Gut Microbiota Integrative Wellness

REVIEW

Bioelectronic medicine for restoring autonomic balance in autoimmune diseases

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ABSTRACT

The aim of this mini-review is to introduce most prevalent autoimmune diseases, emphasize the importance of sympatho-parasympathetic imbalance in these autoimmune diseases, demonstrate how such imbalance can be effectively treated using the bioelectronic medicine, and describe potential mechanisms of bioelectronic medicine effects on the autoimmune activity at the cellular and molecular levels.

Key words: vagus nerve stimulation, sacral nerve stimulation, sacral neuromodulation, autonomic functions, thyroiditis, psoriasis, inflammatory bowel disease, type 1 diabetes

AUTOIMMUNE DISEASES

A low (usually undetectable) level in autoimmunity is normal and even essential for lymphocyte selection and immune system homeostasis, while a moderate level of autoimmunity can be detected as circulating autoantibodies and small tissue infiltrates but generally does not cause clinical symptoms. When a high level of autoimmunity is sustained for a few days or weeks, it becomes pathogenic and starts to generate clinical symptoms of various autoimmune diseases (AIDs). AIDs are caused by a chronic malfunction of the immune system, when it recognizes auto-antigens in our own molecules and cells as harmful to us, initiating a cascade of pro-inflammatory molecular and cellular events leading to destruction of our own tissues. Due to heterogenicity of affected tissues and organs throughout our body, various AIDs are diagnosed by different specialties of physicians, making it difficult to estimate the overall prevalence of AIDs. A recent epidemiological study in Spain[1] indicated an overall prevalence of about 11%, with the cumulative prevalence of 8.5% (or three quarters of all AIDs) attributed to the thyroiditis, psoriasis, inflammatory bowel disease (IBD), type 1 diabetes, rheumatoid arthritis (RA), and polymyalgia rheumatica (Table 1). The list of prevalent AIDs may soon be extended to include the Post-coronavirus disease (COVID) syndrome, since autoimmunity play a critical role in its development.[2] As can be seen on Table 1, the most commonly affected organs are the thyroid gland, skin, small and large intestines, pancreas, skeletal muscles, joints, and kidney. Other organs can also be affected, such as the liver (*e.g.* primary biliary cholangitis, primary sclerosing cholangitis, and autoimmune hepatitis) and bladder (*e.g.* interstitial cystitis), but with a prevalence below 0.2%.[3,4]

SYMPATHO-PARASYMPATHETIC BALANCE IN AIDS

Despite a heterogenicity of autoimmune responses in AIDs, one emerging common theme is the involvement of the autonomic nervous system with two main components, the sympathetic and parasympathetic branches, jointly regulating the immune functions throughout the body.[5] The degree of sympatho-parasympathetic balance (SPB) can be readily measured by calculating the spectral parameters of heart rate

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Table 1: List of major AIDs describing the affected organs and estimated prevalence based on data from the epidemiological study in Spain[1]

Autoimmune disease	Affected organs	Prevalence, %
thyroiditis	thyroid gland	4.8
psoriasis	skin	1.6
inflammatory bowel disease	small and large intestines	0.9
type 1 diabetes	pancreas, skeletal muscles	0.6
rheumatoid arthritis	joints	0.6
polymyalgia rheumatica	skeletal muscles	0.4
spondyloarthritis	joints	0.3
celiac disease	small intestine	0.3
lichen	skin	0.3
glomerulonephritis	kidney	0.3
Sjögren's syndrome	secretory glands	0.3
vitiligo	skin	0.2
total		11%

AIDs: autoimmune diseases.

variability (HRV) in the electrocardiogram.[6,7] The HRV assessment of autonomic activity gained popularity due to its accuracy and reproducibility, when the assessment is performed at specific physiological conditions (*e.g.*, physical activity or post-prandial state).[8] The HRV assessment is also simpler while providing a similar accuracy compared with the traditional autonomic tests, such as deep breathing, Valsalva maneuver, and orthostatic stress (tilt table) test.[9,10] Using the HRV measure of SPB, a clinical study in thyroiditis patients uncovered considerable sympathetic dominance before the therapy and a recovery of SPB after a 6-month thyroid hormone replacement therapy.[11] Similarly, considerable sympathetic dominance was observed in patients with psoriasis,[12] IBD,[13–16] type 1 diabetes,[17–19] RA,[20–22] and polymyalgia rheumatica.[23] Furthermore, the HRV measure of SPB was shown to correlate with severity of the autoimmune response and to be predictive of the AID progression, as seen in the IBD,[13,14] type 1 diabetes,[17–19] and RA.[20–22]

BEM NERVE TARGETS

Recently, advances in the neural interface technology led to a development a new therapeutic approach termed the bioelectronic medicine (BEM) that aims to restore the SPB in the autonomic nervous system.[24] In this section, we will review the autonomic nerves that have been clinically targeted by the BEM.

