



## Long-term high fructose and saturated fat diet affects plasma fatty acid profile in rats

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Received Mar. 23, 2011; Revision accepted Aug. 29, 2011; Crosschecked Dec. 1, 2011

**Abstract:** As the consumption of fructose and saturated fatty acids (FAs) has greatly increased in western diets and is linked with an increased risk of metabolic syndrome, the aim of this study was to investigate the effects of a moderate (10 weeks) and a prolonged (30 weeks) high fructose and saturated fatty acid (HFS) diet on plasma FA composition in rats. The effects of a few weeks of HFS diet had already been described, but in this paper we tried to establish whether these effects persist or if they are modified after 10 or 30 weeks. We hypothesized that the plasma FA profile would be altered between 10 and 30 weeks of the HFS diet. Rats fed with either the HFS or a standard diet were tested after 10 weeks and again after 30 weeks. After 10 weeks of feeding, HFS-fed rats developed the metabolic syndrome, as manifested by an increase in fasting insulinemia, total cholesterol and triglyceride levels, as well as by impaired glucose tolerance. Furthermore, the plasma FA profile of the HFS group showed higher proportions of monounsaturated FAs like palmitoleic acid [16:1(*n*-7)] and oleic acid [18:1(*n*-9)], whereas the proportions of some polyunsaturated *n*-6 FAs, such as linoleic acid [18:2(*n*-6)] and arachidonic acid [20:4(*n*-6)], were lower than those in the control group. After 30 weeks of the HFS diet, we observed changes mainly in the levels of 16:1(*n*-7) (decreased) and 20:4(*n*-6) (increased). Together, our results suggest that an HFS diet could lead to an adaptive response of the plasma FA profile over time, in association with the development of the metabolic syndrome.

**Key words:** High fructose and saturated fatty acid diet, Metabolic syndrome, Plasma fatty acids, Adaptive response, Rats  
 doi:10.1631/jzus.B1100090      **Document code:** A      **CLC number:** Q547; Q956

### 1 Introduction

Over recent decades, fructose consumption has increased dramatically in industrialized countries as manufacturers have turned to using fructose instead of sucrose to sweeten processed foods and beverages. Similarly, the intake of saturated fat has risen during the same period. It has been reported that the current high dietary intake of fructose and saturated fat con-

tributes to the epidemic of the metabolic syndrome (Astrup and Finer, 2000; Malik *et al.*, 2006), which is generally considered to be an association of impaired glucose tolerance, hypertension, dyslipidemia, hyperuricemia, and central obesity (Balkau *et al.*, 2002; Chen *et al.*, 2007). Rodents fed with high-fructose and/or high-fat diets develop metabolic abnormalities such as hyperinsulinemia, insulin resistance (IR), and dyslipidemia (Basciano *et al.*, 2005; Buettner *et al.*, 2007; Abdullah *et al.*, 2009). Many studies have shown that IR is directly associated with lipid disorders like an increase in plasma fatty acid (FA) levels

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or changes of FA composition in the cell membrane. Both induce alterations in insulin action and the signaling pathway (Griffin *et al.*, 1999). The proportions of plasma and tissue FA depend on various processes, e.g., dietary intake, intestinal absorption, endogenous synthesis, metabolism, and storage (Ma *et al.*, 1995), in which different enzymes such as desaturases and elongases play a major role (Kim and Ntambi, 1999). The composition of plasma FA can be used as a risk indicator of disease (Aro, 2003), since an altered FA composition has been related to metabolic and cardiovascular disorders (Riccardi *et al.*, 2004). There is evidence that dyslipidemia in fructose and saturated fat fed rats is accompanied by an increase in saturated fatty acids (SFAs) and monounsaturated fatty acids (MUFAs) and by a decrease in polyunsaturated fatty acids (PUFAs) (Girard *et al.*, 2005). However, how the metabolic syndrome affects the lipid profile of plasma and which FA mainly contributes to its development, remain to be investigated. A comprehensive understanding of the plasma FA profile may provide more insights into metabolic syndrome progression associated with a high fructose and saturated fatty acid (HFS) diet. As far as we know, no previous study has determined the changes in plasma FA composition induced by a prolonged HFS diet (30 weeks). We hypothesized that after an HFS diet prolonged to 30 weeks, changes in plasma FA may occur concomitantly with the development of the metabolic syndrome. This fat- and fructose-rich diet largely mimics that of Western societies (Grundy, 1998). Consequently, the aim of this study was to investigate the effects of short-term (10 weeks) and long-term (30 weeks) HFS consumption on plasma biochemical parameters and FA profiles in response to IR development.

