



Adrenergic regulation of immune cell function and inflammation

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Abstract

The sympathetic nervous system integrates the functions of multiple organ systems by regulating their autonomic physiological activities. The immune system is regulated both locally and systemically by the neurotransmitters epinephrine and norepinephrine secreted by the adrenal gland and local sympathetic neurons. Immune cells respond by activation of adrenergic receptors, primarily the β 2-adrenergic receptor, which signal through heterotrimeric G-proteins. Depending upon the cell type, adrenergic signaling regulates a variety of functions in immune cells ranging from cellular migration to cytokine secretion. Furthermore, due to the diurnal oscillation of systemic norepinephrine levels, various immune functions follow a circadian rhythmic pattern. This review will highlight recent advances in our understanding of how the sympathetic nervous system regulates both innate and adaptive immune functions and how this regulation is linked to circadian rhythms.

Systemic pathways of adrenergic regulation

The sympathetic nervous system controls a myriad of biological processes, and, perhaps, the most well-studied regulators of this system are the neurotransmitters epinephrine (E) and norepinephrine (NE). They both bind and signal through the adrenergic class of G-protein-coupled receptors whose members are differentially expressed on various cells and tissues throughout the body. The receptors are divided into α - and β -family members, and their selective expression, coupled to unique G- α downstream second messengers, conveys unique signals to individual cell types. In this way, E and NE can simultaneously regulate distinct functions in many organ systems.

The immune system is intimately connected to the sympathetic nervous system [1]. Early studies demonstrated that both primary and secondary lymphoid tissues are innervated by post-ganglionic sympathetic nerve fibers that predominantly secrete NE as their primary neurotransmitter [2–12]. Immune cells come in direct contact with the dendrites of these neurons. Both innate and adaptive immune cells express

adrenergic receptors, primarily the β 2-adrenergic receptor (ADRB2), enabling them to directly respond to the sympathetic nervous system [12].

Sympathetic nerves secrete NE in response to pathogenic organisms (reviewed in [12]). While signaling through pattern recognition receptors (PRRs) promotes inflammatory cytokine secretion from antigen-presenting cells, neurons themselves express various Toll-like receptors (TLRs), enabling them to respond directly to certain pathogen-associated molecular patterns (PAMPs) [13–19]. Both viral and bacterial infections elicit bursts of NE secretion from sympathetic neurons, and PAMPs such as lipopolysaccharide (LPS) drive NE release within seconds upon exposure. This intimate relationship between sympathetic neurons and immune cells creates a direct conversation between the two organ systems and establishes reciprocal pathways of regulation. In general, adrenergic signaling is immunosuppressive in nature and has been reviewed extensively. In this review, we will provide an update on novel and recent research into adrenergic regulatory pathways that impact immune function and homeostasis.

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Control of innate responses—antigen presentation, innate sensing, and cytokine secretion

Inflammation is a delicately balanced process that utilizes cytotoxic elements to sterilize tissues, and collateral damage is a necessary but dangerous component. Without checks and

balances, immune cells proceed without limits to destroy cells and tissues within infected areas, and various immune suppressors are in place to limit this destruction. Immune tolerance and suppression collectively limit the magnitude of inflammation, which is necessary for overall survival. Along with well-characterized mechanisms such as central and peripheral tolerance, checkpoint inhibition, and cytokine-mediated suppression, adrenergic signaling is a potent suppressive pathway that limits both inflammatory cytokine signaling and priming of T cells. In addition to the known effects of glucocorticoids, early studies demonstrated that both E and synthetic β 2-agonists could dramatically suppress TNF- α secretion in macrophages responding to LPS [20].

We and others have demonstrated that ADRB2 signaling suppresses inflammatory cytokine secretion from both macrophages and dendritic cells in response to LPS [21, 22]. In our study, we found that this pathway was not exclusive to a TLR4 agonist, as β -agonists, including NE, suppressed virtually all TLR pathways encompassing both intracellular and extracellular sensors [23]. While some components of this pathway may be directly blocking NF- κ B activation [24], IL-10, highly induced by NE, acts in an autocrine fashion to block TNF- α and other inflammatory cytokines. Consequently, deletion of the ADRB2 in macrophages and dendritic cells leads to a severe loss of IL-10 secretion and elevated systemic TNF- α levels in vivo in response to LPS. In fact, ADRB2 loss was found to be lethal in LPS-induced sepsis models, highlighting its critical role in protection against harmful endotoxemia [21, 23]. A single exogenous treatment of IL-10 can rescue ADRB2-deficient mice from lethal LPS toxicity, and antibody blockade of the IL-10R reverses the protective effect of NE. Consequently, IL-10 induction may represent the primary downstream target of the anti-inflammatory properties of E and NE.

