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Decreased Gene Expression of Lipoxin A4 Receptor May Contribute to Nonallergic Rhinitis Pathogenesis

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ABSTRACT

Background: Rhinitis is a prevalent chronic inflammatory illness of the nasal mucosa. Arachidonic acid-derived lipoxin A4 (LXA4) has long been recognized to exert crucial anti-inflammatory and pro-resolving effects on inflammatory responses through a specific receptor named LXA4 receptor/formyl peptide receptor-2 (ALX/FPR2). This study aimed to determine the serum level of LXA4 and the relative mRNA expression level of *FPR2* in peripheral blood cells of patients with rhinitis (allergic and nonallergic) compared to healthy individuals.

Materials and Methods: The study groups consisted of 37 patients with Allergic Rhinitis (AR), 16 patients with Nonallergic Rhinitis (NAR), and 20 sex- and age-matched healthy individuals. The measurement of LXA4 serum level was performed by the Enzyme-Linked Immunosorbent Assay (ELISA) technique, and the analysis of *FPR2* mRNA expression level was performed by quantitative real-time PCR method.

Results: The serum concentrations of LXA4 decreased in AR and NAR patients compared to healthy controls; however, this difference was not statistically significant ($P>0.05$). Besides, the mRNA expression level of *FPR2* in peripheral blood cells of patients with nonallergic rhinitis was significantly lower than that in allergic rhinitis ($P<0.05$).

Conclusion: Our results suggest that reduced gene expression of *FPR2* may contribute to developing persistent and chronic nasal mucosa inflammation seen in NAR patients. Therefore, stable analogs of LXA4 and its receptor agonist may help develop new therapeutic approaches for rhinitis.

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Introduction

Rhinitis is a chronic inflammation of the nasal mucosa characterized by the excessive mucosal influx of inflammatory cells such as eosinophils, basophils, mast cells, neutrophils, macrophages, B and T cells [1, 2]. The two major forms of rhinitis have commonly been defined in the clinic, including Allergic Rhinitis (AR) and Nonallergic Rhinitis (NAR) [3]. Acute inflammation is a salutary response of the host to eliminate and eradicate the invading pathogens or damaging agents. Although acute inflammation is necessary to host survival and health, non-resolving inflammation can lead to many chronic inflammatory disorders, including asthma, multiple sclerosis, rhinitis, rheumatoid arthritis, and atherosclerosis [4].

Recently, researchers have found that omega-3 and omega-6 fatty acids-derived compounds, known as Specialized Pro-resolving lipid Mediators (SPMs) or immunoresolvents, play crucial anti-inflammatory and pro-resolving actions. Lipoxins (LXs) are the lead members of SPMs and are imperative for the timely resolution of acute inflammation [5].

LXs are generated enzymatically from an omega-6 fatty acid called Arachidonic Acid (AA) by transcellular biosynthesis after cell-cell interaction of various cells, including neutrophils, platelets, eosinophils, and airway epithelial cells [6, 7]. The anti-inflammatory functions of LXs are exerted via LXA4 receptor/formyl peptide receptor-2 (ALX/FPR2; also known as formyl peptide receptor like 1 or FPRL1), which is a G Protein-Coupled Receptor (GPCR). FPR2 is expressed by numerous cells, including human neutrophils, Natural Killer cells (NK cells), eosinophils, monocytes, airway epithelium, and macrophages, type 2 Innate Lymphoid Cells (ILC2), synovial fibroblasts, intestinal epithelial cells, and T cells. Additional receptors can also interact with LXs, which include G Protein-coupled Receptor-32 (GPR32), Aryl Hydrocarbon Receptor (AHR), estrogen receptor, and Cysteinyl Leukotriene Receptor (CysLTR) [8, 9].

