MINI-REVIEW

Vagal tone: effects on sensitivity, motility, and inflammation

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Key Points
• The vagus nerve is involved in the control of gastrointestinal sensitivity, motility and inflammation.
• A low vagal tone, as assessed by heart rate variability, is a marker of autonomic dysfunction that might favor dysfunction of the gastrointestinal tract.
• Restoration of vagal tone is a therapeutic target in some gastrointestinal diseases. Vagus nerve stimulation, either invasive or non-invasive, opens therapeutic avenues.

Abstract
The vagus nerve (VN) is a key element of the autonomic nervous system. As a mixed nerve, the VN contributes to the bidirectional interactions between the brain and the gut, i.e., the brain-gut axis. In particular, after integration in the central autonomic network of peripheral sensations such as inflammation and pain via vagal and spinal afferents, an efferent response through modulation of preganglionic parasympathetic neurons of the dorsal motor nucleus of the vagus and/or preganglionic sympathetic neurons of the spinal cord is able to modulate gastrointestinal nociception, motility, and inflammation. A low vagal tone, as assessed by heart rate variability, a marker of the sympatho-vagal balance, is observed in functional digestive disorders and inflammatory bowel diseases. To restore a normal vagal tone appears as a goal in such diseases. Among the therapeutic tools, such as drugs targeting the cholinergic system and/or complementary medicine (hypnosis, meditation...), deep breathing, physical exercise, VN stimulation (VNS), either invasive or non-invasive, appears as innovative. There is new evidence in the current issue of this journal supporting the role of VNS in the modulation of gastrointestinal functions.

Keywords inflammatory bowel disease, motility, pain, vagal tone, vagus nerve stimulation.

INTRODUCTION

In the current issue of this journal, Frokjaer et al. assessed, in healthy volunteers, the effects of transcutaneous vagus nerve stimulation (VNS) and deep slow breathing on validated cardiometrically derived parameters of vagal tone, musculoskeletal pain thresholds, descending pain modulation and gastroduodenal motility in a randomized, sham-controlled, single-blind, crossover trial. They showed that transcutaneous VNS increased: [i] vagal tone, [ii] thresholds to bone pain, [iii] frequency of antral contractions, and [iv]
gastro-duodenal motility index. These data have potential therapeutic implications in the domain of chronic pain and gastrointestinal motility disturbances but also inflammatory disorders of the gastrointestinal tract as observed in functional dyspepsia, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and others.

The VN is a key part of the autonomic nervous system (ANS), composed of the parasympathetic and sympathetic nervous systems. Information regarding the extent of its involvement in the regulation of the digestive tract homeostasis is rapidly expanding and provides new insights from a therapeutic point of view. The VN is the longer nerve in the body; it is a mixed nerve containing approximately 80% afferent and 20% efferent fibers² supplying mostly visceral organs. Vagal afferents are activated by gastrointestinal and pancreatic hormones, mechanical distortion of the mucosa, luminal osmolarity and ingested macronutrients, and are involved in the regulation of food intake, pancreatic exocrine and endocrine secretion, and cardiac and respiratory rhythm generation.

In normal resting conditions, there is a balance between the parasympathetic and sympathetic nervous systems as indexed by heart rate variability (HRV).³ This balance is modified in acute stress condition because stress induces a parasympathetic withdrawal and stimulates the sympathetic nervous system.⁴ This balance is restored after acute stress but in chronic stress conditions it can be disrupted for long periods. Stress is involved in the pathophysiology of functional and organic diseases of the gastrointestinal tract such as functional dyspepsia, IBS, IBD [Crohn’s disease, ulcerative colitis].⁵,⁶ An imbalance between the ANS and the hypothalamic pituitary adrenal [HPA] axis has been reported in such diseases.⁷ This imbalance is often the consequence of an imbalance between the prefrontal cortex [PFC] and the amygdala which innervate central autonomic network [CAN] areas.⁸ Thus, an abnormal vagal tone could be the cause and/or the consequence of such an imbalance. Consequently, restoration of normal vagal tone could be of interest in the medical management of such diseases either through drugs targeting the cholinergic system, complementary medicine [hypnosis, meditation…], deep breathing, physical exercise, VNS. This might favorably prevent an individual’s risk profile.

In this mini-review, we highlight the anatomy of the ANS with a special focus on the VN and the central ANS and the control/evaluation of vagal tone in normal and pathological conditions through HRV. We will focus on the role of vagal tone on sensitivity, motility, and inflammation of the gastrointestinal tract. Finally, we will review nonpharmacological ANS modulation therapies, focusing on VNS, commenting on novel technologies and strategies on the horizon.

