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Role of hydrogen sulfide in skeletal muscle biology and metabolism

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Abstract

Hydrogen sulfide (H_2S) is a novel endogenous gaseous signal transducer (gasotransmittor). Its emerging role in multiple facets of inter- and intra-cellular signaling as a metabolic, inflammatory, neuro and vascular modulator has been increasingly realized. Although H_2S is known for its effects as an anti-hypertensive, anti-inflammatory and anti-oxidant molecule, the relevance of these effects in skeletal muscle biology during health and during metabolic syndromes is unclear. H_2S has been implicated in vascular relaxation and vessel tone enhancement, which might lead to mitigation of vascular complications caused by the metabolic syndromes. Metabolic complications may also lead to mitochondrial remodeling by interfering with fusion and fission, therefore, leading to mitochondrial mitophagy and skeletal muscle myopathy. Mitochondrial protection by H_2S enhancing treatments may mitigate deterioration of muscle function during metabolic syndromes. In addition, H_2S might upregulate uncoupling proteins and might also cause browning of white fat, resulting in suppression of imbalanced cytokine signaling caused by abnormal fat accumulation. Likewise, as a source for H^+ ions, it has the potential to augment anaerobic ATP synthesis. However, there is a need for studies to test these putative H_2S benefits in different patho-physiological scenarios before its full-fledged usage as a therapeutic molecule. The present review highlights current knowledge with regard to exogenous and endogenous H_2S roles in skeletal muscle biology, metabolism, exercise physiology and related metabolic disorders, such as diabetes and obesity, and also provides future directions.

Keywords

Hydrogen sulfide; skeletal muscle; ATP; mitochondria; diabetes; obesity

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Hydrogen sulfide (H_2S) is a novel endogenous gaseous signal transducer and its emerging role in multiple facets of inter- and intra-cellular signaling as a metabolic, inflammatory, neuro and vascular modulator has been increasingly realized. It is produced enzymatically by different prokaryotes and eukaryotes. Since detection of the endogenous H_2S presence, the perception of H_2S as a poisoning gas has been changed. While liver has been

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documented to generate majority of the endogenous H_2S, kidney also produces decent levels of H_2S [1]. Production of H_2S in other organs is relatively very less [1]. In addition to organ specific differences in H_2S production, species specific variations within H_2S production were also reported. For example, in contrast to the mouse scenario, the ability of rat brain tissue to generate H_2S is comparable to the rat liver tissue [2]. Discovery that H_2S production in cardiovascular tissue and the role of H_2S as a vasodilator and modulator of hypertension [3], has numerous implications in regulation of nutrient supply to different end organs. Recently, it was also observed that mouse colon tissue also makes significant levels of H_2S [4]. These studies have highlighted broader distribution of H_2S generating enzymes in different tissues and H_2S function in multiple tissue homeostasis.

The total H_2S pool in the body at any given time is dynamic and can come from diverse sources. For instance, gut bacteria were also reported to engender significant amount of H_2S [5]. Furthermore, human diet that is rich in organosulfur compounds such as garlic, onions, leeks and chives have been reported to contribute to H_2S pool and to exert significant influence on the metabolic state and hypertension [6]. Nonetheless, regulated H_2S production at defined tissue milieu and sub-cellular spaces occurs through specific enzymes. Thus far, three main enzymatic contributors of endogenous H_2S have been identified namely: cystathionine γ-lyase (CSE), cystathionine β-synthase (CBS), and 3 mercaptopyruvate sulfurtransferase (3MST) enzymes [7]. These enzymes use sulfur containing amino acids cysteine and homocysteine as substrates to produce H_2S in a single or multi-step process. The enzymes CBS and CSE have been demonstrated to localize in cytoplasm, and 3MST is localized mainly in mitochondria although small quantities of this enzyme may also be present in cytosol [8, 9]. Excellent reviews detailing molecular pathways of endogenous H_2S production with necessary co-factors are available for readers and are not discussed in detail in the present review [10–14]. Here we will provide an overview of perceived and predicted functions of H_2S in skeletal muscle biology, exercise physiology, bio-energetics and metabolic disorders, such as diabetes and obesity.

