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Aspirin-Sensitive Respiratory Disease

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Key Words

asthma, COX-1 and COX-2 inhibitors, cysteinyl leukotrienes, nasal polyps, PGE₂

Abstract

Aspirin-sensitive respiratory disease (ASRD) is a condition characterized by persistent and often severe inflammation of the upper and lower respiratory tracts. Patients develop chronic eosinophilic rhinosinuitis, nasal polyposis, and asthma. The ingestion of aspirin and other cyclooxygenase-1 (COX-1) inhibitors induces exacerbations of airway disease that may be life-threatening. Thus, aspirin sensitivity is a phenotypic marker for the syndrome, yet nearly all affected individuals can be desensitized by the administration of graded doses of aspirin, leading to long-term clinical benefits. Patients with aspirin sensitivity are often able to tolerate selective COX-2 inhibitors. The pathogenesis of ASRD is underpinned by abnormalities in eicosanoid biosynthesis and eicosanoid receptor expression coupled with intense mast cell and eosinophilic infiltration of the entire respiratory tract. This review focuses on the molecular, cellular, and biochemical abnormalities characterizing ASRD and highlights unanswered questions in the literature and potential future areas of investigation.

ASRD: aspirin-sensitive respiratory disease

NSAIDS: nonsteroidal anti-inflammatory drugs

FESS: functional endoscopic sinus surgery

INTRODUCTION

On the tenth of August of 1897, Felix Hoffmann, a pharmacist working at the Bayer factory in Germany, succeeded in synthesizing acetylsalicylic acid. By March 1899 this compound had been named aspirin and was being marketed by Bayer. Aspirin has since become the most widely used medicine of all time (1, 2). In 1922, Widal described the association of aspirin sensitivity, asthma, and nasal polyps. He also pioneered the first aspirin challenges and desensitization (3). However, aspirin-sensitive respiratory disease (ASRD) became widely recognized only after Samter & Beer published two articles in the late 1960s (e.g., Reference 4), and the combination of aspirin sensitivity, asthma, and nasal polyposis became known as Samter's triad.

Today ASRD is recognized to be an aggressive phenotype of airway disease that often runs a protracted course. Compared with aspirin-tolerant individuals, patients with ASRD are more likely to experience irreversible airflow obstruction (5), to suffer frequent exacerbations (6), to be diagnosed with severe asthma and be prescribed high-dose oral steroids by their physicians, and more often to require intubation for their severe asthma (5).

DEFINITION

The clinical syndrome of ASRD is characterized by a combination of chronic rhinosinusitis progressing to chronic hyperplastic eosinophilic sinusitis, moderate-to-severe asthma, and nasal polyposis. Previous exposure to aspirin is not a risk factor for the development of ASRD, but once established, ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDS) induces an acute worsening of rhinosinusitis and asthma. Aspirin sensitivity therefore is a valuable phenotypic marker for a disease that often responds poorly to steroids and that is characterized by intractable inflammation of the upper and lower respiratory tracts.

CLINICAL FEATURES AND NATURAL HISTORY

ASRD has high morbidity, and symptoms are almost always lifelong once ASRD develops. There is no discernable relationship to an atopic diathesis (5), and ASRD may develop in patients with no prior history of IgE-mediated respiratory disease or manifest in individuals who already have allergic rhinitis and/or allergic asthma. However, unlike atopic asthma it is rare in childhood, with peak ages of onset between 29 and 34 years observed in two large studies documenting the natural history of the disease (7, 8). Typically the condition progresses from the upper to the lower respiratory tracts (4, 8), and approximately half of all patients relate a viral upper respiratory tract infection as the inciting event (8).

Like all adult asthma, ASRD affects women more frequently than men; in women the onset of symptoms is often earlier, and the disease is more aggressive (8). Persistent rhinorrhea and nasal congestion are usually the earliest symptoms. In an average patient, within two years of onset the disease progresses to the lower respiratory tract with asthma, and within four years aspirin sensitivity and nasal polyposis develop (8). Approximately 20% of aspirin-sensitive patients have evidence of generalized mast cell degranulation and experience urticaria (20%) or angioedema (8%) following aspirin challenge (8). In some series the percentage of patients with systemic reactions following aspirin challenge has been reported to be greater than 50%, suggesting heterogeneity within the phenotype (9).

Aspirin-sensitive individuals average one episode of sinusitis every ten weeks (7) and have marked thickening of the basement membrane suggestive of sinusoidal mucosal remodeling (10). At the time of surgery, subjects typically have a larger volume of polyp tissue than do aspirin-tolerant patients, and surgery often results in only a transient relief of symptoms. Six months following functional endoscopic sinus surgery (FESS) and polypectomy, patients with ASRD have significantly higher

rates of symptom recurrence (nasal blockage, facial pain, postnasal drip, and anosmia) in addition to regrowth of nasal polyps (11). On average patients with ASRD will require ten times as many resections of their nasal polyps compared with their non-aspirin-sensitive counterparts (11), and the frequency of FESS polypectomy in ASRD correlates with the density of mast cells and eosinophils in polyp tissue (12). FESS leads to a reduction in lower respiratory tract symptoms with decreased inhaled corticosteroid use and improved asthma symptom scores at six months and one year follow-up (13).

PREVALENCE

The exact prevalence of ASRD in adults is unclear because many asthmatics routinely avoid NSAIDs and patients who experience a mild worsening of their asthma after ingesting NSAIDs may not correlate this with aspirin sensitivity. The prevalence of ASRD also varies depending on the population studied (severe asthmatics, patients with nasal polyps and chronic rhinosinusitis, patients with rhinitis alone) and the technique used to make the diagnosis (population-based questionnaire, physician assessment, or aspirin challenge). A higher prevalence of ASRD is invariably found when asthmatic patients are challenged with aspirin rather than when patient questionnaires are relied upon to make the diagnosis. If patient questionnaires are used as the sole means of assessing for the presence of aspirin sensitivity, the prevalence of ASRD ranges from 0.6% (14) to 2.5% (15) in the general population and from 3.8% (16) to 11% (15) in asthmatics. On the basis of oral aspirin challenges in selected asthmatic populations, the prevalence rises to approximately 20% (17). Conversely, in a study of more than 6000 patients with nasal polyps, it was estimated that 14% of individuals were also aspirin sensitive (18).

It is important to recognize ASRD clinically because it is associated with near-fatal asthma (8, 19), although it remains uncertain if this is because of accidental/unknown NSAID inges-

tion or because of the severity of underlying disease. In a survey of 500 patients with ASRD, 15% of patients who were diagnosed were unaware of their aspirin-sensitive status prior to challenge (8). Estimates vary, but an incidence of ASRD in 14% of rapid-onset, near-fatal/fatal asthma attacks has been reported (20), and it is estimated that between 11% and 15% of all intensive-care admissions with asthma involve aspirin-sensitive patients (21, 22). Lack of patient and doctor awareness, aggravated by limited access to aspirin challenges, therefore may have potentially grave consequences.

THE DIAGNOSIS OF ASRD

The mechanism of aspirin sensitivity remains unclear, but most commentators agree that reaction to aspirin is not immunologically mediated. There is no evidence of an IgE-mediated response to aspirin, and patients do not have positive skin prick tests to aspirin or other NSAIDs. The fact that on first exposure the effect of aspirin is often mimicked by a wide variety of other NSAIDs precludes drug hapten-antibody recognition and makes the scenario of immunological reactivity highly unlikely. Furthermore, despite avoidance of aspirin, chronic inflammation of both the upper and lower respiratory tracts is ongoing and progressive, confirming that the ingestion of NSAIDs is not responsible for inducing the disease. Szczeklik et al. (23) first proposed a nonallergic mechanism of ASRD more than 30 years ago.

