АВТОКАТАЛИТИЧЕСКИЙ ЦИКЛ В ПАТОГЕНЕЗЕ САХАРНОГО ДИАБЕТА: БИОХИМИЧЕСКИЕ И ПАТОФИЗИОЛОГИЧЕСКИЕ АСПЕКТЫ МЕТАБОЛИЧЕСКОЙ ТЕРАПИИ С ПОМОЩЬЮ НАТУРАЛЬНЫХ АМИНОКИСЛОТ НА ПРИМЕРЕ ГЛИЦИНА

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В настоящей работе проведена систематизация (классификация) биохимических и физиологических процессов, вызывающих нарушения в организме человека при развитии заболевания сахарным диабетом (СД). Развитие заболевания рассмотрено как взаимодействие и взаимоусиление двух групп параллельных процессов. Одна из них имеет молекулярную природу и связана с нарушением системы регуляции активных форм кислорода (АФК), включающей в себя NADPH оксидазы, рецепторы конечных продуктов гликирования (RAGE), митохондрии, пероксиредуктазную систему клеток и иммунную систему. Вторая группа процессов имеет патофизиологическую природу, связана с нарушениями микроциркуляции и метаболизма в печени. Проведенный в работе детальный анализ литературных данных по биохимии диабета позволил построить блок-схему развития этого заболевания во времени. При этом были выделены два типа автокаталитических процессов: автокатализ в каскаде биохимических реакций и «перекрестный» катализ, при котором биохимические и патофизиологические процессы усиливают друг друга. Разработанная модель развития диабета показала возможность применения фармакологически активного естественного метаболита глицина в качестве средства, тормозящего процесс развития диабета. Несмотря на то что глицин является заменимой аминокислотой, при СД уже на ранних стадиях заболевания часто наблюдается снижение концентрации глицина в крови, что может дополнительно усугублять течение болезни. Показано, что глицин является потенциальным блокатором ключевых автокаталитических циклов, включающих биохимические и патофизиологические процессы. Проведенный на базе разработанной модели анализ действия глицина полностью согласуется с результатами клинических испытаний, в которых глицин показал себя в качестве эффективного лекарственного средства, улучшающего биохимические показатели крови больных СД и препятствующего развитию диабетических осложнений.

КЛЮЧЕВЫЕ СЛОВА: сахарный диабет; глицин; микроциркуляция; конечные продукты гликирования; воспаление; активные формы кислорода

AUTOCATALYTIC CYCLE IN THE PATHOGENESIS OF DIABETES MELLITUS: BIOCHEMICAL AND PATHOPHYSIOLOGICAL ASPECTS OF METABOLIC THERAPY WITH NATURAL AMINO ACIDS ON THE EXAMPLE OF GLYCINE

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In this work systematization (classification) of biochemical and physiological processes that cause disorders in the human body during the development of diabetes mellitus is carried out. The development of the disease is considered as the interaction and mutual reinforcement of two groups of parallel processes. The first group has a molecular nature and it is associated with impairment of ROS-regulation system which includes NADPH oxidases, RAGE receptors, mitochondria, cellular peroxireductase system and the immune system. The second group has a pathophysiological nature and it is associated with impairment of microcirculation and liver metabolism. The analysis of diabetes biochemistry based on different published references yields a creation of a block diagram evaluating the disease development over time. Two types of autocatalytic processes were identified: autocatalysis in the cascade of biochemical reactions and "cross-section" catalysis, in which biochemical and pathophysiological processes reinforce each other. The developed model has shown the possibility of using pharmacologically active natural metabolite glycine as a medicine inhibiting the development of diabetes. Despite the fact that glycine is a substitute amino acid the drop in the glycine blood concentration occurs even in the early stages of diabetes development and can aggravate the disease. It is shown that glycine is a potential blocker of key autocatalytic cycles, including biochemical and pathophysiological processes. The analysis of the glycine action based on the developed model is in complete agreement with the results of clinical trials in which glycine has improved blood biochemistry of diabetic patients and thereby it prevents the development of diabetic complications.

KEYWORDS: diabetes mellitus; glycine; microcirculation; advanced glycosylation end products; inflammation; reactive oxygen species

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Diabetes mellitus (DM) is a disease characterised by impaired glucose uptake by cells and an increase in blood glucose levels. The two main forms of DM are type 1 and type 2 (DM1 and DM2). In DM1, the pancreatic β-cells that synthesise insulin are completely destroyed as a result of an autoimmune reaction [1]. In DM2, there is loss of sensitivity of the peripheral tissues to insulin (insulin resistance), mitochondrial dysfunction [2] and insulin and glucagon secretion in response to glucose is often impaired [3]. Treatment of DM is extremely serious; in Russia more than 4 million people suffer from the disease [4]. Common manifestations of both types of diabetes include elevated blood glucose and cholesterol levels and increased glycation of proteins and lipids and inflammatory responses. Major impairments to the vital bodily functions in DM include microvascular lesions, ischaemia and tissue injury in the kidneys, eyes, heart, brain and lower limbs.

