Hibernating mitochondria, the cool key to cellular protection and transplant optimization

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DOI:
10.33612/diss.160451743

Gasotransmitters in health and disease: a mitochondria-centered view

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Published: Curr. Opin. Pharmacol. (2019)
DOI: 10.1016/j.coph.2019.07.001

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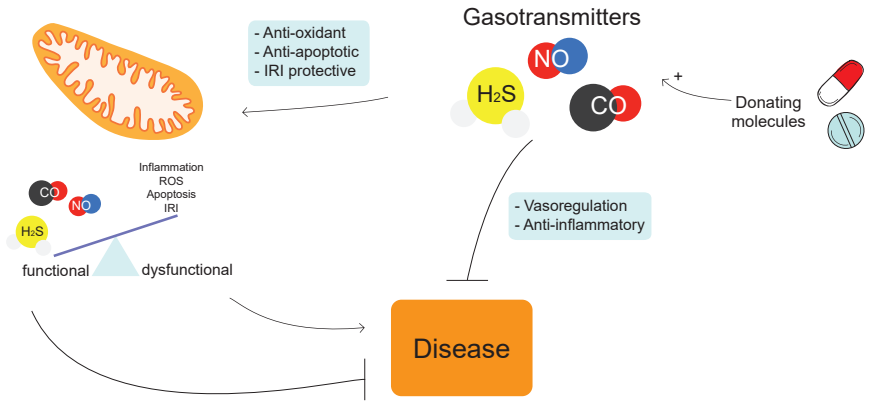
ABSTRACT

Gasotransmitters have long been recognized to fulfill important roles in homeostasis with disbalances having been linked to various pathologies, including inflammation and cardiovascular diseases. In addition to known pathways mediating the actions of gasotransmitters, the effects of gasotransmitters in regulating mitochondrial function is emerging. Given the fact that mitochondria are key organelles in energy production, formation of reactive oxygen species and apoptosis, they have been recognized as important mediators of preserving health and developing disease. Preserving or restoring mitochondrial function by gasotransmitters may therefore mitigate several diseases. Here we discuss the actions of gasotransmitters, focusing on their role in mitochondrial function and their therapeutic potential.

GRAPHICAL ABSTRACT



INTRODUCTION

Gasotransmitters are small, chemically reactive, short-living molecules that played crucial roles in the development of life. Nitric oxide (NO) and carbon monoxide (CO) are the first described and best-known gasotransmitters, whereas hydrogen sulfide (H_2S) has been discovered more recently. This third gasotransmitter gained more interest nowadays. Given the fact that gasotransmitters diffuse freely across cellular membranes, they are well equipped to regulate a broad range of important cellular functions in various cell types throughout the body. These include cardinal roles in regulating vascular tone[1], neuro-modulation[2], paracrine cell signaling[3] and mitochondrial function. Due to the effect on important cellular functions, a disturbance in gasotransmitter bioavailability is linked to a variety of pathological conditions. The mitochondrion is one of the targeted organelles of gasotransmitters and their actions modulate mitochondrial function, including important features such as adenosine triphosphate (ATP) production, reactive oxygen species (ROS) formation and initiation of the apoptotic cascade, all important mediators in inflammation and disease.

This review provides a concise overview of recent findings of gasotransmitters influencing inflammation, disease, and the role of mitochondria herein. It also explores avenues to target enzyme activity or supply gasotransmitter donors as therapeutic interventions.

GASOTRANSMITTER SYNTHESIS AND BIOAVAILABILITY

NO is formed by the conversion of L-arginine to L-citrulline, an oxidative process regulated by three subtypes of nitric oxide synthases (NOS) with different expression levels in different cells: neuronal (nNOS), endothelial (eNOS) and inducible (iNOS). Within a cell, iNOS and nNOS are mainly cytosolic, but subcellular distributions are described for nNOS[4]. eNOS is membrane bound, to facilitate release of NO to the extracellular environment.

CO is synthesized by conversion of heme to biliverdin through heme oxygenase (HO), an enzyme known to exist in three isoforms: HO-1, HO-2 and HO-3. HO is mainly located in the endoplasmic reticulum (ER), but, similar to NOS, has also been reported to be present in the mitochondria[5].

H_2S is derived from conversion of cysteine, catalyzed by cystathionine β-synthase (CBS), cystathionine γ-lyase (CSE) and cysteine aminotransferase (CAT), all three mainly located in the cytosol. However, in line with the mitochondrial NO and CO, CBS and CSE translocate to mitochondria during cellular stress such as hypoxia[6]. Additionally, H_2S is produced directly within mitochondria by 3-mercaptopyruvate

sulfur-transferase (3MST), an enzyme located in mitochondria[7].
Summarizing, the production of gasotransmitters is regulated by different enzymes, of which spatial expression patterns differ within organs and cell types. Of notice, all gasotransmitters can be produced near or inside mitochondria, indicative of an important role in mitochondrial function.

