Histol Histopathol (2021) 36: 505-514

http://www.hh.um.es

Histology and Histopathology
From Cell Biology to Tissue Engineering

REVIEW **Open Access**

Effect of sulfur dioxide on vascular biology

Huijun Cai[1] and Xinbao Wang[2]

[1]Department of Traditional Chinese Medicine, Beijing Friendship Hospital, Capital Medical University, and [2]Department of Pediatrics, Beijing Friendship Hospital, Capital Medical University, Beijing, PR China

Summary. Gasotransmitters, such as nitric oxide, carbon monoxide and hydrogen sulfide, can be generated endogenously. These gasotransmitters play important roles in vascular biology, including vasorelaxation and inhibition of vascular smooth muscle cell (VSMC) proliferation. In recent years, sulfur dioxide (SO_2) has been considered as the fourth gasotransmitter. SO_2 is present in air pollution. Moreover, SO_2 toxicity, including oxidative stress and DNA damage, has been extensively reported in previous studies. Recent studies have shown that SO_2 can be endogenously generated in various organs and vascular tissues, where it regulates vascular tone, vascular smooth cell proliferation and collagen synthesis. SO_2 can decrease blood pressure in rats, inhibit smooth muscle cell proliferation and collagen accumulation and promote collagen degradation, and improve vascular remodelling. SO_2 can decrease cardiovascular atherosclerotic plaques by enhancing the antioxidant effect and upregulating nitric oxide/nitric oxide synthase and hydrogen sulfide/cystathionine-γ-lyase pathways. SO_2 can also ameliorate vascular calcification via the transforming growth factor - β1/Smad pathway. The effect of SO_2 on vascular regulation has attracted great interest. SO_2 may be a novel mediator in vascular biology

Key words: Sulfur dioxide, Mediator, Vascular, Biology

Introduction

Gasotransmitters have common characteristics; they are small gas molecules, are endogenously generated by enzyme catalysis, can freely pass through membranes without a membrane receptor, have special functions at physiological concentrations and have specific cellular and molecular targets (Wang, 2002, 2003). The toxic effect of sulfur dioxide (SO_2) has been extensively examined in previous studies, which have demonstrated that inhalation of SO_2 is harmful to various organs (including the brain, lungs, heart, liver, stomach, intestine, spleen, kidney, and testis) in mice (Meng, 2003); however, endogenous SO_2 production has been detected in various organs and vascular tissues. The protective roles of SO_2, including reduction of lung injury (Chen et al., 2015; Zhai et al., 2019), myocardial injury induced by ischemia reperfusion injury or isoproterenol (Jin et al., 2008, 2013; Wang et al., 2011; Chen et al., 2012; Huang et al., 2013) and myocardial fibrosis (Wang et al., 2018; Zhang et al., 2018a,b), alleviation of atherosclerotic lesions (Li et al., 2011) and abatement of hippocampal cell death (Zare Mehrjerdi et al., 2018), have been reported. Furthermore, SO_2 may be a mediator in the vasculature, and regulate vascular tone and alleviate vascular remodelling and atherosclerosis (Sun et al., 2010; Li et al., 2011; Zhang et al., 2020). Therefore, SO_2 may be the fourth gasotransmitter in the cardiovascular system (Huang et al., 2016a).

Endogenous SO_2/aspirate aminotransferase system in vascular tissue

Endogenous SO_2 can be generated in various tissues, including the heart, lung, stomach, intestine, liver, pancreas, spleen, renal and brain (Luo et al., 2011). Endogenous SO_2 is produced by sulfur-containing amino acid metabolism. First, L-cysteine is metabolized to form sulfur-containing amino acids and then oxidized to L-cysteine sulfinate in a reaction catalysed by cysteine dioxygenase. L-cysteine sulfinate is transformed into β-sulfinyl pyruvate by aspirate aminotransferase (AAT) and then decomposed to pyruvate and SO_2 (Shapiro, 1977; Stipanuk et al., 1990). SO_2 dissociates into its derivatives, bisulfite and sulfite (HSO_3^-/SO_3^{2-}, molar ratio of 1:3), *in vivo* and is then oxidized to sulfate and excreted in the urine (Stipanuk, 1986). In activated neutrophils, hydrogen sulfide (H_2S) can also be transformed into sulfite in a reaction catalysed by

Corresponding Author: Dr. Xinbao Wang, Department of Pediatrics, Beijing Friendship Hospital, Capital Medical University, Yongan Str. No. 95 West District, Beijing 100050, PR China. e-mail: xinbaowang2008@163.com

DOI: 10.14670/HH-18-290

nicotinamide adenine dinucleotide phosphate-oxidase (Mitsuhashi et al., 2005) (Fig. 1).

SO_2 can be generated in both vascular endothelial cells and smooth muscle cells (SMCs), but is mainly produced in vascular endothelial cells (Du et al., 2008). AAT, a key SO_2-producing enzyme, was detected by in situ hybridization in rat aorta. AAT1 and AAT2 are two isoenzymes of AAT. The results showed that AAT1 and AAT2 mRNA expression was much higher in endothelial cells than in vascular smooth muscle cells (VSMCs). The concentration of SO_2 in rat plasma was found to be 16.77±8.24 μmol/L, while the content of SO_2 was different in the arteries. The highest content of SO_2 was found in the aorta (5.55±0.35 μmol/g protein), followed by the pulmonary artery, mesenteric artery, tail artery and renal artery (3.27±0.21, 2.67±0.17, 2.50±0.20 and 2.23±0.19 μmol/g protein, respectively) (Du et al., 2008).

The generation of SO_2 can be increased by acetylcholine and decreased by noradrenaline (Meng et al., 2009). AAT1 overexpression or knockdown can directly regulate the generation of SO_2. In the supernatant of cultured pulmonary artery fibroblasts, the concentration of SO_2 was increased by AAT1 overexpression and decreased by AAT1 knockdown (Liu et al., 2016). Similarly, in the supernatant of cultured pulmonary artery SMCs, the generation of SO_2 was increased by AAT1 overexpression and decreased by AAT1 knockdown. SO_2 generation can be also auto-regulated. In cultured human umbilical vein endothelial cells, a high dose of SO_2 (100 μM) significantly decreased AAT activity and porcine purified AAT1 protein (Song et al., 2020). Furthermore, SO_2 was able to induce S-sulfenylation of AAT1 at Cys192; however, the thiol reductant DTT or a mutated plasmid of AAT1 containing a site-directed cysteine 192-to-serine (C192S) mutation reversed the above effects of SO_2. These data indicate that endogenous SO_2 generation can be auto-regulated by sulfenylation of AAT1 at Cys192. Additionally, the generation of SO_2 is involved in pathological conditions. The content of SO_2 was decreased in the plasma and lung tissue of rats with hypoxia-induced pulmonary hypertension but was upregulated by SO_2 treatment (Sun et al., 2010). The SO_2 concentration in myocardial tissue was significantly decreased by 41.9% in rats with isoproterenol-induced myocardial injury and increased following the administration of SO_2 derivatives (Liang et al., 2011).

