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Gaseous mediators (H_2S, NO and CO) a new approach in gastrointestinal protection

Mediadores gaseosos (H_2S, NO y CO) un nuevo enfoque en la protección gastrointestinal

Elizabeth Arlen Pineda-Peña [a], Aracely Evangelina Chávez Piña [b]

Abstract:

Gastrointestinal damage is generated by a wide range of harmful agents, and is the result of the activation of inflammatory, oxidant and cytotoxic mechanisms, that together overwhelm the "mucosa defense" of the gastrointestinal (GI) tract. It is currently known that mechanism by which gastric damage is generated are slightly different from those that generate intestinal damage. The treatments available on the market such as citoprotectors, the use of selective cyclooxygenase 2 (COX-2) inhibitors, the co-prescription of acid suppressive agents and the use of prostaglandin analogues are mainly focused on the mechanisms of gastric damage, and their use has begun to be limited due its adverse effects at intestinal and cardiovascular level. Due to its multifactorial origin, the prevention and treatment of gastrointestinal damage requires effective therapies that can protect both gastric and intestinal level modulating more than one mechanism. Recently, it has been reported the contribution of gaseous mediators such as nitric oxide (NO), hydrogen sulfide (H_2S) and carbon monoxide (CO) in many physiological processes in the gastrointestinal tract, including the maintenance of GI mucosal barrier integrity, the decrease of inflammatory mediators and the reduction of oxidative stress. Experimental evidence has shown promising results regarding the gastric safety of these gasotransmitters, especially those coupled to nonsteroidal anti-inflammatory drugs (NSAIDs). This review will try to give a general overview of the mechanisms of gastric and intestinal damage, their main differences, the existing therapies for their treatment, and the information available on gastransmitters with a brief description of roles of each of these gaseous molecules.

Keywords:

Gasomediators, Gastrointestinal damage, H_2S, NO, CO.

Resumen:

El daño gastrointestinal se genera por la acción de diversos agentes nocivos y es el resultado de la activación de mecanismos inflamatorios, oxidantes y citotóxicos que en conjunto superan la "defensa de la mucosa" del tracto gastrointestinal (GI). Actualmente se sabe que los mecanismos por los que se genera el daño gástrico son ligeramente diferentes a los que generan el daño intestinal. Los tratamientos disponibles en el mercado como los citoprotectores, el uso de inhibidores selectivos de la ciclo-oxigenasa 2 (COX-2), la prescripción de agentes supresores de ácido y el uso de análogos de prostaglandinas, se centran principalmente en los mecanismos de daño gástrico, y su uso ha comenzado a ser limitado debido a sus efectos adversos a nivel intestinal y cardiovascular. Debido al origen multifactorial, la prevención y el tratamiento del daño gastrointestinal requiere terapias efectivas que puedan proteger tanto a nivel gástrico e intestinal modulando más de un mecanismo. Recientemente, se ha informado la contribución de los mediadores gaseosos óxido nítrico (NO), sulfuro de hidrogeno (H_2S) y monóxido de carbono (CO) en procesos fisiológicos en el tracto gastrointestinal, incluido el mantenimiento de la integridad de la barrera de la mucosa GI, la disminución de los mediadores inflamatorios y la reducción del estrés oxidativo. La evidencia experimental muestra resultados prometedores en cuanto a la seguridad gástrica de estos gasotransmisores, especialmente los acoplados a los antiinflamatorios no esteroides (AINE). Esta revisión pretende dar una visión general de los mecanismos de daño gástrico e intestinal, sus principales diferencias, las terapias existentes para su tratamiento y la información disponible de los gasotransmisores con una breve descripción de las funciones de cada una de estas moléculas gaseosas.

Palabras Clave:

Gasotransmisores, Daño gastrointestinal, H_2S, NO, CO.

