



Review

The Interplay between Autonomic Nervous System and Inflammation across Systemic Autoimmune Diseases

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Abstract: The autonomic nervous system (ANS) and the immune system are deeply interrelated. The ANS regulates both innate and adaptive immunity through the sympathetic and parasympathetic branches, and an imbalance in this system can determine an altered inflammatory response as typically observed in chronic conditions such as systemic autoimmune diseases. Rheumatoid arthritis, systemic lupus erythematosus, and systemic sclerosis all show a dysfunction of the ANS that is mutually related to the increase in inflammation and cardiovascular risk. Moreover, an interaction between ANS and the gut microbiota has direct effects on inflammation homeostasis. Recently vagal stimulation techniques have emerged as an unprecedented possibility to reduce ANS dysfunction, especially in chronic diseases characterized by pain and a decreased quality of life as well as in chronic inflammation.

Keywords: autonomic nervous system; sympathetic system; parasympathetic system; inflammatory reflex; innate immunity; adaptive immunity; systemic autoimmune diseases; inflammation; gut microbiota



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1. Introduction

The autonomic nervous system (ANS) has two main components, the sympathetic and the parasympathetic branches, that dynamically regulate the visceral functions [1]. Previous and recent findings are confirming the strong reciprocal interrelation between ANS and the immune system. Since ANS can regulate inflammation in chronic and acute conditions, autonomic dysfunction can have a pivotal influence on the onset and progression of many diseases where the immune response is involved, such as autoimmune diseases [2–4]. Given these premises, in the present review we will explore the interaction between immunity and ANS, focusing on the mutual contribution with both the innate and the adaptive immunity. Subsequently, we will explore from a more clinical point of view, what is currently known about ANS in three systemic autoimmune diseases in which immunity and inflammation are the main pathological processes such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and systemic sclerosis (SSc).

2. Autonomic Nervous System and Innate Immunity

The immune system is a complex interplay between immune cells, receptors, and self and non-self peptides. Innate immunity is the first response to microbes where pattern recognition receptors (PRRs) elicit the activation of immune/inflammatory processes after recognition of conserved pathogen-associated molecular patterns (PAMPs) that are present

on bacteria, viruses, and fungi [5] or towards damage- (or danger-) associated molecular patterns (DAMPs) and others. Among PRRs, Toll-like receptors (TLRs), nod-like receptors, C-type lectin receptors, and many others have a role in inducing innate immune responses; when PRRs are present on antigen-presenting cells, mainly dendritic cells (DCs), they can induce also the adaptive immune response [6]. Furthermore, DCs play a pivotal role in contributing to either immune activation or maintaining the immune tolerance that is crucial to preventing autoimmunity [7,8]. Defensins, complement, granulocytes, and natural killer (NK) cells are components of innate immunity, determining inflammation that initially has a protective role from external or internal agents that have to be removed [5,9].

A deep interaction between the immune system and the nervous system is nowadays well documented and, in particular, innate immunity contributes to the development of the central nervous system (CNS) through microglia cells that are the main innate immune cells present in the brain [10,11]. TLRs are expressed on microglia surface responding to pathogenic or damaging insults [12–14]. Furthermore, immune cells and innate immune cells maintain the functioning and homeostasis of the nervous system and an imbalance of this equilibrium, due for example to chronic inflammation, can cause a severe impairment with consequent alteration of cognitive functions [15].

