REVIEW

Cardiovascular Effects of Gasotransmitter Donors

M. CEBOVÁ[1], M. KOŠÚTOVÁ[1], O. PECHÁŇOVÁ[1]

[1]Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Bratislava, Slovak Republic

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Summary

Gasotransmitters represent a subfamily of the endogenous gaseous signaling molecules that include nitric oxide (NO), carbon monoxide (CO), and hydrogen sulphide (H_2S). These particular gases share many common features in their production and function, but they fulfill their physiological tasks in unique ways that differ from those of classical signaling molecules found in tissues and organs. These gasotransmitters may antagonize or potentiate each other's cellular effects at the level of their production, their downstream molecular targets and their direct interactions. All three gasotransmitters induce vasodilatation, inhibit apoptosis directly or by increasing the expression of anti-apoptotic genes, and activate antioxidants while inhibiting inflammatory actions. NO and CO may concomitantly participate in vasorelaxation, anti-inflammation and angiogenesis. NO and H_2S collaborate in the regulation of vascular tone. Finally, H_2S may upregulate the heme oxygenase/carbon monoxide (HO/CO) pathway during hypoxic conditions. All three gasotransmitters are produced by specific enzymes in different cell types that include cardiomyocytes, endothelial cells and smooth muscle cells. As translational research on gasotransmitters has exploded over the past years, drugs that alter the production/levels of the gasotransmitters themselves or modulate their signaling pathways are now being developed. This review is focused on the cardiovascular effects of NO, CO, and H_2S. Moreover, their donors as drug targeting the cardiovascular system are briefly described.

Key words

Nitric oxide • Carbon monoxide • Hydrogen sulphide • Heart • Vessels • Cardiovascular system

Corresponding author

M. Cebová, Institute of Normal and Pathological Physiology, Slovak Academy of Sciences, Sienkiewiczova 1, 813 71 Bratislava, Slovak Republic. E-mail: martina.cebova@savba.sk

Introduction

Gasotransmitters are endogenously produced gaseous molecules that function as neurotransmitters and signal mediators to target enzymes, ion channels, and different transporters.

The physiological importance of the first molecule from the family of gasotransmitters, known as nitric oxide (NO), was recognized 30 years ago (Furchgott and Zawadzki 1980, Ignarro *et al*. 1988). The Nobel Prize in Physiology or Medicine has been awarded in 1998 for the discovery of "nitric oxide as a signaling molecule in the cardiovascular system". The class of endogenously generated gaseous transmitters includes also carbon monoxide (CO) and hydrogen sulphide (H_2S) (Szabo 2010, Peers and Steele 2012). Other gaseous molecules such as ammonia or methane are also candidates for this class (Wang 2014). All of them were initially considered to be toxic; but it has recently been determined that at low levels the endogenous NO, CO, and H_2S may provide protective physiological roles within the cardiovascular system and compensatory modulations during cardiac stress and injury (Calvert *et al.* 2010). All three gases have been shown to modulate ischemia/reperfusion injury by inducing a number of cytoprotective mechanisms that include induction of vasodilatation, inhibition of apoptosis, modulation of mitochondrial respiration, activation of antioxidants, and

Fax +420 241 062 164, e-mail: physres@biomed.cas.cz, www.biomed.cas.cz/physiolres

inhibition of inflammation. While their actions are similar, there are some differences in the mechanisms by which these gasotransmitters induce their effects. NO and CO share at least one common mechanism of action: both activate soluble guanylate cyclase (sGC). The affinity of NO to sGC is, however, approximately 30 to 100 times greater than that of CO (Li and Moore 2007). Yet there is no evidence that H_2S actually interacts with sGC. It has been suggested, however, that endogenous H_2S might increase the cGMP level by inhibiting PDE activity (Di Villa Bianca *et al.* 2015).

All three gasotransmitters are produced by specific enzymes. NO is produced by NO synthases (NOS) from the amino acid L-arginine. Three NOS isoforms, collectively known as NOS1, NOS2 and NOS3, were originally termed neuronal, inducible and endothelial NOS, respectively (Garvin *et al.* 2011). Recently, the effects of still putative mitochondrial NOS (mtNOS) have been proposed (Zaobornyj and Ghafourifar 2012). CO is generated by heme oxygenases (HO) during heme degradation (Wu and Wang 2005). There are three heme oxygenases (HO-1-3) (Yoshida *et al*. 1974, Maines *et al*. 1986, McCoubrey *et al.* 1997). H_2S is mainly produced within the metabolism of L-cysteine by the enzymes cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE or CTH) and 3-mercaptopyruvate sulfurtransferase (3-MST) (Wang 2012). Recently, an additional pathway for endogenous H_2S production has been described that involves D-cysteine, 3-MST, and D-amino acid oxidase (Shibuya *et al.* 2013).

This review is focused on the cardiovascular effects of three endogenously produced molecules termed as gasotransmitters: NO, CO, and H_2S. Moreover, their donors as drug targeting the cardiovascular system are described.