THE AUTONOMIC NERVOUS SYSTEM AND THE CENTRAL AUTONOMIC NETWORK

Visceral information conveyed by vagal and spinal afferents are integrated in the CAN containing brain regions highly interconnected and distributed throughout the neuraxis involved in the autonomic, endocrine, motor, immune, and behavioral responses.⁹ These regions include: the frontal, insular, and anterior cingulate cortices; the amygdala [central nucleus]; several areas of the hypothalamus, in particular the paraventricular nucleus [PVH]; the midbrain periaqueductal gray matter; the parabrachial nucleus in the pons; and, in the medulla, the nucleus tractus solitarius [NTS], the first relay station for general visceral afferents, ventrolateral reticular formation and raphe nuclei. This brain network can be divided roughly into structures such as the frontal cortex, which are involved in higher level executive functions, and structures such as the hypothalamus and limbic system, which are involved in homeostatic functions. These areas receive converging visceral and nociceptive inputs and, after integration, generate stimulus-specific patterns of autonomic responses via projections to preganglionic sympathetic neurons in the spinal cord and parasympathetic neurons of the dorsal motor nucleus of the VN to modulate the ANS and thus the vagal tone. Many of these areas are also components of pain modulatory circuits and control nociceptive processing via projections to the spinal and trigeminal dorsal horns. The CAN is a complex system including many positive and negative feedback loops governing both sympathetic and parasympathetic outputs. Because of this complexity, it is difficult to predict the final results of activity of this system since prefrontal activation might induce enhancement of sympathetic activity in one situation but enhancement of vagal activity in another.

VAGAL TONE AND THE CENTRAL AUTONOMIC NETWORK

Vagal tone could be explored via the cardiac vagal tone by means of HRV measurement.⁵ However, correlations between cardiac vagal tone and, for example, gastrointestinal vagal tone require further study, particularly under pathophysiological conditions. There is no a priori reason why vagal output from the nucleus
Vagal tone and sensitivity

Classically, pain arising from the viscera is mediated exclusively by spinal afferents and there is evidence that the sympathetic nervous system is involved in pain generation in chronic pain states. There is growing evidence that the VN modulates nociceptive processing in the spinal cord and the brain. Studies have shown that vagal afferents respond to nociceptive mechanical and chemical stimulation and this leads to brainstem representation of nociceptive signals. The increase in NTS c-fos expression observed in response to noxious gastric distention is attenuated by vagalotomy but persists after spinal cord transection. It has been suggested that nociceptive input through the VN may contribute to the affective-emotional rather than to the sensory-discriminative aspect of pain. Thus, the VN may indirectly modulate abdominal hyperalgesia. Electrical stimulation of abdominal vagal afferents inhibits or facilitates somatic nociceptive impulse transmission in the spinal dorsal horn, and depresses nociceptive behavior, depending on whether unmyelinated or myelinated vagal afferents are excited. Patients with VNS for epilepsy and depression often report improvement of pain. There is evidence for a relationship between VN activity and pain, based on the fact that the VN inhibits factors that are etiologic to pain such as inflammation, oxidative stress, and sympathetic activity, activates brain regions that can oppose the brain ‘pain matrix’, and finally influences the analgesic effects of opioids. Administration of cholecystokinin (CCK)-8 enhances memory retention in the mice after aversive training; this effect is blocked by vagotomy indicating that CCK-8 may produce its effect on memory retention by activating vagal afferents. Thus, in a number of gastrointestinal disorders, such as IBS, nutrient content may contribute to painful visceral perception by enhancing visceral aversive memory via vagal afferent pathways. Activation of vagal afferents is part of the mechanism that not only gives rise to vago-vagal reflex but also can modulate brain cortex neuronal activity and plays a role in the behavioral control of nociception and memory storage processes. It is well known that a hot drink or a nourishing meal are relaxing and help to calm anxiety suggesting that enhanced sensory vagal inputs originating from the gut modulate attitude and behavior. Vagus nerve stimulation suppresses experimentally induced pain through activation of vagal afferents which terminate in the NTS; NTS neurons then innervate the CAN and the nucleus raphe magnus and locus coeruleus, to cause subsequent activation of descending inhibitory pain pathways. Low-intensity VNS that activates vagal afferent Aδ fibers reduces visceral pain suggesting that a group of vagal afferents innervating viscera may have functions related to visceral pain inhibition.