The largest and most dominant parasympathetic nerve is the vagus nerve. The BEM that is targeting the vagus nerve can modulate the activities of multiple internal organs, as the vagus nerve directly innervates the heart, lungs, liver, esophagus, stomach, pancreas, small intestine, and proximal colon, while its innervation of kidneys, spleen, adrenal medulla, and reproductive organs is debated.[25] At the cervical (neck) level, the vagus nerve can be easily accessed without laparoscopy to allow simple surgical placement of the stimulating electrode cuff.[26] At the abdominal level, the vagus nerve is located rather deep in the body and requires a laparoscopic surgery for placing the electrode cuffs on the anterior and posterior vagal nerve trunks.[27] The vagus nerve stimulation (VNS) at the cervical level is the Food and Drug Administration (FDA)-approved for treating epilepsy,[28] depression,[29] and stroke.[30] Clinical trials are ongoing in the US for the RA,[31,32] heart failure,[33,34] asthma,[35] post-COVID syndrome,[36] and nephrotic syndrome[37] and in the EU for Crohn's disease.[38] The abdominal VNS was previously FDA-approved for treating obesity, but that approval was since reversed,[39] citing a rather its modest effect on weight loss compared to bariatric surgical procedures.[40]

The sacral nerve is nearly as large as the cervical vagus and is most easily accessible (also without laparoscopy) inside the sacral foramina allowing simple surgical placement of a stimulating lead along the nerve.[41] Unlike the vagus nerve, which is nearly 100% parasympathetic, the sacral nerve at the S2-S4 levels contains the parasympathetic as well as somatic fibers, including both the afferents and efferents.[42] The sacral nerve stimulation (SNS) can modulate the activities of multiple pelvic organs, including distal colon, anorectum, bladder, urethra, and genitals.[43] The SNS is FDA-approved for treating overactive bladder[44] and fecal incontinence[45] and is approved for constipation in the EU[46] but not in the US. Clinical trials are ongoing or recently completed for the RA,[47] irritable bowel syndrome,[48,49] and endometriosis.[50]

Unlike the parasympathetic nerves that arise from two

discrete anatomic locations (cervical brainstem and sacral spinal cord), the sympathetic nerves arise at multiple sympathetic ganglia along the torso,[51] with each sympathetic nerve typically following an artery by splitting into multiple fascicles that surround the artery to form a neurovascular bundle.[52] These sympathetic fascicles cannot be easily dissected from the artery wall, so a stimulating electrode (*e.g.* a cuff or a patch) has to be placed around the artery without compromising its pulsatility.[52–54] Delicate arterial cuffs for applying the BEM therapy were recently developed by Galvani Bioelectronic[52,53] and applied at the splenic nerve for treating the RA.[55,56]

In addition to stimulating the parasympathetic and sympathetic nerves carrying both the afferent and efferent information, yet another BEM approach is to stimulate the autonomic nerves containing 100% afferent fibers that relay visceral information into the brainstem autonomic centers. Surgically, one of the autonomic afferent nerves, the carotid sinus nerve, is readily accessible by placing a stimulating patch electrode on a surface of the carotid artery at a level of the carotid sinus without compromising its pulsatility.[54] Such patch-based BEM therapy is FDA-approved for treating the heart failure.[57] An alternative surgical approach for accessing the carotid sinus nerve is to insert an intra-arterial stent in the carotid artery at a level of the carotid sinus (also without compromising the arterial pulsatility), with the stent transiently expanding during each cardiac systole to apply mechanical pressure on the nerve endings.[58] Such stent-based BEM therapy is being clinically evaluated in the US for treating the hypertension.[59,60]

Yet another BEM approach for activating the vagus nerve is *via* the somato-vagal reflex induced by electrical skin stimulation on the leg or arm at the locations corresponding to specific acupoints, such as Zusanli (ST36, on the leg) and Neiguan (PC6, on the arm).[61–68] Electrical stimulation at these acupoints was shown to be effective in treating sepsis,[69,70] ulcerative colitis,[71] and RA.[72]

ANTI-INFLAMMATORY EFFECTS OF BEM

As described in the previous section, various BEM approaches and nerve branches are available for modulating the activities of the parasympathetic and sympathetic nerves. Therefore, it is important to determine which of these might be best for treating individual AIDs. Twenty years ago, Dr. Kevin Tracey suggested that VNS can be applied to suppress autoimmune activation in multiple immuno-competent organs, such as the spleen, lymph nodes of the small intestine, and adrenal medulla.[73] The anti-inflammatory effect of VNS on the spleen attracted a lot of attention, once clinical efficacy was demonstrated for several spleen-mediated AIDs, such as the RA[74,75] and lupus.[76] The anti-inflammatory effect of VNS on the small intestine was demonstrated in the Crohn's disease.[77,78] The animal studies suggest that the anti-inflammatory effects of VNS on two immuno-competent organs, spleen and small intestine, are mediated *via* different abdominal branches of the vagus.[79–82] The same abdominal branch of the vagus controls both the spleen and the adrenal gland: it passes through the sympathetic celiac ganglion,[83] where it makes no synaptic connections with the splenic nerve,[84] so the VNS effect on the spleen is likely mediated by direct vagal synapses on the spleen,[85] while the VNS effect on the adrenal medulla is likely indirectly mediated by the synaptic connections between the vagus and the adrenal nerve (the vago-sympathetic reflex).[86,87] The VNS also has an anti-inflammatory effect on other organs, such as the liver, lungs, and upper genital tract, with preclinical studies demonstrating its efficacy in the rodent models of pulmonary arterial hypertension,[88] hepatitis,[89] and endometriosis.[90] Therefore, future clinical studies may be designed to apply VNS at the organ-specific abdominal branches in order to achieve better efficacy and avoid the side effects seen in the cervical VNS, particularly on the heart (bradycardia) and lungs (dyspnea and bronchospasms).[91,92]

