Physiological functions of Vagus Nerve: Current and future applications

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Abstract:

The vagus nerve represents the parasympathetic autonomic nervous system. Research done about the physiological functions of vagus nerve is still preliminary. The afferent role of the vagus has not been described much in the literature. Most of the people know about the efferent role of vagus nerve. Now a day research shows bi-directional communication between the brain and gut via vagus nerve. It connects emotional and cognitive areas of the brain with gut functions. Vagus nerve has immune-modulatory properties also. Vagus nerve plays important role in the relationship between the gut, brain, and inflammation. The brain gut axis could be a therapeutic target for gastrointestinal, psychiatric disorders and inflammatory bowel disease (IBD). There could be new treatment options like vagus nerve stimulation (VNS) and meditation techniques. So in the present narrative research article we tried to focus on the different physiological functions of vagus nerve mostly afferent vagal functions and different therapeutic methods which could be used in gastrointestinal, psychiatric disorders and inflammatory bowel disease.

Key words: *vagus nerve, brain gut axis, vagus nerve stimulation*

Introduction:

Vagus nerve, the tenth cranial nerve has been the less understood cranial nerve. The vagus nerve is a mixed autonomic nerve originating from the medulla oblongata and travels from the brain stem bilaterally along the neck, esophagus and innervate the viscera. It provides an extensive afferent and efferent network of innervation. The vagus nerve is the main

contributor of the parasympathetic nervous system. The vagal efferent fibers are approximately 10–20% of all fibers, and the vagal afferents fibers are 80–90% of all fibers from the intestinal wall to the brain. (Tubbs RS et al, 2015) Though afferent fibers are much more in quantity, we know very little about the role of these fibers.

The vagus nerve helps regulate the body's autonomic functions, which are related to emotional tasks. Most people are more familiar with the vagus nerve's efferent functions only. The vagus nerve is the regulator of autonomic functions such as heart rate and gastric tone.

Sensory functions of the vagus nerve includes, sensation from the skin behind the ear, external ear canal, throat and visceral sensory information from the larynx, esophagus, trachea, lungs, heart and digestive tract, sensation of taste from the root of the tongue.

Motor functions of the vagus nerve include stimulating muscles in the soft palate, pharynx, larynx and lowers resting heart rate, involuntary contractions in the digestive tract.

The right vagus nerve supplies the sinus node and produces sinus bradycardia. Stimulation of the left vagus nerve which supplies the AV node can produce heart block. The Valsalva maneuver can terminate many kinds of SVT by producing transient heart block.

The afferent role of the vagus has not been described much in the literature. Brain-gut axis is the bidirectional communication between the brain and the gut which consists of the vagus nerve, endocrine, immune links. It regulates gastrointestinal homeostasis and connects cognitive and emotional areas of the brain with gut functions. (Carabotti M et al, 2015)

Enteric nervous system neurons are also in close contact to cells of the innate immune system and regulate their functions. The gut is an important control center of the immune system and the vagus nerve has immune-modulatory properties. (Goverse G et al., 2016)

Vagus nerve plays important roles in the relationship between the gut, brain, and inflammation. So the present study was done to review functions of vagus nerve beyond inhibitory parasympathetic functions. Research on vagus nerve functions will help in developing new therapeutic techniques and physiological maneuvers. The brain gut axis is becoming a therapeutic target for gastrointestinal, psychiatric disorders and inflammatory bowel disease (IBD). There are new treatment options like vagus nerve stimulation (VNS), acoustic stimulation and meditation techniques. These treatments have been shown to be beneficial in mood and anxiety disorders (George MS et al., 2008) as well as in inflammation. (Koopman FA et al., 2016)

Vagus nerve: Physiological and anatomical link between the Central and Enteric nervous system-

