ANSC/NUTR 601
GENERAL ANIMAL NUTRITION
Stearoyl-CoA desaturase, VLDL metabolism, and obesity

I. Stearoyl coenzyme A desaturase and obesity in rodents

A. Stearoyl coenzyme A desaturase (SCD) is the Δ9 desaturase.

1. Rodents have several SCD isoforms.
2. SCD1 is expressed primarily in the liver of rodents.

B. Mice that are SCD1-deficient have reduced body weight, even when fed high-fat diets.

1. SCD1 knockout causes reduced Δ^9 desaturase activity primarily in liver of mice.
2. Reduction in body weight in caused by marked reduction in body fat.

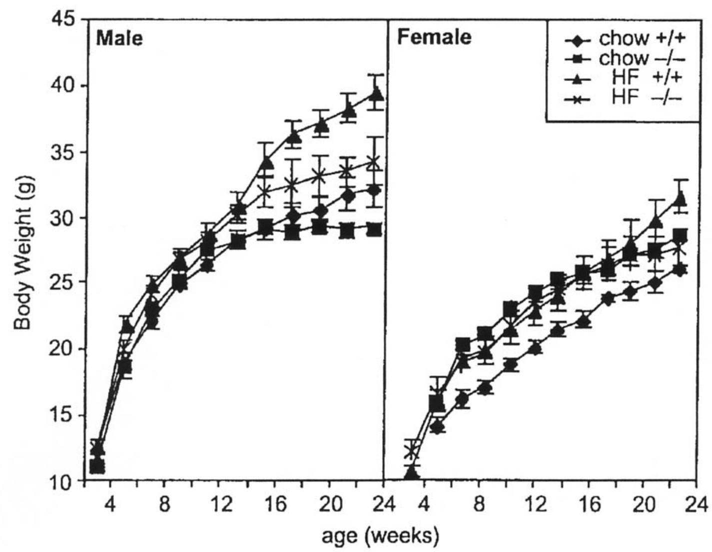
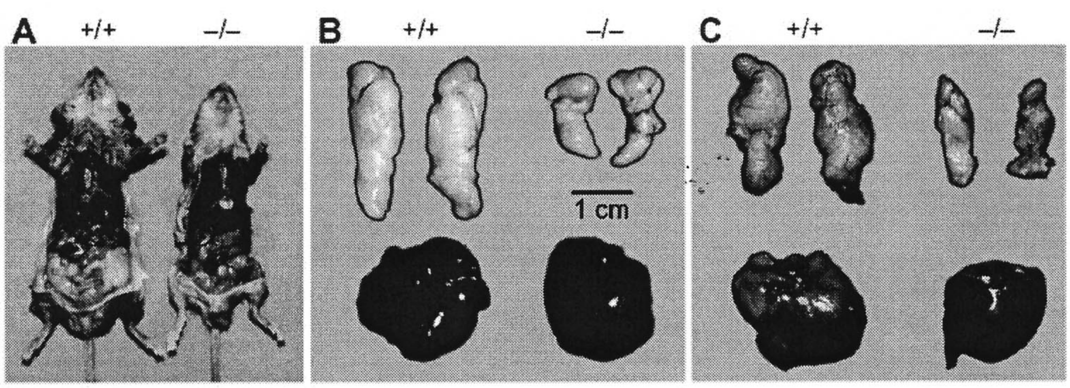


Fig. 1. Body weight of male and female wild-type and *SCD1*−/− mice fed a chow or high-fat diet.

3. Obese mice have much larger fat pads, although liver size does not differ.

Obese and wild-type mice **Organs from high-fat fed mice** **Organs from chow-fed mice**



C. Hepatic SCD1 is over-expressed in obese mice.

1. Pair-feeding obese mice eventually depresses hepatic SCD1 gene expression.
2. Treating obese mice with leptin drastically decreases adiposity and hepatic SCD1 gene expression.
    a. Genetically obese mice have depressed leptin concentrations.
    b. Leptin is expressed in adipose tissue, so in normal mice, more adipose tissue leads to higher leptin.

