NO- and CO-donors: An emerging class of pharmaceuticals in current medicine

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Received 22 August 2011

In recent years, two small diatomic molecules namely, nitric oxide (NO) and carbon monoxide (CO) have been shown to play key roles in human physiology. Depending on their concentration (in the nano-to-micro molar range), these two molecules exhibit distinct physiological or pathological effects. Several exogenous NO-donors have found use as medication for blood pressure control and as anti-infective agents. CO-donating compounds have shown promises in controlling tissue damage. Demand for new and efficient NO- and CO-donors for controlled delivery of these two messenger molecules to biological targets has grown over the years and the market for such drugs is expanding at a fast rate. Inorganic and bioinorganic chemists have already contributed significantly in this area. It is expected that they will play an important role in the future design and development of these drugs.

Keywords: Nitric oxide, Carbon monoxide, NO-drugs, CORM, Heme oxygenase, Nitrosyl compounds, Carbonyl compounds, Signal transduction, Cytoprotective activity

During the past few decades, two surprisingly unusual and “toxic” molecules, namely, nitric oxide (NO) and carbon monoxide (CO), have been shown to play critical roles as signaling molecules in various biological pathways. Although the chemistry of these two “inorganic” molecules has been studied by researchers involved in chemistry, atmospheric science, toxicology and forensic science for quite sometime, their occurrence in human physiology and in recent years their utility as drugs have added new paradigms in biology and medicine. Both molecules are known to be toxic; CO enjoys notoriety as the “silent killer” and NO as the source of “smog” in polluted urban air. That very low concentrations of these two gaseous molecules are nevertheless essential for life therefore comes as a shocker.

Extensive research in the area of signal transduction led to the discovery of the role of NO in blood pressure regulation, innate immune response during pathogen invasion and chronic infection, neurotransmission and cellular apoptosis. Despite use of NO-donating drugs like glycerin trinitrate and sodium nitroprusside in tackling hypertensive episodes since the beginning of nineteenth century, the identity of the true agent responsible for the observed relief came into light as late as 1979 when the so-called “endothelium derived relaxation factor” (EDRF) was identified as NO. Similarly, although formation of CO in human tissue was discovered in 1940, the cytoprotective effects of CO were recognized only during the 1990s. Clearly, the mechanisms by which these two tiny uncharged molecules are produced in controlled amounts on demand and utilized effectively without exerting any apparent toxicity in mammalian tissues are new discoveries and more studies are required to achieve a thorough understanding of the roles of these diatomic signaling molecules in human biology.

Intense research activity on the physiological and pathological pathways of NO and CO has also ushered a new era of drug design targeted toward selected delivery of these molecules to biological sites to elicit desired effects. Numerous NO-donating drugs and a few CO-releasing materials (CORMs) have been synthesized and several of such products have found use in hospitals to combat selected maladies. As one expects, the literature is quite extensive and hence only a few selected articles and recent reviews are provided as reference in this focused critical review. One also must realize that our understanding in these fields is still developing and much remain to be discovered. This is particularly true in the case of CO for which the mechanisms by which it exerts its biological functions are still at an exploratory stage. Finally, this review intends to point out to the roles that inorganic chemists could play in completing the story of these toxic twins.
Sources of NO and CO in Mammals

The enzyme nitric oxide synthase (NOS) \(^{21}\) produces endogenous NO from L-arginine (Scheme 1). In the linings of blood vessels, the endothelial isoform of this enzyme (eNOS) generates nanomolar levels of NO, which in turn activates soluble guanylate cyclase (sGC) to generate cyclic guanosine monophosphate (cGMP). Diffusion of cGMP into the smooth muscle of the inner linings causes vasodilation and regulates blood pressure to maintain a steady flow.\(^ {3,14}\) In addition, NO inhibits blood platelet adhesion and prevents thrombus (clot) formation.\(^ {22}\) The second isoform, namely, neuronal NOS (nNOS) is found in neuronal cells which affords NO necessary in neuronal signaling pathways.\(^ {1,4}\) The third isoform is the inducible NOS (iNOS) which is widespread in the body and is an important part of our innate immune system. At the onset of pathogen invasion, this enzyme is over-expressed in macrophages, hepatocytes and smooth muscle cells and generates micromolar levels of NO. Along with various reactive oxygen species (such as peroxide, superoxide and OH radical) also present in infected tissues, NO reduces microbial loads as part of our immune response.\(^ {5,16}\)