Here, we describe a model for the development of metabolic disorders in DM. The model is based on two groups of parallel processes activated during the course of the disease development: a cascade of biochemical reactions associated with the synthesis of reactive oxygen species (ROS) and a cascade of pathophysiological processes gradually leading to impaired microcirculation of blood and induction of ischaemia in the patient's tissues. The primary result of this study is the effect of the interaction between the two abovementioned subsystems. Due to positive feedback, consistent autocatalytic amplification occurs, with a destructive effect on the organism. This cycle occurs at the second stage of the disease development (Fig. 1) and is independent of insulin signalling and blood glucose concentration. It is important to emphasise that the model is entirely based on experimental data, and each component displayed in the cascades Fig. 1 was observed in real experiments. A detailed description of all the elements of the scheme, as well as components of the relevant literature sources, are given in Table 1, which also enables the biological effect of the amino acid glycine to be traced at each stage of the pathology development.

A number of clinical studies showed that low glycine levels are associated with impaired carbohydrate metabolism, including DM [5–7], at the second stage, based on the developed model; therefore, the possibility that the amino acid glycine acting to weaken the autocatalytic diabetes development cycle was investigated. We found that glycine (a significant pro-inflammatory factor) deficiency contributes to the manifestation of the disease and aggravates its course. On the contrary, compensation of aminoacetic acid deficiency caused a breakdown of positive feedback, as confirmed by several clinical studies that demonstrate the ability of glycine to normalise the biochemical parameters of the blood in patients with diabetes, to prevent and reverse diabetes complications [8–12]. The biochemical causes of glycine deficiency in DM are also discussed in the present study.

MODEL OF AUTOCATALYTIC DEVELOPMENT OF METABOLIC DISORDERS IN DIABETES

We developed a scheme reflecting the development of metabolic disorders in DM over time based on previous studies and analysis of the literature data (Fig. 1). As noted in the Introduction, within the framework of the model developed, the course of the disease is considered to be an interaction and mutual reinforcement of two groups of concurrent processes. One of the groups has a biochemical nature and is associated with increased levels of ROS in cells and tissues. Activation this cascade is triggered by an increased levels of GEPs in diabetes. The second group of processes has a pathophysiological nature and is associated with an impaired microcirculation. Metabolic disorders of the liver in DM create an atherogenic lipid profile that causes disturbance at the molecular level and impairs functioning of the endothelium, eventually leading to atherosclerotic vascular remodelling. It is important to emphasise that insulin deficiency and/or insulin resistance is a common basis of these pathological changes; however, during early stages of disease development, the process becomes autocatalytic. Cyclic systems of reactions occur, practically independent of blood insulin or glucose concentrations. This phenomenon is referred to as 'metabolic memory' [47]. The main autocatalytic cycles of oxidative stress enhancement are described below in more detail.

Primary induction of ROS synthesis in diabetes: a biochemical autocatalytic cycle of ROS-dependent signal amplification of RAGE

GEPs are powerful inflammatory factors and are formed non-enzymatically by attachment of glucose or dicarbonyl intermediates to proteins and lipids. They accumulate in the blood and extracellular matrix and locally activate RAGE receptors, which are present in the plasma membranes of endothelial cells and vascular smooth muscle, neurons, some types of leukocytes and epithelial cells [16]. One of the major consequences of the activation of the RAGE signalling cascade is the increased generation of ROS by NOX [48] and the release of inflammatory cytokines by cells, primarily interleukin-6 [49]. The primary activation of RAGE in diabetes occurs due to the glucose-dependent formation and accumulation of GEP (component 2 in Fig. 1). Increased levels of ROS as well as RAGE signalling represent the initial stage of diabetes development. At this point, the disease ceases to depend on blood glucose levels and becomes autocatalytic in nature, since RAGE-induced synthesis of ROS increases RAGE transcription [50] via activation of the transcription factor NF-κB [19]. In addition, an increase in ROS levels leads to glucose-independent formation of GEPs [51], thereby increasing the number of RAGE-receptor agonists and enhancing its signal. The presence of these feedback mechanisms has been demonstrated experimentally, for example, in diabetes, chronic activation of NF-κB is observed [52] and the amount of the RAGE-receptor protein is significantly increased [47].