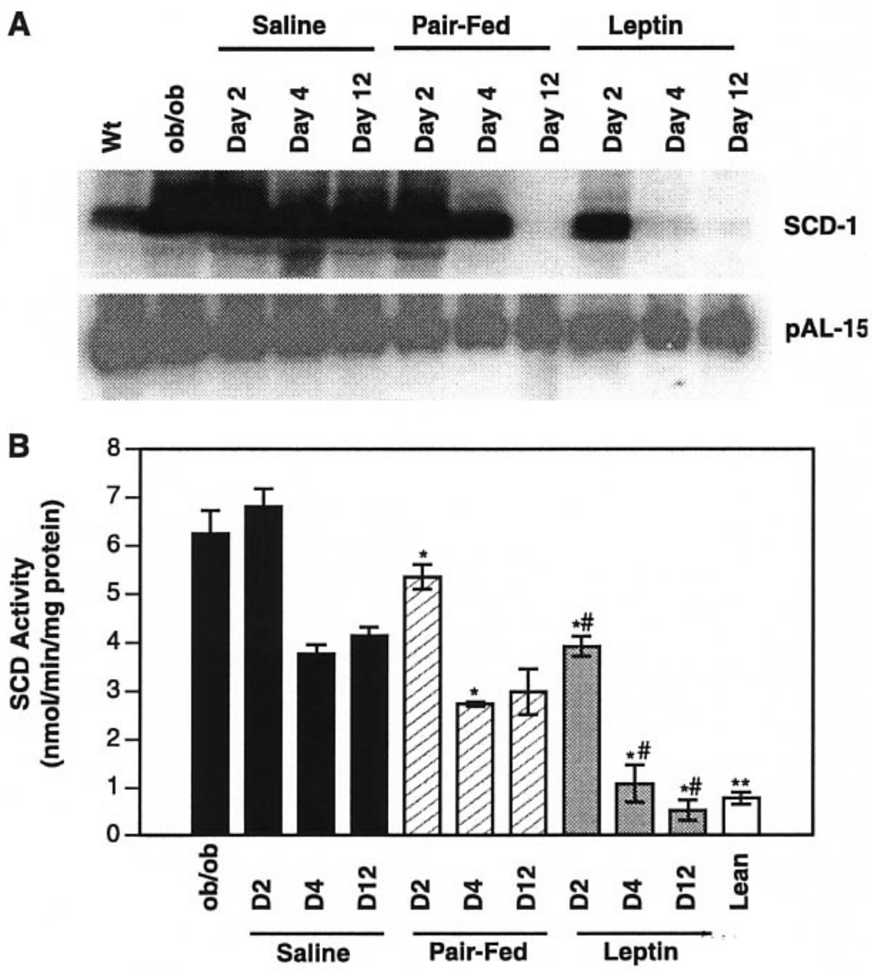
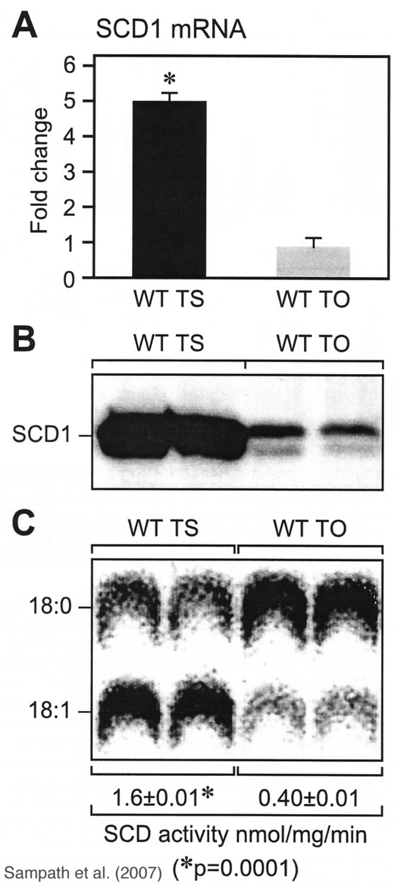


Fig. 1. Leptin-specific down-regulation of SCD-1 RNA levels and enzymatic activity. (**A**) As shown from an independent time-course experiment, Northern blots of liver RNA samples were hybridized with radioactively labeled cDNA probes specific for SCD-1 and the small mitochondrial RNA pAL-15 (loading control). (**B**) SCD enzymatic activity was measured as in (*11*, *19*). Activity is expressed as nanomoles minute^{-1} milligram^{-1} protein. Error bars indicate the SEM, $n = 3$ for each group. *$P < 0.05$ versus saline treated, #$P < 0.05$ versus pair fed, **$P < 0.0005$ untreated lean versus untreated *ob/ob*.

