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Influence of diet on the development and regulation of lipogenic enzymes in adipose tissue

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In the rat, the suckling–weaning transition is characterized by a profound change of nutrition. During the suckling period, the pups ingest exclusively milk, which is a high-fat low-carbohydrate diet (Henning, 1981). Toward the end of the second postnatal week of the suckling period, the pups begin to nibble the solid-food diet of the adult rat, which is a high-carbohydrate low-fat diet and weaning is completed after 4 weeks (Redman & Sweeney, 1976; Henning, 1981). During the first two postnatal weeks, the plasma thyroxine and glucocorticoid concentrations rise (Henning, 1978; Walker *et al.* 1980) and food intake is not subjected to a circadian rhythm (Walker *et al.* 1974; Redman & Sweeney, 1976; Henning *et al.* 1979). The typical rhythm of food intake of adult rats begins after 4 weeks (most food consumption occurring during darkness). The nutritional changes at weaning are accompanied by an increase in plasma insulin and a decrease in plasma glucagon concentrations (Girard *et al.* 1977).

At birth, the rat is devoid of white adipose tissue and the size of fat pads remains very small during the suckling period. However, following weaning, a considerable increase in the size of white adipose tissue occurs (Hahn & Novak, 1975; Cryer, 1982; Greenwood & Hirsch, 1984). The accumulation of fat in white adipose tissue results from two processes: (1) the uptake of circulating triacylglycerol under the action of lipoprotein lipase (*EC* 3.1.1.34) and (2) the *de novo* synthesis of fatty acids from glucose (lipogenesis). It has been reported that lipoprotein lipase activity is low at birth, increases during the first ten postnatal days (during the active phase of adipocyte proliferation) and decreases to extremely low values before increasing after weaning (Cryer, 1982). However, as lipoprotein lipase is an early marker of adipocyte differentiation, the metabolic significance of these changes is not obvious. The absence of fat accumulation in white adipose tissue despite the high level of circulating triacylglycerol during the suckling period suggests that lipoprotein lipase is not in an active form. The migration of lipoprotein lipase from the adipose cells to the vascular epithelium, where this enzyme hydrolyses circulating triacylglycerol, has been shown to be controlled by insulin. The low concentration of plasma insulin during the suckling period could limit adipose tissue lipoprotein lipase activity and the marked increases of plasma insulin after weaning could play an important role in activation of lipoprotein lipase (Cryer, 1982). The rates of glucose utilization in vivo and of lipogenesis are very low in white adipose tissue during the suckling period and markedly increase after weaning onto a high-carbohydrate (HC) diet (Hahn, 1970; Tsujikawa & Kimura, 1980; Gandemer *et al.* 1982; Issad *et al.* 1988). Basal and insulin-stimulated glucose metabolism are also very low in isolated adipocytes during the suckling period but increase markedly after weaning onto a high-fat (HF) diet (Tsujikawa & Kimura, 1980; Issad *et al.* 1989). In contrast, weaning

onto an HF diet entirely prevents the increase in the rate of glucose utilization in vivo, in the rate of lipogenesis and the increase in sensitivity to insulin of white adipose tissue (Tsujikawa & Kimura, 1980; Issad *et al.* 1988, 1989). The aim of the present paper is to review the nutritional and hormonal factors involved in the regulation of lipogenic enzyme gene expression in adipose tissue during the suckling–weaning transition.

CHANGES IN LIPOGENIC ENZYME ACTIVITIES IN ADIPOSE TISSUE DURING THE SUCKLING–WEANING TRANSITION

The activities of three major lipogenic enzymes: fatty acid synthase (*EC* 2.3.1.85; FAS), acetyl-CoA carboxylase (*EC* 6.4.1.2; ACC) and ATP-citrate lyase (*EC* 4.1.3.8; ATP-CL) and of phosphoenolpyruvate carboxykinase (*EC* 4.1.1.32; PEPCK) were studied. PEPCK is an enzyme involved in glyceroneogenesis, a pathway similar to the first part of gluconeogenesis. This enzyme is involved in the generation of glycerol-3-phosphate in adipose tissue and is important for the maintenance of fatty acid esterification in situations of glucose shortage (Ballard *et al.* 1967; Reshef *et al.* 1970). In the adipose tissue of adult rats, starvation increases the activity and synthesis of PEPCK, whereas refeeding has the opposite effects (Hopgood *et al.* 1973). It was chosen as a negative marker of lipogenic enzyme gene expression.

