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From neuroimunomodulation to bioelectronic treatment of rheumatoid arthritis

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Abstract

Neuronal stimulation is an emerging field in modern medicine to control organ function and reestablish physiological homeostasis during illness. The nervous system innervates most of the peripheral organs and provides a fine tune to control the immune system. Most of these studies have focused on vagus nerve stimulation and the physiological, cellular and molecular mechanisms regulating the immune system. Here, we review the new results revealing afferent vagal signaling pathways, immunomodulatory brain structures, spinal cord-dependent circuits, neural and non-neural cholinergic/catecholaminergic signals and their respective receptors contributing to neuromodulation of inflammation in rheumatoid arthritis. These new neuromodulatory networks and structures will allow the design of innovative bioelectronic or pharmacological approaches for safer and low-cost treatment of arthritis and related inflammatory disorders.

Keywords

bioelectronic medicine; neuroimmunomodulation; rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by deleterious inflammation in the joints, hyperplasia of synovial tissues and damage of the joint cartilage and bone [1]. RA is the most common type of autoimmune arthritis, affects approximately 0.5–1% of the population worldwide, causes morbidity and reduces mobility and life expectancy [2]. Although its etiology is unknown, RA is a multifactorial process not well understood. Both, inflammatory cells and cytokines are found in the synovial fluid and

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contribute to joint inflammation and tissue damage in arthritis. Currently, there is no cure for RA and the most effective treatments are the new biological disease-modifying antirheumatic drugs (bDMARDs) that neutralize cytokines (such as TNF, IL-1β and IL-6) or their receptors [3–5]. The most common treatments for RA include the use of monoclonal antibodies that neutralize TNF as Remicade® (infliximab), a chimeric IgG1κ antibody (composed of human constant and murine variable regions), and Humira® (adalimumab), a human monoclonal antibody in rheumatoid arthritis. Likewise, Enbrel® (etanercept), a fusion recombinant protein of the human eTNF receptor 2 and the Fc end of the IgG1, also binds and neutralizes TNF. Biological agents targeting IL-6 (sirukumab, olokizumab and clazakizumab), IL-6 receptor (tocilizumab and sarilumab) or IL-1 receptor antagonist (IL-1Ra; anakinra) have also provided beneficial effects in RA patients [6–10]. These drugs decrease joint inflammation in RA, but they are very expensive and increase the risk of opportunistic infections and immunosuppression [11–13].

Recent studies on neuromodulation revealed the potential of the nervous system to control organ function and re-establish physiological homeostasis during illness [14–18]. These results encouraged investigators to analyze the potential of neuromodulation for treating infectious and inflammatory disorders. The autonomic nervous system can be divided into the enteric, sympathetic and parasympathetic divisions that control physiological homeostasis including the urogenital, cardiovascular and gastrointestinal systems. Likewise, the nervous system modulates the immune system to re-establish immune homeostasis after infections, trauma and other immunological challenges. Nerve stimulation and bioelectronic medicine is an emerging field in modern medicine to control organ function and re-establish physiological homeostasis during illness [14]. Vagus nerve, the main nerve connecting the brain with the viscera, is a bidirectional nerve with afferent signal toward the brain and efferent signals toward the viscera. An initial study showed that efferent vagal projections attenuates inflammation in endotoxemic mice [19], while the afferent vagal fibers activate the hypothalamic–pituitary–adrenal (HPA) axis [20,21]. These results encouraged many investigators to analyze the potential of vagal stimulation in multiple inflammatory disorders such as RA [22–27]. Our results concur with other investigators in showing that neuronal stimulation attenuates inflammation in RA both in experimental and clinical settings [24,28,29]. This article reviews the recent advances in neuroimmune interactions, bioelectronic medicine and the potential of neuronal stimulation for treating arthritis.

