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Glucocorticoid therapy increases COX-2 gene expression in nasal polyps *in vivo*

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ABSTRACT: The aim of the present study was to evaluate the *in vivo* regulation of cyclooxygenase-2 in nasal polyps.

In total, 65 patients with nasal polyps were randomly (3:1) treated with (n=51; 33 with asthma) or without (n=14) oral prednisone and intranasal budesonide for 2 weeks plus intranasal budesonide for 10 additional weeks. Biopsies were obtained at baseline and after 2 and 12 weeks of treatment. All samples were analysed for cyclooxygenase-1 and cyclooxygenase-2 mRNA. Attempts were made to detect cyclooxygenase-2 protein.

At baseline, cyclooxygenase-1 and cyclooxygenase-2 expression did not differ between polyps from nonasthmatic and asthmatic patients. Cyclooxygenase-1 mRNA was unchanged by glucocorticoid treatment, while cyclooxygenase-2 mRNA increased in glucocorticoid-treated patients at week 2 compared with baseline and then decreased at week 12. Within subgroups, increased cyclooxygenase-2 mRNA was found at week 2 in polyps from nonasthmatic and asthmatic patients compared with baseline. At week 12, cyclooxygenase-2 expression remained high in nonasthmatics while it decreased in asthmatics. Cyclooxygenase-2 protein was not detected under any circumstances.

Glucocorticoid therapy enhances cyclooxygenase-2 expression *in vivo* in nasal polyps, a finding that does not follow the generally accepted assumption that cyclooxygenase-2 expression is suppressed by glucocorticoids.

KEYWORDS: Cyclooxygenase-1, cyclooxygenase-2, glucocorticoids, nasal polyps

Prostaglandin (PG) endoperoxidase synthase, known as cyclooxygenase (COX) is the rate-limiting enzyme in the biosynthesis of PG. There are two distinct enzymes, COX-1 and COX-2. While COX-1 is constitutively expressed in most cells, the expression of COX-2 is generally low under basal conditions but is usually induced by inflammatory mediators, mitogens and growth factors. Many observations indicate that the expression of COX-2 plays key roles in inflammation and tumorigenesis [1].

Over-expressed COX-2, in response to stressful signals, has been shown to be a major source of PG. PG can exert opposing effects on inflammatory response in the airways. Mast cells release PGD_2, which is partly responsible for the bronchoconstriction that usually occurs in immediate allergic responses. In contrast, PGE_2 can exert both beneficial and adverse effects. Inhalation of a high PGE_2 dose causes bronchoconstriction while a low dose prevents exercise-induced bronchoconstriction, early- and late-phase allergic airway reactions, and aspirin-induced broncoconstriction [2–4]. Together, the experimental data and clinical findings indicate that COX-2 induction may be a friend or a foe in the lung [5, 6].

Despite the fact that the COX-2 enzyme is induced in states of inflammation, this is not the case in the nasal polyps of asthmatic patients, which show no increase in the expression of the enzyme [7, 8]. This lack of upregulation of COX-2 in the inflamed tissue of nasal polyps is more marked in asthma patients with aspirin intolerance, where the level of COX-2 expression is even lower than in aspirin-tolerant asthmatics [8–10]. The mechanisms responsible for this abnormal response are, as yet, unclear. Whether down-regulation of COX-2 is involved in the formation of nasal polyps or is a collateral consequence of the nasal inflammatory process remains to be elucidated.

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TABLE 1 Demographic data and clinical characteristics of the study population

	Nontreated group	GC-treated group		
		Without asthma	With asthma	
			ATA	AIA
Patients n	14	18	16	17
Sex % female	14.3	16.7	25.0	47.0
Age yrs	52.5±4.8	53.8±3.8	48.6±4.7	49.1±2.9
Skin prick test % positivity	28.6	27.8	25.0	29.4

Data are presented as mean±SEM unless stated otherwise. GC: glucocorticoid; ATA: aspirin-tolerant asthma; AIA: aspirin-intolerant asthma.

