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Review article

Influence of gut microbiota on the development of insulin resistance

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Abstract
Insulin resistance (IR) is an important problem of humanity, which leads to development of many metabolic disorders. Currently the pathogenic mechanism of the development of IR is not completely investigated. Nevertheless, there are some hypotheses explaining the development of this condition. These include such hypotheses as the hypothesis of thrifty genotype, thrifty phenotype, hormonal, stress, good and bad calories, chronic metabolic inflammation, microbiotic and integrated model suggested by Professor Rainer Straub. In this article, the microbiotic theory will be considered in detail, explaining the mechanism of the development of peripheral tissue insensitivity to insulin in dysbiosis due to amplification of transmission by proinflammatory molecules from the intestine to the bloodstream and activation of systemic inflammation, disruption of the "gut-brain-periphery" mechanism and impaired receptor interactions of active intestinal metabolites of the gut microbiota (GM) at the level of cells of metabolic organs. The value of this theory is that its factors affect all links in the pathogenesis of the development of IR, reflected in the integrated model of Professor Straub. In this review the influence of GM and metabolic processes of human body on the development of IR will be considered in detail, data from clinical studies about the influence of GM (its composition, active metabolites, individual bacterial strains) on the development of IR and the role of chronic metabolic inflammation in this process will also be presented. In addition, attention will be paid to bidirectional effects of GM and metformin, as well as to data from clinical studies on changes in GM in healthy people and people with IR under the influence of metformin and how GM affects the pharmacokinetics of this drug. The possibility of IR correction through the use of dietary fiber will also be considered.

Keywords: insulin resistance, type 2 diabetes mellitus, gut microbiota, metformin, gut microbiota metabolites

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INTRODUCTION

For the first time, the term insulin resistance (IR) was introduced by Himsworth and Kerr to specify an insufficient response to exogenous insulin administration in patients with type 2 diabetes mellitus (t2DM) and obesity. Subsequently, it was used to determine the condition accompanied by tissue resistance to hypoglycemic effect of insulin. However, currently, due to understanding that insulin regulates not only metabolism of carbohydrates, but also metabolism of proteins and fats, as well as functions of endothelium and expression of a number of genes, the term IR is considered to mean a combined change in some parameters of metabolism and mitogenic processes [1]. Thus, according to the American Diabetes Association, IR is a disfunction of the integrated biological response (metabolic and molecular genetic) to insulin (exogenous and endogenous), a disruption of metabolism of carbohydrates, fats, proteins, as well as changes in synthesis of deoxyribonucleic acid, regulation of gene transcription, as well as in differentiation and growth of cells and tissues of the body [2]. With the development of IR at the level of the main metabolic tissues (muscle, fat and liver), glucose transport into cells is disrupted, lipolysis, glycogenolysis, gluconeogenesis and protein catabolism are activated. This leads to an increase in blood glucose levels, the accumulation of triacylglycerides in blood, which depose in liver and muscles. Thus, in a situation of lack of the main energy resource, cells begin to use alternative energy sources for their vital activity [3].

In connection with these metabolic disorders, failures in many specialized pathways occur, playing the leading role in the development of multiple organ dysfunction. Thus, in the state of IR, relaxation of smooth muscle cells of arteries is disrupted due to lack of energy necessary to activate the synthesis pathways of nitrogen oxide (NO). This leads to a spasm of the vascular wall and, as a result, to its damage. Therefore, IR is often accompanied by arterial hypertension (AH) and the atherosclerotic process. In kidneys, this situation is aggravated by hyperactivation of the renin-angiotensin-aldosterone system, which stimulates the development of vasoconstriction of the efferent arteri-

ole, which leads to the development of glomerular hypertension [4]. At the adipocyte level, energy deficiency leads to activation of lipolysis, which increases the amount of free fatty acids (FFA) in the blood. FFA accumulate in the liver, steatohepatitis and non-alcoholic fatty liver disease develop [5]. Dysbiosis develops in the intestine under IR conditions, the synthesis of short-chain fatty acids (SCFAs) and the production of glucagon-like peptide-1 (GLP-1) by L-cells decreases [6].

However, a more important consequence of IR is the development of carbohydrate disorders. Hyperglycemia occurs as a result of the fact that, against the background of IR, the activation of the cascade of intracellular proteins is disrupted, leading to a sharp decrease in the transport capacity of type 4 glucose transporters (GLUT-4), located primarily in the membrane of adipocytes and myocytes. As a result, glucose does not rush into cells and intracellular energy deficiency develops [4]. To overcome the insensitivity of peripheral tissues to the action of insulin, beta-cells of the pancreas increase insulin production. This leads to an excessive accumulation of energy in insulin-dependent tissues. Over time, due to prolonged hyperglycemia, compensatory IR develops, causing both glucose and insulin levels to increase in blood. This results in the formation of the "vicious circle": high levels of insulin lead to tissue IR, and IR leads to an increase in blood glucose, in response to which insulin levels increase. In addition, excessive energy accumulation in dependent tissues increases the amount of visceral fat, which contributes to its hypervascularization and increased synthesis of proinflammatory cytokines in adipose tissue secondary to reduced production of adiponectin, responsible for tissue sensitivity to insulin [4,6]. As a result, the chronic hyperglycemia leads to stress of the endoplasmic reticulum and attenuation of pancreatic β-cells. Insulin production decreases progressively, t2DM develops [5].

