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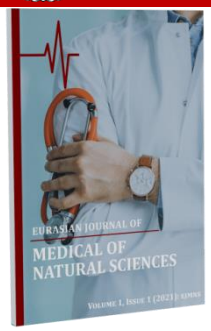

LEUKOTRIENE RECEPTORS, THEIR IMPORTANCE IN MEDICAL PRACTICE AND THE DRUGS ACTING ON THEM

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ABSTRACT

Strong lipid mediators, leukotrienes (LTs), such as cysteinyl LTs (CysLTs) and LTB4, play a key role in the pathogenesis of asthma symptoms. There are at least two known receptor subtypes for CysLTs: CysLT1 and CysLT2. The activation of the CysLT1 receptor mediates the majority of the pathophysiological consequences of CysLTs in asthma, such as increased airway smooth muscle activity, microvascular permeability, and airway mucus secretion. Asthma exacerbations, severe asthma, and airway hyperresponsiveness may all be influenced by LTB4. CysLT1 receptor antagonists can be administered orally as monotherapy in patients with persistent mild asthma, despite the fact that they are typically less efficacious than inhaled glucocorticoids. CysLT1 receptor antagonists can be used in conjunction with inhaled glucocorticoids for people with more severe asthma. By using this therapeutic approach, asthma can be better controlled and the amount of glucocorticoid that is inhaled can be decreased without sacrificing effectiveness. Since the sensitivity to CysLT1 receptor antagonists varies, it is important to identify subgroups of asthmatic patients who react to these medications in order to treat their condition. CysLT1 receptor antagonists' possible anti-remodeling action may be crucial for stopping or undoing structural alterations in asthmatic airways. The function of LTs in asthma is covered in this review, along with the potential therapeutic benefits of pharmacologically modifying the LT pathway.

Introduction. About twenty years ago, leukotriene receptor antagonists (LTRAs)—montelukast, zafirlukast, and pranlukast, in the far East—were introduced as supplemental drugs for people with asthma and allergic rhinitis. Although LTRAs are generally safe medications, they only help a small percentage of patients, particularly those whose allergic or eosinophilic inflammation is significantly influenced by leukotrienes. some medications can lessen the requirement for corticosteroids in some patients. According to recent Medicaid and

Medicare data, two-thirds of adolescent and adult patients with mild asthma (Global INitiative on Asthma step 2) are on an LTRA because they are typically well tolerated and are therefore often prescribed to pediatric patients with allergic disorders and to adults with mild disease [1-4]. However, shortly after LTRAs were introduced, case reports and later real-world cohort studies indicated a higher chance of neuropsychiatric (NP) symptoms, particularly montelukast, developing soon after beginning to take these medications. In order to notify physicians, these symptoms were included to the package insert's adverse events section. However, due to the rarity of the instances, several medical professionals have questioned if NP symptoms and LTRA use are indeed related. Only a small correlation between montelukast consumption and the likelihood of receiving an antidepressant prescription was discovered by a recent Danish registry; this link is thought to be of little clinical significance [5-9]. Although leukotriene receptor antagonists (LTRAs) are commonly used to treat asthma and allergy rhinitis (AR), since the US Food and Drug Administration's first Drug Safety Communication in 2008, there have been worries regarding the possibility of neuropsychiatric events (NPEs). The relationship between LTRA use and NPEs in children, adolescents, and young adults with asthma or AR is assessed in this study. Each receptor subtype may have a unique role in physiology and pathology, as suggested by the various expression profiles, tissue distribution, sensitivity to endogenous ligands, heterodimerization, and cross-regulation of CysLTRs, as well as the frequency of asthma-associated polymorphisms in CysLT2R. It was suggested that CysLT2R-selective or dual antagonists could enhance the treatment of severe asthma cases based on an animal asthma model produced by LTC4. Additionally, ischemia situations and acute brain traumas have been demonstrated to improve when CysLT2R, which is mostly expressed in cardiovascular and brain tissues, is selectively inhibited [10-14]. The studies sought to determine whether exposure to LTRA was associated with longer risk periods for NPEs. We evaluated the incidence of NPEs between the times when patients were subjected to and were not exposed to LTRAs using a self-controlled case series (SCCS) approach, in which each case serves as its control. The lack of precise understanding regarding the selectivity and functional mechanisms of CysLTRs, which necessitates high-resolution structural data, hinders the development of more effective medicines against asthma and related disorders. Here, we present the findings of comprehensive mutagenesis and computer modeling studies, as well as four crystal structures of CysLT2R in association with three dual CysLT1R/CysLT2R antagonists. We now have a comprehensive structural understanding of the receptors mediating the action of cysteinyl leukotrienes in their inhibited, inactive form, in addition to the recently revealed structures of CysLT1R in interaction with zafirlukast and pranlukast [15-21].

The main purpose of this presented analytical manuscript is to briefly comment on the research work carried out on leukotriene receptors in terms of their importance in medical practice and the drugs that affect them.

