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REVIEWS: CURRENT TOPICS

Biological effects of conjugated linoleic acids in health and disease☆

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Abstract

Conjugated linoleic acid (CLA) is a mixture of positional and geometric isomers of octadecadienoic acid [linoleic acid (LA), 18:2n-6] commonly found in beef, lamb and dairy products. The most abundant isomer of CLA in nature is the *cis*-9, *trans*-11 (c9t11) isomer. Commercially available CLA is usually a 1:1 mixture of c9t11 and *trans*-10, *cis*-12 (t10c12) isomers with other isomers as minor components. Conjugated LA isomer mixture and c9t11 and t10c12 isomers alone have been attributed to provide several health benefits that are largely based on animal and in vitro studies. Conjugated LA has been attributed many beneficial effects in prevention of atherosclerosis, different types of cancer, hypertension and also known to improve immune function. More recent literature with availability of purified c9t11 and t10c12 isomers suggests that t10c12 is the sole isomer involved in antiadipogenic role of CLA. Other studies in animals and cell lines suggest that the two isomers may act similarly or antagonistically to alter cellular function and metabolism, and may also act through different signaling pathways. The effect of CLA and individual isomers shows considerable variation between different strains (BALB/C mice vs. C57BL/6 mice) and species (e.g., rats vs. mice). The dramatic effects seen in animal studies have not been reflected in some clinical studies. This review comprehensively discusses the recent studies on the effects of CLA and individual isomers on body composition, cardiovascular disease, bone health, insulin resistance, mediators of inflammatory response and different types of cancer, obtained from both in vitro and animal studies. This review also discusses the latest available information from clinical studies in these areas of research.
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Keywords: Conjugated linoleic acid; Bone; Fat mass; Cancer; Insulin resistance; Inflammation; Cardiovascular health

1. Introduction

Conjugated linoleic acid (CLA) refers to a group of polyunsaturated fatty acids (PUFA) that exist as positional and stereoisomers of octadecadienoic acid. There is no methylene group separating the double bonds of CLA as there is in linoleic acid (LA). Instead, conjugated double bonds (i.e., the two double bonds are separated by one single bond) in either *cis* (c) or *trans* (t) configuration are present predominantly in positions 8 and 10, 9 and 11, 10 and 12, or 11 and 13. They are found naturally in ruminant food products such as beef, lamb and dairy because of the process of bacterial biohydrogenation of LA in the rumen [1–3]. Conjugated LA was discovered quite accidentally when Pariza and Hargraves [4] were investigating the carcinogenic properties of grilled beef. To their surprise and contrary to their expectations, the fatty acids present in grilled beef exhibited anticarcinogenic rather than procarcinogenic properties. Ever since that discovery, CLA has been reported to have several beneficial effects in health-related disorders using animal models and cell cultures derived from humans and animals. Thus, CLAs have been shown to have antiadipogenic [5–7], anticarcinogenic [8–15], antiatherogenic [16–19], antidiabetogenic [20,21] and anti-inflammatory properties [22–25].

Although there are 28 different CLA isomers, the major isomer in natural foods is the c9t11 isomer accounting for more than 90% CLA intake in the diet [26]. Conjugated LA isomers can be prepared commercially by heating LA under alkaline conditions or by partial hydrogenation of LA [27,28]. Health benefits of CLA have been attributed to mainly two of its isomers: *cis*-9, *trans*-11 (c9t11) and *trans*-10, *cis*-12 (t10c12). Structures of the parent LA, c9t11 and t10c12 CLA isomers are shown in Fig. 1. The most commonly used CLA is the mixed isomer preparation containing (approximately 40–45%) equal levels of the

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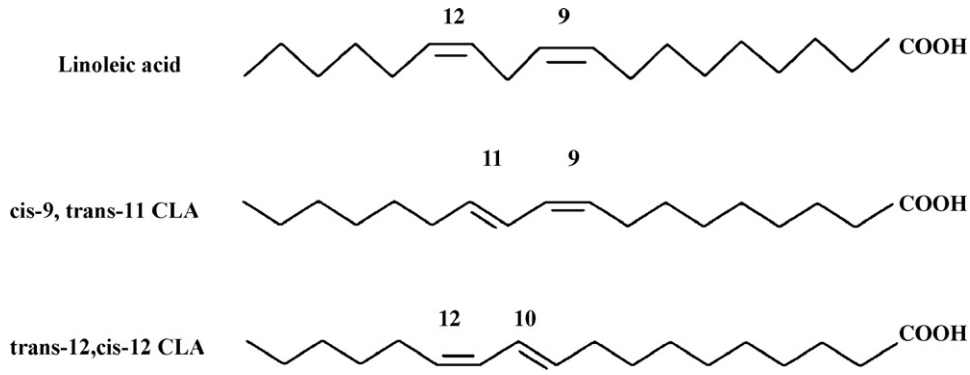

