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The role of gasotransmitters in neonatal physiology.

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Abstract

The gasotransmitters, nitric oxide (NO), hydrogen sulfide (H_2S), and carbon monoxide (CO), are endogenously-produced volatile molecules that perform signaling functions throughout the body. In biological tissues, these small, lipid-permeable molecules exist in free gaseous form for only seconds or less, and thus they are ideal for paracrine signaling that can be controlled rapidly by changes in their rates of production or consumption. In addition, tissue concentrations of the gasotransmitters are influenced by fluctuations in the level of O_2 and reactive oxygen species (ROS). The normal transition from fetus to newborn involves a several-fold increase in tissue O_2 tensions and ROS, and requires rapid morphological and functional adaptations to the extrauterine environment. This review summarizes the role of gasotransmitters as it pertains to newborn physiology. Particular focus is given to the vasculature, ventilatory, and gastrointestinal systems, each of which uniquely illustrate the function of gasotransmitters in the birth transition and newborn periods. Moreover, given the relative lack of studies on the role that gasotransmitters play in the newborn, particularly that of H_2S and CO, important gaps in knowledge are highlighted throughout the review.

Keywords

nitric oxide; NO; hydrogen sulfide; H2S; carbon monoxide; CO; newborn; neonate; fetus; vasculature; ventilatory control; gastrointestinal tract

I. INTRODUCTION

Nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S), the three gases categorized as gasotransmitters [1], have each followed a similar course in the history of biomedical science: from initial consideration as merely environmental toxins to the eventual realization that they are endogenous signaling molecules. This revelation, and the subsequent study of the physiological role of these gasotransmitters, has extended understanding of inter- and intracellular signaling mechanisms in several ways. First, unlike canonical receptor-ligand membrane transduction pathways, these gases diffuse across lipid

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membranes and can thus signal between cells and intracellular compartments more freely than larger signaling molecules. Second, the gasotransmitters can interact with a longer and more varied list of targets than larger conventional signaling molecules that are often selective for only one receptor. Third, the chemical reactivity of NO and H_2S, and the bioactivity of many of their reaction products, confers a level of complexity to their signaling capabilities that goes well beyond simple ligand-receptor interactions characteristic of more classical signaling molecules. Finally, oxygen exerts an influence on the activity of gasotransmitters by a variety of mechanisms, positioning them as more versatile players in oxygen-sensing than can be achieved with most other second messenger systems.

A defining characteristic of neonatal physiology is the need to adapt to extrauterine life, a transition that includes dramatic and rapid changes in cardiovascular function, several-fold increases in tissue dissolved oxygen levels, and transformative modifications in how oxygen, carbon dioxide, nutrients, and wastes are exchanged with the environment. Studies in adult humans and animals have demonstrated that gasotransmitters play an important role in regulating many of the systems that are critical to the birth transition and neonatal homeostasis, such as vascular tone and ventilatory control. In some cases the roles of gasotransmitters have actually been studied in newborns, but most work, particularly for H_2S and CO, has been done in adults and can only be tenuously extrapolated to the newborn. This is despite the fact that gasotransmitters would seem to be ideal candidates as signaling molecules for the rapid, oxygen-sensitive changes that occur at birth.

In this review, we present a summary of the work that has been done to characterize the role of gasotransmitters in neonatal physiology. We also highlight understudied areas where gasotransmitters can be reasonably expected to play a key role in the newborn. It is our hope that this article will not only be useful to the neonatal physiologists looking to include gasotransmitters in their studies, but that it will also point out aspects of newborn physiology that may offer useful insights into the signaling mechanisms of gasotransmitters in general. This review provides an overview of gasotransmitters as they pertain to the newborn, and the reader interested in more detail about gasotransmitters is referred to summaries in the field [2–5].

II. DETERMINANTS OF TISSUE CONCENTRATIONS

The gasotransmitters have a relatively short half life in biological tissues, ranging from a few milliseconds in blood to seconds in most tissues. As a result, concentrations of their free gaseous forms can fluctuate rapidly in response to changes in the rates of either production or clearance. Both enzyme-dependent and enzyme-independent pathways have been found for all three gasotransmitters, although enzyme-dependent production appears to be the predominant endogenous source [6–9].

All three of the gasotransmitters rapidly react with or bind to hemoglobin, and thus the blood serves as a reservoir depot as well as a pathway for biochemical clearance. Clearance of NO and H_2S can also occur by various redox reactions, while CO is chemically inert. In this section we will briefly summarize the pathways of synthesis and clearance that

determine the concentrations of free NO, H_2S, and CO. The rates of both production and metabolism of the gasotransmitters are also influenced by O_2 concentrations, and thus we will discuss how gasotransmitter levels are affected by the dramatic changes in PO_2 that occur at birth.

Nitric oxide

The concentration of free NO in circulation is believed to be at or below low nanomolar levels, while the perivascular concentration of endogenous NO is generally estimated to be at or below mid-nanomolar levels [10,11]. These concentrations are the result of a balance of several NO-producing, NO-preserving, and NO-consuming, pathways. These include the synthesis of NO by NO synthase (NOS), preservation of NO in the form of various NO adducts that can be converted back into NO, and rapid NO-scavenging reactions that oxidize NO to nitrate. In the newborn, most of these pathways are altered so as to decrease NO availability [12–18].

NO Synthesis.—De novo NO is produced endogenously by endothelial or neuronal NO synthases (eNOS or nNOS) that are present constitutively [19], or by inducible NO synthase (iNOS) that can be upregulated in various tissues in response to inflammatory stimuli [20]. NO production by NOS is of significant developmental importance, as eNOS deficiency correlates with defective angiogenesis in hypoplastic human fetal lungs [21], and mice deficient for eNOS display a range of abnormalities including fetal growth restriction, reduced survival, an increased rate of limb abnormalities [22,23], and impaired myocardial angiogenesis and morphology [24,25].

Several factors indicate that overall production of NO by NOS enzymes is decreased during the postnatal period. First, postnatal levels of all three NOS isoforms are generally reported to be decreased compared to the fetus [12–15]. Second, asymmetric dimethylarginine (ADMA), an endogenous competitive inhibitor of NOS, is increased in neonates [26], especially in preterm males [27,28]. Third, plasma concentrations of nitrite, which serve as an index of NOS activity [29–31], are similar in fetal umbilical and maternal blood, but fall by more than 50% within minutes after birth and remain low for a week or more. This phenomenon is particularly pronounced in preterm infants [17,18]. Therefore, NO biosynthesis by NOS appears to be suppressed in newborns. Availability of L-arginine, the primary substrate of all three NOS isoforms and an essential amino acid in newborns [32], is also a determinant of NOS activity. Although plasma L-arginine concentrations in term infants are comparable to those of adults, they are markedly lower in premature infants [32–34] as well as term infants with pulmonary hypertension [35,36], suggesting L-arginine deficiency may also contribute to decreased NO production in some neonatal pathologies [37,38].

NO storage and metabolism.—For some time after the discovery of NOS, it was widely held that the NO it produced was metabolized rapidly via irreversible pathways that ended with nitrite and nitrate, two anions once thought to have little physiological relevance. However, work over the past two decades has now established a number of mechanisms by which endogenous NO can be preserved in the form of NO-derived adducts that either retain

NO-like bioactivity or are capable of releasing free NO again. These NO-active compounds (NOx) include nitrosothiols (SNOs), heme and iron-nitrosyls (hemeNO and FeNO), and dinitrosyl iron complexes (DNICs). Even nitrite and nitrate are now widely acknowledged to contribute to NO signaling, the former by reduction to NO in reaction with various metal-containing enzymes [39] and the latter by bacterial nitrate reductase enzymes that convert nitrate to nitrite [40]. Somewhat ironically, early experiments that detected vasodilation by what was later determined to be NO were likely stimulating the release NO from these NOx species using ultraviolet light rather than by activation of NO production by NOS [41]. These NOx species constitute a significant reservoir of NO in the circulation and within tissues, but the relative concentrations of these compounds and how they are formed and regulated is still largely uncharacterized, particularly in the fetus and newborn.

As mentioned above, although circulating NOx concentrations are very well maintained in adults [31] plasma concentrations of NOx fall abruptly at birth and are maintained at levels well below those of the fetus and adult for the first few days of life [17,18]. This phenomenon may be partly due to reduced NOS levels and activity. In addition, neonates display markedly lower dietary nitrate and nitrite intake [42], lower rates of bacterial nitrate-to-nitrite reduction [16], and greater renal nitrite and nitrate excretion [18,43,44]. The extent to which this birth-related fall in NOx levels contributes to neonatal physiology remains to be determined.

Effects of O_2 on NO levels.—Oxygen availability is a key determinant of both production and consumption of NO [45], and the question thus arises how the increase in O_2 concentrations at birth may affect steady-state concentrations of NO. Briefly, O_2 is required for the production of NO from L-arginine by NOS. Although the Km of eNOS for O_2 (23 μM) is low enough that NO production in the fetus is likely not limited by O_2 availability, the Km for iNOS (135 μM) and nNOS (350 μM) [46] is markedly higher than fetal dissolved O_2 concentrations (arterial ~25 to 30 μM) and thus NO production by these NOS isoforms would seem to be oxygen-limited. Nonetheless, there is evidence that nNOS does function in the sheep fetus, as selective inhibition of nNOS has been found to attenuate post-ischemic brain injury [47].

In addition to NO production by NOS, the production of NO from NOx species such as nitrite is also O_2-dependent. Under hypoxic conditions the production of NO from the reaction of nitrite with deoxygenated heme iron becomes more prevalent [39]. In the case of hemoglobin, this reaction ($NO_2^- + Hb + H^+ \rightarrow NO + MetHb + OH^-$) has been proposed to result in NO-mediated vasodilation that is maximal at oxyhemoglobin saturations of approximately 50% [48]. However, although fetal hemoglobin facilitates this reaction approximately twice as fast as adult hemoglobin [49] and deoxyhemoglobin is more prevalent in the fetus than in the adult, nitrite only produces vasodilation at supraphysiological concentrations in fetal lambs [50], calling the physiological relevance of this reaction into question. For many of the other heme-containing proteins, such as cytoglobin, myoglobin, and neuroglobin, O_2-affinity is so great that availability of the deoxygenated heme for reducing nitrite would appear to be limited at physiological O_2 tensions in the adult [39]. Nonetheless, although the mechanisms remain undefined, there is abundant evidence that nitrite contributes to NO-dependent signaling pathways in the adult,

and that this is potentiated by hypoxia [40]. The physiological relevance of nitrite-derived NO at fetal O_2 tenions, or of the markedly reduced nitrite levels in the newborn are not yet understood. They conceivably relate to the redistribution of cardiac output among organs that takes place at birth.

