REVIEW

Nature’s marvels endowed in gaseous molecules I: Carbon monoxide and its physiological and therapeutic roles

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\textbf{Abstract} Nature has endowed gaseous molecules such as O\textsubscript{2}, CO\textsubscript{2}, CO, NO, H\textsubscript{2}S, and N\textsubscript{2} with critical and diverse roles in sustaining life, from supplying energy needed to power life and building blocks for life’s physical structure to mediating and coordinating cellular functions. In this article, we give a brief introduction of the complex functions of the various gaseous molecules in life and then focus on carbon monoxide as a specific example of an endogenously produced signaling molecule to highlight the importance of this class of molecules. The past twenty years have seen much progress in understanding CO’s mechanism(s) of action and pharmacological effects as well as in developing delivery methods for easy administration. One remarkable trait of CO is its pleiotropic effects that have few parallels, except perhaps its sister gaseous signaling molecules such as nitric oxide and hydrogen sulfide. This review will delve into the sophistication of CO-mediated signaling as well as its validated pharmacological functions and possible therapeutic applications.

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1. Introduction

There are many ways of looking at life on earth, depending on the specific context. However, at a fifty-thousand-foot view, life needs three key components to sustain: an appropriately organized physical structure, well-coordinated signaling mechanisms to mediate the functions of the physical structure, and energy to power life. Missing any of the three components, life would cease to exist. In modern biology, the discussions of physiological and pathological processes of life commonly (and rightfully) involve the examination of DNA, RNA, proteins, peptides, saccharides, lipids, metal ions, essential nutrients such as amino acids and carbohydrates, and signaling molecules including hormones, neurotransmitters, cytokines, chemokines, metabolites, and other small molecules. Often overlooked is a group of gaseous molecules that play critical roles in sustaining life. With this article, we hope to look at some of the life’s processes from a “gas”-centric perspective. As such, we hope to highlight the diverse roles that nature has endowed upon a relatively small number of gaseous molecules by starting with a brief description of how they help to sustain life on a global level, then transitioning to their endogenous signaling roles in mammals, and finally zeroing in on one example, carbon monoxide, to unveil the amazing roles that this small molecule plays in health and disease and its promise as a potential therapeutic agent.

If one looks at life on earth, a central issue to consider is how to capture and use energy to power life. Long before atmospheric oxygen was available for aerobic respiration, Earth’s atmosphere was abundant with gases such as methane, nitric oxide, hydrogen sulfide, and carbon monoxide, which early life probably harnessed for energy in redox mechanisms. In Earth’s modern ecosystem, solar energy is the dominant form of energy sustaining life through photosynthesis. In this context, it is amazing to see how two gaseous molecules serve as the key conduits of energy flow among species that rely on solar energy: oxygen and carbon dioxide. While phototrophs capture and store solar energy by transforming carbon dioxide into organic compounds and splitting water to emit oxygen, heterotrophs, such as human, consume such organic compounds as an energy source through “burning” or oxidation by oxygen with carbon dioxide and water as the ultimate end products of the organic component. Consequently, the reciprocal redox cycling of these two small gaseous molecules forms the chemical basis for powering life on earth that relies on solar energy. The story of nitrogen is just as intriguing; microorganism’s end products of the organic component. Consequently, the oxidation by oxygen with carbon dioxide and water as the ultimate end products of the organic component. Consequently, the oxidation by oxygen with carbon dioxide and water as the ultimate end products of the organic component.

At an individual organism level, the ability for humans to use oxygen for oxidation of organic molecules in a controlled fashion through an intricate web of enzymes is what allows us to capture the energy stored in these organic compounds and to survive on this earth. Even the byproduct, carbon dioxide, is not simply a waste or a bystander; it helps to regulate pH, stimulate breathing, and influence the hemoglobin’s affinity for oxygen (the Bohr effect). While a small portion of carbon dioxide is transported as carbaminohemoglobin, carbonic anhydrase is the enzyme responsible for converting carbon dioxide into (bicarbonate reversibly and is an important target for drug design for a variety of pathological conditions including cancer, neuropathic pain, fluid retention, epilepsy, and glaucoma, among others.