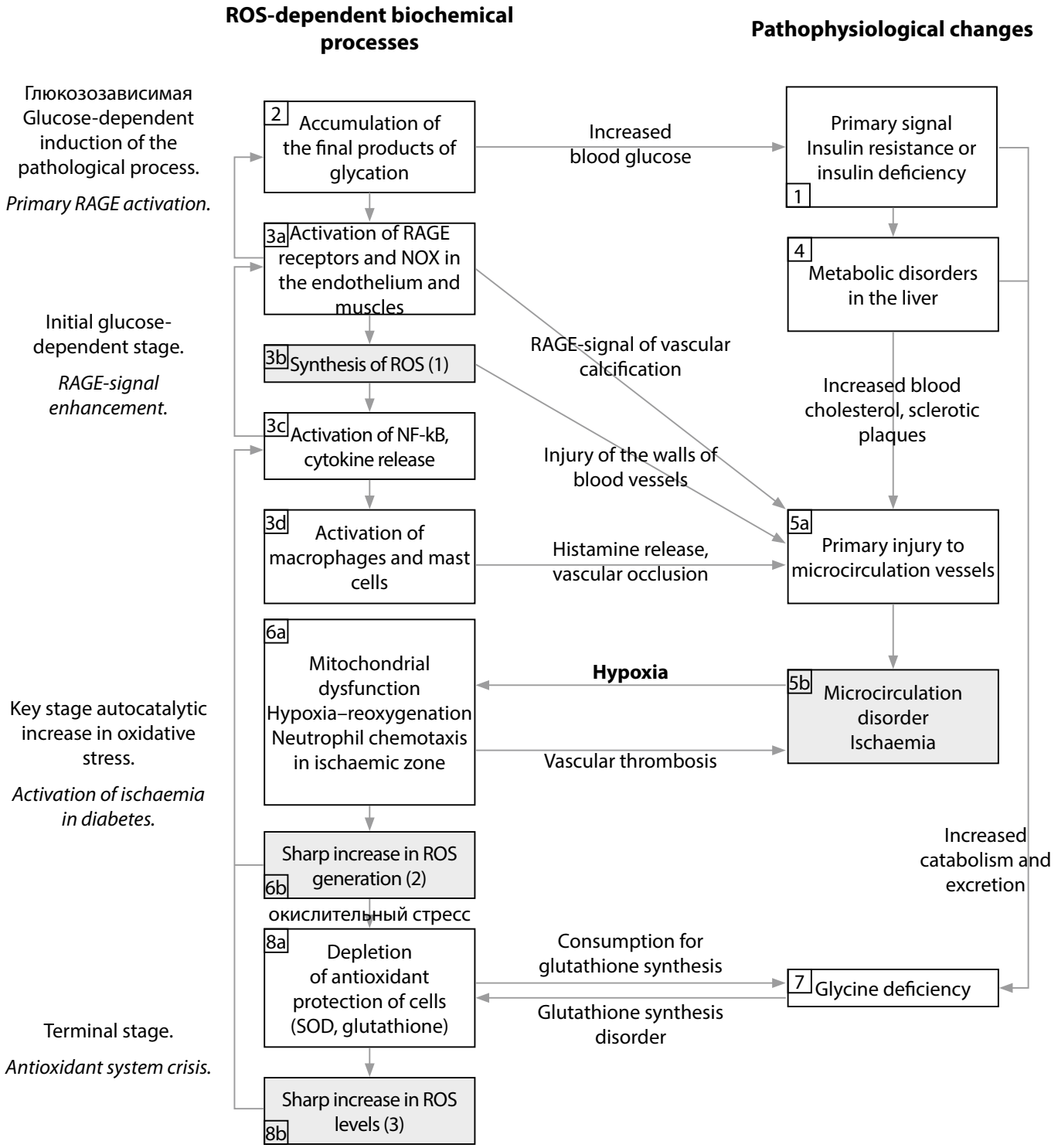

Fig. 1. Scheme of increased reactive oxygen species levels and the development of the inflammatory process in diabetes mellitus. Description of the numbered stages with references to the literature, as well as a description of glycine action at each stage, are given in Table 1. Autocatalytic cycles are described in detail in the text. Abbreviations: ROS, reactive oxygen species; RAGE, receptors of advanced glycation end-products; NOX, NADPH oxidase; NF-κB, nuclear factor kappa-light chain enhancer of activated B cells; SOD, superoxide dismutase.