[a] Carrera Médico Cirujano, Facultad de Estudios Superiores (FES) Zaragoza, Universidad Nacional Autónoma de México, CDMX, México. https://orcid.org/0000-0002-1196-429X, Email: arlen.pineda@gmail.com, ea.pineda@comunidad.unam.mx

[b] Laboratorio de Farmacología, Escuela Nacional de Medicina y Homeopatía (ENMyH), Instituto Politécnico Nacional (IPN), CDMX, México. https://orcid.org/0000-0002-0607-2545, Email: arapina@yahoo.com

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INTRODUCTION

Gastrointestinal damage includes gastric ulcers, peptic ulcers or intestinal ulcers characterized by deep erosions of the gastric or intestinal mucosa with the presence of perforation and bleeding in its most severe forms, it is considered a serious public health problem.[1,2] Gastrointestinal damage is associated with the consumption of irritating substances such as tobacco smoking, alcohol, irritating food consumption, the chronic use of drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy, radiotherapy, and even situations of continuous stress.[3,4] It has been reported that gastrointestinal damage occurs from imbalance between those harmful agents and protective mechanisms, where an overwhelmed mucosal defense leads to changes in cell membrane integrity, gastric cellular redox state, depletion of endogenous prostaglandins (PGs) production and activation of inflammatory pathways.[5,6,7] To reduce the appearance of gastrointestinal ulcers in the susceptible population, well-established therapies have been developed such as the use of selective Cyclooxygenase 2 (COX) inhibitors, the co-prescription of acid suppressive agents and the use of prostaglandin analogues.[8,9] These therapies have little effectiveness, very defined prescription criteria and even the appearance of adverse effects at the intestinal level.[8] Recently, the cytoprotective effect of endogenous gaseous mediators such a as nitric oxide (NO), hydrogen sulfide (H_2S) and carbon monoxide (CO) reported *in vitro* and *in vivo* studies, have increased the interest in their use for the treatment and prevention of gastric and intestinal damage, and even inflammatory diseases.[1,10,11]

GASTRIC AND INTESTINAL INJURY MECHANISMS (A GENERAL OVERVIEW)

In the past decades, several experimental models have been used to elucidate the mechanisms by which gastric damage is generated (Figure 1).[12] These models allowed the search for new therapies by providing valuable and specific information on the possible mechanisms involved.[13,14] There are several experimental models with different mechanisms of injury for example: the pylorus ligation and acetic acid-induced gastric damage models mainly provide information on mucus reduction and excess of hydrochloric acid (HCl) production; ethanol-induced, cold-water immersion induced ulcer and cold-restraint stress induced gastric damage model, which provide information on local damage to tissues mainly due to sub-epithelial hemorrhages, cellular exfoliation, inflammatory cell infiltration, mucosal oedema, and oxidative stress increase; the model of NSAIDs-induced gastric damage provides information on the mucosal blood flow decrease, oxidative stress increase and inflammatory effect; and even the combination of all the models that seek to evaluate ulcer healing.[7,15,16] More recently, experimental animal models that are looking for gastrointestinal toxicity (GIT), shows that enterohepatic cycling in rodents is higher and bacteria are more abundant throughout their small intestine than in humans.[17,18] However, intestinal ulcer formation features many similarities across these species and the model of oral administration and intraperitoneal injection of NSAIDs caused quantitatively and qualitatively very similar results.[18] For this reason, they are the most used experimental models to study the mechanisms of damage and possible treatments.[19]

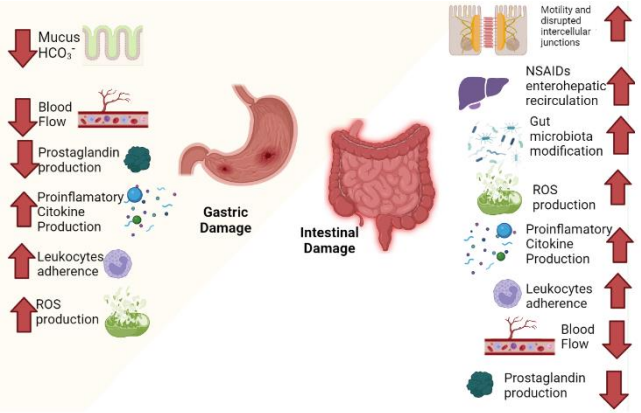

Figure 1. The mechanism implicated in the pathogenesis of gastric and intestinal damage, including the local actions of topical irritant effect on the epithelium and systemical actions.[5,6]

