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ENTERIC NERVOUS SYSTEM: A REVIEW

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ABSTRACT

Enteric nervous system directs and regulates the breakdown, absorption and elimination of food in our digestive system. However, alongside its digestive functions, enteric nervous system has also gained importance because of the discovery of its bidirectional link with intestinal flora, which has recently started to be considered as a separate organ in addiction to its digestive functions. Enteric nervous system contains approximately 100 million nerve cells, operates both independently and in coordination with the central nervous system, interacts with many neurotransmitters and is related to many conditions and structures such as the intestinal flora, mood, immune system and the efficiency of food utilization. It has a clinical importance on account of the diseases it is associated with. Recent studies focus on the connections between the intestinal flora, enteric nervous system and mechanisms of disease development. In order to understand these studies and pathological mechanisms it is essential to know the structure, connections and functioning of enteric nervous system. Considering these, we addressed the enteric nervous system and its communications with other structures of the digestive system.

Keywords: Enteric nervous system, immunization, intestinal flora, mood

INTRODUCTION

The brain in our skull is not the only organ that affects our behavior and our mental balance. Enteric nervous system found in our abdomen is also referred to as "second brain", and has in many aspects similar characteristics with the brain in our skull: It can operate independently or it can affect our behavior by sending signals through the vagus nerve (1). Therefore, aside from spinal afferent nerves, the vagus nerve is dominant in the enteric nervous system, with its afferent and efferent branches (2, 3).

Enteric nervous system (ENS) is known for its content of second highest number of neurons in the organism (2, 3). As evidence, it is thought that the length of our second brain, from the throat to the anus, is approximately 9 meters long and contains nearly 100 million nerve cells. This number is much higher than the nerves of the spinal cord and our peripheral nervous system, which enables us to perceive sensations such as heat, pain and pressure and respond to these properly (4). Due to this aspect, enteric nervous system is known as the assemblage of neurons, which forms the administrative center of intestines. ENS enables this administration by controlling motility, exocrine and endocrine secretions and the microcirculation of digestive system; and by organizing immunoregulatory inflammatory processes (5).

Enteric nervous system consists of neurons embedded in the intestinal wall. Aside from their other functions, these neurons enable us to sense environmental dangers and determine our reactions. For example, under stress, our brain can favor unhealthy food. What makes these foods more appealing is not the brain in the skull, but the second brain in our intestines (1).

The enteric nervous system originates from the vagal segment of the neural crest, which migrates to the proximal part of the gut and later spreads throughout the whole digestive system in distal direction (5).

For this reason, ENS can be considered as an altered part of central nervous system. This system enables the communication formed by the sympathetic and parasympathetic afferent and efferent neurons (5).

The region of the central nervous system associated with the enteric neurons is known as the autonomic

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neural network (4). Neuronal cell bodies in the ENS are associated with neural branches of two main plexuses named myenteric (Auerbach's) plexus (MP) and submucosal (Meissner's) plexus (SP). MP spreads throughout the whole intestine, running between the longitudinal and circular muscle layers and basically provides these two muscle layers with motor and mucosa with secretomotor innervation. MP also runs to gallbladder, to the submucosal ganglions of pancreas and to enteric ganglions. Besides, many important collaterals of myenteric neurons extend to sympathetic ganglions (5).

Aside from the ability of ENS to function independently, it is thought that CNS plays an important role in the coordination of various functions of ENS (1). The tight connection of ENS with CNS, formed by both motor and sensory pathways of sympathetic and parasympathetic nervous system can be demonstrated as a proof for this (4).

Aside from the influence of the CNS, there are 4 main objectives of the ENS:
•Smooth cells which are responsible of the motility of the digestive system,
•Secretory cells of the mucosa,
•Endocrine cells of the digestive system,
•Immunomodulatory and inflammatory cells that maintain the mucosal blood flow during intestinal secretion and generate microcirculation of the digestive system and mucosal immunological, allergical and inflammatory responses (5).