Major autocatalytic cycle of mutual strengthening of pathophysiological and ROS-dependent biochemical processes

Along with activation of the ROS-dependent cascade, weakened insulin signalling induces liver dysfunction in parallel (component 4 in Fig. 1), leading to increased blood cholesterol levels, the formation of atherosclerotic deposits on the walls of blood vessels, impaired blood circulation and induction of ischaemia in tissues (component 5 in Fig. 1). This process is greatly enhanced by ROS synthesis reactions (described above) and is associated with RAGE activation (component 3 in Fig. 1). Signalling of this receptor induces a several pathological processes, namely vascular calcification [18], ROS-dependent vascular injury [25] and release of histamine by mast cells (mastocytes) [17]. Histamine induces dilation of blood vessels and an increase in their permeability, which leads to reduction in blood pressure in the capillaries and capillary dropout with erythrocytes. Histamine release aggravates impaired blood microcirculation and tissue ischaemia. Chemotaxis of neutrophils occurs in the ischaemic lesion zone, which

Table 1. DECODING OF FIGURE 1 WITH INDICATION OF PRIMARY TARGETS OF GLYCINE

No.	Description of key processes	Biological effect of glycine
	INDUCTION OF THE PATHOLOGICAL PROCESS	
1	As DM progresses, pancreatic β-cells are either completely destroyed (DM1) or their number significantly decreases (DM2). With a more pronounced dysfunction of β-cells, high blood glucose levels cease to inhibit the secretion of glucagon [3]. In DM2, insulin resistance develops in adipose tissue, muscles and liver.	Glycine increases insulin secretion by stimulating the glycine receptor in pancreatic β-cells [13], contributing to the normalisation of blood glucose levels in DM2 and in the early stages of DM1.
2	Disorder of the biological action of insulin leads to decreased glucose transport into the cells, which leads to an increase in the concentrations of glucose and ketone bodies (due to increased metabolism of fats) in the blood of patients with diabetes. Glucose and ketone bodies cause non-enzymatic glycation of proteins and lipids and the formation of glycation end-products (GEPs). GEPs either circulate in the blood or are retained in the extracellular matrix.	Glycine reduces the intensity of gluconeogenesis in the liver, which contributes to the reduction of blood glucose concentrations in DM [14]. Glycine enters into chemical reactions with aldehydes, carbonyl groups of proteins and glucose, thereby reducing protein glycation [15].
3	(a) Increased amounts of GEPs leads to activation of RAGE receptors located in many cell types, including endothelial cells, vascular smooth muscle, macrophages [16] and mast cells [17]. (b) Activation of RAGE involves the synthesis of ROS with NADPH oxidase (NOX) [18]. (c) ROS activates the transcription factor NF-κB [19] which, on the one hand, activates the antioxidant protection of cells, and on the other, stimulates the development of inflammation via the release of cytokines. (d) Increased concentrations of inflammatory cytokines causes chemotaxis of immune cells to the pre-inflammatory zone. Activation of RAGE receptors in macrophages and mast cells also stimulates their activity. As a result of immune system activity, ROS concentrations increase further.	Stimulation of the glycine receptor leads to glycine inhibition of excessive activity of immune cells [20]. Activation of the chlorine channel of the glycine receptor causes membrane hyperpolarisation and prevents activation of calcium-dependent cascades associated with the release of inflammatory cytokines and the generation of ROS. In endothelial cells, the glycine receptor activation blocks NOX activity [21].
4	In cases of insulin resistance or an immediate lack of insulin, a disturbance of lipid metabolism in the liver occurs, disturbing the balance of lipoproteins and increasing levels of cholesterol and triglycerides in the blood [22].	Glycine stimulates NMDA receptors in the brain region that controls liver function, normalises lipid metabolism [23] and reduces gluconeogenesis [14].
	ACTIVATION OF ISCHAEMIC PROCESSES IN DIABETES	
5	Disorders of the microcirculation in diabetes occur for the following reasons. - Early formation of an atherogenic lipid profile in DM accelerates atherosclerotic changes in the walls of blood vessels. - Activation of RAGE in vascular smooth muscle cells stimulates their transdifferentiation into osteoblasts and vascular calcification [18]. - Mast cells produce histamine which dilates blood vessels, increases the permeability of their walls and leads to a sharp decrease in pressure in the capillaries, aggregation of red blood cells and cessation of blood flow [24]. - Increased ROS concentrations stimulate lipid peroxidation and the formation of malondialdehyde, which causes collagen cross-linking and vascular injury [25]. - At the acute stage of inflammation, neutrophils cause capillary dropout with aggregates of neutrophils, platelets and red blood cells [26].	- Glycine normalises levels of triglycerides and cholesterol in blood [27], preventing the development of atherosclerosis in DM. - Glycine promotes vasodilation in the brain [28], peritoneum [29] and kidneys [30] of rats. Unlike histamine, glycine does not cause cessation of blood flow and even, conversely, prevents this negative effect of histamine [31]. The vasodilating effect of glycine is likely due to its effect on glycine receptors in endothelial cells [21, 32]. - In ischaemia, glycine reduces lipid peroxidation and the formation of malondialdehyde [33], reducing secondary vascular injury.

