# Selectivity of fatty acids on lipid metabolism and gene expression

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Triacylglycerols represent the main form of storage for a wide spectrum of fatty acids. Their utilization first involves mobilization from adipose tissue through lipolysis. The release of individual fatty acids from adipose tissue is selective *in vitro* and *in vivo* in animal studies and also in human subjects. Generally, fatty acids are more readily mobilized from fat cells when they are short-chain and unsaturated. This selectivity could affect the storage of individual fatty acids in adipose tissue, and their subsequent supply to tissues. The nature of the dietary fats could affect lipid homeostasis and body fat deposition. Dietary fish oil influences adipose tissue development in a site-specific manner as a function of diet and feeding period. A diet high in *n*-3 polyunsaturated fatty acids (PUFA) results in a preferential partitioning of ingested energy towards oxidation at the expense of storage. Fatty acids are important mediators of gene expression in the liver. Indeed, genes encoding both glycolytic and lipogenic enzymes and key metabolic enzymes involved in fatty acid oxidation are regulated by dietary PUFA. White adipose tissue could also be a target for PUFA control of gene expression. The treatment of pre-adipose cells by fatty acids induces the expression of numerous genes that encode proteins involved in fatty acid metabolism. The mechanisms of PUFA-mediated repression of gene expression in adipocytes seem to be different, at least partly, from those described in liver. Tissue-specific and site-specific factors are possibly involved in the specific effect of PUFA on gene expression, although other mechanisms cannot be excluded.

## Résumé

Les acides gras sont stockés sous forme de triacylglycérols dans les adipocytes. La première étape dans l'utilisation des acides gras de réserve est leur mobilisation à travers la lipolyse. La mobilisation des acides gras adipocytaires est sélective et dépend de leur structure moléculaire. Pour un nombre donné de doubles liaisons, la mobilisation d'un acide gras diminue quand sa longueur de chaîne augmente. A longueur de chaîne donnée, la mobilisation d'un acide gras augmente avec le nombre de doubles liaisons. Cette sélectivité démontrée *in vitro* chez l'animal et chez l'homme est également opérante *in vivo* dans des conditions de déplétion des réserves adipeuses ou après stimulation de la lipolyse. La sélectivité de la mobilisation des acides gras adipocytaires est une propriété intrinsèque que leur confère leur structure moléculaire et représente une propriété métabolique générale du tissu adipeux. Il a été montré que cette sélectivité est en accord avec une partition différentielle des triacylglycérols entre une phase apolaire lipidique (substrat) et une phase polaire aqueuse (cytosol contenant les lipases), basée sur les propriétés physico-chimiques que leur confère la structure moléculaire des acides gras. Le stockage d'un acide gras résulte notamment d'un équilibre entre son incorporation et sa mobilisation. Les acides gras polyinsaturés (AGPI) *n*-3 sont sélectivement stockés dans le tissu adipeux et il est décrit une relation inverse entre leur facilité de mobilisation et leur incorporation *in vivo*. Les AGPI d'une façon générale et les AGPI *n*-3 d'origine marine en particulier influencent le développement du tissu adipeux en limitant son hypertrophie. Ces résultats sont retrouvés dans de nombreux modèles animaux normopondéraux et génétiquement obèses. Cet effet semble dépendant de la teneur du régime en AGPI *n*-3. Il est sélectif en fonction de la localisation anatomique des dépôts adipeux et de la durée du traitement nutritionnel. Les effets des AGPI *n*-3 sont dus en partie à des modifications de l'activité lipolytique adipocytaire, de l'oxydation des acides gras et de la lipogénèse hépatiques, et de la thermogenèse induite par l'alimentation. D'une

**Abbreviations:** ACC, acetyl-CoA carboxylase; aP2, adipocyte lipid-binding protein; BAT, brown adipose tissue; DHA, docosahexaenoic acid; EPA. eicosapentaenoic acid; FAS, fatty acid synthase; FFA, free fatty acids; PPAR, peroxisome proliferator-activated receptors; PUFA polyunsaturated fatty acids; SCD1, stearoyl-CoA desaturase 1; TAG, triacylglycerols; UCP, uncoupling protein.

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https://doi.org/10.1017/S002966519900083X Published online by Cambridge University Press

façon générale, l'ingestion de ce type d'acides gras favorise l'oxydation des lipides au détriment de leur stockage dans le tissu adipeux. Les effets biologiques des AGPI s'exercent en partie à travers la modulation de l'expression de gènes codant pour des protéines impliquées dans le métabolisme lipidique et glucidique hépatique et adipocytaire. Leur effet sur l'expression génique peut être soit positif, soit négatif. Au niveau hépatique, les acides gras à longue chaîne et surtout les AGPI *n*-3 peuvent induire la transcription de gènes codant pour différentes enzymes impliquées dans l'oxydation des lipides. Inversement, les AGPI sont également susceptibles de réprimer l'expression de certains gènes impliqués dans la lipogenèse. L'effet inhibiteur est fonction du degré d'insaturation de l'acide gras. Au niveau adipocytaire, la sélectivité de l'effet des acides gras sur l'expression génique est moins nette. Dans le tissu adipeux *in vivo*, les AGPI *n*-3 répriment l'expression de nombeux gènes codant pour des protéines impliquées dans le métabolisme adipocytaire mais aussi codant pour des facteurs de transcription. Cet effet est corrélé positivement à la taille des adipocytes ce qui suggère un effet antiadipogénique des AGPI *n*-3. Les mécanismes moléculaires responsables de l'effet des acides gras pourraient faire intervenir des récepteurs nucléaires qui se fixeraient sur des séquences de reconnaissance dans la région promotrice des gènes concernés et affecteraient leur niveau de transcription. Les AGPI sont également susceptibles d'affecter la stabilité de certains transcripts. Les effets géniques des AGPI pourraient aussi être médiés par les eicoanoïdes.

**Polyunsaturated fatty acids: Dietary obesity: Gene regulation**

## Selectivity of individual fatty acid storage and mobilization

Triacylglycerols (TAG) represent the main form of storage for fatty acids; their utilization first involves mobilization from adipose tissue through lipolysis (Coppack *et al*. 1994). While many studies have dealt with the lipolytic process for fatty acids as a whole, little is known about the release of individual fatty acids. The idea of a selective release of free fatty acids (FFA) from adipose tissue has already been proposed, but no strong evidence has yet been reported to support the hypothesis. All previous *in vitro* and *in vivo* studies support the idea of either a selective metabolism (Hollenberg & Angel, 1963; Hunter *et al*. 1970) or, on the contrary, a random process (Stein & Stein, 1962; Spitzer *et al*. 1966; Hudgins & Hirsch, 1991). It should be noted that all the studies conducted to date were based only on the comparison of four to eight fatty acids with chain length and unsaturation ranging from $C_{14}$ to $C_{18}$ and from zero to three double bonds respectively, which might account for the fact that rather inconsistent conclusions have been drawn from the results. However, adipose tissue TAG contain a wide spectrum of fatty acids, ranging in chain length from $C_{12}$ to $C_{24}$ with from zero to six double bonds, which depend mainly on the fatty acid composition of the diet (Field & Clandinin, 1984; Body, 1988). No study has considered in detail the release of long-chain saturated, monounsaturated and polyunsaturated fatty acids (PUFA). This omission represents a major gap in our knowledge, because adipose tissue is the reservoir of fatty acids used as energy substrates, notably during energy depletion, and also as components of cell membranes (Murphy, 1990; Clandinin *et al*. 1991) from which some of them may be used as precursors of eicosanoids (Bruckner, 1992; Lands, 1992). Thus, whether fatty acids are randomly or selectively released during lipolysis, and how the molecular structure of fatty acids affects their mobilization rates from fat cells, has been a subject of debate.

