

CONJUGATED LINOLEIC ACID: IMPLICATIONS FOR HUMAN HEALTH

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Conjugated linoleic acid (CLA) is being sold as a panacea that has the capability of reducing or eliminating cancer, preventing heart disease, improving immune function, and altering body composition to treat obesity or build lean body mass. Unfortunately, there has been very little published human research on CLA. This review will examine the literature on CLA and discuss the animal research on which the above claims are made. The limited human studies will be presented with an evaluation of the potential uses of CLA for human health and disease.

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INTRODUCTION

In 1979, Michael Pariza and coworkers [1] at the University of Wisconsin-Madison published a study in which they investigated the effect of cooking time and temperature on the generation of mutagenic activity in hamburger meat. In addition to mutagenic activity, they reported mutagenic inhibitory activity from both cooked and uncooked ground beef [1, 2]. Further studies showed that applying both crude extracts [3] and synthetically prepared CLA [4] to the back of mice inhibited 7,12-dimethylbenz[a]anthracene (DMBA)-induced epidermal papillomas and decreased tumor incidence. The substance was identified as isomeric conjugated derivatives of linoleic acid, or conjugated linoleic acid.

Table I
Health effects of CLA

Anticarcinogenesis
Immunomodulation
Decreased cachectic response
Enhanced cell-mediated responses
Decreased inducible eicosanoid production
Body composition alteration
Decreased fat mass
Increased lean mass
Antiatherosclerosis

CLA is found naturally in many animal products, especially those from ruminant sources [5] where it is synthesized by rumen bacteria from linoleic acid [6], although CLA can also be synthesized in non-ruminants [7] and found in non-ruminant meat sources [5]. Increased dairy fat consumption has been shown to be associated with increased CLA levels in human adipose tissue [8] and human milk [9]. CLA can also be synthesized in the laboratory from pure linoleic acid or from sources high in linoleic acid such as sunflower oil, safflower oil, or corn oil by a reaction using heat and basic conditions [5]. With this method, 95% linoleic acid (c9, c12) substrate can be converted into c9, t11 (~43%) and t10, c12-octadecadienoic acid (~44%). In the past several years, commercial sources of CLA have become available, each with different isomeric compositions. This abundant availability of CLA has rapidly advanced our understanding of CLA's myriad of biological activities. Table I shows the health effects of CLA.

CLA AND CARCINOGENESIS

A significant body of literature describes the anticarcinogenic effects of CLA in various cancer models. Using a rat breast cancer model, Ip and coworkers [10] found that CLA decreased mammary tumor incidence and weight, and that this protective effect was dose dependent for CLA levels in the diet up to 1% (no additional protection above the 1% level). Further studies showed that dietary exposure of rats to CLA limited to the time period of mammary gland development was

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sufficient to suppress mammary tumors subsequently induced by methyl-nitrosourea when CLA was no longer in the diet [11]. CLA was not found to be as effective at inhibiting tumorigenesis when added to the diet after initiation unless it was fed continuously for 5 months. Another study showed that CLA inhibited mammary tumor development despite the level or type of fat used in the diet. To study different levels of fat, the investigators used a blend of fat similar to that present in the typical US diet at levels of 10, 13.3, 16.7, or 20% by weight of diet. To study types of fat they used diets with fat consisting exclusively of corn oil (unsaturated fatty acids) or predominantly of lard (saturated fatty acids) [12]. When CLA was fed at levels from 0.5% to 2%, CLA accumulated in rat mammary tissue in a dose-dependent manner [13]. Incorporation of CLA and the ability of CLA to suppress tumorigenesis was not affected by linoleic acid levels of 2% or 12% in the diet [13]. CLA provided in the diet as enriched butter fat (primarily the *c9*, *t11* isomer in the triglyceride form) was effective in reducing terminal end bud density (see the mechanism discussion below) similarly to CLA provided as a mixture of free fatty acids [14]. When CLA was removed from the diet, decreasing tissue levels of CLA paralleled increasing occurrence of new mammary tumors [15]. When human breast cancer cells (MDA-MB468) were inoculated into severe combined immunodeficient (SCID) mice fed CLA, local tumor growth was decreased relative to mice on the control diet, and metastasis of cancer cells to lungs, peripheral blood, and bone marrow was prevented [16]. The most direct evidence for a protective effect of CLA in human cancer to date is from a preliminary study using human breast adipose tissue obtained from patients at the time of surgery for carcinomas or benign tumors. Adjusting for age, menopausal status, and body mass index (BMI), an inverse association was found between the level of CLA in the breast adipose and the risk of breast cancer [17].