Aspirin causes time-dependent covalent modification and irreversible inhibition of cyclooxygenase-1 (COX-1) and competes directly with arachidonic acid for binding to the cyclooxygenase site (24). Serine 530 is the site of acetylation of ovine COX-1 by aspirin (24). X-ray crystallographic studies have established that when serine 530 is acetylated by aspirin, the acetyl group protrudes into the cyclooxygenase active site and interferes with arachidonate binding (24). There is a correlation between in vitro potency of COX-1 inhibition by a drug and the risk of precipitation of aspirin-induced asthma (23). Aspirin also

COX: cyclooxygenase

PG: prostaglandin

5-LO:

5-lipoxygenase

CysLT: cysteinyl
leukotriene

CysLTR: cysteinyl
leukotriene receptor

EP: E-prostanoid

LX: lipoxin

acetylates cyclooxygenase-2 (COX-2) but does not block substrate binding. Hence the resulting enzyme maintains its cyclooxygenase activity and is still able to oxygenate arachidonic acid to exclusively form 15-hydroxy-5,8,11,13-eicosatetraenoic acid (15-HETE), which then undergoes transcellular biosynthesis to produce 15-*epi*-LXA₄ (lipoxin A₄) (25).

Presently, a diagnosis of aspirin sensitivity can be definitively established only by aspirin challenge in which patients receive increasing doses of oral aspirin, or inhaled or nasal lysine aspirin. As well as being time consuming, aspirin challenges are not without risk, and greater than a third of patients have been reported to experience late reactions following bronchial aspirin challenge (26). Flow-cytometric determination of basophil activation induced by aspirin (27) and aspirin-triggered 15-HETE generation in peripheral blood leukocytes (PBLs) may be highly specific and sensitive in vitro diagnostic tests (28), but this possibility has to be fully validated.

THE PATHOPHYSIOLOGY OF ASRD

Mediators and Mechanisms

Unlike preformed mediators such as histamine that are released upon mast cell or basophil stimulation and cytokines that typically require gene transcription and mRNA translation for production, the leukotrienes (LTs) and the prostaglandins (PGs) are synthesized *de novo* upon cellular activation.

Once released from the cell membrane by cytosolic phospholipase A₂ (cPLA₂), unesterified arachidonic acid may be metabolized through two main pathways: the COX pathway, which yields the prostanoids, or the 5-lipoxygenase (5-LO) pathway to form the unstable intermediary LTA₄. LTA₄ is metabolized to either LTB₄ or the cysteinyl leukotrienes (CysLTs), depending on distal enzymes differentially expressed in leukocytes (29) (**Figure 1**).

The pathophysiology of ASRD is characterized by abnormalities in the biosynthesis of

eicosanoid mediators and eicosanoid receptor expression. The biochemical hallmark of ASRD is enhanced CysLT production both at baseline (30, 31) and following aspirin challenge (32, 33). The nasal and bronchial mucosa of aspirin-sensitive patients is rich with eosinophils and mast cells (34, 35), both abundant sources of CysLTs (36). Furthermore, there is upregulation of the cysteinyl leukotriene 1 receptor (CysLT₁R) on target cells in ASRD (37), and one consequence of this upregulation may be enhanced end-organ responsiveness to CysLTs.

Conversely, on inflammatory cells, there is downregulation of the E-prostanoid 2 (EP2) receptor, which binds the anti-inflammatory prostanoid prostaglandin E₂ (PGE₂) (38). There is evidence that PGE₂ ameliorates aspirin-induced disease, at least partly by inhibiting excessive CysLT synthesis (39, 40). The effect of reduced EP2 receptor expression in ASRD on downstream signaling pathways is as yet unclear. It is possible that the halting of the inflammatory process by PGE₂ is critically impaired owing either to deficient PGE₂ production and/or to abnormal PGE₂ receptor expression in aspirin-sensitive patients. Reduced synthesis of anti-inflammatory lipoxins (LXs) also correlates with ASRD (41–43). LXs are functional antagonists of the CysLTs, and therefore diminished capacity to generate LXs may contribute to the uncontrolled, chronic inflammation that characterizes this phenotype of airway disease.

Inflammatory Pathways

Biopsy studies from the respiratory tract in aspirin-sensitive patients show elevated numbers of eosinophils and mast cells as compared with their aspirin-tolerant counterparts (34, 35). Both mast cells and eosinophils are critical effector cells, important cellular sources of CysLTs, and are responsible for perpetuating the devastating inflammation seen in ASRD (36).

Extensive infiltration of eosinophils and mast cells was noted in bronchial biopsies from aspirin-sensitive patients ten years ago (34).

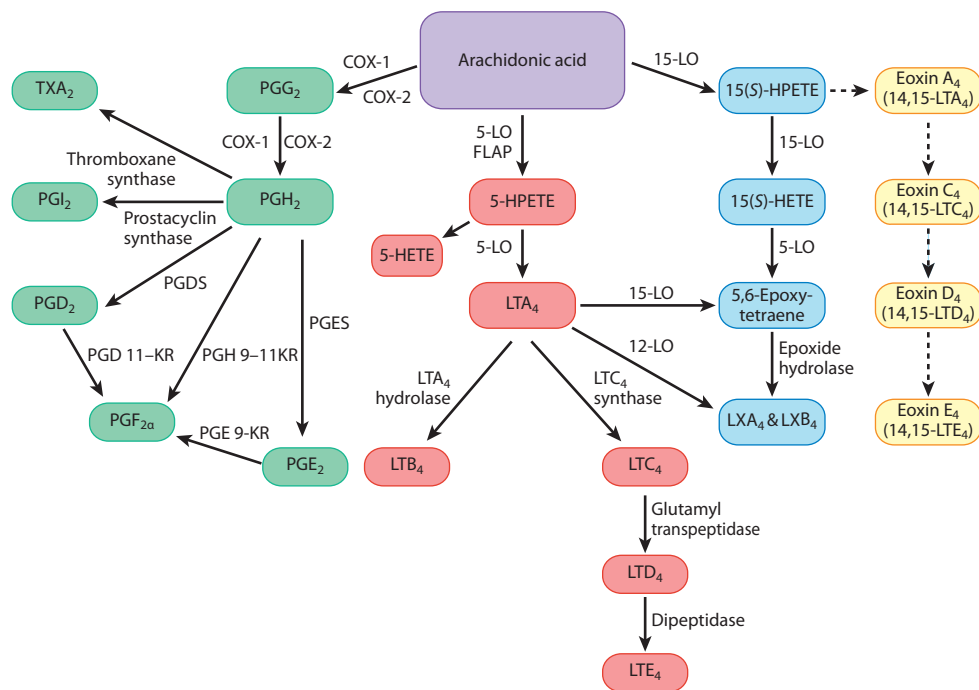


Figure 1

Schematic representation of the metabolism of arachidonic acid by the cyclooxygenase and the 5- and 15-lipoxygenase (LO) pathways. Once released from the cell membrane by cytosolic phospholipase A₂ (cPLA₂), arachidonic acid may be metabolized through two main pathways: the cyclooxygenase (COX) pathway to yield the prostanoids or the 5-lipoxygenase (5-LO) pathway to form the unstable intermediary LTA₄, which, then depending on distal enzymes differentially expressed in leukocytes, is metabolized to either LTB₄ or the cysteinyl leukotrienes (CysLTs). COX-1 and COX-2 catalyze a bifid reaction in which first arachidonic acid is oxidized to prostaglandin G₂ (PGG₂) and then PGG₂ is reduced to prostaglandin H₂ (PGH₂). PGH₂ serves as a substrate for the prostaglandin synthase (PGS) or prostaglandin ketoreductase (PGKR) enzymes, which are responsible for the production of the five principal bioactive prostanoids generated *in vivo*: PGE₂, PGF_{2α}, PGD₂, PGI₂ (prostacyclin), and TXA₂ (thromboxane). 15-Lipoxygenase (15-LO) catalyzes the hydroperoxidation of arachidonic acid, with the insertion of one molecule of oxygen at position 15 to form 15-HPETE. The products of arachidonic acid also include lipoxins (LXs) and eoxins (EXs). The dotted arrows refer to an as-yet-unconfirmed pathway for EX synthesis (124).