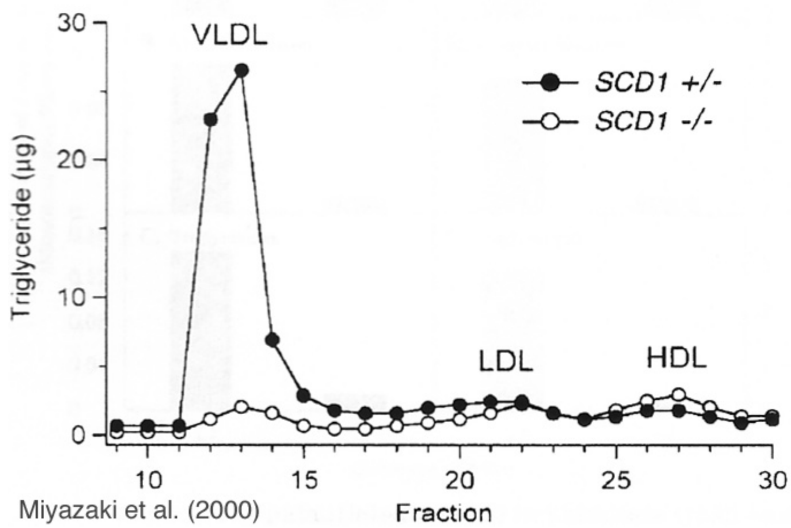
D. Reduction of body fat via hepatic SCD1

1. Hepatic SCD1 activity is required for VLDL synthesis.
2. Oleic acid stimulates ACAT activity (palmitoleic acid may also stimulate ACAT activity).
3. Oleic acid also is a primary substrate for the ACAT reaction.
4. Increased cholesterol ester promotes VLDL synthesis.



Left: SCD gene expression and activity in livers of wild type (WT) mice fed tristearin or triolein. Triolein strongly depressed both SCD gene expression and activity.

Bottom: VLDL synthesis in heterozygous (*SCD1+/-*) and homozygous (*SCD1-/-*) knockout mice. VLDL synthesis was abolished in the homozygous SCD1 knockout mice.



II. Stearoyl coenzyme A desaturase and obesity in cattle

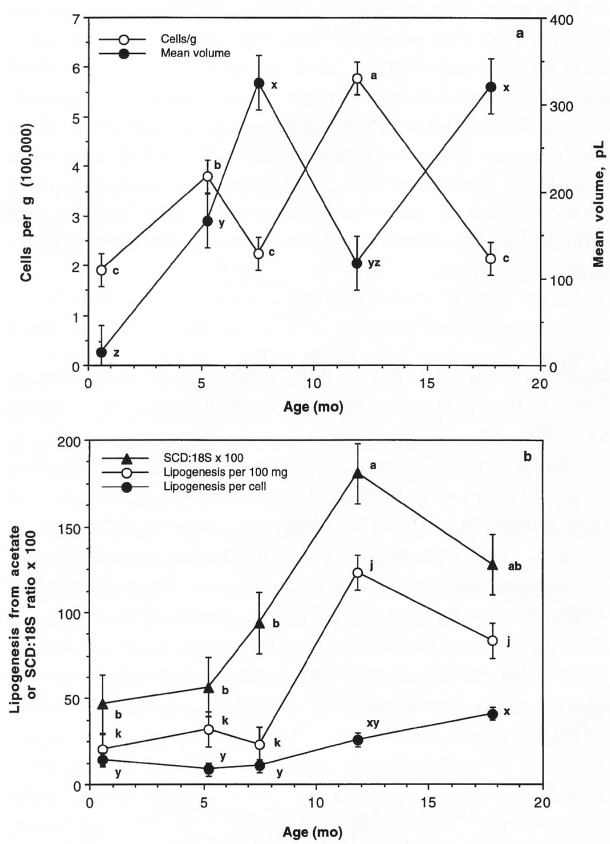
A. Livestock species (pigs, sheep, and cattle) express at most two SCD isoforms.

1. SCD1 (all tissues)
2. SCD5 (a pseudogene primarily in the brain)

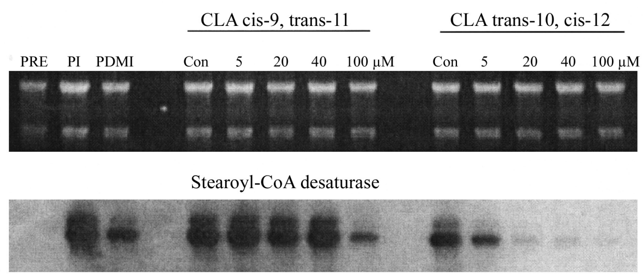
B. Stearoyl-CoA desaturase gene expression is essential for bovine adipose tissue development.

