Pulmonary Pharmacology & Therapeutics xxx (2011) 1–9

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/ypupt

Review

Conjugated linoleic acid (CLA): Is it time to supplement asthma therapy?

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ARTICLE INFO

Article history:
Received 14 January 2011
Received in revised form
15 March 2011
Accepted 20 March 2011

Keywords:
Conjugated linoleic acid
Complementary and alternative medicine
Adipokine
PPARgamma
Asthma

ABSTRACT

The limitations and side effects of existing asthma therapies prompt interest in complementary and alternative therapies. Conjugated linoleic acids (CLA) are a family of natural fatty acids found primarily in beef and dairy products. These molecules have a variety of biological properties which suggest potential benefit in asthma, including effects on energy regulation, lipid metabolism, inflammation and immune function. Here we review the evidence for these effects from pre-clinical and clinical studies, their significance in the context of human asthma, and discuss the potential role for CLA supplementation in asthma management.

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1. Introduction

Asthma is a large and increasing worldwide health problem, and despite advances in pharmaceutical treatments, it remains a major burden in terms of morbidity and resource utilization [1]. Existing therapies including long- and short-acting beta-agonists and inhaled corticosteroids have proved effective in relieving symptoms and managing the disease in a majority of patients, but are not without problems. Tachyphylaxis may complicate beta-agonist use [2], while local and systemic side effects of inhaled corticosteroids including oral candidiasis, osteoporosis, glaucoma, hypothalamic-pituitary-adrenal axis suppression and growth retardation are well documented [3]. Many patients are fearful of side effects and are resistant to long-term therapy with these agents. No drug has been shown to alter the natural progression of asthma, or to prevent the alterations in structural cells and tissues which occur over time in asthma (airway remodeling) resulting in irreversible airway obstruction [4].

Consumer interest in complementary and alternative medicine, including nutritional supplementation, continues to grow. Broad based population surveys in the United States indicate that a growing number of patients use complementary therapies with or instead of their prescribed therapies for a range of acute and chronic conditions [5]. The National Institutes of Health's National Center for Complementary and Alternative Medicine (NCCAM) reports that the 2007 National Health Interview (NHI) Survey found 38% of adults and 12% of children in the United States using some form of complementary and alternative medicine (CAM) [6]. There exist therefore both therapeutic and consumer-driven imperatives to define effective complementary therapies for asthma.

How then will the clinician evaluate potential CAM where the evidence is frequently scant and the traditional requirements of drug development and licensing are not met? A physician may "tolerate" a CAM where there is biological plausibility of benefit and evidence that the proposed therapy is not harmful. For most physicians, recommendation or prescribing of a therapy requires additional evidence of efficacy in human studies. This review will discuss the role of Conjugated Linoleic Acid (CLA) in asthma in terms of biologic plausibility of benefit (including evidence from *in vitro*, animal and human studies of metabolic and anti-inflammatory effects relevant to asthma), safety, and finally evidence of benefit in clinical studies in asthma.

2. CLA – diverse biological effects

Conjugated linoleic acids (CLA), first discovered in 1985, [7] are natural constituents of foods derived from the fat tissues and products of animals, particularly ruminants such as cows and goats, as a result of lipid biohydrogenation and hepatic desaturation. CLA is synthesized *in vivo* from linoleic acid by rumen bacteria and may also be synthesized during heat processing of animal-derived foods

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1094-5539/$ – see front matter © 2011 Published by Elsevier Ltd.
doi:10.1016/j.pupt.2011.03.005

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like milk and meat [89] (Fig. 1). Meat from ruminant animals contributes 25–30% of the total CLA intake in western populations, with the remainder coming from dairy products [89].

CLA first came to the attention of clinicians and the general public due to its metabolic effects on obesity, body composition and insulin sensitivity as a potentially useful adjunct in the treatment of obesity and the metabolic syndrome [10]. Subsequently a huge range of biological properties have been attributed to these molecules, including but not limited to effects on inflammation, carcinogenesis and atherosclerosis [11–13].

CLA represents a heterogeneous group of positional and geometric isomers of linoleic acid with over 25 isomers reported to occur naturally in dairy fats [14]. The predominant isomer in milk and meats derived from ruminant species is *cis*-9, *trans*-11, representing 75–80% of total CLA [15]. The remainder consists mostly of *trans-10, cis-12* [9,16,17], with negligible proportions of the other isomers (Fig. 1). This contrasts with commercial preparation of CLA (usually from sunflower oil), in which the proportions of the two main isomers are usually equal, although the chemical method for synthesis allows manipulation of the ratios of the two isomers [9,16,18]. The purified isomers have different biological actions, due largely to differing effects on activity of the transcription factor peroxisome proliferator-activated receptor gamma (PPAR-γ) [19], which will be detailed below. Isomer *trans-10, cis-12* is thought to be responsible for catabolic effects of increased lipolysis and fat oxidation, while *cis-9, trans-11* is the active anabolic agent [17], and is predominantly anti-inflammatory [13]. Both isomers have anti-cancer activity, but mediated by different effects on lipid metabolism, oncogene regulation and modulation of apoptosis [11]. It is important to note that the multiple biological effects seen in animal models and human studies to date have largely been produced by feeding mixtures of CLA isomers in approximately equal amounts, although literature regarding the effects of supplementation with individual isomers is evolving.

3. Asthma – a disease of CLA deficiency?

Epidemiologic data demonstrate a large increase in the prevalence of asthma in the developed world over the latter half of the twentieth century, although this increase may have reached a plateau in some countries in recent years [20]. The rapidity of the changes is such that it cannot be attributed to genetic factors, but must be the result of other factors including environmental exposures. Putative environmental influences include cigarette smoke, air pollution, allergen exposure and exposures to infection and microbial substances. Apart from cigarette smoke [21], data establishing a causal relationship between these factors and risk of asthma is inconsistent (reviewed in [20]). Numerous studies have examined the potential contribution of diet to asthma pathogenesis – both in terms of specific foods acting as allergen or immune modulator and more importantly, linking increasing asthma prevalence to the obesity epidemic.

Fatty acids play a complex role in cell metabolism and structure. The polyunsaturated fatty acids (PUFAs) are critical mediators of eicosanoid production: the n-6 PUFAs are precursors of arachidonic acid which is metabolized by lipoxygenase and cyclo-oxygenase to produce prostaglandins and leukotrienes which in turn are implicated in airway inflammation and hyperactivity; the n-3 PUFAs in contrast competitively inhibit the metabolism of arachidonic acid and produce less active prostanoids [22]. Dietary changes including the increased consumption of vegetable oil and margarine has resulted in an increase in absolute and relative PUFA consumption in recent decades, while the ratio of n-6 to n-3 PUFAs is markedly increased over historical estimates [23]. Although not definitive, cumulative epidemiologic data suggests that n-3 PUFAs may be protective while n-6 PUFAs increase the risk of airways inflammatory disease (reviewed in [24]).

Similar to n-3 PUFAs, dietary levels of CLA have reduced greatly in recent decades. Meat and milk from grass-fed cows is 2–3 times higher in CLA than that from grain-fed animals. As the primary sources of this natural fatty acid product are limited to ruminant animal meat and milk products, changes in human diets along with the changes in the practices of feeding cattle mean that the estimated amount of CLA in our diet has been reduced by up to 90%. It has been estimated that in the 1960's and 1970's trans fatty acid intake was between 7 and 13 g/day [25–27] and given the amount of total CLA in food [28,29,8] there would have been an average intake of CLA of 3–4 g/day. Today, estimates of dietary intake using

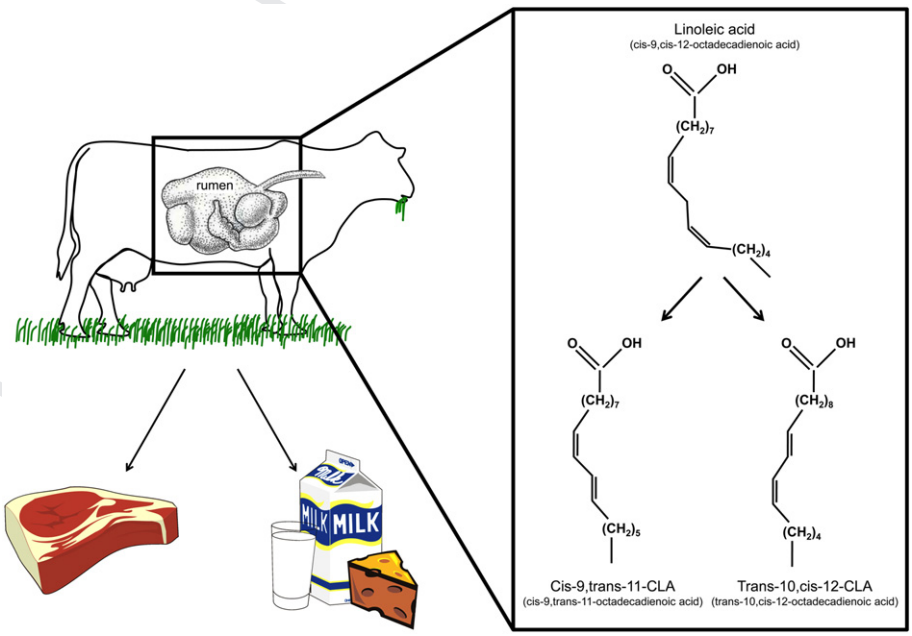

Fig. 1. CLA sources and structure. Dietary CLA is derived predominantly from the tissues and dairy products of ruminant animals, particularly grass-fed cows, by lipid biohydrogenation and hepatic desaturation of linoleic acid.

