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Mini Review

Potential role of hydrogen sulfide in diabetes-impaired angiogenesis and ischemic tissue repair

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ABSTRACT

Diabetes is one of the most prevalent metabolic disorders and is estimated to affect 400 million of 4.4% of population worldwide in the next 20 year. In diabetes, risk to develop vascular diseases is two-to four-fold increased. Ischemic tissue injury, such as refractory wounds and critical ischemic limb (CLI) are major ischemic vascular complications in diabetic patients where oxygen supplement is insufficient due to impaired angiogenesis/neovascularization. In spite of intensive studies, the underlying mechanisms of diabetes-impaired ischemic tissue injury remain incompletely understood. Hydrogen sulfide (H_2S) has been considered as a third gaso-transmitter regulating angiogenesis under physiological and ischemic conditions. Here, the underlying mechanisms of insufficient H_2S-impaired angiogenesis and ischemic tissue repair in diabetes are discussed. We will primarily focuses on the signaling pathways of H_2S in controlling endothelial function/biology, angiogenesis and ischemic tissue repair in diabetic animal models. We summarized that H_2S plays an important role in maintaining endothelial function/biology and angiogenic property in diabetes. We demonstrated that exogenous H_2S may be a theraputic agent for endothelial dysfunction and impaired ischemic tissue repair in diabetes.

1. Introduction

Diabetes is one of the most prevalent metabolic disorders and is estimated to affect 400 million of 4.4% of population worldwide in the next 20 year [1]. Diabetes has a 2- to 4-fold increased risk to develop vascular diseases compared to non-diabetes [2]. Refractory wounds and critical ischemic limb (CLI) are two of major ischemic vascular complications in diabetic patients where oxygen supplement is insufficient due to impaired angiogenesis/neovascularization. Accumulative studies demonstrated that impaired biology/function and angiogenic property of endothelial cells (ECs) play a critical role in diabetes-induced deficiency of angiogenesis/neovascularization [3–5]. However, the underlying mechanisms remain incompletely understood.

Insufficient gaso-transmitters, including nitric oxide (NO) and1) carbon monoxide (CO) have been considered as crucial regulators of EC dysfunction in diabetes [6]. In the last decades, hydrogen sulfide (H_2S), a "toxic gas with strong odor of rotten eggs", has been found in biological system and considered as the third gaso-transmitters regulating many biological functions [7]. Especially, insufficient production of H_2S has been linked to different pathogenesis of cardiovascular diseases such as hypertension, endothelial dysfunction, myocardial infarction and ischemic limb injury [4,5,8–10], and emerged as an important regulator in diabetes-impaired endothelial cell (EC) function/biology, angiogenesis, wound healing and ischemic lamb repair [4,5]. Administration of H_2S rescued endothelial dysfunction in diabetic animal models [11]. Recently, we provided strong evidence that insufficient production of H_2S plays a crucial role in diabetes-impaired microvascular endothelial function and angiogenesis in ischemic hindlimb (IHL) of db/db mice [4,5]. In this review, we will summarize the current understanding of the role of H_2S in diabetes-impaired EC function, angiogenesis, wound and IHL repair.

2. Endogenous H_2S biosynthesis

In mammalian tissues, H_2S is mainly produced by three pyridoxal-5′-phosphate (PLP)-dependent enzymes, cystathionin-β-synthase (CBS), cystathionine-γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST) in the transulfuration pathway of homocysteine metabolism [12–15]. CBS is predominantly expressed in the central nervous system whereas CSE is abundantly expressed in cardiovascular system [16]. Protein expression of CSE was detected in cultured bovine aortic ECs and human umbilical vein ECs, and endothelial layer of vascular tissues in

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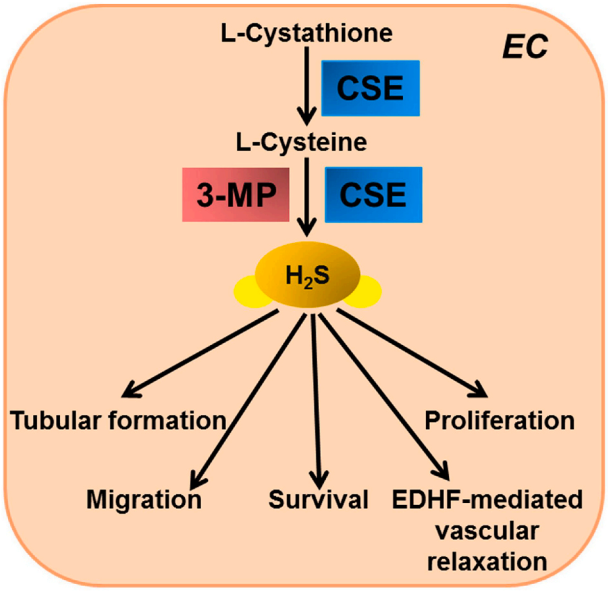

Fig. 1. H_2S synthesis and function in vascular endothelial cells. In vascular endothelial cells (ECs), H_2S is mainly generated by CSE. H_2S plays important role in maintenance of vascular homeostasis, endothelial function and reparative property of ECs. H_2S: hydrogen sulfide; CSE: cystathioine-γ-lyase; 3-MST: mercaptopyruvate sulfurtransferase.

wild-type mice [4,5,17]. H_2S is produced in both vascular ECs and VSMCs mainly by activation of CSE [5,17–21]. Recent studies have shown 3-MST, along with cysteine aminotransferase (CAT), which produces H_2S in the brain as well as in the vascular endothelium (Fig. 1) [15,22]. Physiological level of H_2S is in wide range between 15 nM and 300 μM depending on detection methods and the tissues analyzed [23–31]. In fact, the concentration of free H_2S in vascular tissues is around 100 times greater than that in the other tissues [26,32], implying that H_2S is critical in the regulation of vascular homeostasis, endothelial function and angiogenic property of ECs.

