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ORIGINAL CONTRIBUTION

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Hepatic lipid and carbohydrate metabolism in rats fed a commercial mixture of conjugated linoleic acids (Clarinol G-80™)[1]

Summary *Background* Conjugated linoleic acids (CLAs) exert numerous effects in animal models as well as in humans. Among other things, CLAs decrease plasma lipid levels and bring about hepatic steatosis. The latter effects are attributed to an agonistic action of CLAs on the peroxisome-proliferator-activated receptor family primarily responsible for activating genes involved in lipid metabolism and are related to changes in mRNA levels. Such changes are not necessarily reflected in changes in activity of controlling enzymes. *Aim of the study* To investigate the effects of CLAs treatment on lipid metabolism, we determined lipid concentrations in plasma, lipoproteins and liver and measured the activity of a number of key enzymes in hepatic lipid metabolism as differences in lipid concentrations should be related to changes in enzyme activities. These variables were determined with the rat as a model. *Methods* Rats were fed a control diet or a diet containing 1.15 % *trans*-10, *cis*-12 isomer and 1.11 % *cis*-9, *trans*-11 isomer as part of a commercial mixture of CLAs. After 2 w the animals were killed, and plasma and liver fractions isolated. Subsequently, lipid concentrations of cholesterol, triacylglycerols and phospholipids were determined in the isolated lipoproteins. In livers homogenates, the concentrations of glycogen, cholesterol, triacylglycerol and phospholipids and the activities of enzymes catalyzing pacesetting steps of metabolism were determined, i. e. acetyl-CoA carboxylase, fatty acid synthase, diacylglycerol acyltransferase, 3-hydroxy-acyl-CoA dehydrogenase, citrate synthase and phosphofructokinase. *Results* CLAs induced a lowering of the cholesterol levels in total plasma and in LDL and HDL lipoproteins and of phospholipid concentrations in LDL and HDL. CLAs treatment decreased the hepatic activity of diacylglycerol acyltransferase and had no effect on any of the other enzyme activities. *Conclusions* In other studies enhanced specific activities of ACC and FAS were found in livers of mice using the same or similar methods and experimental protocol as in the present study. The lack of effect of CLAs treatment on hepatic key enzymes of fatty acid synthesis and oxidation in Wistar rats questions the use of this strain for studying the mechanism(s) underlying CLA's effects on these parameters. However, in the rat model we observed reduced levels of cholesterol in total plasma and in LDL and HDL. Therefore, some aspects like loss of body fat are better studied in mice; for other aspects like reduction in serum cholesterol level the rat may be the model of choice.

Key words rats – dietary CLAs – liver – enzymes – plasma lipoproteins

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Abbreviations

ACC	acetyl-CoA carboxylase
CS	citrate synthase
CPT-I	carnitine palmitoyltransferase-I
CLAs	conjugated linoleic acids
DGAT	diacylglycerol acyltransferase
FAS	fatty acid synthase
3-HAD	3-hydroxy-acyl-CoA dehydrogenase
PPAR	peroxisome-proliferator-activated-receptor
TAG	triacylglycerols
TCC	tricarboxylate carrier

Introduction

Conjugated linoleic acids (CLAs) refer to a group of positional and geometric isomers of octadecadienoic acid ($C_{18:2}$) in which the double bonds are conjugated, i. e. contiguous rather than the double bonds of linoleic acid which are separated by a methylene group [1]. CLAs are formed as a result of microbial isomerization of dietary linoleic acid and desaturation of oleic acid derivatives in the rumen of ruminants [2]. Therefore, they are naturally present in edible fats from ruminant origin like milk fat and beef tallow [3, 4].

It has been well documented that dietary CLAs and in particular the *trans*-10, *cis*-12 isomer, exhibit numerous effects, including inhibition of chemically-induced carcinogenesis in several rodent models [2] and reduction of atherosclerosis in rabbits [5] and hamsters [6]. CLAs exhibit several effects on hepatic lipid metabolism. Mice fed CLAs-supplemented diets develop hepatomegaly due to lipid accumulation [7, 8]. Also in humans, CLAs appear to exert a number of effects including reductions in LDL, HDL and total cholesterol [1] and body weight [9]. At present, the issue is controversially discussed in the context of the recommended increase in CLAs in health foods. Four of the eight published human studies found small but significant reductions in body fat with CLA supplementation; however, the reductions were smaller than the predicted errors for the methods used. The other four human studies found no change in body fat with CLA supplementation. These studies also reported that CLA supplementation increased the risk factors for diabetes and cardiovascular disease [10].

