*Biochem. J.* (1985) **225**, 307–313
*Printed in Great Britain*



# Hepatic $\Delta^6$-desaturase activity in lean and genetically obese *ob/ob* mice

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(*Received 1 June 1984/Accepted 9 October 1984*)

1. Hepatic $\Delta^6$-desaturase activity is primarily located in the mitochondrial fraction in mice. 2. Both $\Delta^6$- and $\Delta^5$-desaturase activities are increased in the liver of young (6-week-old) obese mice. 3. The increase in hepatic $\Delta^6$-desaturase activity in obese mice does not occur until weaning. 4. Neither restriction of food intake nor hyperinsulinaemia normalize hepatic $\Delta^6$-desaturase activity of obese mice. 5. Both cold acclimation and tri-iodothyronine (30 $\mu$g/day per kg) decreased hepatic $\Delta^6$-desaturase activity of obese mice to levels observed in lean mice, whereas the increase in activity in obese mice was still maintained after the induction of hypothyroidism.

Many membrane-bound enzymes and receptors require specific phospholipid or acyl-chain environments for optimal activity (see Sanderman, 1978). Several membrane-associated processes are defective in the genetically obese (*ob/ob*) mouse. These include the $(Na^+ + K^+)$-dependent ATPase (York *et al.*, 1978; Lin *et al.*, 1979; Hughes & York, 1983), adenylate cyclase activity of white adipocytes (Dehaye *et al.*, 1978; French & York, 1984), the glucose-transport system of muscle (Cuendet *et al.*, 1976), hepatic 5'-nucleotidase (French *et al.*, 1983) and microsomal NADPH:cytochrome *P*-450 oxidoreductase (Hyslop *et al.*, 1982). Indeed, some authors have proposed that a generalized membrane defect may be closely associated with the expression of the defective *ob* gene (Chang *et al.*, 1975; Dehaye *et al.*, 1978).

The acyl-chain composition of membrane phospholipids is altered in obese (*ob/ob*) mice, the proportion of unsaturated fatty acids being increased in comparison with the membrane phospholipids of lean mice (Winand *et al.*, 1973; Rouer *et al.*, 1980; Hyslop *et al.*, 1982; York *et al.*, 1982; French *et al.*, 1983). The activity of $\Delta^9$-desaturase, the enzyme responsible for the desaturation of $C_{16:0}$ and $C_{18:0}$ fatty acids to $C_{16:1}$ and $C_{18:1}$ respectively, is increased in both liver and adipose tissue of obese mice (Enser, 1979; Enser & Roberts, 1982). However, many of the changes in membrane phospholipid fatty-acyl composition described in obese mice involve the increased incorporation of long-chain polyunsaturated fatty acids. These are synthesized by sequential desaturation and elongation of the essential fatty acids, linoleic ($C_{18:2,\,\omega-6}$) and linolenic ($C_{18:3,\omega-3}$) acids (Naughton, 1981), the synthesis occurring mainly in the liver of adult rodents, but also in the brain during foetal and neonatal stages of development (Cook, 1978). The desaturation stages, utilizing the $\Delta^6$- and $\Delta^5$-desaturases, are slower than the elongation steps in the synthesis of long-chain polyunsaturated fatty acids (Brenner, 1977; Naughton, 1981). The activity of $\Delta^6$-desaturase is affected by a number of hormone and nutritional influences, including dietary essential fatty acid levels (Peluffo *et al.*, 1976), insulin (Brenner *et al.*, 1968), adrenaline (Brenner, 1977) and thyroid hormones (Gomez-Dumm *et al.*, 1977; Faas & Carter, 1981, 1982). Since the obese mouse is hyperinsulinaemic and may have defective thyroid function (Bray & York, 1979), we investigated the effects of both endocrine and nutritional status on the activity of the $\Delta^6$- and $\Delta^5$-desaturase enzymes of obese mice.