In addition to enzymatic synthesis pathways, endogenous H_2S can also be produced through non-enzymatic processes which have not been well understood or characterized. Studies have reported that many factors are involved in non-enzymatic production of H_2S, including glucose, glutathione, inorganic and organic polysulfides and elemental sulfur [33]. H_2S can be generated from glucose either via glycoclysis or from phosphoglyconate via NADPH oxidase or reacting with sulfur-containing amino acid methionine, homocysteine or cystenine [34]. H_2S can be also produced by direct reduction of glutathione and elemental sulfur through reducing equivalents of the glucose oxidation pathway [35]. Moreover, thiosulfate results from a reduction reaction involving pyruvate is an intermediate of sulfur metabolism from cysteine and a metabolite of H_2S that can also lead to the production of H_2S [35].

H_2S can be enzymatically oxidized to sulfur atom in mitochondria by sulfide:quinone oxidoreductase [36]. This sulfur atom is then transferred to reduced glutathione to form glutathione persulfide (GSSH) and then may be either oxidized to sulfite (SO_3^{2-}) by sulfur dioxygenase (persulfide dioxygenase, protein deficient in ethylmalonic encephalopathy, ETHE1) or transferred to sulfite by thiosulfate:cyanide sulfurtransferase (TST, rhodanese) to form thiosulfate ($SSO3^{2-}$) [37,38]. Sulfite is further oxidized to sulfate ($SO4^{2-}$) by sulfite oxidase. It was suggested that physiological concentration of H_2S is maintained by its efficient oxidation [39]. However, under low oxygen supply (oxidative stress), H_2S metabolism is compromised. Pathophysiological role of $SO4^{2-}$ remain unclear.

3. H_2S signaling mechanisms

H_2S exerts its biological effects mainly via three routes: 1, Reactive oxygen species (ROS)/reactive nitrogen species (RNS) scavenging; 2, Metal center interaction; 3, S-persulfidation [40]. Compared to the first two routes, S-persulfidation, normally called S-sulfhydration, is the key process for H_2S-mediated biological effects. S-sulfhydration is the process in which a thiol (R–SH) is converted into a perthiol (R–SSH). S-sulfhydration modulates the biological activity of proteins by decreasing the pK_a and increase in nucleophilicity of perthiols with respect to thiols [41]. S-sulfhydration modification as a new post-translational modification is involved in many pathophysiological process including cell survival/death, differentiation, proliferation/hypertrophy, metabolism, endoplasmic reticulum (ER) stress, vascular relaxation, inflammation, oxidative stress [42]. Recently, insufficient Keap1 S-sulfhydration in ECs has been suggested to be involved in pathogenesis of atherosclerosis in STZ-induced diabetic low-density lipoprotein receptor $(LDLr)^{-/-}$ mice [43]. S-sulfhydration modification of targeted proteins from H_2S may provide novel targets for therapeutic/prevention of ischemic tissue repair in diabetes.

4. H_2S in diabetes

The synthesis of H_2S is known to be reduced in diabetic patients and animal models [43,44]. Plasma H_2S was significantly decreased in high fat diet-induced diabetic $LDLR^{-/-}$ mice [43]. In streptozotocin (STZ)-induced diabetic rats, blood H_2S level were lower compared with age-matched non-diabetic rats [45]. Endogenous H_2S production was also found to be reduced in type 2 diabetic animals [5,46,47]. Plasma H_2S levels were significantly reduced in non-obese diabetic mice [46]. Renal CSE and CBS expression and H_2S production are markedly lowered in spontaneous diabetic Akita mice [44]. Deficient CSE delayed the onset of STZ-induced type 1 diabetes, and diabetes was accompanied by increased pancreatic CSE and CBS protein expression [48]. Recently, we examined H_2S production in small mesenteric arteries of type 2 diabetic db/db mice and non-diabetic db/+ mice with two different methodologies [5]. Using a florescent probe, we found that H_2S production in small mesenteric arteries was decreased to 65% in db/db mice compared with that in db/+ mice. By RP-HPLC detection, we also found that free sulfide levels were reduced to 63.7% (45.9 pM/mg) in the small mesenteric arteries of db/db mice compared with that of db/+ mice [5]. By gas chromatography chemiluminescence and florescent probe, we found that H_2S production was markedly reduced in bone marrow cells (BMCs), plasma and thigh skeletal muscles from db/db mice [4]. We also found that high glucose dose-dependently reduced H_2S production in human microvascular ECs [4]. It has been demonstrated that the negative association between type 2 diabetes and H_2S is reinforced by decreased plasma H_2S levels [45,49]. Understanding the mechanisms of insufficient H_2S-impaired EC function may provide therapeutic targets for ischemic tissue injury in diabetes.