In addition, exogenous NO can be generated \emph{in vivo} via delivery of a wide range of organic nitrite and nitrates (such as GTN), S-nitrosothiols (such as SNAP), diazeniumdiolates (also known as NONOates), and inorganic compounds like sodium nitroprusside (SNP) (Fig. 1).\(^ {7,9}\) Most of these compounds have been employed as systemic NO-donor drugs to modulate the concentration of NO to control hypertension, skin and wound infections and destruction of malignant tissues. For example, glycerin trinitrate (Fig. 1) is widely used (under the trade name Nitrostat\textsuperscript{TM} and others) for angina pectoris (chest pain) and solution of SNP is often used for the immediate control of hypertension in intensive care units. Synthetic chemistry plays a critical role in the design of such NO-donating drugs and most pharmaceutical companies are engaged in quest for new and efficient NO drugs with less side effects and better efficacies.

In mammalian tissue, CO is produced via catabolism of heme by the enzyme heme oxygenase (HO).\(^ {23}\) Present in almost all tissues, this enzyme causes ring-opening of the porphyrin macrocycle with the elimination of CO and a green pigment biliverdin.

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![Scheme 1 - Formation of NO from L-arginine by NOS](image1)

![Fig. 1 - Some common NO-donating drugs](image2)
The iron is recycled while biliverdin is further transformed into bilirubin (Scheme 2) and eventually excreted from the body via the urinary pathway. The constitutive isoform HO-2 takes care of the regular heme processing in the liver and spleen; up to 7 cc of CO is produced from such heme catabolism in an adult human per day. Tissue injury often results in elevated levels of localized heme degradation by the inducible form of HO namely HO-1. The typical purple-to-greenish yellow color of bruises results from the rapid heme degradation at the damage site and serves as an easy visible example of this process in our body. A small amount of CO is also produced from lipid peroxidation, xenobiotics (such as halomethanes) and bacteria. CO produced in tissues, binds hemoglobin in the blood and is carried away to the lungs where it is exhaled as CO gas. In diseased states such as asthma, cystic fibrosis and diabetes, elevated production of CO is easily detected in exhaled air.

**Chemistry of NO and CO**

Both NO and CO are nonpolar gaseous molecules which readily diffuse through the lipid bilayers of mammalian cells. NO has one unpaired electron in the π* antibonding level and hence is paramagnetic. This unpaired electron gives rise to its high reactivity; NO readily reacts with dioxygen to afford N₂O₃, NO₂ and other NₓOᵧ species (collectively known as reactive nitrogen species, RNS) which constitute a major portion of smog in urban air. NO is quite soluble in water (1 mM at body temperature) and is converted to NO₂⁻ (Eq. 1) and NO₃⁻ through metabolic pathways and is excreted via the urinary path.²⁴ Although increased concentration of nitrite and nitrate in the urine of patients with chronic inflammation, sepsis or acute microbial infection was noted in the earlier part of twentieth century, their connection with elevated level of iNOS activity in the body has only been recently realized.²⁵ NO also reacts (at a diffusion-controlled rate) with O₂⁻ (and other ROS) to produce peroxynitrite ONOO⁻, which causes rapid nitration of aromatic amino acid residues of proteins (such as super oxide dismutase, SOD). These nitrated proteins serve as hallmarks of inflammation.²⁶

\[
4\text{NO} + \text{O}_2 + 2\text{H}_2\text{O} \rightarrow 4\text{NO}_2^- + 4\text{H}^+ \quad \text{(1)}
\]

CO is a colorless, odorless and tasteless gas with no unpaired electron (diamagnetic). Compared to NO, it is quite inert and resists oxidation (to CO₂) and has low solubility in water.²⁷ Both CO and NO are good ligands and bind transition metals to give carbonyls (metal complexes of CO) and nitrosyls (metal complexes of NO) that constitute a major portion of what is known as organometallic chemistry.²⁸,²⁹ Although both molecules are weak σ-donors, strong π-backbonding results in strong metal-ligand bonding in all these complexes. Extensive research in this area by inorganic chemists have afforded numerous such species, some of which have been employed as exogenous CO- and NO-donating agents to modulate CO and NO concentrations in biological targets (vide infra).