FAS, ACC and ATP-CL activities are very low in white adipose tissue of 15-d-old suckling rats but increase twentyfold after weaning onto an HC diet (Tsujikawa & Kimura, 1980; Coupé *et al.* 1990). In contrast, the activity of PEPCK was threefold lower in HC-weaned rats than in the suckling rats (Coupé *et al.* 1990). In an attempt to determine whether the nutrition or the stage of development was involved in the changes observed, the activities of lipogenic enzyme were measured in 30–35-d-old rats weaned onto an HF diet. Weaning onto an HF diet prevents the increase of FAS, ACC, ATP-CL and the decrease of PEPCK activities observed when suckling rats are weaned onto an HC diet (Fig. 1; Tsujikawa & Kimura, 1980; Coupé *et al.* 1990). This clearly shows that the nutritional changes are important for the normal development of lipogenic capacity in adipose tissue.

CHANGES IN LIPOGENIC ENZYME mRNA CONCENTRATIONS IN ADIPOSE TISSUE DURING THE SUCKLING–WEANING TRANSITION

There is very little information available concerning the precise time-course of changes of lipogenic enzyme activities in adipose tissue, their dietary and hormonal regulations or the molecular mechanisms involved (transcriptional or post-transcriptional regulation). The recent availability of specific cDNA probes for FAS (Nepokroeff *et al.* 1984; Yan *et al.* 1985), ATP-CL (Elshourbagy *et al.* 1990), ACC (Bai *et al.* 1986) and PEPCK (Yoo-Warren *et al.* 1981) has prompted us to study the role of hormones and of nutrients in the changes of the expression of these genes in adipose tissue at weaning in the rat. In adult rats, changes in the activities of these enzymes are related to variations in their rate of synthesis (Nakanishi & Numa, 1970; Volpe & Marasa, 1975). Thus, the increased enzyme activities at weaning are probably linked to an increased protein mass.

In an attempt to investigate early events involved in the synthesis of these enzymes, we have measured the concentrations of their specific mRNA. In suckling and HC-weaned

