Reduced Prostaglandin D2 Production by Airway Fibroblasts in Nonsteroidal Anti-inflammatory Drug-Exacerbated Airway Disease

Roca-Ferrer J[1,2], Machado-Carvalho L[3,4], Picado C[1,2]
[1]*Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain*
[2]*Centro de Investigaciones en Red de Enfermedades Respiratorias (CIBERES), Madrid, Spain*
[3]*Department of Biology and Environment, School of Life Sciences and Environment, University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal*
[4]*Center for Research and Technology of Agro-Environmental and Biological Sciences (CITAB-UTAD), University of Trás-os-Montes and Alto Douro (UTAD), Vila Real, Portugal*

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Nonsteroidal anti-inflammatory drug (NSAID)–exacerbated airway disease (N-ERD) is caused by a nonallergic hypersensitivity reaction precipitated by aspirin and other NSAIDs. N-ERD is clinically characterized by the co-occurrence of asthma and chronic rhinosinusitis with nasal polyposis (CRSwNP). There is evidence that N-ERD is associated with the dysregulation of arachidonic acid (AA) metabolism [1].

AA is mobilized from membrane phospholipids by phospholipases and is converted by cyclooxygenases (COX) into prostaglandin H_2, which is subsequently metabolized to prostaglandins (PGs), thromboxanes, and prostacyclin, with the contribution of specific synthases. There are 2 COX isoforms: COX-1 and COX-2. COX-1 is constitutively expressed, while COX-2 is induced, and its expression increases markedly under inflammatory conditions. AA is also catalyzed by 5-lipoxygenase (5-LO) to generate cysteinyl leukotrienes (CysLTs) [1].

Reduced synthesis of prostaglandin E2 and overproduction of prostaglandin D_2 (PGD_2) and CysLTs are characteristic of N-ERD. Elevated levels of leukotriene E_4 and PGD_2 are observed at baseline in different body fluids (nasal, bronchial, and urine samples). Following ingestion of aspirin and other NSAIDs, COX-1 inhibition decreases the biosynthesis of PGE_2 but enhances the release of CysLts and PGD_2, both of which are responsible for upper airway symptoms (nasal congestion, nasal discharge) and lower airway symptoms (bronchoconstriction). In contrast, selective COX-2 inhibitors are well tolerated [1].

PGE_2 reduces the activity of 5-LO, resulting in reduced CysLT production [2], and inhibits the production of thymic stromal lymphopoietin, the cytokine involved in PGD_2 production by mast cells and eosinophils [3]. It is commonly accepted that the impaired PGE_2 synthesis in N-ERD accounts for the excessive production of both CysLTs and PGD_2 at baseline. The further reduction in PGE_2 synthesis by NSAIDs contributes to the surge in CysLTs and release of PGD_2, which result in exacerbated airway disease [1].

One of the intriguing observations in N-ERD is the dissociated production of PGE_2 and PGD_2, 2 prostanoids with a common COX metabolic pathway [1]. Reduced PGE_2 production has been reported in airway fibroblasts and epithelial cells associated with diminished expression of inducible COX-2 [4-6]. It was recently suggested that low PGE_2 production would contribute to excessive release of alarmins such as TLSP from airway cells. This, in turn, would increase the metabolic activity of the COX pathway, thereby increasing PGD_2 production by mast cells and eosinophils [7].

If this observation in inflammatory cells is applied to the respiratory epithelium of patients with N-ERD, we would expect that, via an autoregulatory mechanism, the excessive production of thymic stromal lymphopoietin would also increase the activity of the COX pathway in the epithelium, leading to increased synthesis of the prostanoids PGE_2 and PGD_2 in epithelial cells. As mentioned above, this is not the case for PGE_2, whose production is reduced [4-6]. However, very little is known about the regulation of PGD_2 in the structural cells of the respiratory epithelium; only 1 previous study reported deficient production of PGD_2 in nasal polyp fibroblasts from N-ERD patients with respect to healthy controls [5].

Our study hypothesizes that, in the respiratory epithelium (fibroblasts, epithelial cells) of patients with N-ERD, there is an intrinsic alteration of the COX pathway, particularly COX-2. This reduces its capacity for prostanoid synthesis, impacting the production of both PGE_2 and PGD_2.