Similar changes have since been observed in the upper airways with inferior turbinate biopsies from patients with ASRD demonstrating intense inflammation and elevated numbers of total and activated eosinophils, mast cells, and T lymphocytes (35) and nasal polyps from aspirin-sensitive patients revealing substantial eosinophilic and mast cell infiltration compared with aspirin-tolerant patients (44). Aspirin-sensitive patients show a significant increase in the mobilization of leukocyte and eosinophil progenitor cells from the bone mar-

row for up to 20 h after bronchial aspirin challenge (9). This increase, coupled with decreased apoptosis of inflammatory cells in the airway, is a likely contributory factor to the persistent inflammation characterizing the syndrome (44).

Mast cells are found in three distinct microsites in the airways of asthmatic patients: the bronchial smooth muscle, the bronchial epithelium, and the airway mucus glands (45). In ASRD, mast cells are seen in the epithelial cell layer but not in the mucosa of nasal polyps (46). In aspirin-sensitive patients,

ICAM-1: intercellular adhesion molecule-1

RV: rhinovirus

AHR: airway hyperresponsiveness

BAL: bronchoalveolar lavage

significantly higher levels of the mast cell chemoattractant stem cell factor (SCF) have been detected in both mRNA and protein levels from cultured epithelial cells taken from nasal polyp explants (12). The mechanism responsible for an increased expression of SCF in nasal polyp epithelial cells from aspirin-sensitive patients is not known. But because SCF promotes mast cell survival, acts as a major growth and differentiation factor (48, 49), and is chemotactic for human mast cells (50), its upregulation may partially explain the increased numbers of mast cells seen in ASRD and their ongoing activation.

The epithelium in asthma is particularly susceptible to infection with respiratory viruses. Rhinovirus (RV) is able to preferentially invade the bronchial epithelium in asthmatics, using intercellular adhesion molecule-1 (ICAM-1) and very low-density lipoprotein receptors to enter the cell (51). The release of tryptase by mast cells upregulates ICAM-1 expression in airway epithelium (52). Enhanced expression of ICAM-1 as well as of the adhesion molecule vascular cell adhesion molecule-1 (VCAM-1) and very late-activation antigen-4 (VLA-4) has been demonstrated in nasal polyps from aspirin-sensitive patients (53). In individuals who are clinically free of symptoms of a respiratory tract infection, human RV is found in the bronchial mucosa in significantly higher numbers of asthmatics (73%) versus normal controls (22%) (54). Furthermore, there is profound impairment of virus-induced interferon- β (IFN- β) mRNA expression in asthmatic cultures, and this leads to poor clearance of virus and apoptosis by epithelial cells (55). Investigators have observed a correlation between sequestering RV and diminished pulmonary function, eosinophilic inflammation of the bronchial mucosa, and serum eosinophilia (54).

Hence infective exacerbations in asthma arise on a background of impaired epithelial host defense (55), and chronic infection with RV is associated with clinically worse disease (54). ASRD is an acquired condition, and patients will often describe "a cold that never cleared up" as heralding the onset of the syn-

drome. This observation may be highly significant and has led commentators to propose that a chronic viral respiratory tract infection may be the underlying event that both incites and perpetuates the inflammatory cascade in aspirin sensitivity (56). Presently the ability of the airways in patients with ASRD to clear viral infections is little explored, and whether there is a substantial difference in IFN- β expression between aspirin-sensitive and aspirin-tolerant asthmatics is unknown.

Mast cells are a major source of the proinflammatory cytokine tumor necrosis factor- α (TNF- α) in the airways and also release the autacoid mediators histamine, prostaglandin D₂ (PGD₂), and LTC₄ (45), all of which are potent contractile agonists of airway smooth muscle and are capable of inducing airway hyperresponsiveness (AHR), excessive mucus secretion, and edema of the bronchial mucosa. There is conflicting evidence whether mast cells from aspirin-sensitive individuals following exposure to aspirin are directly activated to release these mediators (57–60).

Mast cells cultured from peripheral blood progenitors in aspirin-sensitive patients and activated by anti-IgE overproduced CysLTs by almost 200% compared with aspirin-tolerant patients (57). However, neither basal or IgE-induced release of histamine nor CysLTs were upregulated when the cells were incubated with aspirin. PGD₂ release from mast cells was also suppressed following incubation with aspirin in the same study (57). Conversely, in vivo studies suggest that mast cells are directly activated by aspirin in ASRD. Aspirin-sensitive patients have raised levels of the PGD₂ metabolite (9 α ,11 β -PGF₂) and tryptase in their blood prior to exposure to aspirin, and following challenge in most patients, these levels rise further still (58). After segmental bronchial challenge of asthmatics with lysine aspirin, an aspirin cogener that can be made into an aerosol, a significant reduction in the numbers of tryptase-positive mast cells in the bronchial mucosa and an increase in mucosal infiltration of eosinophils are seen (59). Bronchoalveolar lavage (BAL) from aspirin-sensitive

patients after segmental lysine aspirin challenge has shown a trend toward increased histamine release with no inhibition of PGD_2 production, although the same study found no increase in tryptase or eosinophil cationic protein (ECP) levels (60). Overall these findings suggest that chronic ongoing mast cell activation is a feature of ASRD at baseline, and this may be aggravated further as a result of aspirin provocation. However, a mechanism for direct mast cell activation by aspirin is unclear.

Mast cells secrete the proinflammatory cytokines interleukin (IL)-4, IL-5, and IL-13, and raised IL-4 and IL-6 levels have been measured in exhaled breath condensates from aspirin-sensitive patients (61). IL-5 promotes eosinophil development, priming, differentiation, and survival (62). It also stimulates translocation of 5-LO to the nucleus and upregulates 5-lipoxygenase-activating protein (FLAP) in human eosinophils, thereby enhancing the ability of eosinophils to produce CysLTs (63). In bronchial biopsies from aspirin-sensitive patients, IL-5 expression in mast cells and eosinophils is significantly increased (64). In vivo studies measuring IL-5, both in BAL and serum from aspirin-sensitive patients, have recorded no baseline increases in IL-5 production compared with levels in aspirin-tolerant asthmatics (60, 65). However, within 15 min of lysine aspirin challenge, an increase in numbers of eosinophils with a corresponding increase in IL-5 has been measured in BAL fluid in individuals with ASRD (60).

