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Pathogenesis of Disorders of the Motor Function of the Large Intestine in Functional Constipation

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Aim: to analyze the scientific literature on the role of various factors in the mechanisms of development of functional constipation and to summarize the current data on its leading pathogenetic mechanisms.
Key points. Constipation occurs in 15 % of the adult population in the world and leads to a significant decrease in the quality of life, and in combination with some other symptoms may indicate the presence of an organic pathology of the gastrointestinal tract. The pathogenetic basis of functional constipation (FC) with slow intestinal transit is a decrease in colonic motor function, which is confirmed by the results of high-resolution manometry. FC is characterized by disturbances in such motor patterns of the colon as low and high amplitude propagating contractions, segmental non-propagating contractions, and general increases in pressure. The main FC mechanisms associated with neurogenic dysregulation include impaired function of the gray and white matter of the brain, as well as an increase in the tone of the sympathetic nervous system with a concomitant decrease in the influence of cholinergic nerves innervating the large intestine. A key role in the FC development belongs to a decrease in the pool of interstitial cells, which play the role of an intestinal pacemaker, due to slowing of their self-renewal. FC-associated changes in the enteric nervous system include a relative excess of the contribution of inhibitory influences and a decrease in the activity of cholinergic and serotonergic neurons that stimulate intestinal motility. A certain role in the occurrence of reduced motor function of the colon may have an imbalance in the production of intestinal hormones synthesized by enteroendocrine cells, namely, a deficiency of motility stimulants, which include motilin, gastrin, ghrelin and cholecystokinin, as well as a relative excess of hormones that suppress motility (somatostatin and vasoactive intestinal polypeptide). Changes in the composition of the intestinal microbiota can also contribute to the FC occurrence, which is associated with a dysfunction of the metabolite profile produced by intestinal bacteria.
Conclusions. Functional constipation is a classic multifactorial disease, in the etiology of which the adverse effects of the genotype are combined with multiple acquired risk factors. A more complete understanding of the molecular mechanisms of the FC development can serve as the basis for the emergence of new effective treatments for this common pathology.
Keywords: colonic motor function, functional constipation, slow transit constipation, high amplitude propagating contractions, intestinal hormones, enteric nervous system, intestinal microbiota
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Патогенез нарушений моторной функции толстой кишки при функциональном запоре

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Цель обзора: представить современные данные о ведущих звеньях патогенеза функционального запора.
Основные положения. Запор встречается у 15 % взрослого населения в мире и приводит к значимому снижению качества жизни, а в сочетании с некоторыми другими симптомами может свидетельствовать о наличии органической патологии желудочно-кишечного тракта. Патогенетической основой функционального запора (ФЗ) с медленным кишечным транзитом является снижение моторной функции толстой кишки, которое подтверждается результатами манометрии высокого разрешения. ФЗ характеризуется нарушениями таких

моторных паттернов толстой кишки, как низко- и высокоамплитудные пропульсивные сокращения, сегментарные непропульсивные сокращения и общее повышение давления. Основные механизмы ФЗ, связанные с нейрогенной дисрегуляцией, включают нарушение функции серого и белого вещества головного мозга, а также повышение тонуса симпатической нервной системы при сопутствующем уменьшении влияний холинергических нервов, иннервирующих толстую кишку. Значимая роль в развитии ФЗ принадлежит уменьшению пула интерстициальных клеток, играющих роль кишечного водителя ритма, вследствие нарушения процесса их самообновления. Сопутствующие ФЗ изменения в энтеральной нервной системе включают относительное превышение вклада тормозных влияний и уменьшение активности холинэргических и серотонинэргических нейронов, стимулирующих кишечную моторику. Определенное значение в возникновении сниженной моторной функции толстой кишки может иметь дисбаланс выработки кишечных гормонов, синтезируемых энтероэндокринными клетками, а именно, дефицит стимуляторов моторики, к которым относятся мотилин, гастрин, грелин и холецистокинин, а также относительный избыток гормонов, подавляющих моторику (соматостатин и вазоактивный интестинальный полипептид). Изменения состава кишечной микробиоты также могут способствовать возникновению ФЗ, что связано с нарушением профиля метаболитов, продуцируемых кишечными бактериями.

Заключение. ФЗ представляет собой классическое мультифакториальное заболевание, в этиологии которого неблагоприятные влияния генотипа сочетаются с множественными приобретенными факторами риска. Более полное понимание молекулярных механизмов развития ФЗ может послужить основой для появления новых эффективных методов лечения этого распространенного заболевания.