## Materials and methods

Obese (*ob/ob*) and lean (*ob/?*) mice were bred from heterozygote (*ob/?*) parents in the University animal facilities. The Southampton colony was derived from original stock of undetermined background strain provided by the Institute of Animal Genetics, Edinburgh, Scotland, U.K. Pups were weaned at 21 days on to mouse chow (Christopher Hill, Poole, Dorset, U.K.) and were maintained in plastic cages in a room at a temperature of 22–25°C with a 12h-light/12h-dark cycle (08:00–20:00h) unless otherwise stated in the text. Pre-obese *ob/ob* mice (17 days old) were identified by their enhanced fall in rectal tempera-

ture after exposure to a 14°C environment for 15min (Trayhurn & James, 1978).

Some mice were trained to eat in a meal-feeding pattern by limiting the availability of mouse chow to a 2.5h period each day (09:00–11:30h) for 13 days.

A hypothyroid state was induced in eight lean and eight obese mice by feeding an iodine-deficient diet (Special Diet Services, Witham, Essex, U.K.) and providing a 0.5% (w/v) perchlorate drinking solution for 14 days. Hyperthyroidism was induced by tri-iodothyronine injections (30$\mu$g/day per kg, subcutaneously twice daily) for 14 days.

All animals were killed between 11:30 and 12:00h on the day of the experiment, unless otherwise stated.

Desaturase enzyme activities were assayed either in the 10% (w/v) homogenates of liver and brain in 100mM-phosphate buffer, pH7.4, containing 2mM-reduced glutathione, or in the microsomal and mitochondrial fractions prepared from these homogenates by differential centrifugation. Liver was homogenized in buffer at 4°C. Homogenates were centrifuged at 1000*g* to sediment the nuclear fraction. The supernatant was subsequently centrifuged at 15000*g* for the mitochondrial pellet, and this supernatant at 105000*g* for the microsomal fraction in an MSE Pegasus ultracentrifuge. All fractions were resuspended in phosphate buffer, pH7.4, containing 2mM-reduced glutathione and used immediately for assay of desaturase enzyme activities.

Both $\Delta^6$- and $\Delta^5$-desaturase enzyme activities were assayed by the method of Cook (1978). Reactions were initiated by the addition of 1mg of protein to preincubated flasks containing 100mM-phosphate buffer, pH7.4, 0.2mM-CoA, 2mM-$MgCl_2$, 2mM-ATP, 0.5mM-NADH, 0.05% (v/v) Triton WR 1339 and 25$\mu$M-$^{14}$C-labelled substrate fatty acid containing 300000d.p.m. in a final volume of 2ml. The substrate fatty acid for $\Delta^6$-desaturase assays was [1-$^{14}$C]linoleic acid ($C_{18:2,\omega-6}$) (sp. radioactivity 56mCi/mmol) and for $\Delta^5$-desaturase assays was [2-$^{14}$C]eicosa-8,11,14-trienoic acid ($C_{20:3,\omega-6}$) (sp. radioactivity 55mCi/mmol). Reaction mixtures were incubated at 37°C for 3min. The reaction was stopped by addition of 10% (w/v) KOH in methanol. After heating at 65°C for 30min the fatty acids were extracted from the acidified mixture with diethyl ether/light petroleum (b.p. 60–80°C) (1:1, v/v) and dried over anhydrous $Na_2SO_4$. The fatty acids were methylated in 500$\mu$l of freshly prepared diazomethane (1mM) in diethyl ether at 4°C for 1h. After removal of excess diazomethane by evaporation under $N_2$, the fatty acid methyl esters were separated by t.l.c. on silica-gel G containing 5% (w/w) silver nitrate (Cook, 1978), with ethyl acetate/toluene (7:3, v/v) as developing solvent. Radiolabelled fatty-acid methyl esters were located on a t.l.c. scanner. Radioactivity was counted in a Phillips PW 4700 liquid-scintillation counter after addition of Beckman Ready Solv scintillation fluid (Beckman RIIC, High Wycombe, Bucks., U.K.) to scraped areas of silica gel. Recovery of radioactivity from the plates was in excess of 80%. All results were corrected for recovery.

