^+$ T cells.
Sulfatide treatment reduced the percentages of IFN-γ, TNF-α and IL-17 positive cells among $CD4^+$ T cells (A, B and C). Percentages of IL-4 or IL-10 positive cells and Treg cells among $CD4^+$ cells were not different between two groups (D, E and F). Sulfatide treatment upregulated the ratios of Treg cells to Th1 and to Th17 cells (G and H). These data come from two independent experiments. The results are expressed as mean ± SEM (*$p < .05$, **$p < .01$).

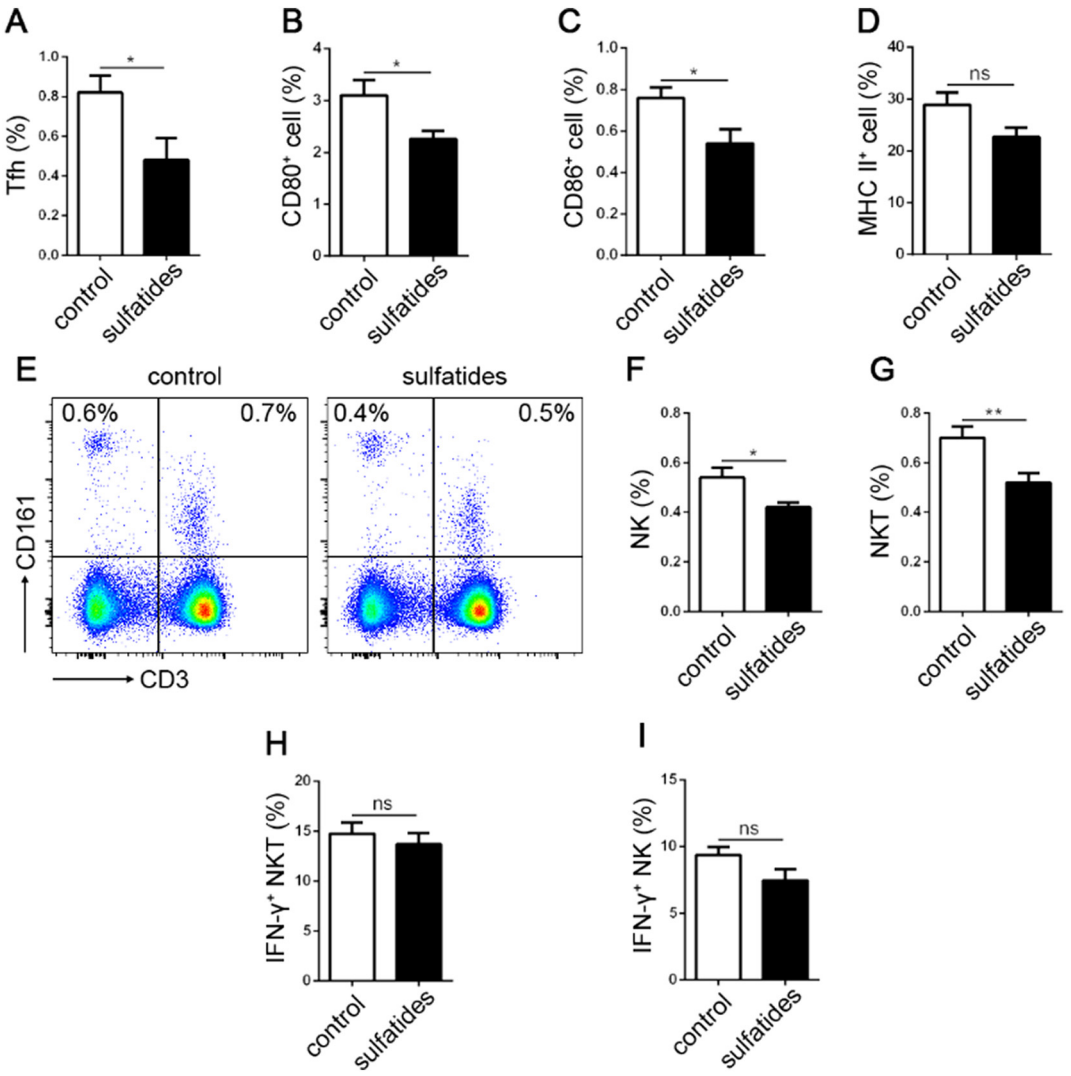

Fig. 3. Effects of sulfatide treatment on Tfh cells, antigen-presenting cells, NK cells and NKT cells in EAN.
Percentages of lymph node Tfh cells among $CD4^+$ T cells were reduced in sulfatide treated group (A). Sulfatide treatment suppressed lymph node CD80 and CD86 positive cells compared with control groups (3B and 3C). There was a trend but not statistical difference of decrease in MHC II positive cells in lymph nodes after sulfatide treatment (3D). The percentages of lymph node NK ($CD3^-CD161a^+$) cells and NKT ($CD3^+CD161a^+$) cells among MNCs were reduced in sulfatide treated group (E), while there were no difference in IFN-γ-secreting NK or NKT cells (F and G). These data come from two independent experiments. The results are expressed as mean ± SEM. ($*p < .05$, $**p < .01$).

pathogenesis of EAN (Zhang et al., 2013). Thus, the differences of Th1, Th2, Th17, and Treg cells in sulfatide-treated EAN rat lymph nodes were analyzed by flow cytometric analysis. Our data showed that the percentages of Th1 and Th17 cells among $CD4^+$ cells were decreased after sulfatide treatment (Fig. 2A, B). Meanwhile, tumor necrosis factor (TNF-α) positive cells among $CD4^+$ T cells