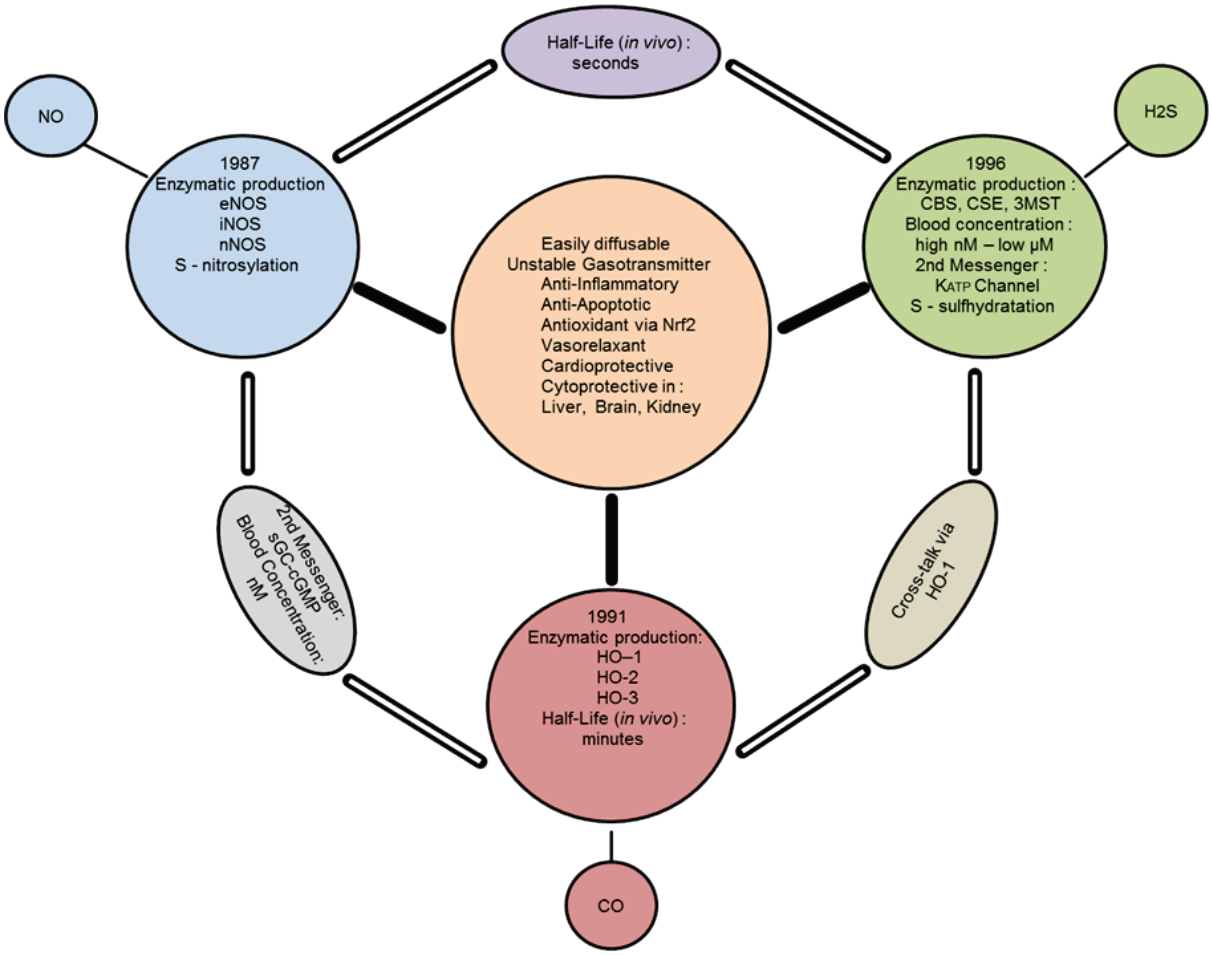

Fig. 1. The endogenous enzymatic production of nitric oxide (NO), carbon monoxide (CO) and hydrogen sulphide (H_2S) that provides effective cytoprotection *via* regulation of multiple signaling pathways. CBS, cystathionine β-synthase; cGMP, cyclic guanosine monophosphate; CSE, cystathionine γ-lyase; eNOS, endothelial nitric oxide synthase; HO-1, heme oxygenase 1; iNOS, inducible NOS; KATP, ATP-sensitive K^+ channel; 3MST, 3-mercaptopyruvate sulfurtransferase; nNOS, neuronal NOS; Nrf2, nuclear-factor-E2-related factor-2; sGC, soluble guanylyl cyclase.

NO in normal and pathological conditions

Nitric oxide originates from the amino acid L-arginine. Its formation is catalyzed by one of three different isoforms of NOS that differ in enzymatic activity, regulation (transcriptional, translational, and posttranslational mechanisms), expression and compartmentalization in cells and tissues. Three distinct NOS isoforms are called NOS I, II, and III. These correspond to the inducible (iNOS), neuronal (nNOS), and endothelial (eNOS) isoforms, typically with high, medium, and low activities, respectively (Bredt and Snyder 1990, Förstermann *et al*. 1991). Still putative fourth isoform – mtNOS may represent a mechanism of fine regulation of the mitochondrial respiratory complexes (for review see Zaobornyj and Ghafourifar 2012). Particular isoforms were described in various cells of cardiovascular system including cardiomyocytes, endothelial cells, and vascular smooth muscle cells (Radomski *et al*. 1990, Schulz *et al.* 1992). Within the heart, eNOS is expressed predominantly in the coronary and cardiac endothelium, whereas nNOS is expressed in the cardiomyocytes (for review see Tirziu and Simons 2008, Pacher *et al.* 2007).

Nitric oxide may affect myocytes in a number of different ways. NO signaling *via* cGMP-dependent or independent pathways modulates the function of downstream proteins *via* specific posttranslational modifications such as phosphorylation by cGMP-dependent protein kinase (PKG) or S-nitrosylation. Interestingly, an increase in intracellular cGMP induced by natriuretic peptides or cGMP analogues was recently shown to modulate both sarcolemmal and mitochondrial ATP-sensitive K^+ channel opening in ventricular cardiomyocytes, which suggests further, diverse actions of NO (Burley *et al.* 2014). The main physiological effects of NO derived from eNOS and nNOS include reduction of the contractile frequency of cardiomyocytes, attenuation of cardiac contractility, acceleration of relaxation and increasing distensibility of cardio-myocytes, and improvement of the efficiency of myocardial oxygen consumption. Under the conditions of enhanced cardiac reserve and cardiac hypertrophy, NO derived from eNOS modulates receptor-mediated signaling, which ultimately leads to a moderate inhibition of cardiac contractility (Yue and Yu 2011, Knowles *et al.* 2011). NO derived from the complex of nNOS-ryanodine receptor (RyR) stabilizes RyR calcium release and increases the efficiency of Ca^{2+} cycling in sarcoplasmic reticulum by the inhibitory effects. However, besides the above-mentioned inhibitions of NO derived from eNOS and nNOS, NO derived from iNOS generally prevents mitochondrial permeability transition pore opening by inhibiting mitochondrial respiration under the conditions of the myocardial ischemia-reperfusion injury and heart failure (Yue and Yu 2011).

