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Review Article

Gasotransmitters: a review

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ABSTRACT

The gaseous molecules produced endogenously with several physiological functions are called gasotransmitters. Even though initially, they were predominantly thought to be of neuronal origin, recent research has clarified that they have roles far beyond that. Their primary function is maintaining the integrity of the cardiovascular system and many other parts. From the available knowledge, we have just started to learn about their roles in physiological systems that could be translated to pharmacological drug development and therapeutics. Most of the process that remains in the form of preclinical research has to go a long way toward utilizing them in therapeutics. This review addresses the various levels at which they could be potentially exploited as therapeutics and their recent entry into clinical trials.

Keywords: Gasotransmitters, NO, CO, Medical gases, H2S, Neurotransmitters

INTRODUCTION

What are Gasotransmitters- gasotransmitters are a class similar to neurotransmitters. These molecules differ from other bioactive endogenous gaseous signaling molecules based on a need to meet distinct characterization criteria. The currently accepted gasotransmitters are carbon monoxide, nitric oxide, and hydrogen sulfide.[1]

Nitric oxide, carbon monoxide and hydrogen sulfide (NO, CO, H_2S) are distinctive from classic neurotransmitters and humoral factors while sharing common characteristics. These endogenous gaseous transmitters fall within the definition of gasotransmitters, measured by the following criteria:[2] 1. They are small molecules of gas. 2. They are freely permeable to membranes. As such, their effects do not rely on the cognate membrane receptors. They can have endocrine, paracrine, and autocrine effects. In their endocrine mode of action, for example, gasotransmitters can enter the bloodstream, be carried to remote targets by scavengers and released there, and modulate functions of isolated target cells. 3. They are endogenously and enzymatically generated, and their production is regulated. 4. They have well-defined and specific functions at physiologically relevant concentrations. Thus, manipulating the endogenous levels of these gases evokes specific physiological changes. 5. Their functions can be mimicked by their exogenously applied counterparts. 6. Their cellular effects may or may not be mediated by second messengers but should have specific cellular and molecular targets.

PHYSIOLOGY AND HISTORY OF GASOTRANSMITTERS

The gasotransmitter family may contain many new unknown endogenous gaseous molecules, such as NH_3 and acetaldehyde. It is necessary to note that the effects of gasotransmitters need not always be beneficial.[2]

NO

The nitrate-containing compounds have been used since the advent of nitroglycerin for medicinal purposes. NO,

and its critical role in endothelium-dependent vasorelaxation revolutionized the concepts of cell signal transduction.[3] The enzymatic NO synthesis from L-arginine occurs in almost every cell type, catalyzed by NO synthases. Abnormal NO metabolism has been described as the pathogenic process of many diseases. The incomplete list of disease conditions involving NO is hypertension, diabetes, ischemia-reperfusion, cardiac damage, heart attack, inflammation, cerebral thrombosis, erectile dysfunction, aging, degenerating neuronal diseases, septic shock, sunburn, anorexia, tuberculosis, and obesity.[2]

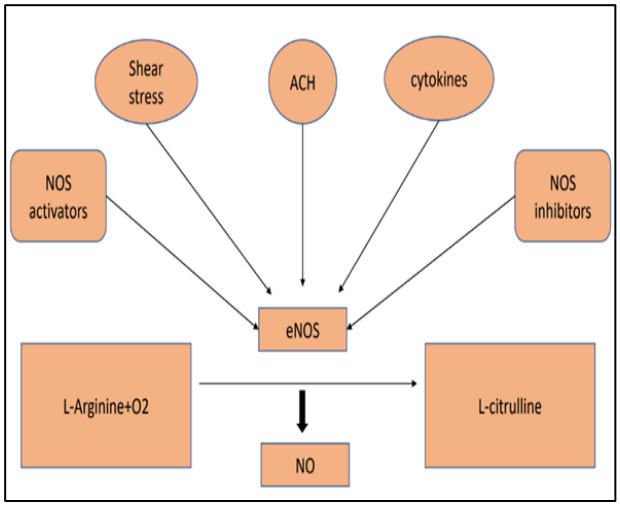

Figure 1: Depiction of stimulus for NO pathway.