IL-13 is predominantly produced by Th2-polarized CD4^+ T cells, but it is also synthesized by non-T cells, including mast cells, basophils, and eosinophils (66). Its production is upregulated in human eosinophils in response to IL-5 and GM-CSF stimulation (67). IL-13 both enhances leukocyte production of LTD_4 (36) and increases expression of the CysLT_1R on bronchial smooth muscle (68). Both IL-4 and IL-13 also enhance bronchial smooth-muscle proliferation in fibroblast growth factor 2-primed cells (69). IL-13 alone may mediate some of the main physiological consequences of asthma, namely AHR, mucus hypersecretion,

and subepithelial fibrosis (66). The importance of IL-13 in the pathogenesis of airway inflammation has been underscored by the correlation between IL-13 overexpression in sputum and bronchial biopsies and severe asthma (70). Furthermore, IL-13 selectively downregulates PGE_2 biosynthesis in human airway epithelial cells from both asthmatic and normal subjects (71). IL-13 inhibits COX-2 and mPGES-1 (a membrane-bound form of prostaglandin E synthase) while upregulating the PGE_2 -metabolizing enzyme 15-prostaglandin dehydrogenase (15-PGDH), and these enzymatic changes correlate with decreased supernatant PGE_2 levels (71). These findings underline the likely importance of transcellular interactions between epithelial cells and leukocytes in vivo. IL-13 also induces apoptosis in lung epithelial cells and is implicated in airway remodeling by upregulating profibrotic genes in primary lung fibroblasts (72). We are not aware of any published studies examining IL-13 production in ASRD or the functional consequences of enhanced or diminished cytokine production.

Finally, a dysfunctional respiratory epithelium that is increasingly vulnerable to damage is a well-recognized feature of asthma. Researchers have extensively described the concept of a disordered epithelium orchestrating an inflammatory response that repairs incompletely and interacts with multiple environmental factors to produce a chronic wound scenario in chronic asthma (73). An elevation of epithelial EP1 and EP2 receptor expression has been observed in the inflamed nasal mucosa of aspirin-sensitive patients (38). This is significant because PGE_2 administration protects against airway obstruction, i.e., it is bronchoprotective; PGE_2 also promotes wound healing and repair in the respiratory epithelium (74).

The 5-Lipoxygenase Pathway, Cysteinyl Leukotrienes, and Their Receptors

The CysLTs are critical proinflammatory mediators in asthma. They have considerable

IL: interleukin

15-PGDH:

15-prostaglandin dehydrogenase

uLTE₄: urinary leukotriene E₄
LTC₄S: leukotriene C₄ synthase

importance in the pathogenesis of ASRD. As well as being potent activators of inflammatory cells, they are powerful bronchoconstrictor agonists. LTC₄ and LTD₄ are approximately 1000-fold more potent than histamine in contracting human bronchi in vitro (75). In mild asthmatics neither bronchial responsiveness to LTD₄ nor the amount of urinary LTE₄ (uLTE₄) that can be recovered without specific antigen challenge is attenuated by inhaled corticosteroids (76). CysLTs induce mucus hypersecretion from goblet cells and augment leukocyte adhesion to endothelial cells (36). They also act directly on endothelial cells to induce microvascular permeability (36). Moreover, they are implicated in airway remodeling and enhance the capacity of lung fibroblasts to proliferate to known mitogens and to lay down collagen (36). Finally, the CysLTs, while being generated by eosinophils, monocytes, and mast cells, can activate these cells in both an autocrine and a paracrine manner (36). The CysLTs act as

chemoattractants for inflammatory leukocytes, and inhalation of LTE₄ increases infiltration of neutrophils and eosinophils into asthmatic airways (77).

A distinguishing feature of ASRD is up-regulation of the 5-LO pathway at baseline, which is enhanced further with the addition of NSAIDs. Christie et al. (78) quantitated uLTE₄ levels as a measure of global CysLT production in aspirin-sensitive patients. A mean sixfold-higher resting uLTE₄ level was detected in aspirin-sensitive compared with normal or non-aspirin-sensitive patients prior to oral aspirin challenge, with a further fourfold increase following aspirin challenge (78) (**Figure 2**). Inhalation challenge with lysine aspirin also induced a similar rise in uLTE₄ (79). Long-term desensitization with oral aspirin resulted in significant blunting of uLTE₄ production, but levels nonetheless remained elevated compared with those of aspirin-tolerant individuals (80).

There is broad overlap in uLTE₄ concentrations between aspirin-tolerant and aspirin-sensitive patients, thereby precluding the clinical use of uLTE₄ as a diagnostic test for ASRD. Nevertheless, the increase in CysLT levels in all bodily fluids studied following aspirin challenge is a unique feature of ASRD (65, 78, 79, 81, 82). To date, whether enhanced CysLT production in ASRD is the result of a predetermined abnormality in the production of CysLTs or is the consequence of greater numbers and activation of eosinophils and mast cells remains unanswered—although these possibilities are not mutually exclusive.

LTC₄ synthase (LTC₄S) is a critical enzyme in CysLT production and conjugates LTA₄ with reduced glutathione in mast cells, basophils, eosinophils, and other inflammatory cells to yield LTC₄ (36). Circulating blood eosinophils from aspirin-sensitive patients have more mRNA for this enzyme (83), as do nasal polyps from aspirin-sensitive individuals compared with aspirin-tolerant subjects (43). Immunostaining in nasal polyps resected from aspirin-sensitive individuals demonstrates a fourfold-higher expression of LTC₄S in the polyp mucosa compared with expression

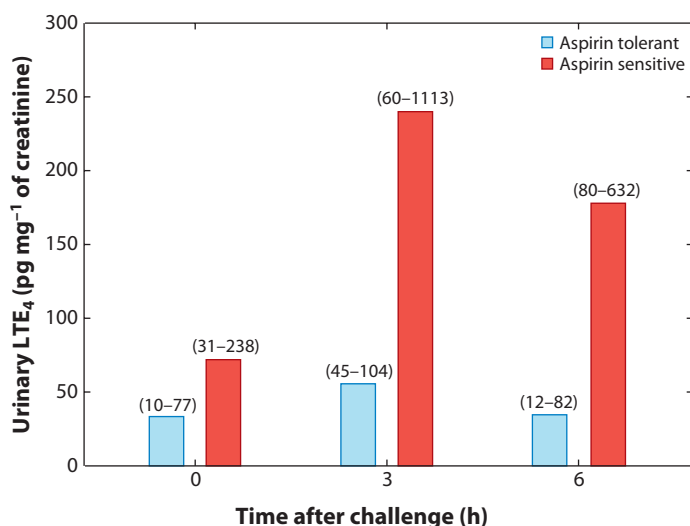


Figure 2

The time-dependent changes in urinary LTE₄ concentrations after lysine aspirin challenge in six aspirin-sensitive patients. After lysine aspirin challenge in patients with ASRD, urinary LTE₄ concentrations increased from 72 pg mg⁻¹ (geometric mean) to 240 pg mg⁻¹ at 3 h and to 178 pg mg⁻¹ at 6 h. The increase in urinary LTE₄ concentrations over time was significant ($p < 0.025$). Aspirin-tolerant individuals displayed no significant increase in urinary LTE₄ concentrations. (Adapted with permission from Reference 79. Copyright American Thoracic Society.)

in aspirin-insensitive subjects (46). LTC₄S is also overexpressed in the bronchial mucosa in ASRD, with fivefold-higher expression compared with aspirin-tolerant subjects (84). This expression of LTC₄S in the bronchial mucosa appears to reflect enzymatic activity, with a correlation between CysLT levels measured in BAL fluid and the numbers of LTC₄S-immunoreactive cells. Furthermore, LTC₄S upregulation in aspirin-sensitive patients correlates with bronchial responsiveness to lysine aspirin challenge (84). The cells in the airways expressing elevated LTC₄S include eosinophils (46) and mast cells (85).

