Published in final edited form as:

Curr Rheumatol Rep. 2023 January ; 25(1): 1–11. doi:10.1007/s11926-022-01094-2.

Neuromodulation as a Potential Disease-Modifying Therapy for Osteoarthritis

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Abstract

Purpose of Review—The following review discusses the therapeutic potential of targeting the autonomic nervous system (ANS) for osteoarthritis (OA) treatment and encourages the field to consider the candidacy of bioelectronic medicine as a novel OA treatment strategy.

Recent Findings—The study of OA pathogenesis has focused on changes occurring at the joint level. As such, treatments for OA have been aimed at the local joint environment, intending to resolve local inflammation and decrease pain. However, OA pathogenesis has shown to be more than joint wear and tear. Specifically, OA-related peripheral and central sensitization can prompt neuroplastic changes in the nervous system beyond the articular joint. These neuroplastic changes may alter physiologic systems, like the neuroimmune axis. In this way, OA and related comorbidities may share roots in the form of altered neuroimmune communication and autonomic dysfunction.

Summary—ANS modulation may be able to modify OA pathogenesis or reduce the impact of OA comorbidities. Moreover, blocking chronic nociceptive drive from the joint may help to prevent maladaptive nervous system plasticity in OA.

Keywords

Osteoarthritis; Vagus nerve stimulation; Neuroimmune axis

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Author Contribution CJC and KDA conceptualized this review. CJC drafted the manuscript, with critical contributions from LSD, KJO, and KDA. All authors approved the final version of the manuscript and figures.

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not include any human or animal research that was performed by the authors.

Introduction

Individuals suffering from osteoarthritis (OA) experience a lower quality of life, chronic pain, and greater healthcare expenses. Developing treatment strategies for OA begins by understanding the pathophysiology of the disease. While the etiologic causes of OA vary, the pathophysiology of chronic OA is well characterized as maladaptive joint remodeling in response to changing mechanical loads [1], cellular stress [2], and chronic low-grade joint inflammation [3]. These maladaptive changes result from the joint's attempt to restore homeostasis; however, healthy homeostasis never returns to the OA-affected joint due to the limited capacity of cartilaginous structures for self-repair [4]. The destruction of the OA-affected joint first produces peripheral sensitization due to both chronic inflammation and shifting joint mechanics. Here, in the early stages of OA, activation thresholds in joint nociceptors are altered by joint inflammation and other pathologic factors, and joint loading causes movement-evoked pain [5]. Over time, prolonged peripheral sensitization can result in lower thresholds in dorsal horn neurons [6–8] (central sensitization) or damage to joint innervation (neuropathic pain) [9–11]. These known neuroplastic components relating to OA pain raise the question of whether OA also prompts functional shifts in other neural communication axes. Specifically, do neuroplastic changes in OA extend to neuroimmune communication involving the autonomic nervous system (ANS)?

Recent reviews have suggested that dysfunction of the ANS occurs with OA pathophysiology [12, 13•, 14•]. Moreover, recent evidence has suggested crosstalk occurs between the joint and ANS [15]. While the physiological links between OA and ANS crosstalk are not yet fully characterized, the ANS has a known role in controlling peripheral inflammation via the neuroimmune axis. As such, shifts in ANS balance could increase susceptibility to inflammatory insult or make it more difficult for inflammatory pathologies to resolve [16–18]. Therefore, ANS dysfunction could act as a risk factor for OA by increasing susceptibility to and/or speeding OA pathogenesis. Such relationships imply that therapies targeting ANS function could alter OA pathophysiology.

