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Role of adenosine monophosphate-activated protein kinase as a regulator of cell energy balance in patients with metabolic disorders. Literature review

L. V. Zhuravlyova, Yu. D. Stoianova

Kharkiv National Medical University

The combination of diabetes mellitus type 2 and gout is common. It has been established that prolonged hyperuricemia leads to insulin resistance and suppresses the effects of insulin, which is why the study of pathogenetic links in the formation of metabolic disorders in synergistic pathologies is relevant. AMPK has been shown to be a regulator of cell energy balance, which plays an important role in preventing the development of insulin resistance. The purpose of this review is to determine the impact of AMPK on carbohydrate, lipid and purine metabolism in patients with diabetes mellitus type 2 and gout. The realization of the effects of AMPK on metabolic processes in the human body occurs in two main ways — inhibition of anabolism and stimulation of catabolism, which will be discussed in the article. It is advisable to consider the mechanisms of action of indirect activators of AMPK as potential components for the comprehensive treatment of patients with metabolic disorders. The mechanisms of activation and inhibition of AMPK are not investigated enough, but it is known that AMPK plays a significant role in the main metabolic processes in the human body. The mechanisms of cell sensitivity to most energy-containing molecules and substances directly depend on the AMPK activation degree. The presence of these dependencies may be evaluated in the case of metabolic diseases. Thus, further study of the effects of AMPK and its influence on carbohydrate, lipid and purine metabolism is necessary, due to the possibility of predicting the formation of insulin resistance, the severity of diabetes mellitus type 2 in combination with gout, and optimizing treatment in patients with comorbid pathology.

Key words:
diabetes mellitus type 2, gout, adenosine monophosphate-activated protein kinase, insulin resistance.

Diabetes mellitus (DM) has a steady upward trend in morbidity. According to the IDF 2019, about 463 million adults (aged 20 to 79) are diagnosed with diabetes. A progressive increase in the incidence of diabetes is also observed in Ukraine. According to the Center for Medical Statistics of the Ministry of Health of Ukraine, 1.22 million patients are registered, 84 % of cases are diabetes mellitus type 2 (T2DM). T2DM is a disease that leads to disability or premature mortality due to both complications of diabetes and the development of comorbid pathology [21].

One of the central pathogenetic links of T2DM and synergistic pathologies is the formation of insulin resistance (IR). This condition contributes to diseases such as coronary heart disease (CHD), arterial hypertension (AH), heart failure (HF), chronic kidney disease (CKD), non-alcoholic fatty liver disease (NAFLD), gout and others [3]. In addition, the presence of T2DM in patients, due to accelerated atherogenesis and the presence of micro-and macroangiopathies, increases the risk of cardiovascular pathology, which causes higher mortality in this pathology compared with patients without T2DM [27].

It is known that the combination of T2DM and gout in patients is quite common [2]. Thus, IR is noted in 60 % of patients with gout, T2DM — in

КОНТАКТНА ІНФОРМАЦІЯ

Журавльова Лариса Володимирівна

д. мед. н., проф., зав. кафедри внутрішньої медицини № 3 та ендокринології

http://orcid.org/0000-0002-0051-3530

E-mail: prof.zhuravlyova@gmail.com

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20 % of patients [15]. Increased uric acid (UA) is associated with an increased risk of cardiovascular disease. Studies have shown that hyperuricemia (HU) increases IR and inhibits the effects of insulin, which is a pathogenetic pathway for the development of T2DM [17], so the study of biochemical relationships between purine and carbohydrate metabolism is relevant. In the case of HU, uric acid induces oxidative stress, which reduces the bioavailability of NO, and as a result leads to inactivation of GLUT4 translocation [24]. Also due to the development of hyperinsulinemia, renal excretion of UA in the proximal tubules of the kidneys decreases, which leads to HU, forming a «vicious circle» [18]. However, a critical decrease UA in plasma is associated with the development of cognitive dysfunction. Therefore, maintaining a normal level of UA is one of the priorities in the treatment of patients with comorbid pathology.

Considering the concept of «insulin resistance» in more detail, we can conclude that this process is accompanied by a decrease in glucose uptake by tissues, the formation of compensatory hyperinsulinemia and disturbance of energy balance of cells due to reduced glucose supply to insulin-dependent tissues [19]. To carry out metabolic processes in the cell requires a sufficient amount of substrate for the synthesis of adenosine triphosphate (ATP) in mitochondria by oxidative phosphorylation. When the level of cellular ATP is significantly reduced, alternative pathways of energy metabolism of cells are activated, in which the enzyme adenosine monophosphate-activated protein kinase (AMPK) plays a key role. According to Ross F. and co-authors, AMPK is recognized as a regulator of energy balance at the cellular level [20].

