Expression and nutritional regulation of Stearoyl-CoA desaturase genes in the ruminant mammary gland: relationship with milk fatty acid composition

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Chapter 13
Expression and Nutritional Regulation of Stearoyl-CoA Desaturase Genes in the Ruminant Mammary Gland: Relationship with Milk Fatty Acid Composition

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Introduction

In lactating ruminants, stearoyl-CoA desaturase (*SCD*) gene expression in the mammary gland focused particular attention due to its implication in milk technological and nutritional qualities for human consumers. Indeed, the mammary enzyme SCD or Δ9-desaturase by introducing a cis double bond between carbons 9 and 10 of the fatty acids (FA) has a key role in the synthesis of milk monounsaturated FA and specific conjugated linoleic acid (CLA) isomers only found in ruminant products. Then, in milk, about 60 % of oleic (cis-9-18:1; a major milk FA), 50–56 % of palmitoleic (cis-9-16:1), 90 % of myristoleic (cis-9-14:1), and >60 % of the major isomer of CLA (cis-9, trans-11-18:2 or rumenic acid) originate from mammary gland synthesis by the action of SCD enzyme on circulating stearic (18:0), palmitic (16:0), myristic (14:0), and vaccenic acids (trans-11-18:1), respectively. This action is very important due to the impact of milk fat concentration and FA profile in determining milk nutritional quality. Indeed, certain saturated FA (mainly 12:0, 14:0 and 16:0) and trans-FA are considered to exert negative effects when consumed in excess, whereas others (4:0, anteiso-15:0, cis-9-18:1, 18:3*n*-3, and some CLA isomers) have potentially positive effects on human health (Parodi 2005; Shingfield et al. 2008b). For example, cis-9, trans-11-18:2, the major isomer of CLA in ruminant milk, exhibits anticarcinogenic and antiatherogenic (Wahle et al. 2004) properties in animal models. Thus, by contributing to the synthesis of FA that are beneficial from the point of view of human nutrition, e.g., cis-9, trans-11-CLA and to a lesser extent cis-9-18:1, SCD contribute to improve the nutritional quality of milk fat. In addition, by introducing a cis-9 double bond to FA,

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SCD contribute to lower the milk fat melting point (Parodi 1982). Differences in mammary gland level of SCD protein may help in explaining the substantial variation in milk fat content of these fatty acids and thus studies on the regulation of SCD activity and gene expression in the mammary gland have focused major interest in the last decades. Overall, different experiments have been conducted in dairy ruminants for studying the effect of nutrition on milk fat secretion and composition in relation with the regulation of mammary lipogenic gene expression and in particular of *SCD* gene. For this purpose measures were performed at the level of the mammary tissue and milk fat and different variables were determined as follows: (1) mammary *SCD* transcript abundance (*SCD1* and *SCD5* mRNA), (2) mammary SCD activity, (3) the in vivo Δ9-desaturation by a chemical tracer technique, and (4) milk FA Δ-9 desaturation ratios (4 milk ratios of the pairs of FA that represent a product/substrate relationship for SCD: cis-9-14:1/14:0, cis-9-16:1/16:0, cis-9-18:1/18:0, cis-9, trans-11-CLA/trans-11-18:1), which are less invasive indicators commonly used as a proxy for Δ9-desaturase activity due to the difficulty in measuring the activity.

This chapter reviews the present knowledge on *SCD* genes expression in the ruminant mammary gland, in particular, the known effects of nutritional factors in relation with milk FA composition and the effect of specific FA studied using in vitro models. In addition, the known or putative molecular mechanisms underlying these regulations are presented.

Functions of SCD in the Mammary Gland of Ruminant

Milk fat is composed of ca. 98 % of triglycerides (TG) whose FA have a dual origin: (1) either they are de novo synthesized in the mammary gland (Fig. 13.1) from circulating acetate and 3-hydroxybutyrate, produced by ruminal fermentation of carbohydrates and by rumen epithelium from absorbed butyrate, respectively, thus resulting in short and medium chain FA (C4:0 to C16:0) that represent 40–50 % of the FA secreted in milk or (2) they are imported from the plasma, where they are either released by the enzyme lipoprotein lipase (LPL) (Barber et al. 1997) from triglycerides circulating in chylomicra or very low density lipoprotein (VLDL), or derived from the plasma non-esterified fatty acids (NEFA) that circulate bound to albumin, for long-chain FA (≥C18), as well as ca. one half of the 16:0 and very low amount of 14:0 depending on the diet composition. Whatever their origin, these FA may be desaturated by SCD, but not elongated, in the secretory mammary epithelial cells (MECs) (Chilliard et al. 2000). In lactating ruminants, mammary glands have high levels of *SCD* mRNA (Ward et al. 1998; Bernard et al. 2005a) and activity (Bickerstaffe and Annison 1970; Kinsella 1970; McDonald and Kinsella 1973; Bernard et al. 2005b, 2009a, b). The protein SCD is located in the endoplasmic reticulum and catalyses the Δ-9 desaturation, introducing a cis double bond, of a spectrum of fatty acyl-CoA substrates, mainly from C14 to C19. This reaction requires NADH, oxygen, and an electron transport sequence comprising NADH-cytochrome *b*5 reductase, cytochrome *b*5, and SCD. The preferred substrate of SCD

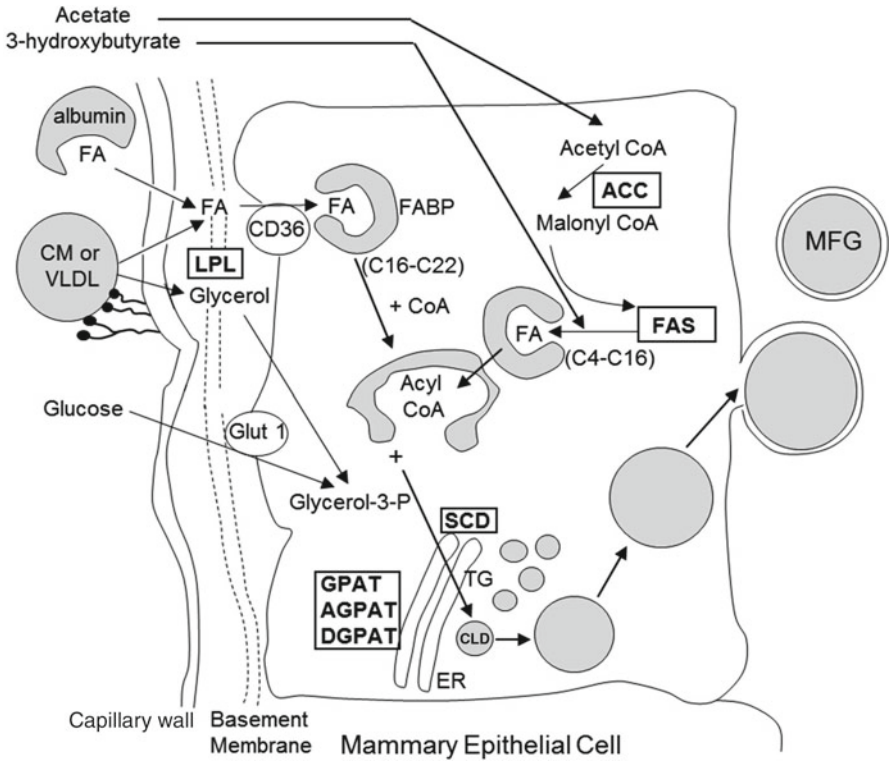

Fig. 13.1 Milk fat synthesis in the ruminant mammary epithelial cell (from Bernard et al. 2008). *ACC* acetyl CoA carboxylase, *AGPAT* acyl glycerol phosphate acyl transferase, *CD36* cluster of differentiation 36, *CLD* cytoplasmic lipid droplet, *CoA* coenzyme A, *CM* chylomicron, *DGAT* diacyl glycerol acyl transferase, *ER* endoplasmic reticulum, *FA* fatty acid, *FABP* fatty acid binding protein, *FAS* fatty acid synthase, *Glut 1* glucose transporter1, *GPAT* glycerol-3 phosphate acyl transferase, *LPL* lipoprotein lipase, *MFG* milk fat globule, *SCD* stearoyl-CoA desaturase, *TG* triglyceride, *VLDL* very low density lipoprotein

is stearic acid leading to the synthesis of oleic acid, the major unsaturated fatty acid found in milk triacylglycerol. In bovine, a number of other saturated acyl-CoA also serve as substrates for SCD including 10:0, 12:0, 14:0, 15:0, and 17:0 (Shingfield et al. 2008b) as well as trans-FA such as trans-7- and trans-12-18:1 (Palmquist et al. 2005; Shingfield et al. 2007). Thus, trans-7, cis-9-18:2 (CLA) in milk originates almost exclusively from the action of Δ9-desaturase on trans-7-18:1 in the mammary gland (Corl et al. 2002). In addition, recent results also suggest that conjugated linolenic acids (CLnA) such as cis-9, trans-11, trans-13-18:3, and cis-9, trans-11, trans-15-18:3 in milk are synthesized endogenously via the action of Δ9-desaturase on trans-11, trans-13-18:2, and trans-11, trans-15-18:2 in the mammary gland, respectively (Lerch et al. 2012). All these trans-18:1 or trans-18:2 FA that may serve as substrate for mammary SCD originate from the ruminal biohydrogenation of the major FA found in the diet delivered to ruminant.