Increased expression of LTC₄S in ASRD may be genetically regulated. A transversion of adenine (A) to cytosine (C), 444 nucleotides upstream of the translational start site (−444A/C), in the promoter region of the LTC₄S gene correlates with an elevated risk of ASRD (86, 87). This single-nucleotide polymorphism (SNP) has been associated with an increased prevalence of ASRD in Japanese studies (86) and severe steroid-dependent ASRD in European populations (87). However, the SNP is only weakly associated with asthma, and not at all with ASRD, in Australian populations (88). It is not associated with asthma or ASRD in the United States (89). The Japanese study observed no relationship between this polymorphism and the LTC₄S activity found in eosinophils. The authors therefore hypothesized that, although this polymorphism might have some effect on the development of ASRD, it was probably acting in linkage disequilibrium with another causatively important and as-yet-unidentified mutation (86). The presence of the LTC₄ −444C allele in aspirin-tolerant patients and the lack of its universal expression in ASRD confirm that this SNP does not represent a unique pathophysiological feature delineating aspirin-sensitive from aspirin-tolerant individuals. Future studies are required to understand why NSAIDs do not induce a rise in CysLT levels in non-aspirin-sensitive individuals.

CysLTs act on at least two rhodopsin-class G protein-coupled receptors: CysLT₁R and CysLT₂R. The sequences of these two recep-

tors are highly divergent, with a 38% homology (90). The evidence for separate cysteinyl leukotriene receptors (CysLTRs) was initially based on differences in biological activity of the individual LTs, the effects of LT receptor antagonists, and radioligand binding studies. In 1999 a previously cloned orphan G protein-coupled receptor was deorphanized and shown to have the pharmacological properties of the CysLT₁R (91, 92). The screening of public databases for novel orphan GPCRs led to the identification of the CysLT₂R in 2000 (93, 94). Both the CysLT₁R and the CysLT₂R are expressed on granulocytes, monocytes, and macrophages (36).

Whereas the CysLT₁R mediates airway smooth-muscle contraction, mucus hypersecretion, microvascular leakage, and swelling of the airways, the CysLT₂R mediates the inflammatory response, possibly through the modulation of chemokine gene transcription, and contributes to vascular permeability and tissue fibrosis (36). The expression of the CysLT₁R is upregulated by proinflammatory cytokines, including IL-13, which augments CysLT₁R expression on human lung fibroblasts, thereby permitting bronchial smooth muscle to respond to LTC₄ and release eotaxin (95). There is emerging evidence of pharmacological cross talk between both sets of receptors, and knockdown of the CysLT₂R stimulates LTD₄-dependent proliferation of cord blood-derived human mast cells. The absence of the CysLT₂R was associated with an upregulation of CysLT₁R expression at the cell surface and enhanced LTD₄-induced ERK phosphorylation (96).

The discovery of the two CysLTRs rapidly opened the way for experiments to determine whether the expression of the CysLT₁R or the CysLT₂R differed in patients with aspirin sensitivity compared with their aspirin-tolerant counterparts. In 2002, Sousa et al. (37) reported that the percentage of inflammatory cells expressing the CysLT₁R in nasal biopsies was fivefold higher in aspirin-sensitive patients compared with aspirin-tolerant individuals. There was no upregulation of the CysLT₂R (97) or

the LTB_4 receptor (37). Desensitization with aspirin led to downregulation of the CysLT_1R in nasal inflammatory cells (37), but substantial amounts of CysLTs continued to be produced (80). Sousa et al.'s (37) results may explain why subjects with ASRD demonstrate greater airway responsiveness to aerosolized LTE_4 than do non-aspirin-sensitive subjects (98, 99).

Several studies have reported biological properties of the CysLTs that are not readily explained on the basis of the recognized pharmacological properties of the CysLT_1R and CysLT_2R , suggesting that there may be further distinct, uncharacterized CysLT receptors or that postreceptor signaling may be differentially regulated in a ligand-specific fashion (100–103). Cumulative findings from a series of radioligand binding studies indicated that there are two separate receptors mediating the actions of LTC_4 and LTD_4 (100, 104, 105) and that the effects of LTE_4 may also be mediated through the LTD_4 receptor (100). In 1984, Lee and coworkers (100) established that prior exposure to LTE_4 , but not to LTC_4 or LTD_4 , enhanced contractility to histamine in guinea pig tracheal spirals in a time- and dose-dependent fashion. Furthermore, LTC_4 , LTD_4 , and LTE_4 all elicited the same magnitude of contraction of tracheal smooth muscle (100). Finally, the authors observed that the rank order of potency of CysLTs to induce contractility was different between guinea pig tracheal smooth muscle ($\text{LTE}_4 > \text{LTD}_4 = \text{LTC}_4$) and guinea pig parenchymal strips ($\text{LTD}_4 > \text{LTE}_4 > \text{LTC}_4$) (106). These observations lent further credence to the idea of three different receptors binding CysLTs .

Evidence for a third CysLT receptor subtype in human tissue was initially based on studies reporting that LTC_4 -induced vasoconstriction of human and porcine isolated pulmonary arterial preparations was insensitive to CysLTR antagonists, including the nonselective $\text{CysLT}_1/\text{CysLT}_2$ receptor antagonist BAY u9773 (102, 103). At approximately the same time, Bandeira-Melo et al. (107) demonstrated that LTC_4 acts as an intracrine mediator of eosinophil cytokine secretion and that this is

mediated by an intracellular G protein-coupled receptor distinct from CysLT_1 and CysLT_2 .

Further indirect evidence for a third CysLTR in humans arose from the finding that, compared with nonasthmatic subjects, asthmatics show an extraordinary bronchial hyperresponsiveness to LTE_4 but that bronchial hyperreactivity to LTC_4 and LTD_4 is magnitudes smaller. Therefore, compared with the airways of normal subjects, the airways of asthmatics are approximately 14-, 15-, 6-, 9-, and 219-fold more responsive to histamine, methacholine, LTC_4 , LTD_4 , and LTE_4 , respectively (108). Patients with ASRD demonstrate an even greater preferential bronchoconstrictor response to LTE_4 but not to LTC_4 (99) and are more-than-tenfold more vulnerable to the bronchoconstrictor effects of LTE_4 when compared with aspirin-tolerant individuals (98). Prior exposure to LTC_4 , LTD_4 , and LTE_4 also enhances subsequent airway responsiveness to histamine in asthmatic patients, but not in normal controls (109). LTE_4 is an end metabolite of CysLT biosynthesis and is therefore likely to persist for the longest time at the site of release. Taken together, these data suggest that LTE_4 is a critical mediator in asthma and in particular in ASRD.

CysLT_1R and CysLT_2R ligate the CysLTs with an affinity order of $\text{LTD}_4 > \text{LTC}_4 \gg \text{LTE}_4$ (CysLT_1) (92) and $\text{LTC}_4 = \text{LTD}_4 \gg \text{LTE}_4$ (CysLT_2), respectively (93). In view of the pharmacologically defined differential sensitivity of both CysLTRs to their ligands and the low affinity of both CysLT_1R and CysLT_2R to LTE_4 , it is difficult to understand why LTE_4 but not LTD_4 or LTC_4 demonstrates such differential effects if the ability of the CysLTs to induce bronchoconstriction is mediated solely through CysLT_1R or CysLT_2R . Some commentators have suggested that chronic exposure to grossly raised CysLT concentrations may lead to dysregulation of the CysLT_1R , resulting in the receptor developing increased affinity for a ligand (LTE_4) that is normally several logs less potent (110).