The mitochondrial marker enzyme, succinate:cytochrome *c* oxidoreductase, and the microsomal enzyme NADPH:cytochrome *P*-450 reductase were assayed as previously described (Hyslop *et al.*, 1982; Holt & York, 1982). Protein was assayed by the method of Bradford (1976), with bovine serum albumin (fraction V) as standard.

All reagents were purchased from Sigma Chemical Co. (Poole, Dorset, U.K.). Radiochemicals were obtained from Amersham International (Amersham, Bucks., U.K.).

All results were assessed for statistical significance by Student's *t* test for unpaired or, where appropriate, paired, data.

## Results

$\Delta^6$-Desaturase activity in liver homogenates from animals aged 7–56 days is shown in Fig. 1. Activity was low in the suckling animal, but rose after weaning and had doubled by 56 days. A marked elevation in $\Delta^6$-desaturase activity was seen in the liver of weaned obese mice (30% higher than in lean mice). However, no differences in $\Delta^6$-desaturase activity were apparent in suckling lean and pre-obese mice distinguished by their susceptibility to hypothermia at 18 days of age. Similarly, no bimodal distribution of $\Delta^6$-desaturase activity was discernible in 24 8-day-old pups from three litters of known heterozygote parents, although such litters would have been expected to contain approximately six pre-obese mice. In contrast, brain $\Delta^6$-desaturase activity, which decreased with age before weaning, was similar in 56-day-old lean and obese mice.

The subcellular distribution of hepatic $\Delta^6$-desaturase activity of lean mice is shown in Table 1. The highest enzyme activity, observed in the mitochondrial fraction, was 2-fold greater than that in the microsomal fraction. Even allowing for the presence of significant microsomal contamination of the mitochondrial fraction, as indicated by the marker enzymes, these data suggest that $\Delta^6$-desaturase activity is located principally in the mitochondria of mouse liver. The presence of significant succinate:cytochrome *c* reductase activity suggested that the $\Delta^6$-desaturase activity in

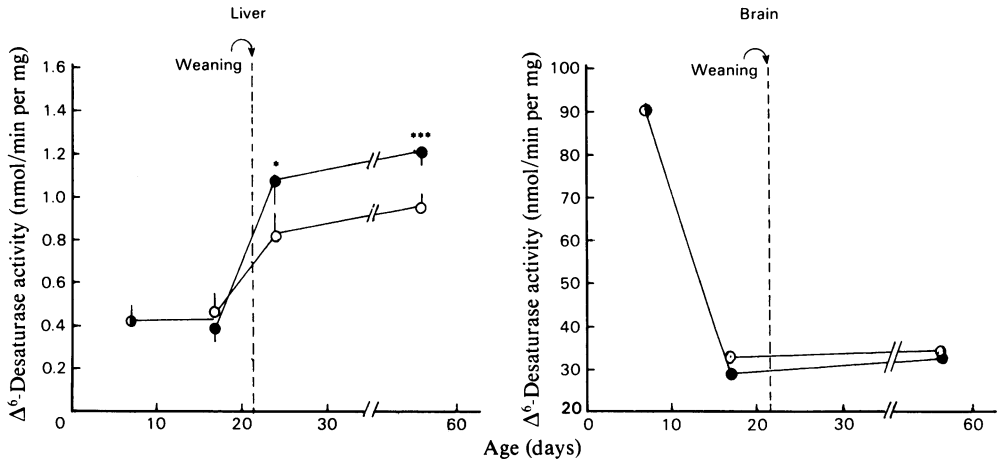


Fig. 1. *Δ⁶-Desaturase activity in homogenates of liver and brain of lean (○) and obese (●) mice at different ages*
Values represent means ± S.E.M. for at least five mice at each age. Since it was not possible to distinguish lean and pre-obese mice at 8 days of age, the value given is that for the three entire litters (8 pups/litter) from known heterozygote (*ob/ob*) parents. $*P<0.05$; $***P<0.005$ compared with lean mice.

