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Role of stearoyl CoA desaturase on conjugated Linoleic acid concentration in bovine milk: review

Papel de la estearoil CoA desaturasa sobre la variabilidad en los niveles de ácido linoléico conjugado en la leche bovina: revisión

Papel do estereaoil CoA desnaturase na variação dos níveis do ácido linoléico conjugado em leite bovino. Revisão

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Summary

Interesting health benefits have been attributed to the intake of conjugated linoleic acid, CLA ($C_{18:2}$ cis-9, trans-11), which is the main isomer of linoleic acid, and is present in bovine milk. Among those benefits are: cancer prevention, diminished risk for the onset of type II diabetes and cardiovascular disease, modulation of the immune response, and reduction of preeclampsia risk in primigravid women. Although an adequate nutrition of cows has permitted to increase the amount of CLA in their milk, there is variation in CLA concentrations among cows consuming the same diet. It has been suggested that this variation is due either to changes in the activity of stearoyl CoA desaturase (SCD), changes in the gene expression, or to alterations in the ruminal process of biohydrogenation. Research conducted in semimembranosus muscle and subcutaneous adipose tissue of cattle suggests there are two isoforms of SCD.

Key words: *cattle, conjugated linoleic acid, stearoyl CoA desaturase, trans-vaccenic acid, variability.*

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Resumen

Al isómero mayoritario del ácido linoléico, $C_{18:2}$ cis-9, trans-11 (Ácido Linoléico Conjugado, ALC) en la leche bovina, se le han atribuido propiedades benéficas para la salud humana, entre las que está su efecto en la prevención del cáncer, disminución de los factores de riesgo para la presentacion de diabetes tipo II y de enfermendades cardiovasculares, modulación de la respuesta inmune como también, en la reducción del riesgo de preeclamsia en mujeres primigrávidas. Aunque se ha logrado elevar la concentración de ALC en leche mediante sistemas de alimentación adecuados, existe variabilidad en su concentración para individuos de una misma especie y sometidos a la misma alimentación. Para explicar dicha variabilidad, se ha sugerido que esta se debe a cambios en la actividad de la Estearoil CoA Desaturasa (ECD), de la expresión genética diferencial o a alteraciones en el proceso de biohidrogenación ruminal. Trabajos realizados en músculo semimembranoso y tejido adiposo subcutáneo en bovinos, sugieren la presencia de dos isoformas de la ECD.

Palabras clave: *ácido linoléico conjugado, ácido trans-vaccénico, bovinos, estearoil CoA desaturasa, variabilidad.*

Resumo

Ao isómero maioritário do ácido linoléico, $C_{18:2}$ cis-9, trans-11 (Ácido Linoléico Conjugado, ALC) no leite bovina, tem-se atribuído propriedades benéficas para a saúde humana, entre as quais estão: seu efeito na prevenção do câncer, diminuição dos factores de risco para a apresentação da diabetes tipo II e de doenças cardiovasculares, modulação da resposta imune, como também, a redução do risco da pré-eclâmsia em mulheres primigrávidas. Embora tem-se logrado elevar a concentração dos ALC no leite mediante sistemas de alimentação adequados, existe a variabilidade na sua concentração para indivíduos da mesma espécie e submetidos a uma alimentação semelhante. Para explicar a variabilidade, tem-se sugerido que é causada por mudanças na actividade do Estearoil CoA Desaturase (ECD), da expressão genética diferencial ou às alterações no processo de biohidrogenação ruminal. Trabalhos realizados no músculo semimembranoso e tecido adiposo subcutâneo em bovinos, sugerem a presencia de duas isoformas do ECD.

