Fatty acids, inflammation, and asthma

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Fatty acids and consequently diet play an essential role in the formation of inflammatory mediators involved in the pathogenesis of asthma. Because intake variations of omega-6 (n-6) and omega-3 (n-3) fatty acids ultimately determine cell membrane incorporation, changes in diet have the potential to modify downstream production of inflammatory mediators derived from these compounds. It has long been hypothesized that decreasing the n-6/n-3 ratio could reduce the production of more proinflammatory mediators while increasing the formation of downstream metabolites that can serve to limit or resolve inflammation. In turn, these changes would result in improved asthma outcomes or would lower the risk for asthma incidence. This review will focus on the role of fatty acid inflammatory and resolving mediators and will summarize the clinical and epidemiologic data on how diet and obesity alter fatty acid profiles that can contribute to asthma. (J Allergy Clin Immunol 2014;133:1255-64.)

Key words: *Asthma, diet, obesity, fatty acids, n-6, n-3, inflammation, resolution*

Abbreviations used

AA:	Arachidonic acid
AHR:	Airway hyperresponsiveness
AIA:	Aspirin-intolerant asthma
cLA:	Conjugated linoleic acid
CRTH2/DP2:	Chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes
CysLT:	Cysteinyl leukotriene
DHA:	Docosahexaenoic acid
EPA:	Eicosapentaenoic acid
GPCR:	G protein–coupled receptor
LA:	Linoleic acid
LO:	Lipoxygenase
LT:	Leukotriene
LXA_4:	Lipoxin A_4
n-3:	Omega-3
n-6:	Omega-6
OA:	Oleic acid
PG:	Prostaglandin
PPARγ:	Peroxisome proliferator activator receptor γ
PUFA:	Polyunsaturated fatty acid

Chronic airway inflammation is coordinated by a complex web of inflammatory mediators, including interleukins, adhesion molecules, inflammatory enzymes, and lipid mediators. Rigorous study in the area of lipid mediators has revealed that these mediators are produced at specific points during the processes of inflammation and resolution. Some lipid mediators promote inflammation, whereas others are made at later stages in the process and promote a return to cellular homeostasis in the resolution phase. When transition to the resolving phase from an inflammatory response to an acute injury does not occur or a state of chronic inflammation manifests, the system is overwhelmed, and negative physiologic consequences occur. Such is the case in asthma, a disease mediated by chronic airway inflammation leading to bronchoconstriction and, potentially, airway remodeling.

Most of the lipid mediators that regulate inflammation are metabolites derived from omega-6 (n-6) or omega-3 (n-3) fatty acids, including arachidonic acid (AA; 20:4n-6), linoleic acid (LA; 18:2n-6), eicosapentaenoic acid (EPA; 20:5n-3), and docosahexaenoic acid (DHA; 22:6n-3; Fig 1). Through enzymatic oxidation by COX, lipoxygenase (LO), cytochrome P450 (CYP) enzymes, or reactive oxygen species, oxygenated metabolites are formed, many of which possess biological actions. n-6 fatty acids are generally described as proinflammatory, and n-3 fatty acids are generally described as anti-inflammatory. In general, this is true; however, it has been realized that although a fatty acid mediator might be proinflammatory in one disease or tissue, it can be anti-inflammatory in another, as is the case for the AA-derived prostaglandin (PG) E_2.

The main AA-derived mediators of inflammation in asthma are PGs and cysteinyl leukotrienes (CysLTs).[1,2] There are many other eicosanoids that have been implicated; however, their roles remain somewhat controversial compared with PGs and leukotrienes (LTs). Therefore this review will focus only on PGs and LTs as inflammatory mediators. Proresolving fatty acids are formed in response to an inflammatory event and accelerate a return to cellular homeostasis. Most of these are n-3–derived metabolites and include resolvins, protectins, and maresins. The one exception is the lipoxin family, which is derived from AA.[3,4] The formation of these proresolving fatty acids requires the enzymatic activity of 5- and 15-LO, typically from 2 different cell types.[4] A third category of lipid mediators are the anti-inflammatory electrophilic fatty acids. This group is derived from both n-6 and n-3 fatty acids and include metabolites that contain an α, β-unsaturated carbonyl, epoxide, or the addition of a nitro group on an alkene.[5] A plethora of recent studies have shown that they have pleiotropic signaling actions that mediate inflammation by upregulating anti-inflammatory pathways and downregulating proinflammatory signaling. Lastly, the implications of fatty acid dietary intake on asthma will be discussed.