One of the underlying mechanisms of diabetes-impaired H_2S production is suggested to be related to hyperglycemia-enhanced H_2S consumption through mitochondria-derived reactive oxygen species (ROS) signaling pathways in ECs [50]. ROS scavenger or mitochondrial uncoupling agents prevented H_2S consumption in high glucose-treated ECs [50]. Another underlying mechanism may be related to down-regulation/inactivation of H_2S synthesis enzymes [5,44,47,48]. In good accordance with above studies, we also provide strong evidence that superoxide generation was enhanced whereas H_2S production was reduced in the lung ECs and/or small mesenteric arteries of db/db mice (Table 1) [5]. Moreover, we demonstrated that decreased H_2S production in microvascular ECs is also related to downregulation of CSE levels although studies to understand the underlying mechanisms of diabetes-downregulated CSE level are warranted [5]. Taken together, diabetes is associated with increased ROS-linked H_2S consumption and CSE-mediated H_2S reduction which might be related to increased

cardiovascular risk in human and experimental models. The underlying mechanisms of diabetes-impaired H_2S production are still needed to be explored.

5. H_2S as ROS modulator in diabetic ECs

Reactive oxygen species (ROS) generated from ECs is a key factor in the pathogenesis of diabetic complications [51]. H_2S was found to be beneficial against oxidative stress via 2 distinct mechanisms: 1) acts as a direct scavenger of ROS; 2) upregulates antioxidant defense system. Accumulative evidence show that H_2S prevents diabetes-impaired EC biology/function via inhibition of oxidative stress. H_2S reduced ROS formation, improved function and metabolic state of ECs under hyperglycemic condition [50]. H_2S decreased ROS production and apoptosis in hyperglycemic ECs [52], and alleviated vascular abnormality in the aorta of diabetic rats via attenuating NADPH oxidase activity [53]. H_2S decreased high glucose-induced autophagy in ECs though the nuclear factor erythroid2-reated factor 2 (Nrf2)-ROS-5′ adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [54]. Administration of sodium hydrosulfide (NaHS) protected excessive autophagy in arterial ECs of db/db mice via enhancing superoxide dismutase/catalase activity [54]. NaHS improved endothelial function and decreased oxidative stress in STZ-treated diabetic mice [55]. Recently, study also provided an evidence that mitochondria-specific H_2S donor AP123 and AP39 prevented hyperglycemia-triggered oxidative stress and metabolic abnormalities in microvascular ECs [56].

6. H_2S affects metabolism in diabetes and ECs

Although numerous studies reported that H_2S production is reduced in diabetes, the role of H_2S in the metabolism in diabetes remains controversial. Studies have reported that H_2S is essential for maintaining insulin bioactivity and glucose uptake. H_2S was required for vitamin D-induced GLUT4 translocation and glucose uptake [57]. H_2S reduced production of inflammatory cytokine, a known causal factor for the development of insulin resistance in adipose and other metabolic tissues, from resident adipose macrophages [58]. Endogenous glucose production was reduced in CSE KO mice [59]. H_2S may directly stimulate gluconeogenesis via sulfhydration of pyruvate carboxylase, a key enzyme in gluconeogenesis [60]. Mitochondria plays a critical role in cell survival and death by regulating ATP synthesis through lipid and glucose metabolism. Increasing evidence indicate that mitochondrial function changes are implicated in diabetes-impaired EC function [61]. It was found that H_2S protected the vascular endothelium in hyperglycemia by preserving mitochondria function [50]. Mitochondria-targeted H_2S donors AP123 and AP39 increased the electron transport at respiratory complex III and improved the cellular metabolism in high glucose-treated microvascular ECs [56].

7. H_2S is an endothelium-derived hyperpolarizing factor (EDHF)

Endothelium is a single layer of squamous ECs that lines the interior surface of blood vessel lumen. Endothelium is the first target of pathological stimuli from blood. Endothelium mediates blood flow homeostasis and fulfills tissue metabolic demands by supplying nutrients and oxygen. Endothelium regulates vasomotor tone and organ perfusion by releasing by releasing vasodilator substances such as nitric oxide (NO), prostacyclin (PGI_2), and endothelium-derived hyperpolarizing factor (EDHF), and vasoconstrictor substances, such as angiotensin II, endothelin-1, thromboxane A_2 and prostaglandin H_2, in response to pathophysiological stimulation [62,63]. EC impairment thus endothelial dysfunction (ED) which is characterized by an impairment of endothelium-dependent vascular relaxation is an early event in the development of cardiovascular disease. EDHF-mediated vascular relaxation is defined by endothelium-dependent relaxation when production of NO and PGI_2 is blocked. It is generally accepted that NO predominantly controls relaxation of macro-vasculature, whereas EDHF primarily controls relaxation of micro-vasculature and becomes more important when vessel diameter decreases [64–66]. Although extensively studied, the nature of EDHF remains unclear. Many EDHF candidates have been reported including NO, CO, H_2O_2, C-type natriuretic peptide, PGI_2, EETs, trihydroxyeicosatrienoic acid [20,65,67,68]. Current studies support the concept that EDHF-mediated.

