**Review**

**Isomer specificity of conjugated linoleic acid (CLA): 9E,11E-CLA**

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Abstract

Conjugated linoleic acids (CLA) were identified in 1980’s, since then it has been intensively studied due to its various beneficial health effects such as anti-inflammatory, anti-atherogenic, anti-carcinogenic and anti-diabetic/obesity effects. Isomer specificity of a number of CLA isomers, especially predominant isomer 9Z,11E- and 10E,12Z-CLA, is now recognized. However, the less prevalent CLA isomers have not been well characterized. Recently, studies have reported the distinctively different effects of 9E,11E-CLA in colon cancer cells, endothelial cells, and macrophage cells compared to the rest of CLA isomers. In this review, various effects of CLAs, especially anti-inflammatory and anti-atherogenic effects, will be discussed with focusing on the isomer-specific effects and potential mechanism of action of CLA. At last, recent studies about 9E,11E-CLA in in vitro and animal models will be discussed.

Key Words: Conjugated linoleic acid (CLA), 9E,11E-CLA, anti-inflammatory, isomer-specificity

Overview of conjugated linoleic acids

CLAs are fatty acids that are mainly found in foods derived from ruminant animals (Pariza & Ha, 1990). They are geometrical and positional isomers of its parent molecule, linoleic acid (cis-9,cis-12-18:2, n-6 (LA)). The cis-9, trans-11 (9Z,11E-octadecenoic acid, C18:2) isomer, also known as rumenic acid (RA), is generated via biohydrogenation of dietary linoleic acids by ruminant microflora and is the most abundant natural CLA isomer (over 75-80% of total CLA). It is not clear whether humans are able to produce RA from other fatty acids (Yurawecz, 1999); however, it is likely that the majority of RA found in the human body originates from the diet. Estimated CLA intake for humans is between 0.5 and 1 g/d (Ip et al., 1994); however, more recent estimates suggest that CLA and RA intakes are much lower (Yurawecz, 1999). For example, the average intake is 430 mg/day for men and 350 mg/day for women in Germany, 212 mg/day for men and 151 mg/day for women in the USA, and 500-1,000 mg/day in Australia (Yurawecz, 1999).

Studied for its potential beneficial effects of CLA on animal health have focused on anti-inflammatory, anti-atherogenic, anti-carcinogenic, and anti-diabetic/anti-obesity effects; however, the beneficial effects of CLA in humans is inconclusive (Kelly, 2001; Pariza et al., 2001; Rainer & Heiss, 2004; Wahle et al., 2004; Whigham et al., 2000). It is important to note that a majority of the CLA studies was performed with a chemically synthesized CLA mixture, although in recent years, some were done with relatively pure 9Z,11E-CLA or 10E,12Z-CLA isomers. CLA supplements which predominantly contain two major CLA isomers are on the market; however, the safety of CLA is a concern in public health. To obtain beneficial amounts of CLA, one must ingest 10-200 times what can be achieved in diet (Gaullier et al., 2002). Although animal studies on CLA showed that it is reasonably safe and well-tolerated in rats, dogs, and pigs (OHagan & Menzel, 2003; Pariza, 2004; Scimeca, 1998), whether the same is true for humans is not known. Gaullier et al. (2002) stated that CLA enriched with 9Z,11E- and 10E,12Z-CLA may be better for human consumption than one enriched with 8E,10Z-, 9Z,11E-, 10E,12Z-, and 11Z,13E-CLA. In spite of these conclusions, concerns on CLA safety remain due to its adverse effects which induce fatty liver, insulin resistance, and lipodystrophy in mice and increase C-reactive protein levels, lipid peroxidation, and reduction of milk fat in humans (Pariza, 2004); therefore, it is essential for long-term human studies to make solid conclusions on recommending a proper amount of CLA supplementation to the public. It is also important to consider differences in CLA isomers in terms of both benefits and potential toxicity.