The distal colon is controlled by a branch of the sacral nerve (the pelvic splanchnic nerve) rather than by the vagus.[93] Accordingly, the anti-inflammatory effect of SNS on the colon and bladder have been observed in the clinical studies for treating ulcerative colitis[94] and interstitial cystitis,[95] while the anti-inflammatory effect of SNS on other pelvic organs (*e.g.* ovaries and prostate) has not been clinically evaluated.

Since the vagus and sacral nerves contain both the afferent and efferent parasympathetic fibers, the anti-inflammatory effect of VNS and SNS could be due to either a direct activation of these parasympathetic efferents and/or the activation of the parasympathetic afferents projecting to the brainstem parasympathetic control centers and resulting in activation of the vagal and sacral efferents.[96,97] Moreover, the vago-sympathetic reflex has been proposed, where the abdominal vagal efferents in the celiac ganglion activate the sympathetic efferents in the greater splanchnic nerve, including the splenic nerve[98–103] and adrenal nerve.[104] With that rationale, Galvani Bioelectronics recently initiated clinical trials in the US and UK, where a direct splenic nerve stimulation (rather than VNS) is being used to treat the RA.[55,56] No other sympathetic nerves have been targeted to date in clinical studies aiming to provide anti-inflammatory therapy to patients with AIDs.

CELLULAR AND MOLECULAR MECHANISMS OF THE ANTI-INFLAMMATORY EFFECTS OF BEM

The BEM anti-inflammatory therapies targeting the spleen (*i.e.* VNS and splenic nerve stimulation) are shown to activate the choline acetyltransferase (ChAT)- and β2 nicotinic acetylcholine receptor (β2 nAChR)-expressing T cells, which in turn activate the anti-inflammatory α7 nAChR-expressing macrophages resident in the spleen; while the BEM anti-inflammatory therapies targeting the intestines (*i.e.* VNS and SNS) activate the enteric neurons, which in turn activate the anti-inflammatory α7 nAChR-expressing macrophages resident in the intestinal mucosa.[105–107] In both the spleen and intestines, activation of the α7 nAChR-expressing macrophages inhibits the release of pro-inflammatory cytokines.[107,108] Interestingly, while the intestinal mucosa contains both the α7 nAChR-expressing macrophages and the α7 nAChR-expressing dendritic cells, only the former were shown to be activated by the VNS.[109] BEM-initiated activation of the α7 nAChR-expressing macrophages in the intestines restores a healthy balance among resident T cells by reducing prevalence of pro-inflammatory ones, such as the T-helper 17 (Th17) cells, and increasing prevalence of anti-inflammatory ones, such as the regulatory T (Treg) cells.[107] Additional and less-explored BEM-initiated mechanisms in the intestines involve enhancing the barrier function of the epithelial cells[110,111] and suppressing infiltration of neutrophils and monocytes into the intestinal tissue.[112] Cellular and molecular mediators of the anti-inflammatory response in the adrenal medulla are not well-studied, with a recent animal study showing that the anti-inflammatory response to a low-level (0.5 mA) somatic afferent stimulation at ST36 uses the vagal supraspinal pathway, which induces NPY+ adrenal chromaffin cells to secrete epinephrine, norepinephrine, and dopamine; while the anti-inflammatory response to a high-level (3 mA) somatic afferent stimulation at ST36 uses the sympathetic spinal (rather than vagal supraspinal) pathway, which induces NPY+ splenic neurons to secrete norepinephrine.[104,113,114]

SUMMARY

High prevalence of AIDs and demonstration of the sympathetic dominance in most AID patients create an opportunity for applying the BEM to restore the SPB as a means of inducing a well-demonstrated beneficial anti-inflammatory effect on the autoimmune activity. The BEM clinical toolbox is already quite extensive and includes cervical and abdominal VNS, SNS, splenic nerve stimulation, and carotid nerve stimulation, with many smaller autonomic nerve branches potentially targetable as well, as the neural interface technology is miniaturizing in the coming years. The BEM therapies have already been applied for treating IBD (both the Crohn's disease and ulcerative colitis), RA, and lupus. As we learn more about the potential mechanisms of the BEM therapy at the cellular and molecular levels and develop smaller neural interfaces, the range of AIDs treated by the BEM is likely to expand rapidly.

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Conflicts of interest

Victor Pikov is an employee at Medipace Inc and owns stock in Medipace Inc. No financial support from Medipace Inc or any other commercial entities was provided for writing this review.

Data sharing

No additional data are available.

