



Metabolic origin and bioactive properties of odd and branched-chain fatty acids in ruminants' milk. Review



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Abstract:

Milk odd and branched-chain fatty acids (OBCFA) are a group of lipids that represents less than 5 % of the total fatty acids (FA) and that includes a group of molecules, among which the most abundant are the isomers of the pentadecanoic (15:0, *iso*-15:0 and *anteiso*-15:0), hexadecanoic (*iso*-16:0), and heptadecanoic (17:0, *iso*-17:0 and *anteiso*-17:0) FA. OBCFA are synthesized by rumen microorganisms from the molecules produced during feed fermentation processes. Recent research indicates the possibility of endogenous synthesis of some odd (15:0 and 17:0) and branched-chain (*iso*-1:0 and *anteiso*-17:0) FA. The presence of these FA in milk is influenced by dietary factors, mainly the starch *vs* fiber proportion, forage to concentrate ratio, and the supplementation with fat sources that change the lipid metabolism, which modifies the OBCFA profile of milk. Milk and dairy products are the main and almost only source of OBCFA in the human diet. Despite their low concentration, OBCFA possess bioactive properties that have been shown in different investigations. This article reviews the metabolic origin, bioactive properties, and most recent nutritional strategies directed to manipulate the contents and profiles of OBCFA in milk fat.

Key words: Ruminant, Fatty acids, Milk, Dairy products, Rumen, Lipids.

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Introduction

The lipids in milk are physically in the form of globules, which form an emulsion with the aqueous phase of milk. Inside these globules reside the triglycerides (TG), which are molecules of esterified glycerol with three FA. TG (more than 95 % of total lipids), and thus, they are mainly responsible for the properties of milk lipids, and their characteristics vary in function of the FA composition. Although milk fat has more than 400 different FA⁽¹⁾, only 30 or 40 are present at concentrations higher than 0.1 %. The FA profile of milk and dairy products is mainly related to dietary factors, followed by ruminant species, and, to a lesser extent, genetic factors, milk yield, and lactation status.

Based on their structure, FA are classified as saturated or unsaturated FA. Most saturated FA have an even number of C atoms, ranging from 4 up to 20 C. Although the most abundant are those with a chain length of 10 to 20 C atoms, the ruminant milk fat is characterized by significant amounts of short-chain FA, especially 4:0 and caproic acid (6:0). Among the unsaturated FA, which can have one to four bonds, the most abundant (15 to 20 %) is oleic acid (*cis*-9 18:1). The presence of small amounts of linoleic (2 %) and α -linolenic (0.5 %) acids in milk derives from the diet, and since both are not synthesized in tissues, they are considered essential FA.

Ruminant milk also contains odd and branched-chain FA (OBCFA). Those with an odd number of C atoms represent 2 % of the total FA; 15:0 and 17:0 are the most abundant and representative (Table 1). Branched-chain FA represent a similar proportion and include a higher number of molecules, classified as *iso* and *anteiso*, with variable concentrations in dairy products. Although the concentration of OBCFA in fat milk is lower than 5 %, their presence is of great relevance because they work as indicators of ruminal function and, in humans, as indicators of the intake of dairy products. Branched-chain FA, especially *anteiso*, have lower melting points than their unbranched counterparts; this allows them to contribute to the fluidity of milk fat.

Table 1: Content of odd and branched-chain fatty acids (g/100 of total fatty acids) in dairy products

Fatty acid	Milk		Butter	Yogurt	Cream	Cheese
	(7)	(58)				
<i>iso</i> 13:0			(59)			
<i>iso</i> 14:0	0.05-0.13		0.09	0.17	0.12-0.13	0.00-0.05 0.00-0.22
<i>iso</i> 15:0	0.14-0.22		0.22	0.10	0.14-0.15	0.00-0.11 0.02-0.42
<i>iso</i> 16:0			0.21	0.34	0.29-0.30	0.24 0.00-1.18
<i>iso</i> 17:0			0.27	0.31	0.16-0.25	0.27-0.30 0.05-0.30
<i>iso</i> 18:0				<0.01	0.00-0.04	<0.01 0.00-0.09
<i>anteiso</i> 13:0			0.08			
<i>anteiso</i> 15:0	0.32-0.45		0.46	0.63	0.62-0.63	0.46-0.49 0.38-0.88
<i>anteiso</i> 17:0			0.50	0.38	0.56-0.59	0.36-0.37 0.29-0.61
15:0	0.84-1.31	0.89				
17:0	0.45-0.66	0.52	0.55-0.90			