The release of up to fifty-two different individual fatty acids was recently studied by comparing the fatty acid composition of FFA with that of fat cell TAG from which they originated through lipolysis (Raclot & Groscolas, 1993). For most of the fatty acids, the relative proportion by weight in FFA was significantly different from that in the TAG. Compared with TAG, released FFA were enriched in some PUFA and depleted in long-chain saturated and monounsaturated fatty acids. The mobilization of the most-readily-mobilized fatty acid (18:5*n*-3) was 15-fold higher than that of the least (24:1*n*-9). Among major fatty acids, the mobilization of eicosapentaenoic acid (20:5*n*-3; EPA) was five times higher than that of 20:1*n*-9. For a given number of double bonds, the mobilization decreases with increasing chain length, whereas for a given chain length, it increases with increasing unsaturation. Thus, fatty acids are not mobilized in direct proportion to their content in adipose tissue TAG, but selectively according to molecular structure. Generally, fatty acids are more readily mobilized from fat cells when they are short-chain and unsaturated, and when their double bonds are closer to the methyl end of the chain. In addition to this previous work, more recent studies have sought to determine whether the mobilization of fatty acids is a general metabolic property of adipose tissue, the nature of the underlying mechanisms, and the physiological relevance and implications for health.

### *Selective mobilization and incorporation of fatty acids: a general metabolic feature of adipose tissue*

The question as to whether individual fatty acids are released *in vivo* according to the same selective pattern that might be expected from studies of adipocytes *in vitro* needed close examination. Compared with fed rats, the fatty acid composition of adipose tissue TAG was clearly affected during fasting, indicating a selective *in vivo* mobilization of fatty acids (Raclot & Groscolas, 1995). The

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relationships between the molecular structure of fatty acids and their mobilization demonstrated *in vitro* are valid *in vivo*. The influence of the molecular structure of fatty acids on their relative mobilization has been confirmed in rabbits in which lipolysis was stimulated *in vivo* by comparing the composition of plasma FFA with that of adipose tissue TAG (Connor *et al*. 1996). Similar results have also been obtained recently *in vivo* with interscapular brown adipose tissue (BAT), despite an unexpected selective retention of linoleate (18:2*n*-6) in TAG during fasting (Groscolas & Herzberg, 1997).

Adipose tissue from animals fed on a laboratory-chow diet or semi-synthetic high-fat diets containing fish oils differing in their fatty acid composition was used throughout most of these experiments. It might be that the dietary treatment could be responsible for confounding effects due to the recent enrichment of adipose tissue in specific fatty acids. Then, it could be proposed that the preferential mobilization of the most-highly-unsaturated fatty acids is related to their high proportion in dietary fat according to the 'last in – first out' hypothesis (Ekstedt & Olivecrona, 1970). However, this situation was not observed, and the mobilization rate of individual fatty acids depended on molecular structure according to the same relationship as those described previously, whatever the dietary treatment and, consequently, whatever the fatty acid composition of adipose tissue (Raclot & Groscolas, 1993; Raclot *et al*. 1995*b*). Thus, the selectivity of fatty acid mobilization is an intrinsic property which originates from molecular structure and represents a general metabolic feature of adipose tissue (Table 1).

Until now, it was still believed that the mobilization of fatty acids in human subjects was proportional to their content in adipose tissue (Hudgins & Hirsch, 1991). However, it has been shown recently that the systemic plasma pattern of FFA is not strictly related to their content in adipose tissue TAG (Halliwell *et al*. 1996). Thus, the question of whether some fatty acids are preferentially mobilized from human adipose tissue as shown in animal studies, where a consistent picture has emerged that the fatty acid mobilization rate depends on molecular structure, needed close examination. The composition of FFA released by isolated fat cells from human subjects in their normal dietary state was compared with that of the TAG from which they originated through lipolysis (Raclot *et al*. 1997*b*). In human adipose tissue, the relative mobilization differed among the thirty-four well-identified fatty acids. FFA were high in some PUFA and low in long-chain saturated and monounsaturated fatty acids. The relationships between molecular structures of fatty acids and mobilization rates demonstrated in animal studies were found to be valid also in human subjects.

These findings could have implications for the storage of fatty acids in adipose tissue, and for their subsequent supply to tissues. The control of PUFA storage in adipose tissue is still poorly understood. The fatty acid composition of adipose tissue TAG largely reflects that of the diet, but does not exactly follow it (Body, 1988), so that the proportion of PUFA in adipose tissue is lower than that of the diet (Field & Clandinin, 1984). Whether the relative incorporation of certain fatty acids is selective *in vivo* and how their selective mobilization from adipose tissue can affect their storage are also considered here (Table 1). The preferential release of some highly-unsaturated fatty acids can partly explain their low proportion in adipose tissue TAG compared with the diet (Lin & Connor, 1990). In a recent study, the net *in vivo* incorporation of fatty acids into adipose tissue TAG and their net *in vitro* mobilization were determined concurrently (Raclot & Groscolas, 1994). *n*-3 PUFA are selectively stored in and released from adipose tissue with opposing facility, providing evidence that the higher mobilization of some fatty acids partly explains their lower storage. The selectively-retained very-long-chain monounsaturated and saturated fatty acids might have been expected to be highly represented in adipose tissue compared with the diet, but this situation was not observed (Lin & Connor, 1990; Raclot *et al*. 1995*b*). Thus, the natural composition of adipose tissue TAG does not necessarily reflect the different rates of fatty acid mobilization from adipose tissue. Indeed, fatty acid availability as well as enzyme selectivity and/or rate of mobilization and re-uptake probably affect the composition of adipose tissue. Differential rates of oxidation of saturated and unsaturated fatty acids (Hovik & Osmundsen, 1987) can contribute to the explanation of their selective storage in adipose tissue (Leyton *et al*. 1987).

**Table 1.** Selectivity of fatty acid incorporation into and mobilization from adipose tissue triacylglycerols

| Selectivity of fatty acid | Species | Site | Experimental conditions | Reference |
|---|---|---|---|---|
| Mobilization | Rat | Retroperitoneal | *In vitro* (adipocytes) | Raclot & Groscolas (1993) |
| | Rat | Retroperitoneal or inguinal | *In vitro* (adipose fragments) | Raclot & Groscolas (1994) |
| | Rat | Retroperitoneal or epididymal Mesenteric or inguinal | *In vitro* (adipocytes) | Raclot *et al.* (1995*b*) |
| | Rat | Retroperitoneal | *In vivo* and *in vitro* (adipocytes) | Raclot & Groscolas (1995) |
| | Rabbit | Mesenteric or inguinal | *In vivo* | Connor *et al.* (1996) |
| | Man | Subcutaneous | *In vivo* | Halliwell *et al.* (1996) |
| | Man | Subcutaneous | *In vitro* (adipocytes) | Raclot *et al.* (1997*b*) |
| | Rat | Brown adipose tissue | *In vivo* | Groscolas & Herzberg (1997) |
| Incorporation | Rabbit | Intraabdominal | *In vivo* | Lin & Connor (1990) |
| | Rabbit | Intraabdominal | *In vivo* | Lin *et al.* (1993) |
| | Rat | Abdominal or epididymal | *In vivo* | Sheppard & Herzberg (1992) |
| | Rat | Retroperitoneal or inguinal | *In vivo* | Raclot & Groscolas (1994) |
| | Man | Subcutaneous | *In vivo* | Leaf *et al.* (1995) |

