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Review

Hydrogen sulfide-releasing anti-inflammatory drugs for chemoprevention and treatment of cancer

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ABSTRACT

For many years it has been recognized that inhibition of cyclooxygenase enzymes is effective in reducing the incidence of many types of cancer, but the adverse effects of these drug, particularly in the gastrointestinal and cardiovascular systems, limits their utility. Recently developed hydrogen sulfide-releasing anti-inflammatory drugs may be a promising option for cancer chemoprevention. In this paper we review evidence suggesting that these novel compounds are effective in a range of animal models of various types of cancer, while exhibiting greatly reduced toxicity relative to currently marketed non-steroidal anti-inflammatory drugs. Some of the possible mechanisms of action of hydrogen sulfide-releasing anti-inflammatory drugs are also discussed.

Contents

1. Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of drugs, sharing the common feature of inhibiting activity of the cyclooxygenase (COX) enzymes [1]. In doing so, NSAIDs reduce the production of prostaglandins and thereby reduce inflammation. These drugs are widely used to treat inflammatory disorders, including osteoarthritis and rheumatoid arthritis. Over the past 5 decades, considerable evidence has accumulated to suggest that regular use of NSAIDs, including aspirin, can also markedly reduce the incidence of various types of cancers, and particularly of cancers in the gastrointestinal (GI) tract [2–5]. However, the propensity of NSAIDs to cause ulceration and bleeding in the GI tract [1,6] has significantly limited the widespread use of these drugs for chemoprevention. Selective inhibitors of COX-2, which were developed on the premise that they would be more "GI-safe", have been shown to be effective in reducing the incidence of several types of cancer [7–9]. However, these drugs are not as GI-safe as had initially been suggested [10], and can cause significant cardiovascular and renal adverse effects [11,12], greatly limiting their utility as chemopreventative agents [11].

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H_2S is increasingly recognized as an important signaling molecule in many tissues [13]. Its effects in the GI tract have been very well characterized, including anti-inflammatory, cytoprotective and pro-healing actions [13,14]. Endogenous synthesis of H_2S is markedly and rapidly increased subsequent to injury to the GI mucosa [15–17]. Indeed, in a model of colitis, an up-regulation of H_2S synthesis and a significant decrease in H_2S oxidation were found to occur specifically at sites of tissue injury (not in immediately adjacent tissue) [17]. Suppression of H_2S synthesis in these circumstances leads to amplification of inflammation, aggravation of tissue injury and impairment of healing [15,16]. On the other hand, administration of H_2S donors increases mucosal resistance to damage induced by a wide range of damaging agents [17–20], accelerates ulcer healing [15,21,22], reduces visceral pain perception [25,26], and attenuates inflammation [23,24,27–31]. The potent cytoprotective actions of H_2S have been exploited in the development of novel, gastrointestinal-safe, H_2S-releasing anti-inflammatory drugs [13,15,27–29,31].

While most studies of H_2S and cancer have focused on colonic cancer, there is considerable evidence that H_2S-based chemoprevention will be effective for a broader range of tumours. Thus, in addition to reviewing recent studies of GI cancer chemoprevention, we have discussed emerging evidence (*in vitro* and *in vivo*) supporting similar approaches for prevention and treatment of melanoma.

2. Chemoprevention and treatment of intestinal cancers

2.1. Aberrant crypt foci model

One of the most common *in vivo* models for studying factors that will affect colon cancer development is the azoxymethane-induced aberrant crypt foci (ACF) model in rodents [32–35]. Administration of this carcinogen over a period of weeks results in the formation of ACF in the colon. These lesions bear close similarity to ACF in human colon cancer, and left untreated, will develop into tumours [32–35]. Mainly because of its simplicity and reproducibility, the azoxymethane-induced ACF model has been widely employed for testing potential chemoprevention strategies, including NSAID-induced chemoprevention [33,34].

We examined the effects of treatment with ATB-346 (H_2S-releasing derivative of naproxen; Fig. 1) in mice with azoxymethane-induced ACF, comparing the effects of this novel drug to those of naproxen [36]. Weekly treatment of mice with azoxymethane for 4 weeks resulted in the development of an average of ~50 ACF in each animal's colon. During the first 2 weeks, the mice were treated orally, twice daily, with vehicle (control group), an anti-inflammatory dose of naproxen (10 mg/kg), an equimolar dose of ATB-346 or an equimolar dose of the H_2S-releasing moiety of ATB-346 (TBZ; 4-hydroxythiobenzamide). One week after the final administration of azoxymethane, the mice were euthanized and the colons were removed and stained for blind quantification of the number of ACF [36].