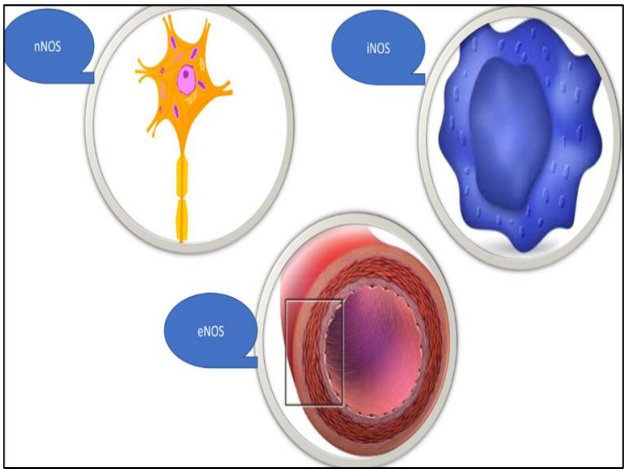

Figure 2: Types of NOS (nitric oxide synthase).

CO

The first indication of endogenous CO was given by Saint-Martin and Nicloux in 1898. In 1950, Sjostrand provided experimental evidence for the endogenous production of CO.[5] Three isoforms of microsomal heme oxygenases (HOs) are involved in enzymatic CO production *in vivo*.[2] Endogenous CO plays a vital role in long-term potentiation (LTP) as a retrograde messenger in the brain.[6] CO modulates the proliferation and apoptosis of smooth muscle and endothelial cells; its source comes from vascular walls. Relaxation of smooth muscles by CO has also been known.[7]

Regarding heme metabolism regulation, HO catalyzes the degradation of heme, as well as the production of CO, biliverdin, and ferrous iron. However, CO was not considered for its beneficial effects on HO until recently. The discovery of NO led to further research on membrane/receptor-independent signaling by gas molecules. In 1991, Marks and colleagues pioneered the resurgence of CO as a physiological signaling molecule.[8,9]

H_2S

Two pyridoxal-5'- phosphate-dependent enzymes, cystathionine-beta-synthase [CBS] and cystathionine-gamma-lyase [CSE], are responsible for the endogenous H_2S in mammalian tissues, which use L-cysteine as the primary substrate.[10] H_2S is produced by the nonenzymatic reduction of elemental sulfur using reducing equivalents obtained from glucose oxidation. The elimination of H_2S takes place via the kidney. These enzymes were characterized initially in the liver and kidney.[11] Homocysteine, a precursor of H_2S, is extensively studied because of its role in atherosclerosis. At physiological concentrations, H_2S reduced KCl-stimulated releases of the corticotropin-releasing hormone.[12] NaHS, a donor of H_2S, produces a concentration-dependent hyperpolarization and reduced input resistance of CA 1 neuron or dorsal raphe neurons.[13] This concentration range is physiologically relevant to the brain.[14] On applying weak tetanic stimulation, NaHS facilitated the induction of long-term hippocampal potentiation in rats by enhancing the NMDA-induced inward currents.[15] In the heart and blood vessels, H_2S has been demonstrated at physiological concentrations to relax vascular smooth muscle cells.[16,17]

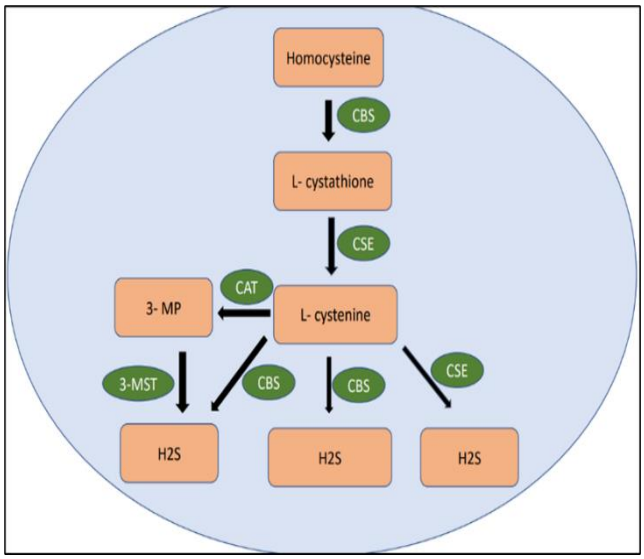

Figure 3: Endogenous source of H_2S production.

Table 1: Comparison of the action modes of neurotransmitters and gasotransmitters.

