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Editorial

Mediator release in aspirin-induced reactions

A proportion of subjects (10% to 30%) with asthma are intolerant of aspirin and other NSAID drugs.^{1,2} Aspirin ingestion in these subjects is followed by the onset of bronchoconstriction, rhinitis, and/or urticaria. In the most severe case, there may be anaphylaxis. AIA tends to occur in the third to fourth decade of life, and subjects are characteristically nonatopic. Nasal polyps are common. Most subjects with aspirin sensitivity may be desensitized to aspirin by the administration of increasing doses of aspirin orally. This may lead to an improvement in the severity of asthma and of nasal symptoms.

The mechanism of aspirin sensitivity is unknown. Subjects with AIA are also intolerant of other NSAID drugs, and the capacity of these agents to provoke asthma is related to their potencies as inhibitors of the cyclooxygenase enzyme.³ After successful desensitization to aspirin, subjects are then able to ingest other NSAID drugs without adverse effects. Since asthmatic attacks may be precipitated by several drugs with different chemical structures, chemical cross-reactivity as an explanation for aspirin sensitivity is most unlikely. In recent years the concept of aspirin-precipitated asthma, which is linked to the release of inflammatory mediators and especially to inhibition of the cyclooxygenase pathway in the respiratory tract of sensitive patients, has gained increasing support.

Abbreviations used

NSAI:	Nonsteroidal anti-inflammatory
LTA ₄ , LTB ₄ , LTC ₄ , LTD ₄ , LTE ₄ :	Leukotrienes A ₄ , B ₄ , C ₄ , D ₄ , and E ₄
AA:	Arachidonic acid
AIA:	Aspirin-induced asthma

AA is released from cell-membrane phospholipids by the action of phospholipase A₂. This substrate is metabolized by the cyclooxygenase pathway to the prostaglandins and thromboxane A₂, or by the 5-lipoxygenase pathway to leukotrienes.⁴ Specifically, the 5-lipoxygenase generates LTA₄ via an intermediate from AA. LTA₄ is metabolized by an epoxide hydrolase to LTB₄ or by LTC₄ synthetase to LTC₄. LTC₄ is cleaved to LTD₄ and then to LTE₄ by γ -glutamyl transpeptidase and by dipeptidase, respectively. The sulfidopeptide leukotrienes, LTC₄, LTD₄, and LTE₄, are potent spasmogens for nonvascular smooth muscle and comprise the activity previously recognized as slow-reacting substance of anaphylaxis.

When the enzymatic cascade for leukotriene biosynthesis was discovered, it was postulated that AA could be diverted from the cyclooxygenase pathway to the 5-lipoxygenase pathway when the cyclooxygenase was inhibited by drugs, such as aspirin. This would result in augmented generation of the spasmogenic leukotrienes, resulting in AIA. However, di-

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rect evidence for this hypothesis was limited. Pretreatment of sensitized human airways *in vitro* with indomethacin led to an increased generation of LTC₄ after an IgE-dependent challenge,⁵ suggesting that inhibition of cyclooxygenase may result in an increased generation of spasmogenic leukotrienes.

With the development of techniques for measuring the sulfidopeptide leukotrienes in complex biologic fluids, enhanced generation of leukotrienes in aspirin sensitivity has now been established. In patients with aspirin-induced rhinitis, the nasooocular reaction after ingestion of aspirin is associated with increases in concentrations of both LTC₄ and histamine in nasal lavage fluid.⁶ It is interesting to note that at the small doses of aspirin required to induce these responses (60 to 150 mg), no decrease in prostaglandin E₂ was demonstrated. After aspirin desensitization, ingestion of 650 mg of aspirin did not induce a nasooocular reaction, and concentrations of both LTC₄ and histamine did not increase in the lavage fluid. At this larger dose of aspirin, concentrations of prostaglandin E₂ decreased.