The pathogenesis of gastric damage suggests multiple mechanisms including the local actions of topical irritant effects on the epithelium and systemical actions, generated mainly by the increase of inflammatory activity and the production of reactive oxygen species (ROS) and oxidative stress.[16, 20, 21] In the local actions, mucosal insult commonly by erosive agents, acid secretion increase, mucosal blood flow decreases or drug "ion trapping" phenomenon, leads to cellular osmotic imbalance, followed by uncoupling of the oxidative phosphorylation in mitochondria, decreased the intracellular ATP concentration and the subsequent production of reactive oxygen species (ROS).[7,14,20,22] ROS generation increase the gastric levels of malondialdehyde (MDA) while the levels of antioxidant molecules such as superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GSH-Px) decresed.[5,23,24] These actions result in the increased permeability and subsequent mucosal damage characterized by cellular exfoliation, mucosal oedema formation, epithelial lifting and disruption of the vascular endothelium.[20,25]

The systemic effects in gastric damage produced as a consequence of both cyclooxygenase enzymes (COXs) and prostaglandins (PGs) inhibition, such as prostaglandin E_2 (PGE_2) and prostaglandin I_2 (PGI_2), begin with the inhibition of the secretion of mucus and bicarbonate and alterations in the microcirculation.[6,7,26,27] In addition, the non-prostaglandin-mediated pathway of mucosal damage (by NSAIDs), includes the ROS production and inflammatory response triggered by local damage of gastric epithelium.[20,27] Which increase inflammatory soluble mediators release, such as tumor necrosis factor-alpha (TNF-α), interleukin 1beta (IL-1β), interleukin 6 (IL-6) and interferon-gamma (IFN-γ), that triggers a massive

neutrophil polymorphonuclear leukocytes (PMN) recruitment to the vascular endothelium by an increase in nuclear factor-κB (NFκβ) activity, an increase in the expression of integrins (CD11 and CD18) in endothelium, high affinity adhesion molecules, such as intermolecular adhesion molecules 1 (ICAM-1) and vascular cell adhesion molecule (VCAM), myeloperoxidase (MPO) and leukotriene B_4 (LTB_4) in neutrophils.[7,14,28,29,30] The excessive neutrophil adhesion to the vascular wall produces a reduction in gastric mucosal blood flow and the release of proteases and ROS production that increases epithelial necrosis.[7,14]

The mechanisms of gastric damage are well documented, most of research assuming that the mechanism of intestinal damage is the same as in gastric damage. However, substantial differences between them have been identified (Figure 1), therefore it is necessary to design new effective therapeutic alternatives.[10] Some authors consider intestinal injury mechanisms as a multi-hit process, where the topical (luminal) effects are considered a "first hit" and the subsequent inflammatory response can be considered a "second hit" which aggravates and enhance the topical effects.[19] These luminal effects are characterized by interactions of the drug (and/or metabolites) with the enterocytes membranes, alteration of their biophysical properties, increased intestinal permeability, possible induction of endoplasmic reticulum (ER) and mitochondrial stress.[18,22,31] Experimental findings suggest that inhibition of COX pathway by NSAIDs may shunt the metabolism of arachidonic acid (AA) into the other direction, such as the lipoxygenase (5-LOX) pathway, that could lead to oxidative stress due to increased production of superoxide from the 5-LOX-catalyzed peroxyradical formation and the possible decrease in glutathione (GSH) due the reduction of peroxyradicals.[19] Unlike the gastric mucosa, there is no proof that the reduction in mucus secretion and excess in HCl production contributes to the development of intestinal lesions associated with NSAID administration and interestingly drugs suppressing acid secretion have been shown to even aggravate small bowel injuries.[32,33]