1. SCD is expressed immediately after differentiation in cell culture.
2. *trans*-10, *cis*-12 CLA depresses SCD gene expression and lipid filling of preadipocytes.
3. SCD is expressed during growth is young steers.
4. SCD gene expression precedes lipid filling and lipogenesis.

Right: Adipocyte volume and cells/g adipose tissue (top) and SCD gene expression and lipogenesis (bottom) in adipose tissue of Angus steers during growth.



Below: SCD gene expression during differentiation of bovine preadipocytes. Preadipocytes were incubated in differentiation medium (PI, pioglitazone and insulin) with or without CLA isomers.



C. Stearoyl-CoA desaturase gene expression and fatty acid composition

1. In cattle fed grain-based diets, SCD activity increases with age.

2. Because of the increase in SCD gene expression and activity, all monounsaturated fatty acids increase in grain-fed cattle.

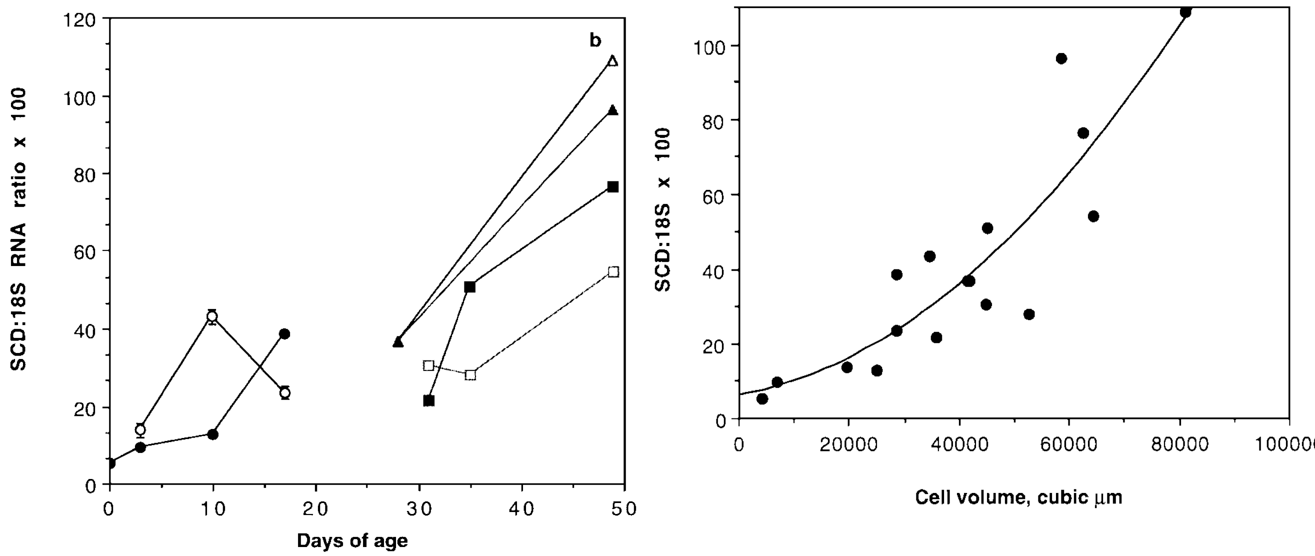
III. Stearoyl coenzyme A desaturase and obesity in pigs

A. Adipocyte volume increases markedly after weaning in piglets.

B. SCD gene expression in subcutaneous adipose tissue also increases markedly after weaning.

1. Obese pigs have higher SCD gene expression than contemporary pigs.

2. Adipose tissue from obese pigs has larger adipocytes than adipose tissue from contemporary pigs.



Changes in *SCD* gene expression (left panel) and the relationship between *SCD* gene expression and adipocyte volume (right panel) in obese (open symbols) and contemporary crossbred pigs (closed symbols). Circles, suckling pigs; triangles, pigs fed a high-fat, milk-based diet; squares, pigs fed a low-fat, grain-based diet. There was a highly significant correlation between adipocyte volume and *SCD* gene expression (R^2 = 0.79, P < 0.001).

