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Review Article

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Vagus Nerve Function in Gut-Brain Communication

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Abstract

The brain-intestinal axis plays an important role in maintaining the body's homeostasis. Nutrition can minimise and improve the undesirable negativities that can occur in the brain-intestinal axis. The gut microbiota is composed of the central nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, the autonomic nervous system and the enteric nervous system. This feature of the enteric nervous system allows it to be described as the 'second brain'. Communication between the brain and the gut (second brain) creates a bidirectional system. The primary neuron that transmits gastrointestinal signals and contains sensory nerve fibres is the vagus nerve. The sensory neurons of the vagus nerve innervate the internal organs and the brain, perceiving and transmitting various sensory signals. This function enables communication between the gut and the brain. Although the vagus nerve is a nerve of broad physiological importance in maintaining homeostasis in the body, it also has important functions in the control of the intestinal, cardiovascular, immune, endocrine and respiratory systems. Before food is eaten, the vagal nerves in the gastrointestinal tract send detailed information about the food to the brain, which receives and processes the information. The brain receives and processes the information, initiating intestinal peristalsis for the digestion and absorption of the ingested food, and the secretion of hormones necessary for the end of the meal and the feeling of satiety. The vagal nerves in the gastrointestinal tract therefore play an important role in the control of food intake. Various alterations in the gut microbiome can lead to metabolic disorders such as obesity and diabetes by regulating metabolic pathways and the host's eating behaviour through the brain-gut axis. Therefore, novel therapies targeting the gut microbiome and the vagus nervous system may be a potential treatment for obesity.

Keywords: Vagus nerve, Brain-intestinal axis, Second brain, Appetite

Introduction

Nowadays, the gut and microbiota are thought to cause health-related changes, and how the brain communicates with the gut is being investigated (1). Many studies have shown that the vagus nerve stimulation (VNS) plays an important role in brain-gut communication, appetite control, food intake regulation, obesity and autonomic nervous system (ANS) control (2,3). Energy balance, food intake and food expenditure are controlled by a complex system. The vagus nerve is the cranial nerve with the longest, largest and most extensive fibre network, communicating with fibres in the abdomen, trunk and neck (2,4). The vagus nerve is an important part of the cranial nerve. This complex nerve consists of 20% motor and 80% sensory fibres. The vagus nerve is an important nerve that controls autonomic reflexes such as maintaining body homeostasis, intestinal peristalsis, heartbeat, breathing, blood pressure, swallowing/coughing and

responses to inflammation in the body, and provides the connection between the brain and the gut (3,5). Studies have shown that regulation of the vagus nerve is effective in the recovery of diseases associated with impaired ANS (5,6).

Gut microbiota and metabolites may target the brain via vagal stimulation or immuno-neuroendocrine mechanisms. It regulates the transmission of signals in the appetite and food reward system, which has a significant impact on homeostasis and energy balance, the incidence of adiposity and obesity (7). The relationship between the brain-gut axis and obesity has been the subject of many studies. Research has linked the gut microbiota to obesity through the direct regulatory effect of the brain-gut axis on appetite-related hormones; glucagon-like peptide 1 (GLP-1), ghrelin and leptin. It has been concluded that the brain-gut axis plays an important role in altering appetite and influencing eating behaviour via the vagus nerve (7). The gut microbiota and microbiome is an important organ that may contribute to the development of some metabolic diseases. This effect on the gut highlights the importance of the brain-gut axis and vagus nerve stimulation in treatment, given the global prevalence of metabolic diseases such as obesity, which has increased in recent years (8). The aim of this study was to determine the functions of the vagus nerve between the brain and the gut (second brain), to evaluate the functions of the vagus sensory nerves in appetite regulation, to investigate the function of the ANS and how the vagus nerve provides communication between the central nervous system (CNS) and peripheral organs.

Enteric Nervous System

The enteric nervous system (ENS) is the largest part of the peripheral nervous system (PNS). On average, it contains the same number of nerve cells as an adult spinal cord. It is a unique organ that forms a neural network that includes two separate ganglionic plexuses, called the myenteric and submucosal plexuses, and thousands of ganglia that maintain neural continuity. Among the internal organs, the ENS has the gastrointestinal system (9). Vagal afferent fibres innervating the enteric nervous system are mainly generated by primary innervating afferent neurons synapsing with enteric nervous system and intestinal epithelial cells. The information transmitted by the primary innervating afferent neurons follows the vagal and spinal afferent pathways to reach the sympathetic ganglion and then the CNS. This transmission is realised by the activation of efferent pathways involving the autonomic nervous system. In this way, the enteric nervous system is directly linked to emotional arousal and central autonomic brain circuits (8). In addition, the ENS controls all intestinal functions in the PNS and regulates the functions of the intestine. It is also involved in many important functions such as absorption and secretion of ingested nutrients, blood flow, regulation of the immune system and gastrointestinal (GI) motility (9).

Cranial Nerves

The PNS is divided into the cranial nerves and the spinal nerves. It consists of a total of 43 pairs of nerves. Of these, 31 pairs are spinal nerves and the remaining 12 pairs are cranial nerves. Cranial nerves provide sensory and motor innervation to the structures of the head and neck. The cranial nerves consists of neural processes associated with the brainstem and cortical structures. It is responsible for the internal and external transmission of information from the brain. Unlike

the spinal nerves, the nuclei of the cranial nervesare functionally separate nuclei within the brainstem. The cranial nerves are numbered anatomically from I to XII and grouped according to their developmental function (sensory, motor, mixed). In particular, the posterior and lateral nuclei tend to be afferent and the anterior ones efferent. Cranial nerves I, II and VIII are considered to be afferent. Cranial nerves III, IV, VI, XI and XII are considered to be efferent nerves (10,11).

Vagus Nerve

The vagus nerve emerged from research on the glossopharyngeal nerve in the early 20th century. Through the sensory pathway, the vagus nerve transmits disease-related and life-sustaining information from the body to the brain. The sensory nerves transmit both signals from the environment and signals from internal systems to the brain. The senses of sight, smell, hearing, taste and touch perceive messages from the environment and transmit them to the brain to trigger a response. The information transmitted is extremely important for the body to meet basic physiological needs, maintaining homeostasis and organ integrity. The vagal afferent neuron extends a unipolar projecting axon bidirectionally to the brain and body (5).

