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A gentle introduction to gasotransmitters with special reference to nitric oxide: biological and chemical implications

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Abstract: Nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) are gaseous molecules of major impact in biology. Despite their toxicity, these molecules have profound effects on mammalian physiology and major implications in therapeutics. At tiny concentrations in human biology, they play key signaling and regulatory functions and hence are now labeled as "gasotransmitters." In this literature survey, an introduction to gasotransmitters in relevance with NO, CO and H_2S has been primarily focused. A special attention has been given to the conjoint physiological, pathophysiological and therapeutic aspects of NO in this work. In addition to the aforementioned elements of the investigation being reported, this report gives a detailed account of some of the recent advancements covering the NO release from both the nitro as well as nitroso compounds. The importance of the metallic center on the eve of producing the reduction center on NO and to develop photolabile properties have been elaborated within the effect of a few examples of metallic centers. Also, theoretical investigations that have been reported in the recent past and some other current theories pertaining to NO chemistry have been enlightened in this review. From the overall study, it is eminent that a number of facts are yet to be explored in context with NO for deeper mechanistic insights, model design for these molecules, other key roles and the search to find the best fit formalism in theoretical chemistry.

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Introduction

In the 1980s, nitric oxide (NO) was discovered to be one of the most important physiological regulator (Ignarro 1987, 1989), playing a key role in signal transduction and cytotoxicity, possibly one of the biggest surprises in biological chemistry. Since then, it is considered as a fundamental component in the fields of neuroscience, physiology and immunology. On the basis of these, NO was voted as "Molecule of the Year" in 1992 by the journal "Science," published by New York Academy of Sciences (Koshland 1992, Stamler et al. 1992). The importance of the molecule became a front page news in 1998 when Robert F. Furchgott, Louis J. Ignarro and Ferid Murad were awarded the Nobel Prize for Medicine and Physiology for identifying NO as a signaling molecule in the cardiovascular system. To date, NO has been associated with numerous physiological pathways including platelet aggregation and adhesion, neurotransmission, synaptic plasticity, vascular permeability, hepatic metabolism, senescence and renal function (Ignarro 2000, Kalsner 2000, Butler and Nicholson 2003, Vincent 2010). At higher (μM) levels, NO also plays a key role in host immunity (Fang 1999) and tumor suppression (Moncada et al. 1998, Burke et al. 2013). The list of abbreviations or acronyms used in the discussion is given in Table 1.

Similarly, carbon monoxide (CO) has long been considered an enemy to human health because of its harmful nature, causing death by asphyxiation. It is produced as a byproduct in the combustion of fossil fuels, in metabolism and in the burning of tobacco (Wu and Wang 2005). The toxicity of CO is attributed in part to its high affinity to hemoglobin (Hb; Douglas et al. 1912, Haldane 1927, Weaver 1999, Gorman et al. 2003). Not understanding the significance of this discovery at the time, the endogenous synthesis of CO was seen as a metabolic waste product of heme oxygenase (HO)-catalyzed heme degradation (Tenhunen et al. 1968, Barinaga 1993).

Table 1: List of abbreviations/acronyms used in the text.

Abbreviation/acronym	Full form	Abbreviation/acronym	Full form
H_2S	Hydrogen sulfide	TST	Thiosulfate:cyanide sulfurtransferase
NO	Nitric oxide	CNS	Central nervous system
CO	Carbon monoxide	ER	Endoplasmic reticulum
μM	Micromolar	ROS	Reactive oxygen species
COHb	Carboxy hemoglobin	NOS	NO synthase
HO	Heme oxygenase	SOD	Superoxide dismutase
ppm	Parts per million	PTP	Protein tyrosine phosphatise
nM	Nanomolar	PERK	Protein kinase-like ER kinase
CSE	Cystathionine-γ-lyase	EDHF	Endothelium-derived hyperpolarizing factor
CAT	Cysteine aminotransferase	ATP	Adenosine triphosphate
CBS	Cystathionine-β-synthase	NMDA	*N*-Methyl-D-aspartate
3-MST	3-Mercaptopyruvate sulfurtransferase	LTP	Long-term potentiation
EDRF	Endothelium-derived relaxing factor	GABA	γ-Aminobutyric acid
P5P	Pyridoxal-5′-phosphate	V-H^+ATPase	Vacuolar-type H^+ATPase
Hcy	Homocysteine	LP	Lipopolysaccharides
SAM	*S*-Adenosyl-L-methionine	VD	Vascular dementia
Aβ	Amyloid-β	MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
AD	Alzheimer's disease	DS	Down's syndrome

However, the breakthrough discovery detailing the possible physiological role CO may play in the mammalian system came in 1987 when Brune and Ullrich showed that, like NO, CO can also activate soluble guanylate cyclase (sGC; Verma et al. 1993). Since then, CO was found to have effective anti-inflammatory, anti-apoptotic and anti-proliferative properties (Wu and Wang 2005). In a similar fashion, hydrogen sulfide (H_2S) has been known for hundreds of years as a poison and toxic pollutant (Mancardi et al. 2009). Fiedler in 2008 reported this gas as an anxiety inducer. Long-term exposure (even low concentration) may decline cognitive performance (Firorucci et al. 2006, Kobayashi and Fukushima 2008, Gupta et al. 2010). Finally, it came to surprise when in 1989 endogenous sulfide was reported to be present in the tissues of brain in rat (Warenycia et al. 1989) and in normal human post-mortem brainstem (Goodwin et al. 1989). It is now recognized that H_2S is produced endogenously in mammals in the brain, blood vessels, liver and kidney at low micromolar levels via the action of cysteine metabolic enzymes: cystathionine-β-lyase (CSE), cystathionine-β-synthase (CBS) and 3-mercaptopyruvate sulfurtransferase (3-MST; Li et al. 2011). H_2S is thought to be involved in various physiological and pathological processes in human beings. It is now being considered as the third gasotransmitter after NO and CO (Wang 2002, Zhao et al. 2002, Lowicka and Beltowski 2007, Tinajero-Trejo et al. 2013).

In the microbial world, all three gases have important long-recognized roles: NO is an intermediate in denitrification (Lundberg et al. 2004) and is detoxified by pathogens (Fang 2004, Bowman et al. 2011), CO is an unusual carbon and energy source (King and Weber 2007), and H_2S is well known to all microbiologists as a product of anoxic sulfate respiration (Slonczewski and Foster 2009). Each gas is reported to have valuable therapeutic applications (Bannenberg and Vieira 2009, Szabo 2010). In our continuous interest toward gasotransmitters and the design of their metallic models (Mir et al. 2017a, Mir and Maurya 2018a,b), this review article is a simple and lucid introduction of its form. After presenting the inputs of the signaling concept, the article is mainly confined to the physiological and pathophysiological role of NO.

Signaling molecules: concept of "gasotransmitter"

Signaling molecules (Mustafa et al. 2009) may be in all sizes and chemical dispositions, ranging from relatively large proteins, lipids and peptides through biogenic amines and amino acids, to gaseous molecules. On the basis of the variations in the properties of signaling molecules that depend upon their chemical nature, signaling molecules are broadly classified as neurotransmitter and gasotransmitter. Chemicals traditionally recognized as neurotransmitters are compounds produced by neurons and stored in vesicles until stimulation of the neurons trigger their release (Figure 1, top). They bind

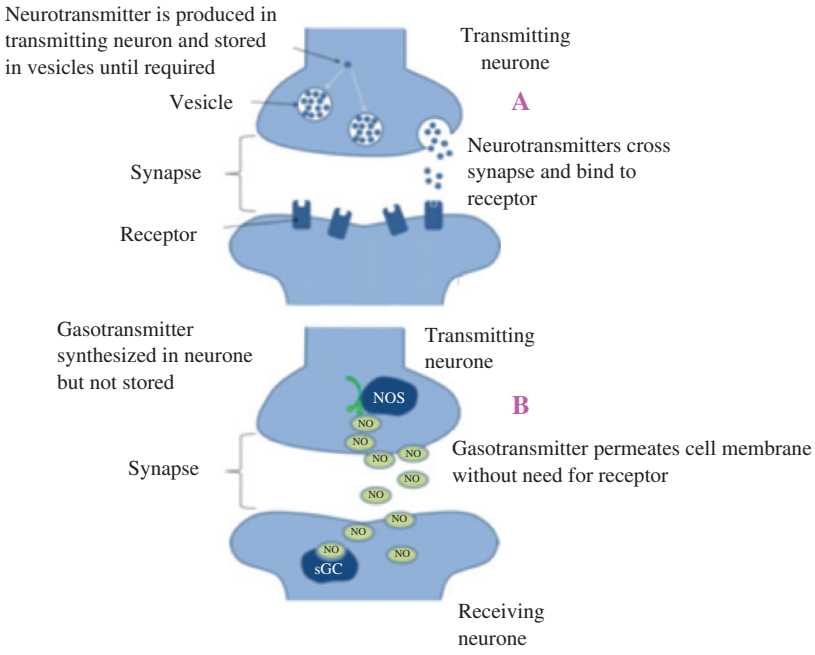


Figure 1: Schematics of the mechanism of neurotransmitter (1-1a, top) and gasotransmitter (1-1b, bottom) action.

to specific membrane receptors in a neighboring cell to produce a physiological effect. Amine, amino acid and peptide neurotransmitters share a number of features. They are stored in synaptic vesicles, so that with each nerve impulse, only a small proportion of the stores is released, leaving a large safety net of reserve pools. Release involves exocytosis, in which the vesicle fuses with the plasma membrane to expel its contents. These neurotransmitters bind to receptor proteins on the external surface of adjacent membranes. Inactivation occurs by reuptake of neurotransmitters into the releasing nerve terminal or adjacent glia, by enzymatic degradation, or by simple diffusion away from the synapse. Gasotransmitters are a subfamily of endogenous molecules of gases or gaseous signaling molecules (Li et al. 2011). They function without receptors because they are freely permeable to cell membranes (Figure 1, bottom; Wang 2004, Allan and Morris 2014). Unlike neurotransmitters, gasotransmitters are not stored in vesicles;' thus, they must be rapidly synthesized in response to stimulation. There is no exocytosis upon the release of gasotransmitters, and in fact, gases are not contained by membranes at all. They can freely enter a cell with no need for receptors or active endocytosis to influence a cell. The term "gasotransmitter," which refers to a gaseous messenger molecule involved in any signaling process, was first coined by Rui Wang in 2002. The criteria for establishing signaling molecules as gasotransmitter are as follows:

(i) They are small gaseous molecules.
(ii) They are freely permeable to cell membranes.
(iii) They are endogenously and enzymatically produced and regulated.
(iv) They have specific well-defined biological roles at specific concentrations.

The scientific community was thrilled with the final verdict that the mysterious endothelium-derived relaxing factor (EDRF), a vasorelaxant substance synthesized and secreted from endothelial cells, was a gaseous molecule (Furchgott and Zawadzki 1980). The conclusion that NO is an endogenous gaseous molecule, termed gasotransmitter, triggered the exploration of other possible gasotransmitters, including CO and H_2S (Wang 2002).

The discovery of NO, CO and H_2S as small signaling gasotransmitters has developed a new type of science that endogenously derived gases could elicit crucial biological functions, as well as contribute to the pathogenesis of human diseases (Hermann et al 2012). Several other gases are currently under investigation to determine if they too act as endogenous mediators, including acetaldehyde, sulfur dioxide, dinitrogen oxide and ammonia. Overall, these new insights have improved our understanding of the physiological importance of gasotransmitters not only in physiological functions but also in the pathogenesis of human diseases.