In a murine model of asthma, Intravenous (IV) injection of a stable analog of LXA4 (LXa) reduced airway infiltration of leukocytes and generation of their mediators, including Interleukin (IL)-5, IL-13, eotaxin, prostanoids, and CysLTs, confirming its ability to inhibit Airway Hyper-Responsiveness (AHR) and pulmonary inflammation. In addition, pulmonary inflammation and tissue infiltration of eosinophils triggered by eicosanoid decreased in transgenic mice expressing human *FPR2* in their leukocytes [10]. LXs also increase the level of an anti-inflammatory transcription factor called Peroxisome Proliferator-Activated Receptor-γ (PPAR-γ) [8]. Furthermore, LXs can serve as an antagonist for cysteinyl leukotriene receptor termed CysLT1R, thereby competing with Leukotrienes (LTs) [11]. Indeed, LXA4 functions as an agonist with the highest affinity for FPR2 and also can reduce the production of Leukotriene B4 (LTB4) by human neutrophils [12, 13]. In severe cases of asthma, Bronchoalveolar Lavage Fluid (BALF) and activated whole blood levels of LXA4, as well as the gene expression level of *FPR2* in peripheral blood granulocytes, significantly decreased, suggesting that these striking reductions exaggerate asthma [14, 15].

This study aimed to investigate the importance of LXA4 and its receptor in rhinitis pathogenesis. Hence, the serum levels of LXA4 and gene expression of *FPR2* were evaluated in peripheral blood cells of patients with rhinitis compared to healthy individuals.

Materials and Methods

Study participants

Subjects were selected among outpatients who attended the Allergy Clinic of Dr Mohammad Kermanshahi Hospital located in Kermanshah Province, Iran (Table 1). Clinicians discerned all patients based on the Practical Guideline for Managing Allergic Rhinitis [16]. A total of 29 common allergens were utilized for a Skin Prick Test (SPT) (listed in Table 2). Meanwhile, histamine dihydrochloride (10 mg/mL) and normal saline were applied as positive and negative controls; respectively. Atopy was assessed as having a wheal reaction equal to or greater than 3 mm in diameter. The positive and negative SPT was considered as allergic rhinitis and nonallergic rhinitis, respectively. The controls were healthy and lacked a history of allergic diseases. The study was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (KUMS), and written informed consent was obtained from all participants.

Sample collection

Peripheral venous blood (10 mL) was collected from all participants and then aliquoted into the CBC and clot tubes. To separate the serum, fresh blood samples in clot tubes were centrifuged at 4000 rpm for 5 minutes. The separated sera were kept at -70°C until further analysis.

Measurement of LXA4 and total IgE concentrations in serum

The Enzyme-Linked Immunosorbent Assay (ELISA) kits of total IgE and LXA4 were purchased from Padtan Elm and Eastbiopharm companies, respectively. The serum levels of total IgE and LXA4 were measured in duplicate by the ELISA method following their manufacturer's protocol. Finally, optical density and the concentration of each sample were read at 450 nm wavelength using an ELISA reader device named STAT FAX 4200.

Evaluation of ALX/FPR2 gene expression

Total RNA was isolated from fresh whole blood using the column method (Favorgen Biotech Corp., Taiwan) according to the manufacturer's recommendations. Reverse transcription was performed by a cDNA synthesis kit (Favorgen Biotech Corp., Taiwan) with a random hexamer primer, according to the manufacturer's instruction. All RNA and cDNA samples were stored in a freezer at -70°C until used. Quantitative real-time PCR was performed by light cycler 96 (Roche) using SYBR® green real-time master mix (Favorgen Biotech Corp., Taiwan). The desired primers were designed by using Beacon Designer™ Software (Primer Biosoft, USA). The designed primer sequences for the *FPR2* gene were forward 5′- GCTTAGCTGCTGGTGCT -3′ and reverse 5′- CAGACTCATAGGACACTTCTTCA -3′. The relative quantity of target mRNA in samples was computed and normalized to the corresponding *GAPDH* mRNA transcript level as a control housekeeping gene. Primer sequences designed for the *GAPDH* gene were forward 5′- CTTCCAGGAGCGAGATCCCT -3′ and *GADPH* reverse 5′- AATGAGCCCCAGCCTTCTC -3′. Eventually, relative mRNA expression ratios were computed using the Pfaffl method with this formula ($R= (E_{target})^{\Delta Ct\ target\ (control-sample)}/(E_{Ref})^{\Delta Ct\ Ref\ (control-sample)}$) [17].

Data analysis

All data were expressed as Mean±SD. The Kruskal-Wallis test was used to determine differences between groups. The correlations were according to the Spearman rank test. Statistical analysis and graph drawing were done using SPSS software v. 16 (SPSS, Chicago, IL, USA) and GraphPad Prism version 6 (GraphPad Software, La Jolla, California, USA). P values less than 0.05 were considered significant.