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*Mechanism of selective fatty acid mobilization from white fat cells*

Among the mechanisms that might explain the selective mobilization of fatty acids, the differential hydrolysis of adipose tissue TAG can be considered. Hormone-sensitive lipase, which catalyses the rate-limiting step during lipolysis, has been reported to hydrolyse preferentially the outer positions (*sn*-1 and *sn*-3) of the TAG backbone (Belfrage *et al*. 1984). Highly-mobilizable fatty acids as well as weakly-mobilizable fatty acids were found mainly in the outer positions of adipose tissue TAG (Raclot *et al*. 1995*a*). Thus, the selective mobilization of fat cell fatty acids seems unrelated to the positional distribution in TAG. Lipolysis is also widely described to work at the lipid–water interface; i.e. for conditions where only small amounts of substrate are directly available to the enzyme (Brockerhoff & Jensen, 1974; Brockman, 1984). Thus, selective mobilization of fatty acids might be the result of a preferential location and resulting increased accessibility to hormone-sensitive lipase of certain TAG according to physicochemical properties (e.g. polarity). Using liquid–liquid partition chromatography, it has been shown that the fatty acid composition of the most-polar adipose tissue TAG and their fatty acid enrichment is consistent with their mobilization rate (Raclot, 1997). The selectivity of fatty acid mobilization from fat cells could originate from a heterogeneous distribution of TAG according to polarity that would lead to a selective accessibility of substrate (Fig. 1). This process does not exclude other putative selective steps. Indeed, adipocyte lipases (mainly hormone-sensitive lipase) are capable of exhibiting hydrolytic selectivities for substrates that might explain the pattern of fatty acid release (Gavino & Gavino, 1992). A differential binding of fatty acids to binding proteins during transport can also be considered. Further studies are needed to demonstrate clearly the mechanisms by which the molecular structure of fatty acids affects their metabolic fate. To date, there is no clear evidence that this selectivity is oriented towards a special demand by tissues, so that for all fatty acids their relative mobilization from adipose tissue is that which could be expected from their molecular structure.

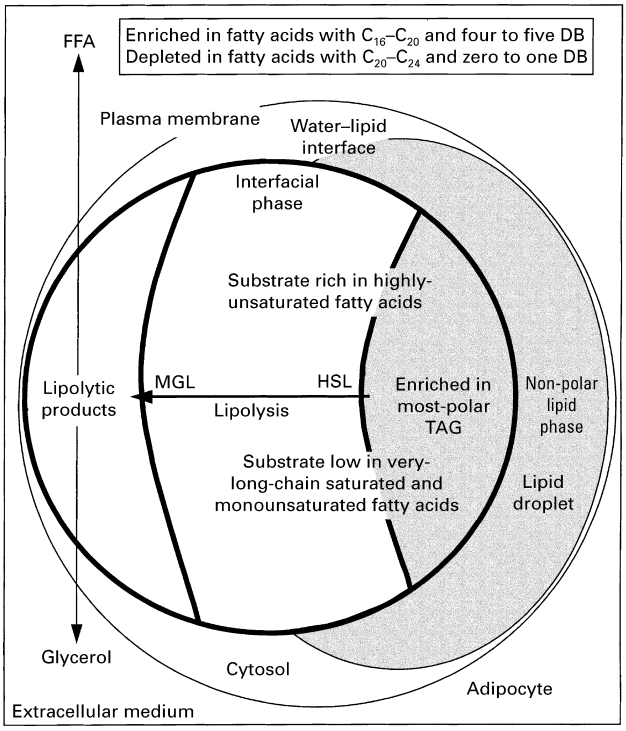


**Fig. 1.** Possible mechanism for selective fatty acid mobilization from white fat cells. The basis of selective fatty acid mobilization would depend on a heterogeneous substrate distribution submitted to hydrolysis. The most-polar triacylglycerols (TAG) would be more abundant at the interface than in the droplet core and, as a consequence, they would be preferentially hydrolysed. Hence, the released free fatty acids (FFA) would be enriched in polyunsaturated fatty acids (including highly-mobilized fatty acids which are $C_{16}$–$C_{20}$ and have four to five double bonds (DB)) and depleted in very-long-chain saturated and monounsaturated fatty acids (i.e. weakly-mobilized fatty acids which are $C_{20}$–$C_{24}$ and have zero to one DB). On this model, the non-polar phase includes TAG and diacylglycerols, and the interfacial phase contains monoacylglycerols, protonated FFA and soaps including ionized FFA. It is commonly stated that the lipolytic enzymes, if water-soluble, must penetrate through an interfacial layer of polar lipids to reach substrate molecules. HSL, hormone-sensitive lipase; MGL, monoacylglycerol lipase.

*Physiological relevance and implications for health*

These findings could have important implications for methodology, epidemiology, physiology and health. When studying the metabolism of total fatty acids in adipose tissue, the choice of the tracer fatty acid should be made carefully. The use of a tracer fatty acid mobilized at the same rate as the total fatty acids (relative mobilization 1) could drastically under- or overestimate the metabolic rate of specific fatty acids such as highly-unsaturated and long-chain saturated and monounsaturated fatty acids. Similarly, the fatty acid composition of adipose tissue TAG is used in human subjects as a biomarker of dietary fatty acid intake in studies dealing with the relationships between health disorders and environmental factors such as dietary changes (van Staveren *et al*. 1986). The use of adipose tissue fatty acids as biomarkers of dietary intake in epidemiological studies (Tjønneland *et al*. 1993) should be made with care, particularly for the assessment of long-term dietary intake of lipids of marine origin. It should probably now be recommended that the adipose tissue content of docosahexaenoic acid (22:6*n*-3; DHA) rather than EPA should be used as a marker for the long-term dietary intake of *n*-3 PUFA. Among other health implications, the selective supply of fatty acids to tissues should also be taken into account. Fatty acids released from adipose tissue are not used only as energy substrates. Indeed, it is interesting to consider that some highly-unsaturated fatty acids have metabolic effects through modulation of gene expression in the liver (Clarke & Jump, 1994; Jump *et al*. 1996) and in adipocytes (Sessler & Ntambi, 1998).