The mechanisms of intestinal injury have mostly been identified thanks to NSAIDs- induced intestinal damage models, suggesting that both COXs (COX-1 and COX-2) and PGs (PGE_2 and PGI_2) helps maintaining intestinal mucosal integrity, acting as potent vasodilators that neutralize back-diffusing acid, dilutes and removing any potentially toxic substances that have entered the subepithelial space when epithelial barrier function is compromised.[33,34,35] It is also of interest that NSAIDs are metabolized in the liver and conjugated with a glucuronic group for its excretion in bile, while the bacterial enzyme β-D-glucuronidase enhances their resorption in the ileum leaving the NSAIDs in its free form, leading to the harmful re-exposure of the intestinal mucosa to these compounds.[35,36] The effects of inflammatory pathway activation on the intestine damage is more related to bacteria and bacteria-derived proinflammatory mediators invading mucosal layers beyond the epithelium, Toll-like receptors (TLR) mediated signaling pathways are activated by lipopolysaccharides (LPS)-mediated, and neutrophils begin to infiltrate into the damage areas.[19] Toll-like receptors (TLRs) such as Toll-like receptor 4 (TLR_4) (expressed on monocytes and macrophages in the lamina propria), activates NFκβ, followed by activation of the proinflammatory cytokines, such as TNF-α.[19,35] TNF-α is involved in enterocyte apoptosis and aggravating the damage by enhanced ROS or proteases production. Finally, it is reported that an increase of enteric gram-negative bacteria contributes to NSAID enteropathy, since these bacteria can metabolically convert NSAID glucuronides and facilitates higher amounts of free drugs at intestinal level.[19,36] Also, bacteria could invade the deeper layers of the mucosa when the tight junctions become more permeable after a toxic insult and subsequently activate TLR_4 and inflammatory pathway.[19,37] However, new experimental models are needed in order to understand clearly the mechanisms of small intestine ulceration and provide potential strategies for further clinical treatment.

CURRENT THERAPIES AGAINST GASTROENTEROPHATY

The multifactorial origin of gastrointestinal damage had not been considered for the development of gastroprotective therapies.[37] The eradication of *Helicobacter pylori* treatments has not decreased the cases of gastrointestinal damage, it is evident that the mechanisms described (above) for the gastrointestinal damage are becoming more important for the development of new therapies.[3,38] The current therapies assumed that both damages shared the same mechanisms.[35] As it has been recently observed, the mechanisms have marled differences, so not all therapies would be useful to treat both types of damage. The therapies for gastrointestinal damage prevention and treatment, considers first the co-prescription of acid suppressive or cytoprotective agents, and second, the use of selective COX-2 inhibitors.[8]

The co-prescription of acid suppressive or cytoprotective agents includes the use of prostaglandins analogues (such as Misoprostol), the evidence reports that its effectiveness in reducing the gastrointestinal damage is accompanied by marked adverse events including diarrhea, abdominal pain, the inconvenience of multiple daily dosing, and the potential abortifacient activity in women of child-bearing potential.[8,19] Meanwhile, the use of Sucralfate and antacids as a useful treatment to neutralize gastric acid and forming a protective coat in the epithelium, it is not a therapy with convincing long-term results and even its use in the intestine is not consistent.[19,39]

On the other hand, it is known that the use of acid secretion inhibitors only treats one of the factors that generates gastric damage and could increase duodenal ulcers by altering the pH of the gastric content, the activation of proteolytic enzymes (such as pepsin) and increase the absorption of certain drugs such as NSAIDs.[8,19,35,37] The two main acid suppressive agents are the H_2-receptor antagonists and the proton pump inhibitors (PPIs). H_2-receptor antagonists (mainly ranitidine and cimetidine),

reduces gastric damage but also increase the risk of intestinal ulcer bleeding because of masking warning symptoms such as headache, stomachache or sickness.[8] Also, both can interact with a number of administered drugs by affecting the hepatic metabolism or to an effect on the absorption of concomitantly administered drugs.[40,41] Recently US Food and Drug Administration (FDA) reported that "acceptable" levels of N-nitrosodimethylamine (NDMA) were found in commercial ranitidine tablets, where the NDMA final quantity could vary due to the subsequent conditions of storage.[41,42] NDMA is a chemical shown to induce tumor formation in the gastrointestinal tract, liver, lungs, and kidneys in animals.[41] Taken together, nowadays H_2-receptor antagonists can no longer be recommended to prevent NSAID gastropathy.[8] In the case of proton pump inhibitors (PPIs), omeprazole is the most prescribed as a co-therapy against gastric damage, and its effective to treat gastric and duodenal ulcers, it is important to consider that the mucosa of the intestine does not have a proton pump.[37,43] Therefore, the protective effect of PPIs in the intestine could be attributed to its recently reported antioxidant activity.[44] PPIs actually exacerbate NSAID-induced enteropathy, which means that patients with the concomitant use of PPIs agents with both selective and nonselective NSAIDs are highly susceptible for intestinal ulcers.[8,37,45] The evidence indicates that PPIs administration generates changes the intestinal flora, by a substantial increase in Gram-negative bacteria and a significant decrease in the numbers of actinobacteria in the intestinal mucosa.[35,46] Gram-negative bacteria can metabolically convert NSAID glucuronides and facilitate higher amounts of free drugs at intestinal level.[19,36] In addition to dysbiosis, the adverse effects reported from the use of omeprazole include nephrotoxicity, anemia and malabsorption.[37,43,47,48]