Clinically, E, NE, and other vasopressors are administered as front-line therapeutics in sepsis-associated hypotension with the primary goal of restoring blood pressure [25, 26]. In septic patients, there is a pivotal shift in cytokine profiles shortly after E administration highlighted by a marked reduction in serum TNF- α coupled with a rise in IL-10 [27–29]. Given the important role of IL-10 in suppressing both local and systemic inflammatory processes, the induction of this immunosuppressive cytokine by E and NE underscores the critical role of the sympathetic nervous system in mitigating the damaging effects of inflammation. This comes at a cost, however, since the very processes that eliminate infection are inhibited by IL-10, potentially allowing pathogen replication and spread. Nonetheless, there is clear evidence that adrenergic stimulation provides dual protection in sepsis by restoring blood pressure and by suppressing inflammatory cytokines.

In addition to suppressing inflammatory cytokines, ADRB2 signaling also modulates various other innate cell activities, which have downstream effects on both B and T

cell responses. For example, β 2-agonists suppress the pro-Th1-inducing cytokine IL-12 in dendritic cells while increasing IL-10 secretion, thus blocking Th1 responses [30–32]. This may be due, in part, to the effects of NE on driving alternative M2 macrophage development, which is characterized by an anti-inflammatory phenotype dominated by IL-10 rather than TNF- α and other inflammatory cytokines [21]. Indeed, these suppressive effects are seen in the innate response of NK cells to virus infection, as loss of ADRB2 enhances IFN- γ and lytic activity of NK cells in response to MCMV [33].

Antigen presentation to T cells is a hallmark activity of innate cells including DCs, macrophages, monocytes, and B cells. Early studies indicated that NE could suppress IFN- γ -induced MHC-II expression on astrocytes [34, 35] and other tissue resident antigen-presenting cells, such as langerhans cells [36]. Thus, β 2-agonists can promote tolerance by limiting antigen presentation, and recent studies have demonstrated that ADRB2 signaling limits the magnitude of CD4⁺ T cell priming by suppressing cross-presentation in dendritic cells [37]. Interestingly, the opposite has been observed in B cells, where adrenergic signaling increases the ability of B cells to present antigen and activate CD4⁺ T cells [38], through the co-stimulatory molecules B71/B72 [39]. B cell help is enhanced in this situation resulting in elevated IgG1 secretion overall [38, 40].

Although expression of α -ARs may be low on immune cells, there is some evidence that the α 1-adrenergic (ADRA1) may act to amplify cytokine secretion in innate cells, placing α and β receptors in opposing roles in regulating cytokine-mediated inflammation [41]. Whether the ADRA1 is acting directly to drive cytokine secretion from innate cells is unclear; however, blockade of the α 1-AR suppresses cytokine-mediated inflammation in the context of bacterial infections. Indeed, it has been suggested that blocking the α 1-adrenergic receptor may be a viable therapeutic intervention to suppress the cytokine storm observed in severe COVID-19 patients [42].

Regulation of T cell effector functions

Cytokines have a profound impact on T cell function and their development into distinct subsets of effector and memory cell populations. For example, IL-12 secreted by DCs drives Th1 and CD8⁺ CTL development in response to both bacterial and viral infections [43, 44]. Other cytokines, such as IL-2, IL-4, IL-10 and IFN- α/β promote alternative pathways of Th2, Treg, and memory cell development [45–52]. Early studies demonstrated that CD4⁺ T cells express the ADRB2 [53, 54], and more recent studies identified differential expression on subsets of effector and memory CD8⁺ T cells [55, 56]. CD4⁺ T cells regulate multiple aspects of effector and memory