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3-day dietary records range from 50 to 430 mg/day, varying greatly with geographical location, sex and age [29–31]. Women in general have lower CLA intakes [32]. CLA is found in breast milk (with levels determined by maternal diet) but not in infant formula [16]. Though controversial, and certainly multifactorial, breastfeeding appears to be protective against the development of allergic disease [33], and CLA in breast milk may contribute to this effect.

While the temporal relationship of decreasing CLA consumption and increasing asthma prevalence is provocative, robust epidemiologic data linking CLA dietary intake to asthma does not exist at this time. Diets rich in milk fat, a source of CLA, are however associated with a lower risks of asthma symptoms [34,35]. Further rigorous epidemiologic studies are required to dissect out the potential contribution of CLA to this effect, while studies examining the effect of CLA supplementation on the development and progression of asthma would be required to consolidate this link.

4. Obesity, asthma and CLA

While the data linking individual dietary constituents to asthma are frequently inconsistent, there exists a powerful body of evidence supporting an association between asthma and obesity [36]. In the past this association has been attributed to a functional interaction: asthma symptoms result in limitations on physical activity resulting in weight gain, while truncal adiposity adversely affects pulmonary physiology and worsens symptoms. It is now accepted that the paradigm is more complex. Importantly, a large number of prospective studies have demonstrated that obesity precedes the development of asthma (suggesting causation) with an odds ratio for incident asthma in obese adults of almost 2 in a recent meta-analysis [37]. This effect was confirmed in another large cohort study of almost 120 000 individuals where the relative risk for incident asthma of a 3 unit increase in body mass index (BMI) was 1.21 [38]. The effect of dietary-induced weight loss has been evaluated in only one study to date, reporting improvements in asthma symptoms and peak flow measurements [39].

Obesity constitutes a pro-inflammatory state. Obesity-related changes in adipose-derived hormones, cytokines and other factors may affect airway hyper-responsiveness and inflammation [40]. Recent studies have highlighted the importance of adipokines – inflammatory molecules derived from adipocytes, levels of which are directly related to fat mass. The adipokine leptin is increased in obesity, stimulates pro-inflammatory cytokine production, and is a predictor of asthma (independent of weight) [41]. In contrast, adiponectin declines with obesity and has the potential to negatively regulate allergic inflammation in the lungs [42]. A recent study found lower levels of adiponectin in asthmatic subjects compared to controls, postulating a potential protective role for adiponectin in asthma [43]. Weight loss, specifically reduction in fat mass, may therefore have important anti-inflammatory benefit in asthma and emerges as a specific goal in asthma management.

Many animal studies using 50/50 mixtures of *cis*-9, *trans*-11 and *trans*-10, *cis*-12 isomers report favorable metabolic effects of CLA resulting in reduced fat deposition and increased lean body mass. These effects are attributed to reduced energy intake, inhibition of fatty acid metabolism and lipogenesis, decreased adipocyte size, and increases in fat oxidation (reviewed in [44]). Subsequent studies using purified isomers attribute most of these effects solely to the *trans*-10, *cis*-12 isomer (reviewed by Wang [45]).

Studies in human subjects have largely used CLA mixtures rather than single isomers, with a large variation in dose (0.7 g/day–6 g/day) and duration (4 weeks–24 months) of supplementation. Unsurprisingly, the effects have been thus inconsistent, while in general the effect size has been smaller than that observed in animal studies. These studies are analyzed in detail in a number of excellent reviews [44,46], and can be summarized as follows: studies in normal weight humans demonstrate no weight loss, although loss of fat mass is variably reported, while a statistically significant weight loss is reported in some studies of obese subjects. In an attempt to reconcile methodologic differences in existing studies, Whigham et al performed ameta-analysis adjusting for dose and found that a dose of 3.2 g/day produced a modest reduction in body fat [47]. Two studies using single isomer of *trans*-10, *cis*-12 showed a reduction in body fat, although overall weight was unchanged indicating an increase in lean body mass [48,49]. While the weight loss in humans is smaller than that seen in animal studies, the significant loss of fat mass may be clinically important in the context of inflammatory diseases including asthma.

Looking specifically at adipokines, a variety of animal studies have shown that CLA supplementation induced reductions in plasma leptin levels, which were attributed to reduction in fat mass or possibly food consumption [50,51]. Interpretation of results from human studies is again confounded by large variation in formulation, dose, duration and study populations. Supplementation with 8 g/day *trans*-10, *cis*-12 CLA reduced plasma leptin levels in type II diabetics [52], while only transient changes were observed with 3 g/day CLA in healthy women [53]. Effects of CLA on adiponectin are more complex, reflecting direct regulatory effects as well as responses to changes in body composition. *In vitro* studies demonstrate that the *trans*-10, *cis*-12 isomer of CLA decreases adiponectin production from adipocytes by PPAR-γ-dependent transcriptional and post-translational mechanisms [54]. Importantly, co-incubation with the *cis*-9, *trans*-11 isomer mitigates these effects, likely via opposing effects on PPAR-γ expression and function. This was reflected in a human study of post-menopausal obese women supplemented with CLA mixture, where significant reduction in weight and fat mass was achieved with no change in serum adiponectin levels [55]. It would appear therefore that optimal modulation of adipocytokines in the context of airway inflammation would require a combination of both isomers such that the beneficial effects of fat loss and reduced circulating leptin (mediated by *trans*-10, *cis*-12 isomer) are not compromised by potentially deleterious reduction in adiponectin. Further human studies in this area are required.

5. CLA: asthma, inflammation and immunity

The metabolic effects of CLA resulting in fat loss and modulation of adipokines are potentially beneficial in terms of respiratory mechanics and systemic inflammation, which in turn may apply to airway inflammation in asthma. These effects in human studies are small however and their clinical relevance in isolation is uncertain. CLA can also directly reduce airway inflammation by a variety of PPAR-γ-dependent and -independent mechanisms which may synergize to produce clinically significant reductions in airway inflammation and hyper-reactivity.

Asthma is a chronic inflammatory disorder of the airways involving a complex interplay between resident cells of the airway (epithelium, connective tissue and smooth muscle) with infiltrating and resident immune cells, particularly mast cells, eosinophils and activated T helper lymphocytes [56]. The resulting airway inflammation and bronchoconstriction result in the characteristic symptoms of wheeze and dyspnea, and over time results in airway remodeling and chronic airflow limitation. These processes are driven by the release of inflammatory mediators in including cytokines (most importantly the Th-2 cytokines e.g. IL-4, IL-5, IL-L3), growth factors, lipid mediators and immunoglobulins. We will review the evidence for CLA-mediated regulation of these processes.

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5.1. PPAR-γ

Peroxisome proliferator-activated receptors (PPAR) are a family of nuclear receptors which directly and indirectly regulate transcription of a wide variety of genes important in energy regulation, homeostasis and immune responses. PPAR-γ activation in particular has been implicated as an important negative regulator of inflammatory responses through a number of mechanisms including transcriptional regulation of cytokines, chemokines and cell survival factors and transrepression of pro-inflammatory transcription factors including NF-kB and AP-1 [57]. The importance of PPAR-γ in human inflammatory disease is underlined by association of the PPAR-γ Pro12Ala polymorphism with multiple sclerosis, an autoimmune disease of the central nervous system [58] and with atherosclerosis, an inflammatory disease of blood vessels [59], while both this Pro12Ala and another (His449His) polymorphism were associated with asthma in a Korean cohort [60]. PPAR-γ is expressed in airway epithelial cells [61,62] and expression is increased in the airway epithelium of asthmatics compared to healthy controls [63]. PPAR-γ expression is also reported in airway smooth muscle, endothelial cells and inflammatory cells including eosinophils [61,64].

