NeuroSolutions 100 Clinical Review

In Office Trigeminocervical and Vagal Nerve Stimulation for Painful Diabetic Neuropathy

March 2024

NeuroSolutions 100

Clinical Overview

- ✓Activates Spinal Cord (TCN) and Vagus Nerve Simultaneously
- ✓Potential to Restore Autonomic Imbalance
- ✓Potential to Block Inflammation via the Cholinergic Anti-Inflammatory Pathway
- ✓Potential to Put Order Back into the Disordered Metabolic State
- ✓Potential to Reduce Pain, Blood Sugar, Narcotic Urge/Hyperalgesia

PNS —> VNS —> PENS

- 1966: Sheldon, Trigeminal Neuralgia, Open surgical CNS placement
- 1967: Wall & Sweet, Sciatic pain, Open surgical PNS placement
- 1980: Law, Stump Implantation, Open surgical PNS placement
- 1984: FDA Approval of Open Surgical PNS
- 1997: FDA Approval of Open Carotid Sheath VNS
- 1999: Weiner & Reed & Alo, Percutaneous PNS = PENS
  - Trigeminocervical Nucleus (TCN) for Occipital Headache (Goadsby, et. al)
- 2021 (December): NS100 combined TCN-VNS PNS/PENS
  - Neurostimulator/Neuromodulation Division of FDA (Predicate = Sprint PNS)

NS100 Combined TCN-VNS Neurostimulator

Neuromodulation Division of the FDA cleared Trial PNS/PENS/VNS Class II Medical Device as non pharmacologic aid to reduce the symptoms of chronic pain associated with diabetic neuropathy.

•4 independent, programmable, titanium electrode arrays precisely implanted activating:

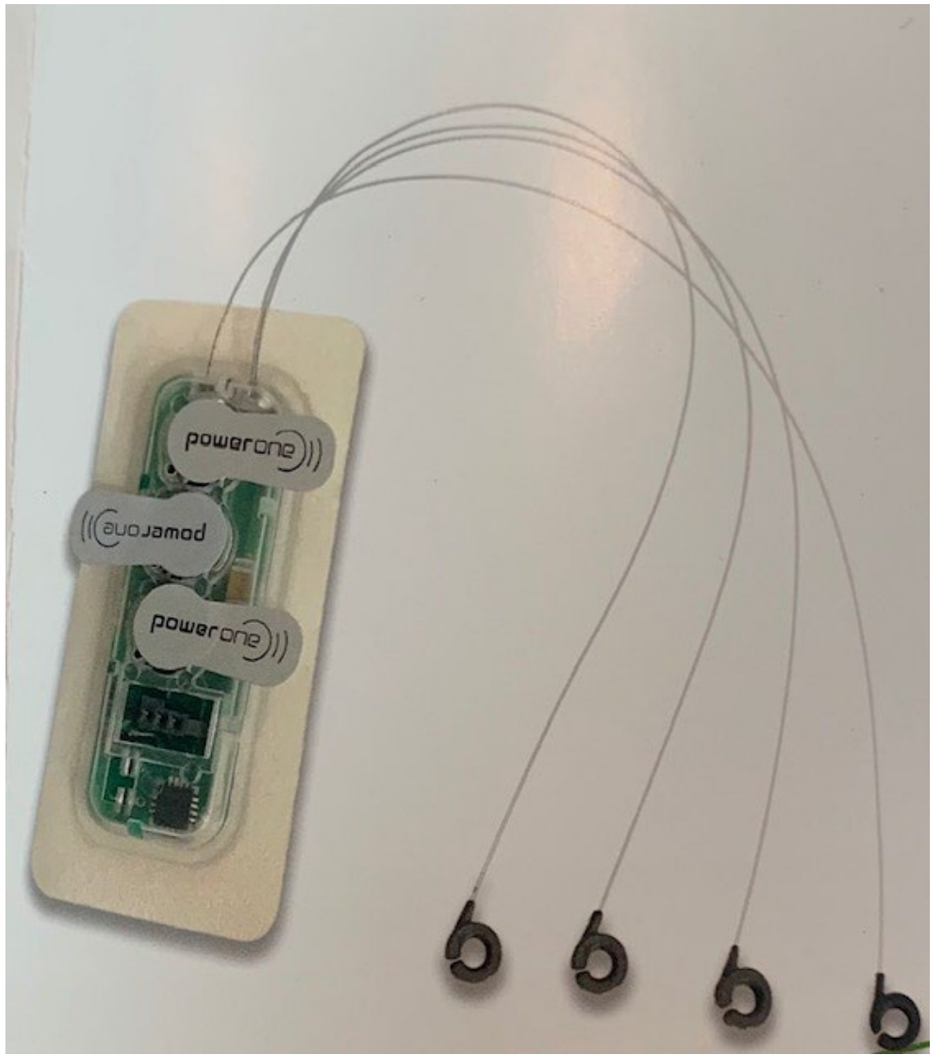
•TrigeminoCervical Nucleus
- •C1-2-3 Cervical Spinal Roots (LON,GAN)
- •Trigeminal Nerve (ATN)

•Vagus Nerve (ABVN)
- •Opioid, Nicotinic, Cannabinoid Receptors

•PANS > SANS
- •Cholinergic Anti-inflammatory Pathway

•Vagal Control of the Metabolic State
- •Neuroendocrine
- •Immune Response

•Can increase quality of life and functionality by minimizing medication side effects (e.g. opioids, NSAIDS, tricyclics, anti-epileptics, etc.), improving diagnostic accuracy (e.g. narcotic hyperalgesia) and potentially modifying end-organ disease state. (Level 1 RCT)



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NS 100 and Painful Diabetic Neuropathy (PDN)

NS 100

- FDA cleared Class II Medical by Device Division of Neuromodulation and Physical Medicine Devices
- On Label for chronic pain due to diabetic neuropathy
- Reimbursed by Medicare (including CA Medicare) and broadly by commercial payers
- Temporary device worn up to 20 days, implanted in office or outpatient setting

PDN

- PDN has a high negative health and economic burden
- The standard-of-care for PDN has limited efficacy with a considerable side-effect profile

Proven NS 100 Treatment Outcomes

<u>Using NS100 Promotes Immediate and Long-Term Patient Outcomes</u>

ON LABEL

- Reduces/eliminates pain*

CASCADE OF BENEFITS

- Increases exercise ability, function and wellness*
- Potential for reducing Comorbidities (cataracts, stroke, heart attacks, ED readmissions, wounds, amputations, ancillary medications..)
- Reduces Insomnia / Irritability / Stress*
- Potential to reduce Insulin, oral hypoglycemics
- Potential to reduce and keep blood sugar under control
- Potential to reduce office visits/encounters

*Based on scientific evidence/internal data

Trigeminocervical Stimulation Mechanisms

HEADACHE
The Journal of Head and Face Pain

Peripheral Neurostimulation for the Treatment of Chronic, Disabling Transformed Migraine

Charles A. Popeney DO, Kenneth M. Aló MD

First published: 27 March 2003 | https://doi.org/10.1046/j.1526-4610.2003.03072.x |

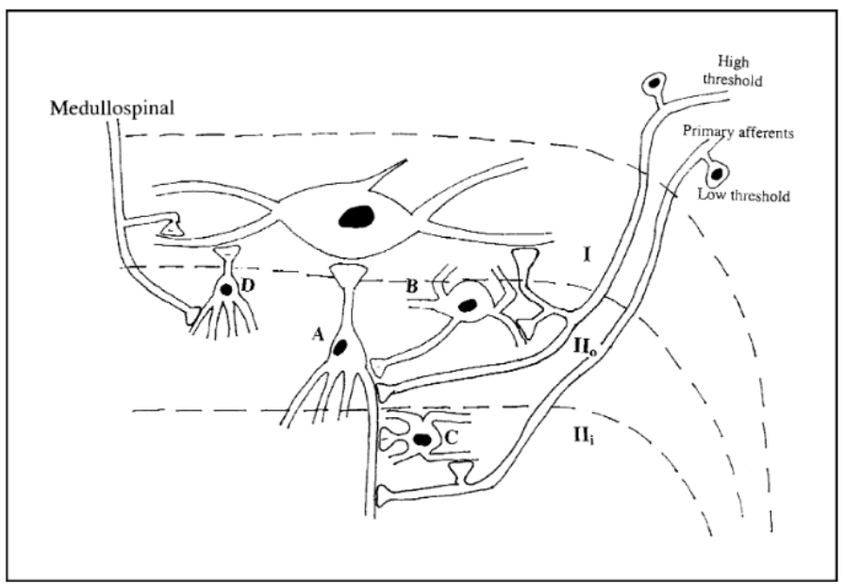


Fig 4.—Local circuitry in the superficial dorsal horn. Nociceptive inputs transmitted via high-threshold and low-threshold primary afferent fibers. The schema also illustrates possible descending control mechanisms (D). These may be exerted directly upon dorsal horn projection neurons. Polysynaptic inhibition and excitation occur.

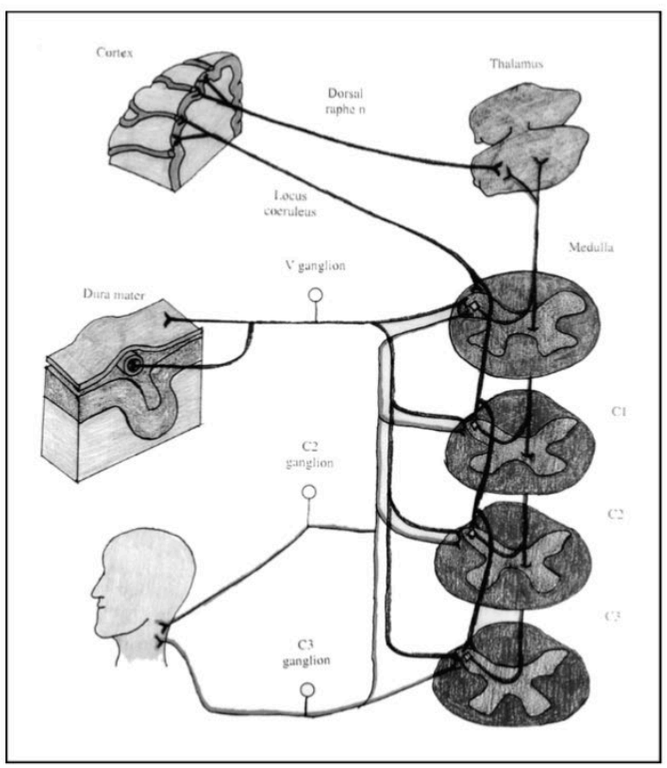


Fig. 2.—Pain transmission and modulation via trigeminovascular and trigeminocervical systems. Anterior intracranial structures dura mater, blood vessels via trigeminal ganglion, C1 through C3 input via C1 through C3 ganglion, and descending inhibitory pathways through the locus coeruleus converging on the same neuron of the trigeminocervical complex.[8]