were also decreased (Fig. 2C). However, there were no significant differences in the percentages of Th2 cells or interleukin-10 (IL-10) positive cells between the control group and sulfatide treatment group (Fig. 2D, E). Also, we did not observed any differences of Treg cells between these two groups (Fig. 2F). As a result, sulfatide treatment could upregulate the ratios of Treg cells to Th1 and to Th17 cells (Fig. 2G, H).

3.3. Sulftide treatment inhibits lymph node Tfh cells and antigen presenting cells

It has been shown that B cells play a dual role in EAN (Brunn et al., 2010). Tfh cells are the major T cell subset involved in helping B cell proliferation and differention. Thus we determined percentages of Tfh cells in different groups and found that sulfatides depressed the percentages of Tfh cells in lymph nodes.

Previous study demonstrated sulfatides ameliorates the pathogenesis of EAE by suppressing dentritic cells (Maricic et al., 2014), the impacts of sulfatides on lymph node antigen presenting cells were investigated. Our results showed rats treated with sulfatides exhibited reductions of lymph node CD80 and CD86 positive cells compared with control group (Fig. 3B, C). A trend but not statistical difference of decreases in MHC II positive cells in lymph nodes were also observed after sulfatide treatment (Fig. 3D).

3.4. Sulftide treatment inhibits NK and NKT cells

We also test the effects of sulfatide treatment on lymph node NK and NKT cells' functions. We found that the percentages of NK and NKT cells among lymph node MNCs were decreased after sulfatide treatment (Fig. 3E, F, G). However, we did not observe any difference in IFN-γ-secreting NK or NKT cells (Fig. 3H, I).