The physiological effect of SO_2 on vascular biology

The effect of SO_2 on vascular tone

SO_2 and its derivatives can relax vascular tissue in an endothelium-dependent or endothelium-independent manner (Meng et al., 2009; Wang et al., 2009). The effect of SO_2 on aortic ring relaxation is much stronger than that of SO_2 derivatives (Zhang and Meng, 2009). The median concentrations of the maximum vasorelaxation effect of SO_2 and its derivatives were 1.24±0.09 mM and 7.28±0.12 mM, respectively (Zhang and Meng, 2009). The mechanisms of SO_2-mediated and SO_2 derivative-mediated vasorelaxation differ.

The effect of SO_2 on endothelium-dependent relaxation

At basal and low concentrations (<450 μM), the vasorelaxation effect of gaseous SO_2 is endothelium dependent, which is related to the large-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel (Li and Meng, 2009; Zhang and Meng, 2009). SO_2 can also relax the aortic rings associated with increased cyclic guanosine monophosphate (cGMP), while the soluble guanylate cyclase (sGC) inhibitor 1H-[1, 2, 4] oxadiazolo [4,3-a] quinoxalin-1-one (ODQ) can reverse this effect of SO_2. The protein levels of sGC and protein kinase G (PKG) dimers were also upregulated. These data indicate that the increased cGMP induced by SO_2 occurs through sGC activation. In addition, SO_2 can reduce the activity of phosphodiesterase type 5, a cGMP-specific hydrolytic enzyme. Therefore, SO_2 upregulation is related to

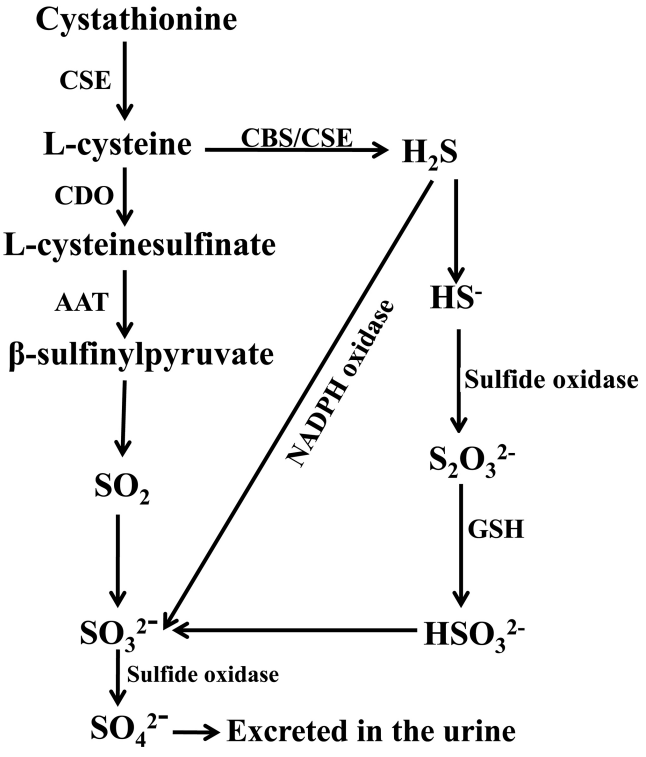

Fig. 1. The generation and metabolism of endogenous SO_2. Abbreviations: SO_2: sulfur dioxide; H_2S: hydrogen sulfide; CBS: cystathionine β-synthase; CSE: cystathionine γ-lyase; CDO: cysteine dioxygenase; AAT: aspartate aminotransferase; 3MST: 3-mercaptopyruvate sulfurtransferase; GSH: glutathione; NADPH: nicotinamide adenine dinucleotide phosphate.

hydrolysis inhibition. These data indicate that the sGC/cGMP/PKG pathway is involved in the vasodilation effect of SO_2 (Yao et al., 2016).

In endothelium-intact rings, SO_2 derivatives (sodium sufite and sodium bisulfite) (0.5-8 mM) relaxed aortic rings in a dose-dependent manner. The NOS inhibitor (L-NAME) reduced the vasorelaxation effect of SO_2 at low doses but not at high doses (≥2 mM). These data indicate that the relaxation induced by SO_2 is associated with NOS activation (Wang et al., 2009). At low concentrations of sodium bisulfite (≤500 μM), vasorelaxation is endothelium dependent. The vasorelaxation induced by bisulfite is mediated by the cGMP pathway and BK_{Ca} channels (Meng et al., 2012).

The effect of SO_2 on endothelium-independent relaxation

At high concentrations (>500 μM), the vasorelaxation effect of gaseous SO_2 is endothelium-independent and related to the adenosine triphosphate-sensitive potassium (K_{ATP}) channel and L-type Ca^{2+} channel (Zhang and Meng, 2009). Du et al. (2008) found that SO_2 derivatives relaxed aortic rings in a dose-dependent manner (1-12 mmol/L). SO_2 reversed the vasoconstriction effect induced by the L-type Ca^{2+} channel agonist, Bay K8644. These data indicate that the mechanism of SO_2 vasorelaxation is related to the inhibition of the L-type Ca^{2+} channel. At high concentrations of bisulfite (≥1000 μM), vasorelaxation is endothelium-independent. The underlying mechanism is related to K_{ATP}, Ca^{2+}-activated K^+ (K_{Ca}) and L-type Ca^{2+} channels (Wang et al., 2009; Meng et al., 2012). Furthermore, the vasorelaxation effect of SO_2 is related to the inhibition of Ca^{2+} entry and partially related to an increase in prostacyclin (Meng and Zhang, 2007). SO_2 and its derivatives inhibit L-Ca^{2+} channels by decreasing the expression of Cav1.2 and Cav1.3 in the rat aorta. SO_2 activated K_{ATP} channels by increasing the expression of Kir6.1, Kir6.2, SUR2B, α, and β1 (Zhang et al., 2014). In the presence of 14 mg/m^3 gaseous SO_2, the activation of K_{ATP} channels is increased by the upregulation of Kir6.1, Kir6.2, and SUR2B expression. In addition, L-type Ca^{2+} channels are decreased by downregulated Cav1.2 and Cav1.3 expression in rat aortas (Zhang, et al., 2016a,b). These data indicate that SO_2 regulates K_{ATP} and L-type Ca^{2+} channels by controlling their subunits.