Table 1. *Subcellular distribution of hepatic Δ⁶-desaturase activity*
The values represent the means ± S.E.M. for three individual preparations.

| Fraction | Δ⁶-Desaturase (nmol·min⁻¹·mg⁻¹) | Δ⁶-Desaturase (Total nmol·min⁻¹) | Succinate:cytochrome *c* reductase* (nmol·min⁻¹·mg⁻¹) | NADPH:cytochrome *P*-450 reductase† (nmol·min⁻¹·mg⁻¹) |
|---|---|---|---|---|
| Nuclei | 0.52 ± 0.02 | 60.0 ± 15.3 | 163.4 ± 45.4 | 18.7 ± 9.2 |
| Mitochondria | 1.08 ± 0.11 | 90.3 ± 21.4 | 180.8 ± 56.2 | 71.0 ± 30.2 |
| Microsomal | 0.53 ± 0.02 | 15.1 ± 3.7 | 5.2 ± 0.3 | 150.6 ± 33.2 |
| 105000*g* supernatant | 0.18 ± 0.02 | 28.1 ± 8.4 | 4.5 ± 0.7 | 11.1 ± 6.2 |

* Mitochondrial marker enzyme.
† Microsomal marker enzyme.

the low-speed nuclear fraction was probably a reflection of mitochondrial contamination. Δ⁶-Desaturase activities of both the mitochondrial and the microsomal fractions were optimal under the incubation conditions described. Activities were not altered significantly by 2-fold increases in the concentrations of ATP, $Mg^{2+}$, CoA or NADH added either individually or collectively to the incubation cocktail (Table 2). Mitochondrial Δ⁶-desaturase activity was linear for up to 6 min under the incubation conditions described in the Materials and methods section. In all subsequent experiments an incubation time of 3 min and the standard incubation conditions described in the Materials and methods section were used.

A similar predominance of Δ⁶-desaturase activity was observed in the mitochondrial fractions of obese mouse liver (Table 2). However, hepatic mitochondrial Δ⁶-desaturase activity was significantly increased in obese mice in comparison with their lean littermates, whereas there were no significant differences in microsomal Δ⁶-desaturase activity. Hepatic mitochondrial Δ⁶-desaturase activity was lower and similar in 17-day-old suckling lean and pre-obese mice ($0.65 \pm 0.02$ and $0.58 \pm 0.05$ nmol·min⁻¹·mg⁻¹ for four lean and four pre-obese mice respectively), in confirmation of the previous observations on hepatic homogenates.

Mitochondrial preparations were used in all subsequent studies on the regulation of Δ⁶-desaturase activity. Hyperphagia, a characteristic of the obese (*ob/ob*) mouse, does not appear to be present in the suckling pre-obese mouse (Rath & Thenen, 1979). To investigate whether the increased hepatic Δ⁶-desaturase activity in obese mice was secondary to their hyperphagia, the effect of starvation and pair-feeding to lean littermates was studied. Obese mice were individually pair-fed with lean mice during a daily feeding period restricted to only 2.5 h. This feeding regime, which reduced food intake of lean mice by 30% and removed differences in feeding frequency between lean and obese mice, also reduced serum insulin (as

Table 2. *$\Delta^6$-Desaturase activity in hepatic mitochondria and microsomes of lean and obese mice at 8 weeks of age*
Enzyme activity was assayed under the incubation conditions described in the Materials and methods section or in the presence of additional concentrations of cofactors as shown. Values represent means for the number of observations shown in parentheses; S.E.M. values are presented when the number of observations exceeds three. $^{**}P<0.01$; $^{***}P<0.001$ compared with lean group.