In man, LTC₄ is rapidly converted enzymatically in blood to LTD₄ and then to LTE₄, which is excreted in the urine.⁷ Thus, measurement of urinary LTE₄ may act as a marker for the systemic release of the sulfidopeptide leukotrienes. Christie et al.⁸ have measured urinary LTE₄ in subjects with asthma with aspirin sensitivity before and after ingestion of aspirin. The results were compared with results of placebo-challenge in the same aspirin-sensitive individuals and with results of aspirin and placebo-challenge in subjects with asthma without aspirin intolerance. The baseline LTE₄ levels in the urine of aspirin-sensitive subjects with asthma was significantly higher than levels of subjects with asthma without aspirin intolerance.⁸ Furthermore, there was a significant average fourfold increase in the urinary LTE₄ concentrations after aspirin provocation in aspirin-sensitive subjects with asthma that accompanied the decrease in FEV₁. There was no significant change in either urinary LTE₄ levels in aspirin-sensitive subjects after placebo challenge or in the control subjects with asthma without aspirin intolerance.

An additional hypothesis for the mechanism of aspirin sensitivity suggests that there is an increased target-organ sensitivity to the leukotrienes. Arm et al.⁹ demonstrated that the airway reactivity of patients with aspirin sensitivity to LTE₄ was significantly augmented compared to that of a group of subjects with asthma who were not aspirin sensitive, despite both groups of patients having comparable airway histamine responsiveness. Arm et al.⁹ further demonstrated that after desensitization of patients to aspirin, the

target-organ responsiveness to LTE₄ markedly decreased, suggesting that the efficacy of desensitization to aspirin may relate, in part, to a selective down regulation of leukotriene receptors in the airways.

If the mechanism of aspirin sensitivity is related to increased synthesis of leukotrienes and/or increased target-organ sensitivity to leukotrienes, then the response to aspirin should be attenuated in the presence of a leukotriene receptor antagonist. Smith et al.¹⁰ have recently demonstrated that the novel, specific, and potent leukotriene receptor antagonist, SK&F 104353, administered by inhalation, attenuated the response to aspirin in five of six subjects studied by between 43% to 74%. SK&F 104353 had no effect in the remaining subject. The variability in protection may have been due to inadequate dosage or variability in aerosol deposition. Alternatively, it may suggest that there are additional mechanisms eliciting AIA. Although additional studies are clearly indicated, the findings from this initial study support the hypothesis that the sulfidopeptide leukotrienes contribute significantly to the response to aspirin in most patients with aspirin-sensitivity.

The mechanisms of the augmented release of eicosanoid mediators are not known. Enhanced generation of the bronchoconstrictor leukotrienes after aspirin challenge in susceptible subjects may be due to the removal of prostanoid metabolites that regulate the lipoxygenase or, less likely, by the shunting of AA metabolism from the cyclooxygenase to the 5-lipoxygenase pathway.

The cellular source for abnormal mediator release is not known. In this regard, the article in this issue of the JOURNAL by Bosso et al.¹¹ has provided intriguing data. These authors have demonstrated that in those subjects who experienced moderate to severe systemic reactions after aspirin ingestion, there were marked elevations in tryptase levels, and significant increase in plasma histamine in all three subjects. This finding provides strong evidence that in some individuals with aspirin sensitivity who have marked reactions to aspirin, there is mast cell activation and mediator elaboration. It is not clear why the other 14 patients, who experienced similar respiratory reactions without extrapulmonary symptoms during aspirin ingestion, did not have detectable increase in tryptase and histamine. This finding may be related to heterogenous mechanisms for aspirin sensitivity or, more likely, to the fact that the other subjects did not have such severe systemic symptoms. It would have been of interest to measure urinary LTE₄ levels in this study.

The increase in histamine levels in patients with AIA has previously been reported by Szmít et al.¹²

The evidence for mast cell activation is supported by a preliminary study in which urinary histamine was measured mass spectrometrically, with negative ion chemical ionization, in two subjects with mastocytosis who developed reactions.¹³ In both subjects reported, there was significant increase in histamine levels after aspirin ingestion, and these increases were accompanied by substantial increases in PGD₂ metabolites observed in the urine.

Thus, aspirin-provoked anaphylactic and asthmatic reactions in susceptible subjects appear to be related, at least in part, to enhanced mediator release, such as leukotrienes and histamine, from mast cells and to enhanced airway sensitivity to the leukotrienes.

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