Endogenous production of NO, CO and H_2S

Nitric oxide (NO)

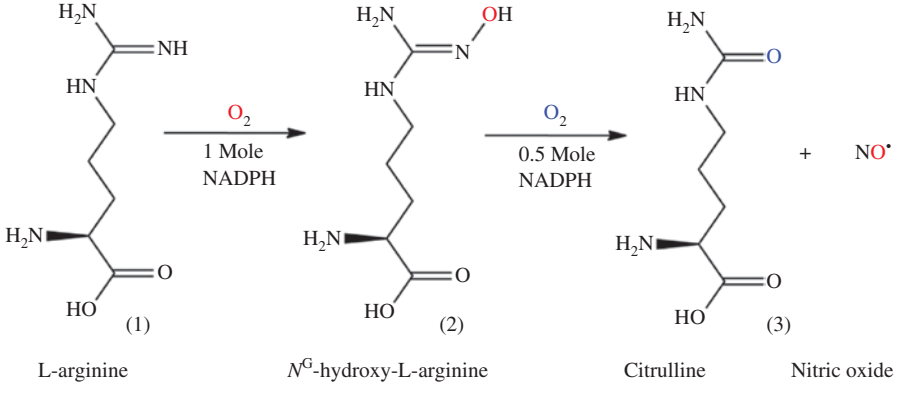
The biosynthesis of NO in bulk is catalyzed by a small family of multidomain, heme-containing enzymes (hemeproteins) called nitric oxide synthases (NOSs) that specifically catalyze the oxidation of L-arginine (**1**) to N^G-hydroxy-L-arginine(**2**) and eventually to L-citrulline (**3**) and NO (Scheme 1). The overall reaction is a five-electron oxidation, with three electrons contributed by nicotinamide adenine dinucleotide phosphate (NADPH) and two from O_2. The NOS catalytic cycle is composed of two successive O_2-dependent mono oxygenation reactions with a stable intermediate, N^G-hydroxy-L-arginine (NHA; Santolini 2011). Considering the breadth of physiologic actions purported for NO, it is not surprising that there are multiple isoforms of this enzyme. These include a constitutive neuronal NOS (nNOS or NOS I; Schmidt et al. 1991), an endotoxin- and cytokine-inducible NOS (iNOS or NOS II; Hevel et al. 1991, Stuehr et al. 1991) and a constitutive endothelial NOS (eNOS or NOS III; Pollock et al. 1991). These isozymes are encoded by three distinct genes (Marsden et al. 1993, Xu et al. 1993). All NOS isoforms produce NO from oxygen and the guanidine nitrogen of L-arginine.

In the linings of blood vessels, the endothelial isoform of this enzyme (eNOS) generates nanomolar levels of NO, which in turn activates sGC to generate cyclic guanosine monophosphate (cGMP). Diffusion of cGMP into the smooth muscle of the inner linings causes vasodilation and regulates blood pressure by maintaining a steady flow (Ignarro 2000, Murad 2006). In addition, NO inhibits blood platelet adhesion and prevents thrombus (clot) formation (Keefer 2003). The second isoform, namely, nNOS, is found in neuronal cells that afford NO necessary in neuronal signaling pathways (Kalsner 2000). The third isoform is the iNOS that is widespread in the body and is an important part of our innate immune system. At the onset of pathogen invasion, this enzyme is overexpressed 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 (Fang 1999, 2004).

Structure and function of NOS

Mammals produce three NOS isoforms: eNOS (cardiovascular system), nNOS (nervous system/brain) and iNOS (immune system). The crystal structures of the heme domain for all three isoforms have been determined. It is a remarkably complex homodimeric enzyme with isoforms ranging in size from ~300 to 360 kDa for the holoenzyme. Each NOS monomer consists of two major regions sheltering five cofactors (Figure 2). The C-terminal reductase region contains flavin adenine dinucleotide and flavin mononucleotide with the reduced form of NADPH as a co-substrate (Marletta et al. 1998), while the N-terminal oxidase region includes a cysteine-coordinated P450-type heme active site (McMillan and 1995, Crane et al. 1997), a tetrahydrobiopterin (BH_4) cofactor (Mayeret al. 1991) and the arginine substrate binding pocket. Homodimerization of the oxidase region is mediated by an inter-dimeric Zn^{II}-tetrathiolate (Ludwig and Marletta 1999). Although NOS executes monooxygenase chemistry typical of a P450-type heme, the overall structure of the oxidase region is entirely different from the archetypal cytochrome P450 fold (Crane et al. 1997). Besides this, the connecting part between the reductase and oxidase areas serves as a docking interface for calmodulin (CaM), a small regulatory, calcium-binding protein.

NOS catalysis begins at the heme of the oxidase region. The oxidase heme works electrons shuttled from



Scheme 1: Biosynthesis of NO.

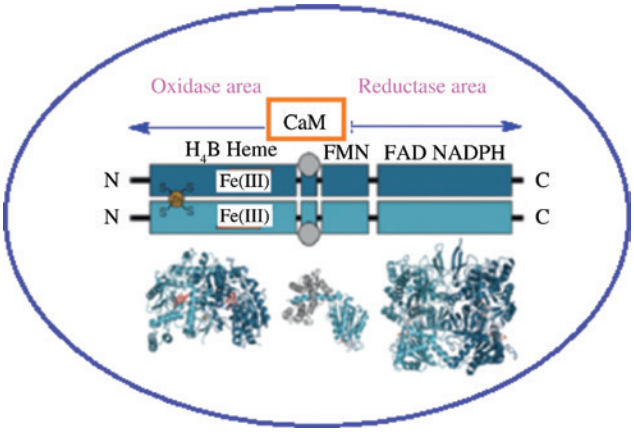


Figure 2: Organization of NOS with representative structures.

the reductase region to activate O_2. Arginine substrate binds within 4 Å of the O_2-binding face of the heme, stabilized by a salt bridge with Glu-377 and an extended hydrogen-bonding network (Figure 3). The essential BH4 cofactor also binds in close proximity to the heme, hydrogen bonding to a heme propionate that in turn hydrogen bonds to the α-amino group of the substrate arginine. The BH_4 is sandwiched between two conserved aromatic residues (Phe-476 and Trp-463) that provide stabilizing π-stacking interactions (Aoyagi et al. 2001).

The reductase region is responsible for feeding electrons to the oxidase domain from the NADPH electron donor. Two flavin cofactors, flavin adenine dinucleotide and flavin mononucleotide, are engaged to shuttle electrons from NADPH (Hevel et al. 1991, Mayer et al. 1991). The structure of the NOS reductase region is well characterized and bears striking structural similarities to other NAD(P)H-binding flavoproteins (Figure 4). Indeed, the NOS reductase domain shares 60% sequence similarity and concomitant structural homology with cytochrome P450 reductase (Garcin et al. 2004).

The small region between the oxidase and reductase domains is crucial for the regulation of NOS activity. This large α-helical linker presents a recognition motif for CaM. Ca^{2+}-triggered binding of CaM to the linker region is a prerequisite for efficient electron transfer from reductase to oxidase regions (Panda et al. 2001). The requirement for CaM/Ca^{2+}-binding convenes a strict point of regulation over NOS activity, coupling intracellular Ca^{2+}levels with NO production. The regulatory role of the CaM-binding region is crucial for reversible control overproduction of NO signals from eNOS and nNOS in vasculature and nerve tissue, respectively (Roman et al. 2002). In contrast, iNOS activity is controlled by transient transcriptional upregulation in immune cells. The iNOS binds CaM irreversibly even in the presence of low, intracellular Ca^{2+} levels and is, therefore, constitutively activated (Roman et al. 2002).

Mechanism of NOS Catalysis

NOS catalysis proceeds in two steps. The first step, conversion of L-arginine to NHA, is generally thought to proceed as a traditional P450 reaction. The main difference is that BH_4 serves as the source of the electron required to reduce the oxy complex to the peroxy level (Hurshman et al. 1999, Wei et al. 2001, 2003) to form a cationic pterin radical (Stoll et al. 2010). Presumably, the radical is reduced back to BH_4 by the flavin reductase. The second step of the reaction, the oxidation of NHA to L-citrulline and NO, has been more challenging to unravel. However, data from several sources are consistent with one of the two mechanisms shown in Figure 5. In the non-BH_4 radical mechanism, the proximal O atom of the oxy complex abstracts an H atom

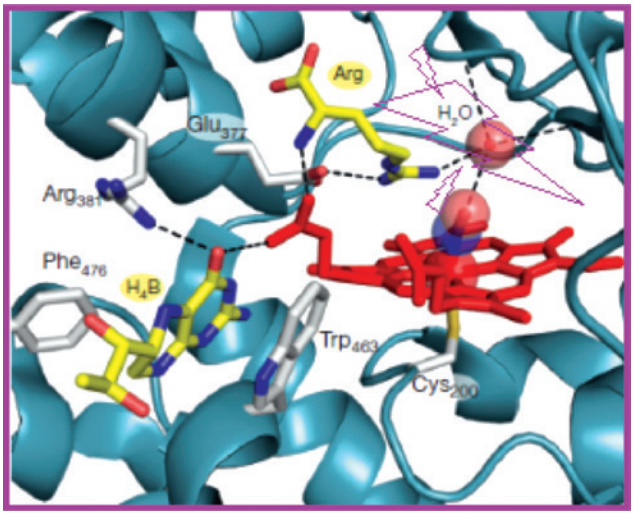


Figure 3: Substrate and cofactor interactions in heme pocket.

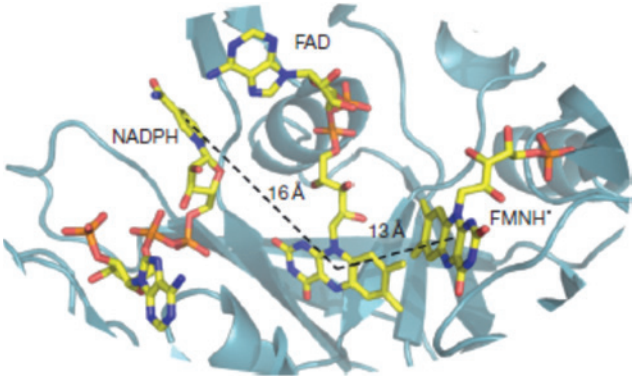


Figure 4: Redox cofactors of the NOS reductase area.

from NHA to give the hydroperoxy species (Huang et al. 2001). The cyclic intermediate collapses to give the products. In the BH_4 radical mechanism, the oxy complex does not abstract the H atom of NHA, but instead BH_4 reduces the oxy complex to the peroxy intermediate followed by the formation of the cyclic intermediate. This intermediate collapses to give NO^- and L-citrulline. The BH4 radical then is reduced by NO^- to give NO. A BH_4 radical does indeed form during the oxidation of NHA, but at the end of the reaction cycle, the radical is reduced back to BH_4 (Wei et al. 2003). What remains unknown is how the BH_4 radical is reduced. Forming NO^- as shown in Figure 5 balances the electron count, but the precise mechanism of back electron transfer to the NO^- radical remains an open question. The mechanism by which NO is formed is similar for all types of NOS.

Carbon monoxide (CO)

Long before the concept of gasotransmitters was even established (Wang 2004), the scientific community was aware that living organisms can endogenously synthesize CO (Sjöstrand 1949, 1951, Coburn et al. 1963). In 1966, it was reported that CO was generated through the degradation of senescent red blood cells, but it took 20 more years to identify and characterize the enzyme HO, which is responsible for the generation of CO by breaking down heme (Tenhunen et al. 1968). Rapid degradation of free heme is physiologically important because of heme toxicity. In the heme degradation process, three reaction products are generated: CO, ferrous iron and biliverdin-IX a (blue-green pigment), which is then further converted into bilirubin-IX a (yellow pigment) by the action of biliverdin reductase (Figure 6; Tenhunen et al. 1968). The iron is recycled, while biliverdin is further transformed into bilirubin and eventually excreted from the body via the urinary pathway. This process can be easily observed when one gets a bruise. During an injury, a dark red/purple coloration is observed, which arises from deoxygenated Hb that is released from the lysed red blood cells. The released heme is then oxidatively degraded by HO with the formation of biliverdin, which is responsible for a green tinge. Later, biliverdin is reduced into bilirubin resulting in a yellow coloration (Johnson et al. 2003). Although most of the heme oxidation occurs in the liver and spleen, HO is ubiquitously expressed in mammalian cells (Tenhunen et al. 1968). This gives HO the potential to continuously produce CO.

