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Peristalsis and regulation of gastrointestinal motility: From mechanisms to pathophysiology

A. M. Halinska*,**, O. V. Severynovska*, O. O. Halinskyi**

*Oles Honchar Dnipro National University, Dnipro, Ukraine
**Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, Dnipro, Ukraine

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Oles Honchar Dnipro National University, Nauky av., 72, Dnipro, 49045,Ukraine. Tel.: +38-098-051-42-01. E-mail: eseverinovskaya@gmail.com

Institute of Gastroenterology of the National Academy of Medical Sciences of Ukraine, Slobozhanskii av.,96, Dnipro, 49074, Ukraine. Tel.: +38-098-212-93-33. E-mail: biolog.anastasia@gmail.com

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Gastrointestinal motility is determined by a complex interaction of neuronal, humoral, and cellular-muscular mechanisms that ensure the movement of partially digested food along the gastrointestinal tract, regulate digestion processes, and control sphincter function. This review presents a systematic study of the anatomical and functional organization of the gastrointestinal tract with a special emphasis on peristalsis and coordination of sphincter activity. Particular attention is paid to the structural and functional role of the SIP syncytium, including interstitial cells of Cajal, cells expressing platelet-derived growth factor receptor-α, and smooth muscle cells in the generation of slow waves and intercellular signaling. Important molecules like calcium ions, nitric oxide, and inositol triphosphate, which are crucial for starting and adjusting muscle contractions, are examined. The data on neurohumoral regulation of motility involving such mediators and peptides as acetylcholine, vasoactive intestinal peptide, motilin, cholecystokinin, and glucagon-like peptide-1 are also summarized. The differences in how motility is controlled based on sex and age are examined, particularly how estrogens and nitric oxide signaling affect this. The pathophysiology of central motility disorders, including esophageal achalasia, functional dyspepsia, gastroesophageal reflux disease, and duodenogastric reflux, is studied, considering the role of esophageal hernia. Modern diagnostic methods are considered, including high-precision manometric study, functional lumen assessment technologies, and long-term monitoring of acidity in the esophagus. The presented data emphasize the close relationship between the molecular mechanisms, cellular structure and clinical manifestations of gastrointestinal motility disorders. The study highlights the need for an integrative and interdisciplinary approach to analyzing gastrointestinal motility, which can improve diagnostic accuracy and enable personalized treatment.

Keywords: gastrointestinal motility; peristalsis; nitric oxide; calcium; pyloric sphincter; lower esophageal sphincter.

Introduction

Gastrointestinal motility is a life-sustaining physiological process that ensures the movement, mixing and evacuation of partially digested food and regulates stomach–intestinal communication. Several regulatory systems, from the molecular to the neurological, must work together for this function to be effective. Disturbances in gastrointestinal motility underlie a wide range of functional and organic diseases of the digestive system, including delayed gastric emptying, insufficient relaxation of the lower esophageal sphincter, reflux of contents from the small intestine into the stomach and retrograde reflux from the stomach into the esophagus. A comprehensive understanding of motility-regulating processes and physiological events is vital for targeted therapeutic plans for such conditions. This article intends to offer a complete overview utilizing cellular, molecular and neurohumoral regulation pathways as examples. *Description of gastrointestinal motility*. Particular attention is paid to key signaling molecules, in particular nitric oxide, calcium ions, and inositol triphosphate, as well as the involvement of specialized interstitial pacemaker cells in generating rhythmic electrical activity known as slow waves. The review also considers modern methods of functional diagnostics, demographic factors, including sex and age differences, and pathophysiological conditions associated with motility disorders. The present work aims to combine classical physiological concepts with the latest scientific data within the framework of a single model of motility regulation that is relevant for both experimental research and clinical practice in gastroenterology.

Anatomical organization of gastrointestinal motility

The esophagus is a 25 cm-long muscular tube connecting the pharynx to the stomach and contains two functionally important sphincters, the cricopharyngeal and the cardiac sphincter (Cock & Omari, 2018; Pellrud & Ahlstrand, 2018). The esophageal wall consists of four main layers, including the muscular coat formed by the proximal portion, which comprises striated muscle. The esophageal wall consists of four main layers, including the muscular coat formed by striated muscle in the upper third and smooth muscle in the lower part. Innervation is provided by both somatic pathways and the enteric nervous system, which allows the coordination of complex motor patterns. The tone of the lower esophageal sphincter is maintained by both muscular (myogenic) and neural (neurogenic) mechanisms. In particular, the neurotransmitter acetylcholine activates the lower esophageal sphincter via type III muscarinic receptors, while nitric oxide and vasoactive intestinal peptide cause its relaxation via signaling pathways involving cyclic guanosine monophosphate and cyclic adenosine monophosphate (McCallum, 1999). Several studies descrybe more profound aspects of these processes. For example, several sources discuss the role of intracellular calcium ions, myosin phosphorylation, and the involvement of protein kinase A and protein kinase G in regulating lower esophageal sphincter tone (McCallum, 1999). It is also noted that the relaxation of the lower esophageal sphincter is an active physiological process, while its mechanical opening can occur passively (Sidhu & Triadafilopoulos, 2008). Changes in lower esophageal sphincter tone may be influenced by external factors, including food consumption, intragastric pressure, body posture, and specific drugs (Tack & Pandolfino, 2018). Gastroesophageal reflux is a disorder of the lower esophageal sphincter, which is accompanied by the reverse movement of gastric contents into the esophagus. This process is mediated by the enteric nervous system, which depends on the activity of nitric oxide (Hunt et al., 2015). It is initiated in response to distension of the upper stomach. It involves sensory fibers of the vagus nerve, the nucleus of the solitary tract in the brainstem, and inhibitory neurons of the enteric nervous system. Studies have shown that this type of lower esophageal sphincter relaxation lasts longer than swallow-induced relaxation, is independent of pharyngeal activity, and can be induced even during diagnostic procedures such as esophageal pressure measurement using manometric methods (Schu-

tyser et al., 2020). Lower esophageal sphincter dysfunction may manifest as decreased tone, which is typical in gastroesophageal reflux disease, increased tone, as in sphincter relaxation disorder known as achalasia, or loss of coordination between sphincter function and esophageal peristalsis. In systemic sclerosis, the lower esophageal sphincter loses its basal tone, and the muscular layer of the esophagus loses the ability to generate peristaltic waves (Chen et al., 2019; Schutyser et al., 2020). Some publications emphasize that the tone of the lower esophageal sphincter changes depending on the phases of the cyclic motor activity of the gastrointestinal tract, known as the migrating motor complex, which is especially relevant in the context of gastric motility (McCallum, 1999). The functional state of the lower esophageal sphincter can be regulated by various pharmacological agents. In particular, stimulants such as metoclopramide, domperidone, and bethanechol increase the level of the neurotransmitter acetylcholine. In contrast, inhibitors, including nitrate-containing drugs, calcium channel blockers, and phosphodiesterase type 5 inhibitors such as sildenafil, decrease sphincter tone by enhancing nitric oxide-mediated signaling pathways or by reducing intracellular calcium ion concentrations (Gangula et al., 2011).