Beyond carbon dioxide and oxygen, three other gaseous molecules are recognized as endogenous signaling molecules in human: nitric oxide (NO), hydrogen sulfide (H2S), and carbon monoxide (CO). These three small signaling molecules are often referred to as “gasotransmitters”, with some dissent. They have similar and overlapping roles at times. Research on NO led to the 1998 Nobel prize in Physiology and Medicine being awarded to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad for their seminal contributions. It is also important to note one thing. Though these three molecules are gaseous in the pure form under normal conditions, they largely exist in the body in the dissolved form, allowing for the possible interconversion of these two forms depending on location and conditions. These gaseous molecules also share three important traits: rapid diffusion, easy permeation through various barriers, and rapid excretion without the need for metabolism (especially CO) through exhalation. Among these three gaseous signaling molecules, NO has the shortest half-life, and thus is most suited for local signaling unless meta-stable precursors such as S-nitrosothiols are involved. HNO, the one-electron reduced and protonated congener of NO, exhibits some biological activities similar to that of NO. Hydrogen sulfide is much more stable, but still undergoes rapid conversions to a variety of species through ionization, redox reactions, sulfur excretion, or chelation to metal ions. CO is relatively metabolic inert except for its high affinity for certain transition metals such as nickel and iron and undergoes minimal chemical transformation in mammalian cells under physiological conditions, and thus is suitable for both local and global signaling over time as the biological half-life in humans is in the range of hours. Recent years have seen sulfur dioxide (SO2) emerging as a possible signaling molecule. It is endogenously produced and has well-recognized biological functions. Another interesting gaseous molecule is molecular hydrogen (H2), which has been extensively studied for its possible pharmacological effects. To the best of our knowledge, there is no human enzyme that produces H2. Therefore, it would not be considered as an endogenous signaling molecule in the traditional sense. However, bacteria in the gut is known to produce H2. Then, could H2-mediated signaling be part of the bacteria-host symbiotic relationship? Furthermore, some pathogens also use H2 as fuel, such as Helicobacter pylori. In terms of therapeutic application, it is very interesting to note that hydrogen-rich water is already commercially available in some parts of the world including China and Japan. We defer to several excellent recent reviews for in-depth discussions of this subject. There are also other gaseous molecules in the body including CH4 (gut bacteria), NH3, and N2. That play various roles in normal human physiology.

Available data on these gaseous species offers a complex and sophisticated picture of how a human body uses gaseous molecules for sustaining and controlling normal physiology. They also offer opportunities for developing therapeutic agents. Covering all these gaseous molecules would require more than a book. In this article, we start with one endogenous gaseous signaling molecule: carbon monoxide (CO)!

Below we discuss the molecular, physiological, and pharmacological traits of CO. We will also briefly discuss some of CO’s known molecular mechanisms of actions. As is true with everything life is CO has two sides: it possesses very promising therapeutic utilities at low doses and is poisonous at high doses. Further, it is very important to point out that CO has a high enough
safety margin for such applications. Fig. 1 summarizes the Yin and Yang sides of CO, the details of which are described in subsequent sections.

2. CO is endogenously produced, can diffuse throughout the body, and is essential for life

In mammals, CO is produced mostly by heme degradation by an enzyme called heme oxygenase (HO)\(^34\), which has two enzymatically active isoforms (HO-1 and HO-2) and is present in all cells. Daily production of CO is on the scale of about 400 µmol per day\(^35\), largely as part of red blood cell turnover\(^35,36\). However, there are other secondary sources including cytochrome P450 reductase\(^37\), human acireductone dioxygenase\(^38\), tyrosinase\(^39\), lipid peroxidation\(^40\), and numerous minor sources\(^36,41\). Further, microbiome sources of CO have not been extensively studied and could turn out to be very important in health and disease\(^42,43\). Regardless of the source, CO mostly exists in the form of carboxyhemoglobin (COHb) because of its 240-fold higher affinity to hemoglobin than oxygen and essentially reaches to all parts of the body through blood circulation. CO is known to be highly permeable and diffusible through both endothelium and skin epithelium\(^44,45\). There is strong evidence that orally administered CO donors allow delivery of CO into the systemic circulation\(^46,47\). Therefore, some common barriers for drug delivery, such as the intestinal barrier and blood–brain barrier are not considered a major issue for CO, which is capable of diffusing in and out of the blood circulation. However, because of CO’s affinity for hemo- globin, at any given time the proportion that diffuses into tissues is thought to be less than 20%\(^48\).