Vascular relaxation is elicited by the opening of Ca^{2+}-activated potassium channels (K_{Ca}) in both ECs and vascular smooth muscle cells (VSMCs) [5,18,19,77].

Several lines of evidence indicate that H_2S has a role in the regulation of vascular tone. H_2S induced vascular relaxation in aorta [78–80], gastric artery [81], mesenteric artery [5,82], and internal mammary artery [83]. Accumulative evidence indicate that H_2S is an EDHF [5,17–20,82,84–86]. H_2S induced cell hyperpolarization by patch clamp [86]. By myograph, H_2S induced endothelium-dependent vascular relaxation in the presence of eNOS inhibitor and cyclooxygenase inhibitor [5,18–20,85]. Moreover, H_2S induced vascular relaxation in the presence of eNOS and cyclooxygenase (COX) inhibitor to a greater extent in the rat mesenteric artery than that in the rat aorta [17–19]. Removal of endothelium completely abolished the H_2S-induced relaxation in human and rat mesenteric arteries [18,82]. Endothelium-dependent vascular relaxation to acetylcholine in small mesenteric arteries was virtually abolished in the presence of eNOS and COX inhibitor in CSE knockout mice [20,85], suggesting H_2S is a EDHF. Moreover, studies also found that the vascular relaxation in response to H_2S is achieved via activation of ATP-sensitive potassium channel (K_{ATP}) in smooth muscle cells [19] and endothelial and/or muscular small- (SK_{Ca}), intermediate- (IK_{Ca}) and big- (BK_{Ca}) conductance calcium-activated and voltage-sensitive (K_v) potassium channel [87–91].

8. H_2S in diabetes-impaired vascular relaxation

H_2S exerts protective effects against hyperglycemic stress in the vascular endothelium and exhibits protective effects in animal models of diabetic complication [7,45,49,50,55,92–94]. We and others reported that H_2S deficiency plays an important role in the pathogenesis of cardiovascular complications in diabetes [3,5,45,49,50,55,92–95]. Low levels of H_2S in the blood of diabetes and overweight patients and STZ-treated rats cause vascular inflammation [45,49]. Exogenous H_2S is beneficial for prevention/therapeutics of diabetes-induced cardiovascular complications, such as rescued oxidative stress, endothelial dysfunction and cardiomyopathy in STZ-induced diabetic mice/rats [55,95]; reduced blood pressure and prevented the progression of diabetic nephropathy in spontaneously hypertensive rats [92]; decreased reactive oxygen species (ROS) and vascular inflammation markers in high glucoses-treated human monocytes [93]; improved metabolic state and mitochondria function of ECs under hyperglycemia condition [50].

Although many studies reported that H_2S production was decreased in diabetes, vascular relaxation response to H_2S was enhanced in thoracic aorta, mesenteric, pulmonary and carotid arteries of STZ- or alloxan-induced diabetic animal models [96–98]. Diabetes-enhanced vascular relaxation response to H_2S has been suggested to be a compensatory mechanism overcome insufficient H_2S production and impaired endothelial function by increasing sensitivity of vasculature to H_2S [5,96,99]. However, the molecular/signaling pathways of enhanced EDHF-mediated endothelium-dependent vascular relaxation in response to H_2S remain unclear. It has been showed that glibenclamide (K_{ATP} channel blocker) decreased maximum relaxation response to NaHS in the thoracic aorta, pulmonary and mesenteric arteries isolated from either 4- or 12-week-STZ-induced diabetic rats [96]. Moreover, vascular relaxation of rabbit carotid artery in response to NaHS was diminished by charybdotoxin (BK_{Ca}/IK_{Ca} blocker), 4-amynopiridine (K_v channel blocker) and glibenclamide in the carotid arteries of alloxan-induced diabetic rabbits but not in that of non-diabetic rabbits [97]. However,

Table 1
H_2S levels in diabetes.