More recently, indication of a putative third receptor in human bronchi has come from a

study by Yoshisue et al. (111), who observed enhancement of mitogenesis of bronchial fibroblasts by LTD₄ in the presence of epidermal growth factor; neither two specific CysLT₁R antagonists nor the dual antagonist (BAY u9773) prevented this enhancement. The absence of mRNA for both the CysLT₁R and the CysLT₂R in bronchial fibroblasts suggested that this mitogenic response may be mediated by a third, uncharacterized receptor (111). The orphan G protein–coupled receptor 17 is a dualistic receptor, intermediate in phylogeny between the CysLTRs and the P2Y pyrimidiner-gic receptors that bind both uracil nucleotides and CysLTs (112). It has been identified as a putative candidate for a third CysLT receptor and as yet has no assigned pathological or physiological role (36).

Aspirin Desensitization

Nearly all aspirin-sensitive individuals can be desensitized to aspirin (113, 114). Once successfully desensitized, most patients will experience improved symptomatic control, require fewer FESS polypectomies, have a reduced requirement for oral corticosteroids, and have fewer hospital admissions for asthma (115). Aspirin desensitization remains an add-on treatment in patients with moderate-to-severe ASRD. This is particularly true for those individuals in whom symptoms are poorly controlled despite optimal medical therapy, who require unacceptably frequent doses of oral corticosteroids, or who require multiple surgeries to resect nasal polyps.

In a series examining outcomes in 172 patients taking 650 mg of aspirin bd for more than a year, 67% of patients derived clinical benefit, whereas 9% did not improve and 14% stopped because of side effects, most often intractable urticaria or gastritis (115). Thus, aspirin desensitization produces definitive improvements in both upper and lower respiratory tract symptoms in the majority of patients with ASRD (115). In a typical desensitization regimen, patients receive escalating doses of oral aspirin over two to five days until 325–650 mg of as-

pirin twice daily is tolerated (115). Daily administration of up to 1300 mg of aspirin per a day may be required to maintain this state. The frequency of aspirin-induced side effects does not vary for maintenance doses of 325 mg or 625 mg of aspirin bd (115).

Despite its success as a therapeutic modality, the precise mechanism by which desensitization occurs is incompletely understood. Arm and colleagues demonstrated that prior to aspirin desensitization LTE₄ was 1870 times more potent than histamine in inducing a 35% fall in specific airway conductance. Within 24 h of successful desensitization with oral aspirin, there was a mean 33-fold decrease in airway responsiveness to LTE₄ but no change in airway responsiveness to histamine (98) (**Figure 3a,b**). These data suggested that successful aspirin desensitization may partly be explained by selective receptor downregulation. Investigators from the same laboratory noted that successful aspirin desensitization occurred despite substantial release of CysLTs after aspirin challenge (80), supporting the view that receptor tachyphylaxis rather than reduced CysLT production was responsible for the desensitized state. In 2002, Lee and colleagues (37) confirmed that aspirin desensitization was associated with significant downregulation in CysLT₁R in inflammatory cells.

The 15-Lipoxygenase Pathway

Products from the 15-lipoxygenase (15-LO) pathway include 15-HPETE, LXs, and eoxins (EXs) (**Figure 1**). Comparatively little is known about the biological function of 15-LO, but its expression is upregulated by the Th2 cytokines IL-4 and IL-13 in the upper and lower respiratory tracts (116, 117), and its expression is significantly increased in the bronchial submucosa of patients with asthma or chronic bronchitis compared with control subjects (118).

Nicknamed the “good” lipids for asthma (119), LXs were discovered by Serhan and colleagues (120) more than 20 years ago. These compounds are trihydroxytetraene eicosanoids that are generated via the sequential actions

EX: eoxin

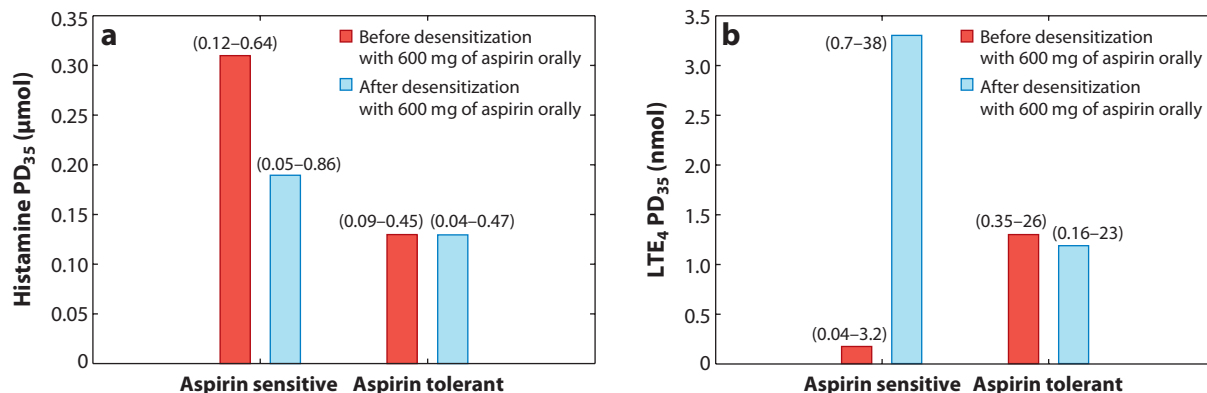


Figure 3

(a) The PD₃₅ [geometric mean (range)] to histamine before and after desensitization with 600 mg of oral aspirin in five aspirin-sensitive and five aspirin-tolerant subjects. Oral desensitization with 600 mg of aspirin was not associated with a significant change in the geometric mean histamine PD₃₅ in aspirin-sensitive or aspirin-tolerant patients. (b) The PD₃₅ [geometric mean (range)] to LTE₄ before and after desensitization with 600 mg of oral aspirin in the aspirin-sensitive and aspirin-tolerant subjects shown in panel a. Oral desensitization with 600 mg of aspirin led to the geometric mean PD₃₅ to LTE₄ increasing from 0.17 nmol to 3.3 nmol after desensitization. (Data from Reference 98.)

of two or more lipoxygenases. There are three principal biosynthetic pathways for their formation. The first involves cooperation between 15- and 5-LO, the second involves acetylation of COX-2 by aspirin to trigger 15-epi-LXA₄ biosynthesis, and the third involves interactions between 12-LO and 5-LO. Interaction of leukocytes with epithelium, endothelium, or platelets results in the formation of LXA₄ (5S,6R,15S-trihydroxy-7,9,13-*trans*-11-*cis*-ecosatetraenoic acid) and its positional isomer lipoxin B₄ (LXB₄; 5S,14R,15S-trihydroxy-6,10,12-*trans*-8-*cis*-ecosatetraenoic acid). The LXs modulate leukocyte trafficking and vascular tone, and in contrast to CysLTs they have potent anti-inflammatory effects (121). A reduction in their levels may be a feature of ASRD (41, 43, 122).

In patients with ASRD, LX synthesis from stimulated whole blood is reduced compared with aspirin-tolerant subjects (41, 122), although researchers have more recently suggested that diminished LXA₄ synthesis is a feature of severe asthma regardless of aspirin sensitivity (123). The only in vitro study to measure LXs from the respiratory tract in patients with aspirin sensitivity found significant downregulation

of 15-LO expression with a corresponding decrease in LXA₄ production (43). Patients with ASRD upregulate CysLT₁R expression on inflammatory leukocytes (37) but may have decreased levels of LXs to compete with CysLTs for binding at their cognate receptor. Therefore, diminished capacity to generate LXs may contribute to the uncontrolled, chronic inflammation that characterizes this phenotype of asthma.