Variables	Release	Reuptake	Removal mechanism	Revert direction	Membrane receptors
Neurotransmitters	Exocytic vesicle	Yes	Enzyme dependent	Pre to the post-synaptic membrane	Necessary
Gasotransmitters	Cytoplasmic release	No	Non-Enzyme dependent	Bidirectional	Not-Necessary

NO AS A DRUG TARGET

Increased understanding of the essential role of nitric oxide (NO) in diverse physiologic processes and diseases has stimulated the development of multiple pharmacologic strategies to target the NO pathway. These approaches include therapies that directly or indirectly release or "donate" NO.

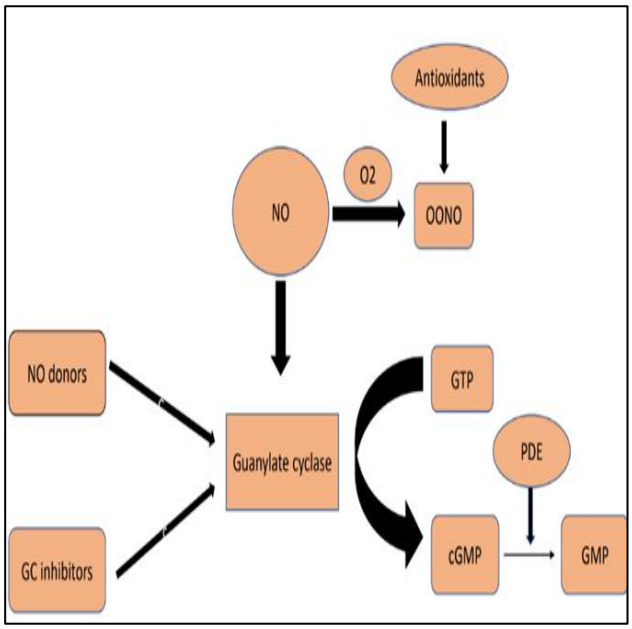

Figure 4: NO pathway.

NO donors

Several pharmacologic tools range from S-nitro-acetyl penicillamine (SNAP) to nitroprusside to the most long-acting NO donors, such as NOC-18.[18] NO donors have been used in patients like amyl nitrate, glyceryl trinitrate, and isosorbide dinitrate.[19] Other nitro vasodilators also possess the property of generating NO, like sodium nitroprusside.[20,21] Recently, a wide range of novel NO donor classes have emerged. Some of these drug classes are interesting for their potential therapeutic applications.

NO releasers

NO-releasing drugs are pharmacologically active compounds that release NO *in vivo* or *in vitro*. The important ones are as follows.

Sodium nitroprusside

In sodium nitroprusside (SNP), NO is incorporated as a nitrosyl group. SNP remains an effective, reliable, and commonly used drug for rapidly reducing significant hypertension regardless of the etiology, afterload reduction when blood volume is average / or the increased, and intraoperative-induced the blood pressure alterations.[22]

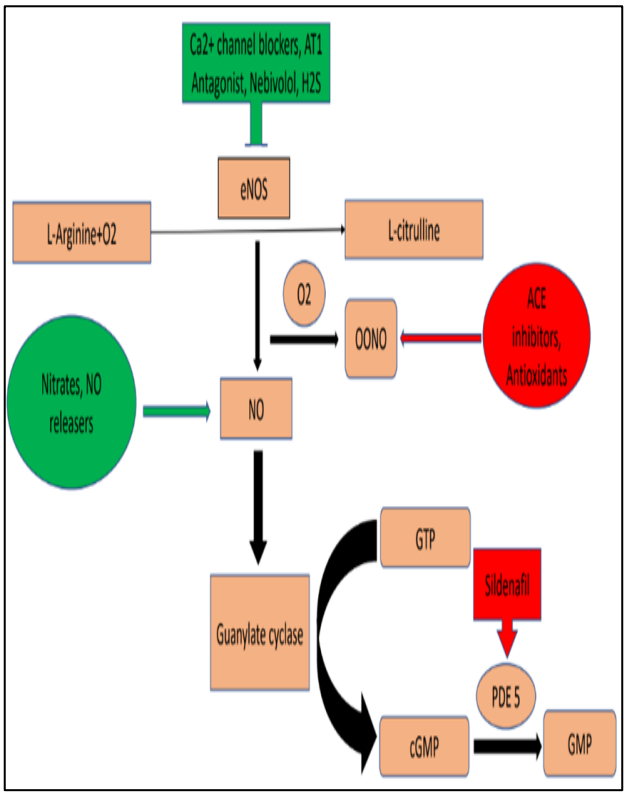

Figure 5: Drugs targeting NO pathway.