Three isoforms of HO have been identified, but only two, HO-1 and HO-2, appear to be active enzymes (Otterbein and Choi 2000). Initially, it was believed that the known antioxidant properties of both biliverdin and bilirubin could readily account for the benefit in the scenario of tissue injuries and other diseases involving oxidative stress processes. Thus, CO was thought of as an unimportant byproduct that was rapidly removed by Hb. Only 2 years later, it was discovered that CO had similar vasodilatory effects as those observed for NO. This finding generated

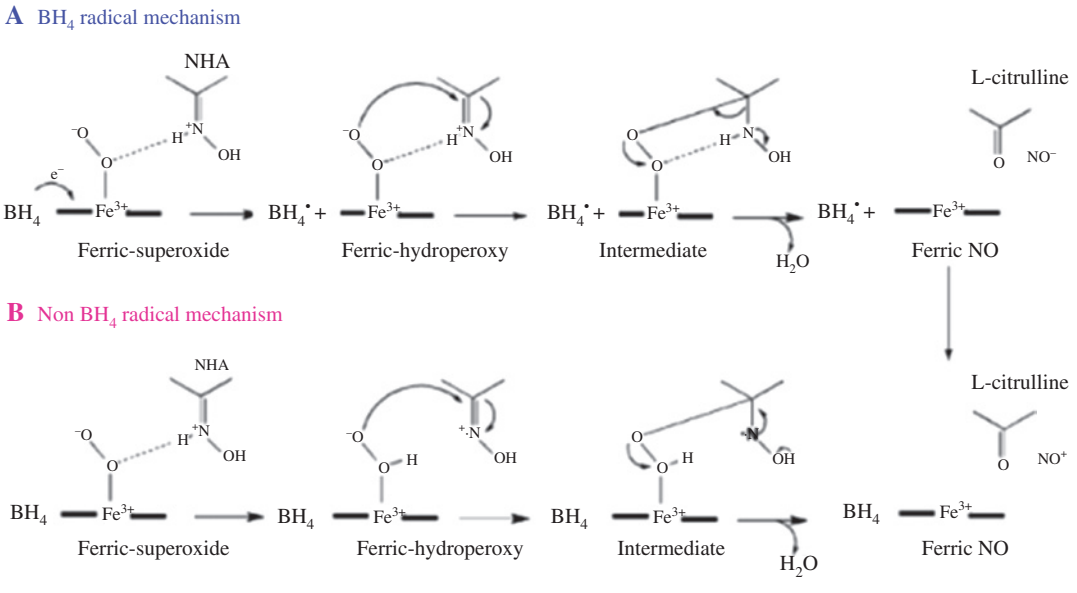


Figure 5: Two possible mechanisms (A) and (B) for the oxidation of N^G-hydroxy-L-arginine (NHA) by NOS.
In the BH4 radical mechanism, BH4 reduces the oxy complex to the peroxy species, which then forms the cyclic intermediate. This collapses to give L-citrulline and NO^-. The BH_4 radical then is reduced by NO^- to give NO. In the non-BH_4 radical mechanism, the source of the electron is the substrate itself rather than BH4, which gives the ferric-peroxy species. The cyclic intermediate then collapses to give the final products.

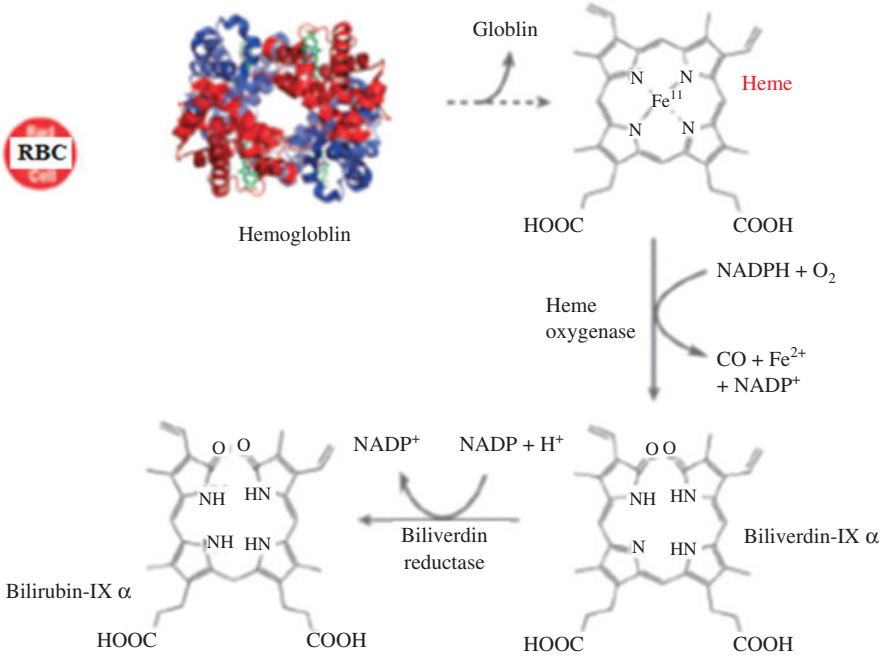


Figure 6: Mechanism of hemoglobin degradation of red blood cells with the generation of CO by heme oxygenase (HO).

the hypothesis that CO may also have a biological role as a mediator of cellular functions similar to NO and led to the clear proposal "…that CO is a neural messenger associated with physiologic maintenance of endogenous cGMP concentrations" (Verma et al. 1993). This discovery spurred an extensive investigation of the biological roles and mechanisms of action of CO, which firmly established CO as an important gaseous messenger molecule.

Hydrogen sulfide (H_2S)

In mammals, H_2S is endogenously produced by enzymatic reactions, even if some nonenzymatic pathways are involved in the biochemistry of H_2S. It is present in micromolar concentrations in blood (Zhao et al. 2001). In fact, in mammalian tissues, H_2S is synthesized from L-cysteine either via pyridoxal-5′-phosphate (P5P)-dependent enzymes, CBS and CSE (Wang 2012), or via the more recently described P5P-independent cysteine aminotransferase (CAT)-3-MST pathway (Shibuya et al. 2009) with important regulatory roles in the nervous and cardiovascular systems and in the regulation of cell and whole-body metabolism (Szabo 2010). L-Cysteine is a sulfur-containing amino acid derived from alimentary sources, synthesized from L-methionine through the so-called "*trans*-sulfuration pathway" with homocysteine as an intermediate (Figure 7) or liberated from endogenous protein (Yap et al. 2000, Meier et al. 2001).

Figure 8 summarizes the pathways that catalyze the endogenous H_2S production. Fascinatingly, these

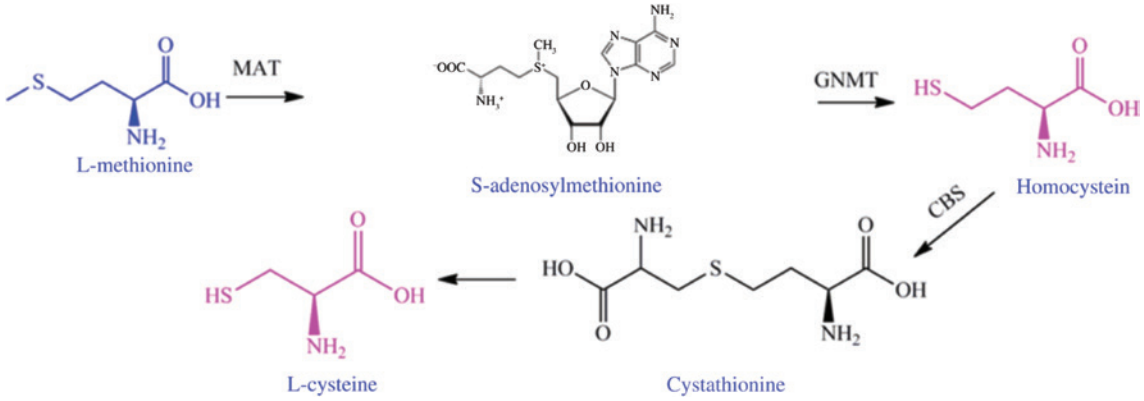


Figure 7: Synthesis of L-cysteine from L-methionine through *trans*-sulfuration pathway (Mancardi et al. 2009).
MAT: methionine adenosyltransferase; GNMT: glycine *N*-methyltransferase; CBS: cystathionine β-synthase.

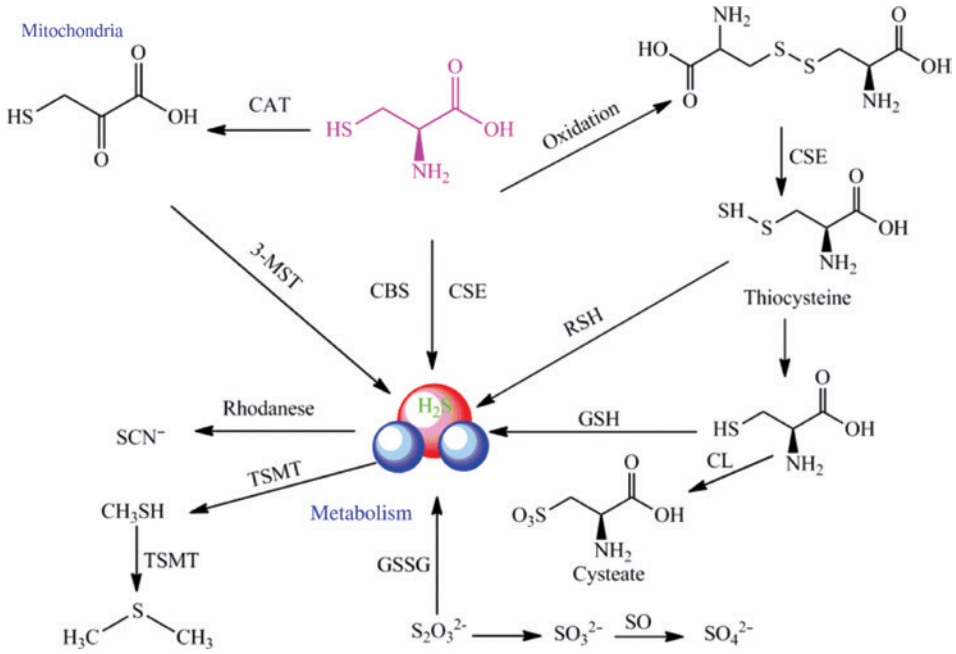


Figure 8: Biosynthesis pathways of H_2S generation in mammalian cells.
CSE: cystathionine-γ-lyase; CBS: cystathionine β-synthase; CAT: cysteine aminotransferase; 3-MST: 3-mercaptopyruvate sulfurtransferase; GSSG: oxidized glutathione; GSH: reduced glutathione; TSMT: thiol *S*-methyltransferase; RSH: a thiol-bearing intermediate; CL: cysteine lyase; SO: sulfite oxidase.

enzymes are evolutionarily conserved and ensue in many lower species as well as in mammals. H_2S is produced from L-cysteine by four separate pathways (Caliendo et al. 2010, Li et al. 2011, Chan and Wallace 2013): (i) CBS acts on L-cysteine to produce H_2S and L-serine; (ii) CSE forms thiocysteine from cystine, which then rearranges to form H_2S; (iii) CAT catalyzes the reaction of L-cysteine with keto acids (e.g. α-ketoglutarate) to form 3-mercaptopyruvate, which is then desulfurated by 3-MST to form H_2S; and (iv) cysteine lyase converts L-cysteine and sulfite to L-cysteate and H_2S. P5P is required as a necessary cofactor by CBS, CAT, CSE and cysteine lyase, whereas 3-MST is zinc dependent. CAT and 3-MST are both mitochondrial and cytosolic, whereas CBS and CSE appear to be exclusively cytosolic. Manifold chemical and biochemical catabolic fates await newly synthesized H_2S, and many more are probably still to be discovered (Geng et al. 2004, Whiteman et al. 2004, Chang et al. 2008, Li et al. 2011), viz., peroxynitrite, superoxide and hydrogen peroxide.