Fievez *et al*⁽⁷⁾; O'Donnell-Megaró *et al*⁽⁵⁸⁾; Shingfield *et al*⁽⁵⁹⁾; Ran-Ressler *et al*⁽⁴³⁾.

Although a great proportion of the OBCFA in milk fat is synthesized during the fermentative processes in the rumen, recent studies have suggested that a small amount could be endogenously synthesized (e.g., mammary gland). Moreover, in the last decade, increasing evidence suggests that OBCFA could have an important role in human health. Therefore, their presence in dairy products should be viewed positively, as these products are almost the only source of these components in the diet. This review aimed to update the information about the origin and synthesis of these FA in ruminants, reviewing the influence of the type of feed on their milk content, and compile evidence on the nutritional benefits of OBCFA in humans.

Origin of odd and branched-chain fatty acids

Ruminal synthesis of OBCFA

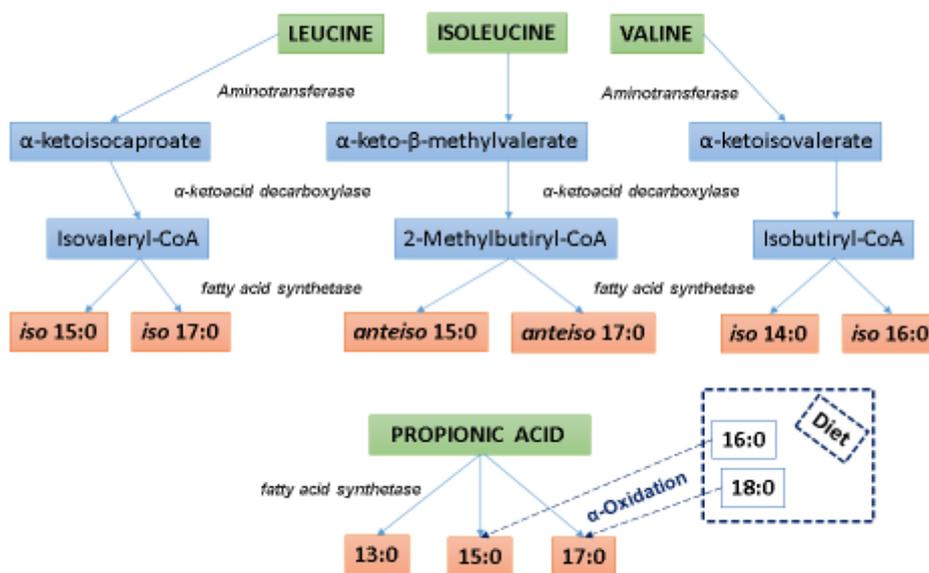
The fat in ruminant milk has higher concentrations of OBCFA than the milk of other mammals. Vlaeminck *et al*⁽²⁾ compiled data from numerous studies about the composition of OBCFA in milk and showed that the main OBCFA are isomers of the tetradecanoic

(*iso*-14:0), pentadecanoic (15:0, *iso*-15:0 and *anteiso*-15:0), hexadecanoic (*iso*-16:0), and heptadecanoic (17:0, *iso*-17:0 and *anteiso*-17:0) FA.

The OBCFA are mainly synthesized during the microbial fermentation processes in the rumen. Rumen bacteria contain between 50 and 90 g/kg of lipids in their dry matter, and approximately 5 % of these lipids are OBCFA, which are preferentially located in the membranes⁽³⁾. Protozoa have less total OBCFA than bacteria (110 vs 160 g/kg of total FA), although they possess a higher proportion of *iso* 16:0 and *anteiso* 17:0⁽⁴⁾.