Ключевые слова: моторная функция толстой кишки, функциональный запор, запор с медленным транзитом, высокоамплитудные пропульсивные сокращения, кишечные гормоны, энтеральная нервная система, кишечная микробиота

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Introduction

The prevalence of constipation in the adult population in most countries of the world is estimated at 15 % [1], but in people over 60 years of age it has increased to 33 % [2]. At the same time, constipation cannot be considered a manifestation of normal aging [3]. According to epidemiological studies, constipation is the fifth most common symptom of gastrointestinal dysfunction [4]. Constipation results in significant economic losses. In the United States alone, approximately $800 million is spent annually on laxatives [5]. Much more is spent on complex diagnostic tests, hospitalization and surgical treatment. The classification of constipation according to its etiology includes two variants — primary and secondary. The most common is primary or functional constipation (FC), in which there is no organic disease of the gastrointestinal tract or other systems that could lead to constipation [6]. Traditionally, all cases of FC are classified into three groups: constipation with normal intestinal transit, delayed transit, and pelvic floor dysfunction [1]. Classification of FC by intestinal transit time is generally very tentative, since at least 40 % of patients with normal transit actually have colonic motor dysfunction [7]. On the other hand, some patients with delayed transit have normal fasting colonic motility and a normal response to food intake and bisacodyl. Nevertheless, according to classical ideas, a decrease in colonic motility is the main link in the pathogenesis of delayed transit constipation [8]. Decreased secretory function, manifested by decreased mucus production by goblet cells and mucus glands, and decreased secretion of anions and water by colonocytes, may be of some, albeit secondary, importance [9]. Under both physiologic and pathologic conditions, colonic motility is influenced by many different internal and external factors. These include neurogenic influences, largely related to the function of the central nervous system, as well as those mediated by the stimulatory action of the parasympathetic nervous system and the inhibitory influence of the sympathetic nervous system [10]. Very important is the enteric nervous system (ENS), which is a set of neurons and glial cells whose cell bodies are located directly in the intestinal wall. However, it should be noted that the completely denervated intestine retains motor activity due to a myogenic response [11]. Motility is stimulated by bile acids and many intestinal and extra-intestinal hormones [9]. Metabolites of the intestinal microbiota, whose relationships with the host organism are considered in the context of the concept of the

"microbiota — gut — brain" axis, are also important in the regulation of colonic motor function [12]. Motility disorders can be associated with changes in the composition of the diet in the form of a relative deficit of non-digestible fiber in it and with the use of various drugs. This review analyzes the scientific literature on the role of various factors in the mechanisms of FC development.

Patterns of colonic motor activity and its impairment in FC

The first translational Consensus on terminology and definitions in the field of colonic motor function [13], according to which seven colorectal motor patterns are currently distinguished in humans (Table), played an important role in harmonizing general ideas about the types of colonic motor activity. It is useful to identify four motor patterns that, according to data from clinical studies, are characterized by significant changes in FC. These include 1) one-step pressure increases [14]; 2) segmental non-propulsive contractions, which do not increase in FC after ingestion [15]; 3) low amplitude propagating contractions (LAPCs), which have been shown to decrease in intensity or frequency in some studies [16]; 4) high amplitude propagating contractions (HAPCs), which have been shown to decrease in intensity or frequency in FC in the vast majority of studies [8, 17]. HAPCs occur spontaneously or under the influence of intestinal distention and chemical agents in the cecum and extend into the descending colon, sigmoid colon and rectum (approximately 5 % of cases). They are accompanied by the transit of intestinal contents over a considerable distance and are associated with relaxation of the internal anal sphincter, and precede defecation. Assessment of HAPC frequency and amplitude by high-resolution manometry can be used to diagnose various disorders of colonic motility, as there is evidence of increased HAPC frequency in irritable bowel syndrome (IBS) with diarrhea [19]. Recent studies using high-resolution manometry have attempted to further subdivide delayed transit constipation into subtypes using criteria such as the presence of spontaneous and neostigmine-induced HAPCs, the presence of LAPCs, and a preserved motility response to awakening and feeding [20]. The authors identified four subtypes of delayed transit constipation, with the most common third subtype characterized by the absence of HAPCs, preservation of LAPCs, and decreased motor response to waking and food intake. The rarest and most severe variant of delayed transit constipation, occurring in 5 % of cases, develops in the complete absence of HAPCs and LAPCs, including in response to waking and feeding.

Three groups of methods are currently used in clinical and research practice to assess colonic motor function in humans:

1. Methods of assessing colonic motor function by intestinal transit time include: scintigraphic assessment of intestinal transit time, in which transit is assessed by the dynamics of brightness of indium-labeled carbon particles immersed in a polymer capsule [21]; use of dynamic observation of the passage of orally administered radiopaque contrast markers [22]; use of the SmartPill telemetric capsule, which contains autonomous pressure, temperature, and pH sensors [23]. The passage of the capsule through the gastrointestinal tract allows real-time or retrospective evaluation of not only intestinal transit time, but also elements of motor and secretory function.

2. Methods of assessing colonic motor function by intraluminal pressure are the most common and informative and include high-resolution manometry and barostat application. The technique of colonic manometry has undergone significant technical improvements in recent years due to the closer placement of fiber optic pressure sensors on the catheter (the distance between adjacent sensors is 10 mm) [17]. Modern high-resolution manometry allows evaluation of a number of characteristics of the propagating wave of colonic contraction, including amplitude, velocity, direction, and area of propagation from the point of origin to the point of attenuation. Manometry is complemented by the barostat technique, which is a hollow polyethylene balloon in which a constant pressure is maintained, and the volume of fluid or air is varied according to the severity of intestinal contractile activity [24]. Unlike manometry, the barostat allows measurement of the volume — pressure relationship and recording of basal intestinal tone and wall relaxation but does not allow assessment of the spatial character of contraction wave propagation [25].

