Alterations in membrane function, organization and composition in the obese *ob/ob* mouse

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In recent years, in vitro investigations with model membrane systems have been used to show the influence of membrane composition or fluidity, or both, on the activity of membrane-associated proteins. These studies have been supported by investigations on native membranes in which the lipid fluid environment has been perturbed or into which differing lipids have been equilibrated (for reviews, see Sanderman, 1978; Houslay & Gordon, 1983; Stubbs & Smith, 1984). While such artificial systems clearly illustrate the interdependence of lipid composition to membrane protein function, the demonstration that dietary manipulation may also alter membrane composition and influence the activity of membrane-associated proteins (Innis & Clandinin, 1981; McMurdine *et al.* 1983; Wahle, 1983) suggests that such interrelations are of physiological significance to the cell and animal. Membrane phospholipids also serve the role of eicosanoid precursors and changes in the relative amounts of individual polyunsaturated fatty acids may influence membrane function through the production of prostaglandins, thromboxane and leukotrienes. Obesity entails the deposition of excess lipid, particularly triacylglycerols and cholesterol, within cells and is often reported to be associated with a change in fatty acid composition (Bray & York, 1979). In the light of the ability to influence membrane composition by diet, it would be surprising if the presence of abnormal quantities of lipid within cells did not influence the composition and function of membranes. In the present paper, I would like to review studies of membrane function in obesity, with particular regard to the function of integral membrane proteins. The review will concentrate on the genetically-obese *ob/ob* mouse, since it is on this animal model of obesity that the majority of research has been conducted.

Membrane function in the ob/ob *mouse*

Table 1 lists a number of membrane-associated processes which have been reported to be abnormal in the *ob/ob* mouse. The diversity of these abnormalities in the function of membrane-localized proteins is evident from Table 1, but our knowledge of the causes of these changes is, for most of the examples, rather superficial. Impaired basal glucose uptake into muscle of *ob/ob* mice has been shown using both isolated soleus muscle (Cuendot *et al.* 1976; Le Marchand-Brustel *el al.* 1978) and perfused hind-limb preparations (Oshima *et al.* 1984). This impairment does not appear to be related to the developing insulin insensitivity of the muscle, which is clearly demonstrable by the poor response of

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Table 1. *Some alterations in membrane function in obese mice*

	References*
1. Transport and secretion:	
Glucose transport	Cuendot *et al.* 1976
Calcium transport	Fraser & Trayhurn, 1984
Sodium–potassium transport	Flier *et al.* 1981
Insulin secretion	Beloff-Chain *et al.* 1973
2. Receptors	
Adrenergic	Begin-Heick, 1981
Insulin	Kahn *et al.* 1973
Vasopressin	Assimacopoulos-Jeannet *et al.* 1984
Glucagon	Assimacopoulos-Jeannet *et al.* 1984
Angiotensin II	Assimacopoulos-Jeannet *et al.* 1984
32 kdalton protein of brown adipose tissue mitochondria	Hogan & Himms-Hagen, 1980
Lectin binding	Chang *et al.* 1975
3. Enzymes	
Adenylate cyclase (*EC* 4.6.1.1)	French & York, 1984
5′-Nucleotidase (*EC* 3.1.3.5)	French *et al.* 1983
$[Na^+ + K^+]$ATPase (*EC* 3.6.1.8)	Hughes & York, 1983
Microsomal NADPH-cyt P_{450} oxidoreductase (*EC* 1.6.2.4)	Hyslop *et al.* 1982
Microsomal ethoxycoumarin-*o*-ethyl transferase (*EC* 2.2.1.99)	Rouer *et al.* 1980
Mitochondrial oxidative enzymes	Katyare & Howland, 1980
4. Other	
Immune system, T-cell function	Meade & Sheena, 1979

*Further references are given in the text.

both glucose transport and metabolism to insulin stimulation. Neither does the reduction in glucose transport result from increased oxidation of free fatty acids and the consequent impairment of glucose metabolism and transport (Cuendot *et al.* 1976). However, it is of note that both basal glucose transport into hind-limb muscle of *ob/ob* mice and its responsiveness to insulin were normalized after adrenalectomy (Oshima *et al.* 1984). Further, basal glucose transport and its coupling to the insulin receptor may be sensitive to its phospholipid environment within the membrane (Czech, 1980).