In aortic rings, the levels of cyclic adenosine monophosphate (cAMP) and prostaglandin I_2 (PGI_2) and the activities of adenylyl cyclase (AC) and protein kinase A (PKA) were significantly increased by SO_2 treatment. The cAMP/cGMP ratio was also significantly increased. These data indicate that the vasorelaxation effect of SO_2 is related to the PGI_2-AC-cAMP-PKA signalling pathway (Meng et al., 2007). The expression of endothelial nitric oxide synthase (eNOS) and the generation of NO were increased by SO_2 in the rat aorta (Li et al., 2010; Lu et al., 2012). The level of cGMP was also increased. These data indicate that the vasodilation effect of SO_2 is partly related to the upregulation of the eNOS-NO-cGMP pathway (Li et al., 2010). Smooth muscle relaxation due to SO_2 (3 μM) can be enhanced by NO (3 or 5 nM), which suggests that the vasoactive effect of SO_2 is synergistic with NO (Li and Meng, 2009). These data indicate that some crosstalk exists between SO_2 and NO. In aging rats with aortic endothelial dysfunction mediated by D-galactose induction, SO_2 improved endothelial dysfunction by inhibiting oxidative stress injury. In addition, SO_2 downregulated the angiotensin II/AT1R pathway (Dai et al., 2018). In endothelial inflammatory injuries, H_2S decreased the generation of endogenous SO_2 by inhibiting the activity of AAT through the sulfhydration of AAT1/2. When the hydrogen sulfide/cystathionine-gamma-lyase pathway was inhibited, the generation of endogenous SO_2 was increased and played a protective role (Zhang et al., 2018a,b). Vasodilation induced by a low concentration of SO_2 (30 μM) can be partially inhibited by LY294002 and N(G)-nitro-l-arginine methyl ester (Zhang et al., 2020). Additionally, SO_2 significantly increased the protein expression of phosphatidylinositol 3 kinase (PI3K), phosphorylated-protein kinase B (p-Akt), and p-eNOS; however, high-dose SO_2 (300 μM or 1500 μM) decreased the protein expression of PI3K, p-Akt, and p-eNOS and increased the NO and cGMP content and NOS activity. These data indicate that PI3K/Akt/eNOS and NO/cGMP are involved in the vasodilatation effect of SO_2. Furthermore, a high dose of SO_2 (1500 μM) significantly increased caspase-3 and caspase-9 content, indicating that a high dose of SO_2 might be detrimental to blood vessels.

The relaxation effect of SO_2 on aortic rings is much stronger than that of SO_2 derivatives (sodium sufite and sodium bisulfite, 3:1 M/M), but the mechanisms differ (Table 1). At low concentrations of gaseous SO_2, the vasorelaxation effect of SO_2 is mainly through the cGMP pathway or BK_{Ca}, while at high concentrations it is through K_{ATP}, L-Ca^{2+} or BK_{Ca}. In contrast, the vasorelaxation effect of low concentration SO_2 derivatives is through the NO/NOS pathway, while those of high concentration depend on K_{ATP}, L-Ca^{2+}, BK_{Ca} or the cAMP/PKA pathway. Therefore, at high concentrations, the vasorelaxation effects of SO_2 and its derivatives are related to K_{ATP}, L-Ca^{2+} or BK_{Ca} channels, while the mechanisms at low concentrations differ.

The effect of SO_2 on vascular smooth muscle cells

The excessive proliferation and hypertrophy of VSMCs contribute to vascular wall thickness and play important roles in vascular remodelling (Vogel et al., 1997). Liu et al. (2014) showed that SO_2 inhibited VSMC proliferation by decreasing DNA synthesis and inhibiting the progression of the cell cycle from the G1 phase to the S phase. VSMC proliferation is increased by

AAT1 or AAT2 knockdown and decreased by AAT1 and AAT2 overexpression. Following platelet-derived growth factor-BB-stimulated proliferation of VSMCs, SO_2 dephosphorylated extracellular-regulated protein kinase (ERK) 1/2, mitogen-activated protein kinase (MAPK) kinase1/2 and RAF by inhibiting the activity of the RAF proto-oncogene serine/threonine-protein kinase. Furthermore, SO_2 stimulated the cAMP/PKA pathway, which inhibited ERK/MAPK transduction in VSMCs. These data indicate that the inhibitory effect of SO_2 on VSMCs occurs through cAMP/PKA signalling, which leads to inhibition of the EKR/MAPK pathway (Liu et al., 2014). In mice with angiotensin II-induced hypertension, SO_2 decreased systemic hypertension and aortic thickening. The increased expression of proliferating cell nuclear antigen (PCNA) and P-ERK was also inhibited by SO_2 in the aorta. The inhibitory effect of SO_2 on VSMC proliferation was attenuated by the ERK phosphorylation inhibitor PD98059. These data indicate that ERK mediates the inhibitory effect of SO_2 on VSMC proliferation (Wu et al., 2016). SO_2 also promoted VSMC apoptosis by down-regulating the expression of B-cell lymphoma 2 (Bcl-2) and increasing the expression of Fas and caspase-3 in spontaneously hypertensive rats (Zhao et al., 2008a). Endothelin-1 increased the expression of PCNA and Ki-67 and enhanced VSMC migration but decreased SO_2 production and AAT activity in VSMCs (Tian et al., 2020). SO_2 treatment also inhibited the increased expression of PCNA and Ki-67 induced by endothelin-1 (Song et al., 2020). Additionally, endothelin-1 significantly increased the generation of reactive oxygen species, accompanied by SO_2/AAT pathway downregulation, and N-acetyl-L-cysteine (a reactive oxygen species scavenger) and glutathione reversed these effects. Therefore, endothelin-1 promotes VSMC proliferation and migration and is related to SO_2/AAT pathway downregulation via reactive oxygen species production.

The effect of SO_2 on vascular collagen

Abnormal vascular collagen synthesis and degradation play an important role in the process of vascular remodelling. In spontaneously hypertensive rats, SO_2 significantly decreased the expression of type I and III collagen in the thoracic aorta (Zhao et al., 2008b). In the stretch-induced accumulation of pulmonary artery fibroblasts, the protein expression of collagen I and III and TGF-β1 and the phosphorylation of Smad2/3 increased, but the SO_2/AAT1 pathway was downregulated (Liu et al., 2016). AAT1 overexpression reversed the above effect induced by stretching, while AAT1 knockdown mimicked the effect of stretching. The TGF-β1/Smad2/3 inhibitor SB431542 reversed the deposition of collagen I and III induced by AAT1 knockdown or stretching. The TGF-β/Smad pathway is also involved in high blood flow–induced pulmonary hypertension in rats. The content of SO_2 and the expression of AAT1 were downregulated. SO_2 treatment

Table 1. Regulatory effects and mechanisms of SO_2 on vascular tone.

Treatment administered	Concentration	Mechanism	Endothelium dependent	Method	Reference
SO_2 gas	<450 μM; >500 μM and <2000 μM	cGMP	Yes; No	Isolated aortic rings	Li and Meng, 2009
	30, 300 μM; 1500 μM	BK_{Ca}; K_{ATP}, L-Ca^{2+}	Yes; No	Isolated aortic rings	Zhang and Meng, 2009
	1500 μM	K_{ATP}; Kir6.1, Kir6.2, SUR2B; BK_{Ca}; BK_{Ca}α, BK_{Ca}β1; L-type Ca^{2+}; $Ca_v1.2$, $Ca_v1.3$	No	Isolated aortic rings	Zhang et al., 2014
	14 mg/m^3	K_{ATP}; Kir6.1, Kir6.2, SUR2B; BK_{Ca}; BK_{Ca}α, BK_{Ca}β; L-type Ca^{2+}; $Ca_v1.2$, $Ca_v1.3$	-	Inhalation	Zhang et al., 2016
	300 μM; 1500 μM	eNOS-NO-cGMP	Yes; No	Isolated aortic rings	Li et al., 2010
	1, 50, 300 μM	sGC/cGMP/PKG	-	Isolated aortic rings	Yao et al., 2016
SO_2 derivatives	0.5, 1 mmol/L	NOS; Voltage-gated Ca^{2+}	Yes; -	Isolated aortic rings	Wang et al., 2009
	0.5-8 mmol/L; 2, 4 mmol/L	K_{ATP} and K_{Ca}	No		
	2, 4, 8 mmol/L	PGI_2-AC-cAMP-PKA	No	Isolated aortic rings	Meng et al., 2007
	6 mmol/L	L-type Ca^{2+}	No	Isolated aortic rings	Du et al., 2008
	1500 μM	K_{ATP}; Kir6.1, Kir6.2, SUR2B; BK_{Ca}; BK_{Ca}α, BK_{Ca}β; L-type Ca^{2+}; $Ca_v1.2$, $Ca_v1.3$	No	Isolated aortic rings	Zhang et al., 2014
	3.7 mg/kg	NO	-	Intraperitoneal injection	Lu et al., 2012
	1, 2, 4 ,6 ,8, 10, 12 mmol/L			Isolated aortic rings	
	30 μM; 300 μM; 1500 μM	PI3K/Akt/eNOS NO/cGMP	-	Isolated aortic rings	Zhang, et al., 2020
$NaHSO_3$	400 μM; 2000, 4000 μM	BK_{Ca}, cGMP; K_{ATP}, L-type Ca^{2+}	Yes; No	Isolated aortic rings	Meng et al., 2012

