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[1]Oliinyk T. M., [2]Rozova K. V., [3]Kovalchuk O. I., [4]Raskaliei T. Ya., [4]Raskaliei V. B., [1]Khmelnytska Yu. K.

THE PARTICIPATION OF HUMORAL MECHANISMS IN THE REGULATION OF THE CONTRACTILE ACTIVITY OF SMOOTH MUSCLE TISSUE OF THE INTESTINE

[1]National University of Physical Education and Sports of Ukraine (Kyiv, Ukraine)
[2]Bogomoletz Institute of Physiology of National Academy of Sciences of Ukraine (Kyiv, Ukraine)
[3]Taras Shevchenko Kyiv National University (Kyiv, Ukraine)
[4]Bogomolets National Medical University (Kyiv, Ukraine)
tanyna1980nmu@gmail.com

The large intestine is the most distal part of the alimentary canal, the main function of which is to prepare undigested food residues for removal from the body and evacuate them to the outside. This is ensured by the implementation of the contractile function of the smooth muscle tissue of the intestinal wall, which is characterized by rhythmic phasic, tonic and high-amplitude propulsive contractions. The amplitude and frequency of these contractions are determined by the complex interaction of complex nervous, humoral and myogenic regulation mechanisms. Nervous effects on smooth muscle tissue are realized due to the implementation of metasympathetic enteric motor reflexes and innervation of extra-organ nerves. They add up with numerous and complex humoral effects. The stimulating effect on the motor function of the intestine is determined by the influence of purines and some regulatory peptides, and serotonergic and tachykininergic effects play a modulating role in this complex regulatory process. The final point of application of humoral effector effects is the secretion of acetylcholine by cholinergic excitatory motoneurons and the release of nitric oxide and vasoactive intestinal peptide. It is worth noting that, in addition to the above, a number of other endogenous biologically active substances (short-chain fatty acids, neurotrophic factors, sex hormones, histamine, prostaglandins, etc.) take part in the modulation of the contractile activity of the smooth muscle tissue of the colon. However, the deep nature of the mechanisms that exert regulatory effects on the contractile activity of the smooth muscles of the colon wall is still not sufficiently understood.

Key words: *motor function, contractile activity, smooth muscle tissue, regulation.*

Connection of the publication with planned research works.

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Introduction.

The motor function of the gastrointestinal tract (GIT) is one of the important components in the implementation of the processes of digestion and further assimilation of the nutrients of the food. The coordinated activity of the smooth muscle cells of the wall of the alimentary canal ensures the mechanical processing of chyme (its grinding, mixing) with its further advancement through the alimentary tract in strict accordance with the periods of secretory activity and chemical processing of food products in certain departments of the gastrointestinal tract [1, 2].

The consistent and coordinated movement of portions of chyme in the small and large intestines is determined by the contractile activity of the muscle layer of their wall. Contractions of smooth muscle cells of the intestinal wall ensure the motor function of the large intestine as an organ. The motor function ensures the deposition of ingested food in the intestine as a result of the receptor relaxation of smooth muscle tissue, and also carries out the mixing of chyme with the components of digestive juices in the area adjacent to the mucous membrane of the intestine, ensures the movement of the contents of the intestines to the exit from the rectum, as well as the evacuation of portioned the contents of the rectum to the outside [3, 4].

The aim of the study.

To systematize information from the scientific literature on the peculiarities of the humoral mechanisms of regulation of the motor function of the large intestine.

Main part.

Motility disorders are one of the most common symptoms of gastrointestinal tract pathology. With some degree of convention, they can be divided into primary and secondary. Primary motility disorders are associated with organic pathology (developmental abnormalities, acquired diseases, etc.), while secondary (functional) disorders are determined by disorders of nervous, humoral, metabolic, and local regulation of the contractile activity of the smooth muscle tissue of the intestinal wall. Disturbances in the regulation of motor activity of the large intestine can be etiological factors in the occurrence of such pathological phenomena as irritable bowel syndrome, diarrhea, constipation, etc [5, 6]. Functional disorders of the motor function of the intestine (dyskinesia) can be the only manifestation of the pathology of the functions of the gastrointestinal tract, but are more often accompanied by a violation of secretion, digestion (maldigestion), absorption (malabsorption), the state of the microflora (dysbacteriosis), the activity of the local link of immune protection, etc [7, 8]. The progression of one functional disorder inevitably leads to a violation of the remaining functions of the gastrointestinal tract.

