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Original research article

Parainfluenza virus infection enhances NSAIDs–induced inhibition of PGE2 generation and COX-2 expression in human airway epithelial cells

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ABSTRACT

Purpose: Respiratory viral infection and nonsteroidal anti-inflammatory drugs (NSAIDs) may affect arachidonic acid (AA) metabolism in the airway epithelium, however their joint effect has not been studied. We hypothesized, that alternations of AA metabolism in human airway epithelial cells (ECs) – induced by Parainfluenza virus type 3 (PIV3) – may be modified by concomitant treatment with NSAIDs.

Materials and methods: Nasal (RPMI 2650) and bronchial (BEAS-2B) epithelial cells were cultured into confluence and then infected with PIV3. Prostaglandin E2 (PGE2) and 15-hydroxyeicosatetraenoic acid (15-HETE) levels in cell supernatants were measured by ELISA and expression of cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LO) and 15-lipoxygenase (15-LO) mRNA in cells was evaluated after reverse transcription with real-time polymerase chain reactions.

Results: PGE2 generation was decreased by PIV3 infection in the upper airway epithelial cells, and increased in the lower airway epithelial cells. Both naproxen and celecoxib induced significant reduction in PGE2 release in both infected and non-infected upper and lower airway epithelial cells. However, in PIV3-infected epithelial cells celecoxib inhibited PGE2 release and COX-2 expression to significantly higher degree as compared to non-infected cells. 15-HETE generation or COX-1, 5-LO and 15-LO expression were not affected by the virus infection or by NSAIDs.

Conclusion: Virus infection in airway epithelial cells enhances inhibitory effect of NSAIDs on prostaglandin E2 generation.

1. Introduction

Respiratory virus infections are the most frequent cause of acute respiratory illness and may exacerbate chronic inflammatory diseases of the upper and lower airways [1–3]. In response to virus infections, airway epithelium generates several active molecules including interferons, cytokines, chemokines, and eicosanoids which in turn modulate virus replication, but may also induce development of local inflammation [4–6]. Prostaglandin E2 (PGE2) and 15-hydroxyeicosatetraenoic acid (15-HETE) are two major arachidonic acid (AA) metabolites generated by airway epithelial cells (ECs) in health and disease and are implicated in the pathophysiology of the airway epithelium. Prostaglandins, which are lipid metabolites derived from AA by the coordinated action of two enzymes: cyclooxygenases (COX-1 and COX-2) and prostaglandin E synthase (PGES), exert multiple effects on host immune function and are involved in diverse physiological and pathophysiological processes [7]. Respiratory viruses potently affect prostaglandin generation in the airway epithelium in a cell type and virus selective manner, and both enhancement and inhibition of cyclooxygenase-2 (COX-2) expression and PGE2 generation by respiratory viruses have been documented [8,9].

15-HETE is formed by 15-lipoxygenase (15-LO) and was reported to be involved in airway remodelling and epithelial inflammatory response to injury or bacterial infection [10,11].

Nonsteroidal anti-inflammatory drugs (NSAIDs), which by inhibiting COX-1/COX-2-derived prostaglandin generation may reduce inflammation, have been widely used for the treatment of pain and fever associated with respiratory infections. However, the effect of

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COX-1/COX-2 inhibition on the pathophysiology of respiratory infections is still controversial. Treatment of common cold with NSAIDs may relieve some (e.g. sneezing, headache, muscle or joint pain), but not other (e.g. cough, nasal discharge) symptoms, and does not affect disease duration [12]. Although beneficial effects of NSAIDs in the treatment of influenza have been suggested [13] no randomized placebo-controlled trials of NSAIDs use in influenza infection in humans have been reported. On the contrary, antipyretics have been consistently shown to increase the risk of mortality during influenza infection in experimental animals [14]. Furthermore, NSAIDs may deteriorate the course of community–acquired pneumonia [15] and prolong hospitalization in patients with pleuro-pulmonary infections [16], which often complicate influenza illness.

The use of both COX-2 and COX-1 inhibitors, have been associated with an increased risk of acute myocardial infarction (AMI), and the cardiovascular events, related to the effect of inhibitors on the generation of beneficial PGE and PGI [17–20]. Recent studies suggested that NSAIDs used during respiratory infections may have a join effect on the risk of AMI [21], and stroke [22] but the underlying mechanism has not been completely revealed [23].