3. Visualization methods to assess the colonic motor function, among which magnetic resonance imaging (MRI) has dominated until recently. MRI is particularly important for the diagnosis of defecation disorders, as there are characteristic signs of paradoxical contraction of the anus muscles and absence of rectal contraction [26]. Currently, MRI is also used to assess the axial movement of colonic contents, the volume of the contents, and the velocity of its transit [27]. Although the duration of a dynamic MRI acquisition can theoretically be unlimited, in practice it is limited to a rather short time interval (5–30 min) due to both economic considerations and patient discomfort. For these reasons, MRI can only be considered as an adjunct method to assess colonic motility,

Table. Patterns of motor activity of the large intestine and their disturbances in functional constipation
Таблица. Паттерны моторной активности толстой кишки и их нарушения при функциональном запоре

Motor pattern ***Моторный паттерн***	**Definition** ***Определение***	**Frequency** ***Частота***	**Modulation** ***Модуляция***	**Change with constipation** ***Изменение при запоре***
Immediate increase in pressure *Одномоментное повышение давления*	Simultaneous increase in pressure in various parts of the colon *Одновременное повышение давления в различных отделах толстой кишки*	1–2 cycles per minute *1–2 цикла в мин*	Increased after waking up and eating *Усиление после пробуждения и приема пищи*	Reduced for constipation with slow transit *Снижение при запоре с медленным транзитом*
Pressure change at the haustra boundary *Изменение давления на границе гаустр*	Rhythmic increase in pressure at one point or at several points at a distance of 4–5 cm *Ритмичное повышение давления в одной точке или в нескольких точках на расстоянии 4–5 см*	3 cycles per minute *3 цикла в мин*	No data *Нет данных*	No changes *Нет изменений*
Intragaustral activity *Интрагаустральная активность*	Waves of contraction propagating in both directions *Волны сокращения, распространяющиеся в обоих направлениях*	3 cycles per minute *3 цикла в мин*	Increased after eating *Усиление после приема пищи*	No changes *Нет изменений*
Segmental non-propulsive contractions *Сегментарные непропульсивные сокращения*	Rhythmic contractions propagating in an ortho- or retrograde direction *Ритмичные сокращения, распространяющиеся в орто- или ретроградном направлении*	2–6 cycles per minute *2–6 циклов в мин*	Increased after eating *Усиление после приема пищи*	No gain after eating *Отсутствие усиления после приема пищи*
Slow retrograde contractions *Медленные ретроградные сокращения*	Slow (< 0.5 cm/s) retrograde contractions with reach > 40 cm *Медленные (< 0,5 см/с) ретроградные сокращения с захватом > 40 см*	Do not repeat *Не являются повторными*	Do not change *Не изменяются*	No data *Нет данных*
Low amplitude propulsive contractions *Низкоамплитудные пропульсивные сокращения*	Isolated propulsive contractions > 1 min apart *Изолированные пропульсивные сокращения с интервалом > 1 мин*	Do not repeat *Не являются повторными*	Increased after waking up and eating *Усиление после пробуждения и приема пищи*	Either no change or decrease *Отсутствие изменения либо снижение*
High amplitude propulsive contractions *Высокоамплитудные пропульсивные сокращения*	Waves of peristalsis (> 75 mmHg) involving more than 20 cm of bowel, associated with defecation *Волны перистальтики (> 75 мм рт. ст.) с захватом более 20 см кишки, ассоциированные с дефекацией*	Can repeat (4–23 times a day) *Могут быть повторными (4–23 раза в сут.)*	Increased after waking up and eating *Усиление после пробуждения и приема пищи*	Significant decrease *Значимое снижение*

but not as an alternative to high-resolution manometry. In 2023, the first attempt was made to use abdominal ultrasound (AUS) to assess colonic motility in healthy volunteers [28]. AUS allows the acquisition of 4–5 cm of colon length, i.e. 2–4 haustra are analyzed. Software identifies the edges of the haustra and measures the change in distance between them. Using this approach, segmental non-propulsive contractions with a frequency of 2–6 cycles per minute have been characterized. Rarer phenomena associated with spontaneous motor activity are not visualized by AUS. The advantages of AUS for the assessment of motility include non-invasiveness, no need for sedation, and cost-effectiveness.

Thus, improvements in technology have provided researchers with a wide arsenal of instrumental methods that allow reliable verification of colonic motor dysfunction in FC. Among these methods, high-resolution manometry is the leader in terms of "diagnostic value/economic costs" ratio. The most urgent task for the coming years is the standardization of measurements and the development of universal recommendations for the interpretation of their results, which should provide basis for multicenter studies.