The motor activity of the smooth muscle tissue of the intestinal wall during digestion, in accordance with the general course of the digestive process and the conditions created inside the intestine, is regulated by a complex integral combination of complex central and peripheral nervous and humoral factors, as well as due to the implementation of local (myogenic) mechanisms

[9]. Nervous influences, which are realized through extra-organ nerves and thanks to the implementation of metasympathetic enteric motor reflexes, add up to numerous and complex humoral effects [10].

The contractile activity of smooth muscle cells of the intestinal wall is determined by the multilevel interaction of regulatory mechanisms. However, despite the many-year history of research on this issue, there are still a number of gaps in the structure of morphological knowledge in the understanding of how the input data of nervous, humoral and myogenic mechanisms are combined into a single integrated complex effect with the aim of optimal regulation of the motor function of the intestines.

The contractile activity of the smooth muscle tissue of the intestinal wall is under the control of the structural and functional syncytium of excitable formations. The morphological elements of this syncytium are peculiar «rhythm drivers» (pacemaker interstitial cells of Cajal) [11-13] and a diffusely scattered network of excitatory cells (neurons, enterochromaffin cells, other secretory cells). The functioning of the above nerve formations is sensitive to the influence of biologically active substances of local and remote action [14, 15].

Humoral regulation of the motor function of the intestines is carried out both at the systemic level and due to the production of various intestinal hormones, which ensure the coordinated work of different departments of the digestive tract, turning them into a single «technological conveyor». Violation of the secretion of locally produced intestinal peptides, other biologically active substances, as well as their relationship with nervous regulation, leads to involvement in the emergence and development of dysfunctional processes in other departments of the gastrointestinal tract. Local regulation of the motility of the gastrointestinal tract is carried out due to the influence of numerous factors of humoral regulation (intestinal peptides, prostaglandins, kinins, nitric oxide, histamine, etc.) [16, 17] on pacemaker cells and directly on smooth myocytes. The smooth muscle cells of the intestinal wall contain various specific receptors: cholinergic, dopamine, opiate, 5-HT4 receptors, etc., thanks to which consistency is achieved in the work of the gastrointestinal tract and the passage of its contents is carried out.

One of the main regulators of the motor function of the intestines is the hormone motilin, which is synthesized in the upper part of the duodenum [18]. Receptors to motilin were found on neurons of the enteric nervous system. Motilin has a vasodilatory effect, but its leading function is the launch of migrating motor complexes. It is assumed that it plays the role of the main regulator of gastrointestinal motility in the breaks between meals [19]. Peripheral administration of motilin stimulates the secretion of pepsin, the activation of contractions of the gallbladder, and the start of the secretion of pancreatic enzymes.

Serotonin (5-hydroxytryptamine), which is 90% synthesized in the gastrointestinal tract by enterochromaffin cells (EC cells, Kulchytsky cells), serves as one of the important regulators of the contractile activity of smooth myocytes of the intestinal wall [20, 21]. Serotonergic neurons are widely represented in the enteric nervous system. They are mainly localized in the structure of Auerbach's nerve plexus of the human intestine [22]. Serotonergic preganglionic fibers are located mainly in the intermuscular nerve plexus. Some neurons of the prevertebral ganglia are also serotonergic [21-23].

The results of morphological studies prove that the synthesis and secretion of serotonin is an intermediate stage in a multi-level complex of activating stimuli of the motor function of the intestines [23]. An increase in the secretion of serotonin with increasing pressure inside the intestine serves as evidence that the release of this biologically active factor is activated by mechanical deformation, as well as chemical stimulation of Kulchytsky cells [24, 25]. The numerous effects of serotonin on the activity of the gastrointestinal tract are determined by their affinity for specific 5-HT receptors [26]. There are seven types of similar receptors in the structures of the alimentary canal. 5HT1A, 5-HT3 and 5-HT4 receptors are localized on enteric neurons [27-29]. The contractile activity of the proximal parts of the colon is determined by the interaction of serotonin with 5-HT1 receptors; in the middle and distal sections of the colon, serotonin acts on both 5-HT1 and 5-H2 receptors [27, 30, 31].