REFERENCES

1. Sisó-Almirall A, Kostov B, Martínez-Carbonell E, *et al.* The prevalence of 78 autoimmune diseases in Catalonia (MASCAT-PADRIS Big Data Project). *Autoimmun Rev.* 2020;19(2):102448.
2. Anaya JM, Herrán M, Beltrán S, Rojas M. Is post-COVID syndrome an autoimmune disease? *Expert Rev Clin Immunol.* 2022;18(7):653–666.
3. Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. *Autoimmun Rev.* 2003;2(3):119–125.
4. Davis NF, Brady CM, Creagh T. Interstitial cystitis/painful bladder syndrome: epidemiology, pathophysiology and evidence-based treatment options. *Eur J Obstet Gynecol Reprod Biol.* 2014;175:30–37.
5. Bellocchi C, Carandina A, Montinaro B, *et al.* The Interplay between Autonomic Nervous System and Inflammation across Systemic Autoimmune Diseases. *Int J Mol Sci.* 2022;23(5):2449.
6. Valenza G, Citi L, Saul JP, Barbieri R. Measures of sympathetic and parasympathetic autonomic outflow from heartbeat dynamics. *J Appl Physiol (1985).* 2018;125(1):19–39.
7. Adjei T, von Rosenberg W, Nakamura T, Chanwimalueang T, Mandic DP. The ClassA Framework: HRV Based Assessment of SNS and PNS Dynamics Without LF-HF Controversies. *Front Physiol.* 2019;10:505.
8. Ali MK, Chen JDZ. Roles of Heart Rate Variability in Assessing Autonomic Nervous System in Functional Gastrointestinal Disorders: A Systematic Review. *Diagnostics (Basel).* 2023;13(2):293.
9. Ramanathan R, Jayabal M, Subramaniam M, Selvaraj V. Comparison of heart rate variability and classical autonomic function tests between type 2 diabetes mellitus and healthy volunteers. *Indian J Clin Anat Physiol.* 2020;7(1):27–31.