1.1 H_2S role in skeletal muscle biology

Species specific differences were reported with regard to expression of CBS and CSE enzymes in skeletal muscles. Human skeletal muscles express significant amounts of CBS and CSE [15], whereas mouse skeletal muscles completely lack these enzymes (data in communication and [15]). A recent report suggested that all the three enzymes (CBS, CSE, 3-MST) were present in detectable levels in the rat skeletal muscles [16]. Nonetheless, their expression is very low when compared to that of the liver and kidney. Only human skeletal muscles express CBS and CSE enzymes that are comparable to the expression levels in liver in relative abundance. Given that skeletal muscles are the dominant organ, consequences of such contrasting CBS and CSE expression variation over cysteine and homocysteine metabolism and H_2S signaling are currently unknown. Expression levels of 3MST were not determined in rodent skeletal muscles thus far. Our results (in communication) indicated that mouse skeletal muscles express non-detectable levels of this enzyme. As we only examined the presence of these enzymes in one particular mouse stain (C57) at present, there is a need for confirmation of these findings in other mouse stains before any further conclusions. Nevertheless, studies from ovine and bovine tissues also indicated that skeletal muscles

express the least amount of 3MST when compared to that of the other tissues [17]. In contrast to mouse skeletal muscles, rat muscles were shown to express considerable levels of 3MST [18]. Contribution of these species specific H_2S production differences in skeletal muscle biology and function are currently unknown.

Nonetheless, studies suggested that with age there is an increase in plasma homocysteine (Hcy), precursor for H_2S, levels which is correlated with enhanced risk for decline in physical function [19, 20]. However, it is not clear whether such decline in physical function is because of changes in H_2S levels as well. Due to complete lack of H_2S producing enzymes in mouse skeletal muscles (data communicated), the author has proposed to utilize the mouse skeletal muscles as a unique place to unravel the biology of the H_2S signaling and homocysteine abundance (hyperhomocysteinemia). As the homozygous CBS knockout mice give birth to healthy offsprings [21], it is more unlikely that CBS might have any determinant role during embryonic development. Interestingly, however, higher expression levels of CBS were observed in mouse limb buds of embryonic age E9.5 and E 10.5 [22], suggesting H_2S might involve in tissue specification during the embryonic stage. Future studies are necessary to test if H_2S plays any role in limb bud specification as H_2S can also be produced by the other two enzymes (3MST and CSE). The possible causes for non-detectable levels of H_2S producing enzymes in adult mouse muscles could be due to epigenetic modifications or inbred mouse strain differences, which need to be clarified further.

In lieu of paucity of the knowledge with regard to the H_2S role in skeletal muscle biology, here we are proposing a hypothetical model where in H_2S might exert therapeutic potential in skeletal muscle wasting/fibrosis, resulting from metabolic complications, such as diabetes and obesity. Although there is a need for direct evidence for its role in skeletal muscle function, studies from other tissues/organs do suggest such possibilities [3, 23]. Here we have hypothesized that H_2S presence might reverse abnormal epigenetic changes caused by metabolic syndromes and produce beneficial effects on skeletal muscle vasculature and mitochondrial function (Fig.1). For instance, treatment of brain endothelial cells with H_2S donors has been shown to alter quantities of DNA methyl transferases, which regulate gene expression at promoter level through CpG methylation [24], and thereby confers protection against oxidative damage. Moreover, epigenetic alterations associated with vascular pathologies have been documented [25, 26]. Given that metabolic syndromes induce vascular fibrosis and stiffening [27] and altered gap junctional content and communication at both micro and macro vascular level [28], it is plausible that presence of H_2S might exert protective role through epigenetic changes and restore vascular function. Likewise, protective nature of H_2S in mitochondrial integrity and function were also reported [29, 30]. All these features of H_2S reverse muscle damage and ameliorate metabolic myopathy (Fig. 1).