The precursors of the microbial synthesis of branched-chain FA in the rumen are leucine, isoleucine, and valine, branched-chain amino acids obtained from the diet (Figure 1). Initially, the rumen microbiota transforms these amino acids into short branched-chain carboxylic acids; isovaleric, 2-methylbutyric, and isobutyric, respectively; linked to Coenzyme A. Subsequently, the microbial FA synthase (FAS) elongates the FA chains. The even-numbered *iso* FA originate from the isobutyric acid; the odd-chain *iso* and *anteiso* FA originate from the isovaleric and 2-methylbutyric acids, respectively. The precursor of medium odd-chain FA (13:0, 15:0, and 17:0) in the rumen is propionic acid, which results from the fermentation of specific ration components, although the 15:0 and 17:0 FA can also originate by α -oxidation from the 16:0 and 18:0 FA in the lipids in the diet.

Figure 1: Synthesis of odd and branched-chain fatty acids by the rumen microbiota



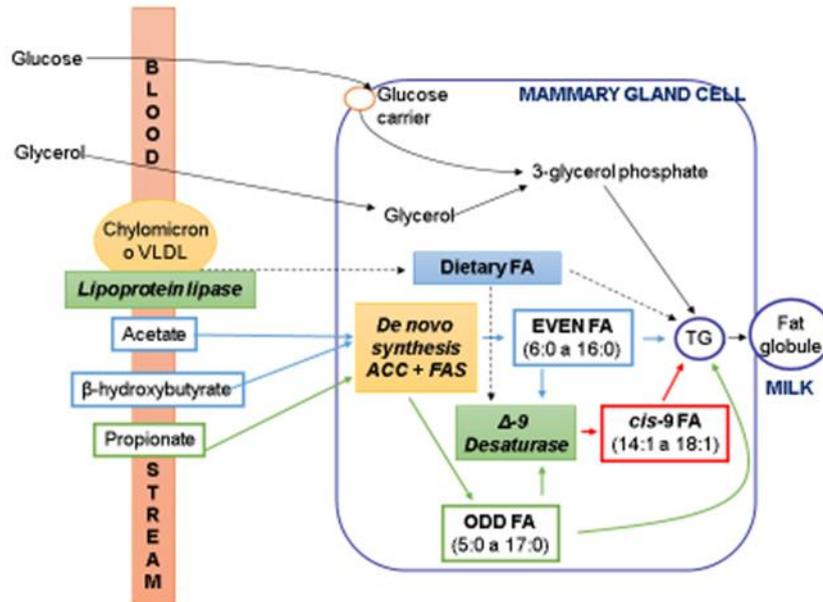
Adapted from Vlaeminck *et al*⁽²⁾

After ruminal digestion, the OBCFA profile is strongly associated with the activity of the microorganisms in this digestive cavity⁽²⁾. Thus, the OBCFA profile variation reflects the relative abundance of the different microbial species in the rumen ecosystem^(5,6). Cellulolytic bacteria, those with enzymes that hydrolyze cellulose, such as *Ruminococcus flavefaciens*, *Ruminococcus albus*, or *Butyrivibrio fibrisolvens*, possess significant contents of *iso* OBCFA⁽⁷⁾. Higher proportions of *anteiso*-15:0 would indicate the presence of bacteria specialized in the fermentation of pectin and sugars⁽⁸⁾, such as *Prevotella* spp., *Lachnospira multiparus*, and *Succinovibrio dextrinosolvens*. Amylolytic bacteria, such as *Succinivibrio dextrinosolvens*, *Succinimonas amylolytica*, *Ruminobacter amylophilus*, *Selenomonas ruminantium*, and *Streptococcus bovis*, have lower proportions of branched-chain FA, but higher proportions of odd-chain FA.

