Too many COX (cyclo-oxygenase) spoil the broth: aspirin-sensitive asthma and 5-lipoxygenase

Jane A Mitchell, Maria G Belvisi

This Editorial was initially submitted in 1995 to Thorax as a hypothesis driven article. Nevertheless, at the time it was thought to be too controversial and unsubstantiated by any scientific evidence. However, with the publication of the journal of Sousa's work showing that COX-2 is increased in asthmatic airways, our original hypothesis is better supported. The potential for COX-2 in asthma and aspirin-sensitive asthma is discussed below.

**Scientific basis**

The induction of COX-2 in the lung may occur either locally in pulmonary structures after airway damage, for example, resulting in an increase in cytokines (fig 1). COX-2 may also be induced in lung tissues after cytokines are elevated, as part of a systemic response to infection (fig 1). Indeed, we and others have shown that COX-2 is induced by inflammatory cytokines in different human pulmonary cells including airway epithelium,4 airway smooth muscle,5,6 lung macrophages and activated leucocytes.7 With the wide range of effects produced by prostanoids it is surprising that NSAIDs do not have more therapeutic uses in lung diseases. However, NSAIDs have been useful in the treatment of cough induced by angiotensin converting enzyme inhibitors.8 These studies illustrate the known modulatory action of prostanoids on sensory nerve function resulting in sensitisation of the cough reflex.9

**Therapeutic potential**

We would suggest that, as in other organs,9 lung tissues express COX-2 during inflammatory events such as those that occur in asthma. Indeed, the report by Sousa et al10 in the current issue of Thorax confirms that COX-2 is present in asthmatic tissue. Why then are NSAIDs unsuccessful in the treatment of asthmatic symptoms? Moreover, in a subgroup of asthmatic subjects aspirin actually causes asthma typical of generalised flush, ocular and nasal congestion, and an acute (often severe) asthmatic attack. These patients also appear to have an increased number of COX-2 expressing mast cells.10 The answer to this question may lie in the biochemical processes that occur in this group of "aspirin-sensitive" asthmatic subjects. To date, aspirin-sensitive asthma has been attributed, at least in part, to the shunting of arachidonic acid from the COX pathway to the 5-lipoxygenase (5-LO) pathway resulting in the production of leukotrienes.11 The "shunting hypothesis" has been an attractive one as leukotrienes contribute to allergic and inflammatory reactions by several mechanisms including constriction of smooth muscle and stimulation of airway mucous production. In addition, increased levels of leukotrienes have been detected in patients with aspirin-sensitive asthma.12 We would like to put forward an alternative hypothesis to explain how aspirin-sensitive asthma is initiated.

We propose that, in sensitive patients, COX-2 predominates and is modified biochemically by aspirin, blocking the normal prostanoid profile and facilitating the production of 5-LO products (fig 1). This hypothesis is supported by recent evidence showing that aspirin is, indeed, able to modify the products formed by purified COX-2.13 In the presence of aspirin COX-2, but not COX-1, is modified to form 15-HETE (normally a 15-LO metabolite). Furthermore, the normal metabolites of COX-2 and all the metabolites of COX-1 are blocked by aspirin. Consequently, in patients where COX-2 predominates these observations would suggest that, in the presence of aspirin, arachidonic acid is still utilised by COX and the metabolites merely diverted.

How then can the "COX-2 hypothesis" explain the apparent involvement of leukotrienes in aspirin-sensitive asthma? Recently Claria and Serhan14 showed that endothelial cells treated to express COX-2 produced 15-HETE in the presence of aspirin which, in turn, was metabolised by 5-LO in associated neutrophils forming a group of novel metabolites known as the 15-epilipoxins.14 However, the functional consequences of the production of these compounds remains unknown. We have shown that various airway cells can be induced to express COX-2 and that, under these conditions, the normal conversion of...
arachidonic acid to prostaglandin E$_2$ is blocked by aspirin and that 15-HETE is formed. It is tempting, therefore, to speculate that in susceptible patients COX-2 predominates and is modified by aspirin to form 15-HETE which, in turn, can be further metabolised by 5-LO present in leucocytes to form 15-epi-LIPoxins and other metabolites (fig 1). This putative pathway for the generation of 5-LO products may well result in the formation of mediators which cross-react with known leukotrienes and account for the observed effects in aspirin-sensitive asthma. Perhaps the most convincing evidence in favour of the “COX-2 hypothesis” and the consequent production of novel 5-LO-derived mediators is that, although leukotriene receptor antagonists attenuate the airway obstruction induced by aspirin challenge, the 5-LO inhibitor zileuton provides complete inhibition of the airway response to oral aspirin challenge.

These clinical observations show that 5-LO activity can modulate asthma without the necessary contribution of conventional leukotrienes. Nevertheless, it should be noted that aspirin-sensitive asthma is not a disease solely linked to aspirin but is indicative of a response to a number of NSAIDs.

**Conclusions**

There is now an overwhelming weight of evidence to suggest that COX-2 is the predominant isoform in inflammation. It therefore seems likely that, in lung diseases such as asthma, COX-2 is expressed in lung structures and contributes to both defence and inflammatory processes. The modification of COX-2 by aspirin resulting in the diversion of arachidonic acid to novel 5-LO products brings a new aspect to the role of leukotrienes in asthma. It therefore remains to be seen what other NSAIDS – including the novel COX-2 selective compounds – do to COX-2 metabolism of arachidonic acid. Furthermore, the pharmacological profile of novel COX-2 derived metabolites such as 15-epi-LIPoxins on airway and lung functions should reveal not only the validity of this hypothesis, but also new aspects to lipid mediators in the lung.

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