Neurochemistry International 130 (2019) 104320

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Adrenergic control of lymphocyte trafficking and adaptive immune responses

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ARTICLE INFO

Keywords:
Adrenergic nerve
β_2-adrenergic receptor
Lymphocyte trafficking
Adaptive immune response
Diurnal rhythm
Inflammation

ABSTRACT

Since the beginning of the last century, substantial evidence has suggested that various aspects of the immune system are influenced by the activity of the nervous system. However, the cellular and molecular basis for the neural control of immune responses has emerged only in the past decade. Recent studies have shown that adrenergic nerves control trafficking of immune cells through cell-type-specific mechanisms. Activation of the β_2-adrenergic receptor expressed on lymphocytes enhances signals mediated by a particular set of chemokine receptors, and consequently inhibits their exit from lymph nodes. This mechanism is involved in the diurnal variation of adaptive immune responses and the progression of inflammatory diseases. In the present review, we focus on the role of adrenergic nerves in the control of lymphocyte trafficking and adaptive immune responses in physiological and pathological conditions.

1. Introduction

The primary function of the sympathetic nervous system is to mediate "fight-or-flight" responses represented by increased heart rate and blood pressure (McCorry, 2007). The sympathetic nervous system consists of pre- and post-synaptic neurons. The presynaptic neurons arise from the thoracic and lumbar regions of the spinal cord and form synapses on postsynaptic neurons in sympathetic ganglia that are aligned along the spine. The postsynaptic neurons are adrenergic, which release noradrenaline from their termini. Noradrenaline induces cellular responses through G protein-coupled adrenergic receptors that are classified into five subclass: α1, α2, β1, β2, and β3.

Studies during 1980s and 1990s provided first mechanistic insights into the control of immune responses by adrenergic nerves. Morphological studies demonstrated that both primary and secondary lymphoid organs are innervated by adrenergic nerves, establishing the anatomical connection between the sympathetic nervous system and the immune system (Felten et al., 1985). Notably, in secondary lymphoid organs, including spleen and lymph nodes (LNs), adrenergic nerves terminate around B cell follicles. It was also reported that noradrenaline binds to the surface of lymphocytes through the β_2-adrenergic receptor (β_2AR) (Brodde et al., 1981). Additionally, stimulation of β_2AR was found to regulate differentiation and functions of helper T (Th) cells in *vitro* (Ramer-Quinn et al., 1997; Sanders et al., 1997). These findings indicated that adrenergic inputs could directly act on immune cells and alter their behaviors.

The cellular and molecular basis for adrenergic control of immune responses has emerged over the past decade. Although a study showed that adrenergic nerves control emigration of neutrophils from blood to peripheral tissues by modulating the expression of chemokines and adhesion molecules in vascular endothelial cells (Scheiermann et al., 2012), it had remained unclear how the inputs from adrenergic nerves influence trafficking of lymphocytes among lymphoid organs and peripheral tissues. Our recent study demonstrated that inputs from adrenergic nerves control lymphocyte recirculation through LNs in a cell-intrinsic manner. This marks a sharp contrast to the role of adrenergic nerves in controlling neutrophil trafficking that depends on the alternation of environmental cues (Nakai et al., 2014). Based on our recent findings, we here discuss the role of adrenergic nerves in the control of lymphocyte trafficking and adaptive immune responses in physiological and pathological conditions.

2. Adrenergic control of lymphocyte egress from LNs

It has been known that adrenergic stimulation induces a rapid increase of granulocyte numbers, but decrease of lymphocyte numbers in blood (Benschop et al., 1996). Because lymphocyte predominantly express β_2AR among five subclasses of adrenergic receptors (Sanders, 2012), we investigated the role of β_2AR in the regulation of lymphocyte trafficking. As expected, intravenous administration of a selective β_2AR

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https://doi.org/10.1016/j.neuint.2018.10.017
Received 30 June 2018; Received in revised form 9 October 2018; Accepted 17 October 2018
Available online 19 October 2018
0197-0186/

