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Functional Properties of Bioactive Components of Milk Fat in Metabolism

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Abstract: Milk fat contains a number of components having functional properties. Milk fat has fatty acids and membrane lipids that may exert antimicrobial effects either directly or upon digestion. Both sphingolipids and their active metabolites, ceramides and sphingosines, were determined as effective bactericidal agents on pathogens like *Listeria monocytogenes*. In addition, studies with experimental animals have shown that feeding sphingolipids inhibits colon carcinogenesis, reduces serum LDL cholesterol and regulates immune system. It has been long known that the fat-soluble vitamins (A and E) are important in human nutrition. Provitamin A (β-carotene) has desirable properties in addition to its role of forming vitamin A, such as being an antioxidant and possibly causing tumour suppression. Butyric acid, a short chain fatty acid and a natural component of the animal metabolism, plays role in cell growth control, cell differentiation and inhibition of colon cancer. In recent years conjugated linoleic acid (CLA), a fatty acid found in milk fat, has been extensively reviewed. A wide range of health benefits of CLA has been shown in animal models including inhibition of carcinogenesis and atherosclerosis as well as immune stimulation. Furthermore, recent studies have also showed that CLA prevents the development of diabetes in the obese rats.

Key words: Milk fat, sphingolipids, conjugated linoleic acid, butyric acid

Introduction

Bovine milk fat represents a rich source of biologically active molecules, many of which offer potential for commercial exploitation in health-promoting functional food products (Gill, 2002). Several milk fat-derived molecules can modulate immunity, reduce serum LDL (low density lipoprotein) cholesterol, inhibit carcinogenesis and act as an effective bactericidal agent on pathogens.

The important features of milk fat from the consumer's point of view are the flavour, the traditional image, spreadability (of butter) and the health perception. These must be considered as a bundle and any changes in one characteristic should not have adverse affects on the others (Boland *et al*., 2001).

Sphingolipids, conjugated linoleic acid (CLA), butyric acid, ether lipids, vitamin A and D are the most known bioactive components of milk fat that offer different functional properties in metabolism.

The aim of this review is to evaluate the functional properties of milk fat components. Furthermore the effects of these components on metabolism and human health will be taken into consideration.

Sphingolipids: Sphingolipids are located in cellular membranes, lipoproteins (especially LDL) and other lipid-rich structures, such as skin. Sphingolipids are critical for the maintenance of membrane structure, especially that of "microdomains" ; they modulate the behaviour of growth factor receptors and extracellular matrix proteins and serve as binding sites for some microorganisms, microbial toxins and viruses (Vesper *et al*., 1999).

Both complex sphingolipids (sphingomyelins, cerebrosides, globosides, gangliosides or sulfatides) and their digestion products (ceramides and sphingosines) are highly bioactive compounds that have profound effects on cell regulation (Vesper *et al*., 1999). Ceramide may be hydrolyzed intracellulary by ceramidase to produce sphingosine. Sphingosine is also associated with a number of cell-regulating pathways. It is a potent inhibitor of protein kinase C, which is closely associated with tumour progression and metastatic potential and can modulate the activity of some other protein kinases and enzymes involved in cell regulation (Parodi, 1997). Because ceramide and sphingosine participate in major antiproliferative pathways of cell regulation that suppress oncogenesis, they have been termed tumour suppressor lipids (Parodi, 1999).

Therefore it has been explored whether milk sphingolipids can induce apoptosis in human colon cancer cells in culture (HT29 cells), and suppress carcinogenesis when fed to experimental animal models for colon cancer. Studies have shown that ceramides and sphingoid bases induce apoptosis in HT29 cells and feeding sphingolipids to Min mice, which have a genetic defect similar to that found in many human colon cancer risk (Vesper *et al*., 1999).