The unsaturation of fatty acid chain is a major determinant of the melting temperature of triglycerides (TG), thus determining the fluidity of milk fat. The fundamental function of mammary SCD in maintaining the physical properties of TG is even increased in ruminants due to the large biohydrogenation processes of dietary PUFA that occur in the rumen which led to the synthesis of saturated FA (mainly 18:0) as well as of numerous intermediates, in particular, trans-FA (Shingfield et al. 2010) that could be further taken up by the mammary gland. Indeed, whereas it is well established that endogenous synthesis of cis-9-18:1 via the action of SCD on 18:0 in the mammary gland is an important point of regulation in milk TG synthesis and maintenance of milk fat fluidity, the presence of a cis- or trans-double bond as well as of short-chain FA and saturated FA also intervene in the maintenance of milk fat fluidity (Chilliard et al. 2000). In this way, a meta-analysis of milk FA yield in relation to duodenal flows (Glasser et al. 2008) showed an interdependence of C18 and C4 to C16 probably due to the esterification step of milk fat synthesis, which involves a putative balance between long-chain and de novo synthesized FA to maintain milk TG fluidity. In the same way it was proposed that, under certain dietary conditions, decreases in the availability of 18:0 for endogenous synthesis of cis-9-18:1 combined with an increase in trans-18:1 at the mammary gland could be a possible mechanism to explain part of the decrease in milk fat secretion (Loor et al. 2005a; Gama et al. 2008). Thus, the ability to maintain milk fat melting point within physiological values could play a role in the regulation of milk fat secretion when milk FA composition varies, for example, in response to feeding factors. In this context, the hypothesis of a contribution of milk fat fluidity to the regulation of milk fat secretion has been proposed (Timmen and Patton 1988; Chilliard et al. 2000) and was confirmed recently in a meta-analysis on cow, goat, and ewe milk FA composition and estimated melting point (Toral et al. 2013a). In addition, studies in goats (Chilliard et al. 2006) on the effect of the CSN1S1 genotype on milk FA profile have reported higher Δ9-desaturation ratios in defective vs. high genotypes suggesting higher expression of SCD in defective genotypes in which the synthesis of short-chain FA is lower. This result led to the hypothesis that higher SCD expression could compensate for the concomitant decrease in short-chain FA and thus to maintain the milk fat melting point in defective genotypes.

Characterization of SCD Genes

Multiple isoforms of *SCD* have been found in most species examined to date. Some rodent genomes (as mice) contain four *SCD* isoforms (*SCD1–4*) with different expression profiles according to tissues. For example, murine *SCD1* is expressed predominantly in lipogenic tissues (Ntambi et al. 1988), while *SCD2* is preferentially expressed in brain and neuronal tissues (Kaestner et al. 1989), *SCD3* is expressed in sebocytes, preputial gland, and Harderian gland (Zheng et al. 2001), and *SCD4* expression is restricted to the heart (Miyazaki et al. 2003). Up to now, the genomes of many other species, including chickens, pigs, cows, and humans, have

been found to contain two *SCD* isoforms. Then, in humans: *SCD1* is highly expressed in adipose tissue and liver while a second *SCD* gene, termed *SCD5*, is highly expressed in brain and pancreas (Wang et al. 2005). In addition to tissue-specific expression profile, there is evidence to suggest that some SCD protein isoforms may differ in their preferred substrate specificity. For example, murine SCD1, SCD2, and SCD4 have been shown to desaturate both palmitoyl-CoA and stearoyl-CoA, while murine SCD3 desaturates palmitoyl-CoA but not stearoyl-CoA (Miyazaki et al. 2006). The tissue and substrate specificity of SCD isoforms suggests that each may have a distinct physiological role.

In ruminants earlier studies reported only one *SCD* gene, generating a transcript of 5 kb in size which was characterized in sheep (Ward et al. 1998), cows (Chung et al. 2000), and goat (Bernard et al. 2001). When compared, the coding region of the caprine *SCD* mRNA shares 98, 95, 90, and 86 % identity with the ovine, bovine, porcine, and human *SCD1* mRNAs, respectively. This *SCD* isoform was highly expressed in lipogenic tissues, adipose tissue, and the lactating mammary gland and was recently renamed *SCD1* since the discovery of the *SCD5* isoform characterized in ruminant species (Lengi and Corl 2007, 2008). In these species *SCD5* is mainly expressed in the brain (Lengi and Corl 2008). In addition to *SCD1* a significant expression of *SCD5* was reported in the lactating mammary gland in cows (Gervais et al. 2009; Jacobs et al. 2011) and goats (Bernard et al. 2010) with probably different regulation for these two isoforms (Gervais et al. 2009; Jacobs et al. 2011). However, both the regulation of the expression and the contribution of *SCD5* isoform to FA Δ-9 desaturation process are still unknown.

SCD1 transcript in goat presents an unusually long (3.8 kb) 3′-UTR sequence which derives from a single exon (Bernard et al. 2001), as observed for human (Zhang et al. 1999), rat (Mihara 1990), and mouse (Ntambi et al. 1988). In the caprine, the 3′-UTR is characterized by the presence of several AU-rich elements as observed in the 3′-UTR region of mouse (Kaestner et al. 1989; Sessler et al. 1996), rat (Thiede and Strittmatter 1985; Mihara 1990), and human (Zhang et al. 1999) *SCD1* transcripts, which could be mRNA destabilization sequences as suggested by Sessler et al. (1996). These AU-rich elements have been shown to play active roles in the mRNA degradation (Vakalopoulou et al. 1991) which is responsible for their turnover. In addition, these motifs could be possible targets of polyunsaturated fatty acids effects on *SCD* mRNA, as proposed by Ntambi (1999) for *SCD1* and *SCD2* mRNA in mouse adipocytes. Otherwise, SCD5 transcript in bovine and ovine was of 2.6 kb in length (Lengi and Corl 2007, 2008) with a 3′UTR corresponding to half the mRNA length.

SCD1 gene was localized on bovine and caprine chromosomes 26q21 and on ovine chromosome 22q21 (Bernard et al. 2001), and *SCD5* was localized on bovine chromosome 6 (Lengi and Corl 2007) and on ovine chromosome 6 (Lengi and Corl 2008). In caprine *SCD1* gene spans about 15 kb and has six exons varying in size from 131 (third exon) to 4,047 (sixth exon) bp, and five introns varying in size from 600 to 3,700 bp (Bernard et al. 2001; Fig. 13.2). This structural organization is similar to *SCD1* gene reported in human (Zhang et al. 1999) and rodents (Ntambi et al. 1988; Kaestner et al. 1989; Mihara 1990). The genomic structure of bovine

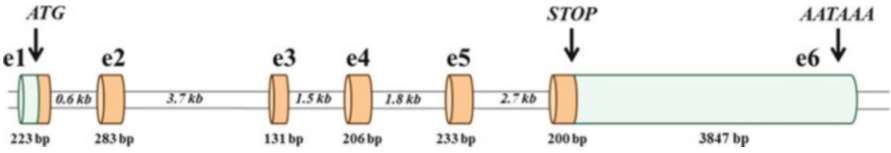

Fig. 13.2 Structural organization of the caprine SCD1 transcription unit. Overall structural organization of the caprine SCD1 gene deduced from PCR analysis. *Open bars* represent introns and exons are depicted by *large*, *green* (UTR) or *orange* (TR) *boxes* (from Bernard et al. 2001)

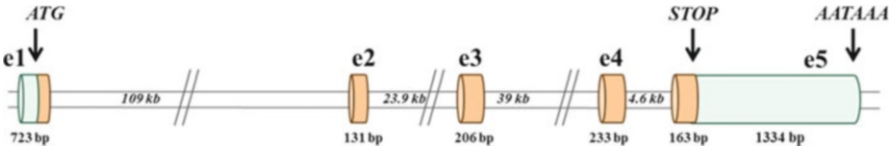

Fig. 13.3 Structural organization of the bovine SCD5 transcription unit. Overall structural organization of the bovine SCD5 gene adapted from Lengi and Corl (2007). *Open bars* represent introns and exons are depicted by *large*, *green* (UTR) or *orange* (TR) *boxes*

SCD5 deduced from known bovine genomic DNA sequence showed that *SCD5* is organized into five exons and four introns in a fragment tenfold longer than *SCD1* spanning more than 175 kb (Lengi and Corl 2007) and is similar to human *SCD5* (Fig. 13.3). Despite the length difference of their genes, the SCD1 and SCD5 encoded proteins are of similar size and are, respectively, composed of 359 and 335 amino acids (AA). Sequence alignment shows 65 % identity between bovine SCD1 and SCD5 at the amino acid level. Both proteins share highly conserved three histidine motifs that are catalytically essential for the desaturase activity. Conversely to SCD1 protein, the N-terminus of the SCD5 protein lacks the conserved PEST (peptide sequence rich in proline, glutamic acid, serine, and threonine). This sequence is present in proteins that have a short intracellular half-time with the hypothesis that PEST sequence acts as a signal peptide for protein degradation (mediated by proteasome or calpaïn). These data suggest that the regulation of SCD1 and SCD5 proteins may differ.

Little is known in ruminant on the molecular mechanisms controlling *SCD* genes expression (see section "Knowledge on the Signalling Pathways Mediating Nutritional Regulation of SCD Gene Expression in Ruminants"). The promoter region of the bovine *SCD1* gene have been studied (Keating et al. 2005) and an area of 36 bp in length was identified as having a critical role in the transcriptional activation and was designated the *SCD* transcriptional enhancer element (STE). Otherwise, a recent study regarding the possible common transcription factors between bovine *SCD5*, expressed in brain and nervous tissue, and rodent *SCD2*, expressed in nervous tissue, demonstrated that early growth response 2 (EGR2) and sterol regulatory element binding protein 1a (SREBP-1a) may bind to the same DNA site in the bovine *SCD5* promoter (Lengi and Corl 2012).