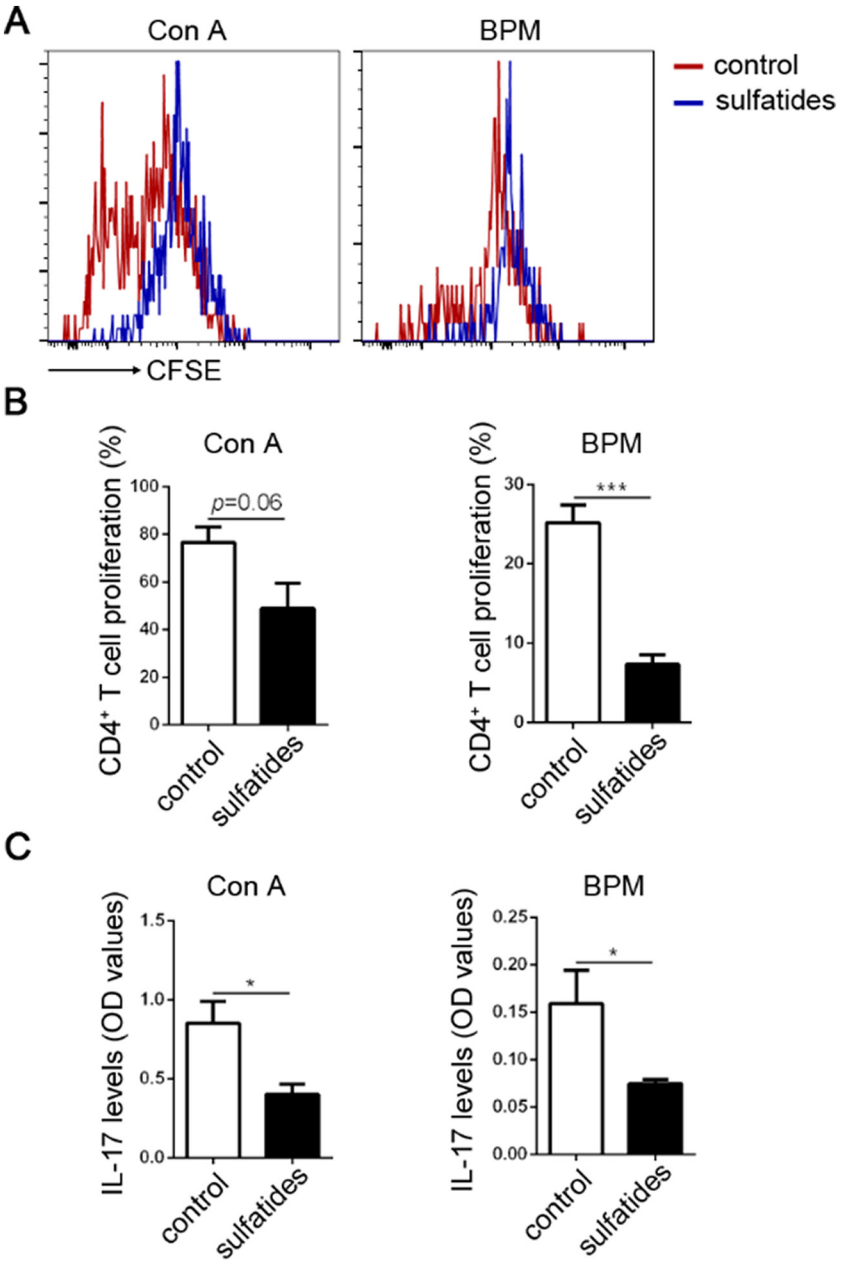

Fig. 4. Sulfatides significantly suppressed lymphocyte proliferation and IL-17 secretion.
Lymph node MNCs from both groups were obtained on day 13 p.i, and then cells were stained by CFSE and cultured in vitro in the presence of Con A or BPM for 72 h. $CD4^+$ T cell proliferation was detected by flow cytometry (A and B). The concentrations of IL-17 in the MNC culture supernatants in the presence of BPM or Con A were detected by ELISA (C). These data come from one independent experiments. The results are expressed as mean ± SEM. (*$p < .05$, **$p < .01$, ***$p < .001$).

3.5. Sulfatides inhibits T cell proliferation and IL17 secretion in vitro

To evaluate the effects of sulfatides on lymphocyte proliferation, lymphocytes from both group were stained by CFSE and cultured in vitro in the presence of Con A or BPM for 72 h. Compared with control group, $CD4^+$ T cell proliferations were inhibited after sulfatide treatment both in Con A and BPM stimulation conditions (Fig. 4A, B). The levels of IL-17 in MNCs' culture supernatants in the presence of Con A or BPM were also suppressed after sulfatide treatment (Fig. 4C).

3.6. Sulfatide treatment does not prevent inflammatory cell infiltration in peripheral nerve system

To investigate whether sulfatide treatment could prevent inflammatory cell infiltration in peripheral nerve system, the sciatic nerves of rats were harvested and stained with HE and immunohistochemistry. HE examination showed lots of inflammatory cells infiltrated in all groups and there was no difference among these groups (Fig. 5A). We also did not found any difference of macrophage cell infiltration as is show by immunohistochemical stain of macrophage cell biomarker, CD68 molecular (Fig. 5B).