Mechanisms of intestinal motility disorders in FC

The decrease in the frequency of occurrence, as well as the decrease in the amplitude of propulsive contractions of the muscular layer of the colonic wall, which is the basis of the development of constipation with delayed transit, can be caused by various mechanisms. Reduction of motor function can be mediated by dysfunction of higher integrative circuits of the central nervous system, sympathovagal imbalance and morphofunctional disorders of the ENS. No less important are changes in the level of production or receptor signaling of hormones that affect the contractile colonic function. Changes in the composition of the intestinal microbiota associated with individual genotype, sex, age, and various modifiable factors also have an indirect effect on colonic motility. The main pathogenetic factors involved in the development of colonic hypokinesia are discussed below.

Central and autonomic regulation disorders

The neurogenic regulation of the colonic motor function is based on a hierarchical principle, according to which the highest coordination is performed by the cerebral cortex and subcortical nuclei, and the central and peripheral structures of the autonomic nervous system, as well as the ENS, act as subordinate parts of regulation, although endowed with considerable autonomy. Disorders at any of these levels can contribute to a decrease in the normal colonic motor activity and, consequently, to the occurrence of FC. The tremendous advances in neuroimaging techniques in recent years have provided unique opportunities to detect structural and functional brain changes in patients with FC [29]. For example, resting-state functional MRI has allowed us to associate the presence of FC with disorders in the function of parts of the brain responsible for emotional perception, namely the anterior insula, orbitofrontal cortex, dorsal anterior cingulate cortex, and hippocampus [30]. The work of L. Liu et al. using resting-state functional MRI in combination with graph theory showed that patients with FC are characterized by a decrease in functional connectivity of the brain, mainly between the thalamus, rostral anterior cingulate cortex, and supplementary motor area [31]. These dysfunctions are accompanied by subtle morphological changes in certain parts of the brain that may be associated with differences in white matter microstructure [32]. In particular, high-resolution MRI revealed morphometric differences from controls in areas of the brain responsible for emotion processing, error detection mechanisms, and control of motor function in FC patients [33]. A recent study using voxel-based morphometry and MR tractography showed that there is a significant change in brain gray matter volume in areas such as the anterior cingulate cortex, left insula, and right middle frontal gyrus [34]. Using functional MRI, graph theory, and functional connectivity analysis, X. Yu et al. (2023) identified disorders in the visual and somatosensory neural networks of the brain, as well as the passive mode neural network of the brain in patients with FC [35]. It is obvious that an in-depth analysis of the neurophysiological dysfunctions that occur in FC may become the basis for the development of personalized treatment schemes in the future.

Direct innervation of the colon is carried out by branches of the vagus nerve, as well as the lumbar internal and pelvic nerves. The "external" colonic innervation, which is different from the "internal" ENS, is carried out by the pre- and postganglionic fibers of the autonomic nervous system, which are part of the above-mentioned mixed nerves. Classical physiological experiments have shown that the influences of the sympathetic and parasympathetic nervous systems on colonic motor function are antagonistic, which is also true for most other visceral functions [36]. The central part of the sympathetic nervous system is represented by neurons of hypothalamic nuclei located along the lamina terminalis (subfornical organ, median preoptic nucleus, vascular organ of the lamina terminalis). Neurons of the above

structures form connections with the paraventricular nucleus, which integrates information from these and other sources and influences preganglionic neurons of the lateral intermediate nucleus of the spinal cord both directly and through the rostral ventrolateral medulla [37]. The axons of neurons of the lateral intermediate nucleus of the spinal cord transiently pass through the ganglia of the lumbar portion of the sympathetic chain and further enter the lumbar innominate nerve [38]. These fibers switch to postganglionic fibers in the 2nd order ganglia, which are part of the superior and inferior mesenteric nerve plexuses. Transection of sympathetic nerves innervating the colon, as well as pharmacological blockade of alpha-adrenergic receptors, results in increased motor function [39]. In contrast, stimulation of pre- and postganglionic sympathetic fibers suppresses spontaneous colonic contractions [40].

The anatomical organization of the parasympathetic innervation of the colon includes a central part represented by neurons located in the dorsal motor nucleus of the vagus nerve (in the medulla oblongata) and in the sacral portion of the spinal cord [41]. Preganglionic parasympathetic fibers pass within the vagus and pelvic nerves and reach the cell bodies of cholinergic neurons that are part of the ENS. Transmission at these junctions is mediated by H-cholinoreceptors and inhibited by ganglion blockers. Experimentally, bilateral transection of the pelvic nerve leads to a decrease in colonic tone and a decrease in its spontaneous motor activity. Thus, in this case, there is a complete absence of HAPCs and bolus defecation in dogs, which is replaced by the defecation of individual small fecal lumps [42]. Bilateral pelvic nerve transection in rats is associated with an increase in intestinal transit time for the first 3 days, followed by partial recovery, which may be explained by a compensatory increase in the expression of transient receptor potential ankyrin 1 (TRPA1) [43] and serotonin 5-HT_3 receptors [44] in the intestinal mucosa. Clinically, pelvic nerve branch injury may occur after pelvic surgery, especially hysterectomy, and after complicated labor. There is convincing evidence that in some cases severe constipation is associated with impaired parasympathetic colon innervation [45, 46]. Electrical stimulation of the pelvic nerve in cats is associated with a marked increase in propagating peristalsis with evacuation of the colonic contents [47]. It is important to note that the prokinetic effect of stimulation of parasympathetic fibers within the pelvic nerve is significantly reduced by simultaneous stimulation of the lumbar innominate nerve [48]. These data suggest that sympathetic nerves exert an inhibitory effect on colonic motility by suppressing tonic excitatory parasympathetic activity.