It was reported [11] that CLAs act as agonist of the peroxisome-proliferator-activated-receptor (PPAR) family. PPARs are known to be DNA-binding transcription factors primarily responsible for activating genes involved in lipid transport and catabolism. Other transcription factors such as liver-X-receptors (LXRs) and sterol responsive element-binding protein 1 (SREBP1) are important factors in regulating hepatic lipid metabolism by controlling de novo fatty acid synthesis [9]. Clément et al. [12] showed that in the diet the *trans*-10, *cis*-12 isomer of CLAs triggers the ectopic production of mRNAs for PPAR, adipocyte lipid-binding protein, FAS and SREBP1a in the liver. These observations suggest that CLAs play a significant role in the modulation of lipid metabolism, accounting for their anti-carcinogenic, anti-atherogenic and anti-diabetic properties.

Observations based on changes in mRNA levels are not necessarily reflected in changes in metabolic activity. Therefore, the present study was undertaken to investigate the effects of CLAs on body weight, food intake and variables of lipid and glucose metabolism with the rat as a model. We measured liver and plasma lipid concentrations and the hepatic activities of enzymes catalyzing pace-setting steps of fatty acid oxidation, fatty acid synthesis and glucose metabolism, i. e. acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), diacylglycerol acyltransferase (DGAT), tricarboxylate carrier (TCC), 3-hydroxy-acyl-CoA dehydrogenase (3-HAD), citrate synthase (CS) and phosphofructokinase (PFK). There are only a very limited number of publications dealing with the effects of enriched isomers of CLA. A mixture of partially enriched isomers in commercial products may be used as an additive to food and feed. Thus, we have employed such a commercial preparation, i. e. Clarinol G-80™.

Materials and methods

Chemicals

[1,5-^{14}C]Citrate, L-[*methyl*-^{3}H]carnitine, [1-^{14}C]palmitoyl-CoA and [1-^{14}C]acetyl-CoA, were purchased from New England Nuclear (Dreieichenhain, Germany). Other chemicals were obtained from Roche (Mannheim, Germany) or Baker (Deventer, The Netherlands). The commercial mixture of CLAs, Clarinol G-80™ (Table 2), was provided by Loders Croklaan B. V. (Wormerveer, The Netherlands).

Animals and diets

The experimental design was approved by the animal experiments committee of the Utrecht Faculty of Veterinary Medicine. Male outbred Wistar rats (HsdCpb:Wu, Harlan-CPB, Zeist, The Netherlands), aged 6 weeks, were used. They were housed three per cage in a room with a 12 h light-dark cycle (lights on, 07.00–19.00 hours). During a one week pre-experimental period, all animals were fed a pre-experimental diet. The pre-experimental diet contained 180 g animal fat/kg (stearic acid-rich fat plus olive oil) instead of the experimental fats, but was otherwise identical to the experimental diets. At the end of the pre-experimental period, the rats were divided over two groups of 12 rats each, the groups being strati-

fied for body weight, plasma triacylglycerols (TAG) and cholesterol concentrations. The groups either received the control diet with stearic acid-rich fat plus olive oil or the test diet with 30 g/kg Clarinol G-80™, a commercial mixture of CLAs containing 38.2 % *trans*-10, *cis*-12 isomer and 36.9 % *cis*-9, *trans*-11 isomer, at the expense of an identical amount of corn starch. The composition of the experimental diets is presented in Table 1. The test diet contained 1.1 % of the *trans*-10, *cis*-12 isomer of CLAs, the supposedly biologically active isomer [12]. In Table 2 is given the fatty acid composition of the CLAs-containing preparation. The animals had free access to feed and tap water. The experimental period lasted 14 d.

