Effects of diet on fatty acid metabolism

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It has, of course, been known for a long time that diet can profoundly affect the amounts and nature of the lipids in the animal body. It is only fairly recently, however, that some measure of control of lipid metabolism by dietary manipulation has become possible. This has come about mainly as a result of advances in our knowledge of the digestive processes (see Lough, 1970; Garton, 1974; Leat & Harrison, 1975) and of the enzymes involved in lipogenesis (see Romsos & Leveille, 1974). Much of the recent research in these fields has been stimulated by the possible connexion between diet and cardiovascular disease on the one hand and, on the other, by the needs of the animal industry for more control over the deposition of fat in meat-producing animals, such as the ox, sheep and pig, and over the composition and output of milk fat.

In this brief review it is not possible to consider more than a few aspects of the relationship between diet and lipid metabolism and attention will accordingly be focussed first on several over-all effects on the amounts and fatty acid (FA) composition of tissue and milk lipids, and, secondly, on the influence of diet on enzymes which regulate the biosynthesis of FA. Even within these confines the original literature is so extensive that the papers and reviews to which reference is made were selected rather arbitrarily to illustrate some of the recent advances in our knowledge of the influence of diet on lipid metabolism.

Effects of diet on amounts and composition of tissue lipids

Liver and plasma lipids. Many investigations (mostly with rats and rabbits) have been conducted on the accumulation of liver lipids in response to various dietary components, especially carbohydrates (Allen & Leahy, 1966; Macdonald, 1966*a*; Bailey, Taylor & Bartley, 1968), leading to the conclusion that fructose as such, or as a constituent of sucrose, promotes hepatic lipogenesis to a greater extent than does glucose or any other carbohydrate. Several studies have recently been reported in which rats fed on protein-free diets have subsequently been given 'repletion' diets containing various sugars and, in one of these investigations, Aoyama & Ashida (1973) found that fructose stimulated lipogenesis to the greatest extent. In other similar studies Aoyama & Ashida (1972) observed that sucrose-induced fatty liver could be prevented when the repletion diet also contained a high proportion of fat in the form of lard. Further experiments by Aoyama, Yoshida & Ashida (1974) revealed that the effect of dietary fat in suppressing enhanced synthesis of liver lipids in fructose-fed rats was associated

with the presence of linoleic acid, saturated and mono-unsaturated FA being ineffective. These findings are complementary to those of Reiser, Williams, Sorrels & Murty (1963) who, using rats and mice respectively, found that utilization of acetate for hepatic FA synthesis was markedly depressed when the animals were fed on diets rich in linoleic acid. Thus, whereas fructose stimulates FA synthesis in liver, linoleic acid depresses it. The reasons are not fully understood, though the fructose effect may at least in part be related, as discussed by Bailey *et al.* (1968), to the fact that it is more rapidly converted to pyruvate (and hence acetate) than is glucose, the metabolism of which involves the rate-limiting enzyme phosphofructokinase (*EC* 2.7.1.11), which is not required for the conversion of fructose to triose phosphates (see Hue, 1974).

In man and laboratory animals it has been repeatedly shown that a high carbohydrate intake results in enhanced levels of serum triglycerides (TG) (e.g. Kuo & Bassett, 1965; Kaufmann, Poznanski, Blondheim & Stein, 1966), particularly when fructose is the main source of dietary carbohydrate (e.g. Macdonald, 1966*b*; Hill, 1970). Waddell & Fallon (1973), in work with rats, showed that whilst both dietary glucose and fructose increased hepatic capacity to utilize glycerol or *Sn*-glycero-3-phosphate for TG synthesis, only the animals fed on fructose showed sustained, increased levels of serum TG. It was concluded that the dissimilar responses to the two sugars could be ascribed to differences between rates of removal of TG from plasma, possibly associated with differences in insulin levels (cf. Bruckdorfer, Khan & Yudkin, 1972; Maruhama & Macdonald, 1972). There is also evidence (Chevalier, Wiley & Leveille, 1972) that, in fructose-fed rats, a shift takes place in the site of lipogenesis from adipose tissue to liver.

