Acta Clin Croat 2005; 44:353-358 Review

# EFFECT OF ASTHMA THERAPY ON CEREBROVASCULAR DISEASE AND NEURODEGENERATION

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SUMMARY – After a short time of clinical experience, COX-2 inhibitors such as Viox and Rofecoxib were removed from the market because they increased the incidence of stroke and acute myocardial infarction. Recent studies have shown that COX-1/COX-2 inhibitors also have very similar side effects. The next step in asthma therapy was the introduction of 5-lipoxygenase inhibitors (Zileuton) and Cysleukotriene antagonists (Zafirlukast, Montelukast, Prankulast). There was a very good drug response within the first 4-13 weeks in mild or moderate asthma patients but side effects such as hypersensitivity reactions, dyspepsia, elevations of liver function tests and increased bleeding tendency were also present (large trials). At this point, we should ask ourselves what should be the alternative and strategies in asthma therapy, which would not affect other systems. Some recent studies have shown that there are some 6% of people in the population who have variant 5-LOX genotype (lacking the common allele) and increase in inflammatory products and intima-media thickness as well. Also, there are a number of studies investigating dietary intake of n-6 (arachidonic acid) and n-3 polyunsaturated (eicosapentaenoic acid) fatty acids, and its effect on leukotriene synthesis. Eicosapentaenoic acid is a poor substrate for COX-2 and the products of eicosapentaenoic acid inflammatory eicosanoids of series 3 and 5 are less inflammatory potent than the products of arachidonic acid inflammatory eicosanoids of series 4. We suggest that asthma patients should substitute n-6 polyunsaturated fatty acids with n-3 polyunsaturated acids in their daily diet in order to decrease eicosanoid series 2 and 4 production and to prevent cardiovascular and cerebrovascular disorders and neurodegeneration.

Key words: *Cerebrovascular disorders – etiology; Cerebrovascular disorders – complications; Asthma – therapy; Asthma – complications; Neurodegenerative diseases – prevention and control; Neuroprotective agents – adverse effects*

## Introduction

Asthma is a major global public health problem, especially in modern western countries, with a prevalence of around 5% in adults and 10% in children below age 10[1]. In addition to the genetic predisposition, there are a number of external factors such as exposure to infective agents or other potentially allergenic substances that influence the type of immune response. Current understanding of the asthma immunopathophysiology clearly relies on the Th1/Th2 cytokine ratio, which is in cross-regulation with arachidonic acid (AA) metabolites[1,2]. The allergic disease immune response can also be modulated through the inhibition of the enzyme cascade responsible for prostanoid and leukotriene synthesis (Figs. 1 and 2). There is clear evidence that people who have variant 5-LOX genotype (lacking the common allele) have an increase in inflammatory products and artery wall intima-media thickness as well[3]. A novel approach of supplementary food intake of eicosapentaenoic acid (EPA) in asthma therapy should be investigated[4]. EPA is a poor substrate for COX-2 and good substrate for 5-LOX as a precursor of $LTB_5$, which is less potent in immune response than the series 4 leukotrienes (Fig. 1)[5,6]. Therefore, EPA could be very potent in modulating asthma immunopathophysiology and its effect on other systems and organs[7-9].

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Received October 10, 2005, accepted in revised form November 7, 2005

## Fatty Acid Metabolism and Brain Aging

Linoleic acid and α linoleic acid are essential fatty acids and precursors of the n-6 (AA) and n-3 (EPA) series of fatty acids, respectively. AA is the first precursor in the leukotriene and prostanoid synthesis, it is esterified to membrane phospholipids in mammalian cells, and can be liberated by the action of phospholipase 2; its further metabolism depends on the cell type and physiologic stimulus (Fig. 1). Cyclooxygenase (COX) catalyzes the first step in AA metabolism to prostanoids, thromboxane-2 ($TXA_2$) and prostaglandins (PG) D, E, F, I series 2. There are two forms of the enzyme: COX-1, which is considered to be involved in AA metabolism in physiologic reactions, and COX-2, which is considered to be primarily involved in inflammatory response. $PGE_2$ is known to be a highly potent cerebral vasoconstrictor leading to enhanced vascular permeability that induces the formation of vasogenic edema. $TXA_2$ also influences vasoconstriction, however, it also activates platelet aggregation and adhesion molecules[10]. Another key enzyme in AA metabolism is 5-lipoxygenase, which possesses two catalytic activities: conversion of AA to 5-hydroeicosatetraenoic acid (5-HETE) and subsequent