**Anti-inflammatory effects**

Levels of fatty acids are known to have a great impact on immune function. Dietary fat intake directly influences the fatty acid profile of blood lipids and cells. The immune-modulating effects of saturated and polyunsaturated fatty acids have been...
reported (Calder & Grimble, 2002). However, the available knowledge about the effects of CLA on immune function in animals or humans is limited. The inflammatory-modulating effects of CLA are mainly observed in in vitro and animal models, while CLA’s anti-inflammatory effects are not conclusive in human studies. Chicks and rats fed 0.5% CLA for 4 wks gained weight even after LPS injection, whereas chicks and rats without CLA lost weight. This led to the idea that CLA inhibited the catabolic effects of endotoxin (Cook et al., 1993). CLA fed mice had higher levels of IL-2 compared to control diet fed mice (Hayek et al., 1999; Wong et al., 1997), while TNF-α and IL-6 levels were decreased (Rahman et al., 2007). However, Kelley et al. (2002) reported that both 9Z,11E- and 10E,12Z-CLA significantly and similarly increased TNF-α and IL-6 levels without altering prostaglandin levels in CLA fed mice.

In in vitro models, CLA was positively related to anti-inflammatory effects. For example, Yu et al. (2002) showed that CLA reduced TNF-α and IL-6 levels induced by IFN-γ, at least partially by a PPARγ-dependent pathway. CLA induced IFN-γ and IL-2 levels in Juckat T cells (Luongo et al., 2003). Moreover, IL-10 receptor and IL-10 levels were induced by CLA in mouse dendritic cells (Loscher et al., 2005). In human epithelial cells, 9Z,11E-CLA attenuated cell growth and reduced IL-8 levels while 10E,12Z-CLA had no effect (Jaudszus et al., 2005).

The results from human studies focusing on anti-inflammatory effects of CLA are inconclusive. Song et al. (2005) demonstrated that CLA supplementation could be beneficial in humans (3 g/d CLA for 12 wks) by enhancing IgA, IgM, and IL-10 but inhibiting IgE, TNF-α, and IL-1β. In addition, CLA boosted the hepatitis B vaccination in healthy human subjects although it did not alter other aspects of immune function including NK cell activity, lymphocyte proliferation, and production of TNF-α, IL-1β, IL-6, IL-2, IL-4, IFN-γ, and PGE2 (Albers et al., 2003). In contrast, other human studies showed no significant relationship between CLA and anti-inflammatory effect (Albers et al., 2003; Kelley et al., 2000; Nugent et al., 2005; Ramakers et al., 2005; Ritzenthaler et al., 2005; Tricon et al., 2004a). There were no changes on the levels of PGE2, leukotriene B4, IL-1β, and TNF-α that were induced by LPS in young healthy women (Kelley et al., 2000).

The regulation of immune functions by CLA does not seem to be affected by a single mechanism. CLA affects the production of eicosanoids either directly or indirectly, enhances PPARγ activation, attenuates the NF-κB pathway, or directly decreases pro-inflammatory cytokines to have beneficial effects on inflammation which ultimately influence metabolic syndromes including obesity, insulin resistance, and atherosclerosis (Zulet et al., 2005). CLA decreased the production of eicosanoids such as PGE2, PGF2α, and LTB4 (Li & Watkins, 1998; Sugano et al., 1998), although the reduction of the eicosanoid production was not consistent (Hayek et al., 1999; Kelley et al., 2000). The mechanism by which CLA reduces AA-derived eicosanoids can be explained as follows: (1) CLA displaces AA in phospholipids; (2) CLA competes with LA for desaturation and elongation; (3) CLA or CLA metabolites may act as substrates or antagonists for enzymes involved in the prostaglandin production process; and (4) CLA-derived eicosanoids themselves may have anti-inflammatory properties. The PPARγ subtype is highly expressed in adipose tissue and macrophages (Olefsky, 2001). Most importantly, PPARγ plays a critical role in the regulation of inflammation (Cuzzocrea et al., 2004). Various CLA isomers activate PPARγ in RAW 264.7 cells and decrease pro-inflammatory cytokines induced by IFN-γ (Yu et al., 2002). NF-κB is a transcription factor that is involved in cytokine gene expression, cellular adhesion, cell cycle activation, apoptosis, and carcinogenesis. CLA negatively regulates inflammatory mediators via the NF-κB pathway by inhibiting IκB phosphorylation (Cheng et al., 2004). Finally, CLA could exert direct anti-inflammatory properties by regulating the gene expression of inflammation mediators (Loscher et al., 2005; Luongo et al., 2003; Song et al., 2005), perhaps due to effects on NF-κB or PPARγ.