Vagal regulation of the innate immune system in endotoxemia

Endotoxemia is the standard experimental model used to study the innate immune responses to bacterial infection [30,31]. The injection of bacterial endotoxin (Lipopolysaccharide; LPS), a cell membrane component of Gram-negative bacteria, activates macrophages to produce inflammatory cytokines such as TNF, IL-1β and IL-6 [30,32]. Overzealous TNF production can be more dangerous than the original infection, and can cause cardiovascular collapse, septic shock and multiple organ failure in severe sepsis [33,34]. The original studies in endotoxemic mice indicated that electrical stimulation of the parasympathetic vagus nerve inhibits the production of proinflammatory, but not anti-inflammatory (e.g., IL-10) cytokines from macrophages [14–16,19,33,35]. Since macrophages M1 and M2 phenotypes are categorized by the production of proinflammatory (e.g., TNF) and anti-

inflammatory (e.g., IL-10) cytokines, it has been suggested that vagal signaling can induce macrophage switch from M1 to M2 profile [36–38].

The vagus nerve is the crucial neurosensitive conduit with around 80% of sensory afferent fibers and represents the most studied example of neuroimmune crosstalk. This mechanism can be divided into two different anatomical portions based on vagal pathways. First, the afferent sensitive nerve can be activated by inflammatory factors in the periphery and transmit the information to the brain [15,39]. The brain processes the information and can activate multiple neuronal pathways to control peripheral inflammation, including the HPA axis and the sympathetic nervous system [20,21,40,41]. Second, the brain can also activate efferent pathways such as the efferent motor vagus nerve that innervate specific organs and will contribute to counteract peripheral inflammation [19]. These systems can also interact between them, and the vagus nerve (which does not innervate the spleen) can activate the sympathetic splenic nerve to release norepinephrine in the spleen (Figure 1A) [42–43]. Multiple studies suggest that the preganglionic vagus nerve can activate the post-LPS-ganglionic splenic nerve through the mesenteric ganglia. Although recent studies argue the synaptic connection from vagal preganglionic neurons to splenic postganglionic neurons [44,45], most studies concur in the lack of cholinergic innervations in the spleen and the joints and synovial capsule [46]. Most studies in sepsis suggest that neurogenic splenic norepinephrine activates β2-adrenoceptors of periarteriolar cholinergic lymphocyte sheet surrounding splenic nerve [28,42,47–49]. These lymphocytes can produce acetylcholine, which inhibits TNF production in the macrophages of the marginal zone [15,50,51]. This modulatory signaling depends on α−7 nicotinic acetylcholine receptors (α7nAChRs) expressed in macrophages because electrical vagal stimulation attenuates serum TNF levels in wild-type but not in α7nAChRs-KO mice [52]. In this neuroimmune pathway, the parasympathetic vagus nerve and sympathetic splenic nerve are connected as a sequential part of the same pathway. These models of functional organization of the nervous system can help to design novel therapeutic strategies co-stimulating different neuronal networks to achieve the most effective control of inflammation.

Efferent vagal & cholinergic regulation of inflammation

The potential of efferent vagal signaling to control inflammation in several critical disorders including infectious diseases [14,34], ischemia and reperfusion [53–55], postoperative trauma [56], hemorrhage, resuscitation [55], pancreatitis [57], endotoxemia [19], septic shock and severe sepsis [58,59] was demonstrated in multiple experimental studies. Most of these studies show that vagal stimulation inhibits TNF production in macrophages. This strategy is similar to using neutralizing anti-TNF antibodies, which were actually first used in endotoxemia to prevent septic shock [60]. Unfortunately, anti-TNF antibodies therapies failed in clinical trials for sepsis for two main reasons. First, sepsis induces an acute ‘early’ production of TNF that peaks within the first 2 h after the infection, and serum TNF levels return to a baseline by the time the patients arrive to the hospital. Thus, anti-TNF therapies are effective to ‘prevent’ experimental sepsis when the treatment is started before the septic challenge, but they provide a very narrow therapeutic time-window in clinical settings. Second, sepsis is characterized by the production of multiple inflammatory factors that can cause sepsis even in TNF-knockout mice [60–63]. Unlike sepsis, RA is characterized by a

chronic production of TNF and neutralizing anti-TNF therapies are currently the most effective treatment for arthritis [13].