No.	Description of key processes	Biological effect of glycine
6	(a) Microcirculation disorder causes tissue hypoxia and a decreased rate of mitochondrial respiration. During hypoxia, fatty acid oxidation ceases and fatty acids and ceramides accumulate, blocking the activity of mitochondrial complexes I and III, respectively [34]. As a result, under hypoxic conditions, the main electron carriers (NADH, coenzyme Q10, cytochrome C) are transferred to the reduced state. With glucose deficiency (due to impaired glucose transport in DM), cells are especially vulnerable to hypoxia, since cessation of fatty acid oxidation deprives cells of their main energy source. (b) Spontaneous reoxygenation causes a sharp increase in ROS generation. Enhancing the inflammatory signal (cytokines, ROS) leads to chemotaxis in the focus of neutrophil ischaemia, causing an even greater release of ROS [35]. High ROS concentrations enhance the NF-κB/RAGE cascade and microvascular injury (feedback).	In the acute phase of ischaemia, glycine has a cytoprotective effect and prevents apoptosis and necrosis [36–38], due to its effects on glycine receptors. During hypoxia–reoxygenation, glycine reduces the synthesis of ROS by mitochondria and also helps to restore their phosphorylation activity [34, 39, 40] and prevents the mitochondrial pore opening in cardiomyocytes [41]. Activation of glycine receptors in neutrophils reduces their release of inflammatory cytokines and generation of ROS [42].
	ANTIOXIDANT SYSTEM CRISIS	
7	Glycine deficiency occurs during the early stages of DM2 development [7]. It may be caused by increased excretion of glycine from the body [43] (see text for more details), increased glycine decarboxylase in hepatocytes or accelerated glycine cleavage under the influence of glucagon [44]. Glycine deficiency is aggravated by increased glycine consumption for glutathione synthesis [11].	Consumption of glycine compensates for its deficiency. Normalisation of the liver under the action of glycine may also contribute to reduced glycine catabolism. Glycine also eliminates mitochondrial dysfunction in glycine-deficient cells [45].
8	(a) A substantial and long-term increase in ROS concentrations contributes to protein injury, depletion of the antioxidant system and glutathione deficiency [46]. Glutathione deficiency is exacerbated by a lack of glycine and/or cysteine for its synthesis [11]. (b) The inability of the cell's antioxidant system to neutralise ROS leads to an increase in oxidative damage, dysfunction of mitochondria and other organelles, the inclusion of stress signalling systems and apoptosis.	Consumption of glycine and cysteine restores the rate of glutathione synthesis to normal values and reduces oxidative stress in DM patients [11].

Notes: the numeration corresponds to Figure 1.

generates large amounts of ROS and contributes to the formation of blood clots in the vessels [26].

Thus, the ROS-dependent cascade of reactions impairs microcirculation, leading to significant intervals in the blood supply to body tissues. Under conditions of increased hypoxia, mitochondrial respiratory function of is impaired and the redox centres in the mitochondria are repeatedly restored (component 6 in Fig. 1). The intermittent supply of oxygen creates conditions of hypoxia–reoxygenation, under which ROS synthesis increases several fold [53], and vascular injury and thrombosis increase [54].

Terminal stage of oxidative stress: antioxidant system crisis

An increase in ROS levels above a certain critical level induces apoptosis and cell death. In most cases, the role of free radical scavengers is performed by cysteine and glutathione, which function as part of the peroxidectase system of the cell. At high rates of ROS generation, depletion of the reduced forms of these SH reagents occurs since the rate of their regeneration system is lower than the rate of ROS synthesis. When the glutathione pool is depleted, control over ROS synthesis and accumulation in the cell is lost, mitochondrial injury occurs [55] and cell apoptosis occurs [56] (component 8 in Fig. 1). In DM, glutathione deficiency is associated with a lack of cysteine and glycine, necessary for its synthesis [11]. A decrease in blood glycine concentrations is observed at the early stages of DM development [43] and is one of the causes of early depletion of the antioxidant system of DM patients (component 7 in Fig. 1).

The interrelated deficiency of glycine and glutathione may be a consequence of a chronic inflammatory process that causes accelerated glutathione consumption or may be due to other reasons, such as an increased rate of cleavage and excretion of these compounds in diabetes. Similar to glucuronic acid, glycine and glutathione are conjugated to poorly soluble compounds (xenobiotics, aromatic compounds) for their excretion from the body by the kidneys [57]. This process can be accelerated in DM and cause an increased excretion of glycine from the body. In particular, it was suggested that glycine may be used for excretion of β-oxidation products and branched-chain amino acids that are also increased in the blood with DM [43].