Transfer of OBCFA from the intestinal tract to the mammary gland

The preponderant role of rumen microorganisms in the presence of OBCFA in dairy products is well known⁽⁹⁾. However, recent reports^(2,10) have questioned the strictness of the correlation between the content of OBCFA in the intestinal fluid and the milk fat. Theoretically, disarrangements could occur during the transfer of these FA from the intestinal tract to the internal tissues, particularly in the mammary gland. These disarrangements could occur during the intestinal absorption process or during the transport through the bloodstream. Like other FA that reach the small intestine, OBCFA are absorbed in the jejunum. Apparently, the intestinal absorption of microbial FA would be higher⁽¹¹⁾, but the few available data are not enough to render a definitive conclusion.

After being absorbed, the OBCFA and remaining FA are esterified in the glycerol by the intestinal epithelial cells to form TG and phospholipids (PL), and transported, first to the lymphatic system and then to the bloodstream, where they form part of macromolecular complexes, such as chylomicrons and very low density lipoproteins (VLDL). Chylomicrons and VLDL contain different types of lipids (TG, PL, cholesterol esters (CE), and free fatty acids), but each one differs in composition since each type of FA selectively binds to the different fractions. The transfer of the FA from the bloodstream to the cytoplasm of mammary gland cells occurs after their release from these macromolecules by the lipoprotein lipase enzyme (Figure 2).

Figure 2: Metabolic pathways of fatty acid synthesis in the mammary gland cells of ruminants

ACC: acetyl-CoA carboxylase; FAS: fatty acid synthase; FA: fatty acid; TG: triglycerides; VLDL: very low-density lipoproteins.

The main targets of the lipoprotein lipase are the FA of the TG. On the contrary, the characteristic FA of the CE and PL fractions are more poorly transferred to milk fat because this enzyme has a low affinity for these FA. Fievez *et al*⁽⁷⁾ reported that the branched-chain FA are more abundant in the CE and TG than in the PL or free fatty acids. However, these last two fractions are richer in odd-chain FA. Nevertheless, the available literature about the distribution of OBCFA between the different types of plasma lipids is still too scarce to predict trends or forecast consolidated metabolic behaviors. Therefore, it would be worth exploring the metabolic processes in the mammary gland cells in detail to find the mechanisms responsible for the differences in the OBCFA profiles between rumen fluid and milk.

Endogenous synthesis of OBCFA

Most of the saturated FA with an even number of C atoms in the milk fat are synthesized *de novo* in the epithelial cells of the mammary gland⁽¹²⁾. Their synthesis occurs from the blood-circulating acetate and β -hydroxybutyrate molecules generated in the rumen during the fermentation of carbohydrates in the diet. Acetyl-CoA carboxylase (ACC) and FAS are the two enzymes responsible for this *de novo* synthesis in the mammary gland (Figure 2). The first step in the synthesis consists of the activation of acetate to acetyl-CoA,

followed by the condensation of two acetyl-CoA molecules to form malonyl-CoA. This step is catalyzed by the ACC. Subsequently, FAS regulates the chain elongation of the FA synthesized *de novo*. If the initial substrate instead of acetate was propionate, methylmalonate, or volatile branched-chain FA (isovaleric, isobutyric, and 2-methylbutyric), then the final products of the *de novo* synthesis would be odd-chained FA, non-terminal methyl-substituted FA, or *iso* and *anteiso*, respectively, as it occurs in the rumen (Figure 1).

The first studies in this field demonstrated that 15:0 and 17:0 could be synthesized *de novo* in the mammary gland of ruminants using propionyl-CoA instead of acetyl-CoA as the primer molecule⁽¹³⁾. The elongation of this molecule, catalyzed by FAS, would explain the presence in milk of 5:0, 7:0, 9:0, and 11:0, as well as the increase in the amounts of 13:0, 15:0, and 17:0 compared to those already generated in the rumen and transferred from the duodenum. The importance of this endogenous synthesis was confirmed in subsequent studies^(10,14,15). Theoretically, these odd-chained FA (13:0, 15:0, and 17:0) could also be metabolized to *cis*-monounsaturated by the delta-9 desaturase enzyme. However, only the conversion from 17:0 to *cis*-9 17:1 seems to be of quantitative importance⁽¹⁶⁾ (Figure 2).