responses through selective cytokine secretion [57], and both naive and in vitro polarized Th1 cells preferentially express ADRB2 with limited expression on Th2 cells [53, 54]. Stimulation of polarized Th1 cells suppressed IFN- γ secretion while having little effect on IL-4 or IL-5 secretion from Th2 cells. Furthermore, NE stimulation can tip the balance toward Th17 development due to effects on dendritic cell priming [32]. In contrast, while the ADRB2 is more highly expressed on effector and memory effector CD8⁺ T cells, NE and β -agonists effectively suppress IFN- γ and TNF- α secretion from all CD8⁺ subsets, and this suppression was specific for TCR-induced functions as stimulation with IL-12 + IL-18 was unaffected by NE to suppress IFN- γ secretion [56]. In addition, ADRB2 signaling effectively suppresses cytolytic activity in CD8⁺ CTLs. In contrast, ADRB2 signaling has been shown to enhance NK cell expansion and effector function in vivo in response to virus infection [58]. It is unclear yet how the adrenergic pathway influences long-term memory T cell development. Thus, the overall activities of NE on T cells seem to fall in line with its immunosuppressive effects on innate cells described above.

While adrenergic signaling modulates activation-induced cytokine expression, conversely, cytokine responsiveness modulates expression of the ADRB2 on T cells, creating a reciprocal feedback loop during innate priming of T cells during infection [59]. For example, IL-2 activation enhances ADRB2 expression in T cells [59] while IL-12 increases its expression on both CD8⁺ T cells and NK cells [56, 58], making them more sensitive to the effects of NE stimulation. Given the immunosuppressive effects of NE, increasing the intrinsic expression of ADRB2 may provide the cells with an additional layer of modulation that can prevent over activation and limit collateral damage during effector responses. Indeed, chemical sympathectomy with 6-hydroxydopamine potently accelerates the CD8⁺ T cell response to influenza [60], indicating a clear role for NE in suppressing the overall magnitude of the CTL response. In some cases, ADRB2 signaling may promote Th2 responses and suppress Th1 development in the absence of overt infection. In HSV DNA vaccine-challenged mice, treatment with the β 2-specific agonist salbutamol elicited Th2 driven immune response indicated by high levels of HSV specific IgG1 antibodies compared with IgG2a, providing protective immunity to mucosal challenge with live virus [61].

In addition to suppressing overt T cell-mediated inflammation, ADRB2 activation can potentially promote T cell tolerance by driving Treg development [62–64]. ADRB2 signaling promotes Treg development by inducing FoxP3 expression in CD4⁺ T cells [63]. This pathway may be accentuated in the context of tolerance to self-antigens presented by resting DCs, as NE can promote IL-10 secretion in these APCs [23, 65]. Curiously, however, FoxP3 induction was independent of IL-10R activation [63], and other studies have shown a direct

induction of Treg activity by ADRB2 activation on Treg cells [66]. Regardless of the precise mechanism, these studies highlight the role of adrenergic signaling in suppressing effector T cell responses in both CD4⁺ and CD8⁺ T cells and potentially driving inducible Treg development in peripheral CD4⁺ T cells to self-antigens.

Inflammation in the context of chronic disease

Stimulation of the sympathetic neurons that innervate secondary lymphoid organs has been shown to suppress inflammation in a variety of chronic diseases. For example, pioneering work from Tracey and colleagues has shown that electrical stimulation of the vagus nerve significantly suppresses inflammation by blocking secretion of inflammatory cytokines both locally and systemically (reviewed in [67, 68]). The complex mechanisms underlying this suppression involve acetylcholine and the α 7-nicotinic receptor [69]. Under certain conditions, release of NE by the splenic nerve stimulates T cells, promoting their secretion of acetylcholine which can suppress innate cell cytokine secretion [70, 71]. This pathway is powerful and has been harnessed to treat a variety of chronic inflammatory diseases. The mechanism of vagus nerve suppression relies on acetylcholine production from immune cells since secondary lymphoid organs are only innervated by sympathetic nerves that secrete NE rather than acetylcholine. However, it is quite likely that NE acts directly on macrophages and DCs to suppress inflammatory cytokine secretion, particularly in response to PAMPs [72, 73].

