Conjugated Linoleic Acid and the Control of Cancer and Obesity

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The effects of conjugated linoleic acid (CLA) in animals are reviewed. In most of the CLA preparations that have been investigated to date for biological activity, two CLA isomers are present in about equal concentrations: cis-9,trans-11 CLA, and trans-10,cis-12 CLA. The occurrence of these isomers in foods and their production by rumen microorganisms are discussed. Potential mechanisms of action as regards the effects of CLA on cancer and body composition are reviewed, including recent evidence that body composition changes are produced by the trans-10,cis-12 CLA isomer. Evidence is presented indicating that CLA may modulate cellular response to tumor necrosis factor-alpha (TNF-α). The mechanistic implications of this finding are considered.

Key Words: conjugated linoleic acid; body composition; cytokines; tumor necrosis factor-α.

CLA (conjugated linoleic acid) is the acronym for a class of positional and geometric conjugated dienoic isomers of linoleic acid (Fig. 1). Ha et al. (1987) coined the term when they reported biological activity (i.e., anticarcinogenic activity) associated with CLA isolated from grilled ground beef, and CLA produced from linoleic acid by base-catalyzed isomerization. Since then, substantial interest has developed in the biochemical actions of CLA and its potential use in foods, feeds, and pharmaceuticals (Doyle, 1998).

The major dietary sources of CLA are animal foods, especially foods derived from ruminant animals (e.g. dairy products and beef). Only trace amounts of CLA occur naturally in plant lipid but various CLA isomers are produced during the chemical hydrogenation of fats, for example in margarine manufacture (Carpenter and Slover, 1973).

The cis-9,trans-11 isomer is the principal dietary form of CLA (Chin et al., 1992; Kramer et al., 1997; McGuire et al., 1997; Parodi, 1997; Sehat et al., 1998). The cis-9,trans-11 isomer of CLA is produced in the rumen of cattle and other ruminant animals during the microbial biohydrogenation of linoleic acid (Kepler et al., 1966). Thereafter cis-9,trans-11 CLA may be directly absorbed (Chin et al., 1994) or biohydrogenated to vaccenic acid (trans-11-octadecenoic acid). Vaccenic acid, after absorption, may then be converted by delta-9 desaturase back to cis-9,trans-11 CLA (Griinari et al., 1998; Holman and Mahfouz, 1980; Pollard et al., 1980).

In addition to vaccenic acid, trans-10-octadecenoic acid is also found in cow’s milk (Griinari et al., 1998). Verhulst et al. (1987) isolated a microorganism that converts linoleic acid to trans-10,cis-12 CLA, so it is possible, by analogy to vaccenic acid, that trans-10-octadecenoic acid may form in the rumen via microbial metabolism of linoleic acid to trans-10,cis-12 CLA, which is then biohydrogenated at the cis-12 bond. Since mammals do not possess delta-12 desaturase, it follows that the trans-10,cis-12 CLA found in ruminant tissues would originate from trans-10,cis-12 CLA absorbed from the gastrointestinal tract. However, Park and Pariza (1998) presented evidence that commercial horse sera may contain substantial levels of trans-10,cis-12 CLA. Since the horse has a hindgut fermentation area (rather than a rumen) where long-chain fatty acid absorption is minimal, the finding of apparent trans-10,cis-12 CLA in a sample of horse sera indicates that the origin of CLA isomers in the blood may be more complex than currently thought.

The Biological Effects of CLA

Current worldwide scientific interest in CLA was stimulated by its identification as an anticarcinogenic principal from grilled ground beef (Ha et al., 1987). We have also established that feeding CLA (0.5% of diet) to rodents or chickens protects them from the catabolic effects of immune stimulation (Miller et al., 1994). Dietary CLA was shown to reduce the development of atherosclerosis in rabbits fed an atherogenic diet (Lee et al., 1994). CLA enhanced feed efficiency in young rats (Chin et al., 1994), indicating that CLA may regulate energy metabolism and nutrient partitioning, a conclusion that was verified by Park et al. (1997). These findings have all been independently confirmed and expanded by other investigators (Doyle, 1998; for an updated listing of the scientific literature on CLA since 1987, which expands weekly, see the internet address http://www.wisc.edu/fri/clarefs.htm). Most recently, Park et al. (1999) established that the trans-10,cis-12 CLA isomer is responsible for body composition changes in mice in vivo, as well as the inhibition of lipoprotein lipase activity and the enhancement of lipolysis in cultured 3T3-L1 mouse adipocytes. In contrast the cis-9,trans-11 isomer was without activity in this regard.

Taken together, these findings indicate a broad range of

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biological activities for CLA that beg the question of underlying mechanism. One intriguing possibility for a general mechanism, which could explain many of the biological effects of CLA, is that one or more of the CLA isomers may act through modified eicosanoid intracellular signaling to alter cellular responses to certain cytokines, in particular tumor necrosis factor-α (TNF-α) (Pariza, 1997).