ENTERIC NERVOUS SYSTEM AND IT'S INTERCONNECTED STRUCTURES

While enteric nervous system carries out its functions, it influences and is influenced by several structures. Which structures are closely associated with the enteric nervous system?

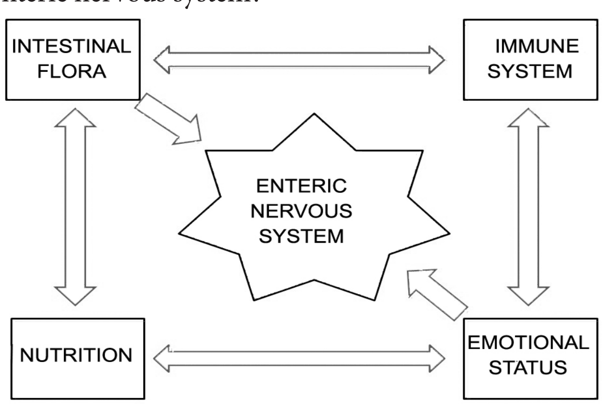

Figure 1: Structures associated with the enteric system

Figure 1.There are many factors associated with the enteric nervous system apart from those mentioned above, however there are four main topics that we want to emphasize. These are, first and foremost, the intestinal flora, then immunity and mood. Some of these regulate the function of enteric nervous system directly and some indirectly. These factors are associated not only with the enteric nervous system, but also with each other. Shown above are the enteric nervous system and their interactions.

If we focus on these factors separately:

1.INTESTINAL FLORA

The bowels have a surface area of 400-500 m2 and constitute one of the most dense and complex ecosystems in the vertebrates. It contains all kinds of symbiosis, first and foremost mutualism, commensalism and parasitism. More than 500 species of bacteria with a number varying between 1014 - 1015 is found in this environment, which is rich of nutrients and has a stable temperature (6).

Most of these bacteria are found in the colon and they make the colon metabolically most active organ in the body. 60% of feces consist of these bacteria. More than 99% of bacteria in the intestines are anaerobic, but anaerobic bacteria are more common in the cecum (7, 8).

Aerobic Bacteria	Anaerobic Bacteria
Bifidobacterium	Escherichia
Clostidum	Enterococus
Bacteroides	Streptecoccus
Eubacterium	Klebsiella

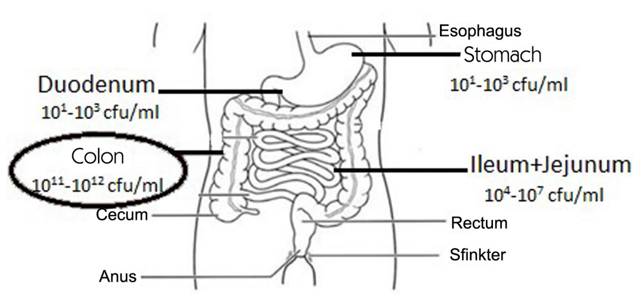

Figure 2: Bacteria dispersal in the digestive system.

Figure 2. The density of bacteria increases from the stomach and the duodenum to ileum+jejunum. In the colon it reaches a cellular density much more than all known ecosystems. Most common aerobic and anaerobic bacteria species are enlisted (7).

Intestinal Flora, Our Nervous System and Our Mood

In some studies, the intestinal flora is considered as another organ. The vegetative nervous system formed by the flora in this region has a role in multiple aspects, such as our momentary emotional status and it directs our eating and drinking habits. Studies show the importance of the intestinal flora in the gut-brain connection. It is discovered that, since the infancy stage, there is a constant communication between the bacteria in our gut and our brain. This communication is involved in shaping the circuits of the brain. It has effects on anxiety and memory, creates changes in our fear center -the amygdala- and in the hippocampus, which is found in the depths of the brain (9).