In the context of autoimmunity, studies have focused on the role of NE in the central nervous system (CNS) in mouse models of experimental autoimmune encephalomyelitis EAE [74]. Early studies found a direct correlation between elevated NE and reduction in severity of CNS inflammation [75]. Depletion of central adrenergic nerves lowered NE levels and significantly increased the severity of EAE as compared with controls. Moreover, treatment with L-DOPA, a NE precursor with non-tricyclic NE selective reuptake inhibitor atomoxetine, increased CNS NE levels and reduced EAE symptoms. Furthermore, the downstream transcription factor NR4A1 was shown to be critical in NE-mediated suppression of neuroinflammation through effects on macrophage recruitment and activation [76]. Recently, a direct role for ADRB2 on immune cells was found to be critical for the anti-inflammatory properties of NE in EAE [77]. In humans, there is some evidence that expression of both dopaminergic and adrenergic receptors on lymphocytes may be considered as a contributing biomarker in the progression of MS [78].

Allergic asthma is another well-studied chronic inflammatory disease, perhaps in which the role of NE and β 2-agonists is most notable in restoring lung function and promoting

airway clearance [79, 80]. Allergic asthma is generally classified as a “type 2” response, being heralded by innate lymphocyte-2 (ILC2) and their induction of allergen-specific Th2 cells leading to IgE secretion in responding B cells (reviewed in [81, 82]). Th2 cells were the original hallmark cellular phenotype that characterized allergic conditions, and multiple signaling pathways converge to drive their development, including IL-4, IL-33, and TSLP [83]. Recently, CD8⁺ Tc2 cells have also been shown to play a distinct role in asthma pathogenesis [84]. Type 2 responses are guided by innate cytokines that drive the development of Th2, Tc2, and other inflammatory phenotypes such as Th17 cells. ILC2 cells, in particular, have been shown to play a key role in early priming events, acting as a potent source of Th2-inducing cytokines such as IL-4. Recently, Moriyama et al. [85] found that the ADRB2 played a significant role in ILC2 suppression, and deletion of the ADRB2 led to exacerbated type 2 responses in gut mucosal tissues. Perhaps, the most potent counter-regulatory cytokine found to inhibit this pathway is the antiviral cytokine IFN- α/β [51, 86]. IFN- α/β suppresses the development and cytokine secretion potential of CD4⁺ Th2 cells [50, 87]; it can also reverse the Th2 phenotype of pre-committed cells, even from allergic subjects [88]. This suppression is accomplished by blocking the induced expression of the key Th2 transcription factor GATA3 [50, 89]. This is particularly important in the context of upper respiratory viral infections which drive the secretion of IFN- α/β [90, 91] as specific Toll agonists have been proposed as therapeutic agents to reverse the allergic phenotype. Yet, viral infections are a particular nuisance in allergic diseases, causing severe exacerbations of allergic asthma. This is a significant conundrum with the use of β -agonists, since recent studies have found that both IgE stimulation and NE can suppress virus-induced IFN- α/β secretion from dendritic cells [92–95]. Nonetheless, while β -agonists had very little effect on IL-4 secretion from Th2 cells in vitro [54], ADRB2 activation can prevent Th2-mediated inflammation with respect to allergic stimulation [96]. This places the use of β -agonists in a very precarious situation when treating allergic airway diseases impacted by respiratory viruses. The stimulation of the adrenergic pathway indeed restores lung function and may temporarily suppress acute Th2 cytokine secretion in vivo, yet it also suppresses IFN- α/β , which is key to reversing the Th2 state and blocking viral replication [86].

Regulation of trafficking and circadian involvement

Over the last 10 years, there have significant advances in the area of “chrono-immunology” and the role circadian rhythms play in immune function [97–99]. Circadian rhythms evolved in virtually all life forms in order to regulate biological

processes that cycle with the needs of the organism as a function of light/dark cycles. In higher organisms, light signals are converted to biological oscillations of a set of core transcription factors that regulate a myriad of processes throughout the body, and immune cells are no exception to this. Light entrainment regulates expression of the core transcription factor Bmal1/2 within the suprachiasmatic nucleus (SCN) subregion of the hypothalamus [100]. As night falls, Bmal1 is extinguished by the action of the cryptochrome proteins Per and Cry. This oscillation regulates the expression of genes with the SCN to release neurotransmitters that entrain cells throughout the body. One of these external entrainment pathways is regulated by the sympathetic nervous system, and the secretion of NE is a major component to that systemic entrainment process. NE levels typically rise in response to light entrainment and fall at night.