Serotonin receptors of the 5-HT2 subtype are more often localized in the interenteric plexus and the longitudinal muscle layer of the intestinal wall; in the circular muscle layer, on the contrary, they occur in the smallest amount. An interesting fact is that the isoform of the serotonin receptor 5-HT4D is present only in the structure of the intestine and is not found in other organs [32, 33]. At the same time, the activation of 5-HT4 receptors can lead to both an increase and inhibition of the motor activity of the large intestine.

Some scientists are of the opinion that neuronal cholinergic pathways are involved in increasing the motor function of the intestine [34, 35], while inhibition of the contractile activity of the intestine is mediated by a direct effect on smooth muscle cells with the participation of blocking nitrergic pathways [36, 37]. Activation of 5-HT4 receptors on myenteric excitatory cholinergic neurons of the colon promotes the secretion of acetylcholine from them. Blockade of these receptors on the circular smooth muscle cells of the intestine leads to its relaxation [38, 39].

The synthesis and release of serotonin largely determines the implementation of the peristaltic reflex [40, 41], the implementation of which is the summation of the «ascending excitatory» and «descending inhibitory» components [41, 42]. It is characteristic of serotonin to excite myenteric neurons [43, 44]. Activation of 5-HT3 and 5-HT4 receptors leads to activation of both components of the peristaltic reflex. This, in turn, is the functional basis of propulsive activity of the intestine. The peristaltic reflex is closed at the level of the enteric nervous system with the participation of non-adrenergic non-cholinergic inhibition mechanisms.

Initiation of 5-HT4 receptors also takes place with the participation of tachykininergic pathways, which account for approximately one third of the number of myenteral neurons [43, 44]. Tychikinin peptides (substance P, neurokinins A and B) are important mediators of myenteral neurons [45, 46]. The main effect of substance P and other tachykinins is to stimulate the contractile activity of the gastrointestinal tract, and

substance P in combination with acetylcholine is one of the main excitatory neurotransmitters for muscle contraction processes.

Modulation of the contractile function of smooth muscle cells of the intestinal wall is mediated by the binding of tachykinins to specific receptors on the surface of these cells. Tachykinins can interact with other enteric transmitters in the physiological control of motor activity of the gastrointestinal tract [47]. Tachykininergic pathways are involved in the stimulation of motor activity of the digestive tract by agonists of 5-HT_4 receptors [48]. Thus, the main activating factor in the regulation of contractile activity of smooth muscle cells of the intestinal wall is a synergistic combination of tachykininergic and serotonergic factors.

The regulation of the motor function of the intestines with the participation of regulatory peptides is interesting. Regulatory peptides are distinguished by a wide spectrum of physiological activity, capable of manifesting both distant systemic effects, and can affect the main functions of the alimentary canal in a paracrine manner [49, 50]. Each of the regulatory neuropeptides causes several effects at once, some of which act as regulators and modulators for the synthesis of other peptides. A specific feature of their action is the fact that the effects of regulatory peptides, which are secreted by peptidergic fibers of the enteric nervous system, may differ in their mechanism of action from the effects of gastrointestinal hormones and parahormones of a similar chemical nature [50].

The effects of regulatory peptides depend not only on the concentration, but also on the mechanism of activation of the corresponding function [49, 51]. The functional role of neuropeptides in the regulation of the contractile activity of the colon has been studied quite well, so we consider it necessary not to focus our attention on it.

The NO-ergic system plays a significant role in the regulation of the motor function of the large intestine and in the possibility of its interaction with the departments of the enteric and even the central nervous system [52, 53]. The action of nitric oxide differs from the mechanism of action of real classic and tissue hormones, as it bypasses receptors and directly regulates the contractile activity of smooth muscle cells, diffusing through the plasma membrane. The effector response of the cell to the influence of nitric oxide consists in the activation of potassium channels, suppression of the permeability of calcium channels and a decrease in the sensitivity of smooth muscle cells to calcium ions, which causes their relaxation [54, 55]. In healthy people, nitric oxide reduces the tone of the colon [56].

Short-chain fatty acids affect local and distant motility of the gastrointestinal tract through mechanisms that are not fully understood. In the large intestine, where they are produced thanks to intestinal microflora, short-chain fatty acids suppress peristaltic activity and are able to activate tonic motor function [57, 58]. Under the conditions of their presence in the terminal part of the ileum, they are able to cause propulsive contractions of the intestinal wall. Through a humoral pathway that probably involves the release of polypeptide YY, short-chain fatty acids from the ileum and colon alter upper motility, inducing relaxation of the proximal stomach and lower esophageal sphincter, thereby reducing gastric emptying [57, 59]. One of the characteristic features of the effects of short-chain fatty acids is the dose dependence of motor reactions of the gastrointestinal tract. One of the presumed physiological functions of the motor effects of short-chain fatty acids may be maintenance of the physicochemical balance of the luminal environment in the distal parts of the large intestine. The participation of these factors in the joint processes with other humoral factors in the regulation of the motility of the proximal parts of the intestines cannot be excluded [60, 61].