Leukotriene biosynthesis and metabolism. 5-LO activity is the source of leukotrienes. Several phospholipase A2 enzymes break arachidonic acid, which is esterified on plasma membrane phospholipids. It is then liberated and converted into LTA4. LTA4 hydrolase then

converts this leukotriene into LTB4, and LTC4 synthase or other membrane-associated proteins in the eicosanoid and glutathione metabolism superfamily (MAPEG), such as microsomal glutathione transferase 2 (MGST2), convert it into LTC4. A γ-glutamyl transpeptidase subsequently breaks down LTC4 into LTD4, which is subsequently broken down into LTE4 by a dipeptidase. With an estimated half-life of less than three seconds, LTA4 is extremely reactive. Because of the common cysteine in their side chains, LTC4 and its metabolites, LTD4 and LTE4, are referred to as cysteinyl-LTs [5-11]. Varied cells have varied intracellular distributions of 5-LO. Granulocytes, monocytes, macrophages, mast cells, and B lymphocytes are the primary cells that express 5-LO. Large quantities of LTC4 can be produced by mast cells and eosinophils using an endogenous supply of arachidonic acid. In vitro, human bronchial fibroblasts spontaneously generate cysteinyl-LTs and LTB4 and constitutively express 5-LO, FLAP, LTA4 hydrolase, and LTC4 synthase. Through the transcellular metabolism of LTA4 produced by active neutrophils, cells that do not express 5-LO, such as platelets, erythrocytes, endothelial cells, and epithelial cells, can also produce cysteinyl-LTs and/or LTB4. Following intracellular synthesis, certain carrier proteins transfer cysteinyl-LTs and LTB4 into the extracellular environment, where they could be targets for future antileukotriene medications [12-22].

Receptors and Mechanism of Action of Leukotrienes. Two G-protein coupled receptor subtypes for cysteinyl-LTs (CysLT1 and CysLT2), that have 38% amino acid identity, have been identified. There is evidence that supports the existence of distinct CysLT receptors. Increased vascular permeability induced by LTE4 in mice lacking CysLT1 and CysLT2 receptors suggests the existence of a third cysLT receptor that responds preferentially to LTE4. A G-protein-coupled receptor (GPCR) GPR17, that responds both to cysteinyl-LTs and to uracil nucleotides, is a ligand independent, constitutive negative regulator for the CysLT1 receptor and suppresses CysLT1 receptor-mediated function at the cell membrane. Most of the effects of cysteinyl-LTs relevant to the pathophysiology of asthma are mediated by activation of the CysLT1 receptor that is expressed in monocytes and macrophages, eosinophils, basophils, mast cells, neutrophils, T cells, B lymphocytes, pluripotent hemopoietic stem cells (CD 34+), airway smooth muscle cells, bronchial fibroblasts, and vascular endothelial cells [5-14]. Most of the effects of cysteinyl-LTs relevant to the pathophysiology of asthma are mediated by activation of the CysLT1 receptor [1,2] that is expressed in monocytes and macrophages, eosinophils, basophils, mast cells, neutrophils, T cells, B lymphocytes, pluripotent hemopoietic stem cells (CD 34+), airway smooth muscle cells, bronchial fibroblasts, and vascular endothelial cells [13,15,23]. The CysLT2 receptor is expressed in human peripheral basophils [19], endothelial cells [10], cultured mast cells [14], and in nasal eosinophils and mast cells in patients with active seasonal allergic rhinitis [4]. In human cultured mast cells, CysLT2 activation may elicit IL-8 generation with potential neutrophilic inflammation [24] that is a characteristic of acute and severe asthma.

Leukotrienes' Biological Impact on Airways. Asthma patients have pathophysiological reactions brought on by cysteine-LTs. The strongest endogenous bronchoconstrictors are cysteine-LTs. In vitro, LTC4, LTD4, and LTE4 exhibit comparable contractile action on the smooth muscle of the human airway. Studies using

bronchoprovocation on healthy participants have verified this effect. LTC4, LTD4, and LTE4 inhalation causes hyperresponsiveness in asthmatic patients. Cysteinyl-LTs improve microvascular permeability in the lungs of experimental animals and increase mucus secretion in isolated animal and human airways. Patients with asthma may experience bronchial obstruction as a result of these effects. Cysteinyl-LT inhalation promotes eosinophil recruitment into the airway mucosa and increases the number of sputum eosinophils in asthmatic individuals [1,7,9,17,21]. Cysteinyl-LTs have a number of actions that add to the inflammatory processes that define asthma in addition to their local effects in the airways. Cysteinyl-LTs increase eosinophil survival in response to mast cell and lymphocyte paracrine signals; induce leukocyte migration from the bone marrow into the circulatory system; cause chemotaxis of eosinophils, increasing their cellular adhesion and transendothelial migration across the vessel wall into the airways; prime progenitor cells to differentiate into mature blood cells and modulate leucopoiesis induced by granulocyte-macrophage colony stimulating factor, interleukin (IL)-5, and IL-3 and prime progenitor cells to differentiate into mature blood cells. The decreased Th2 cell-dependent inflammatory response in LTC4 synthase indicates that cysteine-LTs play a key role in lung inflammation brought on by allergen challenge [19-24].

