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Neural and humoral mechanisms controlling the peristaltic function in the digestive tract

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Abstract
Peristalsis events in the human gastrointestinal tract play a crucial role in the digestion process, providing the movement of food from the upper part of the alimentary canal to the lower part. Peristaltic contractions of the organs of the digestive system mean synchronous contractions of the walls of the organ, providing movements of the food products from the "input" to the "output". It is believed that peristaltic contractions result in complete (or almost complete) blocking of the lumen of the tubular organs of the digestive system.

Keywords Enteric nervous system · Interstitial cells of Cajal · Enteric glia

The peristaltic function is mostly based on various forms of coordinated contractions of the smooth muscle tissue of the esophagus, stomach, small and large intestines, and bile ducts, as well as the sphincter activity. The peristaltic function provides mechanical processing of food and its advancement through the alimentary canal. The striated muscle tissue involved in chewing, swallowing, and defecation events is observed only in the upper and lower parts of the alimentary canal.

The function of the digestive tract is regulated by both neural and humoral mechanisms. In the regulation of the functions of the digestive system, local and central levels can be distinguished. Regulation at the local level is provided by the enteric nervous system (proprial neural structures of the digestive system) and the endocrine system of the gastrointestinal tract. The level of central regulation is represented by "digestive" structures of the CNS (in the spinal cord, brain stem, etc.), which provide implementation of the specific conditioned and unconditioned reflexes. Herein, a review of the respective (mostly modern) literary sources published within the last 10 years is elucidated (with some involvement of the classical scientific literature).

The activity of the digestive system is controlled by the autonomic (vegetative) nervous system (ANS). The ANS includes two main parts, the central and the peripheral. The nuclei of the brain stem and spinal cord form the central part of the ANS, while the ganglia, plexuses, and nerve trunks constitute the peripheral part. Functionally, the ANS should be divided into two main parts, the sympathetic and parasympathetic compartments. These two divisions exert opposite effects on the organs of the digestive system. During sympathetic activation of the ANS, inhibition of peristalsis in the digestive tract and activation of sphincters can be observed. In contrast, peristalsis increases during parasympathetic activation, sphincters relax, and the secretory activity is stimulated. The parasympathetic nervous system ensures digestion and rest processes, whereas the sympathetic nervous system enables the body to cope with stressful situations.

The sympathetic nervous system, in its central part, includes the nuclei of the thoracic and upper lumbar lateral horns of the spinal cord, while the parasympathetic nerves comprise the autonomic nuclei of the III, VII, IX, and X cranial nerves, as well as the sacral segments of the spinal cord. The nuclei are composed of multipolar interneurons, whose axons extend beyond the central structures and form synapses with neurons of the autonomic ganglia, whereas their dendrites make contact with the axons of the pseudounipolar neurons of the spinal ganglia or associative neurons of the spinal cord. The ganglia of the ANS may be located either inside or outside the organ. The intramural plexus (or ganglion) is situated in the wall of the digestive tract.

The digestive tube includes several layers, including the mucous membrane, submucosa, muscular layer, and outer

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coat. Depending on the region of the digestive tract, the muscular layer may be composed of either smooth muscle tissue or striated skeletal muscle. The oral cavity, pharynx, upper third of the esophagus, and the caudal part of the rectum contain striated skeletal muscle tissue, whereas the lower part of the esophagus, stomach, small intestine, and large intestine include smooth muscle within the muscular layer.

The intestinal wall includes enormous components of the endocrine and immune systems of the organism, as well as the so-called enteric nervous system (ENS) [1]. The latter, according to the number of cellular elements and functional significance, can be compared without exaggeration to the spinal cord. The ENS may be considered the third component of the ANS.

The digestive system is connected to the CNS through the extrinsic innervation of the ANS and a system of stress hormones [2]. The ENS consists of intrinsic sensory neurons (intrinsic primary afferent neurons), excitatory and inhibitory interneurons, and motor neurons. The complexity of the ENS allows it to function independently. Sensory neurons receive the external input, after which interneurons integrate the signals [3]. More than ten peptide mediators have been identified in the neurons of this system. These include cholecystokinin, enkephalin, substance P, vasoactive intestinal polypeptide, etc. In addition, acetylcholine also serves in this case as an ENS mediator.