In the endothelium, the interaction of eNOS with caveolin-1 in the caveolae is critical for eNOS activity (Feron and Balligand 2006). Endothelial NOS plays a key role in controlling blood flow and maintaining an antithrombotic and anti-inflammatory luminal surface. On the other hand, iNOS is induced by inflammatory stimuli in leukocytes, epithelial cells and macrophages to mediate pathogen killing. NO synthesized and released by vascular endothelial cells is an important regulator of vascular tone, leukocyte adhesion, platelet aggregation and vascular smooth muscle-cell proliferation (Balligand *et al.* 1993, Bolli *et al.* 1997, Buchwalow *et al.* 2001, Torres-Resgado *et al.* 2007). Interestingly, eNOS expression was not affected by cardiovascular risk factors such as hypertension, obesity, and insulin resistance (Bouvet *et al.* 2007, Fulton *et al.* 2004). Paradoxically, it was found to be increased in various pathological states that are associated with oxidative stress (Zhen *et al.* 2008, Ding *et al.* 2007, Li *et al*. 2002, Puzserova and Bernatova 2016). This effect might be partly mediated by limiting the availability of NO, thereby exerting a negative feedback on NOS expression through the activation of nuclear factor kappa B (NF-κB) (Pechanova and Simko 2009, Pechanova and Simko 2010, Zhen *et al*. 2008, Vranková *et al*. 2009).

It is generally believed that increased production of ROS in the heart and vessels plays an important role in the pathology of hypertension and other cardiovascular diseases; but so far, the clinical studies that used different antioxidants have yielded rather contradictory results (for review see Pechanova and Simko 2009). For example, one of the largest studies involving more than twenty thousand individuals with high cardiovascular risk did not observe any reduction of blood pressure after five years of treatment with the combination of ascorbic acid, synthetic vitamin E, and β-carotene. Moreover, substantially increased plasmatic concentrations of applied vitamins did not result in any significant reduction of the five-year morbidity and mortality from cardiovascular reasons (Heart Protection Study Collaborative Group 2002). Temporarily increased ROS generation in hypertension is not necessarily harmful, as

it may stimulate the activity of the antioxidant defence system and improve the NO signaling pathway, resulting in the establishment of a new equilibrium between increased oxidative load and the stimulated NO pathways, thus maintaining sufficient NO availability (Dröge 2002, Pechanova and Simko 2010, Bernatova 2014). However, in hypertension associated with obesity or diabetes, ROS may favor the activation of proinflammatory NF-κB-dependent pathways. Under these conditions, activation of NF-κB increases levels of cytokines IL-6 and TNF-α that may affect the phosphorylation of tyrosine kinases and decrease NOS activity with a final decrease in NO generation (for review see Belin de Chantemele and Stepp 2012). The increased production of ROS and decreased availability of NO have been suggested to be responsible also for endothelial dysfunction in the models of hypertriglyceridemia (for review see Zicha *et al.* 2006). Several studies also reported prevention or improvement of endothelial dysfunction by different polyphenolic antioxidants and NO donors (Pechanova *et al.* 2006, Pechanova *et al.* 2015). Sufficient production of NO is therefore essential for the prevention and treatment of severe cardiovascular diseases.

NO donors as a drug targeting cardiovascular system

NO donors are pharmacologically active substances that either spontaneously release NO or are metabolized to NO or its redox congeners. NO donors may provide a wide scope for pharmacotherapy in cardiovascular medicine. The organic nitrates (glyceryl trinitrate, isosorbide mononitrate) and NO-metal complexes (sodium nitroprusside, diazeniumdiolates), S-nitrosothiols and (benzo) furoxans are the most commonly used NO donor drugs (Serafim *et al.* 2012). Glyceryl trinitrate (GTN, also known as nitroglycerin) is the best-studied nitrate. It is used mainly in relief of acute pain associated with angina. On the other hand, preparations with a slower NO release, such as isosorbide mononitrate (ISMN), are used for the treatment of chronic angina. The other clinically relevant NO donor is sodium nitroprusside (SNP). SNP is used for the rapid lowering of blood pressure in hypertensive crises and as the gold standard NO-dependent but endothelium-independent vasodilator in clinical and experimental studies. The major complications of SNP therapy are hypotension and toxicity from accumulation of cyanide. These complications usually occur in patients with renal insufficiency when treated for more than 24 h (Hollenberg 2007, Thomas *et al.* 2009). S-nitrosothiols have far less stringent metabolic requirements, and this may be why they do not induce nitrate tolerance with long-term use. They have been shown to induce vasodilatation longer than other types of NO donors (Alencar *et al.* 2003, Nacharaju *et al.* 2012).

Nitrate tolerance, however, has become a limiting factor for clinical use of NO donors. Extended use of nitrate vasodilators induces nitrate tolerance that leads to tachyphylaxis and to aggressive side effects, including increased oxidative stress, endothelial dysfunction and cardiac autonomic dysfunction (Eroy-Eveles and Mascharak 2009, Gori and Parker 2008). The tolerance has been shown to depend on the type of nitrate and the dosing schedule.