CO is considered essential for life with multiple targets\(^49–52\), and the physiological roles of the CO–HO axis have been extensively studied over the past twenty years\(^53–55\). HO-1 is inducible in response to various stress signals and is cytoprotective and anti-inflammatory. During stress, increased production of CO is on the order of 4000 µmol per day\(^56\), which can be measured in exhaled breath\(^57–59\). Lack of HO-1 results in a pro-inflammatory phenotype. Though inflammation promotes malignant growth and contributes to cancer progression\(^60–62\), the effect of HO-1 on cancer is more complex than inflammation alone\(^63\). Further, HO-1 knockout animals were reported to die within a year with indications of inflammation in multiple organs, which is consistent with the known anti-inflammatory role of CO\(^63\).

It is clear that CO is essential in sustaining life, has multiple targets and thus pleiotropic effects (see below), has high diffusivity, and is very stable. Therefore, CO’s effect can be both local and global as well as long-lasting. Further, CO has overlapping targets and functions with NO and H\(_2\)S. As a result, the study of CO’s physiological and pharmacological functions needs to take a holistic approach by combining molecular-level details with global-level network interactions and feedback controls.

3. CO is known to be important in balancing human immunity and has anti-inflammatory, cytoprotective, and organ-protective effects

One of the most widely studied properties of CO is its anti-inflammatory, cytoprotective and organ-protective effects, with a large number of publications supporting this view\(^64–66\). CO has been shown to be protective of organs such as kidney\(^68–71\), heart\(^72,73\), liver\(^74,75\), brain\(^76,77\), and gastrointestinal (GI) system\(^78–84\), among others\(^7,8\) after various injurious events such as ischemia–reperfusion injury, trauma, and chemically induced injury. Along a similar line, CO seems to show beneficial effects
in treating autoimmune-related conditions\textsuperscript{85–87}. In addition, CO has been examined in animal models of sickle cell disease\textsuperscript{46}, preeclampsia\textsuperscript{88,89}, and gastroparesis\textsuperscript{90} and shown to have beneficial effects. The pleiotropic health effects of CO suggest its network-like pharmacological functions and speak to its unique traits and importance in maintaining overall human health. All these suggest the need to take a holistic approach to understanding CO’s true physiological and pharmacological functions.

4. CO has been reported to help the body in fend off bacterial infection and in sensitizing cancer toward chemotherapy

One of the remarkable traits of CO is its ability to suppress pathologically relevant inflammation while still strengthening the body’s ability to fend off infection and other pathological changes. This is very different from other anti-inflammation therapies such as corticosteroids and anti-tumor necrosis factor (TNF)-α agents. For example, CO has been shown to be beneficial in treating bacterial sepsis, which requires the ability to suppress inflammation while still allowing the body to fight off the infection\textsuperscript{91,92,93}. In a recent study, Otterbein and colleagues\textsuperscript{93} have shown that macrophages can sense CO and kill bacteria through activation of inflammasome. Similarly, CO blocks the proinflammatory cytokine TNF, while enhancing expression of the anti-inflammatory cytokine IL-10 in macrophages and in tissue\textsuperscript{94,95}. CO likewise has a direct manner of action against pathogens by inhibiting bacterial oxidases and essential hemoproteins\textsuperscript{96}. In the area of cancer, CO has been shown to sensitize cancer cells toward chemotherapy\textsuperscript{39,77} through an anti-Warburg effect, and to help overcome cisplatin resistance\textsuperscript{38,99}, while simultaneously offer protection of organs such as the heart, kidney, and liver that are prone to chemically-induced injuries\textsuperscript{77,100–105}. Very few, if any, known therapies can offer such seemingly directional controls in achieving therapeutic effects. One can also say that CO helps to restore a balance in eradicating pathological changes.

