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COMMON NEUROHORMONAL MECHANISMS OF DEVELOPMENT, POSSIBILITIES OF THEIR RATIONAL THERAPY OF ENTERAL FAILURE AND METABOLIC SYNDROME

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Abstract. Common neurohormonal mechanisms in the development of enteropathy and metabolic syndrome (MS). MS is characterized by an increase in visceral fat mass, decreased sensitivity of peripheral tissues to insulin and hyperinsulinemia, which cause disorders of carbohydrate, lipid, purine metabolism and hypertension. This is associated to some extent with the presence of common neurohormonal mechanisms in the development of enteropathy and MS. The paper gives the physical, laboratory and instrumental methods for identifying SI dysfunctions in patients with MS. Therapy for the latter is of particular interest in the context of SB functional recovery. The authors discuss the possibilities of enteropathy therapy in patients with MS; thus there is not only SI functional recovery, but also improved overall metabolic processes.

Keywords: review, metabolic syndrome, small bowel function, enteropathy.

Introduction. Metabolic syndrome (MS) is a complex of deep metabolic disorders accompanied by abdominal obesity, arterial hypertension (AH), dysliepidemia, type 2 diabetes mellitus (DM-2) or impaired glucose tolerance and associated insulin resistance (IR) [1]. The clinical significance of disorders united by the framework of this syndrome lies in the fact that their combination significantly accelerates the development of atherosclerotic vascular lesions, which, according to WHO experts, occupy the first place among the causes of death and disability of the population of industrialized countries. Its prevalence is 2 times higher than DM, and in the next 25 years it is expected to increase the growth rate of MS by 50% [2].

The problem of MS is multidisciplinary and is most acute in cardiology, endocrinology and gastroenterology [3]. As a result of complex studies, L.B. Lazebnik and L.A. Zvenigorodskaya [4] revealed pathological changes in the esophagus in 72% of MS patients, liver and biliary tract diseases in 64%, pathological changes in the stomach and duodenum in 66%, pancreatic (pancreatic) diseases in 18%, colon diseases in 74%. Recently, there has been great interest in studying the role of the small intestine (SI) in the development of MS, which is one of the central organs in the regulation of metabolism [5, 6]. At the same time, the features of hydrolysis-resorption disorders in the SI remain insufficiently studied, little attention is paid to the state of the motor-evacuation function of the gastrointestinal tract

(gastrointestinal tract) and correction of violations of the functional state of the SI in MS.

Common neurohormonal mechanisms in the development of enteropathy and MS. MS is characterized by an increase in visceral fat mass, decreased sensitivity of peripheral tissues to insulin and hyperinsulinemia, which cause disorders of carbohydrate, lipid, purine metabolism and hypertension [7]. According to the recommendations of the International Diabetes Federation (2005), the mandatory criterion for MS is the central type of obesity — a waist circumference of more than 102 cm in men, more than 88 cm in women for the Caucasian race [8]. The main cause of obesity is an energy imbalance between an excess of energy intake into the body in the form of food components and its reduced expenditure with low motor activity [9]. The withdrawal of digestive substances from the external environment and their entry into the internal environment of the body is mainly provided by SI [10]. Secretion, cavity and membrane digestion, absorption, adsorption, active transport, diffusion, exudation, insorption, exorption, exfoliation, segmental and peristaltic movements of the intestine of various lengths and spike activity occur here. The process of assimilation of nutrients in the SI can be represented as three successive stages: oral digestion, membrane digestion, absorption of the final products of hydrolysis — glucose, amino acids, fatty acids, cholesterol (Ch) and monoglycerides, followed by the resynthesis of triglycerides in the enterocyte [11, 12].

