

THE VERSATILE ROLE OF THE VAGUS NERVE IN THE GASTROINTESTINAL TRACT

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ABSTRACT

The vagus nerve, the major nerve of the parasympathetic nervous system, innervates several organs from the neck to the abdomen. The vagal branches contain afferent (i.e. sensory) and efferent (i.e. motor) fibres contributing to a bidirectional communication between the visceral organs and the brain. The extensive vagal innervation of the body indicates that vagus nerve has a multitude of physiological functions. Specifically, the gastrointestinal (GI) tract is densely innervated by the vagus nerve and the latter plays a crucial role in GI functions such as food intake, digestion, and GI barrier function. In addition, the vagus nerve has immunomodulatory properties suggesting that activation of the parasympathetic innervation of the GI tract could act as a new therapeutic tool to treat intestinal immune diseases. This review summarises the anatomical and physiological properties of the vagal innervation of the GI tract.

Keywords: Parasympathetic nervous system, vagus nerve, gastrointestinal tract.

TOPOGRAPHICAL ANATOMY OF THE VAGUS NERVE

The vagus nerve, the main contributor of the parasympathetic nervous system, is the tenth cranial nerve originating from the medulla oblongata in the central nervous system. Within the medulla, the cell bodies of vagal preganglionic neurons are found in the nucleus ambiguus (NA) and the dorsal motor of the vagus (DMV). These nuclei supply fibres to the vagus nerve, which emerges from the cranium via the jugular foramen.¹ At the level of the jugular foramen, the superior jugular ganglion of the vagus provides cutaneous branches to the auriculus and external acoustic meatus.^{2,3} Just distally, there is a second ganglion, referred to as the nodose ganglion, collecting sensory innervation from visceral organs. The cell bodies of afferent (i.e. sensory) neurons are located in the

latter ganglion and project to the nucleus of the solitary tract (NTS). This nucleus relays input to the medulla in order to regulate the cardiovascular, respiratory and gastrointestinal (GI) functions.⁴

The cervical vagus descends within the carotid sheath alongside the carotid artery and internal jugular vein. Cardiac vagal branches leave the cervical vagus and join the cardiac plexus. The left and right recurrent laryngeal nerve, arising at the level of the aortic arch and subclavian artery respectively, also contribute to the cardiac innervation. Besides the heart, both vagi innervate the lungs through the pulmonary plexus.¹

INNERVATION OF THE GI TRACT

More distally, the left and right vagus run with the oesophagus through the diaphragmatic hiatus. Upon entering the abdominal cavity, the left and right vagus become the anterior and posterior

vagus, respectively.^{1,5,6} However, one has to keep in mind that each trunk receives fibres from both cervical vagus nerves.⁵ The number of posterior and anterior trunks passing through the diaphragmatic opening is variable, up to two in the former and three in the latter.⁵ The anterior trunk distributes gastric branches to the anterior aspect of the stomach and gives off a hepatic branch. Besides innervating the liver, the hepatic stem gives off branches to the pylorus and the proximal part of the duodenum and pancreas. On the other hand, the posterior trunk distributes one gastric branch to the proximal posterior aspect of the stomach and another to the coeliac plexus, which innervates the spleen and GI tract reaching as far as the left colonic flexure.^{1,5,6} The large intestine receives additional parasympathetic innervation through the pelvic splanchnic nerve (S2-S4), which terminates in the pelvic plexus and emerges as the colonic and rectal nerve.⁷⁻¹⁰

The afferent vagus nerve innervates the GI tract via vagal terminals both in the lamina propria^{11,12} and in the muscularis externa.¹³⁻¹⁵ However, the efferent vagus nerve fibres only interact with neurons of the enteric nervous system (ENS). The ENS consists out of a dense meshwork of nerve fibres, situated in the submucosal (i.e. submucosal plexus) and external muscular compartment of the intestine (i.e. myenteric plexus).¹⁶ By means of electrophysiological and anterograde tracer studies, it was demonstrated that preganglionic parasympathetic fibres (i.e. both vagal and sacral innervation) directly interact with multiple postganglionic myenteric neurons by formation of varicosities, whereas few vagal fibres communicate with submucosal neurons.¹⁷⁻²⁰ The preganglionic innervation of the GI tract displays a typical rostro-caudal gradient with the highest density of innervated myenteric neurons in the stomach and duodenum followed by a progressive reduction in the small intestine and colon.¹⁷ The fact that gastric myenteric neurons are activated by vagal input was also demonstrated immunohistochemically with the detection of c-Fos and phosphorylated c-AMP response element binding protein (p-CREB), which are markers for neuronal activity.^{21,22} As activation of neurons within one ganglion is initiated after the same latency period, Schemann et al.²⁰ suggest that the vagal input to the ENS is monosynaptic. However, this is not confirmed by other studies.²² Currently, three distinct vagal afferent terminals have been described.