Abnormalities in calcium transport both at the cellular and subcellular levels have been reported in *ob/ob* mice. The stimulation of Ca uptake into adipocytes by a variety of hormones and by cyclic AMP was absent in *ob/ob* mice (Dehaye *et al.* 1979). Isolated mitochondria from liver and brown adipose tissue of *ob/ob* mice showed increased rates of ^{45}Ca uptake and release compared with those of lean mice (Fraser & Trayhurn, 1984), indicative of an activation of the Ca^{2+} uniporter.

Hyperinsulinaemia is a common characteristic of obesity in both man and animal models (Bray & York, 1979). There is considerable evidence to suggest that this hyperinsulinaemia may, in some models of obesity at least, be secondary either

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to any hyperphagia or to an altered autonomic regulation of the pancreatic β-cells, parasympathetic stimulation predominating over sympathetic inhibitory influences (Bray & York, 1979; Jeanrenaud, 1981), or to enhanced stimulation by pituitary β-cell tropin (Beloff-Chain *et al.* 1979; Billingham *et al.* 1982). However, an increased insulin secretory response to a number of stimuli was also evident in isolated islets incubated in vitro when separated from all nervous, endocrine and nutrient influences (Beloff-Chain *et al.* 1973; Lavine *et al.* 1977).

The binding of numerous hormones to their plasma membrane receptors is altered in the obese *ob/ob* mouse. The reduction in the number of insulin receptors on hepatic, adipocyte and muscle plasma membranes has been attributed to a down regulation of the reception number in the presence of a high circulating insulin concentration (Kahn *et al.* 1973; Soll *et al.* 1975; Le Marchand-Brustel & Freychet, 1978; Grundleger *et al.* 1980). The number of β-receptors on white adipocytes of *ob/ob* mice has been shown to be reduced compared with those of lean mice, although the affinity remains normal (Begin-Heick, 1981; French & York, 1984). However, the β_2-subtype predominates in *ob/ob* mice rather than the β_1-subtype as in lean mice (Begin-Heick, 1981). The absence of any vasopressin regulation of hepatic glycogenolysis or lipogenesis in the *ob/ob* mouse has recently been attributed to the complete absence of vasopressin V_1-type receptors in the liver, whereas renal vasopressin V_2-type receptors are present in normal numbers and have normal affinity (Assimacopoulos-Jeannet *et al.* 1984). Vasopressin V_2 receptor effects are mediated through adenylate cyclase (*EC* 4.6.1.1) whereas the V_1 receptor effects are mediated through the phosphoinositide regulation of Ca transport. The numbers of specific receptors for angiotensin II and glucagon are also reduced in hepatocytes of *ob/ob* mice and result in a reduction in sensitivity and maximal response of phosphorylase phosphatase (*EC* 3.1.3.17) to angiotensin II and a reduction in sensitivity only for glucagon (Assimacopoulos-Jeannet *et al.* 1984). The explanation of these reductions in a specific-binding of vasopressin, glucagon and angiotensin II are, as yet, unclear but do not appear to reflect down regulation in response to elevated levels of circulating hormone.

Membrane fluidity and membrane lipid composition have been shown to affect the specific binding of a variety of hormones to their receptors. Temperature-induced reduction in fluidity and increases in membrane phospholipid acyl unsaturation have been associated with an increase in the number of insulin receptor sites (Gould *et al.* 1979; Ginsberg *et al.* 1981). Reconstitution experiments with β-receptors from turkey erythrocyte membranes suggest that phospholipids, in particular phosphatidylethanolamine, are important in obtaining maximal binding (Kirolovsky & Schramm, 1983) whereas experiments using phospholipase treatment have suggested that the phospholipid polar head groups might also influence β-receptor binding, although the interpretation of these latter experiments has been queried (Loh & Law, 1980).

The specific binding of [^{3}H]GDP to the 32 kdalton protein of brown adipose tissue mitochondria has been used extensively to illustrate the deficiency in the thermogenic proton conductance pathway of obese rodents. However, the apparent

