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Modulation of inflammation and immunity by dietary conjugated linoleic acid ☆

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ABSTRACT

Conjugated linoleic acid (CLA) is a mixture of positional and geometric isomers of linoleic acid. This family of polyunsaturated fatty acids has drawn significant attention in the last three decades for its variety of biologically beneficial properties and health effects. CLA has been shown to exert various potent protective functions such as anti-inflammatory, anticarcinogenic, antiadipogenic, antidiabetic and antihypertensive properties in animal models of disease. Therefore, CLA represents a nutritional avenue to prevent lifestyle diseases or metabolic syndrome. Initially, the overall effects of CLA were thought to be the result of interactions between its two major isomers: cis-9, trans-11 and trans-10, cis-12. However, later evidence suggests that such physiological effects of CLA might be different between the isomers: t-10, c-12-CLA is thought to be anticarcinogenic, antiobesity and antidiabetic, whereas c-9, t-11-CLA is mainly anti-inflammatory. Although preclinical data support a benefit of CLA supplementation, human clinical findings have yet to show definitive evidence of a positive effect. The purpose of this review is to comprehensively summarize the mechanisms of action and anti-inflammatory properties of dietary CLA supplementation and evaluate the potential uses of CLA in human health and disease.

1. Introduction

Conjugated linoleic acid (CLA), first described in 1985, refers to a class of positional and geometric isomers of conjugated dienoic derivatives of linoleic acid. As many other polyunsaturated fatty acids (PUFA) and their metabolites, dietary CLA has been proposed as a promising avenue for the development of novel and safer nutritional interventions against inflammation (Xu et al., 1999). Interest on the biological function and health benefits of dietary CLA dates back to 1987, when Ha et al. (1987) observed the ability of CLA to inhibit chemically-induced skin neoplasia in mice. This initial discovery lead to a series of studies that identified a broad range of beneficial biological properties of CLA, including but not limited to effects on weight loss, food and energy intake, alteration of body composition, cancer, enhancement of immune function, and inflammation (Lee et al., 1994; O'Shea et al., 2004; Kelley et al., 2007; Whigham et al., 2007; Mitchell and McLeod 2008). The antiobesity, anticarcinogenic, anti-inflammatory and antidiabetic effects of CLA have been widely described in animal studies (Park et al., 1997; West et al., 1998; de Lany et al., 1999; Ostrowska et al., 1999; Park et al., 1999; Tsuboyama-Kasaoka et al., 2000; Whigham et al., 2000; Bassaganya-Riera et al., 2001a; Ryder et al., 2001; Sisk et al., 2001; Bassaganya-Riera et al., 2002; Hontecillas et al., 2002; Terpstra et al., 2002; Yamasaki et al., 2003b; Bassaganya-Riera et al., 2004; O'Shea et al., 2004; Bassaganya-Riera and Hontecillas, 2006; Evans et al., 2010; Moon, 2014). However, such effects seem to be inconsistent and less significant in humans. This review will comprehensively summarize the mechanisms of action and anti-inflammatory properties of CLA supplementation in animals and humans with a focus on mucosal inflammation.

Inflammation is a complex physiological response to noxious stimuli and conditions such as pathogens or non-microbial endogenous molecules that result in tissue injury and cell damage (Ferrero-Miliani et al., 2007). It is induced by chemical mediators produced by damaged host cells and serves as a protective mechanism regulated by the interaction of multiple pro-inflammatory and immunomodulatory signaling pathways that aim to eliminate harmful stimuli, remove necrotic cells and tissue, and initiate the healing process (de Cassia da Silveira et al., 2014). Such inflammatory processes require the movement and interaction of the major cells of the immune system, including basophils, neutrophils, mast cells, T cells, B cells and so on. These events are controlled by a number of extracellular mediators and regulators

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such as cytokines, growth factors, eicosanoids, complement and peptides, along with equally complex intracellular signaling control mechanisms, which regulate immune cell maturation, activation and function as well as tissue-level homeostasis (Punchard et al., 2004; Medzhitov, 2008).

Inflammation underlies the pathogenesis of many widespread diseases including inflammatory bowel disease (IBD), rheumatoid arthritis, osteoarthritis, atherosclerosis, obesity, diabetes, asthma and allergy, bacterial and viral infections, and cancer (Medzhitov, 2008; Koeberle and Werz, 2014). It is exceedingly complex and plays a crucial role in mammalian physiology. Current drug development approaches to suppress inflammation mainly focus on: (1) Agonists of the glucocorticoid receptor (glucocorticoids), (2) interference with eicosanoid biosynthesis (non-steroidal anti-inflammatory drugs), and 3) Pro-inflammatory cytokine signaling blockade (Biological drugs targeting tumor necrosis α (TNFα) and interleukin 1 (IL-1) signaling) (Medzhitov, 2008). Such pharmacological strategies are strongly focused on a limited number of key molecules that are thought to be essential for each particular disease. However, some of these treatments result in poor therapeutic efficacy, significant side effects or adverse compensatory mechanisms (Medzhitov, 2008). Hence, CLA may offer an opportunity as a novel alternative and complementary intervention capable of disrupting the inflammatory process without undesired adverse side effects.