THEORIES OF THE DEVELOPMENT OF INSULIN RESISTANCE

The mechanisms of the development of insensitivity of peripheral tissues to insulin have not been fully investigated. Therefore, in order to understand which main factors lead to the development of IR, it is necessary to consider the best known theories of its occurrence and investigations confirming or refuting these theories.

The first theory. The "thrifty genotype" hypothesis

The first theory explaining the mechanism of IR development at the level of adipose and muscle tissue is the *"thrifty genotype hypothesis"*, described in 1962 by James Neal. According to this theory, a population genetically adapted to an environment with a caloric deficiency has a "thrift gene" in the genome, which contributes to the accumulation of energy during a period of abundance in order to use it later during fasting. This gene "turns on" the rapid activation of glycogenesis and lipogenesis by increased insulin synthesis at the time of food intake. Due to this, there is an accumulation of sufficient reserves of energy resources for prolonged starvation period. During the fasting period, due to lipolysis, fatty acids and ketone bodies accumulate in the blood, leading to a decrease in glucose utilization by tissues and, as a consequence, IR. This IR contributes to less utilization of glucose remaining in the blood, which is necessary to provide energy to the nervous and the immune systems during fasting [7].

There are data confirming and refuting this hypothesis. On the one hand, in 1999, Hegele et al. conducted a study in which the genetic mutation associated with hyperglycemia among the indigenous peoples of Sandy Lake was identified, allowing to explain the high prevalence of t2DM in residents of Ontario province in Canada. The authors of the study suggested that this mutation was a consequence of the presence of a "thrift gene" in this nation which in the past helped the inhabitants of the province survive during a period of prolonged starvation [8]. However, Hegele himself later questioned his conclusions. He came to a conclusion that mutation of one gene is unlikely to lead to the development of t2DM even during the period of "abundance" and the era of sedentary lifestyle [9]. Later, many genetic studies around the world refuted the presence of the "thrift gene". Thus, according to the study of Ayub et al., in which 65 loci of samples of African, European and East Asian origin were evaluated, no signs of positive selection of the "thrift gene" were found [10]. In addition, Speakman et al., built a mathematical model that refutes the existence of the "thrift gene". According to this model, if this gene really existed, it would certainly have achieved evolutional fixation – this allele would be considered as the most advantageous because it would increase life expectancy during starvation due to energy storage [11]. Thus, this theory has lost its relevance in the 21st century due to the lack of scientific evidence.

The second theory. The "thrifty phenotype" hypothesis

The next theory of the development of IR is the *"thrifty phenotype theory"*. According to this theory, during maternal fasting throughout pregnancy, there is a shortage of fetal nutrition, leading to hemodynamic, metabolic, hormonal changes. In the future, these changes may contribute to the development of endocrine disorders in the newborn, leading to a number of diseases in adulthood, such as t2DM, chronic kidney disease, idiopathic hypertension, obesity, etc. The fact is that one of the consequences of nutritional deficiency is IR, which is explained by the physiological adaptation of the fetus to glucose deficiency and persists for a lifetime [12].

The validity of this theory is confirmed by the study of Hales et al., in which the offspring of female rats were fed a low-calorie low-protein diet during pregnancy and showed a decrease in the sensitivity of hepatocytes to the action of insulin and glucagon [13]. However, this theory does not take into account other mechanisms of the occurrence of IR in the fetus, which may be more significant. Thus, the study of Nakano et al. demonstrates a decrease in the levels of total adiponectin and high-mo-

lecular adiponectin in the serum of premature infants compared to mature infants [14]. What is important, adiponectin is secreted by adipocytes and plays a key role in the sensitivity of tissues to insulin and also notably is that high-molecular adiponectin is its active form. The number of adipocytes in premature infants is reduced, therefore, in the future, a "dysfunction" of adipose tissue is formed and IR develops [14]. Thus, the "thrifty genotype hypothesis" explains only one way of the formation of IR in a fetus with a nutritional deficiency, so we cannot consider it completely legitimate.

The third theory. Hormonal hypothesis

The next theory is *the hormonal theory* of IR, which claims that the imbalance between counterinsular hormones and insulin, that occurs in certain endocrine pathologies, leads to such metabolic disorders as increased appetite, inhibition of lipogenesis, stimulation of gluconeogenesis, decreased sensitivity of tissues to insulin, etc. Such pathologies include Cushing's syndrome/disease (increased cortisol), acromegaly (increased growth hormone), pheochromocytoma (increased catecholamines), glucagonoma (increased glucagon), etc. [2]. Thus, a group of scientists led by Guarnotta conducted a cross-sectional study among 192 patients with active endogenous Cushing's syndrome, which revealed a disruption of glucose metabolism in all subjects, including those with slightly elevated cortisol levels [15]. However, it should be taken into consideration that this hypothesis demonstrates only a pathological path of IR formation. With rational therapy, the hormonal imbalance can be corrected with the subsequent restoration of the proper level of insulin and a decrease in the IR of target tissues.