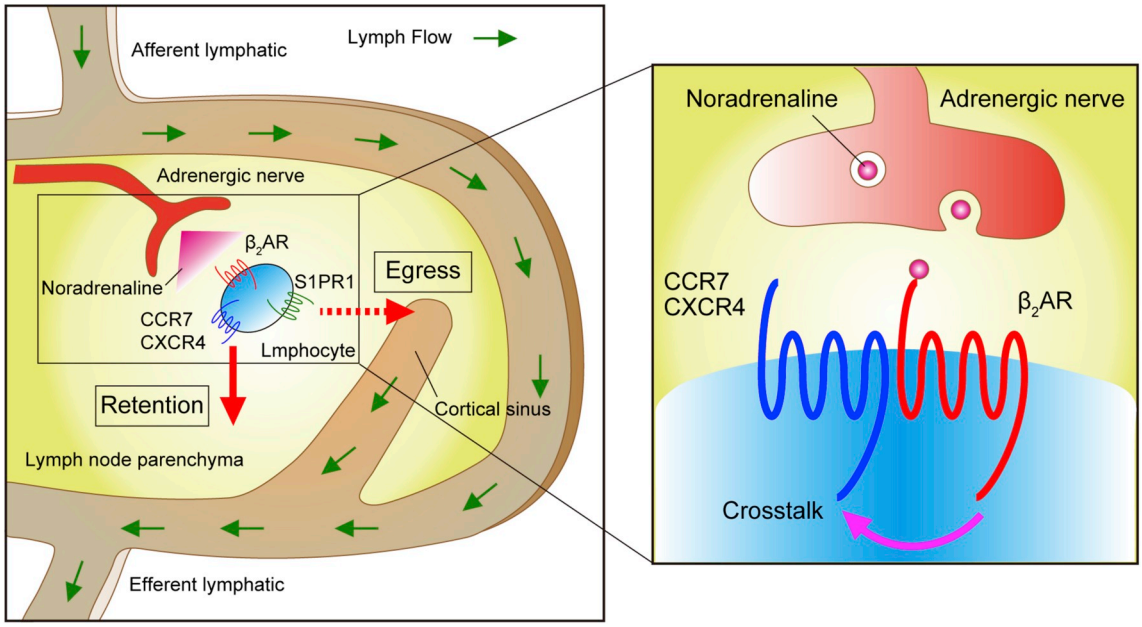

Fig. 1. Adrenergic control of lymphocyte trafficking through LNs. Inputs from adrenergic nerves through lymphocyte β_2AR enhance retention promoting signals mediated by CCR7 and CXCR4, and consequently inhibit lymphocyte egress from LNs.

agonist clenbuterol rapidly decreased blood lymphocyte numbers in mice (Nakai et al., 2014). Additionally, we found that agonist stimulation of β_2AR induced a concomitant reduction of lymphocyte numbers in lymph. The lymphopenic effect was predominant in B cells compared with T cells, which was consistent with the highest expression of β_2AR in B cells among murine lymphocytes. The effect of the β_2AR agonist on circulating lymphocyte numbers was abrogated in irradiated wild-type mice reconstituted with β_2AR-deficient bone marrow cells, which lacked β_2AR expression in the hematopoietic compartment. In contrast, irradiated β_2AR-deficient mice receiving wild-type bone marrow cells, which lacked β_2ARs in the non-hematopoietic compartment, responded normally to the β_2AR agonist. These observations suggested that β_2AR stimulation causes lymphopenia through cell-intrinsic mechanisms.

Continuous recirculation of lymphocytes through lymphoid organs is important for immunosurveillance of the entire body. After entering a LN from blood, lymphocytes spend several hours to survey antigens in the LN, exit into lymph and eventually return to the blood stream (Cyster and Schwab, 2012). Therefore, we speculated that the reduction of lymphocyte numbers in blood and lymph after β_2AR stimulation might result from inhibition of lymphocyte egress from LNs. To test this hypothesis, we treated mice with the β_2AR agonist together with neutralizing antibodies against α4 and αL integrins, which are essential for lymphocyte entry to LNs. After lymphocyte entry is blocked, the numbers of lymphocytes in LNs are decreased over time because of their egress into lymph without any supply from blood. Thus, the frequency of lymphocyte egress from LNs can be assessed by measuring the extent of decrease in lymphocyte numbers (Lo et al., 2005). We found that treatment with the β_2AR agonist attenuated the reduction of lymphocyte numbers in LNs (Nakai et al., 2014), indicating that β_2AR stimulation inhibits lymphocyte egress from LNs.