Glucocorticoids (GCs) represent the most effective treatment for several clinical conditions and are used for their anti-inflammatory effects in the treatment of nasal polyps [11]. GCs have been shown to modulate the expression of several genes involved in inflammatory responses. One of the target genes for GC action appears to be the COX-2 gene, suppressed through both transcriptional and post-transcriptional mechanisms [12–14].

However, the ability of GC to decrease COX-2 expression in the airways is not entirely clear. At least one group has found that GC can decrease COX-2 expression in the bronchial mucosa of asthma patients [15] but others have reported no change in its expression in either bronchial mucosa of patients with asthma [16] or nasal polyps after GC therapy [10]. Similarly, *in vitro* studies also show disparate results, with some reports showing a decrease [12–14] and others an increase [17] in the expression of COX-2 after the exposure of various cells and tissues to GC.

It is difficult to determine the true effect of GC on COX-2 in airways, as the *in vivo* studies are comparison studies of different groups of patients in cross-sectional studies [10, 15, 16] and the *in vitro* studies vary widely with regard to the type of cells, the methodology used and the duration of exposure to treatment [10, 12–14].

The only way to clarify whether GC increase or decrease COX-2 expression *in vivo* is through a prospective study comparing the level of expression of the enzyme in tissues obtained from the same subjects before and after GC therapy. With this objective in mind, serial nasal polyp biopsies were performed on patients treated with GC and the local COX-2 mRNA and protein expression was evaluated.

SUBJECTS AND METHODS

Study subjects

A total of 65 patients (74% male, age 51±2 yrs) with diagnosis of severe nasal polyposis were selected, comprising patients without asthma and patients with either aspirin-tolerant or aspirin-intolerant asthma (ATA and AIA, respectively). Severe nasal polyposis, atopy, asthma and aspirin sensitivity were diagnosed as described elsewhere [18, 19] (see supplementary material). All subjects agreed to participate in the study, which was approved by the Ethics Committee of the Hospital Clinic from Barcelona (Spain). Table 1 summarises the subjects' demographic data and clinical characteristics.

Study design

The study design used herein has been previously reported [18]. After a 4-week washout period with no intranasal or oral steroids, patients were randomised (3:1) into two groups. 1) The GC-treated group included 51 patients who received oral prednisone (30 mg daily for 4 days followed by a tapering of 5 mg every 2 days) and intranasal budesonide (400 μg *b.i.d.*) for 2 weeks (w2), followed by intranasal budesonide (400 μg

TABLE 2 Inflammatory cell counts of nasal polyp biopsies from nontreated or glucocorticoid (GC)-treated patients

Group	Cases n	Mononuclear cells	Eosinophils	Neutrophils	Total inflammatory cells
Nontreated					
Baseline	7	928 (484–1893)	169 (86–215)	34 (13–69)	1127 (721–2531)
Week 2	7	1277 (711–1482)	227 (117–1039)	42 (12–195)	1641 (1373–2181)
GC-treated					
Baseline	22	892 (581–1351)	243 (100–480)	3 (1–14)#	1207 (832–2101)
Week 2	20	1040 (582–1785)	20 (5–39)***	20 (1–43)*	1168 (634–1807)
Week 12	18	1061 (540–1503)	22 (3–85)*	6 (1–26)	1294 (579–2191)

Data are presented as median (interquartile range) cells·mm^{-2}, unless otherwise stated. Total inflammatory cells correspond to the sum of mononuclear cells, eosinophils, and neutrophils. *: $p<0.05$; ***: $p<0.001$; both compared with baseline from GC-treated group (Wilcoxon test). #: $p<0.01$ compared with baseline from the nontreated group (Mann–Whitney U-test).