Vagal fibres provide a bidirectional transfer of information between the brain and peripheral organs. In this transmission, most of the neurons are vagal afferent fibres that carry sensory information from the visceral organs to the brain; the remaining fibres are vagal efferent fibres that carry motor information to control peripheral organ function (12). The peripheral sensory vagus nerve is located in the carotid sheath towards the carotid artery, with major branches to the abdomen, chest and neck. Vagal nerves innervate many important tissues and organs, including the stomach, heart, larynx, ear, lungs, trachea, intestines, oesophagus, pancreas, liver and thyroid. Within each target organ, vagal afferent neurons vary in size, structure and molecular characteristics. They can have a variety of terminals with different anatomical structures and cellular connections to the interacting target organ. Each type of terminal is likely to identify and detect specific sensory points. Centrally, vagus axons pass through the skull and target the brainstem (5). The vagus nerve innervates a large number of peripheral organs; sensory information is transmitted from each of these organs to the brain via vagal afferent fibres, and the brain controls the motor function of each organ by sending signals via vagal efferent fibres. Chronic nutrition affects the response of vagal afferent neurons. It refers to two different neurochemical phenotypes that can stimulate or inhibit food intake. Chronic preference for energy-dense foods reduces the sensitivity of vagal afferent neurons to environmental cues and the constitutive expression of neuropeptides and orexigenic receptors. This disruption of vagal afferent signalling leads to obesity and hyperphagia (12). VNS is a form of neuromodulation that stimulates the vagus nerve. It was first approved for epilepsy, depression and stroke rehabilitation. Later, VNS was approved by the US Food and Drug Administration (FDA) as a treatment to reduce food intake and body weight in obese patients. The first implanted and invasive forms of vagus nerve stimulation emerged as applications. Invasive vagal stimulation requires surgery, is expensive and difficult to access. Its invasive nature and cost limit the use of vagus nerve stimulation in patient populations and make it difficult to study the mechanisms involved (13, 14, 15). A non-invasive form called transcutaneous ear VNS (taVNS), which stimulates the ear branches of the vagus nerve that innervate the human ear, has emerged. This

form of VNS is increasingly being used in clinical trials due to its lower cost and non-invasive nature. The gastrointestinal effects of VNS work through a cholinergic anti-inflammatory pathway and the combination of several systems along the brain-gut axis (16). Long-term administration of VNS reduces body weight and food intake in many species, including humans (17).

Appetite Regulation in the Central Nervous System

The hypothalamus is the regulatory centre for energy metabolism and food intake. Physiological control of appetite is provided by orexigenic (ghrelin) and anorexigenic hormones (leptin, cholecystokinin (CCK) and GLP-1) produced by peripheral organs such as the gut, adipose tissue and pancreas (18). In peripheral organs, hormones are secreted by enteroendocrine cells. They make up only 1% of the epithelial cells in the gastrointestinal system. Hormones secreted by enteroendocrine cells interact with vagal afferent nerves (8). Vagal afferents are regulated by hormonal, neural and mechanical signals. Foods ingested release gastrointestinal peptides that bind to specific receptors on vagal afferents (19). İnformation signals from peripheral organs are transmitted to the hypothalamus via the bloodstream or vagal afferent neuron. The information transmitted to the hypothalamus leads to the eating behaviour necessary for eating. There are many peptides that regulate appetite. These peptides are expressed and interact in complex ways in the cranial Nerves system and peripheral organs. Such peptides reach the mucosal part of the digestive tract and are sent to the solitary nucleus and hypothalamus, where the vagus afferent pathway regulates the electrical function of the vagus nerve. Among the hormones, peripheral peptides other than ghrelin suppress appetite via the vagus nerve. Appetite is regulated by peripheral tissues and the hypothalamus. Leptin is secreted by adipocytes and interacts with the arcuate nucleus of the hypothalamus in the circulation. Glucagon-like peptide-1 (GLP-1) and ghrelin act on the hypothalamus via the vagus nerve. Circulating appetite-stimulating and appetite-suppressing peptides act via gamma-aminobutyric acid (GABA), leptin and melanocortin receptors (MC4R). A-melanocyte stimulating hormone is controlled by the pro-opiomelanocortin (POMC) neuron. Agontia-related regulatory peptide (Ag RP) is an inverse antagonist of MC4R and both are involved in appetite regulation. Neuropeptide Y (NPY)/Agrp neurons, suppression of POMC neurons via GABA receptors play an important role in the regulation of appetite. The red lines in Figure 1 represent hypothalamic inhibition and the blue lines represent hypothalamic reinforcement (20). Enteroendocrine cells in the gut secrete orexigenic hormones that stimulate food intake in the fasting state and anorexigenic hormones that inhibit food intake in the satiated state. Vagal afferent neurons in the nodose ganglia are chemoreceptors that sense these hormones and mechanoreceptors that sense tension at their terminals in the gut. Satiety signals from the vagal afferent are transmitted to the nucleus tractus solitari (NTS) in the hindbrain. NTS neurons become active and reduce the duration and size of the meal. It sends signals to higher order neurons in the forebrain to regulate energy haemostasis or maintain the reward mechanism and/or to vagal efferent neurons of the dorsal motor nucleus (DMN) in the hindbrain to control meal size and duration. Vagal efferent fibres activate excitatory and inhibitory neurons to control digestion and absorption. Gastric hormones can be divided into two categories: those that regulate gastric acid secretion (gastrin, histamine, gastrin) and those involved in appetite control (leptin, ghrelin and nesfatin-1). Ghrelin is secreted in the fasting state, when there is no food in the stomach, and stimulates food intake. Ghrelin inhibits

the vagally mediated satiety effects of CCK and reduces vagal afferent sensitivity to gastric tone. Leptin, on the other hand, is secreted into the stomach with food intake and regulates meal duration and size by increasing mucosal tension sensitivity (12). In the fasting state prior to food intake, gastric enteroendocrine cells produce the orexigenic hormone ghrelin via a vagal pathway involving the hindbrain and hypothalamic ventromedial nucleus to increase appetite. Once food reaches the duodenal epithelium, it binds to enteroendocrine cell receptors where CCK induces the secretion of several hormones, including secretin and GIP, which regulate intestinal homeostasis. CCK receptors are activated by vagal afferent nerves and transmit information to the NTS, contributing to satiety. CCK then acts on vagal terminals to slow gastric emptying and induce pyloric sphincter contraction. GIP activates specific receptors on beta cells and stimulates insulin secretion. It thus acts on the hypothalamus to induce a feeling of satiety. As the food passes from the duodenum to the jejunum, nutrients and bile acids activate intestinal enteroendocrine cells to secrete GLP-1, CCK, PYY, NTS, GIP and secretin. The receptors for these hormones, except for GIP, are located on vagal afferent nerves. In addition, GLP-1, CCK and PYY receptors are located in the terminals of the enteric nervous system. Activation of all these receptors is involved in the feeling of satiety in the system (8).