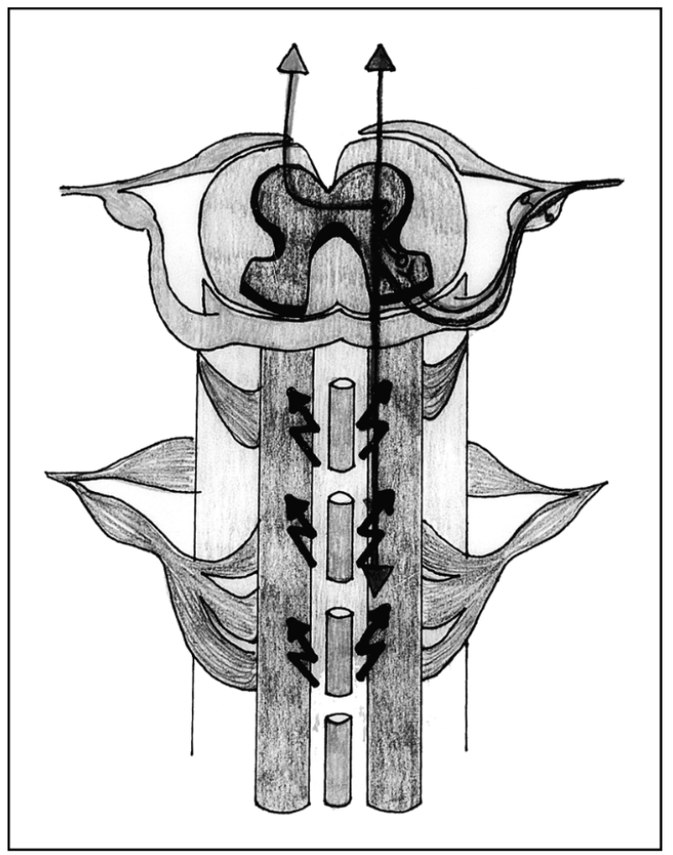
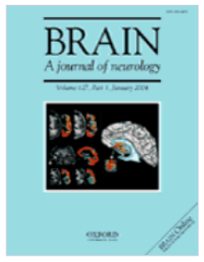


Fig 3.—Mode of action of spinal cord stimulation. Antidromic excitation of low-threshold fibers in dorsal columns is believed to activate inhibitory circuits in the dorsal horn. The simultaneous orthodromic activation of dorsal columns may activate supraspinal-gating mechanisms.[13]

Trigeminocervical Stimulation Mechanisms



Volume 127, Issue 1
January 2004

Article Contents

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JOURNAL ARTICLE

Central neuromodulation in chronic migraine patients with suboccipital stimulators: a PET study

FREE

Manjit S. Matharu ✉, Thorsten Bartsch, Nick Ward, Richard S. J. Frackowiak, Richard Weiner, Peter J. Goadsby

Brain, Volume 127, Issue 1, January 2004, Pages 220–230,
https://doi.org/10.1093/brain/awh022
Published: 01 January 2004 **Article history** ▾

Abstract

Electrical stimulation of primary sensory afferents is known to have an antinociceptive effect. Animal and functional imaging studies suggest a role for supraspinal structures in this response. Eight patients with chronic migraine (≥15 days per month of attacks of migraine without aura), who had shown a marked beneficial response to implanted bilateral suboccipital stimulators, were studied. Stimulation evoked local paraesthesia, the presence of which was a criterion of pain relief. On stimulation, the headache began to improve instantaneously and was completely suppressed within 30 min. On switching off the stimulation, the headache recurred instantly and peaked within 20 min. PET scans were performed using regional cerebral blood flow (rCBF) as a marker of neuronal activity. Each patient was scanned in the following three states: (1) stimulator at optimum settings: patient pain□free but with paraesthesia; (2) stimulator off: patient in pain and no paraesthesia; (3) stimulator partially activated: patient with intermediate levels of pain and paraesthesia. All scans were processed and analysed using Statistical Parametric Mapping (SPM) 99. There were significant changes in rCBF in the dorsal rostral pons, anterior cingulate cortex (ACC) and cuneus, correlated to pain scores, and in the ACC and left pulvinar, correlated to stimulation□ induced paraesthesia scores. The activation pattern in the dorsal rostral pons is

Trigeminocervical Stimulation History

Neuromodulation
TECHNOLOGY AT THE NEURAL INTERFACE

ORIGINAL CONTRIBUTIONS | VOLUME 7, ISSUE 2, P103-112, APRIL 2004

Peripheral Nerve Stimulation for the Treatment of Occipital Neuralgia and Transformed Migraine Using a C1-2-3 Subcutaneous Paddle Style Electrode: A Technical Report

Michael Y. Oh, MD • Juan Ortega, MD • J. Bradley Bellotte, MD • Donald M. Whiting, MD • Kenneth Aló, MD

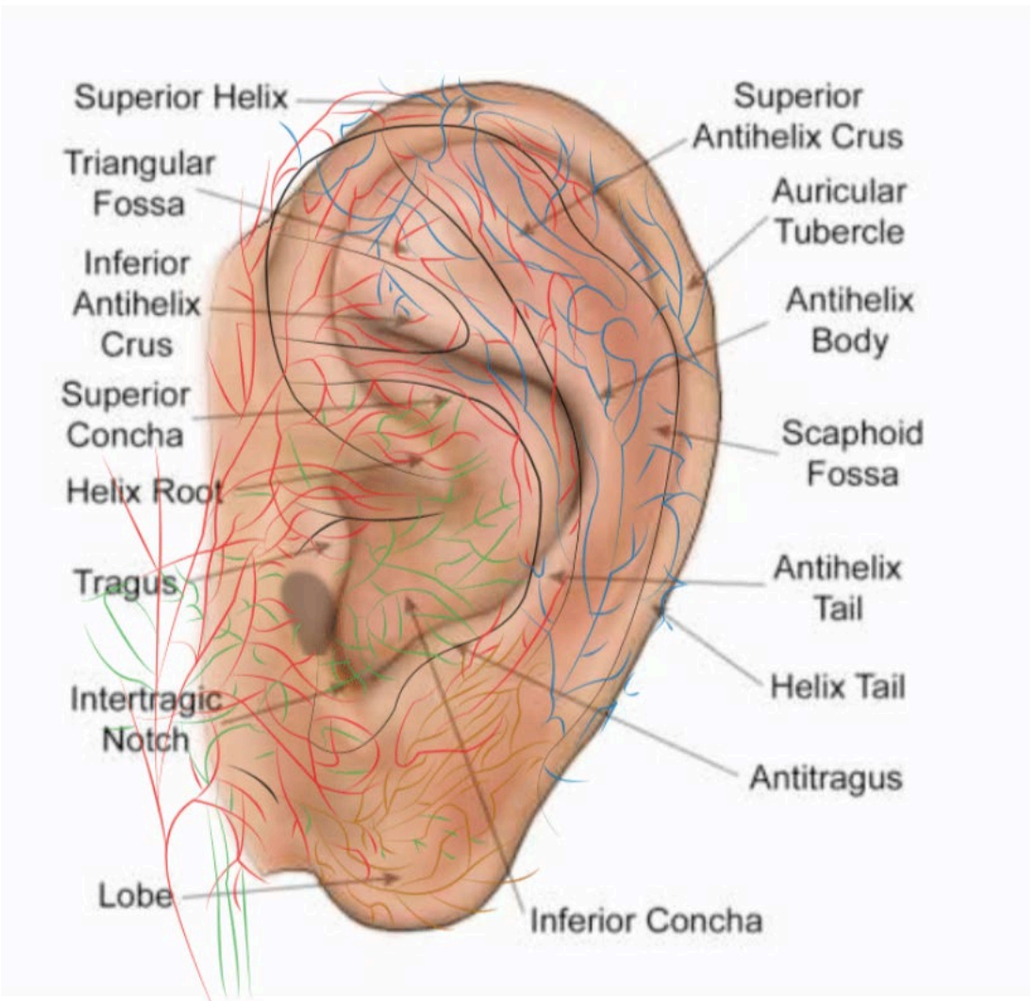
DOI: https://doi.org/10.1111/j.1094-7159.2004.04014.x

