CONJUGATED DIENES OF LINOLEIC ACID AND TUMORIGENESIS

SPRZĘŻONE DIENY KWASU LINOLOWEGO I ROZWÓJ NOWOTWORU

Streszczenie

Sprzężone dieny kwasu linolowego (CLA), będące kwasami tłuszczowymi obecnymi w żywności, w produktach pochodzenia zwierzęcego i roślinnego, są obiektem intensywnych badań dotyczących wykorzystania ich walorów leczniczych.

Niniejszy artykuł przeglądowy podsumowuje wiedzę o przeciwnowotworowych właściwościach CLA.

H a s ła: sprzężone dieny kwasu linolowego – nowotwór.

Summary

Conjugated dienes of linoleic acid (CLA) are fatty acids widely found in food of animal and plant origin. CLA has been the subject of extensive investigation regarding its possible benefits on a variety of human diseases.

This short review summarizes the state of knowledge about the anticancer and antitumor properties of the CLA.

K e y w o r d s: conjugated linoleic acid – cancer.

Conjugated dienes of linoleic acid (CLA) are fatty acids widely found in food – in animal and plant products. CLA are family of 13 fatty acids, however the 2 most prevalent isomers in dairy products are cis-9, trans-11 C18:2 and trans-10, cis-12 C18:2 [1]. CLA are formed in the stomach of ruminants as a result of the bacterial anoxic biohydrogenation of linoleic acid [1]. In small quantities, CLA are also synthesized in the intestines of monogastric animals; small amounts of them were also found in fish muscles. On the other hand, oils and margarines, and other products based there upon, are a minor source of CLA [2, 3]. It is estimated that the content of dienes in partially hardened vegetable fats does not exceed 50 mg per 100 g of fat [4, 5, 6]. The most important dietary sources of CLA in human nutrition are milk and milk products, and the intramuscular fat of ruminant animals. It is estimated that CLA content in dairy products ranges 2.9–26 mg per gram of fat, of which the cis-9, trans-11 C18:2 isomer constitutes 73–93% of the total CLA content. Beef contains on average from 3.1 to 8.5 mg of CLA per each gram of fat. The main isomer isolated from beef is also the cis-9, trans-11 C18:2, constituting 57–85% of CLA. It is estimated that 100 g of fat in beef may contain on average from 100–400 mg of the cis-9, trans-11 C18:2 isomer, which constitutes about 85% of the total amount of all dienes [5, 6]. Conjugated dienes of linoleic acid were also found in human tissues and human milk. Their origin in the human body may be 2 – fold: they are delivered with the diet and used for the synthesis of triacylglycerols, and they are probably (although this is not yet supported by hard evidence) formed as a result of the free-radical peroxidation of linoleic acid, e.g. within an inflammatory area [5, 7, 8].

Conjugated linoleic acid has been the subject of extensive investigation regarding its possible benefits on a variety of human diseases. In some animal studies, CLA has been shown to have a beneficial effect on sclerotic lesions associated with atherosclerosis, be a possible anticarcinogen, increase feed efficiency, and act as a lean body mass supplement [9]. Studies conducted on human and animal models showed that trans-10, cis-12 C18:2 isomer
is substance which might be responsible for the control of adipose tissue mass. This isomer reduced the absorption and accumulation of lipids through inhibition of lipoprotein lipase and stearoyl-CoA desaturase, and decreased the content of triacylglycerols in the liver by 32% [10]. The second most prevalent isomer cis-9, trans-11 C18:2 displayed an opposite effect. The divergent effect of both CLA isomers on lipid metabolism and appetite regulation was also confirmed in laboratory animals [11]. CLA also exert an effect on adipose tissue mass through their action on leptin secretion [12]. It was proven that CLA are a factor lowering the amount of leptin secreted into the plasma in animal and human bodies [13].

