

Aspirin-intolerant asthma: role of cyclo-oxygenase enzymes

Aspirin-induced asthma and rhinitis (AIAR) appear to be precipitated by the inhibition of cyclo-oxygenase (COX). By inhibiting COX pathway aspirin diverts arachidonic acid metabolites to the lipoxygenase pathway. There are two isoforms of COX, namely COX-1 and COX-2. Metabolites derived from COX-1 are involved in cellular housekeeping functions. COX-2 can be induced in cells exposed to proinflammatory substances and growth factors. Recent studies have reported that patients with AIAR have decreased activity of COX-2 and lower production of PGE₂ in the upper airway and peripheral blood cells. Considering the protective effect of exogenous PGE₂ on aspirin-induced bronchoconstriction and the interdependence of PGE₂ and cisteinyl leukotriene production, a reduced PGE₂ synthesis may render aspirin-sensitive patients more susceptible to the inhibitory effect of NSAIDs drugs and also lead to an increase in cisteinyl leukotriene release.

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Introduction

Cyclo-oxygenase (COX), also known as prostaglandin-endoperoxidase synthase, converts arachidonic acid into PGH₂, which is further metabolized by other enzymes into various prostaglandins (PGs), prostacyclin and thromboxanes (1).

There are two isoforms of COX, namely COX-1 and COX-2, with similar molecular weights. The metabolites derived from COX-1 are involved in cellular housekeeping functions. Activation of COX-1 leads, for instance, to the production of prostacyclin, which is cytoprotective when released by the gastric mucosa. COX-2 can be induced in cells exposed to proinflammatory substances and growth factors (1).

Non-steroidal anti-inflammatory drugs (NSAIDs) are used to treat acute and chronic inflammatory disorders. The anti-inflammatory mechanism of NSAIDs is caused by a reduction of prostaglandin (PG) synthesis due to the direct inhibition of COX. The ability of NSAIDs to inhibit COX-2 may explain their therapeutic potential as anti-inflammatory drugs, whereas inhibition of COX-1 may account for their unwanted side-effects, such as gastric damage and toxic effects on the kidney (1).

Inhibition of the COX pathway may cause contrasting nasal and bronchial responses in patients with rhinitis and asthma. In most patients, NSAIDs do not provoke any reaction, but they cause bronchoconstriction and nasal obstruction in about 5–10% (2). Intriguingly enough, in a limited number of patients (less than 1%) NSAIDs may induce bronchodilation and nasal decongestion.

The cyclo-oxygenase pathway in aspirin-induced asthma

Aspirin-induced asthma and rhinitis (AIAR) appear to be precipitated by the inhibition of COX. Recent studies have reported that NSAIDs which inhibit COX-2 but not COX-1 are very well tolerated by NSAID-intolerant patients (2, 3).

Most aspirin-sensitive asthma patients present a typical clinical syndrome involving aspirin sensitivity, bronchial asthma and chronic rhinosinusitis with nasal polyposis. The basic mechanism underlying aspirin sensitivity is not immunological, and seems to be related to the inhibition of COX, with a subsequent release of cisteinyl leukotrienes (LTs), and possibly other mediators as well (2, 3).

The COX pathway appears to play a crucial role in the explanation of the AIAR syndrome. The existence of an abnormality in the COX pathway has been suggested as a possible explanation for the high and selective sensitivity of some asthma patients to the inhibitory action of NSAIDs (3). The following observations support the COX theory:

1) NSAIDs with anticyclo-oxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive patients (3).

2) There is a positive correlation between the capacity of NSAIDs to inhibit COX *in vitro* and their capacity to induce bronchospasm in the sensitive patient (4).

3) NSAIDs which have no effect on COX activity do not precipitate asthma attacks (2).

4) Prostaglandin E₂ (PGE₂) release is markedly reduced in the nasal polyp epithelial cells (5) and peripheral blood cells (6) of aspirin-sensitive patients.

5) PGE₂ administered by inhalation inhibits aspirin-induced bronchoconstriction and the accompanying increase in LT release (7).