O_2 is also required for the predominant pathways of NO consumption in biological tissues, and thus rates of NO consumption would be expected to vary by more than 10-fold across the range of fetal-to-newborn tissue O_2 tensions (Figure 2). The O_2-dependence of NO consumption in tissues does not appear to be due to simple NO autooxidation, as it proceeds by different kinetics and is markedly faster in biological matrices than in aqueous buffer [45,51,52]. In adult plasma, the conversion of NO to nitrite has been attributed to ceruloplasmin [53], but this may not be the predominant mechanism of NO consumption in neonates as fetal plasma NO consumption does not correlate with ceruloplasmin concentrations in sheep or humans [54]. Thus, the mechanisms of O_2-dependent NO consumption and whether these pathways change developmentally, remain unanswered questions.

Hydrogen Sulfide

The study of H_2S is fraught with many of the same challenges as NO in that it reacts rapidly by numerous pathways in biological tissues, and assays that reliably distinguish between free H_2S and its metabolites have been difficult to establish [55]. Most recent work indicates that the physiological concentration of free H_2S is low nanomolar or less in blood, and tens of nanomolar in tissues [55]. These concentrations are determined by a dynamic equilibrium between rates of H_2S synthesis and consumption. Likewise, although H_2S production is not O_2-dependent, H_2S consumption is, and thus birth-related changes in O_2 levels are likely to affect H_2S steady-state levels.

H_2S synthesis and storage.—H_2S is synthesized from the sulfur in cysteine or its derivatives by the tissue specific-enzymes cystathionine-γ-lyase (CSE), cystathionine-β-lyase (CBS), and 3-mercaptopyruvate sulfurtransfurase (3-MST) (Figure 3) [9]. CSE and CBS are absent or sparse and levels of activity are relatively low in the human fetus and newborn [56]. Hepatic CSE expression and activity increase rapidly after birth reaching mature levels at about 3 months of age [57,58]. Availability of cysteine, a conditionally essential amino acid in preterm infants [59,60], may also be limited during neonatal life. Therefore, like NO, H_2S biosynthesis also seems to be developmentally unfavored in the newborn. However, significant physiological importance of H_2S has been indicated in neonates. Pulmonary vascular development and lung alveolarization are impaired in $CSE^{-/-}$ and $CBS^{-/-}$ mouse pups [61] and $CBS^{-/-}$ mice have a high mortality rate after the third and fourth postnatal weeks [62]. CBS deficiency is also associated with severe abnormalities of the eye, skeleton, vasculature, and central nervous system [63].

H_2S is a reactive molecule with a half life of seconds to minutes in the body [64,65]. At physiological pH, H_2S exists at equilibrium with HS^- (28% vs 72% at 25°C) [66]. Pathways for the clearance of free H_2S are shown in Figure 3. They include: 1) mitochondrial oxidation to produce sulfite, thiosulfate, or sulfate; 2) binding to heme (ferric preferred over

ferrous) to form an H_2S complex which then leads to polysulfide and thiosulfate formation; 3) reaction with thiols, although prior oxidation of either H_2S or the reactant thiol is required, to make persulfide; 4) assemblies of iron-sulfur clusters; and 5) oxidation to hydrogen thioperoxide, sulfenic acid, or sulfinic acid. Akin to NO, the concentrations of H_2S metabolites are much higher than that of the free H_2S itself. It was largely due to assay methods that did not distinguish between H_2S and these metabolites that endogenous H_2S concentrations were previously overestimated [55].

Similar to NO, some H_2S metabolites can also regenerate free H_2S by various pathways, and thus serve as a stable storage form of H_2S [67–69]. Sulfane sulfur such as persulfide is one example of labile sulfur compounds that can release H_2S by reduction [70]. So far, knowledge about the physiological role of these sulfur compounds is very limited [67,71]. Information is even more sparse with regard to the fetus and newborn, with only one study measuring urine thiosulfate as a marker of whole body H_2S turnover in newborns. This work found that preterm newborns at greatest risk of microvascular dysfunction also have the highest levels of H_2S turnover, suggesting that overproduction of this gasotransmitter may play a role in the pathology of these patients [72].

Effects of O_2 on H_2S levels.—Unlike NO and CO, O_2 is not required to produce H_2S. However, the predominant pathways for H_2S consumption do require O_2, and thus O_2 tensions tend to be inversely proportional to free H_2S concentrations. This has been demonstrated in tissue homogenates from several vertebrate organs including the salamander gastric tract [73], trout gill and heart [74,75], rat lung [76], seal and bovine pulmonary arteries [77], and mouse brain and liver [55]. In the adult lung, the O_2-dependence of H_2S consumption has an EC_{50} of approximately 5 mmHg PO_2, and an E_{max} of >30 mmHg, which encompasses the physiological range of fetal tissue PO_2s (~5 to 25 mmHg) [78]. Although H_2S concentrations are largely unstudied in the fetus and newborn, extrapolation of what is known about O_2-dependence of H_2S metabolism in adult tissues would predict that H_2S concentrations are markedly elevated in the fetus and then to fall rapidly within minutes after birth. Tests of this hypothesis using assays of H_2S concentrations are needed.

Carbon monoxide

Interest in CO grew in the early 1900’s because of its danger in marsh gas of mines, where it was harm workers by occupying the O_2 binding sites of hemoglobin. Carbon monoxide differs from NO and H_2S in that it is, for the most part, chemically inert in vivo. Tissue CO concentrations are thus the result of a relatively simple equilibrium between its rate of production and the rate at which it diffuses into perfusing blood and is then eliminated from the lungs. Like NO and H_2S, CO binds avidly to deoxyhemoglobin, which has an affinity for CO that is much greater than that of O_2 [79]. As a result, although total concentrations of CO in blood are ~95 μM (based on 15 g/dl hemoglobin and 1% carboxyhemoglobin), concentrations of free CO are ~0.002 μM [80,81]. Likewise, mean tissue concentrations of free CO are also thought to lie in the low nanomolar range, with possible local increases as a result of surges in CO production [80]. As discussed in this section, CO also differs from NO and H_2S in that overall tissue concentrations are elevated during the neonatal period.

Synthesis.—CO is generated from the oxidative degradation of heme by one of two different heme oxygenases designated HO-1 and HO-2. HO-1, also known as heat-shock protein 32, is inducible, responding to a long list of known stimuli such as oxidative stress, hypoxia, hyperoxia, ischemia, and hyperthermia [82]. The CO-producing reaction also releases free Fe^{2+} and biliverdin, with subsequent reduction of biliverdin to produce bilirubin (Figure 4). Newborns are exposed to many of these stresses as a result of the normal birth transition. Accordingly, circulating levels of HO-1 mRNA are upregulated during the first 2 or 3 days after birth in neonates [83], and are also found to be elevated in pig and mouse lungs [84] and rat liver [85] in the days following birth.

The availability of heme substrate is a rate-limiting factor in heme oxygenase activity. Metabolism of heme as a result of red blood cell turnover represents the largest source of CO production in the body [86]. Accordingly, due to the higher hematocrit and shorter red blood cell half-life during the neonatal period, whole body CO production is found to be twice of that of the adult [87]. In addition, CO production in the near-term fetus is higher than the immature fetus and adult, also suggesting an augmented role for CO in the perinatal period [88,89].

CO storage and metabolism.—As mentioned above, CO is not significantly catabolized in vivo. After generation, CO rapidly equilibrates between tissue and blood by diffusion and binds to protein-bound the ferrous hemes with a half life of usually tens of minutes. The sole route of elimination of CO is via exhalation in the lung [90,91]. Heme-CO, such as carboxyhemoglobin (COHb), therefore reflects endogenous CO production and represents the main storage form of CO in the body (Figure 4). It has been suggested that COHb might be useful as a marker for high hemoglobin turnover to allow an earlier identification of newborns at risk of hyperbilirubinemia [92]. Moreover, COHb levels during the early postnatal period may serve as a practical marker for subsequent development of bronchopulmonary dysplasia, a disease associated with increased CO production [93,94]. However, COHb levels can be confounded by multiple factors such as postnatal age, gestational age, hemoglobin concentration, oxyhemoglobin saturation, ambient CO levels, and blood pH [95].

Effects of O_2 on CO levels.—O_2 is a substrate, along with heme, for the production of CO by both HO-1 and HO-2. However, the affinity of these enzymes for O_2 is so high (~0.013 to 0.03 μM [96]) that it would seem unlikely that O_2 availability is a limiting factor for HO activity even in the relatively hypoxic environment of the fetus (Figure 2). Fetal COHb concentrations are higher than those of the mother [97], although the extent to which this is due to fetal HO activity as opposed to the equilibrium of CO exchange between maternal and fetal blood has not been measured directly. However, CO competes with O_2 for binding to the ferrous heme of many proteins including hemoglobin (220-fold greater affinity than O_2, P_{50} = 0.0094 to 0.022 mmHg [79]), myoglobin (39-fold greater affinity than O_2, P_{50} = 0.07 mmHg [79]), and cytochrome c oxidase (2.5-fold greater affinity than O_2, P_{50} = 0.27 mmHg [98]). As a result, if tissue CO production is held constant, an increase in PO_2 results in an increase in P_{CO} due to a decrease in the availability of hemes for CO-binding [80]. Likewise, for any given P_{CO}, an increase in PO_2 results in a decrease in CO

binding to heme. Due to this relationship, the rate of CO scavenging by hemoglobin is inversely proportional to blood PO_2, and modeling of this phenomenon suggests that blood at normal fetal arterial oxyhemoglobin levels would scavenge tissue CO at a rate that is roughly twice that of blood at newborn oxyhemoglobin levels [80]. This interdependence of PO_2 and P_{CO} would be strongest when the PO_2 is at or near the P_{50} of the heme for O_2. Thus, the fetus would be more strongly impacted by this phenomenon than the adult, since the fetal arterial and venous PO_2 gradient normally encompasses the P_{50} of fetal hemoglobin for O_2. Experimentally, however, hypoxia in the newborn piglet results in an increase in CO concentrations in the cerebrospinal fluid [99], possibly suggesting rates of CO production are elevated in response to hypoxia.