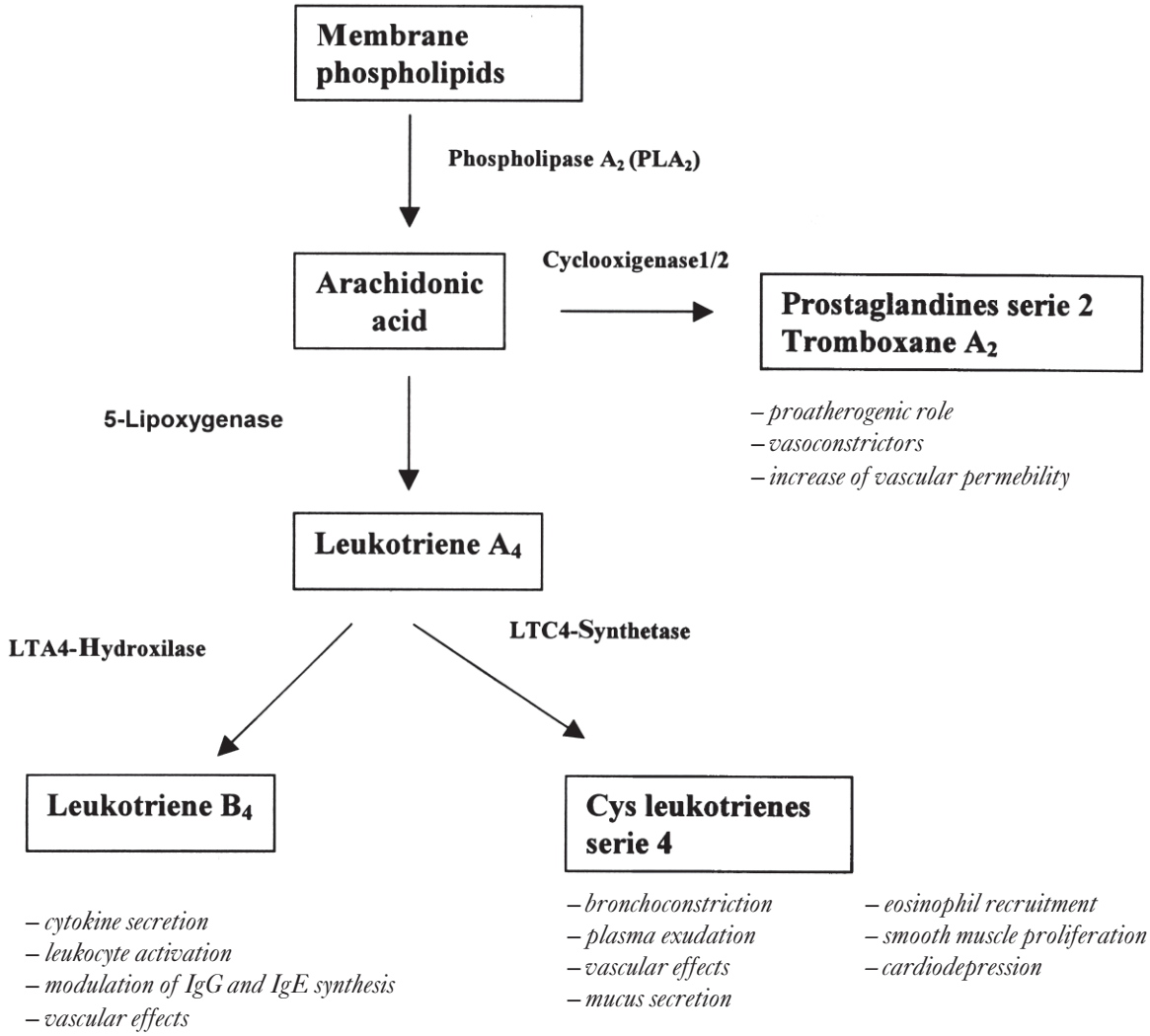


*Fig. 1. Methabolism of arachidonic acid and main pathophysiological effect of eicosanoides. Dietary supplementation of arachidonic acid with eicosapentaenoic acid (poor substrate for cox) will decrease production of 2 and 4 series of eicosanoides and induce production of 3 and 5 series of eicosanoides, which are less potent metabolites. Therefore the EPA would decrease immunopathophysiological effects of eicosanoides*