Therapies that target the ANS include non-pharmacologic physiotherapy [19] and exercise[20], as well as the use of vagus nerve stimulation (VNS). In VNS, electrical stimulation of the vagus nerve is used to increase parasympathetic tone and produce systemic (e.g., circulating cytokines and monocytes) and local (e.g., joint inflammation) anti-inflammatory effects. The anti-inflammatory effects of VNS have been shown in rheumatic joint diseases such as RA [21], introducing the question of whether VNS could be effective for related, but less inflammatory diseases, like OA. These anti-inflammatory effects may be especially therapeutic in the later stages of OA, when inflammation is more pronounced and patient mobility and activity is more affected, limiting access to rehabilitative- and exercise-based therapies. In addition to VNS, bioelectric modification of nociceptive signals has been used as a pain-targeting therapy in OA [22]. Bioelectric blockade or modification of nociceptive signals could have protective effects on neuroplastic shifts in the peripheral and central nervous systems. As such, this review serves to discuss the potential disease-modifying effects of neuromodulation in the context of OA and encourage the field to consider neuro-modulation as a treatment strategy for OA.

OA and Autonomic Dysfunction

OA involves a vicious cycle of progressive joint damage and inflammation, chronic pain, limited mobility, and the onset of chronic comorbid disease (blue/solid lines in Fig. 1). In parallel, autonomic dysfunction occurs at high rates in conditions that are prevalent in patients with OA (e.g., hypertension, obesity, diabetes, and aging), and a dysfunctional ANS could contribute directly to OA pathogenesis (orange/dashed lines in Fig. 1).

Autonomic Dysfunction with Common OA Comorbidities

The relationship between ANS dysfunction and a patient's susceptibility to OA is highlighted by common OA comorbidities and risk factors. For example, the incidence of OA in patients with obesity [23–25], hypertension [26–28], and diabetes [29, 30] are significantly high; in all three diseases, attenuated parasympathetic function has also been noted. Furthermore, attenuated parasympathetic function is seen in OA risk factors such as aging [31, 32] and physical inactivity [33–36]. Due to the role of the parasympathetic nervous system in regulating peripheral inflammation, ANS dysfunction may present a risk factor for OA.

Figure 1 describes how a dysfunctional ANS may contribute to OA pathogenesis. Specifically, the immune ramifications of low vagal tone may simultaneously worsen OA and exacerbate comorbidities. For example, moderate exercise may both increase parasympathetic activity [36] and decrease joint swelling and symptoms in OA [34]. On the other hand, obese individuals also show a dysfunctional ANS through lower vagal tone [23–25] and corresponding increases in systemic inflammation [37]. Importantly, autonomic dysfunction in obese individuals is reversible with weight loss [38], and obese OA patients who have lost at least 10% of their body weight also show improvement in OA symptoms [24]. While the parallel improvement in ANS function and OA symptoms does not prove a definitive link between the ANS and OA, comorbidities that tend to lead to ANS dysfunction (e.g., aging, obesity, diabetes) also tend to increase the incidence of OA; and therapies that tend to improve ANS function (e.g., exercise, weight loss) also tend to improve OA symptoms.

Therapeutic avenues that rebalance the ANS might achieve similar OA symptom relief as seen with exercise and weight loss. For example, bioelectronic stimulation of the vagus nerve can address low vagal tone. This could be especially beneficial for OA patients who lack mobility, may not be able to engage in physiotherapy or physical exercise, or may need initial assistance in implementing a lifestyle change to incorporate more exercise and activity. As with the selection of any therapeutic, the benefits of VNS must outweigh the known side effects [39, 40]. Therefore, additional studies are needed to evaluate the utility of VNS and justify its usage for OA management.

Crosstalk Between the Autonomic Nervous System and the Joint

Joint-level changes in OA are hypothesized to shift ANS function through the brain-joint axis, as depicted by Fig. 2. First, joint-level changes such as cartilage breakdown [41], synovial inflammation [42–44], and bone remodeling [4] occur in early OA. Following

these joint-level changes, chronic joint inflammation fails to resolve, causing sensitization of peripheral nociceptors. Following the sensitization of peripheral nociceptors, altered neuroimmune communication occurs between the OA joint and the nervous system, which may lead to pathologic shifts in brain-joint axis function.