SO_2 derivatives: $NaHSO_3^-$/$NaSO_3^{2-}$, molar ratio of 1:3; AC, adenylate cyclase; Akt, protein kinase B; BK_{Ca} channel, large conductance calcium-activated potassium channel; cAMP, cyclic adenosine monophosphate; cGMP, 3′-5′-cyclic guanosine monophosphate; K_{Ca}, calcium-sensitive potassium channel; K_{ATP}, ATP-sensitive potassium channel; NOS, nitric oxide synthase; PKA, protein kinase A; L-type Ca^{2+}, L-type calcium channel; sGC, guanylate cyclase; PGI_2, prostaglandin I_2; PI3K, phosphatidylinositol 3 kinase; PKG, protein kinase G.

inhibited collagen accumulation and TGF-β1/Smad2/3 pathway activation. These data indicate that the endogenous SO_2/AAT1 pathway mediates stretch-induced collagen deposition through the TGF-β1/Smad2/3 pathway (Liu et al., 2016). Additionally, SO_2 was able to improve pulmonary arteriolar remodelling by inhibiting the proliferation and migration of pulmonary arterial smooth cells in rats with hypoxia-induced pulmonary hypertension. Furthermore, SO_2 downregulated the mRNA expression of Wnt7b, Sfrp2 and Cacna1f, but upregulated the mRNA expression of Dkk1 in lung tissues (Luo et al., 2018). These data indicate that the effect of SO_2 on improving pulmonary arterial remodelling is related to the Dkk1/Wnt signalling pathway.

The endogenous SO_2/AAT pathway is also involved in the process of collagen formation in VSMCs. In TGF-β1-treated VSMCs, endogenous SO_2 synthesis and AAT1 or AAT2 knockdown promoted collagen deposition (Huang et al., 2016b). In contrast, AAT1 or AAT2 overexpression increased SO_2 generation and inhibited collagen I and III expression induced by TGF-β1. In addition, procollagen I and III mRNA and tissue inhibitors of matrix metalloproteinase (MMP)-1 were inhibited, but MMP-13 expression increased. These data indicate that SO_2 inhibits collagen formation and promotes collagen degradation. Furthermore, AAT1 or AAT2 downregulated the phosphorylation of type 1 TGF-β receptor (TβR1) and Smad2/3 in TGF-β1-stimulated VSMCs. The TGF-β1/Smad signalling pathway inhibitor SB431542 decreased the collagen formation induced by AAT knockdown in VSMCs. A similar effect was also found in ectopically expressed AAT or the exogenous addition of SO_2 derivatives during AAT knockdown in VSMCs (Huang, et al., 2016b). These data indicate that the TGF-β1/TβRI/Smad2/3 pathway mediates the effect of SO_2 on improving collagen remodelling.

The pathophysiological effect of SO_2 on vascular related diseases

The effect of SO_2 on hypertension and vascular remodelling

Hypertension is the most common chronic disease and an important risk factor for cardiovascular and cerebrovascular diseases. Meng et al. (2003) found that SO_2 and its derivatives significantly decreased blood pressure in a dose-dependent manner. Additional studies showed that SO_2 derivatives significantly decreased blood pressure in spontaneously hypertensive rats and reduced pulmonary hypertension induced by monocrotaline, hypoxia or high pulmonary blood flow (Sun et al., 2010; Lu et al., 2012; Luo et al., 2013). The mechanism is related to the SO_2 vasodilation effect.

Vascular remodelling is an important step during the pathogenesis of hypertension (Ponticos and Smith, 2014) and is accompanied by SMC proliferation and migration and extracellular matrix (ECM) deposition. The ECM is mainly composed of collagen, fibronectin, laminin, heparin sulfate proteoglycan perlecan, and other macromolecules. Type I and III collagen are the main types of media and adventitia in normal and injured arterial walls (Myllyharju and Kivirikko, 2001; Xu and Shi, 2014). SO_2 significantly decreased systolic blood pressure by 26%, ameliorated vascular remodelling, and reduced the ratio of the media to lumen radius in spontaneously hypertensive rats (Zhao et al., 2008b) (Table 2).

In rats with monocrotaline-induced pulmonary hypertension, SO_2 reduced pulmonary hypertension, ameliorated pulmonary vascular structural remodelling, and reduced the relative medial thickness and relative medial areas of the pulmonary artery (Jin et al., 2008). The underlying mechanism involved the upregulation of the antioxidant activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px). SO_2 significantly inhibited collagen synthesis and promoted collagen degradation. Transforming growth factor (TGF)-β1 expression was decreased by SO_2 in pulmonary arteries. AAT1 overexpression inhibited the activation of the TGF-β/TGF-β1/Smad2/3 signalling pathway. In contrast, AAT1 knockdown increased the phosphorylation of Smad 2/3 and aggravated the deposition of type I and III collagen in TGF-β1-treated pulmonary arterial fibroblasts (Liu et al., 2016). These data indicate that the TGF-β/Smad pathway is involved in the SO_2-mediated reduction in collagen accumulation in monocrotaline-induced pulmonary artery remodelling. The protective effect of SO_2 was also found in rats with hypoxic pulmonary hypertension. SO_2 reduced pulmonary hypertension, improved vascular structural remodelling and inhibited pulmonary arterial SMC proliferation. In addition, SO_2 downregulated the expression of Raf-1 and mitogen-activated protein kinase kinase-1 (MEK-1) and decreased the ratio of p-ERK/ERK. These data indicate that the MAPK pathway is involved in the protective effect of SO_2 (Sun et al., 2010).