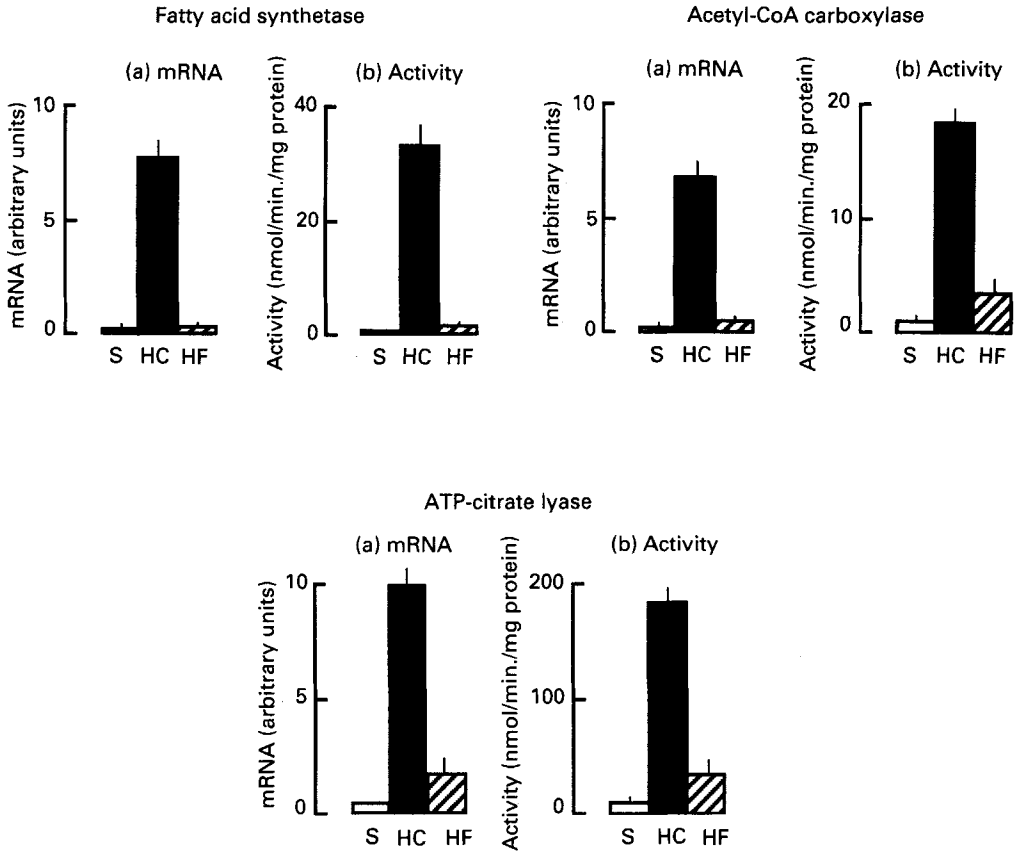

Fig. 1. Fatty acid synthase (*EC* 2.3.1.85), acetyl-CoA carboxylase (*EC* 6.4.1.2) and ATP-citrate lyase (*EC* 4.1.3.8) mRNA and activities after weaning onto a high-carbohydrate (HC) or a high-fat (HF) diet. The suckling rats (S) were 15-d old and the weaned rats were 30 or 35-d old and had been weaned onto an HC or HF diet at 21 or 25 d. Values are the means with their standard errors, represented by vertical bars, of four to seven determinations. Redrawn from Coupé *et al.* (1990) and Tsujikawa & Kimura (1980).

rats, the mRNA concentrations vary in parallel with the changes of enzyme activities (Coupé *et al.* 1990). FAS and ACC mRNA are barely detectable in the adipose tissue of suckling rats, but are markedly increased after weaning onto HC, whereas PEPCK mRNA presents a totally inverse variation (Coupé *et al.* 1990). Similar findings have been obtained for ATP-CL mRNA (D. Perdereau and J. Girard, unpublished results). The FAS, ACC and ATP-CL relative mRNA concentrations are respectively six- to seventeenfold higher in HC-weaned rats than in suckling rats. Conversely, PEPCK mRNA concentration is sixteenfold lower after weaning onto the HC diet. Weaning onto an HF diet prevented the changes of FAS, ACC, ATP-CL and PEPCK mRNA concentrations observed when suckling rats were weaned onto an HC diet (Coupé *et al.* 1990).

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TIME-COURSE OF CHANGES IN mRNA CONCENTRATIONS DURING THE SUCKLING–WEANING TRANSITION

In order to determine the kinetics of the increase of FAS, ACC and ATP-CL mRNA, and the disappearance of PEPCK mRNA that occur at weaning onto the HC diet, suckling rats were artificially weaned. To avoid any starvation period that occurs during a premature (15 d) artificial weaning, the suckling rats were kept with their mother until 21 d of age, and then abruptly weaned onto an HC diet. Since suckling rats begin to nibble the mother's food from 15 d of age, the mothers were fed on an HF diet, having verified that nibbling a solid carbohydrate-free diet by the pups did not modify the studied variables. The FAS, ACC, ATP-CL and PEPCK mRNA concentrations do not increase between 15 and 21 d. FAS, ACC, ATP-CL mRNA concentrations on one hand, and PEPCK mRNA concentration on the other hand, show totally opposite time-course (Coupé *et al.* 1990; D. Perdereau and J. Girard, unpublished results). FAS, ACC and ATP-CL mRNA concentrations are barely detectable before weaning and reach 68, 21 and 94% of the maximal value respectively in the first 24 h. Corresponding values are 90, 81 and 100% after 48 h and are maximal 96 h after the weaning for all enzymes. In contrast, PEPCK mRNA concentration falls to its lowest value in the first 24 h and remains very low thereafter (Coupé *et al.* 1990). Weaning onto an HC diet results in a threefold increase in plasma insulin concentration after 24 h and the plasma insulin concentration remains elevated until the rat is 25 d old. Enzyme activities follow a similar pattern to that of mRNA but with a lag period of about 24 h, suggesting that transcriptional regulation plays an important role in activity levels.

CARBOHYDRATE FEEDING IN 21-D-OLD SUCKLING RATS

To further assess the role of carbohydrates in the large variations in FAS, ACC, ATP-CL and PEPCK mRNA concentrations occurring at weaning onto an HC diet, 21-d-old suckling rats were force-fed with a mixture of sucrose and starch (Coupé *et al.* 1990). Blood glucose and plasma insulin concentrations rapidly increase in carbohydrate-fed rats to reach maximal values after 1 h and remain elevated during the following 5 h. At 4–6 h after carbohydrate feeding FAS and ACC mRNA concentrations increase by respectively six- to eighteenfold and PEPCK mRNA concentration falls to 20% of the suckling values. FAS, ACC and PEPCK mRNA do not change significantly when 21-d-old suckling rats are force-fed with the lipid portion of the HF diet.