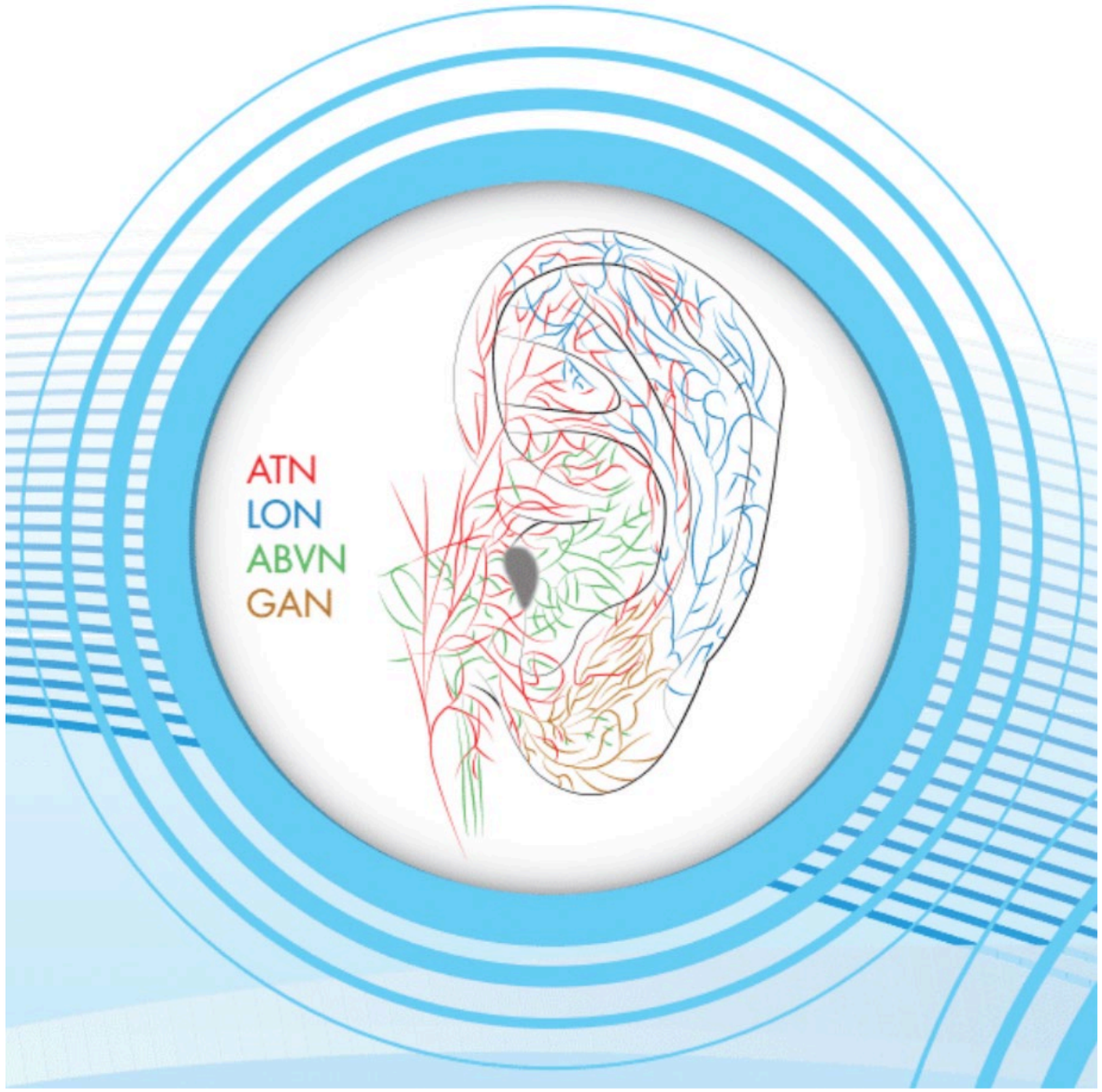
ABSTRACT

In this article we will discuss the treatment of Occipital Neuralgia (ON) and Transformed Migraine (TM) using a paddle style surgical stimulator lead. A paddle style electrode may have advantages to the cylindrical style in reducing migrations from cervical tension or anchor dislodgement. It should be considered in refractory "neuropathic" cervicocranial syndromes such as ON and TM before moving on to more aggressive surgical interventions.

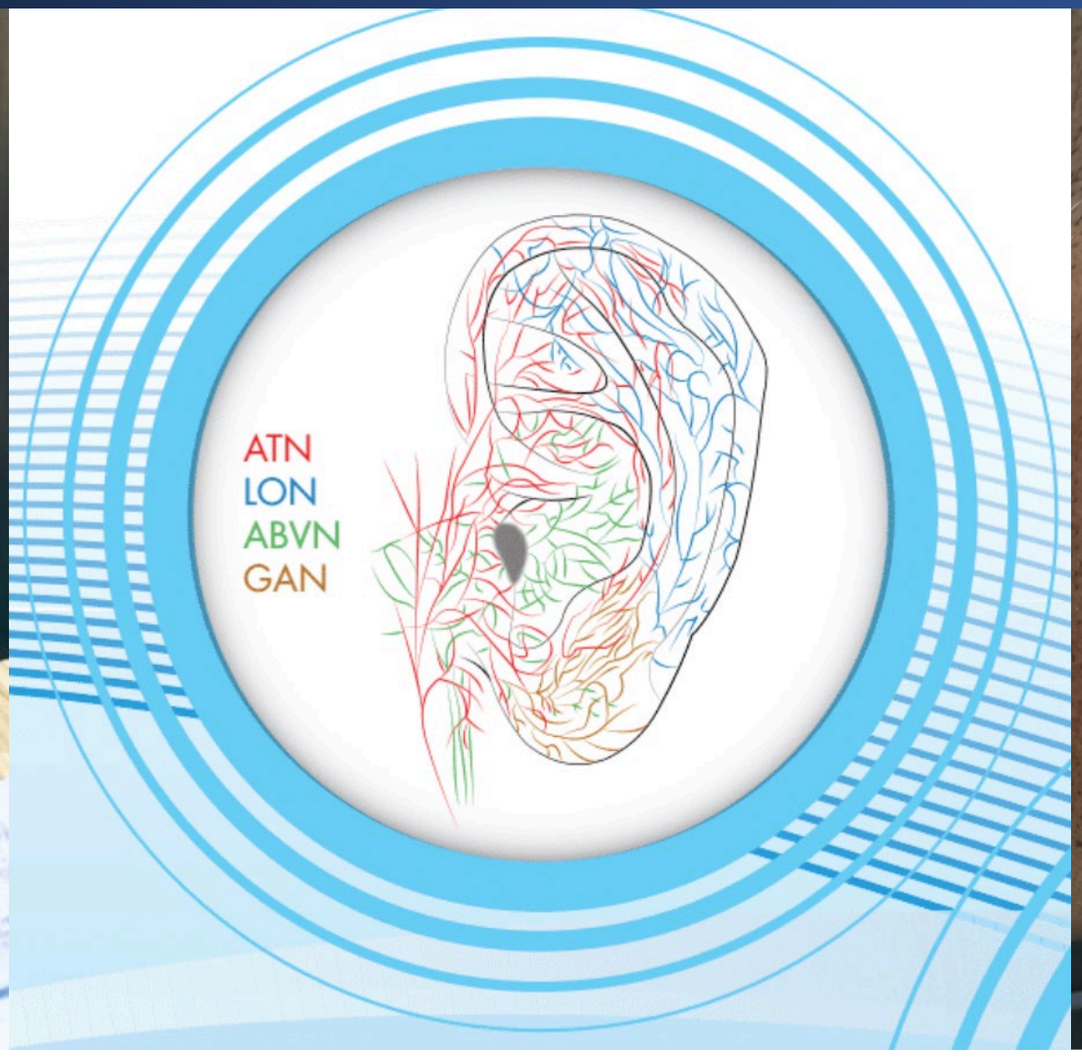
Trigeminocervical and Vagal Peripheral Branches

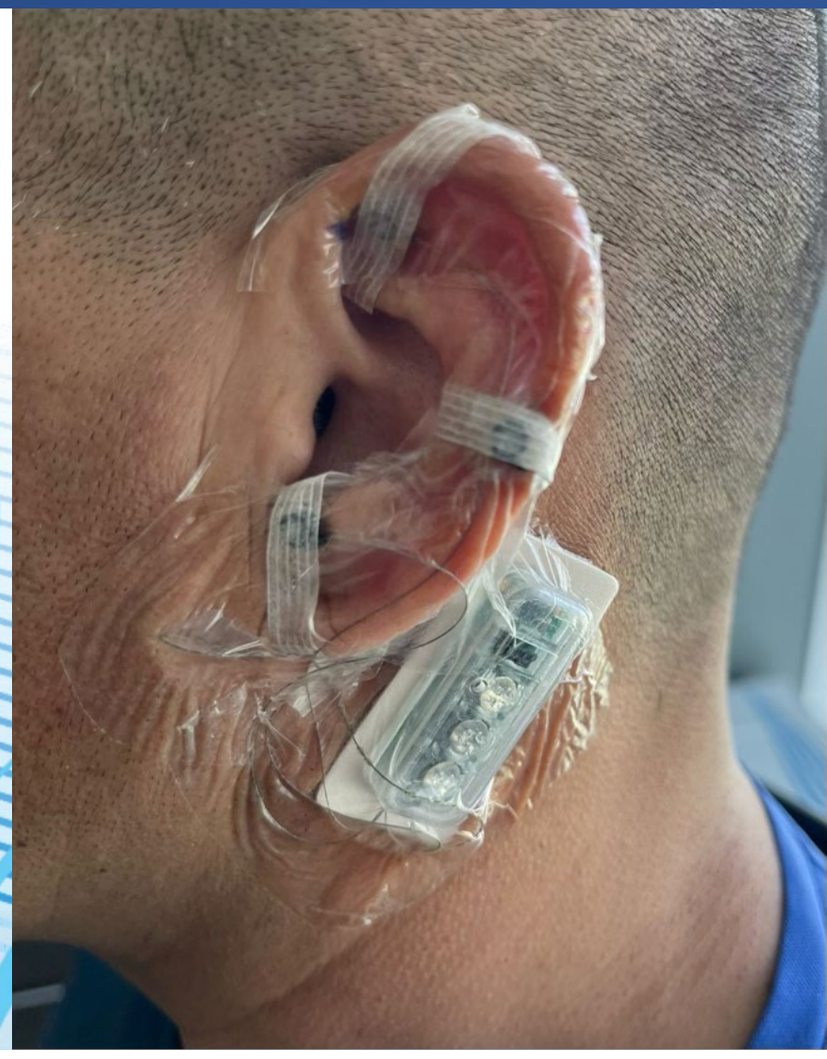
ABVN – Auricular branch of the Vagus Nerve
GAN – Greater Auricular Nerve
ATN – Auricular Temporal Nerve
LON – Lesser Occipital Nerve





NS100 Office/Outpatient Implant





Real-time closed loop impedance drop locates the <u>TCN</u> (ATN, LON, GAN) and <u>Vagus</u> (ABVN) for precise titanium electrode array implantation.

20 minute procedure worn for 20 days (MD/DO and NP-PA in certain states)

Receptor Specific Programming Activation
<u>(Fixed vs. Sweep)</u>

Receptor Specific Activation (Fixed vs. Sweep)

Endorphin	Receptor	Frequency (Hz)	Location
NK cells	Immune	4	Widespread
Beta-endorphins	μ	2-4	Mid-brain/PAG
Enkephalins	δ	2-4/15	Dorsal Horn
Dynorphins	κ	100	Brainstem/Spine
Orphanin	μ	2/15	Widespread CNS
5-HTP	5-HTPF	20-50	Hypothalamus
Oxytocin	OXTR	2-15/30	CNS
Dopamine	D1	2,15-30	Prefrontal
NOS	Epithelium	2,15-30	Widespread

