

EDITORIAL

Aspirin-sensitive asthma

Affecting between 5 and 20% of adult asthmatics, with a usual onset in the third decade and a preponderance in the female population [1–3], aspirin-sensitive asthma has remained, since its initial description at the beginning of the century, a spectacular but elusive disorder.

The first insights into its pathophysiology arose 15 years ago, after several studies had reported the absence of markers for an immunological process, including the lack of aspirin-specific antibodies, of aspirin-induced skin reactivity and of passive cutaneous transfer of aspirin sensitivity [reviewed in 2,3]. In a series of important observations, Szczeklik *et al.* [4] showed that besides aspirin, various chemically distinct non-steroidal anti-inflammatory drugs (NSAIDs) also induced severe asthmatic attacks in these patients; and that all these drugs shared the common pharmacological property of being inhibitors of the cyclo-oxygenase pathway, i.e. inhibitors of the synthesis of prostaglandin endoperoxides, the unstable precursors of prostaglandins (PG) and thromboxane A₂. Drugs that do not inhibit cyclo-oxygenase do not usually induce bronchospasm in aspirin-sensitive asthmatics.

It should be noted that these distinctive features appear as hallmarks of aspirin-induced asthma, but do not seem to apply to other forms of intolerance to aspirin (i.e. the acute urticarial/angioedematous adverse reactions, that might involve classical IgE-mediated mechanisms).

These findings have led to the widely accepted hypothesis that in aspirin-sensitive asthmatics, NSAID-induced blockade of the cyclo-oxygenase pathway might divert arachidonate metabolism from the cyclo-oxygenase to the lipoxygenase pathway, leading to an excess of bronchoconstrictor leukotrienes and to a lack of bronchodilator PGE₂ in the respiratory tract [2–4]. Recently, it was proposed that NSAIDs remove the inhibitory effect of PGE₂ on cytotoxic lymphocytes directed against virally infected cells from the respiratory tract [5]. These hypotheses, however, have not been substantiated by any experimental evidence, and do not address two important features of the disorder. First, NSAIDs do not adversely affect all asthmatic patients, nor all patients with viral infection of the respiratory tract. Secondly, although the very name of aspirin-sensitive asthma refers to the

NSAID-induced bronchospasm, a significant proportion of these patients evolve, despite the complete avoidance of cyclo-oxygenase-inhibiting drugs, towards a chronic course of asthma, and sometimes rapidly become severe therapeutic-resistant asthmatics. This suggests that NSAIDs might reveal and exacerbate in these patients an underlying disorder whose onset and progression do not depend on any drug intake.

The lack of identification in aspirin-sensitive asthma of any cellular model, or of any *in-vitro* abnormality has been frustrating and has hampered further exploration of pathogenesis. In this respect the article by Pearson and Suarez-Mendez in the present issue of the journal represents an important contribution that confirms a series of observations that were made several years ago in our laboratory, including the identification of an abnormal platelet response to NSAIDs in aspirin-sensitive asthmatics. Joseph *et al.* [6,7] had shown that platelets have a membrane receptor for IgE (Fc ϵ RII) that allowed them, upon interaction with the relevant antigen, to efficiently kill parasites and to generate a low but detectable secretion of oxygen-derived radicals; suggesting a direct participation of platelets in IgE-mediated allergic reactions. We then found that platelets from patients with aspirin-sensitive asthma had a similar, but non IgE-mediated, *in-vitro* response to the cyclo-oxygenase-inhibiting NSAIDs that induce asthmatic attacks in these patients [8,9].

The generation, in the presence of cyclo-oxygenase inhibiting NSAIDs, of mediators cytotoxic for parasites appeared specific for the disease [8] and has now been found to be present in over 60 patients, and absent in over 60 controls. A low generation by platelets of oxygen-derived radicals was also observed in our initial study in 14 patients, and not in 10 controls. This abnormal platelet response appeared at least partly restricted to the platelet because patient leucocytes did not kill parasites or generate any respiratory burst in the presence of NSAIDs [8].

Pearson and Suarez-Mendez report, firstly, the generation of a low respiratory burst by platelets from atopic patients when triggered by anti-IgE antibodies or allergen and, secondly, the generation of a similar response by platelets from aspirin-sensitive asthmatics when triggered by two chemically distinct cyclo-oxygenase-inhibiting NSAIDs. They also extend their observations to the new finding of a reduced basic activity of the glutathione peroxidase (GPX) enzyme from patient platelets. The specificity of the abnormal platelet response to NSAIDs is

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confirmed, since it was not observed with platelets from healthy or atopic controls. At variance with our own previous studies, however, is their finding that the platelet respiratory burst is only detectable in 8/25 (32%) of the patients tested, a finding that the authors attribute to a heterogeneity of the disease.

In view of the fact that these authors seem to have confirmed the platelet response and its specificity, the discrepancy appears relatively minor. We would nevertheless like to comment as follows.

(1) The authors observed platelet reactivity to anti-IgE antibodies in 13/29 (45%) of atopic patients only. Although heterogeneity in atopic patients might exist, we feel that there might be a more general problem concerning sensitivity of the studies of the respiratory burst of platelets.