Also in vitro, trans-10, cis-12 C18:2 fat – lowering effects has been shown – preadipocytes incubated with the addition of the trans-10, cis-12 C18:2 reduced the triacylglycerol (TAG) content in the cells [14]. Reduction of TAG content by CLA may be reversible, and the bodyweight reducing properties of CLA may result from inhibition of lipogenesis by the trans-10, cis-12 C18:2 isomer. Moreover, the trans-10, cis-12 C18:2 isomer may lower concentrations of triacylglycerols in preadipocyte cultures through an increase in the rate of oxygenation of fatty acids [14, 15]. When the trans-10, cis-12 C18:2 isomer was added to the cellular culture it enhanced incorporation of glucose and oleic acid into the cellular lipid fraction [16].

CLA and cancer

Both the major isomers of CLA: cis-9, trans-11 C18:2 and trans-10, cis-12 C18:2 were considered as potential inhibitors of the tumorigenesis. In experiments conducted on animals, CLA inhibited the development of chemically induced cancer [17, 18] – e.g. altered the latency and metastasis of the highly metastatic transplantable line in mouse mammary tumor [19]. In 2002, it was announced that CLA isomers might protect against the development of breast cancer in post-menopausal women [20]. These results were confirmed by studies conducted with the use of 2 cell lines in cultures of the human breast cancer cells MDA – MB-231 and MCF-7. In these studies it was reported that CLA might inhibit the development of breast cancer through regulation of the expression of the key enzymes e.g. stearoyl-CoA desaturase (SCD) [21]. In this year, it was shown that CLA may inhibit human breast cancer through activation of the apoptosis via the estrogen receptor alpha – ER α (about 75% of breast cancers are estrogen ER α positive) [22].

Considerable evidence demonstrates that anticancer activity of CLA may be also associated with inhibition of the angiogenesis (by depression of growth factors secretion). Dietary CLA decreased serum levels of vascular endothelial growth factor (VEGF) and whole mammary gland levels of VEGF and its receptor (Flk-1) in the cells. Additionally, CLA inhibited angiogenesis in vitro in the dose-dependent manner [23, 24].

How CLA alter tumorigenesis

CLA could alter tumorigenesis by:

a) interfering with components of the cell cycle;
b) increasing cells death either by way of necrosis or by way of apoptosis;
c) and by modification of an immune system [25].

Interfering with components of the cell cycle – CLA inhibited level of the cyclins D and A, and up-regulate of p53 expression

CLA could reduce tumor cell proliferation by modifying cell cycle proteins that regulate this process. CLA are factors that can alter the expression key for cell cycle proteins: cyclins and their kinases and regulatory factors: p53 and p16 and p27 – (cyclin-dependent kinase inhibitors – cdk inhibitors) [25, 26, 27]. Cell cycle progression is a complex process designed to allow accurate duplication of genetic material before cells are permitted to divide. Progression through each cell cycle phase is controlled by programmed activation (deactivation of cyclin) cyclin-dependent kinases. Activity of each kinase is regulated by specific interactions with cyclin-dependent kinase inhibitor (e.g. p16, p21, p27) and posttranslational modification [28]. Ip et al. demonstrated that feeding CLA or cis-9, trans-11 C18:2 – rich butter fat for 4 wk reduces the expression of cyclins D and A in the terminal – end buds and alveolar clusters of the mammary epithelium [27]. Cyclins D and A are proteins involved in facilitating entry of the cells into the cell cycle and progression through S phase, respectively [25]. Expression of cyclin D and activation of cyclin D/cdk 4/6 kinase is response for the initial entry into mammalian cells (G1 phase), whereas the cyclin A/cdk 2 activity pushes the cells through G2 phase [29, 30]. Cyclin D belongs to the family of cyclin proteins which function as the regulatory subunits of the cyclin-dependent kinase holoenzymes that regulate entry into and progression through the cell cycle [29]. Work by Ip at al. demonstrated that isomer cis-9, trans-11 C18:2 reduced in vitro expression of 2 cyclins complexxes: cyclins D/cdk 4/6 kinase and cyclin A/cdk 2 [27].