2. CLA isomers

CLA is a mixture of positional and geometric octadecadienoic acid isomers derived from linolenic acid, a 18-carbon polyunsaturated fatty acid that contains two double bonds in the cis configuration (*cis*-9, *cis*-12 octadecadienoic acid) (Kennedy et al., 2010). CLA present in mammalian tissues is directly derived from diet or, in smaller amount, from the gastrointestinal microflora (Gorissen et al., 2010). CLAs are natural constituents of foods derived from animal fat tissues and dairy products as a result of lipid biohydrogenation and hepatic desaturation. They are naturally produced in the rumen of cattle as intermediates of the gut bacterial fermentation of dietary linoleic acid to stearic acid and desaturation of oleic acid derivatives (Kepler et al., 1971; Griinari et al., 2000). Specifically, microbes in the gastrointestinal tract of ruminant animals such as cows and goats convert linoleic acid into different isoforms of CLA through biohydrogenation (Medina et al., 2000), a process that changes the location and configuration of one or both double bonds of linoleic acid in such a manner than the two double bonds are no longer separated by two single bonds. This results in the formation of several dozen octadecadienoic acid isomers that contain a single pair of conjugated double bonds (two double bonds separated by a single bond) (Marcy et al., 2004). Alternatively, there is evidence that non-ruminant animals can endogenously produce isomer *cis*-9, *trans*-11 by the delta-9 desaturation of *trans*-11 vaccenic acid (TVA), the primary isomer for ruminant TFAs (Corl et al., 2001, 2003; Kay et al., 2004). Bioconversion of TVA to *c*-9,*t*-11 CLA has been confirmed in mice (Santora et al., 2000), rats (Corl et al., 2003) and humans (Kuhnt et al., 2006).

The proportion of CLA in dairy products ranges from 0.34% to 1.07% of total fat (2.9 to 8.92 mg CLA/g of fat), whereas CLA content in raw or processed meat product ranges from 0.12% to 0.68% (Dhiman et al., 2005; Mendis et al., 2008). In 1992, soon after CLA's first isolation from extracts of grilled ground beef, Ha et al. thoroughly studied the concentrations of CLA in different commercially available foods (Chin et al. 1992). Such efforts resulted in creation of a database containing more than 90 food items including meat, poultry, dairy products, seafood, plant oils, infant foods and processed foods. Results revealed that CLA content in common foods is highly variable, probably due to several factors such as the nutritional status or age of the animal source, thus indicating the possibility of large variations in the CLA dietary intake.. Nonetheless, the average daily intake of CLA is estimated to range from 152 to 212 mg for American non-vegetarian women and men, respectively, and 97.5 mg/day for the British (Ritzenthaler et al., 2001; Kennedy et al., 2010; Mushtaq et al., 2010).

There have been 28 naturally occurring CLA isomers described to date. The *c*-9,*t*-11 CLA isomer, also known as rumenic acid, is the most predominant isomer in meats and milks from ruminant species, representing approximately 90% of total dietary CLA intake. The isomer *trans*-10, *cis*-12 comprises the remaining 10%, with negligible proportions of the other isomers (Fig. 1) (Wallace et al., 2007). Such percentages contrast with chemically synthesized and commercial preparations of CLA, which usually contain equal proportions of the two abundant isomers cis-9, trans-11 and trans-10, cis-12 (Parodi, 1997; Sebedio et al., 1999; Wang and Lee, 2013).

Most of CLA's beneficial properties are elicited by its two main isomers: c9, t11-CLA and t10, c12-CLA (Khan and Vanden Heuvel, 2003). In some cases an effect is produced by only one of the isomers, whereas in other situations the effect results from the synergism of both isomers (Zabala et al., 2006; Halade et al., 2010). Moreover, individual CLA isomers can result in differential effects, and the effect of variable isomer concentrations in CLA mixtures are difficult to predict (Khan and Vanden Heuvel, 2003). For instance, t-10, c-12-CLA is involved in catabolic processes of increased lipolysis and fat oxidation, whereas c-9, t-11-CLA seems to be the active anabolic agent and is predominantly anti-inflammatory (Wang and Lee, 2013). Both isomers seem to have anti-carcinogenic properties, although they are thought to be mediated by different effects on lipid metabolism, oncogene regulation and modulation of apoptosis (Kelley et al., 2007).

The majority of research to date has been performed using mixtures of CLA isomers due to the initial cost and difficulty to

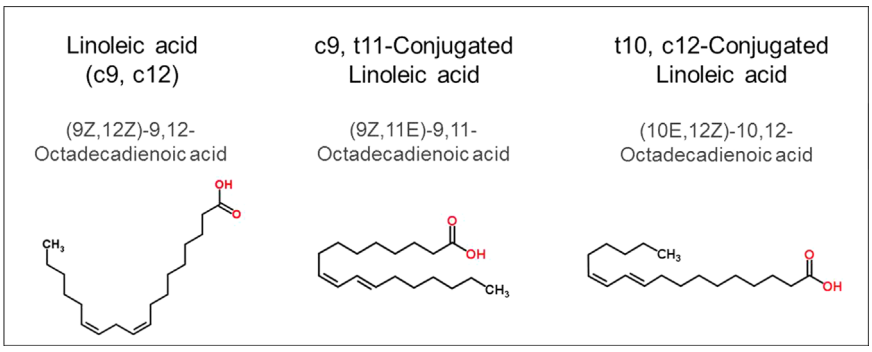

Fig. 1. Structure of linoleic acid, *cis*-9 *trans*-11 CLA isomer and *trans*-10 *cis*-12 CLA isomer.