Collection and preparation of samples

Blood and liver samples were taken between 09.00 and 12.00 h as described previously [13]. Lipoproteins were isolated from fresh plasma by density gradient centrifugation [14]. VLDL, LDL, IDL and HDL were collected on the basis of their densities [13]. Isolated lipoprotein fractions were frozen and stored at –20 °C until analyses. Subcellular liver fractions were prepared by homogenization and differential centrifugation exactly as reported previously [15]. Isolated mitochondria were immediately used for analyses of TCC and CPT-I activity. Isolated microsomes were stored at –80 °C until analysis a few weeks later. Aliquots of the hepatic homogenate were also used to measure the levels of TAG [16] and glycogen [17]. One part of the liver sample was homogenized immediately with a loose-fitting Dounce homogenizer (five strokes) in a medium containing (mmol/L): 50 Hepes (pH 7.5), 0.25 mannitol, 4 citrate, 6.16 EDTA and 5 β-mercaptoethanol. The crude homogenate was centrifuged at 12,000 x g for 5 min and the supernatant was frozen quickly in liquid nitrogen and stored at –80 °C until analyzed for the activities of FAS and ACC.

Table 1 Composition of the diets

Components	Control diet	CLAs diet
Casein	200	200
Corn oil	20	20
Stearic acid-rich fat	120	120
Olive oil	60	60
Clarinol G-80™*	–	30
Corn starch	441	411
Molasses	50	50
Cellulose	50	50
$CaCO_3$	12	12
$MgCO_3$	2	2
$NaH_2PO_4 \cdot H_2O$	15	15
KCl	8	8
Vitamin mix**	12	12
Mineral/trace element mix**	10	10
Total	1000	1000

* Clarinol G-80™ contained 79.4 % total CLAs; the two major CLA isomers are *cis*-9, *trans*-11 (36.9 %) and *trans*-10, *cis*-12 (38.2 %)
** The composition of these two premixes has been described by Terpstra et al. [31]

Table 2 Fatty acid composition of the conjugated linoleic acid (CLAs)-containing preparation[1]

	CLAs (Clarinol G-80™)
16:0 (Palmitic acid)	4.8
18:0 (Stearic acid)	1.6
18:1n-9 (Oleic acid, *cis*-9)	11.6
18:2n-6 (Linoleic acid, *cis*-9, *cis*-12)	1.3
18:2n-6 (*trans*-9, *cis*-12)	0.8
18:2 (CLA, rumenic acid, *cis*-9, *trans*-11)	36.9
18:2 (CLA, *trans*-10, *cis*-12)	38.2
18:2 (CLA, *cis*-9, *cis*-11)	0.8
18:2 (CLA, *cis*-10, *cis*-12)	0.8
18:2 (CLA, *trans*-9, *trans*-11 and *trans*-10, *trans*-12)	1.2
18:2 (CLA, 11, 13)	1.5
18:2 (Main CLA isomers (*cis*-9, *trans*-11 + *trans*-10, *cis*-12)	75.1
Oxidized CLAs	0.2
20:0 (Arachidonic acid)	0.1
20:1n-11 (Gondoic acid)	0.1
22:0 (Behenic acid)	0.1
Other Fatty Acids	0.0
Total	100
Total CLAs	79.4
Free Fatty Acids as Oleic Acid	0.72
Saturated Fatty Acids	6.7
Peroxide Number mEquivalent O_2/Kg)	0.7

[1] Data as provided by the manufacturer (Loders Croklaan B. V., Wormerveer, The Netherlands) and expressed in % of fatty acid methyl esters

Enzyme assays

TCC activity in freshly isolated mitochondria was assayed essentially as reported [18]. Briefly, freshly isolated rat-liver mitochondria were resuspended in 100 mmol KCl/L, 20 mmol Hepes/L, 1 mmol EGTA/L, 2 µg rotenone/ml (pH 7.0), and loaded with L-malate as described previously [19]. The rate of exchange [^{14}C]citrate/malate catalyzed by the carrier was measured at 9 °C. The transport was started by addition to the mitochondrial suspension of 0.5 mmol [^{14}C]citrate/L and stopped by addition of 12.5 mmol 1.2,3-benzene tricarboxylic acid/L. The mitochondria were then re-isolated by centrifugation. The radioactivity, extracted from mitochondria after their osmotic disruption, was counted.