Palavras chave: *ácido linoléico conjugado, ácido trans-vaccénico, bovinos, estearoil CoA desnaturase, variabilidade.*

Introduction

Nutraceuticals and functional foods have become a fast growing research topic in recent years. Bovine milk can fit into the nutraceuticals category if its fat has a particular lipid profile. It is interesting to highlight that there is natural presence of CLA in the lipid fraction of milk. This compound is a geometric and positional isomer of linoleic acid ($C_{18:2}$ cis-9, cis-12, LiA), which has been regarded as beneficial for the human health. Such benefits include its cancer prevention properties (Belury, 1995, Bauman and Griinari, 2001), action on type II diabetes (Belury and Vanden, 1999, Yu *et al.,* 2002; Belury, 2003), positive effects on the cardiovascular system (Nicolosi *et al*., 1997; Kritchevsky, 1999, Munday *et al.,* 1999) and modulation of immune cells response (Akahoshi *et al.,* 2002; Iwakiri *et al.,* 2002, Yang and Cook, 2003 ; Akahoshi *et al.,* 2004). Furthermore, in a study conducted in Colombia, it was reported that CLA also has positive effects on primigravid women with risk of preeclampsia (Herrera *et al.,* 2004).

It is known that there is high variability in the content of CLA in bovine milk. This occurs for animals of the same breed, and even under the same diet. It has been suggested that the causes for these variations are changes in the activity of SCD, the gene coding for the enzyme and the biohydrogenation process (Peterson *et al.,* 2002).

The objective of this review is to provide a possible explanation to the variability observed in CLA concentration in bovine milk in terms of the activity and genetics of SCD.

Conjugated Linoleic Acid (CLA)

This acid belongs to a family of geometric and positional isomers of LiA. Unlike natural fatty acids, its double bonds are conjugated, which is defined for the presence of alternating double-single-double bonds in the carbon structure. In other words, the double bonds are located every two carbons (O 'Shea *et al.,* 1998, Bauman *et al.,* 1999) (Figure 1). Near 20 different positional and geometric isomers of CLA have been reported. Those isomers have several positions for the double bonds in the18-carbon chain. Some of these geometric configurations are: cis-trans, trans-cis, cis-cis and trans-trans (Sehat *et al.,* 1998).

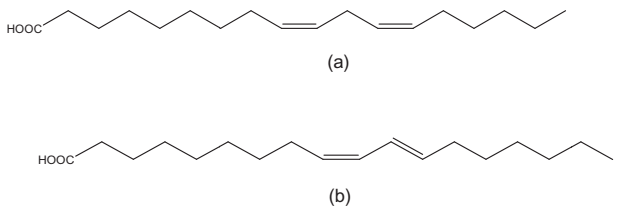

Figure 1. Chemical structures of LiA (a), and CLA (b).

Conjugated linoleic acid is derived from a partial bio-hydrogenation of LiA in the rumen, a process which also generates *trans*-vaccenic acid ($C_{18:1}$ *trans*-11, TVA) from CLA. This TVA can be generated also from α-linolenic acid ($C_{18:3}$ *cis*-9, *cis*-12, *cis*-15, LnA). This TVA is an intermediate compound which is absorbed and subsequently dehydrogenated by SCD between carbons 9 and 10, to produce CLA (Figure 2). It has been reported that 91% of milk CLA is endogenously synthesized by SCD (Kay *et al.,* 2004). It is also known that SCD has increased activity in the mammary gland of lactating cows and in adipose tissue of growing ruminants (Bickerstaff and Annison, 1972; Kinsella, 1972).

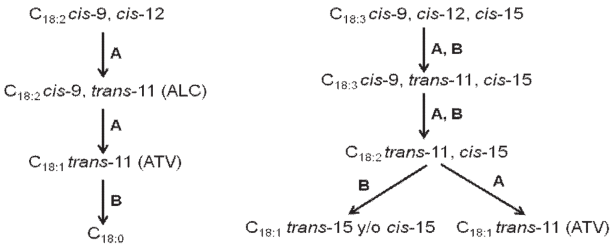

Figure 2. Transformation of unsaturated fatty acids in the rumen.

Role of SCD genotype in the variability of CLA

The creation of a *cis* double bond between carbons 9 and 10 of a saturated fatty acid having between 10 to 18 carbons is an important step in the synthesis of unsaturated fatty acids (Ntambi, 1995, Bauman *et al.,* 1999). The ferric ion, coordinated with SCD, NADPH, cytochrome b_5 reductase, cytochrome b_5 and oxygen, catalyzes the dehydrogenation o f TVA (Figure 3) (Ntambi, 1995; Yahyaoui *et al.,* 2002).