1.2 H_2S and exercise capacity

The influence of acute H_2S exposure on various biochemical parameters in human skeletal muscles during sub-maximal and maximal exercise was reported before [31–33]. The findings from these studies indicated that there was a shift in metabolism from aerobic to

anaerobic side, as there was significant accumulation of lactate in the blood, especially after inhalation of 5 ppm H_2S during maximal power output without significant change in heart rate and power output capacity [32]. Furthermore, inhalation of higher concentrations of H_2S (10ppm) during sub-maximal exercise was reported to cause decline in oxygen uptake by the tissues without any significant change in arterial blood parameters, lactate concentrations, and aerobic and anaerobic metabolic enzyme activities [31]. These studies underscored the fascinating systemic tolerance to external H_2S inhalation without compromising physical performance.

The apparent shift from aerobic metabolism to anaerobic metabolism was mainly owing to significant reduction in the citrate synthase enzyme levels, the regulator of first rate limiting step in citrate cycle during aerobic metabolism, in the skeletal muscles during maximal power output. There were also increased levels of both lactate and lactate dehydrogenase along with decreased levels of cytochrome C oxidase (CytoCOx) after sub-maximal exercise with concomitant H_2S breathing, but these changes are non-significant. Interestingly, the H_2S mediated inhibition of aerobic metabolism was observed only in men but not in women. Causes for such gender related differences in H_2S impact on skeletal muscle metabolism are yet to be known. It is plausible that sex steroids and thyroid levels might act as confounding factors. Although there is a tendency for overdependence on anaerobic metabolism during exercise in the presence of H_2S, long term adaptations of chronic H_2S presence or absence, both in skeletal muscle metabolism, and in overall physical capacity such as hemoglobin and myoglobin levels, and mitochondrial density are not clear.

It was shown that mild mitochondrial uncoupling prolongs yeast lifespan, as it lowers ROS accumulation [34]. Moreover, eccentric exercise causes ROS accumulation [35] leading to mild muscle damage. Given that H_2S can act as a ROS scavenger [36] and/or mild mitochondrial uncoupler, it is of interest to know whether chronic low doses of H_2S exposure might prolong longevity and enhance benefits of exercise by limiting ROS-induced cellular damage to macro molecules.

1.3 H_2S in mitochondrial energy production and function

In many prokaryotes and eukaryotes H_2S can serve as a source for ATP synthesis [37]. As such, its role in mitochondrial energy production and its influence over different mitochondrial enzymes has been studied. A bell shaped dose dependent oxygen consumption rate (OCR) response, at low concentrations stimulation of OCR and at high concentrations inhibition of OCR, was observed after treating isolated rat mitochondria with H_2S donors [29, 38]. Inhibition of cytochrome c oxidase activity and mitochondrial uncoupling were observed after in vitro treatment of human colon carcinoma cells or isolated enzyme system with H_2S donors [38, 39]. Interestingly, there was statistically non-significant reduction in the total ATP production that is accompanied by significant reduction in OCR after the treatment [39]. Mechanisms of such compensatory ATP production in the H_2S presence are not entirely known [39].