In contrast to odd-chained FA, the mammary synthesis of *iso* and *anteiso* FA did not respond to the increase in the availability of its biological precursors, the isovaleric, 2-methylbutyric, and isobutyric FA^(13,14). This observation would indicate that the FAS might not be active in the elongation process, and thus, the *de novo* synthesis would not occur in extraruminal tissues. However, these results would contradict the increased content of *iso* 17:0 and *anteiso* 17:0 in milk fat, compared to the intestinal fluid, reported by other researchers^(2,10,17).

Fievez *et al*⁽⁷⁾ postulated that the lowest values of the *iso* 15:0/*iso* 17:0 and *anteiso* 15:0/*anteiso* 17:0 ratios in milk, compared to those in the duodenal fluid, could be explained if the chain elongation of the *iso* 15:0 and *anteiso* 15:0 molecules was demonstrated to be viable after being absorbed into the bloodstream. In this sense, it seemed striking that the secretion in the milk of *iso* 15:0 + *iso* 17:0 and *anteiso* 15:0 + *anteiso* 17:0 was very similar to the sum of these FA in the duodenum⁽⁷⁾. These data corroborated the hypothesis about the existence of an extraruminal elongase activity on the *iso* and *anteiso* FA with 15 C atoms; it also supported the idea of an almost complete transfer of total branched FA from the duodenum to the milk. In a subsequent study, Vlaeminck *et al*⁽¹⁵⁾ observed higher levels of *iso* 17:0 and *anteiso* 17:0 in milk fat than in the duodenal fluid (Table 2). This fact, along with lower *iso*-15:0/*iso*-17:0 and *anteiso* 15:0/*anteiso* 17:0 ratios in milk, would rule out the post-ruminal *de novo* synthesis of these FA and confirm the predominant role of postabsorption elongases, which would exert their activity on the *iso* 15:0 and *anteiso* 15:0 FA. The lowest value of the *iso* 15:0/*iso* 17:0 and *anteiso* 15:0/*anteiso* 17:0 ratios in the plasma TG, regarding the duodenal fluid samples, would also indicate that the elongation could be taking place in tissues other than the mammary gland.

Table 2. Fatty acid proportion in cow blood plasma

Fatty acid	Assay	Blood plasma				P-value
		Duodenum	Milk	TG	FFA	
<i>iso</i> -15:0	1	12.87 ^d	7.20 ^b	9.13 ^c	6.22 ^a	<0.001
	2	10.45 ^c	5.42 ^a	6.80 ^b	7.54 ^b	<0.001
<i>anteiso</i> 15:0	1	26.98 ^d	14.54 ^b	19.07 ^c	12.47 ^a	<0.001
	2	33.57 ^c	13.22 ^a	15.00 ^{ab}	19.06 ^b	<0.001
<i>iso</i> 17:0	1	5.76 ^a	8.85 ^b	10.02 ^c	13.45 ^d	<0.001
	2	5.79 ^a	6.64 ^a	9.54 ^b	10.09 ^b	<0.001
<i>anteiso</i> 17:0	1	7.32 ^a	13.24 ^b	14.21 ^{bc}	15.50 ^c	<0.001
	2	9.90 ^a	16.18 ^{bc}	14.41 ^b	17.63 ^c	<0.001
C15/C17 ratios						
<i>iso</i> 15:0/ <i>iso</i> 17:0	1	2.28 ^c	0.83 ^b	0.92 ^b	0.48 ^a	<0.001
	2	1.82 ^b	1.18 ^{ab}	0.78 ^a	0.77 ^a	<0.001
<i>ant</i> 15:0/ <i>ant</i> 17:0	1	3.98 ^b	1.10 ^a	1.37 ^a	0.82 ^a	<0.001
	2	3.73 ^a	0.84 ^b	1.10 ^b	1.13 ^b	<0.001

TG= triglycerides; FFA= free fatty acids.

^{a-d} Values in a row with different superscripts are different ($P<0.05$).

Source: Vlaeminck *et al*⁽¹⁵⁾.