Sphingolipids such as ceramide, ceramide-1-phosphate (S1P) have important effects on the development, activation and regulation of the immune system (Cinque *et al*., 2003). In most cases, these molecules are present at low levels in normal milk, although higher levels may be encountered in colostrum and early post-partum milk preparations (Gill, 2002). Associations between sphingomyelin and cholesterol have intrigued researchers for decades. As sphingomyelin affects many aspects of cholesterol transport and metabolism, it may influence atherosclerosis, either directly or by affecting other risk factors such as cholesterol (Vesper *et al.*, 1999). Short-term and long-term feeding experiments with rats have indicated that sphingolipids reduce plasma cholesterol, a risk factor for atherosclerosis (Imaizumi *et al.*, 1992; Kobayashi *et al.*, 1997).

Bovine milk fat may prevent gastrointestinal infections because whole milk consumption is associated with fewer gastrointestinal infections than is consumption of low-fat milk. Generally gram-positive bacteria are lipid sensitive whereas gram-negative bacteria are not. $C_{10:0}$ and $C_{12:0}$ fatty acids and digestion products of sphingolipids appeared to be effective bactericidal agents, whereas digestion products of phosphoglycerides were moderately bactericidal. Gastric triglyceride digestion, rather than intestinal digestion was determined as important in protection against *Listeria monocytogenes*. Thus, milk fat sphingolipids and triglycerides, particularly those containing $C_{10:0}$ and $C_{12:0}$ fatty acids, may protect against food-borne gastroenteritis (Sprong *et al.*, 2001). In rats, high intake of milk fat triglycerides protected against orally administered *Listeria monocytogenes* but not against *Salmonella enteritidis*. The enhanced resistance to *Listeria monocytogenes* was related to an increased release of gastric bactericidal saturated fatty acids (Sprong *et al.*, 2002).

Conjugated linoleic acid: Conjugated linoleic acid (CLA) is a collective term to describe one or more positional and geometric isomers of linoleic acid (cis-9, cis-12 octadecadienoic acid). Conjugated double bonds are usually at positions 9 and 11 or 10 and 12; each double bond can be in either the cis or trans configuration (Parodi, 1997; Ip, 2002). Many reports showed an association between this isomer and several important biological activities including anticarcinogenesis, antiatherogenesis and anabolism (O'Shea *et al.*, 1998). CLA is formed as a result of microbial biohydrogenation in the rumen by a linoleic acid isomerase from rumen bacteria (*Butyrivibrio fibrisolvens*); hence it is found primarily in ruminant animal products and dairy products. Milk fat is the richest natural dietary source of CLA, which is almost entirely the cis-9, trans-11 isomer with an amount of 30mg / g milk fat (O'Shea *et al.*, 1998; Parodi, 1997).

Most of the research on CLA is associated with its anticarcinogenesis properties. CLA reportedly has anticarcinogenesis effects at various stages of cancer development, including initiation, progression and metastasis. Proposed mechanisms of CLA and its anticarcinogenic activities include a reduction in cell proliferation, vitamin A metabolism and prostaglandin metabolism. CLA seems to significantly reduce prostaglandin E_2 synthesis in the mouse epidermis, which could inhibit tumour formation (Rainer and Heiss, 2004).

CLA may impact the immune system. In animals, it is reported that CLA serves as a protection from catabolic effects of immune stimulation (Rainer and Heiss, 2004). CLA supplementation has been shown to exert various responses on lipidemic profiles. Feeding rabbits on atherogenic diet supplemented with CLA (0.5g CLA / rabbit / day) resulted in a reduction of atherogenesis in lipid deposition and in connective tissue development (Lee *et al.*, 1994). CLA is also reported to have antidiabetic effects in rats including improved insulin sensitivity (Rainer and Heiss, 2004).

Butyric acid: Butyric acid, a short chain fatty acid, is a natural component of the animal metabolism (Pouillart, 1998). Butyric acid, present in milk fat and produced in lower bowel due to the fermentation of dietary fibre, promotes differentiation of various cell types (German, 2002). It inhibits cell growth and induces differentiation in a wide spectrum of cancer cell lines including those of the breast and colon, where butyric acid can induce apoptosis and may prevent metastases to the liver (Parodi, 1999).