PPAR-γ is bound and activated to a variable degree by a number of endogenous lipophilic compounds, largely free fatty acids (including linoleic acid and arachidonic acid), oxidized lipids (such as 9- and 13-hydroxyoctadecadienoic acid (HODE), and 12- and 15-HETE), and eicosanoids [65]. 15-deoxy-Δ [12,14] -prostaglandin-J_2 (15-D-PGJ_2) has been identified as an important natural PPAR-γ agonist with potent anti-inflammatory activity [66] and has been shown to limit lung injury in an animal model of pulmonary fibrosis [67]. Synthetic agonists of PPAR-γ (the thiazolidinediones) were developed originally for the treatment of diabetes mellitus due to effects on insulin sensitivity, but have subsequently been investigated for other PPAR-γ-mediated effects, including effects on asthma. Several studies have shown that thiazolidinediones can reduce airway inflammation in cell culture and animal models [68–71] by a variety of mechansisms including regulation of pro-inflammatory [72], anti-inflammatory [70] and Th2 cytokines [70–72], reduced eosinophilia [72,73] and modulation of NF-kB activity [71]. Only two small clinical studies of thiazolidinediones in asthma have been published to date, one in smokers, and both show small but significant improvements in measures of airway hyper-reactivity [74], [75].

CLA also acts as a PPAR-γ agonist and may effect changes in PPAR-γ function by effecting heterodimer binding to the PPRE (Peroxisome Proliferator Response Element), competing with other endogenous PPAR-γ ligands, or by modulating its phosphorylation (Fig. 2). Phosphorylation of PPAR-γ is the major form of regulation [76]. CLA isomers effect PPAR-γ ligand presentation for p38 MAP kinase (*trans*-10, *cis*-12) or ERK (*cis*-9, *trans*-11) and phosphorylation of Serine 82 or Serine 112 residues of PPAR-γ respectively. Specific phosphorylation determines affinity for other ligands and for heterodimer formation with the retinoid X receptor (RXR) and subsequent inhibition or activation of NF-kB and PPRE and thus transcriptional regulation of genes involved in inflammation and metabolism [77,78]. The differing actions of the isomers on PPAR-γ contribute to the divergent activities of these molecules. The *cis*-9 *trans*-11 isomer of CLA is a potent natural activator of PPAR-γ [79] and shares functional similarities with the thiazolidinediones [80] such that many of the anti-inflammatory effects of *cis*-9 *trans*-11 CLA are attributed to activation of PPAR-γ in the nucleus [13]. Examining this mechanism in asthma, the *cis*-9, *trans*-11 isomer of CLA has been shown to reduce airway inflammation (by BAL inflammatory cell count and IL-5) in an animal model of allergic asthma by a PPAR-γ-dependent mechanism [81]. In contrast to the *cis*-9, *trans*-11 isomer, the *trans*-10, *cis*-12 isomer of CLA has recently been shown to be only a weak partial agonist of PPAR-γ, and to inhibit ligand-dependent PPAR-γ activation [76], thus assuming pro-inflammatory activity.

5.2. Eicosanoids

Eicosanoids, including prostaglandins and leukotrienes, are autocrine and paracrine signaling molecules that are generated

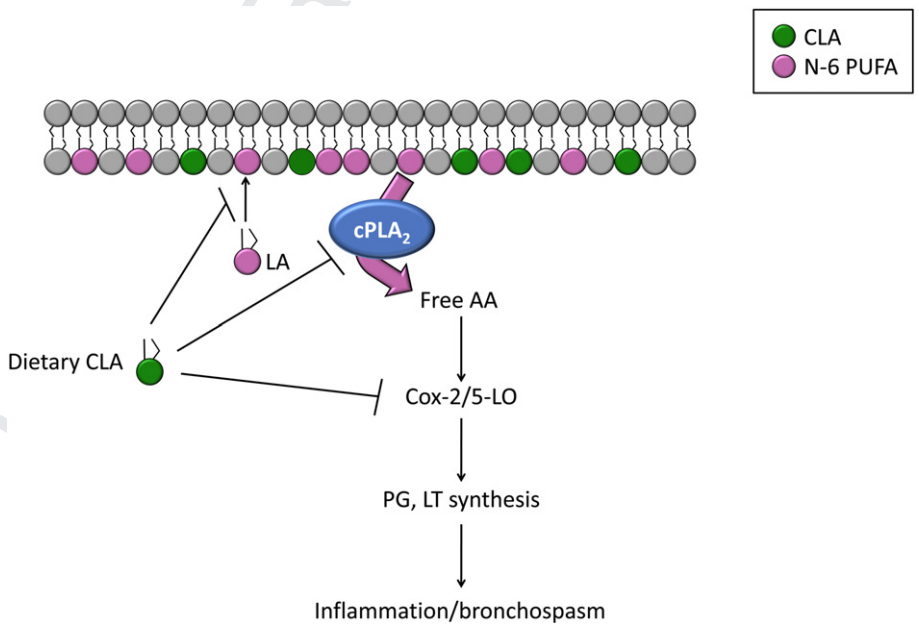

Fig. 2. Schematic of mechanism of CLA-mediated PPAR-γ regulation: CLA isomers bind to PPAR resulting in ligand presentation for p38 MAP kinase (*trans*-10, cis 12) or ERK (*cis*-9, *trans*-11) and phosphorylation of Serine 82 or Serine 112 residues of PPAR respectively. This in turn targets PPAR-γ for ubiquitination and degradation, or for ligand binding and subsequent heterodimerisation with the retinoid × receptor (RXR). This heterodimer promotes transcription of PPRE-dependent and transpression of NF-kB-dependent genes, thus regulating a wide variety of molecules involved in inflammation, apoptosis and metabolism.

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primarily through oxidative metabolism of arachidonic acid (AA) [82]. They play an important role in regulating many aspects of immune function including cytokine production, antibody formation, antigen presentation and differentiation, proliferation and migration of immune cells. Also important in the immunopathology of asthma is their stimulatory effect on the neurohormonal control of airway smooth muscle tone, thus contributing to the airway hyper-reactivity which characterizes the disease.

Production of bioactive eicosanoid mediators (prostaglandins, thromboxanes, leukotrienes) is determined primarily by the availability of substrate fatty acids in the membrane phospholipids and by the amount of n-6 polyunsaturated fatty acid (PUFA) arachidonic acid (AA) relative to other 20-carbon PUFAs (mostly n-3 PUFA) [83]. Increased consumption of long chain n-3 PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) typically found in fish oils results in increased proportions of these PUFAs in membrane phospholipids, partly at the expense of AA [84]. While existing studies fail to provide conclusive evidence regarding efficacy of fish oil supplementation in human asthma, largely because of the lack of large well designed studies [85], evidence of reduction in exercise induced bronchoconstriction associated with reduced airway eicosanoid production is compelling [86].

Similar to n-3 PUFAs, CLA can compete with dietary n-6 PUFAs (primarily linoleic acid LA) at the level of elongases and desaturases for the biosynthesis and membrane incorporation of AA. CLA is itself incorporated into the membrane phospholipids structure where it competes with AA as a substrate for phosholipase A2 (PLA_2) resulting in reduced free AA release [87]. CLA may additionally reduce eicosanoid production by transcriptional regulation of cyclooxygenase-2 (COX-2) [88] and lipoxygenase [89] (Fig. 3). CLA is more potent than EPA or DHA in reducing inflammatory eicosanoid release from a variety of human cell typesincluding vascular smooth muscle cells and immune cells [87,88] and reduces antigen-induced eicosanoid release from sensitized trachea in both *ex vivo* and *in vivo* guinea pig models [90,91]. A recent study of *cis-9 trans 11* CLA supplementation in a mouse model of allergic sensitization reported improved n-3/n-6 PUFA ratio in tissue lipids which was associated with reduced airway hyper-reactivity, however eicosanoid production was not specifically reported [81].