The interaction with innate immunity is not a prerogative of the CNS only and evidence show how the peripheral nervous system and more in specific the ANS have a deep interface with immune cells [16]. Anatomically, the sympathetic branch of ANS is present in immunological organs such as the thymus, spleen bone marrow, and lymph nodes while of interest, no evident traces of the parasympathetic fibers have been demonstrated [16–22]. Moreover, immune cells present adrenergic receptors able to bind norepinephrine that confers the ability to crosstalk with the sympathetic nerves, namely the alpha-adrenergic receptor (α AR) and the beta-adrenergic receptor (β AR), the latter more expressed on innate immune cells [23,24]. The receptors α AR and β AR have effects in opposite directions, where α AR can be considered more stimulatory, while β AR is inhibitory, and under homeostatic conditions, β AR has an overall predominant effect [25]. Altogether, from several studies, norepinephrine inhibits cytokines production, namely TNF α when expressed from monocytes, macrophage, and microglia in response to the lipopolysaccharide (LPS) constituent of the bacterial cell-wall as well as inhibits IL-1 β or IL-6 production [26–30]. Norepinephrine has a direct effect on innate immune cells, increasing circulating NKs and granulocytes [31–33]. Neutrophil chemotaxis and phagocytosis are negatively regulated from norepinephrine; the NK function impairment after stroke seems to be mediated by a noradrenergic neurotransmitter, and the NK response is suppressed by catecholamines [34–40]. The β AR mediated effect of catecholamines suppress macrophage functions including their cytokine production [41,42]. Overall, the activation of the sympathetic nervous system attenuates the innate immunity as also demonstrated in a randomized control trial on human healthy subjects [43].

The parasympathetic branch that includes the vagus nerve has several effects on the innate immune system through the interaction between receptors present on the cellular surface and neurotransmitters, namely acetylcholine [44]. This communication is bidirectional and happens despite the fact that anatomically the parasympathetic fibers have not been individuated in the main immunologic organs such as the spleen and thymus [16,22]. Through vagal afferent fibers, the message that inflammation is present in other body sites reaches the CNS, as demonstrated by animal models of vagotomy in which the lack of vagal contribution determines reduced central responses with a blunted increase in body temperature and cortisol production [45–47]. Evidence of how the vagal afferents are activated by inflammation is not yet completely clear, but it has been suggested that IL-1 β receptors, present especially in the vagal paraganglia, are the main promoters of this afferent reflex to the CNS; moreover, IL-1 β is itself a key contributor in the direct stimulation of the brain to activate the inflammatory cascade [48,49].

The vagus nerve has an anti-inflammatory effect through the release of acetylcholine, mainly through the interaction with the α 7 nicotinic acetylcholine receptor (α 7nAChR)

present on macrophages [50]. On cultures of LPS-stimulated human macrophages, acetylcholine attenuates the production of TNF, as well as of IL-6 and IL-1 β , but not of the anti-inflammatory cytokine IL-10 [51]. The spleen is one of the main targets of vagal action towards the immune system. Indeed, it has been demonstrated how vagal stimulation reduces TNF macrophage production in mice sepsis models [52]. Due to the lack of parasympathetic fibers in the spleen, it has been hypothesized that the innervation is provided by catecholaminergic fibers from the celiac-superior mesenteric plexus ganglia that are under the control of preganglionic neurons of the thoracic spinal cord gray column [19,53–55]. Recently, an electrophysiological study performed on rats excluded the presence of a direct vagal-splenic nerve connection supporting the hypothesis of an effect towards splenic nerves mediated by vagal afferences through the CNS [21,33]. This neuronal modulation of inflammation through vagal afferences and efferences has been termed the “inflammatory reflex” [56]. Overall, the inflammatory reflex is crucial to maintain homeostasis with a balance between pro and anti-inflammatory responses as evident by the increase in morbidity and mortality during sepsis when a vagal depression is present [57–60].