The fourth theory. "Stress hypothesis"

Another reason for the development of IR is *the activation of stress systems*. There is no secret in the fact that chronic stress, mental diseases, starvation, acute inflammation contribute to the development of IR. This occurs due to activation of the hypothalamus-pituitary-adrenal axis in response to stimuli, which leads to the secretion of adrenocorticotropic hormone (ACTH), stimulating the synthesis of cortisol by the adrenal glands [16]. Due to the increased level of cortisol in blood, the synthesis of corticoliberin, which stimulates the release of insulin from β-cells of the pancreas, is reduced. In addition, cortisol causes increased synthesis of proinflammatory cytokines that inhibit the expression of GLUT-4 on membranes of adipocytes and myocytes [17]. The combination of these factors leads to IR. A direct link between cortisol levels and t2DM was demonstrated in the study of Steptoe et al., in which the amount of cortisol in saliva was 36% higher in diabetics compared to the control group. Moreover, patients with t2DM were more likely to report the presence of symptoms of depression, compared with healthy people [18]. However, there are many other pathways of developing IR that do not depend on stress factors, so this hypothesis only partially reveals the causes of IR.

The fifth theory. "Good and bad calories"

There is also the theory of *"good and bad calories"*, explaining the influence of various diets on the development of IR. According to this theory, a diet rich in unsaturated fats improves the sensitivity of tissues to insulin, reduces appetite. A high-carbohydrate diet, on the contrary, leads to an excessive postprandial increase in insulin and, as a consequence, to IR [19]. The secret of polyunsaturated fatty acids is that they have anti-inflammatory potential and, moreover, increase the synthesis of GLP-1. Due to this, the level of postprandial glycemia is quickly corrected, and excessive insulin synthesis does not occur [20]. This hypothesis is confirmed by the study of Gadgil et al., in which a diet rich in unsaturated fats, compared with high-carbohydrate and high-protein diets, was associated with lower level of IR, estimated by the quantitative insulin-sensitivity check index (QUICKI) [19].

The sixth theory. The hypothesis of chronic metabolic inflammation

Another theory of IR is the theory of *chronic metabolic inflammation*. It is worth clarifying that in this context metabolic inflammation is a condition that occurs when the glucometabolic pathways are disrupted in patients with obesity and t2DM, accompanied by an increase in inflammatory cytokines [21]. These proinflammatory cytokines reduce the expression of GLUT-4 and promote the development of IR [3]. Thus, in the study of Molli et al. there is a direct correlation between the presence of metabolic syndrome and IR. Scientists compare the indicators of the IR index (HOMA-IR) and C-reactive protein (CRP) in three groups: metabolically healthy without obesity (the first group), metabolically healthy with obesity (the second group) and patients with obesity and metabolic syndrome (the third group). The level of CRP is approximately equally elevated in patients of the second and the third groups, whereas it is normal among the representatives of the first group. Despite this, HOMA-IR, which confirmed the presence of IR, was elevated only in the group of patients with both obesity and other components of the metabolic syndrome [22]. This hypothesis, like abovementioned ones, considers only one of the ways of the formation of IR, so we cannot consider it as the only true and complete one.

The complex theory. The integrated model of Rainer Straub

Currently, the most relevant is *the complex integrated model* of IR proposed by Professor Rainer Straub (Germany). The essence of this theory is that there are two "egoistic" systems in the body that are hierarchically higher than other systems in the distribution of nutrition – the central nervous system (CNS) and the immune system [23]. When CNS needs an increased amount of energy, it can trigger the development of metabolically dependent tissues due to hyperactivation of the paraventricular nucleus (PVN) and the arcuate nucleus (ARC) of the hypothalamus. PVN, consisting of the hypothalamus-pituitary-adrenal axis and the sympathetic nervous system, is the central core of stress systems. Activation of this nucleus suppresses glucose

uptake by insulin-sensitive tissues, reduces the release of insulin by β-cells of the pancreas, leading to the development of IR. This situation is deteriorated by the hyperactivity of ARC, which is responsible for increasing agouti-related peptide that escalates appetite, reduces the sensitivity of cells to insulin, prevents glucose uptake by brown adipose tissue and slows down energy consumption [24]. When the immune system is overactivated, there is a burst in the level of proinflammatory cytokines and chemokines in blood, leading to the inflammatory processes separated from the regulation of the central nervous system. This delimitation occurs due to production of neurotransmitters and hormones on the periphery and leads to the independent of ACTH synthesis of cortisol and proinflammatory cytokines. Most proinflammatory factors have the ability to increase tissue IR in a variety of ways, for example, by reducing the expression of GLUT-4. It is precisely because of the priority of energy distribution, that increased activity of CNS and the immune system is often accompanied by a painful condition and anorexia, which further exacerbates energy deficiency [23].

Confirmation of the existence of this hypothesis is the systematic review of Sprengell et al., which included 2804 investigations proving the theory that CNS self-regulates its energy content with the highest priority. Thus, with a low level of ATP in neurons, the sympathoadrenal system is activated, increasing the concentration of glucose in blood and reducing the concentration of insulin. Due to this, glucose does not enter insulin-dependent tissues and passes through GLUT-1 to the brain and immune cells [25]. Summing up the hypothesis of Professor Rainer Straub, it is worth mentioning that the more complex the regulation system is organized, the easier it is to disable it. Therefore, a disruption of the sensitivity of receptors, as well as the work of the nuclei of the hypothalamus, the synthesis of neurotrasmitters, the regulation of inflammatory reactions, etc. will inevitably lead to the development of IR.