| | $\Delta^6$-Desaturase activity [nmol·min$^{-1}$·(mg of protein)$^{-1}$] | | | |
|---|---|---|---|---|
| | Mitochondria | | Microsomes | |
| Additions | Lean | Obese | Lean | Obese |
| None | 0.95±0.02 (4) | 1.34±0.02 (4)*** | 0.40±0.05 (4) | 0.61±0.11 (4) |
| +2mM-ATP | 1.02 (2) | | 0.38 (2) | |
| +2mM-$Mg^{2+}$ | 1.13 (2) | | 0.43 (2) | |
| +2mM-$Mg^{2+}$/ATP | 1.91±0.02 (4) | 1.23±0.10 (4)** | 0.36 (2) | |
| +0.5mM-NADH | 0.88 (2) | | 0.44 (2) | |
| +0.2mM-CoASH | 1.15 (2) | | 0.36 (2) | |
| +All of the above | 1.12±0.08 (4) | 1.50±0.11 (4) | 0.41 (2) | |

Table 3. *Effect of food intake on hepatic mitochondrial $\Delta^6$-desaturase activity of lean and obese mice*
Mice were either fed *ad libitum* ('*Ad lib*') or were pair-fed ('Restricted') during a 2.5h restricted feeding period for 13 days. Mice were killed at the end of the 2.5h feeding period. Mice fed *ad libitum* were starved for 17h before being killed ('starved'). Values represent means±S.E.M. for the numbers of animals (*n*) shown. $^{*}P<0.05$; $^{***}P<0.001$ compared with equivalent lean group (Student's *t* test for paired data).

| Animals | Dietary status | *n* | $\Delta^6$-desaturase activity (nmol·min$^{-1}$·mg$^{-1}$) | | Food intake (g/day) | [Insulin] (μ-i.u./ml) | |
|---|---|---|---|---|---|---|---|
| Lean | *Ad lib* | 4 | 0.87±0.04 | $P<0.05$ | 4.96±0.17 | 52±5 | |
| | Restricted | 4 | 0.67±0.04 | | 3.51±0.15 | 65±9 | |
| Obese | *Ad lib* | 4 | 1.10±0.04* | $P<0.01$ | 6.76±0.25 | 350±26*** | $P<0.001$ |
| | Restricted | 4 | 0.80±0.03* | | 3.48±0.19 | 85±12 | |
| Lean | *Ad lib* | 3 | 0.80±0.05 | $P<0.001$ | 4.90±0.24 | 59±8 | $P<0.01$ |
| | Starved | 4 | 1.52±0.06 | | – | 15±5 | |
| Obese | *Ad lib* | 3 | 1.29±0.04 | $P<0.001$ | 6.65±0.23 | 383±37*** | $P<0.001$ |
| | Starved | 4 | 1.65±0.04 | | – | 80±11* | |

measured at the end of the feeding period) of the obese mice to levels similar to those of meal-fed mice. Restriction of food intake to similar levels reduced hepatic $\Delta^6$-desaturase activity in both lean and obese mice, but $\Delta^6$-desaturase activity remained significantly elevated in the obese group (Table 3), as measured at the end of their feeding period, despite the similarity in serum insulin in the two groups of mice. When, however, the $\Delta^6$-desaturase activity was measured 17h after the end of the previous meal, the enzyme activity had risen to similar high values in both lean and obese mice. Chronic treatment of lean mice with insulin (40i.u./day per kg for 3 days) did not increase mitochondrial $\Delta^6$-desaturase activity (0.76±0.06 and 0.77±0.03nmol·min$^{-1}$·mg of protein$^{-1}$ for control and insulin-treated mice respectively, despite a 2-fold increase in serum insulin from 59.7±3.7 to 93.9±6.0μ-i.u./ml) (mean±S.E.M. for four mice in each group).