Molsidomine and pentaerythrityl tetranitrate (PETN) represent more effective tolerance devoid NO donors with a pharmacodynamically beneficial effect. Molsidomine belongs to the sydnonimines group, and it is metabolized to the active linsidomine. PETN is the nitrate ester of pentaerythritol. It is structurally very similar to nitroglycerin. It was found to be the most active drug in cGMP production and in following pathway activation. PETN does not induce oxidative stress (Hinz *et al.* 1998) and evokes endothelium-independent dilatation of the arterial wall (Megson and Leslie 2009). Nicorandil is another vasodilator that is commonly used to treat chronic stable angina. Unlike nitrates, the actions of nicorandil result in "balanced" arterial and venous dilatation that is mediated *via* two distinct anti-angina mechanisms (Kukowetz *et al.* 1991). In addition, nicorandil is not associated with tolerance or rebound angina, and there is some evidence to suggest prognostic benefit due to reduction in oxidative stress during myocardial ischemic reperfusion injury (Horinaka 2011) and the infarct size in rabbit hearts (Argaud *et al.* 2009).

LA 419 is NO donor that has been designed to treat clinical conditions associated with reduced bioavailability of NO (Lacer 2005). The compound LA-419 is an analogue of isosorbide mononitrate. It has been showed to exert anti-ischemic, anti-thrombotic, and anti-atherosclerotic cardiac actions (Lacer 2005, Vilahur *et al*. 2004). Preclinical studies have shown that this agent possesses anti-atherogenic and antioxidant properties that make it applicable for the oral treatment of chronic cardiovascular disorders. LA-419 has beneficial effects in preventing the progression to maladaptive cardiac hypertrophy in a well-characterized model of left ventricle hypertrophy by pressure overload. Ruiz-Hurtado

and Delgado (2010) demonstrate that LA-419 prevents left ventricular remodeling in rats with aortic stenosis at doses that do not affect arterial blood pressure. In their experiment, LA-419 even restored cardiac eNOS expression and enhanced the interaction between eNOS and its positive regulator – heat shock protein 90. LA-419 also re-established the normal cardiac levels of cGMP. In addition, the thiol group of LA-419 improved NO stability by converting NO into nitrosothiols and by protecting the formed NO from the reaction with ROS (for review see Pechanova *et al.* 2015).

Until now, there are several clinical trials that verify the therapeutic potential of NO donors. In general, most of them that focus on pathologies are connected with the cardiovascular system. There is no "typical" NO donor. Each has its own specific characteristics that determine the rate of NO release, peak NO concentration and NO-related species generated for a particular application. Nevertheless, further studies that reveal the complex influence on vascular cell homeostasis are needed to find the key to successful therapeutic use of NO donors.

CO in normal and pathological conditions

Carbon monoxide is a biologically active molecule and is uniquely well established as a gasotransmitter, being a more stable molecule than NO or H_2S. Specific molecular targets of CO are still not known but it acts as a signaling molecule in the cardiovascular, nervous and gastrointestinal systems (Beltowski *et al.* 2004, Olas 2014). CO is the most biologically stable gasotransmitter due to its weak chemical reactivity. CO does not have unpaired electrons, and does not chemically dissociate in an aqueous solution to form different chemical species. Thus, CO might be capable of exerting its effects during longer time periods and distances compared to NO or H_2S (Untereiner *et al.* 2012).

Endogenous CO is generated by heme oxygenases (HO-1 and HO-2) as a final product of heme degradation. The cascade of the reactions leads to the production of ferrous iron (Fe^{2+}), CO and biliverdin, which is rapidly degraded to bilirubin. O_2 and NADPH are necessary for this reaction, which is crucial to iron and bile metabolism, and also induces a production of an effective antioxidant bilirubin. HO-1 expression is inducible, whereas HO-2 expression is constitutive. Both atrial and ventricular cardiac myocytes express HO-1 and HO-2 (Peers and Steele 2012). Just like NO, CO has been shown to act through the activation of sGC increasing cGMP concentrations (Schmidt 1992). However, its effect has lower potential than that modulated by NO (Stone and Marletta 1994, Ma *et al.* 2007). Moreover, there is a fundamental difference in the reactivity of CO compared to NO and H_2S (Fukuto *et al.* 2012). CO binds to transition metal centers due to ambient pressure and temperature and in the absence of special catalysts, whereas the other two species react rapidly with both metal centers and many of the organic constituents of biological systems. This relative inertness and selective reactivity of CO has special implications for both the cellular target structures of CO and the development of delivery systems for CO in potential therapeutic applications (Motterlini and Otterbein 2010). It has been proven that CO is able to activate big-conductance calcium-activated potassium channels with consequent hyperpolarization and relaxation of arterial membrane (Wang *et al.* 1997).

CO is able to modulate important signaling pathways that involve NO/GC, K^+ channels, ROS and MAPKs. The relevant biosynthetic enzyme, heme oxygenase, has a central role in a cellular antioxidant defence and vascular protection, and it may mediate many actions of drugs used in cardiovascular therapy (Muchova *et al.* 2007). Up-regulated HO-1 is expressed in the myocardium and in the coronary circulation after stress such as ischemia/reperfusion (I/R), and it has cardioprotective (Johnson *et al.* 2004, Peers and Steele 2012), anti-apoptotic and cytoprotective effects (Stein *et al.* 2012, Muchova *et al.* 2007, Chan *et al.* 2011). Endothelium and smooth muscle of arterial and venous blood vessels express constitutively HO-2 which may regulate the endogenous CO production and thus modulate the vascular tone.