Diabetic patients/ animals/cells	Method for H_2S assay	Sources of H_2S/free sulfide	H_2S in diabetes vs. non-diabetes	Ref. #
db/db mice	Gas chromatography	Bone marrow cells Plasma Medial tight muscles	↓ ↓ ↓	4
High glucose-treated human microvascular ECs	Florescent dye sulfidefluor 7AM	ECs	↓	4
db/db mice	Florescent dye sulfidefluor 7AM	Mesenteric artery	↓	5
db/db mice	RP-HPLC	Mesenteric artery	↓	5
Akita mice	Spectrophotometer	kidney	↓	[44]
High glucose-treated mouse glomerular ECs	Spectrophotometer	ECs	↓	[44]
High fat diet-induced diabetic LDLR$^{-/-}$ mice	Spectrophotometer	Plasma	↓	[43]
Type 2 diabetic patients and STZ-treated diabetic rats	Spectrophotometer	Plasma	↓	[45]
Non-obese/Ltj diabetic mice	Spectrophotometer	Plasma Aorta	↓ ↓	[46]
STZ-treated mice	Spectrophotometer	Pancreas	↓	[48]
Type 2 diabetic patients	Spectrophotometer	Plasma	↓	[49]
High glucose-treated microvascular ECs (bEnd3)	Spectrophotometer	ECs	↓	[50]
Women with Gestational diabetes mellitus	Sulfide-sensitive electrode (PXS-270)	Plasma	↓	[69]
High fat diet-induced diabetic mice	Gas chromatography	Heart tissue Plasma	↔ ↔	[70]
Type 2 diabetic patients	Spectrophotometry (blood) Methylene blue (plasma)	Blood Plasma	↔ ↔	[71]
STZ-treated diabetic rats	Spectrophotometer	Vascular smooth muscle cells of thoracic aorta	↓	[72]
STZ-treated diabetic rats	Spectrophotometer	Plasma	↓	[73]
Fructose-fed diabetic rats	Methylene blue	Adipose tissue	↑	[74]
STZ-treated diabetic rats	–	Liver Pancreas	↓ ↓	[75]
High glucose treated pancreatic islets	Methylene blue	Pancreatic islets	↓	[76]
STZ-treated diabetic rats	Spectrophotometer	Plasma, liver, pancreas and kidney	Plasma: ↔ Liver: ↑ Pancreas: ↑ Kidney: ↔	[75]

4-amynopiridine did not modify the relaxant response to H_2S in the control rat thoracic aorta [19]. In line with above findings, activity and expression of K_v channels were enhanced in the smooth muscle cells of mesenteric artery of OLETF diabetic rats [98].

Recently, we studied the role of H_2S in diabetes-induced ED in the small mesenteric artery of db/db mice [5]. We were the first demonstrating that H_2S is an effective EDHF in the mesenteric arteries of db/+ and db/db mice [5], because that L-cysteine and NaHS, precursor and donor of H_2S, induced endothelium-dependent response in the presence of L-NAME (eNOS inhibitor) plus indomethacin (COX inhibitor), respectively [5]. Moreover, in good accordance with previous studies that diabetes enhanced vascular relaxation in response to H_2S [96–98], we also provided strong evidence that EDHF-mediated vascular relaxation to NaHS was enhanced in the small mesenteric artery of db/db mice [100]. Finally we found that K_{ATP} blocker, but not any of K_{Ca} blockers, blocked enhanced relaxation to NaHS in the small mesenteric arteries of db/db mice [5]. Our study implicated that increased EDHF-mediated vascular relaxation to H_2S in the small mesenteric artery of db/db mice is via, at least partially, activation of K_{ATP} but not K_{Ca}. Exogenous H_2S and/or K_{ATP} openers may be beneficial for prevention/treatment of micro-vascular complication in diabetic patients. Further studies to examine the therapeutic effects of H_2S and/or K_{ATP} activators on microvascular endothelial function in db/db mice are warranted.

Taken together, in general, the EDHF-mediated endothelium-dependent vascular relaxation to H_2S is enhanced under diabetic condition. The diabetes-enhanced EDHF-mediated vascular relaxation in response to H_2S is suggested mainly by sensitizing/overexpression of different potassium channels, including $K_{Ca,}$ K_{ATP} and K_v. Enhanced endothelium-dependent vascular relaxation to H_2S may be complementary effects to overcome insufficient H_2S production and endothelial dysfunction in diabetes. The differences on the role of $K_{Ca,}$ K_{ATP} and K_v in H_2S-mediated endothelium-dependent vascular relaxation in diabetes may be related to the size and type of vessels, type and severity of diabetes, and species. Whether this complementary effects dependent on the species of animal model and severity/stage of diabetes remain unclear.

9. Low concentration of H_2S mediate vascular constriction

It is noteworthy that low concentration of H_2S has been considered as an endothelium-dependent vascular constriction factor (see review [101,102]). H_2S relaxed phenylephrine-precontracted human internal mammary artery at higher concentrations but induced contraction at lower concentrations [83]. Intravenous infusion of a low concentration of NaHS into the anaesthetized rats significantly increased mean arterial blood pressure [103]. Low concentrations of NaHS induced contraction of aorta from mice/rats [104]. The molecular pathways involved in H_2S-induced vascular contraction were found to be related to decreasing nitric oxide (NO) bioavailability by converting NO to an inactive nitrosothiol and N-nitrosohydroxylamine-N-sulfonate or directly reducing NO production [83,103–105], or down-regulation of cAMP endothelium-independently [106]. The pathophysiological importance of low concentration of H_2S-mediated vascular constriction has been suggested for further investigation [102]. As diabetes markedly reduced H_2S production (Table 1), it would be interesting to study if insufficient H_2S-induced vascular contraction has an impact on impaired blood perfusion in diabetic wound and ischemic hindlimb via restriction of blood/nutrition supply in microvasculature.