Another study about this subject is being conducted in Ireland on a lactobacillus strain. Lactobacillus is a harmless species of bacteria found in the intestines and it is one of the main components of fermented food. Researchers have found that lactobacilli alters the production of gamma-Aminobutyric acid (GABA) receptors, an important neurotransmitter found in the brain cells of mice and correspondingly. These findings suggest that probiotic bacteria could somehow have an effect on our brain (9).

Intestinal Flora and Our Immune System

The effects of flora on our immune system are very important from the aspect that it makes the connection between diseases and the functioning of our gut. It is a fact that cannot be ignored that due to the damaging of our intestinal flora, resulting from the long-term and uncontrolled use of antibiotics, susceptibility to many diseases increases, the recovery time is longer and other problems add on the present disease.

Intestinal bacteria form a natural defense barrier and they have many protective, structural and metabolic effects on the intestinal epithelium. Effects of the flora on the physiology of the intestines are shown by comparative studies conducted on sterilized and colonized animals.

Effects mentioned below are observed in animals

- They became more susceptible to infections,
- Their vascularization is decreased,
- Activity of digestive enzymes is decreased,
- Thinning on the walls of intestinal muscles is observed,
- Production of cytokines and serum immunoglobulin levels are decreased,
- The numbers of Peyer's Patches and intraepithelial lymphocytes decrease, whereas the enterochromaffin cell area is widened. Enterochromaffin cells are a type of gastric intestinal mucosa cells that produces and stores several autacoids like serotonin and prostaglandins. Most important reason for the proliferation of this cell is that the carcinoid tumors of the stomach originate from enterochromaffin-like cells (7, 10).

The intestinal flora also prevents allergens and an overreaction of the body to harmless allergens. Our flora starts to shape our immune system starting from the infancy (8).

2. DIET

In a healthy person, bacteria in the intestinal flora play an important role in the degradation of proteins, carbohydrates and fats found the nutrients we take in our bodies to their building blocks: amino acids, monosaccharides and fatty acids. If we had no intestinal flora, a portion of the carbohydrates we take into our body would not be digested and utilized. Bacteria transform the carbohydrates they ferment into short-chain fatty acids and these fatty acids increase the water absorption capacity of the intestines, decrease the number of harmful bacteria, help the absorption of minerals (especially magnesium, iron and calcium) in the body. These bacteria produce vitamin K and enable its absorption (8).

In addition to all these, diet has important effects on the intestinal flora, too. Correct nutrition is necessary for the health of the intestinal flora, the replacement of microorganisms is managed by correct nutrition. Probiotics modify the balance between the beneficial and harmful bacteria in favor of the beneficial bacteria and functioning of intestinal cells (8).

Probiotic bacteria used as support is usually provided from fermented products such as yoghurt, cheese, pickles, beer, wine, kefir and kumis. A low-sugar and low flour diet, rich in food such as fruits, vegetables, meat and eggs, also strengthen the intestinal flora (8).

Probiotics are carbohydrates that increase the activity of non-pathogenic bacteria, manage their cooperation and that humans cannot digest directly. A shorter description would be: Probiotics are the nutrients of probiotic bacteria. Legume, onion, garlic, banana and leek are important sources of probiotics. Breast milk is also owing to its oligosaccharide-rich ingredients (8).

Following the bi-directional connection between the intestinal flora and nutrition, we should also mention the effect of enteric nervous system on our eating habits. According to the findings of Belgian researchers (9), in fact, certain ingredients of nutrients affect the hormones that send signals to the brain via the enteric nervous system and this contributes to the formation of taste sensation. Studies on mice show that, under stress, mice prefer fatty food (namely, high-energy food) and that this is related to the production of the hormone "ghrelin", which triggers hunger in the brain, by the enteric nervous system. Researchers have determined that mice without ghrelin receptors in their brains do not prefer fatty food under stress. Ghrelin is only one of the many neurotransmitters that connects enteric nervous system and the brain and enables the links between mood and diet.