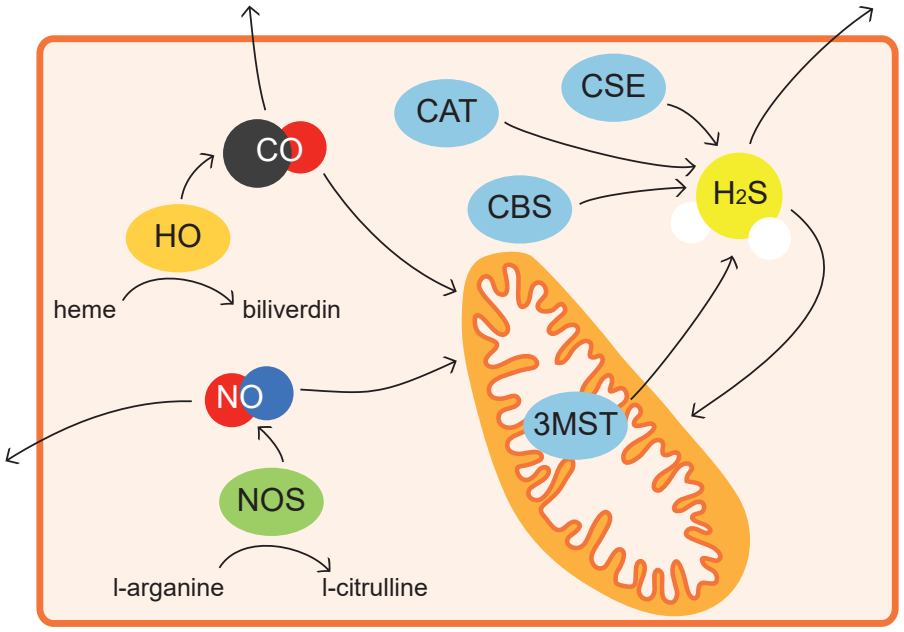


Figure 1. A general overview of the cellular synthesis and bioavailability of gasotransmitters within a cell.
3MST (3-mercaptopyruvate sulfur-transferase), CBS (cystathionine β-synthase), CSE, (cystathionine γ-lyase) and CAT (cysteine aminotransferase) produce H_2S (hydrogen sulfide). HO (heme oxygenase) produces CO (carbon monoxide). NO (Nitric oxide) is produced by NOS (nitric oxide synthase).

GASOTRANSMITTERS IN PHYSIOLOGY AND DISEASE

A plethora of physiological effects of gasotransmitters have been documented over the past decades. For instance, gasotransmitters, both via direct intracellular effects or released in the extracellular space, are known to play an important role in regulation of vascular tone, have capacity of reducing oxidative stress, and induce angiogenesis[8]. More specifically, CO is involved in processes such as regulation of endothelial cell survival and proliferation, protection from ischemia-reperfusion injury (IRI), vasorelaxation and inhibition of pro-inflammatory responses. HO-1 acts as an inflammation neutralizing factor regulated by nuclear-factor-erythroid 2-related factor-2 (Nrf2), as seen in lung inflammation after intestinal IRI[9]. NO

regulates numerous intra- and intercellular processes such as platelet aggregation, endothelial adhesion of leukocytes and relaxation of smooth muscle cells. Moreover, elevated NO levels, upon nuclear-factor-kappa B (NF-kB) activation and signal-transducer-and-activator-of-transcription-1α (STAT-1α) stimulated iNOS activation, represents an important component in the inflammatory response[10]. Excess production of NO, leading to nitrosative stress, is correlated with the severity of liver disease in mice[11]. In contrast, the anti-inflammatory action of NO is revealed in iNOS-knockout high-fat-diet fed mice, that show an increased inflammation leading to liver fibrosis[12]. These concentration-dependent opposing effects stress the requirement of strict regulation of NO production.
H_2S has important anti-inflammatory and antioxidant characteristics, and causes relaxation of blood vessels[13]. H_2S protects endothelial cells from lipopolysaccharide (LPS)-induced inflammation by blocking NF-kB transactivation[14]. In addition, exogenous H_2S treatment decreased inflammation and IRI following intestinal ischemia, whereas eNOS knockout mice were not protected by exogenous H_2S, suggesting that H_2S exerts protective effects via eNOS[15]. NADPH oxidase (Nox), a mitochondrial source of ROS, is identified as a key-signaling pathway responsible for the increased inflammatory response of macrophages in vitro and in septic mice[16,17], which could be ameliorated by endogenous H_2S.
Reduced bioavailability of gasotransmitters and subsequent biological impact has been demonstrated in several disorders such as vascular pathology[18], aging[19] and aging-related pathologies[20], renal pathology[21] and diabetes[22]. These associations suggest causality between alternated gasotransmitter bioavailability and disease pathogenesis.
The various pathways in which gasotransmitters are involved in disease and inflammation become of even more interest when looking at mitochondrial dysfunction, for example in sepsis. David et al. demonstrated lower ATP levels, overproduction of NO and mitochondrial dysfunction in skeletal muscle biopsies of septic patients[23]. Using H_2S and CO, potentiation of mitochondria could preserve tissue function during sepsis, as recently reviewed by Reitsema et al[24]. The authors suggested various future perspectives on therapeutic interventions to increase exogenous and endogenous H_2S production, to specifically inhibit iNOS and to stimulate HO-1 activity, in order to target mitochondrial pathways in sepsis and inflammation.