III. CHEMICAL REACTIVITY AND SIGNALING PATHWAYS

The chemical and physical properties of gasotransmitters lay the foundation for their signaling mechanisms. This section will categorize the known biological targets of gasotransmitters according to their chemical reactivity, with emphasis on ontogeny in the newborn period.

Nitric oxide

The biological targets of NO can be classified into three main categories: free radicals, metals, and thiols. As a free radical itself, NO shows reactivity towards reactants with unpaired orbital electrons, such as other radicals and transition metals. For example, the reaction between NO and superoxide radicals approaches diffusion limited rates [100]. This reaction scavenges NO and produces the peroxynitrite intermediate which typically leads to pro-oxidant events [101]. The birth transition results in a spike in ROS and chelatable metal iron levels [102,103], particularly in preterm infants, making NO more likely to be pro-oxidant in the newborns.

Ferrous iron in heme proteins is the main metal target of NO. sGC with ferrous heme iron, is a specific receptor of NO, and is considered to be the most important biological target of NO. When bound to NO, sGC is activated and produces cGMP which leads to multiple downstream signaling cascades that finally result in vasodilation. Fetuses and neonates have higher lung expression of sGC than adults [104–107]. Likewise, inhibition of NOS activity in fetal sheep in utero significantly attenuates the fall in pulmonary artery pressure and increase in pulmonary blood flow that occurs with the onset of ventilation and increased oxygenation that occurs after birth, consistent with an essential role for NO in the birth transition [108].

Apart from activation of sGC, NO can also mediate signaling via nitrosylation of thiols [109]. Although NO free radical does not readily react with thiols, oxidation of either NO or the thiol, which may be more likely to occur during the transition from fetus to neonate [102,103], can facilitate the formation of nitrosothiols. Once formed, SNOs can readily transnitrosylate other thiol groups, whereby the NO moiety of one SNO is transferred to another thiol group. For example, nitrosoglutathione infused intravenously is found to transfer the NO moiety to plasma proteins within one circulatory transit time [110]. The extent to which SNO formation, either de novo or via transnitrosylation, is targeted to

specific signaling functions is largely understudied in the newborn. At the same time, cellular pathways of SNO degradation are not well characterized but appear to involve denitrosylases such as thioredoxin, which is upregulated by oxygen in the newborn lung [111,112]. This potential of a heightened role for SNO signaling in the newborn period, together with evidence that some nitrosothiols have potent sGC-dependent vasodilatory activity that is greater in fetal vessels than in adult [113], highlights an important knowledge gap in the field.

A third category of NO-mediated signaling which has come to light recently is its effect on gene transcription via epigenetic mechanisms [114]. For example, the activity of jumonji C, an O_{2-} and Fe^{2+}-dependent histone demethylase, is inhibited by NO [115,116]. Histone acetylation may also be under the regulation of NO during neural crest and cranio-facial development [117,118]. There is also evidence that NO influences DNA methylation via regulation of the activity of ten-eleven translocation (TET) enzymes. Similar to jumonjiC, TETs also utilize Fe^{2+} and O_2 [119], and thus their activities might be expected to change markedly during the birth transition when O_2 levels increase and NO levels decrease, although this does not appear to have been studied.

Hydrogen sulfide

Although H_2S is reactive and may play an important role in various biological functions, no specific target comparable to the importance of sGC signaling for NO has yet been identified for H_2S. Metals and thiols are the main biological targets of H_2S. Unlike NO, H_2S does not readily react with ferrous iron in heme proteins such as oxyHb and deoxyHb, nor does it activate sGC. Instead, it binds to the ferric iron in heme and reduces it into ferrous form. For example, H_2S can convert the oxidized ferric form of sGC, which does not respond to NO and might be more abundant in the oxidative neonatal environment [120,121], into the active ferrous form [122]. In addition, H_2S inhibits the cGMP hydrolase activity of phosphodiesterase [123], thereby augmenting the effects of sGC activation by NO. The possibility that excessive oxidation of sGC heme may contribute to the unresponsiveness of some infants to inhaled NO for the treatment of pulmonary hypertension in infants highlights one potential therapeutic potential for H_2S. In addition, methemoglobin levels tend to be higher in newborns due to relatively low plasma methemoglobin reductase levels [124–126]. As a result, H_2S is more likely to react with methemoglobin in neonates, resulting in the production of thiosulfate and polysulfides, which further mediate signaling by H_2S [127].

Although thiols are a main target of H_2S, H_2S does not react with them directly. Instead, the reaction requires prior oxidation of the reactant thiol to disulfide, sulfanic acid, or S-nitrosothiol, or oxidation of the H_2S to HSOH [128]. This results in persulfidation of the reactant thiol by addition of the sulfur atom from H_2S, leading to a disulfide bond. As with S-nitrosylation, addition of H_2S to the thiols of proteins can lead to conformational changes that modify their activity [127]. K_{ATP}, TRPA1, and Keap1 are such targets by this pathway, as they can mediate the signaling of H_2S and its polysulfide metabolites [129]. In addition, similar to transnitrosylation of SNOs, the -SH moiety of persulfides is also readily transferred to other thiol groups, leading to sulfuration of a broad spectrum of targets. In an

oxidative environment, disulfides might be more abundant in neonates after the birth transition [130], potentially rendering more reactive thiol targets for H_2S.

H_2S has long been assumed to be an antioxidant. However, H_2S does not directly react with O_2 and thus this reaction is too slow to account for any significant biological effects [66]. H_2S also does not readily react with ROS such as superoxide or hydrogen peroxide. Although the sequestration of oxidative iron by H_2S has been proposed, autoxidation of H_2S catalyzed by Fenton chemistry can also paradoxically generate considerable ROS leading to toxic effects [131,132]. Investigation is needed to test for the role of H_2S in the regulation of ROS during periods of physiological oxidative stress such as labor and delivery.

Carbon monoxide

Compared with NO and H_2S, CO is quite inert, and thus it is more likely to act as a reserved line of signaling. So far, the search for a specific signaling target of CO has not been successful. Only transition metals in a specific redox state, such as hemes with ferrous iron, have been identified as targets of CO [133]. It has been proposed that the signaling of CO might be mediated exclusively through its interaction, either directly or indirectly, with the transition metals of biological targets. Binding of CO to the ferrous heme of proteins leads to conformational and thus functional changes. Major proteins with high binding affinity for CO include hemoglobin, myoglobin, cytochrome P450 enzymes, and cytochrome c oxidase [134]. sGC has also been proposed to be an important target of CO. However, this activation is about 30-fold less potent than that of NO and the low binding affinity of CO to sGC requires supraphysiological concentrations of CO, raising doubt about the significance of sGC as a target of CO signaling [80].

In contrast to an apparent lack of direct targets for CO, increasing evidence suggests the importance of non-specific effects that result from inhibition of cytochrome c oxidase by competing with O_2 for binding to the heme. This inhibition is proposed to account for the mitochondrial ROS generation that occurs at CO tensions at least as low as 0.19 mmHg (~0.2 μM) [135], as well as ROS-dependent signaling that activates redox-sensitive transcription factors and protein kinases to induce certain antioxidant enzyme systems at tensions as low as 0.076 mmHg (0.08 μM) [136,137]. These concentrations, as well as those observed to have biological effects in piglet pial arteries (0.09 mmHg) [138], are within the predicted range of plausible physiological tissue concentrations [80]. Notably, CO concentrations comparable to those that result from neonatal hyperbilirubinemia or routine low-flow general anesthesia have been associated with oxidative stress and impaired neuronal development in the mouse pup forebrain [139].

IV. VASOACTIVITY OF GASOTRANSMITTERS

Nitric oxide

The first and most widely-known physiological function of NO is ability to vasodilate. NO can be generated by endothelium via simulation with agonists such as acetylcholine and bradykinin, and by blood flow-induced shear stress [140]. It activates sGC to produce cGMP, which leads to modulation of L-type Ca^{2+} and large-conductance Ca^{2+}-activated potassium

channels via cGMP-dependent protein kinase (PKG) [113]. In newborns, the acetylcholine-dependent vasodilation in the skin of the forearm correlates directly with infant body size and head circumference, whereas vasodilation by sodium nitroprusside, which is endothelium-independent, showed no correlation with any anthropometric measures [141]. Thus, endothelial function may be decreased in low-birthweight infants, and is consistent with evidence that low birthweight results in impaired endothelial function later in life [142,143]. Both endothelium-dependent and -independent NO-mediated vasodilation also varies with postnatal age in the newborn piglet, where vasodilation in arteries isolated from animals on the first day of life is markedly reduced compared to vessels taken from animals a few days or weeks later [144,145]. In contrast to the apparent lack of NO-mediated vasodilation of pulmonary arteries from neonatal piglets, NOS inhibition in near-term fetal lambs causes a 50% reduction in birth-related pulmonary vasodilation, suggesting that a significant part of the rise in pulmonary blood flow at birth depends upon an acute release of NOS-derived NO [146–148]. Of note, it is possible that the effects of NO on overall pulmonary vascular resistance may be due to vasodilation of the pulmonary veins as well as the arteries [145,149]. In addition to the pulmonary vasculature, NO also appears to play an important role in mediating the postnatal changes in resistance of intestinal, cerebral, and skeletal vasculatures [150,151].