The functioning of the lower esophageal sphincter is mainly dependent on external factors, including diaphragmatic activity, intraabdominal pressure, body position, food intake, and hormonal influences. It is noted that the antireflux barrier extends beyond the anatomical boundaries of the lower esophageal sphincter to include the upper (proximal) portion of the stomach (Tack & Pandolfino, 2018). Several studies also highlight the synergistic interaction between the lower esophageal sphincter and the muscle fibers of the crura of the diaphragm, which are anatomically and functionally connected via the phrenoesophageal ligament (Mittal & Fisher, 1990; Zifan et al., 2017). The lower esophageal sphincter does not function in isolation but is part of a complex and dynamic system that coordinates the motility of the entire gastrointestinal tract. Its activity is closely related to the motor function of the stomach, the phases of the migrating motor complex, the act of swallowing, the tone of the diaphragm, and central and peripheral mechanisms of nervous regulation (McCallum, 1999; Goyal et al., 2019; Camilleri & Sanders, 2022).

Anatomy and motility of the stomach

Functionally, the stomach is divided into three main motor zones. The proximal section, including the fundus and proximal part of the body of the stomach, functions as the so-called "pressure pump" with a high ability to stretch without increasing internal pressure. This ability is provided by accommodation, i.e. reflex relaxation mediated by the vagus nerve and supported by the action of nitric oxide. This mechanism plays a key role in the reservoir function of the stomach and in the formation of a feeling of satiety. The distal section, including the distal part of the body and antrum, forms a peristaltic pump that ensures mixing and mechanical grinding of the contents. The pyloric region, which includes the terminal antrum and the pyloric sphincter, performs a filtration function, allowing only small particles to pass into the duodenum (Kelly, 1980; Camilleri & Sanders, 2022; Di Natale et al., 2023).

Gastric accommodation is a reflex response to food intake that involves the relaxation of the proximal stomach without a significant increase in pressure (Petersen, 2018). Within the framework of non-adrenergic and non-cholinergic vagal reflexes, nitric oxide plays a key role, which is released by specific neurons and functions as a signaling mediator (Tack et al., 2002; Takahashi, 2003; Verbeure et al., 2021). In addition, this mechanism affects the processes of the formation of the feeling of satiety. Accommodation disorders are associated with gastroparesis and functional dyspepsia, and potential therapeutic strategies include the stimulation of nitric oxide-dependent signaling pathways (Gangula et al., 2011; Achem & Gerson, 2013; Camilleri & Sanders, 2022). Neurohumoral regulation of gastric motility is carried out by integrating the influence of the vagus nerve, enteric nervous system, and gastrointestinal hormones. In the postprandial period, cholecystokinin, glucagon-like peptide type 1, and leptin are activated, which inhibits gastric emptying. In the hunger phase, motilin and ghrelin activate the migrating motor complex (Goyal et al., 2019). Gastric motor activity is coordinated by the pacemaker interstitial cells of Cajal, which generate slow waves, and smooth muscle cells, which mediate contractions. Together with cells expressing the platelet-derived growth factor receptor-alpha, they form the SIP syncytium, a functional electrophysiological complex that mediates coordinated motor activity (Kito, 2011; Camilleri & Sanders, 2022). The types of electrical activity vary depending on the anatomical zone of the stomach. Tonic contractions predominate in the fundus, phasic peristaltic contractions in the body and antrum, and powerful contractions with independent regulation of the sphincter in the pyloric zone (Kim & Malagelada, 1986). During the intermeal period, the migrating motor complex is activated in the stomach, which consists of four phases. Phase I is a period of electrical rest with the generation of slow waves without muscle contractions. Phase II is characterized by rapid, moderate-intensity contractions. Phase III, the so-called “activity front,” involves powerful contractions independent of slow waves and are neuron-mediated. This phase is of clinical importance because insufficient pyloric relaxation can lead to gastric stasis or functional obstruction, while excessive relaxation can lead to duodenogastric reflux. Phase IV is transitional and is accompanied by a gradual decrease in motor activity (Goyal et al., 2019). A number of parameters, such as the caloric content of the diet (high-calorie foods are preserved longer), the osmolarity of the contents (substances with high osmolarity slow down the process), and the aggregate state of the food, affect the rate of gastric emptying. Liquids usually leave the stomach faster, passing through a special functional channel along the lesser curvature – the so-called Magenstraße (Goyal et al., 2019).

Gastric rhythm disorders include tachygastria, more than five cycles per minute, which is accompanied by ineffective peristalsis and gastroparesis; bradygastria, less than two cycles per minute, characteristic of diabetes and neuropathies (Carson et al., 2022; Peralta-Palmezano et al., 2025), and dysrhythmias manifested by unstable, mixed, or retrograde waves (Varghese et al., 2021). An imbalance between excitatory and inhibitory influences from the nervous or humoral regulation leads to various disorders. Pyloric hyperactivity causes delayed gastric emptying, insufficient relaxation leads to vomiting or functional obstruction, and excessive relaxation causes backflow of contents from the duodenum into the stomach (Goyal et al., 2019).

Anatomy, physiology, regulation and clinical significance of the pyloric sphincter

The pyloric sphincter is a region of thickened circular muscle at the border between the antrum of the stomach and the initial segment of the duodenum (Spicer & Sun, 1967). Radiologically, it is defined as a structure approximately 1.2 cm wide, characterized by increased intraluminal pressure compared to adjacent areas (Wuestenberghs & Gourcerol, 2021). Morphologically, the sphincter includes muscle loops that form the pyloric torus, characterized by its segments' independent functional activity (Spicer & Sun, 1967). Unlike the lower esophageal sphincter, the pylorus has greater extensibility and can maintain intraluminal pressure under changing conditions (Wuestenberghs & Gourcerol, 2021). The pylorus is divided into two functional zones: an external muscular zone controlled by gastric slow waves (via the interstitial cells of Cajal in the myenteric layer) and an internal zone regulated by neural mechanisms involving the interstitial cells of Cajal in the intramuscular layer (Camilleri & Sanders, 2022; Soliman & Gourcerol, 2023). This distinction is essential for understanding the sphincter motor pattern and its adaptive capacity to function as a valve.

The pylorus performs not only a barrier function but also a sensorimotor function, regulating the outflow of chyme, taking into account its osmolarity, caloric content, volume, and physical shape (Goyal et al., 2019). Due to the ability to adaptively narrow or expand through muscle restructuring, it selectively passes liquids and small particles, retaining large ones (Ramkumar & Schulze, 2005). In a state of relaxation, the sphincter opens, and when contracted, it closes tightly. However, it is usually in a semi-open state, which allows flexible regulation of the flow of chyme (Ramkumar & Schulze,

2005). The pylorus is controlled by the SIP syncytium, an integrated network of smooth muscle cells, interstitial cells of Cajal, and cells expressing platelet-derived growth factor receptor-alpha (Camilleri & Sanders, 2022). Slow waves generated by the interstitial cells of Cajal in the myenteric layer are responsible for rhythmogenesis, while cells in the intramuscular layer mediate neuronal impulses. Platelet-derived growth factor receptor-expressing cells are involved in inhibitory modulation, mediating the response to nitric oxide and purines. Acetylcholine activates contractions via muscarinic receptors, and enkephalins enhance this effect via opioid receptors, the effect of which can be blocked by naloxone (Suzuki et al., 2006). Relaxation of the sphincter is ensured by the action of nitric oxide and vasoactive intestinal peptide, which activate the signaling cascades of cyclic guanosine monophosphate and cyclic adenosine monophosphate, respectively, as well as purinergic stimulation of SK-type potassium channels (Soliman & Gourcerol, 2023).