In other respects, in order to explain individual differences in milk fat yield and FA composition, in particular in cis-9 monounsaturated FA, studies in ruminants

were focused on the genetic variability of the region containing *SCD* gene. A lot of programs were dedicated to quantitative trait loci (QTL) detection in dairy bovine breeds on milk parameters. In particular, genome-scan for bovine milk fat composition revealed a QTL for the monounsaturated FA and their unsaturation indices on Bos taurus autosome (BTA) 26 corresponding to the chromosome where *SCD1* gene is located (Stoop et al. 2009). These authors have strongly suggested that this BTA26 QTL was caused by a mutation in the *SCD1* gene. Among the single nucleotide polymorphisms (SNP) detected in *SCD1* gene, a nonsynonymous one is located in exon 5 causing a substitution of valine (V) with alanine (A) at position 293 (A293V; Kgwatalala et al. 2007; Schennink et al. 2008). Several studies in different bovine breeds reported significant association between A293V genotypes and milk FA composition with milk of cows carrying the SCD *AA* genotype having a greater content of cis-9-18:1 and a higher cis-9-14:1/14:0 ratio than did milk of cows carrying the SCD *VV* genotype (Kgwatalala et al. 2009b; Mele et al. 2007; Conte et al. 2010), whereas others (Moioli et al. 2007) could not confirm this association. These latter authors suggested a role of regulatory factors acting on the promoter region of *SCD* gene or through activation of the enzyme. In that way, whereas an earlier study on *SCD1* promoter has not allowed the detection of SNP (Keating et al. 2005), a more recent study highlighted a SNP (133A>C) creating a new consensus site for the transcription factor SP1 binding site, which could be responsible for a difference in the milk FA desaturation ratio (Pauciullo et al. 2012). Moreover, different SNPs were also detected in intronic or exonic regions without AA substitution in the protein. However, their linkage with milk yield was particularly studied in haplotypic configuration suggesting that they could be used as potential genetic markers to improve milk performance (Alim et al. 2012). For example, SNP haplotypes identified in the 3′UTR region were reported to be associated with different 10:0 and 12:0 Δ-9 desaturation ratios in bovine milk (Kgwatalala et al. 2009a).

In small ruminants, although less documented, *SCD1* gene polymorphism has also been studied. The first characterization of the caprine *SCD1* mRNA has revealed a polymorphism involving the deletion of a nucleotide triplet (TGT) in the 3′UTR region (Bernard et al. 2001). The analyses of this mutation in haplotype-based configuration with two other 3′UTR SNP were suggestively associated with lower milk stearic FA content and with higher percentages of PUFA (Zidi et al. 2010). An in silico analysis of the secondary structure of *SCD1* mRNA pointed out the 3nt deletion as being involved in a considerable change in the secondary structure of the *SCD1* mRNA. This change could alter the amount of *SCD1* transcripts in MECs (Zidi et al. 2010). In sheep, a QTL analysis for the FA profile showed a QTL for the ratio of rumenic/vaccenic acid in ovine chromosome 22 which coincided with the position of the *SCD* gene (Carta et al. 2008). However, no association of four SNP previously detected (Garcia-Fernandez et al. 2009) has been observed with the ratio of rumenic/vaccenic acid, whereas a possible effect of the *SCD* polymorphism on milk fat percentage has been suggested (Garcia-Fernandez et al. 2010).

Due to its recent discovery, the polymorphism of *SCD5* gene, located on BTA6, has not been studied to the same extend. A recent study revealed that polymorphisms in the *SCD5* gene were among the most representative markers associated

with unsaturated/saturated FA ratio in milk (Rincon et al. 2012). In this study, two SNP were detected within exon 3 which were, respectively, associated with an increase in saturated FA concentration combined with a decrease in monounsaturated FA, and with a decrease in saturated FA combined with an increase in PUFA. Moreover, an intronic mutation named G allele was shown to be associated with a decrease in saturated FA/unsaturated FA ratio and an increase in monounsaturated FA and Δ-9 desaturation ratios for 14:0 and trans-11-18:1 content in Holstein milk (Rincon et al. 2012). However, the mechanism by which this mutation acts needs to be clarified.

Regulation of Mammary *SCD* Genes Expression by Dietary Factors

Effect of Dietary Factors

In ruminants, milk FA composition is greatly influenced by feeding factors (Jensen 2002; Dewhurst et al. 2006; Chilliard et al. 2007). Thus, modification of milk fat content and FA composition by dietary manipulation has been investigated and few studies were performed to relate the effect of diet on milk FA profile to mammary lipid metabolism considering the major lipogenic genes, in particular, *SCD*. The response of *SCD* gene expression to nutritional changes involves the control of events that could occur at transcriptional (e.g., through transcription factors), post-transcriptional (e.g., such as mRNA stability), translational (e.g., its initiation or through microRNA action), and post-translational (e.g., via turnover or regulation of the activity of the enzymatic protein) levels. However, it is often unclear whether the regulatory factors are the dietary components themselves or their metabolites or hormonal changes produced in response to the nutritional changes. Moreover, in most of the studies, it is difficult to conclude on the level of regulation involved since measurements of *SCD* mRNA of the enzyme protein content and activity are not studied simultaneously. Only few studies have investigated the role of diet on the regulation of *SCD* gene expression and activity in ruminants.

As previously mentioned, prior to the characterization of the bovine *SCD5* gene (Lengi and Corl 2007), as only one *SCD* isoform was thought to be present in this species, the gene was simply referred to as *SCD* for *SCD1*. The in vivo trials reporting the nutritional regulation of mammary *SCD1* and lipogenic genes expression have been carried out in mid-lactation cows and goats and mainly with lipid supplements (Table 13.1). In cows, studies have been primarily realized with diets that induce milk fat depression (MFD). These diets belongs to three types: (1) diets rich in starch without addition of lipid supplements (e.g., high grain/low forage diets), but containing a minimal amount of PUFA in dietary feedstuffs; (2) diets with low level of fiber associated with supplemental PUFA of plant origin; (3) diets associated with dietary supplements of marine oils (fish oils, fish meals, oils from marine

Table 13.1 Effect of dietary lipid supplements on mammary *SCD* and lipogenic genes expression and/or enzyme activity in ruminants

Biochemical pathway[a]	Species	Transcript/protein[b]	Response (%)[c]	Nature of lipid supplement	Inclusion rate (g/kg dry matter)	Response of milk fat yield (%)[c]	Reference
Transcription factors							
SREBF1/S14	Bovine	mRNA	−45/−60	Soyabean oil + fish oil[d]	30 + 15	−38	Harvatine and Bauman (2006)
SREBF1	Bovine	mRNA	−30	Sunflower oil + marine algae[e]	27 + 4	−30	Angulo et al. (2012)
	Bovine	mRNA	−31	Linseed oil + marine algae[e]	27 + 4	−31	Angulo et al. (2012)
SREBF1/PPARG	Bovine	mRNA	NS/NS	Soybean oil + fish oil	25 + 10	−50	Invernizzi et al. (2010)
Desaturation and de novo lipogenesis							
SCD1/ACC	Bovine	mRNA	NS	Rapeseed	33	NS	Delbecchi et al. (2001)
SCD1/ACC/FAS	Bovine	mRNA	(−29)/−46/−64	Fish oil	37	−44	Ahnadi et al. (2002)
SCD1	Caprine	mRNA	−43	Oleic sunflower oil	35	+16	Bernard et al. (2005b)
	Caprine	mRNA	−54	Formaldehyde-linseed	112	+8	Bernard et al. (2005b)
SCD	Caprine	Activity	−30	Sunflower oil	55	+17	Bernard et al. (2009b)
	Caprine	Activity	−22	Oleic sunflower oil	35	+16	Bernard et al. (2005b)
	Caprine	Activity	−27	Linseed oil	55	+15	Bernard et al. (2009b)
	Caprine	Activity	−35	Formaldehyde-linseed	112	+8	Bernard et al. (2005b)
SCD1/FAS	Bovine	mRNA	(−25)/−45	Soyabean oil + fish oil[d]	30 + 15	−38	Harvatine and Bauman (2006)
	Bovine	mRNA	−34.5/−31	Sunflower oil + marine algae[e]	27 + 4	−30	Angulo et al. (2012)
	Bovine	mRNA	−45.5/−33	Linseed oil + marine algae[e]	27 + 4	−31	Angulo et al. (2012)
SCD/ACC/FAS	Caprine	Activity	(−17/+12)/+81	Sunflower oil	61	(−3)	Bernard et al. (2009a)
SCD1/ACC/FAS	Caprine	mRNA	(+15/+19/+12)	Rapeseed	146	(+5)	Ollier et al. (2009)
	Bovine	mRNA	(+39/+38/+36)	Safflower seed	135	NR	Murrieta et al. (2006)
	Caprine	mRNA	+166/+72/+74	Safflower oil	50	+26	Li et al. (2012)
	Bovine	mRNA	(−35)/−28/−41	Sunflower oil[d]	10	−27	Peterson et al. (2003)
	Caprine	mRNA	(−7/−8/+5)	Sunflower oil	61	(+7)	Bernard et al. (2009a)
	Caprine	mRNA	(+10/+15/+6)	Sunflower oil	44	+20	Ollier et al. (2009)
	Caprine	mRNA	(+17/+10/+9)	Sunflower oil	55	+17	Bernard et al. (2009b)

(continued)

Table 13.1 (continued)