NO-releasing aspirins

NO-releasing aspirins are nitrate-ester compounds, including NCX-4016 and 2-acetoxy benzoate 2-(2-nitrox)-butyl ester (NCX-4215). The antiplatelet activity of nitro aspirins NCX-4215 and NCX-4016 are compared in vitro with aspirin. The results for maximal inhibition of arachidonic acid-stimulated platelet aggregation.[23] The antithrombotic activity of NCX4016 is present *in vivo* and reduces pulmonary thromboembolism in animal models.[24,25]

Agents modulating the no-pathway

Calcium channel blockers

1,4-Dihydropyridine calcium channel blockers (CCBs) have been used for many years in treating angina pectoris and hypertension. Their action mechanism inhibits the smooth muscle L-type calcium current, decreasing intracellular calcium concentration and inducing smooth muscular relaxation, 1,4-Dihydropyridine CCBs (nifedipine, nitrendipine, and lacidipine) can cause the release of NO from the vascular endothelium.[26] Nifedipine and Lacidipine have dual modes of action that may help explain the beneficial antihypertensive effect of the 1,4-dihydropyridines.[27]

ACE II inhibitors and angiotensin receptor blockers

ACE inhibitors exert beneficial pharmacological effects by increasing vascular NO activity.[28] Chronic ACE inhibition improves endothelial function in patients with high cardiovascular risk.[29] Treatment with an AT-1 antagonist can improve basal NO release and decrease the vasoconstrictor effect of endogenous endothelin-1.[28] The molecular mechanisms involved in the relationship between the ACE inhibitors as well as the NO are still unclear.

Beta-blockers

Some β-blockers may also interfere with the NO pathway. For example, nebivolol causes relaxation in a dose-dependent fashion.[30] Experimental studies have established that nipradilol, another NO-releasing beta-adrenergic blocker, enhances postischemic recovery and limits infarct size.[31] The assumption is that this is due to the activation of the L- Arginine/NO pathway.

Hydroxymethylglutaryl-CoA reductase inhibitors

Statins prevent hypoxia-induced down-regulation of eNOS. Statins block the GTP-binding Ras-like protein, Rho. Inhibition of Rho results in an increase in eNOS expression.[32] Thus, statins can enhance NO's bioactivity and improve endothelial function in patients with atherosclerosis.

Antioxidants and L-arginine

L- Arginine-induced vasodilation is much more pronounced in stenosed vessels.[33, 34] Vitamin C may potentiate NO activity and normalize vascular function in patients with CHD and classical risk factors. Plasma alpha-tocopherol was significantly correlated with the nitroglycerin response. Thus, alpha-tocopherol may preserve endothelial vasomotor function.

Positive clinical trials: CHAOS trial for CHD, SPACE trial for ESRD.[35,36]

Trials with no clinical benefit: GISSI-Prevenzione, HOPE trial.[37,38]

Phosphodiesterase inhibitors

Sildenafil is a selective inhibitor of phosphodiesterase type-5 that is orally effective and acts by NO-mediated mechanisms.[39]

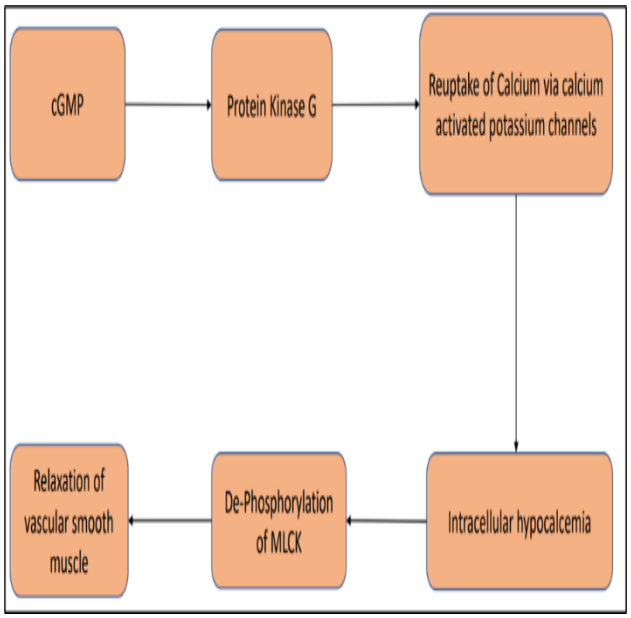

Figure 6: Mechanism of vasodilation by NO.