The total number of neurons within the ENS is approximately 100,000,000 cells, roughly the same number as found in the spinal cord. The ENS includes groups of multipolar neurons and their associated nerve fibers. These structural elements can be observed in the submucosa and between the layers of the muscular coat of the digestive tube, from the esophagus to the anal part of the rectum. The ENS comprises several types of neurons, including excitatory cells that exert a regulatory influence on the peristalsis of the digestive tract [4].

The ENS is capable of self-regulating the functioning of the digestive tube, even without the influence of parasympathetic and sympathetic innervation. At the same time, it is clear that the sympathetic and parasympathetic divisions of the ANS do influence the work of the enteric system. All this has allowed us to formulate the concept of the existence of three divisions in the ANS—the parasympathetic, sympathetic, and enteric.

There is a hypothesis suggesting the existence of a relatively independent subdivision of the ANS, known as the metasympathetic nervous system, which includes the intramural ganglia of the digestive tract (ENS), heart, kidneys, and respiratory system. These microganglia may have a certain level of autonomy in regulating the work of these organ systems, and under physiological conditions are not controlled by the central parts of the ANS and somatic nervous systems. If we rely on this hypothesis, then the metasympathetic nervous system is the third division of the ANS [5]; nonetheless, there is no common single opinion regarding its respective classification.

The microganglia of the digestive tube form the submucosal Meissner plexus and the Auerbach plexus, located between the layers of the muscularis mucosa. Secretory activity, local motility, and blood supply to the mucous membrane are regulated by the Meissner plexus. In turn, the Auerbach plexus is responsible for the peristalsis of the digestive canal [6].

In the myenteric intermuscular plexus, two types of neurons can be found, cells of the first and second types. Cells of the first type receive activation from the CNS through the vagus nerve and lumbar parasympathetic nerves. On the other hand, neurons of the second type can transmit nerve impulses to neurons of the first type, and then to the smooth myocytes of the digestive canal wall. Local reflex arcs are formed using cells of the second type (a sensitive link). The endings of the dendrites of neurons of the spinal ganglia and sensitive neurons of the intramural ganglia provide afferent innervation. It is these nerve fibers that form the sensitive plexus in the muscularis mucosa of the digestive canal. Afferent nerve endings can also be seen in the *lamina propria* of the digestive tube and in the submucosa; they innervate vessels, duodenal glands, villous epithelium, and crypts.

Throughout the digestive tract, from the esophagus to the internal sphincter of the anal canal, the intermuscular nerve plexus contains cells that function as pacemakers. These are the interstitial cells of Cajal (ICC). Smooth myocytes of the muscular coat receive nerve impulses from the ICC, which cause peristaltic contractions with different frequencies—for example, in the duodenum, with a frequency of up to 11–12/min^{-1}, in the ileum (up to 10/min^{-1}), and in the colon (3–4/min^{-1}). Pacemakers generate slow waves of transmembrane potentials. Slow waves do not cause muscle contractions, but create a potential in the muscles close to the activation threshold. In the event of the occurrence of slow waves of action potentials on the plateau, muscle fiber contraction occurs.

Based on results of the *in vitro* studies, it has been proposed that the ICC performs the following functions: generates slow waves, provides neurotransmission between enteric nerves and muscles of the gastrointestinal tract, and acts as mechanoreceptors (roles of the ICC in regulating gastrointestinal motility: *in vitro* vs. *in vivo* studies) [7].

Interstitial cells of Cajal, first characterized by Cajal [8], play an important role in gastrointestinal motility [9]. According to their location in the intestinal wall, the ICC can be classified into the following main subtypes: those located in the myenteric plexus, cells located in the circular and longitudinal muscle layers, those in the deep muscular plexus, and interstitial cells in the submuscular plexus [10].