A schematic overview of some of the involved pathways is given in figure 2.

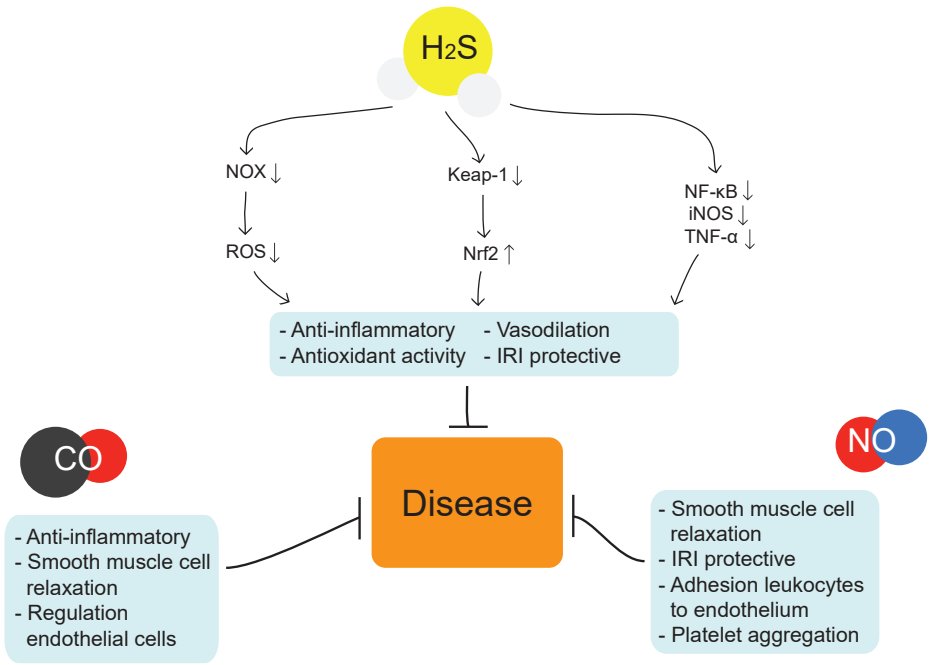


Figure 2. A schematic overview of some of the diseases related pathways gasotransmitters are involved in*. All three gasotransmitters, H_2S (hydrogen sulfide), CO (carbon monoxide) and NO (nitric oxide) show mitigating effects in a variety of diseases.*

MITOCHONDRIAL ASPECTS OF GASOTRANSMITTERS

Mitochondria, often simply referred to as 'the powerhouse of the cell' as they represent the main source of energy using oxidative phosphorylation, also fulfil important regulatory and signaling processes. In oxidative phosphorylation, these cell organelles oxidize substrates using their electron transport chain (ETC; or respiratory chain) comprising five complexes cooperating to build up a proton gradient, which is used to drive the ATP synthase. Gasotransmitters are involved in the regulation of this process, supporting normal physiology.

NO, CO and H_2S all reduce the ETC activity via inhibition of cytochrome c oxidase (COX) in a reversible, fast-acting and dose-dependent manner[25]. Thereby, gasotransmitters are suggested to preserve normal ETC function. Indeed, administration of NO and CO protected mitochondria during hemorrhagic shock[26] and upregulation of HO-1 normalized mitochondrial function and decreases ROS formation in IRI[27]. Also, H_2S protects the ETC by different mechanisms, as extensively described previously[28]. In line, CSE knockout mice are more susceptible to cerebral IRI compared to controls; which could be restored using exogenous

H_2S[29]. Interestingly, on the contrary to NO and CO, H_2S can act as hydrogen donor and functions as substrate for mitochondrial respiration[30].