H_2S

Natural sources of H_2S

Allium vegetables benefit people with cardiovascular diseases. Only three of them, S-allyl-cysteine (SAC), diallyl disulfide (DADS), and diallyl trisulfide (DATS), have correlated with the H_2S signaling pathway.[40] SAC is a significant component in aged garlic extract. It was found that SAC and its analog significantly lowered mortality and improved cardiac function.[41]

Inorganic sulfite salts

NaHS and Na2S have been extensively used in studying the biological effect of hydrogen sulfide. NaHS is used as the H_2S donor, and it decreases inflammatory cytokines such as IL (interleukin)-6 and IL-8 levels and increases anti-inflammatory cytokine IL-10 levels in the plasma and lung tissues.[42] Another potential inorganic H_2S donor is calcium sulfide (CAS), present in Hepar sulphuris calcareum, which is more stable than the former.

Lawesson's reagent and analogs

Lawesson's reagent releases H_2S upon hydrolysis and has been used as an H_2S donor. Compared to inorganic sulfide, the release rate with Lawesson's regent is much slower. In

rats with alendronate (ALD)-induced gastric damage pretreatment with Lawesson′s reagent (27 µmol/kg) attenuated ALD-mediated gastric damage. Lawesson′s reagent also releases H_2S spontaneously upon hydrolysis. GYY4137, a water-soluble derivative of Lawesson′s reagent, showed that GYY4137 suppressed CVB3-induced secretion of enzymes implicated in cardiocyte damage, including LDH and CK-MB, and decreased inflammation.[43, 44]

Controllable H_2S prodrugs

The goal of controllable H_2S prodrugs was to develop H_2S prodrugs that are stable. Some of them are;

Thiol-activated H_2S prodrugs: In 2011, Xian's group developed the first N-mercapto-based derivatives, thiol-activated prodrugs, based on the instability of the N-SH bond. In this mechanistic study, Xian's group found that perthiol could also be a key intermediate in H_2S generation.[45] Perthiol H_2S prodrugs tested for myocardial ischemia/reperfusion (MI/R) injury in a murine model showed a significant reduction in circulating levels of cardiac troponin I and myocardial infarct size per area-at-risk, suggesting that perthiol H_2S prodrugs exhibit cardiac protection in MI/R injury.

Photo-induced H_2S prodrugs: The second type of controllable H_2S prodrugs is light-activated H_2S prodrugs. The first one is gem-dithiol-based- H_2S prodrugs. Then a photo-cleavable design (a 2-nitrobenzyl group) was introduced to protect the gem-thiols group.[46] Based on this strategy, several gem-dithiol-based H_2S prodrugs were prepared-ketoprofen-caged H_2S prodrugs.

H_2S and ace inhibitors[47]

The chemical structure of the drug Captopril contains a thiol moiety. Captopril forms its disulfide in the plasma or reacts with cysteine and glutathione to form mixed disulfides. Other ACE-I inhibitors are prodrugs undergoing hydrolysis in the liver to active forms containing a hydroxyl group. Zofenoprilat has a thiol group, and it is known to increase the levels of H_2S metabolites in the plasma of mice. Pro-angiogenic and anti-apoptotic actions of Zofenopril are reported in association with H_2S release. Spirapril and Temocapril are other sulfur-containing ACE inhibitors.

H_2S in cancer therapy

Enzalutamide and Apalutamide, the androgen receptor antagonists used in prostate cancer treatment, are N-disubstituted thiourea derivatives. The thiourea moiety is assumed to release H_2S and enhance their property of androgen receptor antagonism.[48,49] Observational studies show that enzalutamide and apalutamide are more potent clinically when compared to bicalutamide, which doesn't show this effect.