Investigations into the mechanisms of CLA's effects on mammary carcinogenesis indicate that CLA does not affect total, neutral, or phospholipid levels in mammary tissue, but CLA does decrease mammary epithelium density and DNA synthesis in terminal end buds and lobuloalveolar buds [18, 19]. In addition, studies with estrogen responsive (MCF-7) and unresponsive (MDA-MB-231) human breast cancer cell lines demonstrated that CLA decreased the growth of the MCF-7 cells, but not the MDA-MB-231 cells. This effect on the MCF-7 cells disappeared when the cells were transferred to media without CLA. Furthermore, flow cytometry analysis indicated that more of the MCF-7 cells remained in the G0/G1 phase of the cell cycle and RNA expression of the protooncogene *c-myc* was decreased when the cells were cultured with CLA [20]. The mechanism by which CLA inhibits tumor cell growth appears to be mediated by CLA metabolites of both the lipoxygenase and cyclooxygenase pathways [19, 21, 22]. Recently published data showed that increased levels of dietary

CLA led to increased levels of retinol in mammary tissue (as well as plasma and liver). The authors suggested that this concomitant increase in retinol could have some role in CLA's anticarcinogenic effects in the rat mammary cancer model [23]. There may also be a link between CLA and peroxisome proliferator-activated receptors with regards to anticancer mechanisms, but the evidence is inconclusive at this time and seems to be species dependent [24–27].

Other cancer models have shown CLA to be equally effective. In addition to the aforementioned inhibition of epidermal tumors by externally applied CLA, CLA fed post-initiation with DMBA, but during promotion with 12-O-tetradecanoylphorbol-13-acetate (TPA), reduced skin tumor incidence [28]. In a different mouse model, CLA inhibited benzo(a)pyrene-induced forestomach neoplasia relative to linoleic acid and olive oil treatment [29]. In rats, the number of 2-amino-3-methylimidazo[4,5-*f*]quinoline(IQ)-induced colonic foci was significantly reduced by CLA administration [30]. SCID mice inoculated with DU-145 human prostatic carcinoma cells had decreased local tumor load and decreased metastasis to the lung if fed a diet supplemented with 1% CLA relative to those mice on a control diet or a diet supplemented with 1% linoleic acid. In one-third of the CLA-supplemented mice, the tumors were visibly necrotic and the necrosis progressed until the tumors fell out [31]. Strong evidence for the anticancer abilities of CLA indicate a need to implement clinical investigations of CLA's effect in human patients.

CLA AND IMMUNE MODULATION

Prior to collaborations with Pariza, Mark Cook and coworkers [32] investigated the role of nutrition in immune-induced cachexia. In animal agriculture, enhanced immune function leads to decreased growth resulting in significant commercial losses due to the increased production costs. Conversely, interventions which enhance growth tend to suppress immune function [33]. Cytokines produced during an immune response enhance immune cell proliferation, allowing the host immune system to attack the invading pathogen. However, these cytokines have an overall catabolic effect on non-lymphoid tissues. For example, interleukin-1 (IL-1) and tumor necrosis factor released by macrophages during an immune response can stimulate the breakdown of skeletal muscle and signal production of cholecystokinin, an intestinal peptide which induces anorexia [34, 35]. At the level of the skeletal muscle, IL-1 stimulates production of prostaglandin (PG) E_2 which in turn is responsible for protein degradation [36]. Prostaglandins such as PGE_2 are synthesized from linoleic acid via the cyclooxygenase pathway. This link between linoleic acid and immune-induced cachexia prompted Cook and Pariza to investigate the hypothesis that CLA would protect against immune-induced cachexia.

In three separate trials, Cook and coworkers [37,38] investigated the effect of dietary CLA (0.5%) on bacterial lipopolysaccharide (LPS)-induced growth suppression. In both chickens and rats, CLA supplementation of the diet protected against weight loss induced by LPS injection. Suspecting that this protection against the cachectic response was due to a suppression of the immune system, the investigators also measured several immune parameters including antibody responses to bovine serum albumin and sheep red blood cells, phytohemagglutinin (PHA) foot pad swelling (delayed-type hypersensitivity, DTH), and macrophage phagocytic activity. There were no adverse immune effects in the chickens or rats. In fact, PHA response and macrophage phagocytic activity were enhanced in rats. Mice fed a basal diet or a diet supplemented with 0.5% fish oil lost twice as much weight when injected with LPS compared to mice fed a diet supplemented with 0.5% CLA. Spleen lymphocyte blastogenesis (another measure of immune function) was also increased in mice fed CLA compared to the control- and fish-oil-fed mice.