The specific location of each terminal has correlations with its physiological function.

VAGAL REGULATION OF GI PHYSIOLOGY

Vagal fibres are projected throughout the GI tract and interact with the gut to regulate food intake, digestion, barrier keeping, and immunity. Food intake leads to satiety through the activation of several pathways: the release of various peptides from enteroendocrine cells (EEC), the direct action of certain nutrients (e.g. short fatty acids²³) (Figure 1A), and mechanoreceptor stimulation due to gastric distension (Figure 1B).²⁴ Most afferent vagal endings in the mucosal lamina propria are thought to be chemoreceptors sensing the presence of hormones, peptides and nutrients released by epithelial and neuroendocrine cells.^{23,25-27} In contrast, the terminal vagal structures in the external muscle layers and the myenteric plexus are considered to be mechanoreceptors detecting GI distension.^{13,14} These sensory signals are relayed to the NTS, in which the afferent information is processed. Appropriate vagal efferent output is transmitted from the DMV.¹² The latter has a major metabolic and dietary function, since electrical stimulation of DMV leads to an increased secretion of gastric acid,^{28,29} insulin^{28,30} and glucagon.^{28,31} Moreover, the secretion of gastric acid,³² insulin,³²⁻³⁸ glucagon,³⁵⁻³⁷ and pancreatic polypeptide^{39,40} is also elevated when the peripheral vagus nerve is stimulated (Figure 1). These responses are all abolished by vagotomy,⁴¹ administration of atropine,^{35,40,42} or hexamethonium.^{31,40} Besides its dietary and metabolic functions, the vagus nerve also has effects on the intestinal barrier function through immune cells (i.e. mast cells⁴³) and the activation of enteric glial cells via the ENS.

Dietary Intake and Metabolism Regulation

Chemical stimulation

The EECs respond to nutrient sensing in the lumen by the basolateral secretion of leptin in the stomach⁴⁴ and cholecystikinin (CCK) in the small intestine.⁴⁵ Tracer studies showed that EECs lie in close vicinity to mucosal vagal afferent terminals projecting from the nodose ganglia via the myenteric plexus.^{11,46} The close anatomical position between vagal afferents and EECs enables CCK and leptin to act as paracrine factors, which activate CCK-A²⁶ and Ob-R receptors^{25,27} expressed on afferent fibres, respectively.¹¹

Electrophysiological studies have confirmed these anatomical observations, since CCK stimulates afferent nerve fibres⁴⁷ and nodose ganglion cell bodies⁴⁸ via the CCK-A receptor. Leptin has also been reported to act in synergism with CCK through CCK-A receptors and afferent

vagal fibres.^{27,49} This afferent signalling is further relayed to the NTS.⁴⁹⁻⁵¹ Synergistic vagal activation by CCK and leptin leads to inhibition of food intake.^{49,52,53} In addition, CCK alone inhibits gastric emptying⁵⁴⁻⁵⁶ and stimulates biliary and pancreatic secretion (Figure 1).⁵⁷⁻⁵⁹