As the abnormal membrane composition of *ob/ob* mice may be partially rectified by housing at a thermoneutral temperature (34°C) (Hyslop & York, 1980; French *et al.*, 1983), we decided to investigate the effect of housing temperature on mitochondrial desaturase activity. Animals were housed at a range of temperatures from 4 to 34°C for 14 days before assay of hepatic mitochondrial $\Delta^6$-desaturase activity (Fig. 2). Housing the mice at 34°C did not affect the increased $\Delta^6$-desaturase activity of obese-mouse liver mitochondria, which remained 35% higher than that in lean mice. In contrast, after housing at 12°C, the hepatic $\Delta^6$-desaturase activity of obese mice was decreased towards that of lean mice, which remained unchanged. However, exposure to extreme cold (4°C) for 7 days, after pre-acclimation at 12°C for 7 days, reduced hepatic mitochondrial $\Delta^6$-desaturase activity of both lean and obese mice to similar levels (0.891nmol·min$^{-1}$·mg$^{-1}$ and 0.893nmol

·min$^{-1}$·mg$^{-1}$ for lean and obese mice respectively). $\Delta^6$-Desaturase is inhibited by thyroid hormones (Gomez-Dumm *et al.*, 1977). Since the obese *ob/ob* mouse may be hypothyroid (Bray & York, 1979), the observation that hepatic $\Delta^6$-desaturase activity was normalized in cold-acclimated obese mice prompted an investigation of the effect of thyroid status on the elevated $\Delta^6$-desaturase activity of obese mice. The effect of tri-iodothyronine treatment on hepatic $\Delta^6$- and $\Delta^5$-desaturase activities is shown in Fig. 3. The activity of $\Delta^5$-desaturase was lower than that of $\Delta^6$-desaturase in lean mice, in agreement with a previous report (Sprecher, 1977). Although $\Delta^6$-desaturase and $\Delta^5$-desaturase activities were similarly related in obese mice, the activities of both enzymes were higher than those of the lean controls. Tri-iodothyronine reduced the elevated activities of hepatic $\Delta^5$- and $\Delta^6$-desaturases of obese mice to the levels observed in lean mice, but had no effect on lean mice. In contrast, although the induction of an hypothyroid state increased mitochondrial $\Delta^6$-desaturase activity in both lean and obese mice above the levels observed in the control groups, the activity in the hypothyroid obese mice remained significantly higher (29%) than that in lean hypothyroid mice. Tri-iodothyronine treatment of hypothyroid mice again reduced $\Delta^6$-desaturase activities to similar levels in both lean and obese groups.

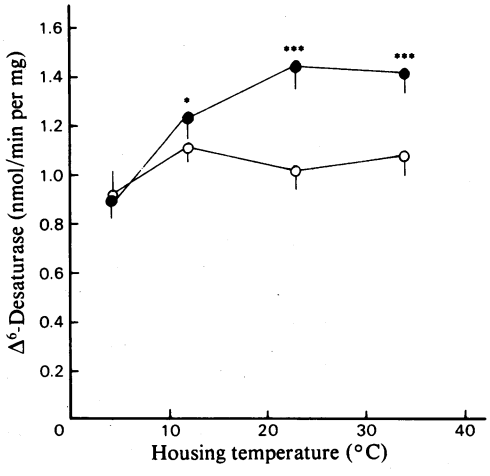


Fig. 2. *Effect of housing temperature on hepatic mitochondrial $\Delta^6$-desaturase activity of lean* (○) *and obese* (●) *mice*
Four lean and four obese mice (7 weeks of age) were acclimated to each temperature for 7 days before being killed. Mice acclimated to a 4°C environment for 7 days were housed at 14°C for the preceding 7 days to prevent any mortality in the obese group. Values represent means ± S.E.M. $*P < 0.05$; $***P < 0.005$ compared with the lean group.