leukotriene $A_4$. Leukotriene $A_4$ hydrolase and leukotriene $C_4$ synthetase are the next two enzymes in the metabolic cascade of AA. $LTA_4$-hydrolase enables the production of leukotriene $B_4$ ($LTB_4$)[11]. $LTB_4$ exerts chemotaxis, activates lymphocyte aggregation, degranulation and superoxide generation leading to increased microvascular permeability through LTB receptors (two classes), which are concerned to be G-protein coupled. The $LTC_4$-synthetase pathway leads to the production of cysteine containing leukotrienes (cys-LT), which also are cerebral vasoconstrictors and together with $PGE_2$ increase vascular permeability and enhance the formation of brain edema. Cys-LT are also very potent bronchoconstrictors and stimulate mucus secretion in the airways. There are at least two types of Cys LT receptors, CysLT1 and 2. CysLT also have depressive effect on cardiac contractility correlated with cardiac vasoconstriction, however, a direct negative inotropic effect on the myocardium may also be involved. CysLT1 receptors are involved in asthma immunopathophysiology. CysLT2 receptors with their abundant distribution in heart and brain tissue are involved in the pathophysiology of ischemic stroke, ischemic heart disease and arrhythmias. 5-LOX enzyme is restrictively expressed in human body and predominantly found in granulocytes, monocytes, macrophages, mast cells, B-lymphocytes, dendritic cells, and neurons in the hippocampus and cerebellum[12]. There are some new data on the influence of 5- LOX activity on AMPA receptor phosphorylation of GluR1 subunits in dorsal hippocampus affecting the strength of synaptic efficacy between the neurons which are widely assumed to underlie memory and learning, confirming that up-regulation of AMPA receptors through the 5-LOX metabolites could be the possible cause of excitotoxicity and contribute to the decreased number of glutamatergic neurons. The nonenzymatic action of 5-LOX may involve the binding of 5-LOX to cytoskeletal proteins; particularly interesting is the interaction of 5-LOX with the coactosin-like protein (CLP) which binds filamentous actin (F-actin) and affects F-actin stability in dendritic spines in the central nervous system (CNS) neurons, and furthermore the stability of synaptic structures[13]. On the other hand, there is a role of 5-LOX in atherosclerosis, through its metabolite autocrine and paracrine effects on the arterial wall endothelial cells, lymphocytes, smooth-muscle