3. Autonomic Nervous System and Adaptive Immunity

Adaptive immunity is the specialized branch of immunity able to respond to specific pathogens and to maintain an immunological memory over time. The main cells involved are lymphocytes B and T. The sympathetic nervous system is able to regulate the mobilization of lymphocytes in the bloodstream through catecholamines that directly interact with β 2AR present on the lymphocytes' surface [61]. Moreover, β 2AR is selectively expressed on naïve T cells, CD4+ T helper (Th) 1, and regulatory T cells (Tregs) and induces T helper differentiation towards a Th1 phenotype through IFN γ /IL-12 interaction in *in vitro* studies, while in *in vivo* the Th differentiation is orchestrated via DCs+ [62,63]. Norepinephrine has an inhibitory effect on cytotoxic CD8+ T cells and modulates Tregs [64–66]. Regarding B cells, catecholamines have an indirect effect on their maturation and on antibodies production through their action on T cells that are necessary as costimulation in the B mediated immune responses [63]. Evidence on a direct effect of β 2AR on B cells is limited; a lack of norepinephrine prevents a normal expression of IgG in mice [67] and norepinephrine induces β 2AR mediated CD86 expression (a costimulator) on B cells [68,69].

Vagal stimulation increases acetylcholine release in the spleen and suppresses TNF- α in control BALB/c mice models of endotoxemia, while it does not reduce TNF- α in nude mice, suggesting that T cells are involved in the inflammatory reflex and that a T cell deficiency impairs the inflammatory reflex [70]. Moreover, α 7nAChR present in T cells also causes a decrease in adhesion molecules expression and lymphocyte proliferation and both nicotinic and muscarinic acetylcholine receptors are present in lymphocytes that regulate their activities producing acetylcholine in a paracrine/autocrine control [71,72]. The role of vagal stimulation in increasing acetylcholine with beneficial effects on inflammation has been recently suggested also in the postural orthostatic tachycardia syndrome (POTS). POTS is a condition characterized by an impairment of the neuromodulation and consequent dysautonomia. Different studies showed a role of autoantibodies in POTS suggesting an autoimmune mediated pathogenesis of this condition [73,74]. In a recent study on a rabbit model of POTS induced by M2 muscarinic acetylcholine receptor-activating autoantibodies immunization, transcutaneous vagus nerve stimulation contributes to increasing acetylcholine with consequent reduction in both inflammation and cardiovagal dysfunction [75].

Overall, once the inflammatory reflex is activated, the sympathetic and parasympathetic branches of ANS act synergistically instead of oppositely as intuitively expected Figure 1. Indeed, as elegantly depicted by Tracey [56], this synergic contribution implies that the vagal afferent fibers signal to the CNS (mainly within the nucleus of tractus solitarius) the presence of peripheric inflammatory/infective stimulus (intercepted for cytokines release and/or pathogens presence), and in response, vagal efferent fibers suppress cytokine release through nicotinic receptors present on macrophages, and throughout the

cholinergic anti-inflammatory pathway. At the same time, the pain caused by the ongoing inflammatory processes can activate the sympathetic branches through the flight-or-fight responses determining norepinephrine release and consequent suppression of inflammation (via the pathways already detailed above) [76,77].