We next examined whether physiological inputs from adrenergic nerves are involved in the control of lymphocyte egress from LNs. We found that β_2AR-deficient lymphocytes exit LNs more rapidly than β_2AR-sufficient lymphocytes (Nakai et al., 2014). Additionally, depletion of adrenergic nerve fibers by 6-hydroxydopamine promoted LN egress of lymphocytes. These findings suggested that physiological levels of adrenergic inputs through β_2AR contribute to retention of lymphocytes in LNs by limiting their egress from LNs. However, β_2AR-mediated signals did not affect lymphocyte entry to LNs.

3. Crosstalk between β_2AR and chemokine receptors

LN egress of lymphocytes strongly depends on sphingoshine-1-phosphate receptor type 1 (S1PR1), through which lymphocytes sense high concentration of S1P in lymph (~100 nmol/L) compared with LN parenchyma (~1 nmo/L) to exit LNs. S1PR1 acts to overcome retention-promoting signals mediated by CCR7, CXCR4, and possibly additional other chemoattractant receptors (Pham et al., 2008; Schmidt et al., 2013). The frequency of lymphocyte egress from LNs appears to be determined by the relative strength of egress-promoting signals versus retention-promoting signals. Thus, we hypothesized that β_2AR-mediated signals might modulate responsiveness of these chemoattractant receptors. Treatment of lymphocytes with the β_2AR agonist enhanced CCR7-and CXCR4-mediated activation of a small GTPase Rac1, whereas S1PR1-mediated Rac1 activation was not influenced by β_2AR stimulation (Nakai et al., 2014). The treatment with the β_2AR agonist alone did not activate Rac1 in lymphocytes, suggesting signaling crosstalk from β_2AR to the chemokine receptors. Consistently, β_2AR stimulation promoted lymphocyte chemotaxis mediated by CCR7 and CXCR4, but not S1PR1. These findings suggested that activation of β_2AR preferentially enhances retention-promoting signals through CCR7 and CXCR4. These chemokine receptors as well as β_2AR are G protein-coupled receptors (GPCRs). Because previous studies showed that different types of GPCRs form heteromeric complexes on the cell surface and mutually control their signals (Fribourg et al., 2011; Gonzalez-Maeso et al., 2008), we tested whether there is a physical interaction between β_2AR and CCR7 or CXCR4. Notably, β_2AR was co-localized on the cell surface and co-immunoprecipitated together with CCR7 or CXCR4, suggesting that β_2AR forms heteromeric complexes with these chemokine receptors (Nakai et al., 2014). We speculate that the physical interaction with β_2AR might be the key to the selective signal enhancement of the chemokine receptors. The effect of β_2AR stimulation on lymphocyte egress from LNs was attenuated by CCR7 deficiency in lymphocytes or pharmacological blockade of CXCR4, confirming that the β_2AR-mediated lymphocyte retention in LNs largely depends on CCR7 and CXCR4 (Nakai et al., 2014). Collectively, the above findings established a model for adrenergic control of lymphocyte trafficking, in which inputs from adrenergic nerves to β_2AR expressed on lymphocytes inhibit their egress from LNs by enhancing retention-promoting signals through CCR7 and CXCR4 (Fig. 1).