**Physiology and Pathology of NO and CO**

The principal targets of both molecules are heme proteins. The high affinity arises from the strong coordinating property of NO and CO (both good π-acid ligands) to iron-porphyrins (an inorganic reaction). It is now established that sGC is activated
upon NO binding to the heme moiety at the active site and displacing a coordinated histidine.\(^3,22\) The five-coordinate NO-bound heme stays within the core of the protein but the overall conformational change of the protein promotes the activation. Activated sGC catalyzes the conversion of guanosine triphosphate to cGMP which causes vasorelaxation of smooth muscle via a signal transduction cascade. In the blood, NO binds specific cysteine (thiol) residue of the \(\alpha\)-subunit of Hb to form a S-nitrosothiol (S-nitrosohemoglobin) and can eventually dissociate to free NO without interacting with the iron center.\(^30\) It thus serves to regulate the lifetime of NO in its bioactive state. It also readily binds the Fe(II) center of hemoglobin (Hb) to afford nitrosyl-Hb. Reaction of NO with oxy-Hb leads to formation of oxidized Hb (met-Hb) and nitrate which is eventually excreted.

NO is a reactive molecule due to its radical-nature (odd electron in the \(\pi^*\) molecular orbital) and has a short lifetime (in seconds) in human tissues.\(^24\) It is readily converted to NO\(^+\) or NO\(^-\) by one-electron oxidation or reduction respectively. For example, reactions of NO with thiols such as glutathione afford S-nitrosoglutathione which acts as a NO-buffer in cellular matrix. As mentioned above, NO reacts rapidly with superoxide (O\(_2^-\)) to produce peroxynitrite (ONOO\(^-\)), a strong oxidizing agent that causes nitration of amino acids and gives to carbonate radicals via reaction with CO\(_2\). The latter radical also mitigates damage to human tissues.\(^26\) NO also induces DNA damage via deamination of bases and inhibits various iron-containing enzymes (such as ribonucleotide reductase, RNR) and enzymes with active thiol (-SH) group.\(^2,3\) As a consequence, excessive levels (in micromolar range) of NO promotes tissue injury and contributes to several diseases including ulcerative colitis, psoriasis, arthritis, Type 1 diabetes, sepsis, multiple sclerosis and Sjogren’s syndrome.\(^5,6,31\) Increased level of NO has also been shown to be detrimental to tumor cells due to direct damage to DNA and inhibition of DNA synthesis.\(^32\) In addition, sudden increases in NO concentration initiates apoptosis (programmed cell death), characterized by changes in the expression of pro- and anti-apoptotic caspases, cytochrome c relocation, chromatin condensation and DNA fragmentation.\(^33\) Interestingly, low concentrations of NO can help tumor angiogenesis by upregulating endothelial growth factors (VEGF), suppressing T-cell proliferation and inhibiting apoptosis. Thus, NO has a double-faced role in cancer biology.\(^34\)

The reactivity of CO toward heme centers in biology is very similar to that of NO. Since the Hb-binding affinity for CO is 250 times greater than its affinity for oxygen, small amounts of CO dramatically reduce the ability of Hb to transport oxygen. Even binding of CO to one heme-containing subunits of Hb reduces the dissociation ability of partially oxygenated Hb to unload O\(_2\) in the tissues and causes severe hypoxia.\(^26\) Because of these binding characteristics CO is a unique threat to human and CO detectors are now required features of modern residences. When inspired air contains CO levels as low as 0.02%, headache and nausea occur; if the CO concentration is increased to 0.1%, unconsciousness will follow. Binding of CO to Hb affords carboxyhemoglobin (CO-Hb), a very bright red compound that causes the skin of CO poisoning victims to appear pink in death, instead of white or blue. In heavy smokers, up to 20% of the oxygen-active sites can be blocked by CO. Unlike NO, CO does not bind to the Fe(III) centers of heme (as in met-Hb) and the binding affinity of NO for the Fe(II) centers of Hb is 1500 times greater that that of CO.

Another biological target of CO is sGC. Like NO, CO activates sGC to produce cGMP (and vasorelaxation) although the extent of activation is much lower than that caused by NO. Binding of CO to the heme center of sGC does not promote loss of histidine ligation (unlike NO) and gives rise to a six-coordinated Fe(II) center. Recent studies have shown that CO provides protection against reperfusion injury. It is believed that binding of CO to the heme centers of cytochrome c oxidase (thus blocking its O\(_2\)-activating activity) is responsible for such protection. CO is also a key player in modulation of calcium-sensitive potassium (BK) channels. Stimulation of HO-2 during hypoxia and CO production stimulates these channels and play important role as an oxygen-sensor in hypoxic pulmonary vasoconstriction.\(^32\)

At low concentrations, CO exhibits anti-inflammatory and cytoprotective effects, both unexpected (and quite surprising) findings for the “silent killer”. For example, CO attenuates endotoxic shocks and allergen-induced inflammation via suppression of inflammatory cytokine production by mitogen activated protein kinase (MAPK) pathways.\(^17\) In animal models, exposure to CO(g) or application of CORMs has been shown to provide protection against organ graft rejections and injury associated with
balloon angioplasty. These beneficiary effects of CO have spurred extensive research activity in the area of developing new CORMs as exogenous CO-donors by synthetic chemists (vide infra).

