Hydrogen sulfide and mitochondria

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There are different opinions about the role of hydrogen sulfide (H₂S) in catalytic and energy processes, but the biochemistry of all possible effects of H₂S is not well studied yet. The enzymatic synthesis of H₂S is catalyzed by cystathionine-γ-lyase, cystathionine-β-synthase, cysteine aminotransferase and in mitochondria by 3-mercaptopyruvate sulfurtransferase only. H₂S may function as an energy substrate to sustain the ATP synthesis under stress conditions, but in high concentration H₂S inhibits respiratory complex IV, blocking electron transport and proton pumping. The interaction between glucose in high concentration, H₂S, and the K_ATP channels may constitute a novel mechanism for the control of insulin secretion. The positive effect of H₂S on the bioenergetic function of mitochondria may be used in therapy of many diseases.

Keywords: hydrogen sulfide, mitochondria, bioenergetics.

Introduction

The knowledge of hydrogen sulfide (H₂S) as a potent signaling molecule greatly advanced over the last years, though the biomolecule is known from the very beginning of the life evolution. H₂S is the hydrogenated sulfur compound with the lowest oxidation state (-2). The description of gas dates back to the 15th century when it was named “hepatic air” [1]. The first chemical synthesis was performed by Carl Wilhelm Scheele in 1777 by mixing metal sulfides with acid, and in 1796 Claude Louis Berthollet studied its chemical composition.

The compound is a flammable, colorless, water-soluble gas denser than air [2]. There are different opinions about the role of H₂S in synthetic, catalytic and energy processes. The ways of the molecule synthesis in mammals were ascertained in the 1940s. In the 1990s, the data on the modulatory and signaling effects of H₂S first appeared. H₂S represents an inorganic reducing substrate for oxidative phosphorylation in mammals [3]. The interest in studying H₂S was triggered by its potential importance for health. The attempt to describe the pathways of formation, to determine a biological role, to characterize and

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explain the physiological effects and to synthesize donors of the biomolecule are promising for innovation of the effective pharmacological treatment. H2S has important effects on mitochondria. The biomolecule influences the mitochondrial electron transport chain. And the reactions with metal centers and thiol oxidation products are possible mechanisms of these biological effects [4].

Key biochemical questions are the role of H2S in the bioenergetic processes and its influence on the diabetes development and its complications. In this review, we give a short overview of the biological role of H2S in mitochondria, the regulation of cellular bioenergetics and the influence on diabetes mellitus.

The enzymology of H2S formation

In mammals, the endogenous H2S is synthesized from homocysteine and cysteine through the enzymes of the transsulfuration pathway. These enzymes are cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), cysteine aminotransferase (CAT) and 3-mercaptopyruvate sulfurtransferase (3-MST). CBS (EC 4.2.1.22), CSE (EC 4.4.1.1) are cytosolic enzymes only, whereas CAT (EC 2.6.1.3) and 3-MST (EC 2.8.1.2) can be present in both cytosol and mitochondria [5]. These enzymes utilize L-cysteine as a substrate that can be taken up with the diet, extracted from endogenous proteins, or synthesized endogenously via trans-sulfuration of serine by L-methionine [6, 7].

3-MST is involved in cyanide detoxification as an enzyme that transfers the sulfane sulfur from substrate to cyanide ion, giving nontoxic thiocyanate and pyruvate. Zink is the cofactor of 3-MST. CAT, CBS, and CSE are pyridoxal phosphate-dependent enzymes that take part in the synthesis of cysteine from methionine and serine. CBS and CSE can execute alternative reactions that yield H2S [5]. The enzyme cystathionine-β-synthase catalyzes the replacement of serine with homocysteine forming cystathionine and water. If cysteine is used instead of serine, the products formed are cystathionine and H2S. CSE catalyzes the elimination of cystathionine to produce cysteine, α-ketobutyrate and ammonia. Alternatively, CSE can form H2S from both cysteine and, less significantly, homocysteine [7, 8].

The rhodanese family enzyme 3-MST catalyzes the formation of pyruvate and a persulfide from cysteine derived 3-mercaptopyruvate. In the availability of thiols, the persulfide can extricate hydrogen sulfide, composing an alternative source of the compound [9].