## 2 Materials and methods

### 2.1 Animal feeding design

Young male Sprague-Dawley rats (180–200 g) purchased from Janvier (Le Genest-St. Isle, France) were maintained in a temperature- and humidity-controlled environment and fed ad libitum. After one week of adaptation under feeding with a standard diet [3.32 kcal/g (1 kcal=4.187 kJ); SAFE, Augy, France], the rats were divided into two groups: a control group

fed with a standard diet for 30 weeks and an HFS group fed with an identical diet except that the total carbohydrates and lipids present in the control diet were replaced by 61.7% fructose and 12% lard, respectively (4.3 kcal/g, SAFE, Augy, France) (Table 1). The animals received the same weight of food once a day, with free access to food and tap water. All the experiments were conducted in compliance with the Centre National Recherche Scientifique guidelines for animal ethics.

**Table 1** Composition of the diets, including their fatty acid profiles

Constituent	Content*	
	Control diet	HFS diet
Protein	19	19
Methionine	0.3	0.3
Starch	62	
Sucrose	3	
Cellulose	5	
Fructose		61.7
Minerals and vitamins	7	7
Choline	0.04	0.04
Lard		12
Soybean and fish lipid sources	3.5	
Main fatty acid		
16:0	15.5	24.0
18:0	–	15.5
16:1( <i>n</i> -7)	2.3	2.6
18:1( <i>n</i> -9)	25.0	43.2
18:2( <i>n</i> -6)	48.0	11.6
18:3( <i>n</i> -3)	0.5	0.8
ΣSFA	17.0	40.0
ΣMUFA	30.0	46.5
ΣPUFA	53.0	13.5

\* The content of each constituent is expressed as g/100 g dry weight; The proportion of each fatty acid is expressed as weight percentage in total fatty acids. HFS: high fructose and saturated fatty acid; ΣSFA: total saturated fatty acids; ΣMUFA: total monounsaturated fatty acids; ΣPUFA: total polyunsaturated fatty acids

### 2.2 Reagents

Butylated hydroxytoluene (BHT) from Sigma-Aldrich was added to methanol (50 µg BHT/ml methanol) to prevent FA oxidation. The internal standard 23:0 methyl ester (Sigma-Aldrich) was dissolved in the methanol-BHT mixture at 100 µg/ml. A standard mixture of 37-component fatty acid methyl esters (FAME) purchased from Supelco was used as the external standard.

### 2.3 Sample collection and biochemical analysis

After overnight fasting, blood was collected from the tail vein of each rat and the plasma was fractionated. Plasmatic levels of total cholesterol, triglyceride (TG), and glucose were determined using an automated analyzer (DXC, Beckman) and kits from Sigma Diagnostic (France). Plasma insulin was assessed using a rat insulin immunoassay kit (Merckodia, France).

### 2.4 Glucose tolerance test

The intraperitoneal glucose tolerance test (IPGTT) was performed after 12 h of fasting. Briefly, glucose (1 g/kg body weight) was injected intraperitoneally and glucose levels were determined with an automated glucometer (Ascensia BRIO, Bayer Diagnostics, France) before injection and 30, 60, 90, 120, and 180 min after injection.

### 2.5 Determination of FA by gas chromatography

The one-step transesterification reaction was performed as described by Masood *et al.* (2005). Briefly, 1.7 ml of methanol, 100  $\mu$ l of acetyl chloride, 100  $\mu$ l of the internal standard solution (containing 10  $\mu$ g of 23:0 methyl ester), and 50  $\mu$ l of plasma were combined in screw-capped glass tubes. The samples were incubated for 60 min at 100 °C in a water bath. After cooling to room temperature, 0.75 ml of hexane was added to the samples. After vortexing, the upper organic phase was collected. This step was repeated twice. The combined organic phases were evaporated to dryness under nitrogen and the lipids were resuspended in 60  $\mu$ l of hexane prior to analysis. Analyses were performed using a Hewlett-Packard 5890 gas chromatography (GC) equipped with a fused silica capillary column (60 m $\times$ 0.25 mm i.d., 0.20  $\mu$ m film thickness; Supelco SP-2340, USA) and a flame ionization detector. Nitrogen was used as the carrier gas and the injection and detection temperatures were set to 270 and 260 °C, respectively. The initial oven temperature was set to 140 °C. After 25 min the oven temperature was increased from 140 to 240 °C at a rate of 4 °C/min and was then maintained at 240 °C for 20 min. The relative amount of each FA was expressed as a percentage of the total FAs and was determined by integrating the area under the peak and dividing the result by the sum of the areas under the peaks corresponding to all FAs present in the sample.

### 2.6 Estimation of desaturase activity

The product/substrate [18:1(*n*-9)/18:0] and [16:1(*n*-7)/16:0] ratios, the [20:3(*n*-6)/18:2(*n*-6)] ratio, and the [20:4(*n*-6)/20:3(*n*-6)] ratio were used to estimate the activities of delta-9 desaturase ( $\Delta$ 9D), delta-6 desaturase ( $\Delta$ 6D), and delta-5 desaturase ( $\Delta$ 5D), respectively (Clore *et al.*, 2000).

