Redox Biology 1 (2013) 313–318

Contents lists available at SciVerse ScienceDirect

Redox Biology

journal homepage: www.elsevier.com/locate/redox

Graphical Review

A tale of two gases: NO and H_2S, foes or friends for life?

Gopi K. Kolluru [a], Xinggui Shen [a], Christopher G. Kevil [a,b,c,*]

[a] Department of Pathology, LSU Health-Shreveport, USA
[b] Department of Molecular and Cellular Physiology, LSU Health-Shreveport, USA
[c] Department of Cell Biology and Anatomy, LSU Health-Shreveport, USA

ARTICLE INFO

Article history:
Received 8 May 2013
Accepted 9 May 2013

Keywords:
Thiol
Redox biology
Cardiovascular disease
Vascular biology
Chemistry

ABSTRACT

Nitric oxide (NO) and hydrogen sulfide (H_2S) have emerged as dominant redox regulators of numerous aspects of cellular and physiological functions within several organ systems included cardiovascular, immune and neurological tissues. Recent studies have begun to reveal that these two gaseous molecules may have redundant or overlapping pathophysiological functions often involving similar molecular targets. However, it remains less clear when and how NO and H_2S may interact under biological and disease processes. In this graphical review, we discuss the current understanding of NO and H_2S interactions and how they may functionally influence each other and what this may mean for biology and mechanisms of disease.

Contents

Introduction

Nitric oxide (NO) has been extensively studied over the last three decades for its role in vascular functions and as a signaling molecule [1]. Nobel winning works from the trio Furchgott, Murad and Ignarro has placed NO as a central endothelial-derived relaxing factor (EDRF) and a key regulator of cardiovascular pathophysiological responses. However, the role of this gaseous molecule is being re-evaluated with the appreciation of a new gasotransmitter hydrogen sulfide (H_2S) that also serves many important regulatory roles in physiological systems. Like NO, H_2S was once thought to simply be a toxic gas but it is now believed to be an important redox-signaling molecule. A decade of studies on H_2S biology have elucidated its role in regulation of vascular homeostasis, neurological function, cytoprotection, anti-inflammation, revascularization and therapeutic angiogenesis; along with modulation of cell survival responses, which is similar to many physiological roles of NO.

Production of either molecule occurs through enzymatic and non-enzymatic pathways. Fig. 1 illustrates H_2S formation via the transulfuration pathway involving CBS and CSE along with cysteine catabolism via MST. It is also possible that H_2S may be obtained through reductive chemistry on thiosulfate, thiocystine and other molecules. Similarly, NO formation predominantly occurs through nitric oxide synthases (NOS's); however, it is increasingly apparent that non-enzymatic generation of NO via various nitrite/nitrate reduction mechanisms also critically regulates bioavailability. The physiological functions of NO [2–4] and

* Corresponding author at: Department of Pathology, LSU Health-Shreveport, USA. Tel./fax:+1 318 675 4694.
E-mail address: ckevil@lsuhsc.edu (C.G. Kevil).