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## Effect of polyunsaturated fatty acids on body fat accumulation and lipid homeostasis

### *Effect of polyunsaturated fatty acids on body fat accumulation*

It is widely reported that high fat intake is closely related to the development of dietary obesity. There is also clear evidence that the nature of the dietary fats could affect lipid homeostasis and body fat deposition, so that not only the amount but also the fatty acid composition of dietary lipids may be relevant (Hill *et al*. 1992). PUFA, particularly those of marine origin, have been shown to affect the development of adipose tissue (Table 2). Several studies report that the intake of high-fat diets containing fatty acids from fish oil high in *n*-3 PUFA limits the hypertrophy of fat depots compared with the intake of high-fat diets containing lard or beef tallow in rats (Parrish *et al*. 1990, 1991; Belzung *et al*. 1993; Hainault *et al*. 1993). Similar results have been obtained with several animal models such as obese Zucker rats (Carlotti *et al*. 1993), mice (Ikemoto *et al*. 1996), obese *ob/ob* mice (Cunnane *et al*. 1986), hamsters (Jones, 1989), and also in human subjects (Couet *et al*. 1997). Feeding fish oil for about 1 month limits the hypertrophy of retroperitoneal and epididymal adipose tissues in rats compared with a diet containing the same amount of lard when the energy intake is similar (Parrish *et al*. 1991; Belzung *et al*. 1993). After such medium-term dietary treatments, the lipid gain in adipose tissues was mainly explained by fat cell hypertrophy. After this feeding protocol the lipid storage in subcutaneous and mesenteric adipose tissues was not affected (Belzung *et al*. 1993). Thus, there are marked regional differences in the limiting effect of *n*-3 PUFA on adipose tissue trophic growth. In addition, the duration of the dietary treatment is a relevant variable. Indeed, in rats, feeding fish oil fatty acids for 3 months, and even more so for 6 months, significantly ($P < 0{\cdot}05$) limits the hypertrophy of the four major fat depots reported previously (Hill *et al*. 1993). On the whole, dietary fish oil influences adipose tissue development in a site-specific manner as a function of diet and feeding period.

The specificity of the metabolic effects induced by dietary fish oil fatty acids has been clearly demonstrated using similar proportions of *n*-3 PUFA, *n*-6 PUFA, saturated and monounsaturated fatty acids in the diets of the experimental groups (Belzung *et al*. 1993; Oudart *et al*. 1997). Thus, the effects of fish oil fatty acids can be ascribed validly to *n*-3 PUFA. The two main *n*-3 PUFA present in fish oil are EPA and DHA, although the respective level at which each fatty acid contributes to the limitation of body fat accumulation is poorly documented. In a recent study, rats were fed for 4 weeks on high-fat diets differing in their fatty acid composition but containing the same amounts of *n*-3 PUFA (EPA, DHA, DHA + EPA), or no *n*-3 PUFA (control). In full agreement with the studies described earlier, *n*-3 PUFA intake influenced adipose tissue development (Oudart *et al*. 1997; Raclot *et al*. 1997*a*). At the end of the dietary treatment, lipid mass and fat cell size decreased in retroperitoneal adipose tissue in the following order: control > EPA > DHA > DHA + EPA (Fig. 2(A)). These results provide evidence for a selective effect of individual dietary *n*-3 fatty acids on body fat accumulation. The clear-cut effect of fish oil on adipose tissue trophic growth could depend on synergistic effects of the two major *n*-3 PUFA.

### *Effect of polyunsaturated fatty acids on lipid homeostasis*

Among putative metabolic pathways that might contribute to explain body fat accumulation during high-fat feeding, the plasma lipid-lowering effects of *n*-3 PUFA could play a central role by affecting substrate delivery to adipose tissues. It is widely documented that fish oil *n*-3 PUFA affect the plasma lipoprotein profile and hepatic lipid

**Table 2.** Selective effects of dietary polyunsaturated fatty acids (PUFA) on body fat accumulation

| Fatty acids in high-fat diets | Species | Effect | Feeding period | Reference |
|---|---|---|---|---|
| *n*-6 PUFA *v.* SFA or MUFA | *ob*/*ob* mouse | ↓ Weight gain | 2 weeks | Mercer & Trayhurn (1987) |
| | Rat | ↓ Body fat | 4 months | Shimomura *et al.* (1990) |
| | Rat | ↓ Body fat | 8 weeks | Matsuo *et al.* (1995) |
| | Rat | ↓ Body fat | 12 weeks | Takeuchi *et al.* (1995) |
| | Rat | ↓ Abdominal fat | 9 weeks | Kawada *et al.* (1998) |
| *n*-3 PUFA *v.* SFA or MUFA | *ob*/*ob* mouse | ↓ Weight gain | 16 weeks | Cunnane *et al.* (1986) |
| | Hamster | ↓ Body fat | 3 weeks | Jones (1989) |
| | Rat | ↓ Epididymal or perirenal fat | 3–5 weeks | Parrish *et al.* (1990, 1991) |
| | Rat | ↓ Subcutaneous or visceral fat | 16–20 d | Hainault *et al.* (1993) |
| | *fa*/*fa* rat | ↓ Visceral or total fat | 8 weeks | Carlotti *et al.* (1993) |
| | Rat | ↓ Epididymal or retroperitoneal fat | 4 weeks | Belzung *et al.* (1993) |
| | Rat | ↓ Epididymal or retroperitoneal fat<br>↓ Mesenteric or subcutaneous fat | 1–3 months | Hill *et al.* (1993) |
| | Rat | ↓ Fat mass gain | 12 weeks | Su & Jones (1993) |
| | Rat | ↓ Epididymal or retroperitoneal fat | 4 weeks | Oudart *et al.* (1997) |
| | Mouse | ↓ Parametrial fat | 19 weeks | Ikemoto *et al.* (1996) |
| | Man | ↓ Body fat | 3 weeks | Couet *et al.* (1997) |
| | Rat | ↓ Perirenal fat | 10 weeks | Cha *et al.* (1998) |
| *n*-3 PUFA *v. n*-6 PUFA | Rat | ↓ Epididymal fat | 2 weeks | Baltzell *et al.* (1991) |
| | Rat | ↓ Epididymal fat | 1 week | Fickova *et al.* (1998) |

MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; ↓, decrease.