Conclusions.

We consider it necessary to note that the modulation of the contractile activity of the smooth muscle cells of the colon wall, in addition to those already mentioned, involves many other endogenous biologically active substances, such as catecholamines, neurotrophic factors, sex hormones, prostaglandins, oxytocin, etc. However, the available body of biological knowledge is still far from ideal regarding the specificity of the deep mechanisms of neurohumoral regulation of the motor function of the large intestine. Accordingly, this actualizes the emergence of new fundamental research on the specified problem.

Prospects for further research.

An experimental study of the intracellular influence of biologically active substances on the contractile activity of the smooth muscle tissue of the large intestine is promising.

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УЧАСТЬ ГУМОРАЛЬНИХ МЕХАНІЗМІВ У РЕГУЛЯЦІЇ СКОРОТЛИВОЇ АКТИВНОСТІ ГЛАДКОЇ М'ЯЗОВОЇ ТКАНИНИ КИШЕЧНИКА

Олійник Т. М., Розова К. В., Ковальчук О. І., Раскалей Т. Я., Раскалей В. Б., Хмельницька Ю. К.

Резюме. Товста кишка людини виконує кілька важливих функцій, включаючи ферментацію поживних речовин, поглинання води та електролітів, а також зберігання та своєчасне видалення фекального вмісту. Ці функції вимагають складної, високо інтегрованої та регульованої активності м'язів товстої кишки, яка має вирішальне значення для підтримання здоров'я та якості життя. Зміни моторної функції товстої кишки беруть участь у генезі симптомів, пов'язаних з такими порушеннями, як функціональна діарея, запор, синдром подразненої кишки тощо. Дослідження функціональної активності гладеньких м'язів товстої кишки значно еволюціонували від міограм м'язових смужок до складних математичних і комп'ютерних моделей просторово-часового відображення рухової та електричної активності кишки і досить добре вивчені. Скоротлива здатність гладенької м'язової тканини стінки товстої кишки визначається складною взаємодією комплексу регуляторних механізмів, серед яких – міогенні механізми, комбіновані місцеві впливіви нейронів ентеральної нервової системи, кишкових нейромедіаторів, нейромодуляторів та гормонів, системними ефектами структур ЦНС тощо. Структурні морфологічні елементи мережі вищеперелічених утворень складають злагоджений функціональний синцитій, аспекти діяльності якого вивчаються на молекулярному, внутрішньоклітинному, тканинному та інших рівнях. Водночас, не дивлячись на значні успіхи сучасної науки у вивченні морфо-фізіологічних аспектів моторної функції товстої кишки, до сих пір залишається багато недосліджених питань стосовно того, які медіатори, циторецептори і внутрішньоклітинні сигнальні молекули в циркулярних і повздовжніх гладеньких м'язах і кишкових нейронах можуть опосередковувати нормалізацію означеної функції при розладах моторики. Розуміння глибинних механізмів регуляції моторної функції гладкої м'язової тканини кишечника наразі ще надто далекі до вичерпного знання і потребують більш поглибленого вивчення.

Ключові слова: моторна функція, скоротлива активність, гладенька м'язова тканина, регуляція.

THE PARTICIPATION OF HUMORAL MECHANISMS IN THE REGULATION OF THE CONTRACTILE ACTIVITY OF SMOOTH MUSCLE TISSUE OF THE INTESTINE

Oliinyk T. M., Rozova K. V., Kovalchuk O. I., Raskaliei T. Ya., Raskaliei V. B., Khmelnytska Yu. K.