5.3. Cytokines

Numerous cell culture studies have demonstrated that CLA reduced pro-inflammatory cytokine production (including IL-6 and TNFα and IL-1β) [92,93], with the effect being largely attributed to the *cis*-9, *trans*-11 rather than the *trans*-10, *cis*-12 isomer [44,92,94]. In an elegant co-culture model of eosinophilic inflammation in asthma, Jaudszus et al demonstrated reduction of both eosinophil-derived ECP (eosinophil cationic protein) and bronchial epithelial cell derived cytokines when cells were pre-treated with *cis*-9, *trans*-11 CLA [95].

Looking more specifically at the Th2 response in animal models, dietary supplementation of mice with either *cis*-9, *trans*-11 or *trans*-10, *cis*-12 CLA reduced *ex vivo* IL-4 production in splenocytes [92,96]. Dietary supplementation with various mixtures of the two isomers had no effect on peripheral blood mononuclear cell IL-4 production in healthy human volunteers however [97]. Similarly, *ex-vivo* production of IL-4 and IL-13 in birch-allergen stimulated peripheral blood mononuclear cells were unchanged following *cis*-9, *trans*-11 CLA supplementation in human subjects with birch allergy, although IL-5 production was reduced [98]. Interestingly in this study, production of the Th1 cytokine IFNγ was also inhibited along with the early response cytokine TNFα.

5.4. Allergic immune responses

IgE is formed duringTh2-mediated antigen-specific immune responses to airborne and food allergens, and regulates the release of a number of important chemical mediators of the allergic response including histamine and leukotrienes. A number of animal studies demonstrate that dietary CLA could increase production of IgA, IgG and IgM from lymph node and spleen lymphocytes while IgE levels were reduced [99,100]. In a mouse model of allergic sensitization, *cis*-9, *trans*-11 CLA reduced total IgE with a trend towards reduced allergen-induced IgE, and ova-

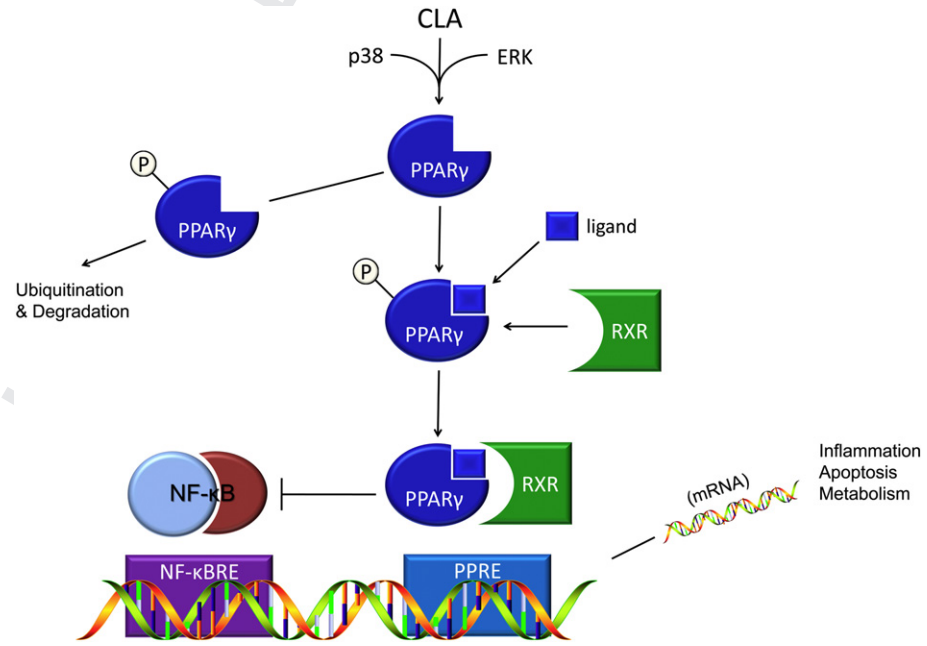

Fig. 3. Schematic of CLA-mediated regulation of eicosanoid synthesis: CLA competes with dietary n-6 PUFA for biosynthesis and phospholipid incorporation of AA, and with AA as a substrate for cPLA2 in the membrane. Eicosanoid production is further inhibited by transcriptional regulation of COX-2 and 5-LO.

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specific IgG1 and IgG2A were also reduced [81]. Immunomodulatory effects in healthy human volunteer studies have been variable, with studies again involving different doses and isomer mixtures. Subjects receiving 1.7 g/day of CLA mounted an enhanced specific immune response to Hepatitis B vaccination [101],, while subjects receiving 3 g/day CLA mixture (1:1 *cis* 9, *trans* 11: *trans* 10,*cis* 12) demonstrated increased IgM and IgA and decreased IgE production [102]. Turpeinin et al found no effect on total or allergen-specific IgE production following 8 weeks CLA supplementation of patients with diagnosed Birch pollen allergy [98]. Of note this study used a lower dose of CLA (2 g/day) and a mixture containing mostly *cis*-9, *trans*-11 isomer (65.3%) with 8.5% *trans* −10, *cis*-12 isomer.

5.5. CLA − anti-viral properties?

Virus infection is known to cause airway tissue damage and inflammation and is a major cause of exacerbation of airway conditions such as asthma. Viral infections account for up to 85% of asthma exacerbations in children [103] and 30% in adults [104]. Despite decades of research, there is no effective treatment, nor any immediate prospect ofeffective vaccines. CLA has been reported to enhance functions critical for the clearance of viruses in a pig model [105] and reduces viral infections and duration in human subjects in an experimental rhinovirus model [106]. This anti-viral effect has been largely attributed to changes in lymphocyte phenotype and effector function. Ongoing work in our laboratory demonstrates additional effects of CLA on the immune function of the airway epithelium. *In vitro* studies, including differentiated air liquid interface cultures of airway epithelial cells, demonstrate that CLA and specifically *cis*-9, *trans*-11 isomer inhibit viral (Respiratory Syncytial Virus) entry, cytopathic effect and virus-induced inflammation [107,108].

6. CLA and human asthma

As we have described, a large body of epidemiologic and preclinical evidence suggests biological plausibility for CLA as a useful therapy in asthma. CLA has been shown to modulate a variety of processes that are important in the pathogenesis of asthma including PPARγ-dependent and −independent inflammation, eicosanoid production and humoral immune responses. Additional effects on body composition and adipocytokines may contribute to therapeutic effect, while anti-viral properties may reduce exacerbation frequency or severity (Fig. 4). The *cis*-9, *trans*-11 isomer appears to be most important for the anti-inflammatory effects while the *trans*-10, *cis*-12 isomer mediates the majority of metabolic effects. Effects in human studies have generally been less potent and less consistent than those observed in cell culture and animal studies, although interpretation of human studies is hampered by large variations in dose, duration isomer composition. In short, CLA has the potential to be a very potent therapy in asthma ……..but can these effects translate into clinical efficacy in human disease?

We have recently completed the first randomized controlled trial of CLA supplementation in asthma. Subjects with mild asthma were randomized to CLA (1:1 *cis*-9, *trans*-11: *trans*-10, *cis*-12) 3 g/day or placebo for 12 weeks in addition to their usual asthma treatment [109]. We found a significant reduction in airway hyperresponsiveness (measured by methacholine challenge) in the CLA group (Fig. 5), associated with weight loss and a reduced leptin/adiponectin ratio in this overweight cohort of asthmatics. The treatment was well tolerated with no significant adverse events and no changes in systemic inflammatory cytokine levels. While encouraging, this study has obvious limitations as a small, single center study of short duration in a specific subset of young (age 19–40) asthmatics with mild disease who were also overweight

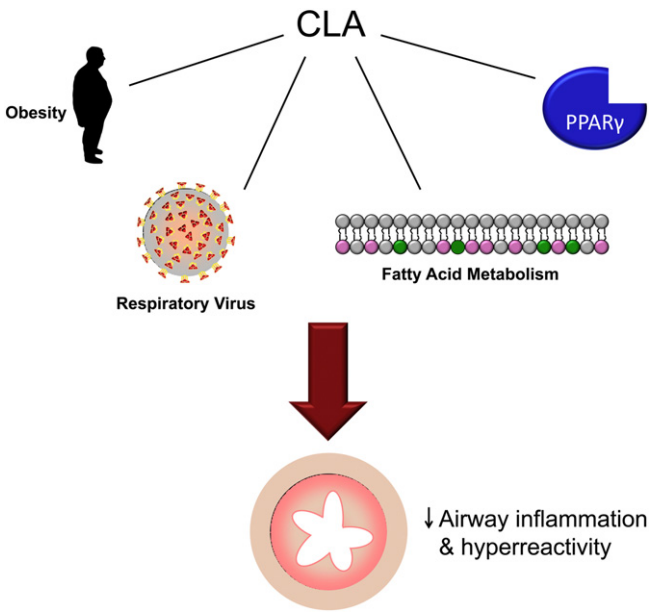

Fig. 4. Proposed mechanisms of effect of CLA in asthma. CLA may improve asthma through favorable effects on body composition and obesity related inflammation, reduction in viral infectivity and virus-induced inflammation, regulation of fatty acid metabolism and inflammatory eicosanoid production and by PPARγ-mediated immune regulation.