10. Videira G, Castro P, Vieira B, *et al.* Autonomic dysfunction in multiple sclerosis is better detected by heart rate variability and is not correlated with central autonomic network damage. *J Neurol Sci*. 2016;367:133–137.
11. Galetta F, Franzoni F, Fallahi P, *et al.* Changes in heart rate variability and QT dispersion in patients with overt hypothyroidism. *Eur J Endocrinol*. 2008;158(1):85–90.
12. Proietti I, Raimondi G, Skroza N, *et al.* Cardiovascular risk in psoriatic patients detected by heart rate variability (HRV) analysis. *Drug Dev Res*. 2014;75 Suppl 1:S81–S84.
13. Hirten RP, Danieletto M, Scheel R, *et al.* Longitudinal Autonomic Nervous System Measures Correlate With Stress and Ulcerative Colitis Disease Activity and Predict Flare. *Inflamm Bowel Dis*. 2021;27(10):1576–1584.
14. Gunterberg V, Simrén M, Öhman L, *et al.* Autonomic nervous system function predicts the inflammatory response over three years in newly diagnosed ulcerative colitis patients. *Neurogastroenterol Motil*. 2016;28(11):1655–1662.
15. Sadowski A, Dunlap C, Lacombe A, Hanes D. Alterations in Heart Rate Variability Associated With Irritable Bowel Syndrome or Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Clin Transl Gastroenterol*. 2020;12(1):e00275.
16. Kim KN, Yao Y, Ju SY. Heart rate variability and inflammatory bowel disease in humans: A systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99(48):e23430.
17. Jaiswal M, Urbina EM, Wadwa RP, *et al.* Reduced heart rate variability among youth with type 1 diabetes: the SEARCH CVD study. *Diabetes Care*. 2013;36(1):157–162.
18. Guan L, Metzger DL, Lavoie PM, Collet JP. Glucose control and autonomic response during acute stress in youth with type 1 diabetes: A pilot study. *Pediatr Diabetes*. 2018;19(5):1020–1024.
19. da Silva AK, Destro Christofaro DG, Manata Vanzella L, Marques Vanderlei F, Lopez Laurino MJ, Marques Vanderlei LC. Relationship of the Aggregation of Cardiovascular Risk Factors in the Parasympathetic Modulation of Young People with Type 1 Diabetes. *Medicina (Kaunas)*. 2019;55(9):534.
20. Lazzerini PE, Acampa M, Capecchi PL, *et al.* Association between high sensitivity C-reactive protein, heart rate variability and corrected QT interval in patients with chronic inflammatory arthritis. *Eur J Intern Med* . 2013;24(4):368–374.
21. Adlan AM, Veldhuijzen van Zanten JJCS, Lip GYH, Paton JFR, Kitas GD, Fisher JP. Cardiovascular autonomic regulation, inflammation and pain in rheumatoid arthritis. *Auton Neurosci*. 2017;208:137–145.
22. Koopman FA, Tang MW, Vermeij J, *et al.* Autonomic Dysfunction Precedes Development of Rheumatoid Arthritis: A Prospective Cohort Study. *EBioMedicine*. 2016;6:231–237.
23. Stojanovich L, Milovanovich B, de Luka SR, *et al.* Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren syndrome and other autoimmune diseases. *Lupus*. 2007;16(3):181–185.
24. Birmingham K, Gradinaru V, Anikeeva P, *et al.* Bioelectronic medicines: a research roadmap. *Nat Rev Drug Discov*. 2014;13(6):399–400.
25. Thompson N, Mastitskaya S, Holder D. Avoiding off-target effects in electrical stimulation of the cervical vagus nerve: Neuroanatomical tracing techniques to study fascicular anatomy of the vagus nerve. *J Neurosci Methods*. 2019;325:108325.
26. Kucia K, Merk W, Zapalowicz K, Medrala T. Vagus Nerve Stimulation For Treatment Resistant Depression: Case Series Of Six Patients - Retrospective Efficacy And Safety Observation After One Year Follow Up. *Neuropsychiatr Dis Treat*. 2019;15:3247–3254.
27. Lee PC, Dixon J. Medical devices for the treatment of obesity. *Nat Rev Gastroenterol Hepatol*. 2017;14(9):553–564.
28. US Food and Drug Administration. Premarket Approval P970003 for VNS Therapy System. FDA US Food and Drug Administration website. Accessed May 4, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003
29. US Food and Drug Administration. Premarket Approval P970003-S050 for VNS Therapy System. FDA website. Accessed May 4, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970003S050
30. US Food and Drug Administration. Premarket Approval P2100007 for Vivistim System. FDA website. Accessed May 4, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P210007
31. ClinicalTrials.gov. Long Term Extension of Safety and Efficacy of Vagus Nerve Stimulator in Patients With Rheumatoid Arthritis (RA). ClinicalTrials.gov website. Published April 27, 2021. Updated April 27, 2021. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT04862117
32. ClinicalTrials.gov. Vagus Nerve Stimulation for Moderate to Severe Rheumatoid Arthritis (RESET-RA). ClinicalTrials.gov website. Published September 07, 2020. Updated March 09, 2023. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT04539964
33. ClinicalTrials.gov. ANTHEM-HFrEF Pivotal Study. ClinicalTrials.gov website. Published February 07, 2018. Updated June 02, 2022. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT03425422
34. ClinicalTrials.gov. Neural Cardiac Therapy for Heart Failure Study (NECTAR-HF) (NECTAR-HF). ClinicalTrials.gov website. Published June 30, 2011. Updated March 03, 2023. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT01385176
35. ClinicalTrials.gov. Relief of Acute Bronchoconstriction/Asthma Using the Non-Invasive AlphaCore Device. ClinicalTrials.gov website. Published February 15, 2012. Updated April 09, 2018. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT01532817
36. Badran BW, Huffman SM, Dancy M, *et al*. A pilot randomized controlled trial of supervised, at-home, self-administered transcutaneous auricular vagus nerve stimulation (taVNS) to manage long COVID symptoms. *Bioelectron Med*. 2022;8(1):13.
37. Merchant K, Zanos S, Datta-Chaudhuri T, Deutschman CS, Sethna CB. Transcutaneous auricular vagus nerve stimulation (taVNS) for the treatment of pediatric nephrotic syndrome: a pilot study. *Bioelectron Med* . 2022;8(1):1.
38. ClinicalTrials.gov. Long Term Observational Study of a Vagal Nerve Stimulation Device in Crohn's Disease. ClinicalTrials.gov website. Published November 01, 2016. Updated August 03, 2017. Accessed March 14, 2023. https://clinicaltrials.gov/ct2/show/NCT02951650
39. US Food and Drug Administration. Premarket Approval P130019 for Maestro Rechargeable System. FDA website. Accessed May 4, 2022. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P130019
40. Bray GA. Therapeutic Management of Obesity. In: Davidson MH, Toth PP, Maki KC, eds. *Therapeutic Lipidology*. Humana, Cham; 2021: 323-339.
41. Tilborghs S, De Wachter S. Sacral neuromodulation for the treatment of overactive bladder: systematic review and future prospects. *Expert Rev Med Devices*. 2022;19(2):161–187.
42. Weledji EP, Marti L. A historical perspective of sacral nerve stimulation (SNS) for bowel dysfunction. *IJS: Short Reports*. 2021;6(3):e25.
43. Gurland B, Aytac E. Anatomy and physiology: Neurologic basis for the function of sacral nerve stimulation. *Semin Colon Rectal Surg*. 2017;28(4):156–159.
44. US Food and Drug Administration. Premarket Approval P970004 for InterStim Therapy System. FDA website. Accessed March 15, 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P970004
45. US Food and Drug Administration. Premarket Approval P080025 for InterStim Sacral Nerve Stimulation Therapy System. FDA website.