The theory of influencing on all elements of the integrated model. The microbiotic hypothesis

Thus, despite the existence of many theories of the development of IR, none of them fully explains the nature of the process of impaired sensitivity of peripheral tissues to insulin. The most universal and complete is the theory of Professor Rainer Straub, which combines the central and the immune regulation of peripheral tissue sensitivity to insulin. However, the integrated IR model does not include ways in which GM influences the development of IR. It is worth noting that GM, due to the action of its active metabolites, is able to influence on all links of Professor Rainer Straub's theory of IR: CNS, inflammation, metabolically active tissues (liver, muscle and fat). For example, the physiological concentration of acetate, serotonin, hydrogen sulfide and secondary bile acids (SBAs) due to their metabolic effects is associated with a reduction in the risk of developing such pathological conditions associated with IR as obesity, hypertension and dyslipidemia. Moreover, GLP-1 and the peptide tyrosine tyrosine (PYY), the synthesis of which is activated by GM, affect CNS, thereby causing insulin-dependent glucose consumption by tissues and decrease in appetite. Additionally, it is important not to forget that the active metabolites of GM contribute to the synthesis of anti-inflammatory cytokines and the integrity of the intestinal wall, preventing the development of systemic mild inflammation, which is the trigger of IR [23].

INTESTINAL MICROBIOTA AND ITS ACTIVE METABOLITES

GM is a complex of a large number of microorganisms, including bacteria, fungi, protea, viruses, archaea living in the gastrointestinal tract [26].

The dominant representatives of GM are bacteria. At the same time, most bacterial genera belong to 2 main types: *Firmicutes* and *Bacteroides* [27]. Intestinal virome consists of a variety of viruses, including eukaryotic viruses, bacteriophages and archaeal viruses [28]. Bacteriophages (families *Siphoviridae, Myoviridae, Podoviridae* and *Microviridae*) make up 90% of intestinal virome, eukaryotic viruses - 10%. In healthy people, intestinal virome demonstrates greater heterogeneity of species and relative intraspecific stability [29]. Fungal GM is not as diverse as bacterial and viral. The main types of fungi are *Candida* and *Phialemonium* [26].

In the host body GM regulates such processes as bile acid metabolism, appetite, synthesis of vitamin K and B-group vitamins, synthesis of essential amino acids, vital activity of the intestinal epithelium, intestinal motility, digestion of complex carbohydrates, homeostasis of glucose and lipids, formation of the immune system [30, 31]. It fulfils these functions thanks to its active metabolites, enzymatic systems, and even particles of its own cells [32, 33, 34].

The main active metabolites of GM are SCFAs: propionate, acetate and butyrate, which are formed in the colon as a result of anaerobic bacterial fermentation of dietary fiber. Cow's milk is also a source of butyrate [35].

Equally important metabolites are indole, serotonin and kynurenines, synthesized in three different ways from exogenous tryptophan. Indole is formed by the direct conversion of tryptophan to GM, which produces the enzyme tryptophanase. Serotonin is synthesized due to the activation of enterochromaffin cells of the intestinal mucosa by tryptamin. At the same time, tryptamin is a product of tryptophan metabolism. The pathway of the formation of kynurenines has not been fully investigated, however, it is believed that they are synthesized due to the activation of indolamine 2,3-dioxygenase under the influence of proinflammatory factors produced, including GM [36, 37].

Another active metabolite of GM is hydrogen sulfide (H2S). The main suppliers of H2S are sulfate-reducing bacteria, hydrolyzing sulfate-containing bindings (amino acids containing methionine or cysteine) [38].

GM is also involved in the biotransformation of primary bile acids (PBAs) to SBAs. This occurs via three main pathways: deconjugation, dehydrogenation, and decarboxyla-

tion. Deconjugation occurs due to hydrolases of bile salts, most of which are synthesized by *Firmicutes* (30%), *Bacteroidetes* (14.4%) and *Actinobacteria* (8.9%). Dehydrogenation is carried out by *Clostridium spp.*, related to *Firmicutes*. In the process of deconjugation and dehydrogenation, lithocholate and deoxycholate are formed [33].

The main effects of active metabolites of GM are listed in the table (*Table*).

THE IMPACT OF GM ON THE DEVELOPMENT OF IR

GM controls the sensitivity of peripheral tissues to insulin due to its active metabolites, the "gut-brain-periphery" mechanism, antiinflammatory activity and maintaining the impermeability of the intestinal barrier for endotoxins and lipopolysaccharides (LPS) of gram-negative bacteria. Consequently, dysbiosis of the GM composition sharply increases the risk of developing IR.