Brain gut axis is the connection between the central nervous system and the enteric nervous system. It is a connecting link between the emotional and cognitive areas of the brain and peripheral intestine. Brain- gut axis is responsible for immune activation and entero-endocrine signaling. The vagal afferents are involved in regulation of the HPA axis, (Howland RH et al., 2014) which is regulator of the adaptive response to stress. Both vagus

nerve and HPA axis together regulate the activities of intestinal functional cells like immune cells, enteric neurons, interstitial cells of Cajal and enterochromaffin cells, epithelial cells. (Mayer EA et al., 2014) Peptide hormones like leptin, cholecystokinin, ghrelin are sensitive to the nutrient content in the gut and regulate hunger and satiety.(Badman MK et al.,2005) Cholecystokinin acts through activation of CCK-1 receptors on vagal afferent fibers and regulates gastric emptying and food intake.(Rehfeld JF et al., 2003) CCK functions as a neurotransmitter and is present in enteric vagal afferent neurons, the thalamus, hypothalamus, basal ganglia, cerebral cortex and dorsal hindbrain. (Little TJ et al., 2005) CCK directly activates vagal afferent terminals in the nucleus tractus soliterious by increasing calcium release. (Rogers RC et al., 2008) CCK can activate neurons in the hindbrain and intestinal myenteric plexus. Circulating ghrelin levels are increased by fasting and fall after a meal. (Murphy KG et al., 2006) Central administration of ghrelin to rats acutely stimulates food intake and chronic administration causes weight gain. (Tschop M, 2000) The action of ghrelin on feeding is abolished in rats that have undergone vagotomy. (Date Y, 2012) Leptin receptors are also present in the vagus nerve. Leptin induce short-term inhibition of food intake and long-term reduction of body weight. (Owyang C, 2011)

Vagus nerve: physiology of anti-inflammatory action:

The gastrointestinal tract is constantly exposed to food antigens, pathogens. Disturbance of symbiotic intestinal microbial flora is a risk factor for intestinal inflammation. (Becker C 2015) Tumor-necrosis factor- alpha (TNF- α) is produced by activated macrophages, dendritic cells in the mucosa in response to pathogens and injurious stimuli. (Tracey KJ et al. 2002) TNF-α causes the cardinal signs of inflammation i.e. heat, swelling, pain, redness in local and systemic inflammation. (Bradley JR et al., 2008). The dorsal vagal complex responds to increased circulating amounts of TNF-α by altering motor activity in the vagus nerve. (Goehler LE et al., 2000)

The anti-inflammatory actions of the vagus nerve are mediated via hypothalamic–pituitary–adrenal axis, splenic sympathetic anti-inflammatory pathway and cholinergic anti-inflammatory pathway.

Norepinephrine released by splenic nerve acts on the β2 adrenergic receptors of splenic lymphocytes which releases acetylcholine (Ach). ACh inhibits the release of TNF-α through α-7-nicotinic ACh receptors in the spleen macrophages.

The ‘cholinergic anti-inflammatory pathway’ (CAIP) is mediated via vagal efferent fibres synapsing with enteric neurons which release ACh at the synaptic junction with macrophages. **(**Bonaz B et al., 2016) ACh binds to α-7-nicotinic ACh receptors of macrophages to inhibit the TNF-α . (Tracey KJ et al., 2009) The CAIP has high speed of neural conductance, which enables to modulate input to the affected region of inflammation immediately. (Browning KN, 2017) The CAIP is important in the intestinal immune response and homeostasis. The CAIP can be a target for the development of novel treatments for inflammatory diseases related to the gut immune system. **(**Bonaz B et al., 2016)

Inflammatory reflex has two principle components - inflammation sensing and inflammation suppressing functions. (Pavlov VA et al., 2012) Pathogenic organisms activate

innate immune cells that release cytokines. Cytokines which activate sensory fibres in the ascending vagus nerve which synapse in the nucleus tractus solitarius. Increased efferent signals in the vagus nerve suppress peripheral cytokine release through macrophage nicotinic receptors and the CAIP. Direct electrical stimulation of the efferent vagus nerve activates the CAIP and inhibits the synthesis of TNF-α in liver, spleen.