In contrast, a high-dose treatment with CO, NO or H_2S can almost completely inhibit mitochondrial activity, especially H_2S showed potential to induce a safe metabolic suppression: a hypometabolic state[31,32]. This hibernation-like state has shown to be protective to IRI, as occurs in e.g. organ transplantation[33].

Besides direct effects on mitochondrial function, gasotransmitters play an important role in (mitochondria-derived) ROS scavenging. Especially NO is a potent antioxidant by virtue of its fast reaction with hydroxyl radicals, superoxides and lipid peroxides[34]. Exogenous H_2S administration protected cardiac tissue from ROS damage in a myocardial injury rat model[35].

In addition to the direct scavenging potential, gasotransmitters are also important in the activation of scavenging pathways, such as Nrf2 and glutathione (GSH). Kelch-like-ECH-associated-protein-1 (Keap1) serves as a negative regulator of Nrf2, during stress free physiology, Keap1 binds to Nrf2 in the cytoplasm and promotes degradation of Nrf2. Cellular stress, such as provoked by ROS, inactivates Keap1 and therefore stabilizes Nrf2, allowing translocation to the nucleus and activation of its target: the antioxidant-response-element (ARE)[36,37]. Alternatively, H_2S can promote the Keap1-dependent Nrf2 stabilization, which helps Nrf2 translocation into the nucleus[38]. Indeed, exogenous NaHS administration in a diabetic stressed rat model resulted in increased nuclear Nrf2 levels, activation of superoxide dismutase (SOD) and limited apoptosis[39]. Besides increasing GSH production, H_2S is believed to redistribute GSH into the mitochondria to directly scavenge the mitochondrial-produced superoxides[40], advocating the interest in the mitochondrial located H_2S production. CO exposure in transplanted rat lungs protected against apoptosis, likely via increased SOD activity and decreased ROS damage[41].

Another important pathway that gasotransmitters are involved in is the opening of the mitochondrial permeability transition pore (mPTP). By mechanisms not yet fully understood, channels can be formed in the inner membrane of mitochondria: the mPTP. Full opening of the mPTP, induced by several factors among which excessive ROS and calcium-overload, results in a loss of mitochondrial membrane potential and oxidative phosphorylation, mitochondrial swelling and a burst of ROS, eventually leading to necrosis or apoptosis[42]. Exogenous H_2S has shown to inhibit apoptosis via blocking mPTP opening and cytochrome c (cyt c) release[43]. Next to mPTP opening, apoptosis can be activated by the Bcl2-family, cyt c release and caspase activation. Both NO and CO are known to suppress the Bcl2-family and caspase activation[44, 45].

Altogether, gasotransmitters have an important role in the cellular energetic state and apoptosis by regulating several mitochondrial- and ROS-related actions, as outlined in figure 3.

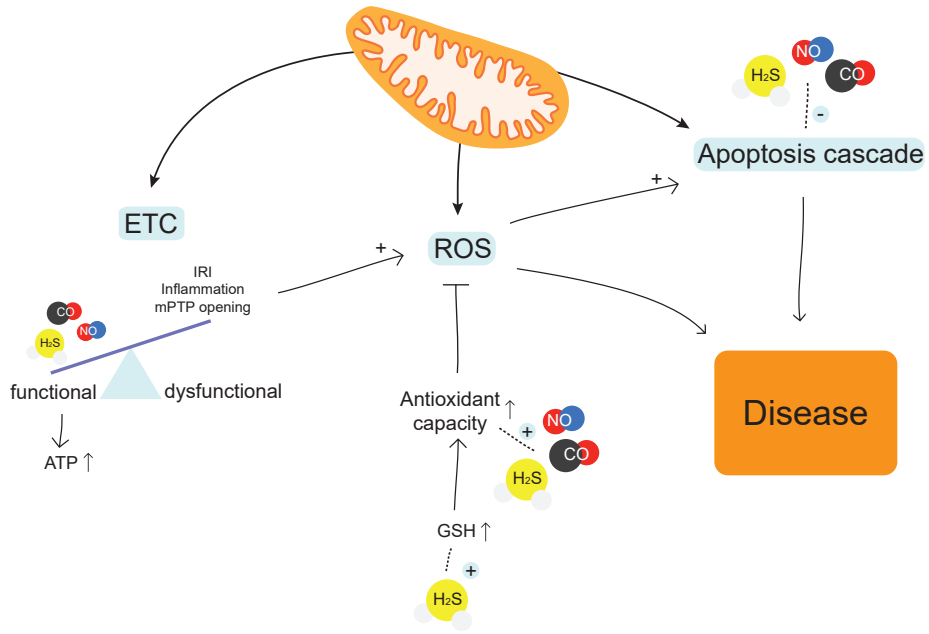


Figure 3. A simplified overview of the interactions between gasotransmitters and mitochondria.
ETC = electron transport chain, ROS = reactive oxygen species, GSH = glutathione.