Biochemical pathway[a]	Species	Transcript/protein[b]	Response (%)[c]	Nature of lipid supplement	Inclusion rate (g/kg dry matter)	Response of milk fat yield (%)[c]	Reference
	Caprine	mRNA	(+22/+2/+10)	Linseed oil	55	+15	Bernard et al. (2009b)
	Caprine	mRNA	(−16/+4/−4)	Linseed oil	62	+14	Bernard et al. (2009a)
	Caprine	mRNA	+121/−26/+52	Linseed oil	50	+34	Li et al. (2012)
	Caprine	Activity	(+11/−3/+64)	Linseed oil	62	+14	Bernard et al. (2009a)
ACC	Bovine	mRNA	−68	Soyabean oil[d]	50	−43	Piperova et al. (2000)
FAS	Caprine	Activity	+68	Sunflower oil	61	(+7)	Bernard et al. (2009a)
	Bovine	Activity	−61/−44	Soyabean oil[d]	50	−43	Piperova et al. (2000)
	Caprine	mRNA	(−21)	Oleic sunflower oil	35	+16	Bernard et al. (2005a)
	Caprine	mRNA	(−1)	Formaldehyde-linseed	112	+8	Bernard et al. (2005a)
	Caprine	Activity	(+27)	Sunflower oil	55	+17	Bernard et al. (2009b)
	Caprine	Activity	(0)	Oleic sunflower oil	35	+16	Bernard et al. (2005b)
	Caprine	Activity	(+30)	Linseed oil	55	+15	Bernard et al. (2009b)
	Caprine	Activity	(−31)	Formaldehyde-linseed	112	+8	Bernard et al. (2005b)
Fatty acid uptake/processing							
LPL	Caprine	mRNA	(−0.03)	Rapeseed	146	(+5)	Ollier et al. (2009)
	Bovine	mRNA	+50	Safflower seed	135	NR	Murrieta et al. (2006)
	Caprine	mRNA	+43	Safflower oil	50	+26	Li et al. (2012)
	Bovine	mRNA	−61	Soyabean oil + fish oil[d]	30+15	−38	Harvatine and Bauman (2006)
	Bovine	mRNA	−30	Sunflower oil[d]	10	−27	Peterson et al. (2003)
	Caprine	mRNA	(+17)	Sunflower oil	61	(+7)	Bernard et al. (2009a)
	Caprine	mRNA	(+23)	Sunflower oil	44	+20	Ollier et al. (2009)
	Caprine	mRNA	(+1)	Sunflower oil	55	+17	Bernard et al. (2009b)
	Caprine	mRNA	+51	Oleic sunflower oil	35	+16	Bernard et al. (2005b)
	Caprine	mRNA	(−1)	Linseed oil	55	+15	Bernard et al. (2009b)
	Caprine	mRNA	(+26)	Formaldehyde-linseed	112	+8	Bernard et al. (2005b)
	Caprine	mRNA	(+13)	Linseed oil	62	+14	Bernard et al. (2009a)

	Caprine	mRNA	+54	Linseed oil	50	+34	Li et al. (2012)
	Bovine	mRNA	−34	Sunflower oil + marine algae[e]	27 + 4	−30	Angulo et al. (2012)
	Bovine	mRNA	−45	Linseed oil + marine algae[e]	27 + 4	−31	Angulo et al. (2012)
	Caprine	Activity	(+42)	Sunflower oil	61	(+7)	Bernard et al. (2009a)
	Caprine	Activity	(+35)	Sunflower oil	55	+17	Bernard et al. (2009b)
	Caprine	Activity	(+13)	Oleic sunflower oil	35	+16	Bernard et al. (2005b)
	Caprine	Activity	(+21)	Linseed oil	55	+15	Bernard et al. (2009b)
	Caprine	Activity	(−17)	Linseed oil	62	+14	Bernard et al. (2009a)
FACL	Bovine	mRNA	−34	Sunflower oil[d]	10	−27	Peterson et al. (2003)
Esterification							
AGPAT/GPAT	Bovine	mRNA	−27/−52	Sunflower oil[d]	10	−27	Peterson et al. (2003)
GPAM	Bovine	mRNA	−10	Sunflower oil + marine algae[e]	27 + 4	−30	Angulo et al. (2012)
	Bovine	mRNA	−26	Linseed oil + marine algae[e]	27 + 4	−31	Angulo et al. (2012)
FA transport							
FABP	Bovine	mRNA	(−25)	Sunflower oil[d]	10	−27	Peterson et al. (2003)
FABP3/FABP4	Caprine	mRNA	(+11)/+36	Sunflower oil	44	+20	Ollier et al. (2009)
	Caprine	mRNA	(+21)/(+11)	Rapeseed	146	NS	Ollier et al. (2009)

Adapted from Shingfield et al. (2013)

[a]*ACC* acetyl CoA carboxylase, *AGPAT* acylglycerol phosphate acyl transferase, *FAS* fatty acid synthase, *FABP* fatty acid binding protein, *FACL* fatty acyl-CoA ligase, *GPAM* glycerol-3-phosphate acyltransferase 1, *GPAT* glycerol phosphate acyl transferase, *LPL* lipoprotein lipase, *SCD* stearoyl-CoA desaturase, *S14* thyroid hormone responsive spot 14, *SREBF1* sterol response element binding protein

[b]Measurement of tissue transcript abundance (mRNA) or protein activity (Activity)

[c]Response reported when treatment effects were significant ($P < 0.10$) and calculated as [((Treatment − Control)/Control) × 100]. Values in parenthesis are not significant at $P < 0.05$. NS, values not reported because unsignificant

[d]Lipid supplementation also accompanied by decreases in dietary forage:concentrate ratio; NR, not reported

[e]Control treatment, supplement of rumen-stable fractionated palm fat rich in 16:0

mammals, and/or algae) which induce MFD whatever the level of starch or fiber in the diet. In these dietary conditions, variable responses of mammary *SCD1* mRNA abundance have been reported in cows: either no variation with high concentrate diets containing sunflower oil (Peterson et al. 2003) or fish oil and soya bean oil (Harvatine and Bauman 2006); or decreases with diets supplemented with plant oils rich in either *n*-3 or *n*-6 fatty acids (FA) plus docosahexaenoic acid (DHA)-rich algae (Angulo et al. 2012) or with rumen "protected" fish oil (Ahnadi et al. 2002); or surprisingly increases with diets supplemented with fish oil and soya bean oil (Invernizzi et al. 2010). From these studies it is difficult to conclude on the effect of the dietary treatments that induce MFD on *SCD1* mRNA abundance and probably that the forage:concentrate ratio and the nature and the level of the PUFA into the diet may intervene to explain such differences. Otherwise, studies in goats have shown that supplementing diets based on grass hay with sunflower-seed oil rich in oleic acid (Bernard et al. 2005b), sunflower-seed oil (18:2 rich), or linseed oil (18:3 rich) decreased SCD activity (Bernard et al. 2009b) but had no effect on mammary *SCD1* mRNA abundance, whereas supplementing grass hay-based diets with formaldehyde-treated linseed (FLS) decreased mammary *SCD1* mRNA without effect on the SCD activity (Bernard et al. 2005b). In contrast, inclusion of sunflower-seed oil and linseed oil in maize silage-based diets (Bernard et al. 2009a) and of soya beans in lucerne hay-based diets (Bernard et al. 2005a) had no effect on caprine mammary *SCD1* mRNA abundance and/or SCD activity. Lastly, in goat, addition of fish oil and starch to a diet containing sunflower-seed oil has no effect on mammary *SCD1* and *SCD5* mRNA abundances (Bernard et al. 2010).

Overall, these observations (Table 13.1) highlight the importance of interactions between the composition of the basal diet and lipid supplement in the goat with the implication that specific PUFA escaping metabolism in the rumen or specific biohydrogenation intermediates may inhibit SCD activity via transcriptional or post-transcriptional regulatory mechanisms.

In vivo Δ-9 desaturase activity has often been estimated by the milk ratios for the pairs of FA that represent a product/substrate relationship for SCD (Bauman et al. 2001) due to the fact that the in vitro activity assay needs fresh materials and is laborious (Legrand et al. 1997). Moreover, ex vivo activity assay is done in optimal conditions (pH, substrate, cofactors) and may differ from in vivo conditions. From the few studies in goats reporting mammary SCD activity together with milk fatty acid composition, the response to dietary lipids of the four FA pair ratios that represent a proxy for SCD activity was related to the response of the SCD activity itself (Bernard et al. 2008). In some experiments with goats, lipid supplements in the diet have been shown to reduce milk FA desaturation ratios but have no effect on SCD activity (Bernard et al. 2009a, b, c). However, it was shown that the milk ratio of myristoleic acid to myristic acid (cis-9-14:1/14:0) gave the best estimation for the response of mammary SCD activity (Fig. 13.4; from Bernard et al. 2008), probably due to the fact that almost all the myristoleic acid present in the milk is likely to be synthesized in the mammary gland from de novo synthesis of myristic acid followed by desaturation by SCD. Indeed, 14:0 and 14:1 even less are poorly represented in feedstuffs used for ruminants, including lipid supplements (except for 14:0