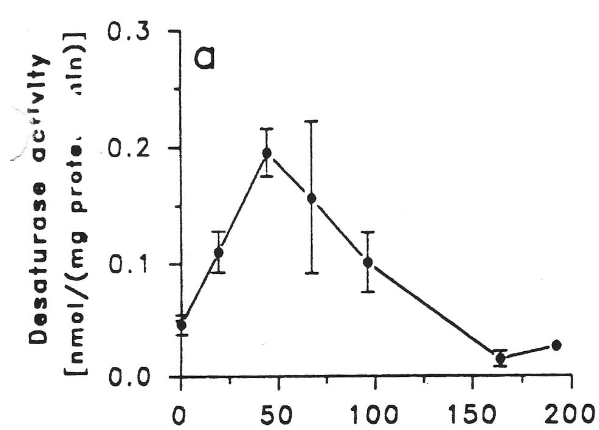
IV. Stearoyl coenzyme A desaturase and VLDL synthesis in poultry

A. Poultry may have a liver-specific isoform of SCD (not yet determined).

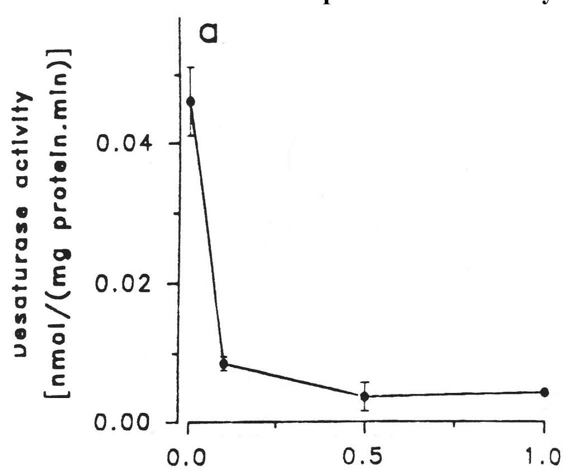
B. Hepatic SCD promotes VLDL synthesis.

1. VLDL synthesis primarily is targeted for egg production.
2. VLDL synthesis may also promote adiposity in poultry.

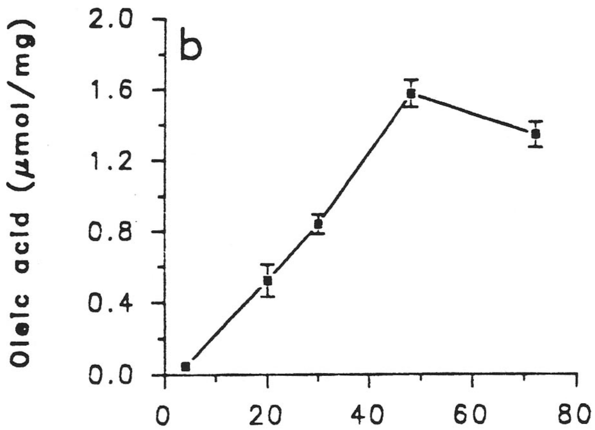
1. SCD activity initially increases during differentiation.



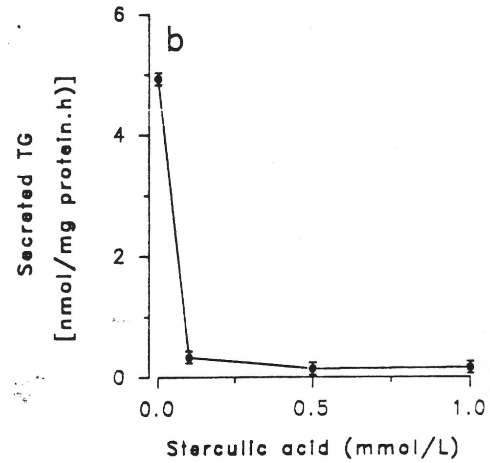
2. Sterculic acid depresses SCD activity.