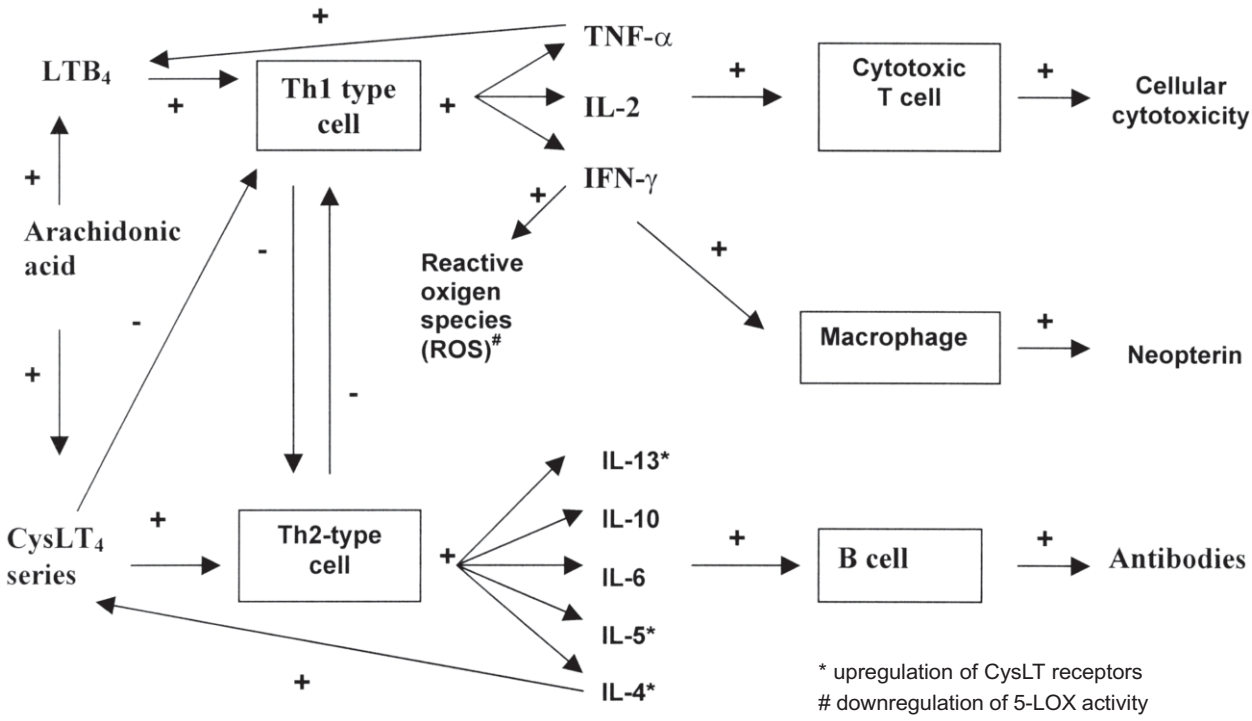


*Fig. 2. Current understanding of asthma pathophysiology clearly relies on the Th2 type of immune response. Both Th1 and Th2 types of immune response are in the interaction with central nervous system immune pathways (NEI) through the production of allergic mediators activating catabolism of AA.*

cells, macrophages and dendritic cells, leading to increased intima-media thickness, atherosclerotic plaque formation, and regional cerebral blood flow changes[3,14,15]. Studies on 5-LOX deficient mice have shown that a 5-LOX overactive pathway may be conductive to anxiety- and depression-like behaviors[16,17].

Some recent studies have shown that there are about 6% of people in the general population who have variant 5-LOX genotypes (lacking the common allele)[3].

Aging dependent hormonal imbalances such as hyperglucocorticoidemia or melatonin deficiency may contribute to 5-LOX up-regulation; on the other hand, epigenetic mechanisms such as DNA methylation might also been involved[18-22].

## Th1/Th2 Immune Response and Neuroendocrine-Immune Networks (NEI)

The current understanding of asthma pathophysiology clearly relies on the Th2-type of immune response. The Th1/Th2-type of immune response ratio plays the key role in the severity of asthma attack[2,7]. Both Th1 and Th2 types of immune response are in interaction with CNS immune pathways (NEI) through the overproduction of allergic mediators. They regulate the cascade of proinflammatory enzymes (PLA, COX-1 and -2, 5-LOX) and induce the production of leukotrienes, which are considered to play crucial roles in NEI (Fig. 2)[23-25].

Th1-type immune response is an important part of adaptive immunity, which is activated in the presence of host cells carrying non-self surface structure such as virus infected or malignant cells. It is characterized by the production of cytokines such as tumor necrosis factor-α (TNF-α), interleukin-2 (IL-2) and interferon-γ (IFN-γ). TNF-α up-regulates $LTB_4$ synthesis[7], IL-2 stimulates cellular cytotoxicity (T cells)[5] and IFN-γ stimulates macrophages on neopterin and reactive oxygen species formation (ROS)[2]. $LTB_4$ up-regulates TH1-type response (Fig. 2)[24].

Th2-type immune response is characterized by interleukin (IL-4,-5,-6,-10,-13) production. IL-4,-5,-6,-10,-13 stimulate formation of specific antibodies (immunoglobulins IgG, IgE up-regulated by 5-LOX)[25,26]. IL-4 up-regulates Cys-LT synthesis. Cys-LT down-regulate Th1-type and upregulate Th2-type immune response[24]. There is a cross-regulation between Th1-type and Th2-type immune response, down-regulating when are activated (Fig. 2)[1,2,7].