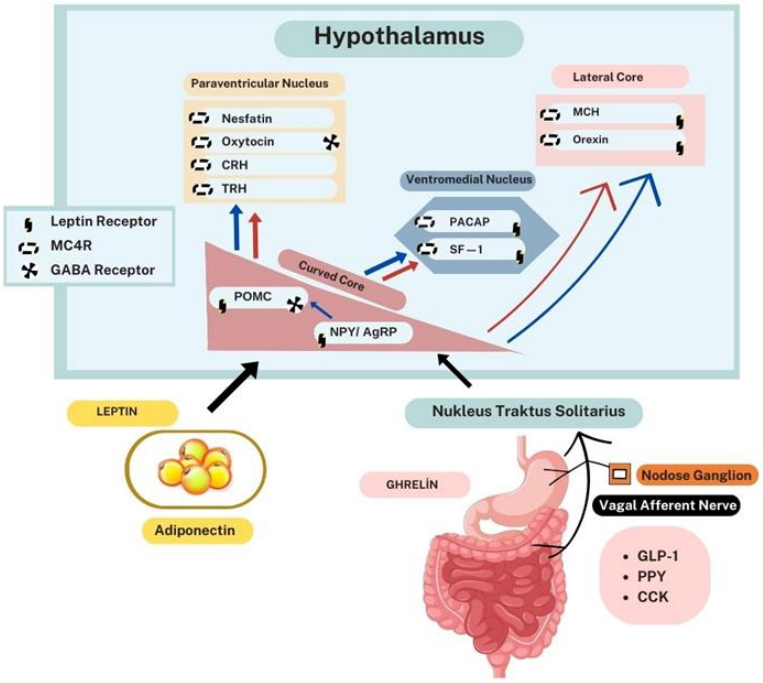

Figure 1. Mechanistic relationship between VA pathway, CNS and peripheral organs in appetite regulation (20). (VA: vagal afferent; CNS: central nervous system; CRH: corticotropin-releasing hormone; TRH: thyrotropin-releasing hormone; MCH: melanin-concentrating hormone; MC4R: melanocortin receptor; GABA: gamma-aminobutyric acid; POMC: pro-opiomelanocortin; NPY: neuropeptide Y; AgRP: agonist-related regulatory peptide; PACAP: pituitary adenylate cyclase-activating polypeptide; SF-1: steroidogenic factor 1; GLP-1: glucagon-like peptide-1; PPY: peptide YY; CCK: cholecystokinin)

Vagal Sensory Neurons and the Gut-Brain Axis

The extrinsic nerve plexus of the gastrointestinal system (GIS) provides the connection between the gut and the brain through spinal and vagal nerve fibres. The brain provides communication by sending efferent sympathetic and parasympathetic nerve fibres to the GI tract (21). The brain-gut axis provides short-term information about the quality and quantity of food consumed and the feeling of satiety after a meal. The brain-gut axis both controls appetite and regulates physiological processes that support systemic changes in energy use, digestion and absorption. Neural pathways influence gallbladder contraction, enzyme secretion, gastric acid secretion, regulation of blood glucose levels, gastric emptying and intestinal motility. Sensory neurons innervate the gut and control food selection and rejection. They are also involved in the control of fluid homeostasis, thirst or high salt intake. The vagus nerve can be accompanied by hunger, 'butterflies' and 'visceral pain', feelings that cannot be clearly defined; it is also stimulated by anxiety and irritability, which are constant in the brain-gut axis in mood control. This arousal may also occur via a reverse reflex circuit, possibly involving transmission from the brain to the gut (5). The brain receives information about food from the GI tract via neuronal afferents, circulating nutrients and gut hormones. The digestive tract is innervated by neurons in its inner and outer periphery. In this way, swallowed food is first perceived in the mouth by taste afferents, which provide information about its taste, food odours by olfactory sensory nerve, and properties such as food temperature and texture by vagus afferents. After ingestion, food is monitored by external nerves in the pharynx, oesophagus, stomach, intestines and rectum. While vagal afferent neurons intensely innervate the proximal small intestine, rectal neurons suppress inversion of the distal intestine (5, 22). In addition to extrinsic inversion, the oesophagus, stomach, intestine and other organs contain a large network of internal (enteric) neurons. Neurons in the ENS are associated with extrinsic motor neurons. The vagus nerve is an important part of the brain-gut axis. If the vagus nerve is severed in the region of the sensory transmitters associated with food (below the diaphragm), motor fibre-mediated transmission is not provided and metabolism, digestion and absorption in the body are impaired. This can lead to unwanted weight loss in the individual. Studies have shown that VNS prevents the feeding method when approached with optogenetic and electrical behaviour (5).

Vagal-Nucleus of the Solitary Tract Nerve Pathway Stimulates Appetite

The feeling of hunger is an extremely important concept for the continuity of life. After a while, the hunger sensation synthesises hormones in the GI tract to induce food intake and the GI tract contracts. The vagus nerve completely innervates the GI tract and provides communication between the gut and the brain. The vagus nerve senses gut hormones and GI contractions depending on the region in which it is located and the type of receptor in that region. In the brain, vagus afferents are important for feeling full after a meal. However, the role of the vagus afferents during hunger is not fully understood. The NTS in the brainstem is the main brain area of vagus afferent integration. The NTS is involved in metabolic control and nutritional regulation. NTS neurons detect nutrients and are sensitive to satiety signals (23). Food intake is suppressed by chemogenetic/optogenetic activation of different NTS neurons. Postprandial chemosensitive and mechanosensitive vagal afferent stimulation results in c-Fos expression, which determines the activation of neurons in the NTS where the vagal afferent fibre terminates

in the hindbrain (12). In one study it was observed that in deserebrated rodents, where communication between the forebrain and hindbrain is disrupted, feeding can be terminated. It has been observed that different types of NTS neurons are involved in satiety in response to nutrient signals. Transmission of peripheral information from subdiaphragmatic vagal afferent neurons to the NTS is sufficient to regulate meal size and duration. However, it has been shown that vagal afferent activation of NTS neurons can indirectly transmit nutrients to high-level forebrain neurons involved in rewards such as conditioned learning (12). Food intake is suppressed by chemogenetic/optogenetic activation of different NTS neurons. Vagal nerves detect orexigenic signals and send this information to the NTS. Thus, the vagal-NTS pathway simultaneously detects orexigenic signals and stimulates feeding. The vagal-NTS pathway is thought to play an important role in this. It is thought to be a vagal-NTS dependent pathway. The NTS pathway from NG to NPY/epinephrine (E) stimulates feeding, whereas the NTS pathway from NG to norepinephrine (NE) inhibits feeding (23).