From a pharmacological perspective, cholinergic agonists such as acetylcholine and nicotine inhibit the production of inflammatory cytokines in macrophages via α−7 nicotinic acetylcholine receptors (α7nAChRs) [35]. Recent studies indicated that α7nAChRs may regulate inflammation through cholinergic mechanisms independent on the vagus nerve, as nicotine can also activate neuronal pathways such as the splenic nerve by binding to neuronal α7nAChRs on the mesenteric ganglia (Figure 1B) [47]. As ganglionic cell bodies express nicotinic receptors, nicotine may act on these neurons to activate the splenic nerve to release neurogenic norepinephrine in the spleen inhibit TNF production in splenic macrophages [33,47,52]. At the cellular level, α7nAChR-agonists can activate several intracellular pathways to control cytokine production in macrophages by inhibiting the NF-κB and Jak2⁄Stat3 pathways as well as inducing miRNA124 [58,64–66]. Treatment with nicotine inhibits serum TNF and high mobility group box-1 (HMGB1; a late proinflammatory cytokine) levels and improves survival in experimental models of polymicrobial peritonitis [58]. Actually, cholinergic agonists such as nicotine have been previously used in clinical trials to control inflammation in ulcerative colitis [67]. These results suggest that specific cholinergic agonists may provide pharmacological advantages for treating autoimmune disorders.

Pharmacological translation for arthritis

The most standard experimental model of arthritis is challenging the animals with type II collagen, a protein mostly found in cartilages [68]. Collagen induces joint inflammation and pathological markers similar to that observed in human arthritis. Given that vagal stimulation inhibits TNF production in endotoxemic animals [19], investigators analyzed whether cholinergic agonists such as nicotine inhibit TNF production in experimental arthritis. Treatment with nicotine can reduce synovial TNF levels, joint swelling, inflammatory factors and histopathological score including both hyperplasia and bone erosion in collagen-induced arthritis [69–71]. However, the mechanism of these anti-inflammatory effects remains controversial. These results concur with recent studies showing that depletion of α7nAchR worsens inflammation in collagen-induced arthritis [72]. Thus, selective α7nAChR-agonists has been considered for treating arthritis due to their potential to inhibits TNF production and joint inflammation in arthritic mice [70,73,74]. Recent studies suggest that nicotinic agonists modulate macrophages by regulating specific subsets of lymphocytes. For example, nicotinic agonists induce T-helper cells shift to a Th2 anti-inflammatory phenotype [75]. Nicotine can also inhibit inflammation in arthritis by reducing IL-17 production by splenic α7nAChR-expressing Th17 cells [76], or preventing macrophage infiltration into the synovial tissues by inhibiting the expression of adhesion molecules such as ICAM-1 [77]. Indeed, RA was originally considered a Th1-mediated disease due to the high levels of TNF and IFN-γ and the lack of Th2-cytokines such as IL-4. However, recent studies show that Th1-cytokines are not the main effectors of arthritis autoimmunity, but a new subset T cells producing IL17 in human arthritic synovial fluid [78–80]. This lineage of Th17 cells is characterized by the expression of transcriptional factor RAR-related orphan receptor gamma-t (RORγ-t) as compared with

classical Th1 (Tbet) and Th2 (GATA3) [81–83]. Thus, inhibiting Th1/Th2/Th17 imbalance can be a potential strategy for treating arthritis [84,85]. Likewise, α7nAChRs in T-regulatory cells can also inhibit cytokine production in macrophages and prevent inflammation in arthritis [86]. Thus, α7nAChR-agonists can limit inflammation even in tissues lacking parasympathetic innervation such as the skin, skeletal muscle and synovial tissue, by regulating non-neuronal cells [46,87–90]. Macrophages and fibroblasts expressing functional α7nAChRs were originally identified in the synovial tissue of the arthritic patients [74,91,92] (Figure 1C). α7nAChR activation in these cells inhibits the nuclear translocation of NF-κB and thereby the production of inflammatory factors such cytokines [93].

Despite the beneficial effects of peripheral nicotinic control of inflammation in experimental sepsis and arthritis, the potential of nicotine-like drugs is limited by their side effects such as toxicity and addiction. Other studies reported that nicotine increases inflammation in experimental arthritis. Nicotine can enhance the formation of neutrophil extracellular traps by human neutrophils and exacerbate inflammation in murine collagen-induced arthritis by inducing autoantigens [94,95]. These results concur with epidemiological studies showing that cigarette smoking can contribute to autoimmune diseases such as arthritis [96]. This discrepancies about the effects of nicotine in arthritic may be due to its administration: pretreatment (before the arthritis induction) with nicotine aggravated adjuvant-induced arthritis severity in rats, whereas the nicotine post-treatment decreased inflammation and clinical score signs of arthritis [97]. Still, the effects and mechanisms of nicotinic agonists on inflammatory diseases such as RA are not totally understood.

