The cyclooxygenase theory of aspirin-induced asthma

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ABSTRACT: Aspirin-induced asthma is a distinct clinical syndrome which affects about 10% of adult asthmatics. In these patients aspirin and several other analgesics precipitate asthmatic attacks. The idea that the attacks might result from the specific inhibition of a single enzyme, namely cyclooxygenase, has gained both experimental and clinical support. It stimulated a number of hypotheses on the mechanism of bronchoconstriction. All these hypotheses, here discussed, operate within the framework of the cyclooxygenase theory. Their major assumption is that inhibition of cyclooxygenase triggers specific biochemical reactions which lead to open asthma attacks.
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The majority of people tolerate aspirin well. Asthmatics, however, are an exception. In about 10% of adults with asthma, but rarely in asthmatic children, aspirin and other non-steroidal anti-inflammatory drugs (NSAID) precipitate asthma attacks. This distinct clinical syndrome is called aspirin-induced asthma (AIA) [1–3]. It appeals to pharmacologists, biochemists and clinicians as a remarkable model for the study of mechanisms operating in asthma.

Many concepts have been advanced to explain the pathogenesis of AIA [3, 4]. The idea that the attacks might result from the specific inhibition of a single enzyme, namely cyclooxygenase, in the respiratory tract has been, perhaps, most discussed. It stimulated a number of hypotheses on mechanisms of bronchoconstriction. All of these hypotheses operate within the framework of the cyclooxygenase theory. Thus, their major assumption, now rather firmly established, is that inhibition of cyclooxygenase triggers specific biochemical reactions which lead to open asthma attacks.

Formulation of the theory

A hypothesis was put forward [5] that in sensitive patients, precipitation of asthma attacks by certain analgesics results from inhibition of cyclooxygenase, leading to an imbalance of prostanoids in the respiratory tract. Cyclooxygenase, an atypical lipoxygenase, is present in most human tissues, including lungs. It introduces two molecules of oxygen into arachidonic acid, converting it into a prostaglandin peroxide. This is the beginning of the metabolic pathway leading to formation of prostaglandins, thromboxane and prostacyclin. Cyclooxygenase is inhibited by aspirin, and several other analgesics; a phenomenon which might explain their pharmacological action [6].

In the early seventies, allergic mechanisms as an explanation for aspirin intolerance were vigorously pursued. Contrary to these concepts, the cyclooxygenase theory proposed that precipitation of asthmatic attacks by aspirin is not based on antigen-antibody reactions, but stems from the pharmacological action of the drug. The original observations [5, 7] that the drug intolerance could be predicted on the basis of its *in vitro* inhibition of cyclooxygenase, have been consistently reaffirmed during the ensuing years [8]. Evidence in favour of the cyclooxygenase theory [3] can be summarized as follows:

1) analgesics with anticyclooxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive patients;

2) analgesics not affecting cyclooxygenase are devoid of bronchospastic properties in these patients;

3) there is a positive correlation between the potency of analgesics to inhibit cyclooxygenase *in vitro* and their potency to induce asthmatic attacks in the sensitive patients;

4) the degree of enzymatic inhibition that is sufficient to precipitate bronchoconstriction is an individual hallmark (thus, if the threshold dose for any anticyclooxygenase in a particular patient is known, one can predict the threshold doses for other analgesics in that patient);

5) *in vitro* anti-cyclooxygenase inhibitors activate platelets to release cytotoxic mediators in aspirin-sensitive asthmatics, but not in the atopic asthmatics or healthy subjects [9, 10];

6) in patients with AIA inhibition of thromboxane A_2 (TXA_2), next to cyclooxygenase enzyme in the arachidonic acid cascade, neither precipitates asthmatic attacks nor alters pulmonary function [11];

7) after aspirin desensitization, cross-desensitization to other analgesics which inhibit cyclooxygenase also occurs [8].