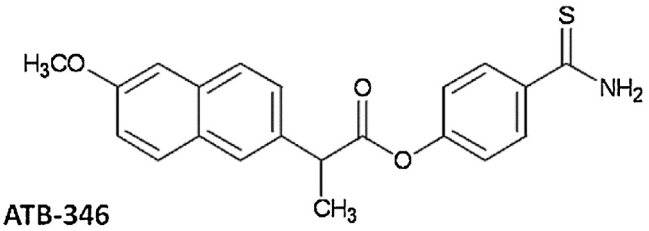

Fig. 1. Structure of ATB-346, a hydrogen sulfide-releasing derivative of the anti-inflammatory drug, naproxen.

Significant beneficial effects were observed with ATB-346 at lower doses than of naproxen. Naproxen was only effective at 10 mg/kg or higher. ATB-346 induced a significant (30%) reduction of ACF at 1/10th the minimally effective dose of naproxen, and a 75% reduction at the highest dose tested (equimolar dose to 30 mg/kg of naproxen) [36]. Administration of the H_2S-releasing moiety of ATB-346 was not effective at any doses tested, consistent with the need for COX inhibition for chemopreventative effects [36]. The enhanced beneficial effects of ATB-346 versus naproxen occurred despite the two drugs producing equivalent suppression of intestinal prostaglandin and whole blood thromboxane synthesis (>90% inhibition). Moreover, when tested in healthy mice, naproxen caused significant small intestinal damage and bleeding, while ATB-346 did not [36]. Similar chemopreventative effects were observed in this model when the mice were treated with an H_2S-releasing derivative of ketoprofen (ATB-352; Fig. 2) that did not produce GI damage, but did suppress COX activity as effectively as the parent NSAID [37].

These studies demonstrated that the combination of COX inhibition and release of H_2S were necessary to achieve optimal chemopreventative effects, as well as sparing the GI tract of damage. Treatment with 4-hydroxy-thiobenzamide (TBZ), the H_2S-releasing moiety of ATB-346, did not significantly alter aberrant crypt foci formation. On first inspection, this may be taken as evidence for a lack of chemopreventative effect of H_2S. However, Sengupta et al. [38] reported that diallylsulfide, a well characterized H_2S donor, significantly reduced ACF formation in rats treated with azoxymethane. Furthermore, the amount of H_2S released from 'unbound' TBZ may not be as great as that released from ATB-346 or ATB-352. Previous *in vitro* studies have shown that the amount of H_2S released from TBZ is substantially less than that released from molecules such as ATB-346 and ATB-352, that consist of TBZ bound to an NSAID [25,39,40]. Further evidence for this comes from *in vivo* studies of the GI safety of ATB-346. While ATB-346 does not produce significant damage in the GI tract, administration of its two components (TBZ and naproxen) resulted in GI damage of comparable severity to that observed with naproxen alone [25,29].

Mechanisms underlying the enhanced chemopreventative effects H_2S-releasing NSAIDs as compared to the NSAID alone may include enhanced suppression of COX-2 [29], as well as H_2S-mediated anti-inflammatory effects [41,42], changes in colonic

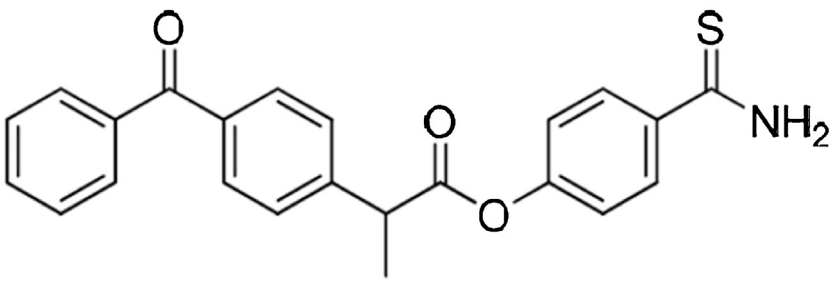

Fig. 2. Structure of ATB-352, a hydrogen sulfide-releasing derivative of the anti-inflammatory drug, ketoprofen.