Chemistry and biology of NO, CO and H_2S

Nitric oxide (NO)

NO has long been considered as an atmospheric pollutant released by cigarette smoke and vehicles (Norman and Keith 1965) that contributes to ozone layer destruction and a precursor of acid rain (Culotta and Koshland 1992). It is a nonpolar gaseous molecule that readily diffuses through the lipid bilayers of mammalian cells. NO has a short half-life (1–5 s) and one unpaired electron, making it a free radical that reacts with other atoms, radicals and molecules (Al-Sa'doni and Ferro 2000). It readily reacts with dioxygen to afford N_2O_3, NO_2 and other N_xO_y species (collectively known as reactive nitrogen species), which constitute a major portion of smog in urban air. NO is a colorless gas with a solubility of 2–3 mM in water (1 mM at body temperature), is converted to NO_2^- and NO_3^- through metabolic pathways, and is excreted via the urinary pathway (Feelish and Stamler 2005). 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 20th century, their connection with elevated level of iNOS activity in the body has only been recently realized (Weitzberg et al. 2010). The reactions of NO with superoxide anion (O_2^-) and other ROS produce peroxynitrite ($ONOO^-$), an oxidative species that causes rapid nitration of aromatic amino acid residues of proteins (such as superoxide dismutase). These nitrated proteins serve as hallmarks of inflammation (Weitzberg et al. 2010). Peroxynitrite ($ONOO^-$), an oxidative species, is responsible for certain types of NO-mediated toxicity *in vivo* (Radi et al. 1991). It can also

interact with oxyhemoglobin to form methemoglobin and nitrate (Doyle and Hoekstra 1981). Studies have explored that NO reacts with the free radical O_2^- ($k = 4.3–6.7 \times 10^9$ M^{-1} s^{-1}) and assumes variable oxidation states by gain or loss of electrons (NO^-, NO^+) (Wink and Mitchell 1998).

The average half-life of NO in tissue is about 3–6 s and in blood 1–2 s (Snyder and Bredt 1992). This short life makes *in situ* studies of NO in living systems extremely challenging. Because of the instability and inconvenient handling of aqueous solutions of authentic NO, there is an increasing interest in using compounds capable of generating NO *in situ*, that is, NO donors.

Carbon monoxide (CO)

As a ubiquitous air pollutant, CO arises primarily from the partial combustion of organic molecules. Its large-scale environmental production results from the oxidation of natural hydrocarbon pools, catastrophic events such as volcanic emissions and forest fires, plant metabolism and oceanic activity (Raub 2005). CO also arises from human activities involving the burning of fossil fuels, in industrial processes, and as a major component of automobile emissions (Von Berg 1999).

CO, a low molecular weight (F.W. 28.01) diatomic molecule, occurs naturally in the gaseous state under atmospheric temperature and pressure (M.P., –205°C; B.P., –191.5°C; density, 1.250 g/l at 0°C; Von Berg 1999). Under ambient conditions, it is a colorless, odorless and tasteless gas with no unpaired electron (diamagnetic). It is soluble in aqueous media (2.3 ml/100 ml at 20°C) and organic solvents (Budavari et al. 1989). CO is relatively stable in biological systems relative to NO, a small gaseous molecule of similar structure and molecular size. Both CO and NO function as heme iron ligands and form complexes with a number of hemo proteins and metalloenzymes (Maines 1997). CO binds only to reduced (ferrous) iron centers, whereas NO may bind to both ferrous and ferric hemes (Omura and Sato 1964, Yonetani et al. 1971).

The clinical manifestations of CO poisoning include dizziness, drowsiness, vomiting, headache and loss of motor coordination (Weaver 1999, Gorman et al. 2003, Penney 2005). Prolonged exposures can cause respiratory difficulty, disorientation, chest pain, loss of consciousness or coma and can ultimately result in death. Chronic exposure to sublethal concentrations may lead to memory loss and other cognitive and neurological complications (Weaver 1999). Symptoms of hypoxic CO poisoning begin to appear at 20% CO-Hb. Death likely occurs in the range of 50–80% CO-Hb (Von Berg 1999). Inhalation studies in rats have revealed that CO can cause oxidative damage in the brain, as evident by increased lipid peroxidation and apoptotic cell death (Thom 1990, Thom 1993, Piantadosi et al. 1997).

Both CO and NO are good ligands and bind transition metals to give metal carbonyls and nitrosyls, respectively, that constitute a major portion of what is known as organometallic chemistry (Mascharak 2012). Although both molecules are weak σ-donors, strong π-back bonding 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.

Hydrogen sulfide (H_2S)

H_2S is a colorless gas with a strong odor of rotten eggs. The detectable level of this gas by the human nose is at a concentration 400-fold lower than the toxic level (Allan and Morris 2014). H_2S is a gas with a structure very similar to that of water, but this is where the similarity ends. The sulfur atom is not as electronegative as oxygen so that H_2S is much fewer polar than water. Because of this, comparatively weak intermolecular forces exist for H_2S, and the melting and boiling points are much lower than they are in water. The boiling temperatures of H_2S and water are −60.7°C and 100.0°C, respectively.

Hydrogen sulfide is a weak acid with pK_a values of 6.98 at 25°C and 6.76 at 37°C. It dissociates in aqueous solution into H^+ and HS^-, which subsequently may decompose to H^+ and S^{2-} ($K_{a1} = 1.3 \times 10^{-7}$ M, $K_{a2} = 1 \times 10^{-19}$ M; Ellis and Giggenbach 1971, Giggenbach 1971, Myers 1986). The undissociated form of H_2S is volatile, while HS^- is not.

$$H_2S \underset{}{\overset{Ka_1}{\rightleftharpoons}} H^+ + HS^- \overset{Ka_2}{\rightleftharpoons} H^+ + S^{2-}$$

Under physiological conditions, i.e. at pH 7.4, one third of H_2S is undissociated and present in biological fluids as H_2S. Conversely, the chemical form S^{2-} is not present in appreciable amounts, as the dissociation of HS^- occurs only at high pH values. According to another report (Bayse 2013), H_2S being a weak acid ($pK_{a1} = 6.76$, $pK_{a2} = 19.6$) exists primarily as SH^- (82%) rather than H_2S (18%) or S_2^- (<0.1%) under physiological conditions. It should be emphasized that H_2S and SH^- may both contribute directly to the biological action of H_2S and that SH^-, the predominant sulfide species under physiological conditions, is a more potent nucleophile than Cys or reduced glutathione, which

readily binds to metal centers in biological molecules (e.g. Hb) or reacts with other compounds. The second pK_a value (pK_{a2}) of H_2S is now settled (Hughes et al. 2009) to be 19 ± 2. Therefore, the sulfide anion S^{2-} is present at extremely low concentrations at pH 7.4, with a mole fraction of 1.7×10^{-12} and is unlikely to participate in the biological chemistry of H_2S.

Hydrogen sulfide is rapidly oxidized, mainly in mitochondria, initially to thiosulfate and subsequently to sulfite and sulfate. This oxidation is not enzymatically driven, while thiosulfate conversion to sulfate and/or sulfite is catalyzed by thiosulfate:cyanide sulfurtransferase. Also, sulfite originating through this reaction is quickly oxidized to sulfate, as sulfate is the major end-product of H_2S metabolism under physiological conditions. However, urinary thiosulfate is considered to be a nonspecific marker of whole body H_2S production (Belardinelli et al. 2001). This readily oxidizing behavior of H_2S disfavors long-range transport under normoxic conditions and also suggests the need for endogenous storage mechanisms (Bayse 2013), such as the formation of thiol hydropersulfides (RS-SH), which constitute a direct parallel to NO storage as nitrosothiols (RS-NO).

H_2S is soluble in many solvents, including water, acetone, carbon disulfide, methanol, ethanol, ether, chloroform and benzene. Some data on the solubility of H_2S in a range of nonaqueous solvents are available (Guenther et al. 2001, Fischer et al. 2002). It is a lipophilic molecule and readily crosses cell membranes. Its solubility in lipophilic solvents is about five times greater than its solubility in water.

At concentrations of <100 ppm, the toxic effects of H_2S in humans include eye irritation, sore throat, dizziness, nausea, shortness of breath and chest tightness (Beauchamp et al. 1964, Reiffenstein et al. 1992). Exposure to H_2S at >1000 ppm concentration may cause severe adverse effects, especially for the central nervous system (CNS) and respiratory depression, ranging from loss of consciousness to death (Kage et al. 2002). The primary cause of death from H_2S poisoning has been attributed to respiratory paralysis (Beauchamp et al. 1964).

Physiological and pathophysiological roles of NO

The catalytic activity of the NOS isoforms (endothelial constitutive, cNOS) involved in signaling is controlled by Ca^{2+} and CaM. After stimulation by the appropriate external signals, there occurs an increase in intracellular-free Ca^{2+}. This then leads to a Ca^{2+}-CaM complex. Each of the four EF hands of CaM binds one Ca^{2+}, and then this Ca^{2+}-CaM complex binds to NOS, thereby activating NOS to synthesize NO (Marletta 2004). NO, being a diatomic free radical gas, diffuses readily from the point of synthesis, can permeate cell membranes, interacts with intracellular molecular sites within both generating and target cells. The best characterized target site for NO is the iron bound in the heme component of ubiquitous enzyme sGC present in the adjacent smooth muscle, stimulating conversion of guanosine 5′-triphosphate (GTP) to 3′,5′-cGMP and mediating the biological effects attributed to cNOS-derived NO (Ignarro and Kadowitz 1985; Figure 9).

Extensive studies have established that the prosthetic heme group of sGC acts as the acceptor site for NO (Humbert et al. 1990), and the presence of the heme group has been shown to be required for the stimulatory effect of NO (Ignarro et al. 1982). Removal of the heme group abolishes NO-induced activation, and the stimulatory effect of NO is restored on the heme reconstitution of the enzyme (Ignarro et al. 1986). The heme group is not covalently bound and exhibits an absorbance maximum at 431 nm (Figure 10). This peak indicates a five-coordinate ferrous heme with a histidine as the axial ligand at the fifth coordinating position (Stone and Marletta 1994). Using site-directed mutagenesis, His-105 of the β_1 subunit has been identified as the axial ligand (Zhao et al. 1998). NO binds to the sixth coordination position of the heme iron and leads to the breakage of the histidine-to-iron bond, yielding a five coordinate nitrosyl-heme complex with an absorbance maximum at 398 nm. The opening of the histidine-to-iron bond is thought to initiate a conformational change, resulting in the activation of the enzyme.