CPT-I activity was assayed in freshly isolated mito-

chondria as the incorporation of radiolabelled carnitine into acylcarnitine as reported [20]. CPT activity that was insensitive to 100 μmol malonyl-CoA/L was always subtracted from the CPT activity experimentally determined.

Measurement of ACC, FAS and DGAT was performed as described previously [21]. The activity of CS, 3-HAD and PFK were determined spectrophotometrically as described [22].

Chemical analyses

TAG (Triglycerides/GB), total cholesterol (CHOD-PAP method) and phospholipids (enzymatic colorimetric method) in plasma, lipoprotein fractions and liver tissue were determined with test kit combinations from Roche as specified in parentheses. Hepatic lipids were extracted with chloroform/methanol (1:2 v/v) [23].

Protein was determined by using the Lowry method [24] with bovine serum albumin as standard.

Statistical analysis

The results were computed with Excel (Microsoft®). Comparison was made using one-way analysis of variance (ANOVA). When a statistical effect was uncovered on the basis of ANOVA analysis, the data were also subjected to the Student's t test. All statistical analyses were performed using an SPSS/PC computer program (SPSS, Chicago, IL). Differences were considered statistically significant at $P < 0.05$.

Results

Food intake, body weight, liver weight and growth rates

The data reported in Table 3 indicate that no significant differences either in body weight and liver weight or in food intake and growth rates were detected among the two groups of rats.

Liver lipids and glycogen content

The CLAs-induced decrease in liver glycogen (by 11%) and increase in TAG content (by 21%) were not significant at $P < 0.05$. No significant changes in hepatic cholesterol and phospholipid content were detected between the two groups of rats (Table 4).

Plasma lipid concentrations

As shown in Table 5, at the beginning of the experiment (d 0) the mean values of plasma cholesterol and TAG were not significantly different between the two groups. At the end of the experimental period (d 14) CLAs supplementation led to a number of alterations in plasma lipids and lipoproteins (Tables 5 and 6). Animals fed the CLAs-supplemented diet exhibited a significant reduction of total plasma cholesterol (by 12%) compared to the control diet. This reduction was primarily due to a

Table 3 Food intake, body weights, relative liver weights and growth rates of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data represent the means ± SD, n = 12. Values for control and test animals are not significantly different

	Control diet	CLAs diet
Body weight (g)		
d 0	256±28	259±30
d 7	287±24	285±23
d 14	322±26	317±23
Relative liver weights (g/100 g body weight)		
d 14	4.0±0.3	4.0±0.4
Feed intake (g/d)		
d 14	28.0±4.3	27.4±4.5
Growth (g/d)		
d 14	4.7±1.2	4.1±1.1

Table 4 Hepatic contents of glycogen, triacylglycerols, cholesterol and phospholipids of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data are expressed in nmol/mg protein and represent the means ± SD, n = 12. Values for control and test animals are not significantly different

	Control diet	CLAs diet
Glycogen	990±327	880±245
Triacylglycerols	68±16	82±23
Cholesterol	29.6±3.0	32.0±4.0
Phospholipids	106±6.8	110±6.0

Table 5 Cholesterol, triacylglycerol and phospholipid concentrations in plasma of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data are expressed in mmol/L and represent the means ± SD, n = 12. Significantly different from the control diet: [a] $P < 0.001$

	Control diet	CLAs diet
Cholesterol		
d 0	2.55±0.32	2.46±0.26
d 14	2.24±0.17	1.97±0.25[a]
Triacylglycerols		
d 0	1.58±0.53	1.65±0.57
d 14	1.82±0.68	1.94±1.03
Phospholipids		
d 14	2.22±0.21	2.04±0.31

significant decrease in the LDL (by 21 %) and HDL (by 16 %) fractions (Table 6). In both groups of rats, TAG concentrations in plasma and lipoproteins did not differ significantly, but a significant decrease in LDL (by 25 %) and HDL (by 16 %) phospholipid levels was observed after CLAs administration, which was associated with a non-significant, 8 % decrease in plasma total phospholipids.