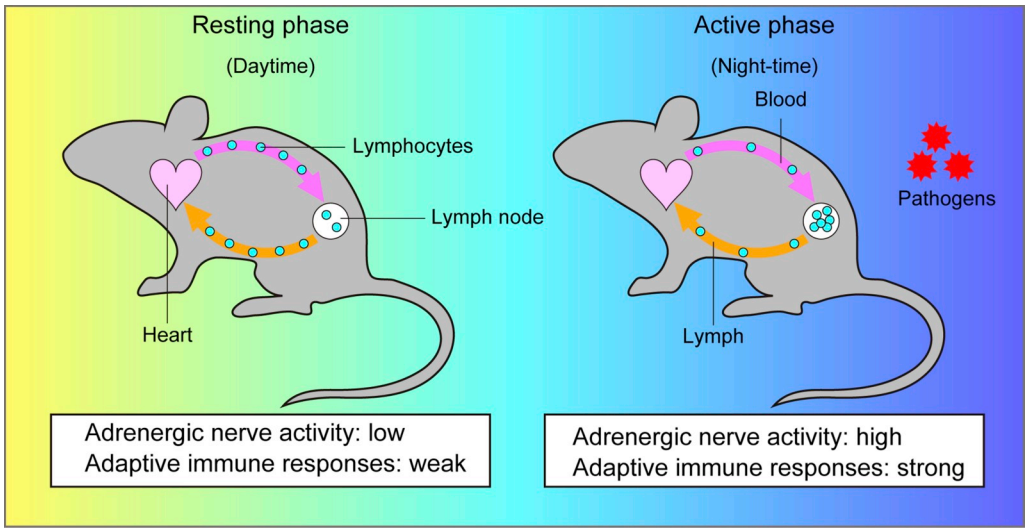

Fig. 2. Diurnal control of lymphocyte trafficking and adaptive immune responses by adrenergic nerves. Neural inputs through β_2AR generate the diurnal variation of lymphocyte egress from LNs and adaptive immune responses. During the period of high adrenergic nerve activity, lymphocyte retention in LNs is enhanced, which promotes induction of the adaptive immune response in LNs. This diurnal variation of lymphocyte trafficking might be favorable to maximize the efficiency of host defense when encounters with pathogens are more likely to occur.

However, further studies are required to reveal the molecular mechanisms of the crosstalk between β_2AR and the chemokine receptors.

4. Diurnal rhythm of lymphocyte trafficking through LNs

The activity of adrenergic nerves exhibits a circadian rhythm according to the rest-activity cycle of the species. The release of noradrenaline from adrenergic nerves increases during the daytime in human, whereas it peaks during the night-time in rodents. Notably, previous studies demonstrated that blood lymphocyte numbers decreased during the period of high adrenergic activity in both human and mice (Haus and Smolensky, 1999; Scheiermann et al., 2012; Suzuki et al., 1997). Additionally, we found in mice that lymphocyte numbers in lymph also displayed a similar pattern of diurnal variations (Suzuki et al., 2016). In contrast, lymphocyte numbers in murine LNs fluctuated in antiphase to those in blood and lymph. The amount of noradrenaline in murine LN was increased toward night-time (Suzuki et al., 2016). Thus, the sequestration of lymphocytes in LNs from blood and lymph coincided with the rise of adrenergic tone. This was consistent with our model in which inputs from adrenergic nerves inhibit lymphocyte egress from LNs (Nakai et al., 2014). To examine whether the frequency of lymphocyte egress from LNs shows diurnal variations, we blocked lymphocyte entry to LNs by treatment with the integrin-neutralizing antibodies during the daytime and night-time. The numbers of lymphocytes remaining in LNs were higher when entry blockade was performed in the night-time (Suzuki et al., 2016), indicating that LN egress of lymphocytes is restricted during the period of high adrenergic nerve activity. The diurnal variation of lymphocyte egress from LNs was diminished by chemical depletion of adrenergic nerves and deficiency of β_2AR expressed on lymphocytes, suggesting that the diurnal variation of lymphocyte trafficking depends on inputs from adrenergic nerves to lymphocyte β_2AR. Although the involvement of CCR7 and CXCR4 signaling in diurnal control of lymphocyte dynamics has not been directly demonstrated, we speculate that the retention-promoting signals mediated by these chemokine receptors might oscillate during a day in response to adrenergic inputs.