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lack of binding sites and of proton translocation may reflect a 'masking' of the protein and its GDP binding sites in the membrane since the quantity of 32 kdalton protein within the membrane of both obese *ob/ob* mice and obese *fa/fa* rats appears to be normal by both immunoassay (M. Ashwell, S. J. Holt and D. A. York, unpublished results) and gel electrophoretic techniques (Hogan & Himms-Hagen, 1980). Chang *et al.* (1975) originally suggested that there was a generalized defect in the production of membrane glycoproteins in *ob/ob* mice from their studies on lectin binding in which they demonstrated that the magnitude of the reduction in binding of concanavalin A and wheat-germ agglutinin to hepatic and renal membranes of obese mice was far greater than the reduction in binding of hormones such as insulin where the receptor is known to be a glycoprotein. Although this suggestion has not been extensively investigated, Sena *et al.* (1982) have shown a gene-dependent reduction in sialic acid residues in the liver and brain of *ob/ob* mice. This work, however, requires validation since the values were expressed on the basis of dry tissue weight rather than membrane protein. Nevertheless, the distribution of the major ganglioside fractions was not significantly different in *ob/ob* mice. Perhaps the best illustration of a membrane glycoprotein change in obesity has been reported by Makula & Goekjian (1982) who demonstrated a reduction in the number of galactose-containing residues and a compensatory increase in non-carbohydrate-containing proteins in adipocyte plasma membranes of obese *fa/fa* rats. The possible interrelations between any generalized defect in membrane glycoproteins and the impaired function of specific membrane glycoproteins, such as the insulin receptor and glucose transporter, remain to be investigated.

The activities of a number of membrane-associated enzymes are altered in the obese *ob/ob* mouse (see Bray & York, 1979). Not only are the activities of the enzymes listed in Table 1 altered in *ob/ob* mice, but the temperatures of inflection in the Arrhenius plots of their activities are also different from those of lean mice (Rouer *et al.* 1980; Hyslop *et al.* 1982; French *et al.* 1983; Hughes & York, 1983; R. R. French and D. A. York, unpublished results). Arrhenius break temperatures are indicative of phase transitions within the membrane lipid which influence the activity of that enzyme. Changes in the break temperature are thought to be indicative of interactions with an altered lipid environment within the membrane bilayer (Houslay, 1985). Thus it has been suggested that the increase in activity and decrease in activation energy of microsomal NADPH-cytochrome P_{450} oxidoreductase (NADPH-cytochrome reductase; *EC* 1.6.2.4) results from its interaction with a more unsaturated phosphatidylcholine in the obese mice (Hyslop *et al.* 1982). Alterations in the phospholipid composition of microsomes may be responsible for the increase in the proportion of glutathione–insulin transhydrogenase (thiol oxidase; *EC* 1.8.3.2) in the latent form in *ob/ob* mice (Varandani & Nafz, 1976). The reduction in activity of plasma membrane [Na^+ + K^+]ATPase in a number of tissues of *ob/ob* mice was correlated with a lack of enzyme units within the membrane as indicated by specific binding of the inhibitor [^{3}H]ouabain (York *et al.* 1978; Lin *et al.* 1978, 1979*b*). However, this now seems

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unlikely since the reduction in [^{3}H]ouabain binding to synaptosomal membranes of *ob/ob* mice was abolished after treatment of the membranes with low concentrations of deoxycholate. Furthermore, the Arrhenius break temperatures for both [^{3}H]ouabain binding and [Na^+ + K^+]ATPase activity were reduced in *ob/ob* mice (Hughes & York, 1983). The findings suggest that the loss of [Na^+ + K^+]ATPase enzyme activity may result from the development of an abnormal membrane lipid environment in the obese mouse. Membrane phospholipids are known to affect [Na^+ + K^+]ATPase activity in a variety of membrane systems (Sanderman, 1978; Jorgensen, 1982).

The impaired isoprenaline stimulation of adenylate cyclase (*EC* 4.6.1.1.) in adipocyte plasma membranes of *ob/ob* mice is associated with a linear rather than bifunctional Arrhenius plot (R. R. French and D. A. York, unpublished results) and was improved after housing the mice at 34° when membrane fluidity was normalized (Hyslop & York, 1980). Such findings suggest that the impaired isoprenaline stimulation of adenylate cyclase in *ob/ob* mice may be associated with changes in membrane fluidity or composition.

Reduced cellular immunity has been demonstrated for both the obese (*ob/ob*) and the diabetic (*db/db*) mouse, whereas the formation of antibodies by B lymphocytes is normal or even enhanced (for reviews see Bray & York, 1979; Meade & Sheena, 1979). In vitro experiments have shown that this impairment in T-cell function in the obese and diabetic mice results from the environment in which it resides rather than from a defect in the T-cell function *per se*. The basis of the inhibitory influences in T-cell function in these obese models is not known. However, once again it is known that diet, in particular its lipid composition, may influence T-cell function possibly through changes in membrane composition (Vitale & Broitman, 1981; Smith *et al.* 1985).