To prove this hypothesis, we performed a dynamic analysis of PGD_2 production in cultured fibroblasts from nasal mucosa (control group) and nasal polyps from N-ERD and non–N-ERD patients. The online supplementary file shows the demographic and clinical characteristics of the study population, as well as information regarding cell culture, the experimental protocol, analysis, and statistics. All the patients provided their informed consent to participate in the study, which was approved by the local scientific and ethics committee.

As previously reported for PGE_2, control of nasal mucosa fibroblasts incubated with IL-1β revealed statistically significant increased production of PGD_2 after 24 hours of incubation (5-fold increase). This cytokine only induced a mild, statistically significant increase in PGD_2 production in non–N-ERD patients at 24 hours (2-fold increase) and no change in N-ERD patients (Figure). This pattern of

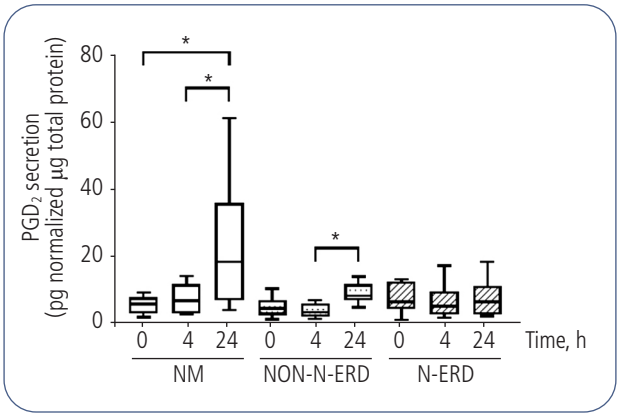

Figure. Time course of IL-1β in secretion of PGD_2 protein. Supernatants were obtained from 150-cm^2 flasks containing quiescent fibroblast cultures incubated for 4 to 24 hours with serum-free media in the presence or absence of 10 ng/mL IL-1β and normalized to the total protein content in cell lysates from the corresponding samples. PGD_2 concentrations were measured using ELISA. Statistically significant difference (P<.05) at 24 hours with respect to the baseline value in control NM. Statistically significant difference (P<.05) at 24 hours with respect to 4 hours in non–N-ERD. NM indicates nasal mucosa; N-ERD, nonsteroidal anti-inflammatory drugs–exacerbated airway disease.

IL-1β–induced PGD_2 expression in fibroblasts mimics that previously observed for PGE_2, supporting the hypothesis that there is an intrinsic anomaly in the regulation of the COX-2 pathway in N-ERD fibroblasts, resulting in deficient production of all prostanoids. Of note, the induction of COX-2 and the subsequent release of prostanoids is also disturbed, albeit to a lesser extent, in NSAID-tolerant individuals [6,8]. It remains unclear whether there is a threshold below which NSAID intolerance develops or whether other, yet unknown cofactors contribute to N-ERD.

While the mechanisms underlying disturbed AA metabolism have yet to be fully elucidated, previous studies demonstrated that the combined action of IL-4, a T_H2 cytokine, and INF-γ, a T_H1 cytokine, can induce disturbances in AA metabolism in healthy nasal mucosa that are similar to those arising spontaneously in N-ERD [9,10].

Our study is limited by the low number of patients included, thus explaining the lack of statistically significant differences between some values. Nasal polyps are usually removed from patients with a poor response to therapy and, therefore, tend to represent the most severe cases. In addition, given that severity may have an impact on AA metabolism, the results obtained should be demonstrated in milder cases.

In summary, our findings support the notion that the disrupted COX-2 pathway, together with the associated reduction in prostanoid production, is primarily localized in the airway epithelium, while inflammatory cells such as mast cells and eosinophils escape this anomaly. Gaining a deeper understanding of the role of the airway epithelium could afford valuable insights into the mechanisms underlying N-ERD.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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César Picado
CELEX
Facultat de Medicina, Primer Pis
Villarroel 170
08035 Barcelona
E-mail: cpicado@ub.edu