The role of active GM metabolites in the development of IR

The main producers of SCFAs are *Faecalibacterium prausnitzii* and *Eubacterium rectale* [40]. Butyrate, the properties of which are known most of all in the lumen of the gastrointestinal tract, fulfils many important functions for the human body. One of the main functions is the most powerful antiinflammatory effect, performed due to the ability to suppress the activity of proinflammatory macrophages and activate regulatory T cells in the intestine. Butyrate also maintains the integrity of the intestinal epithelium, promoting the formation of tight junctions between intestinal cells and increasing mucin secretion. Moreover, butyrate affects insulin synthesis and decreases appetite by increasing the concentration of GLP-1 and PYY in the intestinal lumen. It was confirmed in the study of Zhou et al., in which intravenous administration of sodium butyrate to laboratory animals led to an increase in the concentration of GLP-1 in blood and an increase in insulin synthesis by β-cells of the pancreas [41]. There is also evidence that due to its effects, butyrate can reduce the risk of obesity. Thus, in the study of Li et al. it was reported that butyrate protects against obesity caused by a diet with an excessive fat content. In a 9-week experiment, laboratory animals were divided into 2 groups: the first group received 5% sodium butyrate with food, the second group did not receive butyrate. In the group receiving butyrate, a 22% decrease in food intake was noticed, as well as a marked decrease in body weight and the amount of white adipose tissue compared with the control group [42]. Despite the supporting data on the role of butyrate in weight loss, it is necessary to take into account the fact that butyrate can be metabolized by the liver to form substrates for lipid biosynthesis [40]. It means that high concentrations of SCFAs, butyrate in particular, can lead to obesity and IR. Thus, in the study of Cuesta-Zuluaga et al. it was concluded that high concentrations of SCFAs in the stool of patients were associated with obesity, increased systemic inflammation, dyslipidemia, hypertension and lower diversity of intestinal bacteria. This study confirms the theory that elevated concentrations of SCFAs are a marker of intestinal dysfunction

Table. *Main effects of active metabolites of GM [39]*

Active substance		Clinical effects
Serotonin		• enhancement of gut motility; • increase of mucus secretion; • control of intestinal barrier function; • activation of lipolysis and gluconeogenesis;
Indole		• antiinflammatory effect; • strengthening of intestinal barrier function; • increase in the synthesis of GLP-1; • formation of intestinal biofilm
SBAs		• inhibition of gluconeogenesis; • increase in synthesis of GLP-1; • participation in lipid metabolism: reducing the synthesis of cholesterol and low-density lipoproteins, increasing the synthesis of high-density lipoproteins.
Hydrogen sulfide		• cardioprotective functions: activation of mitochondrial respiration under conditions of myocardial ischemia, vasodilation; • increase in ghrelin synthesis; • decrease in insulin secretion; • activation of synthesis of GLP-1 and peptide YY; • immune regulation
SCFAs	Butyrate	• energy substrate for colonocytes; • proliferation and differentiation of intestinal cells; • control of intestinal cell apoptosis; • strengthening of intestinal barrier function; • activation of intestinal gluconeogenesis; • antiinflammatory effect
	Propionate	• energy substrate for colonocytes; • activation of insulin secretion; • participation in liver gluconeogenesis; • appetite regulation.
	Acetate	• central appetite regulation; • maintenance of intestinal bacteria activity; • lipid metabolism.

and the appearance of conditions associated with this factor [43]. Another confirmation of the effect of excessive concentration of SCFAs on the development of IR is the study of Huang et al., conducted on laboratory animals. In this experiment, pregnant female mice were divided into two groups: some additionally received butyrate, others did not. According to the laboratory parameters of the obtained offspring, it was concluded that a unphysiologically high levels of butyrate during pregnancy are associated with the risk of developing carbohydrate disorders in offspring due to the higher HOMA-IR index in newborns compared with the control group [44]. Thus, SCFAs play an important role in the regulation of insulin synthesis, appetite control, and maintaining the integrity of the intestinal epithelium, however, it is worth mentioning, that different concentrations of these metabolites have different effects on the lipid balance in the body and the risk of obesity and IR.

The metabolic effects of indole are explained by its influence on maintaining the integrity of the intestinal epithelium, increasing the expression of adhesion molecules, suppressing inflammation and the ability to synthesize insulin through stimulation of the production of GLP-1 by intestinal L-cells [45, 46]. Thus, in the study of Abildgaard

et al., in which male rats were fed a diet enriched with indole-3-propionic acid for 6 weeks, was shown that the HOMA-IR index and fasting plasma glucose levels were significantly reduced in the test group. At the same time, no dynamics of IR and glycemia indicators were detected in the control group [47]. The antiinflammatory effect of indole is confirmed in the study of Ma et al., in which indole treatment of cultured liver cells contributed to the expression of the PFKFB3 gene, the main regulatory gene for glycolysis, as well as the suppression of the proinflammatory activity of macrophages dependent on PFKFB3. In addition, in the process of this work, it was found that indole reduces the deposition of fat in the liver and increases the sensitivity of hepatocytes to insulin [48]. Thus, a reduction in the formation of indole in the intestine as a result of GM dysbiosis dramatically increases the risk of developing IR.

Serotonin release is induced by *C. sporogenes* and *Ruminococcus gnavus* [36]. This metabolite enhances insulin synthesis and suppresses the release of glucagon at the pancreatic level; it promotes fat accumulation in the liver, activates lipogenesis and suppresses lipolysis. Thus, serotonin can be called an inducer of "storage" of lipids. However, excessive accumulation of lipids in metabolically active organs is a trigger for the development of IR [49]. Thus, in the study of Young et al., in which the plasma concentration of serotonin was evaluated after intraduodenal glucose administration to obese patients and control group patients, it was found that higher concentrations of serotonin were observed among obese patients. In addition, obese patients had a higher density of enterochromaffin cells compared to the control group, which proves the dominant role of the intestinal pathway of serotonin formation [50]. In addition, high concentrations of serotonin can induce the development of inflammation in the intestine by binding to receptors on mast cells and macrophages [51]. Activation of inflammation at the enterocyte level is associated with an increase in the transmission of LPS into the systemic bloodstream and the development of systemic metabolic inflammation that induces the development of IR [39].