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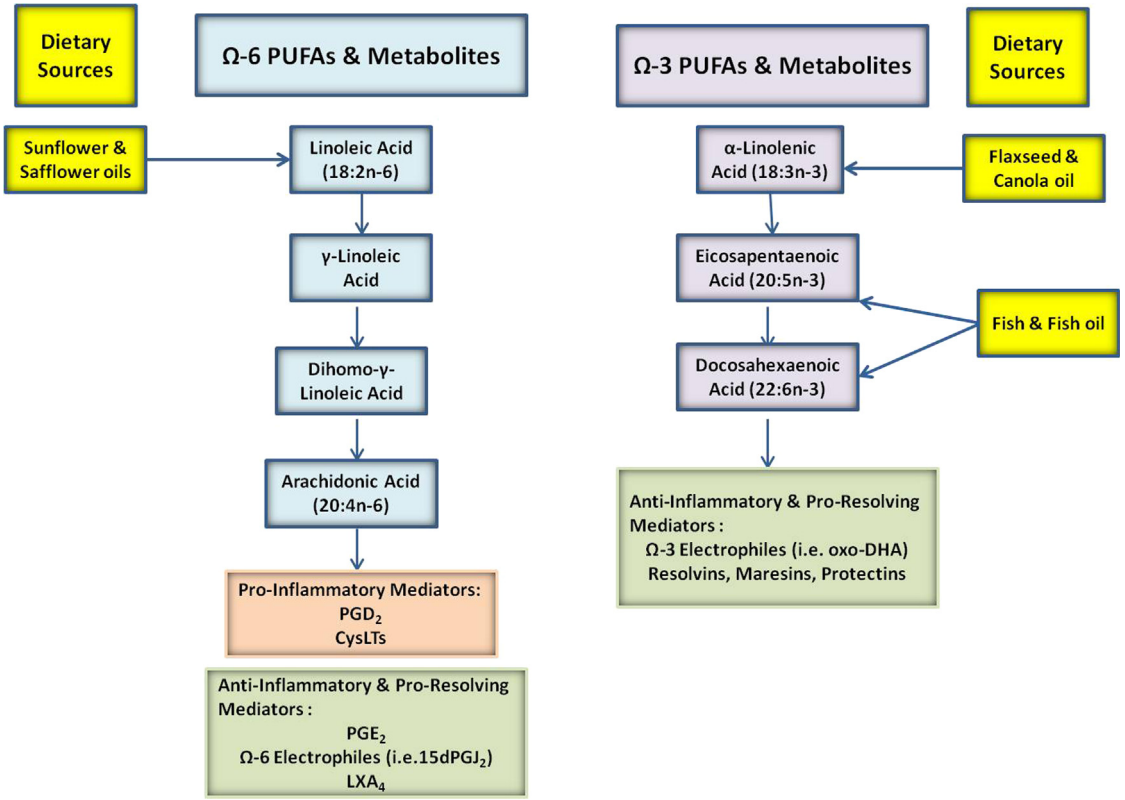

FIG 1. Lipid mediators derived from omega-6 (Ω-6) and omega-3 (Ω-3) fatty acids.

MEDIATORS OF INFLAMMATION

PGs and CysLTs

PGs and CysLTs are metabolites of AA. AA is cleaved from the *sn-2* position of phospholipids by phospholipase A_2. In the case of PGs, AA can be a substrate for either of the COX isoforms COX-1, which is constitutively expressed, or COX-2, which is upregulated in inflammation and primarily responsible for PG formation in asthmatic patients. AA is converted to PGG_2 in one active site and reduced by the endoperoxide active site to PGH_2. Specific synthase enzymes use PGH_2 as a substrate, and the resulting products are thromboxane A_2, PGI_2, $PGF_{2\alpha}$, PGD_2, and PGE_2. PGE_2 is the most abundant PG in the human body and a major metabolite in the lower respiratory tract.[6,7] PGE_2 has been labeled as proinflammatory because of its multiplicity of effects on the immune system, but in the respiratory system PGE_2 is unique in that it has beneficial effects. Cell types that contribute to its production include airway epithelium and smooth muscle, fibroblasts, endothelial cells, and alveolar macrophages.[8] PGE_2 protects against bronchoconstriction, increases relaxation of airway smooth muscle, and has been shown to inhibit the release of mast cell mediators and the recruitment of inflammatory cells.[6] Many, if not all, of these effects are mediated through one of 4 PGE_2 prostanoid G protein–coupled receptors (GPCRs; ie, EP1-EP4).[7]

Although PGE_2 has been exemplified as an anti-inflammatory PG, PGD_2 has been shown to be proinflammatory, despite the fact that they are isomers in which the hydroxyl group and keto group are on opposite sides of the prostanoid ring. Active mast cells generate CysLTs and PGD_2. PGD_2 is mainly produced from mast cells that contain a hematopoietic PGD_2 synthase, and it has been shown that there is a positive correlation of PGD_2 concentration to asthma severity in bronchoalveolar lavage fluid.[8] PGD_2 acts through the thromboxane GPCR, the PGD_2 receptor 1 (DP1), and the chemoattractant receptor–homologous molecule expressed on T_H2 lymphocytes (CRTH2/DP2).[8] The thromboxane GPCR promotes smooth muscle constriction that likely contributes to bronchoconstriction in asthmatic patients. CRTH2 activation on T_H2 lymphocytes, eosinophils, and basophils results in enhanced chemotaxis and activation. CRTH2 receptor binding also induces cytokine production that might play a role in IgE activation by mast cells.[8]

CysLTs

CysLTs are also key mediators of asthma. LTs are derived from AA and synthesized through the 5-LO pathway in conjunction with 5-LO activating protein to catalyze the oxidation of AA to LTA_4. The epoxide ring of LTA_4 is opened by LTA_4 hydrolase to form LTB_4 or it is conjugated to glutathione by LTC_4 synthase to form LTC_4. LTC_4 is transported out of the cell by multidrug resistance–associated protein 1. LTC_4 is then subjected to extracellular metabolism to form LTD_4 (loss of glutamine) and LTE_4 (loss of glycine).[1] These 3 LTs, LTC_4, LTD_4, and LTE_4, comprise the CysLTs. Eosinophils and mast cells are primarily responsible for the synthesis of CysLTs in the context of asthma.[1,2] Bronchoconstriction, the initiation of proinflammatory cytokine production, and airway remodeling have all been attributed to CysLTs. Additionally, CysLTs have been implicated in the trafficking and degranulation of eosinophils in the lungs, increased microvascular permeability leading to pulmonary edema, and increased mucus secretion.[1,9] Unfortunately, only 50% of asthmatic patients show clinical responses to CysLT receptor agonists.[9]