- "Fixed": 1 Hz, 2 Hz, 4 Hz and 10 Hz (low Hz) sequentially …

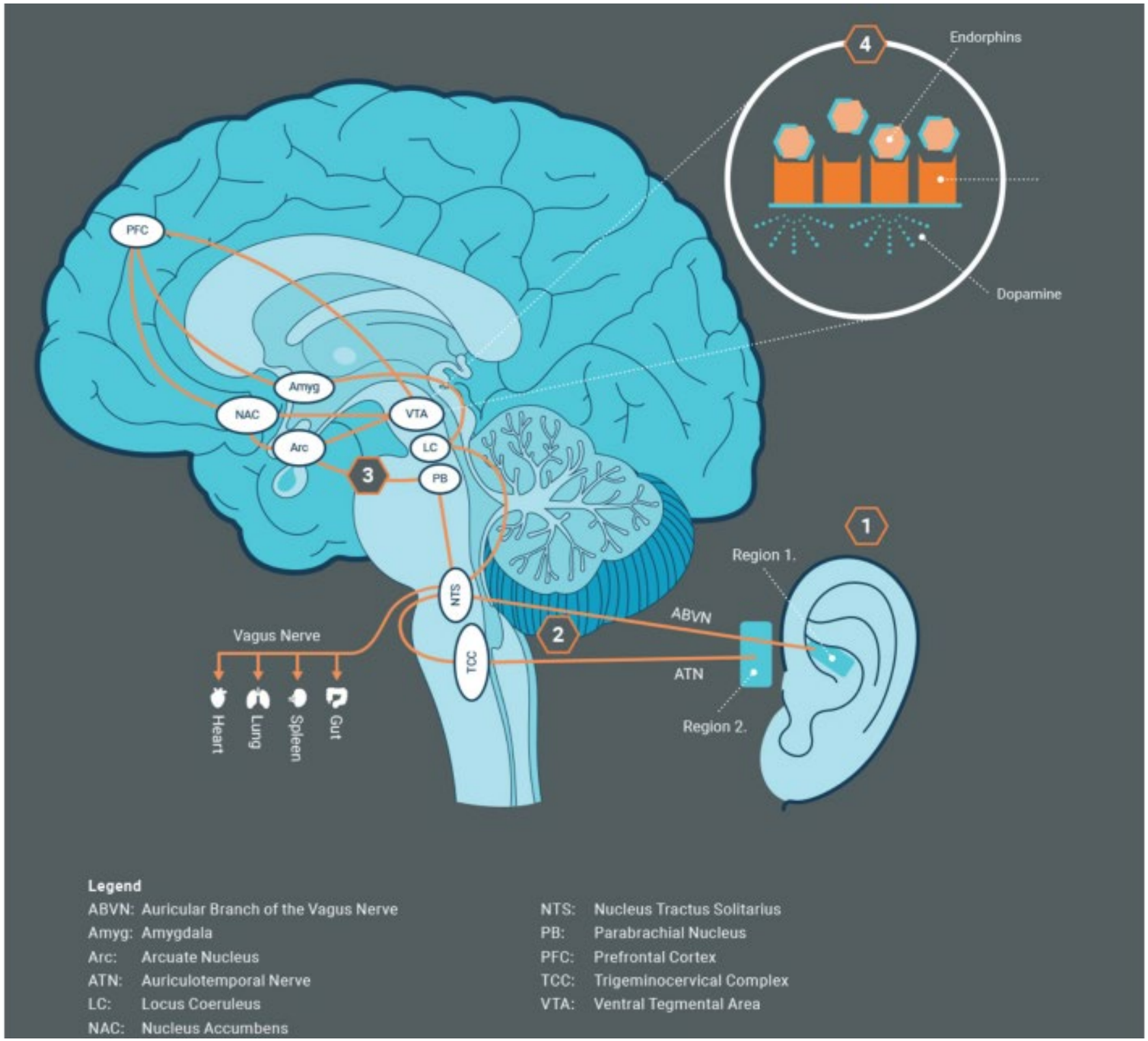
- "Sweep": Ascending 1 Hz, 2 Hz, 4Hz, 10 Hz, 15Hz, 30 Hz and 100 Hz then Descending …*

- Produce measurable Current + Power Densities propagating reproducible physiologic response —>"Nerve Pacing"

- Level 1 RCT…

*battery specific manufacturer data

ATN + ABVN Endorphin Receptor Activation



Diabetic Peripheral Neuropathic Pain.

Double-blind, Randomized, Placebo-controlled Longitudinal Trial TCN/VNS

"Patients who demonstrated good glycemic control had quadratic reductions in pain…"

Comparing Percutaneous Electrical Neuro-Stimulation with Placebo in the Management of Diabetic Peripheral Neuropathic Pain

S. Madhuchander[a,*], S. Gurunath[b]

[a]*Department of OBG, Kakatiya Medical College, Warangal, India*
[b]*Department of Pharmacology, Vaagdevi Institute of Pharmaceutical Sciences, Bollikunta, Warangal, India*

Abstract

Painful diabetic neuropathy is a common phenotype of peripheral neuropathy due to diabetes, affecting up to a third of the general diabetic population. The aim of this study was to evaluate the efficacy of auricular percutaneous electrical neuro-stimulation (PENS) in treating and relieving patients suffering from painful complications of diabetes.

A double-blind, randomized, placebo-controlled longitudinal trial enrolled 89 subjects with pain due to peripheral neuropathy caused by type 2 diabetes mellitus. Patients with pain duration of 4 months involving the lower extremities were randomly assigned to receive either standard (A) or variable-frequency (B) auricular PENS treatment, or a sham device, for 12 weeks, on a week-on week-off basis. Visual analogue scale (VAS) on 10 cm was used to assess pain, while severity of peripheral neuropathy was estimated through the vibration perception test (VPT) and the overall neuropathy limitation scale (ONLS). Insomnia and anxiety/mood severities were appraised by means of, respectively, the insomnia severity index (ISI) and the Hamilton anxiety rating scale (HAS). These 5 measures were repeated each week, alternating between installation and removal of the treatment device. Patients were encouraged to come back and complete the 6 treatments. Parameters of diabetic control were gauged at the first and last visit.

Population size dwindled from initial 89 to 63 subjects remaining after 12 weeks (21 with A, 22 with B). VAS, VPT, ONLS and HAS measures decreased with statistical significance for all 43 individuals in comparison with 20 placebo-treated patients (p-value $\ll 0.001$). Pain scores were found to linearly reduce with time from 7.1 ± 0.6 to 6.5 ± 1.0 over the complete study period with placebo, whereas neurostimulation allowed reductions from 7.2 ± 1.0 to 4.5 ± 1.0. Moderate pain VAS drops were found to be accompanied by drastic plunges in VPT. Study subjects were further sieved according to the decrease of blood glucose measures. Patients who demonstrated good glycemic control (16 out of 43) had quadratic reductions in pain with treatments A and B, from 7.5 ± 0.9 to 4.1 ± 0.6, and from 7.1 ± 1.3 to 3.2 ± 0.7, respectively. Glycemia also determined the decline of anxiety scores. Furthermore, ISI exhibited overall significant decrease ($p \ll 0.001$) for PENS groups in comparison with a raise of insomnia values for the control group. Analgesic requirements decreased by 80% for both treatment groups and only by 7% with placebo. No adverse events were found.

Active PENS treatments improved the neuropathic pain symptoms in all patients who completed the 12 weeks. Their resilience in participating may explain this success. In addition to decreased extremity pain, PENS improved physical activity, sense of well-being, and sleep quality while reducing the need for analgesics.

Central Vagal Circuits Control Glucose Metabolism

AMERICAN JOURNAL OFPHYSIOLOGY
GASTROINTESTINAL AND LIVER PHYSIOLOGY

Am J Physrol Gostrointest UverPhysiol 320: G17S-G182. 2021.
First published November 18,2020:doi:10.1152/a]pgi.00368.2020

REVIEW

Nutrient Sensing, Nutrition, and Metabolism

Musings on the wanderer: What's new in our understanding ofvago-vagal reflexes?VI. Central vagal circuits that control glucose metabolism

Soledad Pitra[1] and Bret N. Smith[1,2]

'Department of Neuroscience. University of Kentucky. Lexington. Kentucky; and [2]Departmem of Physiology. College of Medicine. University of Kentucky. Lexington. Kentucky

Abstract

Neurons in the brain stem dorsal vagal complex {OVq take part in a continuous bidirectional crosstalk. in which they *receive* and respond to a vast array of signaling molecules, Including glucose. Importantly, chronic dysregulation of blood glucose *con•* centration. a hallmark of high prevalence pathologies, such as diabetes and metabolic syndrome, can Induce neuroplasticity in DVC neural networks, which is hypothesized to either contribute *to* Of compensate for the glycemic or Insulinemic dysregulation observed in *these* conditions. Here, we revisrt the topic of vagal *reflexes* to review recent research on the importance of DVC function in regulating systemic glucose homeostasis and the neuroplastlc changes in this brain region that *are* associated with systemic glucose alterations. *We* also discuss the critical connection *between* these nuclei and the gut and the role of central vagal circuits in the favorable outcomes associated with bariatric surgical procedures for metabolic disorders.

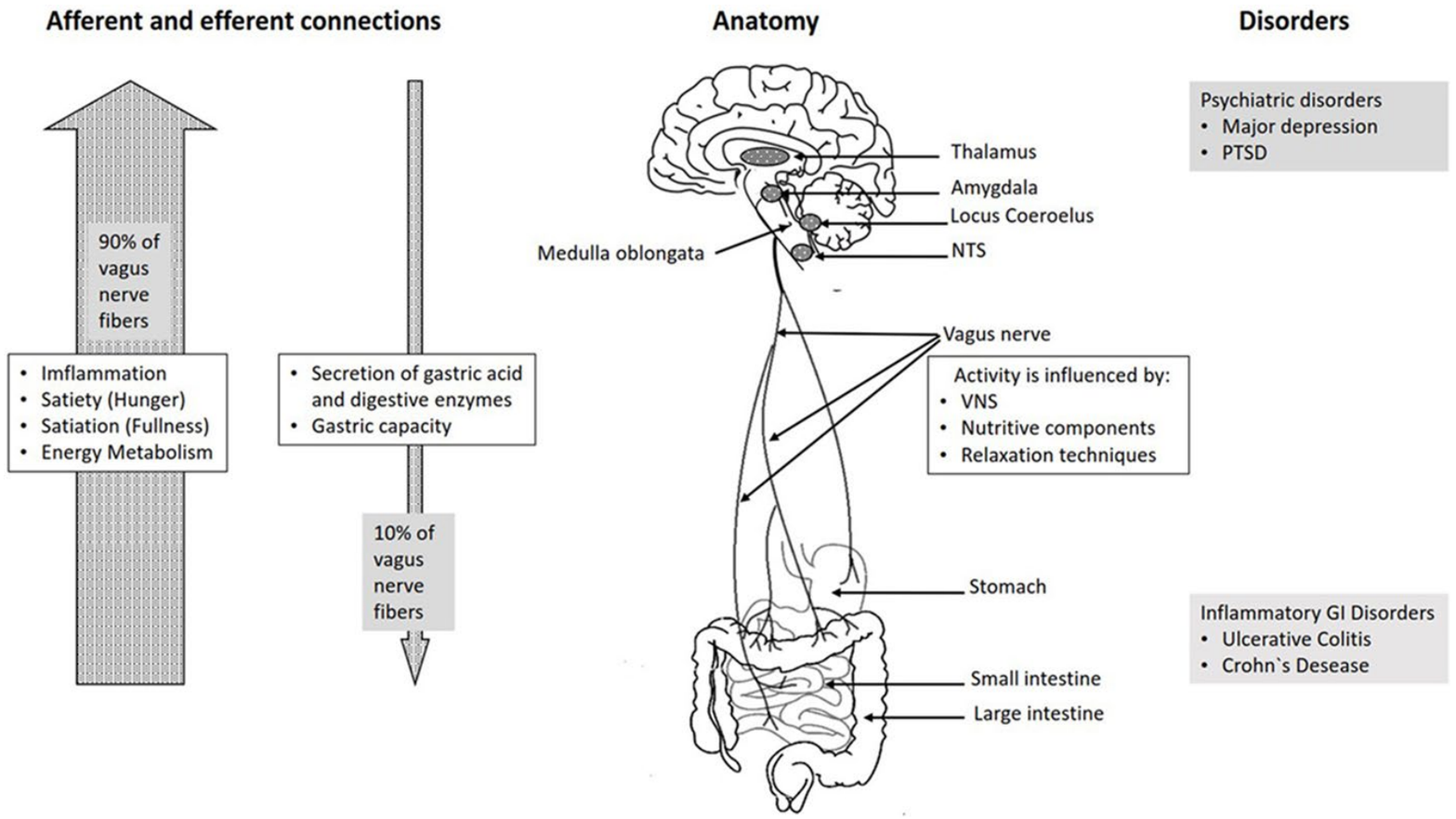
dorsal motor nucleus of the vogus; glucose: diabetes; nucleus tractus solitarlus; neuroplasticity

Vagal Bidirectional Reflexes

- "Wandering", most complex, longest Cranial PN Medulla -> head, neck organs of chest/abdomen. 90% afferent and 10% efferent.