While the significance of the CysLT2 receptor is mainly unclear, the majority of our present understanding of the pathophysiological role of LTs in asthma is restricted to actions mediated by the CysLT1 receptor. Finding people who respond to CysLT1 receptor antagonists may be important for more sensible asthma treatment. CysLT1 receptor antagonists offer people with mild asthma who have prolonged symptoms a therapeutic substitute for inhaled glucocorticoids. However, inhaled glucocorticoids tend to be more efficacious than CysLT1 receptor antagonists. When CysLT1 receptor antagonists are added to inhaled glucocorticoids, asthma control is improved and the dosage of inhaled glucocorticoids can be decreased while still having comparable effectiveness in individuals with more severe asthma who respond to these medications. More research is needed to determine the role of LTB4 in asthma and the possible impact of CysLT1 receptor antagonists in preventing and reversing the structural alterations that define airway remodeling [17-23].

Discussion. CysLT1 and CysLT2, receptors connected to the cysteine leukotriene G protein, control pro-inflammatory reactions linked to allergic diseases. For more than 20 years, selective inhibition of CysLT1R has been utilized to treat asthma and related conditions. More recently, CysLT2R has begun to receive attention as a possible therapeutic target for atopic asthma, brain damage, disorders of the central nervous system, and various cancers. We present four crystal structures of CysLT2R in complex with three antagonists that are dual CysLT1R/CysLT2R. Together with the findings of extensive mutagenesis and computer modeling investigations, the disclosed structures provide insight into the molecular factors influencing CysLTR ligand selectivity and the particular consequences of disease-related single nucleotide variations. Compared to the first generation, the second generation H1-AH was relatively safe for neuropsychiatric events; the fatality rate from first generation H1-AH associated neuropsychiatric events was higher than that of LTRA and ICS; 4 to 6-year-old children were the most likely to experience LTRA associated neuropsychiatric events

reported in FAERS; and the majority of reported cases occurred within the first 10 days after drug initiation [,2,3,7,8,11,12]. The function of CysLT2R in the physiology and pathophysiology of inflammation-related processes is more complicated and still little known than that of CysLT1R, which antiasthmatic medications were able to effectively target 20 years ago. CysLT2R-selective or CysLT1R/CysLT2R dual antagonists may be more effective than the commonly prescribed CysLT1R-selective antagonists, according to recently compiled data, particularly when treating severe asthma. Furthermore, CysLT2R is emerging as a prospective therapeutic target for neurodegenerative diseases and brain damage. Uveal melanoma and other cancer types have been linked to CysLT2R mutants' high constitutive Gq signaling activity. Nevertheless, because CysLT2R's high expression levels have been linked to antitumorigenic activity, its function in cancer is still debatable [11-18]. Important factors influencing ligand binding and selectivity between these two receptors are revealed by the CysLT2R and CysLT1R structures reported in this study. Therefore, our docking investigations enable the explanation of SAR for a number of scaffold derivatives of 3,4-dihydro-2H-1,4-benzoxazine-2-carboxylic acid and recapitulate binding of hundreds of known ligands. In order to understand the distinct roles played by each CysLT receptor subtype in different physiological processes and diseases, these structures will be used as templates for the logical design of a new generation of powerful antagonists with the desired selectivity profiles (receptor selective or dual). These compounds could then be further developed into effective drug candidates or tool compounds [20-26]. Rationalizing the effects of particular SNVs on receptor function is another exciting use for the structural data gathered in this investigation. About 25% of the naturally occurring missense SNVs from 60,000 healthy people that we identified on the CysLT2R structure are found in functionally significant locations that could have an impact on signaling. We are moving closer to personalized medicine as a result of the ongoing expansion of the structural coverage of the GPCR superfamily, the quick accumulation of genome sequencing data, and structure-function studies. These developments should allow for accurate predictions of disease associations and the impact of natural missense variants on drug efficacy and safety profiles [11-21].

Conclusions. In conclusion, although the current study did not find a correlation between LTRA use or exposure duration and the development of NP diseases in Korean adults with asthma, this does not mean that patients with a different genetic background or other age groups (children, adolescents, and adults up to 50 years old) might have this relationship. All things considered, a limited number of patients may have a hereditary propensity to undergo NP changes soon after being subjected to daily LTRA. It appears that montelukast is not the only example of this. It is possible that this occurs at the level of drug metabolism, producing neuroactive compounds. Individuals' genetic backgrounds should be considered in future research on this topic.

Overall, the risk of NPEs with LTRA usage varied by subgroup and risk period. Doctors should advise patients about potential NPEs and prescribe LTRAs based on indications.

LTRA associated neuropsychiatric events reported in FAERS were most frequent in 4 to 6-year-old children. Most reported cases occurred within the first 10 days after drug initiation. The second generation H1-AH was relatively safe for neuropsychiatric events

compared with the first generation. The fatality rate due to first generation H1-AH associated neuropsychiatric events was higher than that of LTRA and ICS. More attention should be paid to specific patients treated with LTRA and H1-AH.

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