Reflex mechanisms also coordinate contractions of the pylorus. The sphincter-antral reflex induces contraction in response to pyloric area stimulation, while the antral-sphincter reflex facilitates relaxation during antral contraction. This link guarantees synchronized gastric emptying (Shafik et al., 2007). From a molecular-electrophysiological point of view, the rhythm of contractions is formed by the participation of Cajal's interstitial cells. Slow waves are accompanied by action potentials that initiate contractions of smooth muscle cells due to the rhythmic release of calcium from the endoplasmic reticulum through inositol-1,4,5-triphosphate receptors and activation of Anoctamin-1 chloride channels. The participation of mitochondria in calcium metabolism ensures the stability of excitatory signal generation (Suzuki et al., 2006).

The most accurate assessment of the functional state of the pylorus is performed using functional luminal imaging technology, which enables one to measure the distensibility and elasticity of the sphincter even under normal intraluminal pressure (Wuestenberghs & Gourcerol, 2021). The method effectively diagnoses gastroparesis, especially with gastric scintigraphy or SmartPill capsule technology. It is also used as an adjunct to high-resolution manometry and acidity measurement in assessing the motility of the lower esophageal sphincter and the esophagogastric junction (Tack & Pandolfino, 2018; Mittal & Vaezi, 2020). Pyloric motility disorders can manifest themselves in four primary clinical forms. In hypertonicity, excessive contraction reduces the efficiency of gastric emptying, causing nausea, vomiting, chyme retention, and early satiety, even in the absence of mechanical obstruction (Wuestenberghs & Gourcerol, 2021; Soliman & Gourcerol, 2023). Hypotonicity promotes duodenogastric reflux, accompanied by dyspepsia and irritation of the gastric mucosa (Ramkumar & Schulze, 2005; Goyal et al., 2019). Sphincter atony occurs in interstitial cells of Cajal deficiency, energy depletion, neuropathies, or under the influence of drugs. It is accompanied by stasis, retroperistalsis, and ineffective gastric emptying, which is especially common in patients with diabetic gastroparesis or after surgery (Suzuki et al., 2006; Camilleri & Sanders, 2022). Functional dystonia is characterized by uncoordinated contractions and relaxations without morphological changes and is caused by dysregulation at the level of the enteric or central nervous system (Shafik et al., 2007).

From a therapeutic point of view, the pylorus is considered a target for endoscopic interventions, such as gastropyloric endoscopic myotomy in treatment-resistant gastroparesis (Soliman & Gourcerol, 2023). Additionally, pharmacological interventions (phosphodiesterase type 5 inhibitors) are being explored, which improve sphincter relaxation by activating nitric oxide-related signaling pathways (Ramkumar & Schulze, 2005). The pyloric sphincter is a complex, multilevel regulatory structure that maintains the physiological balance between the stomach and intestine. Its motor activity is controlled by synchronized interactions between interstitial cells of Cajal, neurotransmitters, smooth muscle cells, and central nervous system mechanisms (Goyal et al., 2019; Camilleri & Sanders, 2022). Understanding this regulatory system is critical for diagnosing and treating functional gastrointestinal disorders. Dysfunction of the pylorus is associated with clinical conditions such as gastroparesis, functional dyspepsia, duodenogastric reflux, and delayed gastric emptying. It is known that the efficiency of pyloric motility depends on the coordinated action of acetylcholine via muscarinic receptors type III, nitric oxide via the cyclic guanosine monophosphate and protein kinase G signaling pathway, and vasoactive intestinal peptide via the cyclic adenosine monophosphate pathway, which affect intracellular calcium dynamics and action potentials in the interstitial cells of Cajal and smooth muscle cells (Suzuki et al., 2006; Camilleri & Sanders, 2022). At the same time, such aspects as calcium metabolism in the interstitial cells of Cajal of the intramuscular layer, the role of mitochondrial activity in maintaining rhythmogenesis, and the influence of age and gender factors on the sensitivity of the pylorus to inhibitory mediators remain insufficiently studied. Clarification of these mechanisms is of interest for developing targeted approaches to treating functional disorders of the gastrointestinal tract.

Regulatory mechanisms and physiological integration of gastrointestinal motility

Gastrointestinal motility results from a complex interaction of myogenic, neurogenic, and humoral mechanisms that coordinate the rhythmic activity of smooth muscles to move, mix, and evacuate contents. Numerous scientific sources (Ward & Sanders, 2001; Faussone-Pellegrini, 2006; Gangula et al., 2011) emphasize a unified understanding of the key components of motor regulation, although there are still discrepancies in the details of the molecular and neurophysiological aspects. The key importance of autonomic control was established back in the 1980s, when it was shown that parasympathetic cholinergic pathways stimulate motility, sympathetic adrenergic pathways inhibit it, and non-adrenergic noncholinergic neurons provide fine inhibitory modulation (Anuras & Loening-Baucke, 1984). Modern ideas about the anatomical and physiological integration of motility were expanded by the concept of the SIP syncytium, a functional complex of smooth muscle cells, interstitial cells of Cajal, and cells with platelet-derived growth factor-alpha receptors (Camilleri & Sanders, 2022).

Myogenic activity is the essential driver of gastrointestinal motility. The slow waves generated by the interstitial cells of Cajal determine the electrical activity of the muscular wall. These waves do not cause contractions by themselves, but when they reach a threshold amplitude, they induce spike potentials that initiate muscle contractions (Kim & Malagelada, 1986). The amplitude of these waves depends on the action of neurotransmitters. Acetylcholine has an excitatory effect, while norepinephrine and prostaglandin E2 have an inhibitory effect. At the molecular level, nitric oxide and its signaling pathway through cyclic guanosine monophosphate and protein kinase G play an important role in inhibitory signaling in the SIP system (Gangula et al., 2011). A decrease in the biological activity of nitric oxide under the influence of oxidative stress is considered one of the possible mechanisms for developing such disorders as gastroparesis and esophageal spasm. Two integrative neuronal pathways that control gastric motility have also been established. These are the ventral excitatory and ventral inhibitory pathways, which link enteric regulation with central coordination via the nucleus of the solitary tract (Goyal et al., 2019). Gastrointestinal hormones play an essential role in humoral regulation. In particular, motilin, cholecystokinin, secretin, vasoactive intestinal peptide, and gastrin modulate motility at different stages of digestion. Their action depends on the phase of the digestive cycle and localization. Thus, cholecystokinin inhibits gastric emptying, while motilin activates the migrating motor complex in the hunger phase (Camilleri & Sanders, 2022).

The functional architecture of the enteric nervous system includes ascending excitatory and descending inhibitory pathways that provide regional coordination of motor activity depending on the digestion phase and the chyme's properties (Schemann et al., 2001). A comparative analysis of the key mechanisms of motor regulation (Table 1) confirms that myogenic activity is the baseline level on which the influence of neural and humoral factors is superimposed (Suzuki et al., 2006; Gangula et al., 2011). Cholinergic action from the vagus nerve enhances the activity of the interstitial cells of Cajal and stimulates phasic contractions. At the same time, adrenergic stimulation

suppresses peristalsis, especially under stress. Non-cholinergic, non-adrenergic neurons, with the help of mediators such as nitric oxide, vasoactive intestinal peptide, and purines, provide the adaptive relaxation necessary for accommodation and sphincter regulation (Ward & Sanders, 2001; Camilleri & Sanders, 2022). Thus, gastrointestinal motility is realized due to the close integration of electrogenic cells, contractile muscles, hormonal regulation, and a complex network of the enteric nervous system. This synchronized mechanism ensures the flexible and efficient coordination of motor activity necessary for normal digestion, absorption, and reflux or obstructive disorder prevention.

