

Does suppression of IL-4 synthesis by aspirin explain the therapeutic benefit of aspirin desensitization treatment?

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After completing aspirin desensitization in patients with aspirin-exacerbated respiratory disease (AERD), treatment with daily aspirin in sufficiently large doses (325-1,300 mg/d) has been shown to significantly suppress inflammatory respiratory disease in most patients.^{1,2} Four clinical observations should be recalled. First, the dose of aspirin that maintains desensitization seems to be independent of the effects of aspirin treatment. For example, 81 mg/d aspirin maintains aspirin desensitization but does not have a measureable effect on disease control. Second, other non-steroidal anti-inflammatory drugs (NSAIDs) can be used to desensitize and maintain desensitization in patients with AERD, but daily treatment with 400 mg of ibuprofen twice daily did not induce therapeutic benefit in 5 patients followed for 1 to 6 months (D. D. S., unpublished data).

Third, daily aspirin treatment of aspirin-tolerant patients who also have nasal polyps pansinusitis, and asthma has not been associated with improvement of symptoms. Finally, about two thirds of patients with AERD also have a comorbid condition of IgE-mediated disease, making it difficult to unwind these dual pathogenic processes and assess efficacy of treatment if directed at only one of the 2 diseases.³

Investigation of AERD continues to advance our understanding of the underlying disease, reactions, desensitization, and the clinical benefit of aspirin treatment. Despite the fortuitous discovery of the beneficial effect of chronic aspirin therapy in patients with AERD some 30 years ago, a satisfactory unifying explanation for its benefit has largely eluded us. A few key observations about the mechanism of the disease and reactions that occur in patients with AERD have been made. Exposure to an inhibitor of COX-1 unleashed a variety of eicosanoid lipid mediators generated from membrane phospholipids. Of these mediators, thromboxane, a potent bronchoconstrictor, is synthesized in increasing amounts in monocytes from patients with AERD when compared with levels in healthy control subjects. Prostaglandin D₂ levels are increased at baseline and increase further during reactions precipitated by any NSAID.⁴ Continued synthesis of leukotrienes, specifically leukotriene (LT) C₄, LTD₄, and LTE₄, might also be important in the pathogenesis of

AERD because increased urinary LTE₄ levels have been found at baseline in some patients with AERD before exposure to aspirin.⁵ After exposure to NSAIDs that inhibit COX-1, marked increases in urinary LTE₄ levels have been measured in patients with AERD. That these levels correlate with the severity of respiratory reactions underscore the fundamental importance of leukotrienes in the pathogenesis of respiratory reactions in patients with AERD.⁵ Overproduction of leukotrienes caused by enhanced transcription of the LTC₄ synthase enzyme has been identified in some patients with AERD and might amplify this key inflammatory pathway.⁶ The importance of this observation is unclear because the same polymorphisms of the LTC₄ synthase gene were also found in some healthy control subjects.

Not only are inflammatory mediators overproduced but also anti-inflammatory regulators are deficient in patients with AERD. Lipoxins, a class of anti-inflammatory mediators, have been investigated in patients with AERD and are present at lower levels in stimulated whole blood.⁷ Prostaglandin E₂ (PGE₂) has bronchoprotective effects when inhaled before aspirin challenge in patients with AERD.⁸ Furthermore, PGE₂ is relatively deficient at baseline in patients with AERD when compared with levels seen in aspirin-tolerant control subjects and healthy control subjects.⁹ PGE₂ functions as a brake on the 5-lipoxygenase enzyme and suppresses mast cell activity. The lower PGE₂ concentrations in inflammatory cells of patients with AERD are further decreased during COX-1 inhibition, resulting in unimpeded leukotriene production.⁸ It seems likely that PGE₂ deficiency plays a major role in vulnerability to NSAID-induced reactions in patients with AERD, but because aspirin disables COX-1 at low doses and COX-2 at higher doses, it is difficult to see how continued depletion of PGE₂ would provide any therapeutic benefit for patients with AERD.