### 2.7 Statistical analyses

All data are expressed as mean $\pm$ standard error of the mean (SEM). Student's *t*-test was used to compare the mean values. Statistical analysis of the data was carried out using the SigmaStat 3.11 software (Systat Software Inc., USA). Differences were considered significant at  $P < 0.05$ .

## 3 Results

### 3.1 Characteristics of metabolic syndrome in HFS-fed rats

The body weight of rats fed with HFS for 30 weeks decreased by 11% relative to the control group, while no significant difference in body weight was observed after 10 weeks of HFS diet (Table 2). The fasting glucose and plasma insulin levels were significantly higher in the HFS group irrespective of the diet duration. Furthermore, the IPGTT revealed a significant increase in blood glucose levels in HFS rats vs. control rats, irrespective of the post-injection time and diet duration (Fig. 1). Plasma TG and cholesterol levels increased in HFS groups relative to the control group (Table 2), suggesting that the HFS intake contributes to dyslipidemia.

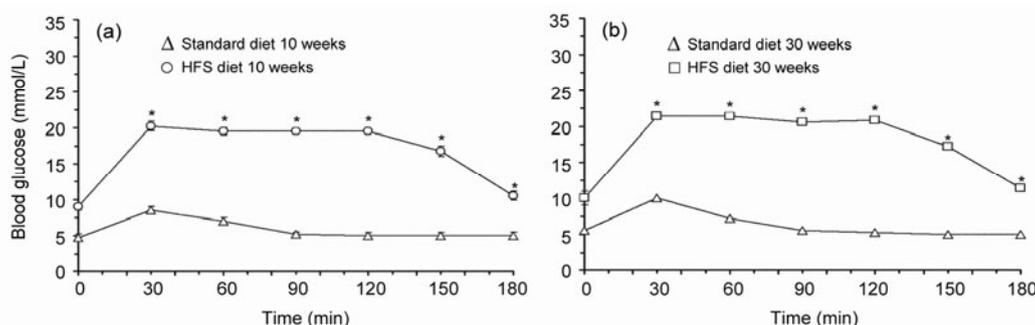
### 3.2 Modification of plasma FA distribution following a prolonged HFS diet

In all experimental groups, the major plasma FAs were palmitic acid (16:0), palmitoleic acid [16:1(*n*-7)], stearic acid (18:0), oleic acid [18:1(*n*-9)], vaccenic acid [18:1(*n*-7)], linoleic acid [18:2(*n*-6)], arachidonic acid [AA; 20:4(*n*-6)] and docosahexaenoic acid [DHA; 22:6(*n*-3)] (Table 3). Compared to the control group, significant differences were observed in the HFS group. The level of 18:1(*n*-9) was more than doubled after 10 and 30 weeks, while the level of 16:1(*n*-7), another product of  $\Delta$ 9D, doubled only after 10 weeks. Among *n*-6 PUFA, 18:2(*n*-6)

**Table 2** Body weight and blood metabolic parameters in rats fed with the standard diet or the high fructose and saturated fat (HFS) diet for 10 and 30 weeks

Diet and feeding time	Body weight (g)	Glucose (mmol/L)	Insulin (ng/L)	Triglyceride (mmol/L)	Cholesterol (mmol/L)
Standard diet 10 weeks	472±8	5.6±0.63	225±12.5	1.4±0.1	1.25±0.12
HFS diet 10 weeks	456±13	8.66±0.43 <sup>a</sup>	480±21.1 <sup>a</sup>	2.1±0.15 <sup>a</sup>	1.67±0.12 <sup>a</sup>
Standard diet 30 weeks	610±11.6	5.4±0.78	229±13.5	1.76±0.1	1.37±0.12
HFS diet 30 weeks	544±8.2 <sup>a</sup>	8.06±0.65 <sup>a</sup>	715±33.8 <sup>a</sup>	2.46±0.1 <sup>a</sup>	1.66±0.12 <sup>a</sup>

Data are expressed as mean±SEM with 8–20 rats in each group. <sup>a</sup>  $P<0.05$  vs. the standard diet

**Fig. 1** Results of the intraperitoneal glucose tolerance test (IPGTT) of rats fed with either the standard diet or the high fructose and saturated fat (HFS) diet for 10 (a) and 30 (b) weeks

Blood glucose was measured after overnight fasting ( $t=0$ ) then at 30, 60, 90, 120, 150, and 180 min following intraperitoneal glucose injection. Data are expressed as mean±SEM with 12 rats per group. \*  $P<0.05$  vs. the standard diet

**Table 3** Plasma fatty acid composition in rats fed with the standard diet or the high fructose and saturated fat (HFS) diet for 10 or 30 weeks