Human parainfluenza virus 3 (PIV3), belonging to the Paramyxoviridae family, is an important cause of upper and lower respiratory tract infections in infants, young children and immunocompromised people [24–26] and is involved in asthma exacerbations in adults [27,28]. In experimental animals, following PIV3 infection, COX-2 cellular expression is upregulated in airway bronchiolar and bronchial ECs and macrophages, suggesting a role for COX-metabolites in regulation of the host inflammatory response during viral infection [29].

We aimed to assess the effect of PIV3 infection on major AA metabolites and enzymes in the airway ECs. We also hypothesized, that PIV3-induced alternations of AA metabolism in human airway ECs may be modified by concomitant treatment with NSAIDs.

2. Materials and methods

2.1. Cell culture

Human nasal ECs – RPMI 2650 were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and were grown as previously described. [30] When the cells reached 90% confluence they were trypsinized and transferred to 24-well culture plates for experiments. Cell viability was assessed using the MTT assay.

Human bronchial epithelial cell line – BEAS-2B was obtained from ATCC (Manassas, VA, USA) and was cultured according to standard protocol. The cells were split twice weekly and after reaching confluence they were transferred to 24-well culture plates for experiments. Human PIV3 was obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA) and propagated in monkey kidney-derived LLC-MK2 cells (ATCC, Manassas, VA, USA).

2.2. Infection of cells with PIV3 and incubation with NSAIDs

RPMI 2650 and BEAS-2B cells cultured into confluence were placed in medium without serum or additives and then infected with PIV3 at multiplicities of infection (MOI) ranging from 0.001 to 1. After 1 h of incubation at room temperature, the inoculum was removed, and the cells were further cultured in minimum essential medium (MEM) supplemented with 2% fetal calf serum (FCS). The cells for mRNA extraction or supernatants for eicosanoid analysis were harvested at relevant time points. In experiments with NSAIDs, PIV3 (0.1MOI) infected and mock-infected cells were incubated for 60 min with either selective (celecoxib: 0.1 μM, 1 μM, 10 μM) or nonselective (naproxen: 1 μM, 10 μM, 25 μM) COX inhibitor. Inhibitors were added 1 h after infection and supernatants were harvested 24 h post infection.

2.3. Measurement of mediators

PGE2 and 15-HETE concentrations in cell supernatants were determined by specific ELISA immunoassays purchased from Assay Designs Inc. (Assay Designs Inc., Ann Arbor, USA). The sensitivity of the immunoassays were as follows: PGE2 100 pg/ml; 15-HETE 69.2 pg/ml.

2.4. Real time PCR

Total cellular RNA was extracted from ECs using RNeasy mini kit (Qiagen, Hilden, Germany) and reverse transcription was performed using Omniscript RT kit (Qiagen, Hilden, Germany). Real-time fluorescent detection PCR product analysis was performed using iQ Sybr-Green Supermix (Bio-Rad, Bio-Rad, Hercules, USA) according to instrument recommendations (StepOnePlus Real Time PCR System, Applied Biosystems, Foster City, CA, USA). Relative quantification of different transcripts was determined with the $2^{-\Delta\Delta CT}$ method using β-actin as an endogenous control. Primers specific for COX-1, COX-2, 15-LO and 5-LO were purchased from Eurogentec (Eurogentec, Liege, Belgium).

2.5. Statistical analysis

Data are presented as means and standard errors of the means. Statistical analyses of the mediator concentrations were performed using Kruskal-Wallis ANOVA, followed by Wilcoxon matched-pairs signed-rank test. Alternatively, Mann-Whitney *U* test was performed. Subsequent post hoc analysis was conducted using the Bonferroni-adjusted α method. All statistical analyses were performed using Statistica version 10 (StatSoft Inc.) Values of p lower than 0.05 were considered statistically significant.

2.6. Ethical issues

The study was approved by ethics committee of the Medical University of Lodz (Lodz, Poland), approval number: RNN/121/12/KE 19/06/2012.

3. Results

3.1. Viability of virus – infected ECs

Following the infection with PIV3 (0.01MOI, 0.1MOI or 1MOI) the cell cultures were observed for 72 h under light microscope. No signs of cytopathic effects in RPMI 2650 or BEAS-2B cultures was observed up to 48 h post infection and when monolayers were stained with crystal violet, no disruption of the cell layer was observed before 72 h post infection. Viability of cells infected with PIV3 – as assessed with MTT – has not changed over 48 h post infection.