Objective — to determine the effect of AMPK on carbohydrate, lipid and purine metabolism in patients with T2DM and gout by the analysis of literature sources for the last 7 years.

AMPK is a heterotrimeric complex consisting of an α-subunit (α-1, α-2) with catalytic activity and two regulatory subunits AMPK-β (β-1, β-2) and AMPK-γ (γ-1, γ-2, γ-3) [8]. The effect of AMPK on cellular metabolism is realized in two main ways — inhibition of anabolism to minimize ATP intake or stimulation of catabolism for ATP production [10]. Let's consider these two paths in more detail.

Inhibition of anabolic processes. AMPK reduces lipid synthesis by inhibiting the phosphorylation of acetyl-CoA-carboxylase and 3-hydroxy-3-methylglutaryl-CoA-reductase, thereby limiting cholesterol synthesis. Inhibition of gluconeogenesis occurs by phosphorylation of CRTC2 (cyclic-AMP-regulated transcriptional co-activator 2) protein, as well as histone diacetylases (HDACs), predominantly class II (most concentrated in skeletal muscle and pancreas). AMPK also controls the metabolism of the nuclear factor hepatocytes-4 alpha (HNF4A) and the transcription factor SREBP1, which are integral regulators of lipid and carbohydrate metabolism [12].

Stimulation of catabolic processes. AMPK is known to promote the active utilization of glucose, phosphorylating proteins TXNIP and TBC1D1, which, in turn, leads to an increase in the number of specific glucose transport proteins GLUT-1 and GLUT-4. In addition, AMPK stimulates the use of lipids by the cell, which is realized through the activation of the enzyme fatty triglyceride lipase (ATGL) [7].

AMPK and carbohydrate metabolism

Glucose, as the primary source of energy, is involved in all key metabolic processes in the human body. The glucose molecule provides not only the formation of ATP in the Krebs cycle by oxidative phosphorylation, but also a substrate for the synthesis of aminoacids, fatty acids and nucleotides. Regulation of gluconeogenesis, transport of glucose to cells by specific transporters is carried out by insulin, but non-insulin-dependent mechanisms are of great therapeutic interest for us. The mentioned above mechanisms include the activation of AMPK [14].

AMPK regulates glycolysis in two ways: by phosphorylating PFKFB3 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase-3) or by inhibiting glucose storage in some tissues by inhibiting multiple isoforms of glycogen synthase (GS). AMPK inhibits gluconeogenesis by blocking the transcription processes and «switching off» of nuclear CRTC2 and class II HDACs, which are necessary co-factors for the transcription of gluconeogenic genes [11].

Numerous studies have shown that activation of AMPK stimulates glucose uptake by skeletal muscle. Moreover, the mechanism of action of AMPK is related to the translocation of GLUT-4, so glucose absorption occurs without a full-fledged trigger mechanism of the insulin-signaling pathway [16]. Therefore, the mechanisms of AMPK reactivation under IR conditions are an important therapeutic area.

AMPK and lipid metabolism

The main source of fatty acid synthesis is acetyl-CoA, which is formed as a result of glucose catabolism. AMPK induces phosphorylation of ACC1 (subunit of acetyl-CoA), thus causing a decrease in cellular levels of malonyl-CoA and blocks the chain of reactions for the formation of fatty acids. Phosphorylation of ACC by AMPK helps to restore the activity of carnitine palmitoyltransferase I (CPT1), the basis of which is the function of the field in the transport of free fatty acids in the mitochondria for β-oxidation. Studies have shown that AMPK has an effect on the synthesis of endogenous cholesterol. In the cytoplasm of liver cells, acetyl-CoA is converted to cholesterol

by sequential reactions [5]. One of the important steps is the conversion of HMG-CoA to mevalonate. AMPK has been shown to inhibit HMGCR activity by phosphorylation, which impairs affinity for NADPH and thus inhibits cholesterol synthesis [22]. AMPK-induced reduction of endogenous cholesterol helps GLUT-4 translocation thereby promoting better glucose uptake by tissues.