Since there is a tissue-specific expression of these enzymes, their contribution to the production of H2S is different. CBS and 3-MST are the main sources of H2S in the nervous system, whereas CSE dominates in cardiovascular tissues and liver [10–13]. One of the major organs regulating endogenous H2S generation through cystathionine-β-synthase and cystathionine-γ-lyase is the kidney [14]. And an alternative pathway for H2S formation is the reduction of some sulfur-containing compounds. For instance, cysteine persulfide (a product of the reactions of disulfides and sulfenic acids with H2S) may be synthesized from cystine in the presence of CBS or CSE [15, 16]; thiosulfate and glutathione can produce glutathione persulfide in the presence of sulfurtransferases [17], and cysteine desulfurases can form a protein-bound persulfide from cysteine. All above
persulfides can release $\text{H}_2\text{S}$ in the presence of necessary reductants [18, 19].

**The role of $\text{H}_2\text{S}$ in the respiratory chain**

The catabolic pathway of $\text{H}_2\text{S}$ in mitochondria contains mitochondrial inner-membrane-bound sulfide quinone reductase (SQR), which fixes $\text{H}_2\text{S}$ to sulfite ($\text{SO}_3^{2-}$) to produce thiosulfate ($\text{S}_2\text{O}_3^{2-}$); thiosulfate sulfurtransferase (TST) another name is rhodanese), reducing sulfite from thiosulfate by fixating the sulfane sulfur on an –SH-containing substrate, for example, glutathione, to form a persulfide (R-S-SH) species; mitochondrial matrix sulfur dioxygenase, which oxidizes the sulfur atom extracted from persulfide, converting it again into sulfite; mitochondrial sulfite oxidase, which further oxidizes sulfite into sulfate $\text{SO}_4^{2-}$. $\text{H}_2\text{S}$ causes protection from the oxidative stress in part by the inner membrane component sulfide quinone oxidoreductase, the latter transferring the electrons from $\text{H}_2\text{S}$ to the electron transport chain and coenzyme Q [19-21].

The most effective system to control the $\text{H}_2\text{S}$ levels appears to be localized in mitochondria and is evolutionary related to the detoxification and energy producing systems. The fact that the evident tissue formation of $\text{H}_2\text{S}$ under aerobic conditions is much lower than that under anaerobic conditions supports the idea that the main consumption pathways of $\text{H}_2\text{S}$ are oxygen-dependent. In mammalian cells, $\text{H}_2\text{S}$ is the first inorganic reducing substrate for oxidative phosphorylation [3].

The mitochondrial hydrogen sulfide oxidation pathway includes several enzymes, and the first is sulfidequinoneoxidoeductase (SQR) localized in the inner mitochondrial membrane. Here, the flavoprotein catalyzes the transfer of electrons from hydrogen sulfide to coenzyme Q producing an intermediate persulfide species that can transfer the sulfane sulfur to a suitable acceptor, possibly glutathione [22, 23]. The sulfane sulfur formed at the expense of SQR can be oxidized to sulfite by sulfur dioxygenase [24] or transferred to sulfite to form thiosulfate by the action of enzymes of the rhadanese family [25].

The findings of Bucci M et al. [26] provide an evidence that $\text{H}_2\text{S}$ acts as an endogenous inhibitor of the phosphodiesterase activity. So, $\text{H}_2\text{S}$ is able to increase mitochondrial energy metabolism by inhibiting phosphodiesterase 2A leading to increased mitochondrial cAMP [4, 27].

The oxidation of hydrogen sulfide in mitochondria is vital in intestinal tissues, in which $\text{H}_2\text{S}$ formation by the microbiota is counteracted by the protective strategies developed by colonocytes. It has been suggested that in these cell types the oxidation of $\text{H}_2\text{S}$ can compete with that of organic substrates, and complexes I and II can act in reverse, accepting electrons from reduced coenzyme Q so as to consume $\text{H}_2\text{S}$ even if cytochrome C oxidase is inhibited [28–32].