The brain-joint axis is simple to describe, yet the driving mechanisms are complex: Afferent sensory stimuli from the joint serve as input to the axis, while feedback is relayed back to the joint through multiple, indirect mechanisms. These mechanisms include modulation of systemic cortisol levels via the hypothalamic–pituitary–adrenal (HPA) axis [45, 46], alteration of gut function [47], and systemic cytokine production [48] and monocyte trafficking [49] from the spleen, among others. In the context of OA, pathologic shifts in the brain-joint axis likely commence once joint inflammation fails to resolve. Specifically, inflammatory mediators within the OA-affected joint (such as TNF-α, IL-1ß, IL-17, and IL-6) sensitize joint nociceptors [50]. Such sensitization produces chronic signaling of peripheral nociceptors, which leads to central sensitization [6, 7]. As nociceptive signals increase from the joint to the brain, functional shifts may occur in other regions of the nervous system, including brain regions that influence ANS balance. Alterations in ANS balance could then derail the healthy function of the brain-joint axis, further exacerbating OA pathogenesis.

For dysfunction of the brain-joint axis to occur, crosstalk between the joint and the central autonomic network must occur, which has been shown for ANS and nociceptive inputs. For example, negative feedback between nociception and vagal tone has been shown in rats [51]. Moreover, in a limited patient cohort, indirect measures of ANS function (galvanic skin response) and changes in the central autonomic network were associated with chronic musculoskeletal pain [52]. In addition, nociception and cardiac autonomic activity, as well as activity in the pain matrix and central autonomic network, have been functionally correlated [53]. Therefore, functional shifts in the ANS and the brain's pain centers could explain why ANS dysfunction is noted in multiple OA-related risk factors and common comorbid conditions. Unfortunately, an understanding of the mechanisms governing plastic changes to the brain-joint axis during OA is lacking. However, these limited findings suggest potential therapeutic opportunities for rebalancing the ANS in chronic musculoskeletal disease, such as OA.

Targeting the Autonomic Nervous System for OA Treatment

Modulating parasympathetic nervous system activity may serve as a potential treatment strategy for OA. Specifically, vagus nerve stimulation (VNS) can increase parasympathetic activity and activate various anti-inflammatory pathways that ameliorate peripheral inflammation [54–58, 59••]. VNS works by depolarizing vagal nerve fibers, causing nerves to fire and transmit both afferent and efferent signals. As shown in Fig. 2 (blue/dashed lines), afferent vagal signals can activate the splanchnic anti-inflammatory pathway, HPA axis, and other regions of the central nervous system, such as sympathetic control centers. On the other hand, efferent vagal signals can activate the cholinergic anti-inflammatory pathway and modify gut health, as shown in Fig. 2 (orange/solid lines). As a result, VNS can

modulate activity in multiple neuroimmune pathways that may drive a combined therapeutic effect in OA, as will be detailed below.

Targeting the Cholinergic and Splanchnic Anti-inflammatory Pathways

VNS can reduce peripheral inflammation, which could potentially decrease joint inflammation in OA. For example, VNS can decrease systemic levels of TNF-α and IL-1ß, while increasing levels of an anti-inflammatory cytokine (IL-10) [60]. Although OA alone often does not have a significant impact on systemic inflammatory levels, reducing systemic pro-inflammatory cytokines may relieve OA-related pain, joint damage, and joint inflammation [61–63]. Moreover, VNS can modify immune cell phenotypes, where VNS alters cell surface ligands on neutrophils and thereby decreases their ability to migrate to a peripheral inflammatory site [64]. Since circulating immune cells can infiltrate synovium to produce synovitis and synovitis is correlated to clinical OA pain, lowering immune cell recruitment to the OA-affected joint could be therapeutic [65, 66]. In addition, following collagen-induced arthritis, 15 days of VNS resulted in reduced pannus formation, less cartilage damage, and decreased bone resorption in the ankle [67].