Thus, the "external" colonic innervation is provided by three main sources: branches of the vagus nerve, internal and pelvic nerves, and each of these pathways provides both the transmission of afferent information to the CNS and carries efferent fibers of the autonomic nervous system [49].

Role of the ENS and interstitial cells

The ENS is represented by neurons and glial cells grouped in intramural ganglia forming two main nerve plexuses, as well as nerve conduits connecting them [50]. The ENS provides a local level of neurogenic regulation of various colonic physiological functions, including secretion of mucus, water and electrolytes, contractile activity of smooth muscle cells of the intestinal wall, vascular tone and immune defense. In this case, the intermuscular plexus (Auerbach's plexus) controls the colonic motor function to a greater extent, while the submucosal plexus (Meissner's plexus) is responsible for controlling secretion, water absorption, and regulation of vascular tone. Since the ENS contains approximately 200 million neurons and 3–5 times as many glial cells, some authors figuratively refer to the ENS as the "intestinal brain" [51]. Despite a significant degree of functional autonomy, the ENS is under the external modulating influence of the autonomic nervous system. All the neurons that make up the ENS can be classified according to their functional specialization as afferent (sensory), interneurons, and motor (efferent) neurons. The most important physiological stimulus for activation of afferent neurons of the ENS is stretching of the colonic wall, which indicates the presence of mechanoreceptor signaling in them [52]. In addition to the neurons themselves, interstitial cells, which act as intestinal pacemakers and depolarize under the action of incoming calcium currents as a result of membrane stretching or chemical stimulation, are of key importance for adequate regulation of colonic motility [53, 54]. In recent years, two distinct subpopulations of interstitial cells have been described: interstitial cells of Cajal and cells expressing platelet-derived growth factor receptor A [55]. Interstitial cells form several plexuses, mainly in the submucosal and intermuscular layers of the intestinal wall and establish gap junctions and electrical contacts with smooth muscle cells, which, under threshold excitation, ensure the formation and propagation of the propulsive wave [56]. A decrease in the number of ENS neurons and interstitial cells in the intestinal wall is one of the most common morphological findings in FC. The first morphometric data on the decrease of interstitial cell density in the intestine of patients

with FC were obtained by C.L. He et al. (2000) [57]. It is known that the number of interstitial cells decreases with age, which may explain the significant increase in the prevalence of FC in the older age group [58]. The results obtained in recent years shed light on the possible mechanisms of the reduction of the interstitial cell pool in FC. It is possible that the leading factor is a disturbance in cell population dynamics with a predominance of programmed interstitial cell death by autophagy over self-renewal processes [59]. MicroRNA-222 and microRNA-129-3p act as epigenetic regulators of interstitial cell autophagy [59, 60].

The influence of efferent neurons of the ENS on colonic motor function is mediated by the type of neurotransmitter synthesized in each type of neuron. As in the case of hormonal regulation of motility, the neurogenic effects of the ENS are based on an antagonistic principle. The major motility-stimulating neurotransmitters are serotonin, acetylcholine, and substance P, and the major inhibitory neurotransmitters are ATP, nitric oxide, and hydrogen sulfide (Fig.). Although there are serotoninergic neurons in the colon, the major amount of serotonin is not produced in the ENS but in the enterochromaffin cells, a type of enteroendocrine cells. On the other hand, serotonin secreted by enterochromaffin cells under the influence of various stimuli acts in a paracrine manner on the receptors of primary sensory cholinergic neurons of the ENS, leading to an increase in peristalsis [61]. It has been shown that ENS sensory neurons express 5-HT_{2B}, 5-HT_3, 5-HT_4, and 5-HT_7 serotonin receptors, the activation of which is accompanied by neuronal depolarization, transmission of impulses to interneurons and then to motoneurons, and culminates in the appearance of a wave of peristalsis [62]. Acetylcholine is a neurotransmitter of pre- and postganglionic neurons of the parasympathetic nervous system, as well as a large population of interneurons and motor neurons of the ENS. Interaction of acetylcholine with muscarinic cholinergic receptors on smooth muscle cells results in their depolarization and stimulation of contraction. Although no impairment of cholinergic neurotransmission in the circular layer of the colonic musculature was found in children with delayed intestinal transit, there was an impaired responsiveness to tachykinins, which are co-transmitters in the terminals of ENS motoneurons [63]. In rats, stimulation of the sacral nerve was associated with attenuation of loperamide-induced constipation symptoms by enhancing cholinergic influences on the smooth muscle layer [64]. Substance P belongs to the neuropeptide family and is expressed by ENS neurons [65]. Substance P has been shown to activate interstitial cells via the NK1 receptor, which has a potent stimulatory effect on intestinal contractile function [66]. A number of studies have shown that in pediatric patients with inert colon, there is a decrease in the density of nerve terminals expressing substance P [67, 68]. Under physiological conditions, suppression of colonic motility is mediated by VIP-ergic and purinergic neurons, as well as by neurons that synthesize gaseous transmitters such as nitric oxide and hydrogen sulfide. For example, hydrogen sulfide inhibits the pacemaker activity of interstitial cells by reducing the inward calcium current [69] and by antagonizing cholinergic and tachykinin neurogenic stimuli [70].