Vagal tone and motility

The VN innervates classically the digestive tract from the esophagus to the splenic flexure while the rest of the digestive tract, i.e., the left colon and rectum, is innervated by the sacral parasympathetic nucleus. However, for some anatomists, the VN innervates all the digestive tract in human. The VN is a major component in the control of upper gastrointestinal
motility, thus a low vagal tone could favor gastrointestinal motility disturbances. Vagal dysfunction is known to contribute to esophageal hypomotility. Physiological vagal input to cholinergic enteric neurons is necessary to maintain a basal gastric tone and vagal cooling induces a decrease in gastric tone. A very low tonic vagal activity is apparently necessary and sufficient to produce basic antral motility, while more sustained vagal activity is necessary for high-amplitude gastric contractions and significant sustained fundic relaxation; the maximal effect of vagal stimulation on amplitude and length of gastric contraction is already reached at 2–4 Hz, with no further increase at 8 Hz. Chewing gum, via activation of cephalic stimulation, is an adequate stimulus to induce vagally mediated normalization of meal-induced antral motility in functional dyspepsia, suggesting that hypomotility is related to inadequate vagal stimulation. Antral dysmotility is a consistent finding in diabetics with delayed gastric emptying and impaired gastric autonomic innervation probably contributes to this dysmotility. Patients with Type 1 diabetes mellitus have impaired meal-induced volume response, possibly as a consequence of reduced vagal tone. Gastric dysmotility in diabetes is thus caused, at least in part, by vagal neuropathy and the VN is important for gastric meal accommodation in man. Stress is well known to delay gastric emptying, alter intestinal transit and colonic motility and inhibit vagal tone; this effect is mediated, at least in part, by corticotrophin-releasing factor. Autonomic dysfunction has been frequently reported in patients with gastrointestinal motility disorders. By stimulating gastrointestinal motility via activation of vagal pathways, gum chewing reduces the duration of postoperative ileus in abdominal surgery. Nicotine gum chewing combines the stimulation of the cephalic-vagal reflex by gum chewing and the activation of the cholinergic anti-inflammatory pathway by nicotine administration; it might be beneficial for the prevention of postoperative ileus. Improving vagal tone through gum chewing, deep breathing, moderate-pressure massage therapy, or other exercises that have a strong effect on heart rate and its variability or through VNS could have prokinetic effects. Further investigations are needed to explore the intestinal component of digestive tract motility under the modulation of vagal tone re-inforcement.

VAGAL TONE AND INFLAMMATION

The VN exerts a dual anti-inflammatory role through its afferents and efferents. Classically, peripheral pro-inflammatory cytokines, such as IL-1beta, activate vagal afferents and then the HPA axis through noradrenergic projections from the NTS to the PVH. More recently, an anti-inflammatory role of vagal efferents has been described by Tracey’s group. Indeed, VNS-induced acetylcholine release from the peripheral terminals of vagal efferents dampens the release of TNF-α by macrophages in a model of endotoxic shock in rats. This effect is mediated via activation of α7-nicotinic receptors on macrophages and defined as the inflammatory reflex, i.e., the cholinergic anti-inflammatory pathway. The same group has described a vagosympathetic link involving a stimulatory effect of the VN on the spleen through an interaction with the splenic sympathetic nerve resulting in the inhibition of TNF-α release by spleen macrophages although this pathway has been recently revisited. We have shown that vagal tone is significantly blunted in IBD in relation with negative affect, and high TNF-α levels. Consequently, low vagal tone has a pro-inflammatory effect. Low vagal tone is a significant predictor of necrotizing enterocolitis, an exaggerated inflammatory response resulting in high levels of pro-inflammatory cytokines, in preterm infants which opens up avenues for its role as a predictive biomarker of this disease. Stress is evoked in the pathophysiology of inflammatory disorders such as IBD, at least through an inhibition of vagal tone either through activation of projections from the hypothalamus to the dorsal motor nucleus of the VN or through modifications of the fronto-amygdaloid complex. We have shown that low frequency (5 Hz) VNS improves colitis in rats and may exert an anti-inflammatory effect in Crohn’s disease patients that exhibit an autonomic imbalance. We showed that VNS induced a clinical, biological, and endoscopic remission at 6 months in the majority (5/7) of patients with mild to moderate active Crohn’s disease and restored autonomic balance toward the homeostatic values observed in healthy subjects. We have also shown, in a case report, that VNS induced significant changes in resting EEG. In particular, activation was observed over the mediofrontal electrodes for both low and high frequency bands with the most important activation for theta band. Significant correlations were detected between EEG and high frequency-HRV for delta, theta, beta, and gamma frequency bands.

