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Hydrogen sulfide and mitochondria

I. V. Gerush, Ye. O. Ferenchuk

Higher State Educational Establishment of Ukraine «Bukovinian State Medical University»
2, Theatralna sq., Chernivtsi, Ukraine, 58002
yelena_f@ukr.net

There are different opinions about the role of hydrogen sulfide (H_2S) in catalytic and energy processes, but the biochemistry of all possible effects of H_2S is not well studied yet. The enzymatic synthesis of H_2S is catalyzed by cystathionine-γ-lyase, cystathionine-β-synthase, cysteine aminotransferase and in mitochondria by 3-mercaptopyruvate sulfurtransferase only. H_2S may function as an energy substrate to sustain the ATP synthesis under stress conditions, but in high concentration H_2S inhibits respiratory complex IV, blocking electron transport and proton pumping. The interaction between glucose in high concentrtaion, H_2S, and the K_{ATP} channels may constitute a novel mechanism for the control of insulin secretion. The positive effect of H_2S 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 (H_2S) as a potent signaling molecule greatly advanced over the last years, though the biomolecule is known from the very beginning of the life evolution. H_2S 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 H_2S 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 H_2S first appeared. H_2S represents an inorganic reducing substrate for oxidative phosphorylation in mammals [3]. The interest in studying H_2S was triggered by its potential importance for health. The attempt to describe the pathways of formation, to determine a biological role, to characterize and

explain the physiological effects and to synthesize donors of the biomolecule are promising for innovation of the effective pharmacological treatment. H_2S 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 H_2S 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 H_2S in mitochondria, the regulation of cellular bioenergetics and the influence on diabetes mellitus.

The enzymology of H_2S formation

In mammals, the endogenous H_2S 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 H_2S [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 H_2S. CSE catalyzes the elimination of cystathionine to produce cysteine, a-ketobutyrate and ammonia. Alternatively, CSE can form H_2S 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 H_2S is different. CBS and 3-MST are the main sources of H_2S in the nervous system, whereas CSE dominates in cardiovascular tissues and liver [10–13]. One of the major organs regulating endogenous H_2S generation through cystathionine-β-synthase and cystathionine-γ-lyase is the kidney [14]. And an alternative pathway for H_2S formation is the reduction of some sulfur-containing compounds. For instance, cysteine persulfide (a product of the reactions of disulfides and sulfenic acids with H_2S) 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 H_2S in the presence of necessary reductants [18, 19].

The role of H_2S in the respiratory chain

The catabolic pathway of H_2S in mitochondria contains mitochondrial inner-membrane-bound sulfide quinone reductase (SQR), which fixes H_2S to sulfite (SO_3^{2-}) to produce thiosulfate ($S_2O_3^{2-}$); 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 SO_4^{2-}. H_2S causes protection from the oxidative stress in part by the inner membrane component sulfide quinone oxidoreductase, the latter transferring the electrons from H_2S to the electron transport chain and coenzyme Q [19-21].

The most effective system to control the H_2S 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 H_2S under aerobic conditions is much lower than that under anaerobic conditions supports the idea that the main consumption pathways of H_2S are oxygen-dependent. In mammalian cells, H_2S is the first inorganic reducing substrate for oxidative phosphorylation [3].

The mitochondrial hydrogen sulfide oxidation pathway includes several enzymes, and the first is sulfidequinoneoxidoreductase (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 rhodanese family [25].

The findings of Bucci M *et al.* [26] provide an evidence that H_2S acts as an endogenous inhibitor of the phosphodiesterase activity. So, H_2S 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 H_2S 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 H_2S 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 H_2S even if cytochrome C oxidase is inhibited [28–32].

H_2S 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 H_2S concentrations, but then decreases as the concentration of H_2S increases. The inhibition of the respiratory chain by exposure to H_2S 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_2S is shown *in vivo* and *in vitro*. The intravenous bolus injection of H_2S transiently decreased blood pressure of rats. The modulatory influence of H_2S on K_{ATP} channels the authors explained by a direct interaction of H_2S 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_2S 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_2S by increasing the CSE expression and stimulating CSE activity. CBS and CSE can translocate to mitochondria under stress conditions, to stimulate mitochondrial H_2S and adenosine triphosphate production [36–38].

Hydrogen sulfide can radically decrease metabolic demand, meaning that the metabolism of H_2S 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_2S inside mitochondria, and stimulates the energy production [34, 36].