## Dietary Intake of Eicosapentaenoic Acid

Supplementary dietary intake of EPA has been reported to provide subjective improvement in rheumatoid arthritis, psoriasis, atopic dermatitis and bronchial asthma. Biochemically, EPA is easily metabolized into the less inflammatory eicosanoids of series 3 and 5 (e.g., $TXA_3$, $PGE_3$ and $LTB_5$)[27]. For example, $LTB_5$ has been demonstrated to be 10 to 30 times less potent as a neutrophil chemoattractant than $LTB_4$[28]. Daily intake of fish oil (EPA precursor) would increase the production of the proinflammatory eicosanoid $LTB_5$ changing the $LTB_4$/$LTB_5$ ratio and decrease the strength of immune response. The ratio of plasma AA and EPA corresponded to the ratio of $LTB_4$ and $LTB_5$ concentrations[29-31].

## Perspectives

Communication between the cells of the immune system depends on the type of eicosanoids they produce and can potentially be modified through dietary supplementation of essential fatty acids in our western diet. In asthma patients who would introduce supplementary EPA food intake, the Th1/Th2 cytokine ratio would be changed, cross-regulating with plasma levels of eicosanoids. The levels of series 3 and 5 eicosanoids would increase and have less influence on Th1/Th2-type immune response than AA metabolites. This mechanism also depends on 5-LOX genotype, and may be decreased or amplified according to the activity of 5-LOX. Populations of special interest are asthma patients with polymorphism in the 5-LOX gene promoter (lacking the common allele) or patients with hormonal imbalance or aging, characterized by up-regulated activity of 5-LOX and increase in the plasma levels of AA metabolites.

Further studies are needed to evaluate correlation of 5-LOX genotype polymorphism, expression of 5-LOX activating protein, supplementary food intake of different concentrations of EPA, plasma lipid serum biochemistry including AA/EPA plasma levels ratio, and levels of circulating proinflammatory factors (especially TNF-α, IFN-γ/IL-4 and LTB4/LTB5 ratio) in the general population, and their effect on asthma immune response, cardiovascular and cerebrovascular disorders, and neurodegeneration.

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Sažetak

## UTJECAJ TERAPIJE ZA ASTMU NA CEREBROVASKULARNU BOLEST I NEURODEGENERACIJU

*I. Zavoreo*

Nakon kratkotrajne primjene u kliničkoj praksi COX-2 inhibitori Viox i Rofecobix su povučeni s tržišta, jer su primijećene nuspojave u smislu povećanja incidencije moždanog i srčanog udara. Kliničke studije su pokazale da COX-1/COX-2 inhibitori imaju vrlo slične nuspojave. Slijedeći korak u terapiji astme bilo je uvođenje 5-LOX inhibitora (Zileuton) i CysLT antagonista (Zafirlukast, Montelukast, Prankulast). Primjena ovih lijekova izazvala je vrlo dobar terapijski odgovor u prvih 4-13 tjedana u bolesnika s blažom i srednje jakom astmom, no zabilježene su i nuspojave kao što su alergijske reakcije, dispepsija, povišene vrijednosti jetrenih proba, povećana sklonost krvarenju. Razmatrajući sve ove činjenice postavlja se pitanje učinkovite terapije astme koja neće utjecati na druge organske sustave. U općoj populaciji oko 6% ljudi ima 5-LOX genotip (nedostaje im uobičajeni alel) kod kojeg je povećana aktivnost 5-LOX, njezinih krajnjih proupalnih proizvoda, a prema nekim istraživanjima i pojačana disfunkcija endotela krvnih žila (povećan IMT). Brojne studije koje su istraživale utjecaj unosa n-6 (arahidonska kiselina) i n-3 (eikosapentanska kiselina) polinezasićenih masnih kiselina na proizvodnju leukotriena pokazale su da je eikosapentanska kiselina loš supstrat za COX-2, te da su proupalni proizvodi serija 3 i 5 manje aktivni od proupalnih proizvoda arahidonske kiseline serija 2 i 4. Upravo zbog tih rezultata povećan unos eikosapentanske kiseline u svakodnevnoj prehrani bolesnika smanjio bi opasnost od kardiovaskularnih i cerebrovaskularnih bolesti te neurodegeneracije.

Ključne riječi: *Cerebrovaskularne bolesti – etiologija; Cerebrovaskularne bolesti – komplikacije; Astma – terapija; Astma – komplikacije; Neurodegenerativne bolesti – prevencija i suzbijanje; Neuroprotektivni lijekovi – štetni učinci*