Accessed March 15, 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P080025

46. Noblett KL, Cadish LA. Sacral nerve stimulation for the treatment of refractory voiding and bowel dysfunction. *Am J Obstet Gynecol*. 2014;210(2):99–106.
47. ClinicalTrials.gov. Sacral Nerve Stimulation for Mild-to-Moderate or Refractory Rheumatoid Arthritis. ClinicalTrials.gov website. Published March 29, 2021. Updated March 04, 2022. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT04821050
48. ClinicalTrials.gov. Subsensory Sacral Nerve Stimulation for Irritable Bowel Syndrome. ClinicalTrials.gov website. Published September 24, 2013. Updated May 17, 2018. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT01948973
49. Fassov J, Lundby L, Laurberg S, Buntzen S, Krogh K. Three-year follow-up of sacral nerve stimulation for patients with diarrhoea-predominant and mixed irritable bowel syndrome. *Colorectal Dis*. 2017;19(2):188–193.
50. ClinicalTrials.gov. Sacral Neuromodulation for Pelvic Pain Associated With Endometriosis. ClinicalTrials.gov website. Published May 04, 2017. Updated May 17, 2021. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT03139734
51. Carnagarin R, Kiuchi MG, Goh G, *et al*. Role of the sympathetic nervous system in cardiometabolic control: implications for targeted multiorgan neuromodulation approaches. *J Hypertens*. 2021;39(8):1478–1489.
52. Donegà M, Fjordbakk CT, Kirk J, *et al*. Human-relevant near-organ neuromodulation of the immune system. *via*. the splenic nerve. *Proc Natl Acad Sci U S A*. 2021;118(20):e2025428118.
53. Sokal DM, McSloy A, Donegà M, *et al*. Splenic Nerve Neuromodulation Reduces Inflammation and Promotes Resolution in Chronically Implanted Pigs. *Front Immunol*. 2021;12:649786.
54. Wilks SJ, Hara SA, Ross EK, *et al*. Non-clinical and Pre-clinical Testing to Demonstrate Safety of the Barostim Neo Electrode for Activation of Carotid Baroreceptors in Chronic Human Implants. *Front Neurosci*. 2017;11:438.
55. ClinicalTrials.gov. Splenic Stimulation for RA. ClinicalTrials.gov website. Published August 12, 2021. Updated October 26, 2021. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT05003310
56. ClinicalTrials.gov. Safety of Splenic Stimulation for RA. ClinicalTrials.gov website. Published July 09, 2021. Updated October 26, 2021. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT04955899
57. US Food and Drug Administration. Premarket Approval P180050 for Barostim Neo System. FDA website. Accessed March 15, 2023. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?id=P180050
58. Kleef MEAM, Bates MC, Spiering W. Endovascular Baroreflex Amplification for Resistant Hypertension. *Curr Hypertens Rep*. 2018;20(5):46.
59. ClinicalTrials.gov. Controlling and Lowering Blood Pressure With the MobiusHD (CALM-DIEM). ClinicalTrials.gov website. Published July 11, 2016. Updated October 12, 2022. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT02827032
60. ClinicalTrials.gov. CALM- 2 - Controlling and Lowering Blood Pressure With the MobiusHD (CALM-2). ClinicalTrials.gov website. Published June 07, 2017. Updated October 12, 2022. Accessed March 15, 2023. https://clinicaltrials.gov/ct2/show/NCT03179800
61. Li YQ, Zhu B, Rong PJ, Ben H, Li YH. Neural mechanism of acupuncture-modulated gastric motility. *World J Gastroenterol*. 2007;13(5):709–716.
62. Ouyang H, Yin J, Wang Z, Pasricha PJ, Chen JD. Electroacupuncture accelerates gastric emptying in association with changes in vagal activity. *Am J Physiol Gastrointest Liver Physiol*. 2002;282(2):G390–G396.
63. Ouyang H, Xing J, Chen J. Electroacupuncture restores impaired gastric accommodation in vagotomized dogs. *Dig Dis Sci*. 2004;49(9):1418–1424.