Overexpression of the gene that codifies the ELOVL6 elongase in ruminants is described in mammary epithelial cells⁽¹⁸⁾, and, more recently, an *in vitro* study evaluated for the first time the role of this enzyme in the regulation of FA elongation⁽¹⁹⁾. Upregulation of ELOVL6 increases the elongation indices of 16:0 and 18:0, which suggests an important role of this enzyme in controlling the chain length of FA in the mammary gland. However, the effects on branched FA are yet to be investigated.

Influence of the cattle diet on the OBCFA contents in milk

The chemical composition of the ration, the proportion of starch and fiber, the forage to concentrate ratio (F/C), and the lipid profile in the diet exert a significant influence on the type of ruminal microbial populations and the microbial synthesis of FA; therefore, the proportion of OBCFA that reaches the small intestine reflects the composition and quantity of rumen microbiota^(2,3,20).

Effects of the basal diet

Among the different diet components, the starch to fiber ratio has an important role in the production of OBCFA through its influence on the microbial ecosystem, particularly on the proliferation of cellulolytic bacterial strains^(21,22). An increase in starch in the rations limits the growth of cellulolytic microorganisms, promoting the proliferation of amylolytic bacteria. As previously described, cellulolytic bacteria possess mainly branched *iso* FA in their membranes⁽⁷⁾ and are sensitive to low ruminal pH values, which are characteristic of feeds with a high starch content⁽²³⁾. Vlaeminck *et al*⁽²⁾ observed that starch-rich diets, characterized by a higher proliferation of amylolytic bacteria, decreased the levels of *iso* 14:0, *iso* 15:0, and *iso* 16:0 (Table 3).

Table 3: Mean content (g/100 of total fatty acids) of odd and branched-chain fatty acids in the milk of ruminants fed with different ingredients

Fatty acid	Shingfield <i>et al</i> ⁽⁶⁰⁾		Vlaeminck <i>et al</i> ⁽²⁾		Patel <i>et al</i> ⁽²⁴⁾		Li <i>et al</i> ⁽²⁵⁾		Cívico <i>et al</i> ⁽²⁷⁾	
	GS	CS	GS	CS	HGS	LGS	HF	LF	HF	HS
<i>iso</i> 13:0	0.03	0.04							0.02	0.01
<i>iso</i> 14:0	0.08	0.06	0.09	0.05	0.08	0.07	0.14	0.13	0.07	0.03
<i>iso</i> 15:0	0.21	0.18	0.24	0.17	0.21	0.18	0.32	0.23	0.17	0.14
<i>iso</i> 16:0	0.21	0.23	0.18	0.16	0.26	0.26			0.19	0.15
<i>iso</i> 17:0	0.74	0.91	0.19	0.23	0.47	0.33	0.38	0.49	0.27	0.23
<i>iso</i> 18:0	0.03	0.01							0.05	0.04
<i>anteiso</i> 13:0	0.05	0.07								
<i>anteiso</i> 15:0	0.39	0.37	0.46	0.46	0.42	0.39	0.49	0.45	0.30	0.22
<i>anteiso</i> 17:0			0.46	0.55			0.89	0.76	0.29	0.26
11:0							0.20	0.22		
13:0							0.09	0.09		
15:0	1.22	0.78	0.95	1.21	1.06	0.94	1.00	0.98	0.82	0.62
17:0	0.63	0.54	0.48	0.55	0.67	0.53	0.73	0.68		

GS= grass silage; CS= corn silage; HGS= high grass silage; LGS= low grass silage; HF= high-fiber; LF= low-fiber; HS= high-starch.

Subsequent studies have confirmed the idea that the fiber and starch ratios influence the content of milk OBCFA (Table 3). Patel *et al*⁽²⁴⁾ reported that an increase in fiber resulting from the presence of grass silage in the rations increased the milk contents of *iso* 15:0, *iso* 17:0, 15:0, and 17:0; while substituting fiber to the detriment of starch in the diet increased the content of *iso* 15:0 in the milk⁽²⁵⁾ and rumen⁽²⁶⁾. These responses were associated with a higher abundance of cellulolytic versus amylolytic bacteria. Moreover,

Cívico *et al*⁽²⁷⁾ measured higher levels of *iso* 14:0, *iso* 17:0, and 15:0 in milk fat when the diet was enriched with fiber and low on starch (Table 3).