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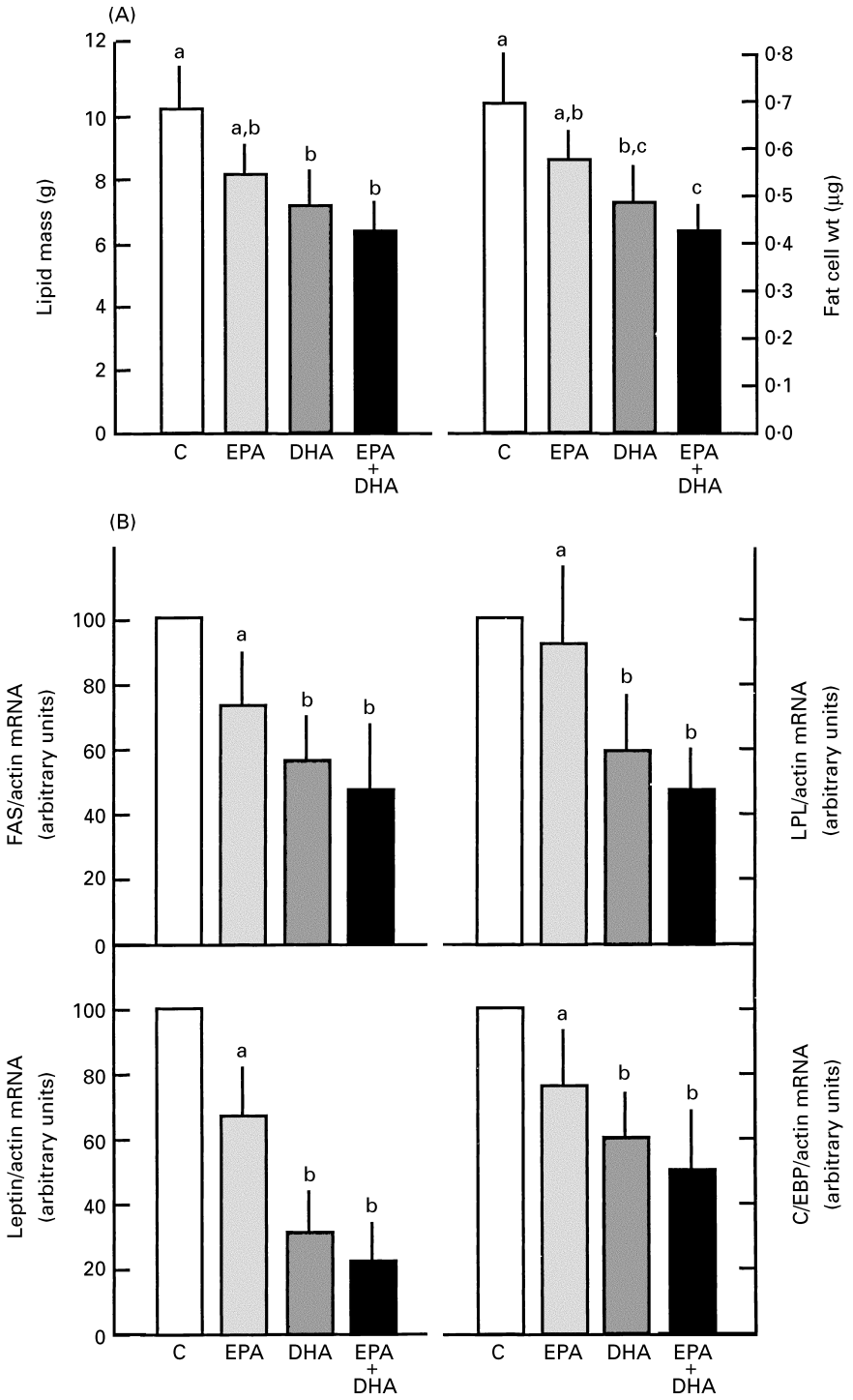


**Fig. 2.** Effect of dietary fatty acids on lipid mass, fat cell weight and gene expression in retroperitoneal adipose tissue. Rats were fed on experimental high-fat diets (200 g/kg) differing in fatty acid composition for 4 weeks. Results of densitometry scanning of autoradiograms are expressed relative to actin mRNA. C (lard plus olive oil), EPA (eicosapentaenoic acid), DHA (docosahexaenoic acid). FAS, fatty acid synthase (*EC* 2.3.1.85); LPL, lipoprotein lipase (*EC* 3.1.1.34); C/EBP, CCAAT/enhancer-binding protein α. Values are means with their standard errors represented by vertical bars. a,b,c, Mean values within each plot with unlike superscript letters were significantly different (Peritz F test for multiple comparisons; $P < 0{\cdot}05$).

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metabolism (Harris, 1989; Nestel, 1990; Rustan *et al*. 1992). Several studies have reported a blood-lipid-lowering effect after administration of *n*-3 PUFA in rodents (Nestel, 1990) and human subjects (Harris, 1989). The mechanism for the inhibitory effect of *n*-3 PUFA on TAG secretion is probably partly via reduced TAG or VLDL synthesis (Harris *et al*. 1990). Fish oil fatty acids suppressed fatty acid synthesis, reduced the activity of esterifying enzymes and increased mitochondrial and peroxisomal oxidation of fatty acids in the liver. In support of the former hypothesis, the hypolipidaemic effect of fish oil fatty acids appears to be mediated through a lowering of lipogenic enzymes such as fatty acid synthase (*EC* 2.3.1.85; FAS) and acetyl-CoA carboxylase (*EC* 6.4.1.2; ACC), glucose-6-phosphate dehydrogenase (*EC* 1.1.1.49) and malic enzyme (*EC* 1.1.1.38; Mohan *et al*. 1991). Fish oil may also exhibit a TAG-lowering effect by inhibition of key hepatic enzymes such as diacylglycerol acyltransferase (*EC* 2.3.1.20; Rustan *et al*. 1992), and phosphatidate phosphohydrolase (*EC* 3.1.3.4; Al-Shurbaji *et al*. 1991), and by inhibition of apolipoprotein secretion (Wong & Marsh, 1988). The effects of different types of dietary fat in the control of hepatic TAG secretion have been clearly shown. *n*-6 and *n*-3 PUFA intake resulted in a diversion of acyl-CoA towards oxidation at the expense of newly-synthesized TAG (Moir *et al*. 1995). An inhibitory effect of dietary fish oil on the synthesis of TAG relative to phospholipids in the liver has also been reported (Yeo & Holub, 1990). The hypolipidaemic effect of fish oil depends on its *n*-3 PUFA composition rather than its *n*-3 PUFA content (Banerjee *et al*. 1992). Indeed, *n*-3 PUFA are selectively metabolized in rat liver (Madsen *et al*. 1998). EPA, in contrast to DHA, inhibits the synthesis and secretion of TAG in the liver (Willumsen *et al*. 1993*a*). The hypotriacylglycerolaemic effect of EPA in rats may be explained primarily by an increased mitochondrial fatty acid oxidation (Willumsen *et al*. 1993*b*). These data are in agreement with a recent study showing that EPA is the hypotriacylglycerolaemic fatty acid of fish oil, and that mitochondria are the principal targets (Frøyland *et al*. 1997). EPA would act as a mitochondrial proliferator, thus increasing the mitochondrial β-oxidation capacity. However, an increased plasma lipid clearance by an enhanced activity of TAG lipases, such as lipoprotein lipase (*EC* 3.1.1.34) or hepatic TAG lipase (*EC* 3.1.1.3), in peripheral tissues can also be validly proposed. Lipoprotein lipase activity has be shown to be slightly affected in adipose tissue but increased in skeletal muscle by fish oil fatty acids (Herzberg & Rogerson, 1989; Baltzell *et al*. 1991). *n*-3 PUFA may also regulate lipid metabolism directly at the level of adipocytes. Insulin has been reported to stimulate the transport of glucose and its incorporation into fatty acids to a lesser extent in adipocytes of animals fed on *n*-3 PUFA than those fed on *n*-6 PUFA, thus leading to decreased lipogenesis (Fickova *et al*. 1998). Experiments with isolated adipocytes showed decreased basal lipolysis after feeding of *n*-3 fatty acids and higher lipolysis on stimulation compared with animals fed on lard (Rustan *et al*. 1993). This finding may reflect an increased hormone-stimulated lipolysis *in vivo* which could contribute to the reduction of adipose tissue trophic growth after *n*-3 PUFA supplementation.