Due to its diffusion limited reaction with NO, superoxide is a determinant of NO bioavailability and thus vascular tone. Under physiological conditions, an increase in the ratio of superoxide and NO leads to vasoconstriction, while a decrease leads to vasodilation. In chronically instrumented fetal sheep, Giussani et al demonstrated that vascular oxidant tone plays an important role in regulating the peripheral vascular resistance via NO-dependent pathways [152–155]. The vascular oxidant tone is operational in late gestation in fetal sheep, and may contribute to the maintenance of arterial blood pressure in the perinatal period. Resetting of this vascular oxidant vascular tone at birth may also be an important factor in the physiological reduction of pulmonary vascular resistance, as exogenous superoxide dismutase results in pulmonary vasodilation in newborn lambs with pulmonary hypertension [156].

It is worth noting that, under some conditions such as hypoxia, NO can also lead to a species-dependent vasoconstriction via biased activation of sGC to produce cIMP instead of cGMP, thus favoring vasoconstriction [157–160]. To our knowledge, such NO-mediated vasoconstriction has not yet been studied in newborns.

As mentioned earlier, some metabolites of NO, such as nitrite, nitrosothiols, and DNICs [161], are capable of preserving its bioactivity and mediating vasodilation. Nitrite levels are markedly decreased in neonates [6,18]. Although we have found that nitrite itself has minimal vasoactivity at physiological concentrations in fetal [50], neonatal [162,163], and adult [164,165] sheep, we have also noted that nitrite potentiates vasodilation by nitrosothiols in adult sheep and rats [164]. We have recently observed the same potentiating effects of nitrite in neonatal lambs. Specifically, as shown in Figure 5, intravenous infusion of nitrosoglutathione (GSNO; 500 μM) produces a dose-dependent systemic hypotension that is markedly accentuated if the lambs are pre-treated with an intravenous infusion of nitrite to raise plasma nitrite concentrations by 2- to 4-fold above basal levels, well below

the 100-fold increases needed for nitrite to cause vasodilation [50]. The mechanism by which nitrite potentiates vasodilation by nitrosothiols remains unclear, but may involve a vascular store of intracellular NOx species as discussed above. The effect of the birth-related fall in circulating nitrite levels on the systemic vascular constriction that is essential to maintaining arterial blood pressure after birth, and the potential role of a vascular NOx store, awaits further investigation.

Hydrogen sulfide

The vasoactivity of H_2S is not as well-defined as that of NO. H_2S has been demonstrated to induce either dilation or contraction, depending on the species, organ bed, and experimental conditions such as type and concentration of H_2S donor used, oxygen tensions, presence of endothelium, substance used for precontraction, and composition of the organ bath buffer [166]. The long list of mechanisms suggested to be involved in H_2S-mediated vasodilation includes opening of ATP- and voltage-sensitive potassium channels (K_{ATP} and K_V, respectively) and Ca^{2+}-dependent potassium channels (SK_{Ca}, IK_{Ca}, BK_{Ca}), closing of voltage-dependent Ca^{2+} channels, release of endothelial NO and hyperpolarizing factor, alteration of intracellular pH and ATP levels, oxidation of protein kinase G 1α, activation of transient receptor potential cation channel, release of calcitonin gene-related peptide, inhibition of phosphodiesterase, reduction of renin release, and inhibition of ACE activity [123,166–170]. The contractile effects of H_2S have been proposed to involve reduction of cAMP concentrations, inhibition of beta-adrenergic vasodilation, inhibition of prostanoid-mediated vasodilation, opening of L-type Ca^{2+} channels, and activation of Na^+,K^+,$2Cl^-$-cotransport [167,171,172].

Investigation of the vasoactivity of H_2S in human vessels is very limited [173–177]. While there are no reports in infants, a few reports from neonates of other species exist. Using a cranial window preparation in piglets, Leffler et al showed that H_2S production by endogenous CSE results in vasodilation of pial arteries [178,179]. They also found that vasodilation by endothelin-1 is mediated by H_2S activation of K_{ATP} and BK_{Ca} channels [180]. In the ductus arteriosus of mice, H_2S is proposed to be an endothelium-derived hyperpolarizing factor [181]. However, no significant ductus arteriosus reactivity was found for endogenous H_2S in chickens [182]. Intriguingly, H_2S has also been proposed as an oxygen sensor in hypoxic vasoconstriction and hypoxic vasodilation of various adult vertebrate species [77,78,183], capable of responding to changes in arterial PO_2 that are within the fetal-to-neonatal range (Figure 2). It is therefore reasonable to speculate that H_2S may play a role in the cardiovascular transition at birth.

Carbon monoxide

Vasodilation is one of the most characterized functions of CO, although it is significantly less potent than NO [5]. The supraphysiological concentrations of exogenous CO necessary to achieve vasodilation have cast some doubt on its role as an endogenous vasodilator. Early studies with cerebral arteries from adult rabbits and dogs found no response to exogenous CO at concentrations more than three orders of magnitude above physiological levels [184]. However, Leffler et al observed significant dilation of piglet pial arteries in response to addition of nanomolar concentrations of CO, and suggested HO-2 could produce adequate

amounts of CO to act as an endogenous dilator [185]. Subsequent work indicates that newborn piglet vessels are more responsive to CO than those of older animals [186,187]. While the vasodilating potency of NO increased over the first few days of life, that of CO decreased [145], suggesting CO may play a compensatory vasodilating role. Using the closed cranial window model in 3 to 7-day-old piglets, endogenous CO has been identified as a cerebral vasodilator during hyperemia, hypotension, and seizures [188–191]. Carbon monoxide also mediates the cerebral vasodilation induced by arachidonic acid, prostaglandin E_2, and ADP [192–194]. Furthermore, work by Parfenova and Leffler has demonstrated that coupling of neuronal activity to cerebral blood flow is facilitated by activation of glutamate receptors leading to increased intracellular Ca^{2+} in astrocytes that then results in activation of calmodulin-dependent HO-2 to produce CO. The resulting CO then stimulates arteriole myocyte K_{Ca} channels to dilate cerebral arterioles [195–201]. Endothelial NO also appears to play a permissive role in CO-induced cerebrovascular dilation in the piglets [202,203]. However, prolonged production of CO can inhibit NOS and reduce NO to elevate cerebrovascular tone [138].

In the lungs, CO might play an important role in reducing pulmonary vascular tone in highland-adapted species. In studies comparing newborn lambs and llamas, a species acclimated to high altitude for over two million years, Llanos *et al* found pulmonary hypertension at high altitude only in the lambs, despite greater pulmonary NO production. In contrast, llamas displayed enhanced production of CO, rather than NO, implicating CO as a key vasodilator in the newborns of highland-adapted species [204–207].

V. GASOTRANSMITTERS IN THE NEONATAL GASTROINTESTINAL TRACT

This section will cover the role of NO, H_2S, and CO in the neonatal gastrointestinal (GI) tract. The GI tract is of particular importance since it has historically emerged as the center of NO recycling, as well as non-enzymatic NO generation. The GI tract also contains microbiota that contribute to gasotransmitter production and elimination. We will therefore explore the enzymatic and non-enzymatic sources of these gasotransmitters in the GI tract, as well as delineate their known roles and mechanisms of action in the normal function of the neonatal GI tract. Where the neonatal-specific research is sparse, as is the case for CO and H_2S, we will point out the known functions in the adult GI tract, then speculate on the potential contributions of these gases in the neonate, as well as highlight the need for more neonatal research.

Nitric Oxide

NOS-independent NO Generation in the GI Tract.—The GI tract is a prominent source of NOS-independent NO production. The rat and adult human oral cavity contain nitrate-reducing bacteria that reduce the physiologically inert nitrate to nitrite, a portion of which subsequently disproportionates into NO and nitrosating species such as N_2O_3 and NO^+ upon acidification in the low pH stomach environment [208], or can circulate in the blood where it may be reduced to NO and contribute to vasodilation, particularly at low oxygen tensions [209–213]. Plasma nitrate can be derived from dietary sources such as beets,

radishes, and leafy vegetables. The salivary glands actively concentrate nitrate from plasma into saliva, raising salivary concentrations by as much as ten-fold [214].

Historically, dietary intake of nitrate/nitrite was viewed as detrimental due to the ability of nitrite to oxidize hemoglobin to methemoglobin, leading to cyanosis, a problem that particularly affects newborn infants. Intake of nitrite-treated meats was also shown to be associated with GI cancer, possibly through the intermediacy of N-nitrosamine formation. Recent research is however increasingly demonstrating more favorable, physiological roles of dietary nitrate/nitrite; dietary nitrate intake is associated with better indices of cardiovascular health such as lower blood pressure, and improved exercise performance as has been reviewed more comprehensively elsewhere [212,215]. Vitamin C and other phenolic compounds have been shown to favor the formation of NO over the potentially detrimental nitrosating species by catalyzing nitrous acid reduction to NO and also reducing the nitrosating species to NO [216,217]. Besides the benefit of protecting from nitrosating species, the NO that is produced in the gastric lumen can easily diffuse into the adjacent epithelium and affect GI function.

Though dietary nitrate can be a significant source of NO or NO-like bioactivity in the adult, it does not seem to be a major source of NO in the neonate. There is essentially very little nitrate-to-nitrite-to-NO conversion in the human newborn in the first weeks of life [6,16]. There are multiple factors that ensure neonatal nitrite levels remain low. First, the infant dietary intake of nitrate and nitrite is only 5% and 0.6% of the normal adult intake, respectively [42,218]. In addition, although the infant salivary glands are able to concentrate nitrate into the saliva similar to the adult, the oral commensal bacteria that are essential for reducing nitrate to nitrite are largely absent during the first few weeks after birth [16]. Furthermore, neonatal saliva production is markedly lower than the adult [16], and preventing adults from swallowing saliva essentially blocks the physiological effects of dietary nitrate [212].

Nitrite can be protonated to HNO_2 (pK = 3.3), and then quickly disproportionates to produce NO. Thus, swallowed nitrite becomes an important source of NO in the stomach when pH is low, and NO concentrations there are found to be orders of magnitude higher than in other portions of the GI tract [219]. However, the neonatal stomach, particularly that of preterm infants, is less acidic than that of the adult [220–222], and thus stomach NO levels would be expected to be much lower.