Key enzymes of hepatic metabolism

We studied the effects of a CLAs-enriched diet on the activities of key enzymes of hepatic lipid synthesis, i. e. ACC, FAS, TCC and DGAT. As shown in Table 7 no significant differences between the two groups were observed as to the specific activities of these enzymes. Interestingly, the CLAs diet induced a significant lowering (by 21 %) of the specific activity of DGAT. To determine whether the test diet had possibly influenced the TAG-synthesizing pathway secondary to the glycolytic pathway, we measured the activity of hepatic PFK. As reported in Table 7, the specific activity of this kinase did not differ between the two groups.

We also explored the effect of feeding the experimental diet on the activities of enzymes involved in fatty acid oxidation, i. e. CPT-I, 3-HAD and CS. The process of fatty acid uptake into mitochondria is controlled by the specific activity and/or the sensitivity to inhibition by malonyl-CoA of CPT-I. Thus, hepatic CPT-I specific activity as well as its sensitivity to inhibition by malonyl-CoA were determined in freshly isolated mitochondria. As reported in Table 8 neither CPT-I activity nor its sensitivity to malonyl-CoA differed between the two groups. In addition, no significant differences were detected for the specific activities of 3-HAD and CS in CLAs-treated and control rats (Table 8).

Table 6 Cholesterol, triacylglycerol and phospholipid concentrations in lipoproteins of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data are expressed in µmol/L plasma and represent the means ± SD, n = 12. Significantly different from the control diet: [a] $P < 0.05$; [b] $P < 0.02$

	Control diet	CLAs diet
Cholesterol		
VLDL	199±95	230±121
IDL	77±53	98±109
LDL	559±139	442±101[a]
HDL	1171±182	982±202[a]
Triacylglycerols		
VLDL	1380±627	1643±937
IDL	351±395	241±176
LDL	145±60	174±115
HDL	68±21	77±27
Phospholipids		
VLDL	362±193	459±330
IDL	89±83	73±59
LDL	317±82	239±59[b]
HDL	910±151	765±115[b]
Ratio Triacylglycerol:cholesterol in VLDL	7.43±2.10	7.33±1.77

Table 7 Hepatic activities of the tricarboxylate carrier (TCC), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), diacylglycerol acyltransferase (DGAT) and phosphofructokinase (PFK) of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data are expressed in nmol/min · mg protein and represent the means ± SD, n = 12. Significantly different from the control diet: [a] $P < 0.01$

	Control diet	CLAs diet
TCC	10.7±2.1	10.1±1.7
ACC	0.27±0.14	0.27±0.08
FAS	4.6±1.4	4.9±1.0
DGAT	0.57±0.10	0.45±0.09[a]
PFK	14.3±2.5	14.0±1.6

Discussion

Dietary supplementation with CLAs at the 1 % level is common practice in the literature and is reported to exhibit maximum activity and to induce numerous responses in animal models as well as in humans, including e. g. reduction of atherosclerosis [25]. In the present study, the principal effect of CLAs treatment was a lowering of the cholesterol concentrations both in total plasma and in LDL and HDL lipoproteins, without a change in its liver content. The reduction in the LDL cholesterol concentration (21 %) was slightly greater than that of HDL cholesterol (12 %). It has been demonstrated that lowering circulating cholesterol, especially LDL cholesterol, can prevent, arrest and even reverse coronary atherosclerosis [26]. Moreover, despite a reduction in plasma HDL cholesterol the ratio of HDL cholesterol to total cholesterol did not change (cf. Tables 5 and 6). The above effects would help to reduce the risk of atherosclerosis [27] and corroborate observa-

Table 8 Hepatic activities of carnitine palmitoyltransferase-I (CPT-I), citrate synthase (CS) and 3-hydroxy-acyl-CoA dehydrogenase (3-HAD) of rats fed a control diet or a diet containing conjugated linoleic acids (CLAs) for 14 d. Data are expressed in nmol/min · mg protein and represent the means ± SD, n = 12. In parentheses: percentage inhibition of CPT-I by 10 µM malonyl-CoA. Values for control and test animals are not significantly different

	Control diet	CLAs diet
CPT-I	3.04±0.40	2.85±0.34
+ 10 µM malonyl-CoA	2.06±0.41 (32.5±7.2)	1.93±0.36 (32.8±6.7)
CS	210±30	203±27
3-HAD	1487±219	1555±177

tions on atherosclerosis in rabbits [5] and hamsters [6]. Interestingly, in a study with humans receiving CLAs, reductions in LDL, HDL and total cholesterol were found [1]. Liver cholesterol synthesis is known to start from acetyl-CoA formed in mitochondria essentially from a carbohydrate source. Mitochondrial acetyl-CoA is then transported, in the form of citrate, on the TCC into the cytosol. Here it is utilized for fatty acid and cholesterol synthesis. In our experiments we did not find any difference in TCC activity between CLAs-fed and control rats. In line with this result, no statistically significant change in liver cholesterol content was found in CLAs-treated rats versus control rats.