The least investigated group of tryptophan metabolites are kynurenines. Currently, it is known that kynurenins are agonists of aryl hydrocarbon receptors, the activation of which causes oxidative stress, an increase in inflammatory factors and premature aging [52]. This is perfectly demonstrated in the investigation of Yu et al., which studied a cohort of patients with elevated levels of kynurenines in blood for 5 years. During the follow-up, 231 out of 985 patients acquired cardiovascular diseases. According to this, it was found that an increased baseline level of kynurenines was associated with a higher risk of myocardial infarction and cardiovascular death [53]. However, the role of kynurenines in the development of IR has yet to be clarified.

H2S is a gas transmitter of endogenous signals in mammals. The peculiarity of H2S is that it has a bimodal mechanism of action: low concentrations have antioxidant, antiinflammatory and cytoprotective effects; high concentrations, on the contrary, have cytotoxic and proinflammatory effects [54]. High amounts of H2S at the pancreatic level decrease insulin secretion by reducing the mass of β-cells [55]. Thus, in the study of Wu et al., Zucker rats with diabetes compared with metabolically healthy animals secondary to IR and hyperglycemia had an increased level of H2S, impaired insulin release and its overall decrease in blood plasma [56]. Thus, it should be assumed that a sharp increase in H2S in the blood is associated with dysfunction of β-cells of the pancreas, which is aggravated in the conditions of IR and leads to the development of carbohydrate disorders.

SBAs are formed from PBAs under the influence of *Firmicutes* (30%), *Bacteroidetes* (14.4%) and *Actinobacteria* (8.9%) [33]. According to Ward et al. ursodeoxycholic acid weakens the release of proinflammatory cytokines and protects against the development of inflammation at the level of intestinal epithelial cells [57]. Moreover, SBAs have a greater affinity for the nuclear receptors of Farsenoid X (FXR) and the type 5 membrane receptors of bile acids (TGR5) compared to PBAs [33]. Activation of the TGR5 receptor located on the membrane of most cells of the human body stimulates the synthesis of GLP-1, increases the sensitivity of tissues to insulin, stimulates energy consumption by increasing the conversion of thyroxine to triiodothyronine, enhances the antiinflammatory effect by inhibiting the nuclear factor kappaβ in macrophages [46]. Activation of the FXR in the liver reduces the synthesis of PBAs by inhibiting cytochrome P450 and increases their oxidation; in the intestine it stimulates the secretion of fibroblast growth factor 15/19, which increases energy consumption [46]. Moreover, the activation of FXR is associated with the expression of the insulin gene [58]. Thus, a decrease in the formation of SBAs in the intestine secondary to GM dysbiosis probably leads to the development of IR, dysfunction of β-cells of the pancreas and the development of metabolic disorders.

The role of inflammation occurring secondary to GM dysbiosis in the development of IR

As mentioned above, GM of a healthy person contributes to maintaining the integrity of the intestinal epithelium. The importance of the integrity of the intestinal barrier is explained by preventing the transmission of microorganisms into the systemic circulation and reducing the risk of systemic inflammation. Intestinal metabolites such as SCFAs and indole, synthesized mainly by gram-positive bacteria, contribute to the preservation of tight junctions between intestinal epithelial cells. This prevents the transport of endotoxins and LPS into the systemic circulation. With GM dysbiosis, the expression of tight junction proteins decreases and an imbalance occurs between the death and regeneration of intestinal epithelial cells, increasing the permeability of the intestinal barrier and activates the development of the systemic inflammatory process [21,59]. In addition, with GM dysbiosis (a decrease in gram-positive and an increase in gram-negative bacteria), the intestinal concentration of zonulin molecules sharply increases. Probably, the binding of zonulin to recep-

tors on tight junctions causes a reduction in the cytoskeleton of colonocytes, leading to increased permeability of the intestinal wall and the development of systemic inflammation [60]. The effects of zonulin were studied in the investigation of Moreno-Navarrete et al., in which an increased concentration of zonulin in men with metabolic disorders was associated with higher levels of body mass index, triglycerides and interleukin-6 (IL-6) in the blood. Moreover, the study showed an inverse correlation between zonulin levels and tissue sensitivity to insulin [60].

Another trigger for the development of the systemic metabolic inflammation secondary to GM dysbiosis is an increase in the LPS of gram-negative blood bacteria. The fact is that after LPS penetrates into the systemic bloodstream, it binds to Kupffer cells in the liver and causes activation of T cells and increases synthesis of proinflammatory cytokines – IL-1, IL-6, IL-8, tumor necrosis factor-α and chemokines [61]. These proinflammatory molecules activate stress-dependent kinases, which phosphorylate the insulin receptor substrate, disrupting the activation of the intracellular insulin cascade and dramatically reducing the transmission of GLUT-4 to the cell surface, leading to the formation of IR [21, 62].