Among the consequences of HO/CO system dysfunction belong increased vascular contractility, unbalanced cellular apoptosis and proliferation in the vascular wall, increased oxidative stress, and hypertension development. Acute application of pharmacological inducers to upregulate the expression of HO-1 or the use of gene delivery method to overexpress HO-1 decreased blood pressure in young spontaneously hypertensive rats (SHR). However, acute manipulation with the expression of HO-1 has not been successful in decreasing blood pressure in adult SHR (Ndisang *et al.* 2004, Mustafa and Johns 2001). HO-1 expression in vascular tissues has been found to be decreased in SHR at a prehypertensive stage. Furthermore, the activities of the

downstream targets of CO – including soluble guanylate cyclase – were also decreased in prehypertensive SHR. These findings show that suppression of HO-1/CO/cGMP signaling pathway precedes the development of hypertension and should support the rise of blood pressure in SHR (Ndisang and Wang 2002). The HO/CO system has also been studied in other models of hypertension, such as Dahl salt-sensitive, phenylephrine-, angiotensin II- and L-NAME-induced hypertension (Teran *et al*. 2005, Johnson *et al*. 1996, Johnson *et al*. 2004, Aizawa *et al*. 2000, Soni *et al*. 2010). Teran *et al*. (2005) suggested that hypertension and surprisingly HO-mediated endothelial dysfunction develop gradually and simultaneously in Dahl salt-sensitive rats on high-salt diets. They also suggested that HO-derived CO underlies the impaired endothelial dysfunction and contributes to hypertension in Dahl salt-sensitive rats on high-salt diets. Johnson *et al*. (2004) also documented that cardiac HO-1 is overexpressed in Dahl salt-sensitive rats. They have also shown that arterial HO-1 immunostaining is enhanced in rats on high-salt diet, but they proposed that coronary HO-1 expression is increased to support coronary vasodilatation in salt-induced hypertension. Also the treatment with the heme oxygenase inducer, heme-L-lysinate, that stimulates formation of heme oxygenase products, reduced blood pressure in rats. Heme-L-lysinate lowered arterial pressure in deoxycorticosterone acetate-salt hypertensive rats and in rats with phenylephrine-induced hypertension, indicating that the vasodepressive actions of heme and CO may be extended to other hypertensive models (Johnson *et al*. 1996). Ndisang *et al*. (2014) offered novel sights on the cardio-protective role of upregulating heme-oxygenase in L-NAME hypertension. The treatment with the heme oxygenase inducer, heme-arginate, improved myocardial morphology in L-NAME hypertensive rats by reducing subendocardial injury, interstitial fibrosis, mononuclear-cell infiltration and cardiomyocyte hypertrophy. Soni *et al*. (2010) concluded that CO-dependent cardioprotective effects seem to be NO-independent because NOS inhibition by L-NAME did not affect CO-mediated protection in isolated perfused rat heart. The upregulation of the HO/CO system, which is followed by increased production of endogenous CO, also increased the concentration of biliverdin and bilirubin, which are considered to be potent antioxidants. Increased concentration of CO can invoke the inhibition of abnormal vascular contractility and vascular remodeling (Rochette *et al*. 2013). Moreover, Aizawa *et al.* (2000) have found that HO-1 upregulation in the kidney of Ang II-induced hypertensive rats can perform a renoprotective effect against Ang II-induced renal injury.

Higher CO levels decrease the production of NO and the formation of $ONOO^-$ in the cardiovascular system (Munoz-Sanchez and Chanez-Cardenas 2014, Throup *et al*. 1999). Cardiotoxic effects of CO cause ischemic and endothelial damage and oxidative stress in the heart (Lippi *et al.* 2012). Long-term CO exposure leads to cardiac fibrosis following myocardial cell death. During experimental CO exposure the cardiac remodeling was accompanied by the alterations in Ca^{2+} homeostasis, uncoupling of eNOS, and pro-arrhythmic changes in cardiac electrophysiology (Reboul *et al.* 2012). Thus, it seems that similarly like NO, CO-induced effects are strongly dependent on the concentration of this gasotransmitter.

CO donors as a drug target for cardiovascular system

Carbon monoxide-releasing molecules (CORMs) are molecules that can release CO under certain biological conditions. The two major classes of CORMs are boranocarbonates and metal carbonyl complexes that contain ruthenium, iron or manganese as metal center (Mann 2010, Motterlini *et al*. 2005, Pitchumony *et al.* 2010, Zobi 2013). CORMs release CO *via* thermal activation or hydrolysis in biological buffers (Desmard *et al.* 2012). In spite of the wide range of therapeutic studies that show the beneficial effects of CO administered as a gas or as a CORM in cardiovascular disease, most of them to date have focused only on the commercially available CORM-2 and water-soluble CORM-3.

CORM-2 (tricarbonyldichlororuthenium(II)) ($[Ru(CO)_3Cl_2]_2$) is the first ruthenium-based CO-releasing molecule with solubility in organic solvents. CORM-2 has a vasorelaxing effect in a concentration-dependent manner on isolated aortic ring sections or afferent renal arterioles (Botros and Navar 2006, Motterlini *et al*. 2002, Marazioti *et al*. 2011, Decaluwé *et al*. 2012). It has been shown that the inhibitor of the guanylate cyclase, quinoxalin-1-one, reduces CORM-2 effect *via* the sGC-cGMP pathway (Motterlini *et al*. 2003, Marazioti *et al*. 2011, Decaluwé *et al*. 2012). K^+ channels also contribute to CORM-2-induced vasodilatation. It has been proven that CO is able to work directly on Ca^{2+}-activated K^+ channels. However, CORM-2 up-regulates the voltage-dependent K^+ channels in mice thoracic aorta (Wang *et al*. 1997, Decaluwé *et al*.