A significant number of primary afferent neurons of the ENS express calcitonin gene-related peptide (CGRP). In early experimental studies, CGRP was shown to suppress peristalsis and intestinal reflexes [71]. Later, however, there was compelling evidence that CGRP-mediated signaling is important for normal peristalsis and its stimulation after a meal. In addition, migraine patients treated with CGRP receptor antagonists and antibodies against CGRP often have secondary constipation [72].

Thus, the ENS is an integral part and a kind of executive link of the complex system of neurogenic regulation of colonic motility. ENS functions in close interaction with other regulatory cell types of the intestinal wall: interstitial cells, mast cells, as well as enteroendocrine and immune cells of the mucosa. The imbalance between prokinetic and inhibitory effects of the ENS in favor of the latter plays an important role in the pathogenesis of FC. The diversity of ENS neurotransmitters and corresponding receptors provides a good basis for the development of new drugs for the treatment of FC.

The role of intestinal hormones

The intestinal mucosa contains 10 subtypes of enteroendocrine cells that are chemosensitive, have a specific distribution pattern, and secrete various intestinal hormones into the blood, some of which affect the motility of the small and large intestine [73]. Motility stimulators include motilin, gastrin, ghrelin, and cholecystokinin. Motilin is secreted by M-cells in the small intestine, acts on a specific G-protein coupled receptor on smooth muscle cells of the gastrointestinal wall, and stimulates peristalsis [74, 75]. It is known that children with FC have significantly lower plasma levels of motilin compared to healthy children, although the occurrence of genetic polymorphisms that may determine the level of hormone production does not differ between the two groups [76]. Gastrin, produced by G-cells in the antrum of the stomach, also stimulates peristalsis, but mainly in the small

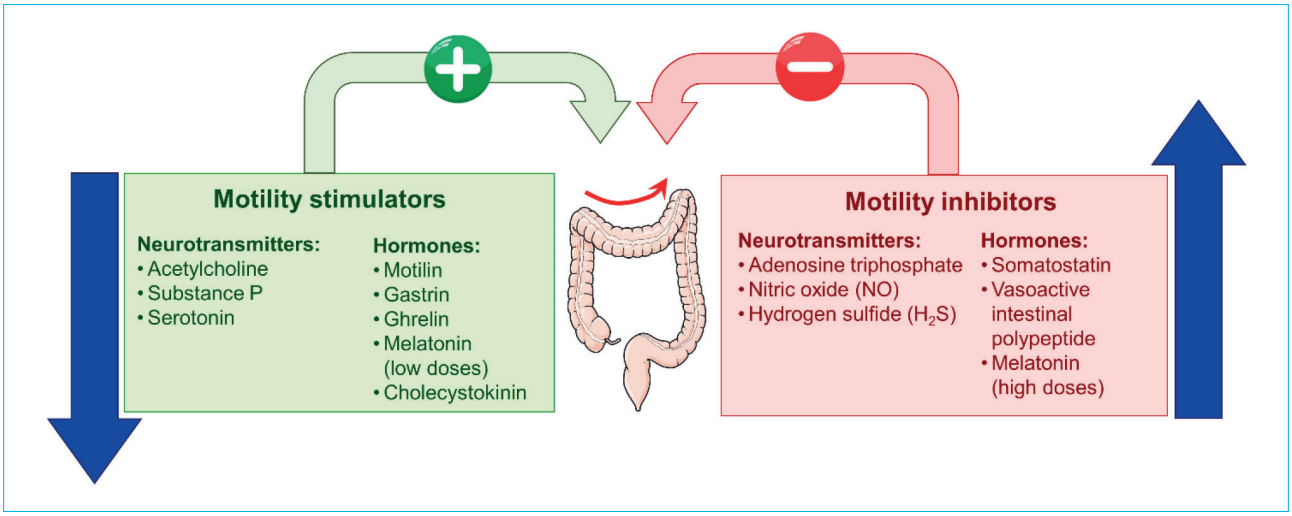

Figure. Imbalance of neurohumoral regulatory molecules as the basis for the pathogenesis of functional constipation. The pathogenesis of functional constipation can be associated with either a deficiency of stimulants or an excess of inhibitors, or, most often, a combination of these changes

