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Review

Sulfur dioxide: foe or friend for life?

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Summary. Sulfur dioxide (SO_2) is a toxic gas and air pollutant. The toxic effects of SO_2 have been extensively studied. Oxidative damage due to SO_2 can occur in multiple organs. Inhaled SO_2 can also cause chromosomal aberrations, DNA damage and gene mutations in mammals. However, SO_2 can also be generated from the sulfur-containing amino acid, L-cysteine. Recent studies have shown that SO_2 has a vasorelaxant effect, and ameliorates pulmonary hypertension and vascular remodeling. SO_2 can also reduce lung injury and myocardial injury in rats. In addition, SO_2 reduces myocardial ischemia-reperfusion injury and atherosclerotic lesions. Therefore, SO_2 exerts both detrimental and protective effects in mammals. Is SO_2 a foe or friend for life?

Key words: Sulfur dioxide, Toxic effect, Physiological effects, Oxidative damage

Introduction

Sulfur dioxide (SO_2) is a common environmental pollutant. Following inhalation by mammals, SO_2 is dissolved in water and dissociates into its derivatives, sulfite and bisulfite (3:1 M/M in neutral solution) (Shapiro, 1977). These derivatives can be distributed throughout the whole body. Therefore, the toxicological effects of SO_2 are stem from its derivatives in mammals. Studies have shown that SO_2 inhalation can cause chromosomal aberrations in mouse bone-marrow cells. SO_2 inhalation causes lipid peroxidation in multiple organs in mice. DNA damage was also observed in blood lymphocytes and in mouse brain, lung, liver, spleen, kidney, and testis cells in a dose-dependent manner (Meng et al., 2005). Therefore, SO_2 is a systemic toxin in multiple organs in mammals.

However, SO_2 can be generated endogenously from the sulfur-containing amino acid L-cysteine in mammals (Stipanuk, 1986, 2004). L-cysteine is converted to L-cysteine sulfinate when catalyzed by cysteine dioxygenase. L-cysteine sulfinate is transaminated to β-sulfinylpyruvate by aspartate aminotransferase (AAT), and is spontaneously decomposed to pyruvate and SO_2 (Shapiro, 1977; Stipanuk et al., 1990). In addition, hydrogen sulfide can be oxidized to thiosulfate by sulfide oxidase, and then catalyzed to SO_2 by the thiosulfate sulfurtransferase of glutathione-dependent thiosulfate reductase (Mitsuhashi et al., 2005). SO_2 can be hydrated to sulfite in plasma, then oxidized to sulfate by sulfite oxidase, and finally excreted in the urine.

Studies have shown that the endogenous SO_2/AAT system exists in multiple organs in rats, including the vascular system, kidney, heart, liver, brain, stomach, lung and spleen (Du et al., 2008; Luo et al., 2011). The concentration of SO_2 in rat plasma was found to be 15.54±1.68 μmol/L (Du et al., 2008). The biological effects of SO_2 were determined in recent studies. SO_2 ameliorated pulmonary hypertension, improved pulmonary vascular remodeling and reduced lung injury in rats (Jin et al., 2008; Sun et al., 2010; Luo et al., 2013). In addition, SO_2 reduced isoproterenol-induced

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myocardial injury, myocardial ischemia-reperfusion (I/R) injury and arterial atherosclerotic lesions in rats (Li et al., 2011). Thus, SO_2 has both detrimental and beneficial effects in mammals.

Toxic effects of SO_2

Oxidative damage caused by SO_2

In Kunming albino mice exposed to 20 ppm (56 mg/m^3) SO_2 for 6 h/day for 7 days, it was shown that the activities of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) were significantly decreased in all organs (brain, lung, heart, liver, stomach, intestine, spleen, kidney, and testis). In addition, glutathione (GSH) content was significantly decreased, and the levels of thiobarbituric acid-reactive substances (TBARS) significantly increased in all organs (Meng, 2003).