- Dorsal Motor + Solitary Nucleus, Nucleus Ambiguus, + Spinal Trigeminal Nucleus (direct from CN V)

- Motor/Sensory/Taste/Chemoreception - baroreceptors, carotid bodies, pharynx, tongue, heart, lungs, liver, pancreas, GI, Anti-inflammatory/Immune (Cholinergic Anti-Inflammatory Pathway)



Vagus Nerve: Real-time Bidirectional IPM "Internal Patient Monitor"

Vagus Nerve Stimulation and Diabetes

Editorial

BIOELECTRONICS IN MEDICINE

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Could vagus nerve stimulation have a role in the treatment of diabetes?

Charles-Henri Malbert*,[1]
[1]Département de Nutrition Humaine, INRA, 35590 Saint-Gilles, France
* Author for correspondence: Tel.: +33 1 (0)2 23 48 50 71; Fax: +33 1 (0)2 23 48 50 80; charles-henri.malbert@inra.fr

"Traditional bariatric surgery is primarily conceived as an intervention that reduces the risk of future disease (i.e., to prevent metabolic or cardiovascular complications of severe obesity) rather than as an approach to treat established disease. On the contrary, metabolic surgery should be considered as a means to achieve the glycemic control necessary to reduce the risk of microvascular complications and cardiovascular disease."

First draft submitted: 28 August 2017; Accepted for publication: 25 September 2017; Published online: 3 November 2017

Type 2 diabetes (T2D) is characterized by relative insulin deficiency caused by pancreatic β-cell dysfunction and insulin resistance in target organs: liver, skeletal muscle, kidneys, brain, intestine and adipose tissue. A total of 171 million individuals were estimated to have diabetes in the year 2000, and this is expected to increase to 366 million by 2030 [1]. T2D was the sixth leading cause of disability in 2015 as a consequence of the morbidity and mortality associated with macro- and micro-vascular complications including cardiovascular disease and stroke, retinopathy, nephropathy and neuropathy. Obesity, physical inactivity and energy-dense diets are common factors that occur in synchrony leading to the pathogenesis of T2D, together with a specific phenotype that appears to increase the risk of cardiovascular death and other life-threatening diseases. However, obesity itself appears an essential contributor since 60% of patients with T2D are obese (body mass index $\geq$ 30 kg/m^2) [2].

Glucose control remains a major focus in the management of patients with T2D. Indeed, while there is a consensus demonstrating that reducing hyperglycemia decreases the onset and progression of microvascular complications, the impact of glucose control on cardiovascular complications is more modest yet likely to be present after many years of improved control. Accordingly, personalized medicine is necessary, balancing the benefits of glycemic control with its potential risks, taking into account the adverse effects of glucose-lowering medications (e.g., particularly

Vagus Nerve Stimulation and Diabetes

Journal of Inflammation Research

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REVIEW

A review of vagus nerve stimulation as a therapeutic intervention

This article was published in the following Dove Press journal:
Journal of Inflammation Research

Rhaya L Johnson[1]
Christopher G Wilson[1,2]

[1]Lawrence D Longo MD Center for Perinatal Biology, Department of Basic Sciences, Loma Linda University, Loma Linda, CA, USA; [2]Department of Pediatrics, Loma Linda University, Loma Linda, CA, USA

Abstract: In this review, we provide an overview of the US Food and Drug Administration (FDA)-approved clinical uses of vagus nerve stimulation (VNS) as well as information about the ongoing studies and preclinical research to expand the use of VNS to additional applications. VNS is currently FDA approved for therapeutic use in patients aged >12 years with drug-resistant epilepsy and depression. Recent studies of VNS in in vivo systems have shown that it has anti-inflammatory properties which has led to more preclinical research aimed at expanding VNS treatment across a wider range of inflammatory disorders. Although the signaling pathway and mechanism by which VNS affects inflammation remain unknown, VNS has shown promising results in treating chronic inflammatory disorders such as sepsis, lung injury, rheumatoid arthritis (RA), and diabetes. It is also being used to control pain in fibromyalgia and migraines. This new preclinical research shows that VNS bears the promise of being applied to a wider range of therapeutic applications.

Keywords: vagus nerve stimulation, pediatrics, inflammation, peripheral nerve stimulation, autonomic circuits

Introduction

Vagus nerve stimulation (VNS) is US Food and Drug Administration (FDA) approved for use in the treatment of epilepsy and depression in patients aged >12 years and is

Vagus Nerve Stimulation and Diabetes

DOI: 10.14814/phy2.14479

ORIGINAL RESEARCH

Physiological Reports

Differential effects of vagus nerve stimulation strategies on glycemia and pancreatic secretions

Sophie C. Payne[1,2] | Glenn Ward[1,3,4] | Richard J. MacIsaac[1,3,4] | Tomoko Hyakumura[1,2] | James B. Fallon[1,2] | Joel Villalobos[1,2]

[1]Bionics Institute, East Melbourne, Vic., Australia

[2]Medical Bionics Department, The University of Melbourne, Parkville, Vic., Australia

[3]Department of Endocrinology and Diabetes, St Vincent's Hospital, Fitzroy, Vic., Australia

[4]Department of Medicine, The University of Melbourne, Parkville, Vic., Australia

Correspondence
Joel Villalobos, Bionics Institute, 384-388 Albert Street, East Melbourne 3002, Vic., Australia.
Email: jvillalobos@bionicsinstitute.org

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Abstract

Despite advancements in pharmacotherapies, glycemia is poorly controlled in type 2 diabetic patients. As the vagus nerve regulates energy metabolism, here we evaluated the effect various electrical vagus nerve stimulation strategies have on glycemia and glucose-regulating hormones, as a first step to developing a novel therapy of type 2 diabetes. Sprague–Dawley rats were anesthetized, the abdominal (anterior) vagus nerve implanted, and various stimulation strategies applied to the nerve: (a) 15 Hz; (b) 4 kHz, or 40 kHz and; (c) a combination of 15 Hz and 40 kHz to directionally activate afferent or efferent vagal fibers. Following a glucose bolus (500 mg/kg, I.V.), stimulation strategies were applied (60 min) and serial blood samples taken. No stimulation was used as a crossover control sequence. Applying 15 Hz stimulation significantly increased glucose (+2.9 ± 0.2 mM·hr, $p = .015$) and glucagon (+17.1 ± 8.0 pg·hr/ml, $p = .022$), compared to no stimulation. Application of 4 kHz stimulation also significantly increased glucose levels (+1.5 ± 0.5 mM·hr, $p = .049$), while 40 kHz frequency stimulation resulted in no changes to glucose levels but did significantly lower glucagon (−12.3 ± 1.1 pg·hr/ml, $p = .0009$). Directional afferent stimulation increased glucose (+2.4 ± 1.5 mM·hr) and glucagon levels (+39.5 ± 15.0 pg·hr/ml). Despite hyperglycemia resulting when VNS, aVNS, and 4 kHz stimulation strategies were applied, the changes in insulin levels were not significant ($p \geq .05$). In summary, vagus nerve stimulation modulates glycemia by effecting glucagon and insulin secretions, and high-frequency 40 kHz stimulation may have potential application for the treatment of type 2 diabetes.

KEYWORDS

bioelectronic medicine, medical devices, peripheral nerve stimulation, type 2 diabetes mellitus

1 | INTRODUCTION

currently diagnosed (Zheng, Ley, & Hu, 2018). The major-

Vagus Nerve Stimulation and Diabetes

DOI: 10.14814/phy2.15257

ORIGINAL ARTICLE

The Physiological Society | american physiological society | Physiological Reports

Blood glucose modulation and safety of efferent vagus nerve stimulation in a type 2 diabetic rat model

Sophie C. Payne[1,2] | Glenn Ward[1,3,4] | James B. Fallon[1,2] | Tomoko Hyakumura[1,2] | Johannes B. Prins[4,5,6] | Sofianos Andrikopoulos[6,7] | Richard J. MacIsaac[1,3,4,6] | Joel Villalobos[1,2]

[1]Bionics Institute, East Melbourne, Victoria, Australia

[2]Department of Medical Bionics, University of Melbourne, Parkville, Victoria, Australia

[3]Department of Endocrinology and Diabetes, St Vincent's Hospital Melbourne, Fitzroy, Victoria, Australia

[4]Melbourne Medical School, University of Melbourne, Parkville, Victoria, Australia

[5]Department of Endocrinology, Royal Melbourne Hospital, Parkville, Victoria, Australia

[6]Australian Centre for Accelerating Diabetes Innovations, University of Melbourne, Melbourne, Australia

[7]Department of Medicine (Austin Health), University of Melbourne, Heidelberg, Victoria, Australia

Correspondence
Sophie C. Payne, Bionics Institute, 384-388 Albert Street, East Melbourne 3002, Vic, Australia.
Email: spayne@bionicsinstitute.org

Funding information
Research reported in this publication was supported by the Bionics Institute Incubation Fund, St. Vincent's Research Endowment Fund (85257), the Cass Foundation Limited (8511), and the University of Melbourne's Early Career Researcher Grants Scheme (1757246). The Bionics Institute acknowledge the

Abstract

Vagus nerve stimulation is emerging as a promising treatment for type 2 diabetes. Here, we evaluated the ability of stimulation of the vagus nerve to reduce glycemia in awake, freely moving metabolically compromised rats. A model of type 2 diabetes ($n = 10$) was induced using a high-fat diet and low doses of streptozotocin. Stimulation of the abdominal vagus nerve was achieved by pairing 15 Hz pulses on a distal pair of electrodes with high-frequency blocking stimulation (26 kHz, 4 mA) on a proximal pair of electrodes to preferentially produce efferent conducting activity (eVNS). Stimulation was well tolerated in awake, freely moving rats. During 1 h of eVNS, glycemia decreased in 90% of subjects (-1.25 ± 1.25 mM h, $p = 0.017$), and 2 dB above neural threshold was established as the most effective "dose" of eVNS ($p = 0.009$). Following 5 weeks of implantation, eVNS was still effective, resulting in significantly decreased glycemia (-1.7 ± 0.6 mM h, $p = 0.003$) during 1 h of eVNS. There were no overt changes in fascicle area or signs of histopathological damage observed in implanted vagal nerve tissue following chronic implantation and stimulation. Demonstration of the biocompatibility and safety of eVNS in awake, metabolically compromised animals is a critical first step to establishing this therapy for clinical use. With further development, eVNS could be a promising novel therapy for treating type 2 diabetes.