5. CO’s remote-conditioning property reflects its health effect in a holistic fashion

Pre-conditioning\textsuperscript{106} and remote ischemic conditioning (RIC)\textsuperscript{107,108} refer to the protective effects of relatively minor ischemic events either locally beforehand or remotely against major damages resulting from ischemia-related events\textsuperscript{109,110}. Despite success in some studies and in pre-clinical models\textsuperscript{111–116}, not all studies observed the same benefit of such conditioning\textsuperscript{117–120}. Thus, a deeper understanding of the mechanism of action might offer a chance to elucidate critical factors that contribute to success in such conditioning and may lead to approaches for pharmacological conditioning\textsuperscript{111}. Mechanistic studies in animal models have led to suggestions of involvement of NO\textsuperscript{113}, hypoxia-inducible factor 1α (HIF-1α)\textsuperscript{80,89}, the PTEN/AKT signaling pathway\textsuperscript{124}, exosomal miR-21\textsuperscript{125}, NF-κB\textsuperscript{126–128}, and iNOS\textsuperscript{129} in pre-conditioning or RIC. Understandably, many such molecular targets are inter-related. No matter what the mechanism is, RIC will likely involve the diffusion of a “signal” from a remote site to the location where ischemic damage happens. CO is such a molecule. HO-1 has been suggested as playing a key role in anesthetic-induced conditioning\textsuperscript{130} and CO has been suggested as a mediator in the conditioning process\textsuperscript{131,132}. In an animal model study, it was shown that inhalation of CO was able to recapitulate the HO-1 induced protective conditioning in a liver ischemic reperfusion injury model\textsuperscript{133}. As discussed in Section 2, there have been many other reports of CO’s role in organ protection after ischemic reperfusion injury\textsuperscript{134–136}. Thus, HO-1 activation and CO production as a result of minor and repeated ischemic events at a remote site could lead to the protection of major ischemic injuries through distance. Again, the chemically inert nature, diffusivity, and long half-life of CO play an important role in allowing CO to be a signaling molecule through distance and over time.

6. There is a large amount of data allowing for some understanding of CO’s molecular mechanism(s) of actions

The examination of CO’s pleiotropic pharmacological effects is supported by extensive and rigorous mechanistic studies, which are very critical to the advancement of this field. Some of the identified molecular targets of CO include the soluble form of guanylyl cyclase, mitochondrial oxidases, nitric oxide synthases, prolyl hydroxylase, neuronal PAS domain protein 2 (NPAS2), the CLOCK transcription factor, Per-2, mitogen-activated protein (MAP) kinases, catalase, PPAR-γ, HIF-1α, Nrf2, ion channels, and cystathionine β-synthase (CBS), among others\textsuperscript{71,95,110,137–141}. A detailed discussion of this aspect would require a separate paper or a book. However, the references provided hopefully would allow readers to delve into the details, should they be interested. The multi-target nature of CO is very remarkable. Understanding the intricate interplay among all the molecular targets in a holistic fashion will be very valuable to achieve a deeper understanding of the “network” effect of CO, especially considering that CO has overlapping targets and functions with NO and H\textsubscript{2}S. Fortunately, this area has attracted a great deal of attention and research activities\textsuperscript{70,10}.

7. CO has healing powers, is safe at therapeutic levels, and yet is harmful or lethal at high levels

Although CO plays an essential role in human physiology in managing inflammation as one of its functions and is being developed for therapeutic applications, there is no doubt that CO is toxic or lethal at high levels. Although the highest recorded non-fatal COHb was 73%\textsuperscript{142}, each year many people die of CO poisoning\textsuperscript{143}. Therefore, it is very important to understand the normal physiological concentration range and safety margin of CO.

In non-smokers, COHb levels averaged about 2% in one study, while smokers averaged 8%\textsuperscript{144}. Hookah smoking has been the subject of clinical trials based on the link between CO inhalation and its vasodilatory mechanism of action (NCT03067701). Interestingly, despite the overall harmful effect of cigarette smoking, some studies found an inverse correlation between smoking and incidents of ulcerative colitis\textsuperscript{145–147} while others offer a different view\textsuperscript{148–149}. Animal model experiments have also duplicated the inverse relationship between smoking and ulcerative colitis\textsuperscript{150,151}. Further research points to CO’s beneficial effects in colitis as a likely molecular link and suggests that the COHb level achieved through smoking is high enough for therapeutic values, though one has to be mindful of all the other harmful substance inhaled during smoking\textsuperscript{70–72,84,152–154}. If one considers the fact that Hb level in a healthy person is about 7.5 mmol/L, the CO concentration in the form of COHb in the blood can range from 150 (non-
smokers) to 600 μmol/L (smokers), which is within human safety tolerance. These concentrations are also comparable to or higher than the peak plasma concentrations of approved drugs such as Tylenol (>100 μmol/L), naproxen (>300 μmol/L), Zantac (1.5 μmol/L), doxorubicin (1–2 μmol/L),[155] imatinib (3.5 μmol/L), and 5-fluorouracil (>300 μmol/L). As a matter of fact, CO has been studied for safety in several human clinical trials. As a result, the U.S. Food and Drug Administration has approved clinical trials with COHb level being as high as 14% as an upper threshold[105]. All indications are that CO can be developed as a safe therapeutic agent with safety margins being higher or comparable to even nutrients such as glucose and potassium as well as therapeutics such as insulin, heparin, digitalis, warfarin, and others.[2-155]