Thus, the inhibition of bronchial cyclooxygenase by aspirin-like drugs appears to set off a chain of reactions leading to asthma attacks in aspirin-intolerant patients. What follows at the biochemical level remains largely unknown, (fig. 1).
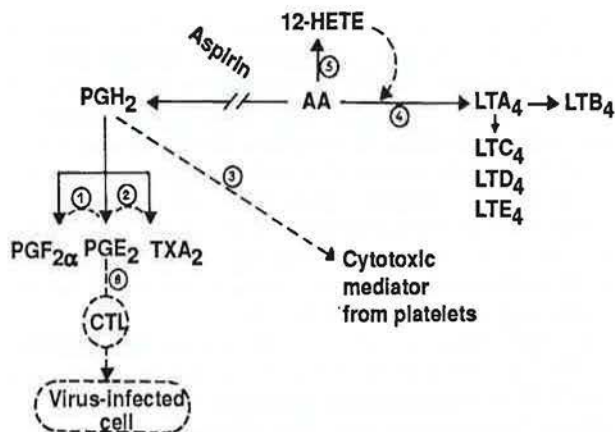

Fig. 1. – Aspirin-induced asthma hypothetical alterations in arachidonic acid metabolism following inhibition of cyclooxygenase by aspirin. AA: arachidonic acid; COX: cyclooxygenase; LOX: lipoxygenase; PGH_2: cyclic endoperoxide H_2; PGI_2: prostacyclin; PGs: prostaglandins; TXA_2: thromboxane A_2; LTA_4: leukotriene A_4; LTB_4: leukotriene B_4; LTC_4: leukotriene C_4; LTD_4: leukotriene D_4; LTE4: leukotriene E_4; 12-HETE: 12-hydroperoxyeicosatetraenoic acid; 15-HETE: 15-hydroperoxyeicosatetraenoic acid; LTX: lipoxin A; LXB: lipoxin B. PGE_2: prostaglandin E_2; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$.

Early explanations

At the time of publication of the cyclooxygenase hypothesis [5], the only eicosanoids known to be produced by the cells of the respiratory tract were prostaglandin E_2 (PGE_2) and prostglandin $F_{2\alpha}$ ($PGF_{2\alpha}$). It was presumed [12], therefore, that although cyclooxygenase was inhibited by aspirin, a selective deficiency among the cyclooxygenase products must also occur, such that bronchodilator PGE_2 was decreased relative to bronchoconstrictor $PGF_{2\alpha}$. This idea was not universally appealing because, although the efficacy of aspirin and certain other NSAIDs as inhibitors of cyclooxygenase was clearly demonstrated, relative effects on (PGH_2)-PGE_2 isomerase and PGH_2-$PGF_{2\alpha}$ isomerase were not.

An early explanation [5], that aspirin-sensitive asthmatics might rely more on PGE_2 than on the β-adrenergic system to keep their bronchi unobstructed, seems unlikely today. These patients, indeed, respond better to inhaled PGE_2 than do other asthmatics [13] but clinical practice leaves no doubt that their lung function also improves substantially following inhalation of β-mimetics.

Participation of leukotrienes

In 1979, when leukotrienes were discovered, it became apparent that arachidonic acid could be diverted from the cyclooxygenase pathway to the 5-lipoxygenase pathway,

if cyclooxygenase had been inhibited. The definition of leukotrienes suggested that they would provide potent mediation of neutrophil influx into the tissue *via* the action of leukotriene B_4 (LTB_4), and a potent stimulation for bronchoconstriction, mucosal permeability and mucus secretion by the actions of leukotriene C_4 (LTC_4), leukotriene D_4 (LTD_4), and leukotriene E_4 (LTE_4). The explanation for aspirin-induced asthma was then postulated as simply being caused by shunting of arachidonic acid from the generation of prostaglandins to the biosynthesis of leukotrienes. In a simplified way, it would be a redirection of flow in a bifurcated vessel: from the blocked arm to an open one. More sophisticated explanations have been put forward. Biosynthesis of leukotrienes could be enhanced by overproduction of 12-hydroperoxyeicosatetraenoic acid (12-HPETE) [14] or removal of inhibiting control of PGE_2/PGI_2 [15]. Both possibilites are a logical consequence of cyclooxygenase pathway inhibition.