In conclusion, the anti-inflammatory action of CLA brings potential therapies for diseases such as atherosclerosis, diabetes, cancers, rheumatism, inflammatory bowel disease and obesity. Meanwhile, the lack of understanding regarding CLA’s mechanism(s) of action, safety issue surrounding CLA as a dietary supplement, and isomer-specific effects on regulating inflammatory mediators require further studies.

**Anti-atherogenic effects**

Atherosclerosis is a complex disease that is influenced in part by inflammation (reviewed in (Ross, 1999)). Interactions between lipoproteins, monocyte-derived macrophages, T cells, and the normal cellular elements of the arterial wall are important contributors for the development of atherosclerosis. CLA-fed rabbits had significantly lower low density lipoprotein (LDL) cholesterol and TG levels as well as a lower ratio of LDL/HDL (high density lipoprotein) and LDL/total cholesterol compared to control diet fed rabbits (Kitchevsky et al., 2000; Lee et al., 1994). In hamsters, CLA reduced total cholesterol, LDL, VLDL (very low density lipoprotein), and TG although there were no changes on HDL levels (Nicolosi et al., 1997). Unlike the results in rabbits and hamsters, the results from mice were somewhat conflicting (Arbones-Mainar et al., 2006; Munday et al., 1999; Nestel et al., 2006; Toomey et al., 2006). A mixture of CLA (9Z, 11E-CLA:10E, 12Z-CLA (80:20 blend)) was tested in ApeE-/- mice and showed a suppression of atherosclerotic lesions by decreasing pro-inflammatory genes (i.e., metalloproteinases (MMP)-9 and PECAM-1) and an increase in apoptotic genes (Toomey et al., 2006). Isomer-specificity of regulation of the lipid profile by CLA isomers was shown in a few studies. Mitchell et al. (2005) showed that 10E,12Z-CLA increased HDL levels in 1% CLA fed hamsters. However, Wilson et al. (2006) reported that 9Z,11E-CLA decreased cholesterol whereas
10E,12Z-CLA increased cholesterol levels in 0.5% CLA isomer fed hamsters. This discrepancy may be due to the relative amount and composition of the CLA mix used in the studies.

Different types of cell lines related to atherosclerosis were used to study the anti-atherogenic effects of CLA in in vitro systems. Decreased levels of 6-keto-prostaglandin F(1α) (6-k-PGF(1α)), a stable breakdown product of PGI₂, were observed in bovine aortic endothelial cells treated with CLA (Coen et al., 2004). CLA increased CD36 (scavenger receptor) in THP-1, human macrophages as well as reduced total lipids, PGE₂, PGI₂, and cytokine-induced NF-κB binding activity in human smooth muscle cells (Ringseis et al., 2006; Weldon et al., 2004). However, CLA failed to inhibit adhesion molecules which are important for the initiation step of atherosclerotic lesion formation, such as ICAM-1, VCAM-1, and E-selectin induced by TNF-α in human aortic EC (Schleser et al., 2006). Although there were no changes in ICAM-1 and VCAM-1 levels by CLA, CLA inhibited the adhesion activity of THP-1 cells to human umbilical vein EC (HUVEC) (Sneddon et al., 2006).

CLA’s fat-lowering effects have been reported in human subjects, although they have not been consistent. Benito et al. (2001) showed no alteration of cholesterol, TG, HDL, and LDL cholesterol levels in human on a 3.9 g/d CLA supplementation (2001) showed no alteration of cholesterol, TG, HDL, and LDL cholesterol levels in human on a 3.9 g/d CLA supplementation for 63 days. Desroches et al. (2005) reported that healthy subjects on CLA had lower total cholesterol, total cholesterol/HDL ratio compared to the subjects on control diet. On the other hand, Mougiros et al. (2001) and Gaultier et al. (2004) reported a detrimental HDL-lowering effect of CLA mix in humans. Tricon et al. (2004b) showed that 10E,12Z-CLA increased a ratio of cholesterol/HDL, LDL/HDL, and TG levels compared to 9Z,11E-CLA in healthy humans. In spite of isomer-specific effects of CLA on lipid profile, the same group reported a similar effect of those two CLA isomers on immune cell function as inhibiting mitogen-induced T cell activation (Tricon et al., 2004a). The CLA isomer-specificity varies depending on the results observed; therefore, studies on pure CLA isomers are needed to elucidate these questions.