It should also be noted that the ROS-dependent inflammatory process itself may be the cause of DM1

[1] and DM2 [58]. Thus, ROS overproduction, which occurs due to the formation of an autocatalytic cycle and the depletion of antioxidant protection, prevents the restoration of normal insulin signalling in diabetes patients. This may also explain why blood glycine levels decrease even before disease manifestation.

MECHANISMS FOR WEAKENING OF PATHOLOGICAL AUTOCATALYTIC CYCLES BY GLYCINE

Systematisation of metabolic disorders in diabetes and the identification of their autocatalytic nature have revealed promising targets for therapeutic intervention for the pathological synthesis of ROS and microcirculation disorders. The amino acid glycine has a biological effect on both of these processes, and is potentially an effective blocking agent of pathological disorders in the cells and tissues of patients with DM. Glycine is a nonessential amino acid and, in healthy young people with adequate nutrition, it enters the body and is synthesised in sufficient quantities. Therefore, it is necessary to reiterate that DM patients tend to have glycine deficiency in the blood [5–7]. The decrease in glycine concentrations is also characteristic of many other diseases associated with severe inflammatory processes, and may be caused by epigenetic changes that disturb its biosynthesis [45]. Its use as a medication is required when glycine concentrations are reduced.

The mechanism of the medicinal effect of glycine is associated primarily with its action as a signalling molecule acting on two types of important receptors, namely, glycine is an agonist of strychnine-sensitive glycine receptors and a co-agonist of glutamate NMDA receptors (NMDARs). Glycine receptors are localised not only in nerve cells, but also in immune [20], endothelial [32] and insulin-producing pancreatic cells [13]. The metabolic effect of glycine is no less important, in particular, it is involved in the synthesis of glutathione, which is a key component of the antioxidant protection of cells. Glycine interferes with glucose-dependent induction of autocatalytic processes as it increases insulin secretion [13] and reduces gluconeogenesis in the liver [14], which contributes to normalisation of metabolism during the earliest stages of the disease (components 1–2 in Fig. 1). If the autocatalytic process has already begun, glycine also helps to weaken the key positive feedback associated with ROS synthesis and microcirculation disorders. The specific components of the metabolic and signalling cascades (see Fig. 1), that are affected by glycine are discussed below.

Glycine reduces RAGE-receptor activity

First, glycine competitively inhibits protein glycation [9] (No. 2 in Table 1), thereby reducing the formation of GEPs and the number of RAGE agonists. Second, glycine reduces oxidative stress, inhibits ROS synthesis by immune cells [20] (Nos. 3, 6 in Table 1) and contributes to maintaining the high levels of glutathione [11] (No. 8 in Table 1). Since expression of the RAGE-receptor gene is implemented by NF-κB signalling [50], which is activated by ROS [19], a decrease in oxidative stress will interfere with RAGE protein synthesis. Thus, glycine reduces the activity of the RAGE receptor both by reducing the concentrations of its agonists and by reducing the ROS-dependent expression of the receptor gene (components 2–3 in Fig. 1).

Glycine improves microcirculation

Glycine prevents the formation of a 'vicious circle' associated with ischaemia, it contributes to normalisation of metabolism in the liver and reduced blood cholesterol levels [23], reduces the pathological activity of immune cells [20] and reduces lipid peroxidation and injury to microcirculation vessels [33] (Nos. 4–6 in Table 1). We previously showed that glycine causes microvascular dilation in the brain [28] and peritoneum [29] of rats. It should be noted that the vasodilation effect of glycine is fundamentally different from the action of histamine. Unlike histamine, which is a typical mediator of inflammation, glycine does not cause aggregation of red blood cells and does not increase the permeability of blood vessels, and, therefore, does not cause cessation of blood flow in the capillaries. Moreover, it was directly shown that glycine prevents the cessation of blood flow under the influence of histamine and restores microcirculation disturbed by histamine in the peritoneal arterioles [31]. The rapid (1–3 min) dynamics of the vasodilating effect of glycine suggests that glycine improves the microcirculation by affecting the glycine receptors in endothelial cells [32]. Modelling the space–time distribution of glucose concentrations near blood vessels using the pial membranes of rats as an example shows that the experimentally observed increase in the calibre of arterioles causes an increase in the amplitude of the gradient of this carbohydrate in the tissue [59]. The vasodilating effect of glycine in the kidneys can also be explained by the activation of NMDAR [30]. Thus, by preventing microvascular injury, vasodilation and anti-histamine action, glycine normalises the microcirculation, eliminating the key cause of increased oxidative stress (component 5 in Fig. 1).