KEYWORDS

autonomic nervous system, bioelectric medicine, directional stimulation, medical devices, metabolic disease, selective peripheral nerve stimulation

Vagus Nerve Stimulation, Diabetes, and ANS Imbalance

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OPEN

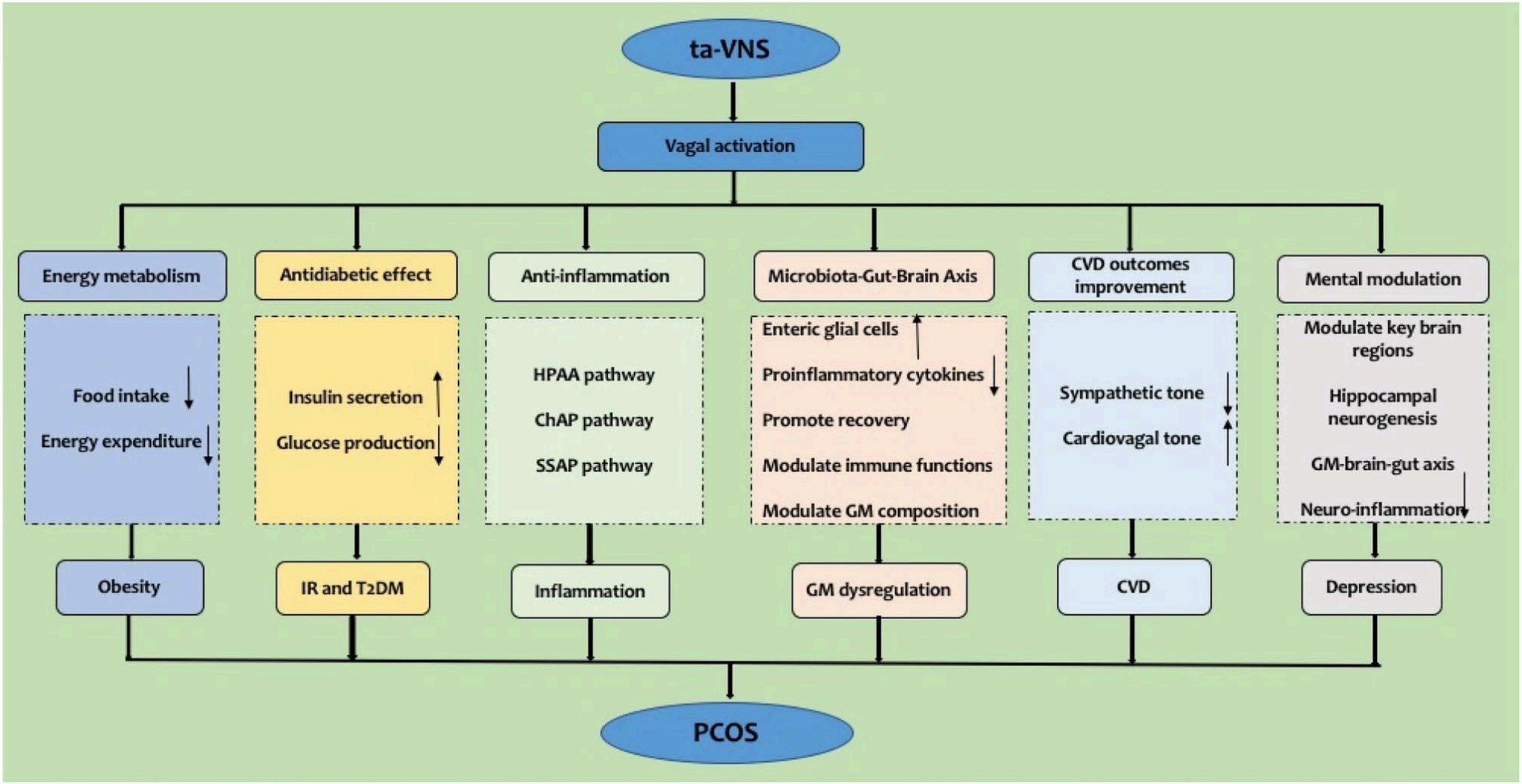
Transcutaneous auricular vagus nerve stimulation as a potential novel treatment for polycystic ovary syndrome

Shike Zhang[1,2], Hui He[3]✉, Yu Wang[4], Xiao Wang[3] & Xiaofang Liu[5]

Polycystic ovary syndrome (PCOS) is a common endocrine disorder in women of childbearing age. The etiology of PCOS is multifactorial, and current treatments for PCOS are far from satisfactory. Recently, an imbalanced autonomic nervous system (ANS) with sympathetic hyperactivity and reduced parasympathetic nerve activity (vagal tone) has aroused increasing attention in the pathogenesis of PCOS. In this paper, we review an innovative therapy for the treatment of PCOS and related co-morbidities by targeting parasympathetic modulation based on non-invasive transcutaneous auricular vagal nerve stimulation (ta-VNS). In this work, we present the role of the ANS in the development of PCOS and describe a large number of experimental and clinical reports that support the favorable effects of VNS/ta-VNS in treating a variety of symptoms, including obesity, insulin resistance, type 2 diabetes mellitus, inflammation, microbiome dysregulation, cardiovascular disease, and depression, all of which are also commonly present in PCOS patients. We propose a model focusing on ta-VNS that may treat PCOS by (1) regulating energy metabolism via bidirectional vagal signaling; (2) reversing insulin resistance via its antidiabetic effect; (3) activating anti-inflammatory pathways; (4) restoring homeostasis of the microbiota-gut-brain axis; (5) restoring the sympatho-vagal balance to improve CVD outcomes; (6) and modulating mental disorders. ta-VNS is a safe clinical procedure and it might be a promising new treatment approach for PCOS, or at least a supplementary treatment for current therapeutics.

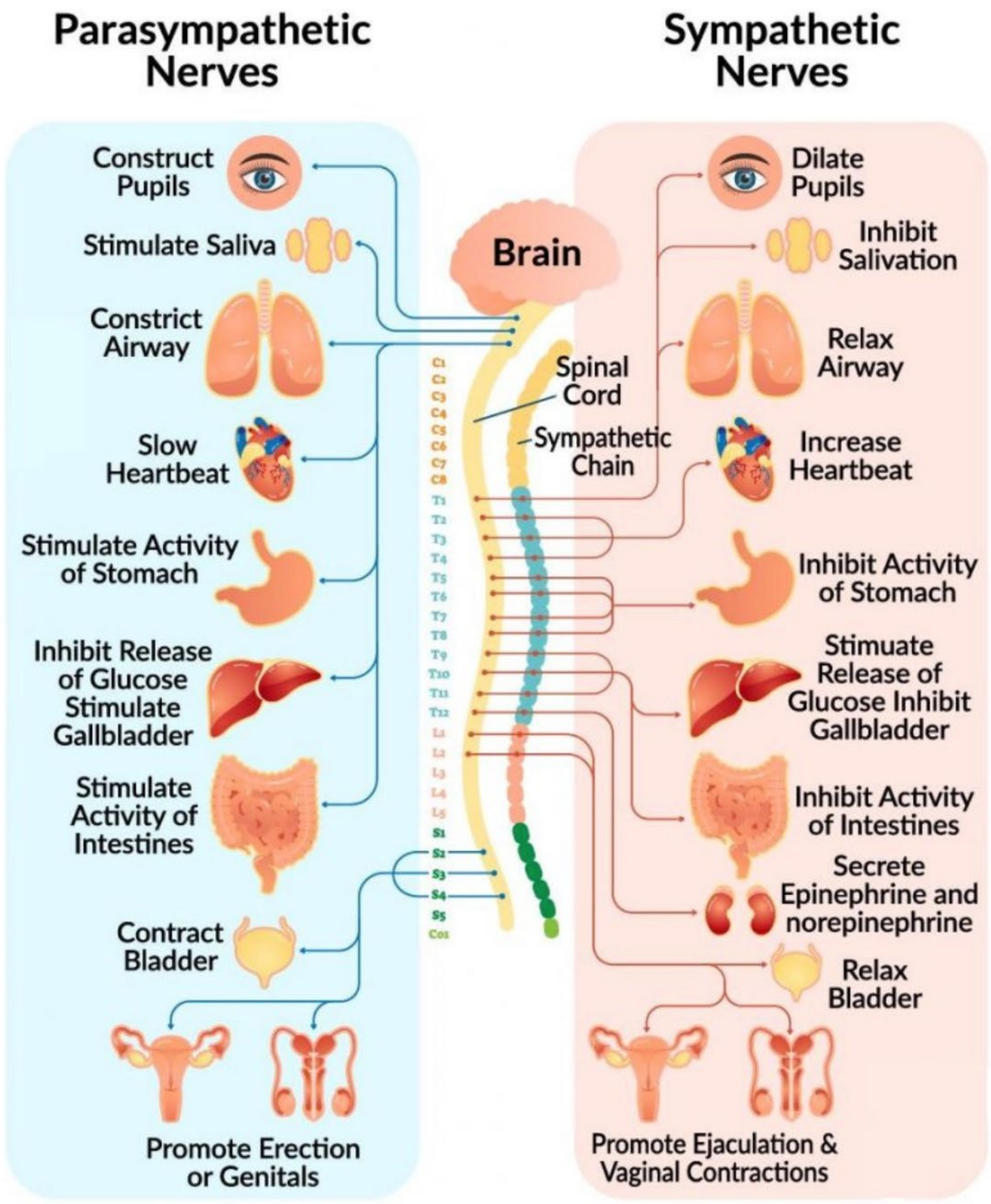
Vagus Nerve Stimulation, Diabetes, and Autonomic Nervous System (ANS) Imbalance

From: Transcutaneous auricular vagus nerve stimulation as a potential novel treatment for polycystic ovary syndrome



Possible pathways and action mechanisms of ta-VNS in the treatment of PCOS. *ta-VNS* transcutaneous auricular vagal nerve stimulation, *PCOS* Polycystic ovary syndrome, *IR* insulin resistance, *T2DM* type 2 diabetes mellitus, *HPAA* hypothalamic–pituitary–adrenal axis, *ChAP* cholinergic anti-inflammatory pathway, *SSAP* splenic sympathetic anti-inflammatory pathway, *GM* gut microbiota, *CVD* cardiovascular diseases.

