

HYPOTHESIS

Aspirin-induced asthma as a viral disease

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Summary

A hypothesis is presented which states that aspirin-induced asthma results from chronic viral infection. This type of asthma has, indeed, a highly characteristic clinical course, reminiscent of viral upper respiratory tract infection. It is suggested that, in response to a virus, a long time after the initial exposure, specific cytotoxic lymphocytes are produced. Their activity is suppressed by prostaglandin E_2 (PGE_2) produced by pulmonary alveolar macrophages. Anti-cyclo-oxygenase analgesics block PGE_2 production, and allow cytotoxic lymphocytes to attack and kill their target cells, i.e. the virus-affected 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-cyclo-oxygenase activity, however, asthma continues to run a protracted course because of chronic viral infection.

Introduction

In some patients with asthma, aspirin precipitates asthmatic attacks. This is a distinct clinical syndrome, affecting about 10% of adult asthmatics [1–3]. Allergic mechanisms for aspirin-induced attacks, based on specific antigen–antibody reactions, have been excluded by extensive immunological studies [4,5]. Furthermore, in aspirin-sensitive patients, asthmatic attacks may be precipitated by several other analgesics with different chemical structures, making immunological crossreactivity most unlikely [6]. In recent years, the concept [7] of aspirin-precipitated asthmatic attacks linked to inhibition of cyclo-oxygenase in the respiratory tract of sensitive patients, has gained wide and firm support.

Inhibition of pulmonary cyclo-oxygenase could have several metabolic consequences. The one most often quoted is the shunting of arachidonic acid from cyclo-oxygenase to the 5-lipoxygenase pathway, leading to overproduction of bronchoconstrictor leukotrienes. Such an explanation, which still remains to be proved, does not answer several basic questions, such as: why should the inhibition of cyclo-oxygenase precipitate attacks only in some, but not in all asthmatics; why should such a reaction occur in subjects who had excellent tolerance to aspirin in the past; and why does this type of asthma, once it develops, run a protracted course despite the avoidance of aspirin and cross-reactive drugs? [6,8]. The hypothesis here presented offers an answer to these questions.

The hypothesis

I propose that aspirin-induced asthma develops as the result of a chronic, viral infection. Part of the immunological response to the infection, expressed by specific cytotoxic lymphocytes, remains under inhibitory control of PGE_2 . Removal of PGE_2 by anti-cyclo-oxygenase analgesics turns off this control mechanism, and allows cytotoxic reactions to proceed. Cytotoxic lymphocytes attack and destroy virus-affected cells of the respiratory tract. Active oxygen species, toxic metabolites and mediators released in the course of these reactions, precipitate attacks of asthma.

While these attacks can be prevented by avoidance of the analgesics with anti-cyclo-oxygenase activity, the basic course of the disease can be altered only by eradication of chronic viral infection.

Viruses as cause of the asthma

Respiratory viruses are probably the most common cause of symptomatic human infections [9]. In normal subjects an upper respiratory tract infection may cause a transient increase in bronchial reactivity [10], and administration of live attenuated influenza virus induces bronchial hyperresponsiveness only in subjects who develop a rise in antibody titre [11]. Empey *et al.* [10] suggested that viral infection damages the respiratory epithelium, thereby exposing airway irritant receptors that would later be activated by various stimulants and irritants. Inflammatory reaction might be initiated in this way. Release of inflammatory mediators from mast cells, eosinophils and neutrophils, as well as damage to epithelium, might expose C-fibre afferent nerve endings, which, via axon reflexes [12], promote secretion of neuropeptides, known to cause bronchoconstriction and an inflammatory reaction. Thus, viral infection can produce disease long after the initial exposure [13].