Recent studies in murine collagen–induced arthritis depict a local non-neural catecholaminergic system modulating pro- and anti-inflammatory cytokines in the initial asymptomatic and secondary symptomatic phases of arthritis, respectively [98]. In the asymptomatic phase, the sympathetic signaling exacerbates collagen-induced arthritis via $CD4^+CD25^+$ T cells [99]. Synovial tissues of the patients with chronic RA show a significant decline in the density of sympathetic nerve fibers [100], similar to that observed in arthritic mice [98]. However, non-neural cells producing catecholamines are found in the synovial tissue and they seem to substitute the sympathetic innervations destroyed during the arthritis progression. These non-neural cells produce catecholamines to reduce local inflammation in the arthritic joints [101]. In the symptomatic phase, catecholamines activate B cells to produce IL-10 and attenuate joint inflammation in arthritis (Figure 1D) [102]. These basic physiological studies on neuromodulation are allowing the design of innovative therapeutic approaches to control inflammation in RA and other inflammatory and infectious disorders.

Vagal afferent signal & central processing of inflammation

Most studies show that the vagus nerve stimulation, focused on the efferent vagal signals toward the periphery, controls systemic inflammation in experimental sepsis by inhibiting splenic TNF production. Although some studies proposed a direct vagal innervation of the spleen [103], most studies suggest that the vagus nerve does not innervate the spleen [44]. Instead, efferent vagal terminals enter the celiac ganglion to activate the splenic nerve [43].

These apparent contradictions from surgical vagotomy and splenectomy provided different results depending on the experimental conditions. For instance, unilateral cervical vagotomy increased inflammation in septic and arthritic mice worsening morbidity and mortality [70,77,104,105].

Selective surgical neurectomies showed that cervical or subdiaphragmatic vagus nerve exerts specific functions transmitting afferent and efferent signals along the anti-inflammatory network. As the cervical vagal trunks are critical for both afferent and efferent nerve signals, its ablation blocks all signals regardless of their origin and processing [106]. The original studies on endotoxemia showed that the spleen has a critical role modulating systemic inflammation by linking both the nervous and immune system [14,51]. The spleen also contributes to sustain the chronic synovial inflammation in peptidoglycan–polysaccharide-induced arthritis in rats [107]. These studies showed that surgical splenectomy prevents the development of collagen-induced arthritis [107,108], but increased acute joint inflammation induced with intra-articular zymosan injection [24,109]. These results show that splenectomy *per se* has different effects on synovial immune response depending on several factors, as the inflammatory stimulus, the disease outcome and the immune cells stimulated. As RA has different inflammatory patterns along its development, these results may explain the debatable effects of splenectomy on clinical arthritis progression [110–112]. Furthermore, surgical splenectomy did not prevent the anti-inflammatory effect of vagus nerve stimulation in intra-articular zymosan-challenged animals or other models of inflammatory diseases [24,109,113], suggesting the existence of other vagal neuroimmune pathways.

In addition to the efferent vagal signal, the afferent vagal signals toward the brain can also contribute to modulate inflammation. Stimulation of the proximal part of sectioned vagus nerve also controls systemic inflammation in endotoxemic animals [47,114,115]. Neurophysiological studies showed that vagus nerve stimulation modulates splenic nerve activity by an afferent pathway (Figure 1E) [44]. Another example is that electrical stimulation of aortic depressor nerve inhibited joint inflammation, cytokine production and neutrophil infiltration in experimental arthritis [109]. The aortic depressor nerve is a critical component of the afferent vagal system that contributes to the baroreflex system, an autonomic neuronal network that maintains cardiovascular homeostasis. Although the vagus nerve is the principal nerve of the parasympathetic system, morphological studies show a subpopulation of tyrosine hydroxylase positive (sympathetic) fibers at the cervical vagus nerve [116,117]. Moreover, the synovial tissue is innervated by adrenergic but not by cholinergic nerves [46]. Afferent vagal stimulation activates specific brain sympathetic-excitatory structures, especially the locus coeruleus (LC) and the paraventricular hypothalamic nucleus, and reduces knee joint inflammation in an acute model of RA (Figure 1F) [24]. Of note, the synaptic connection between vagal afferent signals (toward the NTS) and the LC (a brain noradrenergic nucleus) was mandatory for the vagal anti-inflammatory effects. This vagus nerve-LC-joint network is completely independent of the spleen and the adrenal glands, but is mediated by central and local sympathetic neural networks and synovial β-adrenergic receptors [24,109]. Several studies concur with these findings, reporting the role of sympathetic nervous system [118,119] and β2-adrenoreceptors [48,120] in the neural regulation of immunity. A similar anti-inflammatory effect in mice was also