3.2. Effect of PIV3 infection on AA metabolism in upper airway ECs

Virus–infected RPMI 2650 cells tended to generate less PGE2 already 4 h post infection, as compared to non–infected cells, but statistically significant difference was observed at 8 h after infection (20%, 30.5% and 34% decrease for 0.001MOI, 0.01MOI and 0.1MOI, respectively) and was still present at 48 h after 0.01MOI (27.9% decrease) (Table 1).

In parallel to PGE2 release, the expression of COX-2 mRNA in RPMI 2650 cells statistically significantly decreased already at 4 h after PIV3 infection (by 42%, 42% and 41% for 0.001MOI, 0.01MOI and 0.1MOI, respectively) and was still statistically significantly decreased 8 h post infection. We observed no effect of PIV3 infection on 15-HETE release into cell supernatants and on COX-1 mRNA 5-LO mRNA or 15-LO mRNA expression at any time post infection (data not shown).

Both, infected (0.1MOI) and non-infected, RPMI 2650 cells

Table 1
The effect of PIV3 (0.001MOI, 0.01MOI, 0.1MOI) infection on PGE2 generation and COX-2 mRNA expression in RPMI 2650 cells (n = 8); the results are expressed as mean +/− SEM; * $p < 0.05$.

RPMI	PGE2 (pg/mL)				
	4 h	8 h	24 h	48 h	72 h
control/medium	1991.6 ± 88.9	1858 ± 87.8	1497.1 ± 421.5	2153.4 ± 397.3	1163.8 ± 398.9
PIV3 0.001MOI	1779 ± 140.4	1469.8 ± 112.6 *	1566.6 ± 379.9	2317.8 ± 487.5	957.6 ± 334.0
PIV3 0.01MOI	1690.4 ± 128.2	1291 ± 132.5 *	1424.2 ± 337.6	1552.1 ± 405.1 *	1078.7 ± 319.6
PIV3 0.1MOI	1522.2 ± 160.3	1220.2 ± 81.2 *	1764.8 ± 422.2	1963.4 ± 533.9	1293.8 ± 295.1
	COX-2 mRNA expression (2-ΔΔCT)				
	4 h	8 h	24 h	48 h	72 h
control/medium	1	1	1	1	1
PIV3 0.001MOI	0.58 ± 0.08 *	0.44 ± 0.10 *	0.71 ± 0.18	1.15 ± 0.36	0.57 ± 0.18
PIV3 0.01MOI	0.58 ± 0.12 *	0.43 ± 0.16 *	0.81 ± 0.32	0.63 ± 0.16	0.70 ± 0.23
PIV3 0.1MOI	0.59 ± 0.12 *	0.61 ± 0.15 *	1.6 ± 0.55	0.81 ± 0.22	0.82 ± 0.06

incubated with naproxen (a non-selective COX inhibitor) released statistically less PGE2 into supernatants. The PGE2 inhibition ranged from 75% to 84% for non–infected and from 58% to 76% for infected cells, but no differences in the degree of inhibition were observed between the infected and non-infected cell cultures (Fig. 1a).

Celecoxib, a COX-2 selective NSAID, statistically significantly decreased PGE2 release from RPMI 2650 cells, but in contrast to naproxen, the reduction of PGE2 release was statistically significantly more pronounced (by 54%, 38% and 74% for 0.01, 0.1, 1 μM of celecoxib, respectively) in virus-infected as compared to non-infected cultures (Fig. 1b).

Combined effects of virus and NSAIDs on COX expression in upper airway ECs was not assessed.

Naproxen and celecoxib did not affect 15-HETE release either in infected or non-infected cells (data not shown) and the effect of NSAIDs on COX expression was not assessed in these experiments.

3.3. Effect of PIV3 infection on AA metabolism pathways in lower airway ECs

Virus infection of the BEAS-2B, in contrast to the RPMI 2650 cells, statistically significantly increased the mean concentrations of PGE2 in cell supernatants at 8 h and 24 h after infection. In parallel, PIV3 infection increased the expression of COX-2 mRNA at 8 h and 24 h post infection (Table 2).

There was no effect of virus infection on 15-HETE generation or COX-1 mRNA, 5-LO and 15-LO mRNA expression in ECs (data not shown).