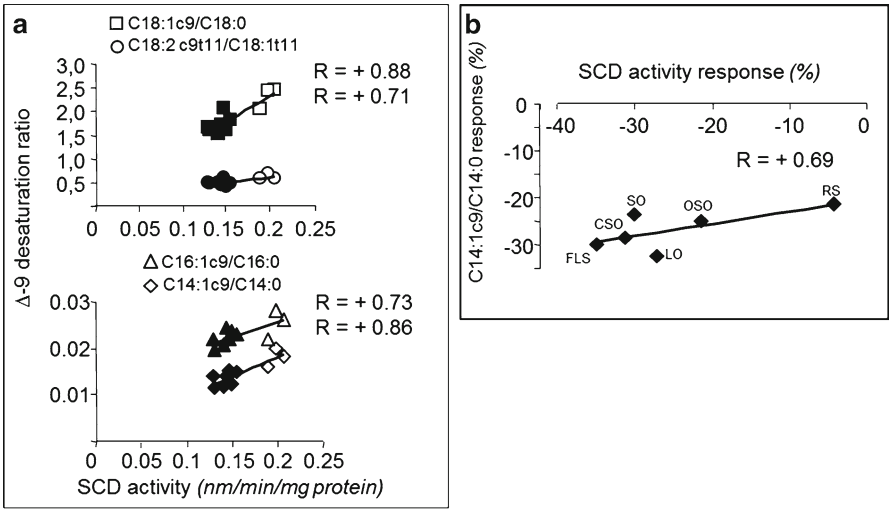

Fig. 13.4 Relationships between milk FA desaturation ratios and stearoyl-CoA desaturase (SCD) activity in 43 goats fed hay-based diet supplemented, or not, with lipids. The lipid supplements were either 3.6 % of lipids from oleic sunflower oil (OSO) or formaldehyde-treated linseed (FLS) (Bernard et al. (2005b)), or 5.8 % lipids from linseed oil (LO) or sunflower oil (SO) (Bernard et al. (2009a)), or 6.5 % whole rapeseed (RS) or 4.5 % of sunflower oil (CSO) (Ollier et al. (2009)) (from Bernard et al. 2008). (**a**) Results are means of the seven lipid-supplemented groups (*black symbols*) and the three control groups (*white symbols*). (**b**) Relationship between the responses (% of the control group) of SCD activity and milk cis-9-14:1/14:0 to the six lipid supplements

in specific lipid supplements such as coconut or krabo oils), and the circulating 14:1 in ruminant is very low (Christie 1981). Otherwise, variable proportions of palmitoleic, oleic, and rumenic acids come from absorption from the digestive tract and/or mobilization of body fat reserves. Consequently, the ratios that involve these latter FA are less indicative of SCD activity even though stearoyl-CoA and palmitoyl-CoA are the preferred substrates for SCD. Indeed, activity of SCD was estimated to contribute to approximately 90 % of cis-9-14:1 compared to 50–56 % of cis-9-16:1, 60 % of cis-9-18:1, and >60 % of cis-9, trans-11-18:2 in bovine milk fat (Enjalbert et al. 1998; Mosley and McGuire 2007; Glasser et al. 2008). Moreover, differential uptake, turnover, and use of different FA of the four pair ratios by the mammary tissue itself may occur.

In other respects, several experiments in goats have provided evidence to support the involvement of post-translational mechanisms in the regulation of SCD activity. Inclusion of cis-9-18:1 enriched sunflower oil (Bernard et al. 2005b), sunflower oil, or linseed oil (Bernard et al. 2009b) in the diet of goats fed grass hay-based diets has been shown to lower mammary SCD activity measured ex vivo without changing mammary *SCD1* mRNA abundance. Otherwise, in goats fed maize silage-based diet, addition of plant oils had no effect on mammary *SCD1* mRNA or SCD activity (Bernard et al. 2009a). However, in four in vivo studies in goats (Bernard et al.

2005b, 2009a, b; Ollier et al. 2009), the relationship between the responses of *SCD1* mRNA and enzyme activity (means per treatment) to the eight lipid supplements (expressed relative to the control) was relatively weak ($r = 0.55$), which may indicate the existence of putative post-traductional regulatory events. In the same way, a recent study in goats using a proteomic analysis suggested an increased protein expression of PSMA5 (proteasome subunit α type 5) and a higher mRNA abundance of *SCD* in the mammary tissue following trans-11-18:1 treatment (by intravenous bolus injection) (Jin et al. 2012). SCD is a short-lived integral membrane protein of the endoplasmic reticulum (Oshino and Sato 1972), and PSMA5 as a part of the ubiquitin proteasome system may be involved in constitutive SCD degradation, and thus could play a role in SCD regulation as further suggested in MAC-T cells (Jin et al. 2012).

Otherwise, in order to determine the in vivo SCD metabolic activity, different methods have been developed and used in ruminants, in particular, to estimate the in vivo conversion of stearic to oleic acid or vaccenic to rumenic acid in the mammary gland. These methods include direct methods, by means of a tracer (for example, [1-^{13}C]trans-11 18:1; Mosley et al. 2006; Bernard et al. 2010), and indirect methods, through quantification of duodenal and milk FA flows (Shingfield et al. 2007; Glasser et al. 2008) or inhibition of the desaturase system using sterculic acid (Griinari et al. 2000; Corl et al. 2001; Kay et al. 2004; Bichi et al. 2012). Studies using these methods provided clear evidence that the endogenous desaturation of stearic and vaccenic acids are the main sources of milk oleic and rumenic acids, respectively. Indeed, about 80 % (Glasser et al. 2008), 80–84 % (Annison et al. 1974), and 63 % (Bichi et al. 2012) of oleic acid comes from stearic acid, respectively, in cows, goats, and ewes. In the same way, 64–97 % (Mosley et al. 2006; Glasser et al. 2008), 63–73 % (Bernard et al. 2010), and 74 % (Bichi et al. 2012) of rumenic acid comes from vaccenic acid, respectively, in cows, goats, and ewes. In addition, few of them provided an estimation of stearic or vaccenic acid desaturation in the mammary gland: for stearic acid it was of 59 % (Mosley and McGuire 2007) and 54 % (Glasser et al. 2008) in cows; for vaccenic acid it was of 25.7 % (Mosley et al. 2006), 28.9 % (Shingfield et al. 2007), 19.8 % (Qiu et al. 2004), 21 % (Glasser et al. 2008) in cows and of 31.6 % in goats (Bernard et al. 2010).

Ruminant Species Specificities

Indirect comparisons from experiments examining in cows and goats the effect of nutrition on milk fatty acid composition outlined several differences in milk cis-9-FA and △-9 desaturation ratios responses to lipid supplements among these two species (Chilliard et al. 2007). As a large proportion of the cis-9-FA secreted in milk is synthesized endogenously via the action of mammary SCD, differences in their concentration may suggest specificities in mammary SCD regulation among species. Indeed, in experiments with goats fed maize silage- or grassland hay-based supplemented with plant oils (Chilliard et al. 2007; Bernard et al. 2009c), the

Table 13.2 Effect of inclusion of sunflower oil (rich in cis-9, cis-12-18:2) into a maize silage-based diet on milk fatty acid secretion and composition (including trans-10, cis-12-, trans-10, trans-12-, trans-9, trans-11-CLA) and milk fatty acid desaturation ratio responses in cows and goats

Species	Bovine		Caprine	
Reference	Roy et al. (2006)		Bernard et al. (2009c)	
Major forage of the diet	Maize silage		Maize silage	
Treatment	Control	Sunflower	Control	Sunflower
Oil inclusion rate (g/kg dry matter)	0	52	0	63
Diet composition				
Concentrate (g/kg dry matter)	520	537	612	545
Neutral detergent fiber (g/kg dry matter)	285	266	310	295
Milk fat content and secretion				
Milk fat output (g/d or response)[a]	1,380	(−44.2 %)	107	(+6.5 %)
14:0 (g/d or response)	156.0	(−67.5 %)	12.0	(−28.5 %)
18:0 (g/d or response)	111.1	(−11.9 %)	4.9	(+96.7 %)
trans-10-18:1 (g/d or response)	5.54	(+837 %)	0.44	(+682 %)
Fatty acid (g/100 g fatty acids)				
10:0	3.46	1.2	10.58	6.91
12:0	3.94	1.65	5.72	3.12
14:0	12.12	7.06	12.07	8.10
16:0	32.32	18.93	29.85	18.78
18:0	8.63	13.62	4.88	9.01
trans-10-18:1	0.43	7.22	0.44	3.23
trans-10, cis-12-CLA	0.003	0.024	0.004	0.064
trans-9, trans-11-CLA	0.006	0.008	0.015	0.059
trans-10, trans-12-CLA	0.004	0.015	0.003	0.024
Milk fatty acid desaturation ratios				
cis-9-14:1/14:0	0.094	0.132	0.019	0.012
cis-9-18:1/18:0	1.92	2.08	2.81	1.74
cis-9, trans-11-CLA/trans-11-18:1	0.40	0.53	0.70	0.50

Adapted from Shingfield et al. (2010)

[a]Response calculated as [((Treatment − Control)/Control) × 100]

relative increases in milk cis-9-18:1 concentrations were lower than observed when comparable diets were fed to lactating cows (Roy et al. 2006; Chilliard et al. 2007). These interspecies differences could be related to a greater sensitivity of the SCD enzyme to the inhibitory effects of PUFA in the goat than the cow (Bernard et al. 2008) and/or to larger increases in the enrichment of trans-FA that may act as inhibitor of SCD in the goat compared to the cows receiving similar diets (such as trans-9, trans-11-CLA in goat milk in Bernard et al. (2009c) compared to bovine milk in Roy et al. (2006); Table 13.2; see section "In Vivo Studies with Specific Fatty Acid Infusion or Injection"). Moreover, the balance between (1) the level and nature of unsaturated FA taken up by the mammary gland and (2) the mammary synthesis of short-chain FA and desaturase activity, which play a role in the regulation of milk fat fluidity (Toral et al. 2013a), may intervene in explaining these interspecies differences. Indeed, it may be hypothesized that the goat which has higher

concentrations of milk short-chain FA (Table 13.2) would require lower level of Δ-9 desaturation for maintaining the milk fat melting point. However, in the absence of direct comparisons between bovine and small ruminant species with similar dietary conditions and stage of lactation, it is difficult to draw clear conclusions on species specificities of SCD regulation.