observed after the stimulation of C1 neurons, a neuronal group located in the medulla oblongata with reciprocal connections with the LC (Figure 1G) [121]. Vagal stimulation has a widespread and stimulatory effect on many specific cortical and subcortical regions of the brain [122–126]. Of note, cortical or vagal stimulation activated similar brain structures: in addition to the LC and paraventricular hypothalamic nucleus, both stimulatory modalities increased the activity of other neural structures involved with autonomic control, as the periaqueductal gray matter, raphe, amygdaloid nuclei and piriform cortex [29]. Actually, stimulation of the piriform cortex reduces joint inflammation in arthritic rats through a LC-dependent sympathetic mechanism. These results reveal, for the first time, a brain map formed by specific neural structures with potential immunomodulatory properties (Figure 1H) [29]. These results concur with clinical studies showing that some arthritic patients that suffered central neural lesions or cerebrovascular accidents, displayed reduced or even absence of arthritis on the affected side [127–130] and clear impairments on the local sympathetic activity and vascular permeability [131,132]. However, the neural or humoral networks between the brain and joint inflammation remained unknown. Further studies indicated that stimulation of primary afferent nociceptors from the inflamed area can attenuate the inflammatory process via a brain feedback toward the HPA axis activation [133–135]. Curiously, this anti-inflammatory effect was potentiated in animals that underwent subdiaphragmatic vagotomy, suggesting that vagal mechanisms are involved in central modulation of peripheral inflammation [134,136]. These results reveal that, in addition to the efferent vagal pathway, afferent vagal signaling modulates peripheral inflammation by activating central neuronal pathways [137,138].

Experimental and clinical studies show that vagal stimulation limits inflammation in RA through central vagal-mediated mechanisms controlling joint arthritis inflammation [27,139]. These physiological mechanisms appear similar to that of the spleen [43]. The vagus nerve can modulate inflammation in the arthritic joints by coordinating with the sympathetic adrenergic system. Unlike the spleen, whose neural activity is modulated via a vagal efferent subdiaphragmatic connection in the celiac-mesenteric ganglia with the splenic nerve, vagal regulation of arthritic joints may be mediated by afferent vagal signals activating central pathways and efferent sympathetic adrenergic networks innervating the joints [140,141].

From a physiological perspective, these studies on neuromodulation depict new models of functional organization of the nervous system to control inflammation [14]. Classically, the sympathetic and parasympathetic systems are described as ‘antagonistic’ mechanisms opposing one another to balance physiological homeostasis. The sympathetic and parasympathetic nervous systems produce antagonistic signals with norepinephrine and acetylcholine to balance both heart beat rate and blood pressure. A characteristic example is the baroreceptor reflex system [142]. Arterial baroreceptors are stretch receptors stimulated by distension of the arterial wall to control blood pressure. If blood pressure falls, baroreceptor firing rate decreases, and the central nervous system activates the sympathetic system to produce norepinephrine and increase the heart rate and blood pressure. Conversely, when blood pressure rises, the baroreceptor reflex activates the parasympathetic nervous system to release acetylcholine and decrease the heart rate and blood pressure. The recent findings of vagal neuromodulation of inflammation in endotoxemia suggest a

different level of functional organization through a ‘sequential’ connection between the parasympathetic and sympathetic systems to inhibit cytokines production.