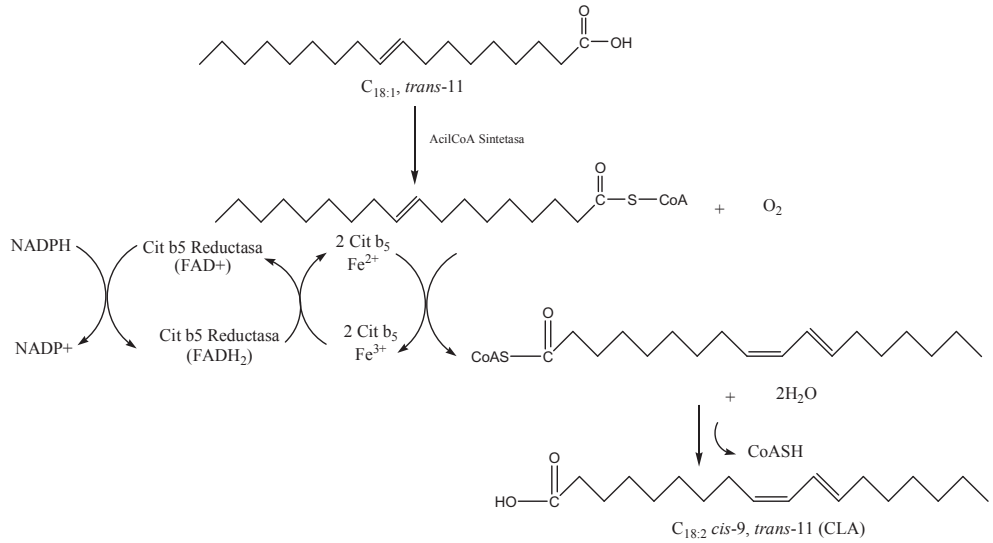

Figure 3. Catalytic action of SCD on TVA for the endogenous synthesis of CLA in mammary gland.

The bovine gene that codifies for SCD has 5,331 base pairs and is located on chromosome 26 (Taniguchi *et al.,* 2004).

The entire length of the gene has been reported in a study in which 20 Japanese black breed steers were used. The same researchers reported they found eight simple nucleotide polymorphisms (SNPs) (Figure 4) (Campbell et al., 2001).

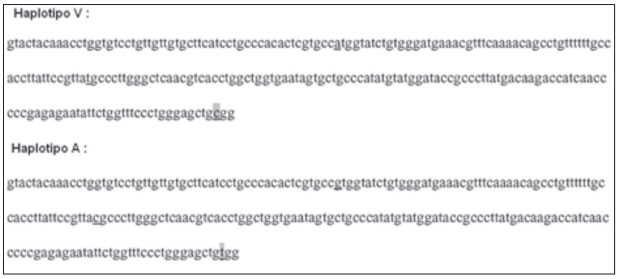

Figure 4. Simple nucleotide polymorphisms in bovine SCD. The gray box shows the substitution of one nucleotide, which causes the replacement of Valine for Alanine (Mele *et al.,* 2007).

Three SNPs have been reported that resulted in two haplotypes detected in the fifth exon. The third SNP caused the substitution of valine (V allele) for alanine (A allele), on the 293 residue of the SCD enzyme (Taniguchi *et al.,* 2004). Besides, they found the relative frequencies of the genotypes of the enzyme were: 27% for AA, 60% for AV and 13% for VV (Mele *et al.,* 2007). They also found that AA genotype was associated with 9.3, 37.9 and 11.7% more total monounsaturated fatty acids (MUFA; $C_{18:1}$ ω9 and $C_{14:1}$ ω5, respectively, in regard to VV genotype (Table 1).

In addition, it was established that the contribution of the genotypes of SCD to the total variation of the other fatty acids was not significant. The same authors, found that the ratio $C_{14:1}$ ω5 / $C_{14:0}$ (which is an estimate of SCD activity) in AA genotype cows was the highest compared with AV and VV genotypes. No significant differences were reported for $C_{16:1}$ ω7/$C_{16:0}$ and $C_{18:1}$ ω9/$C_{18:0}$ ratios. The ratio $C_{14:1}$ ω5/$C_{14:0}$, clearly consistent with the results found for the genotypes studied, suggests there is an effect of genetic variability in the overall composition of fatty acids in milk.