Cell incubation with all three concentrations of naproxen statistically significantly inhibited PGE2 release by both infected (PIV3

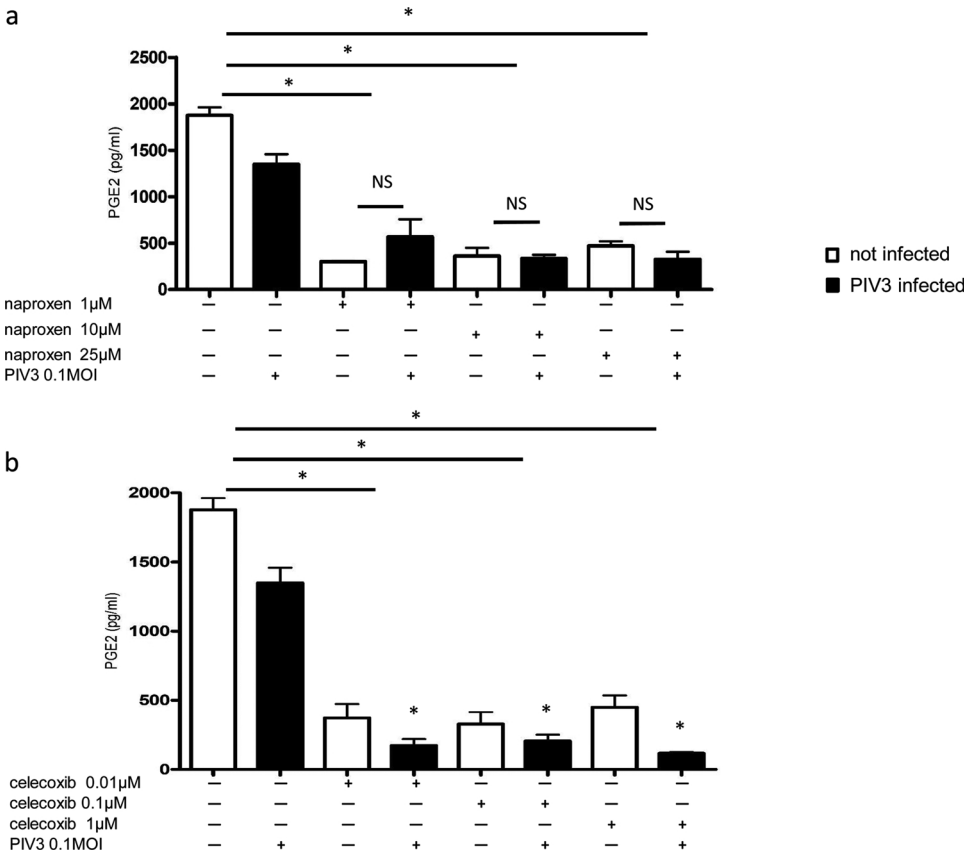

Fig. 1. (a) Inhibition of PGE2 release in not-infected and PIV3-infected (0.1MOI) RPMI 2650 cells by naproxen. Data are shown as mean (+/−SEM) of n = 8 experiments, *$p < 0.05$. (b) Inhibition of PGE2 release in not-infected and PIV3-infected (0.1MOI) RPMI 2650 cells by celecoxib. Data are shown as mean (+/−SEM) of n = 8 experiments,*$p < 0.05$.

Table 2
The effect of PIV3 (0.001MOI, 0.01MOI, 0.1MOI) infections on PGE2 generation and COX-2 mRNA expression in BEAS-2B cells (n = 8); the results are expressed as mean +/−SEM; * $p < 0.05$.

	PGE2 (pg /mL)				
	4 h	8 h	24 h	48 h	72 h
control/medium	1082 ± 151.6	1115.0 ± 198.3	809.0 ± 242.7	848.2 ± 58.21	759.6 ± 80.49
PIV3 0.001MOI	1050 ± 207.6	981.7 ± 235.6	1180.0 ± 285.1	783.7 ± 140.4	666.8 ± 90.44
PIV3 0.01MOI	1307 ± 263.8	1690.0 ± 128.2 *	1619.0 ± 169.6 *	877.4 ± 134.5	814.5 ± 229.9
PIV3 0.1MOI	1390 ± 275.2	1992 ± 88.98 *	1305.0 ± 283.7 *	701.2 ± 137.7	801.8 ± 121.6
	COX-2 mRNA expression (2-ΔΔCT)				
	4 h	8 h	24 h	48 h	72 h
control/medium	1	1	1	1	1
PIV3 0.001MOI	1.06 ± 0.13	1.42 ± 0.32 *	1.29 ± 0.17 *	1.50 ± 0.28 *	0.39 ± 0.07
PIV3 0.01MOI	0.62 ± 0.10	1.54 ± 0.18 *	1.44 ± 0.08 *	0.98 ± 0.08	0.43 ± 0.07
PIV3 0.1MOI	0.84 ± 0.15	1.35 ± 0.18 *	2.13 ± 0.37 *	1.46 ± 0.23 *	0.63 ± 0.05