GLYCINE NORMALISES THE STRUCTURE AND FUNCTION OF MITOCHONDRIA

We previously showed that glycine reduces ROS synthesis of mitochondria after hypoxia in the brain [39] and in the heart [34]. In addition, in brain tissue with anoxia, glycine prevents impairment of the ultrastructure of mitochondria [40]. According to the literature, glycine prevents apoptosis in heart tissues by preventing the opening of the mitochondrial pore [41]. It should also be noted that glycine deficiency itself may cause injury to mitochondria, and its replenishment restores their function [45]. These data show that glycine normalises the work of mitochondria and reduces ROS synthesis by them, and also prevents mitochondria-dependent apoptosis (component 6 in Fig. 1). The ability of glycine to normalise the function of mitochondria is also important because the high rates of mitochondrial respiration provide high insulin sensitivity and prevent the development of DM2 [60].

Glycine protects cells from apoptosis

In the acute phase of ischaemia, glycine protects cells from apoptosis, allowing them to preserve the

Table 2. BRIEF SUMMARY OF CLINICAL STUDIES OF GLYCINE USE IN DIABETES MELLITUS

Study group/ control	Glycine dosage, timing	Primary results of the study	Country, method, reference
DM1 patients with severe encephalopathy: 31 patients/28 patients	100 mg of glycine (+50 mg of citric acid and 200 mg of succinic acid), 3 times a day, 3 months	The number of patients with pre-proliferative and proliferative retinopathy (transition to non-proliferative form) was reduced by 16.8%. Significant positive dynamics of platelet component of haemostasis: the size of the aggregates (25.6%) and the rate of aggregation (20.5%). Indicators of neurological and neuropsychological status of all patients significantly improved.	Russia, open-label randomised study [8]
DM2 patients without complications: 38 patients/36 patients	5 g of glycine once a day, 3 months	Glycated haemoglobin decreased significantly in the group taking glycine (and more than in the placebo group) (from 8.3 ± 1.9% to 6.9 ± 1.3%). Interferon-gamma increased and secretion of tumour necrosis factor receptor TNFα decreased (inflammatory marker).	Mexico, double-blind study [9]
28 DM2 patients with hearing neuropathy/15 DM2 patients without impairment	5 g of glycine 4 times a day, 6 months	Conductivity of the auditory nerve improved in the group receiving glycine but deteriorated in the control group. Glycine increased indices of fasting glucose and glycated haemoglobin to the control level (from 7.2 ± 1.9% to 8.1 ± 1.8%). (The effect may have been caused by stimulation of glucagon secretion with high doses of amino acids).	Mexico open-label study [10]
12 DM2 patients/12 healthy individuals, similar in age, gender, weight index	100 mg/kg of glycine (+100 mg/kg of cysteine) per day, 14 days	The concentration of glutathione in the erythrocytes of DM2 patients was significantly lower than that of the control group (1.65 ± 0.16 vs. 6.75 ± 0.47 μmol/g of haemoglobin). Therapy led to an increase in the concentration of glutathione by 64.4%, an increase in the rate of its synthesis and a decrease in oxidative stress.	USA open-label study [11]
9 healthy individuals/no control	75 mg/kg of glycine, single-dose	In the absence of glucose, glycine increases glucagon secretion. Consumption of glycine along with glucose reduces the maximum increase in blood glucose levels and increases the rate of its absorption by the tissues.	USA open-label study [12]

functionality of tissues and organs, including the brain, heart, kidneys, liver and blood vessels [37]. The efficiency of glycine as an anti-ischaemic drug was confirmed by clinical studies [36] and glycine was prescribed for rehabilitation after ischaemic strokes. Special traits of the cytoprotective actions of glycine in ischaemia are discussed in detail elsewhere [38], and a number of typical features are highlighted, for example, glycine has rapid kinetics of action and does not require transportation into the cell, glycine must be present during the acute phase of ischaemia and its maximum protective effect is achieved when at an extracellular concentration of around 2 mM. These signs indicate that the cytoprotective effect of glycine may be implemented through a special form of the glycine receptor whose activation prevents injury and pathological permeability of cell membranes during ischaemia. The additional intake of glycine and cysteine also enables the rate of glutathione synthesis to be increased to compensate for its deficiency in DM [11]. Thus, glycine interferes with the terminal stage of the development of oxidative stress, leading to apoptosis (or necrosis) of cells (components 7–8 in Fig. 1).

