Review

www.anatomy.org.tr
Received: February 10, 2020; Accepted: April 11, 2020
doi:10.2399/ana.20.008

anatomy
An International Journal of Experimental and Clinical Anatomy

Enteric nervous system, gut-brain connection and related neurodevelopmental disorders

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Abstract

The vagus nerve is the primary neural medium which enables gastrointestinal tract and brain communication. Hippocampus, a region of the brain commonly linked to memory function, is activated by vagus nerve-mediated gastrointestinal signals. Vagal afferent information is received by the medial solitary nucleus and is then transmitted via ascending neural pathways to different regions of the forebrain and hindbrain. Explanation of the exact mechanisms of microbiota and amygdala communication requires further research. By linking microbial activities to progressive structural and functional events in the brain in mice models and in humans, we can suggest that intestinal microbiota is an important contributor to neurodevelopment and neurodegeneration. Further researches revealing these relations may provide new approaches for understanding neurodegenerative, psychiatric and behavioral diseases.

Keywords: enteric nervous system; gut-brain connection; neurodegenerative diseases; vagus nerve

Anatomy 2020;14(1):61–67

Enteric Nervous System and Its Internal Structure

When compared to other peripheral organs of the body, the gastrointestinal tract (GIT) differs from all of them. GIT has a comprehensive internal nervous system called enteric nervous system (ENS), which can control intestinal function, even if it is totally cut off from the central nervous system (CNS).[1] The ENS provides unique innervation of the intestine and is the most neurochemically diverse part of the peripheral nervous system (PNS).[2] The ENS was described by British physiologist John Newport Langley as one of the three autonomic nervous system parts: parasympathetic nervous system, enteric nervous system and sympathetic nervous system.[3] More than 100 million efferent neurons that reach the intestines through the vagus nerve are present in human ENS.[4] Unlike the rest of the PNS, the complexity of managing bowel behavior is a privilege that evolution provides to the ENS, which has led to the ability to manifest complementary neuronal activity and to control gastrointestinal behavior independently of the brain or spinal cord.[5–7] The ENS has at least as many neurons as in the spinal cord but has more neurons than any other group of peripheral ganglia. Unique to PNS, the ENS is regulated in microcircuits with intrinsic primary afferent neurons (IPANs) and interneurons that are capable of initiating reflexes. The phenotypic diversity of enteric neurons is very wide and almost every class of neurotransmitters found in the CNS has been identified in the ENS.[6] Although the ENS can work independently from the CNS, it normally does not; CNS affects the enteric system and the intestine also sends information to the brain. Indeed, 90% of the vagal fibers between the intestine and the brain are afferent, suggesting that the brain is more recipient than a giver in brain-intestinal communication.[6,8]

ENS is located within the tubular digestive system walls, biliary system and pancreas. ENS has myenteric and submucosal plexuses, two ganglioned plexuses in the intestine, where almost all intrinsic nerve cells are present.[9] The myenteric plexus is located between the outer longi-

tudinal and circular muscle layers and runs from the esophagus to the rectum along the full length of the digestive tract. The submucosal plexus is found only in the large and small intestines.[10]

The enteric motor neuron has five broad types and many subtypes; excitatory neurons that excite intestinal muscles, inhibitory neurons that inhibit intestinal muscles, vasodilator/secretomotor neurons, non-vasodilator secretomotor neurons, and neurons that innervate the enteroendocrine cells.[11] In the guinea pig's small intestine, one type of ascending as well as three types of descending interneurons have been identified. Neurons that ascend, which have enkephalin/calretinin/ChAT (ENK/calretinin/ChAT) chemical code, are cholinergic and form chains extending across the intestine, such as descending neurons.[12] The three descending interneuron species that the intestines have are called by the following names and chemical codes: nitric oxide synthase/choline acetyltransferase/vasoactive intestinal peptide ± gamma-aminobutyric acid ± bombesin ± neuropeptide Y (NOS/ChAT/VIP±GABA±BN±NPY), choline acetyltransferase/5-hydroxytryptamine (ChAT/5-HT) and choline acetyltransferase/somatostatin (ChAT/SOM). With the investigation of all these neurons' connections, the hypothesis that ChAT/NOS/VIP neurons involved in local mobility reflexes were related to the transmission of migrating myoelectric complexes (MMCs) of ChAT/SOM neurons. It was found that neurons were directly involved in secretomotor reflexes but indirectly in mobility reflexes in the small intestine and ChAT/5-HT.[11,13] ChAT/SOM neurons have distinctive morphology with branching filament dendritic cell bodies. In the distal colon, filamentous neurons with anal axons are not present but they are present in the colon.[14–16]