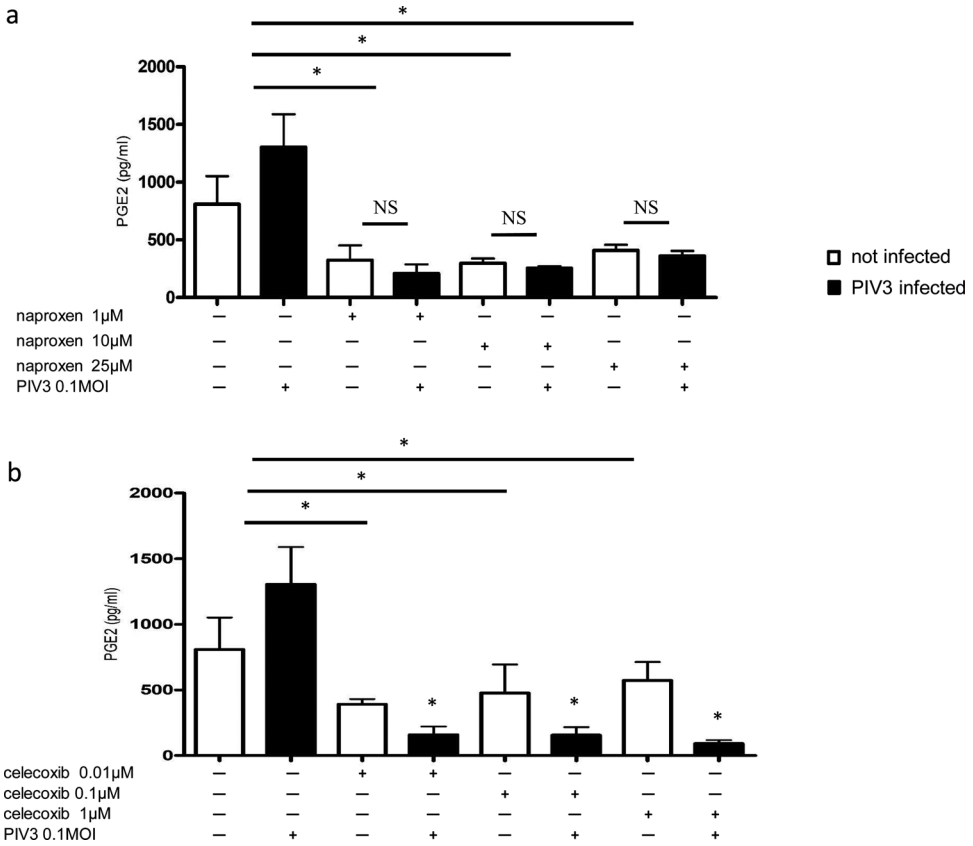

Fig. 2. (a) Inhibition of PGE2 generation in PIV3-infected (0.1MOI) and mock-infected BEAS-2B cells by naproxen. Data are shown as mean (+/−SEM) of n = 10 experiments, *$p < 0.05$. (b) Inhibition of PGE2 generation in PIV3-infected (0.1MOI) and mock-infected BEAS-2B cells by celecoxib. Data are shown as mean (+/−SEM) of n = 8 experiments, *$p < 0.05$.

0.1MOI) and non–infected BEAS-2B cells (Fig. 2a). The inhibition tended to be higher in the infected cells (the mean PGE2 inhibition was 72.5%, 80, 6%; 84% for 1 μM, 10 μM and 25 μM of naproxen, respectively) than in the non-infected cells (49%, 63.3% and 60.1% inhibition, respectively), but the differences between the infected and non-infected cells were not statistically significant. In parallel, COX-2 mRNA expression (but not COX-1 mRNA) was statistically significant, and to similar degree, decreased by naproxen in the virus-infected and non-infected cells (Fig. 3a).