In rats with hypoxia-induced pulmonary hypertension, SO_2 also inhibited the expression of intercellular adhesion molecule 1 (ICAM-1) and nuclear factor-κB (NF-κB) in pulmonary vascular endothelial cells. These data indicate that SO_2 inhibits the inflammation involved in hypoxic pulmonary hypertension (Sun et al., 2010). Furthermore, SO_2 is reportedly a new adipocyte-derived inflammatory inhibitor. In cultured 3T3-L1 adipocytes, the inflammatory factors (monocyte chemoattractant protein-1 and interleukin-8) induced by TNF-α were inhibited by AAT1 overexpression but increased by AAT1 knockdown. NF-κB activation was also inhibited by endogenous SO_2 (Zhang et al., 2016a,b). Therefore, the mechanism by which SO_2 alleviates vascular remodelling is related to its anti-inflammatory effect. Interestingly, an endogenous SO_2/AAT system is also present in macrophages. SO_2 production and AAT

Table 2. Effects and mechanisms of SO_2 on vascular remodelling.

Form of SO_2	Role of SO_2	Mechanisms	Model	References
Na_2SO_3/$NaHSO_3$	Alleviate vascular collagen remodelling	Inhibit abnormal accumulation of collagen type I and III	Spontaneously hypertensive rat	Zhao et al., 2008a
Na_2SO_3/$NaHSO_3$	Alleviate pulmonary vascular structural remodelling	Increase SOD, GSH-Px, and MDA content	Monocrotaline (MCT)-induced pulmonary hypertensive rats	Jin et al., 2008
		Increase plasma SOD, GSH-Px, and CAT levels		
Na_2SO_3/$NaHSO_3$	Improve pulmonary vascular remodelling	Increase H_2S generation	Pulmonary hypertension induced by high pulmonary blood flow in rats	Luo et al., 2013
	Up-regulate endogenous H_2S pathway	Increase CSE protein expression		
		Increase CSE, MPST and CBS mRNA expression		
Na_2SO_3/$NaHSO_3$	Alleviate excessive collagen accumulation	TGF-β1/Smad2/3 pathway	Pulmonary hypertension induced by high pulmonary blood flow in rats	Liu et al., 2016
AAT1 overexpression	Deficiency of endogenous SO_2/AAT1 pathway-mediated collagen accumulation			
AAT1 knockdown			Primary pulmonary fibroblasts	
Na_2SO_3/$NaHSO_3$	Improve collagen remodelling	Inhibit Raf-1, MEK-1, and ERK phosphorylation	Hypoxic pulmonary hypertensive rats	Sun et al., 2010
	Inhibit pulmonary VSMC proliferation	Inhibit NF-kB and ICAM-1 expression		
	Anti-inflammation			
Na_2SO_3/$NaHSO_3$	Attenuate pulmonary arteriolar remodelling	Dkk1/Wnt signalling pathway	Hypoxia-induced pulmonary hypertensive rats	Luo et al., 2018
	Inhibit the proliferation and migration of PASMCs			
Na_2SO_3/$NaHSO_3$	Reduce proliferation and promote apoptosis of smooth muscle cells	Inhibit PCNA expression	Spontaneously hypertensive rats	Zhao et al., 2008b
		Decrease Bcl-2 expression		
		Increase Fas and caspase-3 expression		
Na_2SO_3/$NaHSO_3$	Inhibit vascular smooth muscle cell proliferation	Inhibit the Erk/MAPK pathway, which is mediated by cAMP/PKA signalling	Vascular smooth muscle cells	Liu et al., 2014
AAT1 or AAT2 overexpression and knockdown				
Na_2SO_3/$NaHSO_3$	Inhibit VSMC proliferation	ERK signalling	Angiotensin II-induced hypertensive mice	Wu et al., 2016
	Reduce systemic hypertension and vascular wall thickness	Inhibit PCNA and P-ERK expression	Vascular smooth muscle cells	
AAT1 or AAT2 overexpression	Alleviate collagen remodelling	Inhibit procollagen I and III mRNA and up-regulate MMP-13 expression	Rat A7r5 VSMCs	Huang et al., 2016b
AAT1 or AAT2 knockdown		Downregulate the MMP-1 level		
Na_2SO_3/$NaHSO_3$	Attenuate endothelial dysfunction	Inhibit oxidative stress injury and downregulate the angiotensin II/AT_1R pathway	D-galactose-induced aging in rats	Dai et al., 2018
HDX, NaHS	Inhibit endothelial inflammatory responses	Increase SO_2 production and play a compensatory role while downregulating the H_2S/CSE pathway	Human umbilical vein endothelial cell line (EA.hy926)	Zhang et al., 2018
			Monocrotaline rats	
Na_2SO_3/$NaHSO_3$	Ameliorate vascular calcification	Inhibit Runx2 expression	Vascular calcification induced in rats by vitamin D3 and nicotine; Calcified A7r5 VSMCs	Li et al., 2016
	Increase smooth muscle alpha-actin expression	Downregulate the TGF-β/Smad pathway		
Na_2SO_3/$NaHSO_3$	Decrease atherosclerotic lesions	Increase plasma GSH-Px and SOD activity Reduced plasma MDA level	Atherosclerosis induced by vitamin D3 and high cholesterol in rats	Li et al., 2011
		Up-regulate the NO/NOS pathway		

AAT, aspartate aminotransferase; Bcl-2, B-cell lymphoma 2; CAT, catalase; cAMP, cyclic adenosine monophosphate; CBS, cystathionine-beta-synthase; CSE, cystathionine-gamma-lyase; Dkk, dikkopf-1; ERK, extracellular signal-regulated kinase; GSH, reduced glutathione; GSH-Px, glutathione peroxidase; HDX, L-aspartate-beta- hydroxamate; H_2S, hydrogen sulfide; ICAM-1, intercellular adhesion molecule 1; MAPK, mitogen-activated protein kinase; MDA, malondialdehyde; MEK-1, mitogen-activated protein kinase kinase-1; MMP-13, matrix metalloproteinase-13; MPST, mercaptopyruvate sulfurtransferase; NF-κB, nuclear factor-κB; NO, nitric oxide; NOS, nitric oxide synthesis, PCNA, proliferating cell nuclear antigen; PKA, protein kinase A; SOD, superoxide dismutase; TGF-β1, transforming growth factor-β1;VSMC, vascular smooth muscle cell.

expression can be detected in cultured RAW267.4 macrophages (Zhu et al., 2020). AAT2 knockdown increased the levels of TNF-α and IL-6, which mediate inflammation, and induced macrophage chemotaxis, while an SO_2 donor reversed these effects. SO_2 also decreased macrophage infiltration in mouse hearts treated with angiotensin II. These data indicate that inflammation may regulate macrophages.

The effect of SO_2 on vascular calcification

In rats with vitamin D3-induced vascular calcification, the content of calcium, the activity of alkaline phosphatase (ALP), the osteochondrogenic marker Runx2 and TGF-β/Smad signalling all increased, but SM α-actin decreased (Li et al., 2016). In addition, the plasma level of SO_2 decreased, accompanied by downregulated AAT1 and AAT2 mRNA expression. Vascular calcification was also ameliorated by treatment with SO_2 derivatives. In addition, SO_2 derivatives treatment significantly inhibited the expression of TGF-β/Smad and Runx2 but increased the expression of SM α-actin. In calcified A7r5 VSMCs induced by calcium chloride, treatment with SO_2 significantly decreased calcium deposits and ALP activity and inhibited the TGF-β/Smad pathway. These data indicate that the improvement in vascular calcification induced by SO_2 is related to the downregulation of the TGF-β/Smad pathway (Li et al., 2016). Therefore, the TGF-β/Smad pathway may play different roles in vascular remodelling and calcification.