Table 1

Comparative characteristics of the mechanisms of regulation of gastrointestinal motility under myogenic, cholinergic, adrenergic and non-adrenergic non-cholinergic control

Criterion	Myogenic control	Cholinergic control (parasympathetic)	Adrenergic control (sympathetic)	Non-adrenergic non-cholinergic control	Reference
Origin	Smooth muscle cells, interstitial cells of Cajal, PDGFRα-positive fibroblast-like cells intrinsic muscle activity	From parasympathetic neurons (vagus, enteric nervous system), neurotransmitter acetylcholine	Sympathetic neurons, neurotransmitter noradrenaline	Inhibitory autonomic neurons of enteric nervous system; mediators: NO, vasoactive intestinal peptide, pituitary adenylate cyclase-activating polypeptide, purines	Camilleri & Sanders (2022)
Type of control	Autonomous, cellular	Excitatory neurogenic	Inhibitory neurogenic	Inhibitory/modulatory neurogenic	Goyal et al. (2019)
Mechanism of action	Generation of slow waves by interstitial cells of Cajal causes smooth muscle cells depolarization via Ca^{2+} and Anoctamin-1	Acetylcholine via M3 receptors ↑ Ca^{2+} in smooth muscle cells initiates contraction	Noradrenaline via α_2/β receptors hyperpolarization, ↓ acetylcholine release	NO stimulates ↑cyclic guanosine monophosphate; vasoactive intestinal peptide stimulates ↑ cyclic adenosine monophosphate; purines activates purinergic receptors cause smooth muscle cells relaxation	Suzuki et al. (2006); Gangula et al. (2011)
Target cells	Smooth muscle cells, interstitial cells of Cajal, PDGFRα-positive fibroblast-like cells intrinsic muscle	Intramuscular interstitial cells of Cajal, smooth muscle cells	Enteric nervous system neurons, smooth muscle cells	Intramuscular interstitial cells of Cajal, PDGFRα-positive fibroblast-like cells intrinsic muscle, smooth muscle cells	Camilleri & Sanders, (2022); Koh et al. (2024)
Signal transmission	Via gap junctions between interstitial cells of Cajal and smooth muscle cells	Synaptic transmission in enteric nervous system (via intramuscular interstitial cells of Cajal or directly on smooth muscle cells)	Presynaptic inhibition of enteric nervous system or direct smooth muscle cells innervation	Synaptic action of non-adrenergic non-cholinergic innervation neurons of enteric nervous system	Ward & Sanders (2001)
Effect on motility	Generates basic rhythm (slow waves). Maintains muscle tone	↑ Amplitude and frequency of contractions. Initiates peristalsis	↓ Tone and contraction amplitude. Inhibits vagal stimulation	Causes smooth muscle cells relaxation. Enables accommodation and sphincter regulation	Goyal et al. (2019)
Activity in denervation	Persists	Lost	Lost	Lost	Camilleri & Sanders (2022)
Role in gastrointestinal physiology	Main rhythmic "generator" of motility, independent of central nervous system	Activates motility after food intake, excites smooth muscle cells via enteric nervous system	Maintains inhibitory background, especially under stress/fasting	Provides inhibitory phase of movements, gastric and sphincter relaxation	Gangula et al. (2011)
Modulation of interstitial cells of Cajal and SIP	Interstitial cells of Cajal autonomous activity + Ca^{2+} channels + Anoctamin-1	Depolarizes intramuscular interstitial cells of Cajal, enhances slow waves	Inhibits acetylcholine release, does not directly affect interstitial cells of Cajal	NO inhibits Ca^{2+} in intramuscular interstitial cells of Cajal and reduced slow wave activity	Suzuki et al. (2006)

Table 1 summarizes the main characteristics of the four major mechanisms of gastrointestinal motility regulation: cell-autonomous myogenic control, excitatory parasympathetic (cholinergic), inhibitory sympathetic (adrenergic), and non-adrenergic non-cholinergic neurogenic pathways. Data on the origin, type of signaling, cellular targets, molecular mechanisms of action, role in the physiology of the digestive system, and the effect on SIP syncytium cells, in particular on the interstitial cells of Cajal, are presented. Thus, myogenic control is the basis on which all other regulatory systems interact. The cholinergic system activates the motor response, amplifying myogenic waves. The adrenergic and non-adrenergic systems primarily have an inhibitory effect, providing flexible control over motility depending on conditions such as stress, food intake, or rest.

Cellular physiology modules

In the gastrointestinal tract, nitric oxide functions as a key mediator involved in motor inhibition, the relaxation of the sphincter apparatus, and the regulation of peristaltic activity (Stelzner, 2015). Its action covers both physiological processes and the pathogenesis of functional and organic disorders. In the literature, nitric oxide is recognized as an endogenous gaseous mediator, similar to carbon monoxide and hydrogen sulfide, capable of rapidly diffusing through cell membranes and exerting a local effect (Korbut et al., 2020; Rocha, 2021; Verbeure et al., 2021). The physiological effects of nitric oxide are realized mainly through the activation of soluble guanylate cyclase, which leads to an increase in the level of cyclic guanosine monophosphate and activation of protein kinase G, resulting in a decrease in the intracellular calcium concentration and relaxation of smooth muscles (Gangula et al., 2011; Ma et al., 2018; Liang et al., 2021). In the enteric nervous system, nitric oxide is synthesized with the participation of the neuronal isoform of nitric oxide synthase, which is expressed in neurons of the myenteric plexus. Lying between the longitudinal and circular muscle coats, this structure represents a major component of the intramural control of gastrointestinal motility (Takahashi, 2003; Gangula et al., 2011; Verbeure et al., 2021). In this context, nitric oxide functions as the main inhibitory mediator of non-adrenergic non-cholinergic innervation, participating in the reflex relaxation of the lower esophageal sphincter, pylorus and proximal stomach (McCallum, 1999; Takahashi, 2003; Verbeure et al., 2021). The participation of nitric oxide in the physiological accommodation of the stomach after food intake has been confirmed by a number of studies (Takahashi, 2003; Verbeure et al., 2021).

Disturbances in nitric oxide-dependent neurotransmission are associated with clinical conditions such as gastroparesis, achalasia, gastric accommodation disorders, duodenogastric reflux and functional dyspepsia (Gangula et al., 2011; Szlachcic et al., 2013). Insufficient neuronal NO synthase activity in enteric neurons may interfere with sphincter relaxation, as shown in studies in patients with achalasia (Szlachcic et al., 2013). The level of nitric oxide production may be reduced by the endogenous inhibitor of the synthase, asymmetric dimethylarginine, or under oxidative stress, which reduces its biologi-

cal activity (Gangula et al., 2011; Szlachcic et al., 2013). Additional regulatory mechanisms include phosphorylation, involvement of chaperone proteins such as Hsp90, and S-nitrosylation, which is particularly important in the central nervous system and gastric ganglia (Verbeure et al., 2021).

The functional differences between nitric oxide synthase isoforms are of significant importance. The neuronal isoform mediates neuronal regulation, the endothelial isoform regulates vascular tone, and the inducible isoform is activated by inflammation and has a cytotoxic effect (Calatayud et al., 2001; Takahashi, 2003). Physicochemical limitations to the effectiveness of nitric oxide include its instability, short half-life, and rapid inactivation by superoxide anion, which limits the duration of its action (Konturek & Konturek, 1995; Rocha, 2021). The effectiveness of signaling depends on the tissue microenvironment. Nitric oxide interacts with other gaseous signaling molecules – primarily carbon monoxide and hydrogen sulfide – to complement and enhance their effects. Together they regulate blood tone and antioxidant balance and provide neuroprotection. This combination of molecules shows how meaningful intermolecular interactions are for maintaining homeostasis (Korbut et al., 2020). Clinical manifestations of regulatory effects associated with nitric oxide may be subject to specificity. In women with gastroparesis, a decrease in the biological activity of nitric oxide was revealed, which may be associated with the level of hormones or a change in the sensitivity of receptors (Gangula et al., 2011). Ghrelin stimulates both appetite and gastrointestinal motility and acts through endothelial nitric oxide synthase, indicating a close functional relationship between metabolic processes and motor function (Verbeure et al., 2021).