THERAPEUTIC IMPLICATIONS: ACTIVATION OF VAGAL AFFERENTS/EFFERENTS

Vagus nerve stimulation can be used to modulate gastrointestinal inflammation, motility, and
nociception, in addition to its current use for drug-resistant epilepsy and depression and open new avenues in the therapeutic armamentarium. Implantable VNS is an invasive technique, which poses a risk for adverse events from infection, although the risk is low since the technique is well described and commonly used. To avoid potential bradycardia, VNS electrodes are placed on the left cervical VN which is easily accessible at the level of the neck. ~100 000 patients have been implanted with invasive VNS for epilepsy and depression. Depending on the therapeutic purpose, either anti-inflammatory and/or anti-nociceptive, or prokinetic, one might suggest activating vagal afferents in case of nociception or vagal efferents alone. In addition, one may speculate that activation of both vagal afferents and efferents may be of interest in the domain of inflammation, pain, and gastrointestinal motility. The total charge for the device plus implantation varies from $12 000 to $25 000. By comparison, the cost of a 1 year treatment of biosimilar infliximab is ~6000 euros for the treatment alone in IBD.

Newer non-invasive VNS delivery systems do not require surgery and permit patient-administered stimulation on demand. These non-invasive VNS systems improve the safety and tolerance of VNS and are easy to use, making it more accessible and facilitating further investigations across a wider range of uses. Two non-invasive VNS devices are currently on the market (Fig. 1). NEMOS (Cerbomed, Erlangen, Germany) is an external device that provides transcutaneous auricular VNS (ta-VNS) by using a dedicated intra-auricular electrode (like an earphone) which stimulates the auricular branch of the VN. No clinically relevant adverse events, either cardiovascular or otherwise, have been reported with this device. The recom-
mended daily stimulation duration is 4 h and should be reached daily. Transcutaneous auricular VNS is able to increase HRV and reduce sympathetic nerve outflow in healthy controls. GammaCore (electroCore LLC, Basking Ridge, NJ, USA), is a non-invasive VNS device that uses two stainless steel round discs as skin contacts to deliver a programmable number of stimulation cycles through a transcutaneous low voltage electrical signal to the cervical VN, each lasting 120 s at a frequency of 25 Hz. This device is currently being tested for headache, epilepsy, and gastrointestinal disorders.

Some data is emerging regarding the use of VNS, either invasive on non-invasive, in fibromyalgia, pelvic pain, and headaches [see for review 46]. Lange et al. examined the safety and tolerability of invasive VNS in treatment resistant fibromyalgia and determined preliminary measures of efficacy as a secondary endpoint in this small cohort. Together with what is already known about VNS and its antinociceptive and anti-inflammatory effects, findings from preliminary studies are promising in terms of addressing the hyperalgesia and central sensitization associated with chronic pelvic pain and other chronic pain syndromes.

Ideally, VNS coupled to the detection of HRV would be of interest, particularly in patients with vagal dysautonomia, i.e., vagal hypotony as observed in IBD and IBS. The neurostimulator itself, for example, could also be used to measure HRV. For example, CardioFit (BioControl Medical Ltd., Yehud, Israel) is an implantable VNS device being investigated in heart failure that acts through preferential activation of vagal efferents. The system consists of a stimulator, a sensor lead and a stimulation lead, which are implanted under the skin of the chest. The sensor lead is extended from the stimulator to the right ventricle of the heart, and the stimulation lead is extended from the stimulator to the VN on the right side of the neck. Once activated, the stimulator’s electrical pulses are transferred via the stimulation lead to the VN. The stimulation is designed to correct the autonomic imbalance [sustained sympathetic overdrive and parasymptomatic withdrawal] that is maladaptive in heart failure. Unfortunately, CardioFit is an invasive system. A VNS device coupled to skin conductance evaluation, as a marker of sympathetic nervous system activity, would be of interest as well. In the same way, a VNS device coupled to circulating TNF-α levels would be of interest. Indeed, following intraperitoneal administration of TNF-α, the VN senses changes in peripheral inflammatory status within 3 min, and increases vagal tone in response. This defines a mechanism of inflammation sensing by the brain. Another point, is the improvement of VNS device through a miniaturization of the device and a multi-contact electrode that would stimulate ideally all the fibers components of the VN or selectively afferents or efferents. However, the exact topographic distribution of vagal afferents/efferents in the VN needs to be specified. Although non-implantable devices are attractive, they raise the problem of compliance as observed in the medical treatment of chronic diseases with drugs and which is avoided by the classical invasive VNS.

CONCLUSION

As a bidirectional link between the brain and the gastrointestinal tract the VN is involved in maintaining the homeostasis of gut functions such as sensitivity, motility, and immunity both through its sensing and modulatory roles. A dysfunction of the vagal tone is observed in functional and inflammatory digestive disorders. To restore a normal vagal tone is a therapeutic goal in such diseases where VNS appears as an interesting tool.

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CONFLICTS OF INTEREST

No conflicts of interest exist.

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