Bioelectronic medicine

Bioelectronic medicine is a new medical field that includes electrical engineering, neurophysiology and molecular biology designing novel treatments and diagnostics by using electronic devices to interface with the body [143]. Electric fields could be used to improve the outcome of patients with cancer [144,145]. Bioelectronics medicine has also been proposed as an innovative strategy to control inflammation and organ function by targeting distinct nerves and brain networks [143,146–149]. In 1997, the US FDA approved the use of a pulse generator implanted under the skin below the clavicle to induce electrical vagal stimulation for treating refractory epilepsy [150]. These treatments are proved safe without major side effects, and similar stimulation procedure was also approved in 2005 by the FDA for drug-resistant depression [151].

Growing preclinical and clinical studies evidence the potential of vagal stimulation to reduce inflammation in arthritis. An initial preclinical study demonstrated that cervical vagal stimulation with implantable electrodes reduced inflammation, articular bone loss and clinical score of collagen-induced arthritis in rats [26]. Electrical vagal stimulation with an implanted device (Cyberonics®/LivaNova) in epilepsy patients (n = 7) decreased the TNF, IL-1β and IL-6 production in whole-blood incubated with lipopolysaccharide (LPS) [27]. Also, vagus nerve stimulation for a short period (maximum time: 4 min/day for 84 days) inhibited cytokine production and improved the clinical score in 12 of 17 RA patients in two cohorts (total n = 17; cohort I: RA patients in the early stage of disease refractory to methotrexate treatment; cohort II: RA patients in the late stages of disease refractory to biological therapy) [27,147].

Recently, transcutaneous noninvasive vagus nerve stimulation has become available to replace permanent device implantation in RA patients by using gammaCore© (a cervical vagus nerve stimulator approved for the treatment of various types of primary headaches, including migraine and cluster headaches) [152,153] and Nemos® (a device of auricular branch vagal stimulation used in drug-resistant patients to decrease the seizure frequency) [154]. A preliminary, randomized and blinded pilot trial demonstrated in whole blood culture of healthy volunteers (n = 20) that gammaCore decrease the release of proinflammatory cytokines and chemokines and increase IL-10 anti-inflammatory cytokine as compared with sham stimulation [155]. The bilateral stimulation of cervical vagal nerve with gammaCore increase the cardiac vagal tone and reduces TNF blood levels in healthy subjects (n =20) [156]. Likewise, transcutaneous auricular vagus nerve stimulation can also inhibit blood levels of proinflammatory cytokines in endotoxemic rats [157].

Future perspective

The design of new neuroimmunomodulatory therapies for arthritis will require the study of: the physiological neural networks modulating the immune system, especially in the joints, the specific neurotransmitters and receptors controlling immune cells and their

pharmacological properties, the role of autonomic dysfunction in arthritis and other chronic inflammatory disorders, the design of low-cost bioelectronic devices to control inflammation and organ function through neuronal stimulation; and potential side-effects of these new therapies.

Recent studies indicate that cholinergic regulation of the immune system is not exclusive to the vagus nerve. For instance, high concentrations of norepinephrine (1 mM) can activate splenic lymphocytes to produce acetylcholine, which inhibits cytokine production in splenic macrophages [42,47]. Acetylcholine can also be produced by choline acetyltransferase-expressing T cells that migrate into the spleen after efferent vagal stimulation (Figure 1I) [28]. These results warrant further studies to determine why lymphocytes require such high concentrations of norepinephrine to produce acetylcholine, the specific homing of T cells into the spleen, and their cellular responses. Furthermore, new studies should analyze the role of other organs involved in arthritis, such as the lymph nodes, which modulate the immune response in RA and that are innervated by sympathetic fibers and regulated by β-adrenergic signaling [158].

The stimulation of specific cholinergic pathways by pharmacological agents such as acetyl-cholinesterase inhibitors and β2 adrenergic agonists can be considered as potential strategies to control inflammation in arthritis [159–162]. Recent studies showed that activation of central muscarinic M1 or peripheral M3 receptors reduced inflammation in endotoxemia and delayed the progression of collagen-induced arthritis, respectively [163,164]. It is also known that vagal stimulation releases other neurotransmitters such as the neuropeptide vasoactive intestinal peptide (VIP). VIP has immunomodulatory effects on collagen-induced arthritis and therefore VIP could be used for treating arthritis [165]. The spinal cord is considered the key intermediate between the brain and peripheral sympathetic networks [18,24,166,167]. Therefore, pharmacological or electrical (bioelectronics) strategies modulating the spinal cord excitability could represent therapeutic approaches for treating arthritis. Examples of drugs that modulate spinal neuronal activity and inhibit inflammation in arthritis are GABAb receptor antagonists and cytokine-neutralizing agents, such as p38 MAPK inhibitors and anti-TNF molecules [168].