TABLE 3 Basal expression of cyclooxygenase (COX)-1 and COX-2 mRNAs in the different subtypes of nasal polyps (all patients)

	Cases n	COX-1	COX-2
Without asthma	24	3.29 (0.96–5.93)	0.21 (0.05–0.47)
With asthma	41	3.96 (2.02–6.66)	0.23 (0.06–0.37)
ATA	21	4.81 (2.32–7.18)	0.24 (0.08–0.35)
AIA	20	2.98 (1.65–6.01)	0.20 (0.05–0.61)

Data are presented as median (interquartile range) $\times 10^6$ cDNA copies·μg^{-1} total RNA, unless otherwise stated. ATA: aspirin-tolerant asthma; AIA: aspirin-intolerant asthma. No significant differences in either COX-1 or COX-2 mRNA expression among the different nasal polyp subtypes were found (Mann–Whitney U-test and Kruskal–Wallis).

b.i.d.) alone for 10 additional weeks (w12). 2) The nontreated group included 14 patients who did not receive any steroid treatment over a 2-week period (w2). For ethical reasons, patients from the nontreated group were not kept for more than 6 weeks without any effective treatment. Nasal polyp biopsies were obtained from all patients at baseline, w2 (treated and nontreated groups) and w12 (treated group).

Histological analysis

The inflammatory content of biopsies, *i.e.* mononuclear cells, neutrophils, and eosinophils, was characterised by haematoxylin and eosin staining in 4-μm thick paraffin sections. Sections were counted blindly using an Olympus microscope (×400 magnification). Between 1.6 and 2 mm^2 were counted for each section and cell counts were expressed as the number of positive cells·mm^{-2}. Due to limitations in the amount of tissue obtained at three points (baseline, w2 and w12) and the preferential use of tissues for RT-PCR and protein analysis, the histological analysis could be completed in only 29 patients.

Reverse transcription and real-time PCR

The extraction of total RNA from the specimens and the reverse transcription step were performed as previously reported [9, 10]. Quantification of COX-1 and COX-2 transcripts was achieved by extrapolation to a plasmid double-stranded DNA external standard curve added in each PCR run. The detailed protocol and validation of the real-time PCR assays have been reported elsewhere (see supplementary material) [9].

Western blot and ELISA of COX-2

Total proteins from the nasal polyp biopsies were extracted as described elsewhere [20] and analysed for the expression of COX-2 protein through both Western blot [20] and ELISA using the ZYMED COX-2 ELISA kit (ZYMED laboratories INC, San Francisco, CA, USA). The detection range of the ELISA kit was from 2.15 to 275 ng·mL^{-1} (see supplementary material).

Statistical analysis

Data are expressed as median and interquartile range. Nonparametric statistical analysis was performed by using the Friedman test and Wilcoxon rank test for within-group comparisons, and the Kruskal–Wallis test and Mann–Whitney U-test for between-group comparisons. Spearman rank correlation was used when analysing relationships between data. A p-value of <0.05 was considered to be significant.

The sample size of the study was established from practical considerations. The estimated statistical power for the present sample size (51 GC-treated patients) to detect a two-fold change in the median of the main variable (COX-2 mRNA) was 82% when analysed with a nonparametric approach (Wilcoxon test), with an α error of 5% two-sided.

RESULTS

Subjects

As expected, GC therapy significantly improved clinical symptoms, reduced nasal polyp size and relieved nasal obstruction. A detailed description of the clinical results has been previously reported elsewhere [18].

Histological findings

Except for neutrophils, at baseline, there were no significant differences in the number of inflammatory cells between GC-treated and nontreated control groups (table 2).

There were no significant changes in the inflammatory cell counts between baseline and w2 in the nontreated group (table 2). In contrast, at w2, GC-treated patients showed a marked downregulation in the number of eosinophils, which remained low at w12 and an increase in the number of neutrophils compared with baseline (table 2). The reduction in eosinophils at w2 was found in both nonasthmatic (median 20 (interquartile range 15–38); n=8; $p<0.05$) and asthmatic patients (18 (3–55); n=12; $p<0.01$), compared with baseline (no asthma: 199 (96–339); n=9; asthma: 285 (126–808); n = 13). However, the reduction in eosinophils at w12 was more pronounced in the nonasthmatics (13 (3–71); n=8; $p<0.05$ compared with baseline) than in the asthmatic patients (41 (3–283); n=10; nonsignificant compared with baseline). No differences in the response to GC treatment were apparently found between ATA and AIA patients. However, given the low number of patients available for histological analysis, caution has to be taken when comparing subgroup differences.