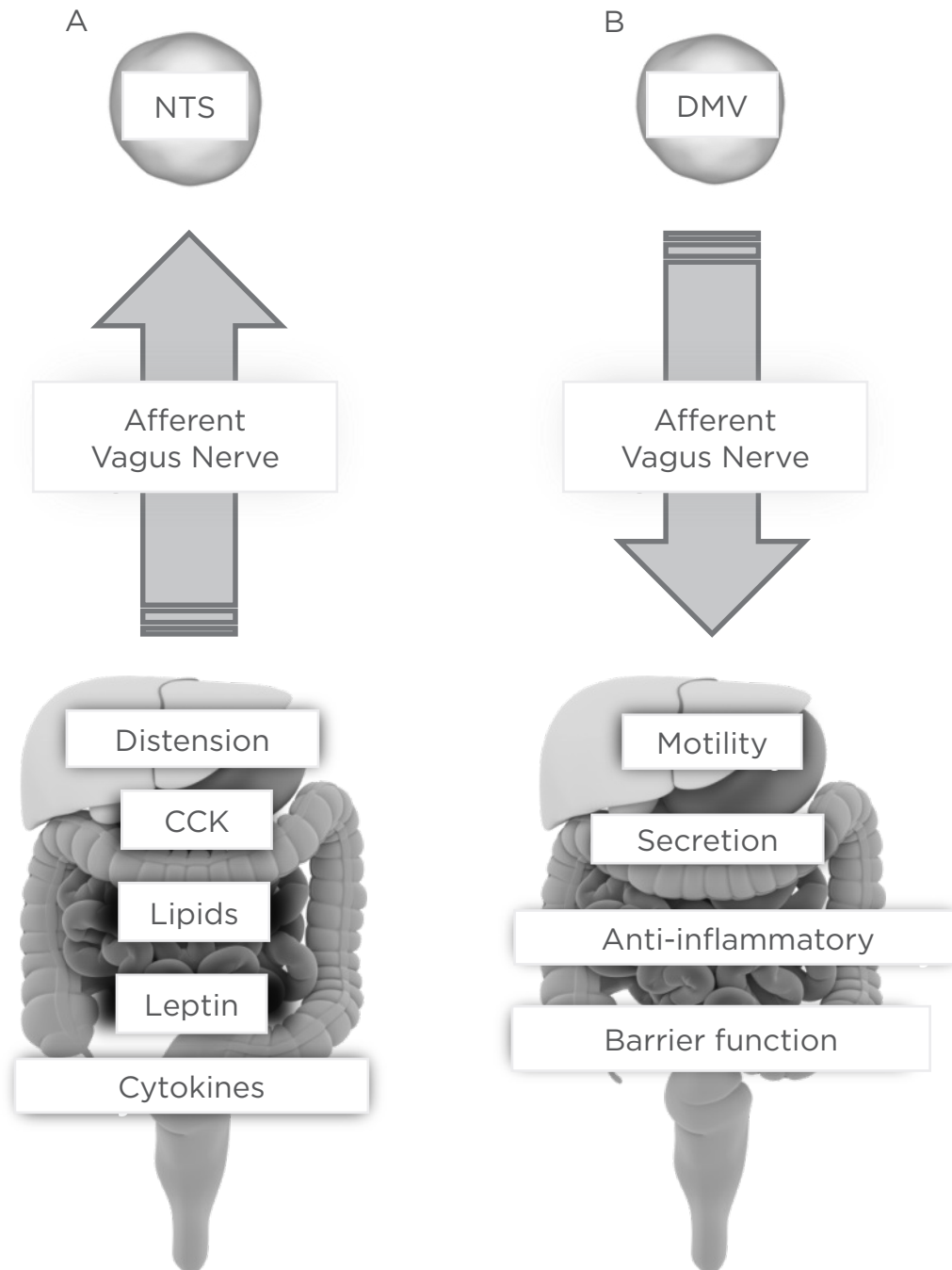


Figure 1. Vagal regulation of gastrointestinal (GI) physiology.

(A) Afferent vagal fibres receive information from the internal milieu of the GI tract via mechanical signalling and chemical (i.e. enteroendocrine hormone release and certain food nutrients) and immunological stimulation (i.e. proinflammatory cytokines).

(B) This sensory information is transmitted to the nucleus of the solitary tract (NTS) to mount an appropriate efferent (i.e. motor) response through the dorsal motor nucleus of the vagus (DMV), such as the secretion of neuroendocrine hormones and variations in GI motility, barrier function, and modulation of the intestinal immune response.