## Discussion

The highest activity of the $\Delta^6$-desaturase was observed in the mitochondrial fractions of mouse liver. This was surprising, as it is generally accepted that the desaturase enzymes are present mainly in the microsomal fraction (Brenner, 1977; Naughton, 1981), although it has long been

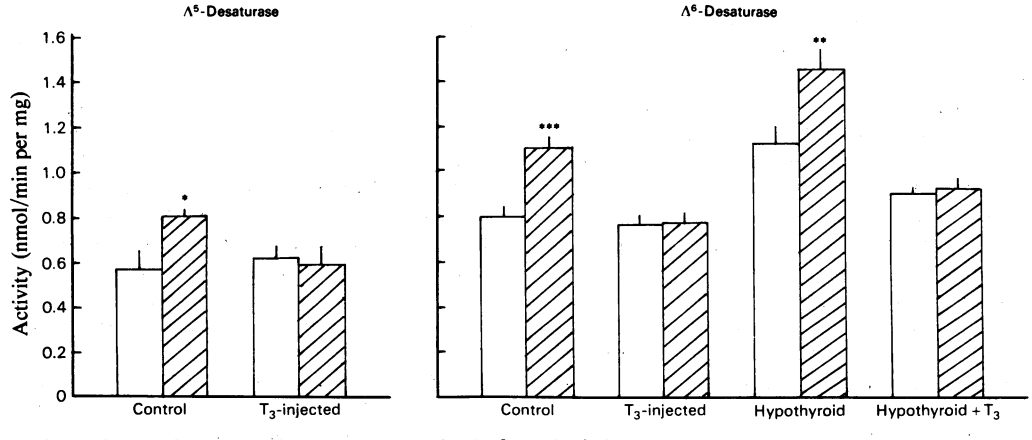


Fig. 3. *Effect of thyroid status on hepatic mitochondrial $\Delta^5$- and $\Delta^6$-desaturase activities of lean* (□) *and obese* (▨) *mice*
Mice (6 weeks old) were injected subcutaneously with either saline (0.9%, w/v) vehicle or tri-iodothyronine ($T_3$) (30 $\mu$g/kg twice daily for 14 days). An hypothyroid state was induced by provision of a low-iodine diet and perchlorate (0.5%, v/v) drinking solution for 14 days, saline vehicle or tri-iodothyronine being injected subcutaneously on days 8–14. Values represent means ± S.E.M. for five mice in each group. $*P < 0.05$; $**P < 0.01$; $***P < 0.005$ compared with lean mice.

recognized that mitochondria are capable of desaturation (Dahlen & Porter, 1968) and elongation (Harlan & Wakil, 1963) of the essential fatty acids. Most of these previous studies used rat liver. Indeed, the activity of mouse hepatic microsomal $\Delta^6$-desaturase reported in the present study was in fact higher than that previously reported for rat hepatic microsomes (Cook, 1978; Faas & Carter, 1981, 1982). The localization of high $\Delta^6$-desaturase activity in murine hepatic mitochondria may represent a species difference. Previous work has also shown that hepatic steroyl ($\Delta^9$-)CoA desaturase activity is increased in obese mice (Enser & Roberts, 1982), principally as a consequence of the increase in substrate supply that results from the excessive rates of hepatic lipogenesis. Such increases in $\Delta^9$-desaturase activity are common to many forms of obesity (Enser & Roberts, 1982; Wahle & Radcliffe, 1977).

Although obese mice have a low proportion of polyunsaturated fatty acids in their liver lipids (Enser & Roberts, 1982; Winand *et al.*, 1969), the proportion in membrane phospholipids is increased when compared with lean mice (French *et al.*, 1983; Hyslop *et al.*, 1982; York *et al.*, 1982). The activity of hepatic $\Delta^6$- and $\Delta^5$-desaturases was increased in the obese mice. These desaturases are rate-limiting enzymes in the biosynthesis of long-chain polyunsaturated fatty acids and are subject to regulation by numerous hormones, in addition to being responsive to substrate and product effectors (Brenner, 1977; Naughton, 1981). Insulin increases hepatic microsomal $\Delta^6$-desaturase activity (Brenner, 1977). However, it is unlikely that the hyperinsulinaemia of the obese mice was responsible for the increase in mitochondrial $\Delta^6$-desaturase activity of obese mice, since (*a*) the severe dietary restriction imposed by meal-feeding and the consequent reduction of serum insulin did not decrease the enzyme activity to the levels of lean mice, and (*b*) chronic treatment of lean mice with insulin did not increase mitochondrial $\Delta^6$-desaturase activity to the levels observed in obese mice.