There is some experimental support for the concept of shift in arachidonic acid metabolism, though clinical evidence is still lacking. In a guinea-pig model of antigen-induced anaphylaxis, pretreatment of animals with indomethacin resulted in an augmentation of the pulmonary mechanical response to intravenous antigen and this was accompanied by an increased generation of LTB_4 [16]. In antigen-challenged sheep lung *in vivo*, cyclooxygenase inhibition enhanced leukotriene production [17]. Pretreatment of passively sensitized human airways with indomethacin resulted in an increased release of leukotrienes from human bronchi in response to both antigen and anti-IgE stimulation [18]. However, others have found [19] that in normal human parenchyma an anti-IgE challenge in the presence of indomethacin does not produce a shift towards leukotriene formation.

Two groups studied the release of leukotrienes into the nasal cavity following aspirin administration to patients with AIA. ORTOLANI et al. [20] noticed an increase in mean LTC_4 concentration in nasal washings of 7 aspirin-sensitive asthmatics following nasal spray provocation with aspirin. However, clinical symptoms occurred within 1–2 min of the challenge, while LTC_4 increase was observed 60 min later. FERRERI et al. [21] used oral aspirin to provoke clinical symptoms in 5 intolerant patients. During the provoked reactions, LTC_4 increased in 3 patients. In 2 of the 5 patients a fall in PGE_2 preceded appearance of clinical symptoms. In the control subjects, ingestion of higher doses of aspirin (650 mg) resulted in a distinct fall in PGE_2 without the release of LTC_4 into nasal washings. A recent study by BISGAARD et al. [22] has cast serious doubt on the validity of mediator measurement in nasal lavage in relation to symptoms following local nasal challenge.

It is not clear in which cells of the respiratory tract alterations in arachidonic acid metabolism might occur. Leucocytes, especially eosinophils, present in large amounts in nasal and bronchial tissue of aspirin-sensitive asthmatics [3, 23] could be considered as a source of leukotrienes. GOETZL et al. [24] suggested a generalized abnormality of the regulation of arachidonic acid oxidative pathways in peripheral blood leucocytes of patients

with AIA. Two recent studies do not support this idea. NIZANKOWSKA et al. [25] studied production by polymorphonuclear leucocytes of 5-dehydroperoxyeicosatetraenoic acid (5-HETE) and LTB_4 in 10 aspirin-sensitive asthmatics and 10 matched healthy controls. The blood cells were obtained before administration of the threshold doses of aspirin, and during the aspirin-induced reactions. Initial levels of eicosanoids determined did not differ between the two groups, and remained unchanged following aspirin challenge. TSUDA et al. [26] measured the production of LTB_4 and LTC_4 in peripheral blood leucocytes stimulated by calcium ionophore A 23187. They compared 4 groups (controls, AIA, atopic and intrinsic asthma) before and after indomethacin challenge. All three asthmatic groups produced more LTC_4 than the healthy controls, but there was no difference between aspirin-intolerant patients and atopic or intrinsic ones. LTB_4 production (as well as PGE_2 and TXB_2) was similar in all four groups. Indomethacin did not affect leukotriene generation in any of the groups studied.