The obesity of the obese *ob/ob* mouse is inherited as a single gene (homozygous recessive trait). It is unlikely that the wide diversity of membrane functional changes could be explained as a pleiotropic expression of this single gene. Since many of the membrane protein functions described in Table 1 are known to be responsive to membrane lipid composition, the possibility that widespread changes in membrane lipid composition may be associated with the obese state and be responsible for some of the membrane functional changes has been investigated.

Fluorescence polarization studies of membranes from obese mice

The fluorescence polarization technique (see Lee, 1985) using a diphenylhexatriene (DPH) probe has been used to compare membrane fluidity in lean and obese *ob/ob* mice. An increase in fluidity (decrease in polarization) is characteristic of a wide variety of cellular and subcellular membranes of the *ob/ob* mouse (Table 2). The Arrhenius break temperatures of DPH polarization are also consistently lower in the membranes of *ob/ob* mice. These findings suggest that the DPH is partitioning into a different lipid environment in the membranes of *ob/ob* mice and are indicative of either a change in lipid organization across the membrane bilayer or altered lipid composition. The latter suggestion seems a more likely explanation

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Table 2. *Diphenylhexatriene (DPH) fluorescence polarization (P_{37}) and Arrhenius break temperature of DPH polarization in membranes from lean and obese mice and rats*

(Values represent means with their standard errors for at least three observations. Where no standard error is given, value represents mean of two Arrhenius plots. Values are from Hyslop *et al.* (1982), Hyslop (1981) or D. A. York, unpublished results)

Membrane	P_{37}				Arrhenius break temperature (°)			
	Lean		Obese		Lean		Obese	
	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Animal: Lean or obese (*ob/ob*) mouse								
Adipocyte plasma	0·249	0·001	0·224	0·003	25·1	0·3	17·6	0·7
Hepatic plasma	0·205	0·001	0·187	0·001	21·2	1·3	15·8	1·2
Salivary gland plasma	0·200		0·185		20·3		17·7	
Pancreatic plasma	0·167		0·152					
Synaptosomal	0·241		0·222		23·3		18·6	
Inner mitochondrial:								
Hepatic	0·197		0·178		19·8		15·4	
Brown adipose	0·178		0·152					
Hepatic microsomes*	0·245	0·002	0·221	0·003	9·5	0·3	6·5	0·2
Muscle sarcolemmal*	0·237		0·206					
Erythrocyte	0·286		0·299		26·0		28·2	
Animal: Lean or obese (*fa/fa*) Zucker rat								
Adipocyte plasma	0·223		0·208		23·7		13·5	
Synaptosomal	0·251		0·237		25·8		19·3	

*Total phospholipid extract from these membranes.

since the total phospholipid extract of *ob/ob* membranes when sonicated into vesicles also shows a reduction in DPH polarization in comparison with phospholipids from lean-mouse membranes (French *et al.* 1983). The erythrocyte membrane of *ob/ob* mice is exceptional in that DPH polarization value is increased in comparison with that of lean mice. This is thought to result from an increased equilibration of cholesterol into the membranes from the hypercholesterolaemic serum. Rouer *et al.* (1980), in their studies of the microsomal enzyme ethoxycoumarin-*o*-ethyl transferase (*EC* 2.2.1.99), were unable to show any difference in DPH polarization at 37° although the Arrhenius break temperatures for DPH polarization and enzyme activities were reduced in the *ob/ob* mice. The apparently normal membrane fluidity in *ob/ob* mice at 37° may be an artefact since these workers failed to separate microsomal membranes from the glycogen granules which would greatly enhance light scattering.