The increase in neutrophil numbers at w2 in all patients (table 2) did not reach statistical significance when they were subdivided in nonasthmatics (w2: 17 (1–47) *versus* w0: 2 (1–13); p=0.07) and asthmatics (w2: 20 (1–40) *versus* w0: 4 (2–30); p=0.07), nor in ATA and AIA patients.

Basal expression of COX-1 and COX-2 mRNA

When all patients were analysed at baseline, no significant differences in COX-1 or COX-2 mRNA expression were found in nasal polyps between nonasthmatic and either ATA or AIA patients (table 3).

COX-1 and COX-2 mRNA expression after treatment with GCs

At baseline, there were no significant differences in COX-1 mRNA expression between treated and nontreated groups (fig. 1a). There were no significant changes in COX-1 mRNA levels between baseline and w2 in the nontreated group, nor between baseline and either w2 or w12 in the treated group (fig. 1a). Within the treated patients, no significant changes in

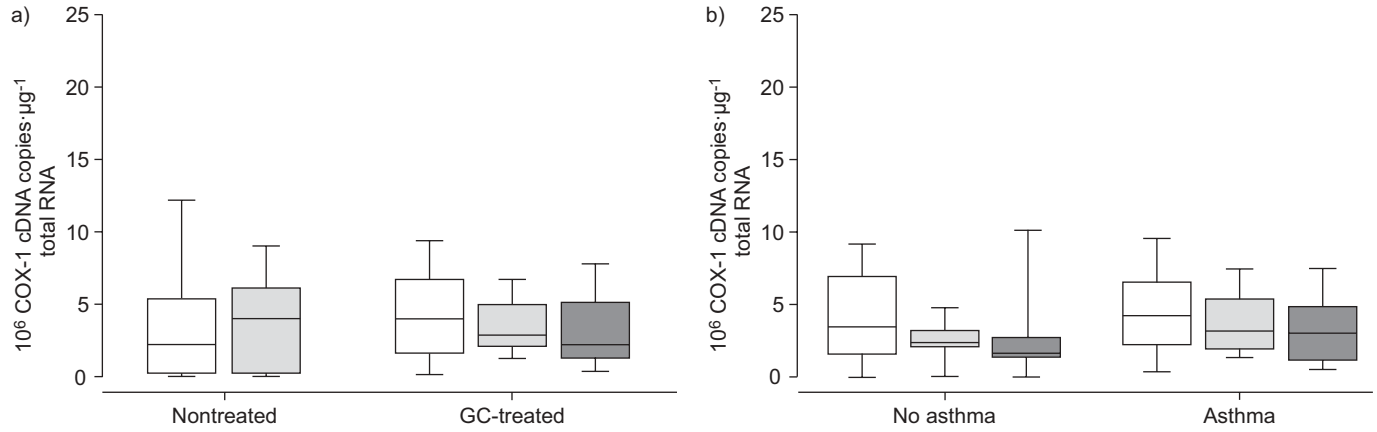

FIGURE 1. Regulation of cyclooxygenase (COX)-1 mRNA in a) nontreated (n=14) and glucocorticoid (GC)-treated patients (n=51) and b) in GC-treated patients who either had no asthma (n=18) or asthma (n=33). Data are presented as box plots with the 25th, 50th (median) and 75th percentile values. Whiskers represent the 10th and 90th percentiles. □: baseline; ▫: week 2; ■: week 12. No significant differences in COX-1 mRNA expression were observed over time for any group (Friedman test and Wilcoxon test).

COX-1 expression were found at w2 and w12 compared to baseline in nasal polyps from both nonasthmatic and asthmatic patients (fig. 1b).