Results

Increased serum levels of total IgE in allergic rhinitis patients

Total IgE serum levels were measured in patients with allergic rhinitis and nonallergic rhinitis and compared the results to healthy controls (Figure 1). A significant increase in total IgE serum levels was observed in patients with allergic rhinitis compared with the healthy controls and nonallergic rhinitis patients ($P<0.05$ and $P<0.01$, respectively). However, there was no significant difference in the serum levels of total IgE between nonallergic rhinitis patients and controls.

No significant difference in the serum levels of LXA4 between patients and controls

LXA4 serum levels were determined in patients with rhinitis (allergic and nonallergic) and healthy subjects (Figure 2). The results illustrated that LXA4 serum levels decreased in rhinitis patients compared to healthy controls. However, this difference was not statistically significant ($P>0.05$). Furthermore, LXA4 serum levels were not significantly different between allergic rhinitis and nonallergic rhinitis patients. No significant correlation was found between serum levels of LXA4 and total IgE in this study.

Table 1. Demographic and clinical characteristics of the study participants

Variables	Healthy Subjects (n=20)	Patients (n=53)		P
		Allergic Rhinitis (n=37)	Non-allergic Rhinitis (n=16)	
Age (Y) Mean±SD	30.92±11.40	34.05±11.27	30.81±13.85	0.49
Sex (Female/Male)	8/12	18/19	8/8	0.84
Race, % white	100	100	100	-
Body mass index (BMI)	23.79	25.48	25.85	0.42
Rhinitis duration (y) Mean±SD	-	7.11±6.05	5.38±3.86	0.29
Seasonal/chronic (n)	0	23/14	1/15	<0.001
Asthma (yes/no)	0	3/34	2/14	0.61
Smoking (yes/no)	0/20	4/33	0/16	0.17

Table 2. List of 29 common allergens with positive Skin Prick tests (Spts)

Mite Mix	7-Grass Mix	Ash	Pepper	Tomato	Acacia
Poplar	plantain	Soya	Pea	Malt	Barely
Bermuda grass	Oak	Aspergillus	Cypress	Maple	Cockroach
Peanut	Almond	Peach	Ginger	Garlic	Tree mix
Timothy	Walnut	P.Rye	Orange	Cypress	

FPR2 gene expression level in non-allergic rhinitis decreased compared to allergic rhinitis patients

Figure 3 shows the relative mRNA expression level of *FPR2* in leukocytes of patients with rhinitis and healthy individuals. *FPR2* mRNA expression level was significantly lower in patients with nonallergic rhinitis than in allergic rhinitis patients (P<0.05). Besides, the mRNA expression level of *FPR2* increased, but not significantly, in allergic rhinitis patients than healthy individuals. No significant difference in *FPR2* mRNA expression was found between patients with nonallergic rhinitis and controls.

Discussion

The current study revealed that patients with allergic rhinitis and nonallergic rhinitis have lower serum levels of LXA4 than healthy subjects. However, this difference was not statistically significant. Moreover, the gene expression level of LXA4 receptor, *FPR2*, in leukocytes of patients with nonallergic rhinitis was low compared to allergic rhinitis patients.

In recent years, the mechanisms involved in the resolution of acute inflammation have attracted great interest in managing and treating inflammatory-based disorders [18, 19]. A timely and successful resolution of acute inflammation is an active and dynamic process governed by omega-6 and omega-3 fatty acids-derived "anti-inflammatory and pro-resolving" lipid mediators such as Lipoxins (LXs) and resolvins [5, 20]. Interestingly, increased airway biosynthesis of LXA4 and expression of its receptor, FPR2, are shown after allergen sensitization and challenge. Signaling through the LXA4-FPR2

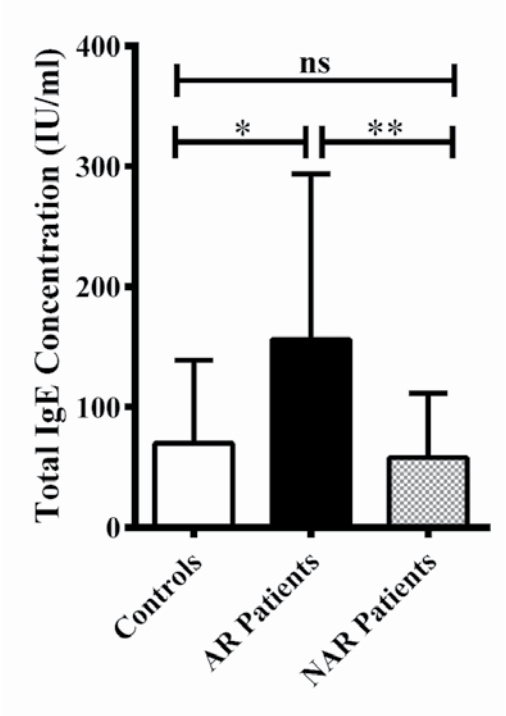

Figure 1. Serum concentrations of total IgE in control, Allergic Rhinitis (AR), and Nonallergic Rhinitis (NAR) groups