Plasma fatty acid composition	10 weeks		30 weeks	
	Control	HFS	Control	HFS
Plasma fatty acid <sup>a</sup>				
14:0	0.50±0.03	0.90±0.08 <sup>a</sup>	0.57±0.16	0.57±0.08
16:0	22.95±0.39	25.07±1.10	21.78±0.43	21.22±0.47 <sup>c</sup>
16:1( <i>n</i> -7)	2.75±0.38	5.82±0.56 <sup>a</sup>	3.65±0.61	2.91±0.24 <sup>c</sup>
18:0	9.51±0.24	10.96±1.15	7.53±0.37	10.85±0.61 <sup>a</sup>
18:1( <i>n</i> -9)	12.15±1.27	30.09±1.66 <sup>a</sup>	12.68±0.39	31.82±1.45 <sup>a</sup>
18:1( <i>n</i> -7)	4.25±0.42	5.03±0.11	5.11±0.48	4.25±0.15 <sup>c</sup>
18:2( <i>n</i> -6)	22.79±1.09	8.65±0.49 <sup>a</sup>	23.96±0.62	8.02±0.30 <sup>a</sup>
18:3( <i>n</i> -6)	0.17±0.06	0.24±0.09	0.23±0.13	0.04±0.02 <sup>d</sup>
18:3( <i>n</i> -3)	0.97±0.35	0.63±0.18	1.29±0.44	0.50±0.06 <sup>a</sup>
20:3( <i>n</i> -6)	0.68±0.09	0.65±0.14	0.73±0.17	0.69±0.05 <sup>b</sup>
20:4( <i>n</i> -6)	18.45±1.85	8.29±1.32 <sup>a</sup>	16.95±1.39	16.09±1.20 <sup>c</sup>
22:6( <i>n</i> -3)	2.68±0.55	0.94±0.09 <sup>a</sup>	3.16±0.36	1.43±0.18 <sup>ad</sup>
24:0	1.03±0.22	0.48±0.13	0.73±0.11	0.26±0.08
Σ <i>n</i> -6 PUFA	42.08±2.77	17.83±1.82 <sup>a</sup>	41.90±1.03	24.85±1.10 <sup>ac</sup>
ΣMUFA	19.16±1.94	40.93±2.09 <sup>a</sup>	21.44±1.29	38.98±1.51 <sup>a</sup>
Desaturase activity (product/precursor FA ratio)				
Δ9D [16:1( <i>n</i> -7)/16:0]	0.12±0.02	0.23±0.01 <sup>a</sup>	0.17±0.03	0.14±0.01 <sup>c</sup>
Δ9D [18:1( <i>n</i> -9)/18:0]	1.29±0.15	3.03±0.40 <sup>a</sup>	1.72±0.11	3.08±0.26 <sup>a</sup>
Δ5D [20:4( <i>n</i> -6)/20:3( <i>n</i> -6)]	31.80±5.82	14.06±1.73 <sup>b</sup>	26.89±6.60	24.43±2.55 <sup>c</sup>
Δ6D [20:3( <i>n</i> -6)/18:2( <i>n</i> -6)]	0.03±0.01	0.07±0.01 <sup>a</sup>	0.04±0.005	0.09±0.01 <sup>a</sup>

Data are expressed as mean±SEM with 4–6 rats per group. \* The proportion of each fatty acid is expressed as weight percentage in total fatty acids. Σ*n*-6 PUFA: total *n*-6 polyunsaturated fatty acids; ΣMUFA: total monounsaturated fatty acids; Δ: desaturase activity. Samples were measured in duplicate. Significantly different from the control group at the same time point: <sup>a</sup>  $P<0.01$ , <sup>b</sup>  $P<0.05$ ; Significantly different from 10-week HFS group: <sup>c</sup>  $P<0.01$ , <sup>d</sup>  $P<0.05$ . The main FA are tabulated

decreased by 62% and by 68% after 10 and 30 weeks of HFS diet, respectively. However, the level of its elongation and desaturation product, 20:4(*n*-6) strongly decreased only after 10 weeks. An HFS diet also caused a decrease in the level of *n*-3 PUFA, 18:3(*n*-3), only after 30 weeks and a decrease in the level of 22:6(*n*-3) after 10 and 30 weeks. The [18:1(*n*-9)/18:0] and [20:3(*n*-6)/18:2(*n*-6)] ratios, used respectively to estimate the  $\Delta$ 9D and  $\Delta$ 6D activities, increased after 10 and 30 weeks, while the  $\Delta$ 9D activity [16:1(*n*-7)/16:0] significantly increased only after 10 weeks. A decrease in  $\Delta$ 5D activity [20:4(*n*-6)/20:3(*n*-6)] was observed only after 10 weeks.