5. Diurnal rhythm of adaptive immune responses

Lymphocytes specific for a given antigen are very rare (estimated to be less than 10 cells per LN), and their population size dictates the magnitude of adaptive immune responses (Moon et al., 2007). Therefore, we hypothesized that the sequestration of lymphocytes in LNs during the active phase might increase the chance of antigen encounter by lymphocytes and potentiate adaptive immune responses. As an approach to favor the likelihood that an antigen is directly delivered to the draining LN within a minimal time lag after injection and supplied to the LN for a limited period of time, we immunized mice in the ear by intradermal injection of a soluble antigen in the form of a non-viscous emulsion containing adjuvants (Pape et al., 2007). Mice were immunized in the daytime and night-time when lymphocyte numbers in LNs exhibited a trough and peak in a day, respectively. We found that night-time immunization enhanced production of antigen-specific antibodies over the daytime immunization, which was accompanied by increased generation of germinal center B cells and follicular helper T cells in the ear-draining LN (Suzuki et al., 2016). These observations suggest that the induction of the humoral immune response in LNs is promoted during the period of high adrenergic nerve activity. Depletion of adrenergic nerves and deficiency of β_2AR abrogated the nocturnal enhancement of the humoral immune response, suggesting that inputs from adrenergic nerves contribute to the diurnal variation of adaptive immunity (Suzuki et al., 2016). Although previous studies showed that β_2AR stimulation had some impacts on B cell responses *in vivo* and *in vitro* (Sanders, 2012), our results obtained from β_2AR-deficient mice showed that β_2AR deficiency did not affect the baseline level of the primary humoral response. Overall, our findings suggested that inputs from adrenergic nerves to β_2ARs generate the diurnal variation of lymphocyte recirculation through LNs, which is reflected in the magnitude of the adaptive immune response (Fig. 2). Blood lymphocyte numbers in humans fluctuate in antiphase to those in mice (Haus and Smolensky, 1999; Suzuki et al., 1997). Considering the fact that adrenergic neve activity in humans and mice shows an opposing oscillation in a day (Suzuki et al., 1997), the same mechanism might operate to generate diurnal variations of lymphocyte trafficking in both humans and mice.

A recent study demonstrated in mice that the core clock protein BMAL1 (brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1) in lymphocytes regulates the expression of CCR7 and S1PR1 at the transcriptional level and contributes to rhythmic lymphocyte recirculation during a day (Druzd et al., 2017). This study suggested that higher CCR7 expression promotes lymphocyte entry to LNs during the night-time, whereas higher S1PR1 expression facilitates lymphocyte egress from LNs during the day time. The sympathetic nervous system plays an important role in synchronization of peripheral circadian clocks through cyclical release of noradrenaline (Dibner et al., 2010). Therefore, adrenergic nerves may contribute to diurnal lymphocyte trafficking directly through β_2AR-mediated enhancement of chemokine receptor signals (Nakai et al., 2014) and by synchronizing the molecular clocks in lymphocytes. It is possible that lymphocyte-intrinsic circadian clocks might also affect antigen priming of B cells