Activated sGC catalyzes the conversion of GTP to cGMP, which causes vasorelaxation of smooth muscle via a signal transduction cascade. In the blood, NO binds specific cysteine (thiol) residue of the α-subunit of Hb to form an *S*-nitrosothiol (*S*-nitroso Hb) and can eventually dissociate to free NO without interacting with the iron center (Angelo et al. 2008). It thus serves to regulate the lifetime of NO in its bioactive state. It also readily binds the Fe(II) center of Hb to afford nitrosyl-Hb. Reaction of NO with oxy-Hb leads to the formation of oxidized Hb (met-Hb) and nitrate, which is eventually excreted.

NO plays a key role in the regulation of several physiological and pathophysiological processes, such as host defense, neuronal communication, regulation of vascular tone, smooth muscle cell replication neurotransmission, glaucoma and neural degeneration, vasodilation, pulmonary hypertension, penile erection, angiogenesis, inflammation, immune response, septic shock, platelet aggregation, gastrointestinal mobility, hormone secretion, gene regulation, Hb delivery of oxygen, stem cell proliferation and differentiation, bronchodilation and wound

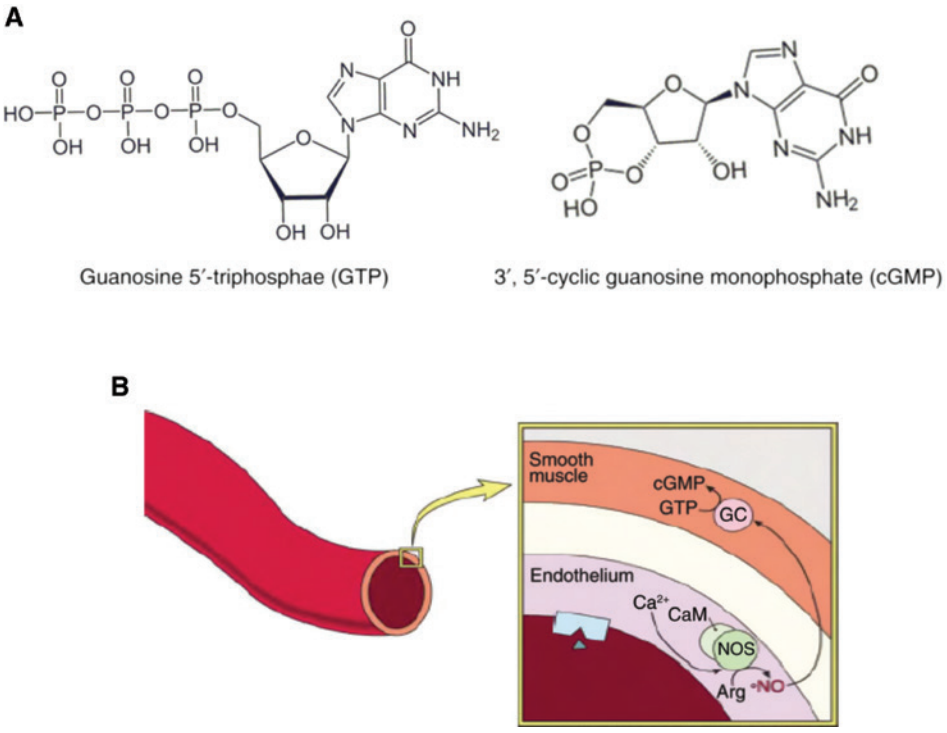


Figure 9: The best characterized target site for NO is the iron bound in the heme component of ubiquitous enzyme sGC present in the adjacent smooth muscle.
(A) Structure of GTP and GMP. (B) Generation of NO by cNOS in smooth muscle mediating the biological effects.

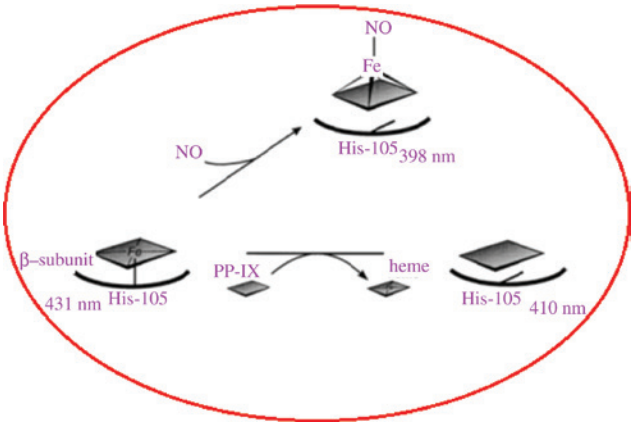


Figure 10: Conformational change in sGC protein:heme as the NO acceptor site of soluble guanylyl cyclase (sGC).
In the nonactivated state, the heme of sGC is five-coordinated with the histidine-105 of the β_1 subunit bound to the fifth coordination position of the heme iron (absorption maximum at 431 nm). NO binds to the sixth coordination position of the heme iron and leads to the breakage of the histidine-to-iron bond so that the fifth coordination position is now free (absorption maximum at 398 nm). Protoporphyrin IX (PP-IX) is able to substitute for the heme group and stimulates the enzyme (absorption maximum at 410 nm).

healing (Török 2008). At higher (μM) levels, NO also plays a key role in host immunity (Fang 1999) and tumor suppression (Moncada et al. 1998, Burke et al. 2013). The latter two properties have inspired many workers to design molecules capable of releasing this innate therapeutic effect (Figure 11) under controlled conditions to elicit salutary effects.

The concentration and location of NO generation strongly dictates the cell signaling pathways induced by this gasotransmitter (Figure 11; Hill et al. 2010). Generation of NO is catalyzed by a family of NOSs (Li and Poulos 2005) that require oxygen and NADPH to oxidize L-arginine to L-citrulline and generate NO. Two of the isoforms, namely, eNOS and nNOS, are constitutive and release pM to nM concentration of NO, while the third one is an inducible NOS (iNOS) that releases μM concentrations of NO when triggered by certain stimuli such as cytokines and pathogen invasion. While all NOS isoforms feature a homodimeric structure that contains N-terminal oxygenase and C-terminal reductase domains, variability exits between the modes of enzymatic activation and O_2 dependence that equate to varied release rates and evolution periods. NO mediates its biological effects mainly by activating sGC and increasing cGMP synthesis from GTP (Murad 2004). However, many NO-cGMP-independent pathways involving inorganic nitrite and nitrate, *S*-nitrosothiols and nitrotyrosine have been discovered recently (Bryan et al. 2009).

To date, NOS has been found in many cell types in various parts of the body (Table 2; Snyder and Bredt 1992).

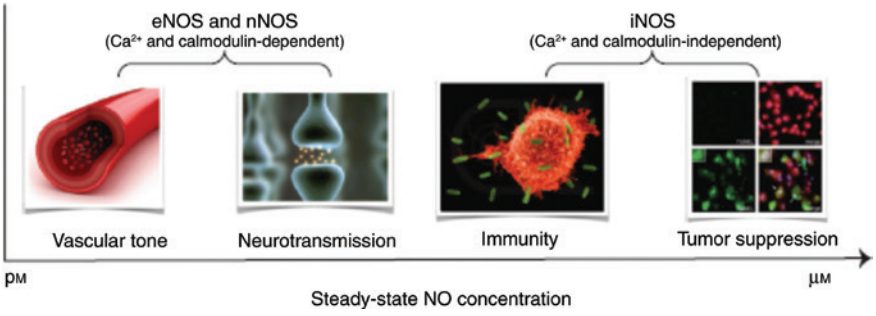


Figure 11: Concentration-dependent pathways dictated by NO.

The monolayer of cells lining the cardiovascular system (the endothelium) produces the largest amount of NO. The endothelium is one of the largest specialized organs in the body, and the total weight of endothelial cells in the human body is about 1.5 kg, which is comparable with the weight of a liver. In the brain, NO is produced by both neuronal and eNOS. NOS is also found in myocytes and skeletal muscles. NO can also act as a cytostatic agent in the immune system. NO can be produced (after induction) by almost every cell in the human body, where it plays a primary role in host defense. In this role, NO may defend the body against invading bacteria, viruses and even cancer. In the corpus cavernosum, nNOS-containing nitregic nerves produces NO, and NO-induced smooth muscle relaxation is mediated by cGMP.

Physiological roles

In the regulation of the cardiovascular system

Vascular endothelial cells contain calcium-dependent (Fleming and Busse 1999) constitutive NOS. Synthesis of NO is stimulated by chemical agonists like bradykinin, acetylcholine, ATP and several other agents that can stimulate the flux of calcium. However, physical agonists like shear stress, flow, electrical current, acupuncture, light and electromagnetic fields can also stimulate NO release in the cardiovascular system. After NOS is turned on by a calcium flux and it biosynthesizes NO for about a minute, it is turned off by phosphorylation. NO synthesized by endothelial cells diffuses out in all directions. Nearly 70–90% of NO released by endothelium is washed away by the blood where it is used to prevent platelet aggregation and the subsequent formation of blood clots. The remaining amount of NO diffuses to the wall of arteries and veins (smooth muscle) and triggers a cascade of events leading to smooth muscle relaxation. Relaxation of the surrounding smooth muscle allows the blood vessel to dilate (increase of vessel diameter), resulting in lowered blood pressure. The cardiovascular system maintains a constant level of NO at a given blood flow. When blood flow increases, the endothelium releases more NO to maintain its constant concentration in the blood stream. When this normal level is not produced, because production is blocked by pathological states such as deposition of cholesterol on the wall of the arteries (atherosclerosis), the vascular muscles do not relax to the appropriate degree, and vasoconstriction ensues. Vasoconstriction increases blood pressure, and decreases flow, and is responsible for hypertension.

Nitroglycerin, discovered by Alfred Nobel, has been used as a drug for cardiac treatment for more than 100 years. It undergoes metabolic degradation in the biological tissue, and one of the degradation products is NO (Agvald et al. 2001), which increases muscle relaxation and can improve blood flow even in atherosclerotic arteries. Platelets in the blood can also release NO. NO released by platelets prevents blood coagulation, formation of thrombin and subsequent blockage of arteries. The pathology of this process leads to coronary thrombosis and is a major cause of stroke.

It has been noted for over 100 years that a heart disconnected from the cardiovascular system and CNS can

Table 2: Nitric oxide synthases in various parts of the body.

Constitutive NOS (eNOS and nNOS)	Inducible NOS (iNOS)
Vascular endothelium	Vascular endothelium
Brain	Vascular smooth muscle
Platelets	Macrophages
Adrenal gland	Kupffer cells
Peripheral nerve	Hepatocytes
Mast cells	Endocardium
Masangial cells	Masangial cells
Myocardium	Lymphocytes
Nitregic nerves	Chondrocytes
	Fibroblasts
	Neutrophils
	Megakaryocytes

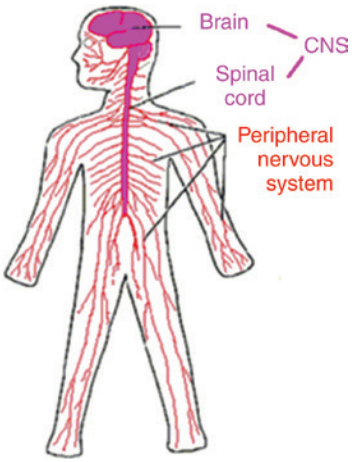


Figure 12: Central nervous system (CNS) and peripheral nervous systems in human.

beat spontaneously for several seconds. The vital functions of the heart are preserved as the concentration of NO is maintained above the 300 nmol/l level. This finding has serious implication for heart preservation strategies for transplantation. Current cold storage preservation solutions permit short time storage of a heart (about 4 h). This is a severe limitation, because surgery itself for heart transplants requires 2–3 h. In the recent past, new solutions have been developed (Minasiana et al. 2015) for heart storage, which preserves the NOS. These new solutions extend the time for heart storage up to 12 h. Under conditions when the heart has to provide extensive work (pumping blood under heavy stress, exercise, etc.), NO is produced by myocytes in addition to endothelial cells. Myocyte NO production is not stimulated by mechanical forces of the heart, but by adrenaline. The release of adrenaline is triggered by the nervous system. The heart is more sensitive to a low supply of NO than to a low supply of oxygen. Cutting-off of NO production/supply in the heart will terminate a human life within 10–15 s, much faster than cutting-off of oxygen supply (5–7 min).