(BMI 27.9 kg/m2). It is however the only clinical trial of CLA in asthma to date.

6.1. Safety

Nutraceuticals are not subject to the same rigorous regulations and testing as pharmaceutical drugs. In the USA, nutraceuticals are classified as food and as such the FDA is responsible for regulation of consumer education, advertising (along with the Federal Trade Commission (FTC)) and scientific standards. Responsibility for ensuring that a dietary supplement is safe before it is marketed lies with the manufacturer [110], who have additional responsibility to report any adverse events related to their products. Due to lack of federal oversight of safety testing, the physician must more carefully consider the safety profile of these products. Critical evaluation of CLA benefits from a large body of rigorous scientific study, being the subject of over 2000 original peer review papers including hundreds of animal studies and over 100 human studies reporting safety data. No acute toxic events were reported in any of these studies and CLA supplementation is considered to be safe [111], however there are some concerns and unresolved questions regarding long-term use in specific patient populations specifically concerning insulin resistance in metabolic syndrome.

The initial enthusiasm for the metabolic effects of CLA with regard to body composition has been tempered by concern regarding potential unfavorable effects on insulin resistance and inflammation which could contribute to the metabolic syndrome with attendant risk of diabetes and cardiovascular disease. A number of studies in obese [112] and diabetic [113] subjects reported reduced insulin sensitivity, specifically with the *trans*-10, *cis*-12 isomer. These results are explained by more recent understanding of the isomer specific effects of CLA on PPAR-γ activation [76]. Supplementation with *trans*-10, *cis*-12 isomer for 12 weeks has resulted in an increased oxidative stress and inflammatory biomarkers in obese men [49], and altered serum lipid concentrations [114]. However, the impaired glucose metabolism and unfavorable effects on lipid profile reported by

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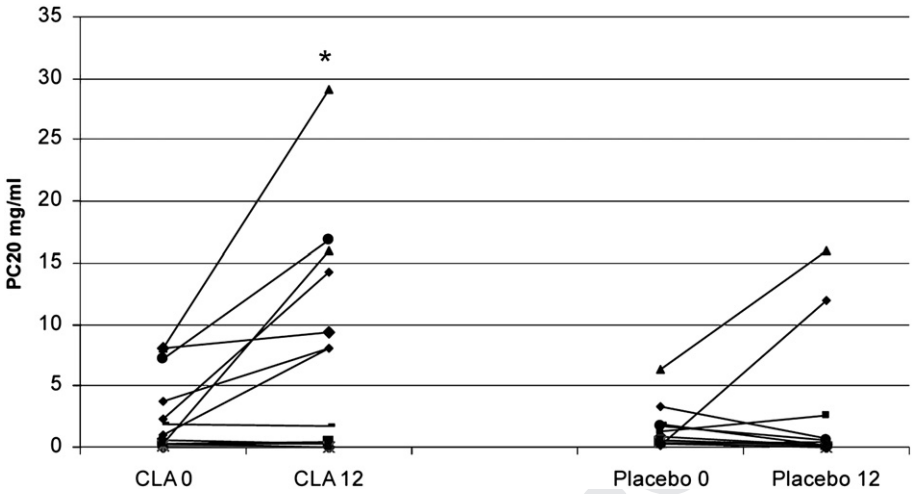

Fig. 5. CLA supplementation improves airway hyper-responsiveness in mild astmatics. Paired data by subject for PC20 by methacholine challenge at baseline (week 0) and after treatment for 12 weeks with either CLA (left) or placebo (right). *$P < 0.02$, paired *t*-test.

Riserus et al was not replicated in other clinical trials using CLA as a mixture of both isomers [115,116], including one study where insulin resistance was accurately tested using the gold standard method of euglycemic hyperinsulinemic clamp [117]. Longer duration supplementation studies are few, but one study where obese subjects were supplemented with 3.4 g/day for 24 months found no clinically significant adverse effects on markers of glucose or lipid metabolism [118]. Effects on markers of systemic inflammation, including CRP as a surrogate of endothelial activation, have been similarly inconsistent. A number of studies found increased CRP levels following supplementation with high doses (4.2–6.4 g.day) of CLA [119,120], although importantly levels remained within the normal range. Other studies found no increase in CRP or other pro-inflammatory markers [113,117], including a study of individual isomers in overweight subjects [121].

Taken as a whole, cumulative safety data suggests that CLA is well tolerated, with the main side effect reported being mild gastrointestinal disturbance, and safe in normal and overweight healthy subjects. Some caution may be recommended in subjects with pre-existing diabetes, insulin resistance and metabolic syndrome, although evidence of adverse effects in these populations is by no means conclusive, and adverse effects of the *trans*-10, *cis*-12 isomer may be offset by co-supplementation with the *cis*-9, *trans*-11 isomer as in most commercially available supplements.

7. Conclusion

As a scientist, many questions remain regarding the use of CLA in asthma. What is the optimal effective isomer formulation? Are the anti-inflammatory effects of the *cis*-9, *trans*-11 isomer most effective and most potent in isolation, or are the *trans*-10, *cis*-12 isomer-mediated metabolic effects and modulation of adipocytokines also required to achieve the clinical effect? Will CLA prove effective only or most potently in specific asthma populations e.g. overweight and obese patients, exercise induced bronchoconstriction or atopic asthmatics? Will the anti-viral properties translate into reduced viral exacerbations in asthma? Is there a role in pediatric asthma and can CLA affect the natural history of the disease? We hope that these questions will be answered by future studies.

For the clinician, the most topical question is whether one is ready to prescribe CLA to asthmatic patients? For patients who are interested in pursuing complementary and alternative therapies as an adjunct to their regular therapy, CLA may be considered to fulfill criteria for “tolerable”; it is generally safe for asthmatics and has proven biological effect in a large body of pre-clinical studies. Evidence points towards potential additional benefits in overweight asthmatics seeking an adjunct to diet and exercise programs. While clinical effect has been demonstrated in the one study published to date, the limitations of this single study preclude routinely prescribing CLA to asthma patients at this time. It is hoped that future studies will define a role for this remarkable molecule in asthma.

Conflicts of interest

The authors declared no conflict of interest.

References

[1] Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy 2004;59(5):469–78.
[2] Haney S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. Clin Rev Allergy Immunol 2006;31(2–3):181–96.
[3] Rossi GA, Cerasoli F, Cazzola M. Safety of inhaled corticosteroids: room for improvement. Pulm Pharmacol Ther 2007;20(1):23–35.
[4] Elias JA, Zhu Z, Chupp G, Homer RJ. Airway remodeling in asthma. J Clin Invest 1999;104(8):1001–6.
[5] Tindle HA, Davis RB, Phillips RS, Eisenberg DM. Trends in use of complementary and alternative medicine by US adults: 1997-2002. Altern Ther Health Med 2005;11(1):42–9.
[6] Barnes P, Bloom B, Nahin R. CDC National Health Statistics Report #12. Complementary and alternative medicine use among adults and children. United States, 2007; 2007.
[7] Pariza MW, Hargraves WA. A beef-derived mutagenesis modulator inhibits initiation of mouse epidermal tumors by 7,12-dimethylbenz[a]anthracene. Carcinogenesis 1985;6(4):591–3.
[8] Chin SF, Liu W, Storkson JM, . Ha YL, . Pariza MW. Dietary sources of conjugated Dienoic isomers of linoleic acids, a newly Recognized class of Anticarcinogens. J Food Comp Anal 1992;5:185–97.
[9] Parodi PW. Cows' milk fat components as potential anticarcinogenic agents. J Nutr 1997;127(6):1055–60.
[10] Park Y, Albright KJ, Liu W, Storkson JM, Cook ME, Pariza MW. Effect of conjugated linoleic acid on body composition in mice. Lipids 1997;32(8):853–8.
[11] Kelley NS, Hubbard NE, Erickson KL. Conjugated linoleic acid isomers and cancer. J Nutr 2007;137(12):2599–607.
[12] Lee KN, Kritchevsky D, Pariza MW. Conjugated linoleic acid and atherosclerosis in rabbits. Atherosclerosis 1994;108(1):19–25.
[13] O'Shea M, Bassaganya-Riera J, Mohede IC. Immunomodulatory properties of conjugated linoleic acid. Am J Clin Nutr 2004;79(6 Suppl):1199S–206S.
[14] Kramer JK, Cruz-Hernandez C, Deng Z, Zhou J, Jahreis G, Dugan ME. Analysis of conjugated linoleic acid and trans 18:1 isomers in synthetic and animal products. Am J Clin Nutr 2004;79(6 Suppl):1137S–45S.
[15] Fritsche J, Rickert R, Steinhart H. Advances in Conjugaed linoleic acid research. Champaign (IL): AOCS Press; 1999.