Immune cells migrating to the joint environment play a critical role in the OA pathogenesis [68]. As such, employing therapies that can decrease the buildup of immune cells in the joint may be effective in treating OA. Interestingly, VNS can reduce the number of circulating immune cells that may migrate to a peripheral site of inflammation, such as the OA-affected joint. Here, VNS decreases serum levels of pro-inflammatory CD11b + /Ly-6c + monocytes in mice, while keeping levels of anti-inflammatory CD11b + / Ly-6c − monocytes unchanged [55]. As such, VNS may reduce the levels of circulating pro-inflammatory monocytes that can migrate to joint tissues. VNS can also decrease the accumulation of inflammatory cells in peripheral inflammatory sites and alter their cellular phenotype. For example, VNS decreases CD11b levels on neutrophils, a beta-2 cell-surface ligand that assists with immune-cell chemotaxis and adhesion to tissues [64]. Chemical VNS produces similar anti-inflammatory results, where the accumulation of inflammatory cells decreased in mice ears following inflammatory lipopolysaccharide challenge [69]. Chemical VNS also lowered chemokines such as IL-8, CCL2, and RANTES in TNF-α-challenged human microvascular endothelial cells [69]. Chemokines, such as CCL2 and IL-8, play an important role in immune cell chemotaxis to an inflammatory site and have been implicated in the pathophysiology of OA [70]. However, to date, no studies have evaluated the impact of VNS on immune cell trafficking to the OA joint. As such, determining if VNS can alter joint inflammation in OA is an important next step.

Targeting the Sympathetic Nervous System

Crosstalk between the two branches of the ANS (the parasympathetic and sympathetic nervous system) occurs regularly to promote body-wide homeostasis. Specifically, afferent vagal fibers relay signals to the nucleus tractus solitarius in the brainstem, the region where afferent vagal signals terminate. Following the activation of the nucleus tractus solitarius, signals can be relayed to other regions of the nervous system, such as sympathetic control regions. In the case of ANS dysfunction, parasympathetic-sympathetic crosstalk may become dysfunctional, shifting healthy peripheral immune homeostasis. As such, better

characterization of the relationship between parasympathetic-sympathetic balance and the OA-affected joint could yield new knowledge on OA pathophysiology and encourage new therapeutic approaches to treat OA.

Indirect activation of the sympathetic nervous system via VNS has shown to impact joint inflammation; this highlights the potential for functional relationships between the sympathetic nervous system and OA pathophysiology. Mechanistically, afferent vagal signals via VNS terminate at the nucleus tractus solitarius, where they can be relayed to subcortical and cortical regions of the brain via ascending pathways [71•, 72•, 73–75]. Following the activation of ascendingpathways by VNS, activity in sympathetic control regions of the brain can be modulated. For example, VNS can alter activity in various sympathetic control regions such as the paraventricular hypothalamic nucleus [72•], locus coeruleus [72•], parietal cortex [71•], and cingulate cortex [71•]. Following the modulation of these sympathetic control regions, joint-innervating sympathetic nerve fibers can release norepinephrine into the joint environment [76]. Here, increases in joint norepinephrine levels have coincided with decreased joint inflammation following VNS in a rat model of arthritis [71•, 72•]. Mechanistically, increases in joint norepinephrine levels may drive changes to chondrocyte metabolism and result in anti-inflammatory effects. For example, norepinephrine decreases the production of catabolic factors in chondrocytes which promote cartilage degradation, a hallmark of OA that results in joint inflammation [77–79]. Apart from the various anti-inflammatory pathways that VNS activates to resolve peripheral inflammation, the information reviewed here suggests the sympathetic nervous system may regulate joint-level inflammation and bone remodeling under OA conditions. As a result, future studies that characterize the relationship between the sympathetic nervous system, joint inflammation, and joint structure could produce new findings on OA pathophysiology.

Dysfunction between parasympathetic-sympathetic crosstalk may increase susceptibility to OA or exacerbate preexisting OA. For example, both sympathetic [52] and parasympathetic [80, 81] dysfunction has been noted in patients suffering from chronic musculoskeletal disease. Moreover, in a preclinical model of OA, sympathectomy resulted in worsened subchondral bone remodeling [82]. Since both the parasympathetic and sympathetic nervous systems work in concert to promote peripheral immune homeostasis, shifts from their normal function may dysregulate neuroimmune homeostasis at the joint level. As a result, these physiological links encourage future preclinical and/or clinical studies that can clarify the relationship between sympathetic dysfunction and joint-level changes within the context of OA.