Total IgE serum concentration significantly increased in AR patients compared to healthy controls and NAR patients (P=0.01 and P=0.005, respectively). However, there was no significant difference between healthy controls and NAR patients in the serum total IgE concentrations. Data are expressed as the Mean±SD (*P<0.05 and **P<0.01).

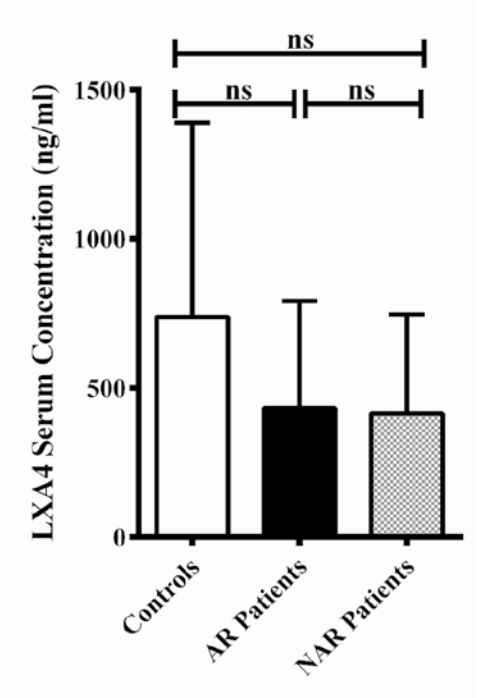

Figure 2. LXA4 serum levels in control, Allergic Rhinitis (AR), and Nonallergic Rhinitis (NAR) groups

Serum levels of LXA4 decreased in AR and NAR patients compared to healthy controls; however, it was not statistically significant. Also, there was no significant difference between AR and NAR patients in the serum levels of LXA4. Data are expressed as the Mean±SD (ns= not statistically significant).

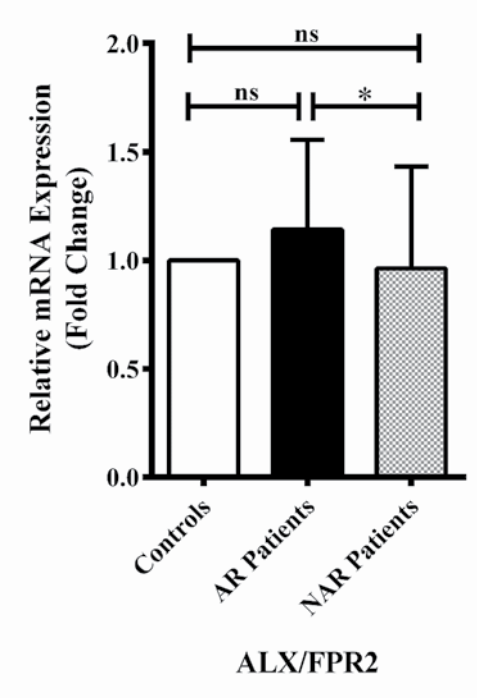

Figure 3. *FPR2* gene expression level in peripheral blood cells of control, Allergic Rhinitis (AR), and Nonallergic Rhinitis (NAR) subjects

The gene expression level of *FPR2* increased in AR patients relative to healthy controls. However, it was not statistically significant. Moreover, the *FPR2* gene expression level was significantly diminished in NAR patients compared to AR patients (P=0.014). Data are expressed as the Mean±SD (ns= not statistically significant, *P<0.05). ALX/FPR2:LXA4 receptor/formyl peptide receptor-2.

axis decreased allergic airway and pulmonary inflammation, as demonstrated by reducing IL-5, IL-13, CysLTs, eotaxin, prostanoids, serum IgE production, as well as eosinophils and T cells infiltration [10].

