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Gaseous mediator-based anti-inflammatory drugs

Oksana Sulaieva[1] and John L Wallace[2,3]

Among the most commonly used drugs, nonsteroidal anti-inflammatory drugs (NSAIDs) remain problematic because of their propensity to cause serious adverse events, principally affecting the gastrointestinal tract. In recent years, the discovery of potent anti-inflammatory and cytoprotective effects of endogenous gaseous mediators (nitric oxide, hydrogen sulfide, carbon monoxide) stimulated efforts to develop novel, combination NSAIDs that suppress prostaglandin synthesis (producing anti-inflammatory and analgesic effects) and release one or more of the cytoprotective gaseous mediators. Gaseous mediator-based anti-inflammatory drugs have reached the human clinical trial stage and show considerable promise as a safer option for treating chronic inflammatory diseases.

Addresses
[1] Department of Histology, Zaporozhye State Medical University, Zaporozhye, Ukraine
[2] Department of Physiology & Pharmacology, University of Calgary, Calgary, Alberta, Canada
[3] Faculty of Medicine, Universidade Camilo Castelo Branco, São Paulo, SP, Brazil

Corresponding author: Wallace, John L (altapharm@hotmail.com)

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Introduction

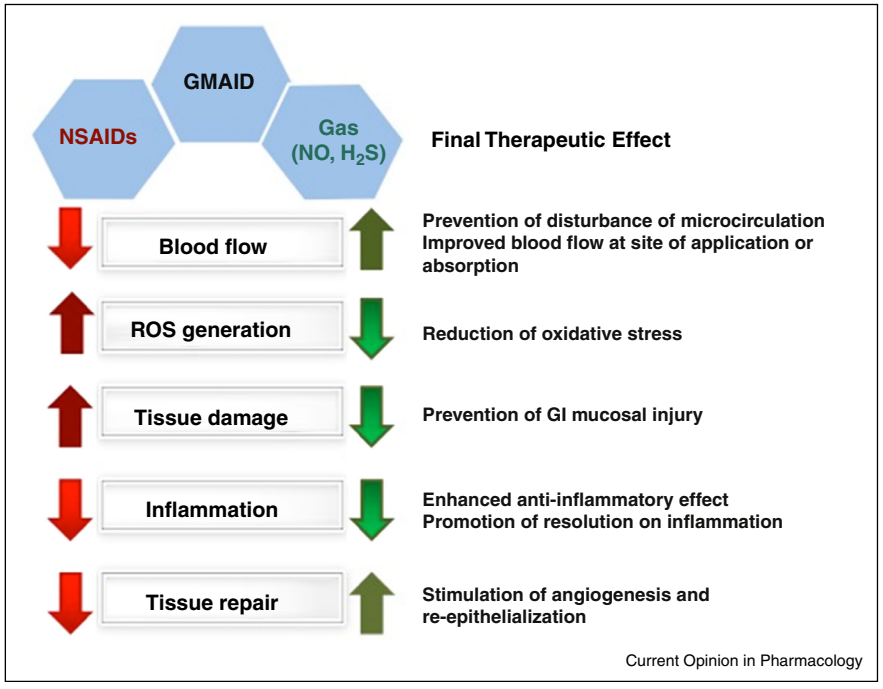
Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly used drugs in the world, employed mainly for reducing pain and inflammation. However, these drugs, particularly when used chronically such as for osteoarthritis and rheumatoid arthritis, often produce significant adverse effects, most notably in the gastrointestinal, renal and cardiovascular systems [1,2]. Numerous strategies have been taken to reduce the incidence of such adverse effects, but none have completely succeeded. Proton pump inhibitors reduce NSAID-induced gastroduodenal damage, but appear to render the small intestine more susceptible to significant ulceration and bleeding [3,4]. Selective inhibitors of cyclooxygenase (COX)-2 also exhibit reduced adverse effects on the upper gastrointestinal (GI) tract, but their safety in the lower GI tract has not been definitively demonstrated and their use carries significant risks for cardiovascular and renal adverse effects [5–7].

In recent years, the discovery of a broad range of physiological roles of gaseous mediators, including nitric oxide (NO), carbon monoxide (CO) and hydrogen sulfide (H_2S) has led to extensive studies of these substances as mediators of GI mucosal defence [8–10,11••]. Having established such roles, efforts were then made to produce novel anti-inflammatory drugs that released one or more of these gaseous mediators, with a goal of producing significant anti-inflammatory effects but with greatly reduced toxicity [12,13•] (Figure 1). This paper provides an overview of these strategies, the mechanisms of action of the novel drugs and an assessment of their clinical potential.