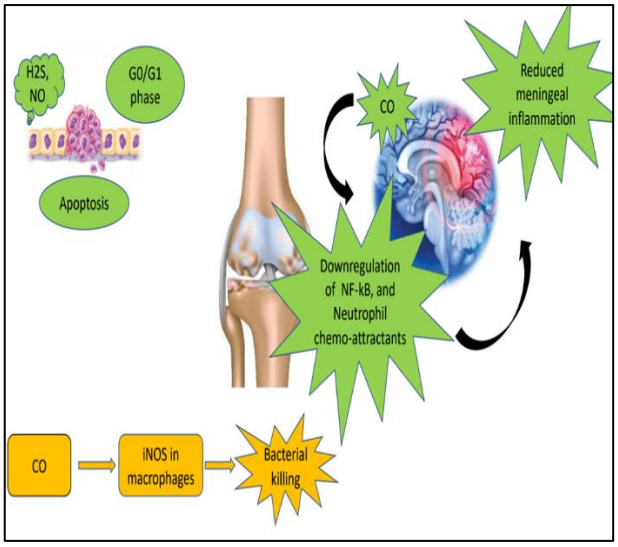

Figure 7: Pulmonary, Cardiovascular, and gastroprotective roles of Gasotransmitters.

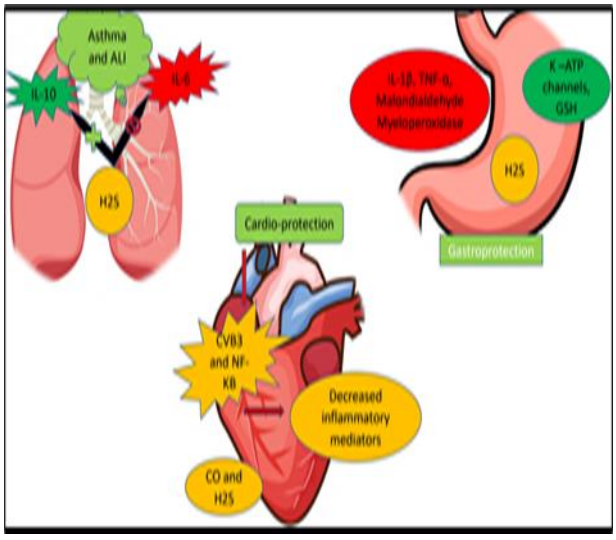

Figure 8: Inflammatory and cell cycle regulatory role of gasotransmitters.

CO

Every cell in a mammalian organism expresses haem oxygenase enzymes and thus has the potential to generate CO, which has crucial physiological roles continuously. The vital role of CO has been confirmed in organisms lacking haem oxygenase 1. For example, a clinical case report identified an individual deficient in HO1 who died prematurely.[50] The Hmox1knockout mouse is embryonically lethal in >95% of all fertilizations. Unlike NO and H_2S, which interact indiscriminately with several intracellular targets, CO reacts exclusively with transition metals. CO is relatively stable because of its chemical reactivity compared with NO and H_2S. It primarily targets metals with a specific redox state, for example, iron, thus offering more flexibility and versatility for the development of CO based pharmaceuticals. Against the

negative attributes associated with CO is the recent emergence of potent protective gas properties related to preclinical efficacy. CO-releasing molecules (CORMs) originated from substantial medicinal chemistry efforts. Although CO is well understood physiologically and pharmacologically, questions remain about the application of inhaled CO as a therapeutic.

CO-RM (Carbon monoxide releasing molecules)

These are exogenous molecules designed to release CO in a controlled fashion. CO has various effects on our organ systems, as evidenced by preclinical studies.[51] CO-RMs are shown to have vasodilatory effects and are delivered to decrease intra-hepatic pressure. These molecules are shown to possess anti-inflammatory activities. CO is also established to have anti-apoptotic effects in normal cells and pro-apoptotic in hyper-proliferative and dysregulated cells.

Types of CO-RM

Transition metal CO-RM: Complexed with iron, molybdenum, ruthenium, manganese, cobalt, rhenium

Photo CO-RM: These are molecules where CO release is induced by light. Photoremovable, Photocleavable, and Photocaged compounds protect them.

ET CO-RM: They release CO by esterase activity in our bodily systems

CO-prodrugs: Methylene chloride, sodium boranocarbonate, deltic acid, squaric acid, croconic acid, rhodizonic acid

Enzyme hybrids: They are based on the synergism of the heme oxygenase system and CO delivery. Some of them are dimethyl fumarate, NRF-2

Others: CarboxyHb infusion, porphyrins, carbon monoxide releasing materials.