A selective energy-dissipative process to counteract body fat accretion during high-fat feeding has been demonstrated (Rothwell & Stock, 1979), and may be implicated in the regulation of energy balance during high-fat feeding according to the fatty acid composition of dietary fat (Trayhurn, 1986). It has been shown that PUFA lead to a higher increase in diet-induced thermogenesis than saturated or monounsaturated fatty acids during high-fat feeding, suggesting that dietary fatty acids could be selectively thermogenic (Takeuchi *et al*. 1995; Oudart *et al*. 1997). Diet-induced thermogenesis is brought about mainly by BAT, which is under the control of the sympathetic nervous system, through the activity of the uncoupling protein (UCP) 1. *n*-6 PUFA are more potent stimulators of the BAT sympathetic nervous system than saturated or monounsaturated fatty acids, as has been assessed by the higher BAT noradrenaline turnover in rats fed on *n*-6 PUFA than that in saturated or monounsaturated fatty acid-fed rats (Young & Walgren, 1994; Matsuo *et al*. 1995). At the cellular level, brown adipocytes from rats fed on *n*-6 PUFA have a higher stimulated respiration rate than those from rats fed on saturated or monounsaturated fatty acids (Ide & Sugano, 1988). In the whole animal the effect was detected by the measurement by indirect calorimetry of postprandial energy expenditure, which is higher in rats fed on *n*-6 PUFA than in saturated or monounsaturated fatty acid-fed rats (Takeuchi *et al*. 1995). *n*-3 PUFA are also potent stimulators of diet-induced thermogenesis, as was clearly shown in BAT from rats fed on a diet enriched with fish oil fatty acids, which had a higher BAT thermogenic activity (Oudart *et al*. 1997) and a higher UCP1 content (Sadurkis *et al*. 1995; Kawada *et al*. 1998) than rats fed on a lard-based diet. The results of all these studies are in accordance with a role for BAT thermogenesis in the limiting effect of PUFA on body fat accumulation. However, the contribution of diet-induced thermogenesis in BAT on the total energy expenditure remains to be clarified. Moreover, the extent to which the recently discovered UCP2 (Fleury *et al*. 1997) and UCP3 (Boss *et al*. 1997), which have a wider tissue distribution than UCP1, might contribute to the limiting effects of PUFA on nutritional obesity also needs close examination. Taken together, these results support the view that a diet high in *n*-3 PUFA results in a preferential partitioning of ingested energy towards oxidation at the expense of storage.

## Effect of polyunsaturated fatty acids on gene expression

Fatty acids are not only used as an energy source and for membrane components, they also serve as important mediators of gene expression (Table 3). The regulation of hepatic gene expression by fatty acids, and notably PUFA, has been extensively reviewed by other workers (Clarke & Jump, 1993, 1994, 1996*a*,*b*, 1997; Baillie *et al*. 1996; Jump *et al*. 1996; Clarke *et al*. 1997; Sessler & Ntambi, 1998). The present review will focus mainly on tissue-specific and site-specific regulation of gene expression by PUFA.

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**Table 3.** Selective effects of polyunsaturated fatty acids (PUFA) on gene expression in liver and adipose tissue

| Selectivity of fatty acid | Animal model | Gene expression | Experimental conditions | Reference |
|---|---|---|---|---|
| *n*-6 PUFA | Mouse | ↓ Liver SCD1 | *In vivo* | Ntambi (1992) |
| | Mouse | ↓ Adipose S14, FAS | *In vitro* | Mater *et al.* (1998) |
| | Rat | ↓ Liver and adipose ACC, FAS | *In vivo* | Foufelle *et al.* (1992) |
| | Mouse | ↓ Adipose GLUT4 | *In vitro* | Tebbey *et al.* (1994) |
| *n*-6 or *n*-3 PUFA | Rat | ↓ Liver PK | *In vivo* or *in vitro* | Liimatta *et al.* (1994) |
| | Mouse | ↓ Liver SCD1 | *In vivo* or *in vitro* | Landschulz *et al.* (1994) |
| | Rat | ↓ Liver FAS, ACC | *In vivo* | Girard *et al.* (1994) |
| | Mouse | ↑ Adipose PEPCK | *In vitro* | Antras-Ferry *et al.* (1995) |
| | Rat | ↓ Liver FAS, S14<br>↑ Acyl-CoA oxidase, cytochrome P450 4A2 | *In vivo* | Ren *et al.* (1997) |
| *n*-3 PUFA | Rat | ↓ Liver S14 | *In vivo* or *in vitro* | Jump *et al.* (1993) |
| | Rat | ↓ Liver PK, GK, ME, FAS, S14 | *In vivo* or *in vitro* | Jump *et al.* (1994) |
| | Rat | ↓ Liver APO A-I<br>↑ Liver Acyl-CoA oxidase | *In vivo* or *in vitro* | Berthou *et al.* (1995) |
| | Rat | ↓ Adipose FAS, LPL, HSL, PEPCK, leptin, C/EBPα | *In vivo* | Raclot *et al.* (1997*a*) |
| | Rat | ↓ Adipose adipsin, aP2, PPAR α | *In vivo* | Okuno *et al.* (1997) |
| | Rat | ↓ Liver ACC, FAS, ATP-CL, ME, G6PDH | *In vivo* | Iritani *et al.* (1998) |

SCD1, stearoyl-coA desaturase (*EC* 1.14.99.5); FAS, fatty acid synthase (*EC* 2.3.1.85); PK, pyruvate kinase (*EC* 2.7.1.40); ACC, acetyl-CoA carboxylase (*EC* 6.4.1.2); GLUT4, insulin-responsive glucose transporter 4; PEPCK, phospho*enol*pyruvate carboxykinase (*EC* 4.1.1.32); GK, glucokinase (*EC* 2.7.1.2); ME, malic enzyme (*EC* 1.1.1.38); APO A-I, apolipoprotein A-I; LPL, lipoprotein lipase (*EC* 3.1.1.34); HSL, hormone-sensitive lipase; C/EBP α, CCAAT/enhancer-binding protein α; PPAR α, peroxisome proliferator-activated receptor α; aP2, adipocyte lipid-binding protein; ATP-CL, ATP-citrate lyase (*EC* 4.1.3.8); G6PDH, glucose-6-phosphate dehydrogenase (*EC* 1.1.1.49); ↓, suppressed; ↑, enhanced.

### *Effect of polyunsaturated fatty acids on hepatic gene expression*

Several studies have established that genes encoding both glycolytic and lipogenic enzymes are regulated by dietary PUFA. On the model of the sucking–weaning transition, the nature of dietary fatty acids were shown to affect FAS and ACC mRNA levels and activities in sucking rats weaned to high-fat diets differing in their fatty acid composition (Girard *et al*. 1994). Weaning to high-fat diets containing saturated long-chain fatty acids (or medium-chain fatty acids) does not prevent the increase in FAS and ACC mRNA levels (and activities) in the liver. On the other hand, *n*-6 PUFA prevent this increase in the liver, but this effect was considerably less important in adipose tissue where a similar trend was nevertheless observed (Foufelle *et al*. 1992). Since the carbohydrate content of all the diets was the same, the repression of genes encoding proteins involved in hepatic lipogenesis is likely to be due to the presence of PUFA in the diet. Indeed, linoleic acid added to high-fat low-PUFA diets markedly decreases the concentrations of mRNA encoding FAS in the liver. The expression of genes encoding hepatic lipogenic (FAS, malic enzyme, and S14) and glycolytic (glucokinase (*EC* 2.7.1.2) and pyruvate kinase (*EC* 2.7.1.40)) enzymes was also repressed in rats fed on a high-fat diet containing fatty acids of marine origin (Jump *et al*. 1994). These effects are rapid and progressive, and a single meal containing fish oil was sufficient to suppress gene transcription of glycolytic and lipolytic enzymes by 60–70 %. After several days on the fish oil diet, the gene transcription of these hepatic enzymes was decreased by 70–90 % when compared with rats fed on a diet supplemented with olive oil. These effects of PUFA on gene expression are gene-specific, since two transcription factors and β-actin were not affected. Thus, *n*-3 PUFA attenuate hepatic glycolytic and lipogenic enzyme gene expression to a similar extent. The suppression of lipogenic enzyme gene expression in rat liver is rapidly brought about by even small amounts of dietary PUFA (Iritani *et al*. 1998). Lipogenic enzyme gene expression was suppressed within 2 h in the liver by PUFA from perilla oil (20 g/kg diet), while a stronger suppression was obtained with 50 g perilla oil/kg diet. *n*-6 and *n*-3 PUFA have similar inhibitory effects on the transcription of various hepatic lipogenic and glycolytic genes, whereas, in contrast, saturated and monounsaturated fatty acids are rather ineffective. PUFA ranging in chain length from $C_{18}$ to $C_{20}$ and in unsaturation from two to five double bonds had effects on hepatocyte gene expression. PUFA had to be at least $C_{18}$ and have two double bonds located at the C-9 and C-12 positions to exert strong inhibitory effects on liver lipogenesis (Clarke & Jump, 1994). The lack of selectivity of *n*-6 and *n*-3 PUFA on hepatic gene expression does not argue for the involvement of an eicosanoid pathway.