The colon is the organ mostly associated with butyrate, which results from fermentation of nonabsorbed carbohydrate by colonic microflora. Buytrate is utilized by colonocytes as an important energy source or passes from the basolateral membrane to the portal circulation where most is rapidly cleared by the liver with little reaching other tissues. Although butyrate inhibits proliferation in colon cancer cell lines, paradoxically, it stimulates proliferation in normal colonocytes. Colonic generation of buytrate is considered one factor associated with the protective effect of dietary fibre for colon cancer (Parodi, 1997). Recent information have showed that butyric acid currently considered as therapeutic purposes in the treatment of colorectal cancer and hemoglobinopathies.

Ether lipids: Alkylglycerols, alkylglycerophospholipids and their derivatives, referred to as ether lipids, by an ether bond in position *sn-1* of the glycerol backbone of triacylglycerols and phospholipids, are potent antineoplastic agents which inhibit growth, show antimetastatic activity and induce differentiation and apoptosis in cancer cells (Parodi, 1997;1999). The therapeutic potential of ether lipids and derivatives is being determined currently in a number of clinical trials (Diomede *et al.*, 1993; Principe and Braquet, 1995).

Milk fat contains small quantities of ether lipids. It has been shown that 1-0- alkyl *sn-1* glycerols liberated from dietary ether lipids are readily absorbed and transported, without cleavage of the ether bond, to the liver and other organs, where they are used to synthesize membrane phospholipids. The use of dietary ether lipids in cancer prevention has not been reported (Parodi, 1999).

Vitamin A and D: It has been long known that the fat-soluble vitamins are important in human nutrition. Vitamin D and A which are found abundant in milk fat, have effects on cancer prevention. The physiological effects of vitamin D are mediated by vitamin D receptors, which are present in a number of organs and have also been detected a variety of human cancer cells, including prostate, colon and breast. In these cancer cells, 1,25 – dihydroxyvitamin D_3 induces biological responses, such as the suppression on growth, induction of apoptosis and induction of terminal differentiation (Parodi, 1999).
Vitamin A and β-carotene are probably the most widely investigated natural anticarcinogens. Epidemiological studies consistently find that people eating more fruits and vegetables rich in β-carotene or having higher blood concentrations of β-carotene had a lower risk of developing several types of cancer, especially lung cancer (Parodi, 1999).
In animals, β-carotene suppress chemically-induced tumours at some sites. The effect is probably enhanced when combined with other micronutrients, such as vitamins E and, glutathione and selenium (Parodi, 1999). Although metabolism of β-carotene in animals is notably different from humans, intervention studies with humans suggest β-carotene may protect against cancer of the aerodigestive tract and colon and probably is more effective during the early stages of carcinogenesis (Van Poppel, 1993). Provitamin A (β-carotene) has desirable properties in addition to its role of forming vitamin A, such as being an antioxidant and possibly causing tumour suppression as reported (Boland *et al.*, 2001).

Conclusion: In many studies it has been reported that milk fat contains a number of components which are metabolically active in metabolism. A variety of health benefits have been associated with sphingolipids and their digestion products, ceramides and sphingosines. They are suggested to be important in prevention from carcinogenesis, reduction of serum LDL cholesterol, regulation of the immune system and inhibition of food-borne pathogens. Conjugated linoleic acid which is a naturally occurring fatty acid found in animal and dairy fats, exhibits a number of health benefits. Reported beneficial health-related effects of CLA include anticarcinogenesis, antiatherogenic, antidiabetagenic and immune modulating properties.
Butyric acid and ether lipids have also been suggested to have an anti-tumour role whereas butyric acid is especially effective in colon cancer prevention. Vitamin A and D and β-carotene are also offered as natural anticarcinogens in numerous reviews.
As health benefits of these bioactive components of milk fat has been studied mostly *in vitro* conditions, *in vivo* researches are not sufficient. So, further research is required to establish the contribution of these dietary components to host metabolism and health.

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