CLA was also shown to up-regulate the expression of p53, the protein that is involved in monitoring the quality of DNA after G0 phase and also induce genes belonging to a family of regulatory molecules known as cdk inhibitors – p16 and p27 [25, 27]. CLA-fed rats expressed the p16 and p27 an in vivo study [25, 27]. An in vitro study (the mutant TM4t marine mammary tumor cells) trans-10, cis-12 C18:2 induced G1 phase arrest by enhance of p53 level [31]. The tumor suppressor gene p53 was significantly up-regulated by CLA in the dose depended way [31].

CLA increasing cells death either by way of necrosis or by way of apoptosis

CLA are fatty acids that disturbed programmed cell death – apoptosis [25]. This process plays a key role in the development and growth regulation of normal and cancerous
cells. Apoptosis involves the activation of a highly regulated series of intracellular events in which the cell actively participates in its own death. Genes such as bcl-2 and proteolytic enzymes as such as the caspases, play an important role in apoptotic cell death in other cell types [32].

As has been shown CLA (especially the trans-10, cis-12 isomer) markedly limited the divisions of cancer through induction of apoptosis and inhibition of DNA synthesis (by the lowering polyamine synthesis and enzyme polymerase activity) [25, 33, 34, 35]. Isomer trans-10, cis-12 C18:2 may also induce apoptosis by inducing apoptosis of pre-neoplastic and neoplastic mammary epithelial cells through ER stress [31]. Ou et al. show that isomer trans-10, cis-12 C18:2 induced a time- and concentration-dependent cleavage of caspases-3 and -9, and release of cytochrome c from mitochondria to cytosol [31]. Also levels of antipapoptotic protein – Bcl-2 were down-regulated after trans-10, cis-12-CLA treatment, whereas proapoptotic protein – Bax were up-regulated by CLA [31].

It was noticed that tumor cells do not possess sufficient antioxidant defense systems compared to healthy cells, and they are more susceptible to oxidative and peroxidative damage. Polyunsaturated fatty acids are the main intracellular substrates for lipid peroxidation, thus PUFA derived reactive lipid compounds could damage cell membranes, change the cellular composition or cytoskeletal assembly, modify membrane transport systems or enzymes or inhibit polymerase reactions and polyamine synthesis. Supplementation of cells with CLA also increased the susceptibility of tumor cells to lipid peroxidation [25]. Cultivation of cells with CLA leads to an increased ROS synthesis, partly by PPAR-alpha mechanism. An increase in ROS concentration in the cell may stimulate apoptosis [36].

Conjugated linoleic acid also up-regulate anticancer defenses through modification of an immune and inflammatory responses and modulation of immune function

Recent publications demonstrated that CLA isomers modulated immune function in humans and animals [35]. In animals CLA reduced immune – induced wasting and enhanced ex vivo lymphocyte proliferation and decreased tumor necrosis factor alpha (TNF-alpha) and interleukin 6 (IL-6) production. In mice, increased lymphocyte proliferation and IL-2 production. Furthermore, evidence suggests that the mixture of CLA isomers exert distinct effects on immune function. Specifically, these isomers have differential effects on specific T cell populations and immunoglobulin subclasses in animal and human studies [37]. CLA improved natural killer cell cytotoxicity and humoral and T cells responses [25] to mitogens [38, 39]. Both isomers increased IL-2 production, proliferation and release of granzyme [37, 40]. Mixtures of CLA also up-regulated the humoral function: increased IgG and IgM, IgA production of spleen lymphocytes in a dose – dependent manner production [41, 42] and reduced macrophage function e.g. reduced the synthesis of inflammatory mediators [43, 44, 45, 46] and/or inflammatory enzymes [47, 48].

References

Conjugated dienes of linoleic acid and tumorigenesis