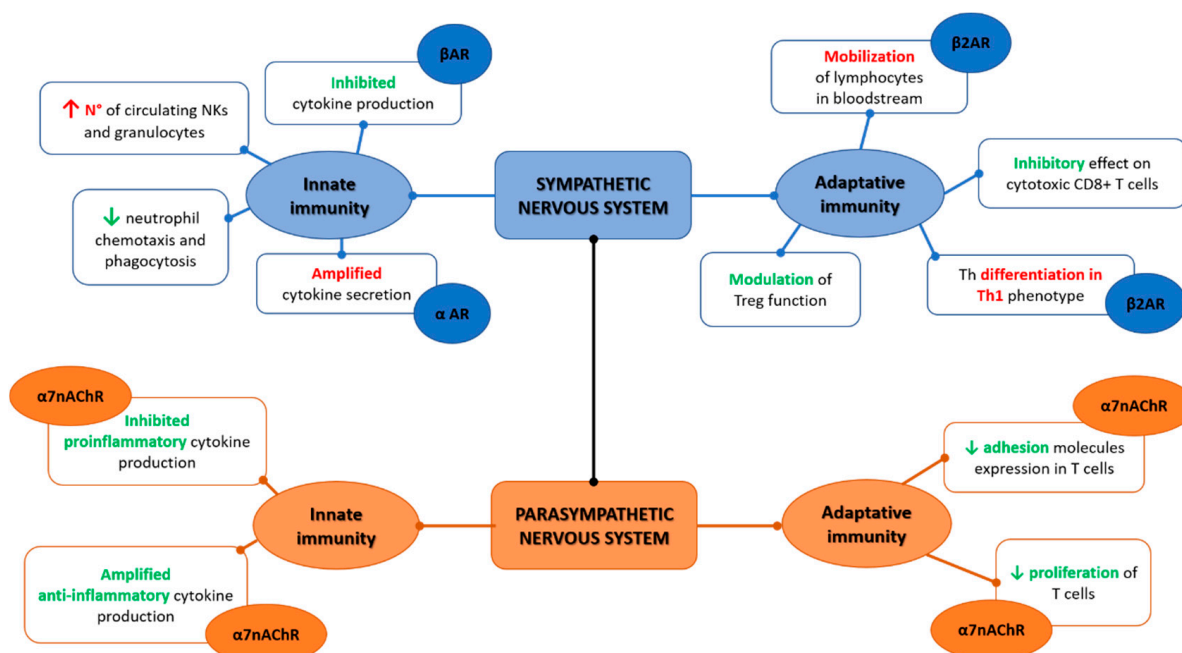


Figure 1. Sympathetic and parasympathetic synergic function on the innate and adaptive immunity.

It is important to add that these mechanisms can have different implications and functioning in acute versus chronic conditions, as described in acute stress that can cause an immune hyperactivation, while chronic stress is typically associated with an immunosuppressive status [78], and what keeps the homeostasis is the dynamic balance between all these regulatory systems; when one system is prevailing, the imbalance can cause, or be the consequence of, a pathological condition, such as for example, chronic autoimmune diseases [79]. Finally, by way of example of the deep bidirectional complex interactions between the nervous system and both innate and adaptive immunity, we could consider the case of celiac disease (CD) in which evidence shows how both innate and adaptive immunity mechanisms are involved [80]. A wide range of neurological disorders, ANS dysfunction included, mediated by antineuronal and antigangliosides autoantibodies have been indeed demonstrated in CD [81–84].

4. Autonomic Nervous System and Gut Microbiota

The gastrointestinal tract (GIT) is considered one of the most extended and important immunological organs because of its enormous abundance of cells of both innate and adaptive immunity residing in the bowel mucosa [85]. In the GIT, the immune system directly interacts with the unique microbiota ecosystems that are hosted there; microbiota includes the whole composition of bacteria, fungi, and viruses that are present in a specific body site, and the gut microbiota has a crucial role from birth, allowing the evolution and development of the immune system as demonstrated by germ-free mice models in which the absence of microbiota is associated with an absent or impaired immune development [86–89]. Moreover, GIT microbiota can regulate the immune interaction with external antigens and maintain the immune homeostasis through its protolerogenic commensal Phyla of bacteria able to metabolize and generate short-chain fatty acids (butyrate, propionate, and acetate) that induce Tregs expansion in the colon [90,91]. A reduction in pro-tolerogenic bacteria, mainly Firmicutes and Bacteroides has been extensively de-

scribed in studies performed on mice models and in patients with inflammatory bowel diseases (IBD) and irritable bowel syndrome (IBS) as well as in systemic autoimmune diseases [92–95].

The brain–gut axis (BGA) is a well-known interaction between the enteric nervous system (ENS) and CNS that also occurs through the sympathetic and parasympathetic branches of ANS [96,97]. Gut microbiota can directly interact with the ENS and indirectly modulate the BGA through neuroendocrine and neuroimmune pathways, all together considered the “brain–gut–microbiota” axis [98,99]. If these mechanisms undergo a dysfunction, an imbalance of this system leads to clinical alteration of the GIT especially with IBS development [100–102]. Moreover, the microbiota is directly associated with mental health disorders as demonstrated in knock-out mice models in which the absence of intestinal microbiota influences the development of behavior, along with neurochemical changes in the brain [102,103]. Microbiota alterations can modulate both the brain functions and the ANS through the vagus nerve, sending signals to the CNS and vice versa [104–107]. A recent study on beta 1 and 2 adrenergic receptor knock-out mice shows that the overall sympathetic reduction increases protolerogenic bacteria, with reduction in circulating CD4+ T cells and reduced IL-17 [108].