At low concentration of SO_2 (22 mg/m^3), the content of TBARS was significantly increased in the lung, brain, liver, heart, stomach, intestine, and testis. In addition, the activity of GSH was significantly decreased in the heart and lung. The activity of SOD was significantly decreased in the heart, liver and intestine (Meng, 2003; Meng and Bai, 2004; Meng et al., 2003a). At high concentration of SO_2 (112 mg/m^3), the activity of GSH was also significantly decreased in the stomach and the activity of SOD was significantly decreased in the lung, liver and testis. The activity of GPx was significantly decreased in the lung and the content of CAT was decreased in the brain, but increased in the intestine (Meng et al., 2003a,b). These results showed that oxidative damage caused by SO_2 varied in organs at different concentrations.

Protein oxidation damage can also occur after SO_2 inhalation. Following exposure to 28 and 56 mg/m^3 SO_2, the level of protein carbonyl was significantly increased in mouse lung, liver, and heart. In addition, DNA-protein crosslinking was increased in these three organs after exposure of SO_2 (Xie et al., 2007). The content of protein carbonyl and the DNA-protein crosslink coefficient were significantly increased in rat hippocampus in a concentration-dependent manner following SO_2 inhalation (14-56 mg/m^3) (Sang et al., 2009). These data indicate that protein oxidation damage occurred in multiple organs after SO_2 inhalation.

Cytochrome P-450s (CYPs) comprise a superfamily of heme proteins which play important roles in the metabolism of steroids, fatty acids, prostaglandins, and leukotrienes, and pharmacokinetics in mammals. P-450s can be decreased by oxidative injury. In male Wistar rats exposed to 56 mg/m^3 SO_2, the gene transcription of CYP1A1 and 1A2 were decreased, and the mRNA and protein expression of c-fos and c-jun were significantly increased in rat lung and liver tissues (Qin and Meng, 2005, 2006b). In addition, SO_2 decreased the mRNA expression of CYP2B1/2 and CYP2E1 in the lung and CYP2B1/2 in the liver of rats (Qin and Meng, 2006a, 2010b). The inhibition of cytochrome P450s might be the mechanism of oxidative damage caused by SO_2, resulting in loss of function and structural damage.

DNA damage caused by SO_2

Male and female mice were exposed to 14, 28, 56 or 112 mg/m^3 SO_2 for 6 h/day for 7 days, the results showed that the extent of DNA damage (measured as olive tail moment) was significantly increased in blood lymphocytes and in brain, lung, liver, spleen, kidney, and testis cells in a dose-dependent manner (Meng et al., 2005). When the mice were treated with SO_2 derivatives (125, 250 or 500 mg/kg) daily for 7 days, these derivatives dose-dependently increased the extent of DNA damage (measured as olive tail moment) in cells from all organs (including brain, lung, heart, liver, stomach, spleen, thymus, bone marrow and kidney) (Meng et al., 2004). These results showed that SO_2 and its derivatives caused DNA damage in various organs.

In addition, the mRNA and protein levels of proto-oncogenes (including c-fos, c-jun, c-myc and Ki-ras) were dose-dependently increased, while those of tumor suppressor genes (Rb and p16) were decreased in rat lung tissues after SO_2 exposure (Bai and Meng, 2005b). In male Wistar rats exposed to 56 mg/m^3 SO_2 for 6 h/day for 7 days, the mRNA and protein expression of c-myc, H-ras and p53 were increased, while those of p16 and Rb were decreased in rat lung tissues (Bai and Meng, 2010a; Qin and Meng, 2010a). In cultured human bronchial epithelial cells, SO_2 derivatives increased the mRNA and protein expression of c-fos, c-jun and c-myc from 0.001 mM to 2 mM. The expression of H-ras and p53 were up-regulated at the highest concentration (0.1-2 mM), while the expression of tumor suppressor genes p16 and Rb were down-regulated (Qin and Meng, 2009). These data indicate that SO_2 up-regulated proto-oncogenes and inhibited tumor suppressor-related genes.