There were no significant changes in COX-2 mRNA expression between baseline and w2 in the nontreated group, while COX-2 mRNA was seen to be increased in treated patients at w2 compared with baseline. COX-2 mRNA expression decreased significantly at w12, compared with w2 (fig. 2a and table 4). Interestingly, a different response to GC treatment was found between nonasthmatic and asthmatic patients (fig. 2b and table 4). Thus, in nonasthmatic patients, increased COX-2 expression was found at w2 and w12 compared with baseline. However, in asthmatic patients, COX-2 expression increased at w2, compared with baseline, and decreased to basal levels at w12. The same apparent pattern of regulation, *i.e.* increase in COX-2 mRNA levels at w2 and return to basal levels at w12, was observed in both ATA and AIA patients, although changes did not achieve statistical significance (table 4).

TABLE 4 Effect of glucocorticoid (GC) treatment on cyclooxygenase-2 mRNA in the different subtypes of nasal polyps

Group	Cases n	Baseline	Week 2	Week 12
Nontreated	14	0.19 (0.02–0.48)	0.21 (0.08–0.55)	
GC-treated	51	0.23 (0.08–0.38)	0.41 (0.20–0.90)**	0.31 (0.09–0.52)$^{\#}$
Without asthma	18	0.23 (0.13–0.44)	0.37 (0.08–1.12)*	0.39 (0.21–0.65)*
With asthma	33	0.23 (0.07–0.37)	0.47 (0.21–0.86)*	0.26 (0.07–0.51)$^{\#\#}$
ATA	16	0.24 (0.11–0.34)	0.55 (0.21–0.92)	0.19 (0.07–0.51)
AIA	17	0.18 (0.05–0.60)	0.40 (0.21–0.69)	0.27 (0.04–0.52)

Data are presented as median (interquartile range) $\times 10^6$ cDNA copies·µg^{-1} total RNA, unless otherwise stated. ATA: aspirin-tolerant asthma; AIA: aspirin-intolerant asthma. *: $p<0.05$; **: $p<0.01$; both compared with baseline (Wilcoxon test). $^{\#}$: $p<0.05$; $^{\#\#}$: $p<0.01$; both compared with week 2 (Wilcoxon test).

A weak but statistically significant negative correlation was found between COX-2 mRNA levels and eosinophil counts ($r= -0.307$; $n=73$; $p<0.01$). However, changes in COX-2 mRNA levels did not correlate with changes in eosinophil numbers after GC treatment. Changes in COX-2 mRNA also did not correlate with the increase in neutrophil numbers at w2.

COX-2 protein expression

COX-2 protein was not detected through ELISA in any tissue or at any time-point. Western blot analysis revealed absence of COX-2 protein at baseline and occasional faint bands corresponding to COX-2 protein after GC treatment in a few tissues, which were difficult to quantify (fig. 3).

DISCUSSION

It is generally accepted that COX-2 is upregulated under conditions of inflammation and that the COX-2 derived eicosanoids are mostly pro-inflammatory. Because eicosanoids are generally considered to be potent pro-inflammatory mediators, their inhibition by GC and nonsteroidal anti-inflammatory drugs (NSAIDs) has been considered a desirable therapeutic goal. However, many recent observations question these assumptions, particularly when they are applied to asthma and idiopathic interstitial lung fibrosis [5, 6, 21].

In asthma and nasal polyps, and most obviously in those patients with aspirin-sensitivity, there are intriguing data to support the existence of a substantial disregulation of the COX-2 pathway. COX-2 and/or PGE_2 levels have been reported to be downregulated in nasal polyps [7–10, 22] as well as in bronchial fibroblasts [23] and bronchial smooth muscle [24] from asthmatic patients. No significant differences in the expression of COX-2 were found between ATA and AIA subjects, which concurs with previous reports showing that kinetic studies are sometimes necessary to demonstrate differences in the expression of COX-2 between ATA and AIA asthma patients [9], and between healthy nasal mucosa