Heart rate variability (HRV) is a functional measure of the autonomic balance. Multiple studies suggest that HRV correlates with inflammation and may reflect autonomic dysfunction contributing to inflammatory disorders [169]. However, this view is still controversial because parasympathetic and sympathetic signaling are essentially organ-specific [104]. In addition, autonomic dysfunction is a common signal in inflammatory diseases, suggesting that the disruption of the parasympathetic⁄sympathetic balance is not specific to a neural system. Lower HRV may correlate to the higher incidence of sudden death in the arthritis patients [170]. Indeed, several studies correlated decreased vagal or increased sympathetic tonus with a worse outcome in RA [169,171]. For example, it has been shown an association between reduced vagal tonus and elevated blood levels of HMGB-1, a proinflammatory cytokine, contributing to arthritis [171]. In fact, high HMGB-1 levels were associated with low α7nAChR expression by peripheral circulating monocytes in the arthritic patients, suggesting a cholinergic signaling deficiency [172]. In summary, HRV is a biological signal with promising application to predict arthritis outcome, and to

investigate the efficacy of pharmacological treatments, as anti-TNF therapies [173], although its mechanisms need further study.

From a bioelectronic perspective, the stimulation of other nerves (e.g., splanchnic nerve) with noninvasive approaches (e.g., pulsed ultrasound) may also provide therapeutic advantages to control inflammation without the side effects observed with conventional invasive methods [119,137,148,174]. Electroacupuncture is another alternative medical treatment with promising use in RA. Stimulation of the sciatic nerve with electroacupuncture controls systemic inflammation in endotoxemic mice through a vagal-adrenal dependent pathway and dopaminergic modulation of the immune cells [175]. This novel neuroimmune pathway could shed light on the mechanisms of electroacupuncture to alleviate arthritis [176–179]. Moreover, from a pharmacological perspective dopaminergic agonists could be used to control inflammation in arthritis due to their ability to inhibit Th17 cytokines [180].

In addition to the promising results on vagal control of joint inflammation, the potential side effects of vagal stimulation in RA are not known. The current use of vagal stimulation for the treatment of refractory epilepsy appears to induce minor side effects related to cervical surgical implantation, as such local infections, vocal cord paralysis and electrode rejection [181,182]. These clinical studies indicate that vagal stimulation does not produce immunosuppression as found with the biological drugs used in the treatment of arthritis. The patients under antirheumatic drug therapy appear to have more severe side effects mainly immunosuppression [11,12]. On the other hand, it has been proposed that neurological disorders can affect peripheral inflammation. For instance, neurological damages increase the susceptibility to infections triggering chronic autonomic output signals [183–185]. A recent study showed that occlusion of one middle cerebral artery (a classic model of stroke) prevents the progression of arthritis [186]. These studies suggest that vagal stimulation may also re-establish neurological function contributing to potential inflammatory disorders.

Conclusion

Despite its recent identification, a large number of studies show the potential of the vagus nerve to control the immune system and attenuate inflammation in both infectious and inflammatory disorders. A growing number of studies show the beneficial effects of cervical vagal stimulation to control experimental and clinical arthritis, even in patients refractory to current antirheumatic treatments. The local (joints) and⁄or systemic (spleen) targets of distinct (afferent⁄efferent) vagal signals may be more complex than anticipate and they need to be described in detail. Moreover, while the sympathetic and parasympathetic nervous systems have been described as opposing functional systems, multilevel interactions between both systems may be responsible for the control⁄exacerbation of inflammation in arthritis and must be clarified in the future. It is also possible that in the experimental models of arthritis, time and⁄or intensity of vagal stimulation influence diverse neuroimmune pathways in isolated or integrative (when more than one pathways are activated simultaneously) mechanisms. A recent study shows a central neural arc that includes vagal afferents-LC-sympathetic innervations in the regulation of joint inflammation. In addition, this novel neuronal network involving cortical-LC-sympathetic signaling could be

stimulated by noninvasive methods such as electrical and magnetic transcranial techniques. Finally, the presence of catecholaminergic and cholinergic non-neural systems in the synovial tissue can provide new therapeutic targets for designing innovative treatments for arthritis.