Fig. 1. Structures of parent LA, c9t11 and t10c12 CLA.

c9t11 and t10c12 isomers. With the advent of technology, enriched or purified c9t11 and t10c12 CLA preparations have become commercially available in recent years, leading to studies examining the effects of these individual isomers in health-related disorders. Most of the studies have used CLA isomer mix, but recent evidence suggests that c9t11 and t10c12 may have myriad effects in different biological systems. Indeed, it has been found that both the isomers exhibit significant biological activities, which often may be similar or opposite. This review focuses on the biological role of CLA and its purified isomers (c9t11 and t10c12) in different models of health-related disorders in cell culture, animals and clinical studies. Unless otherwise mentioned in this review, CLA refers to a mixture containing equal levels of c9t11 and t10c12 isomers.

2. Conjugated LA and body composition

2.1. Animal studies

Park et al. [5] showed for the first time that intake of 0.5% CLA in ICR male and female mice (50% c9t11 and 50% t10c12) results in decreased body fat mass and increased lean body mass. The mechanisms proposed were increased lipolysis, increased fatty acid oxidation or reduced fatty acid uptake in adipocytes. Subsequent studies in different animal models corroborated the findings and showed that CLA containing equal proportions of both isomers decrease fat mass and enhance lean mass [21,29–34]. These studies and others have been discussed in reviews published elsewhere [35–39].

The availability of purified isomers or CLA enriched in either c9t11 or t10c12 isomers prompted new in vivo and in vitro studies, which identified t10c12 isomer to be primarily involved in reduction of fat mass, and not the c9t11 isomer. When hamsters were fed with a hypercholesterolemic diet containing 1% CLA, 0.2% c9t11 CLA or 1% LA, CLA isomer mix-fed animals had the lowest weight gain [40]. Yet, another study showed that intake of t10c12 isomer-enriched diet decreases body fat significantly compared to diet enriched in c9t11 isomer [6]. In a study in Zucker diabetic fatty (ZDF) rats, dietary intake of 1.5% of CLA (47% c9t11+47.9% t10c12) decreased weight gain and fat mass, whereas dietary intake of CLA containing 91% c9t11 had no effect on these parameters, proving that t10c12 is the isomer responsible for loss of fat mass [20]. In vitro studies using purified c9t11 and t10c12 isomers and cultured 3T3-L1 adipocytes provided further supportive evidence that t10c12 was the isomer responsible for the fat-lowering effects of CLA [6,41].

Here we summarize recent information on the impact of CLA or its isomers on body composition. Navarro et al. studied the effect of 6 weeks of supplementation of 0.5% LA, c9t11 CLA or t10c12 CLA in atherogenic diet-fed hamsters. Although there was no difference in body weight, fat mass decreased significantly in t10c12-fed hamsters [42]. In a related study, intake of diet containing 0.5% t10c12 CLA for 6 weeks decreased fat mass in atherogenic diet-fed hamsters [43], but failed to prevent insulin resistance (IR) associated with intake of atherogenic diet. Wargent et al. [44] recently showed that intake of t10c12 CLA isomer for 3 weeks in genetically obese mice decreased gain in body weight and white fat pad weight. In a study using wild-type and stearoyl-CoA desturase 1 (SCD1) null mice, t10c12 CLA decreased fat mass and enhanced mRNA expression of lipogenic enzymes, fatty acid synthase (FAS) and uncoupling protein 2 (UCP-2), suggesting that antiobesity effects of t10c12 CLA is independent of SCD1 gene expression and enzyme activity [45].

Some recent studies have evaluated the impact of the type of dietary fat on the antiadiposity effects of CLA. A recent study showed that CLA isomer mixture (1.5%, 4 weeks) had no effect on adiposity in Sprague–Dawley (SD) rats when given alongside diets rich in either saturated fat (coconut oil) or unsaturated fat [corn oil (CO)] [46]. Another recent study examined the effects of 14 days of CLA mixture intake on body fat in mice previously treated with diets containing soy oil as control, coconut oil [essential fatty acid-deficient (EFAD)] and fish oil for 42 days [47]. Conjugated LA significantly decreased body weight and epididymal fat mass, but not retroperitoneal fat mass in both control and EFAD diet-fed mice. The study suggested that CLA seems to be more effective in lowering fat mass when diet was deficient in essential fatty acids

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