NO in the nervous system

The first evidence of a role for NO as a neurotransmitter was reported by Garthwaite et al. (1988), who demonstrated that stimulation of cerebellar *N*-methyl-D-aspartate receptors by glutamate caused the release of a diffusible molecule with strong similarities to EDRF (Garthwaite et al. 1988). Shortly before this study was published, NO had been identified as the EDRF molecule (Ignarro et al. 1987, Palmer et al. 1987). Subsequently, it was shown that NO acts as a neurotransmitter in both the CNS and peripheral nervous systems by mechanisms that are dependent on cGMP (Sanders and Ward 1992, Garthwaite and Boulton 1995).

NO in the CNS

The nNOS actions in the CNS (Figure 12) have been associated with pain perception, especially at the spinal cord level (Yamamoto et al. 1993), and control of sleep, appetite, thermoregulation (Monti and Jantos 2004), neural development and synaptic plasticity (Dinerman et al. 1994). NO has been proposed as the retrograde messenger that coordinates the enhancement of both pre- and post-synaptic mechanisms involved in two forms of synaptic plasticity, namely, long-term potentiation (LTP) and long-term depression (LTD; Esplugues 2002). LTP is a property of many central excitatory synapses characterized by a prolonged enhancement of synaptic transmission or an activity-dependent increase in synaptic strength, lasting from hours to weeks or even longer. The process by which LTP is induced is not completely clear, but it involves glutamate acting on amino-3-hydroxy-5-methylisooxazole-4-propionic acid or *N*-methyl-D-aspartate receptors. This activates a series of events in which Ca^{2+}/CaM-dependent protein kinase II, NOS and protein tyrosine kinases are implicated. LTP is thought to be a synaptic correlate of learning and memory and is most pronounced in higher brain centers involved in cognitive functions, particularly in the cerebral cortex and hippocampus.

LTD can be observed in higher regions of the brain, although it has been particularly well studied in the cerebellum where it has been proposed as a model for the learning of motor movements (Esplugues 2002). Finally, the role of NO in both forms of synaptic plasticity involves interaction with PSD-95 and related membrane-associated guanylate kinases, underlined by the fact that both LTP and LTD are significantly modified in mice with targeted disruption of PSD-95 (Migaud et al. 1998).

NO in the peripheral nervous system

First debated in the late 1980s (Bowman et al. 1986, Gillespie et al. 1989, Li et al. 1989), it is now well established that NO has a leading role as an inhibitory neurotransmitter of peripheral nonadrenergic, noncholinergic (NANC) nerves. Peripheral nitrergic nerves have a widespread distribution and are particularly important in that they produce relaxation of smooth muscle in the gastrointestinal, respiratory, vascular and urogenital systems.

Gastrointestinal system

In the gastrointestinal tract, the majority of NOS positive fibers are intrinsic, with smooth muscle cells containing sCG next to axon varicosities containing NOS (Ekblad et al. 1994). This neuronally produced NO is implicated in many physiological and pathophysiological reflexes in which changes in gastrointestinal muscle relaxation are noted (Barnette et al. 1990). Dysfunction of the inhibitory NANC nerves in the lower esophageal sphincter results in the motility disorder, achalasia (Mearin et al. 1993), and is probably involved in esophageal spasms and related primary motor disorders in the esophageal body (Yamato et al. 1992). Gastric NANC-mediated relaxation following vagal stimulation, food intake or distension of the antrum or duodenum was among the first NANC effects described (Martinson 1965).

Pulmonary system

The density of extrinsic NOS-containing fibers increases progressively from the top of the trachea to the primary bronchi and then diminishes as the bronchial diameter decreases (Fischer and Hoffmann 1996). Nitrergic nerves are believed to represent the main nervous bronchodilator pathway in humans, and dysfunction of this system may be implicated in the increased tone and hyperresponsiveness observed in asthma (Belvisi et al. 1995). Furthermore, inhalation of NO has become an important therapeutic tool in the treatment of diseases such as acute respiratory distress syndrome, hypoxic respiratory failure, high pulmonary artery pressure, lung transplantation, sickle cell disease and especially pediatric conditions such as neonatal pulmonary hypertension (Weinberger et al. 2001). Indeed, new approaches (Gibson 2001) to the treatment of some of these diseases involve potentiation of NO responses with inhibitors of phosphodiesterase-5.

Vascular system

nNOS is found in the perivascular nerves of various blood vessels and appears to constitute an alternative regional control mechanism (Bredt et al. 1990) for blood flow, independent of eNOS. This neuronally produced NO seems to be particularly relevant in the regulation of cerebral blood flow (Estrada and Defelipe 1998). High levels of nNOS are present in vasodilator nerves in cerebral blood vessels (Thomsen et al. 1993), although, in most cases, nNOS is co-localized with different vasoactive neurotransmitters. In the brain, activity-dependent activation of nNOS is associated with a local increase in blood blow, and this response is prevented by inhibitors of NOS (Iadecola et al. 1993). The initial vascular response to neuronal ischemia and the implication of nNOS in this condition have been the subject of discussion (Esplugues 2002). In addition to this relationship, it has been suggested that blockade of NANC vasodilatation by hemolysate or Hb may contribute to the vasospasm observed in hemorrhages. Abnormal dilatation of cerebral vessels appears to mediate vascular headaches. Furthermore, the finding that blockade of NO synthesis aborts acute attacks of migraine points to the use of the pharmacological manipulation of nNOS in the development of antimigraine compounds (Olesen 2008).

Urogenital system

nNOS is most prominent in the parasympathetic postganglionic in nervation of the urethra. Likewise, stimulation of bladder afferent nerves leads to the release of NO, and chronic irritation of the bladder augments nNOS expression in dorsal root ganglion cells. Finally, bladder hyperactivity provoked by intravesical irritants can be moderated by inhibition of NO synthesis, thus suggesting a role for spinal cord NO in the micturition reflex pathway (De Groat and Yoshimura 2001).

Recent years have seen a major focus on the pharmacological modulation of the NO released by the endothelium and nitrergic nerves (nNOS) and which is involved in penile erection. Part of the physiological process of erection involves the release of NO in the penile corpus cavernosum. This then activates the enzyme guanylate cyclase that results in increased levels of cGMP, leading to smooth muscle relaxation in the corpus cavernosum, resulting in increased blood flow to the penis and an erection. Moreover, sGC stimulation blocked by NOS inhibitors results in impaired erection (Toda et al. 2005). Nitrergic neurones are also implicated in the effects of sexual hormones. For instance, nNOS levels in the penis decrease substantially after castration but return to normal levels following testosterone replacement (Penson et al. 1996). Levels of nNOS diminish with age, and this decrease correlates with impaired erectile responses (Carrier et al. 1997). Similarly, impotence occurring with diabetes mellitus, spinal cord injury and treatments for prostate cancer is now related to damage of the nitrergic structures controlling erection (Goldstein et al. 1998).

Phosphodiesterase-5 is the isoenzyme predominantly responsible for cGMP hydrolysis in the corpus cavernosum, and recently, different isoforms of this isozyme have been described (Lin et al. 2000). Selective inhibition with drugs such as zaprinast or sildenafil restores erectile responses, which are linked to the prolongation of the NO/sGC/cGMP signaling pathway (Gibson 2001). However, this mechanism of action is dependent on a level of integrity of the

nitrergic nerves and a pre-activated endogenous NO-cGMP system. This explains the clinical observation that sildenafil does not aid erection in patients with complete loss of sacral nerve activity nor where there is an absence of sexual arousal (Maytom et al. 1999).

Nitrergic structures also innervate smooth muscle structures in the female urogenital tract and are particularly abundant in the clitoral corpus cavernosum (Burnett et al. 1997) where they appear to be responsible for the NANC erectile response of the clitoris (Cellek and Moncada 1998). There have been few studies of female sexual dysfunction, but existing results suggest that inhibitors of phosphodiesterase-5 may be effective in specific cases, particularly those associated with the use of antidepressant, antipsychotic and antianxiety agents (Shen et al. 1999). Encouraging results have also been obtained with sildenafil in other cases of sexual dysfunction (Sipski et al. 2000), but these need confirmation. The use of sildenafil to aid *in vitro* fertilization is also a possibility as its application in the vagina increases both uterine blood flow and the thickness of the endometrium (Chwalisz and Garfield 2000). Finally, NO appears to be responsible for a tonic inhibition of spontaneous contractile activity in the uterus, while there is evidence of increased biosynthesis of NO during pregnancy and a rapid drop in NOS activity preceding delivery. This points the involvement of nitrergic mechanisms during pregnancy, which promote a relaxed state in the uterus, whereas a decrease in responsiveness to NO would appear to be involved in the initiation of labor (Weiner and Thompson 1997).

Skeletal muscle

The high levels of nNOS expressed in skeletal muscle, particularly the muscle-specific splice variant nNOSm, tend to be located beneath the sarcolemma of fast twitch fibers, emphasizing the role of NO as a modulator of contractile force (Kobzik et al. 1994). NO derived from sarcolemmal nNOS is also implicated in various other physiological functions occurring near the muscle membrane. Myocytes fuse to form muscle myotubes during muscle development, and this process is prevented by inhibition of NO (Lee et al. 1994). In myocyte/motor neuron co-cultures, NO produced at the postsynaptic muscle membrane functions as a retrograde messenger, regulating myotube innervations (Wang et al. 1995). In mature muscle fibers, NOS modulates glucose uptake across the sarcolemma. Although glucose uptake in skeletal muscle is regulated by both rigorous exercise and insulin, inhibition of NO synthesis has a selective action on glucose uptake in the former (Roberts et al. 1997). Interestingly, regular exercise increases nNOS protein expression in the muscle, and this has long-lasting enhancing effects on glucose transport in the muscle (Roberts et al. 1997). Finally, both eNOS and iNOS isoforms are also present in the skeletal muscle, the former mostly related with the control of skeletal blood flow and the latter with inflammatory conditions and responses elicited by cytokines or lipopolysaccharides (Stamler and Meissner 2001).

Several muscular diseases have been linked to a dystrophin deficiency, and although the specific cause is unconfirmed, perturbed NO signaling would seem to be responsible (Brenman et al. 1995). A mutation in the rod-like domain of dystrophin causes Becker's dystrophy and results in a loss of sarcolemmal nNOS, while other components of the dystrophin complex are preserved (Chao et al. 1996).

NO as a regulator of male and female reproductive systems

NO regulates smooth muscle cell tone, platelet aggregation and adhesion, cell growth, apoptosis, neurotransmission and injury as well as infection-induced immune reactions. Because these processes are also associated with the biology, physiology and pathophysiology of various reproductive processes, it is highly likely that NO plays an important role in reproduction. Indeed, in the past decade NO has been recognized as a molecule that importantly regulates the biology and physiology of the reproductive system (Rosselli et al. 1998; Figure 13).

Female reproductive systems

Ovary

Recent findings (Tabraue et al. 1997) provide convincing evidence that NO, both ovarian cell-derived and vascular endothelial cell-derived, plays an important role in the physiology and biology of the ovary with regard to regulation of folliculogenesis and ovulation. The clinical implications of these findings have not yet been addressed. Future studies are needed to investigate whether the ovarian dysfunction observed in certain pathological conditions is associated with decreased vascular and intra-ovarian NO synthesis and whether these defects can be corrected by NO. It may be possible to treat ovarian dysfunction related to decreased perfusion of the ovary in vaso-occlusive disorders either directly by administering NO donors or indirectly via administration of IL-1β.