Abstract. The human colon performs several important functions, including the fermentation of nutrients, the absorption of water and electrolytes, and the storage and timely elimination of fecal contents. These functions require complex, highly integrated, and regulated colonic muscle activity that is critical for maintaining health and quality of life. Changes in the motor function of the large intestine are involved in the genesis of symptoms associated with such disorders as functional diarrhea, constipation, irritable bowel syndrome, etc. Studies of the functional activity of the smooth muscles of the large intestine have significantly evolved from myograms of muscle strips to complex mathematical and computer models of spatio-temporal mapping of motor and electrical activity of the intestine and are quite well studied. The contractile ability of the smooth muscle tissue of the colon wall is determined by the complex interaction of a complex of regulatory mechanisms, including myogenic mechanisms, combined local effects of neurons of the enteric nervous system, intestinal neurotransmitters, neuromodulators and hormones, systemic effects of CNS structures, etc. The structural morphological elements of the network of the above formations make up a coordinated functional syncytium, the aspects of whose activity are studied at the molecular, intracellular, tissue and other levels. At the same time, despite the significant successes of modern science in studying the morpho-physiological aspects of the motor function of the large intestine, there are still many unexplored questions regarding which mediators, cytoreceptors and intracellular signaling molecules in circular and longitudinal smooth muscles and intestinal neurons can to mediate the normalization of the specified function in motility disorders. The understanding of the deep mechanisms of regulation of the motor function of intestinal smooth muscle tissue is currently still far from comprehensive knowledge and requires more in-depth study.

Key words: motor function, contractile activity, smooth muscle tissue, regulation.

ORCID and contributionship:
Oliinyk T. M.: https://orcid.org/0000-0003-4685-1479 ABC
Rozova K. V.: https://orcid.org/0000-0002-6266-4617 BCD
Kovalchuk O. I.: https://orcid.org/0000-0002-6311-3518 CDE
Raskaliei T. Ya.: https://orcid.org/0000-0002-6737-2381 DEF
Raskaliei V. B.: https://orcid.org/0000-0002-5240-6278 DEF
Khmelnytska Yu. K.: https://orcid.org/0000-0002-0231-1879 BD

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Corresponding author
Oliinyk Tetyana Mykolaivna
National University of Physical Education and Sports of Ukraine
Ukraine, 02000, Kyiv, 1 Fizkultury str.
Tel.: +380672580937
E-mail: tanyna1980nmu@gmail.com

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Ostrovska S. S., Abramov S. V., Baibakov V. M., Antonova O. V., Markhon N. O., Khmel O. S., Konovalova O. S.

ANTIOXIDANT EFFECTS OF SELENIUM IN THE TOXIC EFFECT OF CADMIUM (REVIEW OF FOREIGN LITERATURE)

European Medical University (Dnipro, Ukraine)
s.ostr2018@gmail.com

Cadmium (Cd) is one of the main toxic and most widespread heavy metals (HM) affecting public health. Work with Cd pigments, plastic, glass, metal alloys and electrode material in nickel-cadmium batteries, as well as non-occupational exposures such as food, water and cigarette smoke, causes Cd to be absorbed from the environment into the body through the pulmonary and enteric routes, which affects the liver, kidneys, vascular, nervous, reproductive and other organ systems. Scientific studies have shown that the basis of Cd polytropic toxicity is oxidative stress (OS) due to excessive formation of reactive oxygen species (ROS), which leads to cell dysfunction, necrosis or apoptosis. Using natural compounds with antioxidant properties is relevant and essential because natural biologically active compounds are safe and have a positive anti-inflammatory and anti-tumour effect on the body, reducing the adverse effects of toxicants, including Cd. Dietary antioxidants, including selenium (Se), are ingested with food and have an antagonistic effect against Cd-induced carcinogenesis and epigenome disorders, manifested in the mitigating impact of pathological changes. Se does not occur in nature in its pure form, only in the form of any compounds (most often sulfides). Its content in various foods is given. The leader in Se content is Brazil nuts, but the fruit's chemical composition depends on the tree's age, which can live up to 500 years. Se supplementation has proven to be effective against drug side effects, but the narrow range between therapeutic and toxic doses of Se, as well as the dependence of its impact on the form used, dose and method of treatment, makes the choice of an effective supplement a difficult issue. The most recent research concerns its nanoparticles (SeNP), which are a promising new food additive due to their ability to gradually release Se. When ingested internally, SeNP and Si-SeNP demonstrate anti-cancer and antimicrobial properties that can contribute to human health not only as food supplements but also as therapeutic agents.

Key words: *cadmium, oxidative stress, selenium as an antioxidant, therapeutic effects.*

Connection of the publication with planned research works.

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Introduction.

The problem of environmental pollution by toxic substances, including heavy metals, is a growing concern for scientists and the population of different countries. Numerous studies have shown a correlation