There are only limited numbers of studies investigating the effects of chronic aspirin desensitization on inflammatory markers. Current evidence supports the concept that treatment success is not mediated through acetylation of COX-1 enzyme by aspirin. In this issue of the *Journal*, Katial et al¹⁰ advance the idea that a specific cytokine, namely IL-4, measured in the sputum of patients with AERD is the target of aspirin during aspirin treatment in patients with AERD. After oral aspirin challenge, followed by desensitization with aspirin and then treatment with daily aspirin for 6 months, IL-4 levels were remeasured in sputum and found to be markedly reduced from baseline values. Furthermore, in 3 subjects with aspirin-tolerant asthma who also had chronic sinusitis and nasal polyps, aspirin treatment did not decrease IL-4 levels in posttreatment sputum samples. Is this the smoking gun that explains the mechanism of aspirin treatment that is specific for AERD?

The idea is attractive because IL-4 upregulates cysteinyl leukotriene 1 receptors and, through the enhanced expression of signal transducer and activator of transcription 6, leads to

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T_H2 -mediated inflammation. Specific effects of IL-4 also include prolonged eosinophil survival through inhibition of eosinophil apoptosis, induction of vascular cell adhesion molecule to encourage transmigration of eosinophils into tissues, its function as a co-factor for mast cell growth, induction of expression of LTC₄ synthase, and encouragement of differentiation from naive T_H0 lymphocytes to T_H2 cells.¹¹ It is tempting to conclude that the success of aspirin treatment in patients with AERD is due to decreased synthesis of IL-4, thus ameliorating its inflammatory effects, as listed above.¹¹

It is interesting that aspirin inhibited secretion of IL-4 but not IL-13 in the study by Cianferoni et al¹² of normal CD4⁺ T cells. Other NSAIDs, namely indomethacin and flurbiprofen, had no effect in inhibiting the synthesis of IL-4, but the very weak inhibitor of COX-1, salicylic acid, was at least as effective as aspirin in inhibiting IL-4 expression. In the current study by Katial et al,¹⁰ the same IL-4-suppressive effects of aspirin were measured in all 21 study patients with AERD and in none of the 3 control subjects, suggesting impressive specificity for patients afflicted with AERD. If the effects of aspirin on IL-4 levels in patients with AERD are unique to the AERD population, it is unclear why this same effect could be detected *in vitro* in the cells of healthy donors.^{12,13} Perhaps the effect of aspirin is much more pronounced at therapeutic levels in patients with AERD yet occurs to some extent in T cells of all subjects. Perhaps deficiency of PGE₂ provides unrecognized susceptibility to the effects of aspirin on mast cells and eosinophils in patients with AERD.

It seems likely that other NSAIDs do not exhibit similar COX-independent anti-inflammatory properties. However, could a drug exist that does not have much COX antagonism at therapeutic levels but retains the same measurable effect on IL-4 levels in patients with AERD? Sodium salicylate could be a candidate for further study in this regard. Salicylates have minimal effects on COX-1, even at high therapeutic doses, and previous data suggest similar anti-inflammatory effects through IL-4.^{12,14,15} In theory sodium salicylate could be given to a patient with AERD without concern for a significant reaction yet with potential for improvement in the inflammatory disease. In a small study of 9 patients, pretreatment with choline magnesium trisalicylate for 3 days before aspirin challenge attenuated the expected reactions to aspirin.¹⁶ The possibility of a new, nonaspirin, salicylate-based treatment for AERD is worthy of further study.

There are still many questions remaining. Renewed interest in LTE₄, which is released in such striking quantities in patients with AERD, with its own special receptor (CysLT_{ER}) mediating vascular dilatation, might also hold the answer to some of the remaining

questions. Our understanding of the pathogenesis of AERD, reactions, and its treatment is progressing nicely and is clearly enhanced by the study of Katial et al.¹⁰ Many new avenues for further investigation are also opening up before us.

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