5. Autonomic Nervous System and Its Interplay with Inflammation in Systemic Autoimmune Diseases

5.1. Rheumatoid Arthritis

Rheumatoid arthritis (RA) is the most common form of chronic inflammatory arthritis, affecting 1% of the Western population [109]. It represents a real burden on public health as its prevalence is rising with high rates of disability and premature death mainly due to cardiovascular (CV) complications [110]. Patients with RA frequently experience physical disability due to persistent synovial inflammation that eventually leads to joint/bone deformities and chronic pain. Cardiovascular (e.g., ischemic heart disease, heart failure, arrhythmia) and psychiatric comorbidities are not infrequent in RA, and they can markedly impact patients’ quality of life [109].

As in other autoimmune diseases, it has been demonstrated that ANS plays a role in RA. Indeed, ANS dysfunction affects target organs (i.e., heart, kidney, and blood vessels), and it is also strongly interrelated with the onset and perpetuation of chronic inflammation via the ‘inflammatory reflex’ [111]. Signs of autonomic impairment in RA have been observed since the late 1950s [112]; however, the cause–effect and the temporal relationship between the onset of ANS dysfunction and inflammation is still a matter of current research. According to a systematic review based on 40 studies, the prevalence rate of ANS dysfunction among RA patients is 60%. Most of the studies report a reduction in cardiac parasympathetic activity ($n = 20/26$ studies, prevalence 77%) assessed through a reduced heart rate variability (HRV), that is a noninvasive method to investigate the status of cardiovascular autonomic control, and a high Resting Heart Rate (RHR) [113]. Under a physical effort, when compared to healthy subjects, RA patients have a reduced chronotropic response to exercise and slower heart rate recovery post-maximal exercise test [114]. Sympathetic hyperactivity has been documented in approximately half of the studies included in the aforementioned review ($n = 16/30$ studies, prevalence 53%), but the evidence is weaker since its measurement tools (e.g., clinical cardiovascular tests, neuropeptide Y, serum chromogranin, urinary or plasmatic catecholamines, pupillary light reflex, etc.) are less validated, and the results can be altered by concurrent conditions such as arterial hypertension [115]. Parasympathetic nervous system (PNS) hypoactivation and sympathetic nervous system (SNS) hyperactivity may exert their pathogenetic effect directly impacting the CV system and through an impairment of the cholinergic anti-inflammatory pathway. In RA, an imbalance in PNS–SNS stimulation may lead to a defective release and binding of acetylcholine to the $\alpha 7nAChR$ on splenic macrophages and fibroblast-like synoviocytes in the joints with a consequent uncontrolled release of proin-

flammatory cytokines (e.g., TNF, IL-1, and IL-6) and self-sustaining chronic inflammation of target organs (e.g., joint and bone damage and accelerated atherosclerosis) [2,111].