$\text{H}_2\text{S}$ in high concentrations inhibits complex IV, decreases the rate of electron transport and proton pumping [4]. This opposite role as inhibitor determines that the mitochondrial oxygen consumption first increases at low $\text{H}_2\text{S}$ concentrations, but then decreases as the concentration of $\text{H}_2\text{S}$ increases. The inhibition of the respiratory chain by exposure to $\text{H}_2\text{S}$ is associated with toxic effects [33]. It is well-known that ATP contains high-energy phosphate bonds and is produced in mitochondria.
and the cytosol via glycolysis, substrate-level phosphorylation, and oxidative phosphorylation. And energy is released by hydrolysis of the phosphate bond. Many chemoautotrophic and photoautotrophic bacteria and certain animals use sulfide as an energy substrate [34].

In the work [35], the vasorelaxant effect of H$_2$S is shown in vivo and in vitro. The intravenous bolus injection of H$_2$S transiently decreased blood pressure of rats. The modulatory influence of H$_2$S on K$_{ATP}$ channels the authors explained by a direct interaction of H$_2$S and K$_{ATP}$ channel proteins. So, hydrogen sulfide may induce the reduction of disulfide bonds of the K ATP channel protein. In other words, H$_2$S may function as an energy substrate to sustain ATP synthesis under stress conditions, for example, in hypoxia, it may help to produce more ATP [34].

For the first time, the authors showed that NO appears to be a physiological modulator of the endogenous production of H$_2$S by increasing the CSE expression and stimulating CSE activity. CBS and CSE can translocate to mitochondria under stress conditions, to stimulate mitochondrial H$_2$S and adenosine triphosphate production [36–38].

Hydrogen sulfide can radically decrease metabolic demand, meaning that the metabolism of H$_2$S in mitochondria may serve as a means for energy supplementation. The cysteine level inside mitochondria is 3 times higher than in the cytosol. CSE translocation is promoted by the growing level of intracellular calcium levels via the calcium ionophore. The translocation of CSE to mitochondria metabolizes cysteine, produces H$_2$S inside mitochondria, and stimulates the energy production [34, 36].

### 3-MST and its role in the bioenergetic process

In mitochondria a source of H$_2$S is mercaptopyrivate sulfurtransferase, expressed predominantly in kidney cells, liver cells, cardiac cells, proximal tubular epithelium, pericentral hepatocytes, and neuroglial cells [9-13].

The crystal structure of MST reveals a mixture of the product complex containing pyruvate and an active site of cysteine persulfide (Cys248-SSH), and a nonproductive intermediate in which 3-MP is covalently linked via a disulfide bond to an active site of cysteine [19]. According to study [38], in the crystal structure of 3-MST an Asp-His-Ser catalytic triad is positioned to activate the nucleophilic cysteine residue and participate in general acid-base chemistry, whereas the kinetic analysis shows that thioredoxin is likely to be the principal physiological persulfide acceptor for mercaptopyrivate sulfurtransferase.

An additional enzymatic reaction that occurs mainly in mitochondria is the conversion of 3-mercaptopyruvate to H$_2$S and pyruvate. The reaction is catalyzed by 3-MST and needs the activity of CAT, which also is known as aspartate aminotransferase, converting cysteine and -ketoglutarate to glutamate and 3-mercaptoproyvate. α-cysteine that is not generated in mammalian tissues but can be consumed by food is converted by α-aminotransferase to 3-mercaptoproyvate, a substrate for 3-MST [9, 13, 19].

The role of 3-MST in the regulation of cellular bioenergetics is realized in several ways [4, 39]. 3-MP in low concentrations produces H$_2$S and stimulates the effect on bioenergetic parameters, and this process is suppressed by the silencing of 3-MST. A higher activity of
3-MST inhibits the cellular bioenergetic answer, and limiting of SQR suppresses both basal and 3-MP mediated activation of bioenergetic function as well as the L-cysteine-mediated stimulation of mitochondrial oxygen consumption. Cysteine and α-ketoglutarate activate the mitochondrial electron transport, and these effects are attenuated by the CAT inhibitor aspartate. The 3-MP-derived, 3-MST-mediated production of H2S donates electrons into the mitochondrial electron transport chain via SQR at the level of Complex II. The activating effect of enzyme on bioenergetics decreased with oxidative stress. Since 3-MP is the substrate for 3-MST, mercaptic acids structurally similar to 3-MP would inhibit the activity of MST. Incidentally, ketobutyrate, keto-glutarate, and pyruvate were shown to be uncompetitive inhibitors of 3-MST with respect to 3-MP [29, 40–42].