Mechanisms of the Nutritional Regulation of Mammary SCD

In Vivo Studies with Specific Fatty Acid Infusion or Injection

A key role for specific fatty acids on mammary lipogenesis and desaturation was showed from in vivo studies (Shingfield et al. 2010). In particular, studies with specific dietary conditions inducing a dramatic MFD (Bauman and Griinari 2003) underlined the role of specific trans-FA that act as potent inhibitors of mammary lipid synthesis and desaturation process. Indeed, as diet-induced MFD was associated with an increase in milk trans-10-18:1 content (Griinari et al. 1998; Piperova et al. 2000; Loor et al. 2005b) and trans-10, cis-12-CLA (Baumgard et al. 2000), these FA were proposed as candidates for inhibition of mammary lipogenesis (Bauman and Griinari 2001). Studies with post-ruminal infusion of trans-10, cis-12-CLA clearly demonstrated the anti-lipogenic effect of this CLA isomer which was however not always accompanied by a reduction of milk desaturation ratios. Then, post-ruminal infusion studies in lactating cows have established that in amounts above 5 g/day, trans-10, cis-12-CLA typically decreased milk FA desaturation ratios consistent with a decrease in *SCD1* mRNA abundance (Table 13.3). In the bovine, in vivo studies indicated that injection or infusion of trans-10, cis-12-CLA decreased mammary *SCD1* gene transcription (Baumgard et al. 2002; Gervais et al. 2009), whereas no effect was observed on *SCD5* (Gervais et al. 2009). In cows, the responses of mRNA abundances of the lipogenic genes involved in other pathways than desaturation (de novo FA synthesis, FA uptake, transport and esterification) to either diets that induce MFD (Table 13.1) or trans-10, cis-12-CLA infusion (Tables 13.3 and 13.4) showed a large decrease that occurred prior to a decrease in *SCD1* mRNA. It is likely that the responses of lipogenic genes and *SCD1* to these factors reflect a two-step phenomenon which could be related to differences in the response to the transcription factors involved in these regulations (see section "Knowledge on the Signalling Pathways Mediating Nutritional Regulation of SCD Gene Expression in Ruminants"). Otherwise, in the caprine, administration of trans-10, cis-12-CLA directly at the duodenum (Andrade and Schmidely 2006) or fed as calcium salts (Shingfield et al. 2009) was reported to lower milk FA desaturation ratios in the absence (Andrade and Schmidely 2006) or with a small decrease (Shingfield et al. 2009; Table 13.3) in milk fat secretion. Similarly, in the ovine, distribution of trans-10, cis-12-CLA as encapsulated lipids was reported to lower milk fat secretion and FA desaturation ratios (Lock et al. 2006).

Table 13.3 Summary of CLA isomers acting as inhibitors of milk fat synthesis and/or milk fatty acid desaturase ratios in ruminants

Treatment[a]	Species	Dose (g/d)	Duration (h)	Change in milk fat secretion (%)[b]	Milk desaturation ratio response[c] C14/C16/ C18/C18:1 t11	Transfer efficiency into milk (%)	Reference
t10c12-CLA							
Post-rumen	Bovine	13.6	5	–48	–32/NS/–17/–24	12	Baumgard et al. (2002)
	Bovine	5	4×24	–28	–10/NS/NS/–10	28	Perfield et al. (2006)
	Bovine	4.2	4×24	–20	–14/NS/–32/–27	19	Sæbø et al. (2005)
	Bovine	5	5×24	–27	–6/–4/–4/–8	22	Perfield et al. (2007)
Intravenous	Bovine	10	5×24	–32	NS		Gervais et al. (2009)
Post-rumen	Caprine	2	3×24	NS	NR/–21/–50/–45	18	Andrade and Schmidely (2006)
Calcium salt	Caprine	7.5	10×24	–20	–70/–53/–57/–17	2.37	Shingfield et al. (2009)
	Caprine	15	10×24	–28	–74/–50/–63/–2	2.38	
	Caprine	22	10×24	–32	–66/–34/–66/–14	2.19	
Lipid encapsulated	Ovine	2.4	10×24	–16	NS/–24/–6/–8	3.8	Lock et al. (2006)
t10t12-CLA							
Post-rumen	Bovine	5	4×24	NS	–19/–18/–10/–15	17	Perfield et al. (2006)
	Bovine	4.7	4×24	NS	–14/NS/–20/–15	23	Sæbø et al. (2005)
t9t11-CLA							
Post-rumen	Bovine	5	5×24	NS	–29/–11/–8/–13	21	Perfield et al. (2007)

[a]Treatment consists of either infusion, abomasal, duodenal, or intravenous of CLA or addition of CLA to the diet as lipid encapsulated or calcium salt
[b]Response reported when treatment effects were significant ($P<0.10$) and calculated as [((Treatment−Control)/Control)×100]
[c]Response of the milk desaturation ratio (14:1-cis9/14:0) reported when treatment effects were significant ($P<0.10$); NS, values not reported because unsignificant; NR, not reported

Table 13.4 Effect of infusion or injection of trans-10, cis-12-CLA and trans-11-18:1 on mammary mRNA abundances of *SCD1* and lipogenic genes in ruminants

Treatment[a]	Species	Transcript[b]	Dose (g/d)	Duration (h)	Response (%)[c]	Milk desaturation ratio response[d] C9-14:1/14:0	Change in milk fat secretion (%)[c]	Reference
t10c12-CLA								
Post-rumen	Bovine	SCD1	13.6	5	−50	−32	−48	Baumgard et al. (2002)
		FAS/ACC			−40/−39			
		LPL/FABP			−48/−54			
		GPAT/AGPAT			−42/−41			
Intravenous	Bovine	SCD1	10	3×24	NS	NR	−24	Harvatine and Bauman (2006)
		SREBF1/Insig1/S14			−30/−45/−40			
		FAS/LPL			−25/−25			
Intravenous[e]	Bovine	SCD1/SCD5	10	5×24	Tendancy/NS	NS	−32	Gervais et al. (2009)
		ACC/FAS/LPL			−46/−57/tendancy			
		SREBF1			−59			
t11-18:1	Caprine	SCD1	0.3	4×24	+27	+66 (c9t11/t11)	ND	Jin et al. (2012)
Intravenous		ACC/FAS/LPL			−40/−64/NS			

[a]Treatment consists of either post-ruminal infusion and/or intravenous injection of trans-10, cis-12-CLA and trans-11-18:1

[b]Measurement of tissue transcript abundance (mRNA) of *SCD* stearoyl-CoA desaturase 1 and/or 5, *ACC* acetyl CoA carboxylase, *AGPAT* acylglycerol phosphate acyl transferase, *FAS* fatty acid synthase, *FABP* fatty acid binding protein, *GPAT* glycerol phosphate acyl transferase, *Insig1* insulin induced gene 1, *LPL* lipoprotein lipase, *S14* thyroid hormone responsive spot 14, *SREBF1* sterol response element binding protein

[c]Response reported when treatment effects were significant ($P<0.10$) and calculated as [((Treatment − Control)/Control) × 100]

[d]Response of the milk desaturation ratio (14:1-cis9/14:0) reported when treatment effects were significant ($P<0.10$); NS, values not reported because unsignificant; NR, not reported

[e]Control treatment, infusion of cis-9, cis-12-C18:2

From data in ruminant species (Tables 13.1, 13.3, and 13.4), it may be hypothesized that whereas mammary lipogenic genes expression (at the level of the mRNA and protein) in caprine is less sensitive to the anti-lipogenic effect of the trans-10, cis-12-CLA than in cows, for SCD protein the figure could be different with a higher sensitivity in goats. Indeed, indirect comparison from studies in goats (Bernard et al. 2009c) and cows (Roy et al. 2006) with similar dietary conditions (diets based on maize silage and supplemented with 5 % sunflower oil) showed that the four milk FA desaturation ratios decreased in goats, whereas these ratios increased in cows (Table 13.2).

Moreover, post-ruminal infusion studies in cows have shown that in addition to trans-10, cis-12-CLA, trans-10, trans-12- (Sæbø et al. 2005) and trans-9, trans-11-CLA (Perfield et al. 2007) reduced milk FA desaturation ratios (Table 13.3), and therefore, these two latter biohydrogenation intermediates could be specific inhibitors of SCD activity since they were not associated with MFD. In particular, the high response of milk trans-9, trans-11-CLA in goats receiving sunflower oil could play a direct role in the typical decrease of milk FA desaturation ratios in this animal species (Table 13.2). Otherwise, abomasal infusions in cows and ewes (Griinari et al. 2000; Corl et al. 2001; Kay et al. 2004; Bichi et al. 2012) of sterculic oil, known as a strong inhibitor of SCD, and administration of Co-EDTA in the rumen or per os (Shingfield et al. 2006, 2008a; Taugbøl et al. 2008, 2010; Karlengen et al. 2012) decreased the milk FA desaturation ratios without alteration of mammary *SCD1* mRNA abundance (Karlengen et al. 2012) and without decreasing milk fat secretion. It was hypothesized (Shingfield et al. 2008a) that Cobalt interferes with the transfer of electrons from cytochrome b5 to the di-iron protein center of the terminal desaturase protein, thus altering the oxidation–reduction reactions of the conversion of the acyl-CoA substrates. In bovine the concomitant effects of trans-10, cis-12-CLA on mammary *SCD1* mRNA abundance and milk FA desaturation ratios (Table 13.4) suggest an effect at the level of *SCD1* transcription for this CLA isomer. Otherwise, the mechanisms by which trans-10, trans-12 CLA and trans-9, trans-11 CLA decreased milk FA desaturation ratios are not clear and could involve an inhibition of *SCD1* gene transcription or activity.