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[16] McGuire MA, McGuire MK, Parodi PW, Jensen RG. Advances in conjugated linoleic acid research. In: Yurawecz MP, Mossoba MM, Kramer JKG, Pariza MW, Nelson GJ, editors. Champaign: AOCS Press; 1999. p. 296–306.
[17] Parodi P. Advances in conjugated linoleic acid research. Champaign, IL: AOCS Press; 2003.
[18] Saebo A. Advances in conjugated linoleic acid research. Champaign (IL): AOCS Press; 2003.
[19] Khan SA, Vanden Heuvel JP. Role of nuclear receptors in the regulation of gene expression by dietary fatty acids (review). J Nutr Biochem 2003;14(10): 554–67.
[20] Eder W, Ege MJ, von Mutius E. The asthma epidemic. N Engl J Med 2006; 355(21):2226–35.
[21] Strachan DP, Cook DG. Health effects of passive smoking. 6. Parental smoking and childhood asthma: longitudinal and case-control studies. Thorax 1998; 53(3):204–12.
[22] Hoffmann P, Mest HJ. What about the effects of dietary lipids on endogenous prostanoid synthesis? A state-of-the-art review. Biomed Biochim Acta 1987; 46(7):639–50.
[23] Simopoulos AP. Evolutionary aspects of diet, the omega-6/omega-3 ratio and genetic variation: nutritional implications for chronic diseases. Biomed Pharmacother 2006;60(9):502–7.
[24] Fogarty A, Britton J. The role of diet in the aetiology of asthma. Clin Exp Allergy 2000;30(5):615–27.
[25] Hunter JE, Applewhite TH. Isomeric fatty acids in the US diet: levels and health perspectives. Am J Clin Nutr 1986;44(6):707–17.
[26] Hunter JE, Applewhite TH. Reassessment of trans fatty acid availability in the US diet. Am J Clin Nutr 1991;54(2):363–9.
[27] Enig MG, Atal S, Keeney M, Sampugna J. Isomeric trans fatty acids in the U.S. diet. J Am Coll Nutr 1990;9(5):471–86.
[28] Fritsche J, Steinhart H. Contents of trans-fatty acids (TFA) in German foods and evaluation of Daily intake. Fett/Lipids 1997;99:314–8.
[29] Fritsche J, Steinhart H. Amounts of conjugated linoleic acid (CLA) in German foods and evaluation of Daily intake. Z Lebensm Unters Forsch A; 1998:77–82.
[30] Ritzenthaler K, McGuire MK, Falen R, Shultz TD, Mcguire MA. Estimation of conjugated linoleic acid (CLA) intake. FASEB J 1998;12:A527.
[31] Mushtaq S, Heather Mangiapane E, Hunter KA. Estimation of cis-9, trans-11 conjugated linoleic acid content in UK foods and assessment of dietary intake in a cohort of healthy adults. Br J Nutr 2010;103(9):1366–74.
[32] Ritzenthaler KL, McGuire MK, Falen R, Shultz TD, Dasgupta N, McGuire MA. Estimation of conjugated linoleic acid intake by written dietary assessment methodologies underestimates actual intake evaluated by food duplicate methodology. J Nutr 2001;131(5):1548–54.
[33] Greer FR, Sicherer SH, Burks AW. Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121(1):183–91.
[34] Wijga AH, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Neijens HJ, et al. Association of consumption of products containing milk fat with reduced asthma risk in pre-school children: the PIAMA birth cohort study. Thorax 2003;58(7):567–72.
[35] Woods RK, Walters EH, Raven JM, Wolfe R, Ireland PD, Thien FC, et al. Food and nutrient intakes and asthma risk in young adults. Am J Clin Nutr 2003; 78(3):414–21.
[36] Ford ES. The epidemiology of obesity and asthma. J Allergy Clin Immunol 2005;115(5):897–909. quiz 10.
[37] Beuther DA, Sutherland ER. Overweight, obesity, and incident asthma: a meta-analysis of prospective epidemiologic studies. Am J Respir Crit Care Med 2007;175(7):661–6.
[38] Hjellvik V, Tverdal A, Furu K. Body mass index as predictor for asthma: a cohort study of 118,723 males and females. Eur Respir J 2010;35(6):1235–42.
[39] Stenius-Aarniala B, Poussa T, Kvarnstrom J, Gronlund EL, Ylikahri M, Mustajoki P. Immediate and long term effects of weight reduction in obese people with asthma: randomised controlled study. BMJ 2000;320(7238): 827–32.
[40] Weiss ST. Obesity: insight into the origins of asthma. Nat Immunol 2005; 6(6):537–9.
[41] Sood A, Verhulst SJ, Varma A, Eagleton LE, Henkle JQ, Hopkins-Price P. Association of excess weight and degree of airway responsiveness in asthmatics and non-asthmatics. J Asthma 2006;43(6):447–52.
[42] Shore SA, Terry RD, Flynt L, Xu A, Hug C. Adiponectin attenuates allergen-induced airway inflammation and hyperresponsiveness in mice. J Allergy Clin Immunol 2006;118(2):389–95.
[43] Sood A, Qualls C, Seagrave J, Stidley C, Archibeque T, Berwick M, et al. Effect of specific allergen inhalation on serum adiponectin in human asthma. Chest 2009;135(2):287–94.
[44] Bhattacharya A, Banu J, Rahman M, Causey J, Fernandes G. Biological effects of conjugated linoleic acids in health and disease. J Nutr Biochem 2006; 17(12):789–810.
[45] Wang YW, Jones PJ. Conjugated linoleic acid and obesity control: efficacy and mechanisms. Int J Obes Relat Metab Disord 2004;28(8):941–55.
[46] Plourde M, Jew S, Cunnane SC, Jones PJ. Conjugated linoleic acids: why the discrepancy between animal and human studies? Nutr Rev 2008;66(7):415–21.
[47] Whigham LD, Watras AC, Schoeller DA. Efficacy of conjugated linoleic acid for reducing fat mass: a meta-analysis in humans. Am J Clin Nutr 2007;85(5): 1203–11.
[48] Malpuech-Brugere C, Verboeket-van de Venne WP, Mensink RP, Arnal MA, Morio B, Brandolini M, et al. Effects of two conjugated linoleic Acid isomers on body fat mass in overweight humans. Obes Res 2004;12(4):591–8.