Another finding of the present study is that the CLAs induced a change in DGAT activity. Hepatic DGAT is known to be sensitive to changes in the hepatic uptake of fatty acids, uptake and enzyme activity being directly correlated [28]. As the same amount of fatty acids was present in the diet of the control group and the CLAs-fed group, we did not anticipate a change in DGAT activity between the two groups. Much to our surprise the activity of DGAT was significantly lower in the CLAs-fed animals without a change in plasma TAG content. This could be ascribed to a specific effect of dietary CLAs on DGAT activity because in previous work [29] we did not find any difference in DGAT activity in rats fed diets containing similar amounts of oleic or elaidic acid versus stearic acid. The observed decrease in hepatic DGAT activity in the CLAs-fed group is what one would expect if body fat is reduced as was reported for the latter in hamsters [30], mice [31] and pigs [32]. In the present study, hepatic TAG was not decreased, but rather increased (Table 4).

There were no significant differences between the two groups of rats in the activities of key enzymes of fatty acid synthesis, i. e. ACC and FAS. The activity of CPT-I, key enzyme for the oxidation of fatty acids was also unchanged by the dietary treatment. Apparently, the CLAs-diet did not affect hepatic PPAR or liver X receptor as evidenced by a lack of change in the activity of characteristic enzymes like CPT-I and FAS [33] indicating that the Wistar rat species is poorly responsive to CLAs as to fatty acid synthesis and oxidation. The lack of effect of the CLAs-containing diet on the activity of CPT-I supports a similar observation in rat liver by Martin et al. [34]. In addition, we observed no change in hepatic 3-HAD and CS activities following CLAs treatment, thus further emphasizing that hepatic fatty acid oxidation in the rat is not affected by CLAs.

With the same methods and the same experimental protocol as used for the present study, we found in the livers of mice enhanced specific activities of ACC and FAS and unaltered specific activities of 3-HAD and CS [35]. Similar results were obtained in the mice model by Yakahashi et al. [36]. The changes in the activity of the fatty acid synthesizing enzymes in mice are in line with increased mRNA levels [9, 36] and the lack of effect on fatty acid oxidizing enzymes corroborates findings with no change in hepatic CPT-I activity in CLAs-fed mice [37]. It must be pointed out that CLAs may trigger different physiological actions depending on the animal species and perhaps genetic strain of a single species being investigated [2]. The variability in results between the different studies could be due to other factors as well, including apart from species and strain, gender, age, differences in diet composition, in the composition of the CLA isomer mixture used, in dietary concentrations of the different CLA isomers, in duration of feeding the CLAs-supplemented diet and in methodology for determining enzyme activities.

Feeding a mixture of CLAs isomers does not significantly affect body weight or feed intake in rats [38] or rabbits [6]. In addition, no effect is observed in rats on the amount of body fat, liver fat and liver weight [this study, 39]. There is substantial documentation for species differences with regard to CLAs-induced lipid accumulation in the liver. Rats [40] or pigs [2] fed CLAs-supplemented diets exhibited no evidence of lipid accumulation in the liver or enhanced liver weight. Mice, on the other hand, develop liver steatosis following CLAs treatment [9, 31]. In the present study we did not find any appreciable effect on body weight or hepatic lipid accumulation in CLAs-treated rats versus a control group (Table 4). These differences may explain that the results for the lipid metabolizing enzymes found in rats are not always consistent or similar to those observed in mice.

The foregoing considerations question the use of either the mouse or the rat as the animal model of choice for unmasking the mechanism(s) underlying the effects of dietary CLAs treatment. Some aspects like loss of body fat are better studied in mice; for other aspects like reduction in serum cholesterol level the rat may be the model of choice.

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