Bronchial asthma is a chronic inflammatory disease and is associated with airway hyper-reactivity and inflammatory responses. The epidermal growth factor (EGF), epidermal growth factor receptor (EGFR), intercellular adhesion molecule-1 (ICAM-1) and cyclooxygenase-2 (COX-2) genes play an important role in the pathogenesis of asthma. In cultured human bronchial epithelial cells, SO_2 derivatives increased the mRNA and protein expression of EGF, EGFR, ICAM-1, MUC5AC and COX-2 (Li and Meng, 2007; Li et al., 2007a,b). These data indicate that SO_2 may influence asthma by regulating related genes.

Chromosome aberrations and gene mutations induced by SO_2

Following SO_2 inhalation for 4 h/day for 7 days, chromatid-type breaks occurred at concentrations of 14 and 28 mg/m^3, but did not occur at 7 mg/m^3 in mouse bone marrow. Chromosome-type aberrations (isochromatid breaks) occurred following exposure to 56 and 84

mg/m^3 SO_2 (Meng and Zhang, 2002). These data indicate that SO_2 caused clastogenic and genotoxic effects in mice.

In AS52 cells treated with bisulfite (10 mM) for 4 h, the mutant frequency was 4-fold greater than the background frequency. These results showed that bisulfite was a weak mutagen even at high concentration. In spontaneous xathine-guanine phosphoribosyl transferase-mutant AS52 cells, 10 mM bisulfite increased mutant cells to 65% compared with control cells (36%) (Meng and Zhang, 1999). These results showed that bisulfite induced gene mutations.

Apoptosis induced by SO_2

Apoptosis is a type of cell death which can occur naturally or by highly programmed mechanisms. Apoptosis plays important roles in physiological development, growth and immune regulation. Bcl-2 gene is considered a repressor of apoptosis while Bax is a pro-apoptotic gene (Korsmeyer, 1999). In male Wistar rats exposed to 14, 28 or 56 mg/m^3 SO_2 for 6 h/day for 7 days, the mRNA levels of p53 and Bax were dose-dependently increased, while mRNA levels of Bcl-2 decreased following exposure to 28 or 56 mg/m^3 SO_2 in rat lung tissues. In addition, Caspase-3 activity increased in lung tissues. These results showed that SO_2 induced cell apoptosis in rat lungs (Bai and Meng, 2005a). The mRNA levels of p53 and Bax were increased at 28 or 56 mg/m^3 SO_2, while the mRNA levels of Bcl-2 were significantly decreased in rat liver (Bai and Meng, 2005b). SO_2 also dose-dependently up-regulated mRNA and protein expression and the activities of caspase-3, caspase-8, and caspase-9 in rat liver and lung (Bai and Meng, 2010b). SO_2 inhalation at 28 and 56 mg/m^3 increased caspase-3 activity and cell apoptosis in rat hippocampus (Sang et al., 2009).

Pro-inflammatory cytokines can provoke apoptosis by inducing mitochondrial dysfunction accompanied with reactive oxygen species increasing, mitochondrial membrane potential disorder and caspases activation. Tumor necrosis factor (TNF)-α, interleukine-1 (IL-1) β and ICAM-1 are the typical pro-inflammatory cytokines. Following inhalation of 14 and 28 mg/m^3 SO_2, the mRNA levels of TNF-α and IL-1β significantly increased in the heart and lung, but were unaffected by 7 mg/m^3 SO_2. ICAM-1 mRNA levels in the heart and lung were enhanced following SO_2 inhalation at 28 mg/m^3. The ratio of Bax to Bcl-2 was increased by 14 and 28 mg/m^3 SO_2 in rat heart and lung (Yun et al., 2011). These data indicate that SO_2 up-regulated apoptosis-related genes.

Physiological and pathophysiological effects of SO_2

Regulatory effect of SO_2 on vessel tone

SO_2 and its derivatives (sulfite and bisulfite, 3:1 M/M) have a vasorelaxing effect, but there are some differences between them. Studies have shown that the median effect concentrations (EC50) on vasodilation of SO_2 and its derivatives were 1.25±0.1 mM and 7.28±0.12 mM, respectively (Zhang and Meng, 2009). These data indicate that the vasodilating effect of SO_2 is much stronger than that of its derivatives (Fig. 1).