Recently, it was proposed that mitochondria could act as a source for carbon (organic substrates) and sulfide oxidation [40]. While sulfide oxidation provides additional supply of

electrons through a sulfide oxidizing complex [consisting of sulfide quinone reductase (SQR), dioxygenase and sulfurtransferase], the electron flux from organic compound oxidation to quinone pool gets inhibited to keep the electron flux at the same level (because of constant quinine pool) [40]. Hence the presence of H_2S may lead to inhibition of organic compound oxidation and suppression of normal metabolism. Interestingly, when the electron flux from complex I was inhibited by the chemical means, maximal electron flow through the Complex III & IV and maximal OCR were observed in the presence of H_2S donors, suggesting the usage of maximal compensatory electron donation from H_2S when normal metabolism is inhibited [29]. These findings further imply that electron flux from H_2S through SQR and complex I are in competition with each other (Fig. 2). Furthermore, it has been shown that silencing of SQR attenuates L-cysteine stimulated mitochondrial OCR, suggesting that SQR is indispensable for the electron transfer from H_2S [29]. All these studies together imply that 1) SQR complex is the sole oxidizing entity and 2) H2S presence sustains ATP synthesis when normal organic metabolism is inhibited.

Though SQR activities are present in detectable range in liver, kidney and heart tissues, no such noticeable activity was observed in brain tissue, hence the authors suggested that brain has low tolerance for sulfide poisoning, but the other organs exhibit tolerance and possibly preference to H_2S oxidation over carbon oxidation [40]. Although not yet determined, presence of SQR activity in skeletal muscles would explain the earlier observation: H_2S inhalation during acute exercise has no effect, as sulfide oxidation could serve as a potential source for alternative electron flux. Whether such electron flux from sulfide oxidation requires more oxygen consumption [40] awaits further investigation. Nonetheless, coupled respiration and ATP production was observed with chicken liver mitochondria, albeit at low doses of sulfide with reduced oxygen/sulfide ratio [41]. Based on these recent results [40–44], the author proposes the following model, where in SQR complex along with its associated protein entities (not completely defined) could also serve as a proton pump in addition to electron donation to coenzyme Q after sulfide oxidation (Fig. 2). If indeed such a possibility exists, then H_2S can sustain alternative ATP synthesis at low doses in mammalian mitochondria. The future challenge then would be to deliver sustained low levels of H_2S in the mitochondrial matrix without inhibiting CytoCOx function, as higher doses leads to uncoupling.

In addition to the ATP generating role played by H_2S as mentioned above, other protective effects of H_2S on mitochondrial integrity and function have been reported. Furthermore, H_2S was proposed to confer protection of end organs against low oxygen and nutrient supply and its supplementation through chemical donors or enzymatic production was found to protect from ischemic injury in multiple organs including skeletal muscles [18, 30, 45–53]. The protective effects of H2S could be due to the following mechanisms: 1) H_2S upregulated uncoupling proteins (UCPs) in mitochondria attenuated reactive oxygen species (ROS) production thereby prevented mitochondrial injury and consequent neuronal degeneration [54]. Given that uncoupling and ATP generation are mutually exclusive events and H_2S has been implicated in both these processes, it is possible that other factors such as ROS levels, oxygen supply, nutrient supply, functional proteome and available H_2S levels might have a determinant function over the final outcome and suggests dynamic nature of H_2S dependent cellular energy modulation. 2) At very high concentrations H_2S was

proposed to inhibit cytochrome oxidase and metabolism leading to hypothermia and tissue preservation [55]. 3) Inhibition of apoptotic initiation by the H_2S most likely through preservation of mitochondrial integrity [55, 56]. 4) Reducing ability of H_2S was proposed to decrease oxygen utilization during mitochondrial respiration [38].

Together, all these studies imply that H_2S could serve as an alternative route of energy production and suppresses ROS accumulation. These particular abilities of H_2S could offer protection against low nutrient oxygen environments and might also generate enough ATP to withstand temporary adverse conditions. Consistent with this model, recent study also proposed that H_2S can act as an oxygen sensor in hypoxic environments [57]. To conclude, H_2S might orchestrate broader survival signals encompassing from neutralization of ROS species, production of ATP, preservation of mitochondrial function and heat generation to regulation of vascular responses, end organ nutrient supply and regeneration or protection during hypoxia. All these abilities elevate H_2S as a tissue protective molecule especially in cases of crisis and most likely these phenomena also translates in skeletal muscle scenario