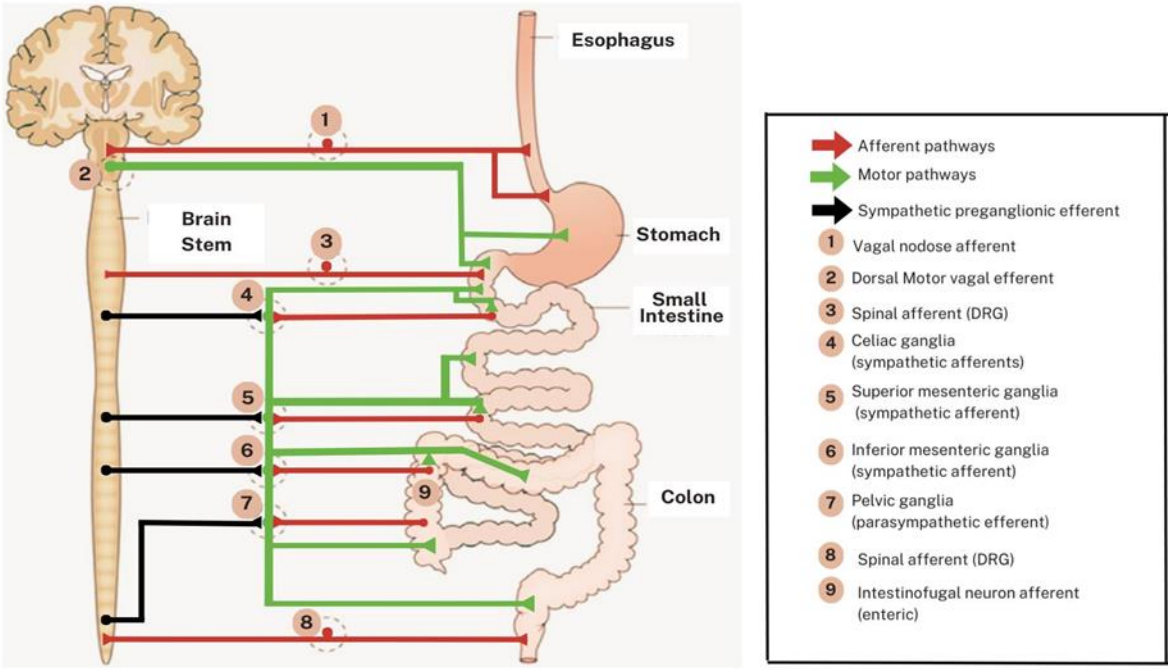

Figure 2. Diagram of the main extrinsic neural pathways between the enteric nervous system and the spinal cord and brain (1)

The main extrinsic motor pathways between the enteric nervous system (ENS) and the brain-spinal cord are coloured green. These motor pathways form the sympathetic and parasympathetic (vagal-motor) nervous systems. In the gut, the parasympathetic nerves are excitatory and the sympathetic nerves are inhibitory. In the upper intestine, the main external sensory nerves of the oesophagus and stomach arise from the vagus nerve, whereas in the colon (lower intestine) the influence of the vagus nerve is reduced and the main external sensory nerves to the colon arise from the spinal afferent nerve. The cell bodies are the nerves in the dorsal root ganglia (DRG) (1).

Nutrient Responses Along the Gut-Brain Axis

It has been suggested that the inclusion of high energy foods in the daily diet has a rewarding effect on the body. Digestion begins at the cephalic stage. The odours, shape and appearance of the food create food-related signals in the body, and signals are sent from the brain to the gut to give the order to prepare to eat. The macronutrients in food taken into the mouth are broken down by the digestive system into free fatty acids, amino acids and glucose. Special epithelial sensory nerves in the gut release glucose into the bloodstream before absorption. Once absorbed, the nutrients have different effects on different tissues. It activates nerve cells in the brain and stimulates the secretion of the metabolic hormone insulin. Enteroendocrine cells (EECs) play an important role in the response to food, and their food-sensing pathways in controlling satiety behaviour are an active area of research. The vagus nerve and rectal afferent nerves do not have direct access to the gut lumen. Therefore, endocrine cells, extraintestinal chemosensory neurons, immune cells, cluster cells and enteric neurons act as secondary neurons receiving sensory input. It is not clear how the enteroendocrine cell communicates with the vagus afferent. However, in the gastrointestinal tract these cells are intermittently mixed and on average make up 1% of the epithelial cells. Relative to the length of the intestine, enteroendocrine cells are the most abundant and hormone-producing cell model in the body. Enteroendocrine cells are similar to intestinal epithelial cells, but some have a shorter life span, while others can remain in crypts for longer. There is no clear information on the continuity of synaptic connections with neurons during enteroendocrine cell action and maturation (22). Enteroendocrine cell -derived hormones are cholecystokinin (CCK), peptide YY (PYY), glucagon-like peptide 1 (GLP-1), ghrelin, neurotensin, somatostatin, serotonin, gastric inhibitory polypeptide (GIP) and secretin hormones. Of these gut hormones, PYY, GLP-1 and CCK are released after ingestion and suppress appetite. Ghrelin, on the other hand, is secreted during hunger, is regulated by food intake and stimulates feeding. These meal-related signals are important in determining meal size and are therefore potential targets for the treatment of excess energy intake and obesity (10). Vagal afferent neurons harbour receptors and neuropeptides associated with the cessation of eating in response to a consumed meal. Vagal neurons innervating the gut communicate the state of eating with two distinct neurochemical phenotypes. After ingestion, gastric tone is increased and CCK is secreted. Circulating leptin increases the sensitivity of vagal afferent neurons to these peripheral signals and enables vagal afferent neurons to express the receptors and neuropeptides necessary to terminate food intake (anorexigenic), while at the same time terminating the expression of receptors and neuropeptides necessary to increase food intake (orexigenic). In the fasting state, ghrelin and cannabinoids are

secreted. The orexigenic fetotype is activated in vagal afferent neurons. The release of orexigenic neuropeptides to the NTS in vagal afferent neurons prolongs meal size and duration, whereas the release of anorexigenic neuropeptides shortens them (12). The mechanosensitivity of gastrointestinal vagal afferents varies with chronic nutritional status. In response to chronic consumption of high fat diets, there is a loss of mechanical and neurochemical plasticity in vagal afferent neurons. Loss of neurochemical flexibility in vagal afferent neurons is an important mechanism in the development of obesity (12). Disruption of vagus afferent signalling is sufficient to induce hyperphagia and obesity (10). GIP and GLP-1 are incretins that alter the metabolism of glucose ingested before it is immediately absorbed into the circulation and rapidly stimulate insulin release. GLP-1 receptor-related molecules are therefore important in the treatment of diabetes. GLP-1 receptor-related molecules are therefore important in the treatment of diabetes. Serotonin, CCK and other gut hormones are involved in the regulation of digestive functions such as gastric emptying, intestinal motility, absorption, exocrine pancreatic and gallbladder secretions. Some vagal afferent neurons express multiple receptors for gut hormones, including PYY, GLP-1 and CCK. CCK mediates calcium transients and activates action potentials. As a result of nerve transection studies, fat was found to reduce AgRP neuron function via vagus nerve and carbohydrate via spinal afferents (22).