The regulation of complex processes of digestion and absorption in the SI is carried out by the central nervous system and the endocrine glands, as well as gastrointestinal hormones. Nervous and hormonal effects interact. To understand the essence of MS, it is important to study the mechanisms of perception and transformation of hormonal signals entering the receptor apparatus of the cell [13]. In the body of a MS patient, hormonal imbalance is observed simultaneously with the accumulation of visceral fat, namely, an increase in the level of insulin, norepinephrine, cortisol, testosterone and androstenedione in women, as well as a decrease in the level of progesterone, somatotropic hormone, testosterone in men [13, 14]. One of the important clinical signs of MS is the presence of hypercorticism. The reasons for the development of abdominal obesity include the age over 30 years, when the activity of the hypothalamus, the adrenocorticotropic hormone system increases with the release of cortisol, which leads to prolonged and excessive secretion of it, accompanying the appropriate distribution of fat. It is known that cortisol stimulates cortisol-dependent lipoprotein lipase on the capillaries of fat cells

of the upper half of the trunk, abdominal wall and visceral fat. As a result, fat deposition increases, adipocyte hypertrophy and characteristic abdominal obesity develop. Abdominal obesity and dyshormonosis are one of the key moments in the development of MS [13, 15].

At the same time, the same hormones take part in the regulation of digestion and absorption processes in the SI [16, 17]. Thus, glucocorticoids have a diverse effect on digestive processes in the gastrointestinal tract: they negatively affect the mitotic process and DNA synthesis in the gastrointestinal tissues, support the inflammatory process [18] and potentiate the development of atrophy in the mucous membrane (MM) of SI [19, 20]. The adrenal cortex—SI connection is not one-sided. Our studies [21, 22] have shown that there are regulatory effects on the adrenal glands of the gastrointestinal tract, including SI, and pituitary-adrenal relationships can change with intestinal lesions.

The root cause that unites all the components of MS is insulin resistance (IR), as a result of which the biological effect of insulin on body tissues decreases [23]. Literature data on the effect of insulin on glucose absorption in the intestine are contradictory. However, most researchers believe that insulin increases the rate of glucose absorption in the SI. The mechanism of this phenomenon is still poorly understood. There is evidence of the direct effect of insulin on the intestine [24]. A number of authors [25, 26] associate its effect on absorption with a change in the periodic motor-secretory activity of TC, an increase in the activity of Na, K-ATPase and the level of glycogen in the intestinal wall. Another mechanism of insulin action is carried out by activating transporters directly in enterocyte membranes, as well as increasing the activity of sucrose and phosphofructokinase [21, 27]. The study of the relationship between fat absorption and insulin levels showed that in the control group there is a positive correlation between the amount of incoming fat from the intestine into the blood and the level of insulin, i.e., against the background of an increase in insulin content, the period of maximum fat accumulation in the blood was reduced and vice versa [22]. It is especially important that the development of hyperinsulinemia leads to a number of pathological disorders that form vicious circles. Prolonged hyperinsulinemia caused by MS contributes to the narrowing of the lumen of arterioles due to the proliferation of their smooth muscle cells, which plays a significant role in the disruption of blood supply, primarily in the liver, pancreas, stomach and intestines, rich in vessels. This, in turn, is fraught with the development of dystrophic and atrophic changes [28]. Stellate cells existing not only

in the liver, but also in the pancreas, lungs, kidneys, intestines [29] are activated, which is naturally accompanied by the development of fibrosis.

In recent years, there has been great scientific and practical interest in studying the role of gastrointestinal hormones in the regulation of insulin secretion, and consequently in the regulation of glucose homeostasis in the human body. In this regard, it should be emphasized that there is evidence in the literature indicating the important role of such gastrointestinal hormones as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (ITP). These hormones are called "incretins", and their effect, which leads to an increase in glucose-dependent insulin secretion by the β-cells of the pancreas, is called the "incretin effect" [30]. It has been proven that after taking glucose, there is a more pronounced increase in insulin secretion compared to that observed after intravenous glucose infusion, accompanied by a similar increase in blood glucose (BG) [31]. These results indicated that not only the interaction of glucose with β-cells of the islets of Langerhans, but also intestinal factors are involved in stimulating insulin secretion [32]. Currently, it is believed that postprandial insulin secretion is approximately 70% due to the potentiating effect of incretins produced by endocrine-like gastrointestinal cells [33].