Calcium is a universal second messenger that is key in regulating gastrointestinal motility. Its functions include initiating electrical activity in pacemaker cells and the provision of contraction of smooth muscle cells through intracellular signaling cascades. Most sources emphasize that the intracellular dynamics of calcium underlie the formation of slow waves, phasic contractions, and tonic tension in the digestive tract (Boev, 1978; Kirchhoff & Geibel, 2006). The primary mechanism of calcium signaling is considered to be the release of calcium ions from the endoplasmic or sarcoplasmic reticulum via ryanodine receptors or inositol-1,4,5-triphosphate receptors (Suzuki et al., 2006; Alfadda et al., 2014; Dulhunty et al., 2018). This activation causes wave-like changes in membrane potential via calcium Anoctamin-1-chloride channels, causing depolarization, an essential phase of contractions. In this case, the interstitial cells of Cajal are considered the main rhythmogenic structures that have the ability to initiate slow waves in the absence of neuronal activity. Calcium oscillations in these cells and muscle fibers are a key mechanism for initiating slow waves that generate electrical activity in the intermuscular and intramuscular space (Suzuki et al., 2006; Van Helden et al., 2010). According to this model, slow waves result from interactions between calcium microdomains coordinated by mitochondria and the endoplasmic reticulum.

Classical physiological studies confirm a direct relationship between action potentials, intracellular calcium influx, and phasic contractions, which became the basis for constructing electrophysiological models of gastric motility (Boev, 1978). More recent approaches suggest that local calcium waves, and not only action potentials, are the key triggers of rhythmic activity of the interstitial cells of Cajal (Van Helden et al., 2010). Ryanodine channels provide rapid release of calcium stores from cellular depots. Their sensitivity is regulated by two factors: molecular structure features and cooperation with additional proteins (Dulhunty et al., 2018). Mitochondria, absorbing and releasing calcium, are actively involved in modulating the frequency of slow waves and forming the cyclic activity of interstitial and smooth muscle cells (Suzuki et al., 2006). Modern concepts are complemented by the mechanism of calcium entry (store-operated calcium entry), activated by the depletion of its reserves in the endoplasmic reticulum. In addition to motor function, calcium imbalance is considered one of the factors of oncogenic transformation, confirming the key role of calcium metabolism in the regulation of proliferative processes (Chang et al., 2021).

The multifunctionality of calcium as a second messenger is manifested in its ability to induce multiple intracellular signaling cascades, including activation of protein kinase C, guanylate cyclase, and serine-threonine kinases. This allows the integration of calcium signals with neurohumoral regulation, in particular in response to acetylcholine, nitric oxide, and vasoactive intestinal peptide (Takahashi, 2003; Suzuki et al., 2006; Chang et al., 2021). The involvement of melatonin-sensitive calcium signaling in regulating gastrointestinal mucosal function is discussed separately. The ability of melatonin to modulate calcium activity in enterocytes through the corresponding receptors emphasizes its role in the functional regulation of the gastrointestinal tract and adaptation to circadian biological rhythms (Allen & Flemström, 2005). Thus, calcium is a key trigger of motor activity in the gastrointestinal tract, realizing its function through multilevel regulation from electrophysiological mechanisms in interstitial cells to cellular signaling, mitochondrial involvement, hormonal modulation, and integration with neural pathways. Calcium signaling is crucial for coordinating myogenic, neurogenic, and humoral motility control.

The interaction of smooth muscle cells, interstitial cells of Cajal, and platelet-derived growth factor receptor-alpha-positive fibroblast-like cells coordinates gastrointestinal motor activity. Together, these elements form a functional syncytium, the SIP complex (smooth muscle cells, interstitial cells of Cajal, PDGFRα$^+$ cells) (Fig. 1 and Table 2), which ensures the generation, transmission, and regulation of rhythmic contractions (Camilleri & Sanders, 2022; Koh et al., 2024). The intermuscular interstitial cells of Cajal, located between the longitudinal and circular muscle layers near the Auerbach plexus, generate slow waves – rhythmic electrical oscillations of the membrane potential that spread to the smooth muscles and provide their periodic depolarization, creating conditions for phasic contractions (Ward et al., 2004; Suzuki et al., 2006). Slow waves have two components – electrotonic, formed by the intermuscular cells of Cajal, and a local total potential formed by intramuscular interstitial cells of Cajal, which participate in neuromuscular transmission (Suzuki et al., 2006). Intramuscular interstitial cells of Cajal are localized in the thickness of the circular and longitudinal muscle layers and interact with both smooth muscle cells and neurons of the enteric nervous system. These cells play a key role in the neurohumoral regulation of motility, responding to neurotransmitters, in particular acetylcholine and nitric oxide (Hirst & Edwards, 2004; Faussone-Pellegrini, 2006; Al-Shboul, 2013). Other types of interstitial cells of Cajal include subserous cells, located beneath the serous membrane and likely involved in mechanical and neuronal signaling (Faussone-Pellegrini, 2006); deep muscular cells, located within the circular muscles of the small intestine and regulating local motility (Ward & Sanders, 2001); as well as cells situated near the submucosal (Meissner's) plexus and presumably influencing the motor activity of the mucous membrane and secretion (Faussone-Pellegrini, 2006). The diagram (Fig. 1) shows that SIP syncytium, which includes smooth muscle cells, interstitial cells of Cajal, and cells expressing the platelet-derived growth factor receptor α, forms an integrated electrophysiological network. This network ensures the coordinated contractions of the muscular wall of the gastrointestinal tract and the adaptive interaction between excitatory and inhibitory influences.

The functional organization of the SIP syncytium is represented by an integrated interaction between smooth muscle cells, interstitial cells of Cajal, and platelet-derived growth factor receptor-α-positive fibroblast-like cells (Fig. 2). Rhythmogenic activity is provided by the interstitial cells of Cajal, inhibitory neurotransmission (in particular, via nitric oxide) is realized by PDGFRα$^+$ cells, and muscle contractions are performed by smooth muscle cells. All these cellular components are electrically coupled via gap junctions, forming a single functional electrophysiological network (Camilleri & Sanders, 2022). Slow waves are generated by rhythmic calcium release from the endoplasmic reticulum with the participation of inositol-1,4,5-triphosphate receptors. These receptors are activated by the second messenger inositol triphosphate, which is formed under the action of neurotransmitters (Suzuki et al., 2006). This leads to the opening of chloride-sensitive Anoctamin-1 channels, causing depolarization of

the interstitial cells of Cajal and initiating the ascending phase of the slow wave (Camilleri & Sanders, 2022).