In these early studies, it was hypothesized that CLA protects against protein degradation at the level of the skeletal muscle by alteration of phospholipid fatty acid composition, which in turn alters the production of eicosanoids such as PGE₂ [37]. Indeed, this was later shown to be the case in several systems. Dietary CLA suppressed the production of PGE₂ in serum and spleen [39], keratinocytes [40], trachea [41], and bone [42]. In fact, Nugteren [43] demonstrated that the elongated and desaturated metabolites of the *t*10, *c*12 isomer of CLA competitively inhibited the conversion of arachidonic acid into PGE₂.

Other reports also indicate that CLA may enhance immune function. Increased lymphocyte proliferation has been demonstrated *in vivo* with porcine blood lymphocytes [44] and *ex vivo* (primary cell culture assays from animals fed CLA) with splenic lymphocytes [45,46], however not all *ex vivo* studies showed an effect from CLA. With the *in vitro* model, investigators demonstrated that CLA decreased IL-2 production and macrophage phagocytic ability, while increasing macrophage killing ability [44]. However, in *ex vivo* models, lymphocytes from CLA-supplemented animals had increased IL-2 production [45,46] and no change in lymphocyte cytotoxicity [45], IL-1 and PGE₂ production, or DTH reaction [46]. In an *ex vivo* rat model, dietary CLA reduced the levels of some cytokines produced by peritoneal macrophages, but not always at both ratios of polyunsaturated fatty acids tested (n-6:n-3 at 7.3:1 and 1.8:1) or at both basal and stimulated levels [47].

Due to the ability of CLA to increase certain aspects of immune function, Cook and coworkers [48] decided to investigate whether CLA would enhance autoimmune diseases or allergic (type I hypersensitivity) reactions. Autoimmune NZB/W F1 mice fed CLA lost significantly less weight compared to control-fed mice once immune-induced proteinuria had developed. In this

model, anti-DNA antibodies appeared sooner in CLA-supplemented mice than in controls, however, the days of survival did not differ between the dietary treatments (i.e. survival after proteinuria developed was increased in CLA-supplemented mice compared to controls). In a guinea-pig model for type I hypersensitivity (i.e. immune reactions such as allergic asthma and other allergies), CLA did not affect antigen-induced tracheal contractions, and in fact, CLA decreased antigen-induced histamine and PGE₂ released from the trachea [41]. Further studies with this model found that CLA decreased the entire profile of prostanoids and cysteinyl leukotrienes in response to antigen challenge without affecting basal eicosanoid production [49]. Sugano and coworkers [50] showed that CLA increased IgA, IgG, and IgM, while decreasing IgE in rat serum and mesenteric lymph node lymphocytes. Leukotriene (LT) B₄ was decreased in a dose-dependent fashion in spleen and lung, but changes in the lung did not reach statistical significance. LTC₄ was significantly decreased in lung by as little as 0.5% dietary CLA. These investigators found no difference in the amount of histamine released from peritoneal exudate cells (spontaneously or after calcium ionophore stimulation), but did see a trend toward decreased stored histamine with increasing levels of dietary CLA (unlike the model for type I hypersensitivity, this model did not involve antigen sensitization of the animal). PGE₂ levels were significantly decreased in the serum, but not in the spleen of CLA-fed rats. Based on these results, CLA may be shifting the immune response from a T_H2-type response (allergic reactions) in favor of a T_H1-type response (cell-mediated functions) [51].

Immunological studies to date indicate that CLA may have implications for human health in promoting maintenance of lean body mass during immune stimulation, especially in wasting diseases such as cancer or AIDS, and during late stages of autoimmune diseases such as lupus. CLA may also help downregulate type I hypersensitivity reactions, leading to less severe immune responses to allergens.

CLA AND BODY COMPOSITION

During the immune studies described above in which CLA was shown to enhance growth, researchers also noticed a difference in the amount of food being consumed between the treatments, which led to the investigation of the role CLA was playing in feed efficiency and body composition.