Currently, the concept of MS is expanding. It began to include hyperandrogenism in women, hyperleptinemia, leptin resistance, myocardial hypertrophy, increased levels of free fatty acids in the blood, sleep apnea syndrome, activation of the sympathetic part of the autonomic nervous system (C-ANS), the presence of oxidative stress, proinflammatory status, prothrombotic status: increased fibrinogen content in the blood, increased adhesive and aggregation platelet abilities, increased activity of plasminogen activator inhibitor-1 [34]. It is especially important that the development of hyperinsulinemia leads to a number of pathological disorders that form vicious circles. For example, hyperinsulinemia increases the tone of C-ANS, which consistently leads to persistent pathological vasoconstriction and a decrease in volumetric blood flow in the capillaries of skeletal muscles — the causes of the progression of IR and further growth of hyperinsulinemia [35]. It has been proven that central obesity also causes activation of C-ANS and baroreflective function [36]. Overeating leads to the activation of C-ANS to maintain energy balance at the cost of all the negative consequences of hypersympathicotonia [35]. Consequently, an increase in the activity of C-ANS can be attributed to a group of reasons leading to the formation of IR. The analysis of the Kerdo index showed [37] that sympathetic tone prevails in 86% of patients with MS. Sympathetic nerve fibers coming out of the segments of the IX—X spinal cord and from the synapses of the

abdominal and mesenteric ganglia inhibit the motor activity of the SI. Electroenterography revealed that 40 minutes after a standard breakfast, 80% of patients had impaired motor function of the SI. At the same time, hypotonic dyskinesia of SI significantly prevailed against the background of a decrease in the frequency of contractions per minute (in 71.5% of patients). The electrical activity of the duodenum (duodenum) after eating (in the postprandial period — PPP) in 70% of patients is low, which indicates an insufficient response of the duodenum to food stimulation in MS. The ratio of the doudenum/jejunum in the food phase in 60% of patients with MS has low values, indicating a decrease in evacuation from the WPC to the jejunum in the PPP. There is a discoordination of motor skills between the ileum and colon, which worsens after food stimulation. The coefficient of rhythm of the duodenum in 40% of patients was reduced in both phases of the study, in 50% it was not changed and only in 10% of cases it was increased. A significant decrease in the rhythm of contractions is observed at the frequencies of the jejunum, iliac and colon both on an empty stomach and in the PPP, which indicates a weakening of the propulsive contractions of the intestine in patients with MS [38].

The functional organization of the digestive system, including the coupling of motility, secretion and absorption, is regulated by a complex system of nervous and hormonal mechanisms [39]. To clarify the role of hormonal factors in disorders of hydrolysis and resorption in SI in MS patients, correlation studies were conducted between hormones and indicators of the functional state of TC. An inverse relationship was found between oral digestion and cortisol levels ($r=-0.38$; $p<0.05$) and insulin ($r=-0.26$; $p<0.05$), i.e. against the background of an increase in the level of cortisol and insulin, there is an inhibition of the processes of oral digestion in the intestine. A direct relationship was found between membrane digestion and insulin levels in the blood ($r=0.49$; $p<0.05$), i.e. unidirectional increase in membrane digestion and insulin levels. There was no relationship between glucose and D-xylose resorption and cortisol levels. A moderate direct relationship was found between the level of insulin and glucose and D-xylose absorption ($r=0.58$; $p<0.05$). With an increase in cortisol levels, there is a decrease in the rate of evacuation from the duodenum ($r=-0.44$; $p<0.05$) and a decrease in the electrical activity of the SI ($r=-0.33$; $p<0.05$) [38]. These data are consistent with the results of other studies [21, 40], which showed that an excess of endogenous corticosteroids in the body has a relaxing effect on the smooth muscles of organs, causing a decrease in their motor skills, the amplitude of contractions, a decrease in pressure in the sphincter area. In addition, the

role of activation of C-ANS, which is a sign of MS, cannot be excluded in the violation of the motility of SI [1, 41, 42].