The concept of arachidonic acid shunting needs an additional assumption that the airways of aspirin-intolerant patients are more sensitive to leukotrienes than those of other patients with asthma [27]. If not, all asthmatic patients would react with bronchoconstriction in response to aspirin-like drugs. Three research groups addressed this problem. VAGHI et al. [28] and BIANCO [29] measured bronchial response to LTC_4 in 10 aspirin-sensitive asthmatics as compared to 10 controls. They were unable to find any significant difference. SAKAKIBARA et al. [30] studied airway responsiveness to methacholine, histamine and LTD_4 in 12 patients with AIA, 13 patients with extrinsic asthma and 12 patients with intrinsic asthma. There were no significant differences in either concentrations of any of the agents producing a 20% fall in forced expiratory volume in one second (FEV_1) or the slope of FEV_1 changes among the groups studied. The only positive finding was somewhat delayed recovery in FEV_1 following challenge with LTD_4 in the aspirin-intolerant group as compared to the others. These two studies do not support the concept of increased bronchial reactivity to LTC_4 or LTD_4. However, the results of ARM et al. [31] suggest a selective increase in airway responsiveness of LTE_4. They measured a 35% fall in the specific airway conductance following histamine and LTE_4 inhalation in 5 subjects with aspirin-induced asthma and in 15 asthmatics without aspirin sensitivity. The airways of aspirin-intolerant patients had a significant, 13-fold increase in responsiveness to LTE_4 relative to histamine when compared to control asthmatics. Interestingly, this hyperresponsiveness to LTE_4 was abolished after aspirin-desensitization.

The concept of diversion of arachidonic acid metabolism from prostanoids to leukotrienes is hard to accept in view of likely compartmentalization of arachidonic acid in the lung [32]. This concept still awaits testing with a powerful, specific leukotriene inhibitor. In a recent trial [33] pretreatment of aspirin-intolerant asthmatics with leukotriene inhibitor failed to prevent aspirin-precipitated bronchospasm. The bioavailability of the inhibitor, administered by inhalation remained, however, uncertain.

Platelet involvement

In the last few years attention has been paid to possible participation of platelets in pathogenesis of bronchial asthma [34, 35], particularly in aspirin-induced asthma [9, 14]. In patients with AIA, aspirin challenge may lead to activation of peripheral blood platelets which parallels the time course of bronchospastic reaction [36]. In contrast to platelet activation, the detection of endogenous platelet-activating factor (PAF) release has not been a consistent finding. Aspirin-induced bronchoconstriction does not seem to be based on the contracting properties of PAF [36].

In 1982, MACLOUF et al. [14] noticed that platelets 12-HETE stimulated the generation of LTB_4 and 5-HPETE in mixed platelet-leucocyte suspension. These authors hypothesized that administration of aspirin to intolerant patients with asthma may lead to increased generation of 12-HPETE in their platelets [37] because of impaired cyclooxygenase and 12-lipoxygenase balance, or because of inhibition of peroxidase activity in platelets. The released 12-HETE could activate 5-lipoxygenase of circulating blood leucocytes and pulmonary macrophages; generated leukotrienes would precipitate asthma.

AMEISEN and co-workers [9, 10] reported that platelets isolated from patients with aspirin-induced asthma react abnormally in vitro to aspirin and other cyclooxygenase inhibitors by generating cytocidal molecules that can kill parasitic larvae. Aspirin-like drugs had no similar effect on platelets from normal donors or allergic asthmatics. This abnormality, according to the authors [38], appears to be associated with the inhibiting properties of the analgesics on the cyclooxygenase pathway, that leads to a defect of the binding of prostaglandin endoperoxide PGH_2 to its receptors on the platelet membrane.

NIZANKOWSKA et al. [25] measured 12-HPETE production by platelets in 10 aspirin-sensitive asthmatics and 10 matched healthy controls before and after administration of the threshold doses of aspirin. Initial levels of 12-HPETE did not differ between the two groups. Following aspirin challenge, 12-HPETE increase to similar levels in both groups. These data do not support a concept that there is a generalized abnormality in arachidonic acid oxidative pathways in platelets of aspirin-sensitive asthmatics. Lack of protective effect of prostacyclin infusions on aspirin challenge also raises doubts about participation of platelets in the reactions discussed [33].

Compartmentalization of eicosanoids in the lungs

An interesting hypothesis was recently proposed by GRYGLEWSKI [39]. It is based on the idea that arachidonic acid metabolism in the lungs is compartmentalized [32]. Thus, PGE_2 is generated by smooth muscle of large

airways, TXA_2 by contractile elements of lung parenchyma, prostacyclin is produced by vascular endothelium, while leukotrienes are released by leucocytes residing in the lungs and by fibroblasts. All these compartments can be stimulated simultaneously by an immunological reaction.