2012). However, CO-induced inhibition of sGC and K^+ channels did not cause an obvious inhibition of CORM-2-induced vasorelaxation (Decaluwé *et al.* 2012). The relaxant abilities of CORM-2 may have a blood pressure lowering effect *in vivo*. CORM-2 applied in a rat model of acute hypertension significantly attenuated L-NAME-induced pressor responses and induced significant vasorelaxation of thoracic aorta (Motterlini *et al*. 2012). Exercise training in hypertensive rats completely renewed the impaired relaxant responses of CORM-2 due to an increased activity of K^+ channels (Boissiere *et al*. 2006). In a rat model of myocardial ischemia-reperfusion injury it has been shown that cardioprotection by CORM-2 is highly concentration-dependent, but independent of coronary endothelium and this cardioprotective effect might be attributed to the activation of K_{ATP} channel present on vascular smooth muscle cells (VSMC) (Soni *et al.* 2010). Another study has described the mechanisms of cardioprotection that occur as a result of the activation of the p38 mitogen-activated protein kinase β and protein kinase C cascades before ischemia and phosphatidylinositol 3-kinase cascade during reperfusion (Soni *et al*. 2012). Moreover, CORM-2 protected cardiomyocytes from I/R-induced apoptosis as well. This probably occurs through the inhibition of mitochondrial apoptotic pathway and by the enhancement of energy metabolism (Zhao *et al*. 2014). After the post-resuscitation phase, CORM-2 eliminated the production of cardiac reactive oxygen species in mitochondria and reduced oxidative stress in the heart (Yao *et al*. 2015).

CORM-3 (tricarbonylchloro(glycinato)ruthenium(II)) ($Ru(CO)_3Cl(glycinate)$) seems to become the most promising CO donor due to its high ability to release CO and to mediate vasorelaxation (Motterlini *et al*. 2003). Vascular effect was also demonstrated by the low response to iCORM-3 (inactivated CORM-3 which is depleted of CO). CORM-3-dependent relaxation was significantly reduced by blocking the K_{ATP} channels with glibenclamide or by blocking the sGC activity with ODQ. This confirms that K^+ channel activation and cGMP partially mediate CORM-3 effect. Interestingly, inhibiting NO production or removing the endothelium significantly decreased vasodilatation by CORM-3, suggesting that factors produced by the endothelium influence CORM-3 vascular activities (Foresti *et al*. 2004). However, Alshehri *et al*. (2013) demonstrated that the foregoing hypotheses are unlikely to make clear the endothelium-dependent and cGMP-dependent relaxant influence of CORM-3 that results from the stimulation of NO synthase. They also find that CORM-3 has a vasorelaxant effect that is independent of endothelium and sGC by direct activation of smooth muscle K^+ channels. In addition, CORM-3 causes vasorelaxation *in vivo* followed by a rapid decline in mean arterial pressure, which is further enhanced by 3-(50-hydroxymethyl-20-furyl)-1-benzyl indazole (YC-1). This substance is known to sensitize sGC to the activation by CO, confirming the engagement of sGC (Foresti *et al*. 2004, Motterlini *et al*. 2005). Pretreatment with 1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-one (ODQ) or charybdotoxin eliminated the CORM-3-induced relaxation in aortas of normotensive and spontaneously hypertensive rats. This indicates a participation of sGC and Ca^{2+}-activated K^+ channels, respectively. Compared with the NO donor, S-nitroso-N-acetyl-D,L-penicillamine, CORM-3-mediated vascular relaxation was maintained for a longer time in SHR aortas. Therefore, CORM-3 is a possible alternative for the treatment of hypertension when the NO donor therapy is not adequate (Failli *et al*. 2012). CO from CORM-3 displayed a positive inotropic effect on isolated perfused rat cardiac tissue. In this case, cGMP and stimulation of Na^+/H^+ exchanger seem to be involved (Musameh *et al*. 2006). CORM-3 also reduced the release of myocardial creatine kinase and attenuated the infarct size (Clark *et al*. 2003). It has cardioprotective effects not only when given at the moment of reperfusion but also when administered 24 to 72 hours before coronary occlusion. This persistent cardioprotective effect of CORM-3 may be helpful as prevention in patients at risk for myocardial infarction (Stein *et al.* 2005). In a mouse model of myocardial infarction, CORM-3 eliminated cardiac tissue damage, decreased infarct size during reperfusion and even significantly prolonged the survival period after organ transplantation (Clark *et al.* 2003).

CORMs are novel CO-specific carriers that can be used in pharmacology for their therapeutic effects. To fully reflect the promise of CO as a therapeutic agent, it is essential to find the novel pathway for CO delivery to injured tissues without concomitant formation of elevated toxic blood levels of carboxyhemoglobin. CORMs appear to have a potential to constitute safe treatments with controlled CO release.

H_2S in normal and pathological conditions

Hydrogen sulphide (H_2S) is easily soluble gas in both water and lipids. At physiological pH, less than

20 % of H_2S exists as an undissociated compound; the rest is dissociated to HS^- and H^+ (Li and Lancaster 2013). From a chemical point of view, H_2S is the simplest thiol of all. Until recently, H_2S was viewed exclusively as a toxic gas and environmental hazard. In general, H_2S damages mainly the brain, kidneys and lungs. However, H_2S is an endogenous, labile molecule that induces a variety of beneficial reactions in the myocardium (Pan *et al*. 2006). Four enzymatic pathways of H_2S production have been found to date. Two are catalyzed by cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE), which are pyridoxal 5′-phosphate-dependent cytosolic enzymes of the transsulfuration pathway in which homocysteine is metabolized to cysteine (for review see Beltowski 2015). In general, it is suggested that CBS is the main H_2S synthase in the nervous system. CSE plays this role in the most peripheral tissues except the liver and kidney, which contain both enzymes in substantial amounts (Singh *et al.* 2009). The third pathway of H_2S generation requires two enzymes: cysteine aminotransferase (CAT) and 3-mercapto-pyruvate sulfurtransferase (3-MST). This pathway operates mainly in mitochondria (Kimura 2013). 3-MST is presented in endothelial cells in the thoracic aorta (Shibuya *et al*. 2009). The distribution and regulation of H_2S-producing enzymes and the wide range of biological effects of H_2S are discussed in separate reviews (Szabo 2007, Elsey *et al.* 2010, Gadalla and Snyder 2010, Kimura 2014, Whiteman and Winyard 2011, Whiteman *et al.* 2011, Wang 2012, Cacanyiova *et al.* 2016). Like the other two gasotransmitters (NO and CO), many of the biological responses to H_2S follow a biphasic dose-response: The effects of H_2S range from physiological, cytoprotective effects at low concentrations up to cytotoxic effects at higher concentrations (Szabo *et al.* 2014). There is growing evidence that H_2S is a critical regulator of cardiovascular functions and plays a protective role in the pathogenesis and development of cardiovascular diseases (Polhemus and Lefer 2014). Hydrogen sulphide may inhibit platelet activation and vascular smooth-muscle cell proliferation. In the vascular wall, H_2S functions as an endothelium-derived relaxing factor (Yang *et al.* 2008, Wang 2009). It is also an endothelium-derived hyperpolarizing factor (Tang *et al*. 2013, Mustafa *et al.* 2011). Altaany *et al.* (2014) suggested that hydrogen sulphide increases the phosphorylation of eNOS and thus reduces blood pressure. Thus, H_2S is a pivotal gasotransmitter that coordinates the S-sulfhydration, S-nitrosylation, and phosphorylation of eNOS to finely tune endothelial function under physiological and pathophysiological conditions.