In Vitro Studies on the Effect of Fatty Acids on Mammary SCD

Few in vitro systems have been developed to investigate the role of specific FA on the regulation of mammary lipogenesis (Table 13.5), including: (1) dispersed bovine mammary epithelial cells (bMECs) (Hansen et al. 1986; Hansen and Knudsen 1987) or primary bMECs (Matitashvili and Bauman 2000); (2) bMEC lines (MAC-T (Jayan and Herbein 2000; Peterson et al. 2004; Kadegowda et al. 2009; Ma and Corl 2012), BME-UV (McFadden et al. 2008)) or the cloned bMECs (Liu et al. 2006; Yonezawa et al. 2008); and (3) mammary slices (Matitashvili et al. 2001; Bernard et al. 2012). Although they are a simplification of physiological conditions, these

Table 13.5 Effect of fatty acid and of agonist or silencer of transcription factor on the regulation of mammary SCD1 and lipogenic gene mRNA abundance and/or enzyme activity in vitro

Biochemical pathway[a]	Transcript/protein[b]	In vitro model	FA supplement/no FA or treatment	Concentration (μM)	Duration treatment (h)	Change in expression or activity (%)[c]	Reference
Nuclear receptors							
SREBF1	mRNA	MAC-T	trans-10, cis-12-CLA	75	48	NS	Peterson et al. (2004)
			cis-9, trans-11-CLA	75	48	NS	
	Precursor protein (125 kDa)		trans-10, cis-12-CLA	75	48	NS	
			cis-9, trans-11-CLA	75	48	−11	
	Mature protein (68 kDa)		trans-10, cis-12-CLA	75	48	−26	
			cis-9, trans-11-CLA	75	48	NS	
SREBF1/ PPARG/S14	mRNA	MAC-T	16:0	100	12	NS/NS/NS	Kadegowda et al. (2009)
			18:0	100	12	NS/NS/NS	
			cis-9-18:1	100	12	−139/NS/NS	
			trans-10-18:1	100	12	−48/NS/NS	
			trans-10, cis-12-CLA	100	12	−189/NS/-73	
			20:5	100	12	−125/NS/NS	
			Rosiglitazone	50	12	+100/NS/NS	
SREBF1	mRNA	BME-UV	T0901317 (T09)	2	8	+416	McFadden and Corl (2010)
	Precursor protein		LXR agonist	2	8	+240	
	Mature protein			2	8	+210	
SREBF1	mRNA	Goat MEC	T0901317 (T09)	0.01/0.1/1	24	+132/+269/+381	Wang et al. (2012)
FAS	mRNA		LXR agonist	0.01/0.1/1	24	+127/+157/+223	
LXRA	mRNA			0.01/0.1/1	24	NS/NS/NS	

SREBF1/S14	mRNA	MAC-T	SREBF1-SiRNA[d]	0.1	48	–90/–95	Ma and Corl (2012)
SREBF1	Precursor protein			0.1	48	Undetectable	
	Mature protein			0.1	48	Undetectable	
Desaturation and de novo lipogenesis							
SCD1	mRNA	MAC-T	trans-11-18:1	50	(90) + 6	NS	Jin et al. (2012)
PSMA5	mRNA	MAC-T	trans-11-18:1	50	(90) + 6	+340	
SCD1	mRNA	bovMEC	trans-11-18:1	200	6 or 72	+200	Matitashvili and Bauman (2000)
			cis-11-18:1			NS	
SCD1	mRNA	MAC-T	trans-10, cis-12-CLA	75	48	–40	Peterson et al. (2004)
			cis-9, trans-11-CLA	75	48	NS	
SCD1	mRNA	MAC-T	16:0	100	12	+95	Kadegowda et al. (2009)
			18:0	100	12	NS	
			cis-9-18:1	100	12	–428	
			trans-10-18:1	100	12	–100	
			trans-10, cis-12-CLA	100	12	–357	
			20:5	100	12	–205	
			Rosiglitazone	50	12	NS	
SCD	Activity	MAC-T	cis-9-18:1/18:0	100	72	–21	Jayan and Herbein (2000)
			trans-11-18:1/18:0	100	72	+72	
ACC/FAS	Activity	MAC-T	cis-9-18:1/18:0	100	72	–27/–35	Jayan and Herbein (2000)
			trans-11-18:1/18:0	100	72	–58/–43	
SCD1	mRNA	MAC-T	SREBF1-SiRNA[d]	0.1	48	–60	Ma and Corl (2012)
ACC/FAS/IDH1	mRNA					–40/–65/–50	
ACSS1/ACSS2	mRNA					NS/–60	

(continued)

Table 13.5 (continued)

Biochemical pathway[a]	Transcript/protein[b]	In vitro model	FA supplement/no FA or treatment	Concentration (μM)	Duration treatment (h)	Change in expression or activity (%)[c]	Reference
SCD1/ACC	Protein					−90/−47	
FAS	mRNA	BME-UV	T0901317 (T09)	2	8	+185	McFadden and Corl (2010)
FAS	mRNA	Goat MEC	T0901317 (T09)	0.01/0.1/1	24	+127/+157/+223	Wang et al. (2012)
SCD	Activity	Goat cell fraction[e]	Oleic (>lin >lnn)[f]	0.8	1	−53	Bickerstaffe and Annison (1970)
Long-chain activation and transport							
ACSL1/FABP3	mRNA	MAC-T	SREBF1-SiRNA[d]	0.1	48	NS/−76	Ma and Corl (2012)
Esterification and protein of milk fat globule							
GPAM/ AGPAT6	mRNA	MAC-T	SREBF1-SiRNA[d]	0.1	48	−20/+22	Ma and Corl (2012)
DGAT1						±70	
Protein of the milk fat globule							
PLIN2/ BTN1A1/ LPIN1	mRNA	MAC-T	SREBF1-SiRNA[d]	0.1	48	−250/NS/−90	Ma and Corl (2012)

[a]*SCD* stearoyl-CoA desaturase, *ACC* acetyl CoA carboxylase, *FAS* fatty acid synthase, ACSS*1* acyl-CoA synthetase short chain family member 1, *ACSS2* acyl-CoA synthetase short chain family member 2, *ACSL1* acyl-CoA synthetase long chain family member 1, *ACSL2* acyl-CoA synthetase long chain family member 2, *IDH1* isocitrate dehydrogenase 1, *S14* thyroid hormone responsive spot 14, *SREBF1* sterol response element binding protein, *PPARG* peroxisome proliferator receptor gamma, *LPIN1* lipin1, *PLIN2* perilipin 2, *BTN1A1* butyrophilin subfamily 1 member A1, *AGPAT6* acylglycerol phosphate acyl transferase 6, *FABP3* fatty acid binding protein 3, *GPAM* glycerol-3-phosphate acyltransferase 1, *DGAT1* diacylglycerol acyl transferase 1

[b]Measurement of tissue transcript abundance (mRNA) or protein activity (Activity)

[c]Response reported when treatment effects were significant ($P < 0.10$) and calculated as [((Treatment − Control)/Control) × 100]; NS, values not reported because unsignificant

[d]MACT-T transfected with sterol regulatory element binding protein SREBP-1 small interfering (si) RNA

[e]Goat subcellular fraction of mammary tissue (post-mitochondrial fraction)

[f]lin linoleic acid, lnn linolenic acid

in vitro systems offer an advantage over in vivo nutritional studies because the effects of specific FA in small amount can be evaluated under controlled conditions. Then, several years ago looking at the effects of specific FA on bovine mammary cell line (MAC-T cells), Jayan and Herbein (2000) showed that, compared to stearic acid, oleic acid decreased SCD activity. Similarly, still using MAC-T cell, Kadegowda et al. (2009) demonstrated that oleic acid, among other long-chain FA including 20:5*n*-3, was the most potent inhibitor of *SCD* gene expression, which is suggestive of a feedback-inhibition mechanism. Furthermore, earlier studies (Bickerstaffe and Annison 1970) observed negative effects of oleic, linoleic, and linolenic acids on goat mammary SCD activity measured on the subcellular fraction of goat mammary gland, which have been partly confirmed by in vivo studies on goat (Bernard et al. 2005b, 2009b). Regarding the effect of trans-FA, only two trans-18:1 isomers have been tested in vitro (Table 13.5). Incubation of trans-11-18:1 with bovine MEC increased *SCD1* mRNA abundance (Matitashvili and Bauman 2000) and SCD activity in bovine MAC-T cell line (Jayan and Herbein 2000), whereas trans-10-18:1 reduced *SCD1* mRNA abundance in bovine MAC-T cell line (Kadegowda et al. 2009). Similarly, in goats, intravenous bolus injection of trans-11-18:1 increased both the expression of *SCD* in mammary tissue (Jin et al. 2012) and milk cis-9, trans-11-CLA, suggesting an upregulation of the expression at the protein level. Otherwise, trans-10, cis-12-CLA (and to a lesser extent cis-9, trans-11-CLA) caused a significant reduction in *SCD* transcriptional activity (Keating et al. 2006) in bovine MAC-T cells, due to the *SCD* transcriptional enhancer element region (STE; see section "Characterization of SCD Genes"). The same study also showed that bovine *SCD* promoter was upregulated by insulin and downregulated by oleic acid, whereas linoleic, linolenic, stearic, and vaccenic acids had no effect. Elsewhere, using bovine and caprine mammary slices, Bernard et al. (2012) did not evidenced significant effect of trans-10, cis-12-CLA on *SCD1* mRNA abundance after 20 h incubation time. Conversely, in bovine MAC-T cell, Kadegowda et al. (2009) demonstrated that trans-10, cis-12-CLA reduced expression of *SCD1* together with *SREBF1*. These two latter studies outline differences of response of different in vitro models for studying lipogenic genes expression.