The F/C ratio in the rations could modify the contents of OBCFA in dairy products. Vlaeminck *et al*⁽²⁾ concluded that a greater proportion of forage in the basal diet contributed to a selective increase of specific OBCFA, such as *iso* 14:0 and *iso* 15:0. However, the levels of *anteiso* 15:0 were less affected. These results are explained by changes in the ruminal ecosystem induced by the variation in the F/C ratio of the diets. An increase in the concentrate would favor the proliferation of amyolytic bacteria which could increase *anteisos* and odd-chain FA. In this line, researchers⁽¹⁰⁾ observed lower levels of 15:0 and 17:0 in the milk of cows fed diets with an elevated F/C ratio.

The analysis of the digestive fluids extracted from goats with duodenal cannulation confirmed that increasing the F/C ratio in the ration increases all the OBCFA synthesized *de novo* by the bacteria⁽⁵⁾. A similar experiment in cows⁽²⁸⁾ had similar results. More recently, Zhang *et al*⁽²⁹⁾ confirmed that the OBCFA profiles in the digestive fluids of bovines are drastically affected by the F/C ratio in the basal diet. The concentrations of 11:0, 13:0, *iso* 15:0, *iso* 16:0, *iso* 17:0, and 17:0 were higher when the proportion of forage in the ration was higher. They also observed that only the *anteiso* 15:0 and 15:0 increased with higher proportions of the concentrate.

Effects of lipid supplementation

The levels of OBCFA in dairy products show a significant decrease when they come from animals whose diet has been supplemented with lipid sources. This pattern, observed in the milk of bovines^(6,30) and small ruminants^(31,32), is characteristic of supplementation with oilseeds rich in unsaturated FA.

These results could be explained by the inhibitory effect of the polyunsaturated fatty acids (PUFA) on the gut microbiota. The severity of the effect of the FA incorporated into the diet on the viability of rumen bacteria is greater as the number of unsaturations increases. The effects would be more pronounced if the geometric configuration of the double bonds is of the *cis* type^(2,3). Furthermore, not all microorganisms would be affected in the same way by the lipid supplementation of the diet. Previous studies have observed that cellulolytic and Gram-positive bacteria are more sensitive to the lipids in the diet than amyolytic and Gram-negative bacteria^(20,33,34).

Branched-chain fatty acids as bioactive components

Neonatal gut microbiota

Recent studies have highlighted the role of branched-chain FA as health-protective bioactive components. The presence of branched-chain FA is very low in adult human tissues; however, they are essential bioactive components in the digestive tract at the final stages of fetal development and after delivery⁽³⁵⁾.

Approximately 30 % of the total FA in the vernix caseosa are branched-chain FA, with a great variety of molecular structures, among which *iso* 14:0 and *iso* 16:0 stand out⁽³⁵⁾. The vernix is a waxy material with a cheese-like texture that covers the skin of the fetus and newborn. It consists of a mixture of fatty secretions originated from the 18th week of gestation from the sebaceous glands. The vernix avoids water loss, protecting the skin of the fetus from dehydration, preventing its hardening, and reducing friction and cracking. Moreover, it helps regulate the temperature of the fetus by acting as an insulating layer. There is no other land mammal that produces vernix-covered neonates; however, the fetuses of aquatic mammals present this same fatty film composed of branched FA⁽³⁶⁾.

A complementary hypothesis postulates that the vernix may have antibacterial activity. This idea is based on the fact that vernix particles are detached from the skin during the last months of pregnancy and pass into the amniotic fluid, increasing its turbidity. In the last trimester, the fetus ingests a significant part of the amniotic fluid, and thus, its intestine impregnates with the branched-chain FA in the vernix⁽³⁵⁾.