The increased activity of mitochondrial $\Delta^6$-desaturase in obese mice was not observed in suckling pre-obese mice, but was apparent within 7 days of weaning. Similarly, the changes in Arrhenius break temperatures of the hepatic plasma-membrane enzymes ($Na^+ + K^+$)-dependent ATPase (Hughes & York, 1983) and 5′-nucleotidase (R. R. French & D. A. York, unpublished work) of obese mice do not appear until after weaning. These changes in Arrhenius characteristics have been associated with changes in membrane composition. The coincident appearance of increased $\Delta^6$-desaturase activity and the changes in Arrhenius break points of membrane enzymes shortly after weaning suggests that the membrane phospholipid acyl composition changes of obese mice may reflect metabolic changes associated with weaning.

The increase in hepatic $\Delta^6$-desaturase activity that normally occurs after weaning is thought to reflect the increased supply of dietary essential fatty acid (Cook, 1978; Naughton, 1981). As the hyperphagia of the obese mouse only develops after weaning, it was possible that this increase in food intake was responsible for the elevated $\Delta^6$-desaturase activity. However, it is unlikely that the $\Delta^6$-desaturase activity of obese-mouse hepatic mitochondria is simply a reflection of increased substrate supply, since $\Delta^6$-desaturase activity remained elevated in the obese mice pair-fed a restricted level of food with lean mice, whereas starvation increased $\Delta^6$-desaturase activity to similar levels in lean and obese mice.

Obese mice exhibit a number of developmental characteristics that have been suggested as indicative of hypothyroidism (Bray & York, 1979; Van der Kroon *et al.*, 1982). However, serum concentrations of tri-iodothyronine are normal, although serum thyroxine concentrations may be decreased at certain ages (Ohtake *et al.*, 1977; York *et al.*, 1978; Mobley & Dubuc, 1979). Tissue and membrane fatty acid compositions are known to be affected by thyroid status (Patton & Platner, 1971; Chen & Hoch, 1977; Faas & Carter, 1981, 1982; French *et al.*, 1983). Similarly, thyroid hormones have been shown to inhibit hepatic microsomal $\Delta^6$-desaturase activity in the rat (Gomez-Dumm *et al.*, 1977; Faas & Carter, 1981, 1982). In the present paper we have reported that the mouse hepatic mitochondrial $\Delta^5$- and $\Delta^6$-desaturase activities were responsive to thyroid status, being increased in hypothyroid animals, an effect that was inhibited by tri-iodothyronine. Tri-iodothyronine reduced the activity of both $\Delta^5$- and $\Delta^6$-desaturases of obese mice down to the levels observed in lean mice without affecting their hyperphagia. This is further evidence that the changes in desaturase activity are not related to dietary intake of substrate. Furthermore, $\Delta^6$-desaturase activity was reduced to similar levels in both lean and obese mice acclimated to a 4°C housing temperature, a condition associated with increasing food intake.

The cold-induced reduction in $\Delta^6$-desaturase activity would be consistent with the physiological regulation of the enzyme by thyroid hormones. However, the maintenance of the difference in $\Delta^6$-desaturase activity in hypothyroid lean and obese mice suggests that factors other than thyroid status may be primarily responsible for the increased $\Delta^6$-desaturase activity observed in obese mice.

This research was supported by a grant from the British Diabetes Association.

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