The role of GM diversity in the development of IR

Undoubtedly, the imbalance of gram-positive and gram-negative bacteria is the cause of the development of IR. This is primarily due to the fact that the dominance of gram-negative bacteria changes the number of active metabolites of GM and increases the level of LPS in the intestinal lumen. In fact, in the study of Medina-Vera et al., it was revealed that in patients with t2DM secondary to IR, there was a sharp increase in *Prevotella copri* (gram-negative bacterium) [63]. However, gram-positive bacteria are activators of energy "storage". This means that with their dominance, IR develops as well [64]. Indeed, in the study of Koliada et al. it was shown that as the body mass index increased, there was an increase in *Firmicutes* (gram-positive bacteria) and a decrease in *Bacteroidetes* (gram-negative bacteria) [64]. However, despite these results, in the study of Hu et al. no difference was found in the ratio of *Firmicutes* to *Bacteroidetes* between patients with t2DM and the control group [65]. The discordant results suggest that not only the imbalance between gram-positive and gram-negative bacteria determines the risk of developing IR, but also the direct quantitative representation of bacteria in the intestine. Indeed, the results of the study of Chen et al. with the participation of 2166 patients, of whom 193 had t2DM, it was shown that the higher the alpha diversity (species diversity) of GM, the lower IR; the smaller the alpha diversity, the greater the risk of developing IR and t2DM [66].

The influence of individual bacterial strains on the development of IR

It is important that not only an imbalance of gram-positive and gram-negative bacteria and a decrease in alpha diversity are associated with the development of IR. There is evidence that individual representatives of GM also affect the sensitivity of peripheral tissues to insulin. Thus, according to Macchione et al., *Akkermansia muciniphila* maintains the impenetrability of the intestinal barrier, reduces the synthesis of inflammatory factors, prevents the development of obesity and, consequently, reduces the risk of developing IR [67]. *Bifidobacterium lactis* and *Lactobacillus gasseri* increase the expression and translocation of GLUT-4 by stimulating insulin-mediated glucose uptake by peripheral tissues. *Lactobacillus rhamnosus* increases the level of adiponectin in white adipose tissue, thereby reducing IR [68]. *Faecalibacterium prausnitzii* reduces IR and the severity of fatty hepatosis by activating the synthesis of SCFAs and GLP-1 [68, 69]. *Roseburia* participates in butyrate synthesis, controls colonocyte apoptosis, activates intestinal gluconeogenesis, induces the production of antiinflammatory cytokines, reducing the risk of the systemic metabolic inflammation leading to the development of IR [68].

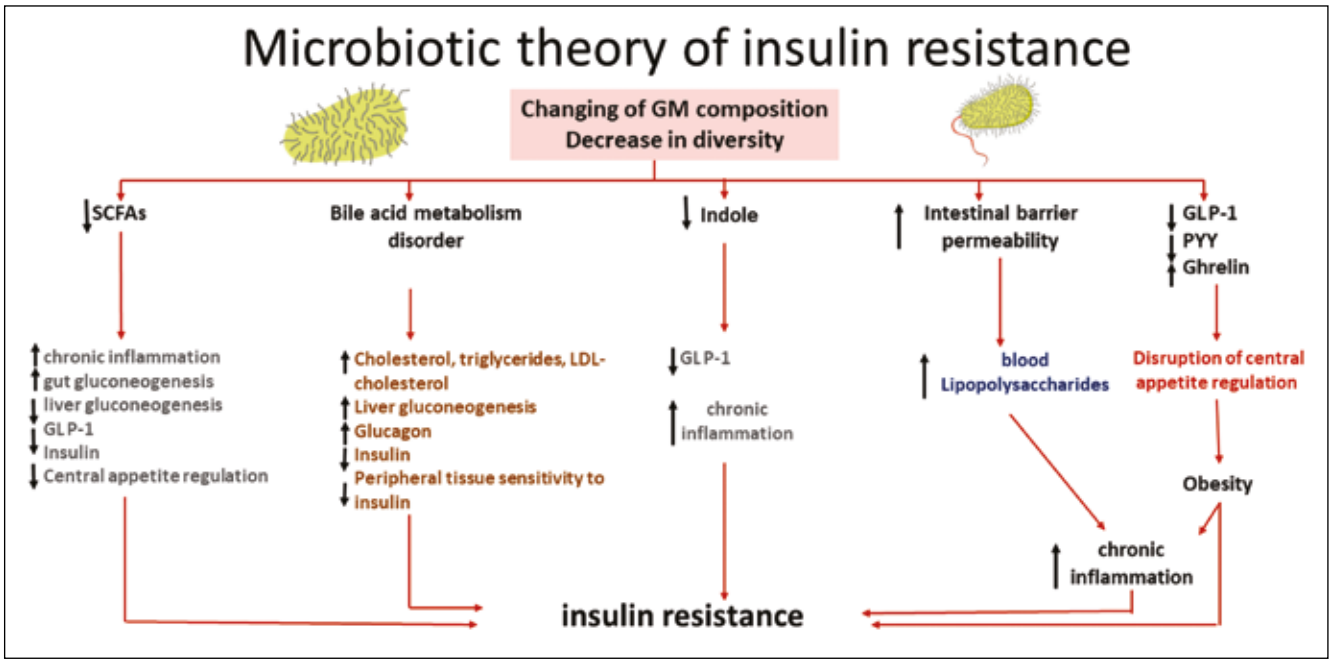
Thus, qualitative and quantitative changes in the composition of GM can induce the systemic inflammation and the development of IR by reducing or sharply increasing the production of active metabolites, alteration of the integrity of the intestinal barrier, increasing the amount of zonulin molecules in blood and enhancing the transport of LPS into the systemic circulation. Thus, we may acknowledge the existence of a microbiotic theory of the development of IR. The microbiotic theory of the development of IR is presented in the figure (*Fig.*).