3. ENTERIC NERVOUS SYSTEM AND IMMUNITY

ENS has various functions. It is responsible from controlling motility, endocrine and exocrine secretions and the microcirculation of the digestive system and also plays an important role in the control of immunoregulatory inflammatory processes and it is as well as responsible of the control of the motility, exocrine and endocrine secretions and maicrocirculation of the digestive system.

Nerves which form the enteric nervous system are under the effect of the autonomous nervous system. Enteric nervous system consists of approximately 100 million neurons and creates a considerably systematic neural network in the gut. This neural network formed by the brain and the enteric nervous system is called the gut-brain axis. With its links to immunity and endocrine mechanisms, this neural network influences intestinal homeostasis (11).

Ganglions consist of interactive nerve cells, terminal branches formed by nerve fibers and glial cells. Glial cells are components of the ENS and resemble the astrocytes in the CNS. Cells called enterochromaffin cells that are responsible of the production of serotonin and prostaglandins in the gastric intestinal mucosa interleukins (cytokines that allow the communication between leukocytes) and the response generated by the cytokines displays MHC-II antigens. This situation shows that enteric glia cells and therefore the ENS has a role in the generation of inflammatory response in the intestine (12).

Ulcerative colitis and Crohn's disease are inflammatory bowel diseases, which have no connections with known agents such as infection, drugs, ischemia and radiation (13). It is suggested that there are many underlying factors that cause inflammatory bowel diseases. Aside from environmental factors; genetics, immunity and some infectious reasons are to count among these. In recent years, there is an increasing number of evidence suggesting that inflammatory cells and immune system have a complex interaction with the enteric nervous system. This complex interaction can be explained like this: Intestines are densely innervated with autonomous nerve fibers and autonomous nerves are in close connection with immune responding cells in the intestines. Stimulation of sensory nerves regulates inflammation on immune responding cells through the neuropeptides. Alterations of nerve fibers are observed in both ulcerative colitis and Crohn's disease. Studies demonstrate that topical application of lidocaine prevents neural transmission and; accordingly, reduction of mucosal inflammation could be possible (14, 15).

Several alterations referred to as neuromatous changes are observed in inflammatory bowel diseases. These are perception of impulses, motility and alterations in secretion. Besides, hypertrophy in submucosal and myenteric nerve plexuses, excessive increase in the number of cells and structural defects (16).

4. CONNECTION BETWEEN MOOD AND ENTERIC NERVOUS SYSTEM

Disorders on every level in brain-gut communication and autonomic function disorders play an important role in the genesis of recurrent abdominal pain (RAP) (2, 3). Recurrent abdominal pain is one of the most common problems in children. Has a reported prevalence of 10-20% in childhood age group. RAP is not a diagnosis; it is only a definition, a symptom. Several diseases can cause this clinical appearance. Organic reasons as well as several psychological problems associated with our emotional world could be underlying these diseases (2, 3, 17).

Until 1980s, RAP was considered as a psychological condition, if no organic cause could be detected. In later years, individual differences and contributing factors to these differences came into prominence, whereas recently biological, physiological and social factors are addressed. Studies in recent years point out that underlying etiology of RAP is related to the enteric nervous system, which is accepted as the second brain, brain-gut relations, motility disorders of the digestive system and especially visceral hypersensitivity (18). This hypersensitivity could be caused by an infection, trauma or inflammation, whereas stress and several psychological factors are also thought to play a role in the ENS becoming overly excitable (3, 19).

5. ENTERIC NERVOUS SYSTEM AND NEUROTRANSMITTERS

More than twenty types of neurotransmitters are found in the neurons of the enteric nervous system. Latest studies reported that this number has reached forty and functions of most these neurotransmitters are discovered. The presence of acetylcholine and serotonin, gamma-Aminobutyric acid (GABA), adenosine triphosphate (ATP), vasoactive intestinal polypeptide (VIP) and nitric oxide (NO) is shown. Numerous ENS neurons contain multiple neurotransmitters and alternative bindings of mediators according to the location of the neurons create alternative functions. Most of the neurons with distinctive functions can use the same neurotransmitters. Neurotransmitters are spread around the myenteric and submucous plexuses (5, 9).