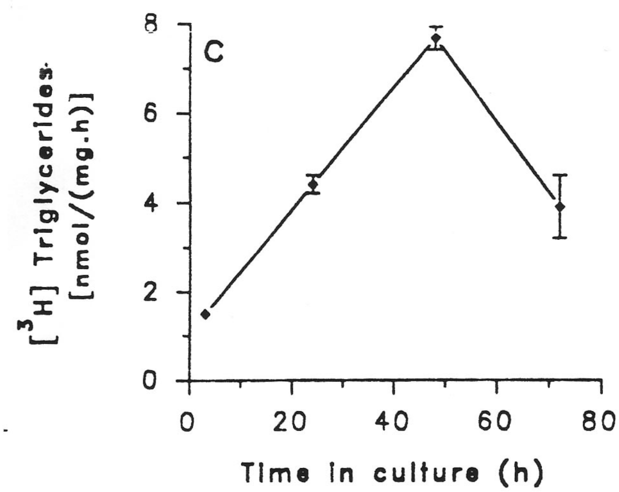
3. Oleic acid in the media from poultry hepatocytes increases during differentiation.



4. Sterculic acid depresses TAG synthesis.



5. Triacylglycerol synthesis increases in cultured hepatocytes.



6. Adding back oleic or linoleic acid restores triacylglycerol synthesis.

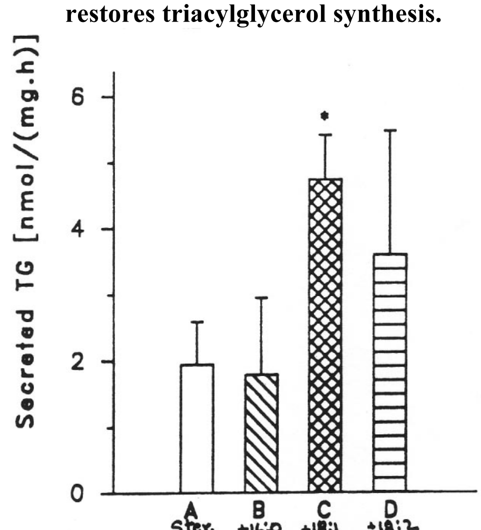


FIGURE 6 Effect of addition of different fatty acids to the culture medium of chicken hepatocytes in which the Δ9-desaturase had been inhibited by sterculic acid.

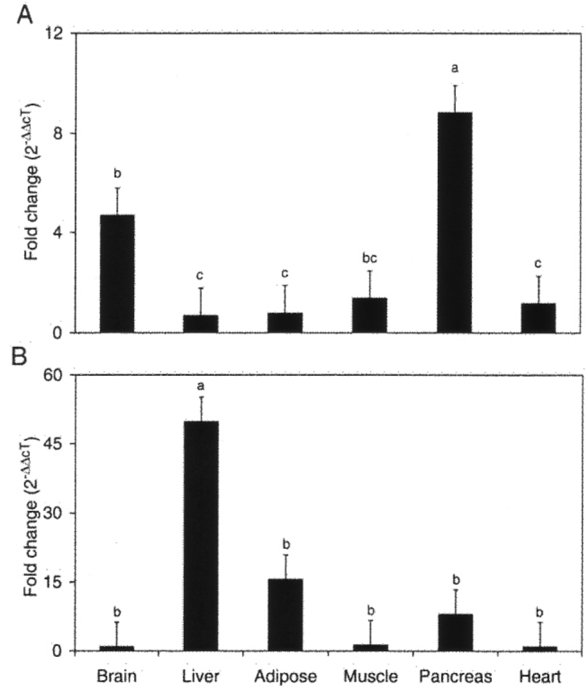


Fig. 4. Analysis of (A) chicken *SCD5* gene expression (B) chicken *SCD1* gene expression using real-time PCR. Real-time PCR was performed using RNA extracted from snap-frozen tissues as indicated (brain, liver, adipose, skeletal muscle, pancreas, heart; $n=3$). Beta actin was used as the endogenous control gene, and skeletal muscle tissue was used as the calibrator for making relative comparisons between tissues. Fold change was calculated using the $2^{-\Delta\Delta cT}$ method. Bars not sharing a common superscript letter within each graph differ ($p<0.05$). Error bars represent the standard error of the mean.