The clinical course of aspirin-induced asthma is reminiscent of viral infection. In the majority of patients the first symptoms appear during the third or fourth decade of life. The disease invariably starts suddenly with symptoms of malaise, nasal discharge, nasal obstruction and sneezing. Cough and expectoration without pneumonia are commonly associated. All these symptoms resolve within a week or two, except for the rhinitis, which is characterized by intermittent, profuse watery rhinorrhea resistant to treatment. Nasal congestion develops and physical examination often reveals nasal polyps. Rhinitis persists, and several months or years later bronchial asthma and intolerance to aspirin develop. The asthma runs a chronic course. It fits into the category of 'intrinsic' or 'infectious' asthma because of a lack of atopic background, usually negative skin tests to common airborne allergens, normal serum IgE levels and frequent clinical exacerbations suggestive of recurrent infection [3]. This onset and course of the disease is so characteristic that a typical case has been constructed [1] and confirmed by many clinicians [2-5].

Inhibition of cyclo-oxygenase triggers asthmatic attacks

Evidence supporting the hypothesis [7] that in sensitive patients, precipitation of asthmatic attacks by certain analgesics results from inhibition of cyclo-oxygenase, leading to an imbalance of prostanoids in the respiratory tract, can be summarized [1-3]. (i) Analgesics with anti-cyclo-oxygenase activity invariably precipitate bronchoconstriction in aspirin-sensitive asthmatic patients; (ii) analgesics not affecting cyclo-oxygenase are devoid of bronchospastic properties in these patients (inhibitors of thromboxane A_2 synthetase, deprived of anti-cyclo-oxygenase activity, are also very

well tolerated by the same patients [15]; (iii) there is a positive correlation between the potency of analgesics in inhibiting cyclo-oxygenase *in vitro* and their potency in inducing asthmatic attacks in the sensitive patients; (iv) the cyclo-oxygenase in nasal polyps of aspirin-sensitive patients has an increased susceptibility to the inhibitory action of aspirin [16], while PGE₂ formation by the nasal polyps from aspirin-sensitive patients is within the control range [16,17]; (v) *in vitro*, cyclo-oxygenase inhibitors activate platelets to release toxic mediators in aspirin-sensitive asthmatics, but not in atopic asthmatics of healthy subjects [18]. Thus, the inhibition of cyclo-oxygenase by aspirin-like drugs appears to set off a chain of reactions leading to asthmatic attacks in aspirin-intolerant patients. What follows at the biochemical level remains largely unknown.

I do not favour the widely held concept that aspirin-like drugs, by blocking the cyclo-oxygenase pathway, divert arachidonic acid metabolism towards leukotrienes C₄ and D₄, which are potent bronchoconstrictors and mucous secretagogues. This concept lacks experimental evidence [19] and is hard to accept in view of the likely compartmentalization of arachidonic acid in the lung [20]. Our negative results with a specific leukotriene inhibitor also argue against the simple shift in arachidonic acid metabolism towards leukotrienes [21]. Here we suggest a different explanation based on PGE₂-mediated control of defence mechanisms.

Cytotoxic response to virus infection

The immune system is equipped with two types of cytolytic lymphocytes [22–24]. The cytotoxic T lymphocytes (CTL), upon priming with antigen, lyse antigen-bearing cells, such as virally infected cells. Natural killer (NK) cells lyse certain tumours or virally infected cells without prior sensitization to any antigen. Natural killer cells are distinct from CTLs in that their lytic ability is not immunologically specific and is also not major histocompatibility complex (MHC) restricted. These are functional categories of cell-mediated cytotoxicity, and more than one type may be manifested by a particular cell [22]. Thus, some MHC-restricted CTLs may express NK activity [25]. Conversely, the viral specific cytotoxic effects may be mediated by more than one subset of lymphocytes [26].

In man, a cell-mediated immune system exists in the respiratory tract that is apparently separate, although not clearly distinct from the systemic cell-mediated immune system [27]. Bronchoalveolar lavage fluid from healthy people contains large granular lymphocytes (LGL). These cells have a potential to express both NK cell and CTL activity [22,28]. Large granular lymphocytes from human lungs are inactive, or possibly inhibited [29], but disclose their cytolytic properties upon stimulation with interleukin-2. The cytotoxic function in cell suspension, prepared from human lung [30] and human bronchial lavage [31], assayed as NK activity, was found to be under the strong suppressive influence of adherent cell populations, the major component of which were pulmonary alveolar macrophages (PAM).