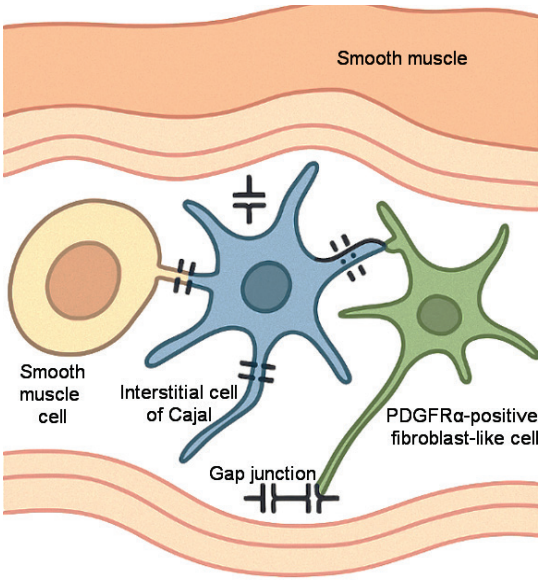

Fig. 1. Functional structure of the SIP-syncytium in the wall of the gastrointestinal tract

The schematic (Fig. 2) illustrates the structural organization and functional integration of interstitial cells of Cajal, smooth muscle cells, and platelet-derived growth factor receptor-α positive cells. Intermuscular interstitial cells of Cajal generate slow waves via calcium-dependent mechanisms, including inositol-1,4,5-triphosphate receptors and anoctamin-1 chloride channels (Suzuki et al., 2006). In contrast, intramuscular interstitial cells of Cajal mediate neuromuscular transmission (Camilleri & Sanders, 2022). PDGFRα$^+$ cells are involved in inhibitory neurotransmission, mainly through nitric oxide-dependent signaling pathways (Gangula et al., 2011). This tripartite system mediates coordinated gastrointestinal motility through electrical coupling and integration of excitatory and inhibitory influences. The component structure of the slow wave consists of the electrotonic part created by the intermuscular cells of Cajal and the local total potential formed by the intramuscular interstitial cells of Cajal (Suzuki et al., 2006). The cyclic release and reuse of calcium in the interstitial cells of Cajal is mediated by mitochondrial turnover. This rhythmogenic activity is sensitive to the action of proton pump inhibitors and calcium chelators, which confirms its pharmacological vulnerability (Suzuki et al., 2006). The frequency of the waves depends on temperature, which indicates the participation of mitochondrial metabolism in rhythmogenesis.

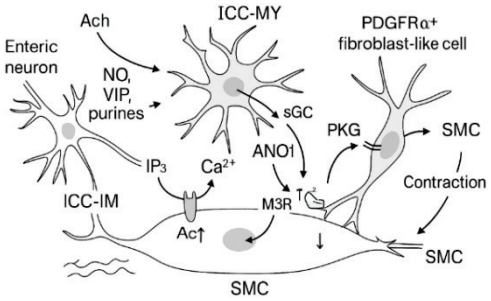

Fig. 2. Cellular and molecular interactions between the SIP syncytium of the scolio-intestinal tract. Ac (ACh) – acetylcholine; T – enteric nervous system terminal; ICC-MY – myenteric interstitial cells of Cajal; ICC-IM – intramuscular interstitial cells of Cajal; PDGFRα$^+$ – fibroblast-like inhibitory cells; SMC – smooth muscle cell; M3R – muscarinic M_3 receptor; Ca^{2+} – calcium ion; IP_3 – inositol trisphosphate; ANO1 – Anoctamin-1 Ca^{2+} -activated Cl^- channel; NO – nitric oxide; sGC – soluble guanylate cyclase; cGMP – cyclic GMP; PKG – protein kinase G; VIP – vasoactive intestinal peptide

Table 2
Functional organization of SIP syncytium based on localization composition and functional specialization

SIP syncytium component	Localization	Function	Reference
Smooth muscle cells	Circular and longitudinal muscle layers	Direct contraction in response to depolarization	Al-Shboul (2013); Camilleri & Sanders (2022)
Myenteric interstitial cells of Cajal	Between circular and longitudinal muscle layers	Generation of slow waves (rhythmogenesis)	Ward & Sanders (2001); Al-Shboul (2013)
Intramuscular interstitial cells of Cajal	Within muscle layers	Transmission of neuronal signals, modulation of contractions	Ward & Sanders (2001); Faussone-Pellegrini (2006)
PDGFRα-positive fibroblast-like cells	Adjacent to smooth muscle cells, in the submucosal and intramuscular space	Inhibitory modulation, signal transmission (including NO), involvement in inhibitory neurotransmission	Faussone-Pellegrini (2006); van Helden et al. (2010)

Neuronal influences modulate the activity of the interstitial cells of Cajal. In particular, acetylcholine stimulates the release of calcium ions, increasing the excitability of the intramuscular interstitial cells of Cajal and the SIP syncytium as a whole, whereas nitric oxide decreases the level of intracellular calcium, suppressing wave activity and reducing smooth muscle contractility (Gangula et al., 2011; Camilleri & Sanders, 2022). The interstitial cells of Cajal express the entire nitric oxide (NO)-cyclic guanosine monophosphate-protein kinase G signaling cascade, making them target cells for inhibitory neurotransmission. Activating this cascade, for example, by inhibiting phosphodiesterase 5 with sildenafil, improves gastric accommodation and motility (Gangula et al., 2011). Thus, the interstitial cells of Cajal, especially their intermuscular and intramuscular types, play a leading role in the rhythmogenesis of gastrointestinal motor activity. The formation of slow waves is ensured by a combination of inositol triphosphate-dependent calcium signaling, mitochondrial function, activation of anoctamin-1 channels, and neuronal regulation via acetylcholine and nitric oxide. All these processes are integrated within the SIP syncytium, providing a holistic coordination of electrical, chemical, and mechanical processes of contraction (Suzuki et al., 2006; Camilleri & Sanders, 2022).

Slow waves generated by the intermuscular interstitial cells of Cajal are fundamental for gastric motor activity. Their rhythmogenesis is determined by intracellular calcium dynamics involving inositol triphosphate, endoplasmic reticulum, Anoctamin-1 channels, and mitochondria. The regulation of the excitation and inhibition of interstitial cells shapes the adaptive response of the stomach to neural and humoral stimuli. Within the SIP syncytium, the interstitial cells of Cajal function as an integral part, providing a coordinated motor response of smooth muscle cells to electrical, chemical, and mechanical stimulation (Camilleri & Sanders, 2022). Since slow waves are a key mechanism for generating rhythmic activity in the gastrointestinal tract, it is essential to consider the molecular factors involved in their formation and regulation. Below is a comparative table (Table 3) summarizing the involvement of calcium, nitric oxide, and inositol-1,4,5-triphosphate in the functioning of the interstitial cells of Cajal and the formation of slow waves.

As can be seen from Table 3, calcium, nitric oxide, and inositol triphosphate play complementary but functionally opposite roles in the rhythmogenesis of interstitial cells of Cajal. Their balanced interaction determines the effectiveness of excitatory and inhibitory signals in coordinating gastrointestinal motility.