DPH polarization in phospholipid vesicles prepared after extraction and separation of membrane phospholipids has been used to identify major differences in phospholipid composition between lean and obese mice. In adipocyte plasma

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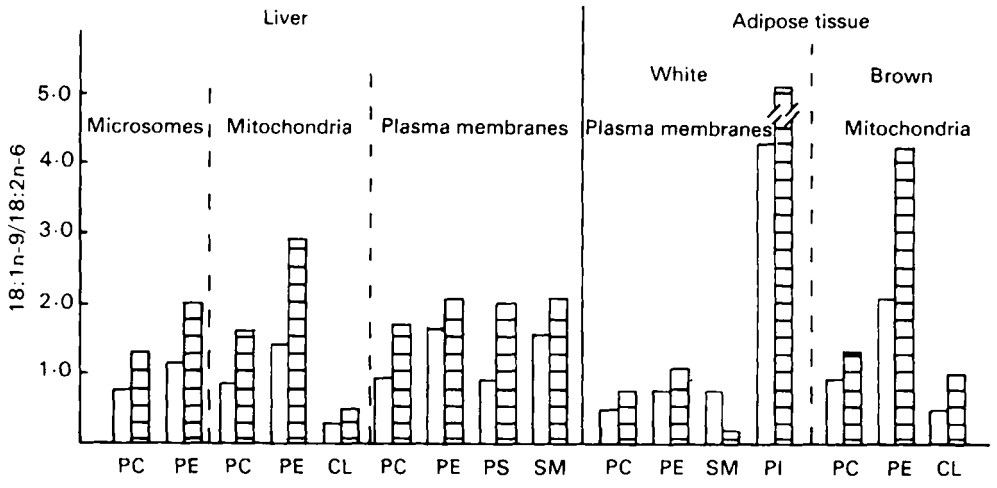

Fig. 1. Ratio, oleic (18:1n-9)/linoleic (18:2n-6) acids in phospholipids of tissue and organelle membranes of lean (□) and obese *ob/ob* (▤) mice. PC, phosphatidylcholines; PE, phosphatidylethanolamines; CL, cardiolipins; PS, phosphatidylserines; SM, sphingomyelins; PI, phosphatidylinositols (18:9).

membranes of *ob/ob* mice the major change appears to be a large increase in the fluidity of phosphatidylethanolamine (York *et al.* 1982) which, by derivitization experiments with trinitrobenzene sulphonic acid, has been shown to be located in the inner half of the bilayer (P. S. Hyslop and D. A. York, unpublished results). In contrast, in hepatocyte plasma membranes, the major change appears to be in the sphingomyelin component (York *et al.* 1982; French *et al.* 1983) which is normally located in the outer half of membrane phospholipid bilayers (Op den Kamp, 1979). Thus it is likely that fluidity changes in the membranes of *ob/ob* mice will not be distributed symmetrically across the lipid bilayer and will show both tissue and organelle specificity. It should also be remembered that specific phospholipid changes may result in a redistribution of cholesterol within the bilayer (Hyslop, 1981).

Similar increases in membrane fluidity, as indicated by lower DPH polarization and lower Arrhenius break temperatures, have also been observed in adipocyte plasma membranes and synaptosomal membranes of Zucker obese *fa/fa* rats (Table 2).

Membrane lipid composition

There have been numerous reports of tissue lipid composition in *ob/ob* mice but relatively few reports specifically on membrane lipids. Varandani & Nafz (1976) showed that hepatic microsomes from *ob/ob* mice contained less phospholipid than those from lean mice and that the proportions of the phospholipids, in particular phosphatidylethanolamine and phosphatidic acid, were altered. A reduction in phospholipid content has also been reported in hepatic plasma membranes of *ob/ob* mice (French *et al.* 1983) whereas both phospholipid and cholesterol content and

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the distribution of phospholipid subclasses of adipocyte plasma membranes were all unaltered (York *et al.* 1982).

Changes in the fatty acyl composition of phospholipids in *ob/ob* mouse membranes are common although there are great variations between individual phospholipids in the same membrane bilayer, between different membrane fractions within the same tissue and between similar membranes in different tissues (Rouer *et al.* 1980; Hyslop *et al.* 1982; York *et al.* 1982; French *et al.* 1983). For example, a large increase in the proportion of docosohexaenoic acid (22:6n-3) in phosphatidylethanolamine has been reported in adipocyte plasma membranes of *ob/ob* mice, whereas the content of 22:6 fatty acids in phosphatidylethanolamine of hepatic plasma membranes is normal (York *et al.* 1982; French *et al.* 1983). However, the one consistent change which has been observed in the membrane phospholipids of *ob/ob* mice is an increase in the ratio, oleic (18:1n-9)/linoleic (18:2n-6) acids, as illustrated in Fig. 1. This may result, in part at least, from an increased desaturation of linoleic acid (18:2n-6) to more unsaturated fatty acids since the activities of both Δ6- and Δ5-desaturase enzymes are increased in *ob/ob* mice (S. Hughes and D. A. York, unpublished results). Normalization of hepatic Δ6-desaturase activity after thyroid hormone treatment was accompanied by correction of the ratio, 18:1/18:2 fatty acids in the phospholipids of hepatic plasma and mitochondrial membranes (Fig. 2.).