The plasma FA composition was not altered in rats fed with the standard diet for 10 and 30 weeks. In contrast, after 30 weeks of HFS diet, we observed significant changes in the plasma FA profiles, compared to 10 weeks of HFS diet. Indeed, the proportion of 16:1(*n*-7) and that of its precursor 16:0 significantly decreased (−50% and −15%, respectively) between 10 and 30 weeks of the diet, while the proportion of 18:1(*n*-9) and that of its precursor 18:0 did not change. The FA 18:1(*n*-7), resulting from an elongation of 16:1(*n*-7), decreased by 16% after 30 weeks of HFS diet compared with the level at 10 weeks. Among *n*-6 PUFA, 18:2(*n*-6) was unchanged and 20:4(*n*-6) showed a two-fold increase between 10 and 30 weeks of the HFS diet. The proportion of 18:3(*n*-6), the desaturation product of 18:2(*n*-6), after 30 weeks of HFS diet decreased by 84% compared to the level at 10 weeks. Furthermore, after 30 weeks of HFS diet, total *n*-6 PUFA increased by 40% while total MUFA was unaltered. Concerning *n*-3 PUFA, no significant changes in the proportions of 18:3(*n*-3) and 22:6(*n*-3) were observed between 10 and 30 weeks of the HFS diet. The  $\Delta$ 9D [18:1(*n*-9)/18:0] and  $\Delta$ 6D [20:3(*n*-6)/18:2(*n*-6)] activities were unchanged between 10 and 30 weeks in the HFS group. In contrast,  $\Delta$ 9D [16:1(*n*-7)/16:0] activity significantly decreased after 30 weeks of HFS diet while  $\Delta$ 5D [20:4(*n*-6)/20:3(*n*-6)] activity increased.

#### 4 Discussion

In this study, we showed that HFS consumption for 30 weeks leads to an increase in glycemia, insu-

linemia, TG, and cholesterol levels and to abnormal IPGTT. These results are in accordance with previous studies showing that fructose and SFA diets induce impaired glucose tolerance, dyslipidemia, and hyperinsulinemia (Thorburn *et al.*, 1989; Girard *et al.*, 2005; Abdullah *et al.*, 2009). The coexistence of glucose intolerance and fasting hyperinsulinemia in HFS-fed rats strongly suggests the establishment of IR throughout the study period. The consumption of HFS affects the hepatic production of FA and leads to an FA imbalance. Indeed, absorbed fructose is delivered to the liver through the portal vein and, once phosphorylated into fructose-1-phosphate, it is either converted to glycerol or metabolized in the glycolytic pathway and then induces an enhancement in the rate of de novo lipogenesis and TG synthesis (Mayes, 1993; Mittendorfer and Sidossis, 2001). More importantly, fructose bypasses the main control point in glycolysis, 6-phosphofructokinase and, unlike glucose, is not limited by feedback inhibition by citrate and adenosine triphosphate (ATP) (Basciano *et al.*, 2005). The increase in the availability of gluconeogenic substrates such as pyruvate, lactate, and glycerol and the accumulation of acetyl CoA resulting from an increase in FA oxidation have been suggested to be the major cause of fasting hyperglycemia in HFS-fed rats. This has been confirmed by the high level of fructose-1,6-bisphosphatase, a key gluconeogenic enzyme (Storlien *et al.*, 1993; Thresher *et al.*, 2000). Furthermore, an increase in circulating FA leads to IR through the inhibition of the insulin signaling system (Dresner *et al.*, 1999). The hypertriglyceridemia induced by a high-fructose and/or high-fat diet is due to an increase in the production of very low density lipoproteins (VLDLs) and/or to a decrease in TG clearance (Zammit *et al.*, 2001; Abdullah *et al.*, 2009). The increase in total cholesterol induced by both lard and high fructose intake (Bantle *et al.*, 1986; Abdullah *et al.*, 2009) results from a higher cholesterol synthesis and/or an alteration of cholesterol metabolism. Furthermore, a moderate duration (10 weeks) of HFS diet induced similar weight gains in both groups, in agreement with previous researches (Girard *et al.*, 2005; Abdullah *et al.*, 2009). In contrast, after a lengthy diet (30 weeks), the weight gain was lower in the HFS group than that in the standard group, even though the HFS diet provides additional calories. This weight difference has

previously been reported in long-term high-fructose diets (Comte *et al.*, 2004) and could be explained by a reduction in food intake in HFS rats, since no diarrhea or changes in physical activity were observed in rats of the HFS group. This observation may indicate an interaction between a high-fructose diet and the regulation of food intake, involving insulin, leptin, and ghrelin hormones (Havel, 2005). Consumption of HFS induces metabolic disorders that are not accompanied by obesity, contrary to consumption of a high energy-starch diet (Berkane *et al.*, 2007).