Table 3
Comparative characteristics of the role of calcium, nitric oxide and inositol-1,4,5-triphosphate in the regulation of the activity of interstitial cells of Cajal and slow waves in the gastrointestinal tract

Parameter	Ca^{2+}	NO	Inositol-1,4,5-triphosphate	Reference
Primary role	Secondary messenger; initiates slow waves by activating Ca^{2+}-sensitive channels	Inhibitory neurotransmitter; reduces excitability of interstitial cells of Cajal and smooth muscle cells	Secondary messenger; triggers Ca^{2+} release from internal stores	Camilleri & Sanders (2022)
Molecular mechanism of action	Activates Ca^{2+}-activated Cl^- channels, causing cell depolarization	Activates soluble guanylate cyclase education cyclic guanosine monophosphate activation protein kinase G, which inhibits Ca^{2+} release	Activation of inositol trisphosphate receptor on the endoplasmic reticulum results in Ca^{2+} release	Gangula et al. (2011)
Source of generation/action	Mitochondrial activity, Ca^{2+}-induced Ca^{2+} release	NO from nonadrenergic noncholinergic neurons or endothelium	Formed via phospholipase C following receptor stimulation	Suzuki et al. (2006)
Impact on slow waves	Determines amplitude, but not frequency	Reduces interstitial cells of Cajal excitability by inhibiting Ca^{2+} release	Increased inositol trisphosphate promotes generation of slow waves through Ca^{2+} release	Suzuki et al. (2006); Camilleri & Sanders (2022)
Key targets/channels	Anoctamin-1 Ca^{2+}-dependent Cl^- channels, T-type Ca^{2+} channels	Soluble guanylate cyclase, protein kinase G, phosphodiesterase-5	Inositol trisphosphate receptors on the endoplasmic reticulum	Suzuki et al. (2006)
Interstitial cells of Cajal activity regulation	Maintains rhythmicity via Ca^{2+} exchange between endoplasmic reticulum and mitochondria	Inhibits excitability by reducing Ca^{2+} in intramuscular interstitial cells of Cajal	Promotes periodic Ca^{2+} release, supporting rhythmogenesis	Camilleri & Sanders (2022)

Methods for studying gastrointestinal motility

Analysis of the motor function of the gastrointestinal tract, including the lower esophageal sphincter and the pylorus, is of fundamental importance in modern gastroenterology. In the scientific literature, a consensus has been formed regarding the need to use multi-instrumental diagnostic approaches to objectively assess the functional state of the sphincters, motor coordination, and clinical interpretation of pathological changes. Among modern diagnostic technologies, endoluminal functional lumen imaging probe occupies an important place due to the ability to assess the gastrointestinal tract distensibility in real-time monitoring. The method is of particular value for examining the pyloric sphincter in gastroparesis, which is confirmed by clinical data (Wuestenberghs & Gourcerol, 2021; Soliman & Gourcerol, 2023). Endoluminal functional lumen imaging probe can detect decreased tissue elasticity even with typical manometric values, which is valuable in stratifying patients with functional disorders of gastric emptying. A similar application of endoluminal functional lumen imaging probe to assess the function of the cardiac sphincter and the esophagogastric junction is also presented in studies (Mittal & Vaezi, 2020), where this method was used to detect achalasia and gastroesophageal reflux disease and monitor the results of therapy. The consistency of such results is confirmed in studies (Tack & Pandolfino, 2018), which emphasize the role of high-resolution manometry as the "gold standard" in the study of esophageal motility, as well as its importance in the modern Chicago classification of motor disorders.

The combined use of high-resolution manometry and pH-impedancemetry used in clinical practice allowing a full assessment of the function of the lower esophageal sphincter and the identification of motility disorders (Ribolsi et al., 2020). According to the Lyon Consensus, the combination of high-resolution manometry and endoluminal functional lumen imaging probe has become the gold standard for diagnostics, allowing unified approaches and objective assessment of treatment outcomes (Gyawali et al., 2018; Tack & Pandolfino, 2018). As an additional tool, the endoluminal functional lumen imaging probe has demonstrated high efficiency in cases where high-resolution manometry does not provide definitive results. A number of studies confirm its diagnostic value in assessing emptying disorders at the gastroesophageal junction, as well as in analyzing pyloric function in patients with gastroparesis (Kahrilas et al., 2018; Chen et al., 2019; Gyawali et al., 2019). In recent years, the method has also been actively used to monitor the effectiveness of interventions such as peroral endoscopic myotomy and pyloromyotomy.

A separate category is made up of studies devoted to specific clinical cases. In particular, extraesophageal manifestations of gastroesophageal reflux disease in children are described in the work (Brodsky & Carr, 2006), which emphasizes the importance of early diagnosis of reflux-associated conditions, including chronic cough, laryngitis, and dysphonia. A retrospective analysis of the pathophysiology of gastroesophageal reflux disease before the introduction of high-resolution manometry is presented in a classic study (Galmiche & Janssens, 1995), which became the basis for subsequent improved approaches. Thus, using a wide range of diagnostic technologies – high-resolution manometry, the endoluminal functional lumen imaging probe, endoscopy, pH meter, and impedance monitoring – illustrates a multi-level strategy for studying gastrointestinal motility. Regardless of the differences in methods and research approaches, all authors emphasize the common trend – the objectification of functional motility disorders for accurate diagnosis and personalized treatment in clinical gastroenterology.

Demographic features of motility regulation

Scientific publications unanimously agree on the importance of sex differences in regulating gastrointestinal motor function. Nitric oxide plays a vital role in this process as a key neurotransmitter, relaxing the smooth muscles of the sphincters and promoting gastric emptying. NO signaling is considered a critical factor in the normal regulation of motility and the development of functional gastrointestinal disorders (Gangula et al., 2011; Iijima & Shimosegawa, 2014). In particular, nitrergic activity is higher in women due to increased expression and dimerization of neuronal NO synthase, which correlates with estrogen levels (Gangula et al., 2011). Such activity, despite the physiological advantage, in disorders can lead to gastroparesis, accommodation dysfunction, and delayed gastric emptying. Nitric oxide is also considered a factor that promotes the relaxation of the lower esophageal sphincter and increases the risk of gastroesophageal reflux. At the same time, estrogens can protect the esophageal mucosa, which probably explains the lower prevalence of severe forms of reflux disease in women (Iijima & Shimosegawa, 2014). However, nitric oxide is considered a key regulator; different aspects of its action focus either on gastric motility (Gangula et al., 2011) or the effects on the esophageal mucosa (Iijima & Shimosegawa, 2014). Sex differences due to the hormonal modulation of NO signaling determine the clinical diversity of manifestations of gastrointestinal pathologies.

With age, the functioning of the gastrointestinal tract changes, associated with a decrease in motility, secretion, blood supply, and neurohumoral regulation. Most sources note that age-related motility disorders are associated with decreased NO-dependent smooth muscle relaxation mechanism efficiency (Marks et al., 1992; Salles, 2009; Ramsay & Carr, 2011). This is also accompanied by a decrease in acid secretion and a disruption of the protective function of the mucosa, which can lead to dyspepsia or ulceration. Decreased esophageal elasticity, impaired peristalsis, and decreased relaxation of the lower

esophageal sphincter in old age are also considered to be a consequence of age-related neuronal changes (Chen et al., 2019; Cock & Omari, 2018). At the molecular level, it has been established that aging is accompanied by a decrease in NO synthase activity and nitric oxide bioavailability, which negatively affects motor function, regulation of vascular tone, and the protective properties of the mucous membrane (Ma et al., 2018; Rocha, 2021; Liu et al., 2023). In addition, using exogenous sources of nitric oxide, particularly dietary nitrates, is proposed to compensate for its deficiency. The focus of individual studies varies. In some publications (Ma et al., 2018; Rocha, 2021; Liu et al., 2023), NO is considered in the context of systemic aging, including the role of microbiota, diet, and cellular signaling. At the same time, in the works (Marks et al., 1992; Salles, 2009), the emphasis is on morphofunctional changes in the mucosa. A decrease in mucosal blood flow, which contributes to its damage even without an increase in acidity, is highlighted as an additional risk factor (Ramsay & Carr, 2011). Age-related changes in esophageal motility are manifested by a decrease in muscle tone, weakening peristalsis, and relaxation of the lower esophageal sphincter, which increases the likelihood of developing dysphagia and aspiration (Cock & Omari, 2018). Nitric oxide acts as a central signaling molecule through which the influence of sex hormones, especially estrogens, and age-related changes is realized. Even without pronounced pathology, a decrease in NO-dependent signal transmission is associated with functional disorders, which is the basis for continuing research.