64. Chen J, Song GQ, Yin J, Koothan T, Chen JD. Electroacupuncture improves impaired gastric motility and slow waves induced by rectal distension in dogs. *Am J Physiol Gastrointest Liver Physiol*. 2008;295(3):G614–G620.
65. Song J, Yin J, Chen J. Needleless transcutaneous electroacupuncture improves rectal distension-induced impairment in intestinal motility and slow waves. *via*. vagal mechanisms in dogs. *Int J Clin Exp Med*. 2015;8(3):4635-4646.
66. Fang JF, Fang JQ, Shao XM, *et al*. Electroacupuncture treatment partly promotes the recovery time of postoperative ileus by activating the vagus nerve but not regulating local inflammation. *Sci Rep*. 2017;7:39801.
67. Pan WX, Fan AY, Chen S, Alemi SF. Acupuncture modulates immunity in sepsis: Toward a science-based protocol. *Auton Neurosci*. 2021;232:102793.
68. Takahashi T. Effect and mechanism of acupuncture on gastrointestinal diseases. *Int Rev Neurobiol*. 2013;111:273–294.
69. Meng JB, Jiao YN, Xu XJ, *et al*. Electro-acupuncture attenuates inflammatory responses and intraabdominal pressure in septic patients: A randomized controlled trial. *Medicine (Baltimore)*. 2018;97(17):e0555.
70. Yang G, Zheng B, Yu Y, *et al*. Electroacupuncture at Zusanli (ST36), Guanyuan (CV4), and Qihai (CV6) Acupoints Regulates Immune Function in Patients with Sepsis. *via*. the PD-1 Pathway. *Biomed Res Int*. 2022;2022:7037497.
71. Ge F, Ji Y, Ma XP. [Clinical effect observation of electroacupuncture combined with medicine in the treatment of ulcerative colitis]. *China Modern Medicine*. 2015;22(06):164–168.
72. Yy, Li Ss, Ben Yh. Clinical observation on electroacupuncture plus long-snake moxibustion for rheumatoid arthritis due to kidney deficiency and cold coagulation. *J Acupunct Tuina Sci*. 2020;18(6):467–473.
73. Tracey KJ. The inflammatory reflex. *Nature*. 2002;420(6917):853–859.
74. Koopman FA, Chavan SS, Miljko S, *et al*. Vagus nerve stimulation inhibits cytokine production and attenuates disease severity in rheumatoid arthritis. *Proc Natl Acad Sci U S A*. 2016;113(29):8284–8289.
75. Genovese MC, Gaylis NB, Sikes D, *et al*. Safety and efficacy of neurostimulation with a miniaturised vagus nerve stimulation device in patients with multidrug-refractory rheumatoid arthritis: a two-stage multicentre, randomised pilot study. *The Lancet Rheumatology*. 2020;2(9):e527–e538.
76. Aranow C, Atish-Fregoso Y, Lesser M, *et al*. Transcutaneous auricular vagus nerve stimulation reduces pain and fatigue in patients with systemic lupus erythematosus: a randomised, double-blind, sham-controlled pilot trial. *Ann Rheum Dis*. 2021;80(2):203–208.
77. Bonaz B, Sinniger V, Hoffmann D, *et al*. Chronic vagus nerve stimulation in Crohn's disease: a 6-month follow-up pilot study. *Neurogastroenterol Motil*. 2016;28(6):948–953.
78. D'Haens G, Cabrijan Z, Eberhardson M, *et al*. P574 The effects of vagus nerve stimulation in biologic-refractory Crohn's disease: A prospective clinical trial. *Journal of Crohn's and Colitis*. 2018;12(supplement 1):S397–S398.
79. Matteoli G, Gomez-Pinilla PJ, Nemethova A, *et al*. A distinct vagal anti-inflammatory pathway modulates intestinal muscularis resident macrophages independent of the spleen. *Gut*. 2014;63(6):938–948.
80. Costes LM, van der Vliet J, van Bree SH, Boeckxstaens GE, Cailotto C. Endogenous vagal activation dampens intestinal inflammation independently of splenic innervation in postoperative ileus. *Auton Neurosci*. 2014;185:76–82.
81. Caravaca AS, Levine YA, Drake A, Eberhardson M, Olofsson PS. Vagus Nerve Stimulation Reduces Indomethacin-Induced Small Bowel Inflammation. *Front Neurosci*. 2022;15:730407.
82. Torres-Rosas R, Yehia G, Peña G, *et al*. Dopamine mediates vagal