Lipoxin concentrations are significantly lower in the sputum of patients with Severe Asthma (SA) than those with mild asthma [21]. Furthermore, in activated whole blood of patients with SA, the LXA4 generation was significantly reduced compared to those with moderate asthma [15]. Also, LXA4 levels in plasma isolated from stimulated whole blood of SA patients have been indicated to be significantly lower compared to patients with mild and moderate asthma [7]. Besides, BALFs levels of LXA4 are significantly lower in SA patients than subjects with non-severe asthma [14]. It was illustrated that LXA4 plasma levels were significantly reduced instantly after exercise challenge in both asthmatic children with positive and negative responses to exercise, suggesting the association between impaired biosynthesis pathways of LXs and development of exercise-induced bronchoconstriction in asthmatic children [22]. Furthermore, the LXA4 levels in stimulated whole blood of children with different degrees of asthma severity (mild, moderate, and severe) are gradually reduced with the exacerbation of asthma [23]. Moreover, it was shown that the urinary concentrations of LXA4 relative to the concentrations of 15 epimers of LXA4 (15-epi-LXA4) were significantly lower in asthmatic patients [24].

A previous study by Shimizu et al. revealed a lower concentration of LXA4 in the nasal secretions of patients having chronic rhinosinusitis with nasal polyposis relative to AR patients [25]. These findings indicate that a defect in the biosynthesis pathway of LXA4 leading to lower LXA4 levels may be implicated in the pathogenesis of chronic airway inflammation. Indeed, stable analogs of LXA4 suppress the extreme accumulation, trafficking, and activation of eosinophils and T cells into the lungs of sensitized and challenged mice [26]. Contrary to previous findings, we found no significant difference between rhinitis patients and healthy subjects in the serum concentrations of LXA4. This discrepancy may partly be due to the different involved sites in rhinitis relative to asthma so that asthma is a chronic inflammatory illness of the lower airways, while rhinitis is a chronic inflammation of the upper airways [27]. The difference in the types of investigated samples can also be another reason (e.g. serum, nasal secretions, etc).

ALX/FPR2 is primarily expressed by multiple cells such as human neutrophils, eosinophils, monocytes, macrophages, T and NK cells, ILC2, fibroblasts, and airway epithelial cells [28-30]. In addition to LXA4, FPR2 is also specifically activated by an omega-3 fatty acids-derived metabolite termed resolvin D1 [31]. In line with our findings, some studies show a reduced FPR2 receptor expression in children and adults with SA [14, 21]. Besides, a lower gene expression of *FPR2* has formerly been reported in inferior turbinates than in nasal polyps [25]. However, inconsistent with our study, another study found no significant difference in gene expression of *FPR2* in Peripheral Blood Mononuclear Cells (PBMCs) of control, mild and severe asthma groups [12].

Based on the findings presented in Table 1, most nonallergic rhinitis patients (93.75%) enrolled in our study had chronic rhinitis, whereas most allergic rhinitis patients (62.16%) had seasonal rhinitis. This issue (chronicity stage of the disease) can be a rational reason for reducing *FPR2* gene expression in the nonallergic rhinitis group. In other words, chronic inflammation in nonallergic rhinitis patients can arise from decreasing the gene expression of *FPR2*.

Conclusion

In conclusion, our findings are the first demonstration of diminished gene expression of *FPR2* in association with nonallergic rhinitis disease. Given the anti-inflammatory and pro-resolving effects of FPR2 in airway inflammation, its reduction may increase the susceptibility of nonallergic rhinitis patients to beget persistent and chronic upper airways inflammation. Our results suggest that stable analogs of LXA4 and its receptor agonist may help develop new therapeutic approaches for rhinitis. Further studies with larger sample sizes and the investigation of pro-inflammatory lipid mediators, particularly LTB4 and cytokines, as well as other LXA4 receptors and LXA4-producing enzymes, are warranted to uncover the precise functions of inflammation-resolution mediators and to be addressed these molecules as therapeutic targets.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of the Kermanshah University of Medical Sciences (Code: KUMS.REC.1395.96).

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Authors' contributions

Conceptualization and supervision: Farhad Salari; Investigation, writing – original draft, and writing – review & editing: All authors; Data collection: Samira Jahangiri; Data analysis: Ali Gorgin Karaji, Alireza rezaiemanesh and Farhad Salari; Funding acquisition and resources: Farhad Salari

Conflict of interest

The author declare there are no conflict of interests.