**Modulatory Activity Between CO and NO**

Close scrutiny of the effects of NO and CO indicate that these gases do not always work independently, but rather can modulate each other’s activity. The cross talk between the production and physiological function of these two messenger molecules is quite intriguing. Since both molecules activates sGC, cross talk is somewhat expected. Indeed, exposure to CO elevates the level of NO in the body and high concentration of OONO (a result of high NO level) is noted in blood platelets and vascular cells. Conversely, elevated levels of NO during hypoxia induce over-expression of HO-1 to protect lung tissues. As a consequence, higher concentrations of CO and NO are noted in patients with asthma and cystic fibrosis. Enhanced HO-1 activity or exogenous CO application has now been shown to offer cytoprotectivity against toxicity arising from overproduction of NO in sepsis, ischemia and other oxidative injuries. A balance between the levels of CO and NO thus maintains tissue health during injury and inflammation.

**Exogenous NO- and CO-Donors**

Although glycerin trinitrate (GTN, Fig. 1) and nitroprusside (SNP, Fig. 1) have been used for many decades to control hypertension, systematic research on exogenous NO-donors has gained significant momentum following the discovery of the physiological roles of NO. In recent years, the cytoprotective role of CO has also inspired syntheses of designed CO-donors to impede tissue injury during oxidative and inflammatory stress. Both organic and inorganic chemists have pivotal roles in such pursuit and selected examples of products of such endeavor are discussed below.

**NO-donating drugs**

Organic nitrates (such as GTN) and nitrites such as isoamyl nitrite (IMN, Fig. 1) are most widely used for blood pressure control. Selected doses of these compounds are metabolized in human to produce NO at desired levels. GTN is employed as pills, ointments, sprays and patches to induce vasodilation. IMN is also used in the hospitals as an inhalant antidote for cyanide poisoning. NO generated from IMN competes with CN at the heme site of cytochrome c oxidase and exerts its inhibitory effects. SNP is the oldest inorganic compound used as an exogenous NO-donor. Although loss of cyanide ligands from SNP in the body often limits its use in tackling prolong hypertension, intravenous injections of SNP are sometimes used in the hospitals to combat hypertensive emergency. The S-nitrosothiol agent SNAP (Fig. 1) has been employed as a NO-donor drug in animals for protection against hemorrhagic shock and SNAP-containing creams have shown success in treating cutaneous leishmaniasis. The diazeniumdiolates such as DEA-NO (commonly known as NONOates) produce 2 equivalents of NO via a pH-dependent pathway (Eq. 2). Discovered by Drago and coworkers during mid-1960, these compounds did not draw attention as NO-donors until 1980. Elegant use of organic synthesis has afforded a series of diazeniumdiolates that can release NO with $t_{1/2}$ values from seconds to days depending on the R group. Toxicity of the amine end products ($R_2NH$) often raises concern in the use of NONOates as NO-donors. However, NONOates derived from benign R groups (such as PROLI-NO, Fig. 1) have now been synthesized. In recent years simple nitrites have been explored as NO-donors. Topical applications of ointments of NaNO$_2$ and ascorbic acid have shown success in treating cutaneous inflammation.

\[ R - N - N - O - \text{Na}^+ \xrightarrow{\text{H}^+} R - N - \text{H} + 2\text{NO} + \text{Na}^+ \] 

(2)

In recent years, NO-donors have been incorporated in various polymeric matrices and such composites have been utilized to deliver NO to selected targets under controlled conditions. Since presence of NO in the vascular system inhibits blood platelet adhesion and clot formation, exogenous NO-donors have been employed to prevent blood clotting on surgical equipments, vascular stents and pacemaker contacts. Since both NO(g) and NO-donating drugs have been shown to drastically reduce microbial (bacterial, fungal and parasitic) loads in human and animal models, agents like SNAP and DEA-NO have been incorporated in different polymeric materials to treat chronic infections, wounds, diabetic leg ulcers via transdermal delivery of NO. These formulations are particularly effective against various
antibiotic resistant strains of common pathogens such as *E. coli* and *Staphylococcus aureus*. In addition to eradication of the pathogens, NO assists in collagen synthesis, tissue regeneration and, hence, the overall wound healing process.