The vasorelaxing effect induced by a SO_2 stock solution was caused by SO_2. SO_2 caused relaxation of rat thoracic aortic rings in a concentration-dependent manner (1-2000 μM) (Du et al., 2008; Wang et al., 2009). At low concentration (<450 μM), the vasorelaxing effect was endothelium-dependent, which was mediated by the big-conductance calcium-activated potassium channel (Zhang and Meng, 2009). In addition, the vasorelaxation effect of SO_2 was endothelium-independent at high concentration (>500 μM). The mechanism was related to adenosine triphosphate

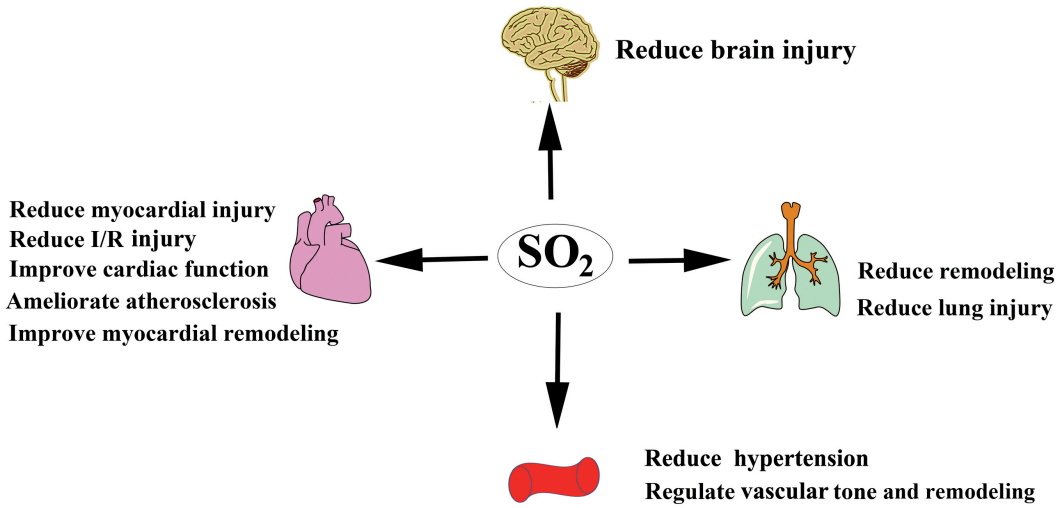

Fig. 1. The protective effect of SO_2 in mammals

sensitive potassium (K_{ATP}) channel activation and L-type calcium channel inhibition (Zhang and Meng, 2009). Furthermore, in the presence of 14 mg/m^3 SO_2, SO_2 activated the big-conductance Ca^{2+}-activated K^+ (BK_{Ca}) channel by up-regulating BK_{Ca} alpha and BK_{Ca} beta1 in rat aorta. SO_2 activated the K_{ATP} channel by up-regulating the expression of Kir6.1, Kir6.2, and SUR2B, and inhibited L-Ca^{2+} channels by down-regulating the expression of Cav1.2 and Cav1.3 in rat aorta (Zhang et al., 2015b). A recent study showed that the soluble guanylate cyclase (sGC)/cyclic guanosine monophosphate (cGMP)/protein kinase G (PKG) pathway was also involved in the vasorelaxation caused by SO_2 (Yao et al., 2016).

The SO_2 derivatives also dose-dependently (0.5-12 mM) caused relaxation of rat aortic rings. The relaxing effect of the SO_2 derivatives was endothelium-dependent at low concentration (<2 mM) and the mechanism was related to NOS activation. At high concentration (≥2 mM), the relaxation effect of SO_2 was endothelium-independent. The mechanism was related to K_{ATP} and K_{Ca} activation, and L-type calcium channels. In addition, the prostaglandin I_2- adenylate cyclase - cyclic adenosine monophosphate - protein kinase A pathway was also involved in the vasorelaxation effect of SO_2. Furthermore, the SO_2 derivatives at 1500 μM activated the K_{ATP} channel by up-regulating the expression of Kir6.1, Kir6.2, and SUR2B. The SO_2 derivatives also activated the BK_{Ca} channel by up-regulating BK_{Ca} alpha and BK_{Ca} beta1, and inhibited L-Ca^{2+} channels by decreasing the expression of Cav1.2 and Cav1.3 in rat aorta (Zhang et al., 2014).