In a study designed to determine if CLA is a growth factor, rats were fed a CLA-supplemented diet during gestation and lactation. Body weights for the pups were significantly higher relative to controls. In addition, when these pups were weaned and fed a CLA-supplemented diet, they continued to weigh more than their control counterparts while consuming the same amount of food, leading to an improved feed efficiency [52].

The improved feed efficiency led Cook and Pariza to investigate the effects of CLA on body composition. Research showed that 0.5% CLA in the diets of mice (ICR) resulted in a decreased body fat of 57% and 60% in males and females, respectively ($P < 0.0001$ and $P < 0.01$). Whole body protein was significantly increased in the CLA-fed mice as well. In these studies, body weights were similar, but feed efficiency of the CLA-fed group was significantly improved [53]. The effect on whole body protein apparently precedes the effect on total body fat [54]. This effect of CLA on body fat in a different strain of mice (AKR/J) fed high fat (45% kcal) and low fat (15% kcal) diets [55] confirmed the results of Park, *et al.* [53]. However, in AKR/J mice, CLA decreased total body protein in one study [55], but increased total body protein in the same strain of mice in a subsequent study [56]. When CLA was withdrawn from the diet of mice, body fat remained reduced and total body protein levels remained elevated relative to control-fed animals for the 8 weeks remaining in the study [54].

Several biochemical studies have been performed in an attempt to elucidate the mechanisms by which CLA affects body composition. Park and coworkers [53] showed that dietary CLA increases carnitine palmitoyltransferase activity, the rate limiting enzyme in β -oxidation, in mice. The same enzyme effect was also reported in rats [27]. Using the 3T3-L1 adipocyte cell line, CLA was shown to inhibit the activity of lipoprotein lipase (the enzyme responsible for cleaving fatty acids off the glycerol backbone so they can be taken up and stored by adipocytes) and decrease the amount of esterified and free glycerol in the cells while increasing the free glycerol in the culture medium (an indication of increased lipolysis) [53]. This is consistent with another report which found that adipocytes from rats fed 0.5% CLA exhibited enhanced norepinephrine-induced lipolysis and hormone sensitive lipase activity (the enzyme responsible for cleaving esterified fatty acids from triglycerides within adipocytes so the fatty acids may be exported) [53]. Another group showed that CLA significantly reduced 3T3-L1 proliferation (measured as tritiated thymidine incorporation) [57]. However, they noted that CLA increased lipid filling of 3T3-L1, which contradicts that Park and coworkers found [53]. This could be due to different methodologies used such as use of albumen-complexed fatty acids vs free fatty acids in the cell cultures and adding CLA at different stage of differentiation of the 3T3-L1 cells. The results by Satory and Smith [57] (increased lipid filling) were refuted by Park and coworkers in a recent publication [54] and are inconsistent with *in vivo* reduced body fat data [53–56]. Another group investigated the effects of CLA on 3T3-L1 cells and found that CLA inhibited differentiation (indicated by glycerol-3-phosphate dehydrogenase activity) and reduced mRNA expression of several proteins typically expressed during differentiation. CLA also reduced cell number in pre-confluent cells, but had no effect on

uninduced post-confluent cells and increased the number of induced post-confluent cells [58]. However, Azain and coworkers [59] showed that dietary CLA decreased rat fat pad size by decreasing cell size but not cell number.

New reports indicate that the *t*10, *c*12 isomer is responsible for the decrease in body fat [60, 61] and that the *c*9, *t*11 isomer may be responsible for the increased growth [61]. The *c*9, *t*11 isomer does not interfere with the ability of the *t*10, *c*12 isomer to decrease body fat, however, the *t*10, *c*12 isomer may interfere with growth stimulation and improved feed efficiency associated with the *c*9, *t*11 isomer [61]. The *t*10, *c*12 isomer has also been shown to be the most effective isomer for increasing carnitine palmitoyl transferase activity (the rate limiting enzyme in β -oxidation of fatty acids) [27].

Another interesting effect of CLA on energy metabolism is its ability to normalize glucose tolerance when supplemented to the diet of pre-diabetic rats [62]. CLA-supplemented rats had significantly lower blood glucose, plasma insulin, and circulating free fatty acids. Evidence of increased aP2 mRNA, a fatty acid binding protein which is upregulated during adipocyte differentiation, suggests that the antidiabetic effects of CLA are at least partially mediated via the adipocytes.