The intestinal microbiome also appears to play an important role in regulating NO bioavailability. Lactobacilli can act as a nitrite sink in the GI tract [223], and dietary supplementation with both lactobacilli and nitrate in rats led to a 3 to 8 fold increase in NO in the small intestine and cecum, but not in the colon [218]. Lactobacilli and bifidobacteria are very prevalent in the diet and GI tract of infants fed breast milk [224], and their prevalence in stool samples increases gradually over the first few weeks of life [225]. In vitro, these bacterial strains are able to convert nitrite into NO, while other strains of bacteria (E. coli and S. aureus) can act as an NO sink to suppress NO concentrations [218]. Intestinal NO gas has also been measured in human preterm infants, and was found to be decreased by antibiotic treatment [226]. Altogether, these results demonstrate how bacteria are important

contributors to NOS-independent NO-generation, and NO metabolism in the human infant GI tract. Moreover, NO-generation by commensal bacteria in the human neonate is even more relevant considering the increasingly common use of probiotics, especially in preterm infants, to minimize risk for necrotizing enterocolitis [227,228].

NO and GI Function.—NO generated from eNOS, iNOS and nNOS contributes to almost all aspects of GI processes and functions such as gastric motility, gastric secretions, preservation of mucosal barrier integrity, mesenteric and intestinal perfusion, and innate immunity against enteropathogens as well as protection against epithelial injury. One of the most prominent roles of NO in the GI tract is its modulation of mesenteric vascular tone in both the fasted state to support basal GI function, and in the postprandial state when blood flow to the gut and intestines increases in support of digestion and absorption.

Normally, the adult small intestine receives about 10 % of cardiac output, about 80 % of which passes to the mucosal and submucosal layers. Total blood flow to the small intestine can increase by almost 100 % in the postprandial phase [229]. Interestingly, blood volume per gram of tissue is higher in the neonatal rat and piglet intestines compared to adults, increasing rapidly in piglets between days 1 and 3 post-birth and then falling gradually with increasing age [230,231]. The fetal-to-neonatal increase in intestinal blood flow is also observed in lambs, with an ~100 % increase in blood flow in 2 to 10-day-old lambs compared to fetal lambs at 90% gestation [232–234]. These flow changes are accompanied by decreases in intestinal postprandial hyperemia in both piglets and newborn lambs [232].

These fetal-to-neonatal-to-adult blood flow and vascular resistance changes have multifactorial causes, but have been shown to be mediated partly through changes in the eNOS → sGC → cGMP vasodilation pathway in the mesenteric arteries. In the piglet, whose GI system closely matches the human system [232], decreases in intestinal vascular resistance are flow-stimulated and NO-mediated. However, the eNOS → sGC → cGMP pathway contributes to the regulation of intestinal vascular resistance to a greater extent in 3-day-old vs. 35-day-old swine as determined by eNOS inhibition in both whole animal and isolated artery experiments [235–237]. In these studies, flow-mediated decreases in vascular resistance were eliminated by L-NAME only in the 3-day-old piglets, which also had greater acetylcholine and substance P-induced relaxation. Furthermore, the cGMP content of 3-day-old piglets was also higher than in 35-day-old piglets following acetylcholine/substance-P-induced relaxation. Of note, NO-mediated vasodilation serves to counterbalance the myogenic vasoconstriction exhibited by mesenteric terminal arteries shortly after birth (1-day-old), in contrast to postnatal day 40 when myogenic vasoconstriction is no longer observed [238,239]. Subsequent studies revealed that the eNOS protein levels are increased two-fold in 1-day-old piglets, compared to fetal or 1-day-old non-fed piglets, and eNOS levels continue to increase until day 10, after which protein levels decreased to day 1 levels [240], correlating with increased sensitivity to NO-mediated vasodilation. Together, these studies indicate that eNOS-dependent vasodilation is of more importance in the newborn piglet than in the fetus or adult.

The mesenteric endothelium regulates blood flow in response to endocrine, neural, and physiologic stimuli most of which utilize the eNOS-dependent pathway as a major

determinant to effect an increase in mucosal blood flow. Neurohormones such as serotonin, acetylcholine, adenosine diphosphate, bradykinin [241], gastrin [242] and cholecystokinin [243] can all bind to luminal endothelial cell receptors, and increase mucosal blood flow in an eNOS-dependent manner, under both basal and postprandial hyperemic conditions. In adult rats, glucose-mediated hyperemia was inhibited by L-NAME, but reversed by L-arginine and L-NAME co-infusion [244], and the NO production requires activation of the adenosine-A2b receptor [245]. Postprandial hyperemia has also been specifically studied in neonatal pigs (3-week old), in which the hyperemia is also inhibited by NO-blockade [246].

Submucosal sympathetic nerves, which are the primary determinants of intestinal blood flow in the adult, contain both adrenergic vasoconstrictor fibers and non-adrenergic non-cholinergic (NANC) vasodilatory fibers. NANC fibers contain nNOS and produce NO as their primary neurotransmitter, and help to increase blood flow through an sGC-dependent mechanism. nNOS derived NO is a significant mediator of gut motility by inhibiting smooth muscle contractility directly, and through inhibiting the release of excitatory mediators. Loss of nNOS signaling is a key feature in the gastroparesis associated with diabetes, showcasing the importance of NO in normal gastric function [247,248]. The importance of nNOS in the human neonate is also apparent in Hirschsprung disease, a common cause of neonatal and infantile large gut obstruction due to dysfunctions in the development of nNOS-containing nerves, involving reduced expression of nNOS mRNA and protein [249,250], and dysfunctional NO transmission to the target cells [251,252]. Studies have consistently described decreases in nNOS-containing myenteric nitrergic cell density from fetus to birth, with continued decreases during the first few years of life [15,253]. The biological relevance of these changes are not well understood.

Hydrogen sulfide and carbon monoxide

Compared to NO, there is a large gap in knowledge about the physiological involvement of CO and H_2S in the adult GI tract, particularly so in the neonate. Of the few studies that are available, most have been performed using exogenous donor compounds and under pathophysiological conditions. While it is still possible to gain hints about the normal physiological function of these molecules from these studies, any conclusions should be made with caution as more research is performed to obtain a clearer picture of all gasotransmitters in both adult and neonatal physiology.

Metabolism of H_2S in the GI tract.—Due to the presence of mainly sulfate-reducing bacteria, which reduce inorganic sulfate (SO_4^{2-}) to H_2S, and other bacteria that reduce cysteine and methionine to H_2S, the adult human gastrointestinal tract, especially the colon, is a site of significant H_2S metabolism and bioactivity [254–256]. The GI tract also contains the CSE and CBS, which produce H_2S from cysteine, especially in the colonic epithelial, smooth muscle, and neuronal cells, and interstitial cells of Cajal, in both animals and humans [257–260]. Similar to both NO and CO, H_2S was historically regarded as a toxin in the GI tract. In fact, since bacteria-derived H_2S is still being implicated in the etiology and pathogenesis of inflammatory bowel diseases such as Crohn’s disease and ulcerative colitis, and also in colorectal cancer [256]. Though there are many conflicting reports in the literature, endogenous H_2S does seem to have some physiological relevance in the GI tract

where it has mainly been implicated in the modulation of gastric motility through its hyperpolarization and relaxation of enteric smooth muscle cells [261,262], involving the S-sulfhydration and activation of K_{ATP} channels, inhibition of Rho/RhoA, [258], inhibition of both L-type Ca^{2+} and BK channels [263], or through crosstalk with NO [264,265]. Similar to NOS and HO-2, expression of CSE and CBS is reduced in Hirschsprung's disease [257], demonstrating the possible importance of H_2S to normal GI motility function in a neonatal or pediatric population group.

Sulfate-reducing bacteria have been observed in the feces of human infants as early as two weeks following delivery, with a prevalence that increases with developmental age [266,267]. The physiological contributions of endogenous and bacterial H_2S to neonatal and infant gastrointestinal health are otherwise unknown due to very limited study, but it is likely that H_2S at low concentrations coordinates with NO and CO to effect the fetal-to-neonatal decrease in intestinal vascular resistance at birth, and as a modulator of both gastric motility and protection. Studies utilizing already-established animal models of neonatal GI disease would likely make an important contribution to understanding the role of H_2S in the neonatal GI tract.

Metabolism of CO in the GI tract.—Unlike its role in NO generation, the GI tract does not seem to be a significant source of bacteria-facilitated CO production. There are however a few reports about some enteric bacteria, specifically some strains of *E.* coli, which express a protein (chuS) with heme oxygenase-like activity [268,269], and might contribute to heme degradation, in vivo CO generation, and to the modulation of the host immune response when added to the GI tract of the adult mouse [270]. This study showed that endogenous production of CO by gut bacteria is feasible, especially in the context of probiotic supplementation, but the relevance of this phenomenon to the human adult and neonate still needs to be studied. Metabolism of CO by the colonic flora has been observed in the adult human, where bacteria play a role in regulating CO levels within the GI tract [271], but the physiological relevance of this potential CO sink and source of CO for the circulation is uncertain. The adult gut lumen is also known to have increased CO due to the action of mucosal heme oxygenases on luminal heme after its uptake into the intestinal mucosa [272]. In the adult, ingestion of meat has been reported to increase intestinal CO levels since the mucosal heme oxygenases can also act on exogenous, meat-derived heme [273]. Since the normal neonate diet does not contain appreciable heme, meat-derived heme is not a feasible source of CO production in the neonate. The differential postnatal changes in intestinal mucosa HO-1/2 expression from the fetal to neonatal to the adult age have also not been characterized, therefore it is not clear how much endogenous CO levels would increase in the event of heme supplied by gastrointestinal bleeding, a common neonatal and pediatric disorder with an incidence of about 6.4% [274]. In neonatal rats, however, enteral heme administration increases CO levels [275].