Pathophysiology of motility disorders

Esophageal achalasia is a primary motility disorder characterized by a complex pathogenesis, well-defined manometric criteria, and variable clinical response to therapy. There is consensus on the key mechanisms of the disease, although views on the etiology and treatment approaches remain varied. The common characteristics are the absence of peristalsis in the distal esophagus and impaired relaxation of the lower esophageal sphincter in response to swallowing, as confirmed by high resolution manometry (Schlottmann & Patti, 2018; Mittal & Vaezi, 2020). The main pathogenetic link is considered to be the loss of inhibitory innervation in the intermuscular plexus, in particular, a decrease in the activity of neuronal NO synthase, which impairs the relaxation of the lower esophageal sphincter (Takahashi, 2003; Groneberg et al., 2016). Deficiency in nitric oxide release is directly related to motor dysfunction and is considered in the clinical classification of achalasia types, which has prognostic value (Mittal & Vaezi, 2020). As for the etiology, hypotheses are put forward about the involvement of immune mechanisms, particularly a possible connection with eosinophilic esophagitis. There is evidence of the presence of eosinophilic infiltrates in the muscular layer of the esophagus, which can be both an accompanying process and a trigger for pathology (Spechler et al., 2018; Rieder et al., 2020). Approaches to therapy also vary. In addition to multidisciplinary management (Schlottmann & Patti, 2018), assessing the biomechanical parameters of achalasia is relevant, allowing the individualization of endoscopic and surgical interventions (Gregersen & Lo, 2018). Thus, achalasia is considered a neurogenic motor disorder based on a deficit of inhibitory innervation. Still, its clinical heterogeneity requires further research, particularly in immunology and biomechanics.

Hiatal hernia is an important anatomical and functional factor in developing gastroesophageal reflux disease. The standard mechanisms of esophageal cleansing are bypassed in its presence, and peristalsis is weakened, contributing to reflux (Tack & Pandolfino, 2018; Babii et al., 2022). The most common form is a sliding hernia (type I), which is characterized by the weakening of the lower esophageal sphincter and decreased resistance in the gastroesophageal junction (Cha, 2020). There is a direct relationship between the volume of the hernial protrusion, the degree of gastroesophageal reflux, and the decrease in pressure in the esophagogastric junction, which serves as a pathogenetic justification for surgical intervention (Mackay & Louie, 2023). The method of choice is Nissen fundoplication, the main goal of which is anatomical reconstruction and restoration of the barrier function. Implementing the respiratory mechanism of reflux with the formation of a hernial chamber makes it possible to passively move the stomach's contents into the esophagus even without swallowing (McCallum, 1999). Manometric and scintigraphic methods confirm a decrease in the functional capacity of the gastroesophageal zone (Tack & Pandolfino, 2018), and delayed gastric emptying accompanying gastroesophageal reflux disease increases symptoms (Galmiche & Janssens, 1995). The diagnostic algorithm includes radiography with contrast, endoscopy, and manometry (Babii et al., 2022). The therapeutic strategy for hernias is determined by the extent of development and the severity of clinical symptoms. Surgical intervention is recommended for large hernias or when severe hernias are evident. For small asymptomatic hernias, you can get by with a conservative approach and dynamic observation (Mackay & Louie, 2023).

Gastroesophageal reflux disease is one of the most commonly diagnosed gastrointestinal diseases, with a variable global prevalence ranging from 8–33% depending on geographic region, lifestyle, and diagnostic criteria (Gyawali et al., 2018). Although reflux occurs in healthy individuals, its pathological nature is determined by symptoms and mucosal damage (Vaezi et al., 1995). The prevalence of gastroesophageal reflux disease does not show significant gender differences (Galmiche & Janssens, 1995; Fass et al., 2021). Clinically, a distinction is made between the nonerosive form, erosive esophagitis, Barrett's esophagus, and extraesophageal manifestations, including cough, laryngitis, and chronic respiratory disease (Brodsky & Carr, 2006; Banting et al., 2020; Woods et al., 2021). The key mechanism of gastroesophageal reflux disease is dysfunction of the lower esophageal sphincter, although in some patients it retains morphological integrity (Souza, 2010; Pacheco-Galván et al., 2011). Esophageal motility also plays a significant role (Mittal & Vaezi, 2020). According to the Lyon Consensus, gastrointestinal motility assessment should be standardized (Gyawali et al., 2018). Complications include strictures, dysplasia, Barrett's esophagus, and adenocarcinoma (Souza, 2010). Oxidative stress is essential in developing complications (Korbut et al., 2020). Laryngopharyngeal reflux is characterized by a mechanism of injury in which pepsin plays a significant role (Krause et al., 2022; Cui et al., 2024). Diagnostic methods include high-resolution manometry, pH-metry, lumen compliance technology, and endoscopy. One of the modern methods of treatment is transcutaneous electroacupuncture stimulation of the lower esophageal sphincter (Liu et al., 2019). Modern surgery again focuses on this anatomical zone, which emphasizes the cyclical nature of the development of antireflux therapy (Mackay & Louie, 2023).

Conclusion

Interconnected cellular, ionic, neural, and humoral mechanisms regulate gastrointestinal motility. The structural basis of this regulation is the SIP syncytium, which includes smooth muscle cells, interstitial cells of Cajal, and PDGFRα^+ cells. The generation of waves depends on the release of calcium through IP_3 receptors, the activation of Anoctamin-1 channels, and the participation of mitochondria. While acetylcholine increases contractions, nitric oxide lowers intracellular calcium, promoting relaxation. Coordinated gastrointestinal tract function depends on peristalsis, sphincter tone, and the enteric neural system. Understanding and treating diseases depends on these physiological systems. Of particular importance are malfunctions of Cajal cells, slow wave disorders, and imbalances between excitatory (acetylcholine) and inhibitory (vasoactive intestinal peptide, NO) mediators. The deficiency of nitric oxide signaling is the pathogenetic factor in achalasia, gastroparesis, and other sphincter dysfunctions. Modern research methods include high-resolution manometry, lumen compliance technology, pH-metry, and scintigraphy. These approaches allow us to evaluate accurate physiological parameters of motor activity, such as compliance, tone, and coordination of contractions and relaxations. In combination with therapeutic measures, such as using nitric oxide donors, phosphodiesterase type 5 inhibitors, and endoscopic myotomy, targeting specific links in impaired motility is possible. The physiological aspects of gastrointestinal motility remain an area of active research. Up-and-coming areas are those related to the detailing of calcium microdomains in the interstitial cells of Cajal

and their interaction with mitochondria, the molecular profile of the SIP complex in different anatomical zones of the gastrointestinal tract, sex and age variations in sensitivity to acetylcholine, nitric oxide and inositol triphosphate, as well as intersystem interactions, such as the influence of the microbiota on neuronal and hormonal regulation of motility. In addition, studying the mechanisms of adaptation of the SIP system to pathological conditions such as inflammation, ischemia, diabetes, and oxidative stress is critical for developing new biomarkers and targeted strategies for treating functional gastrointestinal disorders.

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