2. H_2S and diabetes

Evidence for both pro-diabetogenic and anti-diabetogenic effects of H_2S exists in the literature. Hydrogen sulfide was implicated in hypoinsulinemia and hyperglycemia as higher levels H_2S and CSE expression correlated with reduced pancreatic islet insulin production in Zucker diabetic fatty rats when compared to the control Zucker fatty or lean rats [58]. Further, this study also indicated that the compound (DL-propargylglycine (PPG)) that inhibits H_2S production was able to restore normal serum insulin levels [58]. Based on these findings, it was proposed that H_2S mediated abnormal activation of K_{ATP} channels caused hyperpolarization of pancreatic islets and made them insensitive to hyperglycemia. In a subsequent study, it was also observed that H_2S through p38 MAPK activates endoplasmic reticular stress pathways and causes apoptosis in insulin secreting β-cells [59]. Inhibition of CSE enzyme using pharmacological means resulted in alleviation of acute pancreatitis and lung injury in animal models of pancreatitis [60]. This study suggested that H_2S might augment pancreatic injury and might diminish insulin output. The effects of H_2S over K_{ATP} channels can be explained by its influence as a metabolic suppressor and mitochondrial uncoupler, as described above, and need to be investigated further for mechanistic insights.

In contrast to the above studies, high fructose diet-induced type II diabetes in rats was found to associate with the decline in serum H_2S levels [61]. Interestingly, chronic feeding of raw garlic paste, a commonly used natural food spice containing H_2S donor substances, could not only increase serum H_2S levels but also correlated with improved insulin resistance, reduced triglyceride levels, and enhanced oxidative stress tolerance [61]. Though other studies also reported hypoglycemic effects of garlic extracts in different rat and rabbit models of diabetes, concomitant plasma/serum levels of H_2S were not enumerated in these studies [62–68]. One study indicated no effect of garlic extracts on hyperglycemia [69]. Another recent report suggested that either systemic increase or decrease in H_2S levels by pharmacological means causes reduction in insulin resistance [70], implying varied organ specific metabolic responses to different doses of H_2S.

Future studies are necessary to clarify the above mentioned contradictory nature of H_2S effects on blood glucose and insulin levels. Potential factors for consideration are 1) enhancement of H_2S detection limits without compromising sensitivity and 2) enumeration of long-term effects of H_2S with tandem usage of natural compounds, chemical H_2S donors and endogenous enzymatic enhancers. Different genetic backgrounds and tissue specific responses also need to be evaluated. Notably, the H_2S dose should also be carefully considered to distinguish between physiological and pathological responses.

3. H_2S and obesity

Recently, endogenous CBS and CSE expression and H_2S production were detected in adipose tissues [71]. Although, no significant amount of CBS enzyme have been detected in brown fat, levels of CBS in other adipose tissues (perirenal and epididymal fat) are substantial. Expression of CSE has been more versatile across different adipose tissues. Based on these observations, CSE could act as a main contributor for H_2S production in adipose tissue [71]. The levels of H_2S in adipose tissue are comparable to that of the major endogenous H_2S producing organs [71]. Contribution of 3-MST for adipose tissue derived H_2S and its expression in different kinds of adipose tissues are yet to be unraveled. Along with increase of mice age, adipose tissue was observed to express higher levels of CSE protein and also generated larger amounts of H_2S [71]. As fat mass in any given individual is influenced by age, diet, physical activity and genetic background, determination of adipose derived H_2S contribution to the total plasma H_2S pool would serve to clarify its contribution to metabolic alterations associated with obesity.