The effect on body composition has been demonstrated in pigs in several studies. Pigs fed 1% dietary CLA had reduced feed intakes, improved feed efficiencies, deposited less subcutaneous fat, and gained more lean than pigs fed a diet supplemented with sunflower oil [63]. In another study, pigs were fed a commercial product containing 60% CLA isomers at levels of 0, 0.29, and 0.57%. Backfat thickness in the CLA-fed pigs was reduced as early as day 14 and was maintained below that of the controls over the entire time course of the experiment, reaching a 24% decrease at the time of slaughter. Feed efficiency over the entire period of the trial was also improved in the CLA group [64].

These reports on the effect of CLA on body composition in animals piqued the interest of human nutritionists. However, few human studies have been published to date, and the data for those is available only in abstract form. One study involved 20 normal to slightly overweight subjects in Norway in a randomized, double-blind, placebo-controlled trial. Subjects were given 1.8 g of CLA per day or a placebo for 3 months. Average initial body weights and percent body fat (measured by near infrared) for the control and CLA groups were similar. At the end of the 3-month trial, control subjects had gained weight (0.6 kg) and percent body fat had slightly increased (0.4%). The CLA subjects had slightly, but not significantly, lost weight (0.7 kg), but percent body fat increased from 21.3% to 17.0% ($P < 0.05$) (E. Thom, unpublished data, personal communication).

Another human study involved 24 experienced resistance-trained males matched for body weight and total training volume into two groups [65]. The CLA group received 3.6 grams per day of CLA and the control groups received olive oil capsules for a total

of 28 days. Body composition was measured using dual-energy X-ray absorptiometry (DEXA). There were no significant differences in body mass, percent body fat, lean body mass, or strength performance on exercise tests (bench press and leg press). However, the trends for both exercise tests were improved for the CLA group.

A study with novice male body builders did show an improved strength performance (leg press), greater skinfold-corrected arm girth gain, and greater body mass gain in subjects ingesting 7.2 g of CLA per day compared to those taking a vegetable oil placebo [66]. There was no effect of supplementation on subcutaneous fat measured by skinfold or total body fat, or water distribution measured by bioelectrical impedance analysis, indicating CLA enhanced strength and body mass without increasing body fat.

These human studies were relatively short and involved a lower CLA dose per unit body weight than the animal studies described above. However, data from the human breast cancer study mentioned above in which investigators analyzed breast tissue taken from 360 patients at the time of surgery indicated that there was a significant inverse correlation between body mass index and CLA levels in breast tissue [17]. Further research will be necessary to determine more conclusively if CLA is effective at increasing lean body mass and improving muscle strength in humans.

A human study involving 80 obese subjects was conducted at the University of Wisconsin in Madison. The study was randomized, double-blind, and placebo controlled for a 6-month period. Subjects were counseled to follow a standardized diet and exercise regimen with a modest reduction in calorie intake and modest increase in exercise. The CLA dose was 2.7 g per day. Body composition was assessed by underwater weighing. Mean body weights and percent body fat were similar between the two groups at baseline. There were no significant differences in body weight or percent body fat between the two groups at the end of the 6-month period. Both groups lost about 2.5 kg of weight and about 1 kg of fat. A subpopulation of individuals gained weight during the trial. Within this subpopulation, there were twice as many subjects in the CLA group compared to the control group who gained lean body mass, and the CLA subjects lost body fat on average while the control subjects gained body fat. There were no major side effects in either group [67].

There are several potential reasons why the results seen in this study are dissimilar from the results of the previously described animal studies. The dose used was much lower per unit body weight than that used in the animal studies (about 27 mg per kg body weight per day in the human study vs about 240 mg per kg body weight per day in the pig study). The human subjects were all adults rather than growing animals, and none of the animal studies involved obese animals or restricted caloric intake (animals were always fed *ad libitum*). Two recently published abstracts described studies which ad-

dressed these issues. One study involved human subjects living on a metabolic ward [68]. Researchers determined that CLA supplementation did not affect hunger in these subjects. However, subjects were required to eat a specified number of calories each day based on energy requirements calculated at the beginning of the study. This design did not parallel the *ad libitum* feeding in the animal trials. The second study involved obese mature beagles which typically need to be food restricted to avoid weight gain and body composition changes. The animals were allowed to eat *ad libitum* for 45 minutes each day. CLA supplementation of the diet impeded weight gain and body fat increase relative to animals fed the control diet [69]. Another recent study addressing the issue of feed restriction vs *ad libitum* feeding showed that growing rats that were feed-restricted to about 30% below their required maintenance levels and fortified with CLA had a repartitioning of energy such that body protein was significantly increased and body fat was significantly decreased compared to restricted rats whose diets were not fortified with CLA [70].

