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Review of the roles of conjugated linoleic acid in health and disease

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ABSTRACT

Dietary fatty acids (FA) are increasingly recognized as major biologic regulators and have properties that relate to health outcomes and disease. Conjugated linoleic acid (CLA) is a generic term denoting a group of isomers of linoleic acid (C18:2, n-6) with a conjugated double bond. CLA has attracted increased research interest because of its health-promoting benefits and biological functions. In a variety of studies, CLA has been shown to impact immune function and has protective effects against cancer, obesity, diabetes, and atherosclerosis in animal studies and in different human cell lines. Studies investigating the mechanisms involved in the biological functions of CLA are emerging with results from both in vivo and in vitro studies. Most of the biological effects have been attributed to the c9,t11-CLA and t10,c12-CLA isomers. The purpose of this review is to discuss the effects of CLA on health and disease and the possible mechanisms for CLA activities.

Contents

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Abbreviations: CLA, conjugated linoleic acid; LOX, 5-lipoxygenase; COX, cyclooxygenase; PGE2, prostaglandin E2; TB2, thromboxane B2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IKK, IκB kinase; PPAR, proliferator-activated receptor; TNF-α, tumor necrosis factor-α; LPS, lipopolysaccharide; SCD, stearoyl-CoA desaturase; RXR, retinoid X receptor; LDL, low density lipoprotein; VLDL, very low density lipoprotein; TFG-β1, transforming growth factor β1; UCP-2, uncoupling protein-2; 5-HETE, 5-hydroxyeicosatetraenoic acid; IGF, insulin-like growth factor; NAG-1, nonsteroidal anti-inflammatory drug-activated gene-1.

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1. Introduction

The term conjugated linoleic acid (CLA) describes the positional and geometric isomers of linoleic acid (C18:2, c9,c12), containing a double bond system where each of the two double bonds can be either in cis or trans configuration, and at different positions along the 18 carbon chain, resulting in 28 possible isomers (Banni, 2002), in which the most common and health-associated active isomers are c9, t11-CLA and t10, c12-CLA (Fig. 1).

CLA has received much attention in recent years because of its interesting biological benefits. The main health effects described for CLA include reduction of carcinogenesis, atherosclerosis, inflammation, obesity, diabetes, as well as growth promoting and bone formation-promoting properties (Belury, 2002a; Bergamo et al., 2014; Jaudszus, Foerster, Kroegel, Wolf, & Jahreis, 2005; Kim, Park, & Park, 2014; Park, Albright, Storkson, Liu, & Pariza, 2010; Park et al., 1997; Tricon et al., 2004; Valeille et al., 2006). Most research into the health effects of CLA to date has been conducted with mixed isomers of CLA, typically consisting of a mixture of equal amounts of the c9,t11-CLA and t10,c12-CLA isomers, with a number of other minor isomers in the mixture (Kelley, Hubbard, & Erickson, 2007).

The predominant geometric isomer found in nature is c9,t11-CLA, produced as an intermediate during the biohydrogenation of dietary linoleic acid to stearic acid (C18:0) by ruminant microorganisms, i.e. *Butyrivibrio fibrisolvens* (Kepler, Hirons, McNeill, & Tove, 1966); therefore, c9,t11-CLA is named as rumenic acid. Vaccenic acid (C18:1, t11) can also be converted to c9,t11-CLA by delta9-desaturase in the mammary gland (Bauman, Corla, Baumgard, & Grinari, 2001). CLA is accumulated in the fat of milk and tissues of ruminant animals. C9,t11-CLA represents 80–90% of total milk fat CLA, while t10,c12-CLA is present at approximately 1% of milk fat CLA (Jensen, 2002). Thus, ruminant dairy and meat products are the principal food sources of CLA in the human diet. In recent years, a number of food-grade bacteria have been identified as CLA producers, such as *Bifidobacterium* (Barrett, Ross, Fitzgerald, & Stanton, 2007; Coakley et al., 2003; Gorissen et al., 2010; Rosberg-Cody et al., 2004), *Lactobacillus* (Hosseini, Kermanshahi, Hosseinkhani, Shojaosadati, & Nazari, 2014; Ogawa et al., 2005; Yang et al., 2014), *Lactococcus* (Ogawa et al., 2005) and *Propionibacterium* (Hennessy et al., 2012; Rainio, Vahvaselka, Suomalainen, & Laakso, 2001).

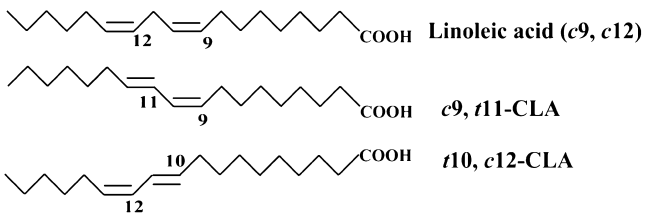

Fig. 1 – Structure of linoleic acid and the most common biologically active isomers of conjugated linoleic acid (CLA).

It has been well established that CLA has a number of biological functions, and a number of publications have reported a variety of microbial CLA producers. The focus of this contribution is to review the current knowledge about CLA and its beneficial effects with associated molecular mechanisms.

2. Beneficial effects of CLA on disease

2.1. *Effects of CLA on cancer*

The role of CLA in cancer prevention is well documented. CLA is an efficient inhibitor of all stages of carcinogenesis; initiation, promotion and metastasis (Belury, 2002b), as well as neovascularization or angiogenesis (Masso-Welch et al., 2002, 2004). Numerous studies, both *in vitro* and *in vivo*, have demonstrated anticancer activity of CLA (Kelley et al., 2007). Animal studies have shown that a mixture of CLA isomers, and either c9,t11-CLA or t10,c12-CLA isomer alone in a range between 0.05 and 1% (w/w) inhibit chemically induced tumors of the mammary gland (Lau & Archer, 2009; McGowan et al., 2013; Rakib et al., 2013), colon (Bassaganya-Riera, Viladomiu, Pedragosa, De Simone, & Hontecillas, 2012; Kelley et al., 2007; Lau & Archer, 2009; Rosberg-Cody, Johnson, Fitzgerald, Ross, & Stanton, 2007), forestomach neoplasia (Chen et al., 2003) and metastasis of inoculated cancer cells (Kuniyasu et al., 2006; Soel, Choi, Bang, Yoon Park, & Kim, 2007). Similarly, *in vitro* studies have demonstrated both the c9,t11-CLA and t10,c12-CLA isomers, as well as a mixture of isomers to be anti-proliferative against a range of different cell lines, including prostate cancer cells (Kim et al., 2006; Lau & Archer, 2009; Ochoa et al., 2004; Song, Sneddon, Heys, & Wahle, 2006), colon cancer cells (Cho et al., 2005, 2006; Lee et al., 2006) and breast cancer cells (El Roz, Bard, Huvelin, & Nazih, 2013; Flowers & Thompson, 2009; Rakib et al., 2013). The c9,t11 and the t10,c12-CLA isomers are reported to inhibit cancers through different models of action