Cytokines are hormone-like mediators of immunity and inflammation that are produced by macrophages and other immune cells when they are stimulated. TNF-α is particularly important in this signaling process. TNF-α (along with interleukin-1) induce a number of effects in immune cells, including the inflammatory response. However, these cytokines also produce biochemical changes in other cells, for example the induction of catabolism in skeletal muscle and changes in cell surface proteins. Additionally, virtually every cell in the body has receptors for TNF-α, and many types of cells (e.g., nerve cells, adipocytes) can also produce this cytokine (Hotamisligil and Spiegelman, 1994).

TNF-α also appears to be a key mediator in many chronic pathologies including cachexia (Freeman and Rubenoff, 1994), atherosclerosis (Ross, 1993), carcinogenesis (Okahara et al., 1994, Suganuma et al., 1996) and (paradoxically) obesity (Hotamisligil and Spiegelman, 1994). The association of TNF-α with so many biological and physiological processes has led Hotamisligil and Spiegelman (1994) to conclude that this cytokine produces a “...bewildering array of biochemical changes in a wide variety of cells [which] is attributable to its capacity for using multiple signaling pathways through its cell surface receptors.”

Accordingly, our working hypothesis is that at least some of the multifunctionality of CLA may be explained by the effects of one or more CLA isomers on the cellular responses to TNF-α (Pariza, 1997; Park et al., 1997).

The data of Figure 2 provide further support for this hypothesis. Mice were fed control diet or diet supplemented with 0.5% CLA for 32 days, then injected with TNF-α as indicated. The CLA-fed mice experienced less weight loss, indicating that they were partially protected against the cachexia that was induced by the cytokine. This provides evidence indicating that CLA may modulate cellular response to TNF-α, possibly through the regulation of eicosanoid production and/or type.

CLA and Cancer

CLA may influence the development and progression of cancer in three ways: by directly affecting the process of carcinogenesis; by reducing excessive body fat accumulation...
which indirectly influences cancer risk; and by reducing cachexia which is associated with advanced cancer and with certain cancer treatment strategies.

There is evidence that CLA may inhibit carcinogenesis at each of the major stages described by Boutwell (1985): initiation (Ha et al., 1987; Liew et al., 1995), tumor promotion (Ip et al., 1994; 1996), progression and metastasis (Cesano et al., 1998). Further, whereas CLA is a potent anticarcinogen, linoleic acid has been shown to enhance experimental carcinogenesis in a number of animal models (Cesano et al., 1998; Ip et al., 1985). Tumor-derived prostaglandin E\(_2\) (PGE\(_2\)) (from lipoxygenase) has been shown to suppress immune defense against tumors (Young, 1994). Accordingly, it would appear that one effect of CLA may be to offset the negative effects of excessive dietary linoleic acid on carcinogenesis without interfering with the essential functions of that nutrient (Ip et al., 1996; Pariza, 1997).

It is likely that the isomers of CLA, like the omega-3 fatty acids of fish oil (Endres et al., 1989, Hellerstein et al., 1989) are metabolized to one or more biologically active forms, which may then act by regulating arachidonic acid metabolites such as PGE\(_2\). Other potential modifiers of cyclooxygenase products (e.g., aspirin) inhibit colon carcinogenesis in animal models and there is encouraging evidence on this from human clinical trials as well (Marnett, 1992).

Alternatively, CLA metabolites may act in their own right, via signal transduction pathways, to affect biological responses effected by TNF-\(\alpha\) and related cytokines. For example, they may influence the expression of cell surface proteins that are associated with neoplastic progression and metastasis (Garofalo et al., 1995; Okahara et al., 1994) as well as atherosclerotic plaque development (Carlos et al., 1990).

CLA may also indirectly affect cancer development via its effects on body composition: e.g., reducing body fat, enhancing lean body mass (Pariza, 1997; Park et al., 1997, 1999). The association of excessive body fat with enhanced cancer risk and the potential for reducing cancer risk through calorie reduction are discussed elsewhere in these proceedings. The hormonal mechanisms involved in cancer modulation by body fat and calorie intake may relate to cancer reduction by CLA as well.

Finally, CLA may have application in cancer chemotherapy strategies. A common characteristic of advanced cancer is severe wasting, the hallmark of cachexia. Cachexia is mediated by cytokines, especially TNF-\(\alpha\) (Hotamisligil and Spiegelman, 1994). Given that dietary CLA reduces the adverse catabolic effects of immune stimulation which include cachexia, it is possible that CLA might be useful in easing this complication of cancer. CLA could also prove useful as an adjunct to chemotherapy with cytokines. Both of these potential applications are supported by the data of Figure 2. The possibility that CLA might have chemotherapeutic applications in its own right should also be investigated.