Vagus nerve stimulation technique and physiology of emotions:

The vagus nerve is connected with many mood regulating limbic and cortical areas via the NTS. (Nemeroff CB,2006) For the treatment of depression chronic vagal nerve stimulation technique is used. Vagal nerve stimulation decreases resting brain activity in the ventromedial prefrontal cortex which in projected to the amygdala modulating emotions. (Pardo JV et al., 2008) Antidepressant action of vagal nerve stimulation is because of chemical changes in monoamine metabolism. (George MS et al., 2005) Norepinephrine is main neurotransmitter of the pathophysiology of depressive disorders.(Moret C et al., 2011) The locus ceruleus contains the largest population of noradrenergic neurons which receives many projections from NTS, which receives afferent input from the vagus nerve. (Pisapia J, 2016) Vagal nerve stimulation leads to an enhancement of the firing activity of noradrenergic neurons and serotonin neurons. Thus vagal nerve stimulation was shown to increase the Norepinephrine concentration in the prefrontal cortex.(Follesa P, 2007)

Vagus nerve and serotonin Interaction:

The neurotransmitter serotonin stimulates peristalsis and induces nausea and vomiting by activating the vagus nerve. In rats increase in serotonin in the dorsal raphe nucleus has been seen after vagal nerve stimulation treatment. (Dorr AE and Debonnel G, 2006) Serotonin produced is essential for the regulation of appetite and sleep and is responsible for feelings of well-being. Serotonin released from the gastrointestinal tract leads to activation of 5-HT3 receptors on the terminals of vagal afferents. (Browning KN, 2015) The central terminals of vagal afferents also have 5-HT3 receptors which increase glutamatergic synaptic transmission in neurons of the nucleus tractus solitaries. Interactions between the vagus nerve and serotonin systems play an important role in the treatment of psychiatric conditions.

Physiological activation of vagus nerve by yoga for treating depressive symptoms:

Yoga can directly stimulate the vagus nerve and regulate autonomic nervous system, cognitive functions and stress coping. Yoga breathing induces increased vagal tone.(Streeter CC et al., 2012) Sudarshan Kriya Yoga stimulates the vagus nerve and causes changes in heart rate, improved cognition and improved bowel function.(Zope S et al., 2013) Iyengar yoga has been shown to decreased depressive symptoms. Iyengar yoga is associated with increased heart rate variability by increasing parasympathetic tone. (Khattab K., 2007)

Conclusion:

The interaction between the gut and the brain is based on neural as well as endocrine, immune links. The vagus nerve afferent and efferent pathways play an important role in the modulation of inflammation, the maintenance of intestinal homeostasis, and the regulation of

food intake, satiety and weight gain. Vagus nerve also plays an important role in the pathogenesis of psychiatric disorders and inflammatory diseases.

Meditation techniques and vagus nerve stimulation has a therapeutic effect by modulating the vagus nerve, mainly due to its relaxing and anti-inflammatory properties. VNS is approved by FDA for depression and seizure prevention and promising therapy for the treatment of severe anxiety disorders. Vagus nerve stimulation is approved for seizures and treatment resistant depression. Psychotropic drugs like serotonin reuptake inhibitors have effects on both the brain and the gastrointestinal tract. Research has great scope in investigating the interaction between vagus nerve and heart rate, psychological and pharmacological treatments and vegal nerve stimulation technique.

Application of the study:

1. Research on brain gut axis will help in treating inflammatory bowel disease, Crohn's disease.
2. Research on anti-inflammatory functions of vagal nerve will help decreasing inflammation in rheumatoid, heart failure due to myocarditis, inflammation in diabetes mellitus.
3. Vagal nerve stimulation techniques can physiologically lower the heart rate and blood pressure.
4. Research about vagus nerve stimulation will help in managing fear. It will help in treating rapid cycling bipolar disorder, anxiety disorders and Alzheimer's disease.
5. Research in Vagus nerve afferent functions will help in understanding pathophysiology of Parkinson's disease and intractable hiccups.

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