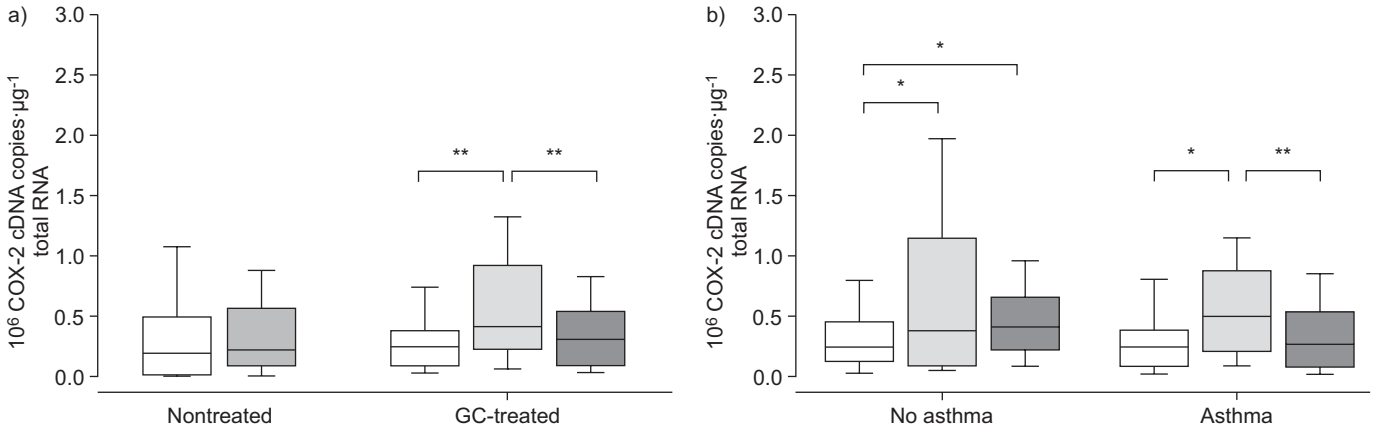

FIGURE 2. Regulation of cyclooxygenase (COX)-2 mRNA in a) nontreated (n=14) and glucocorticoid (GC)-treated patients (n=51) and b) in GC-treated patients who either had no asthma (n=18) or asthma (n=33). Data are presented as box plots with the 25th, 50th (median) and 75th percentile values. Whiskers represent the 10th and 90th percentiles. □: baseline; ▫: week 2; ■: week 12. *: $p<0.05$; **: $p<0.01$ (Wilcoxon test).

and nasal polyps [7]. PGE_2 appears to be a modulator of the airway inflammatory response rather than to act as a pro-inflammatory substance [2–6]. Inhibition of the COX pathway by NSAIDs in asthmatic patients generally has no beneficial effect. Indeed, NSAIDs can precipitate severe asthma reactions in some patients, which can be prevented by pre-treatment with PGE_2 [3].

In contrast to what was expected, the present study shows that GC increased COX-2 mRNA in nasal polyps, a new intriguing finding to add to the altered regulation of COX-2 in this inflamed nasal tissue. The initial intense therapy with systemic and intranasal GC caused a significant increase of COX-2 mRNA in both nonasthmatic and asthmatic patients causing, in the latter, a return to baseline expression levels after prednisone withdrawal and treatment with intranasal GC alone for 10 additional weeks. In parallel, the 2-week oral and intranasal GC treatment provoked a marked reduction in eosinophil numbers and an increase in neutrophils. These differential effects of GC on inflammatory cells have been previously reported and ascribed to the opposing effects of GC on the regulation of apoptosis in eosinophils (increased apoptosis) and neutrophils (decreased apoptosis) [25]. When patients were treated with the less-potent intranasal GC therapy, eosinophil numbers increased in nasal polyps of patients with asthma compared with oral GCs, while in nonasthmatic patients the eosinophilic infiltrate remained low. These findings suggest that the presence of a greater inflammatory activity in the nasal polyps of patients with asthma resulted in an earlier relapse of the eosinophilic infiltrate after prednisone withdrawal. Interestingly enough, COX-2 mRNA expression appears to run in parallel with changes in the inflammatory cell infiltrate. Accordingly, a weak but significant negative correlation was found between COX-2 mRNA levels and eosinophil counts, though changes in COX-2 mRNA did not correlate with changes in eosinophils after GC treatment. Thus, changes in COX-2 mRNA induced by GC treatment may involve a direct effect of GC on the regulation of the COX-2 gene, but may also, at least in part, be a consequence of changes in the tissue cell composition.