6) The COX pathway of aspirin-sensitive asthma seems to be more sensitive to the effect of NSAIDs than that of aspirin-tolerant patients (8).

7) COX-2 mRNA is downexpressed in nasal polyps of aspirin-sensitive patients (9).

8) Aspirin-intolerant asthmatics has a decreased capacity to generate 15-epi-LXA₄, a metabolite that is released when COX-2 is inhibited by aspirin, possibly reflecting either lower COX-2 expression and/or altered sensitivity of this enzyme to aspirin (10).

However, a number of observations do not support the existence of either a decreased production of PGE₂ or an increased susceptibility of the COX pathway to NSAIDs in aspirin-sensitive patients:

1) The abnormalities in the COX pathway have been found in nasal polyps (5, 8, 9) and peripheral blood cells (10) but not in the lower airway, where immunostaining for COX-2 shows no differences in bronchial biopsies of aspirin-sensitive patients as compared to aspirin-intolerant asthmatics (11, 12). It is difficult to reconcile these differences since evidence has been accumulated which suggests that upper airway (rhinosinusitis and nasal polyps) and lower airway (asthma) disease in aspirin-sensitive asthmatics share common pathogenic mechanisms (13–15).

2) Significantly higher baseline bronchoalveolar fluid levels of PGE₂ and other prostanoids have been reported in aspirin-sensitive asthmatics, compared to aspirin-tolerant patients (13). Both nasal instillation and bronchial inhalation of lysine-aspirin reduce nasal (14) and BAL fluid (13) PGE₂ levels, respectively, in aspirin-sensitive patients to the same extent as in aspirin-tolerant patients (12, 13). Nevertheless, assays of BAL and nasal lavage fluids may not reflect mediator concentrations within the bronchial wall. Lavage methods are very useful in the detection of major changes in the release of mediators: for instance, all studies have reported similar marked increases in the production of LTs in aspirin-sensitive patients after aspirin challenge (13, 14, 16). In contrast, the study of PGE₂ levels shows contradictory results: higher (13), similar (14) and lower (16) levels of PGE₂ have been reported in BAL (13, 16) and nasal lavages (14) in

aspirin-sensitive patients, compared to aspirin-tolerant asthmatics. Both increases (13) and decreases (14, 16) in PGE₂ lavage levels after aspirin challenge have been described in aspirin-sensitive asthma. These differences reveal the poor sensitivity of lavage methods in the evaluation of PGE₂. Therefore, the study of the levels of PGE₂ in bronchial and nasal secretions should be used with caution, whether to support or to dismiss its role in aspirin-sensitive asthma.

The COX-2 theory of aspirin-induced asthma

It is generally accepted that the induction of COX-2 and a consequent increase in the production of PGE₂ occur during inflammatory events in various organs and tissues. Although it is commonly assumed that induction of COX-2 expression and the consequent increase in PG synthesis are important in promoting inflammation, some recent studies have suggested that COX-2 up-regulation may also have an anti-inflammatory role in some circumstances, particularly in chronic inflammation (17). It may well be that inadequate regulation of COX-2 may predispose asthma patients to the development of aspirin sensitivity.

Several observations strongly support the notion that the COX pathway is abnormally regulated in aspirin-sensitive asthma (5, 6, 8–10), as reflected in a lowered production of PGE₂ (5, 6, 8, 9). From the viewpoint of the concept that COX-2 up-regulation and increased production of PGE₂ are usually found in inflammatory diseases, the lowered production of PGE₂ detected in aspirin-sensitive asthmatics is an unexpected finding. Considering the protective effect of exogenous PGE₂ on aspirin-induced bronchoconstriction and the interdependence of PGE₂ and LT production (7), a reduced PGE₂ synthesis may render aspirin-sensitive patients more susceptible to the inhibitory effect of NSAID drugs and also lead to an increase in LT release (9). NSAID administration reveals the heightening of the defective regulation of COX-2 and precipitates severe bronchospasm in these patients. The mechanisms responsible for the abnormalities in the COX-2 pathway remain to be clarified.

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