Celecoxib–induced decrease of PGE2 release was statistically significantly higher in the infected as compared to non–infected cells (Fig. 2b). The mean decrease in PGE2 generation in the virus-infected cells was 88%, 89% and 93% and in the non–infected cells 51%, 41% and 29% for 0.01, 0.1, 1 μM of celecoxib, respectively. PGE2 production in the virus-infected cells was lower by 59.6%, 67.4%, 84.1% (for 0.01, 0.1 and 1 μM, respectively) as compared to the non–infected cells ($p < 0.05$). COX-2 mRNA expression was statistically significantly decreased by all three concentrations of celecoxib in both, infected and non-infected, cells as compared to controls. However, two highest celecoxib concentrations (0.1 and 1 μM) inhibited COX-2 expression to statistically significantly higher degree in the infected as compared to the non-infected cells (Fig. 3b).

4. Discussion

This is the first study that assessed the combined effect of respiratory virus infection and NSAIDs on prostaglandin generation and COX-2 expression in the human airway ECs. We have demonstrated, that virus infected ECs were more susceptible to inhibitory effect of celecoxib, a selective COX-2 inhibitor, as compared to mock-infected

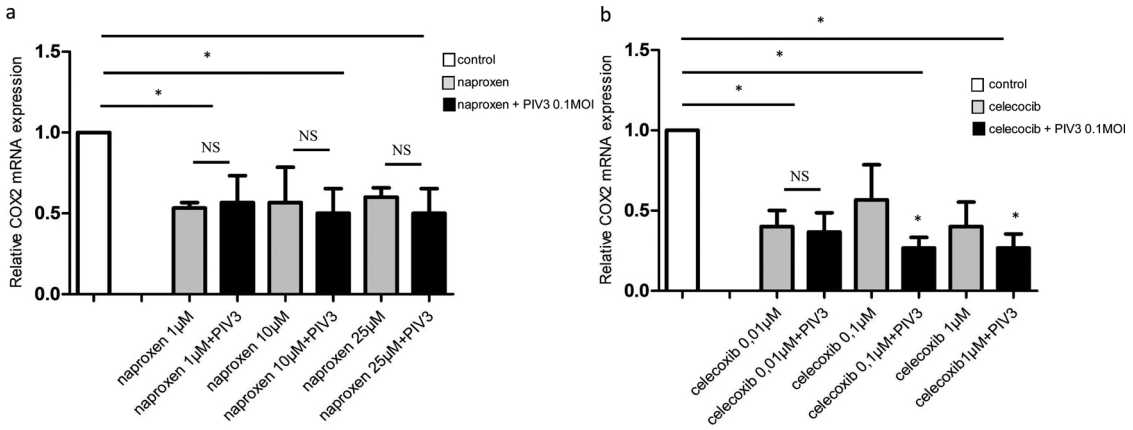

Fig. 3. (a) Inhibition of COX-2 mRNA expression by naproxen in not-infected and infected with PIV3 0.1MOI BEAS-2B cells. Data are shown as mean (+/−SEM) of n = 8 experiments, $^*p < 0.05$. (b) Inhibition of COX-2 mRNA expression by celecoxib in not-infected and infected with PIV3 0.1MOI BEAS-2B cells. Data are shown as mean (+/−SEM) of n = 8 experiments, $^*p < 0.05$.

cells. There was also a tendency to enhance the PGE2 inhibition in ECs by naproxen, a non-selective NSAID in virus infected ECs.

Both, upper airway (RPMI 2650) and lower airway (BEAS-2B), ECs released PGE2 and expressed COX-1 and COX-2 mRNA and these observations are consistent with results of previous studies that demonstrate low levels of COX-1 and COX-2 expression in untreated airway ECs [21,31].

PIV3 infection of the upper airway ECs decreased prostaglandin generation and COX-2 expression, while in the lower airway ECs virus infection increased PGE2 with parallel enhancement of COX-2 mRNA expression. Inhibitory effect of PIV3 on PGE2 generation in ECs is similar to the effect previously reported for Ebstein-Barr virus (EBV, a herpes virus) infection in human monocytes and adenovirus-uteroglobin in lung cancer cells [32,33]. On the contrary, stimulatory effects of PIV3 on COX-2 expression observed in our present study in the lower airway ECs are in line with the study by Radi et al. [29] who documented upregulation of COX-2 by PIV3 in lower airway ECs and in macrophages and by Respiratory Syncytial Virus (RSV) infection in experimental animals. Similarly, Influenza A virus infection in human lung ECs or RSV infection of human alveolar type II – like ECs have been shown to stimulate the expression of COX-2 and PGE2 release [9,34]. These data suggest that the effect of viral infection on prostaglandin pathways may depend on the virus strain and/or is cell-type specific.