PGE₂ as a suppressor of cytotoxic lymphocytes

Suppressor macrophages produce PGE₂ which inhibits cytotoxic activity of lymphocytes [22,29]. This inhibition can be overcome by anti-cyclo-oxygenase analgesics, which block cyclo-oxygenase and deprive PAM or PGE₂ [32].

Interleukin-2 has an important role in the immune response [33]. It stimulates

human lymphoid cells to proliferate and induces their differentiation into cytotoxic effector cells. Thus, it promotes the growth and differentiation of both CTLs and NK cells [24]. Interleukin-2-activated lymphocytes become partly resistant to suppression by PGE_2 [22]. *In vivo*, aspirin augments interleukin-2 production by prevention of macrophage PGE_2 synthesis [34]. Similar observations have been reported for other cyclo-oxygenase inhibitors *in vitro* [35].

I suggest that in response to persistent, chronic viral infection, aspirin-sensitive asthmatics develop virus-specific cytotoxic T lymphocytes, the activity of which is suppressed by PGE_2 . It takes considerable time before such a defensive mechanism can be mounted. The late cellular response to virus infections, such as measles, infectious mononucleosis and cytomegalovirus, is well documented [23]. Indeed, the specific T-cell response to cytomegalovirus may not appear for several months [23].

Once established, the cellular defensive mechanism becomes sensitive to inhibitors of cyclo-oxygenase. The analgesics, which block cyclo-oxygenase and suppress PGE_2 production, allow cytotoxic T lymphocytes to exert their attack against the virus-altered target cells. These could be bronchial epithelium, cells of the subepithelial connective tissue, perhaps smooth muscle cells (Fig. 1).

Cytotoxic lymphocytes recognize the target cells and lyse them by generating hydroxyl radicals [36]. As a result, toxic oxygen intermediates, lysosomal enzymes and mediators are released, which precipitate attacks of asthma. The cytotoxic reaction can be amplified by leukotriene B_4 [37], generation of which becomes enhanced in the absence of inhibitory action of PGE_2 [19]. Furthermore, eosinophils and neutrophils, present in the bronchial tissue of asthmatic patients [38], might add to the irritating and toxic effects of lymphocyte cytolysis through superoxide anions generation, facilitated greatly by the inhibition of production of PGE_2 [39].

The mechanism described might become permanently implanted because of viral shedding in previously infected subjects and subsequent endogenous antigenic exposure of the immunologic repertoire, even in the absence of manifest clinical disease.

Aspirin-precipitated attacks of asthma can be markedly attenuated by a 10-day pre-treatment with glucocorticosteroids [40]. Perhaps steroids exert their protective action through inhibition of T cell proliferation and interleukin-2 production [41]. By

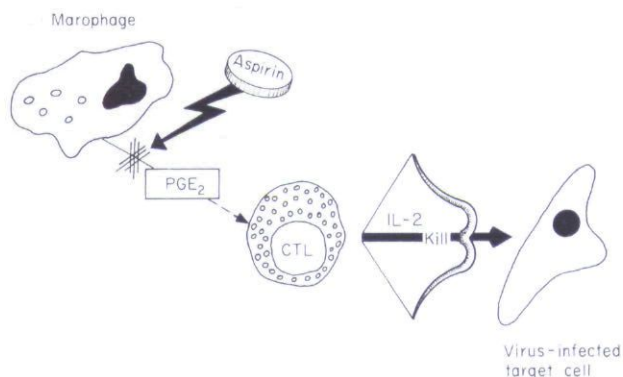


Fig. 1. Aspirin turns off the control mechanism by blocking PGE_2 production in pulmonary alveolar macrophages. As a result, cytotoxic T lymphocytes attack and kill virus-infected cells of the respiratory tract. IL-2: interleukin 2, CTL: cytotoxic T lymphocyte, PGE_2 = prostaglandin E_2 .

doing so they would remove the effector pathway of the mechanism responsible for idiosyncratic reactions to aspirin from the picture.

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