Indeed, the administration of specific CCK-A receptors antagonists (i.e. L364,718) prior to a meal increases food ingestion^{54,60} and gastric emptying, but inhibits pancreatic secretion.^{57,61,62} These effects of CCK are dependent on an intact vagal supply, since vagotomy^{58,63,64} or destruction of small diameter vagal afferent C fibres by capsaicin abolish the actions of CCK.^{54-56,58}

Mechanical stimulation

Besides chemosensory signal transduction, the afferent arch of the vagus is also activated by gastric distension through the stimulation of afferent vagal mechanoreceptor in the GI tract. Two candidate mechanoreceptors of the vagus nerve have been described: the intraganglionic laminar ending (IGLE)¹³ and intramuscular arrays (IMAs).¹⁴

The former terminal consists of aggregates of terminal puncta associated with myenteric neurons as well as connective tissue structures surrounding the myenteric ganglia. IGLEs are the densest in the stomach and become sparse more caudally.^{14,65-67} The close anatomical proximity between the connective tissue layers and the ganglia indicates that IGLEs are able to detect the shearing forces between the orthogonal muscle layers.^{67,68} Electrophysiological studies confirm that IGLE could act as low threshold tension receptors, since distortion of the stomach leads to activation of tension-sensitive vagal mechanoreceptors.^{46,67,69-71}

A second class of prominent vagal mechanoreceptors are IMAs, which consist of parallel arrays of neurite terminals coursing parallel to muscle bundles in the longitudinal or circular muscle layers^{14,66,72} and lie in close vicinity of interstitial cells of Cajal (ICC).^{15,73} IMAs are mostly located in the upper stomach, lower oesophageal and pyloric sphincters.^{14,74-76} Based on the morphological features, IMAs appear to act as stretch receptors sensitive to shearing forces in the long axis. However, electrophysiological studies have not been able to unambiguously determine the true functionality of IMAs.^{15,70,71}

The sensory vagal mechanoreceptors stimulated by gastric distension, are the first trigger of vago-vagal reflexes, such as gastric accommodation,⁷⁷ inhibition of food intake, and antral peristalsis (Figure 1).⁷⁸ Distension also

appears to act in synergy with CCK to increase afferent activity and consequently decrease food intake.⁷⁹⁻⁸³ However, Grundy et al.⁸⁴ disagree to the fact that CCK exerts a direct effect on vagal afferent mechanoreceptors, rather they suggest that the action of CCK is mediated through the sensory vagal chemoreceptors in the mucosa.⁸⁴

The Vagus Nerve as Intestinal Barrier Keeper

Intestinal epithelial cells maintain a strict barrier between the external and internal environment via the expression of tight junctions. The tight junctions consist of a branching network of interacting transmembrane proteins, such as claudins and occludins. The loss of epithelial barrier integrity and thus tight junction expression enables bacterial translocation across the intestinal mucosa, which can initiate detrimental systemic inflammation after severe injuries.⁸⁵ Coimbra et al.⁸⁶⁻⁹⁰ showed that there is increased intestinal permeability after haemorrhagic shock and traumatic brain and burn injuries, characterised by a decreased tight junction expression. Pharmacological, nutritional and electrical stimulation of the vagus nerve prevents the breakdown of the epithelial barrier via the stabilisation of tight junction expression (Figure 1).^{88,89,91-96} Evidence suggests that VNS maintains the epithelial barrier integrity after severe injury by enteric glia activation. Several groups have demonstrated that the activation of glial cells leads to the release of S-nitrosoglutathione (GSNO), which increases the expression of tight junctions and improves mucosal integrity. These observations were confirmed *in vivo* by intraperitoneal (i.p.) injection of GNSO in inflammatory models.⁹⁷⁻¹⁰⁰

Vagus Nerve and Intestinal Immune System: The Cholinergic Anti-Inflammatory Pathway (CAIP)

For many decades, it has been acknowledged that a complex interplay exists between the nervous system and immune cells. The central nervous system (CNS) receives sensory information about the presence of inflammation and responds appropriately via two specific pathways: neuroendocrine and neural routes.¹⁰¹

Afferent arch of CAIP

In light of an overt infection, circular cytokines (i.e. IL-1 and TNF- α) or pathogenic components can be detected by higher brain structures (e.g.

circumventricular organs [CVO]) that are devoid of a blood brain barrier. Indeed, administration of intravenous (IV) endotoxin elicited c-Fos activation in the CVO and NTS.¹⁰²⁻¹⁰⁴ These structures give direct input to motor neurons in the DMV, which project vagal efferents to the spleen. In this way, the vagus nerve is able to modulate the splenic immune response.¹⁰⁴⁻¹⁰⁶