Role of CO in therapeutics

Inflammation

The anti-inflammatory properties of CO and CORMs make them a potential therapeutic application for inflammatory diseases. A typical example of the positive effects of CO can be seen in a mouse model of cerebral malaria. In this model, CO administered three days after parasite infection completely prevented brain edema.[52] Administration of CORM2 or CORM3 resulted in an increased survival rate in mice that had sepsis.[53] Among the various inflammatory and related disorders like rheumatoid arthritis and osteoarthritis, intraperitoneal administration of CORM3 in collagen induced arthritis suppressed the clinical manifestations of the disease. The compound was administered to animals therapeutically, beginning 22 days after the onset of the rash, and the beneficial effect of CORM3 was evaluated after 31 days.[54] Bactericidal effects against Pseudomonas aeruginosa by CORM3 improved survival in mice. When CORM3 is administered in the presence of macrophages, it enhances bacterial killing capabilities that lead to improved survival, primarily driven by the inflammasome.

Cardiovascular disease

In a mouse myocardial infarct model of coronary artery occlusion, intravenous infusion of CORM3 before reperfusion reduced infarct size, fibrillation, and tachycardia. These cardioprotective mechanisms mediated by CORMs probably involve potassium channels, as small amounts of CORMs are lost in the presence of inhibitors of mitochondrial ATP-dependent potassium channels. B-KCa channels are also crucial in several physiological phenomena, including oxygen sensing and vasodilatation.[55] CO prevents intimal hyperplasia by inhibiting hyperproliferative vascular smooth muscle cells in rats, mice, pigs, and primates. In addition to blocking vascular smooth muscle cells, CO increases mobilization and recruitment of bone-marrow derived progenitor cells to the denuded vessel and enhances reendothelialization. CO in vascular smooth muscle cells is NO-independent and requires cGMP and p38 mitogen-activated protein kinase.[56, 57] Coated stents release agents such as rapamycin to block vascular smooth muscle cell proliferation.

Organ transplantation[51]

Transplantation has been the field of study in which most progress has been made in evaluating the beneficial effects of CO. CO has been evaluated in every transplantable organ system as well as islets and has shown results by treating the donor, the organ, or the recipient. In a model for cardiac allograft rejection in rodents, inhaled CO Or $CORM_3$ administered once a day for eight days prolongs heart graft survival. In an experimental model of non-heart-beating donor kidneys in pigs, low concentrations of CORM3 ameliorated a loss in renal blood and urine flow, suggesting a therapeutic potential for the use of CORMs in the clinical setting of organ preservation and transplantation may be feasible. A niche indication for which CO gas and CORMs have produced promising results is the preservation of organs for transplantation. CO gas saturated preservation solution ameliorated intestinal ischemia-reperfusion injury occurring after transplantation. Collectively, the data with transplantation make it clear that CO gas and CORMs reduce vascular injury and improve function at reperfusion. Whether this could be implemented as adjuvant therapy for increasing viable organs or long-term storage for transplantation remains to be tested.

CO-based pharmaceuticals

The desired characteristics of CO-based carbonyls are as follows:[51] Solubility in water, stability to oxygen, the

integrity (or prolonged decay) of the M(CO)y fragment in the circulation, cell membrane permeation and the viable CO release in diseased tissues and they also must exhibit low toxicity and rapid excretion of the scaffold that is left after CO release.

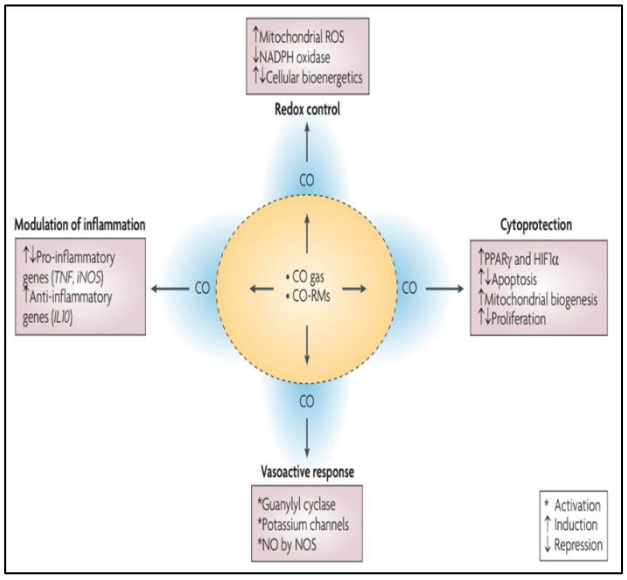

Figure 9: In preclinical models, potential mechanisms of action of carbon monoxide (co) delivered as a gas or co-releasing molecule (co-rM).