4. Discussion

EAN is an animal model of GBS, which is mainly caused by autoreactive T cells and macrophages. In the present study, we found that sulfatide administration ameliorated EAN in Lewis rats induced with BPM. Sulfatide treatment delayed the onset times and decreased the maximal scores of EAN by down-regulating the proportions of both Th1 and Th17 cells in lymph nodes. Compared with control group, cells

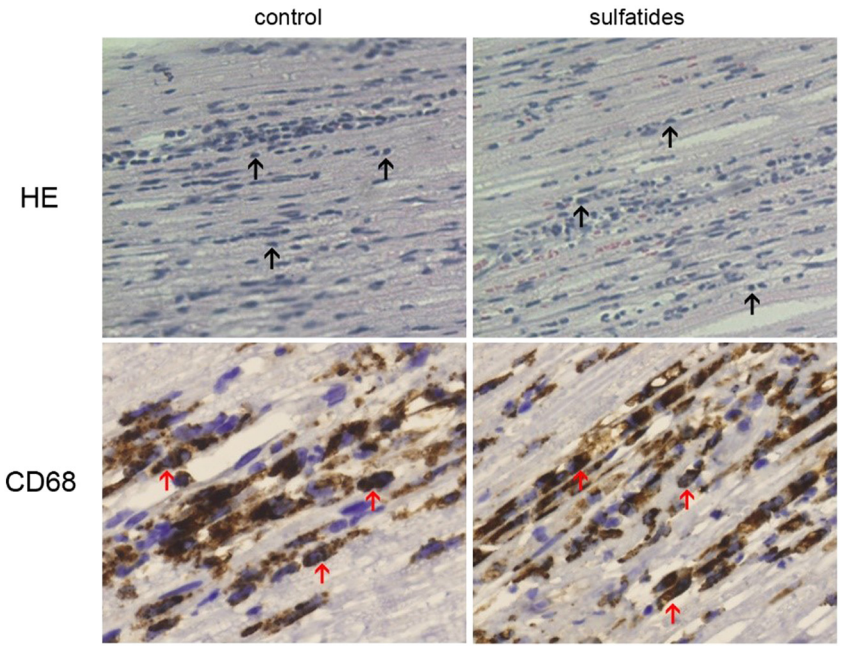

Fig. 5. Sulfatide treatment does not alter inflammatory cell or macrophage infiltration in sciatic nerves.
HE and immunohistochemical stain of sciatic nerve sections from control or sulfatide treated EAN rats. The black arrows indicated the infiltrating inflammatory cells in sciatic nerves. The red arrows indicated the infiltrating macrophage in sciatic nerves. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

from sulfatide-treated rats exhibited lower potential in proliferation and IL-17 secretion in the presence of BPM or Con A in vitro. Moreover, sulfatides also reduced the proportions of NK and NKT cells in lymph nodes.

NKT cells are a kind of T cells, which share some characteristics with NK cells. NKT cells mainly contains two subtypes (type I and type II NKT cells) according to differences in the nature of their T cell receptors (TCRs) (Godfrey et al., 2004). Whereas type I NKT cells are a main subset in the mouse, type II NKT cells are more prevalent in humans (Arrenberg et al., 2009; Exley et al., 2001). Studies of experimental animal models of autoimmune diseases and inflammations indicate that type I NKT cells have a greater propensity to be more pathogenic than protective, while type II NKT cells function predominantly to protect from inflammation and autoimmune disease (Kumar and Delovitch, 2014).

Sulfatide, which is a myelin-derived glycolipid antigen, can be presented to type II natural killer T (NKT) cells by CD1d molecules. Mice injected with sulfatides were significantly protected from EAE (Jahng et al., 2004). The protection from disease was attributed to the ability of sulfatides to inhibit the IFN-γ and IL-4 secretion by pathogenic T cells in the draining lymph nodes (Jahng et al., 2004). Besides, Sulfatide administration after the onset of disease ameliorated the ongoing chronic and relapsing form of EAE in SJL/J mice (Maricic et al., 2014). Sulfatide treatment inhibited Th1 and Th17 response, and led to inactivation of type I NKT cells, DCs and micoroglial cells (Maricic et al., 2014). Moreover, sulfatide-reactive type II NKT prevents inflammatory liver disease and diabetes by suppressing the activation of Type I NKT cells in mice (Halder et al., 2007; Subramanian et al., 2012). However, other researchers found that sulfatide-induced inhibition of T cell was CD1d-independent, and was mediated by galectin-4 (Mycko et al., 2014).