10. H_2S in diabetes-impaired angiogenesis

Angiogenesis is defined as a physiological process through which new blood vessels are sprouted from the preexisting blood vessels [107,108]. Angiogenesis is required for delivering nutrients and waste and supplying immune surveillance [100]. The rate of new blood vessels formation varies with biological age and differs between tissues in healthy organisms [109]. Organisms exhibit rapid angiogenesis during embryonic development [110]. In adults, angiogenesis is observed only in limited number of physiological responses and in tissue-specific manners. Under ischemic conditions, angiogenesis is a critical event for improving blood flow and oxygen/nutrients supply [111]. Under

pathological stimulation, ECs process an angiogenic program to contribute wound healing and tissue remodeling [107]. Enhancing EC function and angiogenesis thereby improving blood perfusion has been suggested as an alternative approach in the treatment of ischemic tissue injury. The process of angiogenesis is complex which contains a series of cellular and molecular events which includes three steps: 1) enzymatic degradation of capillary basement membrane; 2) EC proliferation, migration and 3) tubulogenesis and the formation of capillaries [112–114], which involves the interaction between pro- and anti-angiogenic factors, growth mediators, cytokines, cells and extracellular matrix [115]. Recent studies demonstrated that rather than the amount of single angiogenic factor, balance between endogenous pro- and anti-angiogenic factor plays an important role in the regulation of angiogenesis [116]. Defects in the angiogenic balance may cause a shift towards either excessive or deficient angiogenesis.

Impaired angiogenesis is one of the hallmarks of diabetes which is involved in the pathogenesis of nephropathy, wound and critical limb ischemia in diabetes [4,117–119]. The risk factors involved in diabetes-impaired angiogenesis are suggested to be related to many factors, including hypoxia, chronic inflammation, oxidative stress, hyperglycemia/advanced glycation end products (AGE), connective tissue growth factors, lipoxidation and its products [120]. The underlying mechanisms of diabetes-impaired angiogenesis remain incompletely understood.

Emerging data support the role of H_2S in the regulation of angiogenesis. H_2S promotes EC proliferation, migration, survival, formation of tubular structure and networks [100,107,121–129]. The sufficient concentrations of H_2S to induce angiogenesis are physiological levels [125,130]. H_2S in a dose-dependent manner promoted human umbilical vein endothelial cells (HUVECs) growth, adhesion, migration, tube formation, and in vivo angiogenesis measured by matrigel plug assay [124,125,129]. Silencing of CSE in HUVECs decreased cell proliferation and tube formation [131]. Administration of H_2S increased proliferation and migration in microvascular ECs and recovered microvessel sprouting in CSE-silenced rat aorta [122]. In addition, administration of 3-mercaptopyruvate (3-MP), the 3-MST substrate reserved increased Matrigel plug angiogenesis/neovascularization in mice [132]. Many molecules have been suggested to be involved in H_2S-mediated angiogenesis. Most studies focused on the VEGF signaling in angiogenic response [125,133,134]. The pro-angiogenic effect of vascular endothelial growth factor (VEGF) is mediated by the endogenous production of H_2S [125]. Silencing of CSE by siRNA attenuated VEGF-induced angiogenesis [125]. In addition, H_2S stimulated angiogenesis by increasing the activity of endothelial nitric oxide synthesis (eNOS) [121,135], phosphatidylinositol 3 (PI3)-kinase/protein kinase B (AKT) [130], p38/mitogen-activated protein kinase (MAPK) [125], K_{ATP}^{127}, signal transducer and activator of transcription 3 (STAT3) [124], and sirtuin 1 (SIRT1)/VEGF/cyclic guanosine 5′-monophosphate (cGMP) cascade [123].

Angiogenesis is impaired in diabetes [4,117]. However, the underlying mechanisms of diabetes-impaired angiogenesis remain unclear. A series of multiple mechanisms, including impaired EC biology/function and growth factor response, were suggested to lead to diminished peripheral blood perfusion and decreased angiogenesis in diabetes. H_2S rescued hyperglycemia-impaired migration of HUVECs by upregulating miR-126–3p [136]. Hyperglycemia/diabetes-impaired angiogenesis is associated with an impairment of proangiogenic and bio-energetic effects of 3-MP [132]. NaHS promoted angiogenesis in ob/ob mice is related to decreasing infiltration of neutrophil and macrophage, production of TNF-α, interleukin (IL-6) [137]. H_2S donor diallyl trisulfide (DATS) improved revascularization in STZ-induced diabetic mice via increasing NO bioavailability [138]. H_2S promoted angiogenesis in db/db mice via improving VEGFR and PDGFR, and Angiopoietin-1 (Ang I) [118,128]. Recently we reported that diabetes impairs angiogenesis in db/db mice via eNOS-pT495-mediated reduction of NO [4].

11. H_2S in diabetes-impaired wound healing

It is well known that in the physiological condition (before injury), the vasculature is quiescence in which blood vessel are adequately perfused to deliver sufficient oxygen/nutrients to the tissue [139,140]. There is a proper balance of pro-and anti-angiogenic factors are expressed to maintain a functional vascular network that neither proliferating nor diminishing [139,140]. However, this homeostasis is interrupted leading to an ischemic/hypoxic state when tissue is injured. Under post-injury, numerous proangiogenic factors are produced for formation of angiogenesis in wounds, such as VEGF and transcriptional activator hypoxia-inducible factor (HIF) which promotes angiogenesis by upregulating target genes such as VEGF-A [141].