Cholecystokinin

Cholecystokinin (CCK) synthesis takes place in the small intestine, mainly in the proximal duodenum. Outside the intestine, several neurons in the nucleus of the central nervous system, including the NTS, are also involved in this secretory process (24). There are several forms of CCK, the most common being CCK-8 and CCK-58. In the gastrointestinal tract, CCK is synthesised by I-cells in the small intestine. CCK is mainly released by I-cells in response to the presence of fatty acids and plays an important role in the digestion of food. CCK controls appetite behaviour in the nucleus accumbens region of the brain. CCK co-localises with several neurotransmitters and neuropeptides including serotonin, glutamate, dopamine, endogenous opioid peptides and GABA. This localisation suggests that CCK interacts with these molecules to modulate physiological processes and neuronal signalling in the central nervous system (12). CCK plays an important role in food intake, digestion and postprandial regulation, including delayed gastric emptying, secretion of pancreatic enzymes and inhibition of gastric acid secretion. Amino acids and dietary fats stimulate CCK in enteroendocrine cells in the duodenum and CCK secretion in the intestine. CCK-induced satiety acts via the paracrine pathway and is mainly mediated by the vagus afferent satiety nerves. There are two types of CCK receptors in the body. These are type A (CCK1R) and type B (CCK2R). TypeA has a high affinity for

sulphated CCK. TypeB binds to non-sulphated cholecystokine. Vagus afferents innervating the duodenum express typeA (24). Vagal afferents express the CCK1 receptor and terminate in the propria near the basolateral membrane of I cells. Electrophysiological studies show that vagal afferent discharge is increased by CCK-8 and neurons in the NTS are stimulated by CCK (19). The action of CCK in the system is mediated by activation of CCK1 and CCK2 receptors in vagal afferents. CCK receptors can interact with different G protein subtypes, similar to other GPCRs (25). The vagal-mediated mechanism of action of the CCK1 receptor is to cause contraction of the gallbladder, stimulation of the pancreas and satiety; the mechanism of action of the CCK2 receptor is motility and acid secretion. Disruption of vagal afferent pathways reduces the satiety effect of CCK in mice and rats. CCK1 receptor knockout Otsuka Long-Evans Tokushima Fatty (OLETF) rats showed hyperphagic results. Nakaft mice showed similar results to OLETF rats. These mice tended to consume larger meals (19).

Leptin

Leptin is an anorexigenic hormone secreted by the body's adipose tissues. Leptin is secreted mainly by adipocytes and to a lesser extent by parietal (P) cells of the stomach. Leptin receptors (LEPRe) are found in several regions of the brain, mostly in areas involved in feeding control. Leptin can cross the blood-brain barrier and activates leptin receptors on two subsets of neurons in the arcuate nucleus of the hypothalamus (ARC). Leptin regulates appetite and energy metabolism mainly by binding to the hypothalamic long-form leptin receptor and activating the Janus kinase 2 signal transducer and activator of transcription 3 (JAK2-STAT3) pathway. LEPRe are also expressed by vagal afferents terminating in the stomach (18, 19, 26). Peripheral leptin signalling is mediated by vagal afferents to the CNS. It has been observed that inactivation of the leptin receptor in mice causes obesity and hyperphagia. The main pathway by which leptin enters the CNS to signallingly regulate hepatic lipid metabolism is unknown (26). In particular, leptin activates anorexigenic neurons expressing POMC and inhibits orexigenic neurons expressing neuropeptide Y (NPY) and AgRP. These functions suggest that leptin plays an effective role in the appetite mechanism and suppresses appetite (18). Leptin also affects the function of the hypothalamic-pituitary-gonadal axis. In one study, leptin-deficient ob/ob mice showed reduced satiety and suppression of fertility. However, it is not clear whether leptin contributes to sex differences or to changes in food intake at meal frequencies according to the ovulatory cycle. In another study, conditional deletion of the leptin receptor in vagus afferent neurons in male mice led to an increase in meal duration and portion size, as well as an increase in body weight. This condition resulted in hyperphagia (27). There is a positive correlation

between plasma leptin levels and body fat mass. The stomach synthesises leptin hormone in response to food intake. Leptin increases energy expenditure and suppresses food intake and plays an important role in energy homeostasis. Nerves in the hindbrain and hypothalamus expressing the leptin receptor (LEPRe) mediate the anorexigenic effect of leptin. Direct binding of leptin to the NTS reduces food intake and weight gain. Damage to neurons in the NTS and LEPRe results in reduced satiety signalling in the gut and a reduced cholecystokinin response. This leads to increased food intake. In addition to the CNS, leptin is expressed via vagus afferent neurons innervating the GI tract and induces depolarisation of vagus afferent neurons. Leptin also has a synergistic effect with CCK and Ca+2. In the study, conditional deletion of LEPRe in the vagal afferent neuron in mice causes hyperphagia and a decrease in cholecystokinin-induced satiety. Both parts of the vagus-hindbrain axis, the NTS response to leptin and the vagus afferent, contribute to leptin-induced anorexia. Leptin controls the generation of satiety signals in the gut (24). The development of leptin resistance in peripheral neurons such as the vagal afferent neuron and neurons in the CNS during a high fat diet leads to the failure of this response to positive energy balance. Reduced leptin signalling appears to be an important factor in causing the energy imbalance that leads to obesity (28). A long-term high-fat diet increases bacterial lipopolysaccharide and plasma leptin levels. It decreases leptin sensitivity, known as leptin resistance, by inducing chronic immune activation and inflammation. Leptin resistance in the body leads to an increase in fat mass, body weight and hyperphagia. In the case of reduced sensitivity of the vagal afferent neuron to food-related GI signals and disruption of LEPRe, it is observed that carbohydrate absorption from the gut and long-term energy storage are impaired during HDF feeding (Figure 3) (28).

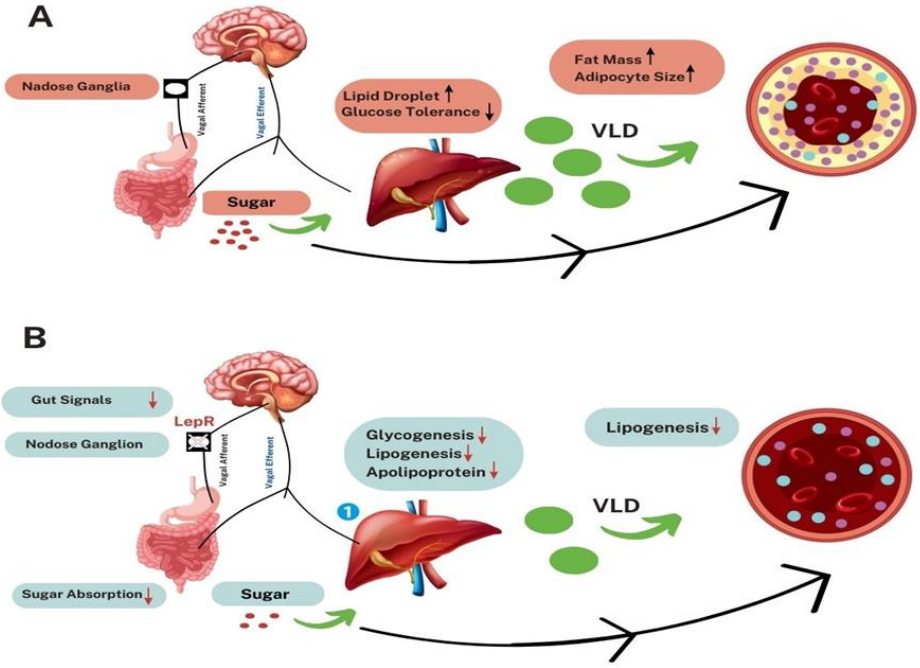

Figure 3. Demonstration of the interaction between VNS and leptin signalling on long-term energy storage and nutrient absorption during feeding (28).