The effect of SO_2 on atherosclerosis

Atherosclerosis is a common fatal cardiovascular disease worldwide. In rats with vitamin D3 and high-cholesterol diet-induced atherosclerosis, SO_2 content and AAT activity were significantly decreased in the aorta (Li et al., 2011). Atherosclerotic plaques formed in the aorta or the coronary artery. SO_2 derivatives treatment significantly decreased the size of atherosclerotic plaques with increasing H_2S content and downregulated cystathionine-γ-lyase (CSE) mRNA expression in the aortas. In addition, SO_2 significantly increased plasma GSH-Px and SOD activities, eNOS activity and NO content (Li et al., 2011). These data indicate that the anti-atherosclerotic effect of SO_2 is related to increased antioxidant activity and NO/NOS and H_2S/CSE pathway upregulation.

Perspective and challenges

Vascular diseases are an important cause of mortality or disability throughout the world and result in a serious financial burden to families. Moreover, vascular diseases are still not well prevented and treated. Recent studies showed that SO_2 could be endogenously generated in mammals, and the endogenous SO_2/AAT pathway is involved in the development of vascular remodelling. Vascular remodelling is a complicated pathological process that can be caused by hypertension, atherosclerotic injury and vascular calcification (Tanaka and Laurindo, 2017; Jaminon et al., 2019) (Fig. 2). Vascular calcification is the inevitable result and a pathological process of atherosclerosis (Faggiano et al., 2019). Hypertension is one of the causes of atherosclerosis. Atherosclerosis is a chronic pathological process in which lipids and complex carbohydrates first accumulate, followed by haemorrhage and thrombosis. Fibrous tissue hyperplasia and calcium deposition then occur, which gradually leads to degeneration and calcification in the arterial middle layer and results in thickening and hardening of the arterial wall and narrowing of the vascular lumen (Kobiyama and Ley, 2018). Interestingly, current studies showed that SO_2 exerts a vasorelaxation effect and decreases hypertension

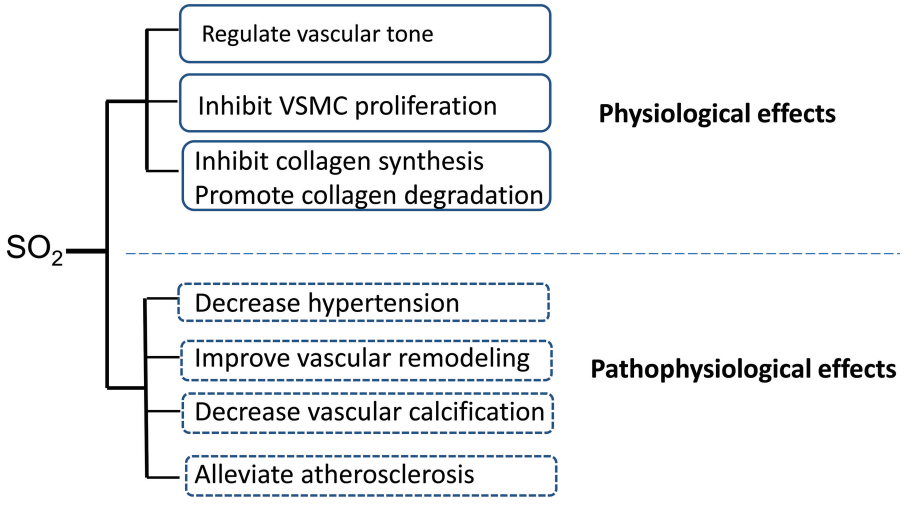

Fig. 2. The effect of SO_2 on vascular biology. SO_2 exerts physiological and pathophysiological effects on the vasculature, including regulating vascular tone, inhibiting smooth muscle cell proliferation and collagen accumulation and promoting collagen degradation. SO_2 can also alleviate vascular remodelling and ameliorate vascular calcification and cardiovascular atherosclerosis. (VSMC: vascular smooth muscle cell)

in rats. SO_2 also alleviates coronary artery atherosclerotic injury and vascular calcification, improves vascular remodelling and regulates the imbalance of collage synthesis and degradation. The gaseous molecule SO_2 may be a novel mediator in vascular biology. In addition, the potential of SO_2 as a drug has also been studied. SO_2 prodrugs can be activated by a bioorthogonal click reaction, and the release rate can be adjusted by the substituents (Wang et al., 2017a). Another SO_2 donor, 2,4-dinitrophenylsulfonamides, can produce SO_2 by thiol activation and strongly inhibits mycobacterium tuberculosis growth (Malwal et al., 2012; Pardeshi et al., 2015). Although this drug has only recently been identified, it shows potential for further clinical application.

Additional studies of SO_2 on vascular diseases are required. For example, 1) SO_2 exerts a vasorelaxation effect and can reduce hypertension, but the effective therapeutic dose and side effects are unclear. 2) In the pathological process of atherosclerosis, the effects of SO_2 on endothelial injury, macrophage, proliferation of smooth muscle cells and low density lipoprotein receptor require further exploration. 3) In the development of vascular calcification, the effects of SO_2 on bone formation related protein, osteoblast-like cells differentiation, matrix vesicles formation and activation of genetic factors, and hormones are still unknown. 4) Vascular remodelling is an inevitable result of various vascular injuries. The mechanisms of SO_2 on abnormal extracellular matrix accumulation, signal pathway proliferation and apoptosis, and endothelial-to-mesenchymal transition remain unclear.

Acknowledgements. We thank Professor Chaoshu Tang from Peking University for his advice and guidance during the revision of this manuscript.

Conflict of interest statement. The authors declare no conflict of interest.

References

Chen S., Du J., Liang Y., Zhang R., Tang C. and Jin H. (2012). Sulfur dioxide restores calcium homeostasis disturbance in rat with isoproterenol-induced myocardial injury. Histol. Histopathol. 27, 1219-1226.

Chen S., Zheng S., Liu Z., Tang C., Zhao B., Du J. and Jin H. (2015). Endogeous sulfur dioxide protects against oleic acid-induced acute lung injury in association with inhibition of oxidative stress in rats. Lab. Invest. 95, 142-156.

Dai J., Liu R., Zhao J. and Zhang A. (2018). Sulfur dioxide improves endothelial dysfunction by downregulating the angiotensin II/AT1R pathway in D-galactose-induced aging rats. J. Renin. Angiotensin Aldosterone Syst. 19, 1470320318778898.

Du S.X., Jin H.F., Bu D.F., Zhao X., Geng B., Tang C.S. and Du J.B. (2008). Endogenously generated sulfur dioxide and its vasorelaxant effect in rats. Acta Pharmacol. Sin. 29, 923-930.

Faggiano P., Dasseni N., Gaibazzi N., Rossi A., Henein M. and Pressman G. (2019). Cardiac calcification as a marker of subclinical atherosclerosis and predictor of cardiovascular events: A review of the evidence. Eur. J. Prev. Cardiol. 26, 1191-1204.

Huang P., Sun Y., Yang J., Chen S., Liu A.D., Holmberg L., Huang X., Tang C., Du J. and Jin H. (2013). The ERK1/2 signaling pathway is involved in sulfur dioxide preconditioning-induced protection against cardiac dysfunction in isolated perfused rat heart subjected to myocardial ischemia/reperfusion. Int. J. Mol. Sci. 14, 22190-22201.