Рисунок. Дисбаланс нейрогуморальных регуляторных молекул как основа патогенеза функционального запора. Патогенез функционального запора может быть связан либо с дефицитом стимуляторов, либо с избытком ингибиторов, либо, чаще всего, с сочетанием этих изменений

intestine [77]. Ghrelin, which is also produced in the stomach, plays an important role in the stimulation of intestinal motility. The mechanism of prokinetic action of ghrelin is related to activation of receptors on neurons of the lateral intermediate nucleus of the spinal cord in its lumbosacral region, which activates ENS neurons and causes propagating peristalsis [78]. Pharmacological activation of central ghrelin receptors improves the clinical course of constipation in Parkinson's disease and spinal cord injury [78]. Children with FC have lower blood levels of ghrelin, and a strong inverse correlation has been found between ghrelin concentration and intestinal transit time [79]. Cholecystokinin is produced by I-cells in the duodenum and jejunum. Most studies have shown that cholecystokinin stimulates intestinal motility via the response regulator SSK1, although the prokinetic effect of cholecystokinin is partially mediated by the peptide YY [80]. The effects of intestinal hormones that stimulate motility are normally counterbalanced by the effects of peristaltic inhibitors, which include somatostatin and vasoactive intestinal polypeptide (VIP). Somatostatin is secreted by D-cells in the stomach, pancreas and small intestine and further inhibits secretion and motility in the small and large intestine [81]. Data on blood somatostatin levels in patients with FC are currently lacking. The second most important hormonal inhibitor of intestinal motility is VIP, which is produced in the intestine, pancreas and brain. The effect of VIP on smooth muscle cells of the gastrointestinal wall is NO-dependent and is mediated by an increase in cytoplasmic cyclic guanosine monophosphate levels [82]. It has been repeatedly noted that the VIP levels in the colonic wall is reduced in chronic constipation [68, 83, 84], which may have an important pathogenetic significance. It should be emphasized that the attribution of some of the above-mentioned substances only to intestinal hormones is rather conditional, since, for example, VIP is both a hormone and a neurotransmitter. Although melatonin is not an intestinal hormone, there is evidence for its effect on colonic motility. Low doses of melatonin have a stimulating effect on motility, while higher doses inhibit it [85]. Thus, all hormones that affect gastrointestinal motility can be divided into stimulators and suppressors. Increased production of suppressors and/or deficiency of stimulators may play an important role in the mechanism of GI motility development.

Disorders of the intestinal microbiota

In recent years, due to the decreasing cost of sequencing methods, studies describing the composition of the intestinal microbiota in patients with FC compared to healthy individuals have begun to appear [86, 87]. Despite some discrepancies in the results of individual studies, in general, changes in the composition of the intestinal microbiota in FC are characterized by a decrease in the number of beneficial bacteria (e.g., *Lactobacilli* and *Bifidobacteria*) with a

simultaneous decrease in total biodiversity and an increase in the representation of pathobionts [88]. The work of T. Yu et al. attempted to characterize enterotypes in constipation with normal and delayed transit compared to controls [89]. It was shown that only patients with delayed transit had lower numbers of *Bacteroides* in the intestinal microbiota and lower plasma butyrate levels than controls. However, the available clinical data do not yet allow a clear interpretation of the results in terms of a causal relationship between changes in the microbiome composition and the occurrence of FC. It is possible that in some cases changes in the microbiota are secondary, for example as a result of increased proliferation of slowly renewing intestinal bacterial species with prolonged intestinal transit time. Of great interest are the molecular mechanisms of the influence of the intestinal microbiota on the colonic motor function. Several microbial metabolites act as mediators, of which bile acids (BAs), short-chain fatty acids (SCFAs), tryptamine, indoles and methane are the most actively discussed in this context. Since it is bacterial 7α-dehydroxylase that converts primary BAs to secondary BAs, the activity of the intestinal microbiota may influence the composition and levels of BAs in the intestinal lumen and blood. BAs activate the G protein-coupled bile acid receptor 1 (TGR5) on enterochromaffin cells of the colonic mucosa, resulting in the release of serotonin, which has a potent prokinetic effect through stimulation of 5-HT_3 and 5-HT_4 receptors on ENS neurons [90]. Tryptamine is produced from tryptophan by certain species of intestinal bacteria and binds to the aryl hydrocarbon receptor (AhR) on intestinal cells [91]. Since intestinal microflora can induce AhR expression in intramural neurons, this contributes to the enhanced effects of tryptamine on these neurons and activation of motility [92]. In addition, indole derivatives are formed from tryptophan under the action of intestinal microflora enzymes, including indoxyl sulfate, the main producers of which are bacteria of the genera *Bacteroides* and *Blautia*. Indoles activate TRPA1 on enterochromaffin cells and promote the serotonin release from these cells [93]. Thus, tryptophan metabolites, the levels of which depend on the composition of the microbiota, may have an important stimulatory effect on colonic peristalsis. The role of SCFAs in the regulation of colonic motility is currently poorly understood. There is evidence that SCFAs have a stimulatory effect on motility mediated by the release of glucagon-like peptide-1 and peptide YY from enteroendocrine cells [94]. The metabolites of the intestinal microflora include motility inhibitors, one of which is methane. Methanogenic bacteria, such as *Methanobrevibacter smithii*, are overrepresented in patients with FC [95], and the level of methane production, as determined by the hydrogen-methane breath test, is associated with intestinal transit time in patients with chronic constipation [96]. A course of antibiotic therapy directed against methanogenic bacteria resulted in improvement in patients with irritable bowel syndrome with constipation [96]. Intestinal dysbiosis associated with increased methane production and/or decreased production of BAs, SCFAs, and tryptophan metabolites may contribute to the development of FC.