H2S is eliminated following the persulfide transfer in these reactions:
\[
\text{MST-SH} + 3-\text{MP} \rightarrow \text{MST-S-SH} + \text{pyruvate} \\
\text{MST-S-SH} + \text{R-SH} \rightarrow \text{MST-SH} + \text{R-S-SH} \\
\text{R-S-SH} + \text{RSH} \rightarrow \text{R-S-S-R} + \text{H}_2\text{S}
\]

**Inhibition of mitochondrial Complex IV by H2S**

Mitochondria is one of the major sources of reactive oxygen species (ROS), that causes serious damage to tissues, the aging process and different diseases. Mitochondrial Complex IV is the last enzyme of the electron transport chain in the inner mitochondrial membrane, and is an essential component of aerobic cell respiration and energy generation. As the final enzyme in the respiratory chain, it receives an electron from each of four cytochrome C molecules, and transfers them to one oxygen molecule, converting the latter to two molecules of water. The process contributes to the generation of transmembrane proton and it has been established that H2S in high concentrations, binds to Complex IV, thereby inhibiting the binding of oxygen [43, 44].

The H2S metabolism occurs in three pathways: oxidation, methylation, and reaction with cytochrome C and other metalloproteins or disulfide-containing proteins. The acute toxicity of hydrogen sulfide at the molecular level has been attributed to the inhibition of cytochrome C oxidase [45]. In [4] the authors used the combination of three effects for explaining the complex mode of inhibition: reduction of the cytochrome a3 center, followed by a reaction with molecular O2; reduction of other centers and ligating the ferrocytochrome a3 hem group.

However, at lower H2S concentrations, a non-competitive type of inhibition has also been supposed (Fig. 1). Once the binding of oxygen to Complex IV is inhibited, the inner mitochondrial membrane potential is dissipated and aerobic ATP generation is blocked [30, 46].

The blocking of Complex IV by sulfide includes not only the inhibition of cytochrome aa3 but also a ‘false substrate’ pathway in which a cysteine radical or copper-cysteine complex reacts directly with molecular oxygen. Then the electrons from sulfide follow the normal oxidative way to Complex III, cytochrome C, and Complex IV and then to atomic oxygen to form water [4, 47].

When compared to other substrates of the mitochondrial respiratory chain (NADH, FADH2, succinate, L-alphaglycerophosphate), the yield of sulfide in terms of electrons to be
used by the respiratory chain is relatively low: two molecules of sulfide are necessary to provide two electrons. It is expensive in terms of oxygen: for the same electron transfer in the respiratory Complexes III and IV, sulfide oxidation needs three times more oxygen. And when it takes place, the yield of energy per one oxygen atom consumed is low in comparison with NADH or FADH₂ generated by oxidation of carbon-containing substrates, so sulfide may appear as a poor energy substrate. Therefore, although the exact role of this process remains to be elucidated, sulfide may serve as an ‘emergency’ substrate, or as a substrate that balances and can complement the electron-donating effect of Krebs cycle-derived electron donors [33, 48–50].

In mitochondria, H₂S acts as a cytoprotective factor inhibiting the activity of cytochrome oxidase following ischemia/reperfusion, upregulating the level of superoxide dismutase, and downregulating the levels of ROS. Inhibition of cytochrome oxidase often occurs in the absence of high H₂S levels in tissue [33, 48].

In the work [47], the authors suggest that H₂S poisons mitochondrial respiratory chain by binding to iron of cytochrome C oxygenase, but it also helps to reduce mitochondrial damage and provides cytoprotection. H₂S also acts both as neuroprotector increasing the production of glutathione [51] and as a modulator of the CSE translocation to mitochondria and the supply of the cell with ATP during hypoxia [34,
Because mitochondria play a key role in cell death pathways, H₂S is involved in regulating apoptosis [52, 53]. Downregulation of the endogenous H₂S/CSE pathway, induced by high salt concentration, was involved in mitochondrion-related human vascular endothelial cell apoptosis leading to the leakage of mitochondrial Cyt-C, which activated Caspase-9 and Caspase-3 [51, 54–55]. Not only the concentration of H₂S directs different mitochondrial outcomes, but it may be also important where H₂S is produced inside the cell.