Targeting the HPA Axis

The HPA axis and the sympathetic and parasympathetic components of the ANS share functional relationships [45, 83]. Specifically, crosstalk between the HPA axis and ANS helps to coordinate stress responses, circadian rhythm [13•], immunity [84], and metabolism [85], among other tasks. In the case of a dysfunctional ANS, the HPA axis may also become dysfunctional, or vice versa. For example, physiological stressors associated with OA such as joint inflammation [86] and pain [87, 88] can chronically alter HPA axis homeostasis.

As a result, ANS dysfunction can take place in the form of parasympathetic withdrawal and overcompensation by the sympathetic nervous system [45, 89].

Since the HPA axis can produce strong immunomodulatory effects via control of endogenous glucocorticoids, dysfunction of the HPA axis via the ANS may worsen an already inflammatory joint environment [84]. Here, defective HPA axis coordination in humans and animals can increase the organism's susceptibility to inflammatory disease [90, 91]. These same systems also play a role in peripheral tissue circadian clocks, which have been suggested to be involved in OA pathogenesis [13•]. Finally, because several studies have reported altered cortisol levels in OA patients, a dysfunctional HPA axis may occur in chronic OA [92–94].

Therapies that rebalance the HPA axis may help restore immune homeostasis and reduce the risk of chronic comorbid disease in OA, including bioelectronic modalities such as VNS. For example, increasing vagal tone through VNS may alter HPA axis function in rats [95, 96]. However, evidence of HPA axis modulation within the context of OA is lacking. Nonetheless, the pathophysiological links between the ANS, HPA-axis, and VNS are clear enough to warrant more study.

Rebalancing the Gut-Brain-Joint Axis in OA

The ANS also plays a role in the maintenance of gut health. Specifically, the parasympathetic and sympathetic branches work in concert to regulate intestinal blood flow, intestinal permeability, and gut microbiome diversity, among other characteristics [47]. As such, chronic conditions that include a dysfunctional ANS could prompt pathological shifts in gut health. For example, a loss of gut microbiome homeostasis has been reported to coincide with obesity-related OA [97, 98]. Both obesity and gut dysbiosis coincide with common OA comorbidities and risk factors where ANS dysfunction is noted, such as physical inactivity [99]. Moreover, since vagal tone influences gut microbiome diversity and intestinal permeability, a shift in vagal function could alter gut health homeostasis.

Since the ANS influences gut wall permeability, therapies that rebalance the ANS could potentially help restore gut health. Specifically, decreasing intestinal wall permeability through VNS may reduce the amount of bacteria and toxins that leak from the gut into the systemic circulation, as shown in Fig. 2. For example, mice challenged with bacterial lipopolysaccharide showed less intestinal permeability along with lower damage and inflammation to the small intestine following VNS [100]. Moreover, these shifts in intestinal permeability were ameliorated with chemical block of acetylcholine receptors, demonstrating a mechanistic link between VNS, the ANS, and the gut [100]. Other groups have evaluated links between the gut microbiome and OA [97]. For example, animals fed a high-fat diet display significantly worse histological scores of knee OA, greater synovial fluid inflammation, greater serum lipopolysaccharide levels, and greater pathological shifts in gut microbiome diversity [97]. Interestingly, increased joint damage was correlated to decreases in Lactobacillus spp., a probiotic that protects the gut barrier [97, 101]. Since altered gut health correlates with OA severity, evaluating whether VNS can rebalance the gut-brain-joint axis is an important next step for evaluating VNS as an OA therapy.

Clinical Applications of VNS for OA

In the clinic, VNS has achieved successful therapeutic results in other joint diseases. For example, VNS has been able to lower inflammation and clinical scores in patients with rheumatoid arthritis [58]. For OA, similar studies are still undergoing preliminary trials; however, one study did clinically evaluate VNS in OA patients. Here, VNS decreased swelling, tenderness, and joint pain in patients presenting erosive hand OA [59••]. Although such data is promising, erosive hand OA is generally more severe than primary OA and may associate with high inflammatory activity. As a result, evaluating whether the reported therapeutic effects of VNS occur in other OA patient populations are needed, as well as determining the optimal stimulation parameters for OA treatment [102].