ANS Imbalance:
Sympathetic Greater Than Parasympathetic



ANS Imbalance => Insulin Imbalance => ⇩ATP + ⇧Glucagon

Loss of Beta Cell Function not Mass

⇩**Pulsation**

Organelle

⇧**Inflammation**

Disorder

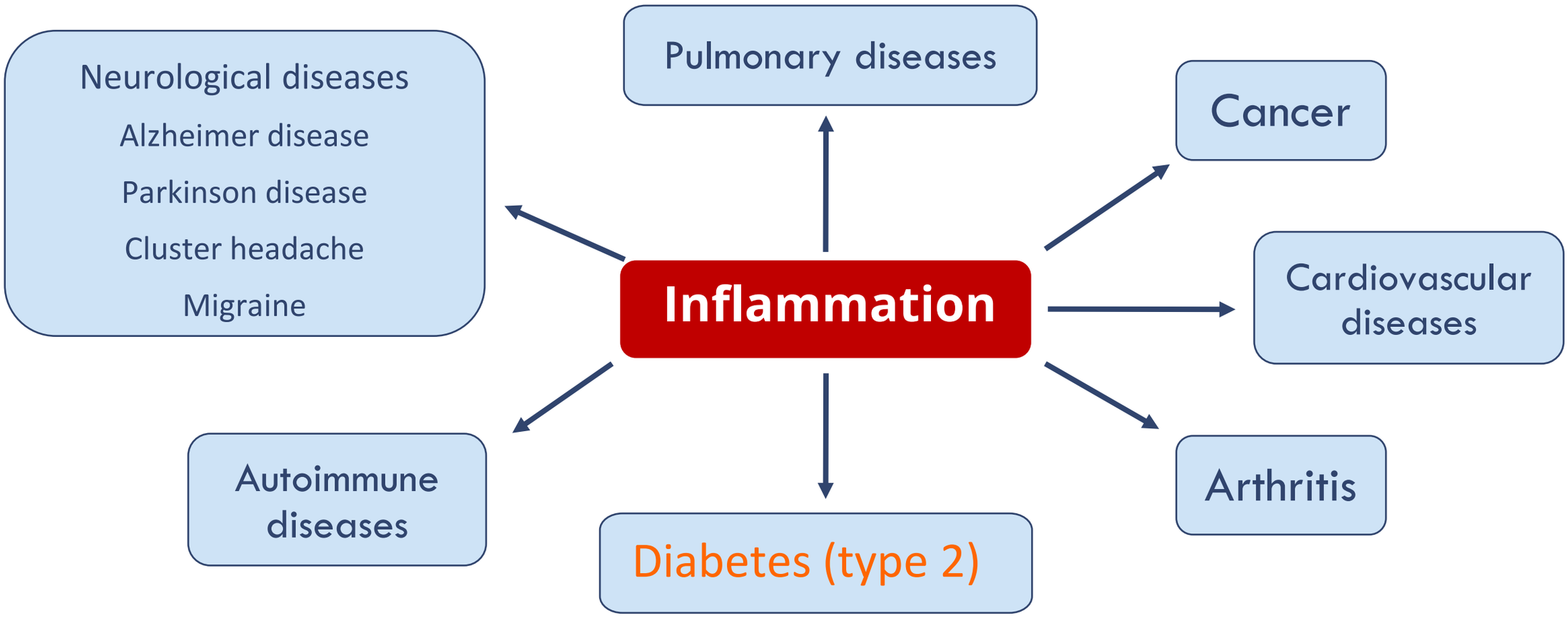
Intracellular Metabolic Failure

Brain and End Organ Vascular Dysfunction (lost dilatation + energy storage) leads to **80% of all Diabetic Comorbidity including Neuropathy**

https://doi.org/10.3390/ijms23031884
Brian Loverage, Tori Tucker, Melanie St. Laurent, Scott Hepford, Michael Alexander, Jonathan RT Lakey (2021) Dynamic diabetes solutions: physiologic insulin resensitization. Medical & Clinical Research 6(8): 656-660.

Metabolic Failure and Chronic Inflammation

Failure to return to a quiescent state may result in chronic inflammation, implicated in many serious medical conditions



ANS + Insulin Imbalance = Type 3 Diabetes = Alzheimer's

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Type 3 Diabetes and Its Role Implications in Alzheimer's Disease

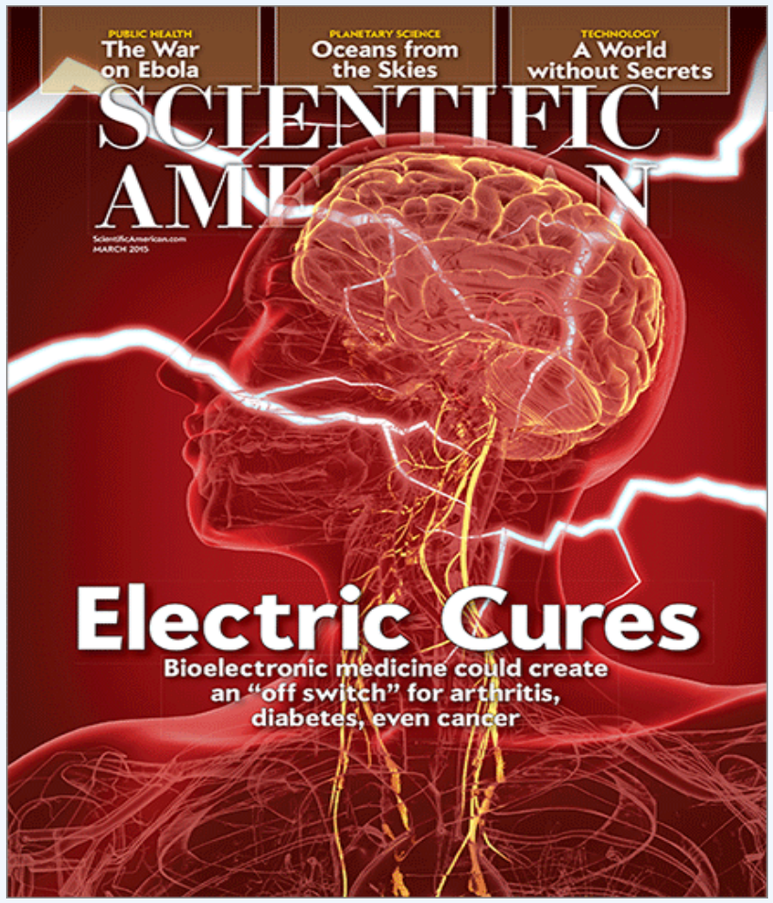
Thuy Trang Nguyen,[1,†] Qui Thanh Hoai Ta,[2,†] Thi Kim Oanh Nguyen,[3] Thi Thuy Dung Nguyen,[4,*] and Vo Van Giau[5,6,*]

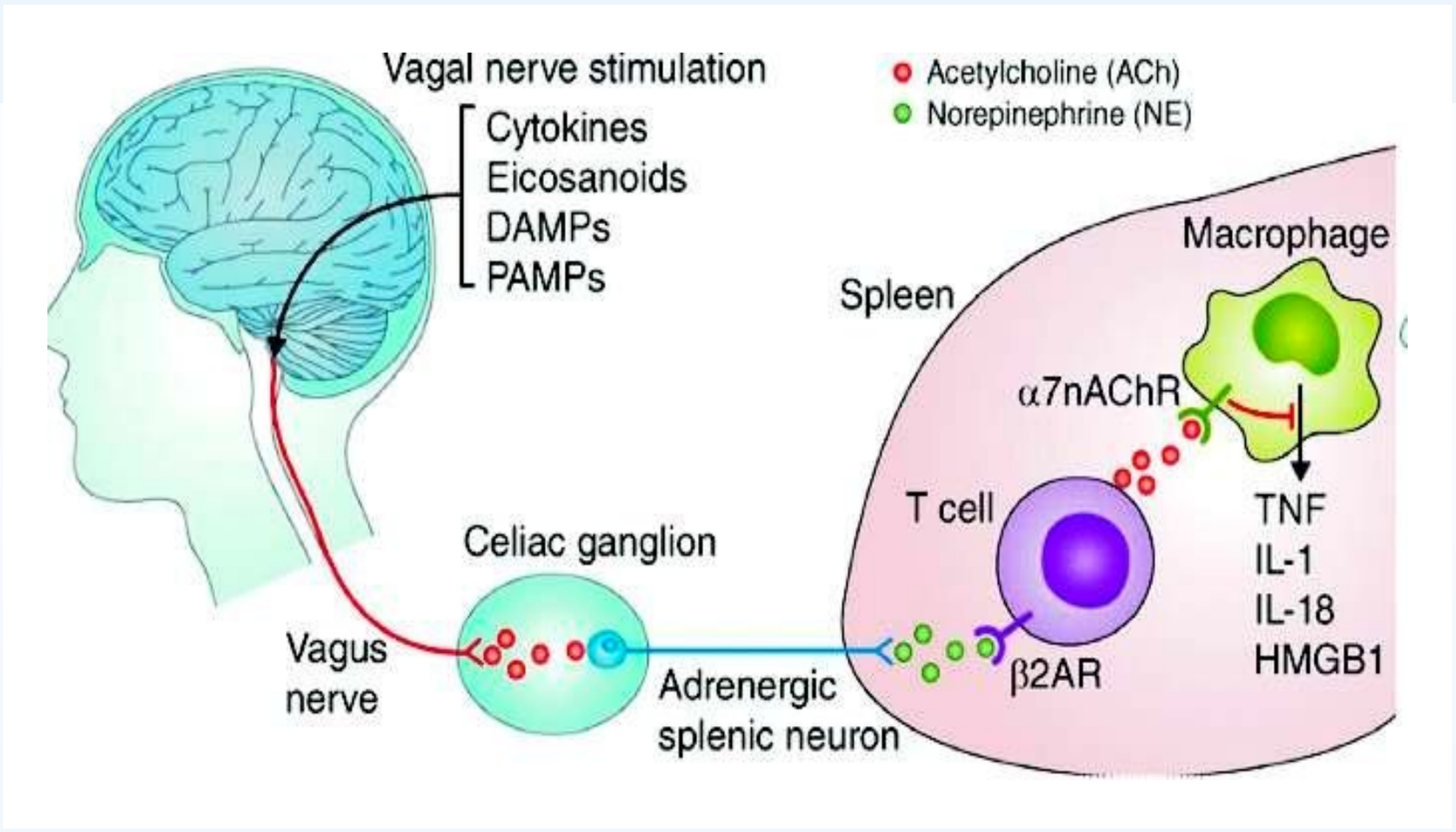
Abstract

The exact connection between Alzheimer's disease (AD) and type 2 diabetes is still in debate. However, poorly controlled blood sugar may increase the risk of developing Alzheimer's. This relationship is so strong that some have called Alzheimer's "diabetes of the brain" or "type 3 diabetes (T3D)". Given more recent studies continue to indicate evidence linking T3D with AD, this review aims to demonstrate the relationship between T3D and AD based on the fact that both the processing of amyloid-β (Aβ) precursor protein toxicity and the clearance of Aβ are attributed to impaired insulin signaling, and that insulin resistance mediates the dysregulation of bioenergetics and progress to AD. Furthermore, insulin-related therapeutic strategies are suggested to succeed in the development of therapies for AD by slowing down their progressive nature or even halting their future complications.