Both non-selective (naproxen) and COX-2 selective (celecoxib) NSAIDs, as expected, inhibited statistically significantly prostaglandin generation in non-infected upper and lower airway ECs. However, in the virus infected upper airway ECs, celecoxib depressed PGE2 generation to a higher degree than in the non-infected cells. Suppressive effect of naproxen, on PGE2 synthesis, was not statistically significantly affected by viral infection. The apparent lack of synergistic effect of naproxen and PIV3 infection on PGE2 generation might be related to the high degree of PGE2 inhibition by concentrations of naproxen used in our experiments. Similarly, in lower airway ECs, celecoxib inhibited PGE2 synthesis to a higher degree in the virus infected cells as compared to the mock-infected cells and the amount of prostaglandins generated was on average lower by 70%. In parallel, COX-2 mRNA expression was more efficiently inhibited by celecoxib in the virus infected cells. Naproxen induced similar inhibitory effect on PGE2 release and COX-2 expression in virus infected and non-infected cells.

Our present study documents a previously not reported interference of viral infection with COX pathway of AA metabolism in airway ECs, reflected by increased susceptibility of prostaglandin synthesis to inhibitory effect of NSAIDs. This effect was statistically significant in celecoxib treated cells, however similar, but not statistically significant, tendency was also observed after cell incubation with naproxen, a non-selective COX inhibitor. Enhanced inhibition of PGE2 generation by celecoxib seems to result from a higher suppression of COX-2 expression in the virus infected cells. However, the mechanism leading to virus-increased susceptibility of epithelial COX to inhibitory effect of NSAIDs remains to be elucidated. Although unstimulated RPMI 2650 and BEAS-2B cells expressed 15-LO and released 15-HETE, neither 15-LO expression nor 15-HETE generation were affected by PIV3 infection, suggesting that PIV-3 infection selectively affects COX pathway of AA metabolism in airway ECs.

Our study may provide some insights into the pathomechanism of recently reported synergistic effect of respiratory virus infections and treatment with NSAIDs on the increased risk of atherothrombotic events such as AMI. In the study by Wen et al. [22] the authors documented that NSAIDs used during acute respiratory infection increase the risk for AMI 3.4-fold if taken orally, and 7.2-fold with parenteral dosing. It is tempting to speculate, that NSAIDs taken during respiratory infection may decrease to lower degree generation of vasoprotective COX metabolites e.g. prostacyclin or prostaglandins, thus increasing the risk of vascular episode.

Interaction of viral infection with AA metabolism resulting in the change in expression in AA-related enzymes in ECs may also shed a new light on the pathomechanisms of aspirin-induced asthma, recently referred to as NSAID-exacerbated respiratory disease (NERD). [35] The pathomechanism of acute aspirin-induced respiratory reaction has been attributed to decreased generation of protective PGE2 resulting from inhibition of COX-1. However, chronic airway inflammation in NERD patients seems to be associated with prostaglandin deficiency resulting from decreased expression of COX-2 in the airway ECs of patients with NERD [36]. It has been hypothesized that NERD develops as the result of viral infection [37], but the effect of infection on the AA metabolism in aspirin-sensitive patients has not been studied. Our observations are in line with the hypothesis that viral infection may alter AA metabolism leading to a decreased expression of COXs and prostaglandin deficiency, characteristic for NERD patients.

5. Conclusions

In conclusion, our study demonstrated that viral infection can modulate AA metabolism in airway epithelium rendering the ECs more susceptible to the inhibitory effect of celecoxib, a selective COX-2 inhibitor.

Conflict of interests

The authors declare no conflict of interests.

Financial disclosure

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The author contribution

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Data Collection: Anna Lewandowska-Polak, Marzanna Jarzębska, Małgorzata Brauncajs, Małgorzata Pawełczyk.

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Data Interpretation: Marek L. Kowalski, Anna Lewandowska-Polak, Joanna Makowska.

Manuscript Preparation: Anna Lewandowska-Polak, Marek L. Kowalski.

Literature Search: Anna Lewandowska-Polak, Marek L. Kowalski.

Funds Collection: Marek L. Kowalski.

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