(VNS: vagus nerve stimulation; VLD: very low density lipoprotein; LepR: leptin receptor)

Glucagon-like Peptide 1 (GLP-1)

GLP-1 is produced in solitary neurons in the CNS brainstem and in peripheral tissues from the proximal colon and small intestine. It is an incretin hormone produced by enteroendocrine L-cells. GLP-1 has two bioactive forms, GLP-17e37 and GLP-17e36 amide. GLP-1 receptors are abundant in the arcuate nucleus and hypothalamus. With its peripheral and central actions, GLP-1 reduces energy intake, increases satiety and can lead to weight loss. It is produced in solitary neurons in the brainstem of the CNS and in peripheral tissues by the proximal colon and small intestine (29). Stable GLP-1 and peripheral GLP-1 analogues can reach neurons in the CNS and cross the blood-brain barrier. Peripheral GLP-1 regulates food intake in the periphery and via the vagus afferent. The main metabolic functions of GLP-1 are to suppress food intake, induce insulin secretion and provide glycaemic control (24). GLP-1 sends information directly to the paraventricular nucleus of the hypothalamus. This provides strong evidence that this is the main site of GLP-1 satiety. GLP-1 acts directly on the paraventricular nucleus. In addition, GLP-1 receptors are expressed by POMC neurons and GLP-1 exerts anorexigenic effects in the arcuate nucleus. Neural circuits are activated and satiety signals such as CCK and GLP-1 occur at the time of food consumption, signalling the end of the meal and ending food intake (29). In adipose and muscle tissue, GLP-1 and GLP-1R agonists have an insulin-like effect by stimulating intracellular glucose transport through phosphorylation of AMP-activated protein kinase (AMPK) and glucose transporter 4 (Glut-4) at the plasma membrane. In addition, GLP-1R agonists have proliferative and cytoprotective effects on beta, alpha and delta cells (8). GLP-1R suppresses food intake via vagal deafferentation and subdiaphragmatic vagotomy. It has been

shown that GLP-1 in NTS neurons can also regulate food intake (10). GLP-1 secretion is stimulated by the gut microbiota when food is consumed. It binds to specific receptors on gastrointestinal and hepatic vagal afferents and is transmitted to the nucleus of the NTS and higher brain centres. Here vagal afferents are redirected to innervate peripheral organs (stomach and pancreas). This is involved in the regulation of food intake and gastric emptying and shows that the incretin effect of GLP-1 on the pancreas is strong (8). In mice with GLP-1R-specific knockdown in the vagal afferent neuron, it was observed that food intake increased, while the response to intraperitoneal injection of GLP-1 to reduce food intake was decreased in these mice (10). The vagus afferents pathway is the main pathway that responds to peripheral GLP-1 and transmits the satiety signal to the CNS. In addition to the vagal afferent neurons, the GLP-1R helps to regulate food intake for GLP-1 in the hypothalamus, mesolimbic system, hindbrain and hippocampus located in the CNS and is expressed in different types of nuclei in the CNS (23). GLP-1R knockdown of NTS neurons increases food intake and meal size. This suggests that satiety induced by gastric distension is mediated by activation of GLP-1R signalling in NTS neurons (10). The response of NTS neurons and the vagal afferent neuron to GLP-1 induces satiety signalling. In conclusion, peripheral GLP-1 is largely mediated by the vagal hindbrain pathway. In mice fed a high-fat diet, GLP-1 causes reduced activation of gut afferent nerves (10).

Gastrointestinal Vagal Afferents, Food Intake and Circadian Rhythm

Intestinal cells are connected to a central system in the suprachiasmatic nucleus (SCN) of the hypothalamus, which contains the circadian rhythm. Absorption and digestion of nutrients to ensure nutritional continuity is provided by the rhythmic biotransformation of the gut clock (30). In response to eating, the GI tract sends neural and humoral signals to the CNS. These signals are combined with the signals present here and the meal is terminated (3). The microbiota and the bacteria in the microbiota ensure that the gut clock works correctly. In this case, the preferred foods are crucial for maintaining the rhythm. At the same time, there is an indirect link between circadian rhythms and feeding times (30). For example, in gastritis vagus afferent, food-related stimuli are formed as daily rhythms. These rhythms are related to the frequency and size of meals and are inversely related to stomach content. An animal study found that gastric vagal afferent neuron sensitivity was lowest during the dark phase, associated with an increase in meal frequency and meal size, and highest during the light phase, associated with a decrease in meal size and meal frequency (3). In a study by Kentish et al. showing that the expression of clock genes (Bmal1, Per1, Per2 and Nr1d1) is involved in vagal afferent cell bodies and that the oscillation in the expression of these genes is associated with changes in the sensitivity of gastric mucosal receptors to stroking, single fibre recordings in afferents from the gastric bulge showed that the response of the gastric mucosal receptor to stroking with Frey hairs at 12 and 15 hours was 3 times higher than the response at 0 hour. According to the results of the study, gastric vagal mechanoreceptors respond differently to ingested food at different hours, suggesting that they have a circadian rhythm (19). Studies in humans and mice have shown that foods with a higher fat content are preferred in the evening compared to the morning, increasing the risk of obesity (30). In order to meet daily energy requirements, it is important to plan the flow of food with sensitivity and dedication (3).

Gut Microbiota

The microbiota has important functions in gut endocrine functions, the satiety system, control of lipid and glucose homeostasis, metabolic function and immune system development, and directly affects the maintenance of homeostasis (21, 31). The gut microbiota plays an important role in the ability of the GI tract to perform its functions (3). The gut microbiota is in regular communication and interaction with body systems and peripheral organs. The microbiota is effective in colonisation resistance, lipid and bile acid metabolism, amino acid anabolism and energy production. The microbiota is influenced by several factors, with diet having a 57% effect (31). Bacteria in the gut can indirectly or directly alter the function of the vagus afferent by affecting their receptors on enteroendocrine cell on the intestinal wall (21, 31). The gut microbiota includes the mechanisms involved in appetite control; it enables enteroendocrine cells to secrete anorexigenic hormones (GLP-1, PPY, CCK), neurotransmitters (5-HT), gut microbial metabolites and peripheral hormones (insulin, leptin and ghrelin). Ig's can also regulate the biological activity of appetite-regulating hormones such as ghrelin and leptin. In addition, the gut microbiota can produce protein sequences identical to appetite-regulating peptides, such as ClpB, which can bind to Ig's to regulate the secretion of anorexigenic hormones from enteroendocrine L-cells by acting directly on anorexigenic neurons (18).

The receptors for short chain fatty acids (SCFAs) produced by the gut are found on the enteroendocrine cell.