To conclusively determine if CLA will have applications for improving human body composition, studies need to be undertaken with higher doses of CLA during which the subjects are not calorie restricted. In addition, studies during active weight gain, either in subjects prone to obesity or obese people who have lost weight, are warranted to determine if CLA will prevent fat gain. Studies involving the prevention of age-related increased in body fat may also prove valuable.

CLA AND ATHEROSCLEROSIS

Considerably fewer studies have been published addressing the role of CLA in atherosclerosis compared to the other topics covered, however, the information available suggests another positive role of CLA in health. An early study found that rabbits fed a diet supplemented with CLA had significantly decreased low density lipoprotein (LDL) cholesterol (the cholesterol attributed to increasing atherosclerosis). There was no significant difference in the high density lipoprotein (HDL) levels, and the LDL:HDL ratio was decreased significantly in the CLA group. Upon histological examination, the researchers found that the percent of the aortic surface that was involved in the atherosclerotic lesions was 12% less in the CLA-supplemented animals (not statistically significant, but biologically relevant). In addition, in the histological evaluation of lipid deposition and connective tissue development in the thoracic and abdominal aortas, the CLA-supplemented group had fewer rabbits classified as severe compared to the control group [71]. Using this same model, Kritchevsky [72] has also found that rabbits fed a CLA-supplemented diet after the development of atherosclerotic lesions had a 30% regression of these lesions. Currently, dose-response effects of CLA are being investigated.

Another group of scientists investigated CLA's effect on atherosclerosis using a hamster model [73]. Hamsters were fed a hypercholesterolemic diet alone (control) or with 1.1% linoleic acid or 0.06, 0.11, or 1.1% CLA added to the control diet. The total plasma cholesterol was significantly decreased by 21–26% in all three CLA groups (not dose-dependently) relative to the control group, and by 8–14% relative to the linoleic acid group. The non-HDL cholesterol was also significantly decreased similarly by CLA. Triglycerides were significantly decreased in the low and medium CLA groups. The mean fatty streak area for all the CLA groups combined was also significantly lower than the controls.

Recently, two other studies using a hamster model have been reported. One group reported a decrease in fasting LDL-, HDL-, and total cholesterol and an increase in VLDL-cholesterol and plasma triglycerides in hamsters fed a diet supplemented with a mixture of the *c*9, *t*11 and *t*10, *c*12 isomer as well as the *t*10, *c*12 isomer alone, but the *c*9, *t*11 isomer alone had no significant effect [26]. The other group reported that dietary CLA (isomer mixture) decreased triglyceride, total cholesterol, and non-HDL cholesterol, but did not affect HDL cholesterol compared to the linoleic acid diet group [74]. In this study, the *c*9, *t*11 isomer alone also had no significant effect. Therefore, although the specific effects of CLA differ somewhat from study to study, the *t*10, *c*12 isomer appears to be the active isomer for the antiatherogenic effects of CLA.

A study using C57BL/6 mice as an atherosclerosis model found some conflicting results. While a 5 g of CLA per kg diet significantly decreased serum triacylglycerol and HDL : total cholesterol ratio compared to control mice, in the highest level of CLA (5 g kg⁻¹) there was no difference in total aortic fatty streak area compared to controls, and at the lower level (2.5 g kg⁻¹) the investigators reported an increase in total aortic fatty streak area compared to controls [75].

The antiatherogenic effects could be explained, at least in part, by a decreased presence of cholesterol in the liver [70] and a decreased secretion of cholesterol by the liver [76] shown in rat models, as well as the ability of CLA to inhibit thromboxane production [49] and platelet aggregation [77]. Further studies using models of atherosclerosis are needed to address conflicting reports and to elucidate other mechanisms by which CLA may be having these effects.

SUMMARY

The amount of published literature describing the biological effects of CLA has expanded dramatically in recent years. Unfortunately, very little of this research has been done in humans. Ongoing research attempts to further elucidate mechanisms involved in these diverse biological responses. Recent findings suggest that not only does CLA affect many different pathways, but that individual

isomers of CLA act differently. In addition to the pressing need to continue uncovering these mechanisms, it is also imperative to determine if these beneficial biological effects can be applied to human health. At this time, it is not possible to state with certainty if CLA supplementation will be beneficial for humans.

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