Systemic NO-donors such as GTN cannot be employed to destroy malignant cells via NO-induced apoptosis due to lack of control on NO release; the drug goes everywhere in the body and NO is released via enzymatic and nonenzymatic (such as heat or pH) pathways. This inexorability of NO release is a major drawback in delivering high concentrations of NO (in micromolar range) to malignant locales since similar levels of NO in other parts of the body initiate life-threatening hypotensive episodes. Controlled delivery of light-triggered NO is however quite feasible and hence photoactive transition metal nitrosyls (NO complexes) have drawn special attention as NO donors.\(^44\) NO has been employed as a ligand in inorganic chemistry for quite sometime and several metal nitrosyls exhibit photoactivity. Although attempts with iron nitrosyls like Roussin’s red and black salt (RRS and RBS, Fig. 2) have been marred by unpredictable NO release and decomposition,\(^45\) ruthenium nitrosyls derived from N-donors (like NH\(_3\), pyridine) (Fig. 3) have shown great promise as biocompatible photoactive NO-donors.\(^{46,47}\) Among the NO-donors shown in Fig. 3, the porphyrin-based nitrosyls are somewhat disappointing. Despite good sensitivity towards light, the high affinity of NO toward metal porphyrins greatly reduces their overall NO delivering capacity; the rates of NO dissociation and recombination are comparable and hence such NO-donors have limited utility. This problem has been circumvented via careful design of non-porphyrin polydentate ligands. Ruthenium nitrosyls such as \([\text{Ru(PaPy})_3](\text{NO})|(\text{BF}_4)_2\) (Fig. 3) exhibit excellent NO photolability due to low NO recombination rates. The polydentate nature of the ligands ensures no ligand dissociation (like SNP) in biological system with such nitrosyls.

The photolability of NO in most metal nitrosyls arise from \(d_x(M) \rightarrow \pi^*(\text{NO})\) transitions.\(^48\) In ruthenium nitrosyls, such transitions occur in the 300-450 nm region. As a consequence, ruthenium nitrosyls exhibit NO photolability upon exposure to UV light which is often detrimental to biological targets. Attachment of suitable dye molecules as light-harvesters has recently afforded ruthenium nitrosyls (Fig. 4) that rapidly release NO upon exposure to visible light.\(^48\) This type of sensitization allows use of ruthenium nitrosyls in NO delivery to biological target without the need of harmful UV light. Some of these dye-nitrosyl conjugates have recently been employed to promote NO-induced apoptosis in cancer cells\(^49\) and eradicate bacterial colonies\(^50\) under the total control of light.

**Fig. 2** – Some common NO-donating inorganic iron nitrosyls. [RRS = Roussin’s red salt, RBS = Roussin’s black salt, Na[(FeNOS)]\(_3\) = Cubane-type iron nitrosyl].

**Fig. 3** – Selected photoactive ruthenium nitrosyls with N-donor ligands used as NO-donors. [Por = porphyrin; bpb and PaPy\(_3\) are non-porphyrin ligands with carboxamido-N donors (see Ref. 47).
The results strongly attest the fact that inorganic chemists could play important roles in this area of drug development.

**CO-donating drugs**

The cytoprotective action of CO has inspired several groups to identify exogenous CO-donors (CORMs) for controlled delivery of CO to safeguard against cardiac tissue damage, organ graft rejection and post-operative complications. Initial studies focused on metal carbonyls like \([\text{Mn}_2(\text{CO})_{10}]\) and \([\text{Ru}(\text{CO})_3\text{Cl}_2]\) (Fig. 5) which release CO upon dissolution and/or exposure to light. These carbonyls were employed as solutions in DMSO to avoid problems related to their solubility in biological media. In recent years, the water soluble \([\text{Ru}(\text{CO})_3\text{Cl(glycinate)}]\) (CORM-3, Fig. 5) has shown promise in a number of studies. Another iron carbonyl, namely \([\text{Fe}(\text{CO})_2(S-N)_2]\) (CORM-S1, Fig. 5), has also been reported to exhibit light-dependent CO liberation. The rates of CO release from the rhenium carbonyl \([\text{Re}(\text{L})_2(\text{CO})_3\text{Br}_2]\) (\(\text{L} = \text{py, im, and other N-donor ligand, Fig. 5}\)) can be varied via change of the N-donor ligand. CORMs are not restricted to transition metal carbonyls. The boranocarbonate anion \([\text{H}_3\text{BCO}_2]^2-\) releases CO with \(t_{1/2} = 21\) min at \(pH\) 7.4. This water-soluble CORM induces vasorelaxation in isolated tissues and causes drop in arterial pressure \(in vivo\) via slow release of CO (and boric acid).