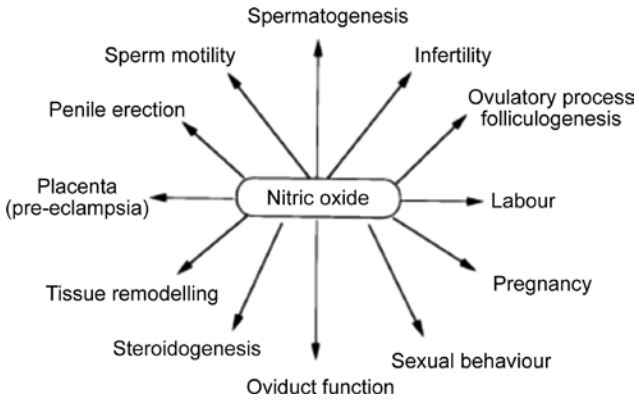


Figure 13: Schematic presentation of role of NO in reproductive system.

Uterus

The uterus undergoes important structural alterations in pregnancy as well as during menstruation. Because NO regulates smooth muscle cell contractility and spontaneous contraction as well as distension of the uterus during pregnancy, the role of NO in regulating the pathophysiology and biology of the uterus has gained intense attention. Uterine vasculature and nerve supply both express NOS activity and have been shown to modulate the contractile effects of multiple vasoactive factors (Magness et al. 1997). Apart from in the vessel wall and neurons, the presence of NOS has been demonstrated in glandular epithelium, endometrial stromal cells, myometrial smooth muscle cells and mast cells, suggesting that NO plays a local role in the control of uterine function (Telfer et al. 1995).

The physiological role of eNOS and iNOS during pregnancy and labor was studied in depth by Buhimischi et al. (1996), who demonstrated that both eNOS and iNOS are upregulated during pregnancy but decreased when labor begins. Gestational differences in the response to NO are well established. It has been shown that, during pregnancy, the relaxing effects of NO are enhanced compared with the uterus during term or preterm labor (Natuzzi et al. 1993). The above findings, together with the observations that (i) nitroglycerine relaxes the uterus to facilitate extraction of retained placenta (Peng et al. 1989), (ii) nitroglycerine arrests preterm labor and prolongs gestation (Lees et al. 1994), (iii) amyl nitrate decreases the magnitude of uterine contractions induced by oxytocin, but not spontaneous activity (Kumar et al. 1965) and (iv) NO donors inhibit uterine contractions in pregnant rhesus monkeys, sheep and rats as well as humans (Jennings et al. 1993), provide compelling evidence that NO differentially controls uterine contractility during pregnancy and labor. The role of NO in pregnancy has recently been reviewed by Sladek et al. (1997).

Cervix and vagina

It was demonstrated by Buhimischi et al. (1996) that rat cervix expresses all three isoforms of NOS, i.e. iNOS, nNOS and eNOS. Furthermore, they demonstrated that expression of iNOS is increased in the cervix and decreased in the uterus, during parturition and preterm labor. Moreover, nNOS, which was not expressed in the uterus during gestation, increased in the cervix during labor. In contrast to nNOS and iNOS, no significant changes were observed in eNOS expression during labor at term. These findings suggest that NOS activity in the uterus and cervix is differentially regulated during labor and may be involved in connective tissue remodeling during cervical ripening. The physiological and biological relevance of NO in pregnancy and labor comes from their finding that the inhibition of NO synthesis by administration of L-NAME (a precursor to NOS inhibitor) prolonged the duration of delivery as well as decreasing cervical extensibility. These findings not only suggest the importance of NO synthesis in the uterus and cervix during labor and pregnancy but also point to the role of various isoforms of NOS in regulating these effects.

NOS activity has also been localized in the vagina. eNOS activity is localized in the stratified squamous epithelial lining and in smooth muscle cells (Chatterjee et al. 1996). The expression of eNOS was maximal during estrus and pro-estrus, suggesting that NO may stimulate vaginal secretion. NOS immunoreactive axons and neurons have also been shown to be present in the vagina; moreover, the most abundant NO-releasing innervation has been shown to be present in the cervix and vagina (Grozdanovic et al. 1994).

NO in the male reproductive system

Regulation of penile erection

Erectile dysfunction (ED) is a widespread problem affecting many men across all age groups, and it is more than a serious quality of life problem for sexually active men. Over 30 million men suffer from ED in the U.S. (Lue 2000), and it is becoming a public health issue. The prevalence of ED is very high and is expected to rise considerably over the next 25 years, impacting more than 300 million men by 2025 (Ayta et al. 1999). ED is defined as the persistent

inability to maintain or achieve a penile erection sufficient for satisfactory sexual performance. Its etiology is multifactorial. Various aspects affect the expression/degree of ED, and risk factors include age, diabetes mellitus, neurologic diseases, smoking and cardiovascular diseases, among others (Hafez and Hafez 2005). Although the disorder has been described for more than 1000 years, the molecular basis and mechanisms of ED have yet to be completely understood. In the last four decades, elucidation of the macroscopic structures of the erectile system (Lue and Tanagho 1987, Mersdorf et al. 1991) ushered in a new era of therapeutic options for erectile disorders. Later, new insights into erectile neurotransmission (Andersson and Holmquist 1994), essentially the NO pathway (Ignarro et al. 1990), resulted in rational alternatives as a treatment (Andersson 2011).

The variety of vital roles played by NO is a direct consequence of its unique chemical properties in the biological cells. NO is small and chargeless; therefore, it can freely diffuse through the cell membrane as well as through cytoplasm just like O_2 and N_2. NO has modest chemical reactivity (making it a somewhat selective reducing or oxidizing agent), allowing its survival at least for several seconds in the biological matrix. NO has an unpaired electron and binds quickly to O_2^- and more slowly to several metals in the biological matrix including iron in Hb. This reaction leads to the eventual disposal of NO in the body. The story of the role of NO is fascinating and far from being complete. It is also an excellent example of utilization of chemistry in solving important medical problems (Maurya and Mir 2014).

Metal nitrosyl complexes as NOS mimics and other manifold significance

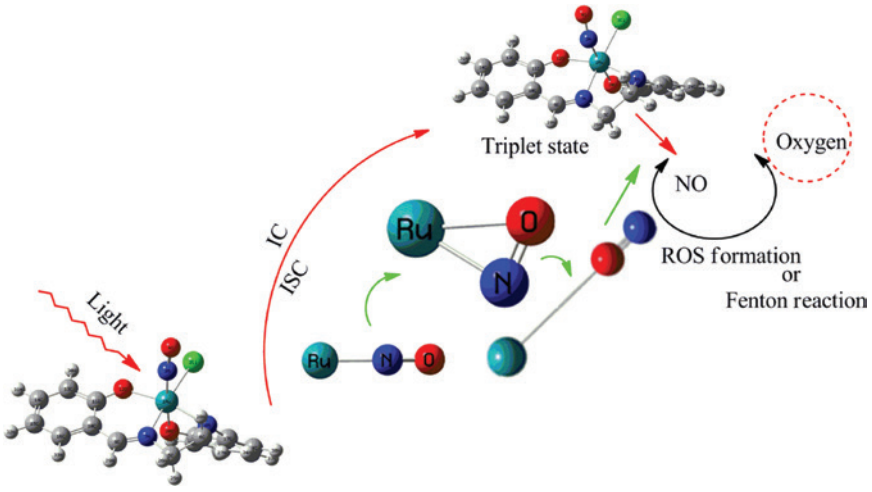
Thousands of metal complexes are tested every year to mimic the biological release of NO. Herein, we discuss the current scenario of NO ligand binded with metals of different nature. The search for new storage release systems, capable of delivering NO to desired targets, has stimulated the chemistry of metal nitrosyl complexes, which has witnessed a substantial progress since the last decade (Tfouni et al. 2003). The chemistry of metal nitrosyl complexes has taken on added significance (Lunardi et al. 2009) in recent years because of the important role involving transition metal in the biological process of NO, as well as the possibility of producing thermodynamically stable and kinetically labile species. Such strategies (Toledo et al. 2004) have focused on the development of pharmacological substances capable of releasing NO at specific rates in tissues, in order to overcome NO deficiency. The great affinity of d^6 and d^5 low-spin and in low oxidation state metal complexes for NO and the versatility of NO on its own right as a ligand make the nitrosyl complexes a good alternative for such a proposal. Iron, ruthenium (Kudo et al. 1997) and manganese are good candidates as a model for NO carriers. Indeed, several iron-based nitrosyls including sodium nitroprusside (SNP, $Na_2[Fe(NO)(CN)_5]$; Butler and Megson 2002) and Roussin's salts (Torsoni et al. 2002) were found to release NO when exposed to light. Despite its well-known toxicity, SNP is largely used as a NO deliverer in clinical practices for blood pressure control in cases of acute hypertension (Patra et al. 2002, 2003, Afshar et al. 2005). Clearly, the number of metal nitrosyls that release NO exclusively when triggered by light and exhibit stability under physiological conditions (pH ~7, presence of oxygen) is very limited.

Ruthenium nitrosyl complexes

Ruthenium nitrosyls are considered as efficient light sensitive compounds. Photoisomerization in relation to such complexes is considered a prominent frontier to carry out a study of NO release. In addition to unfurl ligand-based properties of this class of compounds, solution-based studies are also tried to find the best fit biological relevance. NO lability in such cases along with photolability is a requisite of current medicinal field. PDT has been evaluated as an adjuvant therapy to other therapeutic modalities, including surgery, hyperthermia, radiotherapy, immunotherapy and chemotherapy as new approaches for the treatment of a variety of cancers and nonmalignant disorders (Pavlos et al. 2004).

From Scheme 2, it is clear that spin system change accompanies radiation-less decay, and the transfer of electron to antibonding orbital of NO certifies its release, and thereby, it may enter both pathways, Path 1 and Path 2 of PDT to achieve the target of damaging cancer cells (for description of Path 1 and Path 2, see Mir et al. 2017b: photodiagnosis and photodynamic therapy). Whether the subject would involve Fenton reaction or production of reactive oxidation species to cross biological membrane, both paths can be traced by the application of metal complex.

Study of photo-induced NO cleavage (Yonemura et al. 2001, Yonemura 2009) has shown that the NO release in polyamidoamine functionalized with ruthenium nitrosyl compounds is made through light irradiation ($\lambda = 355$ nm) and one-electron reduction (Eu^{2+}). The record of stability of phosphite coordinated to ruthenium(II) in aqueous media is also an attractive work (Truzzi and Franco 2014).



Scheme 2: Proposed mechanism of PDT by the complex.

NO release in some cases has been stated to be possible only if they are activated by reduction centered on the nitrosyl ligand (Truzzi and Franco 2014). Another important recent advancement in the nitrosyl lability is from a trinuclear ruthenium nitrosyl complex and the relevant *in vitro* cytotoxicity against melanoma cells (Carneiro et al. 2014), and certain ruthenium nitrosyl clusters have been designated as a prodrug, NO releasers. It has also been found that chronic corticosterone administration facilitates aversive memory retrieval and increases glucocorticoid receptors (GRs)/NOS immune reactivity. As retrograde messenger, NO influences the formation of LTP and memory consolidation (Santos et al. 2014). Cell-penetrating ability and cytotoxicity of NO donoring ruthenium complexes are also quite fascinating (Mayer and Bottcher 2014). Some concerns regarding the NO release with anti-HIV and anticancer activities have also been investigated.