Damping Nociceptive Input from the OA Joint into the Brain-Joint Axis

Chronic joint inflammation in OA leads to sensitization of joint nociceptors and results in peripheral and central sensitization. Initially, peripheral sensitization of joint-innervating nociceptors occurs, resulting in the increased and repetitive firing of action potentials to the dorsal horn of the spinal cord [5]. Moreover, prolonged peripheral sensitization can lead to central sensitization [6–8], resulting in the amplification of nociceptive input from the OA joint to the central nervous system. Sensitization of nociceptors results in chronic pain, but can also result in neuroplastic shifts to other physiological axes, such as the ANS. For example, individuals suffering from central sensitization show a dysfunctional ANS [16, 80, 103, 104]. Since the ANS plays a key role in maintaining a healthy brain-joint axis, perturbations in ANS function may exacerbate OA or be a risk factor for developing OA. As shown in Fig. 2, a decrease in nociceptive signals from the OA joint could protect against neuroplastic shifts in the brain-joint axis. Several bioelectric modalities could be used to decrease nociceptive joint signaling, including peripheral nerve block and spinal cord stimulation.

Targeting peripheral nociceptive signals from the OA joint could help manage chronic pain and potentially protect against central sensitization. Some bioelectric therapies transcutaneously stimulate the joint, such as pulsed electromagnetic stimulation [105]. These therapies may be able to decrease nociceptive joint signaling, but they do not specifically target the nervous system, may not have sufficient stimulation parameters to directly affect the nerve, and will also apply stimulation to surrounding tissues [22, 105]. Bioelectric modalities that directly stimulate the nervous system could involve the use of high-frequency alternating current stimulation to induce a nerve conduction block [106–109]. Here, peripheral high-frequency block has been successful in treating neuropathic pain in humans [110] and rats [111]. Additionally, dorsal root ganglia stimulation has been used as a treatment for chronic pain [112, 113] and has been successful in treating preclinical arthritic conditions [114, 115]. However, it is unknown whether these bioelectric pain treatments could also reduce maladaptive ANS plasticity resulting from chronic nociceptive inputs in OA. Therefore, evaluating if peripheral bioelectric stimulation could alleviate sensitization and protect against maladaptive ANS changes in OA should be further studied.

Beyond the peripheral nervous system, spinal cord neurons are another potential site for the modification of nociceptive signals related to OA. When OA causes central sensitization,

neurons in the dorsal horn are sensitized and interneuron circuits are modified [116]. Some of these neurons synapse onto ANS neurons and control ANS spinal reflexes [117]. Since spinal cord pain processing interacts with the ANS, these maladaptive changes at the dorsal horn may both exacerbate OA pathogenesis and further sensitize nociceptive circuits [117]. Spinal cord stimulators are thought to treat pain partially by inhibiting neurons in the spinal cord that control signaling related to the intensity and location of pain, called wide dynamic range neurons [118–121]. Additionally, spinal cord stimulation could inhibit the development of chronic neuropathic pain [122]. Therefore, preventing central sensitivity development in OA could prevent ANS dysfunction [16, 80, 103, 104]. Bioelectric stimulation may also directly or indirectly modulate ANS function in OA; this interaction warrants more examination of how central nervous system networks relate to OA pathogenesis.

Conclusions

Characterizations of OA pathophysiology have emphasized changes to the local joint environment such as cartilage loss, synovial inflammation, and bone remodeling. However, OA pathogenesis also involves maladaptive neuroplasticity, in the form of peripheral and central sensitization, which helps to drive chronic OA symptoms. In this review, we explored how local pathologic factors may modulate systemic ANS function and how disrupted ANS function may propagate both OA-related pain and pathology. Further, OA does associate with other common diseases and risk factors that have known autonomic dysfunction, including aging and obesity.