AMPK and purine metabolism

One of the main mechanisms of damage of internal organs in long-term HU is a impairment of the balance of Na/K-ATPase, which in turn leads to mitochondrial dysfunction, autophagy and inflammation. Despite the fact that the activation of AMPK did not reduce the level of UA in the serum of patients with HU, there was a decrease in the effects of HU-associated cell damage [25]. Presumably, prolonged activation of AMPK is able to reduce lysosomal degradation of Na/K-ATPase, thereby providing protection of cells from the effects of HU-associated inflammation [26].

Thus, AMPK plays a very important role in ensuring metabolic processes in the cell and is an integral part of carbohydrate, lipid, purine and protein metabolism, as shown in Table 1.

Activation of AMPK is possible in the presence of a substance that causes the accumulation of adenosine monophosphate or calcium in the cell. Accordingly, there are direct and indirect activators of AMPK, which are shown in Table 2 [9].

Today AMPK is considered as a potential component for the treatment of patients with metabolic disorders, which primarily include T2DM, obesity, NAFLD, which is why the group of indirect activators of AMPK is promising for further study.

Biguanides are one of the main representatives of indirect AMPK activators. Studies have shown that one of the mechanisms of action of metformin is the activation of AMPK in hepatocytes. AMPK-mediated phosphorylation of acetyl-CoA-carboxylase has been suggested to be a major factor in altering lipid synthesis by metformin, which in turn modulates insulin sensitivity and stimulates muscle glucose utilization [6]. In retrospective studies, AMPK activation was shown to significantly improve the symptoms and course of T2DM in several animal models, including lowering blood glucose levels. Interestingly, inactivation of AMPK in the liver did not affect the effectiveness of treatment, which leads to the conclusion that the key therapeutic target of T2DM is the activation of AMPK of skeletal muscles [13].

Equally important indirect activators of AMPK are glitazones. Studies have shown that treatment of patients with T2DM with this group of drugs caused the release of adiponectin from adipocytes, which triggered the action of AMPK in skeletal muscles, liver, leading to increased glucose uptake, fatty acid oxidation and decreased gluconeogenesis in hepatocytes [4].

It should be emphasized that AMPK activity may be inhibited by conditions accompanied by HU, alcohol abuse, and excessive fructose intake [23]. Elevated UA inhibits AMPK by activating the competing enzyme adenosine monophosphate dehydrogenase (AMPD), which in turn activates gluconeogenesis in liver cells. Studies have shown that HU induces oxidative stress in β-cells of the pancreas, which leads to their damage and disruption of insulin synthesis [11]. However, to date, the accumulated information is not exhaustive and requires detailed study.

Conclusions

It is well known that AMPK plays a significant role in the energy balance of body cells. Moreover, the mechanisms of cell sensitivity to most

Table 1. The main mechanisms of action of AMPK, which are realized in carbohydrate, lipid, protein metabolism

Type of metabolism	Mechanism of action
Carbohydrate	↑ absorption of glucose by tissues ↑ glycolysis ↓ gluconeogenesis ↓ glycogen synthesis
Lipid	↓ synthesis of triglycerides, phospholipids ↓ synthesis of fatty acids ↑ oxidation of fatty acids ↑ absorption of fatty acids
Protein	↑ transcription of genes in response to oxidative stress ↓ synthesis of proteins

Table 2. Direct and indirect activators of AMPK, features of mechanisms of action

Activator	Mechanism of action
Direct	
Salicylates	Activation of β-subunit of AMPK
Thienopyridines	
Benzimidazole	Activation of β_1-subunit of AMPK
Indirect	
Metformin	Increasing the ratio of AMP/ATP, the impact on the first complex of the respiratory chain, which plays a key role in the processes of oxidative phosphorylation
Pioglitazone	
Rosiglitazone	
Quercetin	Increasing the ratio of AMP/ATP, the effect on mitochondrial ATP synthase
α-Lipoic acid	Increased levels of calcium in cells

energy-containing molecules and substances are directly dependent on the level of AMPK activation.

Activation of AMPK reduces the level of inflammation in the presence of GU and gout, normalizing the energy balance of cells by restoring the function of Na/K-ATPase.

The effects of AMPK are related to the translocation of GLUT-4 of skeletal muscles and are realized in the form of glucose delivery to tissues without the involvement of the insulin-signaling pathway under IR conditions. Therefore, it is advisable to use indirect AMPK activators in patients with IR and T2DM.

Therefore, it can be concluded that the mechanisms of AMPK require further more detailed study, especially in the context of metabolic diseases. In addition, modeling the therapeutic effect on AMPK activation could potentially change the treatment tactics of this group of diseases.

Conflicts of interest: none.