3-MST and its role in the bioenergetic process

In mitochondria a source of H_2S is mercaptopyruvate 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 triadis 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 mercaptopyruvate sulfurtransferase.

An additional enzymatic reaction that occurs mainly in mitochondria is the conversion of 3-mercaptopyruvate to H_2S 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-mercaptopyruvate. α-cysteine that is not generated in mammalian tissues but can be consumed by food is converted by α-aminotransferase to 3-mercaptopyruvate, 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_2S 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 H_2S 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, ketoglutarate, and pyruvate were shown to be uncompetitive inhibitors of 3-MST with respect to 3-MP [29, 40–42].

H_2S is eliminated following the persulfide transfer in these reactions:

$$\text{MST-SH} + \text{3-MP} \rightarrow \text{MST-S-SH} + \text{pyruvate}$$
$$\text{MST-S-SH} + \text{R-SH} \rightarrow \text{MST-SH} + \text{R-S-SH}$$
$$\text{R-S-SH} + \text{RSH} \rightarrow \text{R-S-S-R} + H_2S$$

Inhibition of mitochondrial Complex IV by H_2S

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 H_2S in high concentrations, binds to Complex IV, thereby inhibiting the binding of oxygen [43, 44].

The H_2S 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 O_2; reduction of other centers and ligating the ferrocytochrome a3 hem group

However, at lower H_2S 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, $FADH_2$, succinate, L-alphaglycerophosphate), the yield of sulfide in terms of electrons to be

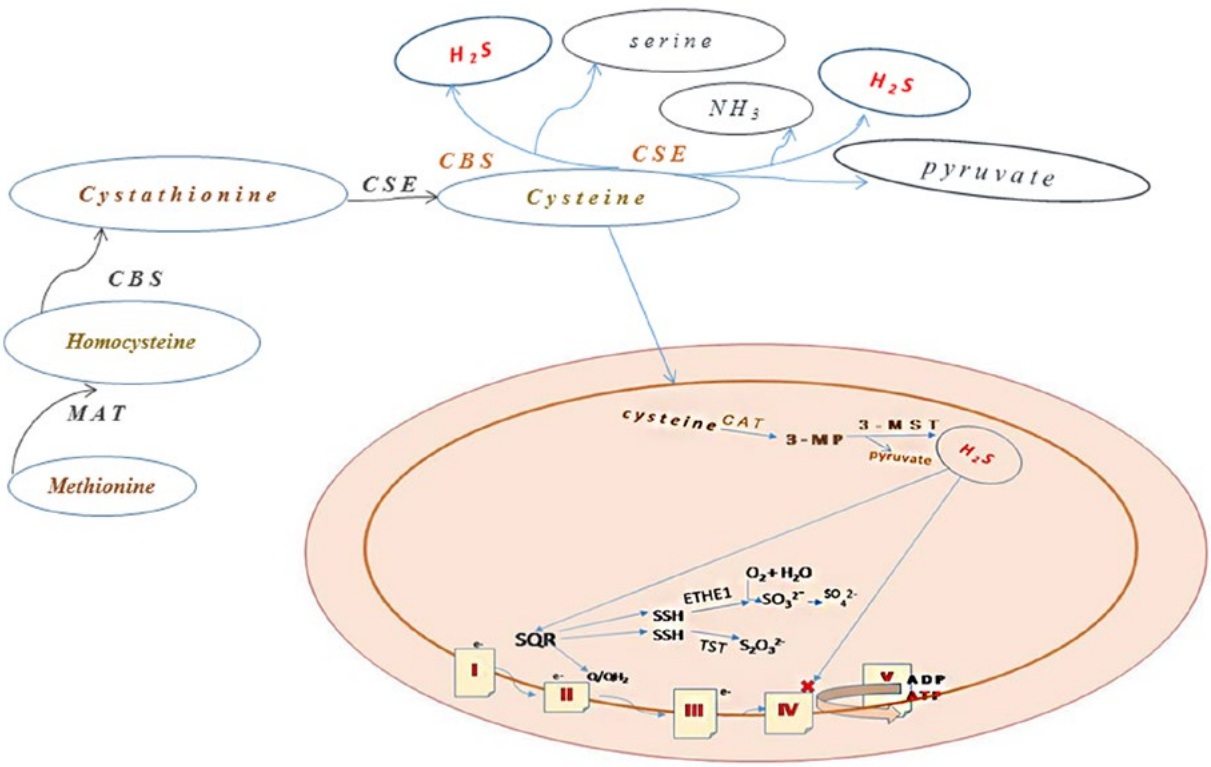

Fig. 1. Synthesis of hydrogen sulfide and its role in the mitochondrial respiratory chain

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 $FADH_2$ 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, H_2S 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 H_2S levels in tissue [33, 48].