This model is supported by experimental studies on animals that showed that treatment with $\alpha 7nAChR$ pharmacological agonists (nicotine, AR-R17779, or GTS-21) reduces the clinical severity of arthritis as well as the expression of proinflammatory cytokines and atherosclerotic plaque in the aorta [2,116]. On the other hand, $\alpha 7nAChR$ knockout mice had higher plasmatic levels of TNF, higher disease severity scores, and joint destruction compared to wildtype [2,117]. Recent data support the existence of a complex interlinkage between ANS dysfunction, chronic inflammation, and disease severity. For example, in RA patients elevated CRP seems to be independently associated with a significant depression of HRV and with QTc prolongation, thus increasing the risk of tachyarrhythmia, when compared to healthy controls or patients with low CRP levels [110,118]. Moreover, in a study conducted on 30 patients with RA, an augmented SNS activity was demonstrated by showing that heart rate and Muscle Sympathetic Nerve Activity (MSNA) were increased, and Cardiac Baroreflex Sensitivity (cBRS) was reduced in RA patients compared to non-RA patients, independently from arterial hypertension presence. In this study, pain was strongly correlated with MSNA (positive correlation) and cBRS (negative correlation), while heart rate had a positive independent association with high sensitive CRP (hs-CRP) and disease activity (DAS28-CRP) [115].

Some authors argue that ANS disturbances may precede the onset of inflammation rather than be its consequence, even though the causal issue is still a matter of debate. Interestingly, subjects 'at risk' for developing RA, which is defined by the positivity of rheumatoid factor (IgM-RF) or anti-citrullinated peptide autoantibodies (ACPA) along with arthralgia or a family history of RA, have a similar resting heart rate to RA patients, that is higher than healthy subjects. ANS impairment may anticipate or predict the onset of clinical disease, as RHR was significantly higher at baseline in those patients who subsequently developed arthritis [119]. Of note, the inflammatory reflex was impaired in subjects with a marked ANS dysfunction, as $\alpha 7nAChR$ was significantly less expressed on peripheral blood monocytes of RA subjects [119]. CV complications account for 50% of premature deaths in RA and lead to a two-fold risk of sudden cardiac death, mainly due to Ischemic Heart Disease, Congestive Heart Failure, and arrhythmias [110].

The immune–autonomic link may also have a crucial role in determining the onset and severity of psychiatric comorbidities observed in patients with RA and other autoimmune diseases. It is well known that RA patients suffer more frequently from Major Depressive Disorder (MDD) and anxiety disorders than the general population [111]. Many mechanisms have been proposed to explain this association. First, peripheral proinflammatory cytokines can directly induce central nervous system (CNS) cells and the hypothalamic–pituitary–adrenal axis (HPA) to overproduce further cytokines and cortisol. Secondly, such cytokines can also alter the metabolism of neurotransmitters (e.g., dopamine, serotonin, and glutamate) causing reduced neuroplasticity. Moreover, anxiety appears to be associated with increased levels of IL-17 in RA [120]. Novel research points out that biological immunosuppressive drugs (e.g., anti-TNF α and anti-IL6 drugs) have a beneficial effect on anxious and depressive symptoms, and interesting perspectives come from studies on vagal nerve stimulation, which appears to ameliorate depression, RA symptoms, and chronic pain [2,121].

5.2. Systemic Lupus Erythematosus

SLE is a systemic autoimmune disease characterized by chronic inflammation, multiple autoantibodies production, immune-complex deposition, and involvement of several organs (joints, skin, lungs, kidneys, and central and peripheral nervous systems) leading to variable clinical presentation and disease severity [122]. Overall, an ANS dysfunction in SLE has been extensively documented, with a prevalence of the sympathetic activity along with a decreased parasympathetic tone [3,123–125]. In particular, a reduced HRV and index of increased sympathetic modulation, is seen in SLE subjects as demonstrated in a study

performed on 35 SLE patients where impaired HRV was also associated with the increase in inflammatory cytokines such as TNF and with disease activity [3]. Several other studies found a decreased HRV in SLE [126–130]. It is widely known that ANS dysfunction is associated with the development of cardiovascular diseases (CVDs), where the sympathetic activity is a mediator of both the onset and progression of CVDs while on the other hand, the parasympathetic control seems to have a protective role with reduced mortality in CVDs [131–133]. In SLE patients, CVDs are a high cause of mortality, especially related to atherosclerosis, and CVD risk is doubled with respect to the general population [134,135]. It could be speculated that this higher cardiovascular risk in SLE reflects the ANS dysfunction mutually linked to chronic inflammation as already postulated for RA. For example, in a mice model of SLE, the restoration of the vagal cholinergic anti-inflammatory pathway, with pharmacological compounds, reduces blood pressure along with inflammation [136,137]. The cardiac autonomic dysfunction may be related to QTc prolongation in SLE as investigated in a study on 91 SLE patients [138]. Overall these studies pave the way for wider future investigations on ANS' mutual contribution with inflammation to disease onset and disease severity, as well as its impact on the cardiovascular system and quality of life in patients affected by SLE.