The immune system does not only communicate with the brain via the circulation. In the case of more localised peripheral inflammation, in which the amount of proinflammatory cytokines is not detectable by the CVO, afferent vagal fibres and adjacent glomus cells are activated by cytokines/chemokines, such as IL-1 and mast cells mediators.¹⁰⁷⁻¹⁰⁹ Electrophysiological studies have reported that mast cell mediators and IL-1 activate afferent vagal fibres (Figure 1).^{108,110,111} Furthermore, both IV and IP administration of endotoxin induced c-Fos activity in primary afferent ganglia (i.e. nodose ganglia)¹¹² followed by increased NTS and splenic activity.¹⁰⁴ The same c-Fos induction was observed in the NTS in response to intestinal anaphylaxis and inflammation caused by surgical manipulation of the gut.¹¹³⁻¹¹⁵ Subdiaphragmatic vagotomy largely abolishes c-Fos activity in NTS and DMV after i.p. injection of endotoxin (i.e. LPS and SEB).^{105,116} Together, these observations strongly indicate that the brain is able to modulate the splenic immune response indirectly via the detection of circulating cytokines and directly via afferent input from sensory fibres.

Efferent arch of CAIP

The splenic immune response plays an important role during systemic inflammation, since splenic macrophages are the major source of TNF- α in sepsis.¹¹⁷ Therefore, the spleen is considered to be the perfect target to modulate the immune response in response to endotoxemia. In light of this, Borovikova et al.¹¹⁸ showed that vagus nerve stimulation (VNS) strongly inhibits splenic TNF- α production in a model of systemic inflammation, introducing the concept of the cholinergic anti-inflammatory pathway (CAIP). This anti-inflammatory response is mediated by the reduced activation of splenic macrophages expressing alpha7 nicotinic receptor (α 7nAChR). Acetylcholine (ACh) released by memory T cells, namely, interacts with α 7nAChR and inhibits the secretion of pro-inflammatory cytokines via the JAK-STAT pathway.¹¹⁹⁻¹²²

Over the years, many studies have demonstrated the beneficial effect of VNS in other inflammatory models such as haemorrhagic shock,¹²³ pancreatitis¹²⁴ and collagen-induced arthritis.¹²⁵ Ourselves and others also extended the concept of CAIP to the GI tract, since the gut is largely innervated by the vagus nerve. Indeed, we and others showed that electrical, nutritional and pharmacological activation of the vagal pathway prevents surgical induced inflammation and thus postoperative ileus (POI).^{122,126-129} CAIP activation also reduced intestinal inflammation in other models: diabetic-induced gastroparesis,¹³⁰ colitis,¹³¹⁻¹³³ and LPS-induced septic ileus.¹³⁴⁻¹³⁷ In contrast, vagotomised mice have a higher susceptibility to develop colitis after dextran sulphate sodium (DSS) administration.^{132,138,139} Moreover, a more severe colitis is also correlated with a reduction of mucosal levels of ACh in a model of depression.^{132,140,141} Like in the spleen, the anti-inflammatory response of CAIP is mediated through α 7nAChR macrophages. Deficiency of α 7nAChR in bone marrow-derived cells significantly abrogated the vagal anti-inflammatory effect, whereas α 7nAChR deficiency in neurons and other cells did not have a significant effect in POI, indicating that the beneficial effect of VNS depends on α 7nAChR expression on immune cells rather on neuronal cells.^{129,142} As in the spleen, the CAIP is not mediated by direct interaction between α 7nAChR macrophages and efferent vagal fibres, but rather via the modulation of cholinergic enteric neurons in proximity of intestinal α 7nAChR expressing macrophages.^{113,129} Other mucosal and submucosal immune cells, such as dendritic cells, mast cells, and T and B lymphocytes also express nicotinic receptors and may, therefore, be involved in CAIP.¹⁴¹

CONCLUSION

To date, electrical stimulation of the vagus nerve is already used as a therapeutic tool for intractable epilepsy and treatment-resistant depression. Currently, the anti-inflammatory effects of VNS are explored in three clinical trials in patients with rheumatoid arthritis (RA), Crohn's disease and postoperative ileus (NCT01552941, NCT01569503 and NCT01572155). Future insight from clinical trials and from basic research will hopefully offer the cholinergic anti-inflammatory pathway as a novel and powerful new therapeutic tool.

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