Regarding the use of selective COX-2 inhibitors (Coxibs) to reduce NSAIDs gastric adverse effects, these drugs at the time showed a decrease in gastric damage. However, specialized studies concluded that Coxibs alters the natural balance between anti-thrombotic and pro-thrombotic action in platelets, leading to an increase in thrombotic cardiovascular events in Coxibs chronic consumption.[8,49,50] Therefore, their use is limited to a certain group of patients with low risk of cardiovascular death.[32,51] Thus, until now there is not a fully effective therapeutic approach either in the prevention or in the treatment of gastroenteropathy.

NEW THERAPEUTIC APPROACH TO GASTROENTEROPHATY

In the understanding of the mechanisms of gastric damage, new studies have reported that gaseous mediators nitric oxide (NO), hydrogen sulfide (H_2S) and carbon monoxide (CO) contribute to many physiological processes in the gastrointestinal tract.[2] These endogenous gaseous mediators are involved in the maintenance of GI integrity, exhibiting gastroprotective action by accelerating ulcer healing and modulating gastric blood flow and gastro-duodenal secretion.[1,32] The emerging evidence shows the potential of gasotransmitters for drugs development against gastrointestinal damage (Figure 2). Therefore, based on the possible therapeutic properties of NO, H_2S and CO, preclinical and clinical studies have shown promising effects of novel gaseous mediators-based NSAIDs, which are the first therapies designed to deal with gastric and intestinal damage.[32]

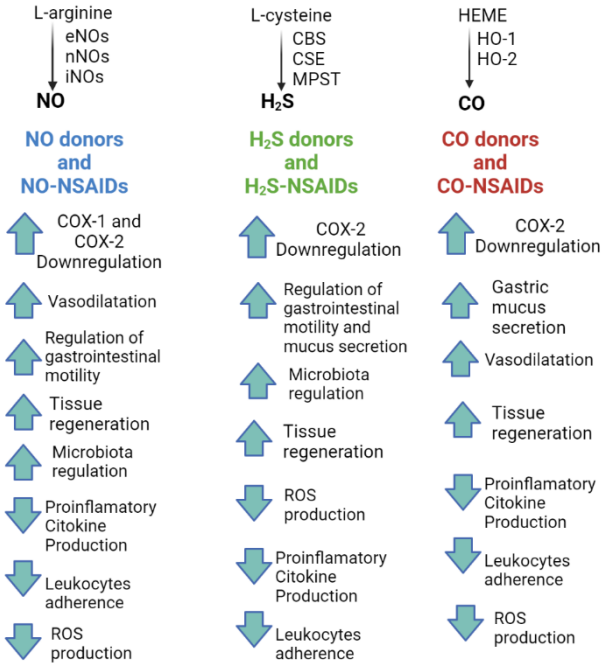

Figure 2. Possible mechanisms of action of NO-, H_2S-, CO-releasing NSAIDs in the gastric and intestinal tract.[2,32]

Nitric Oxide (NO)

Nitric Oxide (NO) is an unstable gas that is produced from L-arginine by constitutive NO synthase (NOS) and inducible NOS (iNOS) enzymatic pathways, with the resulting production of L-citrulline and NO.[52,53] The three NOS isoforms: neuronal NOS (nNOs), endothelial NOS (eNOS) and inducible NOS (iNOS) are involved in the maintenance of GI mucosal integrity at different moments.[2,54] The nNOs isoform located in the neurons of central and peripheral nervous system, and eNOS localized in platelets and endothelial cells, are constitutive isoforms that produce small amounts of NO (pmol/l) in healthy situations.[35,55] While iNOS isoform is located in endothelial cells, smooth vascular muscle, neutrophils, macrophages and hepatocytes, is able to produce high amounts of NO (nmol/l) in response to stress factors or inflammatory cytokines.[2] NO binds and activates guanylate cyclase, thereby stimulating the conversion of GTP to cGMP, which in turn activates protein kinase G (PKG), with downstream phosphorylation cascades leading to effector functions.[54] In the gastrointestinal tract the constitutive NO production is involved in the vagally-mediated accommodation reflex, emptying of the stomach and small bowel motility, furthermore NO contributes in the alkaline production, decrease secretion of acid as well as in vascular perfusion, and tissue regeneration.[2,35,55,56] Nitric oxide (NO)-