Dietary *n*-6 and *n*-3 PUFA also regulate fatty acid oxidation by modulating the expression of genes coding for key metabolic enzymes (Table 3). Interestingly, an increase in liver acyl-CoA oxidase mRNA concentrations was shown in rats fed on fish oils (Berthou *et al*. 1995). Acyl-CoA oxidase is the rate-limiting enzyme involved in the peroxisomal β-oxidation of fatty acids. *n*-3 PUFA induce an increase in acyl-CoA oxidase mRNA concentrations in primary hepatocytes, indicating a direct transcriptional action. Recent data show that the expression of carnitine palmitoyltransferase I (*EC* 2.3.1.21) mRNA was markedly increased after exposure of cultured fetal hepatocytes to long-chain fatty acids, whereas medium-chain fatty acids proved to be ineffective (Chatelain *et al*. 1996). The effect of fatty acids on carnitine palmitoyltransferase I mRNA levels seems to be dose-dependent and also to depend slightly on the fatty acid molecular structure.

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Like hepatic lipogenic and glycolytic enzymes, the expression of the stearoyl-CoA desaturase 1 (*EC* 1.14.99.5; SCD1) gene is markedly suppressed by PUFA *in vivo* (Ntambi, 1992; Table 3). The expression of the SCD1 gene was significantly and selectively decreased by PUFA in murine liver *in vivo* compared with saturated and monounsaturated fatty acids which were rather ineffective. Among the PUFA tested, arachidonic acid, and to a lesser extent α- and γ-linolenic acids and linoleic acid, dramatically decrease the levels of SCD1 mRNA. The suppressive effects of PUFA on expression of the SCD1 gene in rat hepatocytes are selective, increasing according to the degree of unsaturation of the fatty acids (Landschulz *et al*. 1994). The down-regulation of hepatic SCD1 seems to be caused by a reduction of SCD1 gene transcription. It appears clear at present that fatty acids act directly on hepatocyte gene expression. *In vitro* studies have shown that PUFA-mediated repression of mRNA encoding hepatic lipogenic and glycolytic enzymes and SCD1 does not need extrahepatic factors.

The cellular and molecular mechanisms by which dietary PUFA regulate hepatic gene expression are beginning to be elucidated (Clarke *et al*. 1997). It is unlikely that one mechanism will explain fatty acid regulation of gene expression. PUFA inhibit transcription of the hepatic gene encoding enzymes involved in lipogenesis, while inducing expression of genes encoding acyl-CoA oxidase and cytochrome P450 4A2, which are enzymes involved in fatty acid oxidation (Ren *et al*. 1997). PUFA can regulate the expression of genes involved in lipid metabolism through a group of transcription factors called peroxisome proliferator-activated receptors (PPAR; Lemberger *et al*. 1996). The PPARα have been implicated in the effects of fatty acids on gene transcription. However, PUFA have been reported to suppress hepatic FAS and S14 gene expression independently of PPARα (Ren *et al*. 1997). Conversely, PUFA did not induce microsomal and peroxisomal enzyme expression in PPARα-deficient mice, indicating that PPARα are involved in the regulation of these enzymes (Ren *et al*. 1997). Thus, lipogenic and peroxisomal enzymes are differentially regulated by PUFA and two distinct mechanisms are implicated for PUFA control of lipid metabolism in the liver. PUFA could exert their effects through direct regulation of gene expression in the liver (Jump *et al*. 1993). Concerning the hepatic S14 protein, which is possibly involved in the lipogenic pathway, *cis*-regulatory elements of PUFA control have been identified within the proximal promoter at −220 to −80 bp (Jump *et al*. 1993). Dietary *n*-3 PUFA have also been shown to interfere with the insulin or glucose activation of L-pyruvate kinase gene transcription in hepatocytes (Liimatta *et al*. 1994). The *cis*-regulatory targets of PUFA control were located within the proximal promoter region at −197 to −96 bp. This region binds two transcription factors involved in the insulin or glucose regulation of L-pyruvate kinase gene transcription. Thus, PUFA may interfere with hepatic carbohydrate metabolism by regulating gene transcription of a key glycolytic enzyme. It appears that dietary PUFA do not modulate the transcription of hepatic genes via PPAR, but rather through transcription factors related to the carbohydrate response region. The repression of hepatic FAS mRNA concentrations by PUFA is due to an inhibition of gene transcription (Jump *et al*. 1994). The presence of *cis*-acting elements responsive to PUFA are much less clear in the proximal promoter region of the FAS gene (Fukuda *et al*. 1997) and also in that of ATP-citrate lyase (*EC* 4.1.3.8; Fukuda *et al*. 1996). Indeed, PUFA may interfere with the insulin signalling pathway through the sequences responsive to glucose or insulin stimulation (Iritani & Fukuda, 1995). Thus, the molecular basis by which PUFA affect hepatic gene expression probably involves at least two distinct pathways involving either *trans*-acting factors or *cis*-regulatory targets.