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References

[1] Kakli HA, Riley TD. Allergic rhinitis. Prim Care. 2016; 43(3):465-75. [PMID]

[2] Sin B, Togias A. Pathophysiology of allergic and nonallergic rhinitis. Proc Am Thorac Soc. 2011; 8(1):106-14. [PMID]

[3] Tran NP, Vickery J, Blaiss MS. Management of rhinitis: Allergic and nonallergic. Allergy Asthma Immunol Res. 2011; 3(3):148-56. [PMID] [PMCID]

[4] Alessandri AL, Sousa LP, Lucas CD, Rossi AG, Pinho V, Teixeira MM. Resolution of inflammation: Mechanisms and opportunity for drug development. Pharmacol Ther. 2013; 139(2):189-212. [DOI:10.1016/j.pharmthera.2013.04.006] [PMID]

[5] Lotfi R, Rezaiemanesh A, Mortazavi SH, Karaji AG, Salari F. Immunoresolvents in asthma and allergic diseases: Review and Update. J Cell Physiol. 2019; 234(6):8579-96. [DOI:10.1002/jcp.27836] [PMID]

[6] Barnig C, Frossard N, Levy BD. Towards targeting resolution pathways of airway inflammation in asthma. Pharmacol Ther. 2018; 186:98-113. [DOI:10.1016/j.pharmthera.2018.01.004] [PMID]

[7] Celik GE, Erkekol FO, Misirligil Z, Melli M. Lipoxin A4 levels in asthma: Relation with disease severity and aspirin sensitivity. Clin Exp Allergy. 2007; 37(10):1494-501. [DOI:10.1111/j.1365-2222.2007.02806.x] [PMID]

[8] Chandrasekharan JA, Sharma-Walia N. Lipoxins: Nature's way to resolve inflammation. J Inflamm Res. 2015; 8:181-92. [DOI:10.2147/JIR.S90380] [PMID] [PMCID]

[9] Duvall MG, Levy BD. DHA- and EPA-derived resolvins, protectins, and maresins in airway inflammation. Eur J Pharmacol. 2016; 785:144-55. [DOI:10.1016/j.ejphar.2015.11.001] [PMID] [PMCID]

[10] Levy BD, De Sanctis GT, Devchand PR, Kim E, Ackerman K, Schmidt BA, et al. Multi-pronged inhibition of airway hyper-responsiveness and inflammation by lipoxin A(4). Nat Med. 2002; 8(9):1018-23. [DOI:10.1038/nm748] [PMID]

[11] Bonnans C, Chanez P, Chavis C. Lipoxins in asthma: Potential therapeutic mediators on bronchial inflammation? Allergy. 2004; 59(10):1027-41. [DOI:10.1111/j.1398-9995.2004.00617.x] [PMID]

[12] Bonnans C, Vachier I, Chavis C, Godard P, Bousquet J, Chanez P. Lipoxins are potential endogenous antiinflammatory mediators in asthma. Am J Respir Crit Care Med. 2002; 165(11):1531-5. [DOI:10.1164/rccm.200201-053OC] [PMID]

[13] Romano M, Cianci E, Simiele F, Recchiuti A. Lipoxins and aspirin-triggered lipoxins in resolution of inflammation. Eur J Pharmacol. 2015; 760:49-63. [DOI:10.1016/j.ejphar.2015.03.083] [PMID]

[14] Planagumà A, Kazani S, Marigowda G, Haworth O, Mariani TJ, Israel E, et al. Airway lipoxin A4 generation and lipoxin A4 receptor expression are decreased in severe asthma. Am J Respir Crit Care Med. 2008; 178(6):574-82. [DOI:10.1164/rccm.200801-061OC] [PMID] [PMCID]

[15] Levy BD, Bonnans C, Silverman ES, Palmer LJ, Marigowda G, Israel E; Severe Asthma Research Program, et al. Diminished lipoxin biosynthesis in severe asthma. Am J Respir Crit Care Med. 2005; 172(7):824-30. [PMID] [PMCID]

[16] Okubo K, Kurono Y, Fujieda S, Ogino S, Uchio E, Odajima H, et al. Japanese guideline for allergic rhinitis. Allergol Int. 2011; 60(2):171-89. [DOI:10.2332/allergolint.11-rai-0334] [PMID]