A decrease in the rate of passage of food chyme by SI in MS patients contributes to a violation of the ratio of nutrients in the composition of the flow, thereby changing the rate of their transfer from the enteral to the internal environment, exacerbating metabolic disorders. Against the background of suppression of abdominal and parietal digestion, an increase in glucose and D-xylose resorption was found, coupled with a decrease in electrical activity and a slowdown in evacuation by SI in the PPP. With hypomotor dyskinesia of SI, conditions are created in the SPP for a longer exposure of nutrients in the enteral environment. This contributes to an increase in the level of lipids and BG (mainly due to monosaccharides), which, against the background of IR, exacerbates the formation of abdominal obesity in patients with MS [37, 38].

The intestine performs not only hydrolytic and resorption functions, but also endocrine, immune, metabolic and mechanical barrier functions, the preservation of which is a prerequisite for maintaining homeostasis of the internal environment of the body. The weakening of one of them increases the possibility of disruption of gastrointestinal microbiocenosis, translocation of bacteria, and the risk of developing multiple organ failure [43, 44]. Over the past decade, the issue of the influence of the intestinal microbiota on the energy balance of the body has been widely discussed in scientific medical circles. Several hypotheses have been proposed to explain the mechanisms of the microbiota's influence on the metabolism of HC. This is the participation in the formation of secondary bile acids (BA), the increase in the concentration of high-density lipoproteins (HDL) in the blood. The basis of cholesterol homeostasis is the enterohepatic circulation of the BA. The lipid composition of the blood is always changed against the background of deep microecological disorders in the intestine. Gastrointestinal microorganisms interfere with cholesterol metabolism by acting directly on the enzyme systems of host cells that participate in the recycling of LC and synthesize endogenous Ch. The increased multiplication of bacteria in the SI leads to increased deconjugation of bound LC and the formation of their toxic endogenous salts, which disrupt microcirculation in the intestinal wall and increase the absorption of almost 100% LC into the liver. Their synthesis in hepatocytes decreases, the content of HC in blood plasma increases due to the lack of need for its use in the synthesis of LC. The natural mechanism of cholesterol homeostasis is disrupted — enterohepatic circulation of the LC, dyslipoproteidemia is formed [45].

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Violation of intestinal microbiocenosis leads to endotoxinemia, which has a toxic effect on liver function and consequently affects lipid metabolism. Endotoxin is one of the most active biological compounds. It is a complex of liposaccharide, protein and phospholipid forms. The reason for the increased endotoxin content in people suffering from MS is a violation of the function of all known physiological barriers to the path of the toxin in the body. Microcirculatory disorders characteristic of the atherosclerotic process in mesenteric vessels in MS contribute to ischemia of the intestinal wall and increased absorption of endotoxin into the bloodstream [46]. An essential link in the development of MS is intestinal hypoperfusion, intestinal ischemia, which leads to an increase in the permeability of the intestinal wall for endotoxin, and an excess of endotoxin destroys fibrogenesis disorders and the development of atherosclerosis [35, 47].

Diagnosis of enteropathy in MS. The main clinical symptoms of intestinal lesions in MS patients are signs of enteral insufficiency in the form of dyspeptic phenomena, general trophic disorders and symptoms of polyhypovitaminosis (brittle nails, hair loss, dry skin, folfollicular keratosis, angular stomatitis, bleeding gums, glossitis) [6].

When studying the functional state of SI in MS patients, a complex of modern laboratory and instrumental studies is used. The state of absorption and digestion in the intestine is assessed by the degree of assimilation of glucose monosaccharide, sucrose disaccharide and soluble starch polysaccharide [48]. A consistent study of glycemic curves when loaded with different carbohydrates makes it possible to determine the state of hydrolysis and absorption in the intestine and identify the stage of their violation. Fasting BG and the nature of glycemic curves depend not only on the state of the stomach, but also on the rate of absorption of carbohydrates by the liver, muscles, and central nervous system. BG may depend on the state of the motor evacuation function of the stomach and intestines. Therefore, in order to reduce the hormonal effect of BC on BG, special attention is paid to the study of the initial part of the glycemic curve (within 30 minutes after loading with glucose), reflecting mainly the absorption process [5].