Short-chain fatty acids (acetate, butyrate and propionate) are indigestible dietary fibres that are fermented by the gut microbiota. Once absorbed into the circulation, FFA act as energy substrates. In the CNS, they act as signalling molecules and play an active role in the formation of microglia. CXRs stimulate the secretion of gut peptides by acting on specific G protein-coupled receptors. G protein-coupled receptors (GPCRs) are a family of seven transmembrane proteins that regulate various signalling processes by binding to G proteins on the cell membrane. The G protein-coupled receptors are called GPR43 (FFAR2) and GPR41 (FFAR3). These receptors are also expressed in a wide variety of tissues and cell types. GPR43 is expressed in skeletal muscle and fat cells, and GPR41 in the blood-brain barrier, peripheral nervous system, immune cells, colon and heart. This unique ligand specificity suggests that the interaction between the gut microbiome and the host may be mediated by GPR41 and GPR43. (8, 32, 33, 34). Propionate is a potent stimulator of GPR41 and GPR43, whereas acetate and butyrate have a more selective affinity for GPR43 and GPR41, respectively (34). In GPR41 and GPR43 systemic transgenic animal models, different effects were observed in phenotypes associated with metabolic diseases. This effect suggests that GPR41 and GPR43 play an important role in metabolic diseases such as diabetes and obesity (34). In vitro and in vivo studies have shown that propionate, one of the FFAs, stimulates the release of GLP-1 and PYY in humans and is effective in regulating appetite (3, 31). GPR41 and GPR43 have broad health effects on immunity and brain function, gut health and the growth and development of SCFA-producing gut bacteria. A recent study showed that butyrate in the gut microbiome of healthy menopausal women influences skeletal muscle mass through gut microbial synthesis. This effect suggests that GPR41 and GPR43 may play an effective role in sarcopenia (34). CXRs may inhibit appetite by binding to GRP43 and activating the release of leptin, GLP-1, PYY, insulin to

signal the appetite system (18). Results from rodent experiments show that gut microbial diversity and abundance are associated with leptin signalling (18). In a study of leptin treatment, it reduces hypothalamic NPY and AgRP expression in germ-free mice, but has no effect in wild-type mice. In addition, in vivo and in vitro studies show that leptin signalling is inhibited in obese humans and mice with increased intestinal permeability, which directly affects energy metabolism (18). The production of SCFA is influenced by the release of GLP-1. In a study, the G protein-coupled receptor GPR43 is activated when SCFAs are applied to mouse colon cell cultures. Activation of the GPR43 receptor ensures the production of GLP-1. This may interact with bacterial metabolites such as propionate by intestinal L-cells and control GLP-1 production. In another study, the probiotic 'Akkermansia muciniphila' is administered to obese mice to ensure the release of GLP-1 in the microbiota. After treatment, levels of acylglycerols, which are by-products of fat digestion in the gut, increase. It activates a G protein-coupled receptor. This allows L cells to release gut peptides, including GLP-1 (29). According to the results of a 2024 study investigating the effect of intestinal GPR43-specific GPR43 on obesity in KO mice and intestinal receptor function, energy expenditure and food intake were reduced in GPR43 KO mice, resulting in reduced weight gain and energy expenditure. Taken together, these findings suggest a novel role for intestinal GPR43 in mediating the development of obesity (35). One study investigated the effects of GPR41 on energy balance and glucose homeostasis. In the study, mice were fed 2 different diets. The first group was fed a normal diet and the second group was fed a high fat diet. Male mice showed genotype-dependent differences in plasma leptin concentration and body fat mass, with GPR41-KO mice having higher levels compared to wild-type mice. The reduced energy expenditure observed in GPR41-KO mice supports the idea that intestinal SCFAs have a potential role in increasing energy expenditure via GPR41 (34). Dietary recommendations specific to the gut microbiome and GPCRs may have a significant impact on the prevention and treatment of various diseases (34).

Effect of Diet

Dietary content causes differences in microbiota diversity between individuals. Diet is extremely important in the treatment of brain-gut axis dysfunction, neuroinflammation and repair of cognitive dysfunction. Animal and plant based dietary models induce rapid changes in the microbiota. Plant-based dietary models provide diversity in the microbiota and increase the number of beneficial bacteria in the microbiota. With the increase in beneficial bacteria, SCFA production and gut barrier integrity increase, while inflammation decreases. Consuming diets of animal origin or high in simple and refined carbohydrates reduces SCFA production and does not support microbial diversity (21). The stomach wall stretches when food is consumed and the mechanoreceptors in the stomach are activated. It is known that an individual's diet and stomach contents alter the neural responses of mechanoreceptors and feeding behaviour (21). In obesity, afferent neurons are less sensitive to peripheral meal-induced signals such as leptin, gastrointestinal hormones and gastric distension. Leptin resistance occurs in vagal afferent neurons. This prevents appropriate changes in neurochemical expression in response to a meal; instead, vagal afferent neurons continuously express receptors and neuropeptides that promote food intake. Loss of sensitivity to these peripheral signals in vagal afferent neurons directly promotes overeating and weight gain. Thus, vagal afferent signalling is the primary means of short-term control of food intake; however, when chronic high-energy diets are consumed,

dysregulation of vagal afferent neurons that secrete orexigenic signals to the brain results in increased meal size, leading first to hyperphagia and then to obesity (12). Estrogens play an important role in the central regulation of energy homeostasis. The solitary tract has been shown to act in both hypothalamic and extrahypothalamic regions, including the caudal medial nucleus of the hypothalamus, the arcuate nucleus of the hypothalamus and the dorsal raphe nuclei, to control feeding (27, 36). Female rodents are more resistant to obesity induced by a high-fat diet than male rodents, suggesting that oestrogen may protect against obesity (27). In ovariectomised animals, estrogen signalling is absent, resulting in increased energy intake and decreased energy expenditure, leading to obesity. Postmenopausal women whose plasma oestrogen levels are reduced show increased adiposity with lower resting energy expenditure (27, 37). VNS suppresses appetite and reduces the desire to eat in humans and animals. This leads to a decrease in body weight. The stomach becomes distended and a feeling of fullness occurs as the activity of vagal afferent neurons increases. This leads to a decrease in body weight (10). Another study investigated the efficacy of 12 weeks of chronic left cervical VNS via an implanted electrode and bioelectronic interface in rats diagnosed with obesity and metabolic syndrome and fed a high fat diet. The study found that VNS sham stimulation significantly reduced insulin resistance and plasma insulin, visceral fat deposition, triglyceride, total cholesterol and TNF levels. Blood pressure was also reduced, cardiac mitochondrial dysfunction was improved and adiponectin levels were increased. In a study investigating non-invasive ear VNS in rats induced to become obese by a high-fat diet, a significant reduction in body weight and abdominal adipose tissue content was observed (38). In a study of 1883 individuals aged 18-65 years, metabolic syndrome was significantly associated with decreased vagus nerve activity and increased sympathetic activity (38). In humans, electrical stimulation of the left cervical vagus nerve, a procedure used to treat refractory epilepsy and depression, has been reported to cause weight loss and increased energy expenditure via BAT thermogenesis (39). A pilot clinical trial also demonstrated beneficial effects on glucose metabolism with transcutaneous stimulation of the left auricular branch of the vagus nerve (40). There are also side effects associated with the loss of body weight caused by VNS. These side effects include indigestion, abdominal cramps and pain, bloating, reflux, vomiting, flatulence, regurgitation and nausea (10).