5.3. Systemic Sclerosis

Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterized by microvascular impairment, production of several specific autoantibodies, and deposition of fibrosis in the dermal layer, thus contributing to the typical skin thickening (scleroderma) and to the involvement of several major organs such as lungs, heart, gastrointestinal (GI) tract, and kidneys [139]. An ANS dysfunction could explain part of the processes involved in SSc clinical manifestations. For example, a sympathetic overactivity determines prevalent vasoconstriction that is a leading process in the Raynaud phenomenon, the most common and earliest manifestation of SSc due to microvascular damage and related to cold temperatures and stress situations [140]. As described in [141] an HRV impairment is indeed found to be associated with microvascular damage assessed through the nailfold videocapillaroscopy of SSc patients and, interestingly, a study performed on twenty-seven SSc patients found a positive correlation between digital microvascular damage and parasympathetic modulation that promoted VEGF release to stimulate vasodilatation [142].

Along with sympathetic overactivity, ANS dysfunction is characterized also by a decreased parasympathetic function [143]. It begins in the early stages of SSc along with the organ fibrotic involvement (especially of the heart) and correlates with the disease subsets; the more fibrotic forms, such as diffuse cutaneous SSc, present a higher ANS impairment, while patients at the preclinical stage are similar to healthy subjects [144–146]. The presence of cardiac autonomic dysfunction has been extensively investigated in scleroderma patients and is associated with several cardiac manifestations, including left and right ventricular remodeling and cardiac repolarization abnormalities [147–151]. Moreover, HRV at rest is associated with the risk of developing arrhythmias as well as with mortality, and HRV response is impaired in SSc, when compared to healthy subjects during orthostatic stress [141,146,152]. Moreover, the role of ANS in mediating kidney vascular involvement has been studied [4]. The authors postulated that the increased stiffness and a further increase in vascular resistance were the results of sympathetic hyperactivity with a consequent increase in renal resistances detectable in SSc patients. Moreover, the GI affection that occurs in about 90% of SSc patients, has been related to an ANS impairment, especially of the vagal branch, that in physiologic conditions controls both the GI motility and the normal stress response. In SSc, ANS dysfunction is associated with esophageal dysmotility and patients with a severe GI disease have more symptoms of dysautonomia with consequent emotional distress [153–156]. HRV was also used to assess the relationship between dysautonomic symptoms and quality of life in SSc patients, showing that cardiovascular dysautonomia can be related to poor sleep quality, high pain scores, and depressive symptoms with an overall severe impact on quality of life [157].

6. Present and Future Perspectives

Based on the premises above, a substantial amount of data is emerging regarding the effects of vagal stimulation on the neuroinflammatory regulation, not only in models of endotoxemia but also in preclinical models of autoimmune diseases (specifically RA and inflammatory bowel diseases (IBD)) in which vagal stimulation can control inflammatory/immune activation [52,158–161]. New clinical trials that implicate the use of neurostimulators for RA and IBD are emerging [162–165]. Vagal stimulation is nowadays investigated as an efficacious tool to obtain relief from chronic pain and depression pain-related symptoms [166–168]. Furthermore, a direct noninvasive modulation of the vagal nerve using transcutaneous vagus nerve stimulation (tVNS) represents a promising non-pharmacological and noninvasive therapy for cardiovascular and noncardiovascular disorders [169,170].