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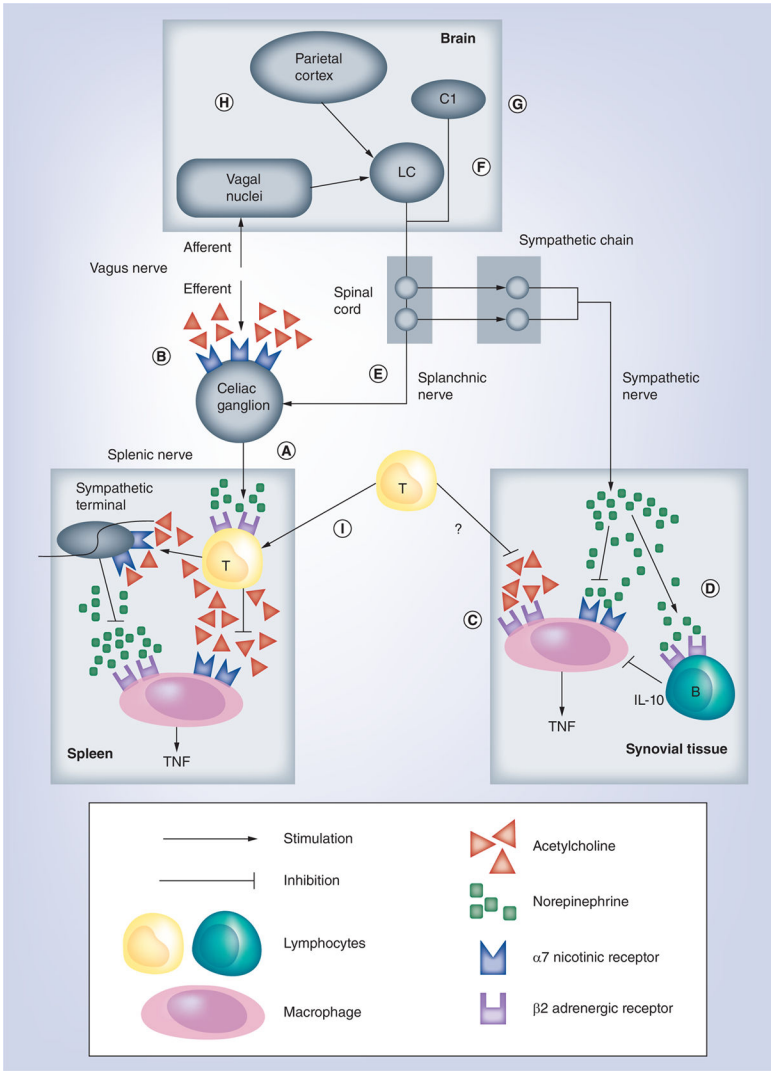

Figure 1. Description of neuroimmune circuits with potential therapeutic use in the treatment of arthritis.

An efferent vagus nerve can inhibit inflammation through the activation of splenic nerve **(A)** by a neuroimmune pathway constituted by alpha-7 nicotinic acetylcholine receptor (α7nAChR)-expressing mesenteric ganglia **(B)** and splenic acetylcholine-producing T lymphocytes. Afferent vagal signaling, sympathetic C1 neurons **(G)** and cortical stimulation **(H)** can prevent local joint inflammation by a mechanism dependent on activation of LC **(F)** followed by stimulation of splanchnic nerve **(E)** or synovial sympathetic innervations **(C & D)**. An articular non-neural cholinergic system improves local inflammation by a mechanism dependent on a7nAchR expressed in macrophage⁄fibroblast **(C)** while a neural adrenergic system inhibits local inflammation by direct (β-adrenoceptors) or indirect (IL-10-producing B lymphocytes) mechanisms **(D).** A recent hypothesis suggests that non-neural acetylcholine can be produced by peripheral T-cells that migrate to organs (e.g., spleen) after vagal stimulation **(I)**. LC: Locus coeruleus.