modulation of the immune system by electroacupuncture. *Nat Med*. 2014;20(3):291–295.

83. Ulloa L, Quiroz-Gonzalez S, Torres-Rosas R. Nerve Stimulation: Immunomodulation and Control of Inflammation. *Trends Mol Med*. 2017;23(12):1103–1120.
84. Bratton BO, Martelli D, McKinley MJ, Trevaks D, Anderson CR, McAllen RM. Neural regulation of inflammation: no neural connection from the vagus to splenic sympathetic neurons. *Exp Physiol* . 2012;97(11):1180–1185.
85. Gonzalez-Gonzalez MA, Bendale GS, Wang K, Wallace GG, Romero-Ortega M. Platinized graphene fiber electrodes uncover direct spleen-vagus communication. *Commun Biol*. 2021;4(1):1097.
86. Ulloa L. Bioelectronic neuro-immunology: Neuronal networks for sympathetic-splenic and vagal-adrenal control. *Neuron*. 2023;111(1):10–14.
87. McKinley MJ, Martelli D, Trevizan-Baú P, McAllen RM. Divergent splanchnic sympathetic efferent nerve pathways regulate interleukin-10 and tumour necrosis factor-α responses to endotoxaemia. *J Physiol*. 2022;600(20):4521–4536.
88. Yoshida K, Saku K, Kamada K, *et al*. Electrical Vagal Nerve Stimulation Ameliorates Pulmonary Vascular Remodeling and Improves Survival in Rats With Severe Pulmonary Arterial Hypertension. *JACC Basic Transl Sci*. 2018;3(5):657–671.
89. Jo BG, Kim SH, Namgung U. Vagal afferent fibers contribute to the anti-inflammatory reactions by vagus nerve stimulation in concanavalin A model of hepatitis in rats. *Mol Med*. 2020;26(1):119.
90. Hao M, Liu X, Rong P, Li S, Guo SW. Reduced vagal tone in women with endometriosis and auricular vagus nerve stimulation as a potential therapeutic approach. *Sci Rep*. 2021;11(1):1345.
91. Fitchett A, Mastitskaya S, Aristovich K. Selective Neuromodulation of the Vagus Nerve. *Front Neurosci*. 2021;15:685872.
92. Noller CM, Levine YA, Urakov TM, Aronson JP, Nash MS. Vagus Nerve Stimulation in Rodent Models: An Overview of Technical Considerations. *Front Neurosci*. 2019;13:911.
93. Skandalakis LJ, Skandalakis JE. Colon and Anorectum. In: Skandalakis L, Skandalakis J, eds. *Surgical Anatomy and Technique*. Springer, New York, NY; 2014: 431-513.
94. Chen Z, Ni M, Li J, *et al*. Su1616–Anti-Inflammatory Effects and Mechanisms of Sacral Nerve Stimulation Performed. *Via*. Acupuncture Needles on Ulcerative Colitis. *Gastroenterology*. 2019;156(6):S-585.
95. Hernández-Hernández D, Padilla-Fernández B, Navarro-Galmés MÁ, Hess-Medler S, Castro-Romera MM, Castro-Díaz DM. Sacral Neuromodulation in the Management of Bladder Pain Syndrome/ Interstitial Cystitis. *Curr Bladder Dysfunct Rep*. 2020;15(1):83–92.
96. Tu L, Gharibani P, Zhang N, Yin J, Chen JD. Anti-inflammatory effects of sacral nerve stimulation: a novel spinal afferent and vagal efferent pathway. *Am J Physiol Gastrointest Liver Physiol*. 2020;318(4):G624–G634.
97. Ye F, Liu Y, Li S, Zhang S, Foreman RD, Chen JD. Sacral nerve stimulation increases gastric accommodation in rats: a spinal afferent and vagal efferent pathway. *Am J Physiol Gastrointest Liver Physiol*. 2020;318(3):G574–G581.
98. Martelli D, Yao ST, McKinley MJ, McAllen RM. Reflex control of inflammation by sympathetic nerves, not the vagus. *The Journal of physiology*. 2014;592(7):1677–1686.
99. Martelli D, Yao ST, McKinley MJ, McAllen RM. Reflex control of inflammation by sympathetic nerves, not the vagus. *J Physiol*. 2014;592(7):1677–1686.
100. Komegae EN, Farmer DGS, Brooks VL, McKinley MJ, McAllen RM, Martelli D. Vagal afferent activation suppresses systemic inflammation. *via*. the splanchnic anti-inflammatory pathway. *Brain Behav Immun*. 2018;73:441-449.
101. Patel YA, Saxena T, Bellamkonda RV, Butera RJ. Kilohertz frequency nerve block enhances anti-inflammatory effects of vagus nerve stimulation. *Sci Rep*. 2017;7:39810.
102. Bonaz B, Sinniger V, Pellissier S. Therapeutic Potential of Vagus Nerve Stimulation for Inflammatory Bowel Diseases. *Front Neurosci*. 2021;15:650971.
103. Tanaka S, Abe C, Abbott SBG, *et al*. Vagus nerve stimulation activates two distinct neuroimmune circuits converging in the spleen to protect mice from kidney injury. *Proc Natl Acad Sci U S A*. 2021;118(12):e2021758118.
104. Liu S, Wang Z, Su Y, *et al*. A neuroanatomical basis for electroacupuncture to drive the vagal-adrenal axis. *Nature*. 2021;598(7882):641–645.
105. Stakenborg N, Boeckxstaens GE. Bioelectronics in the brain-gut axis: focus on inflammatory bowel disease (IBD). *Int Immunol*. 2021;33(6):337–348.
106. Serafini MA, Paz AH, Nunes NS. Cholinergic immunomodulation in inflammatory bowel diseases. *Brain Behav Immun Health*. 2021;19:100401.
107. Mikami Y, Tsunoda J, Kiyohara H, Taniki N, Teratani T, Kanai T. Vagus nerve-mediated intestinal immune regulation: therapeutic implications of inflammatory bowel diseases. *Int Immunol*. 2022;34(2):97–106.
108. Rosas-Ballina M, Olofsson PS, Ochani M, *et al*. Acetylcholine-synthesizing T cells relay neural signals in a vagus nerve circuit. *Science*. 2011;334(6052):98–101.
109. Yang NN, Yang JW, Ye Y, *et al*. Electroacupuncture ameliorates intestinal inflammation by activating α7nAChR-mediated JAK2/ STAT3 signaling pathway in postoperative ileus. *Theranostics*. 2021;11(9):4078–4089.
110. Tu L, Gharibani P, Yin J, Chen JDZ. Sacral nerve stimulation ameliorates colonic barrier functions in a rodent model of colitis. *Neurogastroenterol Motil*. 2020;32(10):e13916.
111. Brégeon J, Coron E, Da Silva AC, *et al*. Sacral nerve stimulation enhances early intestinal mucosal repair following mucosal injury in a pig model. *J Physiol*. 2016;594(15):4309–4323.
112. Meroni E, Stakenborg N, Gomez-Pinilla PJ, *et al*. Vagus Nerve Stimulation Promotes Epithelial Proliferation and Controls Colon Monocyte Infiltration During DSS-Induced Colitis. *Front Med (Lausanne)*. 2021;8:694268.
113. Hu J, Hu W, Tang L, Wang Y. Fundamental Neurocircuit of Anti-inflammatory Effect by Electroacupuncture Stimulation Identified. *Neurosci Bull*. 2022;38(7):837–839.
114. Liu S, Wang ZF, Su YS, *et al*. Somatotopic Organization and Intensity Dependence in Driving Distinct NPY-Expressing Sympathetic Pathways by Electroacupuncture. *Neuron*. 2020;108(3):436–450.e7.