The emerging contributions of CO to the adult gastrointestinal physiology are covered in a number of in-depth reviews [276,277]. Most of the actions of CO parallel those of NO in the GI tract. HO-2 is constitutively expressed in various cells of the GI tract of animals and humans, especially the myenteric interstitial cells of Cajal, and myenteric neuronal cells, both of which are the gut pacemaker cells and mediate gut motility [278–281]. HO-1 tends

to only be induced under injury or inflammation, and can help in gastroprotection [282]. Endogenous CO has been shown to contribute to mesenteric vasodilation since an HO-substrate was shown to vasodilate endothelium-intact, isolated rat mesenteric arteries in the presence of a NOS inhibitor [283]. HO-2-derived CO is also a critical mediator of gastric motility by acting as a hyperpolarizing factor [281,284,285], and by acting as a critical determinant of the membrane potential across myenteric smooth muscle cells [286]. The studies of CO involvement in gastroprotection are of a more pharmacological nature, but do suggest that CO may play a role in the protection of the gut from injury or inflammation [287,288]. Interestingly, HO-2 expression often co-localizes with NOS expression [15,280,289], and in myenteric NANC neurons, is more highly expressed than nNOS [290]. Accordingly, the effects of CO on both gut motility and protection of the gastric barrier are co-mediated by NO [288,291].

Carbon monoxide also seems to play a significant role in the neonatal GI tract, although there are only a few comparative studies between neonates and adults, or in neonates alone. In the neonatal suckling rat, the production of CO by isolated small intestine is not inhibited by tin-protoporphyrin, a competitive inhibitor of HO-1 and HO-2, while the CO production is significantly decreased in the adult rat, suggesting a possible alternative means of CO production in the neonatal intestine. In the same model, gradients of CO production across the intestinal length (duodenum to ileum) have an opposite pattern in the neonatal (ileum > duodenum) vs. adult intestine (duodenum > ileum) [292]. Postnatal changes in HO-2 and nNOS expression in myenteric neurons have also been reported in the pig at fetal, 1 to 2-day-old, and 5 to 6-week-old stages of development. These studies reveal that HO-2 expression increases with age in the neonatal period, and has an opposite pattern to nNOS expression, which decreases with developmental stage [293]. The physiological importance of these differential developmental changes are not yet clear.

VENTILATORY CONTROL

Pulmonary ventilation is an automatic process that begins at birth and usually proceeds without conscious intervention [294]. The control of ventilation is performed by a complex, highly integrative system that maintains the homeostasis of blood O_2, CO_2, and pH within narrow limits by modulating ventilatory rate. This complex system involves the sensing of blood PO_2 or PCO_2/pH by peripheral (aortic and carotid body) and central (medullary) chemoreceptors, as well as input from pulmonary stretch receptors. Gasotransmitters are found to be involved in many aspects of ventilatory control in studies of adults, and likely also play an important role in the initiation and maintenance of ventilation in the neonate, as described in the following sections.

Nitric oxide

The control of ventilation is carefully integrated, mainly in the medullary and pontine portions of the brainstem, into a modulated transmission to effector organs via the involvement of many afferent and efferent neurons, and motor output by respiratory muscles, facial structures and airway effectors [295]. Gasotransmitters, especially NO, have been

implicated in these complex networks of ventilatory control, especially in the observed reflex increase in ventilatory responses to hypoxia and hypercapnia.

These inputs are carefully integrated, mainly in the medullary and pontine portions of the brainstem, into a modulated transmission to effector organs via the involvement of many afferent and efferent neurons, and motor output by respiratory muscles, facial structures and airway effectors [295]. Gasotransmitters, especially NO, have been implicated in these complex networks of ventilatory control especially in the observed reflex increase in ventilation following acute hypoxia (hypoxic ventilatory response, HVR), or the time-dependent increase in ventilation and ventilatory response following chronic hypoxia (ventilatory acclimatization to hypoxia, VAH), and also the increase in ventilation following a rise in $PaCO_2$ (hypercapnic ventilatory response).

NOS has been localized in both the peripheral and central regions associated with the control of breathing. NOS expression has been reported within the nerve fibers innervating the glomus tissue of the carotid bodies, which are the primary peripheral chemoreceptors, in which NO plays an inhibitory role. Accordingly, NOS inhibition results in an increase in the hypoxic ventilatory response [296–298]. The carotid body response, however, may depend on the specific NOS isoform, as nNOS inhibition augments the hypoxic ventilatory response, while eNOS inhibition attenuates it [297]. NOS has also been localized to the areas of the brainstem that are involved in ventilatory control such as the nucleus tractus solitarius — where carotid body efferents terminate [299,300]. Here, NO plays an excitatory role which can be blunted by NOS inhibition resulting in a depression of the hypoxic ventilatory response. NOS also plays an excitatory role in the rostral ventrolateral medulla, where the central chemoreceptors sensitive to low pH are located, and in the nucleus raphe magnus, in which NOS inhibition attenuates the hypoxic ventilatory response [301,302]. NOS has also been localized to the locus coeruleus, which has been reported to have an inhibitory effect on the ventilatory response but can be inhibited by NO, giving NO an overall stimulatory effect towards the ventilatory response [303–305]. NO has also been suggested to play a role in the ventilatory acclimatization to hypoxia (VAH), in which ventilation and ventilatory-oxygen sensitivity is time-dependently increased following chronic hypoxia [306], but a few studies in rats have mostly yielded null results, showing no effect of NOS inhibition on VAH [307–309]. It is important to note that systemic administration of NOS inhibitors might yield confounding results due to opposing effects on the peripheral and central chemoreceptors [310].

The role of NO in ventilatory control is understudied in neonatal subjects. The few studies that exist indicate that NO plays a similar role as in adults. NO is suggested to have an inhibitory role on the carotid body-mediated ventilatory response to hypoxia following endotoxin administration in a newborn piglet model [310,311]. The role of NO has also been explored in the biphasic hypoxic ventilatory response characteristic of newborn mammals, in which the initial increase in ventilation is quickly followed by a depression of the ventilatory rate to levels less than or equal to baseline. The ventilatory depression decreases with increasing developmental age to yield a sustained ventilatory increase with hypoxia. In neonatal rats the transition from biphasic to sustained hypoxic ventilatory response correlates with increased NOS protein expression, and is reversed by NOS inhibition [312].

At least one study, however, has yielded a null result since NOS inhibition did not promote ventilatory depression following hypoxia in hyperoxia-reared neonatal rats [313]. There is the limitation that this study used systemic NOS inhibition, which can confound results due to opposing effects on carotid body and central hypoxic response.

Overall, there is a need for more studies about the role of NO in neonatal ventilatory control, and in both adult and neonatal groups there is still a dearth of knowledge about the molecular pathways through which NO modulates ventilatory control, and also little information about the possible contributions of the metabolites of nitric oxide such as nitrite, nitrosothiols and dinitrosyl iron complexes to the control of ventilation. Nitrosothiols, especially ones with low molecular weight, have however been reported to increase the basal ventilatory rate upon direct administration to the nucleus tractus solitarius, and are a possible candidate for the molecular effector of NOS-mediated ventilatory increase during hypoxia [314,315].

Hydrogen sulfide and carbon monoxide

Endogenous H_2S has also been shown to play a role in the central regulation of respiratory rhythm and in both the central and peripheral response to hypoxia. Both CBS and CSE are expressed in the glomus cells of the carotid body, where H_2S levels are increased by hypoxia, and the H_2S has been suggested to augment sensory excitation by low oxygen [316], although the exact mechanism is still debated [78]. The physiological role of endogenous H_2S in O_2-sensing in the carotid body has also been challenged, since most of the in vitro work depends on exogenous H_2S at concentrations higher than those generated endogenously [317]. None of the research on the role of H_2S on oxygen-sensing in the carotid body appears to have been conducted in a neonatal population for any animal model, which presents an avenue for continued research.

Within the brain, CBS and 3-MST are the predominant H_2S-producing enzymes, and have both been implicated in ventilatory control with specific effects that seem to be dependent on the exact brainstem region. CBS expression has been reported in the rat nucleus tractus solitarius (NTS), where exogenous and endogenous H_2S has been reported to have an excitatory effect on isolated neurons [318,319]. Increased H_2S production has also been reported following hypercapnia in the rat NTS, along with the observation that CBS blockade attenuates the ventilatory response to hypercapnia, further demonstrating the excitatory role of H_2S [319]. CBS expression has also been observed in the rostral ventrolateral medulla, where H_2S has been reported to have a down-modulatory role in the response to hypoxia, a role that is also reported in the anteroventral preoptic region [320,321]. Endogenous H_2S, in contrast, has an excitatory role in both the adult and neonatal pre-Bötzinger complex where it has been suggested to modulate inspiratory rhythm since CBS-inhibition reduces inspiratory burst frequency of brainstem spinal cord (BSSC) and medullary slice preparations from both newborn and adult rats, and also decreases basal inspiratory rhythm of anaesthetized adult rats [322]. Exogenous H_2S and L-cysteine were also shown to increase the burst frequency of neonatal rat medullary brain slices containing the pre-Bötzinger complex after a brief depression, and the L-cysteine activity was abolished by CBS inhibition, and enhanced by S-adenosyl-L-methionine, an allosteric activator of

CBS. In this study, the biphasic effects of H_2S in the neonatal rat medulla were shown to be mediated through K_{ATP} channels and cAMP [323], in different region of the neonatal medulla [323,324]. 3-MST expression has been reported in the adult rat medulla oblongata, and has been shown to be increased with chronic intermittent hypoxia [325], but similar studies have not been reported in the neonate. Overall, there is need for more studies of the contributions of the CBS/3-MST-H_2S pathway in neonatal ventilatory control, and in general more mechanistic studies on the molecular pathways of demonstrated H_2S-mediated modulation in both adults and neonates.