Herein lies an important message that is not always as widely understood in the general public as one would have hoped. As an important historical figure, Paracelsus (a Swiss physician, alchemist, and philosopher, 1493–1541) would say, it is the dose that makes a poison or a remedy[156]. CO’s therapeutic effect at low doses does not diminish its health risk or lethality at high levels, and vice versa. Further, simply because a drug is useful in treating a specific pathological condition does not mean that it is good for a healthy person to take as a preventative measure. This is a message that I (Wang) always tell students: just because taxol is a good drug to treat certain forms of cancer, it does not mean that a healthy person should take taxol to prevent the same cancer because all drugs are inherently toxic if abused. The same message is true for CO as well as medicinal plants, herbal supplements, and natural compounds. Prophylactic usage is very different from treatment and should only be based on proven science. Just because CO has the potential to be used as a therapeutic agent for treating certain conditions such as inflammation, it does not mean that a healthy person can “self-medicate” in any form or fashion. All therapeutic agents should be used only based on clinically proven science and under the supervision of appropriately trained medical professionals. Otherwise, there could be harmful or lethal consequences.

8. Much progress has been made in developing CO-based therapeutics, but challenges remain

Because of the demonstrated pharmacological activity of CO, there is much interest in developing CO-based therapeutics for various indications, as summarized in a few recent reviews[7,8,157–160]. Thus, we shall only provide a brief synopsis without duplicating what is in these reviews. In addition to efficacy, there are two key factors to consider in developing CO-based therapeutics: toxicity and delivery. For toxicity, Sections 1 and 6 specifically address this issue. Three recent reviews address the safety issue in detail and show that for pharmaceutical development, CO has a sufficient safety margin, which is probably higher than or comparable to many approved therapeutics[105,165,166,168]. For delivery, using CO gas as the delivery form actually poses several issues. First, CO is lethal at high doses. A practical problem in using CO in a tank is that it is odorless, colorless, and tasteless, making it hard to detect if leakage happens. Even with the availability of CO detectors, CO leakage still poses a safety issue for healthcare workers and family members in the same household. Further, delivering a precise dose of gaseous CO through inhalation is a challenge by itself and in terms of patient compliance. As a result, there have been strong interests in developing alternative CO delivery methods including oral formulations and metal-immobilized carbonyls as CO-releasing molecules (CORMs)[159]. For those who are interested in more details, there are two earlier reviews and three recent reviews that cover the subject comprehensively[158,161–165]. These include prodrugs with tunable release rates (2 min to days)[153,162,165,170], targeted delivery[170,171,172], triggered release (pH[173–175], reactive oxygen species (ROS)), thiold[177], esterase-sensitive[174,178], photo-sensitive[179] as well as dual-triggered[166,174,177] prodrugs, the ability to deliver two payloads in one prodrug[180], and the ability to target the mitochondria[75,158,171]. These prodrugs have shown anti-inflammatory[162] and antibacterial (H. pylori)[180] effects in vitro and have been studied in animal models of colitis[155], gastric injuries[179], liver injuries[5,178], kidney injuries[11], and systemic inflammation[114] with very pronounced efficacy.

Fig. 2[7,15,155,161–164,168–170,173–175,177,180,104,169,182–200] summarizes the conceptual development of CO delivery forms; and we hope that with this many CO delivery options available, some will eventually be developed into therapeutic agents. Even with all the remarkable progress, it is important to note that challenges remain in areas such as (1) understanding the interplay of dosage, duration of exposure, and efficacy, (2) deciding key parameters to measure in studying CO’s pharmacokinetics[17, (3) tissue-specific delivery when needed, (4) ways to minimize systemic CO exposure when needed, (5) methods for real-time detection of free and bound CO, and (6) a deeper understanding of the consequence of the “network”-like pleiotropic effects of CO at the molecular level. Recently, it has been reported that many of the previously described biological effects of metal-based CORMs, including antimicrobial[200–205], anticoagulation[206–208], and ion channel regulation[209] are actually CO independent. Instead, much of these activities can be attributed to the generation of reactive oxygen species[203–205] and reactivity toward thiol[200], sulfite[10], proteins and enzymes[200,201,208,209,211–217], and electron-deficient organic functional groups such as an aryltin group[218] by certain metal-based CORMs in as well as their general solution chemistry including water-shift reactions[203,219]. All these issues indeed suggest that some of these metal-based CORMs may be more than CO donors per se. Such results further suggest the need to use rigorous controls and assessment of the general molecular reactivity of CO donors and their side products after CO release, whether they are metal-based CORMs or organic prodrugs. Therefore, much more work is needed.