As with diabetes, role of H_2S and its association with obesity are not straightforward. In rodent diabetic models, H_2S was found to inhibit glucose uptake by mature adipocytes in a dose dependent manner with or without insulin presence [71]. Importantly, fructose induced insulin resistance was also correlated with enhanced CSE expression and H_2S production in epididymal fat tissue [71]. Given that fructose enhances de novo fat synthesis, contribution of fructose induced H_2S in fat synthesis is not known. Interestingly, it was recently noted that pharmacological enhancement of H_2S levels also reduced lipolysis [70]. Together these studies suggested that a combination of enhanced lipogenesis and reduced lipolysis are associated with increased H_2S levels and rise in H_2S levels may cause obesity syndrome.

In contrast to the H_2S mediated negative effects observed in animal studies involving diabetic models, a recent human prospective study encompassing small group of participants showed that plasma H_2S levels are negatively correlated with type II diabetes [72]. Furthermore, greater waist to hip ratio (higher in obese people) was independently associated with reduced plasma H_2S levels after adjusting for systolic blood pressure, microvascular function, insulin sensitivity, glycemic control and lipid profile variables [72]. In recent studies, link between H_2S effects and UCPs have been observed [39, 54]. Whether H_2S induces UCPs in different tissues, especially in adipose tissue is currently unknown. Given that UCPs are important regulators of browning of white fat, it is most likely that the negative correlation between H_2S levels and fat accumulation in humans may provide a future therapeutic intervention if H_2S upregulates UCPs in adipose tissue. The contradictory

nature of observed correlations between H_2S and obesity syndrome in different species need to be reconciled further to better understand H_2S mediated signaling in adipose tissues.

Conclusions

The salient points from our review with regard to the functions of H_2S in skeletal muscle biology and metabolism are the following: 1) There are species specific and tissue specific variations with regard to expression of enzymatic endogenous H_2S producers and levels of ambient H_2S production. The significance of such variation is currently unknown. Though there have been significant improvements in detection of H_2S quantities in tissues, there is a need for ultrasensitive, dynamic detection of de novo H_2S production. 2) There are limited studies with regard to the role of H_2S in skeletal muscle biology and disease. 3) Though, H_2S has been perceived to serve as an alternative electron donor and modulates oxygen consumption, its role in mitochondrial function and ATP production is yet to be fully uncovered in different pathophysiological scenarios. 4) Many studies point to the protective function of H_2S on mitochondrial integrity and tissue preservation especially during crisis situations. Yet there is a need for comprehensive delineation of mechanistic aspects of such protection. 5) The role of H_2S in diabetes and obesity is rather controversial and need to be fully illustrated further.

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Highlights

- Tissue and species specific differences in endogenous H_2S generators are present.
- H_2S role in skeletal muscle biology and disease is not yet known.
- H_2S might function in anaerobic ATP generation and mitochondrial protection.
- H_2S role in metabolic diseases is controversial and needs further investigation.