Theoretical studies on certain nitrosyl complexes of ruthenium are already reported, involving their geometry optimization and verification through furnished X-ray data (Mir et al. 2017c) involving the complex in conformation of minimum energy and not in a transition state using Spartan program with B3LYP hybrid density functional theory in conjunction with the 6-31G basis sets and LACVP for the ruthenium atom. In some cases (Carneiro et al. 2011), density functional theory geometry optimization is carried out with the aid of software packages (Schmidt et al. 1993) with a convergence criterion in a conjugate gradient algorithm. It is here to mention that the use of LANL2DZ (Hay and Wadt 1985) effective core potential for ruthenium and the atomic 6-31G(d) basis set (Francl et al. 1982) employed for all other atoms in the complex and B3LYP hybrid functional (Becke 1993) has fetched reliable results as per the reports (Formiga et al. 2008).

Dinitrosyl iron(II) complexes

Electronic structure of dinitrosyl porphyrin metal complexes has remained a highly interested quest since the last decade (Attia et al. 2014) to unravel the respective stereochemistry.

Vanin et al. (2010) suggested a hypothesis that NO and its endogenous derivatives (low molecular *S*-nitrosothiols and dinitrosyl iron complexes (DNIC) with thiol-containing ligands) can move in the intracellular space not only by diffusion but also in an auto wave mode. This hypothesis is based on the previously reported data on auto wave distribution of DNIC with glutathione following the application of a drop of a solution of Fe^{2++} glutathione onto the surface of a thin layer of *S*-nitrosoglutathione solution. According to the report of Mokh et al. (2010), auto wave distribution of NO and its endogenous derivatives in the intracellular space is advantageous over free diffusion, which might entail higher efficiency of their biological action. Regarding NO-derived cellular adducts of their formation and biological fate (Andreyev-Andriyevsky et al. 2011), quantitative measurements reveal that cellular concentrations of DNIC are proportionally the largest of all NO-derived adducts (900 pmol/mg protein, or 45–90 μM). It has been established that DNIC will be formed under all cellular settings of NO production and that the contribution of DNIC to the multitude of observed effects of NO must always be considered.

Cysteine-based dinitrosyl-iron complexes have been found responsible for a long-lasting vasorelaxation

(Chazov et al. 2012). It has been found (Remizova et al. 2011) that intracavernous injections of water-soluble DNIC with glutathione or cysteine (0.4–6.0 μmol/kg) to male rats induce short-term (2–3 min) penile erection along with a short-term drop of arterial pressure and appearance of protein-bound DNIC in cavernous tissue and circulating blood. A comparative study of hypotensive effects of binuclear forms of dinitrosyl iron complexes with glutathione, *S*-nitrosoglutathione and sodium nitrite ($NaNO_2$) on rats in first clinical phase trial has revealed that the latter appeared to be the least efficient, viz., mean arterial pressure decreased by 10 and 30 mm Hg at 25 and 100 lmol/kg of $NaNO_2$ (Landry et al. 2011). In contrast, DNIC and glutathione, *S*-nitrosoglutathione produced an appreciable hypotensive effect when used at much lower concentrations. It has been found that DNIC with glutathione (DNIC-GS) injected into the blood flow of rats at a dose of 0.05 μmol/kg prior to hemorrhage significantly improve cardiac function under conditions of hemorrhagic shock manifested in increased stroke volume, left ventricular work and cardiac output to a level exceeding control values 1.5-fold (Hough et al. 2011, Simontacchi et al. 2012).

Hemoproteins play central roles in the formation and utilization of NO in cellular signaling, as well as in the protection against nitrosative stress (Kolesnik et al. 2013). Strong parallels between the NO-binding kinetics of AxCYTcp, the eukaryotic NO sensor soluble guanylate cyclase and the ferrocytochrome c/cardiolipin complex have led to the suggestion that a distal-to-proximal NO switch could contribute to the selective ligand responses in gas-sensing hemoproteins. In case of plants, exposure to NO increases the nitrosyl-iron complexes content in sorghum embryonic axes (Borodulin et al. 2013). Nitrosyl-Fe complexes formation has been detected in sorghum embryonic axes homogenates incubated *in vitro* in the presence of 1 mM of NO donors: diethylenetriamine NONOate (DETA NONOate), *S*-nitrosoglutathione and SNP. Glutathione dinitrosyl complexes can be easily synthesized in the air at ambient temperature (Wena et al. 2010, Giliano et al. 2011) including consecutive addition to distilled water of glutathione, which decreases the pH of the test solution to 4.0, a bivalent iron salt (e.g. ferrous sulfate) and sodium nitrite at the molar ratio of 2:1:1, with a subsequent increase in pH to neutral values.

Comparative antitumor effect of curcumin and dinitrosyl iron complexes against melanoma cells has indicated a synergistic cytotoxic effect on mouse melanoma B16-F10 cells *in vitro* (Lewandowska et al. 2012, Burgova et al. 2014). The water-soluble *o*-phenanthroline derivative bathophenanthroline disulfonate (BPDS) had shown an antitumor effect on DNIC with glutathione during incubation of HeLa cells in Eagle's medium**.** It has been assumed that EDTA or BPDS induced pro-apoptotic effect of DNIC with thiosulfate or glutathione coupled with the ability of decomposing DNIC to initiate *S*-nitrosylation of proteins localized on the surface of HeLa cells. Intraperitoneal injection of dinitrosyl glutathione iron complexes has been reported to suppress endometrioid tumors (Chen and Ellis 2000). The importance of iron ions in HIS-DNIC induced genotoxicity has been confirmed by plasmid nicking assay, implying that there is no direct interrelationship between iron-NO coordination and their mutual toxicity modulation (Garcia et al. 2011).

Manganese(II) nitrosyl complexes:

The NO reduction of some manganese nitrosyl complexes and their studies based on IR spectral data reveal a nonbridging structure (Kaim and Schwederski 2010). However, the sequential reaction of certain dimanganese complexes with NO (5% in N_2) at room temperature and NO_2 present a nitrite ligand bridging the dimetal center through the N and O atoms (Masuya and Hori 1993). Noninnocent ("suspect") behavior of redox active, $NO^+/NO^\bullet/NO^-$ either substrates or supporting components is now even discussable in biochemical context interacting with manganese (Akolekar and Bhargava 2001).

Electron paramagnetic resonance based studies on manganese(II) nitrosyl complexes have shown effects of site-specific chemical modification of the distal histidine on ligand-binding structures (Topsoe et al. 2011). The surface chemistry of NO with respect to manganese metal surface has also attained a good research momentum. Adsorption of NO and CO and the co-adsorption of (NOCCO) and (COCNO) over the manganese(II) exchange studied by infrared spectroscopy have shown to be effected by pressure, temperature and evacuation on these NO/CO species (Blokhin et al. 2013, Jiang et al. 2013). Thus, it is possible to use NO as a probe molecule to obtain detailed atomic-scale information on hydrotreating catalysts and the origins of activity differences.

Selective catalytic reduction of nitrogen oxides (NO_x) with ammonia is one of the processes for cleaning the flue gas, and using diffuse reflectance infrared Fourier transform spectroscopy of Fe-Mn/TiO_2 revealed that surface OH species are consumed during NO adsorption, indicating that O_2 could promote the dehydration reaction of the manganese oxides to produce active oxygen and greatly enhance the amount of NO complexes on the catalyst (Ford and Wecksler 2005). The role in metathesis by the application of cyclopentadienyl-Mn(CO)(NO)$SnCl_3$

pronounces the industrial relevance of manganese(II) nitrosyl complexes (Afshar et al. 2005).

Chemical mechanisms relevant to the roles played by nitrogen monoxide species in mammalian bioregulation and immunology have proved very useful in probing these mechanisms (Ford and Wecksler 2005). Keen interests are developed to build strategies to deliver NO to biological targets upon demand for such goals as the sensitization of radiation damage in hypoxic tissue. One such strategy would be to employ a precursor that displays relatively low thermal reactivity but is photochemically active to release NO. This proposition has led us to investigate the flash and continuous photolysis kinetics of a number of different nitrosyl complexes. Manganese nitrosyls have found potential application in inhibiting papain by the *S*-nitrosylation inhibiting the hydrolytic ability triggered by light induction (Afshar et al. 2005). Mn porphyrins allow us to design optical and electrochemical selective HNO sensors (Doctorovich et al. 2011). Mn(II)-substituted myoglobins have been found applicable in nitrite reduction toward understanding necessary components of Mb nitrite reductase activity to nitric oxide, drawing increasing attention as a protective mechanism to hypoxic injury in mammalian physiology (Heinecke et al. 2012).

Nitroso compounds

Nitroso compounds are any of a class of organic compounds having molecular structures in which the nitroso group (-N=O) is attached to a carbon or nitrogen atom. *N*-Nitroso compounds were known almost 40 years ago to be present in food treated with sodium nitrite, which made a fish meal hepatotoxic to animals through formation of nitrosodimethylamine. Since that time, *N*-nitroso compounds have been shown in animal experiments to be the most broadly acting and the most potent group of carcinogens (Lijinsky 1999). Biologically, some enzymes, like nitrosoglutathione, are capable of promoting the transnitrosylation of proteins, when NO groups are transferred between thiol groups. Studies indicate that these *S*-nitroso modifications are rarely found and suggest that this event may constitute a pivotal signaling mechanism. These *S*-nitroso modifications give rise to a subset of *S*-nitrosoproteins, formed mainly by plasma albumin (*S*-NO-albumin). Albumin can be further nitrosated by *trans-S*-nitrosation, serving as a source of thiol residues (Panis 2014). One of the main drawbacks in consuming these products is that a large portion may remain undigested in the body and may result in disturbance of health state. This is because the covalent bonds are in organic forms, so inorganic nitrosyl complexes should replace these products to be human-friendly and easily digestible (Maurya and Mir 2014).

Concluding remarks

The insights that have been presented so far in this paper have improved our understanding of the physiological importance of gasotransmitters not only in physiological functions but also in the pathogenesis of human diseases. The exploration of NO as an endogenous gaseous molecule, termed gasotransmitter, triggered the investigation of other possible gasotransmitters, including CO and H_2S. Several other gases including acetaldehyde, sulfur dioxide, dinitrogen oxide and ammonia are currently under investigation to find if they could be accepted as gasotransmitters. Although many questions of known gasotransmitters have been solved, there are still some queries that have not yet been addressed. For instance, the biosynthesis of NO^- balances the electron count but the precise mechanism of back electron transfer to the NO^- radical remains an open question. The mechanism by which NO is formed is similar for all types of NOS. On one hand, because of the instability and inconvenient handling of aqueous solutions of authentic NO, there is an increasing interest in using compounds capable of generating NO *in situ*, that is, NO donors. On the other hand, the rapid oxidizing behavior of H_2S disfavors long-range transport under normoxic conditions, and hence, the need for endogenous storage mechanisms is suggested, e.g. in association with NO stores as nitrosothiols (RS-NO). Hence, NO associated H_2S study is of present continuous interest. Many studies have proven the clinical relevance of the subject molecules, but the arena of human clinical trials are yet to be opened. Besides treating dreadful diseases like cancer and diabetes by their virtue, a major void is yet to be filled to create flawless disease-controlling strategies. In addition to the above, the fruitful behavior of metal nitrosyls is remarkable. Photoactive metallic systems are supposed to act as intelligent NO donors in this context. The applicability of nitrosyls over nitroso compounds is a persuasion toward the continuous interest of synthesizing metal complexes of NO. In association with experimental measures in nitrosyl chemistry, it is to be emphasized here that the various theoretical formalisms are in process to find the best fit formulae to speculate or infer the relevant chemical descriptors of this class of compounds.

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