releasing NSAIDs (NO-NSAIDs), was developed by chemically adding a nitroxybutyl or a nitrosothiol moiety to the parent NSAID via a short-chain ester linkage.[57] Although, NO-NSAIDs protective effect could be attributed mainly to its vasodilator action, animal studies have demonstrated that NO-NSAIDs protect gastric mucosal by mechanisms independent of prostaglandins.[58,59,60] Such as inhibition of the release of the proinflammatory cytokines, reduced adherence of neutrophils and their infiltration of gastric tissue resulting in diminished reactive oxygen species (ROS) production and decreased oxidative stress.[32,58,61,62] Moreover, NO-NSAIDs can regulate the tight junctions of the gastric and intestinal epithelial cells through mechanisms involving inhibition of protein and lipid oxidation and the maintenance of redox homeostasis.[63] The absence of toxic GI effects of NO-NSAIDs, such as NCX-4016 (NO-aspirin) and NCX-530 (NO-indomethacin) against HCl/ethanol-induced damage.[35,59,64] Is also confirmed NCX-4016 (NO-aspirin) GI safety in either normal or diabetic rat stomachs.[65] The strong evidence of the therapeutic potential of NSAIDs in several clinical scenarios, together with their gastric safety, has made it possible to explore their use at higher doses and in conjunction with other medications, if necessary.[66,67] Some of these NO-NSAIDs have entered phase II studies in patients with type 2 diabetes and peripheral arterial disease or completed phase III clinical trials.[35,57,68,69,70] However, there is still a long way to go to determine which NO-NSAIDS will see their commercial therapeutic application.

Hydrogen sulfide (H_2S)

Although it has long been known as a toxic gas with a peculiar odour, hydrogen sulfide (H_2S) it has recently been described as a gaseous transmitter.[71] Under physiological conditions, H_2S is produced using L-cysteine (L-Cys) as the substrate mainly by cystathionine-β-synthase (CBS) and cystathionine-γ-lyase (CSE) enzymes, which are expressed in the enteric nervous system (ENS) and brain neurons.[72,73] While mercaptopyruvate sulfurtransferase (MPST) in mitochondria uses 3-mercaptopyruvate as substrate to produce H_2S.[73] H_2S concentrations can vary according to tissue, but have been reported to be between 50 and 160μM.[74] In addition to this 'H_2S synthesizing enzymes', some non-enzymatic routes for H_2S generation have been identified, where H_2S could be produced and metabolized by microbiota within the gut using cysteine degradation or even a source of H_2S such as hydrogen sulfide (NaHS).[32,75,76] This additional source of H_2S, could locally increase the concentration of H_2S above safe limits, which could generate some pathologies.[75,76] However, it has been suggested that the intestinal epithelium may serve as a "metabolic barrier" to the diffusion of bacteria-derived H_2S into the lamina propria, since H_2S is rapidly inactivated by a complex of mitochondrial enzymes collectively referred to as the "sulfide oxidation unit".[74,77,78] Recently, the properties of H_2S in the gastrointestinal tract have been evidenced, in part due to the development of H_2S-releasing drugs (Figure 2).[79,80] H_2S acts as a signaling molecule that maintains the integrity of the mucus layer, participating in the control of motility and vascular tone in gastrointestinal tract .[81,82] H_2S also has roles in glycemia control in gastrointestinal organs.[83,84] It has been reported that H_2S donors can prevent the decrease of gastric mucosal blood flow caused by NSAIDs.[85,86] In addition, H_2S contributes to protect the gastrointestinal mucosa and against lesions induced by NSAIDs and other noxious factors.[32,62,87,88,89,90] Where the protective effects of H_2S in gastrointestinal mucosa could be attributed to its properties to enhanced mucosal microcirculation, suppression of pro-inflammatory cytokines expression, decrease of the TNF-α signaling and leukocyte adherence.[32,74,91] It is important to mention that H_2S-donnors (such as ATB-429) have been reported their ability to accelerate the healing of colonic ulcers in rodents.[92,93] Which seems to be particularly important due to the need for an effective therapy against the intestine NSAID adverse effects.[94] Until now, there are promising advances in the development of H_2S donor drugs for the treatment of inflammatory pathologies which shows gastric and intestinal safety. Such as ATB-429 an H_2S-releasing derivative of mesalamine, with significant anti-inflammatory and antinociceptive effects on inflammatory bowel disease (IBD) in murine model.[92] ATB-337, an H_2S-releasing diclofenac, decreases paw edema evoked by carrageenan and protects from intestinal damage.[95] Similarly, H_2S-releasing ketoprofen ATB-352, reported a decrease in the inflammation and concomitant bone resorption in experimental model of periodontitis.[96] Furthermore ATB-346 that is an H_2S-releasing naproxen derivative that exhibits an anti-inflammatory activity and gastric safety in a murine model of arthritis.[97] Recently, ATB-346 has completed a phase I and phase II clinical trial that revealed the safety and good tolerability.[94,98,99] H_2S is a strong candidate to be exploited as a therapeutic agent, especially coupled to NSAIDs, since it could maintain and enhance anti-inflammatory properties without causing damage to the gastrointestinal mucosa.