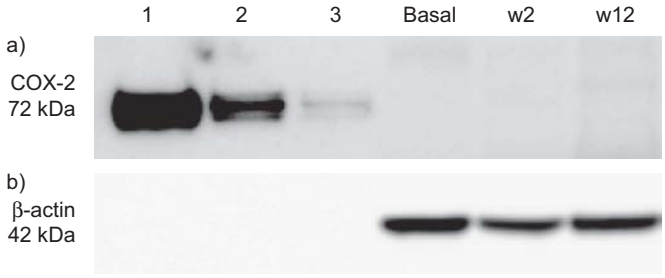

FIGURE 3. a) Representative image of cyclooxygenase (COX)-2 protein in a nasal polyp detected through Western blot at baseline (basal) and after 2 (w2) and 12 weeks (w12) of glucocorticoid (GC) treatment. 1, 2 and 3 denote serial dilutions of the COX-2 standard (11, 5.5 and 2.75 ng, respectively). Note the absence of COX-2 at baseline, w2 and w12. b) Western blot for β-actin, demonstrating a similar protein load in all lanes.

COX-2 protein was not detected either at baseline or post-GC treatment. This is not an unexpected result because COX-2 protein is not usually found by Western blot at baseline in either nasal mucosa or bilateral nasal polyps [7, 14]. Potent inflammatory stimuli are usually needed to induce the production of detectable levels of COX-2 protein in *in vitro* studies [7]. COX-2 protein can also be found *in vivo* in diseases with demonstrated high production of PGs such as cystic fibrosis [20]. Since COX-2 protein was not detected under any circumstances, it is unknown whether the mild GC-induced increase in COX-2 mRNA found in the present study results in an increased translation to COX-2 protein. It is also unknown if GC treatment in the present study has any effect on prostaglandin production.

It is unclear whether the GC effect on COX-2 mRNA expression occurs in inflamed nasal tissue only or whether it can also take place in healthy nasal mucosa. For ethical reasons, nasal biopsies from healthy subjects before and after GC therapy could not be obtained.

Interestingly enough, the present observation concurs with another previously reported by DWORSKI *et al.* [26], who unexpectedly also found that COX-2 mRNA expression significantly increased in alveolar macrophages and blood monocytes from atopic asthma patients treated with 30 mg of

prednisone for 7 days, while the same treatment resulted in a decreased expression of COX-2 mRNA in the same cells from healthy subjects. In contrast with the results obtained *in vivo*, the expression of COX-2 mRNA was significantly inhibited when stimulated monocytes from atopic asthmatic patients and healthy subjects were exposed to dexamethasone *ex vivo* [26].

Thus, in spite of the fact that in this study the GC-induced increase of COX-2 mRNA might be partly ascribed to the effects of GC on the inflammatory infiltrate, the present results, together with those reported by DWORSKI *et al.* [26], support the hypothesis that GC therapy upregulates COX-2 expression *in vivo* in cells and airway tissues of patients with asthma and nasal polyps.

The present authors cannot find an explanation for the increased expression of COX-2 with GC therapy in asthma/nasal polyps. Based on the dichotomy in the effect of GC *in vivo* with respect to the *ex vivo* situation found by DWORSKI *et al.* [26], the present authors hypothesise that components of the inflammatory process that underlie asthma and nasal polyps might be responsible for the restricted expression of the COX-2 gene. GC therapy might reduce the activity of one or more of these components, which would allow a partial release of the restrained COX-2 gene expression.

In summary, the present study provides evidence that glucocorticoid therapy can enhance the expression of cyclooxygenase-2 mRNA in nasal polyps. These results, together with previous observations, support the notion that the regulation of cyclooxygenase-2 in nasal polyps does not follow either the generally accepted notion that this enzyme is upregulated under conditions of inflammation, or the assumption that cyclooxygenase-2 expression is suppressed by glucocorticoids. Identification of the mechanisms involved in these distinct responses may help to better understand the role of prostanoids in the regulation of inflammation in airway diseases.

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