In animal models, these CO-donors have induced vasodilatation, inhibited platelet aggregation, and provided protection against ischemia, reperfusion injury and lung inflammation. However, unlike NO-based pharmaceuticals, the understanding of the physiology of CO is somewhat limited at this time and protocols for safe delivery of CO to treat human diseases are only in their developing phase. Consequently, CORMs have yet to be employed in clinical trials (in human). Also the number of biocompatible CORMs is quite limited. Inorganic chemists could fill this void by synthesizing new CORMs for human trials.

**Future Challenges**

Successful delivery of NO or CO selected targets with exogenous NO- and CO-donors depends critically on their (a) stability in biological media, (b) toxicity, (c) dispersive properties and (d) ease of exiting the body. The synthetic challenges are therefore quite demanding. In addition, clear understanding of
the physiology and pharmacology of these drug molecules is essential. The chemistry of metal complexes with CO (metal carbonyls) and NO (metal nitrosyls) is an established field of inorganic chemistry. However, this field needs to be revisited with specific requirements in mind. Conventional organometallic ligands such as cyclopentadiene or allylic fragments might not be useful in the synthesis of NO- and CO-donors for pharmacological use because of their toxicity. Since controlled delivery is a primary requirement, one must think of a triggering mechanism for the release of these small molecules. Two such triggers have drawn attention in recent years. The drug can release NO or CO upon reduction by cellular reductant such as glutathione or upon exposure to light. In order to confer such property to the designed drug, one has to make good use of the redox parameters and fundamental principles of photochemistry. For stability, the chemist has to design a multidentate ligand and to avoid toxicity the design should include more tolerable units such as amino acids. Solubility in biological media often restricts use of specific compounds as drugs. The design of exogenous NO- and CO-donors therefore must consider the overall solubility of the final compound. The kinetic parameters of NO or CO release for these donors also have to be calibrated properly for slow or rapid delivery of these small molecules to elicit the desired drug effects.

For targeted delivery, accumulation of the drug at or near a specific site is a primary requirement. Recent developments in biocompatible polymers offer a wide variety of vectors that could be used to place the drug-polymer composites close to the desired biological targets. Inorganic chemists could make use of silicate-based hydrogels, zeolite-based porous carriers and related polymers to deliver NO- or CO-donors as bandages, patches, or powders. Even systemic drugs such as GTN and SNP (Fig. 1) can be employed in this manner. Expertise in material chemistry will be quite helpful in designing such composites in the future. Examples of NO- and CO-donors as shown in Figs 2-5 demonstrate the diverse nature of “inorganic” drugs that could be designed for more precise and efficient delivery of NO or CO to biological targets. Although syntheses of these kinds of molecules fall right within the boundaries of inorganic and bioinorganic chemistry, a systematic and synergistic approach will be essential in the future development of this emerging field of designed NO- and CO-donating drugs.

Conclusions

Research to date has clearly established that both NO and CO are essential signaling molecules and modulation of their in vivo concentration could be the key to treatment of several maladies. Severe toxicity of these two molecules however requires strict control on such manipulation. Exploration of the biochemical pathways of NO and development of NO-based pharmaceuticals had an early start (in 1970s) while the role of CO in human physiology has begun to emerge since 1990s. As a consequence, medical application of exogenous CO-donors has not yet been achieved while NO-donating drugs are routinely prescribed or employed in hospitals around the world. The high level of research activity in the area of CO physiology is a strong indication that suitable CORMs will eventually transpire as a new set of pharmaceuticals. It is true that the “toxic” label of these two gases will not go away any time in the future. However, compounds that could deliver either of these two toxic twins safely and selectively to biological targets to elicit desired drug actions will always be welcome in health and medicine.

Acknowledgement

The author acknowledges support from the National Science Foundation (grants CHE-0553405 and CHE-0957251) for support of his research in the area of development of NO- and CO-donors.

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