Relationship between a High-Fat, High-Carbohydrate Diet and the Vagus Nerve

Gastric vagus afferent tone receptors, reduced mechanosensitivity and reduced neural activation in response to gastric distension are observed in the hypothalamus of obese individuals. Hyperphagia and obesity are observed in individuals fed a high energy diet over a long period of time. When the neural responses of these individuals to food intake are studied, it is understood that they develop a defence against imbalance or loss of body weight. The responses of the gastric vagus nerves formed against gastric distension are reduced and it becomes difficult for the individual to achieve ideal body weight (3,10). Studies of obese rats fed a high-fat diet have shown that the perception of gastric mechanoreceptors is reduced by up to 55% and that these rats consume more energy due to increased food consumption (28). The situation of constantly consuming more than the daily energy requirement causes the expression of neuropeptides and various receptors in the stomach and vagus afferent sensitivity to decrease. In animals fed a high fat diet, there is a decrease in gastric distension and satiety due to afferent sensitivity to the jejunum. It has also been reported that the same effects are observed in animals fed a high fat

diet for short periods, although not continuously. Consumption of a lower fat diet reduces satiety signalling via the vagal afferent neuron and alters the expression of appetite hormone receptors. This is not seen in obesity-resistant rats fed a high-fat diet (41). In an animal experiment, the first group consisted of mildly obese mice fed a low-fat diet (10.5% energy from fat) and the second group consisted of mice fed a high-fat diet (60.3% energy from fat), and it was observed that these two groups exhibited similar behaviours. In addition, when these two groups were compared with mice fed a standard diet containing a moderate amount of fat (18% energy from fat), it was observed that there was less change in vagal tone during gastric emptying after food ingestion. The body weight, waist circumference and body mass index of mice fed a high-fat diet were more similar to the mildly obese mice fed a low-fat diet than to mice fed a standard diet. In this study, it was observed that the change in vagal tone was less in mice fed the Group 1 and Group 2 diets. This suggests that the fat content of the diet is not solely responsible for the development of bloating and the feeling of fullness. In addition, although it is not definitively clear whether a high carbohydrate diet causes vagus afferent disruption, it can be said that the fact that a high carbohydrate diet causes vagus afferent disruption similar to a high fat diet is related to the similarity that occurs in mice fed with groups 1 and 2. A minimal change in vagal tone provides the feeling of satiety (41). In another study, it was found that with the digestive system removed, vagal afferent neuron could not be activated and the rats did not feel full and were constantly engaged in eating behaviour (42). Another study in mice showed that long-term feeding of a high-fat diet disrupted the vagus afferent response to GLP-1, resulting in a disruption of the satiety signal (10). In another study, disruption of vagus nerve signals that provide communication between the brain and the gut in mice and rats resulted in a lack of satiety after a meal. In addition, long-term feeding of a high-fat diet causes regression of vagal afferent neuron, a decrease in satiety hormone sensitivity and hyperphagia in mice (42). Another study investigated the efficacy of 12 weeks of chronic left cervical VNS via an implanted electrode and bioelectronic interface in rats diagnosed with obesity and metabolic syndrome and fed a high fat diet. The study found that VNS sham stimulation significantly reduced insulin resistance and plasma insulin, visceral fat deposition, triglyceride, total cholesterol and TNF levels. Blood pressure was also reduced, cardiac mitochondrial dysfunction was improved and adiponectin levels were increased. In a study investigating non-invasive ear VNS in rats induced to become obese by a high-fat diet, a significant reduction in body weight and abdominal adipose tissue content was observed (38). In a study of 1883 individuals aged 18-65 years, metabolic syndrome was significantly associated with decreased vagus nerve activity and increased sympathetic activity (38). In humans, electrical stimulation of the left cervical vagus nerve, a procedure used to treat refractory epilepsy and depression, has been reported to cause weight loss and increased energy expenditure via BAT thermogenesis (39). A pilot clinical trial also demonstrated beneficial effects on glucose metabolism with transcutaneous stimulation of the left auricular branch of the vagus nerve (40).Long-term VNS reduces body weight and food intake in many species, including humans (42). A study in 2020 showed that vago-vagal reflex mechanisms play a role in the beneficial effects of chronic subdiaphragmatic VNS in high-fat diet-induced obese animals (38). In one study, obese rats were stimulated with trascutaneous ear VNS. The results of the study supported that VNS prevented weight gain by increasing BAT pain and B-adrenergic receptor and uncoupling protein1 (UCP1) mRNA expression in the BAT. The effects of VNS are accompanied by afferent signalling. A number of studies have shown that

increased Fos expression in the NTS is associated with reduced weight gain (12, 19). Data from these studies showed that consumption of a high fat diet caused inhibition of the vagus nerve between the brain and the gut (19).Data from all these studies have shown that VNS inhibition between the brain and the gut occurs after consumption of a high-fat diet (12, 19).

Conclusion

When it comes to digestion and metabolic regulation, vagus nerve is undoubtedly one of the most important connections between the gut and the brain. The vagus nerve plays an important role in nutrient intake, digestion, absorption and satiety. Control of satiety; while gastritis is involved in the induction of satiety via the vagus afferent, the vagus afferent of the proximal small intestine is involved in the formation of satiety and satiety due to chemosensitivity. Food intake is regulated by satiety hormones such as GLP-1, CCK and PYY secreted by enteroendocrine cells in the gut. These hormones have the ability to directly control vagus afferent terminals in the intestinal mucosa, which are close to enteroendocrine cells. Therefore, hyperphagia and obesity may result from the disruption of vagus afferent signalling. Feeding a high-fat diet reduces the VNS, causing a decrease in the satiety hormones secreted in the gut and their transmission to the brain. This leads to hyperphagia and obesity. In obese and overweight individuals, impaired vagus afferent leads to excessive food intake. The reduced effect of the satiety hormones secreted by the gut leads to an increase in body weight. Obese patients are usually fed a high fat diet. This diet causes a decrease in the secretion of the hormone leptin in obese people. Reduced leptin in the body causes a lack of satiety and leads to constant eating behaviour in the individual. Plastic changes in the vagus occur in metabolic diseases such as obesity and diabetes. These changes can adversely affect gastrointestinal function. A clear understanding of the molecular and cellular mechanisms mediating these events may provide new therapeutic targets for prevention and/or treatment. Neuromodulation of the vagus nerve may be used in the treatment of obesity.

When VNS is applied to obese individuals, it can lead to a decrease in food intake and body weight. Vagus nerve stimulation prevents weight gain in response to a high-fat diet. Clinical studies have shown that vagal nerve stimulation promotes weight loss in obese hosts on a high-fat diet and in patients with depression or epilepsy. Approaches and molecular targets are proposed for the development of future pharmacotherapy of the vagus nerve for the treatment of obesity. In conclusion, there is strong evidence that the vagus nerve plays a role in the development of obesity and is an attractive target for the treatment of obesity.

Compliance with Ethical Standard

Conflict of interests: The author declares that for this article they have no actual, potential, or perceived conflict of interests.

Ethics committee approval: The author declares that this study does not include any experiments with human or animal subjects; therefore, no ethics committee approval is needed.

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