TREATMENT PERSPECTIVES

Exogenous administration of gasotransmitters is an emerging therapeutic option. The oldest and most used donor is the acute NO donor nitroglycerin, causing vasodilation and acute pain relief during angina pectoris. Another clinically relevant NO donor in current use is sodium nitroprusside (SNP), also playing an important role in vasorelaxation. Based on these successes, several NO donors were synthesized, among which NO donors coupled to other medication, such as NO-NSAID[46]. Additionally, more downstream NO-interfering drugs were tested, such as the highly specific phosphodiesterase 5 (PDE5) inhibitor sildenafil[47]. Sildenafil treatment showed an increased activity of the NO and cGMP pathway and protection against oxidative damage and apoptosis in diseases such as diabetes[48] and cardiovascular dysfunction[49]. In contrast, most recent findings in pregnant women with fetal growth restriction revealed detrimental effects of sildenafil treatment[50]. In line with the functions of CO, carbon monoxide-releasing-molecules (CORMs) have shown anti-apoptotic, anti-inflammatory, and antioxidant effects[51]. Widely used under experimental conditions are H_2S donors NaHS and Na_2S. These sodium salts lead to a fast and high concentration of H_2S. Ideally to induce a hypometabolic state[32], but not suitable for precise and sustained

administration. A potential alternative can be found in sodium thiosulfate (STS). STS showed positive effects on hypertension and renal injury[52]. The potential of STS on reducing cardiac ischemia is now being clinically tested.
Recently, slower H_2S donating molecules have been synthesized, such as GYY4137, AP39 or DATS-MSN, which show promising results in IRI by exploiting the protective properties of H_2S. Sun X et al. suggested that DATS-MSN shows superior anti-apoptotic, antioxidant and anti-inflammatory abilities over NaHS[53]. AP39, a mitochondrial targeted H_2S donor, has shown very potent protective effects in an organ transplantation model[54]. Interestingly, also (ROS)-triggered H_2S donors[55] and slow-releasing NO/H_2S hybrid molecules are invented[56] with promising effects against heart failure[57].

CONCLUSION

Gasotransmitters play a vital role in various diseases, with a central role for its effects on mitochondria. H_2S, CO and NO all have their specific roles in maintaining accurate mitochondrial function or inducing mitochondrial distress and show a broad variety of potential therapeutic properties: influencing ETC activity, direct scavenging, activation of scavenging pathways and suppression of apoptosis. These effects qualify gasotransmitters as potential efficacious drugs and, recently, have led to the synthesis of long-lasting and slow releasing donors for therapeutic use. Although promising results have been obtained in experimental disease models, sufficient clinical studies are lacking. This urges the need for more extensive research and maybe even new compounds. A mitochondrial targeted combination of H_2S-NO-CO donor is an attractive concept to protect mitochondria from noxious insults; whether this concept is actually applicable remains to be seen in the near future.

Acknowledgements
We like to thank Maaike van der Meulen for designing the artworks.

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Chapter 6 • A mitochondrial view on gasotransmitters

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ABBREVIATIONS

3MST	3-mercaptopyruvate sulfur-transferase
ARE	antioxidant response element
CAT	cysteine aminotransferase
CBS	cystathionine β-synthase
CO	carbon monoxide
CORMs	CO-releasing molecules
COX	cytochrome C oxidase
CSE	cystathionine γ-lyase
Cyt c	cytochrome c
ER	endoplasmic reticulum
ETC	electron transport chain
GSH	glutathione
H_2S	hydrogen sulfide
HO	heme oxygenase
IRI	ischemia-reperfusion injury
Keap1	kelch-like ECH-associated protein 1
LPS	lipopolysaccharide
mPTP	mitochondrial permeability transition pore
NF-kB	nuclear factor kappa B
NO	nitric oxide
NOS	nitric oxide synthases
Nox	NADPH oxidase
Nrf2	nuclear-factor-E2-related factor-2
PDE5	phosphodiesterase 5
ROS	reactive oxygen species
SNP	sodium nitroprusside
STAT-1α	signal transducer and activator of transcription-1α
STS	sodium thiosulfate
TNF-α	tumor necrosis factor-α