The hypothesis postulates that in patients with AIA cyclooxygenase of large airways is more susceptible to pharmacological inhibition than that of lung parenchyma. In consequence, an ingestion of anti-cyclooxygenase drug causes an increase in TXA_2/PGE_2 ratio. The most likely explanation for an augmented selective susceptibility of bronchial cyclooxygenase to analgesics is chronic viral infection of the upper airways of patients with AIA [40, 41]. This chronic infection might either change the biochemical characteristics of cyclooxygenase in upper airways or make it easily accessible to analgesics. If the hypothesis is right, then simultaneous pretreatment of patients with TXA_2 synthetase inhibitor and TXA_2/PGH_2 receptor antagonist should protect them against the aspirin-induced bronchoconstriction.

Viral infection

Viruses have been implicated in pathogenesis of asthma [42, 43], including aspirin intolerance [4, 40], though in the latter case no explanation was offered as to how viral infection could be linked with cyclooxygenase-dependent mechanism. Such explanation has been given by a recent hypothesis [41].

The hypothesis postulates that aspirin-induced asthma results from chronic viral infection. In response to a virus, a long time after the initial exposure, specific cytotoxic lymphocytes are produced. Their activity is suppressed by PGE_2 produced by pulmonary alveolar macrophages. Anti-cyclooxygenase analgesics block PGE_2 production, and allow cytotoxic lymphocytes to attack and kill their target cells, i.e. virus-infected cells of the respiratory tract. During this reaction, toxic oxygen intermediates, lysosomal enzymes and mediators are released, which precipitate attacks of asthma. These acute attacks can be prevented by avoidance of all drugs with anti-cyclooxygenase activity. However, asthma continues to run a protracted course because of chronic viral infection.

The hypothesis is bases on the following concepts:
1) The clinical course of aspirin-induced asthma is reminiscent of viral infection [44, 45].
2) Latency or semi-latency of viruses is being increasingly recognized [46, 47]. In man, a notable example is Epstein-Barr virus, causing infection which persists for life, and is subject to reactivations. Interestingly, some of the clinical manifestations of acute Epstein-Barr virus infection, such as Guillain-Barré syndrome, hepatitis or suppression of haematopoiesis may be caused by secondary immune responses to latently infected lymphocytes [48].
3) Cytotoxic T-lymphocytes form a part of the human immune system in the respiratory tract. They increase in numbers in response to viral infections and are highly specific.
4) Lung macrophages produce PGE_2 which suppresses immunological response [49], including cytotoxic activity of lymphocytes [50, 51]. This inhibition can be overcome by anti-cyclooxygenase analgesics, which deprive macrophages of PGE_2.

Several of the hypotheses presented here are now being actively tested. New hypotheses might be expected to emerge as the role of other eicosanoids, such as 15-lipoxygenase products, become more clear. Though aspirin-induced asthma guards its secrets well, it attracts more and more scientists and clinicians, convinced that unravelling the mysteries of this syndrome will give new insight into the pathogenesis of asthma.

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La théorie de la cyclooxygénase pour l'asthma induit par l'Aspirine. A. Szczeklik.
RÉSUMÉ: L'asthme induit par l'Aspirine est un syndrome clinique bien défini, qui atteint environ 10% des asthmatiques adultes. Chez ces patients, l'Aspirine et d'autres analgésiques peuvent déclencher des crises asthmatiques. L'idée que la crise pourrait résulter de l'inhibition spécifique d'une seule enzyme, en l'occurrence la cyclooxygénase, trouve des confirmations à la fois expérimentales et cliniques. Elle a stimulé un certain nombre d'hypothèses sur les mécanismes de la bronchoconstriction. Toutes ces hypothèses décrites ici se dévéloppment dans le cadre de la théorie de la cyclooxygénase. Leur supposition principale est que l'inhibition de la cyclooxygénase stimule des réactions biochimiques spécifiques que conduisent à des crises d'asthma franc.
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