Nitric oxide

NO is a potent vasodilator, inhibits leukocyte adherence to the vascular endothelium, and increases gastroduodenal mucus and bicarbonate secretion [8,14]. All of these actions can enhance GI mucosal defence, and thereby reduce the severity of mucosal injury [8]. Endogenous NO plays an important role in ulcer healing [15] and NO donors can accelerate their healing, and promote resolution of inflammation in the GI tract [16,17]. For these reasons, NO-releasing NSAIDs were developed and tested extensively in animal models [12,18], with an aim of producing compounds that were potent anti-inflammatory drugs, but with improved GI safety. Several pharmaceutical companies attempted to develop NO-NSAIDs for clinical use, including NicOx and NitroMed. NicOx made the most progress in this regard, advancing their lead drug (Beprana) through phase 3 clinical trials. However, in the wake of the cardiovascular problems recognized for selective COX-2 inhibitors and other NSAIDs [5], the regulatory barriers to approval of a novel NSAID were greatly increased, and NicOx decided to focus their resources on other assets in their portfolio. NitroMed were developing NO-releasing NSAIDs in partnership with Merck [19], and when the latter company withdrew their selective COX-2 inhibitor from worldwide markets, the partnership with NitroMed was dissolved, and NitroMed ceased operations shortly thereafter. One of the shortcomings of Beprana was that the GI safety of this drug had not proven to be as great as animal studies had suggested [20]. On the other hand, this NO-releasing naproxen derivative exhibited a significantly reduced propensity to elevate blood pressure, a clinical problem with all NSAIDs [21]. NicOx have focused in recent years on NO-releasing anti-inflammatory drugs for ocular

Figure 1



Targets and actions of the nonsteroidal anti-inflammatory drug (NSAID) and gaseous mediator-releasing moieties to the actions of gaseous mediator releasing-NSAIDs (GMAIDs). In many cases, the gaseous mediator counteracts detrimental effects of the NSAID moeity. Nitric oxide (NO) and hydrogen sulfide (H_2S) produce similar actions to one another. ROS: reactive oxygen species.

indications. For example, the NicOx drug latanoprostene bunod is in phase 3 clinical studies where it was shown to be effective [22]. The rationale for an NO-releasing ocular drug was based on the finding that eNOS plays important role in regulating intraocular pressure [23].

Hydrogen sulfide

H_2S is believed to have supported the earliest forms of life on Earth, and eukaryotes have retained the ability to generate adenosine triphosphate from H_2S [24,25•]. The physiological effects of H_2S are broad [11••], and there has been a significant burst of research activity on this gaseous mediator since early reports that it exhibited neuromodulatory, vasodilatory and anti-inflammatory activities [26••,27••,28••,29–37,38•,39–41,42•,43–45,46•,47–58,59•,60–62]. Very soon after these actions of H_2S were reported, several groups began to develop novel anti-inflammatory drugs that release H_2S, based on the premise that the new drugs would have enhanced activity and/or improved safety profiles. Table 1 lists some of the H_2S-releasing anti-inflammatory drugs that are in commercial development [11••,29].

Most of the drug development activity for H_2S has focused on NSAIDs [11••,29], and there is strong evidence that the H_2S-releasing moiety attached to various NSAIDs markedly reduces the GI toxicity of the NSAID moiety, while not reducing anti-inflammatory activity [13•,30,31]. Indeed, there may be an enhancement of anti-inflammatory activity. ATB-346 is an H_2S-releasing derivative of naproxen [13•]. It has been examined in a wide range of models of inflammation and injury, where it was found to be equal to or more effective than equivalent doses of naproxen [13•,30,31]. For example, in a rat model of adjuvant arthritis, ATB-346 exhibited comparable anti-inflammatory effects to naproxen, but with markedly reduced GI toxicity [32]. On the other hand, in a model of zymosan-induced subdermal inflammation (airpouch model), ATB-346 was found to inhibit cyclooxygenase-2 activity and reduce leukocyte infiltration significantly more effectively than an equimolar dose of naproxen [13•].

ATB-429 is an H_2S-releasing derivative of mesalamine, the first-line therapy for inflammatory bowel disease (Crohn's disease and ulcerative colitis). In animal models, ATB-429 exhibited significantly enhanced anti-inflammatory and pro-healing effects than mesalamine [17]. It also markedly suppresses expression of a number of pro-inflammatory cytokines (TNFα, IL-1, IL-2, IFN-γ, etc.), but not the expression of the anti-inflammatory cytokine, IL-10 [17].

It has been recognized for decades that regular use of NSAIDs can significantly reduce the incidence rates of several types of cancer, particularly those affecting the GI