Similar to H_2S, most studies have historically focused on the toxic effect of CO on ventilation, as CO exposure is frequently employed to model hypoxia [326,327]. However, similar to H_2S, endogenous CO production by constitutive HO-2 expression, has been shown in the brain medullary centers such as the NTS [328–330]. Though studies are fewer, a physiological role for HO/CO and ventilatory control has also been suggested mainly due to proposed crosstalk between CO and H_2S in carotid body O_2-sensing; an inverse relationship has been observed between HO-2/CO and H_2S levels in the carotid body during hypoxia. This relationship involves a reduction in CO levels which allows an increase in H_2S levels leading to stimulation of the carotid body of adult rats [331–334]. Electrophysiological experiments using medullary slices from neonatal rats with and without HO-2 inhibition or HO-2 substrate (hemin) supplementation suggest that endogenous CO has a role in maintaining respiratory frequency, expiratory duration, and respiratory magnitude [335]. These effects are partially mediated by nNOS [336], and can be partially abolished by BK_{CA} channel inhibition [337]. However, more research is needed to persuasively implicate the HO/CO pathway in central ventilatory control, which can be done by using in vivo models, and also studying differences in CO response by different brainstem regions responsible for respiratory control, as has been documented for both NO and H_2S.

CONCLUSION

The revelation four decades ago that NO is produced endogenously and leads to vasodilation sparked a field of study that has now established that NO plays a role in cell signaling throughout the body. While NO production by NOS enzymes and sGC-mediated signaling pathways have been relatively well-characterized, much remains to be learned regarding how NO bioactivity is preserved and regulated in the form of its many metabolites. The same appears to be true for the bioactivity of H_2S and its metabolites. In both cases, progress in the field is hindered by a lack of reliable assay methods capable of distinguishing between specific metabolites, particularly in living tissues where the more important adducts may also be the least stable and challenging to measure. The development of novel tools for determining levels of the specific NO and H2S adducts in living tissues is critical to gaining a better understanding of this important aspect of gasotransmitter signaling.

As we have highlighted throughout this review, the biological roles of all three of the gasotransmitters are intimately linked to O_2 concentrations, whether it be by the effects of O_2 on their production and metabolism, or by virtue of the fact that they often compete with O_2 for the same heme targets that are critical to the O_2-mediated functions. The physiology

of the neonate provides a unique model for studying the effects of gasotransmitters in various organ systems under broad range of O_2 tensions. Previous advances in understanding the effects of NO on vascular tone, and the role that it plays in the fetus-to-neonate transition led to significant improvements in neonatal care, such as the use of inhaled NO gas for treating pulmonary hypertension. It is likely that as the complexities of modes of storage and action of these gasotransmitters are further characterized, particularly with respect to the influence of changes in O_2 concentrations on these pathways, additional novel modes of therapy will appear.

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ABBREVIATIONS

CSE	cystathionine-γ-lyase
CBS	cystathionine-β-lyase
3-MST	3-mercaptopyruvate sulfurtransferase
sGC	soluble guanylate cyclase
cGMP	cycling guanosine monophosphate
NANC	non-adrenergic non-cholinergic

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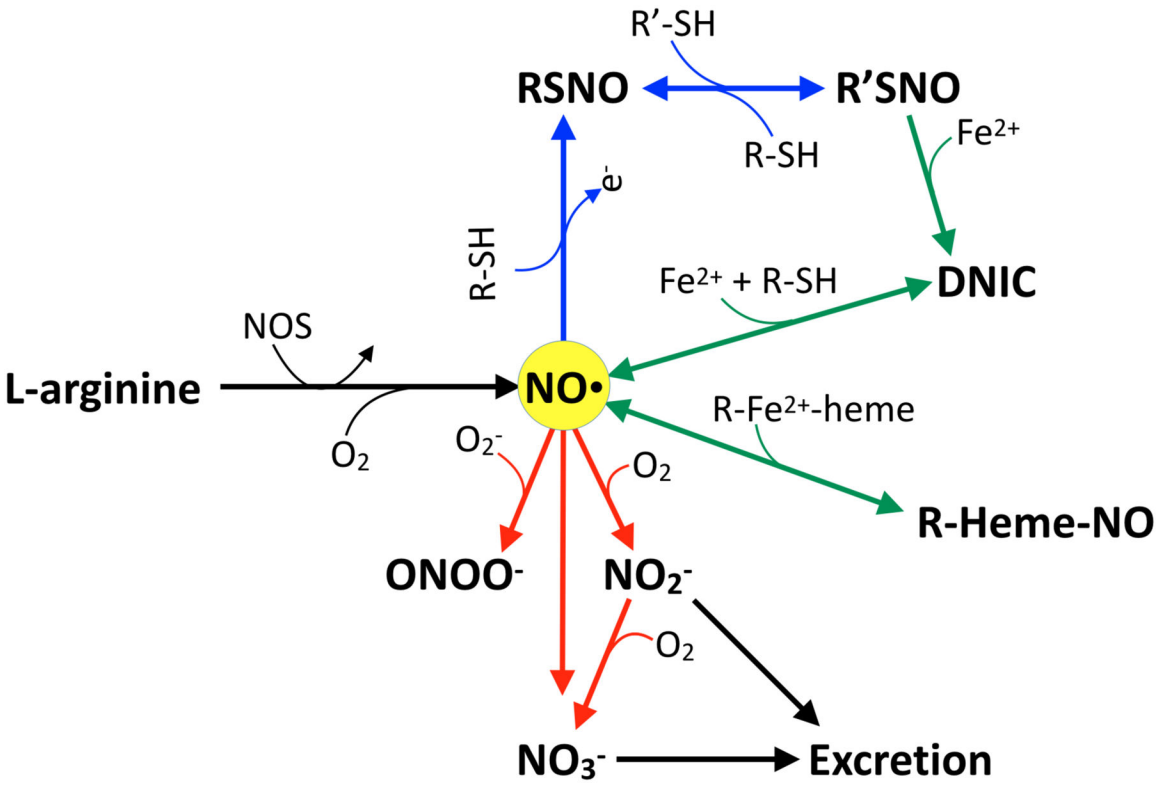

Figure 1. Major pathways of NO synthesis, metabolism, and clearance.

De novo NO is produced from L-arginine by NO synthases (NOS), a reaction that requires O_2. If oxidized, NO free radical (NO·) can form nitrosothiols (RSNO), which are capable of transferring the NO moiety from one thiol to another (blue arrows). NO· and nitrosothiols can also react with heme and nonheme iron to produce heme iron nitrosyl compounds (R-heme-NO) and dinitrosyl iron complexes (DNIC) (green arrows). Finally, NO· can react with superoxide (O_2^-) to produce peroxynitrite ($ONOO^-$), or with O_2 to produce nitrite (NO_2^-) or nitrate (NO_3^-), both of which are excreted in the urine (red arrows). Note that NO_3^- can also be reduced back into NO_2^- by oral bacterial reductases, and that NO_2^- can be reduced back into NO under hypoxic and acidic conditions as described in the text.

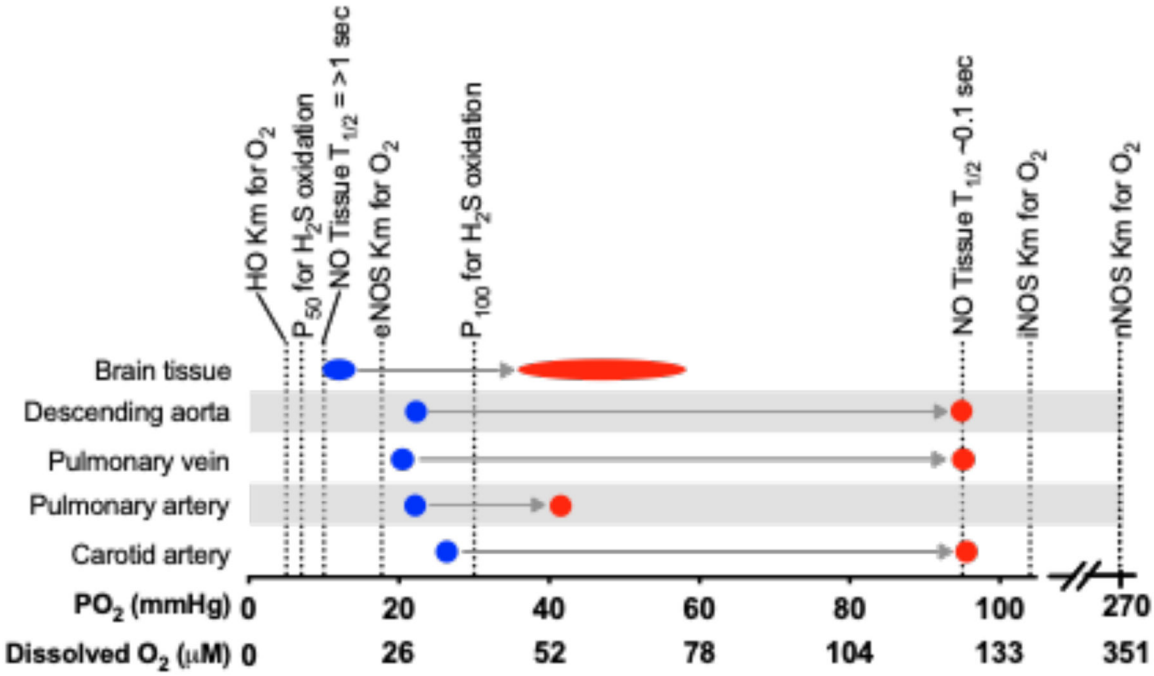

Figure 2. Comparison of the birth-related change in O_2 tensions and dissolved O_2 concentrations (x-axis) with various measures of the O_2-dependence of gasotransmitter concentration.

Blue markers indicate oxygen tensions in utero, red markers indicate oxygen tensions in the newborn and adult. Heme oxygenase (HO) Km for O_2 from [96]. P_{50} and P_{100} for H_2S oxidation from [78]. NO tissue half lives ($T_{1/2}$) from [338]. NO synthase (NOS) Kms for O_2 from [46].