Up to now, there has been no report about the sulfatide-reactive type II NKT cells in rats. The effect and mechanism of sulfatides in EAN were also unclear. In this study, it was explored whether sulfatides could be protective in EAN Lewis rats. Indeed, we found that sulfatide administration ameliorated EAN in Lewis rats induced with BPM. Sulfatide treatment delayed the onset time and decreased the maximal scores of EAN. Although we were not able to distinguish type I from type II NKT cells, the lymph node NKT cells, which include both types of NKT cells, were found to be suppressed by sulfatide treatment. Because sulfatide-mediated type II NKT cell activation result in inhibition of type I NKT cells (Marrero et al., 2015), the decreases of NKT cells might be the net effect of sulfatide treatment. We also observed a reduction of NK cells, which might also be attributed to the suppression of type I NKT cells by activated type II NKT cells, because NK cells were activated following the activation of type I NKT (Carnaud et al., 1999).

Previous study has shown that Th1 cytokines including IL-12, IFN-γ and TNF-α contribute to disease progression in EAN (Bao et al., 2002). IL-17 in cerebrospinal fluid and plasma are raised in GBS (Li et al., 2012). The clinical symptoms of EAN could be ameliorated by decreasing Th1/Th17 cytokines including IFN-γ, TNF-α and IL17A (Xu et al., 2014). Consistent with the previous studies, we found that sulfatide administration inhibited Th1 and Th17 response in vivo in EAN, while there were no differences of Treg cells. As a result, sulfatide treatment could upregulate the ratios of Treg cells to Th1 and to Th17 cells (Fig. 2G, H). Ex vivo studies also showed that $CD4^+$ T cell proliferation and IL-17 production were inhibited after sulfatide treatment both in ConA and BPM stimulation conditions. All these results indicated sulfatides ameliorates EAN symptoms by regulating the balance of Th1/Th17 cells and Treg cells.

Taken together, our study showed that sulfatides alleviated EAN in Lewis rats induced with BPM by regulating the balance of Th1/Th17 cells and Treg cells. Since type II NKT cells are present in humans, sulfatides may have a therapeutic potential in human Guillain–Barré syndrome by activate type II NKT cells.

Conflict of interest

The authors declare no conflicts of interest.

Acknowledgment

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References

Arrenberg, P., Halder, R., Kumar, V., 2009. Cross-regulation between distinct natural killer T cell subsets influences immune response to self and foreign antigens. J. Cell.