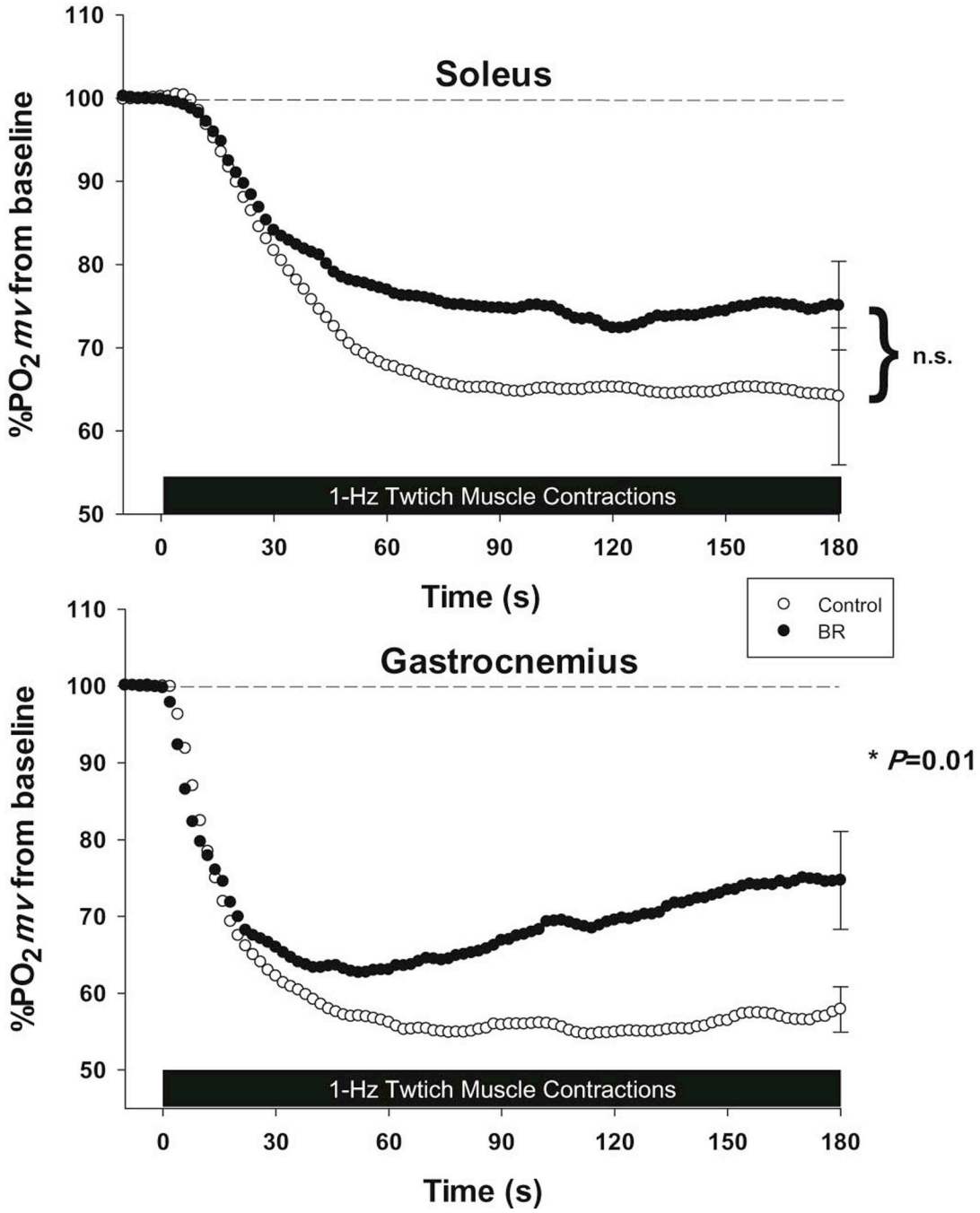

Figure 1.

Hypothetical model for protective function of H_2S in skeletal muscle myopathy/dysfunction induced by metabolic syndromes such as diabetes and obesity. H_2S may reverse changes in epigenetic modifications induced by metabolic syndromes. Metabolic syndromes are perceived to cause vascular [73] and mitochondrial [74] dysfunction potentially through Epigenetic modifications. H_2S by mitigating vascular dysfunction and by preventing mitochondrial damage might reverse deterioration of muscle function as well as alleviation of other symptoms associated with metabolic syndromes.