2213-2317
http://dx.doi.org/10.1016/j.redox.2013.05.001

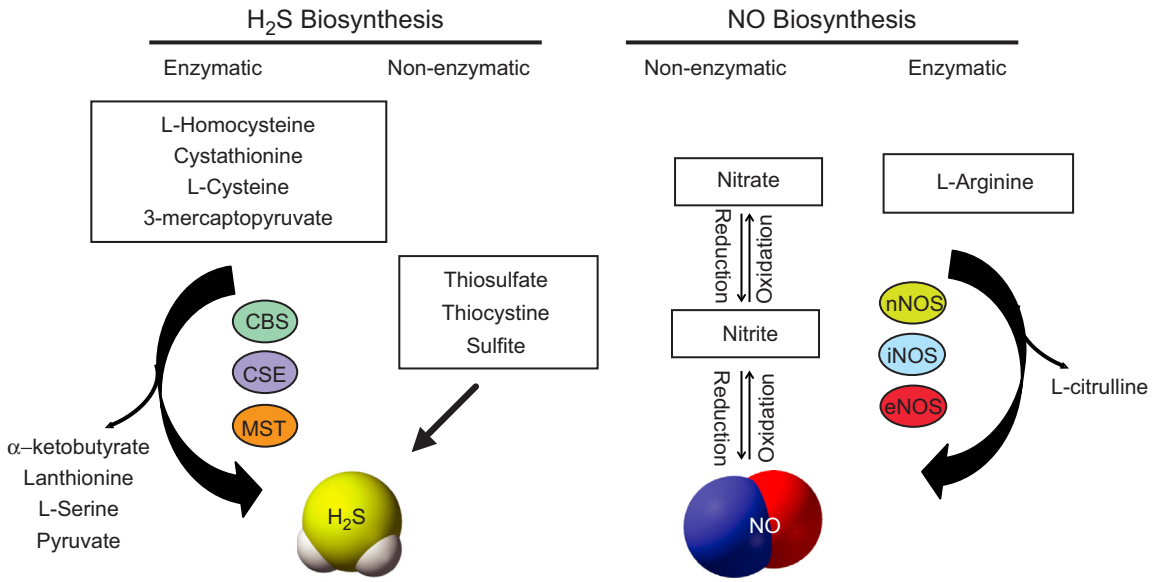

Fig. 1. Biosynthesis of NO and H_2S: NO and H_2S are enzymatically synthesized by three enzymes. H_2S is generated from oxidation of the substrates L-homocysteine, cystathionine, L-cysteine and 3-mercaptopyruvate through the enzymes cystathionine β-synthase (CBS) and cystathionine γ-lyase (CSE) and 3-mercaptopyruvate sulfurtransferase (3-MST). α-ketobutyrate, lanthionine, L-serine and pyruvate are the secondary products formed. NO is produced by three NOS isoforms neuronal, inducible and endothelial NO synthase (nNOS, iNOS and eNOS) that catalyze the oxidation of L-arginine to L-citrulline; Alternatively, production of H_2S occurs non-enzymatically from various storage forms of sulfur like thiosulfate, thiocysteine and sulfite; whereas NO is produced through reduction of nitrite/nitrate under low oxygen conditions.

H_2S [5–7] have been extensively studied and reviewed in the literature. However, the interrelation of NO–H_2S and their subsequent biochemical interactions are complex and currently unclear. While some studies have shown that NO/H_2S positively affect each other's production and function [8–10]; other studies report contrarian, if not directly opposite findings [11–13]. Thus, significant ambiguity remains regarding NO–H_2S chemical interactions and subsequent biological effects. This graphical review discusses the latest understanding of the relationship between these two gaseous signaling molecules and their roles in regulating several biological functions along with important future directions for research.

NO–H_2S signaling

To date, only a small number of reports suggest that NO–H_2S molecules may influence each other in their production and pathophysiological functions [5,14]. Studies demonstrate a common signaling pathway where NO–H_2S crosstalk mediates their effects on vascular functions such as vasodilation, vascular remodeling (migration and proliferation) and angiogenesis [10,14–16]. Recent studies demonstrate H_2S mediated upregulation of NO and vice-versa in regulating angiogenesis and attenuation of ischemia reperfusion (I/R) injury [14,15,17,18]. Fig. 2 illustrates that pro-angiogenic and I/R injury protection of H_2S and its donors may occur through induction of VEGF/VEGFR2 signaling and its downstream effectors such as PI3K/Akt/eNOS in the vascular endothelial cells [8,10,19,20]. Moreover, H_2S has been reported to prevent eNOS degradation and induce eNOS phosphorylation with subsequent NO production via PI3K/Akt activity [21,22] and p38 MAPK pathways [23]. H_2S therapy can also preserve mitochondrial function and modulate cardioprotection through attenuation of oxidative stress via VEGF/Akt/eNOS/NO/cGMP pathway [8]. Reciprocally, pharmacological donors of NO can up-regulate substrate bioavailability for and expression of the H_2S synthesis enzyme cystathionine gamma lyase (CGL/CSE) resulting in H_2S production eliciting vasodilatory effects [14,24–26]. However, it has been

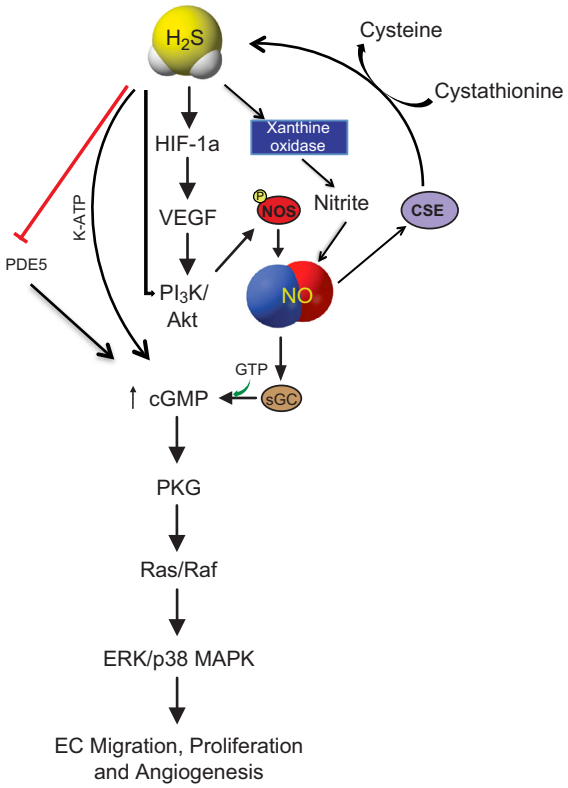

Fig. 2. Common signaling pathways of H_2S and NO: H_2S and NO mediated vascular remodeling aspects through common pathway that include VEGF, HIF-1α, PI3K/AKT upregulated by H_2S. PI3K/AKT induces NOS/NO. H_2S directly effects NO through XO mediated nitrite. Both NO and H_2S are independently involved in upregulating cGMP; H_2S acts through K-ATP and PDE5, NO activates enzyme sGC to increase cGMP production that has downstream signaling effects of EC migration, proliferation and angiogenesis via PKG/Ras–Raf/ERK-p38 MAPK axis.

reported that use of an NO donor can inhibit CBS expression counteracting what has been shown for CGL [13]. Finally, studies have shown that H_2S has opposing effects on NOS/NO