It is well known that the HFS diet modifies liver and plasma FA distribution (Girard *et al.*, 2005; Abdullah *et al.*, 2009). However, the effects induced on plasma FA distribution by a prolonged diet have not previously been investigated. We showed changes in plasma FA compositions after 10 and 30 weeks of the HFS diet. Indeed, the plasma FA profile in HFS-fed rats was characterized by a higher proportion of SFA and MUFA, notably  $\Delta 9$ D products [16:1(*n*-7) and 18:1(*n*-9)], as well as by a lower proportion of *n*-6 PUFA [18:2(*n*-6) and 20:4(*n*-6)]. This profile is consistent with liver and plasma FA composition studies in rats fed with high-fructose and/or saturated-fat diets (Comte *et al.*, 2004; Girard *et al.*, 2005; Abdullah *et al.*, 2009). After 30 weeks of the HFS diet, we observed significant changes in plasma MUFA and *n*-6 PUFA. Indeed, 16:1(*n*-7) levels decreased and 20:4(*n*-6) levels increased between 10 and 30 weeks of the HFS diet while 18:1(*n*-9) and 18:2(*n*-6) levels were unchanged. Our results also showed that alterations of SFA and unsaturated FA levels in HFS-fed rats affect desaturase activities, as estimated from the product/precursor FA ratios. These enzymes

introduce a double bond at the  $\Delta 9$ ,  $\Delta 6$ , or  $\Delta 5$  position of the FA carbon chain (Nakamura and Nara, 2004) and therefore catalyze with elongases the synthesis of long chain MUFA and PUFA (Fig. 2). Furthermore,  $\Delta 9$ D indexes [also known as stearoyl-CoA desaturase (SCD)], estimated from plasma or tissues, were correlated with the expression of the SCD mRNA in several studies (Attie *et al.*, 2002; Hulver *et al.*, 2005; Sjögren *et al.*, 2008). We found that after 10 weeks, an HFS diet induces an increase in  $\Delta 9$ D and  $\Delta 6$ D activities and a decrease in  $\Delta 5$ D activity. Between 10 and 30 weeks of the HFS diet,  $\Delta 9$ D [18:1(*n*-9)/18:0] and  $\Delta 6$ D activities were unchanged while  $\Delta 9$ D [16:1(*n*-7)/16:0] decreased and  $\Delta 5$ D increased. The hepatic activity of  $\Delta 9$ D, which is directly linked to the proportion of SFA substrates, mainly 16:0, is repressed by dietary PUFA intake (Ntambi, 1995). The PUFA regulation of SCD activity allows cellular unsaturated FA balance to be maintained. The main role of SCD is to increase membrane unsaturation in response to an elevation of saturated fat or carbohydrate dietary intake and to reduce the availability of 16:0 by converting it into 16:1(*n*-7). Palmitic acid (16:0) is the main component of phospholipids in membranes and it has been shown to mediate alterations of the insulin signaling pathway, causing IR through an activation of de novo ceramide synthesis (Schmitz-Peiffer *et al.*, 1999). Additionally, 16:0 induces a decrease in the proliferative capacity of rodent and human  $\beta$ -cells, and promotes  $\beta$ -cell apoptosis while 16:1(*n*-7) counteracts the toxic effects of 16:0 (Maedler *et al.*, 2001; 2003). Chronic exposure of pancreatic islets to 16:0 completely abolishes acute glucose-stimulated insulin secretion,