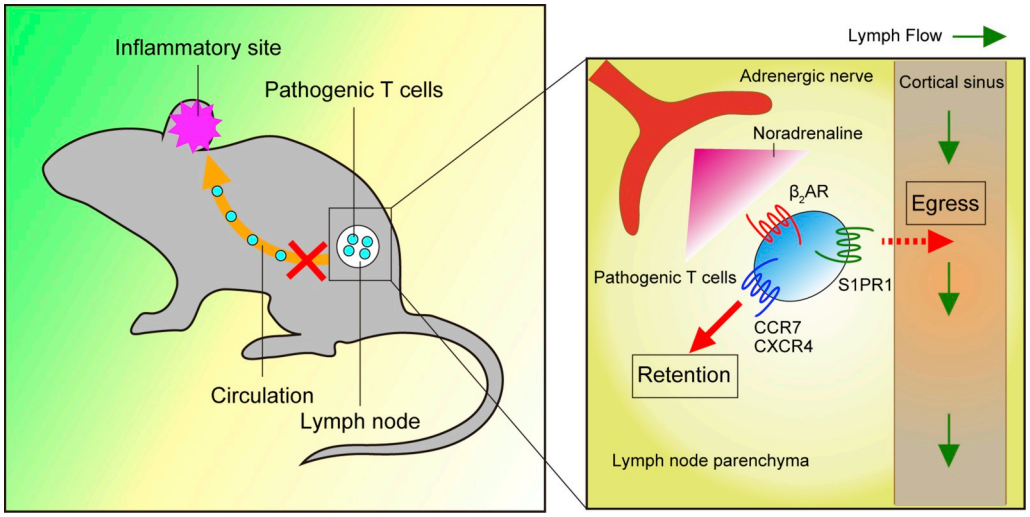

Fig. 3. Adrenergic control of T-cell mediated inflammation. Activation of β_2AR inhibits LN egress of pathogenic T cells and prevents their invasion to inflammatory sites, which could reduce inflammatory responses at the sites.

and $CD4^+$ T cells, and their respective differentiation to germinal center B cells and follicular helper T cells, as demonstrated in the differentiation of interleukin-17-producing Th cells (Yu et al., 2013).

Innate immune cells also exhibit diurnal variation in their trafficking. Inputs from adrenergic nerves were shown to generate a diurnal rhythm in tissue entry of neutrophils by modulating the expression of adhesion molecules and chemokines in vascular endothelial cells (Scheiermann et al., 2012). Neutrophil entry to tissues peaked during the night-time in mice, which was accompanied by more severe tissue inflammation than in the daytime. The core clock component BMAL1 in pulmonary epithelial cells was shown to regulate the transcription of a neutrophil-attracting chemokine CXCL5 and establish circadian oscillation in neutrophil recruitment to the lung (Gibbs et al., 2014). Circulation of inflammatory monocytes also exhibited circadian rhythmicity under the control of BMAL1, which influenced the susceptibility to bacterial infection (Nguyen et al., 2013).

Previous studies, including the above, have suggested that the innate immune system prepares for higher risk of infection during the active phase in a day by recruiting myeloid cells into peripheral tissues and up-regulating pathogen sensors (Curtis et al., 2015; Silver et al., 2012). Our study showed that high adrenergic nerve activity promotes the induction of the humoral immune responses in LNs, suggesting that the adaptive immune system is also poised to mount higher responses during the period of activity. The synchronization of both arms of the immune system might have evolved to efficiently initiate host defense responses when encounters with pathogens are more likely to occur. The time-dependent differences in immune responses can be exploited in clinical settings, such that vaccination during immunologically active phase might ensure potent protection against infections. Indeed, a recent study showed that influenza vaccination in the morning, the period of high adrenergic nerve activity in humans, induced higher antibody responses compared with afternoon vaccination (Long et al., 2016).

6. Adrenergic control of T cell-mediated inflammation

The influences of adrenergic inputs on inflammation are complex, as adrenergic nerves were shown to play both protective and detrimental roles in inflammatory diseases in a context-dependent manner (Bellinger et al., 2008). However, it appears that signals through β_2AR generally act to suppress T cell-mediated inflammatory diseases, including rheumatoid arthritis and multiple sclerosis (MS). An early study showed that administration of tri- or tetracyclic antidepressants or L-dopa, which leads to increase the level of noradrenaline, ameliorated the clinical symptoms of MS (Berne-Fromell et al., 1987). Consistent with this observation, animal studies demonstrated that treatment with β_2AR agonists suppressed experimental autoimmune encephalomyelitis (EAE), an animal model of MS (Chelmicka-Schorr et al., 1989; Wiegmann et al., 1995). However, mechanisms by which signals through β_2AR alter the pathogenesis had been poorly understood. To confirm the role of β_2AR-mediated signals in inflammatory diseases, we employed EAE and delayed-type hypersensitivity (DTH) responses in the skin as representative models of T cell-mediated inflammation. As expected, the clinical symptom of EAE and skin DTH responses in mice were ameliorated by administration of the β_2AR agonist at the disease onset (Nakai et al., 2014). Additionally, in both models, β_2AR-deficient mice developed more severe inflammation compared with wild-type mice, reinforcing the notion that signals through β_2AR act to suppress T cell-mediated inflammation.

