Aspirin-exacerbated Respiratory Disease: A Syndrome of Mast Cell–mediated PgD2 Overproduction

Hypersensitivity reactions to aspirin were first described almost immediately after its introduction, and by 1922, Widal had described the constellation of asthma and nasal polyps with aspirin sensitivity, and also reported on the beneficial effects of aspirin desensitization (1). At this time, the preferred term for this syndrome is aspirin-exacerbated respiratory disease (AERD), recognizing that not all subjects have asthma. Patients with AERD often prove clinically challenging. Sinus surgery and polypectomy are often fruitless as the sinonasal disease rapidly recurs. Similarly, when present, the asthma component can produce a severe phenotype that is refractory to treatment and often associated with progressive irreversible obstruction.

Although a clinical challenge, AERD does offer physicians two forms of therapy that are specific to this disorder: aspirin desensitization and leukotriene (LT) modifiers. A distinguishing feature of AERD is the high constitutive production of cysteinyl leukotrienes (CysLTs) and a further surge during reactions to aspirin and other nonselective cyclooxygenase inhibitors (2). Reflecting the importance of CysLTs, LT modifiers and, in particular, leukotriene synthesis (5-lipoxygenase [5-LO]) inhibitors, reduce polyp size, restore sense of smell, and improve both sinus and asthma symptoms while reducing LTE4 concentrations (3). These data appear to argue that CysLTs are primary mediators of AERD. Similarly, aspirin desensitization followed by continuous high-dose administration of aspirin will suppress nasal polyp growth, improve sinus symptom scores, restore sense of smell, decrease frequency of secondary acute sinus infections, improve asthma control, and reduce the need for oral corticosteroids (4).

It was assumed that aspirin desensitization would work by recapitulating the pathways mediated by 5-LO inhibition, namely, reduction in CysLT production. However, in this issue of the *Journal*, Cahill and colleagues (pp. 704–711) investigated the effects of aspirin therapy on biomarkers of AERD (5). Surprisingly, this study demonstrated the paradox that high-dose aspirin administration after desensitization increases numerous markers of allergic (type 2) inflammation, and specifically actually further increased CysLT production (6). Thus, the two medical treatments we have for AERD have exactly opposite effects on what has been thought to be this central pathogenic mediator.

Finding an explanation for the increase in type 2 inflammation is more straightforward. In AERD, PgE2 (prostaglandin E2) primarily mediates anti-inflammatory effects and, specifically, constrains the activation of eosinophils, basophils, mast cells, and other immune cells (7). The severe hypersensitivity reactions that occur in AERD in response to aspirin reflect the loss of this PgE2 inhibitory pathway, as can be demonstrated by the ability of PgE2 homologs to block reactions (8). In the current study, the authors further support this concept by demonstrating that high-dose aspirin lowers PgE2 concentrations, and thereby enhances several aspects of allergic inflammation, including enhanced mast cell activation with higher levels of tryptase and the CysLTs.

But how is it possible to reconcile this increased production of CysLTs with the clinical benefits observed? In addition to CysLT overproduction, AERD is also characterized by exquisite sensitivity to CysLTs, with CysLT challenges driving enhanced bronchospasm, eosinophil recruitment, and worsening of bronchial hyperreactivity (9). These effects are particularly profound with LTE4 challenges, likely reflecting LTE4 acting through the recently described LTE4 receptor (LTE4R) (10). One explanation for a clinical benefit of aspirin in the face of increased CysLT production would be if aspirin downregulated CysLT receptors or signaling. Reduced CysLT receptor 1 expression does occur (11), although this is less likely to explain any therapeutic benefit given the usual disappointing results with LT receptor antagonists. Nor would this explain the specific decreases in sensitivity to LTE4 challenges (9), arguing perhaps for decreased expression of LTE4R. Reduced LTE4R transcript expression was not reported in the studies performed on peripheral blood in this study. But modulation of LTE4R expression has not been studied in nasal polyps or lung samples, studies clearly needing to be performed. A mechanism for reduced LT receptor expression could be mediated through the reported influences of aspirin on immune and signaling pathways (e.g., stat6 and cytokine production) (12).

There is, however, another more intriguing mechanism by which aspirin could benefit patients with AERD in the face of higher CysLT production. Specifically, perhaps all aspirin is accomplishing is exactly what would be predicted from its mode of action; that is, inhibition of cyclooxygenase. Consistent with cyclooxygenase inhibition, the current study also demonstrates lower thromboxane and PgD2 production. Both thromboxane and PgD2 act through the thromboxane receptor to cause bronchospasm (13). But it is particularly intriguing to consider whether blockade of PgD2 acting through its type 2 receptor (DP2 or CRTH2) could be the primary basis for the clinical benefits observed with aspirin. CRTH2 is expressed on Th2 effector lymphocytes, innate lymphoid type 2 cells, basophils, and eosinophils, and drives recruitment and activation of these cells (14). The increases in circulating $CRTH2^+$ eosinophils and basophils in the circulation that was observed in the current study would be consistent with the "stranding" of these and likely other $CRTH2^+$ cells in the circulation and result in their failure to ingress into respiratory tissue and affect inflammation.

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It is then reasonable to speculate that both aspirin and 5-LO inhibitors benefit AERD through the same final common pathway; namely, the blockade of PgD2 production. The LTE4 receptor is highly expressed on epithelial cells and mast cells. Engagement of these receptors on epithelial cells (15), in part through their secretion of IL-25, IL-33, and TSLP (thymic stromal lymphopoietin), can indirectly drive mast cell activation and PgD2 production. But CysLTs, including especially LTE4, also act directly on mast cells to cause PgD2 production (16). Thus, an intriguing solution to the paradox of both 5-LO inhibitors producing decreased CysLT expression and aspirin administration's increased CysLT expression being beneficial in AERD would be that both agents ultimately act to decrease PgD2.

In summary, this study points to the central role of the mast cell in the pathogenesis of AERD, with mast cell–derived PgD2 potentially being a central pathogenic mediator. And any mechanism that blocks PgD2 pathways, including CysLT synthesis inhibitors, cyclooxygenase inhibitors, or perhaps in the future, CRTH2 antagonists, can form the basis for clinical improvement. ■

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Indoor Endotoxin Exposure and Ambient Air Pollutants Interact on Asthma Outcomes

It is now quite well established that ambient (outdoor) air pollution is a health risk and contributes substantially to the global burden of disease. The mortality and morbidity burden resulting from ambient air pollution has increased during the last 2 decades (1). Human populations breathe complex mixtures of air pollutants, allergens, and irritants. It has been known for some years from small controlled clinical trials that ambient air pollutants such as ozone (O_3) (2), nitrogen dioxide (NO_2) (3), and combinations of these gaseous pollutants (4) interact with allergens on physiological outcomes in people with allergic asthma. Much more has been learned in recent years about the effects of fine particles (particulate matter <2.5 μm in aerodynamic diameter [$PM_{2.5}$]) on asthma and other chronic diseases (5). A major constituent of $PM_{2.5}$ in urban environments is diesel exhaust particles, which have been shown to bind the major grass pollen allergen (6).

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