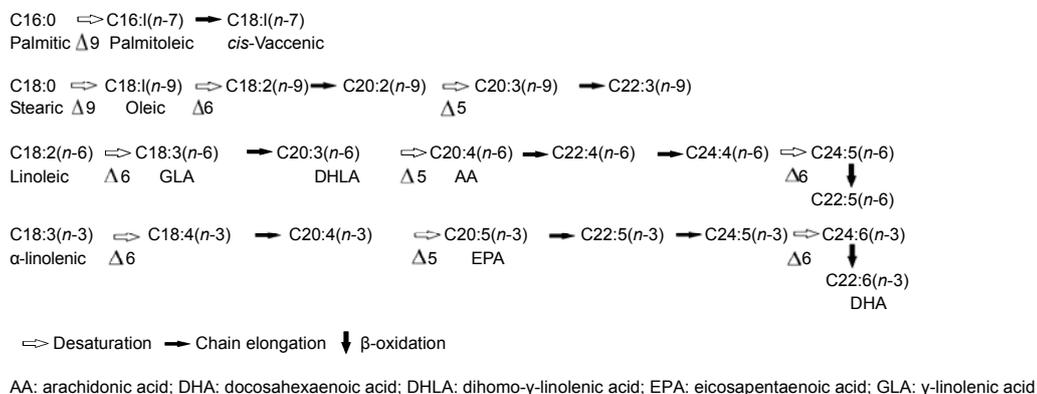


Fig. 2 Fatty acid metabolism

and addition of 16:1(*n*-7) partly restores such glucose stimulation (Maedler *et al.*, 2001; 2003). Palmitoleic acid has a protective role against both pancreatic  $\beta$ -cell cytotoxicity and the deleterious effects on glucose-stimulated insulin release induced by palmitic acid. Our results showed that the protective effects of 16:1(*n*-7) declined when the HFS diet duration increased to 30 weeks. The availability of palmitic acid could also be reduced by increasing its elongation to 18:0, which could subsequently be desaturated to 18:1(*n*-9). Our results showed that the proportion of 18:1(*n*-9) increased after 10 weeks and remained high after 30 weeks of HFS suggesting a sustained activation of  $\Delta$ 9D. The higher proportion of MUFA observed in HFS-fed rats was directly related to the increase in  $\Delta$ 9D activity. Indeed, the HFS diet promotes a higher proportion of MUFA in plasma FA profiles because of its fructose and lard content. Fructose is highly lipogenic. It has been observed in several studies that hepatic de novo FA synthesis (including the desaturation stage) is stimulated after acute fructose ingestion, with fructose providing carbon atoms for both the glycerol and the fatty-acyl parts of TGs (Clark *et al.*, 1974; Chong *et al.*, 2007; Parks *et al.*, 2008). Fructose may also increase the expression of key lipogenic enzymes in the liver. It has been shown to induce the expression of the factor of transcription sterol regulatory element binding protein 1c (SREBP-1c), the principal activator of lipogenic genes including those coding for SCD (Shimomura *et al.*, 1999; Matsuzaka *et al.*, 2004; Miyazaki *et al.*, 2004). Moreover, numerous investigations have shown an enhancement of MUFA production in fructose administration, due to an increase in hepatic SCD (Waters and Ntambi, 1994). Furthermore, dietary saturated fat strongly induces SCD expression involving the activation of the lipogenic transcription factors liver X receptor (LXR) and SREBP-1c (Sampath *et al.*, 2007). An HFS diet that contains high proportions of palmitic acid (16:0) and stearic acid (18:0) may be likely to increase SCD activity. Indeed, the increase in palmitoleic acid [16:1(*n*-7)] as MUFA, which was found to be associated with IR and related disorders, does not directly reflect the proportion of this FA in the HFS diet. The content of palmitoleic acid was very small in the HFS diet and not different from that of the control diet. Rather, it reflects increased endogenous desaturation

of palmitic acid (16:0) by SCD [leading to increased 16:1(*n*-7)], as a consequence of the HFS diet. Thus, the increased proportion of 16:1(*n*-7) in the HFS group after 10 weeks, does not reflect the dietary proportion of this FA, but is due not only to an increase in substrate availability but also to an increase in SCD, activity as indicated by the significantly increased ratio of [16:1(*n*-7)/16:0] used as a surrogate measure of this activity. Regarding oleic acid [18:1(*n*-9)], a large proportion of this FA in plasma is probably of dietary origin, given the high dietary abundance of 18:1(*n*-9) in the HFS diet. Nevertheless, other observations reveal that endogenous 18:1(*n*-9) synthesized by SCD, provides a more readily accessible FA pool than the dietary pool for the synthesis of TGs and cholesterol esters in the liver (Miyazaki *et al.*, 2001; Ntambi and Miyazaki, 2004). In addition, Attie *et al.* (2002) showed that the plasma ratio 18:1(*n*-9)/18:0 used as a desaturation index was correlated with SCD activity. Furthermore, the  $\Delta$ 9-desaturation product of 18:0, 18:1(*n*-9), was required for fructose induction of lipogenic gene expression through dependent and independent mechanisms of SREBP-1c (Miyazaki *et al.*, 2004). In the liver and in skeletal muscle, high  $\Delta$ 9D activity increases the production of malonyl-CoA which is a substrate for de novo lipogenesis and a potent inhibitor of carnitine palmitoyl-transferase I (CPT1), the rate-limiting enzyme of FA  $\beta$ -oxidation (Dobrzyn *et al.*, 2004; Hulver *et al.*, 2005). Therefore, elevated levels of SCD influence the partitioning of FA towards synthesis and storage of TGs and away from  $\beta$ -oxidation. Elevated SCD activity is found in a wide range of disorders including diabetes, atherosclerosis, obesity, and the metabolic syndrome (Ntambi *et al.*, 2002).

Among PUFA, linoleic acid [18:2(*n*-6)] and AA [20:4(*n*-6)] decreased by more than 50% after 10 weeks of HFS diet relative to the control group. Between 10 and 30 weeks of the HFS diet, 18:2(*n*-6) levels were unchanged, while 20:4(*n*-6) exhibited a two-fold increase and  $\gamma$ -linolenic acid [GLA; 18:3(*n*-6)] decreased dramatically.  $\Delta$ 6D and  $\Delta$ 5D are required for the conversion of 18:2(*n*-6) to 20:4(*n*-6) and of  $\alpha$ -linolenic acid [18:3(*n*-3)] to *n*-3 PUFA [eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)] (Fig. 2). The production of AA from linoleic acid requires the formation of two FA intermediates, GLA and dihomo- $\gamma$ -linolenic acid [DHGLA; 20:3(*n*-6)].