Unfortunately, while functional changes in the ANS could cause dysfunction of various physiological systems, such as the neuroimmune axis and/or by increasing the body's susceptibility to OA, studies of the bidirectional relationship between the OA joint and ANS dysfunction remain limited. Bioelectronic medicine modalities such as VNS could potentially modulate ANS functions and activate various neuroimmune pathways such as the cholinergic anti-inflammatory pathway, the splanchnic anti-inflammatory pathway, and the HPA axis. Moreover, the parasympathetic component of the ANS could regulate gut health, which may also relate to OA susceptibility. Thus, VNS could both reduce OA progression or reduce chronic comorbid conditions with OA. Further, bioelectric strategies to block chronic nociceptive signals from sensitized joints in OA might also reduce the risk of pathologic functional shifts to the ANS. To better evaluate the potential of these therapeutic strategies in OA, crosstalk between the ANS and OA joint needs to be explored in more detail, including how neuromodulation influences OA.

Funding

Authors for this publication are supported by the national institute of arthritis and musculoskeletal and skin diseases of the national institutes of health under award number R01AR071431, R01AR071431-S1, the national science foundation under fellowship grant number DGE-1842473, and a graduate student fellowship award from the University of Florida.

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Key Points

- Dysfunction of the autonomic nervous system may be a key driver of OA comorbidities and thus may be a critical component of OA's effects on overall health.
- Vagus nerve stimulation could activate the neuroimmune axis to decrease OA pathogenesis or reduce the risk of OA pathogenesis.
- Blocking chronic OA pain could protect against pathologic shifts in the brain-joint axis and decrease the risk of chronic comorbid disease.

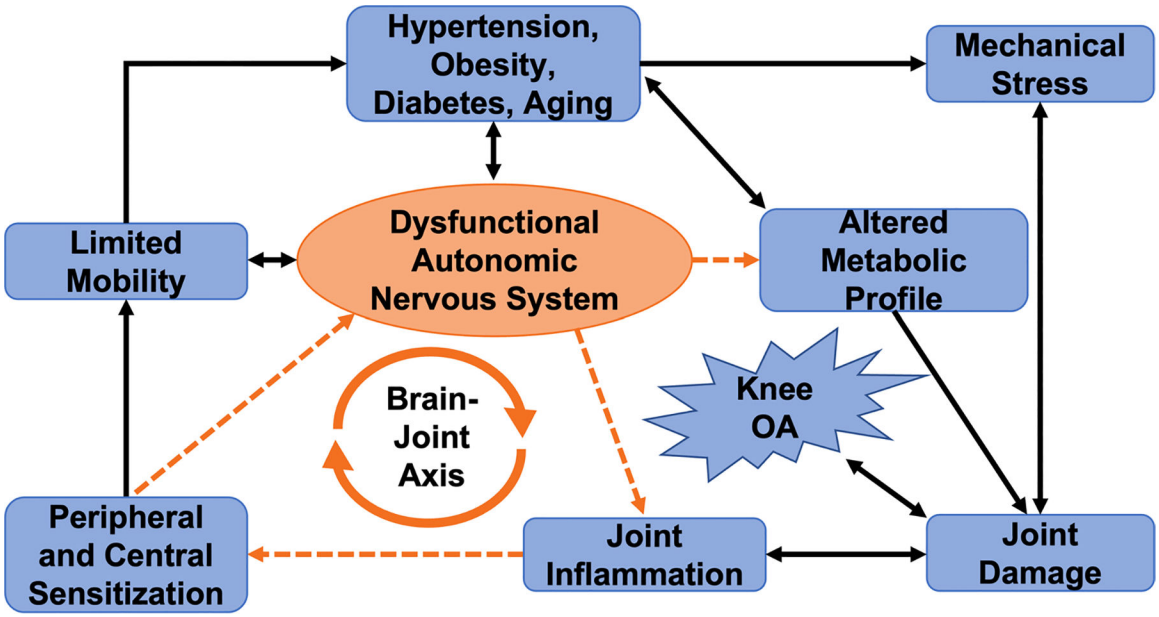

Fig. 1.