Clinical evidence of glycine action in diabetes mellitus

A search of the databases of the literature revealed that in recent years in different countries, studies were conducted into the action of glycine on patients with diabetes. The main parameters of the clinical studies are provided in Table 2. Despite significant differences in the groups studied (various types of diabetes and the severity of diabetic complications), all studies show positive dynamics of the condition of patients with diabetes using glycine therapy. These data reveal that the most noticeable effect of glycine was on parameters associated with microcirculation and the intensity of inflammatory processes, which is consistent with the results of the analysis of the biological action of glycine conducted in the present study. It is worth noting individually that the use of very high doses of glycine (20 g per day) in therapy, as well as its consumption on an empty stomach [12], can provoke an increase in glucagon secretion and lead to increased blood glucose concentrations, and a long-term increase in glycated haemoglobin [10]. Therefore, moderate doses of glycine with food (up to 5 g), on the contrary, contribute to reduced glycation [9], in agreement with results observed using model animals [15]. It should also be emphasised that none of the above studies show noticeable side effects or complaints from patients about worsening of their condition with glycine consumption.

CONCLUSION

In the present study, we formulated a structured model of the stage development of diabetes that occurs under conditions of severe weakening or disappearance

of the insulin signal. In the model, the initial insulin and glucose-dependent stage of the disease is emphasised, including two primary concurrent processes. First, glycation of proteins and lipids activates the RAGE receptor, leading to ROS synthesis. Second, lipid metabolism disorder in the liver leads to increased blood cholesterol levels, and development and progression of endothelial dysfunction.

The second stage of the disease is not directly related to impaired glucose metabolism and insulin signalling. The model of the subsequent development of the disease is based on the interaction of two groups of parallel pathological processes that effectively reinforce each other. Cascades of ROS-dependent biochemical reactions and the stepwise impairment of the microcirculation are associated with each other via positive feedback, resulting in an autonomously increasing autocatalytic cycle of disorders of metabolism and ROS signalling in tissues (Fig. 2). This cycle demonstrates the well-known effect of 'metabolic memory' and is the basis of the glucose-independent stage of diabetes.

The results obtained enable us to redefine DM as a disease that carries the most important traits of a self-accelerating cyclic autocatalytic process. In an autocatalytic cycle, disruption of significant positive feedback discontinues or sharply slows down the entire cyclic process in general. This highlights the prospect of a new approach to the treatment of this disease by targeted blocking of autocatalysis. On the other hand, it can be assumed that, according to the accepted model, the strongest therapeutic effect may be achieved via directional simultaneous blocking of both systems, namely ROS-related processes and the pathophysiological cascade of impaired microcirculation.

Based on the results obtained and the analysis of the biological action of glycine, the present study shows that glycine blocks both the biochemical cascade of reactions associated with ROS synthesis and microcirculation disorders, and may effectively weaken the main autocatalytic cycle in diabetes (Fig. 2). Thus, our study reveals the key components of metabolic changes in diabetes that are potential drug targets, such as the amino acid glycine.

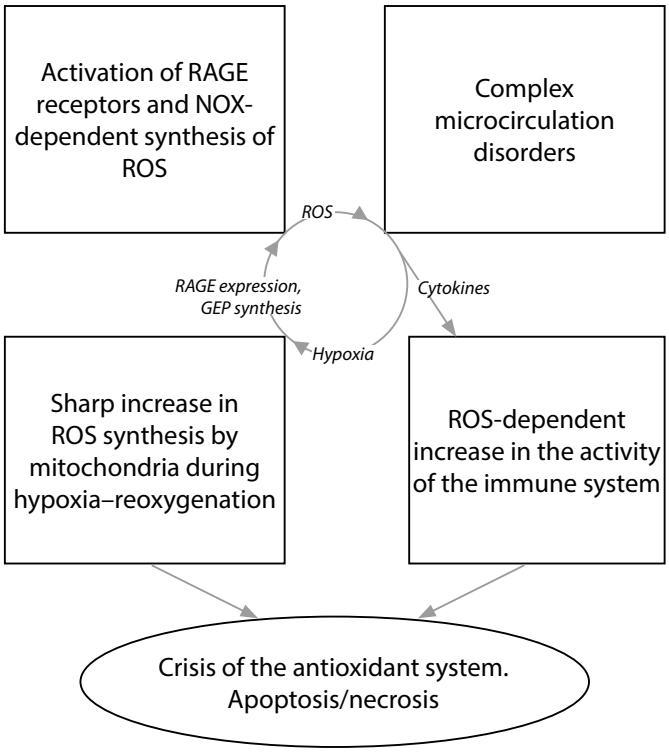

Fig. 2. Scheme of the primary autocatalytic cycle of the mutual amplification of ROS-dependent processes and the pathophysiological process of impaired microcirculation. The degree of immune cell activity increases due to the release of inflammatory cytokines in ROS-dependent activation of NF-κB. As a result of an autocatalytic increase in oxidative stress, there is a depletion of antioxidant protection of cells and apoptosis (or necrosis). Abbreviations: ROS, reactive oxygen species; GEP, glycation end-product; RAGE, receptor of advanced glycation end-product; NOX, NADPH oxidase.

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