DRUG CORRECTION OF IR WITH METFORMIN IN PATIENTS WITH T2DM

Metformin has been acknowledged as the drug of choice in the treatment of t2DM for many years [71]. Its main hypoglycemic effect is considered to be the suppression of gluconeogenesis in the liver, fulfilled due to two targets located in the mitochondria of hepatocytes. These targets include respiratory complex I and mitochondrial glycerol-3-phosphate dehydrogenase, the function of which is suppressed by metformin. This leads to an increase in the AMP:ATP ratio, which reduces the expression of gluconeogenesis genes [72]. In addition, metformin inhibits glucose transport from the intestine to blood by increasing anaerobic glucose metabolism in enterocytes [73]. There is also evidence that metformin is able to enhance the synthesis of GLP-1 by intestinal cells and affect the composition of GM [74].

The fact that metformin is able to change the composition and diversity of GM is proved by a number of studies [75-78]. Thus, according to Wu et al., transplantation of fecal microbiota to mice with carbohydrate disorders from donors who received metformin for 4 weeks led to a marked improvement in glucose tolerance [75]. In the study of Tong et al., it was demonstrated that metformin therapy was associated with an increase in alpha diversity [76]. Elbere et al. showed that metformin therapy was associated with a decrease in the number of three genera

Figure. *Scheme of the microbiotic theory of the development of IR [39,70]*



of the *Peptostreptococcaceae* family in a week after the start of treatment [77], and according to a study by Zhang et al. the level of *Firmicutes*, including *Lactobacillus*, increased in Zucker mice with diabetes secondary to metformin therapy. It was also associated with a decrease in endotoxemia and elevated levels of GLP-1 and insulin in blood [78]. Thus, metformin really changes the composition of GM. This is probably why intravenous administration of metformin has almost no therapeutic effect [27].

GM and the effectiveness of metformin

It is known that the effectiveness of metformin varies from person to person. This means that GM is most likely to affect the hypoglycemic properties of metformin. Currently, the number of studies evaluating the effect of GM on the effectiveness of metformin therapy is sharply limited, however, Koh et al. demonstrated a direct correlation between the intestinal metabolite propionate and blood glucose levels and proved the absence of the hypoglycemic effect of metformin in a group of mice receiving propionate [79]. According to results of this study, we may only judge the indirect influence of GM on the effectiveness of metformin therapy through the prism of excessive levels of propionate. The effects of propionate, other active metabolites of GM and individual intestinal representatives on the action of metformin have yet to be proved in clinical studies.

It is known that GM affects IR by direct action of active metabolites on target tissues and also by changing the pharmacodynamics of metformin. This means that by modulating the composition of GM, it is possible to achieve better results in the treatment of t2DM. One of the possible ways to improve the composition of GM is the use of dietary fiber, which are metabolized by bacteria into SCFAs [80]. In fact, in the study by Liu et al. conducted on laboratory animals, it was shown that the use of *Phellinus linteus* polysaccharide extract for 8 weeks led to an increase in the number of bacteria producing SCFAs [81].

A higher level of active metabolites formed secondary to dietary fiber therapy, as well as the modulation of GM under the action of metformin may contribute to the improvement of the hypoglycemic properties of the latter. Thus, in the work of Zheng et al. it was demonstrated that the combination of metformin and the prebiotic manooligosaccharide contributed to the improvement of glucose tolerance and the restoration of pancreatic islets. In addition, the combined use of these drugs reduced the number of potentially pathogenic *Clostridiales* and increased the number of *Akkermansia muciniphila* and *Bifidobacterium pseudolongum* associated with improved carbohydrate metabolism [82]. Therefore, the addition of prebiotics to hypoglycemic drugs is probably a logical measure that increases the effectiveness of antidiabetic drugs.

Side effects of metformin mediated by GM

Most people taking metformin often have dyspepsia, the development of which is explained by irritation of the gastric mucosa and a decrease in glucose absorption from the intestine into blood [72]. However, there is evidence confirming the role of GM in the development of side effects of metformin. Thus, Elbere et al. revealed a direct connection between side effects of metformin and a number of *Escherichia-Shigella spp* [77]. Bryrup et al. found a direct connection between bacteria of the *Sutterella, Allisonella* and *Akkermansia* families and gastrointestinal manifestations secondary to metformin treatment [83]. Moreover, despite the fact that in the study of McCreight et al. the composition of GM was not evaluated, the authors of the study concluded that intestinal factors were the cause of side effects of metformin, since there was no difference

between the levels of lactate, bile acids, serotonin and metformin in blood between the groups of patients with and without dyspepsia [84]. It is necessary to conduct further investigations evaluating the safety of metformin therapy depending on the initial composition of GM.

CONCLUSION

Due to its active metabolites, GM is able to change the rate of catabolism of human energy resources, affect the concentrations of PBAs and SBAs, control the integrity of the intestinal wall and participate in the development of immune reactions. This means that a change in the qualitative and quantitative composition of GM may increase the risk of developing IR and diseases associated with this condition (t2DM, hypertension, etc.). Metformin is the first choice drug in the treatment of t2DM. It is important that GM is able to influence the effectiveness and safety of therapy with this drug. Currently, there are not enough data on representatives of GM associated with a decrease in hypoglycemic ability and the development of dyspepsia secondary to metformin treatment. Thus, it is necessary to conduct further researches, which would allow to personalize the approach to the initial hypoglycemic therapy depending on the original composition of GM in future.

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