Gastrointestinal motility is important for the transport of ingested food and the absorption of nutrients through the intestine. After a meal, the fundus of the stomach relaxes to accept the ingested food. Peristalsis (distal spreading contractions) is generated in the proximal antrum and spreads distally to the pyloric sphincter. Before reaching the antral contractile front, the pylorus relaxes or opens, and gastric chyme is ejected into the small intestine through the pylorus. In the small intestine, mixed contractile patterns (antegrade, simultaneous, and retrograde) are present in the postprandial state. These mixed contraction patterns are necessary for the absorption of nutrients and the transport of chyme through the small intestine [11]. Contractile patterns in the colon are more complex.

In addition to the rhythmic contractions or peristalsis mentioned previously, the intestines also create and maintain a certain tone. The tone, or the resting pressure of the various sphincters along the intestines, also plays an important role in transporting ingested food through the intestines. Intestinal sphincters include the pylorus and the anal sphincter. A decreased tone can lead to gastroesophageal reflux, while impaired relaxation of the cardiac sphincter during swallowing is one of the main causes of dysphagia. Impaired relaxation of the pyloric sphincter can lead to pyloric stenosis or delayed gastric emptying. In the anus, weakness of the anal sphincter is associated with fecal incontinence, and failure of the anal sphincter to relax is associated with obstructive constipation.

Neurons of the ENS exhibit mechano- and/or chemosensory activity [12]. In addition to direct signal reception, they are able to receive and process messages about the intensity, duration, and structure of stimuli. These neurons usually form a circumferential network surrounding the intestine. Several classes can be listed within the group of neurons of the ENS—for example, those according to their localization (myenteric/submucosal plexus) or the direction of signal transmission. Thus, they can receive, integrate, and amplify signals both locally and through a network (similar to interneurons) [13, 14]. Interneurons can be divided into ascending and descending units. In addition, there are several classes within the interneuron population that can be distinguished neurochemically, and the proportion of interneurons in these classes may differ between parts of the gastrointestinal tract, which may reflect a regional diversity of motor patterns in the intestine [15, 16].

The last group of neurons in the ENS are the motor neurons, which are divided into two subgroups, the inhibitory and the excitatory. They participate in the control of intestinal peristalsis, as they contribute to the contraction and relaxation of circular and longitudinal smooth muscles in a mechanism dependent on acetylcholine (excitatory neurons) or nitric oxide (NO), vasoactive intestinal peptide (VIP), and pituitary adenylate cyclase-activating polypeptide (inhibitory neurons) [1].

Glial cells located in the gastrointestinal tract are also known as enteric glial cells. Initially, they were simply considered a structural support for the ENS; however, it is now well known that they are involved in several important processes corresponding to the gastrointestinal tract [17, 18]. The ratio of neurons to enteric gliocytes in humans is 1:7, which undoubtedly indicates the important function of the latter. In terms of general morphology, ultrastructure, and relationship to neuronal bodies and processes, enteric gliocytes are very similar to astrocytes. Enteric gliocytes can be described as stellate cells with a large number of highly branched processes. The nucleus is quite large, occupying almost the entire cytoplasm. Very often, enteric gliocytes receive synaptic contacts from neurons, indicating that these contacts are the main morphological substrate of neuron-glial relationships.

Enteric gliocytes, according to their morphology, can be classified into four subgroups [19]. Type I enteric gliocytes, called "protoplasmic", are stellate cells with short, irregularly branched processes resembling protoplasmic astrocytes in the CNS. Type II enteric gliocytes (fibrous) are elongated glial units with interganglionic fiber tracts, while type III enteric gliocytes (mucosal) have long, branched processes. Finally, type IV enteric gliocytes (intermuscular) are elongated glial cells that accompany nerve fibers and surround smooth muscle.

Enteric gliocytes play an important role in intercellular communication, the formation and maintenance of the intestinal barrier, as well as the control of gastrointestinal motility, immune response, and the sensitivity of internal organs. Populations of enteric gliocytes originate from a common pool of precursors (neural crest cells) and express a common set of biomarkers (S100, transcription factors, Sox8, Sox9, and Sox 10). Because of the interaction between enteric gliocytes and other cells of the digestive tube wall, gliocytes in the ENS differ from each other structurally.