Perhaps, the most well-documented aspect of circadian control of immune function is in the area of immune cell trafficking through lymphoid tissues [97, 101]. Nakai et al. [102, 103] found that lymphocyte recirculation through secondary lymphoid tissues followed a diurnal circadian pattern. Their retention and release was regulated by interactions with chemokine receptors and required the expression of ADRB2. Further treatment with β -agonists could alter their migration. In addition to trafficking, innate sensing is also impacted by circadian rhythms. Recent studies found that TLR9 is directly controlled by CLOCK, and diurnal oscillations in TLR9 regulated both the innate secretion of pro-inflammatory cytokines and the resulting adaptive response [104]. Whether this effect was regulated by adrenergic signaling was not explored. In humans, during sleep, low levels of sympathetic agonists, such as NE and prostaglandin E2, allow T cells to express β 2-integrins on their cells surface. This expression is normally suppressed by $G\alpha$ -receptor activation during wakefulness when the levels of these neurotransmitters are high [105]. Increased expression of integrins allows for differential recirculation of cells within lymphoid tissues.

In addition to trafficking, circadian rhythms also have the potential to influence an overt immune response in T cells. Indeed, T cells display a periodic oscillation of core circadian factors [106]. Interestingly, recent studies in CD4⁺ T cells found that the CLOCK gene was dispensable for primary effector responses to infection, although there was observed reduction in IL-2 responsiveness [107]. However, the case is quite different for CD8⁺ T cells. Here, loss of the primary oscillator Bmal1 in CD8⁺ T cells significantly altered their development into primary effector cells in response to virus infection [108]. Whether the ADRB2 is responsible for the entrainment of these cells is still an open question. Nonetheless, it is clear that immunity is controlled, in part by circadian oscillations, and identifying specific mechanisms of this regulation could open new avenues of therapeutic intervention. Significant questions remain in this area such as

the role of the ADRB2 in the entrainment of immune cells, the requirement of rhythmic oscillations in effector and memory responses, and whether the time of day of infection influences the outcome of vaccines and immunotherapy.

The gut microbiome has come into focus recently as a key regulator of mucosal immune homeostasis, and perturbations in the microbiome lead to significant inflammatory conditions (reviewed in [109]). Like all organisms, the microbiome operates under the constraints of circadian rhythms and releases a variety of metabolites in a diurnal rhythmic fashion [109, 110]. Recent studies have demonstrated that products from the microbiome can directly regulate inflammatory responses [111–113]. Thus, the microbiome establishes an important circadian rhythmic control of the local immune community at barrier interfaces.

Conclusion

The sympathetic nervous system plays a major role in controlling the biological processes including immune system, mediated via neuromodulators such as epinephrine and nor epinephrine. This neuroimmune communication is enabled by the adrenergic receptors, among which ADRB2 as a pivotal player is differentially expressed on innate and adaptive immune cells. To keep in check the necessary evil “inflammation,” neurosignaling through ADRB2 limits the release of inflammatory cytokines from macrophages and dendritic cells, along with activation of T cells. As revealed by our previous studies, IL10 is a critical target downstream of E and NE to limit inflammation. The suppression of inflammation in varied chronic diseases is also exhibited by NE, which has been utilized for treatment of diseases such as allergic asthma where NE and β_2 -agonists play major roles in restoring normal health conditions. Even the autoimmune diseases such as EAE in mouse have correlated the NE levels with decrease in CNS inflammation, underscoring the role of ADRB2 signaling in suppressing inflammation. Through sympathetic regulation, circadian rhythms also contribute to the timing and magnitude of specific functions of immune system. Recirculation of immune cells through lymphoid tissues and circulation has been well studied and demonstrated in context of circadian regulation. Much remains to be uncovered, and further revelations could open new avenues for the identification and development of prophylactic and therapeutic targets with improved clinical outcomes.

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