[17] Pfaffl MW. A new mathematical model for relative quantification in real-time RT-PCR. Nucleic Acids Res. 2001; 29(9):e45. [DOI:10.1093/nar/29.9.e45] [PMID] [PMCID]

[18] Gilroy DW, Lawrence T, Perretti M, Rossi AG. Inflammatory resolution: New opportunities for drug discovery. Nat Rev Drug Discov. 2004; 3(5):401-16. [DOI:10.1038/nrd1383] [PMID]

[19] Maderna P, Godson C. Lipoxins: Resolutionary road. Br J Pharmacol. 2009; 158(4):947-59. [DOI:10.1111/j.1476-5381.2009.00386.x] [PMID] [PMCID]

[20] Lotfi R, Davoodi A, Mortazavi SH, Gorgin Karaji A, Tarokhian H, Rezaiemanesh A, et al. Imbalanced serum levels of resolvin E1 (RvE1) and leukotriene B4 (LTB4) in patients with allergic rhinitis. Mol Biol Rep. 2020; 47(10):7745-54. [DOI:10.1007/s11033-020-05849-x] [PMID]

[21] Gagliardo R, Gras D, La Grutta S, Chanez P, Di Sano C, Albano GD, et al. Airway lipoxin A4/formyl peptide receptor 2-lipoxin receptor levels in pediatric patients with severe asthma. J Allergy Clin Immunol. 2016; 137(6):1796-806. [PMID]

[22] Tahan F, Saraymen R, Gumus H. The role of lipoxin A4 in exercise-induced bronchoconstriction in asthma. J Asthma. 2008; 45(2):161-4. [PMID]

[23] Wu SH, Yin PL, Zhang YM, Tao HX. Reversed changes of lipoxin A4 and leukotrienes in children with asthma in different severity degree. Pediatr Pulmonol. 2010; 45(4):333-40. [DOI:10.1002/ppul.21186] [PMID]

[24] Yamaguchi H, Higashi N, Mita H, Ono E, Komase Y, Nakagawa T, et al. Urinary concentrations of 15-epimer of lipoxin A(4) are lower in patients with aspirin-intolerant compared with aspirin-tolerant asthma. Clin Exp Allergy. 2011; 41(12):1711-8. [DOI:10.1111/j.1365-2222.2011.03839.x] [PMID]

[25] Shimizu S, Ogawa T, Seno S, Kouzaki H, Shimizu T. Proresolution mediator lipoxin A4 and its receptor in upper airway inflammation. Ann Otol Rhinol Laryngol. 2013; 122(11):683-9. [DOI:10.1177/000348941312201104] [PMID]

[26] Levy BD, Lukacs NW, Berlin AA, Schmidt B, Guilford WJ, Serhan CN, et al. Lipoxin A4 stable analogs reduce allergic airway responses via mechanisms distinct from CysLT1 receptor antagonism. FASEB J. 2007; 21(14):3877-84. [DOI:10.1096/fj.07-8653com] [PMID] [PMCID]

[27] Bergeron C, Hamid Q. Relationship between asthma and rhinitis: Epidemiologic, pathophysiologic, and therapeutic aspects. Allergy Asthma Clin Immunol. 2005; 1(2):81-7. [DOI:10.1186/1710-1492-1-2-81] [PMID] [PMCID]

[28] Chiang N, Serhan CN, Dahlén SE, Drazen JM, Hay DW, Rovati GE, et al. The lipoxin receptor ALX: Potent ligand-specific and stereoselective actions in vivo. Pharmacol Rev. 2006; 58(3):463-87. [DOI:10.1124/pr.58.3.4] [PMID]

[29] Barnig C, Cernadas M, Dutile S, Liu X, Perrella MA, Kazani S, et al. Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. Sci Transl Med. 2013; 5(174):174ra26. [DOI:10.1126/scitranslmed.3004812] [PMID] [PMCID]

[30] Bonnans C, Fukunaga K, Levy MA, Levy BD. Lipoxin A(4) regulates bronchial epithelial cell responses to acid injury. Am J Pathol. 2006; 168(4):1064-72. [DOI:10.2353/ajpath.2006.051056] [PMID] [PMCID]

[31] Pirault J, Bäck M. Lipoxin and resolvin receptors transducing the resolution of inflammation in cardiovascular disease. Front Pharmacol. 2018; 9:1273. [DOI:10.3389/fphar.2018.01273] [PMID] [PMCID]