Refractory wound is defined by slow healing of wound which is one of major microvascular complications in diabetes. In the wound healing process, impaired EC function/angiogenesis contribute to defects in the oxygen/nutrients supply, thus inhibiting normal healing process [142]. In the process of wound healing, angiogenesis is a crucial step which starts at the 3rd days after wounding [140,143]. Dysfunction of angiogenesis has been linked to impaired wound healing in diabetes [4,117,118,128]. For instance, the prevalence of foot ulcers due to impaired wound healing is predicted to be 25% in diabetic patients [144,145]. Many insufficient angiogenic factors, such as vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF-2) and platelet-derived growth factor (PDGF) are involved in diabetes-impaired angiogenesis/wound healing [146–148]. Moreover, several studies also demonstrated that modulation of anti-angiogenic factors and capillary maturation factors are also involved in the pathogenesis of diabetes-impaired wound healing. For example, circulating levels of anti-angiogenic factor pigment epithelium-derived factor (PEDF) were significantly enhanced in patients with diabetic foot ulcers (DFU) [149], suggesting that enhanced PEDF could negatively impact wound healing in diabetes. Local administration of neutralizing antibodies to Ang I on wounded skin reduced maturation of capillary formation in STZ-induced diabetic mice [150]. In addition, several miRNAs (miRs) have also been shown to be involved in diabetic wound healing. miR-27b accelerated the wound healing process in db/db mice [128]. Inhibition of miR-155 reduced oxidative stress, increased angiogenesis and wound healing in STZ-induced diabetic rats [151]. Local administration of let-7b-containing exosomes, nanoscale membrane extracellular vesicles (30–100 nm), from LPS-primed mesenchymal stromal cells decreased inflammatory response and increased wound healing in STZ-induced diabetic mice [150]. miR-191 and -200b expression were increased in diabetic patients with PAD and chronic wounds and positively correlated with higher levels of inflammation associated markers [152,153].

H_2S has been reported to accelerate gastric ulcer and skin burn wound healing [125,130,154]. Topical administration of H_2S improved the recovery from burn wounds in wild-type rats and that genetic ablation of CSE delayed healing in mice [125]. H_2S improves angiogenesis and wound healing in db/db mice via increasing transcription of VEGF, EGF, HIF-1α and eNOS, and protein expression of VEGF, PDGF, and phosphorylated VEGFR and PDGFR [128]. H_2S accelerates wound healing in STZ-induced diabetic mice associated with formation of granulation, anti-inflammation, and the increased level of VEGF [155]. H_2S improved diabetic wound healing in ob/ob mcie via attenuating inflammation [137]. H_2S premised wound to close through inhibition of neutrophil extracellular traps (NET) release-coupled neutrophil death (NETosis) in db/db mice [117]. H_2S improved wound healing via restoration of endothelial progenitor cell functions and activation of Ang 1 in db/db mice [118]. Cysteine/cysteine-rich un-denatured whey protein supplement improved pressure ulcer recovery in diabetic patients [156]. Accumulative evidence indicated that H_2S regulates miR expression (i.e. miR-1, -221, −21, and −133a) [157–160], however, the interaction between H_2S and miRs in diabetic wound healing remain unclear. A recent study suggested that H_2S may rescue diabetes-impaired wound healing via DNMT1 inhibition and

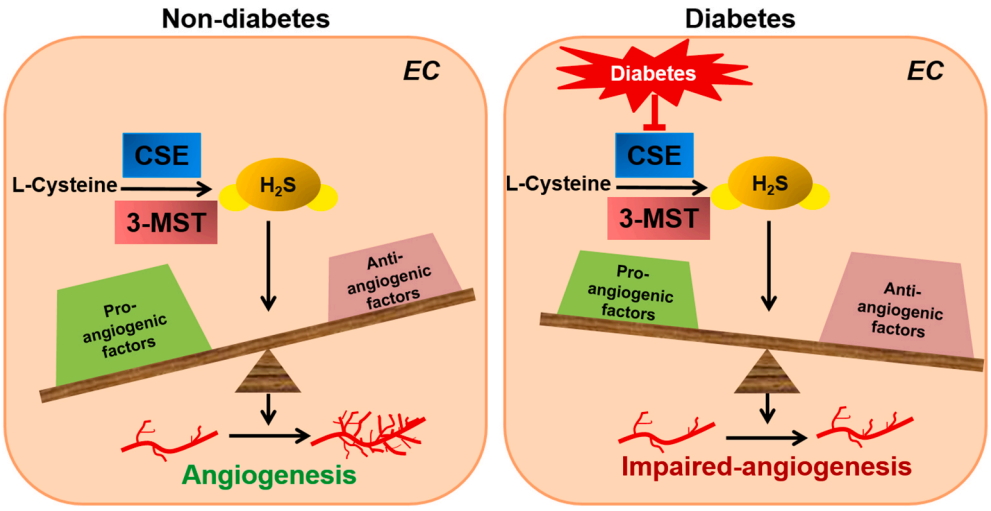

Fig. 2. Mechanistic scheme of H_2S in non-diabetes-(left panel) and diabetic-mediated(right panel) angiogenic property of ECs in response to ischemic tissue injury. H_2S plays an important role in maintaining physiological balance in ECs in response to ischemic tissue injury. Under diabetic condition, insufficient H_2S production impaired angiogenetic property of ECs via disturbing the balance of pro-and anti-angiogenic factors. CSE: cystathionine-γ-lase-lyase; 3-MST: mercaptopyruvate sulfurtransferase.

consequently enhanced miR-126-3 production in ECs [161]. Further studies to understand the role of H_2S in miRs-mediated EC dysfunction will provide novel insights for prevention/therapeutics ischemic tissue injury in diabetes.