In discussing CO-based therapeutics, it is critical to also analyze one issue: pharmacokinetics. As discussed earlier, CO’s biological half-life (t1/2) in humans is commonly cited as about 300 min under atmospheric conditions[20]. However, such studies were mostly in the context of CO poisoning, presumably through inhalation. One may also need to consider the likelihood that the t1/2 may vary depending on the duration of CO exposure and alveolar ventilation[219], the form of CO delivery[170,217,222], and the level of CO in the blood[217,23,223–228]. For example, in a study of human waterpipe usage, COHb level (averaging 6.2% COHb) returned to the baseline level within 8 h, implying a t1/2 of much shorter than 300 min[229]. In any case, CO administration in the form of short inhalation of 1000 ppm (once every min for 10 min) at 40 min interval was sufficient to give a sustain level of COHb[229]. In most animal model studies, once daily administration of CO is commonly used for yielding pharmacological efficacy.
However, the biological half-life of CO as represented by COHb levels seems to vary considerably among porcine, dog, rabbit, rodent, and human. For example, in mice when administered in the form of CO prodrugs, the $t_{1/2}$ of COHb is normally about 1–2 h depending on the route of administration. In porcine after bolus administration of CO-saturated blood, the $t_{1/2}$ of COHb is also about 1 h. There have been other pharmacokinetic studies of COHb profiles using different donors and under different conditions. Such results mean that much more work is needed in examining the relationship between pharmacokinetics and pharmacodynamics, which may vary depending on the specific pharmacological indications.

9. Concluding remarks

With all the discussions above, it is clear that CO is essential to human health, has a wide range of pharmacological effects, and has therapeutic potential. The inter-twined pleiotropic effects of CO mean that we will need to take an integrated and holistic approach to understanding CO’s functional roles, especially in the context of its overlapping functions with NO and H2S. Beyond CO, it is important to note the network-like roles of the various gaseous molecules in sustaining life. This is an area that will require elevated levels of activities to fully tap into the therapeutic potential of these gaseous molecules.

As an afterthought, it is important to note that the conception of the roles of gaseous molecules in life’s processes did not start with the commencement of modern molecular science. Quite to the contrary, the central roles that gaseous entities play in life had been recognized long time ago by human ancestors throughout the ancient civilizations, even though at that time, understanding at the molecular level was in the far distant future. For example, more than five thousand years ago in the ancient India, breath and gas (prana, “प्राण” in Hindu) were acknowledged as a vital element for life in the oldest philosophical medicine system known as “Ayurveda”.

The Yellow Emperor’s Classic of Medicine in Chinese medical records such as the “The Yellow Emperor’s Classic of Medicine” (circa 2nd century BCE). However, all these ancient concepts seem to have a broader meaning than its literal translation of the physical concept of “air” or “gas” and to embody philosophical concepts as well, reflecting the recognition of the vital nature of gaseous entities in life. Finally, it is also interesting to note that one of the earliest medicines that continues its use in modern days is laughing gas, or nitrous oxide, which was first introduced in the 1770’s.

It is our hope that this article will serve as a teaser to nature’s marvels embedded in gaseous molecules and will help to stimulate additional interests in the same. As a result, we look forward to seeing a boom in research activities in this area so that we can collectively take a quantum leap in moving this field forward. We also hope that readers will lend their collective wisdom to the exploration of the holistic roles of gaseous signaling molecules in maintaining human health.

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Author contributions

Xiaoxiao Yang and Binghe Wang drafted this manuscript. Christopher P. Hopper, Wen Lu, and Bowen Ke gave their intellectual input and revised the manuscript.
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Conflicts of interest

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