Some proposed mechanisms for the anti-atherogenic and lipid-lowering effects of CLA include roles for PPARs, sterol regulatory element-binding proteins (SREBPs) and stearoyl-CoA desaturase (SCD) (reviewed in (Bhattacharya et al., 2006)). Further studies using each CLA isomer and long-term clinical studies are needed to establish their potential anti-atherogenic effects and mechanism(s) of action.

**9E,11E-CLA: its effects and mechanism**

The isomer-specific effects of 9Z,11E-CLA and 10E,12Z-CLA are now well-recognized (reviewed in (Evans et al., 2002)). However, the less prevalent CLA isomers have not been intensively studied. Recently, more studies have reported the effects of 9E,11E-CLA in colon cancer cells, endothelial cells, and macrophage cells (Beppu et al., 2006; Lai et al., 2005; Yasui et al., 2007). Lai et al. (2005) showed that among the CLA isomers, 9E,11E-CLA attenuated proliferation of bovine endothelial cells the most by enhancing caspase-3 activity. In the following year, Beppu et al. (2006) reported that 9E,11E-CLA showed the strongest apoptosis among 9Z,11E-, 9Z,11E-, and 10E,12Z-CLA isomer on colon cancer cells, Caco-2 cells. The same researchers further reported the 9E,11E-CLA’s chemopreventive effect in rats fed 0.1% or 1% 9E,11E-CLA for 4 wks (Yasui et al., 2007). Ecker et al. (2007) showed that 9E,11E-CLA, but not 9Z,11E- and 10E,12Z-CLA, induces SREBP target genes such as ABCG-1 via a SREBP-1c-dependent mechanism in primary human monocyte-derived macrophages. Comparison of five different CLA isomers showed that 9E,11E-CLA indeed regulates gene expression distinctively different compared to the rest of CLA isomers in a mouse macrophage cell line, RAW 264.7 (Lee et al., 2008). Thus, isomer specificity of 9E,11E-CLA has been recognized in various cell types.

Although the portion of 9E,11E-CLA in American beef fat and commercial CLA mixtures ranged from 1.5-3.7% of the total CLA isomers (Kramer et al., 1998; Yurawecz, 1999), 9E,11E- and 9Z,11E-CLA were the main CLA isomers in serum isolated from women on 2.1 g of CLA supplementation for 45 days which represented 41% of the CLA total (Petridou et al., 2003). These isomers were also the two major CLA isomers in platelet lipids, 17% and 33% of the total respectively (Al-Madaney et al., 2007). Based on the basal plasma CLA levels in healthy men as 7 μM, the 9E,11E-CLA concentration is estimated to be in the 1-3 μM range (Huang, 1994). Considering 10-fold higher concentration in local areas, 10-30 μM might be a physiologically relevant level of 9E,11E-CLA. Large-scale and economically efficient separation of 9E,11E-CLA is difficult due to its minimal existence in the CLA mixture. Kishino et al. (2002, 2003) reported the bacterial production of 9Z,11E- and 9E,11E-CLA from ricinoleic acid (12-hydroxy-cis-9-octadecenoic acid) and linoleic acid. This biological system for 9E,11E-CLA production may promise the large-scale and selective preparation of 9E,11E-CLA.

**Conclusion**

In spite of intensive studies of CLAs performed over the last two decades, the mechanism of action of each CLA isomer is not well-appreciated yet. In this review, various health-related effects of CLAs were discussed with a focus on superior and/or distinctive characteristics of 9E,11E-CLA. The limited numbers of recent studies of 9E,11E-CLA in in vitro and in vivo studies suggest that this specific CLA isomer appears to have the anti-carcinogenic, anti-inflammatory, and potential anti-atherogenic effects. Although it requires more in vivo and clinical studies before making a solid conclusion, understanding the effects of the individual CLA isomer helps us to make a combination of the CLA isomers in dietary supplements to maximize its healthful effects and minimize its harmful effects.
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