So far, the developed in vitro systems present several limitations: MECs and cultured mammary slices have a limited lifetime, modified cell lines often have abnormal characteristics and low secretory activity. Nevertheless, use of these approaches has allowed to decipher, at least in part, the underlying mechanisms responsible for the inhibitory effects of trans-10, cis-12-CLA on lipogenesis and lipogenic gene expression in primary culture of bMEC (Matitashvili and Bauman 2000), MEC lines (Peterson et al. 2004; McFadden et al. 2008; Kadegowda et al. 2009), and mammary explants (Matitashvili et al. 2001) (see section "Knowledge on the Signalling Pathways Mediating Nutritional Regulation of SCD Gene Expression in Ruminants"). Further research is necessary in ruminants to identify the major regulators of FA desaturation which is hampered by the lack of pure trans-18:1 and 18:2 isomers and by the difficulty to obtain an in vitro functional model for lipid synthesis and secretion (Barber et al. 1997; Bernard et al. 2012).

Knowledge on the Signalling Pathways Mediating Nutritional Regulation of SCD *Gene Expression in Ruminants*

Whereas the signalling pathways involved in the regulation of *SCD* gene expression by dietary factors (e.g., the inhibitory effect of PUFA) have been comprehensively described in rodent tissues (Nakamura and Nara 2004; Ntambi et al. 2004), still little is known about these mechanisms in ruminants. Among the class of transcription factors known as major regulators of lipid synthesis are the sterol response element binding protein (SREBP) family (Eberlé et al. 2004) and peroxisome proliferators-activated receptors (PPARs) (Clarke 2001).

Because different SREBP isoforms have different roles in regulating lipid synthesis, these isoforms have been studied extensively in different species (Brown and Goldstein 1997).

SREBP family is composed of three members: two isoforms of SREBP-1 (a and c) and SREBP-2. Both SREBP-1a and SREBP-1c, which can be differentially expressed in various tissues, are produced from a single gene (*SREBF-1*, located on bovine chromosome 17) presenting alternative splicing. *SREBF1c* and *SREBF1a* use different first exons and both regulate FA synthesis. SREBP-2 is transcribed from a separate gene (*SREBF2*, located on bovine chromosome 5) and regulates the cholesterol biosynthetic pathway (Horton 2002).

Multiple proteins are involved in the SREBP pathway because (1) SREBP are translated as precursor proteins which need maturation steps to become mature that involve several proteins (such as SCAP, INSIG1, 2, S1P, S2P) and (2) the SREBP mature proteins recruit other proteins acting as co-activators to activate the transcription of lipogenic genes to whom belong *LPL*, *ACACA*, *FASN*, and *SCD1* genes.

Regarding PPARs, three different isoforms of PPAR (PPARα, PPARβ/δ, and PPARγ), have been identified and are encoded by three different genes; they exhibit significant differences in tissue distribution and ligands but all function by dimerizing with RXR and binding to the PPAR response element (PPRE) DNA sequence (Sampath and Ntambi 2005).

In lactating cows, in vivo studies have shown the involvement of SREBP-1 and/or PPAR during diet-induced changes in mammary lipogenic gene expression (Angulo et al. 2012; Bionaz and Loor 2008) or in response to 3–5 d intravenous infusions of trans-10, cis-12-CLA (Harvatine and Bauman 2006; Gervais et al. 2009) with the implication that these transcription factors are central elements in the overall regulation of milk fat synthesis.

However, little is known in the ruminant mammary gland on the signalling pathways involved in *SCD* gene expression. Among six in vivo studies (either nutritional or infusion studies) in cows with MFD that measured the mammary mRNA abundances of both lipogenic genes and *SCD1*, only two reported a simultaneous decrease in mRNA abundance of lipogenic genes and *SCD1* (Baumgard et al. 2002; Angulo et al. 2012). Conversely, in the others, either nutritional studies (Ahnadi et al. 2002; Harvatine and Bauman 2006; Peterson et al. 2003) or with intravenous

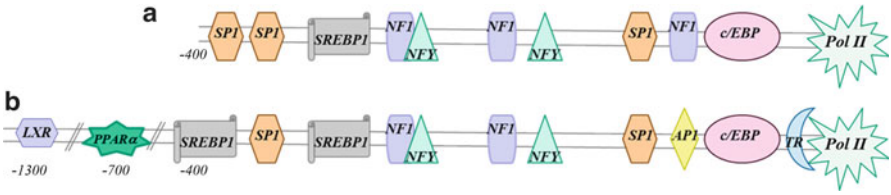

Fig. 13.5 Diagram of the SCD1 gene promoter. The diagram shows the different transcription factors involved in the regulation of SCD1 gene transcription. (**a**) Represents the binding sites of transcription factors deduced by sequence homology between bovine sequence (AY241932) and pig (AY487830) and human (AF 320307). (**b**) Represents elements characterized in human, mouse, and chicken promoters from Mauvoisin and Mounier (2011)

infusion of trans-10, cis-12-CLA (Gervais et al. 2009), a coordinate decrease in the abundance of lipogenic genes was observed with only a tendency to decrease for *SCD1* mRNA suggesting that the transcription of this gene varies less or less rapidly in response to the diet. Probably the other lipogenesis-related transcription factors (e.g., PPARs, SP1, NFY, CEBPs; Fig. 13.5) expressed in the ruminant mammary gland (Bionaz and Loor 2008; Toral et al. 2013b) are involved in the mediation of diet-induced effects on mammary *SCD1* gene expression that may counteract for the effect of *SREBF1*.

Otherwise, in an in vitro study using bovine MAC-T cell line, addition of trans-10, cis-12-CLA and 20:5*n*-3 decreased both *SREBF1* and *SCD1* mRNA abundances with variable effects on the other lipogenic genes and without changing *PPARG* mRNA (Kadegowda et al. 2009). Recently, it was reported that the bovine *SREBF1* gene contained in its promoter responsive elements for both *SREBF1* (SRE) that could allow for a positive feedback regulation by SREBP-1 itself and for liver X receptor (LXR-RE; Lengi and Corl 2010). Therefore, the SREBP-1 responsiveness to LXR activation was demonstrated in BME-UV cell line (McFadden and Corl 2010) using T0901317 (T09), an LXR agonist that resulted in the upregulation of transcription, translation, and proteolytic cleavage of SREBP-1. Because both SRE and LXR-RE have been characterized in *SCD1* gene promoter in human, mouse, or chicken (Mauvoisin and Mounier 2011) and are conserved between species, probably they may also be present in bovine *SCD1* gene promoter. Using bovine MAC-T cell line, Peterson et al. (2004) have demonstrated that the inhibitory effect of trans-10, cis-12-CLA acts through inhibition of the proteolytic activation of SREBP-1, resulting in a reduction in the transcriptional activation of lipogenic genes (*ACACA* and *FASN*) and *SCD1*, without increasing the *SREBF1* expression. The role of SREBP-1 in regulating milk fat synthesis had not been directly evaluated in ruminants until a recent study in MAC-T cells (Ma and Corl 2012) using RNA interference to knock down *SREBF1* (the *SREBF1*-specific siRNA targeted a region of the transcript identical between *SREBF1a* and *SREBF1c* and did not distinguish the two isoforms 1a and 1c) to investigate the specific role of SREBP-1 in affecting the expression of genes encoding key enzymes of milk fat synthesis including *SCD1*. In this study,

FABP3 and *SCD1 mRNAs* were both decreased when SREBP-1 mRNA decreased (and SREBP protein was undetectable), indicating that transport and desaturation of long-chain FA could be regulated transcriptionally by SREBP-1.

Altogether these data underlined the necessity to better characterize the molecular mechanisms involved in the dietary regulation of *SCD* gene expression in ruminant species, and in particular to precise the role of SREBP-1 and PPARs. The observed differences in the response of *SCD* and other lipogenic genes expression to decreased *SREBF1* mRNA abundance (Table 13.1) may suggest a lower threshold response for *SCD* to SREBP-1 level compared to other lipogenic genes which would be in line with the hypothesis of a two-step mechanisms of regulation for these genes, with the implication of other transcription factors in these regulations.

Conclusions

A balance between the endogenously synthesized short-chain FA, the exogenous unsaturated long-chain FA, and the SCD desaturation products must be maintained within the mammary gland in order to preserve the fluidity of milk fat, which emphasizes the importance of knowledge on SCD regulation. Over the last years, the development of studies in ruminants on the nutritional regulation of a few "candidate" genes involved in mammary lipogenesis including Δ9-desaturation (*SCD*) has shown that *SCD* gene regulation differ from other lipogenic genes. Indeed, in cows with dietary conditions that induce a dramatic MFD, a decrease in the mRNA abundance of mammary lipogenic genes was observed which was not always observed for *SCD*. It was hypothesized that the responses of lipogenic genes and *SCD1* to dietary factors that induce MFD in cows occur as a two-step phenomenon, with a first downregulation of lipogenic genes followed by *SCD1*, which could be related to the observed differences in the response to *SREBF1* or to other transcription factors involved in these regulations. In addition, these studies showed that the response of mammary *SCD* mRNA or activity to nutritional factors do not always match with the responses of milk FA Δ-9 desaturation ratios. In goats, *SCD* is regulated at a transcriptional and/or post-transcriptional level, depending on the lipid supplements. Conversely, in cows, data converged to demonstrate that *SCD* mRNA varied little in response to diet except for a decrease when "protected" fish oil or combination of PUFA and DHA-rich algae was fed. Indirect comparison of data from bovine and caprine suggested that SCD in caprine could be more sensitive to the effect of dietary PUFA or their ruminal biohydrogenation intermediates than in cows and that trans-9, trans-11-CLA could play a specific role in the regulation of mammary Δ-9 desaturation in goats receiving PUFA-rich diets. Future experiments examining changes in mammary *SCD* and other lipogenic genes expression in the different ruminant species in response to dietary treatments as well as ruminant *SCD1* and *SCD5* promoter sequencing would provide a more comprehensive insight into the regulation of these genes and their impact in the synthesis of milk fat.

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