The role of H₂S in diabetes mellitus and other diseases

The biological roles of endogenous H₂S are multiple and rapidly expanding. Its regulatory functions span the nervous system, the regulation of cellular metabolism, the regulation of immunological and inflammatory responses, and various aspects of cardiovascular homeostasis. The metabolic pathway of H₂S and mitochondria take part in different pathological processes in the organism, like diabetes mellitus, diseases of heart, liver, and kidney [56–62]. It was experimentally confirmed significant effects of H₂S production or H₂S donors in cardiovascular diseases, including heart failure, ischemic myocardium, atherosclerosis, and hypertension [53, 58, 63–65]. The authors [46, 58] studied the influence of H₂S levels on cardiac mitochondrial content. They found that restoring H₂S levels with H₂S-releasing prodrug, SG-1002, in the heart failure increased cardiac mitochondrial content, improved mitochondrial respiration, and ATP production efficiency, and as a result improved cardiac function. The study [66] indicates the involvement of H₂S in modulation of changes in the permeability of mitochondrial membranes, which suggests that H₂S plays an important role in the development of cardiovascular diseases.

Others authors reported the changes in metabolism of gasotransmitter and a similar protective effect of H₂S in ischemia reperfusion injury of the kidney [28, 54]. In the review [67] the cellular and molecular mechanisms of protection by H₂S in experimental models of chronic kidney disease are discussed.

H₂S regulates some proteins involved in cellular oxidative stress, which could result in a protective effect against aging. It inhibits the mitochondrial ROS production and prevents activation of the adaptor protein p66Shc [68–71] and reduces the advanced glycation end products toxicity by persulfidating its receptor for advanced glycation end products [69]. Some studies of diabetic disease show that increased extracellular glucose induces mitochondrial dysfunction in endothelial cells [34, 57–59, 70]. This causes the inhibition of cellular bioenergetics through the dysfunction of mitochondrial electron transport and the generation of ATP [68, 71–72].

In work [74], the authors studied an important mechanism for the fine control of insulin secretion from pancreatic β-cells. The study demonstrated that an increase in extracellular glucose concentration lowers the endogenous H₂S level. The possible mechanism of interaction among glucose, H₂S, and the K<sub>ATP</sub> channels may constitute a novel mechanism for the control of insulin secretion from pancreatic β-cells in any pathophysiological conditions. The K<sub>ATP</sub> channels are sensitive to the changes in intracellular ATP concentration. Elevation of intracellular ATP level leads to closure of the K<sub>ATP</sub> channels in many metabolically active
cells. In this way, the K\textsubscript{ATP} channel is a coupling factor to link metabolic activity and membrane excitability. When circulating glucose level elevates, the glucose influx into pancreatic β-cells increases as well as the ATP production. Consequential closure of the K\textsubscript{ATP} channels on plasma membrane depolarizes the membrane and opens the voltage-dependent calcium channels. The final eventuality of this chain reaction increased the insulin release due to elevated intracellular free calcium. In the study it was determined that the endogenous H\textsubscript{2}S production from INS-1E cells varies \textit{in vivo} conditions, which significantly affects the insulin secretion from INS-1E cells. H\textsubscript{2}S stimulates the K\textsubscript{ATP} channels in INS-1E cells, independently of the activation of cytosolic second messengers, which may underlie H\textsubscript{2}S-inhibited insulin secretion from these cells.

There is a hypothesis [71] that H\textsubscript{2}S provides physiological reducing and antioxidant intracellular environment within the endothelial cells, which helps to support normal mitochondrial functions. So, ROS from hyperglycemic mitochondria directly reacts with and consumes the intracellular H\textsubscript{2}S, which then induces additional mitochondrial dysfunction, possibly by oxidative modification of mitochondrial proteins. This positive feed-forward cycle may then lead to a mitochondrial dysfunction where molecular oxygen is utilized to produce ROS instead of ATP, and where mitochondrial efficacy is diminished.