Table 1. Fatty acids concentration in bovine milk (g/100 g of milk fat) for three SCD genotypes (Mele *et al.,* 2007).

	Genotype of SCD					
	AA		AV		VV	
Fatty acid (g/100 g milk fat)	Ave*	St. Dev**	Ave	St. Dev	Ave	St. Dev
$C_{14:0}$	8.49	0.25	8.85	0.17	8.88	0.31
$C_{16:0}$	23.92	0.60	24.12	0.41	23.17	0.72
$C_{18:0}$	8.70	0.35	8.91	0.24	8.58	0.42
TVA	0.76	0.03	0.77	0.02	0.74	0.03
$C_{14:1}$ ω-5	0.80^{A}	0.04	0.68^{B}	0.03	0.58^{B}	0.05
$C_{16:1}$ ω-7	1.17	0.05	1.16	0.04	1.10	0.06
$C_{18:1}$ ω-9	18.43^{A}	0.44	17.68^{B}	0.30	16.50^{B}	0.53
CLA	0.37	0.01	0.36	0.01	0.33	0.02
Total MUFA	20.72^{A}	0.47	20.30^{A}	0.32	18.95^{B}	0.57

* Average
**Standard deviation
Means within a row with different superscripts differ significantly (p <0.01).

Although, as mentioned, there were significant differences in the profiles and concentration of fatty acids in milk fat within the same breed, it was also found that while AA genotype produced more than 12% CLA compared with VV, this difference was not significant (Mele *et al.,* 2007). In other words, the genetic factor did not satisfactorily explain the dispersion values registered for CLA under those conditions. However, this effect cannot be ruled out entirely, because there was an experimental constraint, which was the sample size of the population. Although there have been other studies evaluating the effect of SNPs on the SCD and the fatty acids profile in bovine milk fat (Moioli *et al.,* 2007), there are scarce reports determining the effect of genetic variability of SCD on CLA concentration.

Stearoyl CoA desaturase activity

The dehydrogenation index of a fatty acid is considered as a rough measure of the SCD activity. Several indexes have been proposed, such as the ratio: product / substrate (Lock and Garnsworthy, 2003, Thompson *et al.,* 2003), substrate / product (Chouinard *et al.,* 1999) or product / (substrate + product) (Kelsey *et al.,* 2003; Royal and Garnsworthy, 2005).

The main products of SCD activity present in the mammary gland of ruminants are $C_{14:1}$ ω-5, $C_{16:1}$ ω-7, $C_{18:1}$ ω-9 and CLA, which are derived from $C_{14:0}$, $C_{16:0}$, $C_{18:0}$ and ATV, respectively. Taking into account that $C_{14:0}$ is mostly obtained from *de novo* synthesis in the mammary gland, the best indicator of SCD activity is the ratio $C_{14:1}$ ω-5/$C_{14:0}$ (Lock and Garnsworthy, 2003).

It is known that diet is the main factor influencing SCD activity in the bovine mammary gland (Kelsey *et al.,* 2003). According to Lock and Garnsworthy (2003), high levels of SCD activity were observed for cows fed forage-based diets. On the other hand, cows fed grain-forage diets resulted in lower SCD activity. Similarly, Daniel *et al.* (2004) reported high SCD activity in the mammary gland of sheep fed high forage diets.

It has been reported that cobalt inclusion in feed supplements, and abomasal infusion of CLA have resulted in a reduction of SCD activity (Chouinard *et al.,* 1999; Taugbøl *et al.,* 2008).

Besides the effect of the diet, it is known that also breed has a significant effect on SCD activity. It has been reported that Holstein cows present higher SCD activity than Brown Swiss (Kelsey et al., 2003). In a similar work, Vasta et al. (2009) found that Brown Swiss and Jersey breeds exhibited lower SCD activity in comparison with Holstein cows.

A relationship was established between the proportion of A and V alleles and the activity indexes of SCD in Jersey, Piedmont and Varlostana cattle (Table 2). The researchers found that V allele increased $C_{14:1}$ ω-5/$C_{14:0}$ and $C_{10:1}$ ω-1/$C_{10:0}$ indexes. They reported no increase in CLA production for Jersey cattle, and no effect of V allele was detected, which is entirely consistent with its frequency in SCD of this breed (Moioli *et al.,* 2007).