Similar increases in the 18:1/18:2 value of membrane phospholipids have also been observed (P. A. Hyslop and D. A. York, unpublished results) in hepatic microsomes of gold thioglucose-induced obesity and in synaptosomal membranes of the genetically obese rat, suggesting that these changes may be secondary to the development of obesity.

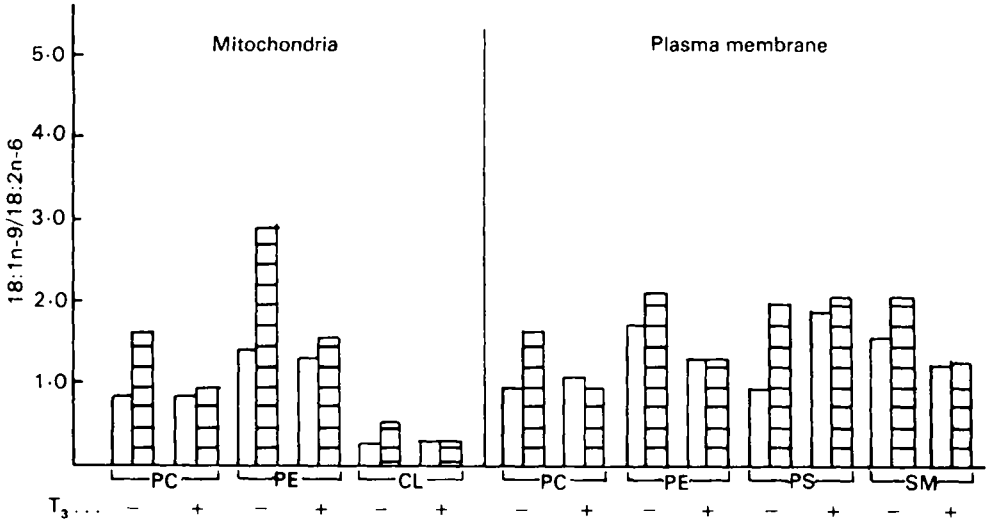

Fig. 2. Effect of triiodothyronine (T_3) on the ratio, oleic (18:1n-9)/linoleic (18:2n-6) acids in liver membrane phospholipids of lean (□) and obese *ob/ob* (■) mice. T_3 was given at a dose of 50 μg/kg per d. PC, phosphatidylcholines; PE, phosphatidylethanolamines; CL, cardiolipins; PS, phosphatidylserines; SM, sphingomyelins.

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Table 3. *Arrhenius break temperatures of* 5′*-nucleotidase* (*EC* 3.1.3.5) *and diphenylhexatriene* (*DPH*) *fluorescence polarization, and sphingomyelin acyl composition in hepatic plasma membranes of lean and obese* (ob/ob) *mice*

(Values for 18:1/18:2 represent means of two measurements of plasma membranes pooled from five animals in each group)

	Control†		32°‡		Triiodothyronine§	
	Lean	Obese	Lean	Obese	Lean	Obese
Arrhenius break temperatures (°):						
DPH polarization:						
Plasma membrane	21·2	15·8••	15·0	21·3••	21·1	21·9
Sphingomyelin vesicles	26·0	30·6••	30·7	23·9••	23·7	25·6••
5′-Nucleotidase activity	23·2	32·1••	29·4	19·2••	17·7	19·4••
Sphingomyelin 18:1/18:2	1·57	2·11	4·73	1·27	1·23	1·30

Significantly different from lean value: ••$P<0.01$.
†Housed at 24–25°.
‡Housed at 32° for 7 d.
§50 μg/kg per d for 6 d.

It is not clear at which stage of development of the *ob/ob* mouse the changes in membrane lipid composition or organization, or both, appear. The changes in [Na^+ + K^+]ATPase activity are not apparent either before weaning (Lin *et al.* 1979*a*; Hughes & York, 1983) or in a cultured preadipocyte line derived from obese mice (Forest *et al.* 1982). However, DPH polarization values and 5′-nucleotidase (*EC* 3.1.3.5) activity of hepatic plasma membranes are already altered immediately before weaning (R. R. French and D. A. York, unpublished results). Such preliminary results suggest that the membrane changes may develop over a period of time around weaning.