For an isolated study of the resorptive process, D-xylose is used, which is not subjected to enzymatic treatment in the intestine. A sample with D-xylose is more informative in the diagnosis of a violation of the resorption function, since D-xylose, absorbed into the TC, is excreted unchanged by the kidneys, without being included in the metabolic processes of the body [49].

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To study the parietal (membrane) digestion, a stress test with sucrose is used. It is known that intestinal disaccharidases are synthesized inside the enterocyte, are located on the microvilli of the membrane and participate in the final hydrolysis of carbohydrates. They are a structural component of the enterocyte membrane [5, 10]. A decrease in the hydrolysis of disaccharides at the level of the brush border of enterocytes is manifested by a decrease in the content of monosaccharides in the blood [50]. In patients with MS, there is a decrease in the assimilation of sucrose disaccharide [37]. A decrease in parietal digestion in SI is associated with a violation of hormonal regulatory mechanisms — hyperproduction of gastrin, glucagon, cGMP and a decrease in cAMP levels. A decrease in the number and damage to the structure of the villi and microvilli of the brush border per unit surface due to concomitant pathology of the digestive organs, disorders of intestinal peristalsis and the phenomena of dysbiosis of the SI lead to a violation of membrane digestion [41].

A flat glycemic curve when loaded with starch indicates a decrease in abdominal digestion in the intestine. Oral digestion is a complex process. It depends on the functioning of the pancreas, the breakdown of food in the stomach and intestines under the action of enzymes. Violation of oral digestion is more associated with a change in the hydrolysis of nutrients in the intestine and occurs mainly due to an uncompensated decrease in the secretory function of the stomach, intestines, pancreas, bile secretion [41, 42]. A significant role in its occurrence is played by a violation of the motor function of the gastrointestinal tract. Violation of the exocrine function of the pancreas also significantly affects the digestive processes and, as a consequence, many body functions due to the role that pancreatic enzymes play in the gastrointestinal tract, providing digestion of all the main components of food: proteins, fats and carbohydrates. The first consequence of these disorders is a violation of intestinal absorption of nutrients and a decrease in the trophological status of the patient [33]. In the process of oral digestion, carbohydrates (starch, glycogen) are broken down by pancreatic amylase to disaccharides and a small amount of glucose. Under the action of proteolytic enzymes, low molecular weight peptides are formed. Fats in the presence of bile are hydrolyzed by pancreatic lipase to di- and monoglycerides of fatty acids and glycerin. Direct and indirect methods of examination are used to identify impaired exocrine function of the pancreas. The former include methods based on the direct determination of enzyme activity in the duodenal contents, and the latter — on the assessment of the degree of cleavage by pancreatic enzymes of certain substrates in the gastrointestinal tract [34].

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The definition of pancreatic elastase-1 in the feces is recognized as the modern "gold standard" for assessing the exocrine function of the pancreas. In essence, this test is direct, since it determines the content of the enzyme, but the medium is not the duodenal content, but feces. Pancreatic elastase-1, unchanged, reaches the distal parts of the intestine, does not break down when passing through the intestinal tract; fluctuations in the activity of elastase in the feces are insignificant, which ensures high reproducibility of the results; this method determines only human elastase, so the test results do not depend on the ongoing enzyme replacement therapy [49]. In patients with MS, there is a decrease in elastase-1 feces [37]. According to the study of fecal elastase-1, in 70% of patients the exocrine function of the pancreas is not impaired, in 20% there is mild or moderate exocrine insufficiency, in 10% there is severe pancreatic insufficiency.

Hydrogen breath test is a non—invasive study of the functional state of the intestine, aimed at detecting disorders of digestion and absorption of certain substances in the SI (sucrose, lactose, fructose, etc.). This test is also used to determine the bacterial overgrowth syndrome, which manifests itself as a digestive disorder [38].