Carbon monoxide (CO)

Carbon monoxide (CO) is a gas mediator that has recently reported protective actions in the gastrointestinal tract.[1,100] CO can be produced by degradation of free heme to biliverdin via the enzymatic activity of heme oxygenase (HMOX) which can be constitutive produced such as HO-2 (expressed in brain, liver and vascular endothelial cells) and inducible such as HO-1 (expressed in human gastric epithelial cells and in inflammatory cells) that can be generated in response to stressful stimuli.[2] The exploration of the effects of CO *in vivo* has serious limitations, since it is not a free radical, CO as a more stable molecule with a long half-life time up in comparison with the others gasotransmitters.[2,35] However, demonstrating the participation of CO in the intestinal tract, has been a difficult task since there are not enough CO donors' molecules that can be useful for experimental studies and the interaction of CO with transition

metals as their molecular are largely unknown.[100,101] The therapeutic approach for the use of CO at the gastrointestinal level, are the recently developed CO-releasing molecules (CO-RMs or CORMs), that had probe to be a safe way of delivering physiologically efficient quantities of exogenous CO to various tissues and organs.[32] The use of CO-RMs in preclinical models has made it possible to identify the activities of CO (Figure 2), including the increase gastric mucus secretion, the maintenance of tissue perfusion in the upper GI tract, particularly in presence of NSAIDs, stimulate duodenal bicarbonate secretion and modulating leukocyte adherence to the vascular endothelium reducing pro-inflammatory cytokine expression by inhibiting NfκB.[102,103,104,105,106] It has been suggested that biological functions of CO are related to the activation of soluble guanylyl cyclase (sGC), the cyclo-oxygenase (COX) pathway or the inhibition of cytochrome P450.[2,107] Also, CO functions as a back-up system for activating sGC when intracellular levels of NO are low.[107,108,109] The preclinical animal studies reports that CORMS offers gastroprotection against gastric mucosal injury induced by ethanol, ischemia/reperfusion and NSAIDs.[110,111,112,113] So far, CO-RMs are metal carbonyl complexes releasing CO dose-controlled and tissue-specific that have only been tested in experimental animal models and cell-lines.[32,114] It is also worth mentioning that CORM-3 have been also pointed out as potential antihypertensive agent.[32,115] More studies in different models and gastrointestinal scenarios will be able to generate the necessary scientific support to take CO-RMs to the next phases of drug research.

CONCLUSIONS

There is an urgent need for the development of gastric safety therapies, these novel strategies should decrease both gastric and intestinal mucosal toxicity as well. The discovery of molecules such as NO, H_2S and CO that could contribute to maintaining many physiological processes in gastrointestinal tract, has allowed the development of gasotransmitters-releasing drugs. Which are specifically designed to maintain the therapeutic properties of the coupled drugs and show unprecedented gastric and intestinal safety. Although their mechanism of action of these gastrotransmitters has been extensively studied yet are not fully understood, therefore, further studies are still needed to understand these emerging gaseous mediator-releasing drugs. That so far represents a clear advantage compared to therapies available on the market to prevent gastrointestinal injury generated by noxious factors. The animal studies as well as clinical trials of these novel compounds have shown encouraging results giving a solid background to prompt the further investigation.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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