Membrane composition and 5′*-nucleotidase activity*

An understanding of the precise relation of the changes in membrane composition to the alterations in membrane function, examples of which are shown in Table 1, awaits further research. However, the increase in 5′-nucleotidase activity in hepatic plasma membranes of *ob/ob* mice may result from changes in sphingomyelin composition (French *et al.* 1983). 5′-Nucleotidase is purified as a sphingomyelin complex (Widnell, 1974; Merisko *et al.* 1981). The Arrhenius break temperature of hepatic plasma membrane 5′-nucleotidase was increased in *ob/ob* mice while the break temperature for DPH polarization in the same membranes was reduced indicating that the enzyme and probe were monitoring different lipid environments. Further studies on animals housed at 34° or treated with triiodothyronine showed a close correlation between the Arrhenius break temperatures for 5′-nucleotidase and DPH polarization in purified sphingomyelin vesicles (Table 3 and Fig. 3; French *et al.* 1983). Alterations of the ratio, (18:1n-9/18:2n-6) in sphingomyelin were associated with parallel changes in

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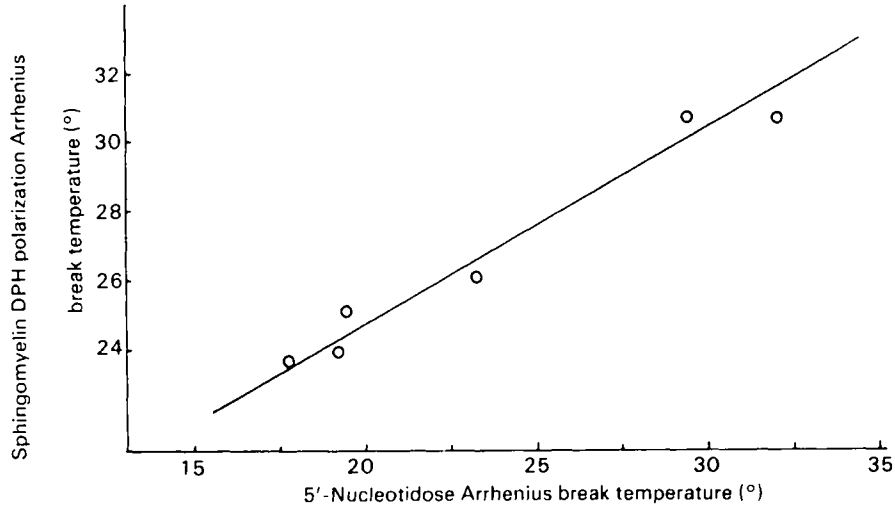

Fig. 3. Relation of Arrhenius break temperature of hepatic plasma membrane 5'-nucleotidase (*EC* 3.1.3.5) to Arrhenius break temperature of diphenylhexatriene (DPH) polarization in vesicles prepared from membrane sphingomyelin. Values are taken from Table 3.

Regression equation: $y = 1{\cdot}84x - 25{\cdot}6$, r 0.97.

Arrhenius break points of enzyme and activity of DPH polarization. No other phospholipid showed any close association of Arrhenius characteristics.

Membrane changes in other obesities

Very few investigations have been reported to date on either membrane composition or function in other forms of obesity. [Na^+ + K^+]ATPase activity is reduced in the diabetic *db/db* mouse but is unaltered in either gold thioglucose-induced obesity or the genetic obesity of the fatty *fa/fa* rat (Bray *et al.* 1978). Hepatic and erythrocyte [Na^+ + K^+]ATPase may be increased in human obesity (Bray *et al.* 1981; Mir *et al.* 1981) although some reports have found a reduction in enzyme activity in the obese (Deluise *et al.* 1980; Beutler *et al.* 1982). Since the majority of obese individuals are hypertriglyceridaemic and hypercholesterolaemic it might be expected that the lipid composition of blood cell membranes might be altered and this could be reflected in changes in cellular function. Studies with the obese mouse have shown that the membrane changes are individual to each tissue or organelle membrane. Thus it is unlikely that a particular change in membrane composition or function will be found universally in all forms of obesity, but rather that the changes may differ according to aetiology, age of onset, diet, etc. Further research is required to investigate the frequency of membrane compositional changes in other forms of obesity and their relevance to the altered metabolic status of obesity.

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