Noteworthy, some authors [4, 52, 38, 70–77] reported that H\textsubscript{2}S exerts protective effects against the development of diabetic complications, at least protecting the mitochondria. The level of sulfide is decreased in diabetes, in part due to an increase in consumption of sulfide by ROS production, which causes the down-regulation of H\textsubscript{2}S-producing enzyme in endothelial cells, CSE. The results of the study [78] evidence that the CSE-produced hydrogen sulfide protects beta-cells from glucotoxicity via regulation of expression of the thioredoxin binding protein-2 levels and thus prevents the development of type 2 diabetes.

H\textsubscript{2}S has a protective effect on endothelial cell apoptosis induced by high glucose level [52]. This effect was linked to the increased superoxide dismutases activity and decreased generation of reactive oxygen species and level of thiobarbituric acid products, which subsequently attenuated the high glucose impaired antioxidative activities. Genetic expression or pharmacological supplementation of H\textsubscript{2}S-producing enzymes in hyperglycaemic cells reduces the mitochondrial ROS formation [38] and exerts the cytoprotective effect, including normalization of mitochondrial bioenergetics (recovery of oxidative phosphorylation, inhibition of glycolysis) [35, 58].

Additionally, sulfide protects against the activation of pro-inflammatory signaling pathways in endothelial cells with hyperglycemia (inflammatory cytokine production and NF-κB activation) [79–81], against reduction in matrix protein synthesis and remodeling [82–84]. However, a specific role of H\textsubscript{2}S in some diseases remains to be investigated.

**Conclusions**

In mammals, the endogenous H\textsubscript{2}S is synthesized from homocysteine and cysteine through the enzymes of the transsulfuration pathway. These enzymes are cystathionine-β-synthase, cystathionine-γ-lyase, cysteine aminotransferase, and mercaptopyruvate sulfurtransferase.
In mitochondria, H$_2$S is produced by mercaptopyruvate sulfurtransferase. H$_2$S may function as the source of electrons to sustain ATP synthesis under stress conditions, but in high concentration H$_2$S inhibits Complex IV, blocking electron transport and proton pumping.

The interaction between glucose in high concentration, H$_2$S and the K$_{ATP}$ channel may constitute a novel mechanism for the control of insulin secretion. The positive impact of H$_2$S on bioenergetic function in mitochondria may have a therapeutic effect against diabetic complications. The problems discussed and the processes of synthesis and regulation of H$_2$S enzymes in mitochondria need further investigation in this promising field of research.

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**Hydrogen sulfide and mitochondria**

Гідроген сульфід і мітохондрія

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Існують різні дані про роль гідрогену сульфіду (H$_2$S) в каталітичних та енергетичних процесах, але біохімічні механізми різноманітних ефектів H$_2$S ще недостатньо вивчені. Ферментативний синтез H$_2$S здійснюється цистатіонін-γ-ліазою, цистатіонін-β-синтазою, цистеїн амінотрансферазою, а в мітохондріях – 3-меркаптопіруват сульфуртрансферазою. H$_2$S може функціонувати як енергетичний субстрат для підтримки синтезу АТФ в умовах стресу, але при високій концентрації молекула інгібуювала комплекс IV, блокуючи перенесення електронів. Взаємодія між високим рівнем глюкози, сірководнем і K$_{ATP}$-каналами може стати новим механізмом контролю секреції інсуліну, а ефект H$_2$S на біоенергетичну функцію можна застосовувати при ускладненнях багатьох захворювань.

**Ключові слова:** гідроген сульфід, мітохондрія, енергетичний обмін.

Сероводород и митохондрия

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Существуют различные данные о роли сероводорода (H$_2$S) в каталитических и энергетических процессах организма, но биохимические механизмы всевозможных эффектов H$_2$S еще недостаточно изучены. Ферментативный синтез H$_2$S осуществляется цистатионин-γ-лиазой, цистатионин-β-синтазой, цистеин аминотрансферазой, а в митохондриях – 3-меркаптопируват сульфуртрансферазой. H$_2$S может функционировать как энергетический субстрат для поддержания синтеза АТФ в условиях стресса, но в высокой концентрации молекула ингибирует комплекс IV, блокируя перенос электронов. Взаимодействие между высоким уровнем глюкозы, сероводородом и K$_{ATP}$-каналом может стать новым механизмом контроля секреции инсулина, а эффект H$_2$S на биоенергетическую функцию возможно применять при осложнениях многих заболеваний.

**Ключевые слова:** сероводород, митохондрия, энергетический обмен.

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