It is well established that lymphocyte trafficking plays important roles in the pathogenesis of inflammatory diseases (Steinman, 2014). Indeed, the functional S1PR1 antagonist FTY720 (fingolimod/Gilenya) has been proven to be effective for the treatment of MS, and approved for clinical use. FTY720 is thought to inhibit egress of autoreactive T cells from LNs and consequently their migration to the target organ (Brinkmann et al., 2010). Thus, LN egress of lymphocyte is an important therapeutic target in T cell-mediated inflammatory diseases. Based on our findings, we hypothesized that β_2AR-mediated inhibition of LN egress of pathogenic T cells might suppress inflammation at the peripheral sites. To test this possibility, we tracked the migration of antigen-specific T cells in the skin DTH model. We found that signals through β_2AR inhibited LN egress of antigen-primed T cells of a central memory phenotype, but not effector memory phenotype (Nakai et al., 2014). The preferential retention of central memory T cells might result from their higher expression of β_2AR (Nakai et al., 2014). Accordingly, β_2AR-mediated signals reduced the numbers of antigen-specific T cells in the circulation and inflammatory sites. It has been suggested that central memory T cells are reactivated by dendritic cells at the inflammatory sites and undergo local differentiation to effector cells to induce inflammation (Kivisakk et al., 2004). Therefore, our findings suggest that β_2AR activation inhibits LN egress of pathogenic T cells and their migration to inflamed peripheral tissues, which might prevent the inflammatory responses (Fig. 3).

Although we demonstrated that β_2AR-mediated effects on lymphocyte trafficking might contribute to the attenuated inflammatory responses, the direct causal connection has not been established. Recent studies showed that stimulation of β_2AR expressed on dendritic cells reduced their capacities for antigen presentation (Herve et al., 2013) and production of pro-inflammatory cytokines, including interleukin-6,

-12, and −23 (Nijhuis et al., 2014). Therefore, β_2AR-mediated alternation of dendritic cell functions might impair reactivation of central memory T cells at inflammatory sites. We speculate that combination of multiple immunomodulating effects of β_2AR signals might act to suppress inflammatory responses. We cannot exclude the possibility that the aforementioned effects on Th cell differentiation might affect the pathology of T cell-mediated inflammation. However, because β_2AR agonist stimulation or β_2AR deficiency did not alter antigen-induced differentiation of Th cells (Nakai et al., 2014), it is unlikely that modulation of Th cell differentiation could suppress inflammation at least in our experimental systems.

7. Conclusion

Our recent studies revealed the mechanism for adrenergic control of lymphocyte trafficking and showed the significance of this mechanism in physiological and pathological conditions. In this regard, our findings provide additional insights into immune regulation by the nervous system. However, our study poses an apparent discrepancy; high adrenergic nerve activity could promote lymphocyte priming in LN but suppress lymphocyte-driven inflammation in peripheral tissues. We speculate that the circadian rhythm of adrenergic nerve activity might hold the key to reconcile these opposing actions of adrenergic nerves on adaptive immune responses. As described above, the enhanced retention of lymphocytes in LNs during the period of high adrenergic activity is favorable for efficient induction of adaptive immune responses in the physically active phase when the chance of encounter with pathogens is increased. Conversely, decreased adrenergic nerve activity allows lymphocytes to egress from LNs and access peripheral tissues, which would facilitate recognition and elimination of pathogens at the sites of infection. Therefore, adrenergic nerves might coordinate adaptive immune responses in LNs and peripheral tissues to maximize the efficiency of host defense by generating the daily rhythm of lymphocyte recirculation.

Conflicts of interest

None declared.

Acknowledgement

We thank members of the Suzuki laboratory for helpful comments on the article. Our studies described in this article were supported by grants from the Japan Society for the Promotion of Science to K.S. (JP15H05656 and JP15K15153) and to A.N. (JP16K19154); the Ministry of Education, Culture, Sports, Science and Technology, Japan to K.S. (JP15H01157).

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