The study of the motor function of SI is carried out using the X-ray method, respiratory tests [39], by the method of radionuclide dynamic scintigraphy [40]. For a deep and detailed study of the motor-evacuation function of all gastrointestinal tract departments in MS patients, peripheral electrogastroenterocology using the gastroenteromonitor GEM-01 Gastroscan-GEM is proposed. In MS patients, types II and III of motor and evacuation function disorders of the upper gastrointestinal tract were identified [31, 32]. Hypokinetic dyskinesia of the duodenum prevails with a decrease in evacuation and the formation of duodenostasis in the PPP, as well as antroduodenal discoordination and duodegastric reflux [38].

Correction of violations of the functional state of SI in MS. The main directions in the treatment of patients with MS are the effect on IR, restoration of carbohydrate and lipid metabolism, prevention of acute and long-term complications associated with vascular and metabolic disorders [2, 33]. Important measures carried out in relation to the correction of metabolic disorders are non—drug - lifestyle changes, smoking cessation, revision of food preferences [44]. However, in most cases, it is difficult to achieve the desired result only by non-drug measures, and there is a need to add drug therapy [35, 36]. There are several pharmacological groups of drugs whose effectiveness in the correction of MS is undeniable [7, 34]. Together with a hypocaloric diet and increased physical activity, in some cases, taking into

account strict contraindications, it is necessary to add drugs that reduce body weight — orlistat, sibutramine to non-drug methods of treating obesity. Biguanides, α-glucosidase inhibitors, and thiazoidinediones are widely used in the correction of carbohydrate metabolism and IR. To normalize lipid metabolism, the use of statins and fibrates is pathogenetically justified.

Recently, the treatment of MS patients from the position of restoring the functional state of the SI has been of interest. A positive therapeutic effect has been established when using pancreatin in combination with actovegin [37]. The basis for the use of the proposed drug combination may be the desire to supplement replacement therapy with pancreatin containing pancreatic enzymes, using actovegin, which activates cellular metabolism by increasing the transport and accumulation of glucose and oxygen, enhancing their intracellular utilization [38, 39]. Actovegin is prescribed at a dose of 5 ml intravenously for 5-10 days, then actovegin 200 mg 1 tablet 3 times a day; pancreatin 10,000 1 capsule 3 times a day at the beginning of a meal. The inclusion of pancreatin in combination with actovegin in complex therapy has a pronounced positive clinical effect: it eliminates the symptoms of dyspepsia and improves trophic processes. In addition, there was an improvement in the membrane and cavity stages of digestion, motor evacuation function of the TC. The beneficial effect of treatment on the motor function of SI is achieved by improving digestion and absorption in the intestine, as well as normalization of autonomous innervation of SI against the background of taking actovegin [39, 40, 41]. A decrease in the level of insulin and IR in patients with MS is associated with the effect of actovegin, which normalizes the utilization of glucose by cells and affects the main pathogenetic links of IR [40], and mini-microspherical pancreatin, which improves the functional state of the pancreatic endocrine apparatus [45]. Against the background of treatment, a decrease in the level of triglycerides compared to the baseline was noted from 2.85±0.34 to 1.53±0.18 mmol/l ($p<0.01$), which is probably due to the effect of actovegin on the main pathogenetic links of IR and triglyceride synthesis in the liver [40]. At the same time, an increase in the concentration of HDL cholesterol was noted (from 0.86±0.14 to 1.26±0.17 mmol/l; $p<0.05$), decrease in total cholesterol (from 6.08±0.16 to 5.19±0.21 mmol/l; $p<0.05$) and a decrease in the atherogenicity coefficient of blood serum (from 5.21±0.28 to 2.93±0.34; $p<0.05$) [47].

Thus, the use of actovegin in combination with pancreatin improves the functional state of the SI and, in addition, favorable changes in general metabolic processes occur against this background in patients with MS.

Conclusion. In patients with MS, clinical and functional signs of SI lesion are detected in 82.9% of cases. The main components of the cascade of metabolic disorders of MS are closely related to the functional state of SI. In this regard, MS therapy is of particular relevance from the position of restoring the functional state of the SI. Certain experience available in the diagnosis and successful treatment of enteropathy in MS patients inspires optimism in achieving positive results in the prevention of MS.

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