Huang Y., Tang C., Du J. and Jin H. (2016a). Endogenous sulfur dioxide: A new member of gasotransmitter family in the cardiovascular system. Oxid. Med. Cell. Longev. 2016, 8961951.

Huang Y., Shen Z., Chen Q., Huang P., Zhang H., Du S., Geng B., Zhang C., Li K., Tang C., Du J. and Jin H. (2016b). Endogenous sulfur dioxide alleviates collagen remodeling via inhibiting tgf-beta/smad pathway in vascular smooth muscle cells. Sci. Rep. 6, 19503.

Jaminon A., Reesink K., Kroon A. and Schurgers L. (2019). The role of vascular smooth muscle cells in arterial remodeling: Focus on calcification-related processes. Int. J. Mol. Sci. 14, 5694.

Jin H.F., Du S.X., Zhao X., Wei H.L., Wang Y.F., Liang Y.F., Tang C.S. and Du J.B. (2008). Effects of endogenous sulfur dioxide on monocrotaline-induced pulmonary hypertension in rats. Acta Pharmacol. Sin. 29, 1157-1166.

Jin H., Wang Y., Wang X., Sun Y., Tang C. and Du J. (2013). Sulfur dioxide preconditioning increases antioxidative capacity in rat with myocardial ischemia reperfusion (I/R) injury. Nitric Oxide 32, 56-61.

Kobiyama K. and Ley K. (2018). Atherosclerosis. Circ. Res. 123, 1118-1120.

Li J. and Meng Z. (2009). The role of sulfur dioxide as an endogenous gaseous vasoactive factor in synergy with nitric oxide. Nitric Oxide 20, 166-174.

Li J., Li R. and Meng Z. (2010). Sulfur dioxide upregulates the aortic nitric oxide pathway in rats. Eur. J. Pharmacol. 645, 143-150.

Li W., Tang C., Jin H. and Du J. (2011). Regulatory effects of sulfur dioxide on the development of atherosclerotic lesions and vascular hydrogen sulfide in atherosclerotic rats. Atherosclerosis 215, 323-330.

Li Z., Huang Y., Du J., Liu A.D., Tang C., Qi Y. and Jin H. (2016). Endogenous sulfur dioxide inhibits vascular calcification in association with the TGF-beta/Smad signaling pathway. Int. J. Mol. Sci. 17, 266.

Liang Y., Liu D., Ochs T., Tang C., Chen S., Zhang S., Geng B., Jin H. and Du J. (2011). Endogenous sulfur dioxide protects against isoproterenol-induced myocardial injury and increases myocardial antioxidant capacity in rats. Lab. Invest. 91, 12-23.

Liu D., Huang Y., Bu D., Liu A.D., Holmberg L., Jia Y., Tang C., Du J. and Jin H. (2014). Sulfur dioxide inhibits vascular smooth muscle cell proliferation via suppressing the cAMP/PKA kinase pathway mediated by camp/pka signaling. Cell Death Dis. 5, e1251.

Liu J., Yu W., Liu Y., Chen S., Huang Y., Li X., Liu C., Zhang Y., Li Z., Du J., Tang C., Du J. and Jin H. (2016). Mechanical stretching stimulates collagen synthesis via down-regulating SO_2/AAT1 pathway. Sci. Rep. 6, 21112.

Lu W., Sun Y., Tang C., Ochs T., Qi J., Du J. and Jin H. (2012). Sulfur dioxide derivatives improve the vasorelaxation in the spontaneously hypertensive rat by enhancing the vasorelaxant response to nitric oxide. Exp. Biol. Med. 237, 867-872.

Luo L., Chen S., Jin H., Tang C. and Du J. (2011). Endogenous generation of sulfur dioxide in rat tissues. Biochem. Biophys. Res. Commun. 415, 61-67.

Luo L., Liu D., Tang C., Du J., Liu A.D., Holmberg L. and Jin H. (2013).

Sulfur dioxide upregulates the inhibited endogenous hydrogen sulfide pathway in rats with pulmonary hypertension induced by high pulmonary blood flow. Biochem. Biophys. Res. Commun. 433, 519-525.

Luo L., Hong X., Diao B., Chen S. and Hei M. (2018). Sulfur dioxide attenuates hypoxia-induced pulmonary arteriolar remodeling via Dkk1/Wnt signaling pathway. Biomed. Pharmacother. 106, 692-698.

Malwal S.R., Sriram D., Yogeeswari P., Konkimalla V.B. and Chakrapani H. (2012). Design, synthesis, and evaluation of thiol-activated sources of sulfur dioxide (SO_2) as antimycobacterial agents. J. Med. Chem. 55, 553-557.

Meng Z. (2003). Oxidative damage of sulfur dioxide on various organs of mice: Sulfur dioxide is a systemic oxidative damage agent. Inhal. Toxicol. 15, 181-195.

Meng Z. and Zhang H. (2007). The vasodilator effect and its mechanism of sulfur dioxide-derivatives on isolated aortic rings of rats. Inhal. Toxicol.19, 979-986.

Meng Z., Geng H., Bai J. and Yan G. (2003). Blood pressure of rats lowered by sulfur dioxide and its derivatives. Inhal. Toxicol. 15, 951-959.

Meng Z., Li Y. and Li J. (2007). Vasodilatation of sulfur dioxide derivatives and signal transduction. Arch. Biochem. Biophys. 467, 291-296.

Meng Z., Li J., Zhang Q., Bai W., Yang Z., Zhao Y. and Wang F. (2009). Vasodilator effect of gaseous sulfur dioxide and regulation of its level by ach in rat vascular tissues. Inhal. Toxicol. 21, 1223-1228.

Meng Z., Yang Z., Li J. and Zhang Q. (2012). The vasorelaxant effect and its mechanisms of sodium bisulfite as a sulfur dioxide donor. Chemosphere 89, 579-584.

Mitsuhashi H., Yamashita S., Ikeuchi H., Kuroiwa T., Kaneko Y., Hiromura K., Ueki K. and Nojima Y. (2005). Oxidative stress-dependent conversion of hydrogen sulfide to sulfite by activated neutrophils. Shock 24, 529-534.

Myllyharju J. and Kivirikko K.I. (2001). Collagens and collagen-related diseases. Ann. Med. 33, 7-21.

Pardeshi K.A., Malwal S.R., Banerjee A., Lahiri S., Rangarajan R. and Chakrapani H. (2015). Thiol activated prodrugs of sulfur dioxide (SO_2) as MRSA inhibitors. Bioorg. Med. Chem. Lett. 25, 2694-2697.

Ponticos M. and Smith B.D. (2014). Extracellular matrix synthesis in vascular disease: Hypertension, and atherosclerosis. J. Biomed. Res. 28, 25-39.

Shapiro R. (1977). Genetic effects of bisulfite (sulfur dioxide). Mutat. Res. 39, 149-175.

Song Y., Peng H., Bu D., Ding X., Yang F., Zhu Z., Tian X., Zhang L., Wang X., Tang C., Huang Y., Du J. and Jin H. (2020). Negative auto-regulation of sulfur dioxide generation in vascular endothelial cells: AAT1 S-sulfenylation. Biochem. Biophys. Res. Commun. 525, 231-237.