Taken together, all of SO_2 and its derivatives have a vasorelaxing effect. SO_2 can be a physiologic endothelium-derived relaxing factor (Wang et al., 2017). The vasorelaxing effect of SO_2 might contribute to its effects of reducing hypertension, improving cardiac function and vascular remodeling.

Effect of SO_2 on cardiac function

In isolated rat heart, perfusion with the SO_2 derivatives significantly decreased left-ventricle developed pressure, ±LV dp/dtmax and heart rate. These data indicate that cardiac function was inhibited by SO_2 (Zhang et al., 2009). Interestingly, the mechanisms were different for SO_2 and its derivatives and they induced negative inotropic effects at different concentrations. At low concentration (10 μM), SO_2 could induce inotropic effects by increasing the activities of protein kinase C, cyclooxygenase, and cGMP. However, the SO_2 derivatives induced inotropic effects by opening the ATP-sensitive potassium channel and by inhibiting calcium influx via the L-type calcium-channel. At high concentrations, (300 and 1000 μM), the mechanism of SO_2 and its derivatives were similar, which may be related to the ATP-sensitive potassium channel, L-type calcium-channel, protein kinase C, cyclooxygenase, and cGMP (Zhang and Meng, 2012). In the presence of 14 mg/m^3 SO_2, the expression of L-Ca^{2+} channel subunits Cav1.2 and Cav1.3 was significantly decreased, while the mRNA and protein levels of the K_{ATP} channel subunits Kir6.2 and SUR2A were significantly increased by SO_2 in rat heart (Zhang et al. , 2015a). These data indicate that the activation of K_{ATP} by SO_2 was related to up-regulation of the expression of Kir6.2 and SUR2A. SO_2 inhibition of L-Ca^{2+} channels was related to down-regulation of the expression of Cav1.2 and Cav1.3 in rat heart.

Effect of SO_2 on ischemia reperfusion

In rat hearts with ligated left coronary artery for 30 min and reperfusion for 120 min, SO_2 derivatives pretreatment for 10 min prior to ischemia (1-10 μmol/kg) decreased myocardial infarct size and reduced the plasma level of the myocardial enzyme creatine kinase and lactate dehydrogenase (Wang et al., 2011a). SO_2 derivatives pretreatment induced the expression of myocardial glucose-regulated protein 78 (GRP78) and phosphorylated eukaryotic initiation factor 2a-subunit (p-eIF2a) before myocardial ischemia, but down-regulated the expression of GRP78 and p-eIF2a after myocardial ischemia reperfusion. Moreover, the endoplasmic reticulum stress (ERS) stimulator, dithiothreitol, mimicked the above effect of the SO_2 derivatives. The ERS inhibitor, 4-phenylbutyrate, reversed the protective effect of SO_2. These data indicated that the augmentation of ERS induced by SO_2 prior to ischemia contributed to protection against subsequent myocardial I/R injury (Wang et al., 2011a). In addition, SO_2 derivatives preconditioning could increase plasma SOD, GSH, and GSH-Px, and reduced malondialdehyde (MDA) level (Jin et al., 2013b). These data indicate that SO_2 derivatives preconditioning induced the activities of antioxidative enzymes which may be related to the protective effect of SO_2. Further studies showed that the phosphatidylinositol 3-kinase (PI3K) inhibitor, LY294002, reversed the protective effect of SO_2 derivatives on myocardial I/R (Zhao et al., 2013). The PI3K/Akt pathway may mediate the protective effect of SO_2. In isolated rat heart with I/R, pretreatment with PD98059, an extracellular signal-regulated kinase (ERK)1/2 inhibitor, abolished improving cardiac function by SO_2. The protective effect of SO_2 may be related to the ERK/mitogen-activated protein kinase (MAPK) pathway (Huang et al., 2013a). Therefore, the mechanisms involved in the SO_2 protective effect on myocardial I/R may be related to the PI3K/Akt pathway, ERK/MAPK pathway and reduced oxidative stress.