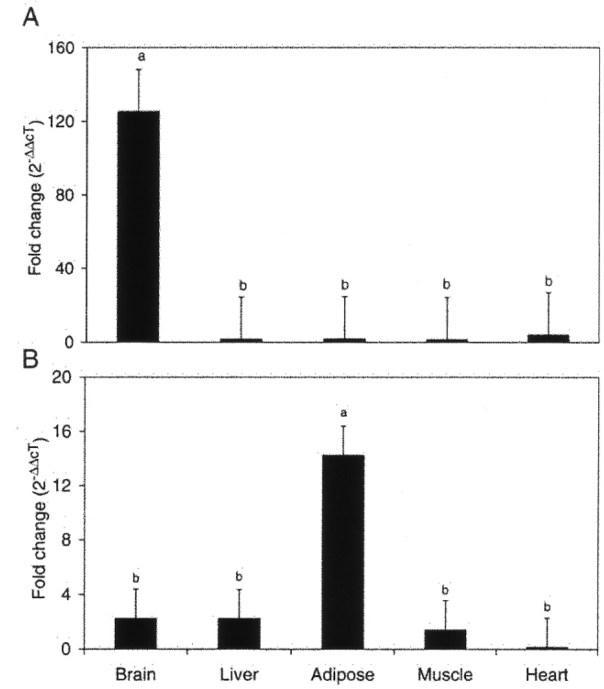


Fig. 5. Analysis of (A) pig *SCD5* gene expression (B) pig *SCD1* gene expression using real-time PCR. Real-time PCR was performed using RNA extracted from snap-frozen tissues as indicated (brain, liver, adipose, skeletal muscle, heart; $n=3$). Beta actin was used as the endogenous control gene, and skeletal muscle tissue was used as the calibrator for making relative comparisons between tissues. Fold change was calculated using the $2^{-\Delta\Delta cT}$ method. Bars not sharing a common superscript letter within each graph differ ($p<0.05$). Error bars represent the standard error of the mean.

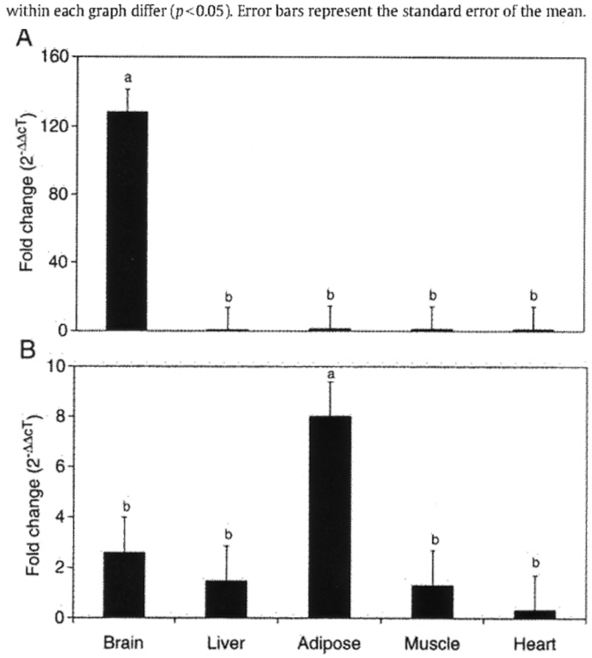


Fig. 6. Analysis of (A) sheep *SCD5* gene expression (B) sheep *SCD1* gene expression using real-time PCR. Real-time PCR was performed using RNA extracted from snap-frozen tissues as indicated (brain, liver, adipose, skeletal muscle, heart; $n=4$). Beta actin was used as the endogenous control gene, and skeletal muscle tissue was used as the calibrator for making relative comparisons between tissues. Fold change was calculated using the $2^{-\Delta\Delta cT}$ method. Bars not sharing a common superscript letter within each graph differ ($p<0.05$). Error bars represent the standard error of the mean.