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Л. В. Журавльова, Ю. Д. Стоянова

Харківський медичний університет

Роль аденозинмонофосфат-активованої протеїнкінази як регулятора енергетичного балансу клітини у хворих із метаболічними порушеннями. Огляд літератури

Відзначено стійку тенденцію до зростання захворюваності на цукровий діабет у світі. Відомо, що цукровий діабет 2 типу є захворюванням, яке призводить до втрати працездатності або передчасної смерті, що зумовлено як його ускладненнями, так і розвитком коморбідної патології. Комбінація цукрового діабету 2 типу та подагри є поширеним явищем. Установлено, що тривала гіперурикемія призводить до інсулінорезистентності та пригнічує ефекти інсуліну, тому дослідження патогенетичних ланок формування метаболічних порушень при синергійних патологіях є актуальним. Доведено, що аденозинмонофосфат-активована протеїнкіназа (AMPK) — це регулятор енергетичного балансу клітини, який відіграє важливу роль у запобіганні інсулінорезистентності. Наведено дані щодо впливу AMPK на вуглеводний, ліпідний і пуриновий обмін у хворих на цукровий діабет 2 типу та подагру. Розглянуто два основні шляхи реалізації ефектів AMPK на метаболічні процеси в організмі людини — пригнічення анаболізму та стимуляцію катаболізму. Висвітлено механізми дії непрямих активаторів AMPK як потенційних компонентів для комплексного лікування хворих із метаболічними розладами. Механізми активації та інгібування AMPK недостатньо вивчено, але відомо, що AMPK відіграє важливу роль у ключових метаболічних процесах в організмі людини. Механізми чутливості клітин до більшості енерговмісних молекул та речовин безпосередньо залежать від ступеня активації AMPK. Наявність цих залежностей можна прослідкувати у разі метаболічних захворювань. Подальше вивчення ефектів AMPK та характеру її впливу на вуглеводний, ліпідний і пуриновий обмін є необхідним через можливість прогнозування формування інсулінорезистентності, ступеня тяжкості цукрового діабету 2 типу в поєднанні з подагрою, а також для оптимізації методів лікування у пацієнтів із коморбідною патологією.

Ключові слова: цукровий діабет 2 типу, подагра, аденозинмонофосфат-активована протеїнкіназа, інсулінорезистентність.

Л. В. Журавлёва, Ю. Д. Стоянова

Харьковский национальный медицинский университет

Роль аденозинмонофосфат-активированной протеинкиназы как регулятора энергетического баланса клетки у больных с метаболическими заболеваниями. Обзор литературы

Отмечена устойчивая тенденция к росту заболеваемости сахарным диабетом в мире. Известно, что сахарный диабет 2 типа является заболеванием, которое приводит к потере работоспособности или преждевременной смерти, что обусловлено как его осложнениями, так и развитием коморбидной патологии. Комбинация сахарного диабета 2 типа и подагры является распространенной. Установлено, что длительная гиперурикемия приводит к инсулинорезистентности и подавляет эффекты инсулина, поэтому исследование патогенетических звеньев формирования метаболических нарушений при синергичных патологиях является актуальным. Доказано, что аденозинмонофосфат-активируемая протеинкиназа (AMPK) — это регулятор энергетического баланса клетки, который играет важную роль в предотвращении инсулинорезистентности. Приведены данные о влиянии AMPK на углеводный, липидный и пуриновый обмен у больных с сахарным диабетом 2 типа и подагрой. Рассмотрены два основных пути реализации эффектов AMPK на метаболические процессы в организме человека — угнетение анаболизма и стимуляция катаболизма. Освещены механизмы действия косвенных активаторов AMPK как потенциальных компонентов для комплексного лечения больных с метаболическими расстройствами. Механизмы активации и ингибирования AMPK недостаточно изучены, но известно, что AMPK играет важную роль в ключевых метаболических процессах в организме человека. Механизмы чувствительности клеток к большинству энергосодержащих молекул и веществ напрямую зависят от степени активации AMPK. Наличие этих зависимостей можно проследить в случае метаболических заболеваний. Дальнейшее изучение эффектов AMPK и характера ее влияния на углеводный, липидный и пуриновый обмен необходимо из-за возможности прогнозирования формирования инсулинорезистентности, степени тяжести сахарного диабета 2 типа в сочетании с подагрой, а также для оптимизации методов лечения у пациентов с коморбидной патологией.

Ключевые слова: сахарный диабет 2 типа, подагра, аденозинмонофосфат-активируемая протеинкиназа, инсулинорезистентность.

ДЛЯ ЦИТУВАННЯ

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