Effect of SO_2 on myocardial injury

In isoproterenol (ISO)-induced myocardial injury in rats, SO_2 treatment improved cardiac function, and ameliorated both myocardial structure injury and cardiomyocyte apoptosis. The mechanism involved the

inhibition of excessive activated endoplasmic reticulum stress induced by ISO (Liang et al., 2011). In addition, SO_2 significantly increased the activities of SOD and glutathione, and decreased hydrogen peroxide and superoxide radical levels. Therefore, the antioxidant effects of SO_2 were involved in the protection of ISO-induced myocardial injury. Disturbance of calcium homeostasis was also involved in myocardial injury. In ISO-induced myocardial injury in rats, SO_2 significantly increased the activity, and protein and mRNA levels of sarcoplasmic reticulum calcium ATPase and the protein phosphorylation level of phospholamban in myocardial tissues (Chen et al., 2012). Thus, the protective effect of SO_2 on myocardial injury may involve decreasing calcium overload in association with up-regulating the expression of sarcoplasmic reticulum calcium ATPase and the phosphorylation level of phospholamban in rat myocardial tissues. In addition, SO_2 reduced cardiomyocyte apoptosis by up-regulating myocardial Bcl-2, down-regulating Bax expression, and reducing caspase-9 and caspase-3 activities in ISO-treated rats (Jin et al., 2013a).

Effect of SO_2 on atherosclerosis

Atherosclerosis is a chronic progressive inflammatory disease and is together with its related diseases the leading cause of death worldwide. Atherosclerosis is a complicated process involving lipid accumulation, oxidative stress, inflammation, vascular smooth muscle cell (VSMC) proliferation, macrophage invasion and foam cell formation. In rats, atherosclerosis was induced by a single dose of vitamin D3 and a high-cholesterol diet for 8 weeks, and the SO_2 derivatives significantly decreased the plasma levels of total cholesterol and low-density lipoprotein-cholesterol. In addition, SO_2 significantly diminished the size of aortic and coronary artery atherosclerotic plaques. The levels of hydrogen sulfide (H_2S) in plasma and aortic tissues were significantly increased by SO_2, but the expression of cystathionine gamma lyase (CSE) mRNA decreased in the aorta. In atherosclerotic rats, the activities of plasma GSH-Px and SOD were decreased, and the level of plasma MDA was increased. However, plasma GSH-Px and SOD were significantly increased and plasma MDA was decreased in rats treated with SO_2 (Li et al., 2011). These data indicate that SO_2 ameliorated vascular atherosclerotic lesions in association with up-regulation of the H_2S/CSE pathway. The protective effect of SO_2 on atherosclerosis was related to inhibition of lipid oxidant damage. Furthermore, in rat vascular calcification induced by vitamin D3 and nicotine for four weeks, SO_2 treatment reduced the content of calcium and alkaline phosphatase (ALP) in plasma and aorta homogenates. In cultured A7r5 VSMCs with calcification induced by 5 μmol/L CaCl2 calcifying media, SO_2 significantly reduced the calcium content and ALP activity. In addition, increased expression of TGF-β and p-Smad2 (ser245/250/255) in calcified cells was down-regulated by SO_2 (Li et al., 2016). These data indicate that SO_2 reduced vascular calcification which was related to down-regulation of the TGF-β/Smad pathway.