V. Stearoyl coenzyme A desaturase, VLDL synthesis, and obesity in humans

A. Livestock species (pigs, sheep, and cattle) express at most two SCD isoforms.

1. SCD1 (all tissues)

2. SCD5 (a pseudogene primarily in the brain)

B. Hepatic SCD activity cannot be easily measured in humans.

1. It is virtually impossible to get liver samples from humans.

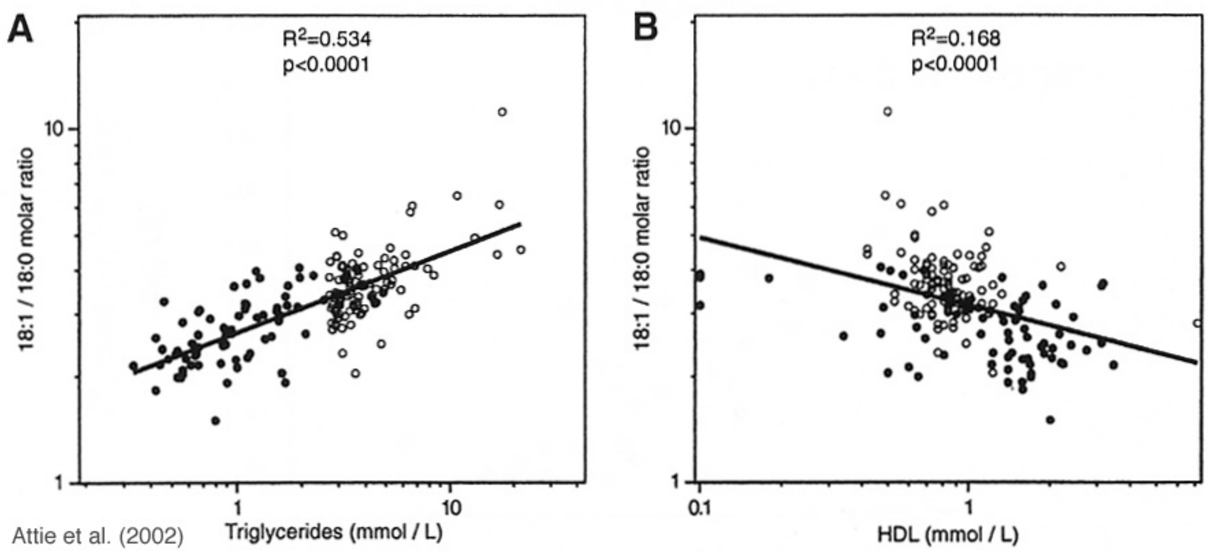
2. Plasma fatty acid indices are used as surrogates for hepatic SCD activity.

C. The plasma oleic:stearic acid ratio, TAG, and HDL cholesterol in men fed high-carbohydrate diets

1. A high plasma oleic:stearic acid ratio is associated with high plasma TAG.

2. A high plasma oleic:stearic acid ratio is associated with low plasma HDL cholesterol.

3. The oleic:stearic acid ratio was increased by a high-carbohydrate diet.



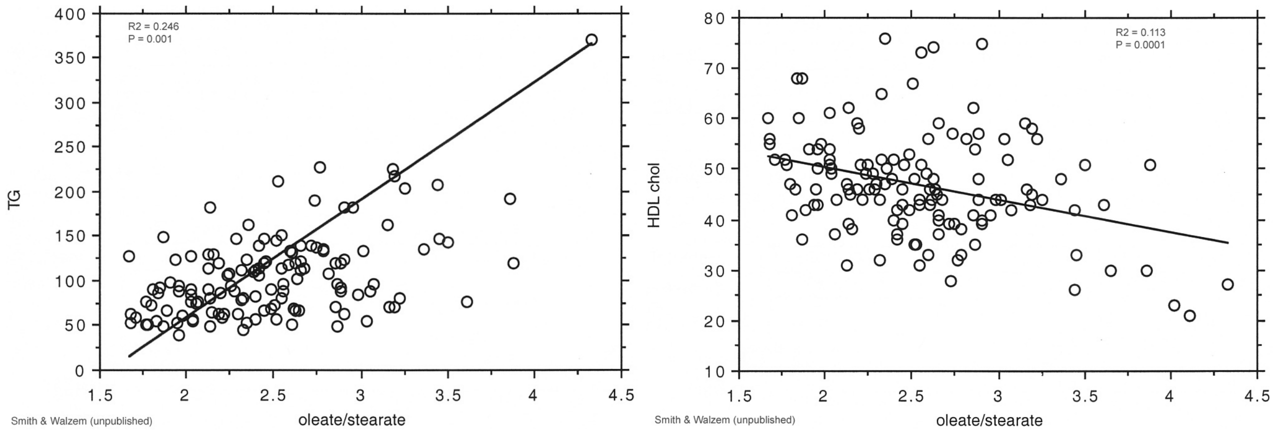
Plasma oleic:stearic acid ratio as a function of triglycerides (left) and HDL (right) in men consuming habitual diets (filled circles) and high-carbohydrate diets (open circles).

D. The plasma oleic:stearic acid ratio, TAG, and HDL cholesterol in men fed high-fat diets

1. A high plasma oleic:stearic acid ratio is associated with high plasma TAG.

2. A high plasma oleic:stearic acid ratio is associated with low plasma HDL cholesterol.

3. Diets high in stearic acid increased the plasma oleic:stearic acid ratio.



Plasma triglycerides (left) and HDL cholesterol (right) as a function of the plasma oleic:stearic acid ratio.