These findings suggest that a direct relationship exists between plasma insulin, blood glucose and the rise in lipogenic enzyme mRNA concentrations. This is in keeping with a recent study showing that the low concentration of ACC mRNA in the adipose tissue of streptozotocin-diabetic rats, is restored to normal levels 6 h after insulin injection (Pape *et al.* 1988). Thyroid hormones have been shown to stimulate the expression of lipogenic enzyme mRNA (Goodridge, 1987; Katsurada *et al.* 1990*a*,*b*). In the present study, it is unlikely that thyroid hormones played a role in the changes of FAS and ACC mRNA concentrations. Indeed, plasma triiodothyronine concentration was not increased in rats weaned onto HC or HF diets compared with 15-d-old suckling rats (Coupé *et al.* 1990). However, it must be pointed out that the plasma concentrations of thyroid hormones had reached the adult level just before weaning (Walker *et al.* 1980; Henning, 1981) and, thus, could play a permissive role in the induction of lipogenic enzymes in response to carbohydrate and insulin.

CHANGES IN LIPOGENIC ENZYME mRNA CONCENTRATIONS IN ADIPOSE TISSUE AFTER WEANING ONTO A BALANCED DIET CONTAINING LONG-CHAIN (LCT) OR MEDIUM-CHAIN TRIACYLGLYCEROLS (MCT)

A number of studies have suggested that diets rich in fat, and particularly diets rich in polyunsaturated fatty acids, decrease the lipogenic capacity of adipose tissue of adult rat (Romsos & Leveille, 1974; Clarke *et al.* 1977; Toussant *et al.* 1981). More recently, it has been shown that diets rich in polyunsaturated fatty acids decrease FAS and ACC mRNA abundance in liver and adipose tissue of adult rats (Clarke *et al.* 1990; Katsurada *et al.* 1990*a*,*b*; Shillabeer *et al.* 1990). Diets containing MCT have been found to have divergent effects on the lipogenic capacity and lipogenic enzyme activities of adipose tissue and liver of adult rats, depending on the amount of MCT in the diet. MCT-rich diets (60% of the energy) have been reported to decrease (Lavau & Hashim, 1978) or to increase (Takase & Hosoya, 1986) the activity of lipogenic enzymes. Diets containing moderate amounts of MCT (30% of the energy) did not affect the activity of lipogenic enzymes (Chanez *et al.* 1991). In order to investigate the effect of the nature of fatty acids in the diet on the changes of FAS and ACC activities and mRNA concentrations occurring at weaning, suckling rats were abruptly weaned at 21 d onto a carbohydrate-rich diet (50% of total energy) containing either LCT or MCT (30% of energy). Suckling rats weaned onto an HC diet were used as controls, since it was previously shown that it induces a maximal increase of FAS and ACC mRNA concentrations and activities (Coupé *et al.* 1990).

Weaning onto the MCT diet does not prevent the increase in FAS and ACC mRNA and activities that occur normally in adipose tissue after weaning onto an HC diet (Foufelle *et al.* 1992*b*, Fig. 2). However, the mRNA accumulation was slightly delayed when compared with that observed in HC-weaned rats. In contrast, the accumulation of FAS and ACC mRNA was less in rats weaned onto the LCT diet when compared with the rats weaned onto the MCT diet. FAS and ACC activities followed a pattern similar to that described for mRNA but the changes were less marked suggesting a post-transcriptional control of enzyme concentration in addition to a translational regulation. Since the carbohydrate content is similar in MCT and LCT diets, it is likely that the lower lipogenic enzyme mRNA and activities after weaning onto the LCT diet were specific for the long-chain fatty acids and not a consequence of a lower carbohydrate consumption. The inability of MCT to inhibit lipogenic enzyme gene expression in adipose tissue after weaning could be simply due to their particular metabolic fate. Medium-chain fatty acids arising from intestinal triacylglycerol hydrolysis are not re-esterified in the intestine and enter the plasma compartment through the portal vein. They are extensively removed from the portal blood by the liver and, thus, adipose tissue is never exposed to high concentrations of medium-chain fatty acids. Another possible explanation of the different effects of MCT and LCT on lipogenic enzyme gene expression relates to the concentration of plasma insulin. Insulin is probably involved in the increased lipogenic enzyme gene expression in adult and weaned rats (Pape *et al.* 1988; Paulauskis & Sul, 1989; Coupé *et al.* 1990; Perdereau *et al.* 1990). In the present study, plasma insulin concentrations were significantly lower in LCT-weaned rats (30 μU/ml) than in MCT-weaned rats (60 μU/ml). This is due to the fact that MCT consumption induces much higher plasma ketone body concentrations than LCT (Yeh & Zee, 1976) and that high plasma levels of ketone bodies stimulate insulin release in the rat (Hawkins *et al.* 1971). Thus, the lower plasma insulin observed in the LCT-weaned rats could be one of