The first step is the  $\Delta 6$ -desaturation of linoleic acid to GLA followed by the elongation of GLA into DHLA. Finally, a  $\Delta 5$ -desaturation of DHLA leads to AA production (Fig. 2). High consumption of fructose during 30 weeks compared to 10 weeks induced an increase in  $\Delta 5D$  activity whereas  $\Delta 6D$  activity was unchanged.  $\Delta 6D$  is the rate-limiting enzyme involved in the conversion of linoleic acid to AA (Vessby, 2000). Thus, the generation rate for  $18:3(n-6)$  and its elongation to  $20:3(n-6)$  might still be regulated by  $\Delta 6D$ . Lower  $\Delta 5D$  levels could be responsible for the decrease in  $20:4(n-6)$  levels in different tissues from diabetic rats (Hu *et al.*, 1994). In diabetic patients,  $20:4(n-6)$  levels increased or decreased depending on the tissues considered (Simopoulos, 1997; Clifton and Nestel, 1998). Metabolic pools of  $20:4(n-6)$  seem to be tissue-specific.  $20:4(n-6)$  is the precursor of  $n-6$  eicosanoids, including the two-series prostaglandins which have greater biological activity than the three-series prostaglandins derived from  $n-3$  PUFA (Hu *et al.*, 1994). This  $20:4(n-6)$  metabolism pathway involves cyclooxygenase and lipoxygenase that use molecular oxygen to generate reactive oxygen species (ROS) that are implicated in IR development and in impaired insulin secretion (Evans *et al.*, 2003). Also, excessive production of  $n-6$  eicosanoids from  $20:4(n-6)$ , such as the two-series prostaglandins, may give rise to pathophysiological signaling (Rustan *et al.*, 1997). The lower proportion of  $20:4(n-6)$  that we observed after 10 weeks of the HFS diet compared to the proportion after 30 weeks seems to be due to a decline in  $\Delta 5D$  activity (Table 3) rather than to an increase in prostaglandin production. The decrease in  $18:3(n-6)$  levels between 10 and 30 weeks of the HFS diet could be explained by an increase in  $20:4(n-6)$  production correlated with an increase in  $\Delta 5D$  activity. On the other hand,  $20:4(n-6)$  is one of the most oxidation-prone FAs (Vazquez *et al.*, 1998) and it activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Shiose and Sumimoto, 2000), generating ROS. The stimulation of neutrophil NADPH oxidase by advanced glycation end-products could be mediated by an increase in  $20:4(n-6)$  production resulting from phospholipase A2 activation (Wong *et al.*, 2003). Furthermore, the lower levels of  $n-6$  PUFA and  $20:4(n-6)$  after 10 weeks of HFS diet compared to the levels after 30 weeks might prevent lipid peroxidation. However, after 30 weeks of the

HFS diet,  $20:4(n-6)$  levels increased, suggesting that this prevention declines over time. Interestingly, other studies have reported an adaptive response of blood pressure and an enzyme adaptation in lipid and carbohydrate metabolism among the long-term effects of a high-fructose diet (Vraná *et al.*, 1978; Mayes and Laker, 1986; Park and Meyer, 1992; Dai and McNeill, 1995; Takagawa *et al.*, 2001).

## 5 Conclusions

In summary, our results showed changes in the plasma FA composition in rats fed for 10 or 30 weeks with HFS, especially in  $16:1(n-7)$  (MUFA) and  $20:4(n-6)$  ( $n-6$  PUFA). These disruptions, associated with the appearance of hyperinsulinemia, could be linked to the development of IR. It remains to be determined whether these FA modifications contribute to IR or are initiated in response to IR. Nevertheless,  $16:1(n-7)$  levels observed after 10 weeks of HFS could counteract the toxicity induced by an excess of palmitic acid and  $20:4(n-6)$  could prevent lipid peroxidation. These changes in FA profile could be considered as preventive mechanisms against fuel excess, as observed in the early stages of IR, rather than as a deleterious response. After 30 weeks of HFS diet, the protective responses of  $16:1(n-7)$  and  $20:4(n-6)$  seem to decrease or disappear with the development of IR associated with the deleterious effects of glucolipototoxicity. It could be hypothesized that, after an HFS diet prolonged to 30 weeks, rats are not able to develop a sustained response that adequately compensates for IR. Further experiments are required to elucidate this phenomenon.

## Acknowledgements

The authors thank Mr. Ben S. ABDOU-RAHAMANE for technical assistance, Dr. Fabienne GUILLAUMOND for precious advice, and Dr. Corinne DELAURENT and Dr. Claude AUBERT for performing the GC analysis of plasma FA.

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