Moreover, the significant amount of branched-chain FA in the meconium (the first feces of the newborn) constitutes a sufficiently relevant indication of the type of microorganisms that begin to colonize the intestinal tract of the newborn, and that would be favored by the presence of these non-fermentable prebiotics⁽³⁵⁾. As previously described, branched-chain FA are among the most important molecules in the membrane of several microorganisms, particularly of most species of the genus *Bacilli*⁽³⁷⁾. A previous report indicated that the substitution of the dietary fat with branched-chain FA in newborn rat pups modifies their microbiome. These changes translate into an increase of the microorganisms that can incorporate branched-chain FA into their membranes, and a simultaneous reduction of the incidence of necrotizing enterocolitis⁽³⁸⁾, one of the major causes of mortality in preterm infants. Furthermore, *in vitro* studies have demonstrated that branched-chain FA reduce mortality and virulence of pathogens such as *Pseudomonas aeruginosa*⁽³⁹⁾.

High concentrations of branched-chain FA, as a consequence of the presence of vernix in the intestinal lumen of the fetus, may have an important role in the growth and metabolism of enterocytes, as well as in intestinal health and regulation. Recent studies have observed that branched-chain FA can be incorporated into the membrane PL of enterocytes, conferring them an anti-inflammatory activity^(40,41). Liu *et al*⁽⁴²⁾ postulated that this incorporation of branched-chain FA to the PL would contribute to the modulation of the biophysical properties of membranes. Branched-chain FA are assigned biophysical functions comparable to monounsaturated FA with *cis* configuration, but they have the advantage of presenting greater oxidative stability due to the absence of double bonds in their structure. Moreover, the lower melting points of branched-chain FA compared to their linear homologous would be associated with the fluidity of cell membranes⁽⁴³⁾.

Other bioactive properties of branched-chain fatty acids

Besides their positive effects on the composition of gut microbiota, branched-chain FA in the diet could help prevent different diseases. The first study that attributes anti-cancer activity to branched-chain FA was published at the beginning of this century⁽⁴⁴⁾. This study describes the inhibitory effects of *iso* 15:0 on cell proliferation and apoptosis induction in prostate cancer, leukemia, and adenocarcinoma cell lines. More recently, Cai *et al*⁽⁴⁵⁾ reported that *iso* 15:0 could contribute to human lymphomas inhibition. Other studies^(46,47) determined that branched-chain FA could also induce apoptosis in breast cancer cells and inhibit tumor development in cell cultures and animal models.

Moreover, a recent study in overweight humans⁽⁴⁸⁾ reported for the first time the possibility that the abundance of *iso* branched-chain FA in blood serum could be inversely correlated with the presence of TG and negatively associated with other characteristic indicators of inflammatory processes. In any case, the beneficial effects of this group of FA require more research to help clarify the mechanisms underlying the prevention of these pathologies.

Odd-chain fatty acids as bioactive components

Different recent studies have demonstrated that 15:0 and 17:0, the most abundant odd-chain FA in dairy products, could benefit human health^(49,50). For example, there is an inverse association between the concentration of these FA in plasma and the risk of developing type 2 diabetes⁽⁵¹⁻⁵³⁾. This result has also been observed in European populations subjected to different diets⁽⁵⁴⁾. Even several prospective studies on cardiovascular diseases have shown that the plasma concentration of these FA would be associated with a lower risk of developing cardiovascular diseases⁽⁵⁵⁻⁵⁷⁾. However, more

detailed research is needed to help elucidate the metabolic pathways involved in these health effects.

Conclusions

Milk and dairy products are the most significant sources of OBCFA in the human diet. Despite their low concentrations, recent investigations have demonstrated their potential as bioactive components and their nutritional importance. Although they derive mainly from the microbial activity in the rumen, there is recent evidence that their formation is not limited to the biochemical processes that occur in the digestive tract of ruminants. The ability of other tissues to endogenously synthesize specific OBCFA must be carefully considered and may encourage very promising lines of research in the future.

Conflicts of interest

Authors declare no conflicts of interest.

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