Stipanuk M.H. (1986). Metabolism of sulfur-containing amino acids. Annu. Rev. Nutr. 6, 179-209.

Stipanuk M.H., De la Rosa J. and Hirschberger L.L. (1990). Catabolism of cyst(e)ine by rat renal cortical tubules. J. Nutr.120, 450-458.

Sun Y., Tian Y., Prabha M., Liu D., Chen S., Zhang R., Liu X., Tang C., Tang X., Jin H. and Du J. (2010). Effects of sulfur dioxide on hypoxic pulmonary vascular structural remodeling. Lab. Invest. 90, 68-82.

Tanaka L.Y. and Laurindo F.R.M. (2017). Vascular remodeling: A redox-modulated mechanism of vessel caliber regulation. Free Radic. Biol. Med. 109, 11-21.

Tian X., Zhang Q., Huang Y., Chen S., Tang C., Sun Y., Du J. and Jin H. (2020). Endothelin-1 downregulates sulfur dioxide/aspartate aminotransferase pathway via reactive oxygen species to promote the proliferation and migration of vascular smooth muscle cells. Oxid. Med. Cell. Longev. 2020, 9367673.

Vogel W., Gish G.D., Alves F. and Pawson T. (1997). The discoidin domain receptor tyrosine kinases are activated by collagen. Mol. Cell. 1, 13-23.

Wang R. (2002). Two's company, three's a crowd: Can H_2S be the third endogenous gaseous transmitter? FASEB J. 16, 1792-1798.

Wang R. (2003). The gasotransmitter role of hydrogen sulfide. Antioxid. Redox Signal. 5, 493-501.

Wang Y.K., Ren A.J., Yang X.Q., Wang L.G., Rong W.F., Tang C.S., Yuan W.J. and Lin L. (2009). Sulfur dioxide relaxes rat aorta by endothelium-dependent and -independent mechanisms. Physiol. Res. 58, 521-527.

Wang X.B., Huang X.M., Ochs T., Li X.Y., Jin H.F., Tang C.S. and Du J.B. (2011). Effect of sulfur dioxide preconditioning on rat myocardial ischemia/reperfusion injury by inducing endoplasmic reticulum stress. Basic Res. Cardiol. 106, 865-878.

Wang W., Ji X., Du Z. and Wang B. (2017). Sulfur dioxide prodrugs: Triggered release of SO_2 via a click reaction. Chem. Commun. (Camb.) 53, 1370-1373.

Wang X.B., Cui H. and Du J.B. (2018). Sulfur dioxide ameliorates rat myocardial fibrosis by inhibiting endoplasmic reticulum stress. Histol. Histopathol. 33, 1089-1097.

Wu H.J., Huang Y.Q., Chen Q.H., Tian X.Y., Liu J., Tang C.S., Jin H.F. and Du J.B. (2016). Sulfur dioxide inhibits extracellular signal-regulated kinase signaling to attenuate vascular smooth muscle cell proliferation in angiotensin II-induced hypertensive mice. Chin. Med. J (Engl). 129, 2226-2232.

Xu J. and Shi G.P. (2014). Vascular wall extracellular matrix proteins and vascular diseases. Biochim. Biophys. Acta 1842, 2106-2119.

Yao Q., Huang Y., Liu A.D., Zhu M., Liu J., Yan H., Zhang Q., Geng B., Gao Y., Du S., Huang P., Tang C., Du J. and Jin H. (2016). The vasodilatory effect of sulfur dioxide via SGC/cGMP/PKG pathway in association with sulfhydryl-dependent dimerization. Am. J. Physiol. Regul. Integr. Comp. Physiol. 310, R1073-1080.

Zare Mehrjerdi F., Shoshtari A., Mohseni F., Khastar H., Norozi P., Asadi Y., Dadkhah M. and Khaksari M. (2018). Sulfur dioxide reduces hippocampal cell death and improves learning and memory deficits in a rat model of transient global ischemia/reperfusion. Iran. J. Basic Med. Sci. 21, 998-1003.

Zhang Q. and Meng Z. (2009). The vasodilator mechanism of sulfur dioxide on isolated aortic rings of rats: Involvement of the K^+ and Ca^{2+} channels. Eur. J. Pharmacol. 602, 117-123.

Zhai Y., Huang X.L., Ma H.J., Zhou X.H., Zhou J.L. and Fan Y.M. (2019). Sulfur dioxide reduces lipopolysaccharide-induced acute lung injury in rats. Cent. Eur. J. Immunol. 44, 226-236.

Zhang Q., Tian J., Bai Y., Lei X., Li M., Yang Z. and Meng Z. (2014). Effects of gaseous sulfur dioxide and its derivatives on the expression of K_{ATP}, BK_{Ca} and L-Ca^{2+} channels in rat aortas *in vitro*. Eur. J. Pharmacol. 742, 31-41.

Zhang H., Huang Y., Bu D., Chen S., Tang C., Wang G., Du J. and Jin H. (2016a). Endogenous sulfur dioxide is a novel adipocyte-derived inflammatory inhibitor. Sci. Rep. 6, 27026.

Zhang Q., Bai Y., Yang Z., Tian J. and Meng Z. (2016b). The molecular mechanism of the effect of sulfur dioxide inhalation on the potassium and calcium ion channels in rat aortas. Hum. Exp. Toxicol. 35, 418-427.

Zhang D., Wang X., Tian X., Zhang L., Yang G., Tao Y., Liang C., Li K., Yu X., Tang X., Tang C., Zhou J., Kong W., Du J., Huang Y. and Jin H. (2018a). The increased endogenous sulfur dioxide acts as a compensatory mechanism for the downregulated endogenous hydrogen sulfide pathway in the endothelial cell inflammation. Front. Immunol. 9, 882.

Zhang L.L., Du J.B., Tang C.S., Jin H.F. and Huang Y.Q. (2018b). Inhibitory effects of sulfur dioxide on rat myocardial fibroblast proliferation and migration. Chin. Med. J. (Engl.) 131, 1715-1723.

Zhang Q., Lyu W., Yu M. and Niu Y. (2020). Sulfur dioxide induces vascular relaxation through PI3K/AKT/eNOS and NO/cGMP signaling pathways in rats. Hum. Exp. Toxicol. 39, 1108-1117.

Zhao X., Jin H.F., Tang C.S. and Du J.B. (2008a). Effects of sulfur dioxide, on the proliferation and apoptosis of aorta smooth muscle cells in hypertension: Experiments with rats. Zhonghua yi xue za zhi 88, 1279-1283.

Zhao X., Jin H.F., Tang C.S. and Du J.B. (2008b). Effect of sulfur dioxide on vascular collagen remodeling in spontaneously hypertensive rats. Zhonghua Er Ke Za Zhi. 46, 905-908.

Zhu Z., Zhang L., Chen Q., Li K., Yu X., Tang C., Kong W., Jin H., Du J. and Huang Y. (2020). Macrophage-derived sulfur dioxide is a novel inflammation regulator. Biochem. Biophys. Res. Commun. 524, 916-922.

Accepted December 15, 2020