[49] Riserus U, Arner P, Brismar K, Vessby B. Treatment with dietary trans10cis12 conjugated linoleic acid causes isomer-specific insulin resistance in obese men with the metabolic syndrome. Diabetes Care 2002;25(9):1516–21.
[50] Takahashi Y, Kushiro M, Shinohara K, Ide T. Dietary conjugated linoleic acid reduces body fat mass and affects gene expression of proteins regulating energy metabolism in mice. Comp Biochem Physiol B Biochem Mol Biol 2002;133(3):395–404.
[51] Yamasaki M, Mansho K, Mishima H, Kasai M, Sugano M, Tachibana H, et al. Dietary effect of conjugated linoleic acid on lipid levels in white adipose tissue of Sprague-Dawley rats. Biosci Biotechnol Biochem 1999;63(6):1104–6.
[52] Belury MA, Mahon A, Banni S. The conjugated linoleic acid (CLA) isomer, t10c12-CLA, is inversely associated with changes in body weight and serum leptin in subjects with type 2 diabetes mellitus. J Nutr 2003;133(1): 257S–60S.
[53] Medina EA, Horn WF, Keim NL, Havel PJ, Benito P, Kelley DS, et al. Conjugated linoleic acid supplementation in humans: effects on circulating leptin concentrations and appetite. Lipids 2000;35(7):783–8.
[54] Miller JR, Siripurkpong P, Hawes J, Majdalawieh A, Ro HS, McLeod RS. The trans-10, cis-12 isomer of conjugated linoleic acid decreases adiponectin assembly by PPARgamma-dependent and PPARgamma-independent mechanisms. J Lipid Res 2008;49(3):550–62.
[55] Norris LE, Collene AL, Asp ML, Hsu JC, Liu LF, Richardson JR, et al. Comparison of dietary conjugated linoleic acid with safflower oil on body composition in obese postmenopausal women with type 2 diabetes mellitus. Am J Clin Nutr 2009;90(3):468–76.
[56] Hamid Q, Tulic M. Immunobiology of asthma. Annu Rev Physiol 2009;71: 489–507.
[57] Daynes RA, Jones DC. Emerging roles of PPARs in inflammation and immunity. Nat Rev Immunol 2002;2(10):748–59.
[58] Klotz L, Schmidt S, Heun R, Klockgether T, Kolsch H. Association of the PPARgamma gene polymorphism Pro12Ala with delayed onset of multiple sclerosis. Neurosci Lett 2009;449(1):81–3.
[59] Regieli JJ, Jukema JW, Doevendans PA, Zwinderman AH, van der Graaf Y, Kastelein JJ, et al. PPAR gamma variant influences angiographic outcome and 10-year cardiovascular risk in male symptomatic coronary artery disease patients. Diabetes Care 2009;32(5):839–44.
[60] Oh SH, Park SM, Lee YH, Cha JY, Lee JY, Shin EK, et al. Association of peroxisome proliferator-activated receptor-gamma gene polymorphisms with the development of asthma. Respir Med 2009;103(7):1020–4.
[61] Denning GM, Stoll LL. Peroxisome proliferator-activated receptors: potential therapeutic targets in lung disease? Pediatr Pulmonol 2006;41(1):23–34.
[62] Pawliczak R, Han C, Huang XL, Demetris AJ, Shelhamer JH, Wu T. 85-kDa cytosolic phospholipase A2 mediates peroxisome proliferator-activated receptor gamma activation in human lung epithelial cells. J Biol Chem 2002;277(36):33153–63.
[63] Benayoun L, Letuve S, Druilhe A, Boczkowski J, Dombret MC, Mechighel P, et al. Regulation of peroxisome proliferator-activated receptor gamma expression in human asthmatic airways: relationship with proliferation, apoptosis, and airway remodeling. Am J Respir Crit Care Med 2001;164(8 Pt 1):1487–94.
[64] Belvisi MG, Mitchell JA. Targeting PPAR receptors in the airway for the treatment of inflammatory lung disease. Br J Pharmacol 2009;158(4):994–1003.
[65] Kersten S, Desvergne B, Wahli W. Roles of PPARs in health and disease. Nature 2000;405(6785):421–4.
[66] Scher JU, Pillinger MH. 15d-PGJ2: the anti-inflammatory prostaglandin? Clin Immunol 2005;114(2):100–9.
[67] Genovese T, Cuzzocrea S, Di Paola R, Mazzon E, Mastruzzo C, Catalano P, et al. Effect of rosiglitazone and 15-deoxy-Delta12,14-prostaglandin J2 on bleomycin-induced lung injury. Eur Respir J 2005;25(2):225–34.
[68] Lee KS, Park SJ, Kim SR, Min KH, Jin SM, Lee HK, et al. Modulation of airway remodeling and airway inflammation by peroxisome proliferator-activated receptor gamma in a murine model of toluene diisocyanate-induced asthma. J Immunol 2006;177(8):5248–57.
[69] Lee SY, Kang EJ, Hur GY, Jung KH, Jung HC, Lee SY, et al. Peroxisome proliferator-activated receptor-gamma inhibits cigarette smoke solution-induced mucin production in human airway epithelial (NCI-H292) cells. Am J Physiol Lung Cell Mol Physiol 2006;291(1):L84–90.
[70] Kim SR, Lee KS, Park HS, Park SJ, Min KH, Jin SM, et al. Involvement of IL-10 in peroxisome proliferator-activated receptor gamma-mediated anti-inflammatory response in asthma. Mol Pharmacol 2005;68(6):1568–75.
[71] Lee KS, Park SJ, Hwang PH, Yi HK, Song CH, Chai OH, et al. PPAR-gamma modulates allergic inflammation through up-regulation of PTEN. FASEB J 2005;19(8):1033–5.
[72] Woerly G, Honda K, Loyens M, Papin JP, Auwerx J, Staels B, et al. Peroxisome proliferator-activated receptors alpha and gamma down-regulate allergic inflammation and eosinophil activation. J Exp Med 2003;198(3):411–21.
[73] Trifilieff A, Bench A, Hanley M, Bayley D, Campbell E, Whittaker P. PPAR-alpha and -gamma but not -delta agonists inhibit airway inflammation in a murine model of asthma: in vitro evidence for an NF-kappaB-independent effect. Br J Pharmacol 2003;139(1):163–71.
[74] Richards DB, Bareille P, Lindo EL, Quinn D, Farrow SN. Treatment with a peroxisomal proliferator activated receptor gamma agonist has a modest