OA as a systemic disease. The traditional vicious cycle is highlighted in blue (solid lines), while the influence of autonomic dysfunction is highlighted in orange (dashed lines)

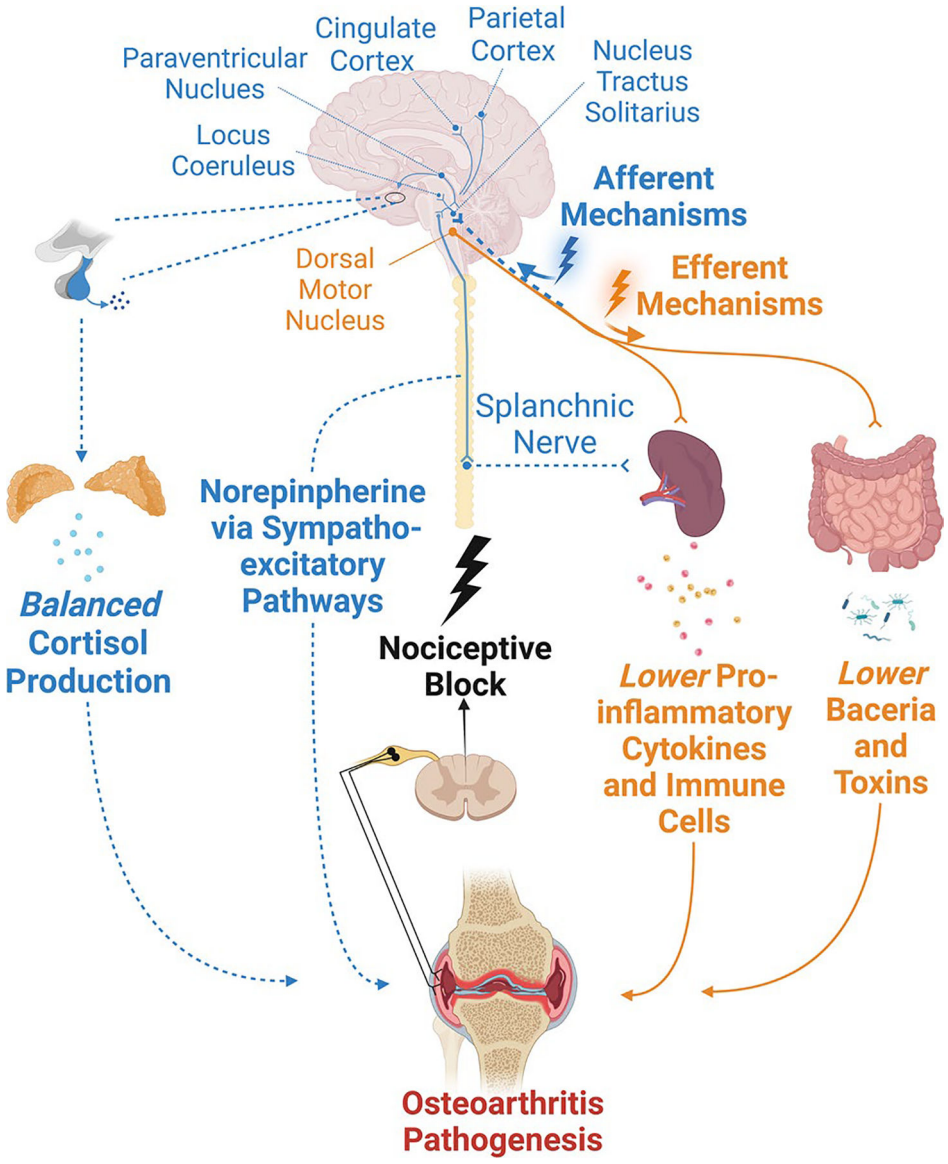

Fig. 2.

Various therapeutic pathways in which bioelectronic medicine could treat OA pathogenesis. Neuroimmune pathways activated via afferent vagal fibers are highlighted in blue/dashed lines and pathways activated via efferent vagal fibers are highlighted in orange/solid lines (created using BioRender.com)