The homeostatic and beneficial effects of CO gas and CO-RMs in animal disease models occur through multiple cellular and molecular mechanisms of action that include redox control, cytoprotection, modulation of vasoactive responses, and modulation of the innate immune response. HIF1α, hypoxia-inducible factor 1α; IL10, interleukin-10; iNOS, inducible nitric oxide (NO) synthase; PPARγ, peroxisome proliferator-activated receptor-γ; ROS, reactive oxygen species; TNF, tumor necrosis factor. Adopted from Moterlini, R., Otterbein, l "The therapeutic potential of carbon-mono-oxide" nature reviews drug discovery 9, 728-43

CURRENT STATUS OF GASOTRANSMITTERS IN THERAPEUTICS

NO

Inhaled NO is FDA-approved for only one indication, persistent pulmonary hypertension of the newborn. NO was tried as NORS (Nitric oxide Releasing Solution) in case of covid illness. This was conducted as a multicentric parallel arm study with primary outcomes, including symptomatology and secondary effects like hospitalization and oxygenation [NCT04337918]. Regarding the safety of nitric oxide, it ranges up to 160ppm for 30 minutes as per the phase I study.[52] In the case of the heart, transplantation inhaled nitric oxide of 20 ppm reduced pulmonary vascular resistance and improved cardiac functioning. Another trial is the phase III REBUILD trial for pulmonary hypertension in patients with idiopathic pulmonary fibrosis [NCT03267108]. Another pilot clinical trial assessing inhaled nitric oxide's safety and efficacy in acute bronchiolitis has shown promising efficacy and safety profile [NCT03053388]. A phase I study on MK-8150 has shown promising results. However, this drug is prone to tolerance even though it acts by a unique mechanism of releasing NO by CYP3A4-mediated metabolism [NCT01590810]. These suggest they could be clinically helpful drugs shortly.

H_2S

A phase I clinical trial involving a novel H_2S prodrug was done. SG1002 capsules were designed to assess safety and changes in H_2S and NO bioavailability in healthy and HF subjects. This trial showed that H_2S enhanced NO's bioavailability in the blood and reduced BNP levels [NCT01989208]. For H_2S in the case of peripheral arterial disease, an observational study showed that H_2S could be potentially used as a prognostic marker [NCT01407172]. This was also assessed for its usefulness in sepsis and stroke in the case of critically ill patients, which showed this correlate well with the severity of disease and outcome [NCT01088490]. A phase IIb study showed that ATB-346 250 mg OD significantly reduced the gastric effects of Naproxen in individuals [NCT03291418]. As the trend says, this gasotransmitter has an immense role in diagnostics than Therapeutics.

CO

Some trials looked into the anti-inflammatory effects of carbon monoxide in the case of lung infections [NCT00094406], and ARDS [NCT03799874], one of which the results were not known, and the other is in the recruiting phase. Inhaled CO in patients with idiopathic pulmonary fibrosis showed no significant difference compared to placebo [NCT01214187]. Another study was planned to assess the effect of CO on post-operative paralytic ileus; unfortunately, the study didn't commence due to administrative reasons. HBI-002, an orally administered liquid containing carbon monoxide (CO), was developed, and its phase I trial is in the beginning stage [NCT03926819]. These suggest that we have a long way to go to unlock the potential of CO as a therapeutic option.

CONCLUSION

The role of these gasotransmitters in homeostatic functions and pathological events is undeniable. But the complexity of these compounds has to be decoded for further progress of research in this field. The failure in clinical trials has proven that we have just started to learn about a complex physiological system with numerous interconnections. The knowledge from this review suggests that these molecules depend on each other for many roles. So, quality research is required to overcome the existing challenges and successful therapeutic development in the future.

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