(2) It should be recalled that the parasite killing response of platelets induced by IgE-dependent stimuli that we described earlier is of a similar, or greater, magnitude than that of monocytes [10] or eosinophils, whereas the generation of oxygen radicals induced by the same stimuli is of several orders of magnitude lower in platelets than in these inflammatory cells. More generally, the cytotoxic response of platelets from any healthy control that can be triggered by various stimuli, including C-reactive protein [11], lymphokines (gamma interferon [12], lymphotoxin [13]), or an antifilarial drug, diethylcarbamazine (DEC) [14] has been much easier to quantify than the generation of platelet respiratory burst. In one case (DEC) the use of electron paramagnetic resonance (EPR) was required for confirmation [14].

(3) We have so far observed an abnormal platelet response to NSAIDs only in patients who react with bronchospasm to NSAIDs (aspirin-induced asthma), and not in patients, whether asthmatic or not, who react with isolated urticaria/angioedema. Regarding platelet GPX activity, the authors show that platelets from the latter patients (6/25 patients) have a normal activity, similar to that of control platelets, and significantly different from the reduced activity detected in aspirin-sensitive asthmatics who react to NSAIDs with bronchospasm. In fact the observation by the authors (p.11) that 'mean platelet GPX activity was similar in those subjects with positive and negative *in-vitro* platelet chemiluminescent response to ASA' suggests that the eight patients who had a platelet respiratory burst in response to NSAIDs were indeed in the aspirin-induced asthma group. If this is the case, the platelet respiratory burst to NSAIDs in patients with aspirin-induced asthma, taken as a homogeneous group, would be in 8/19 (42%), a percentage similar to the anti-IgE antibody triggering the authors observed in atopic patients (45%).

A most important observation by the authors is the

finding of reduced GPX activity in platelets from patients with aspirin-sensitive asthma. This reduced activity was observed in the absence of NSAIDs, and might therefore be directly related to the underlying biological abnormalities involved in the disorder. GPX plays a significant role in degrading H_2O_2 . How does this reduced activity participate in the pathogenesis of the disorder? How, in particular is it related to the abnormal response to cyclo-oxygenase inhibiting NSAIDs?

The extreme view that the effect of NSAIDs is completely independent of their common inhibitory property on cyclo-oxygenase and related to a different effect that they would share on an unrelated target appears unlikely. We have observed that drugs chemically similar to aspirin, such as sodium salicylate and salicylamide, that are devoid of cyclo-oxygenase-inhibiting property and well tolerated by aspirin-sensitive asthmatics, do not activate their platelets [8]. Inhibitors of thromboxane synthetase (the enzyme that converts PG endoperoxides, the cyclo-oxygenase products, into thromboxane A_2) did not activate patient platelets [8], an observation that correlated with the later finding by Szczeklik *et al.* [15] that these drugs do not induce bronchospasm in aspirin-sensitive asthmatics. Interestingly, the unstable PGH_2 endoperoxides, and their stable analogues, prevented patient platelet response to NSAIDs [8]. Finally, selective antagonists of the platelet PGH_2 receptor induced the same abnormal response as NSAIDs in platelets from the patients but not from controls [16]. This suggested to us that an ongoing synthesis of PGH_2 and interaction of PGH_2 with its platelet receptor might play a critical role in patient platelets that NSAIDs would interrupt. GPX down-regulates the cyclo-oxygenase pathway by removing peroxy products required for initiation of the reaction. We feel that there might be a relation between the role played by PGH_2 endoperoxides in patient platelets and a reduction in the activity of an enzyme, GPX, that normally down-regulates the bioavailability of these endoperoxides in the cell. Is the lowered GPX activity a cause or a consequence of the disorder? Is it related to a defect in synthesis of the enzyme? The hypothesis of the authors that nutritional deficiency of selenium could be involved is appealing.

Altogether, the important point is that a cellular model of the disease, the platelet, appears now to be available. In the complex network of inflammatory cells involved in asthma, it is, however, unlikely that the platelet represents the only cell reflecting the sensitivity of patients to NSAIDs. Goetzl *et al.* [17] have reported that NSAIDs have an excessive inhibitory effect on PG synthesis by patient basophils, but that this effect can be detected only when the basophils are stimulated by IgE. It is possible that, in the absence of additional triggering events,

inflammatory cells or cells of the respiratory tract have no easily detectable *in-vitro* abnormal response to NSAIDs. The fact that the platelet is a cell without a nucleus might account for the existence of less complex regulatory mechanisms and could explain the apparent suitability of this cell for *in-vitro* studies of aspirin-sensitive asthma. On the other hand, for the very same reason, platelets represent a problem for the use of molecular biology probes. Therefore, although further exploration of the platelet model is essential to appreciate its possible role in the pathogenesis of asthma, a search for an additional cellular model appears important in order to understand this puzzling disorder and to be able to test in optimal conditions new preventive and therapeutic approaches.

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