Effect of SO_2 on pulmonary hypertension and vascular remodeling

In monocrotaline (MCT)-induced pulmonary hypertension in rats, SO_2 derivatives treatment significantly decreased mean pulmonary artery pressure and ameliorated pulmonary vascular structural remodeling, and increased the plasma and lung tissue levels of SOD and GSH-Px. These data indicate that the protective effects of SO_2 on pulmonary hypertension were related to the promotion of antioxidative capacities in vivo (Jin et al., 2008). In pulmonary hypertension induced in hypoxic rats, SO_2 administration prevented pulmonary hypertension and pulmonary vascular structural remodeling. In addition, SO_2 could down-regulate the expression of Raf-1, mitogen-activated protein kinase kinase-1 (MEK-1) and p-ERK/ERK in lung tissues, and inhibited pulmonary VSMC proliferation (Sun et al., 2010). Hydroxamate (SO_2 inhibitor) also reversed the protective effect of SO_2 on pulmonary hypertension (Sun et al., 2010). These data indicate that the SO_2 /AAT pathway also mediated the protective effect of SO_2 on pulmonary hypertension. In pulmonary hypertension induced by high pulmonary blood flow, SO_2 derivatives treatment significantly reduced systolic pulmonary artery pressure and decreased the muscularization of pulmonary arteries. In addition, SO_2 increased the production of H_2S and the protein expression of cystathionine-gamma-lyase. These data indicate that SO_2 reduced pulmonary arterial pressure in association with up-regulation of the endogenous H_2S pathway (Luo et al., 2013).

Furthermore, SO_2 inhibited VSMC proliferation by suppressing the extracellular signal-regulated kinase/mitogen-activated protein kinase pathways. However, the extracellular signal-regulated kinase/mitogen-activated protein kinase pathways could be inhibited by cyclic adenosine monophosphate (cAMP)/protein kinase A signaling (Liu et al., 2014). Also AAT1 overexpression inhibited collagen I and III expression induced by stretch, and AAT1 knockdown increased the expression of collagen I and III in pulmonary artery fibroblasts. However, SB431542, a transforming growth factor-beta 1/Smad2/3 inhibitor, eliminated the accumulation of collagen I and III induced by AAT1 knockdown (Liu et al., 2016). These data indicate that the endogenous SO_2/AAT1 pathway mediated the process of stretch-induced abnormal collagen accumulation by transforming growth factor-beta 1/Smad2/3 signaling in pulmonary artery fibroblasts. In addition, AAT1 or AAT2 knockdown aggravated collagen deposition in transforming growth factor-beta 1 induced VSMCs. However, AAT1 or AAT2 overexpression inhibited collagen I and III expression

induced by transforming growth factor-beta 1 in VSMCs. Also, AAT1 or AAT2 overexpression inhibited the mRNA expression of procollagen I and III, increased the expression of matrix metalloproteinase-13 and inhibited the phosphorylation of transforming growth factor-beta1 receptor and Smad2/3 (Huang et al., 2016a). These data indicate that endogenous SO_2 regulated collagen synthesis and degradation via the transforming growth factor-beta 1/ Smad2/3 pathway in VSMCs.

Effect of SO_2 on lung injury

In lung injury induced by lipopolysaccharide, polymorphonuclear neutrophil apoptosis is significantly increased, and treatment with SO_2 solution (25 μmol/kg) can reverse this effect. SO_2 treatment also significantly increased the protein level of caspase-3 and Bax, but increased that of Bcl-2 in polymorphonuclear neutrophils. These data indicate that the protective effect of SO_2 on pulmonary injury was associated with the regulation of polymorphonuclear neutrophil apoptosis (Ma et al., 2012). In oleic acid-induced acute lung injury in rats, the content of SO_2 and the protein expression of AAT1 and AAT2 were significantly decreased due to severe lung tissue injury. SO_2 donor administration reversed these effects. SO_2 alleviated lung injury and inhibited the levels of MDA and OH-, but increased the levels of SOD, GPx and total antioxidant capacity. These data indicate that the SO_2/AAT1/AAT2 pathway is involved in the protective effect of SO_2 in association with inhibition of oxidative stress (Chen et al., 2015).