Keywords: Alzheimer's disease, hypometabolism, type 2 diabetes, type 3 diabetes, insulin resistance

Modulating Immune Inflammation | Vagal ANS



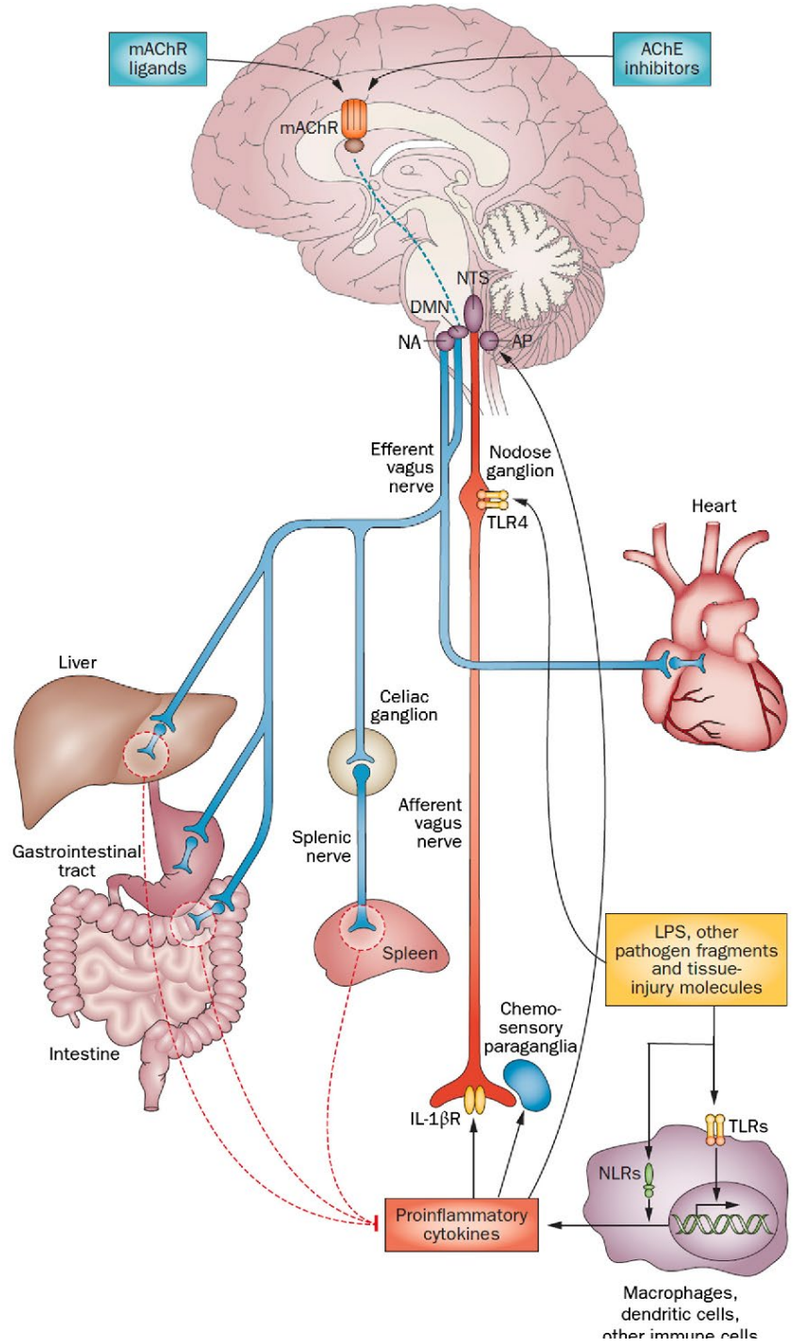


The system has evolved a control circuit to modulate immune responses to prevent excessive inflammation

Vagal Autonomic Nervous System (ANS).

Vagal Nerve Stimulation Blocks Inflammation through the Cholinergic Anti-Inflammatory Pathway

The CAP was first associated with the spleen, but liver, brain, lung, pancreas and intestinal pathways have now been reported.



Bonaz, et al., Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation, Journal of Physiology, 594 (20), 5781–5790 (2016).

Synergistic Vagal Control of Pain + Glucose

CNS: attenuates nociception, reduces cortical spreading depression, seizure and narcotic withdrawal, and autonomic restoration of vagal tone-imbalance; increases lymphatic flow,

Cardiac: Reduces heart rate and blood pressure

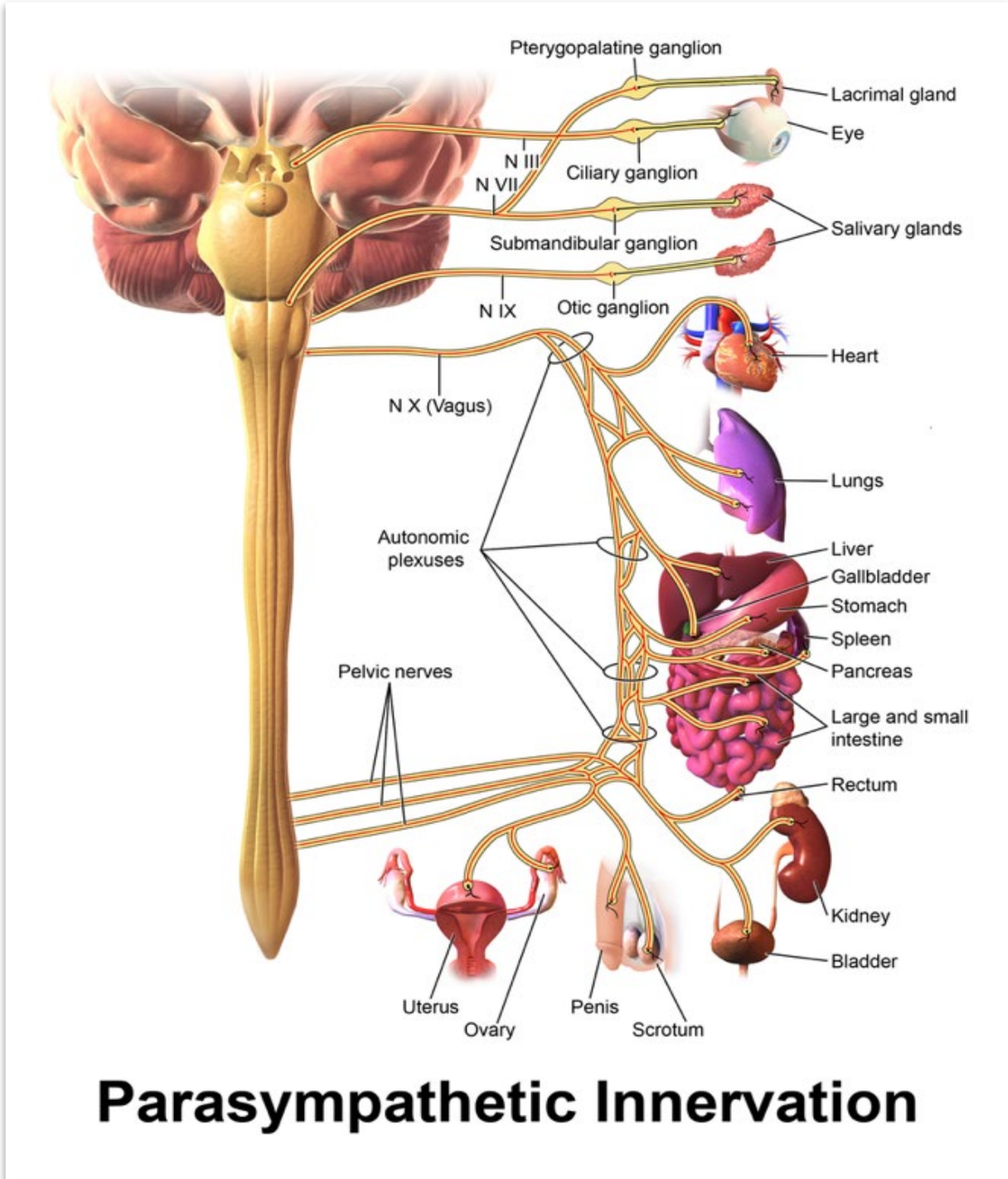
Pulmonary: Increases bronchodilation

Hepatic/Pancreas: Regulation/Restoration of Gluconeogenesis (Insulin Balance)

Gastrointestinal: Increases GI motility, neuroendocrine reflexes, and secretions; satiation

Splenic: Detection and regulation of systemic Inflammation - Cholinergic Anti-Inflammatory Pathway

Multiple Synergistic Pain Relieving Mechanisms



Trigeminocervical and Vagal Nerve Stimulation for Painful Diabetic Neuropathy

NeuroSolutions 100

- Successful clinically in mitigating pain for up to 6 months**
- Can decrease need for prescription pain medication and aid in opioid withdrawal treatment
- Potentially diagnose and Remove Narcotic Hyperalgesia from DPN pain presentation
- Improve patients' function, insomnia, depression, anxiety and quality of life
- Central Antidromic Inhibition of WDN of Dorsal Horn

**Potential Vagal Control of Metabolic State - Improvement in Inflammatory bidirectional reflexes and Glucose to maintain Pain control

NS100 Combined TCN-VNS Neurostimulator

THANK YOU