### *Effect of polyunsaturated fatty acids on adipose tissue gene expression*

The fact that the effects of PUFA on gene expression are rapid in the liver and much slower in adipose tissue argue in favour of a tissue-specific phenomenon (Jump *et al*. 1993; Girard *et al*. 1994). While PUFA seem to down-regulate gene expression, saturated and unsaturated fatty acids are able to up-regulate gene expression both in liver (Meunier-Durmort *et al*. 1996) and in adipose tissue (Amri *et al*. 1991; Grimaldi *et al*. 1992). Hence, white adipose tissue could also be a target for PUFA control of gene expression (Table 3). Treatment of pre-adipose cells with fatty acids induces the expression of numerous genes that encode proteins involved in fatty acid metabolism. Long-chain fatty acids induce the expression of the adipocyte lipid-binding protein (aP2) gene in pre-adipocytes (Distel *et al*. 1992; Grimaldi *et al*. 1992). Irrespective of their degree of unsaturation, fatty acids with chain lengths longer than $C_{12}$ seem able to activate the aP2 gene (Amri *et al*. 1991). Bromopalmitate, a non-metabolized long-chain fatty acid, was even more potent than natural fatty acids in inducing aP2 gene expression, indicating that induction of aP2 in pre-adipocytes is due to unprocessed fatty acids (Grimaldi *et al*. 1992). Fatty acids lead to the conversion process of pre-adipose cells to adipose cells (Amri *et al*. 1991). Since the expression of early markers such as lipoprotein lipase are not affected after fatty acid supplementation, fatty acids do not appear to trigger the first stage of differentiation. On the contrary, fatty acids act on the late differentiation process by increasing the expression of terminal differentiation-related markers. For instance, the expression of the angiotensinogen gene, which is a late marker of adipose cell differentiation, has been shown to be regulated by fatty acids in pre-adipose cells (Safonova *et al*. 1997). In this framework, it has been proposed that during high-fat or high-carbohydrate feeding, high levels of fatty acids originating from circulating TAG such as chylomicrons and VLDL might induce hypertrophy and hyperplasia of adipose tissue. On the other hand, in rats fed on fish oil, the plasma lipid-lowering effects of *n*-3 PUFA could led to a decreased fatty acid availability from circulating TAG, which in turn may contribute to the limiting of adipose tissue development.

Previous studies have shown that PUFA prevent excessive adipose tissue growth, but the mechanisms underlying these effects remain unclear. Since fatty acids have been shown to play a central role in the regulation of adipocyte-related genes, the nature of dietary fatty acids could influence the regulation of the expression of adipose tissue proteins involved in lipid storage or mobilization. In addition,

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experiments carried out on rats fed on high-fat diets containing *n*-3 PUFA suggest that the regulation of adipose tissue gene expression by PUFA would have to be site-dependent to help explain their selective effects on body fat accumulation (Belzung *et al*. 1993). There are big metabolic differences depending on the fat depot location. These site-specific differences hold also for the expression of genes encoding various proteins in adipose tissue (Cousin *et al*. 1993; Tavernier *et al*. 1995). The respective level at which each of the fatty acids could contribute to the regulation of gene expression, or whether one of the two main *n*-3 PUFA (EPA and DHA), or a mixture of both fatty acids, can substitute for native fish oil was unknown for adipose tissue. The effects of *n*-3 PUFA of marine origin on expression of several gene-encoding enzymes, transcription factors and leptin were examined in retroperitoneal adipose tissue (Fig. 2(B)), which responded differentially when oils of marine origin (EPA, DHA or EPA + DHA) replaced lard plus olive oil (controls; Raclot *et al*. 1997*a*). The inhibitory effect of EPA on gene expression was approximately half that of DHA, thus showing that *n*-3 PUFA are differentially effective in regulating adipose tissue gene expression. EPA and DHA may act through different mechanisms to repress gene expression in retroperitoneal adipose tissue since the two fatty acids appear to work synergistically.

Viewed another way, the mRNA encoding these various proteins might also be considered as markers of adipocyte phenotype (Ailhaud *et al*. 1992; Cornelius *et al*. 1994; MacDougald & Lane, 1995). The similar repression of mRNA encoding proteins involved in adipose tissue homeostasis would indicate that the regulation by *n*-3 PUFA is not strictly gene-specific. The mRNA encoding these various proteins are closely related to fat cell size induced by the dietary manipulations (Fig. 2), but seem unrelated to the fatty acid composition of adipose tissues. *n*-3 PUFA could affect gene transcription in white adipose tissues in a site-dependent manner by a mechanism that would require factors other than fatty acids *per se*. The suppression of gene expression by fish oil fatty acids might suggest that an eicosanoid pathway is involved in generating reactive intermediates. PUFA, and notably DHA, are strong cyclooxygenase (*EC* 1.14.99.1) inhibitors and consequently inhibit prostaglandin synthesis. Prostaglandins play a critical role in the adipocyte differentiation process (Forman *et al*. 1995; Kliewer *et al*. 1995). With these observations, it seems reasonable to propose that *n*-3 PUFA exert an anti-adipogenic effect in adipose tissue in a site-specific manner by down-regulating prostaglandin synthesis. Evidence in support of this concept also comes from a recent study showing that when compared with saturated and polyunsaturated oils perilla oil (high in α-linolenic acid (18:3*n*-3)) prevents the development of visceral adipose tissue by down-regulating adipocyte differentiation (Okuno *et al*. 1997). Indeed, the expression of the late genes of adipocyte differentiation was repressed in rat epididymal adipose tissue after perilla oil feeding. This finding suggests that *n*-3 PUFA limit the development of visceral adipose tissue by suppressing the late phase of adipocyte differentiation. In future research, it might be interesting, therefore, to use adipose cells at different stages of differentiation to separate the specific effects of fatty acids on gene expression from their overall effect on the differentiation process.

In order to further address the molecular basis by which PUFA might influence adipose tissue gene expression, it has been shown that PUFA act directly on adipocyte gene expression (Grimaldi *et al*. 1992; Amri *et al*. 1994; Sessler *et al*. 1996; Mater *et al*. 1998). This finding indicates that PUFA-mediated regulation of adipose tissue gene expression would not necessarily need extra-adipose factors. For instance, phospho*enol*pyruvate carboxykinase (*EC* 4.1.1.32) mRNA was strongly induced (about tenfold) by fibrates and DHA compared with oleic acid in adipocyte cell line 3T3-F442A, and the role of a PPAR in fatty acid signalling has been postulated (Antras-Ferry *et al*. 1995). It is interesting to note that DHA is a strong activator of PPARγ2, which is a transcription factor specifically expressed in adipose tissue. Following activation by fatty acids, induction of PPARγ2 mRNA would increase expression of CCAAT/enhancer-binding protein α, leading to activation of adipogenic genes (Tontonoz *et al*. 1994). A recent report studying the effect of PUFA on lipogenic gene expression in adipocytes showed that arachidonic acid and EPA repressed the mRNA encoding FAS and S14 (Mater *et al*. 1998). The arachidonic acid had a higher potency for inhibiting lipogenic gene expression, but its effect was blocked by an inhibitor of cyclooxygenase. These findings suggest that the mechanism for control involves an eicosanoid pathway in adipocytes. The mechanism of PUFA-mediated repression of lipogenic gene expression in adipocytes is different from that described in liver. PUFA also decrease SCD1 mRNA levels in 3T3-L1 adipocytes (Sessler *et al*. 1996). PUFA suppress the expression of the SCD1 gene in adipocytes by decreasing mRNA stability. Indeed, PUFA did not alter the transcription rate of the SCD1 gene, but caused a 3-fold decrease in the half-life of the SCD1 mRNA. It seems that the eicosanoid pathway is not required for the repression of SCD1 mRNA expression by arachidonic acid. SCD 1 mRNA levels in adipocytes are differentially decreased by other PUFA such as linoleic and linolenic acids and EPA, indicating that the repression of SCD1 mRNA expression is a selective response to PUFA. Thus, PUFA regulate SCD1 gene expression through different mechanisms in liver and adipose tissue.

Numerous possibilities exist with regard to the control of gene expression by PUFA in liver and adipose tissue. Several lines of evidence argue against PPAR as the PUFA response factor. Tissue-specific and site-specific factors are possibly involved in the specific effects of PUFA on gene expression, although other mechanisms cannot be excluded. New insights into the regulation of gene expression by PUFA are expected in future studies.

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