H_2S relaxes the thoracic aorta, but its relaxation effect was significantly weaker than its effect on vena portae or ileum (Hosoki *et al.* 1997). Furthermore, endothelium-dependent vasorelaxation effects of H_2S are more prominent in peripheral resistance arteries than they are in large-conduit arteries, which require membrane hyperpolarization of both endothelial and vascular smooth muscle cells (Mustafa *et al.* 2011). Hosoki *et al.* (1997) and others have also found the synergic effect of NO and H_2S. To date, mechanisms of primary hypertension have not been fully understood. NO and CO have been found to play important roles in the pathogenesis of hypertension, as mentioned above. But does H_2S also play a role in spontaneous hypertension? A variety of studies have focused on the association of H_2S with hypertension (Yang *et al.* 2008, Pan *et al*. 2015, Ahmad *et al*. 2012, Zhong *et al*. 2003). Intravenous bolus injection of H_2S induced a transient dose-dependent decrease in mean arterial pressure in anesthetized rats (Zhao *et al*. 2001). The CSE-deficient mice developed severe endothelial dysfunction and hypertension within 8 weeks of birth; however, H_2S replacement reduced systolic blood pressure in both $CSE^{-/-}$ and $CSE^{+/-}$ mice (Yang *et al.* 2008). These authors suggested that the H_2S synthases/H_2S pathway confers a protection against hypertension. In SHR CSE gene expression was downregulated in the development of hypertension and plasma level of H_2S, as well as its production rate were lower in SHR than in WKY rats. Therefore, CSE is a specific enzyme for H_2S production in the thoracic aorta, and its decreased activity in hypertension may lead to a smaller H_2S production. It can result in a decrease of circulating H_2S (Yan *et al.* 2004). Administration of exogenous H_2S lowers blood pressure and prevents the progression of diabetic nephropathy in SHR (Ahmad *et al.* 2012). Exogenous H_2S effectively inhibited the development of L-NAME-induced hypertension in rats (Zhong *et al.* 2003).

In vitro, H_2S and NaHS relaxed rat thoracic aorta and portal veins preconstricted with norepinephrine. Importantly, H_2S also relaxed mesenteric arteries (Cheng *et al.* 2004) which are as peripheral resistance vessels more significant for the regulation of vascular resistance and blood pressure than large conduit arteries.

H_2S donors as a drug target for cardiovascular system

Potential targets for H_2S donors include arterial hypertension, atherosclerosis, myocardial hypertrophy, heart failure, ischemia-reperfusion injury of various organs such as the heart, brain, kidney, lung, liver or intestine (Kashfi and Olson 2013, Sikora *et al.* 2014). H_2S donors have also been shown to prevent platelet aggregation (Zhong *et al*. 2014) and thrombus formation in venules (Kram *et al.* 2013).

In most studies, the inorganic sulphide salts, sodium hydrosulphide (NaHS) and sodium sulphide (Na_2S) are used. These compounds increase H_2S/HS^- concentration due to dissociation and pH-dependent balance between HS^- and H_2S in aqueous solutions. There are many mechanisms involved in the protective effect of NaHS, such as activation of K_{ATP} channels and protein kinase B/Akt, increase in Nrf2 signaling. Yan *et al*. (2004) showed that, after injecting NaHS for 5 weeks, the plasma level of H_2S, the production rate of H_2S and the CES expression in aorta of NaHS-treated SHR were increased significantly compared to those of control SHR. Also, systolic blood pressure decreased much at the same time and the medial cross-sectional area and medial stress were reduced, suggesting that aortic structural remodeling is attenuated by the increased level of H_2S in SHR. Other investigators showed that daily treatment of SHR with NaHS for 8 weeks not only lowered blood pressure but also reduced the hypertrophy of intramyocardial arterioles and ventricular fibrosis in these animals. These results suggest a long-term vasculoprotective effect of H_2S (Shi *et al*. 2007). Similar data have been reported by Zhao *et al*. (2008) who noted that chronic NaHS administration in SHR reduced aortic collagen-1 content and ^{3}H-proline incorporation.