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effect in the allergen challenge model in asthma: a randomised controlled trial. Respir Med 2010;104(5):668–74.
[75] Spears M, Donnelly I, Jolly L, Brannigan M, Ito K, McSharry C, et al. Bronchodilatory effect of the PPAR-gamma agonist rosiglitazone in smokers with asthma. Clin Pharmacol Ther 2009;86(1):49–53.
[76] Kennedy A, Chung S, LaPoint K, Fabiyi O, McIntosh MK. Trans-10, cis-12 conjugated linoleic acid antagonizes ligand-dependent PPARgamma activity in primary cultures of human adipocytes. J Nutr 2008;138(3):455–61.
[77] Gardner OS, Dewar BJ, Graves LM. Activation of mitogen-activated protein kinases by peroxisome proliferator-activated receptor ligands: an example of nongenomic signaling. Mol Pharmacol 2005;68(4):933–41.
[78] Kelly DP. The pleiotropic nature of the vascular PPAR gene regulatory pathway. Circ Res 2001;89(11):935–7.
[79] Moya-Camarena SY, Vanden Heuvel JP, Blanchard SG, Leesnitzer LA, Belury MA. Conjugated linoleic acid is a potent naturally occurring ligand and activator of PPARalpha. J Lipid Res 1999;40(8):1426–33.
[80] Houseknecht KL, Vanden Heuvel JP, Moya-Camarena SY, Portocarrero CP, Peck LW, Nickel KP, et al. Dietary conjugated linoleic acid normalizes impaired glucose tolerance in the Zucker diabetic fatty fa/fa rat. Biochem Biophys Res Commun 1998;244(3):678–82.
[81] Jaudszus A, Krokowski M, Mockel P, Darcan Y, Avagyan A, Matricardi P, et al. Cis-9, trans-11-conjugated linoleic acid inhibits allergic sensitization and airway inflammation via a PPARgamma-related mechanism in mice. J Nutr 2008;138(7):1336–42.
[82] Harizi H, Corcuff JB, Gualde N. Arachidonic-acid-derived eicosanoids: roles in biology and immunopathology. Trends Mol Med 2008;14(10):461–9.
[83] Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr 2006;83(6 Suppl):1505S–19S.
[84] Healy DA, Wallace FA, Miles EA, Calder PC, Newsholm P. Effect of low-to-moderate amounts of dietary fish oil on neutrophil lipid composition and function. Lipids 2000;35(7):763–8.
[85] Reisman J, Schachter HM, Dales RE, Tran K, Kourad K, Barnes D, et al. Treating asthma with omega-3 fatty acids: where is the evidence? A systematic review. BMC Complement Altern Med 2006;6:26.
[86] Mickleborough TD, Lindley MR, Ionescu AA, Fly AD. Protective effect of fish oil supplementation on exercise-induced bronchoconstriction in asthma. Chest 2006;129(1):39–49.
[87] Urquhart P, Parkin SM, Rogers JS, Bosley JA, Nicolaou A. The effect of conjugated linoleic acid on arachidonic acid metabolism and eicosanoid production in human saphenous vein endothelial cells. Biochim Biophys Acta 2002;1580(2–3):150–60.
[88] Ringseis R, Muller A, Herter C, Gahler S, Steinhart H, Eder K. CLA isomers inhibit TNFalpha-induced eicosanoid release from human vascular smooth muscle cells via a PPARgamma ligand-like action. Biochim Biophys Acta 2006;1760(2):290–300.
[89] Ochoa JJ, Farquharson AJ, Grant I, Moffat LE, Heys SD, Wahle KW. Conjugated linoleic acids (CLAs) decrease prostate cancer cell proliferation: different molecular mechanisms for cis-9, trans-11 and trans-10, cis-12 isomers. Carcinogenesis 2004;25(7):1185–91.
[90] Whigham LD, Cook EB, Stahl JL, Saban R, Bjorling DE, Pariza MW, et al. CLA reduces antigen-induced histamine and PGE(2) release from sensitized guinea pig tracheae. Am J Physiol Regul Integr Comp Physiol 2001;280(3):R908–12.
[91] Whigham LD, Higbee A, Bjorling DE, Park Y, Pariza MW, Cook ME. Decreased antigen-induced eicosanoid release in conjugated linoleic acid-fed guinea pigs. Am J Physiol Regul Integr Comp Physiol 2002;282(4):R1104–12.
[92] Yang M, Cook ME. Dietary conjugated linoleic acid decreased cachexia, macrophage tumor necrosis factor-alpha production, and modifies splenocyte cytokines production. Exp Biol Med (Maywood) 2003;228(1):51–8.
[93] Yu Y, Correll PH, Vanden Heuvel JP. Conjugated linoleic acid decreases production of pro-inflammatory products in macrophages: evidence for a PPAR gamma-dependent mechanism. Biochim Biophys Acta 2002;1581(3):89–99.
[94] Turek JJ, Li Y, Schoenlein IA, Allen KGD, Watkins BA. Modulation of macrophage cytokine production by conjugated linoleic acids is influenced by the dietary n-6:n-3 fatty acid ratio. J Nutr Biochem 1998;9(5):258–66 (9).
[95] Jaudszus A, Foerster M, Kroegel C, Wolf I, Jahreis G. Cis-9, trans-11-CLA exerts anti-inflammatory effects in human bronchial epithelial cells and eosinophils: comparison to trans-10, cis-12-CLA and to linoleic acid. Biochim Biophys Acta 2005;1737(2–3):111–8.
[96] Kelley DS, Warren JM, Simon VA, Bartolini G, Mackey BE, Erickson KL. Similar effects of c9, t11-CLA and t10, c12-CLA on immune cell functions in mice. Lipids 2002;37(7):725–8.
[97] Nugent AP, Roche HM, Noone EJ, Long A, Kelleher DK, Gibney MJ. The effects of conjugated linoleic acid supplementation on immune function in healthy volunteers. Eur J Clin Nutr 2005;59(6):742–50.
[98] Turpeinen AM, Ylonen N, von Willebrand E, Basu S, Aro A. Immunological and metabolic effects of cis-9, trans-11-conjugated linoleic acid in subjects with birch pollen allergy. Br J Nutr 2008;100(1):112–9.
[99] Sugano M, Tsujita A, Yamasaki M, Noguchi M, Yamada K. Conjugated linoleic acid modulates tissue levels of chemical mediators and immunoglobulins in rats. Lipids 1998;33(5):521–7.
[100] Yamasaki M, Chujo H, Hirao A, Koyanagi N, Okamoto T, Tojo N, et al. Immunoglobulin and cytokine production from spleen lymphocytes is modulated in C57BL/6J mice by dietary cis-9, trans-11 and trans-10, cis-12 conjugated linoleic acid. J Nutr 2003;133(3):784–8.
[101] Albers R, van der Wielen RP, Brink EJ, Hendriks HF, Dorovska-Taran VN, Mohede IC. Effects of cis-9, trans-11 and trans-10, cis-12 conjugated linoleic acid (CLA) isomers on immune function in healthy men. Eur J Clin Nutr 2003;57(4):595–603.
[102] Song HJ, Grant I, Rotondo D, Mohede I, Sattar N, Heys SD, et al. Effect of CLA supplementation on immune function in young healthy volunteers. Eur J Clin Nutr 2005;59(4):508–17.
[103] Johnston SL, Pattemore PK, Sanderson G, Smith S, Lampe F, Josephs L, et al. Community study of role of viral infections in exacerbations of asthma in 9-11 year old children. Bmj 1995;310(6989):1225–9.
[104] Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. Bmj 1993;307(6910):982–6.
[105] Bassaganya-Riera J, Pogranichniy RM, Jobgen SC, Halbur PG, Yoon KJ, O'Shea M, et al. Conjugated linoleic acid ameliorates viral infectivity in a pig model of virally induced immunosuppression. J Nutr 2003;133(10):3204–14.
[106] Hayden F, O'Shea M. Effect of conjugated linoleic acid on experimental rhinovirus Illness. Anti-viral therapy advances conference; 2004. Tuscon, AZ.
[107] Vancouver, Canada Singhera GK, MacRedmond R, Dorscheid DR. PPAR-Dependent inhibition of viral airway inflammation by CLA. Am J Respir Crit Care Med 2009;1(79):A2815. 2009.
[108] Singhera GK, MacRedmond R, Wadsworth SJ, Dorscheid DR. CLA inhibits RSV entry and cytopathic effect in isolated airway epithelial cells. Am J Respir Crit Care Med 2010;179:A6187. 2010.
[109] MacRedmond R, Singhera G, Attridge S, Bahzad M, Fava C, Lai Y, et al. Conjugated linoleic acid improves airway hyper-reactivity in overweight mild asthmatics. Clin Exp Allergy 2010;40(7):1071–8.
[110] USFDA. Dietary supplements - Consumer Information http://www.fda.gov/Food/DietarySupplements/ConsumerInformation/ucm110417.htm#safe.
[111] Pariza MW. Perspective on the safety and effectiveness of conjugated linoleic acid. Am J Clin Nutr 2004;79(6 Suppl):1132S–6S.
[112] Riserus U, Vessby B, Arner P, Zethelius B. Supplementation with trans10cis12-conjugated linoleic acid induces hyperproinsulinaemia in obese men: close association with impaired insulin sensitivity. Diabetologia 2004;47(6):1016–9.
[113] Moloney F, Yeow TP, Mullen A, Nolan JJ, Roche HM. Conjugated linoleic acid supplementation, insulin sensitivity, and lipoprotein metabolism in patients with type 2 diabetes mellitus. Am J Clin Nutr 2004;80(4):887–95.
[114] Riserus U, Smedman A, Basu S, Vessby B. Metabolic effects of conjugated linoleic acid in humans: the Swedish experience. Am J Clin Nutr 2004;79(6 Suppl):1146S–8S.
[115] Noone EJ, Roche HM, Nugent AP, Gibney MJ. The effect of dietary supplementation using isomeric blends of conjugated linoleic acid on lipid metabolism in healthy human subjects. Br J Nutr 2002;88(3):243–51.
[116] Gaullier JM, Berven G, Blankson H, Gudmundsen O. Clinical trial results support a preference for using CLA preparations enriched with two isomers rather than four isomers in human studies. Lipids 2002;37(11):1019–25.
[117] Syvertsen C, Halse J, Hoivik HO, Gaullier JM, Nurminiemi M, Kristiansen K, et al. The effect of 6 months supplementation with conjugated linoleic acid on insulin resistance in overweight and obese. Int J Obes (Lond) 2007;31(7):1148–54.
[118] Gaullier JM, Halse J, Hoye K, Kristiansen K, Fagertun H, Vik H, et al. Supplementation with conjugated linoleic acid for 24 months is well tolerated by and reduces body fat mass in healthy, overweight humans. J Nutr 2005;135(4):778–84.
[119] Smedman A, Basu S, Jovinge S, Fredrikson GN, Vessby B. Conjugated linoleic acid increased C-reactive protein in human subjects. Br J Nutr 2005;94(5):791–5.
[120] Steck SE, Chalecki AM, Miller P, Conway J, Austin GL, Hardin JW, et al. Conjugated linoleic acid supplementation for twelve weeks increases lean body mass in obese humans. J Nutr 2007;137(5):1188–93.
[121] Ramakers JD, Plat J, Sebedio JL, Mensink RP. Effects of the individual isomers cis-9, trans-11 vs. trans-10, cis-12 of conjugated linoleic acid (CLA) on inflammation parameters in moderately overweight subjects with LDL-phenotype B. Lipids 2005;40(9):909–18.

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Please cite this article in press as: MacRedmond R, Dorscheid DR, Conjugated linoleic acid (CLA): Is it time to supplement asthma therapy?, Pulmonary Pharmacology & Therapeutics (2011), doi:10.1016/j.pupt.2011.03.005