In RA, VNS might have a beneficial anti-inflammatory effect in patients who did not fully respond to drug therapy (corticosteroids and synthetic or biologic disease-modifying antirheumatic drugs). Indeed, in a study after 42 days of 60 s stimulation 1–4 times daily, there was a drop in TNF levels and a significant clinical improvement of at least 20% in approximately 70% of patients treated. These beneficial effects were nullified by a 2 week discontinuation of VNS, which was associated with an additional increment in TNF production and DAS28-CRP [2].

In SLE, the scientific background that justifies the future use of VNS is depicted in [171]. Moreover, recently a double-blind sham-controlled pilot study was conducted on 18 SLE patients with pain, in which tVNS significantly reduced pain and fatigue, compared to sham-stimulation and joint scores after 5 and 12 days [172]. One study investigated the effects of a tVNS on 17 SSc patients with upper GI tract dysfunction versus nine healthy controls, showing an altered HRV in SSc and normalization of sympatho-vagal balance with improvement of the GI symptoms score after prolonged use of tVNS [173].

Therefore, advancing the knowledge of the interplay between the autonomic nervous system, inflammation, and autoimmune diseases could be a great opportunity for several fields, such as bioelectronics medicine. Since new pathophysiological mechanisms have been revealed, instruments and protocols could be developed, expanding the possibilities of nonpharmacological treatment and rehabilitation in autoimmune and inflammatory diseases. Figure 2.

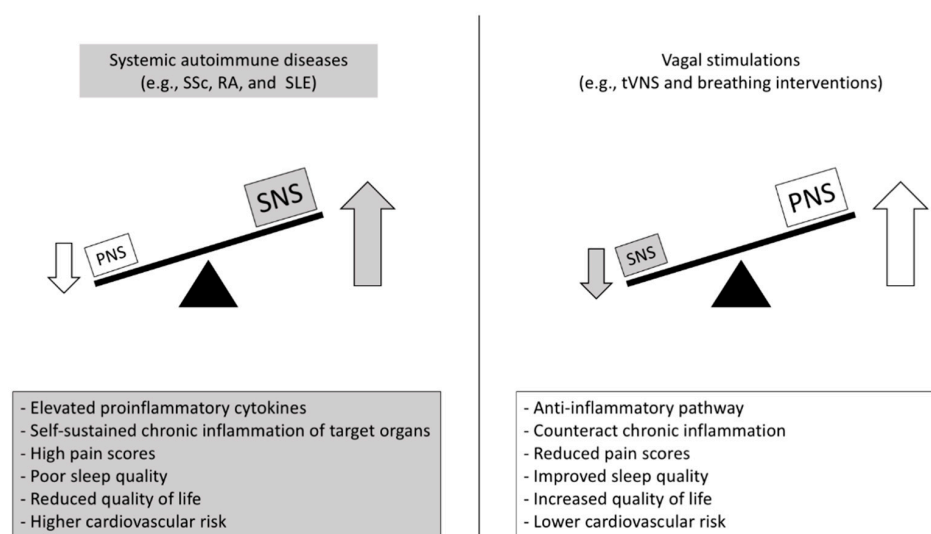


Figure 2. Putative autonomic- and inflammatory-mediated mechanisms and clinical outcomes in autoimmune diseases and promising countermeasures. SNS: sympathetic nervous system; PNS: parasympathetic nervous system; SSc: Systemic sclerosis; RA: Rheumatoid arthritis; SLE: Systemic lupus erythematosus; tVNS: transcutaneous vagus nerve stimulation.

7. Conclusions

The evidence of the interplay between ANS and the immune system are multifaceted and are at the basis of the clinical pictures (such as organ inflammation, pain, CV involvement, and fatigue) of diseases where chronic inflammation is implied. In particular, the potential benefit for a nonpharmacological intervention in systemic autoimmune diseases based on vagal stimulation is an emerging field of interest that is worth further study to confirm its efficacy in improving the symptoms and quality of life of these patients.

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