Many studies have noted that reflexes occur in the isolated intestine, even after the cut-off of the extrinsic nerves feeding the intestines and after a certain period of time for the ends to degenerate. This indicates the presence of IPANs (sensory neurons) in the intestine.[17,18]

Intestinal secretomotor neurons of two types have been identified that are cholinergic and non-cholinergic, and also the release of IPANs in the mucosa from the ends of these neurons, indicates that these cells may have secretomotor effects.[11] It has been shown that non-cholinergic neurons use VIP or a related peptide as their main transmitter and mediate the majority of the local reflex response. The point of innervation of ACh/calretin neurons and the secretory glands is the mucosal base where the former have collaterals against submucosal arterioles but ACh/NPY neurons don't supply innervation to the arterioles.[11]

Gut-Brain and Vagus Nerve

The vagus nerve serves as the first neural communication mediator between the brain and the gastrointestinal (GI) system. The vagus nerve transmits energy state signals through the vagal afferent (sensory) nerves from the intestine to the brain. There are separate afferent fibers innervating GI organs to determine intestinal nutrient content or stomach volume.[19–21] Afferent fibers mentioned include cell bodies inside the nodose ganglia synapsing with the CNS. The medial nucleus of the solitary tract (mNTS) in the caudal brain stem acquires vagal afferent/sensory information in the brain and the information is then transmitted via ascending neural pathways to the various hindbrain and forebrain regions.[22] Vagal-mediated signaling from the GI organs is first received in the mNTS area of the brain.[23] GI-mediated signals, such as direct vagus nerve stimulation, mechanical tension in the stomach, and intestinal infusion, activate neurons in a region of the brain that is classically affiliated with memory control, feeding behavior, and learning; the hippocampus (HPC).[22,24–27] Studies of Clark et al.[28–30] have shown that unilateral cervical vagus nerve stimulation and stimulated vagal afferents by inactivation of the vagal efferents, improve inhibition-avoidance retention memory in rats, while in humans, vagus nerve stimulation increases retention in recognition memory as stimulation occurs upon learning.

The vagus nerve promotes neurotrophic and neurogenic signaling. The endogenous relevance of vagal signaling, particularly the vagal afferent pathways of the innervated intestines, abnormal and cognitive control is not well understood. The neural pathways that enable transmission of vagal mediated energy-state signals between hippocampal neurons and the GI pathway have not totally clarified. Furthermore, the neural pathways which cater for the transmission of vagal mediated energy-state signals between the GI pathway and hippocampal neurons are not completely understood. MNTS, where sensory inputs from the digestive system synapse here, sends projections to several brainstem and forebrain regions, but not directly to the HPC.[31–33] This shows that communication between mNTS and HPC is made through multiple nerve projection pathways. The potential brain region reserve location that binds mNTS to the ventral CA1 HPC (one of the subregions of the HPC) was defined as the locus coeruleus (LC) and the medial septum (MS).[31] In the world of gut-brain connection, HPC is a new player. GI signal with in-meal saturation signals (eg, gastric bloating, intestinal food infusion) activates cerebral blood flow (CBF) in hippocampal neurons in rodents.[24,34]

In addition, HPC blood flow is strongly actuated after gastric vagal nerve stimulation in people suffering from obesity.[27]

Suarez et al.[22] noted that the gastrointestinal derived vagal sensory signaling supports hippocampus-dependent memory function by way of brainstem–septal nerve pathway, in this way initializing a previously unbeknown act for the axis of the brain-gut in memory control. Other studies have shown that vagal nerve stimulation, mimicking afferent signaling from the intestine, has been successfully used to treat depression, and also increases memory as well as learning in both humans and animals.[35,36] Potentially, luminal microbiota can affect behavior, mood, and brain development via signals transmitting by the vagus nerve.[6,37–39]

The amygdala is a small, almond-like structure and is considered one of the most important parts in the limbic system and has a vast record of scientific research in emotion processing with its role in behavior modulation.[40,41] Because it is located centrally in the temporal lobe, the amygdala complex is highly joined to multiple brain regions. Amygdala receives sensory input from thalamus and cortical regions, as well as various other sites in the limbic system, including hippocampus and the prefrontal cortex.[42]

There are noradrenergic projections extending directly and indirectly from NTS to amygdala.[43] Thus, visceral information received by the vagus nerve may ultimately affect amygdala activity. In fact, vagus nerve stimulation has been shown to stimulate norepinephrine release in the amygdala,[44] increasing behavioral outcomes in preclinical fear extinction models and clinical trials of major depressive disorder, and regulating connections to the amygdala prefrontal cortex.[45,46] In contrast, the interruption of vagal communication in the subdiaphragmatic disruption of the vagus nerve has been shown to reduce fear depletion but to reduce anxiety-like behavior in rats.[47]