In 2008, details of EXs, a novel group of compounds that are metabolites of the 15-LO pathway, were published. Feltenmark et al. (124) isolated human eosinophils from whole blood and stimulated them with arachidonic acid. This led to the formation of 15(S)-HETE, 12(S)-HETE, and a new product that had an UV absorbance maximum at 282 nm and a shorter retention time than did LTC₄ on RP-HPLC. Positive-ion electrospray tandem mass spectrometry identified the product as 14,15-LTC₄, which in eosinophils could be further metabolized to 14,15-LTD₄ and 14,15-LTE₄; these three products were named EXC₄, EXD₄, and EXE₄, respectively. Mast cells derived from cord blood and nasal polyps could also produce EXC₄ when stimulated with arachidonic acid.

Incubation of eosinophils with arachidonic acid favored EXC_4 production, whereas stimulation with calcium ionophore led almost exclusively to LTC_4 production. Receptor-mediated stimulation of eosinophils with LTC_4 , PGD_2 , and IL-5 also triggered the release of EXs. An endothelial cell monolayer was used to demonstrate that EXs induced vascular leakage and were almost as potent as CysLTs in this regard. However, EXs did not appear to induce smooth-muscle contractility (124). Clearly these potentially important proinflammatory mediators may induce many of the pathological features characteristic of ASRD, and studies will be required to elucidate any role they may have in the pathogenesis of ASRD.

PGE₂, E-Prostanoid Receptors, and ASRD

PGE₂ is the most abundant PG in the human body, and the lung has been described as a privileged site for its beneficial anti-inflammatory effects (125). In the airways PGE₂ is widely regarded as the prostanoid with the most prominent immunomodulatory, antifibrotic, and bronchodilating properties. It is the predominant PG synthesized by the bronchial epithelium, and injury to the airway epithelium decreases the production of PGE₂ and leads to an overproduction of CysLTs by leukocytes such as bronchial macrophages (126). As well as being generated by airway smooth muscle (127), PGE₂ also influences the bronchial remodeling process in the human lung by inhibiting the transition of fibroblasts into myofibroblasts via its actions on the EP2 receptor (128). PGE₂ therefore has the potential to reverse at least three of the cardinal features of ASRD: enhanced CysLT production, smooth-muscle hyperplasia, and airway epithelial damage.

It has been more than a decade since pretreatment with aerosolized PGE₂ was shown to attenuate lysine aspirin-induced bronchoconstriction in ASRD (40, 129) and to completely abolish any rise in uLTE_4 excretion (40). In

IgE-activated mast cells cultured from peripheral blood cell progenitors in aspirin-sensitive patients, 10^{-6} M PGE₂ significantly reduced CysLT production while not inhibiting PGD_2 or histamine production (57). In a second in vitro study, stimulating peripheral blood leukocytes (PBLs) with aspirin prior to incubation with PGE₂ induced modest but significant decreases in CysLT production in aspirin-sensitive patients, and this inhibitory effect on CysLT production was also observed in aspirin-tolerant and control subjects (39). In cytokine-primed human neutrophils, PGE₂ inhibits CysLT biosynthesis by inhibiting 5-LO translocation to the nucleus (130), a step at the beginning of CysLT production.

PGE₂ is generated from COX-derived PGH_2 by prostaglandin E synthase (PGES), which occurs in multiple forms, two of which are membrane bound (mPGES-1 and mPGES-2) and one of which is cytosolic (cPGES). Of these enzymes, COX-1 along with mPGES-2 and cPGES are constitutively expressed, whereas COX-2 and mPGES-1 are induced by inflammatory stimuli. In vitro, mPGES-1 functionally couples to COX-2 and localizes to the nuclear membrane (131), whereas cPGES couples to COX-1 (131). The cellular function of mPGES-2 is less clear and appears to be constitutive; mPGES-2 is functionally coupled with both COX-1 and COX-2 (131). PGE₂ is rapidly degraded by the PGE₂-metabolizing enzyme 15-PGDH (132). There is evidence of a reciprocal relationship between COX-2 expression and 15-PGDH expression in the lung and in human airway epithelial cells in both asthmatic and normal subjects: IL-13 significantly downregulates COX-2 and mPGES-1 while upregulating 15-PGDH (71). The relative expression of mPGES and 15-PGDH in aspirin-sensitive patients is not yet defined.

The close relationship between CysLT production and its inhibition by PGE₂ in ASRD has led to suggestions that aspirin-sensitive patients are particularly dependent on the anti-inflammatory effects of PGE₂ and that the anti-inflammatory effects of PGE₂ are impaired

because of reduced production, or abnormal EP receptor expression and signaling, or both. A number of studies in the literature address PGE₂ production in aspirin-sensitive patients. However, most of these have involved the stimulation of PBLs, which are remote from the site of the disease or prolonged culture of tissues in vitro. Kowalski et al. (42) examined eicosanoid production in PBLs from aspirin-sensitive patients. At baseline PBLs generated similar amounts of PGE₂ as compared with aspirin-tolerant patients. Stimulation with calcium ionophore significantly increased PGE₂ production, and incubation with aspirin inhibited PGE₂ biosynthesis, but there was no difference between both groups (42). Kowalski et al. (133) also measured PGE₂ production in cell culture supernatants from nasal polyp epithelial cell explants. This group found diminished PGE₂ production at baseline in aspirin-sensitive patients but observed, on treatment with aspirin, a similar relative inhibition of PGE₂ production in aspirin-sensitive and control subjects. Bronchial fibroblasts derived from aspirin-sensitive patients stimulated for 18 h with cytomix (a cell-stimulating mixture of lipopolysaccharide, IL-1 α , and TNF- α) also produced less PGE₂ than did fibroblasts from aspirin-tolerant patients, although spontaneous production was equivalent in both groups (134). Although all these experiments have yielded valuable data, the use of individual cell types excluded the possibility of transcellular eicosanoid biosynthesis. In vivo studies have measured PGE₂ release in nasal lavage fluid, exhaled breath condensate, and BAL fluid in aspirin-sensitive and aspirin-tolerant patients (135–139). The findings from these studies are inconsistent, and it is difficult to draw any firm conclusions from the results. However, no in vivo study has found diminished levels of PGE₂ at baseline in aspirin-sensitive patients, and some studies have reported a relative overproduction of PGE₂ in aspirin-sensitive patients (135, 138).

PGE₂ ligates four G protein-coupled receptors designated EP1–4 (139). Expression of the EP2 receptor in nasal mucosal inflamma-

tory cells in aspirin-sensitive patients is reduced (38). Furthermore, a functional SNP of the EP2 gene, believed to be associated with a decrease in the transcription level of the receptor, is associated with an increased risk of aspirin-sensitive asthma and rhinosinusitis (140). Together these findings suggest that diminished EP2 receptor expression may be a cause of the excessive CysLT production in ASRD.

The Cyclooxygenase Pathway and ASRD

Since Szczeklik first proposed that the precipitation of acute attacks of asthma and rhinosinusitis in susceptible patients was a consequence of aspirin inhibiting COX-1, a second isoform of COX (COX-2) has been discovered. Both isoforms manufacture prostanoids (**Figure 1**) and are products of distinct genes expressed in normal human respiratory epithelium. COX-1 is constitutively expressed and is concerned with basal prostanoid production or housekeeping functions, whereas COX-2 is upregulated in response to inflammatory stimuli. Immunostaining in human and porcine endothelial cells suggests that COX-1 is expressed and confined to both the perinuclear zone and the cytoplasm. COX-2 localizes to the nucleus alone in a resting-state cell (141), but with cell activation it relocates to the nuclear envelope and the cytoplasm (141).