Motilin, somatostatin, prokinetic agents and opiates initiate migrating motor complex activity. Tonic inhibition of motility and relaxation of sphincters are enabled by neurons containing VIP and NO. A cause of achalasia disorder is the malfunction of inhibitory neurons of the myenteric plexus of oesophagus, containing VIP and NO (5). NO and VIP are the two main neurotransmitters that help non-adrenergic, non-cholinergic nerves to relax the smooth muscle cell. The connection between these two molecules is still a matter of debate and there are studies indicating that NO and VIP are cotransmitters and are simultaneously released from enteric inhibitory nerves (20).

Among the neurotransmitters of the enteric nervous system, serotonin (5-HT, 5-hydroxytriptamine) has gradually gained importance. Serotonin is released from the enterochromaffin cells. 5-HT3 and 5-HT4, which are 5-HT receptors, control gastrointestinal sensation, motility and secretions (21). Serotonergic receptors are linked to depression, food intake and obesity, bipolar disorders, obsessive compulsive and anxiety disorders, sleep, analgesia, nausea and vomiting, drug addictions. An increase in the serotonin level in synapses decreases food intake and prevents obesity and sleep disorders like insomnia, eliminates the depression seen after the withdrawal from an addiction. Selective serotonin reuptake inhibitors (SSRI), monoamine oxidase (MAO) inhibitors that degrade excessive serotonin in the cell body, tryptophan and hydroxytryptophan supplements are used (22). The combined use of some of these drugs increases the serotonin level and leads to the clinical condition known as the serotonin syndrome (fever, diarrhea, changes in mental state, myoclonus, agitation, tremor, increase in reflexes) (23). 95 percent of the body's serotonin production is found in the intestines. Selective serotonin reuptake inhibitors, antidepressant drug treatments known as SSRIs raises serotonin levels. It is an expected condition that the side effects of drug treatments, which cause chemical alterations in the brain, are digestive complaints. A drug that prevents the release of serotonin from the intestines is shown to prevent postmenopausal osteoporosis in rodents. Serotonin released from the second brain could play a role in autism, which is the earliest recognizable developmental disorder in the early childhood (1, 9).

Neurotransmitter-ENS connection showed that regulating the levels of released neurotransmitters could treat many diseases. There are data that suggests that acupuncture initiates norepinephrine, serotonin and dopamine release. In 1977, researchers showed the first attempt to use acupuncture method to evaluate patients with psychosomatic symptoms and under drug therapy. Participants experienced a reduction in tension, restlessness, sadness, headache, cephalic paresthesia and loss of appetite during the study. The authors viewed acupuncture as a safe and potentially effective method of treating depression (24).

Researchers have studied the effect of electroacupuncture on levels of neuropeptide Y (NPY) over 4 weeks in a small pilot study of six patients with major depression. During acupuncture therapy, NPY plasma levels decreased in five patients. This finding was associated with clinical improvement of depression. Acupuncture allows the release of serotonin and other neurotransmitters and therefore is a practice that deserves further research in the treatment of depression as an alternative for antidepressants, which have numerous side effects (24).

CONCLUSION

Enteric nervous system is a system with many regulatory features such as the intestinal flora, our mood and our diet. They are in tight connection with neurotransmitters while carrying out these functions.

Enteric nervous system is a neural structure that especially through the afferent and efferent fibers in the vagus nerve, the neurotransmitters it releases and its connections with the autonomous nervous system. As a consequence of these tight connections, any condition that affects our intestines can also show its effect on the central nervous system. Likewise, a problem in our intestines can reach our central nervous system and affect our mood.

It is shown that the our enteric nervous system deserves more attention with its hundred million nerves (which is the second highest number after the brain), its influences on our central nervous system and the results that emerge with the help of our CNS.

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