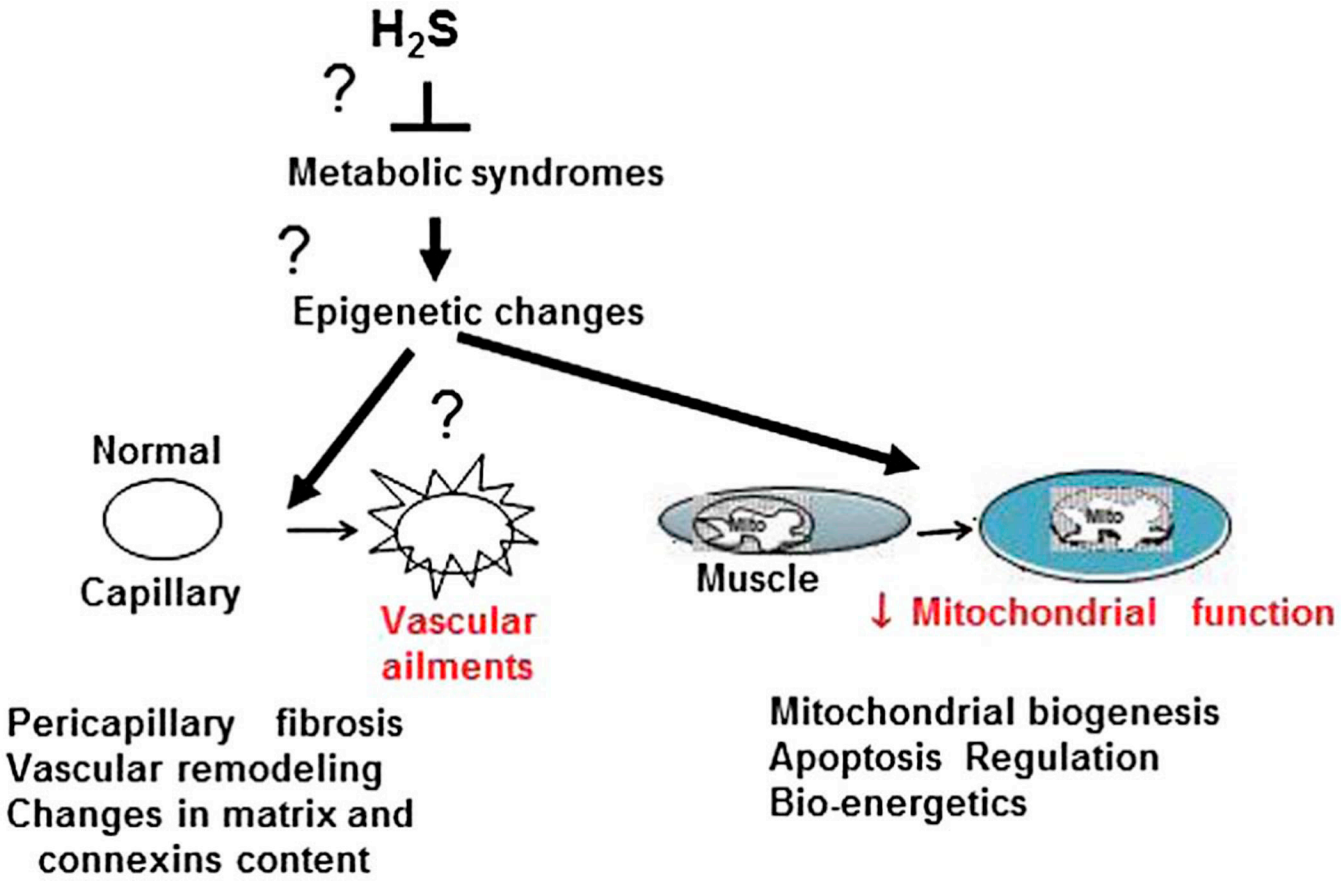

Figure 2.

H_2S mediated ATP generation in mitochondria. In this hypothetical model, H_2S not only supply electrons but also serves as a source for protons. The yet to be fully characterized protein complex may function to supply electrons to quinines and also contribute to proton gradient necessary for ATP generation as a byproduct during H_2S metabolism in mitochondria. The hypothetical protein functional unit most likely involves SQR complex proteins as well [40]. Both cytoplasmic and mitochondrial pool of sulfur containing compounds (such as cysteine) contributes to the H_2S production by locally residing enzymes. Both oxygen (during hypoxic cases) or other compounds as in anaerobes [75] (during hibernation or ischemia) might accept final electrons. Presence of H_2S inhibits organic compound oxidation.