In the work [47], the authors suggest that H_2S poisons mitochondrial respiratory chain by binding to iron of cytochrome C oxygenase, but it also helps to reduce mitochondrial damage and provides cytoprotection. H_2S 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,

36, 37]. Because mitochondria play a key role in cell death pathways, H_2S is involved in regulating apoptosis [52, 53]. Downregulation of the endogenous H_2S/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 H_2S directs different mitochondrial outcomes, but it may be also important where H_2S is produced inside the cell.

The role of H_2S in diabetes mellitus and other diseases

The biological roles of endogenous H_2S 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 H_2S 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 H_2S production or H_2S donors in cardiovascular diseases, including heart failure, ischemic myocardium, atherosclerosis, and hypertension [53, 58, 63–65]. The authors [46, 58] studied the influence of H_2S levels on cardiac mitochondrial content. They found that restoring H_2S levels with H_2S-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 H_2S in modulation of changes in the permeability of mitochondrial membranes, which suggests that H_2S plays an important role in the development of cardiovascular diseases.

Others authors reported the changes in methabolism of gasotransmitter and a similar protective effect of H_2S 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.

H_2S 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 H_2S level. The possible mechanism of interaction among glucose, H_2S, and the K_{ATP} channels may constitute a novel mechanism for the control of insulin secretion from pancreatic β-cells in any pathophysiological conditions. The K_{ATP} channels are sensitive to the changes in intracellular ATP concentration. Elevation of intracellular ATP level leads to closure of the K_{ATP} channels in many metabolically active

cells. In this way, the K_{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_{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_2S production from INS-1E cells varies *in vivo* conditions, which significantly affects the insulin secretion from INS-1E cells. H_2S stimulates the K_{ATP} channels in INS-1E cells, independently of the activation of cytosolic second messengers, which may underlie H_2S-inhibited insulin secretion from these cells.

There is a hypothesis [71] that H_2S 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_2S, 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_2S 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_2S-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_2S 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 antioxidant activities. Genetic expression or pharmacological supplementation of H_2S-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_2S in some diseases remains to be investigated.

Conclusions

In mammals, the endogenous H_2S 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_2S is produced by mercaptopyruvate sulfurtransferase. H_2S may function as the source of electrons to sustain ATP synthesis under stress conditions, but in high concentration H_2S inhibits Complex IV, blocking electron transport and proton pumping.

The interaction between glucose in high concentration, H_2S and the K_{ATP} channel may constitute a novel mechanism for the control of insulin secretion. The positive impact of H_2S 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_2S enzymes in mitochondria need further investigation in this promising field of research.

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Гідроген сульфід і мітохондрія

І. В. Геруш, Є. О. Ференчук

Існуть різні дані про роль гідроген судьфіду (H_2S) в каталітичних та енергетичних процесах, але біохімічні механізми різноманітних ефектів H_2S ще недостатньо вивчені. Ферментативний синтез H_2S здійснюється цистатіонін-γ-ліазою, цистатіонін-β-синтазою, цистеїн амінотрансферазою, а в мітохондріях – 3-меркаптопіруват сульфуртрансферазою. H_2S може функціонувати як енергетичний субстрат для підтримки синтезу АТФ в умовах стресу, але при високій концентрації молекула інгібує 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_2S на біоенергетичну функцію можна застосовувати при ускладненнях багатьох захворювань.

Ключові слова: гідрогену сульфід, мітохондрії, енергетичний обмін.

Сероводород и митохондрия

И. В. Геруш, Е. А. Ференчук

Существуют различные данные о роли сероводорода (H_2S) в каталитических и энергетических процессах организма, но биохимические механизмы всевозможных эффектов H_2S еще недостаточно изучены. Ферментативный синтез H_2S осуществляется цистатионин-γ-лиазой, цистатионин-β-синтазой, цистеин аминотрансферазой, а в митохондриях – 3-меркаптопируват сульфуртрансферазой. H_2S 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_2S на биоэнергетическую функцию возможно применять при осложнениях многих заболеваний.

Ключевые слова: сероводород, митохондрия, энергетический обмен.

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