Enteric gliocytes support the transmission of nerve impulses between neurons and ensure the maintenance of homeostasis. These cells transfer to neurons the necessary components for the synthesis of neurotransmitters, such as GABA, nitric oxide, and glutamate. In addition, gliocytes support the transmission of nerve impulses by regulating the bioavailability of neuroactive substances in the extracellular environment [20]. Because of the presence of specific receptors (ATP, ADP, glutamate, noradrenaline, serotonin), enteric gliocytes can also find and modulate the activity of neurons. Additionally, they initiate the functioning of the intracellular signaling mechanisms in response to the release of neurotransmitters by neurons [21].

Enteric gliocytes influence enteric transmission by releasing neuroactive substances. An increase in Ca^{2+} ions in the intestinal tube wall leads to the release of ATP, an important neurotransmitter and neuromodulator in the ENS.

Subepithelial enteric gliocytes are in very close contact with epithelial cells, nerve fibers, and myocytes of the blood vessels, making this population of cells a significant component in the regulation of intestinal barrier function [22, 23]. The intestinal barrier limits the penetration of bacteria, viruses, and toxins. Epithelial permeability has been shown to increase after destruction of enteric glia. In transgenic mouse models, where enteric glia were selectively removed, inflammation occurred in the intestinal wall, and the integrity of the epithelial barrier was compromised [24].

In a recent review, it was suggested that enteric glia may be a novel factor in the pathogenesis of abdominal pain [25]. Abdominal pain is a common symptom of both acute and chronic gastrointestinal diseases. In irritable bowel syndrome, a disorder associated with a disruption of the brain-gut axis [2], visceral hypersensitivity is a major feature. This pathology is characterized by abdominal pain in combination with impaired peristalsis (either accelerated, with predominant diarrhea), slowed (with predominant constipation), or having a mixed type.

It should also be noted that, in addition to the ENS, paracrine and endocrine regulation, which is instigated by cells of the dissociated neuroendocrine system, plays an equally important role in the processes of self-regulation and coordination of peristalsis of the digestive tube [5].

In the epithelial layer of the mucous membrane of the digestive tube and the pancreas, there are also endocrine cells that participate in the implementation of humoral-hormonal mechanisms of regulation. Humoral excitation and inhibition are carried out by biologically active substances of various structures (histamine, serotonin, acetylcholine, etc.), as well as by the products of nutrient hydrolysis that enter the blood and provide the final (intestinal) phase of juice secretion. Among the hormonal mechanisms, the most important are gastrointestinal hormones (gastrin, secretin, cholecystokinin-pancreozymin, etc.). Gastrin is synthesized by cells located in the mucous membrane of the antrum of the stomach and, to a lesser extent, the duodenum. These agents enhance the secretion of the stomach, pancreas, and intestinal glands, and they increase the motility of the gastrointestinal tract [26, 27].

Secretin is synthesized by cells of the duodenal and small intestinal mucosa under the influence of the hydrochloric acid present in the gastric content. The hormone increases the secretion of bicarbonates by the pancreas and inhibits the secretion of hydrochloric acid in the stomach. Cholecystokinin-pancreozymin is produced by cells of the proximal small intestinal mucosa. It enhances the motility of the gallbladder and bile secretion, the secretion of pancreatic enzymes and pepsin in the gastric juice, and it increases the motility of the small intestine. Intestinal hormones regulate the secretion of water, electrolytes, enzymes, motor activity, and absorption of substances in the digestive tract. The role of local regulatory mechanisms in the small and large intestines is especially great [28]. The local regulatory apparatus (nerve ganglia, biologically active substances, intestinal hormones, etc.) largely coordinates the interaction of the stomach, intestines, pancreas, and biliary tract independently.

Thus, the structural and functional basis responsible for the regulation of intestinal peristalsis is a complex system of interactions between neurons of the ENS, interstitial cells-pacemakers, and components of enteric glia. In addition, paracrine and endocrine regulation, provided by cells of the dissociated neuroendocrine system, also play an equally important.

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Declarations

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The authors declare that they have no conflict of interest

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