Numerous neurodevelopmental complications are also linked to abnormalities in the amygdala. Changes in amygdala efficacy, volume (properties affected by the intestinal microbiota)[48–51] and/or connectivity have been reported in individuals diagnosed with attention deficit hyperactivity disorder,[52] schizophrenia,[53,54] and autism spectrum disorders (ASD).[55,56]

Link between the Gut Microbiota-Brain and Neurodevelopmental Disorders

In humans, the gastrointestinal tract is collectively colonized by trillions of microorganisms called intestinal microbiota. This gut microbiota regulate host physiology in many aspects, including the maturation and function of the immune system.[57–59] Furthermore, increasing evidence suggests that intestinal microbiota have effects on brain development, function and regulation of behavior.[37,60,61]

Brain development in mammals is a complex process that lasts until adolescence and in humans lasts until early adulthood. In addition, the brain development process involves the passage of cells over longer distances to create specific circuits underlying behavior, as well as the migration of cells to extraordinary, large-scale long distances during certain fetal development.[62,63] The biggest portal in the molecular universe is the intestine hence it has been shown that various dietary ingredients interact directly with the brain development and trigger functional changes in the grown-up brain.[64,65] Recent research has found evidence that the intestinal microbiota has long-term effects on health, such as leading and easing developmental processes in the brain.

The mammalian microbiome consists of a unique combination of many different microorganisms (i.e. bacteria, fungi, archaea, and viruses) in the body. There are many pieces of research showing the effect of the intestinal microbiome on CNS function, but most of these researches are preclinic, rather than human investigations.[61,66] These include diet management, interventions that bolster the growth of beneficial bacteria (like prebiotics), administration of specific bacterial strains (like probiotics), antibiotic treatments, germ-free mice (microbiota deficient), fecal microbiota transplantation and C-section.[67] Recent reports of studies on mice models show that disruption of the microbiome will contribute to the understanding of the pathology of various neurological diseases. According to evidence from rodent models, there is a direct link between intestinal microbiota, stress and anxiety.[68] Research on human and animal models has linked intestinal bacteria with the function and development of the immune system. Microbiota includes all types of immune cells, and specific microbes that increase or ameliorate immunological disorders like asthma, inflammatory bowel disease and type 1 diabetes.[69] There are many animal models research based on the potential role of the microbiome in neuropsychiatric disorders like depression, anxiety,[68] autism spectrum disorder,[70] schizophrenia,[71] Parkinson's disease, and Alzheimer's disease.[72]

Increasing evidence indicates bi-directional nature of communication between intestinal microbial populations and brain.[73–76] De Palma et al.[77] used a maternal separation model in mice and showed deep differences in intes-

tinal microbiota in response to early life stress resulting in an anxiety-like phenotype. It has also been reported that intestinal bacteria have a reciprocal effect where certain bacteria or whole microbial populations have an effect on host stress and depression-like behavior.[78–80] It is not yet clear whether these examples are directly driven by an intestinal-brain interaction or mediated by other physiological factors caused by the disease state. But these reports and others illustrate potential interactive relations between the gastrointestinal tract microbiome and the brain.

Evidences from studies in rodent animal models show that intestinal microbiome plays a role in depressive behavior.[81–83] Approximately 20% of patients with gastrointestinal symptoms have been reported to be associated with depression.[84] According to a hypothesis, depression or subsets of this disorder are the result of a microglial disorder, since the presence of depression commonly leads to either intense inflammatory episodes in the brain or a descend in microglial function.[85] According to latest findings on the role of the microbiota in microglia maturation and activation, it is not difficult to predict that microbiota can trigger depression by affecting microglial maturation and activation.[86,87] In a study on depression, reduced bacterial richness and diversity were addressed and it was reported that depression-like phenotypes could be transmitted to rats by fecal transplantation.[88] More recently, studies on mice and humans have indicated that microbiota has an active role in guiding depression-like behavior and suggests potential new ways of therapeutic development.

In this review, in the light of general information about the enteric nervous system and its internal structure, we evaluate the relationship between microbiota and brain in human as well as animal models through many studies with gut and vagus nerve connections. The vagus nerve is the primary neuron that enables the gastrointestinal tract–brain communication. Vagus nerve mediated gastrointestinal signals activate the hippocampus. Explanation of the exact mechanism concerning microbiota and amygdala communication requires further research. By linking microbial activities to progressive structural and functional events in the brain in mice models and in humans, we can suggest that intestinal microbiota is an important contributor to neurodevelopment and neurodegeneration. Further researches revealing these relations may provide new approaches for understanding neurodegenerative, psychiatric and behavioral diseases.

Author Contributions

EA: designing the review and writing text, EA and KA: literature search, EA, KA, MB and ING: writing text, final check of the manuscript.

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Conflict of interest statement: No conflicts declared.