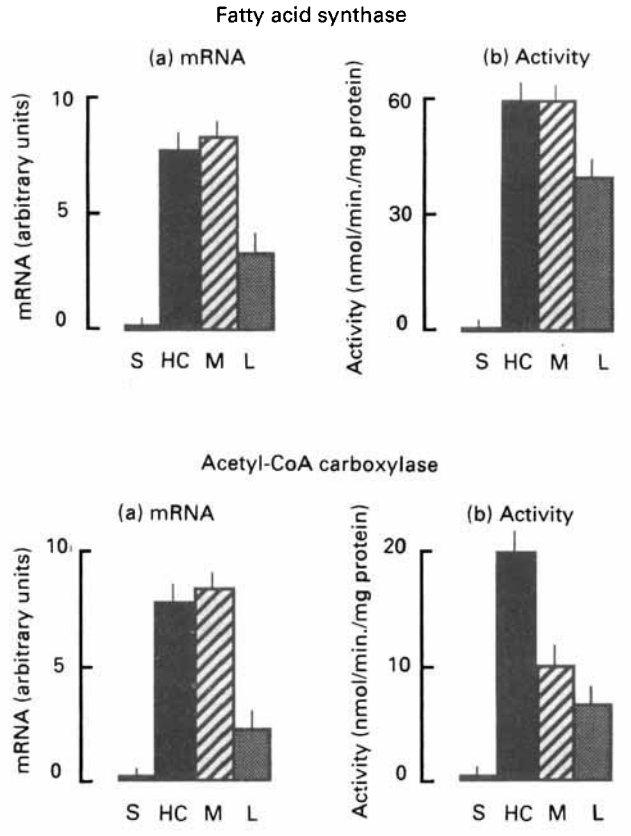

Fig. 2. Fatty acid synthase (*EC* 2.3.1.85) and acetyl-CoA carboxylase (*EC* 6.4.1.2) mRNA and activities after weaning onto a high-carbohydrate (HC) or balanced diets containing medium-chain (M) or long-chain (L) triacylglycerols. The suckling rats (S) were 15-d old and the weaned rats were 30-d old and had been weaned onto an HC or balanced diets containing M or L triacylglycerols at 21 d. Values are the means with their standard errors, represented by vertical bars, for four to seven determinations. Redrawn from Foufelle *et al.* (1992*a*).

the factors contributing to the inhibitory effect of LCT on lipogenic enzyme expression after weaning in comparison with MCT.

CHANGES IN LIPOGENIC ENZYME MRNA CONCENTRATIONS IN CULTURED ADIPOSE TISSUE EXPLANTS FROM SUCKLING RATS

Explants from adipose tissue of 19-d-old suckling rats were cultured 6–24 h in a serum-free minimal essential medium (Foufelle *et al.* 1992*a*). A large accumulation of FAS and ACC mRNA was observed in explants of adipose tissue cultured in the presence of insulin (10^{-7} M) and glucose (5 mM). Insulin did not induce FAS and ACC mRNA accumulation when the culture medium was deprived of glucose, but the effects of insulin on FAS and ACC mRNA levels were markedly potentiated when the glucose concentration in the medium was increased to 10 and 20 mM (Foufelle *et al.* 1992*a*). The

effects of glucose and insulin on FAS and ACC mRNA levels were antagonized by dexamethazone, glucagon and isoproterenol and were potentiated by thyroid hormones. Thus, insulin and glucose are the main factors involved in the initial induction of FAS and ACC mRNA in white adipose tissue.

CONCLUSION

The series of experiments carried out both in vivo and in vitro strongly support the view that the marked increase in lipogenic enzyme mRNA concentrations and activities that occur in white adipose tissue after weaning onto an HC-diet is dependent on an increase in plasma insulin concentration. An increased glucose metabolism in white adipose tissue is necessary to the expression of insulin effects on FAS and ACC mRNA accumulation since insulin is ineffective in vitro in the absence of glucose. It has been suggested recently that glucose-6-phosphate could play an important role in the effect of insulin on lipogenic enzyme gene expression in white adipose tissue (Foufelle *et al.* 1992*a*). Other hormones and substrates could also play a role in the surge of lipogenesis after weaning. The fall in plasma glucagon after weaning onto an HC diet could reinforce the insulin-induced accumulation of FAS and ACC mRNA since this hormone inhibits lipogenic enzyme expression in white adipose tissue. The decrease in the dietary supply of fat and the fall in plasma free fatty acids after weaning onto an HC diet could also potentiate the accumulation of FAS and ACC mRNA since long-chain fatty acids and particularly polyunsaturated fatty acids are potent inhibitors of lipogenic enzyme gene expression.

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