To overcome the limitation of sulphide salts, several slow-releasing H_2S compounds have been synthesized: namely, GYY4137, AP67, and AP72. GYY4137 (morpholin-4-ium 4-methoxyphenyl (morpholino) phosphinodithioate dichloromethane complex) is the most popular among the slow-releasing H_2S donors. It is a water soluble compound that spontaneously decomposes to release H_2S over 3-4 hours after dissolving. Its intravenous injection had no immediate effect on blood pressure in the anesthetized rat but caused a slow fall in blood pressure for up to 2 hours accompanied by a progressive, presumably reflex, rise in heart rate (Li *et al.* 2008). The authors also found that GYY4137 induced vasorelaxation *in vitro* and decreased blood pressure *in vivo*. It reduced secretion of proinflammatory cytokines (TNF-α, IL-1β, IL-6) and decreased COX-2 and iNOS expression in LPS-stimulated RAW264.7 macrophages (Whiteman *et al.* 2010). It also protected cultured cardiomyocytes from hyperglycemia-induced injury (Wei *et al*. 2014), was beneficial in the experimental model of joint inflammation (Li *et al.* 2013), inhibited platelet aggregation *in vitro* and thrombus formation *in vivo* (Grambow *et al*. 2014), restored fetal growth in mice model of preeclampsia (Wang *et al*. 2013), and reduced atherosclerotic lesions in apo-E knockout mice (Liu *et al*. 2013). This inhibitor did not cause cytotoxic effects or alterations in the cell-cycle profile or p53 expression of cultured rat vascular smooth muscle cells (Li *et al.* 2008).

AP67 (4-methoxyphenyl) pyrrolidin-1-ylphosphinodithioc acid and AP72 (4-methoxyphenyl) piperidin-1-ylphosphinodithioc acid can relax precontracted isolated bovine ciliary artery, an effect that is dependent on endogenous production of H_2S (Kulkarni-Chitnis *et al.* 2015). AP39, a sulphide donor with a mitochondria-targeting moiety, has been shown to increase intracellular H_2S probe 7-azido-4-methyl-coumarin. It has also been demonstrated that AP39 is able to prevent glucose oxidase-induced mitochondrial oxidative stress (Szczesny *et al*. 2014).

There is a growing evidence of the development and usage of the stable H_2S donors. These compounds seem to be innovative pharmacotherapeutical tools for treatment of cardiovascular diseases.

Conclusions

NO, CO and H_2S are endogenous gaseous transmitters with different physiological functions. As NO is the most extensively characterized of these transmitters, its properties have portended features of the others. So far it has been shown that all three gasotransmitters induce vasodilatation by activating the sGC/cGMP pathway (NO and CO) or by activating ATP-sensitive K^+ (K_{ATP}) channels (H_2S), they inhibit apoptosis directly or by increasing the expression of anti-apoptogens such as HSP90, HSP70, and Bcl-2, and they activate antioxidants while inhibiting inflammatory actions. Regarding the crosstalk of gasotransmitters, CO and NO have been shown to participate in vasoactivity, influencing growth factors, anti-inflammatory mediators, angiogenesis and vascular remodeling. It has been suggested that NO and H_2S collaborate in the regulation of vascular homeostasis and vasodilatation. Finally, H_2S

can upregulate the HO/CO pathway during hypoxic pulmonary hypertension.

The role of exogenously derived NO has been studied by the administration of NO in the form of authentic NO gas, NO donors, and more recently by nitrite and nitrate. Currently, NO donors represent important drugs in cardioprotection and in the treatment of cardiovascular diseases. CO and H_2S donors are now extensively studied in animal models and human studies. It is expected that the high level of research activity in this area will transpire soon to a new set of pharmaceuticals with protective or therapeutic properties in the cardiovascular system.

Conflict of Interest

There is no conflict of interest.

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Abbreviations

3-MST – 3-mercaptopyruvate sulfurtransferase
AP39 – [(10-oxo-10-(4-(3-thioxo-3H-1,2-dithiol-5yl) phenoxy)decyl) triphenylphosphonium bromide]
AP67 – (4-methoxyphenyl) pyrrolidin-1-ylphosphino-dithioc acid
AP72 – (4-methoxyphenyl) piperidin-1-ylphosphino-dithioc acid
CAT – cysteine aminotransferase
CBS – cystathionine-β-synthase
cGMP – cyclic guanosine monophosphate
CO – carbon monoxide
CORMs – carbon monoxide-releasing molecules
COX – cyclooxygenase
CSE or CTH – cystathionine-γ-lyase
eNOS – endothelial NOS
GTN – glyceryl trinitrate
GYY4137 – morpholin-4-ium 4-methoxyphenyl (morpholino) phosphinodithioate
H_2S – hydrogen sulphide
HO – heme oxygenases
HO/CO – heme oxygenase/carbon monoxide
HS^- – bisulfide
HSP – heat shock protein
I/R – ischemia/reperfusion
IL-1β – interleukin-1beta
IL-6 – interleukin 6
iNOS – inducible NOS
ISMN – isosorbide mononitrate
K_{ATP} – ATP-sensitive K^+ channel
L-NAME – N-nitro-L-arginine methylester
MAPKs – mitogen-activated protein kinases
mtNOS – mitochondrial NOS
Na_2S – sodium sulphide
NaHS – sodium hydrosulphide
nNOS – neuronal NOS
NO – nitric oxide
NO/GC – nitric oxide-sensitive guanylyl cyclase
NOS – nitric oxide synthase
Nrf2 – nuclear-factor-E2-related factor-2
ODQ – 1H-[1,2,4] oxadiazolo [4,3-a] quinoxalin-1-one
$ONOO^-$ – peroxynitrite
PETN – pentaerythrityl tetranitrate
PKB/Akt – protein kinase B or Akt
PKG – cGMP-dependent protein kinase
ROS – reactive oxygen species
($[Ru(CO)_3Cl_2]_2$) – tricarbonyldichlororuthenium(II) dimer ($Ru(CO)_3Cl$(glycinate), tricarbonylchloro (glycinato)ruthenium(II)
RyR – ryanodine receptor
sGC – soluble guanylate cyclase
SHR – spontaneously hypertensive rats
SNP – sodium nitroprusside
TNF-α – tumor necrosis factor alpha
YC-1 – 3-(50-hydroxymethyl-20-furyl)-1-benzyl indazole

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