Pathogenetic rationale for the efficacy of lactulose in functional constipation

Treatment and prevention of constipation is a change in lifestyle, including physical activity, correction of diet with the use of foods rich in fiber. If ineffective, drug therapy is carried out with the prescription of fiber, as well as laxatives. Special preference is given to osmotic laxatives, among them the most studied is lactulose.

Lactulose is a synthetic disaccharide composed of galactose and fructose. Lactulose is a unique drug due to the diversity of its effects and the multidirectional nature of its action. Lactulose is widely used in the treatment of FC and constipation associated with irritable bowel syndrome, diverticular disease, and cystic fibrosis [97]. In addition to its primary laxative effect, lactulose is used in hepatic encephalopathy because it reduces the formation and absorption of ammonia [98]. There are also studies demonstrating the benefit of lactulose in chronic kidney disease (by reducing uremic toxins) and diabetes mellitus [99, 100]. Data on the increase in calcium absorption with the use of lactulose determine its importance in increasing bone density, especially in pediatric and elderly patients [101].

Upon entering the digestive tract, the absorption of lactulose is less than 1 % of the administered dose, so in the colon, the majority of the laxative drug undergoes fermentation by the intestinal microbiota [101]. In this case, there is an increase in the osmotic effect with an increase in intraluminal gas formation, changes in the consistency and quantity of fecal masses, which increases intestinal peristalsis, causing a laxative effect in patients with constipation.

Lactulose has been shown to have a prebiotic effect, depending on the dose and the patient's constitution. Low doses (2–5 g per day) improve the intestinal microbiota by stimulating the growth of beneficial microflora. On average, the prebiotic nature of lactulose has been demonstrated at a dose of 10 g per day [101, 102]. An increase in the abundance of *Bifidobacterium* and

Lactobacillus with an increase in the production of beneficial metabolites (SCFAs) has been confirmed, while bacteria of the genera *Prevotella* and *Ruminococcus*, as well as some pathogenic strains, were inhibited [101, 103]. For example, low-dose lactulose supplementation improves the colonic microbiota in patients with chronic liver disease, including the cirrhotic stage, by reducing *Clostridium difficile* [101]. Changes in the microbiome after lactulose administration have been observed in patients with different body mass indexes. In normal or underweight patients, lactulose treatment promotes the growth of *Bacteroides* and *Parabacteroides*, with decreased growth of these microorganisms in obese individuals. Growth of *Faecalibacterium* spp. and *Dorea* spp. was observed in obese patients in contrast to normal weight patients [101]. In a recent study by S.L. Collins et al. (2018), the disaccharide lactulose was also found to prevent vaginal dysbiosis by promoting the growth of lactobacilli [103].

The use of lactulose along with lifestyle changes improves the course of FC and improves the quality of life of patients. The recommended dose of lactulose for the treatment of constipation is 15–45 mL per day, the maintenance dose is 15–30 mL per day. The effect occurs within a few days, but if there is no effect, it is recommended to increase the dose of the drug [97].

Thus, lactulose has pleiotropic effects, which makes the prescription of this drug effective and safe not only as a treatment for constipation, but also to restore the microbiome of the colon and, as a consequence, to prevent diseases of various organs and systems.

Conclusion

Functional constipation is a classic multifactorial disease, in the etiology of which adverse influences of genotype are combined with multiple acquired risk factors. The main pathogenetic mechanisms of FC associated with neurogenic dysregulation include dysfunction of the gray and white matter of the brain, as well as an increase in the tone of the sympathetic nervous system with a concomitant decrease in the influence of cholinergic nerves innervating the colon. A key role in the development of functional constipation belongs to a decrease in the pool of interstitial cells that play the role of intestinal pacemakers. Changes in the ENS are associated with a relative excess of the contribution of inhibitors (ATP, NO, H_2S) and a decrease in the activity of neurons stimulating colonic motility (acetylcholine, substance P, serotonin). Changes in the composition of the intestinal microbiota may also contribute to functional constipation, which is associated with an impaired profile of metabolites produced by intestinal bacteria. A better understanding of the molecular mechanisms of functional constipation may provide the basis for new effective treatments of this common pathology.

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