12. H_2S in diabetes-impaired critical limb ischemia

The morbidity of critical limb ischemia (CLI) in patients with diabetes, which affects 178 million US adults [1], is extremely high (up to 76% in some studies [162]). Patients with CLI suffer from consequent rest pain, ulcers, cool limbs, and even amputation. Disease severity at the time of presentation and progression of CLI in diabetes has also been noted to be worse [163]. Angiogenesis is a promising target for the treatment of ischemic limbs by providing extra blood for the ischemic region. Pro-angiogenic factors, such as VEGF and basic fibroblast growth factor (bFGF), plays an important role in promoting angiogenesis accompanied with enhanced blood perfusion in ischemic limbs of patients [164]. It is also reported that transplantation of bone marrow- or placenta-derived mesenchymal stem cells (MSCs) significantly improved capillary density and blood flow in ischemic hindlimbs of animal models [165,166]. Pro-angiogenic factors released from MSCs could promote angiogenic differentiation, leading to the stimulation of resident progenitor cells (EPCs) to migrate, proliferate, and differentiate into incorporated ECs [167].

In clinics, H_2S levels in gastrocnemius tissue were attenuated in the setting of CLI in patients [168]. Administration of H_2S was beneficial for ischemic hindlimb (IHL) repair in animal model. S-propargyl-cysteine, a novel water-soluble modulator of endogenous H_2S promoted angiogenesis in IHL of mice via signal transducer and activator of transcription 3 (STAT3)/VEGF signaling [124]. Intraperitoneal injection of low dose, but not high dose, of NaHS significantly improved capillary density, angiographic scores, blood perfusion in IHL which may be mediated by interaction between the upregulated VEGF in the skeletal muscle cells and the VEGFR2 as well as its downstream signaling element AKT in the ECs [129]. H_2S improved angiogenesis and blood perfusion in IHL of $CSE^{-/-}$ mice via peroxidsome proliferator-activated receptor-γ (PPAR-γ)/VEGF axis [169]. DATS enhanced angiogenesis and blood flow in IHL of wild-type mice via stimulation of AKT-eNOS signaling pathway [170]. H_2S also limited cellular damage in myotubes and skeletal muscles of ischemic hindlimbs [171].

We examined role of H_2S in diabetes-impaired biology/function of bone marrow cell (BMC) and IHL repair in db/db mice [4]. We found that H_2S production and CSE expression was significantly reduced in BMCs from db/db mice. Systemic administration of DATS or local transplantation of DATS-treated or CSE-overexpressed BMCs improved capillary density, cell survival and blood perfusion in the IHL of db/db mice [4]. Mechanistically we found that DATS restored NO production and decreased eNOS-pT495 levels in human microvascular ECs. We demonstrated that H_2S and overexpression of CSE in diabetic BMCs may rescue their dysfunction and open novel avenues for cell-based therapeutic of CLI in diabetic patients [4]. Consistent with the effects of DATS in IHL of db/db mice, recent study also revealed that administration of DATS improved angiogenesis and IHL repair in STZ-treated mice via NO signaling pathway [138]. However, the underlying mechanisms of downregulation of CSE expression/activity and insufficient H_2S-induced eNOS-pT495 in diabetic ECs remain incompletely understood.

13. Conclusion

H_2S is an endogenous gas with important physiological function. H_2S plays an important role in maintenance of vasculature homeostasis. The evidence presented above shows that H_2S, mainly synthesized by CSE or 3-MST, stimulates angiogenetic property of ECs. H_2S-induced EDHF-mediated vascular relaxation is enhanced in micro-vasculature in diabetes which may play compensatory effects for overcoming H_2S reduction-induced endothelial dysfunction. Diabetes enhances H_2S-induced EDHF-mediated vascular relaxation in micro-vasculature by opening potassium channels, including K_{Ca}, K_{ATP} and Kv, which varies by type of vessels, diameter of vessels, severity of diabetes and species. Physiological doses of H_2S increase angiogenesis by promoting EC growth, survival migration and tube formation. H_2S production is reduced in plasma/blood, ECs and bone marrow cells in diabetes. Insufficient H_2S production in diabetes impairs angiogenic property and ischemic tissue injury via, at least partially, interrupting the balance between pro- and anti-angiogenic factors (Fig. 2). Although studies showed that administration of H_2S or overexpressing CSE improves EC biology/function, angiogenesis and IHL repair in diabetes, how H_2S impacts on the metabolism of EC and contributes to it angiogenic properties in diabetes remain unclear. In addition, studies for significance of translational medicine of H_2S on diabetes-impaired angiogenesis and ischemic tissue repair in patients are warranted.

14. Declaration of completing interest

The authors declare no conflict of interest.

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