Table 2. Frequency of A and V alleles in Stearoyl CoA desaturase and CLA concentration for three cattle breeds (Adapted from Moioli *et al.,* 2007).

Breed	CLA concentración in milk (g/100 g milk fat)	Allele	
		A	V
Jersey	0.451	0.94	0.06
Piedmontes	0.831	0.42	0.58
Valdostana	1.668	0.65	0.35

It has been established that milk yield, milk fat, parity, and lactation stage do not have a significant effect on SCD activity, which explains why these physiological effects have received little attention (Kelsey *et al.,* 2003; Soyeurt *et al.,* 2008).

Besides the specific dehydrogenation rates of fatty acids, a direct relationship between SCD activity and its expression has been proposed (Vasta *et al.,* 2009). There is little research concerning SCD expression in mammary gland. Literature is more abundant regarding protein expression in muscle and adipose tissue of cattle. In a recent paper Dance *et al.* (2009) reported the effect of breed on fatty acid composition and SCD expression in bovine muscle and subcutaneous adipose tissue. They concluded that changes in SCD expression could contribute to the MUFA and CLA variations observed into the same breed.

The additional reports found on SCD in ruminants are limited to the enzyme activity in relation to its mRNA (Jamberenghi *et al.,* 2007, Pavan and Duckett, 2007). There is a report about the effect of feeding systems and tannin supplementation on the relation between intramuscular fat content, fatty acid composition and SCD expression in lamb *longissimus dorsi* (Vasta *et al.,* 2009). Changes in the activity of SCD may be related to variations in the expression of mRNA and / or protein. The authors found that SCD expression was not affected by tannin supplementation, and also reported no association between SCD expression and the levels of MUFA and CLA ($p > 0.05$). Additionally, they found that feeding concentrate diets affected the MUFA / SFA ratio (saturated fatty acids) but did not affect CLA

/ TVA ratio, which agrees with a previous report conducted on milk fatty acid composition (Mele *et al.,* 2007.) As a possible explanation for this inconsistency, it is argued that CLA and MUFA biosynthesis could be catalyzed by two SCD isoforms. The presence of more than one isoform has been previously reported in other species (Thida *et al.,* 1986, Miyazaki and Ntambi, 2003). Today, we know that there are two isoforms of SCD in ruminants, and both have been found in cattle (Ward *et al.,* 1998, Chung *et al.,* 2000; Lengies and Corl, 2007). Regarding research in other species, four isoforms have been found in mice (Kaestner *et al.,* 1989, Zheng *et al.,* 2001, Miyazaki *et al.,* 2003), two in humans (Zhang *et al.,* 1999, Wang *et al.,* 2005), and many counterparts in rats, sheep, goats and pigs (Lengi and Corl, 2007). It is not clear why such isoforms exist.

Nevertheless, there is evidence of their divergent and specific expression in tissues (Ntambi *et al.,* 1988), and also substrate specificity. An example is Muridae family, where SCD1, SCD2 and SCD4 have shown preference to desaturate palmitoyl-CoA and estaroil-CoA, whereas SCD3 desaturates only palmitoyl-CoA (Miyazaki *et al.,* 2006). This could indicate that the existence of different SCD isoforms has a physiological role (Lengies and Corl, 2007).

Conclusions

The experimental evidence so far suggests that there is an effect of genetic variability in the overall composition of fatty acids in milk, for animals of the same breed under the same diet. Although the genetic factor did not explain the dispersion registered for CLA values, this factor cannot be entirely ruled out, since there was an experimental constraint, which was the sample size of the population, making it necessary to conduct further work to determine the effect of SCD genetic variability on CLA concentration.

A marked influence was found for the effect of diet and breed on SCD activity. Experimental evidence shows that genetic variability among breeds is the factor that exerts such a change in SCD activity.

Based on SCD studies using cattle *semimembranosus* muscle and adipose tissue, it has been suggested the existence of two isoforms of the enzyme, which may preliminary explain why feeding concentrates significantly affected the MUFA / SFA rate, but not the CLA / TVA rate. Consideration also should be given to the existence of several SCD isoforms in some species which is related to their specific substrates and different tissue expression, features which play perhaps some physiological role.

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