In lung injury induced by limb ischemia-reperfusion in rats, SO_2 concentration and GOT activity were significantly decreased in lung tissues. Hydroxamate inhibited SO_2 generation and even aggravated lung inflammation in limb ischemia-reperfusion. SO_2 derivatives treatment significantly reduced lung injury in association with decreased plasma levels of IL-1β, IL-6, and IL-10. Myeloperoxidase (MPO) activity and inflammation in lung tissue were also inhibited by SO_2 treatment (Huang et al., 2013b). Furthermore, in lung injury induced by limb ischemia-reperfusion in rats, MDA and MPO were significantly increased in lung tissues. In addition, the levels of IL-1β, IL-6, IL-10 and TNF-α were increased in plasma and lung tissues. SO_2 administration significantly decreased the levels of MDA and MPO in lung tissues. The levels of IL-1β, IL-6 and TNF-α were also decreased and the level of IL-10 was increased in plasma and lung tissues. The protein expression of P-STAT3, P-Akt, and P-p38 was increased in lung tissue in rats with lung injury induced by limb ischemia-reperfusion. Administration of SO_2 resulted in increased P-Akt and P-p38 protein expression, and decreased P-STAT3 protein expression. LY294002 (PI3K inhibitor) or SB03580 (MAPK inhibitor) reversed the protective effect of SO_2 (Zhao et al., 2016). These data indicate that the protective effect of SO_2 on acute lung injury induced by limb ischemia-reperfusion was related to the JAK2/STAT3, PI3K/Akt, and p38MAPK pathways.

Effect of SO_2 on brain damage

In the recurrent febrile seizure rat model, the plasma and hippocampus levels of SO_2 were increased. The activities of AAT1 and AAT2 were both increased, accompanied by neuronal apoptosis and mossy fiber sprouting in the hippocampus. Preconditioning with a low concentration of SO_2 (1-10 μmol/kg) reduced neuronal damage, neuronal apoptosis and mossy fiber sprouting in the hippocampus of rats with recurrent febrile seizures (Han et al., 2014). These data indicate that SO_2 reduced brain injury induced by recurrent febrile seizures.

Perspective and challenges

SO_2 is a controversial gas. It is considered a toxic gas and an environmental pollutant. SO_2 has toxicological effects in multiple organs, such as oxidative damage, DNA damage, gene mutation, and chromosome aberration. However, studies have shown that SO_2 can be generated endogenously in mammals. In its pharmacological aspect, SO_2 has a vasorelaxing effect and may reduce hypertension in mammals. At the same time, SO_2 can reduce lung injury and ameliorate pulmonary vascular remodeling induced by pulmonary hypertension in rats. In addition, SO_2 can reduce myocardial injury, myocardial ischemia-reperfusion injury, and atherosclerosis. SO_2 can also reduce neuronal damage in the hippocampus of rats with recurrent febrile seizures. The protective effects of SO_2 are related to its antioxidant activity, reduction of cell apoptosis, and regulation of signal pathways. Another study showed that 2,4-dinitrophenylsulfonamides, a donor of SO_2, has excellent inhibitory effects on methicillin-resistant Staphylococcus aureus (Pardeshi et al., 2015). Therefore, the therapeutic effect of SO_2 may be used on cardiovascular diseases and others, though there is a long way for us to go.

The difference in the toxic and protective effects of SO_2 may be related to the following factors: First, exposure to SO_2, normally by inhalation, is harmful, as the effect of gaseous SO_2 is much stronger than that of its derivatives. Second, a low dose of SO_2 is beneficial, while a high dose is harmful in mammals. More and more studies have shown that the endogenous SO_2/AAT system has important effects in mammals. SO_2 is considered a gasotransmitter in the cardiovascular system (Huang et al., 2016b; Wang et al., 2011b, 2014, 2015).

However, there is much work to be done in further studies. First, we need to find the boundary of toxic and beneficial effects of SO_2. Second, what about the effect of SO_2 on other systems, such as digestive system, urinary system, nervous system and endocrine system. Third, the molecular mechanisms of SO_2 need further investigation. Clinical research is also required to determine the therapeutic potential of SO_2.

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Conflict of interest, The authors declare there is no conflict of interest.

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