The majority of aspirin-sensitive patients can tolerate selective COX-2 inhibitors (142). This has led to suggestions that there is a functional COX-2 deficiency in ASRD, COX-2 makes only a trivial contribution to local PGE₂ production in these individuals (143), and therefore aspirin-sensitive subjects do not experience an exacerbation of their symptoms when ingesting a selective COX-2 inhibitor, because there is little or no reduction in airway PGE₂ production. This idea is attractive, but the literature does not unequivocally support the two arms of this hypothesis (diminished COX-2 expression and decreased PGE₂ synthesis).

In 1999, using reverse transcriptase PCR, Picado et al. (144) reported that nasal polyps from aspirin-sensitive and aspirin-tolerant patients with ASRD expressed equivalent levels of COX-1 mRNA but significantly less COX-2 mRNA compared with levels in nasal mucosa from healthy patients. In 2004, a second study from the same research group used real-time PCR to assess relative expression of COX-1 and COX-2 mRNA in three groups of patients: aspirin-sensitive patients undergoing nasal polypectomy, aspirin-tolerant patients undergoing nasal polypectomy, and patients undergoing corrective nasal surgery (145). The investigators also sought to determine whether in the hour following surgery there was a time-dependent upregulation in COX mRNA. The expression of COX-2 mRNA at baseline was lower in both groups of patients with nasal polyps than levels in the nasal mucosa. Over a 1-h time course, the expression of COX-2 mRNA rose significantly in nasal polyps from aspirin-tolerant patients (reaching similar levels as in nasal mucosa), but this upregulation of COX-2 was not seen in the nasal polyps of aspirin-sensitive patients. A comparison between the three cohorts revealed that, although none of the patients undergoing corrective nasal surgery and only 6% of the aspirin-tolerant group were receiving oral corticosteroids at the time of surgery, almost 40% of the aspirin-sensitive group were receiving oral corticosteroids at the time of surgery. The lack of parity between the three groups of patients complicates the interpretation of this study's findings (145).

In a third study, PGE₂ and COX-2 mRNA was measured in homogenized sinonasal tissue of patients with chronic rhinosinusitis with and without nasal polyposis (CRS group), in sinonasal tissue of patients with nasal polyposis and aspirin sensitivity, and in normal nasal mucosa from healthy subjects (NM group) (43). The study groups were comparable with all patients undergoing polypectomy receiving topical nasal corticosteroids and none requiring oral corticosteroids at the time of the proce-

dures. Diminished levels of COX-2 were quantified in patients with nasal polyposis compared with individuals with chronic rhinosinusitis alone. This decreased expression of COX-2 was particularly enhanced in aspirin-sensitive patients and correlated positively with LT production and inversely with PGE₂ measurements. The authors concluded that changes in tissue eicosanoid metabolism appear to be related to the severity of eosinophilic inflammation, rather than aspirin sensitivity per se (43). Nonetheless, this study provides direct evidence supporting the hypothesis that patients with ASRD produce less PGE₂ owing to diminished COX-2 expression. In contrast, when the expression of COX-2 was examined in the bronchial mucosa of aspirin-sensitive and aspirin-tolerant patients with asthma, enhanced COX-2 expression was observed in aspirin-sensitive subjects, with a mean fourfold increase in the percentage of COX-2-expressing cells that were mast cells and a 2.5-fold increase in the number of eosinophils expressing COX-2 (146). Further studies are now clearly needed to elucidate the relative expression of COX-1 and COX-2, particularly in the bronchial mucosa, of patients with ASRD. The functional consequences of COX inhibition also warrant further investigation.

In this respect Mastalerz and colleagues (147) measured PGE₂ urinary metabolites and used these as a biomarker for systemic PGE₂ production in aspirin-tolerant and aspirin-sensitive patients. No differences in urinary PGE₂ metabolites were noted at baseline. However, after aspirin challenge, although non-aspirin-sensitive patients showed diminished systemic production of PGE₂, as demonstrated by a fall in measurable urinary PGE₂ metabolites, no parallel fall was noted in aspirin-sensitive patients. The administration of the selective COX-2 inhibitor celecoxib led to a decrease in the production of PGE₂ metabolites in both groups of patients and challenged the concept that aspirin-sensitive patients can tolerate COX-2 inhibitors because COX-2 induces relatively trivial quantities of

PGE₂. Although it is not possible to directly extrapolate these observations locally to the nasal and bronchial mucosa, the data indicate that COX-2 contributes considerably to overall PGE₂ production and support previous in vivo work that reported no significant decreases in PGE₂ levels after aspirin challenge in patients with ASRD, although levels decreased in all other groups (135).

CONCLUDING REMARKS

ASRD is a chronic inflammatory disorder of the upper and lower respiratory tracts that is characterized by enhanced CysLT production at baseline and subsequent to aspirin exposure (78). It is heterogeneous in its clinical presentation and is probably underrecognized. The inflammatory pathways underlying ASRD are complex, but despite the absence of any animal models, substantial progress has been made in the past ten years in understanding of the pathophysiology of this condition. Gradually a picture has emerged of a phenotype of airway disease in which multiple defects in the inflammatory pathways described above either enhance inflammation or lead to an inadequate anti-inflammatory response.

Approximately half of all patients with ASRD describe a flu-like illness triggering the syndrome (8). This observation, combined with the findings from a study in which pretreatment of aspirin-sensitive individuals with acyclovir abrogated both aspirin-induced bronchoconstriction (148) and the expected increase in uLTE₄ following aspirin challenge, has led some commentators to suggest an infectious component to the disease (56, 149). A latent viral infection could induce many of the features of ASRD, including enhanced CysLT biosynthesis, modification of transcription events in the COX pathway, and treatment-refractory inflammation (149). Furthermore, the reduced ability of the epithelium in asthma to clear RV is now well recognized (54, 55). The hypothesis suggesting that a viral insult in genetically susceptible individuals leads to a chronic viral

infection that then drives ASRD is therefore attractive. But experiments to test this provocative hypothesis are lacking, and studies are required to determine the relevance of chronic infection in perpetuating the inflammatory mechanisms that underpin ASRD.

In recent years, there has been significant interest in the anti-inflammatory prostanoid PGE₂, its biosynthesis relative to COX-2 expression, and its capability to ameliorate ASRD at least partly by reducing excessive CysLT production (40). It remains to be determined whether PGE₂ production is depressed in ASRD. Decreased EP2 receptor expression has been noted in the nasal mucosa of aspirin-sensitive patients, and this may adversely affect local end-organ responses (38). This reduced expression may be genetically determined, as previously reported (140), and these important observations require urgent confirmation. Alternatively, or in addition, *Staphylococcus aureus* enterotoxin B (SEB) may downregulate PGE₂, EP2 receptor expression, and COX-2, so the role of SEB and other superantigens in contributing to ASRD should be tested (150).

Most aspirin-sensitive patients have moderate-to-severe disease, and medications currently available fail to control symptoms in a large proportion of this cohort. Novel therapeutic approaches targeting aspirin-sensitive patients are required. To date there are few specific treatments aimed specifically at managing patients with ASRD. Desensitization with aspirin remains one therapeutic modality specific to ASRD, but its mechanism of action is largely unknown; elucidation of the mechanism(s) will likely yield insights into not only desensitization but also the pathogenesis of ASRD.

In summary, ASRD is a complex phenotype of asthma characterized by severe inflammation of the airways that responds poorly to current medications. Increased understanding of the molecular, cellular, and biochemical basis of ASRD will likely open the way for new diagnostic techniques and therapeutic interventions.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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