Physiol. 218, 246–250.
Bao, L., Lindgren, J.U., van der Meide, P., Zhu, S., Ljunggren, H.G., Zhu, J., 2002. The critical role of IL-12p40 in initiating, enhancing, and perpetuating pathogenic events in murine experimental autoimmune neuritis. Brain Pathol. 12, 420–429.
Brunn, A., Utermohlen, O., Sanchez-Ruiz, M., Montesinos-Rongen, M., Blau, T., Schluter, D., et al., 2010. Dual role of B cells with accelerated onset but reduced disease activity in P0(1)(0)(6)(−)(1)(2)(5)-induced experimental autoimmune neuritis of IgH (0)(/)(0) mice. Acta Neuropathol. 120, 667–681.
Buschard, K., Hanspers, K., Fredman, P., Reich, E.P., 2001. Treatment with sulfatide or its precursor, galactosylceramide, prevents diabetes in NOD mice. Autoimmunity 34, 9–17.
Carnaud, C., Lee, D., Donnars, O., Park, S.H., Beavis, A., Koezuka, Y., et al., 1999. Cutting edge: Cross-talk between cells of the innate immune system: NKT cells rapidly activate NK cells. J. Immunol. 163, 4647–4650.
Coetzee, T., Fujita, N., Dupree, J., Shi, R., Blight, A., Suzuki, K., et al., 1996. Myelination in the absence of galactocerebroside and sulfatide: normal structure with abnormal function and regional instability. Cell 86, 209–219.
Dong, C., Palladino, S.P., Helton, E.S., Ubogu, E.E., 2016. The pathogenic relevance of alphaM-integrin in Guillain-Barre syndrome. Acta Neuropathol. 132, 739–752.
Exley, M.A., Tahir, S.M., Cheng, O., Shaulov, A., Joyce, R., Avigan, D., et al., 2001. A major fraction of human bone marrow lymphocytes are Th2-like CD1d-reactive T cells that can suppress mixed lymphocyte responses. J. Immunol. 167, 5531–5534.
Godfrey, D.I., MacDonald, H.R., Kronenberg, M., Smyth, M.J., Van Kaer, L., 2004. NKT cells: what's in a name? Nat. Rev. Immunol. 4, 231–237.
Halder, R.C., Aguilera, C., Maricic, I., Kumar, V., 2007. Type II NKT cell-mediated anergy induction in type I NKT cells prevents inflammatory liver disease. J. Clin. Invest. 117, 2302–2312.
Jahng, A., Maricic, I., Aguilera, C., Cardell, S., Halder, R.C., Kumar, V., 2004. Prevention of autoimmunity by targeting a distinct, noninvariant CD1d-reactive T cell population reactive to sulfatide. J. Exp. Med. 199, 947–957.
Kumar, V., Delovitch, T.L., 2014. Different subsets of natural killer T cells may vary in their roles in health and disease. Immunology 142, 321–336.
Li, S., Yu, M., Li, H., Zhang, H., Jiang, Y., 2012. IL-17 and IL-22 in cerebrospinal fluid and plasma are elevated in Guillain-Barre syndrome. Mediat. Inflamm. 2012, 260473.
Maricic, I., Halder, R., Bischof, F., Kumar, V., 2014. Dendritic cells and anergic type I NKT cells play a crucial role in sulfatide-mediated immune regulation in experimental autoimmune encephalomyelitis. J. Immunol. 193, 1035–1046.
Marrero, I., Ware, R., Kumar, V., 2015. Type II NKT cells in inflammation, autoimmunity, microbial immunity, and cancer. Front. Immunol. 6, 316.
Maurer, M., Gold, R., 2002. Animal models of immune-mediated neuropathies. Curr. Opin. Neurol. 15, 617–622.
Mycko, M.P., Sliwinska, B., Cichalewska, M., Cwiklinska, H., Raine, C.S., Selmaj, K.W., 2014. Brain glycolipids suppress T helper cells and inhibit autoimmune demyelination. J. Neurosci. 34, 8646–8658.
Norton, W.T., Poduslo, S.E., 1973. Myelination in rat brain: method of myelin isolation. J. Neurochem. 21, 749–757.
Rhost, S., Lofbom, L., Mansson, J., Lehuen, A., Blomqvist, M., Cardell, S.L., 2014. Administration of sulfatide to ameliorate type I diabetes in non-obese diabetic mice. Scand. J. Immunol. 79, 260–266.
Subramanian, L., Blumenfeld, H., Tohn, R., Ly, D., Aguilera, C., Maricic, I., et al., 2012. NKT cells stimulated by long fatty acyl chain sulfatides significantly reduce the incidence of type 1 diabetes in nonobese diabetic mice [corrected]. PLoS One 7, e37771.
Takahashi, T., Suzuki, T., 2012. Role of sulfatide in normal and pathological cells and tissues. J. Lipid Res. 53, 1437–1450.
Wang, X., Zheng, X.Y., Ma, C., Wang, X.K., Wu, J., Adem, A., et al., 2014. Mitigated tregs and augmented Th17 cells and cytokines are associated with severity of experimental autoimmune neuritis. Scand. J. Immunol. 80, 180–190.
Wang, F.J., Cui, D., Qian, W.D., 2018. Therapeutic effect of CD4+CD25+ regulatory T cells amplified in vitro on experimental autoimmune neuritis in rats. Cell. Physiol. Biochem. 47, 390–402.
Xu, H., Li, X.L., Yue, L.T., Li, H., Zhang, M., Wang, S., et al., 2014. Therapeutic potential of atorvastatin-modified dendritic cells in experimental autoimmune neuritis by decreased Th1/Th17 cytokines and up-regulated T regulatory cells and NKR-P1(+) cells. J. Neuroimmunol. 269, 28–37.
Zhang, H.L., Zheng, X.Y., Zhu, J., 2013. Th1/Th2/Th17/Treg cytokines in Guillain-Barre syndrome and experimental autoimmune neuritis. Cytokine Growth Factor Rev. 24, 443–453.
Zhang, M., Liu, R.T., Zhang, P., Zhang, N., Yang, C.L., Yue, L.T., et al., 2017. Parthenolide inhibits the initiation of experimental autoimmune neuritis. J. Neuroimmunol. 305, 154–161.