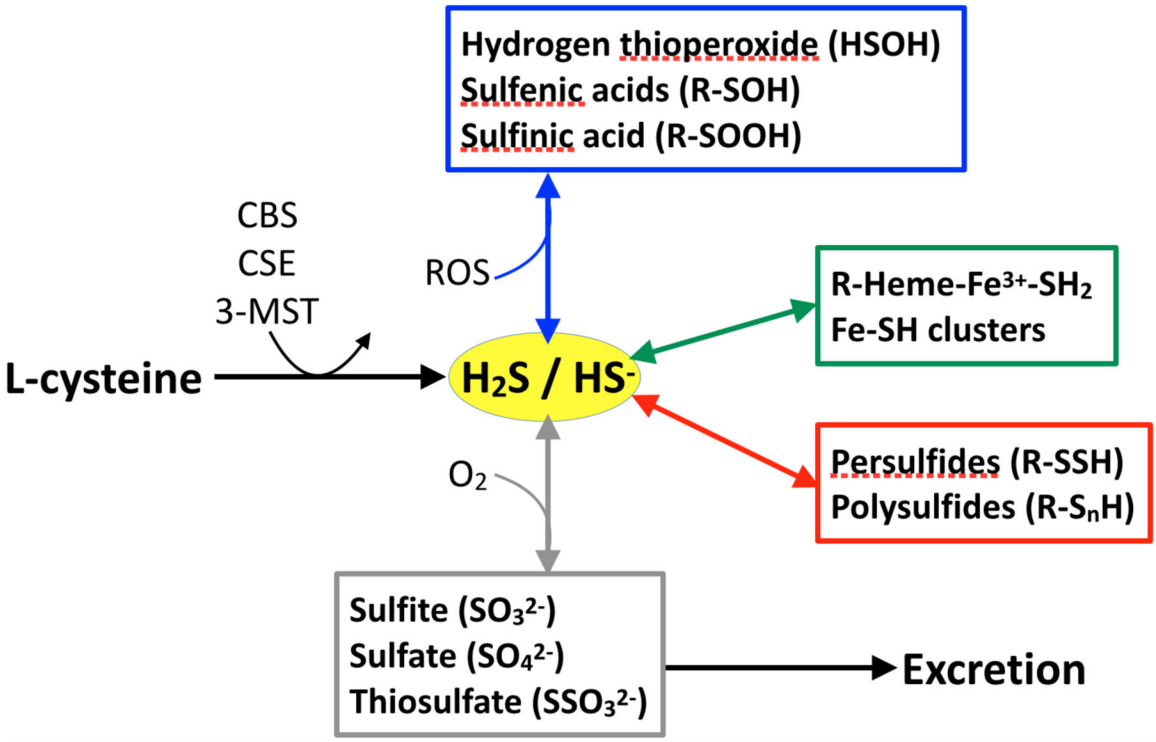

Figure 3. Pathways of H_2S synthesis, metabolism, and clearance.

H_2S is produced from L-cysteine by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3-MST). Oxidation reactions with reactive oxygen species (ROS) are shown in the blue box. Reactions with heme- and nonheme-iron are shown in the green box. Reactions with thiol groups are shown in the red box. Oxidation reactions with O_2 to produce sulfite, sulfate, and thiosulfate are shown in the grey box. The latter constitute the major pool eliminated in the urine. Note that the many of the metabolic pathways shown are not yet well characterized in biological matrices.

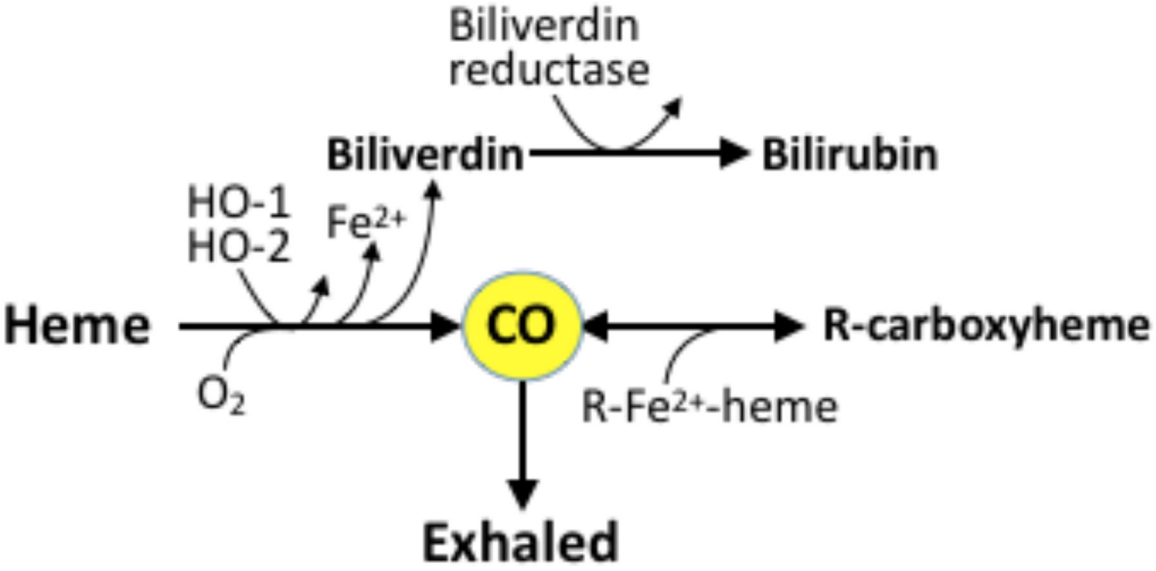

Figure 4. Pathways of CO synthesis, metabolism, and clearance.

CO is formed from heme by heme oxygenases 1 and 2 (HO-1, HO-2) in a reaction that requires O_2 and produces Fe^{2+} and biliverdin. Biliverdin is further reduced to bilirubin. CO can bind to various protein-bound heme moieties such as cytochrome oxidase c in tissues and deoxyhemoglobin in blood. CO is carried to the alveoli in the form of carboxyhemoglobin, where it can be exhaled.

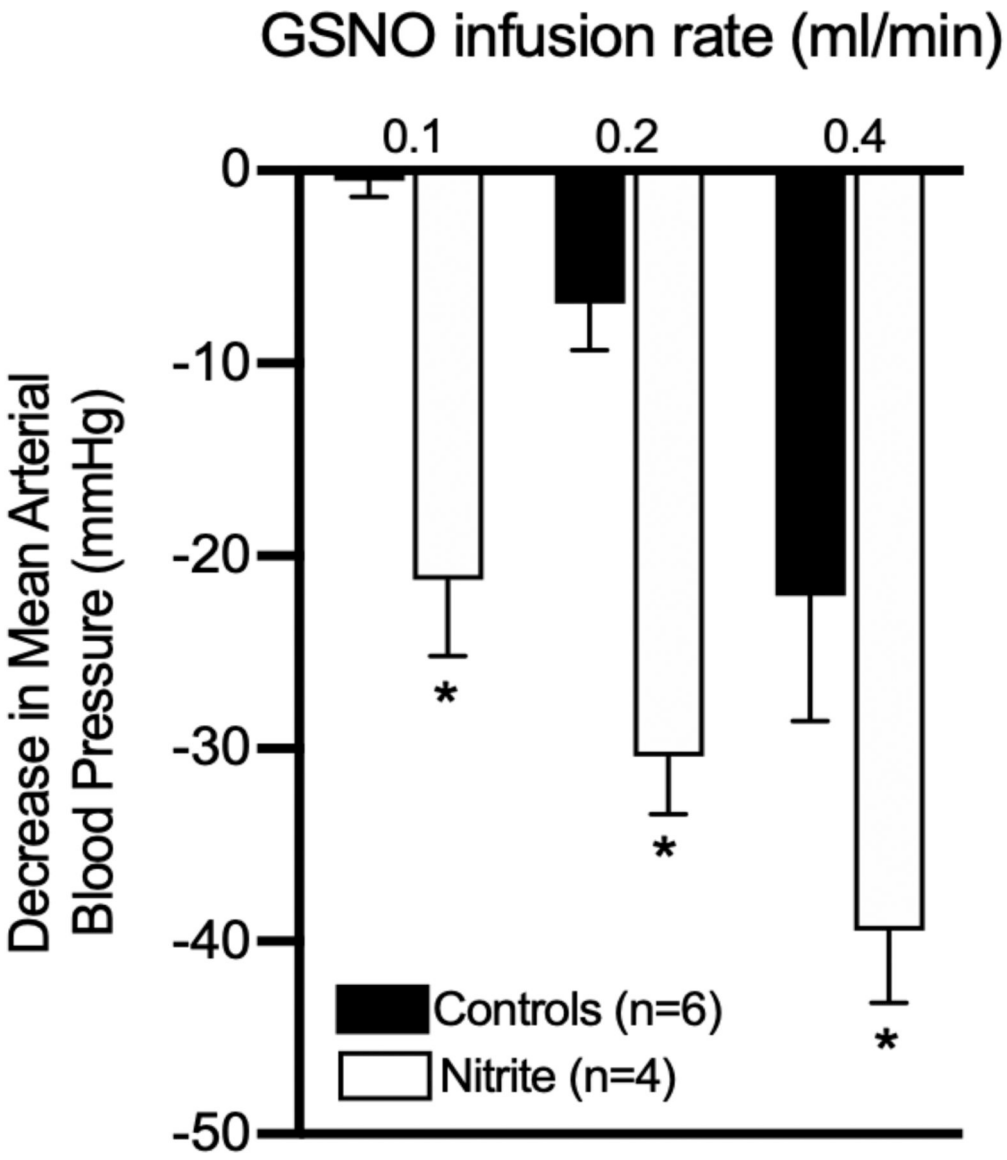

Figure 5. Effect of nitrite on hypotensive response to intravenous infusion of nitrosoglutathione (GSNO) in anesthetized one-day-old lambs.

An intravenous bolus of sodium nitrite to achieve ~2 μM in the blood, which alone does not cause vasodilation [50,165], resulted in a significant potentiation of the hypotensive response to GSNO compared to lambs that received a saline bolus instead of nitrite. These results are consistent with previous observations in adult sheep and rats [164]. ($P < 0.05$ for nitrite vs controls, 2-way ANOVA with Dunnett's post hoc test.)