Fatty livers, due apparently to failure of lipoprotein formation, have been observed in rats (Aoyama, Yoshida & Ashida, 1969) and in children suffering from kwashiorkor (Truswell, Hansen, Watson & Wannenberg, 1969). Protein deficiency in rats (Williams & Hurlebaus, 1965) and sheep (Horgen & Masters, 1963) is associated with increased proportions of oleic and linoleic acids in liver lipids and a reduced proportion of arachidonic acid. Similarly, when rats are fed on lipid-free diets, liver lipids accumulate and their content of oleic acid increases, that of arachidonic acid decreases and eicosatrienoic acid (which characterizes essential FA deficiency) is produced (Alfin-Slater, Aftergood, Wells & Deuel, 1954) and is present in notable abundance in the phospholipids of hepatic plasma membranes, endoplasmic reticulum and mitochondrial membranes (Gerson, 1974). That dietary essential FA are necessary for the maintenance of membrane structure (including enzyme activities) of rat liver mitochondria has recently been demonstrated by Haeffner & Privett (1975).

Depot and milk lipids. Whereas in non-ruminant animals FA derived from dietary lipids can directly modify the composition of depot and milk lipids mainly by adding unsaturated FA to the pools of endogenously-synthesized FA (see Garton, 1963, 1969), the depot lipids of ruminant animals are largely refractory to such effects, owing to bacterial hydrogenation of dietary unsaturated FA in the rumen (see Dawson & Kemp, 1970). Before rumen bacteria become established, young ruminants behave as non-ruminants in so far as the effect of dietary FA on

tissue lipids is concerned (Garton & Duncan, 1969*a*; Stokes & Walker, 1970), but thereafter their depot lipids gradually assume the FA composition of the adult ruminant (Garton & Duncan, 1969*b*; Leat, 1970; Payne & Masters, 1971). Stearic acid, arising from rumen hydrogenation of dietary oleic, linoleic and linolenic acids, accumulates particularly in the TG of internal adipose tissue; the subcutaneous TG appear to result mainly from endogenous synthesis and are similar in composition whether or not lipid is present in the diet (Duncan & Garton, 1967; Duncan, Garton & Matrone, 1971).

The FA of the TG of tissue and milk lipids of ruminants normally contain 1–2% monomethyl-branched components of the *iso*- and *anteiso*-series which derive from the digestion and absorption of rumen bacterial structural lipids (Garton, 1964). Multi-branched acids are also normally present in very small proportions and, of these, phytanic acid (3,7,11,15-tetramethylhexadecanoic acid) and its oxidation products originate as metabolites of the phytol moiety of dietary chlorophyll (see Lough, 1973). Recently a wide range of *anteiso*- and unusual branched-chain FA has been found to occur in considerable amounts (10–20%), together with abnormally high proportions of odd-numbered, straight-chain FA, in the adipose tissue TG of lambs fed on diets rich in certain cereals such as barley, maize and wheat (Garton, Hovell & Duncan, 1972; Duncan, Ørskov & Garton, 1974). The unusual branched-chain FA are a complex mixture comprising mostly monomethyl-substituted acids of chain length 10–17 carbon atoms, together with some di- and trimethyl-branched components (Duncan, Lough, Garton & Brooks, 1974). Rumen fermentation of starch-rich cereals gives rise to considerable amounts of propionate (Ørskov, Fraser & Gordon, 1974) and it was concluded (Garton *et al.* 1972) that, when the lamb's hepatic capacity for gluconeogenesis from propionate was exceeded, propionate could readily be utilized as a primer unit for the synthesis of odd-numbered FA, and that branched-chain acids probably arose as a result of the incorporation of methylmalonate (the carboxylation product of propionate) into FA. Studies in vitro with FA synthetase prepared from lamb adipose tissue have demonstrated that branched-chain FA can arise in this way from methylmalonate (Scaife & Garton, 1975). The normal metabolism of methylmalonate to succinate involves a vitamin B_{12}-dependent enzyme (methylmalonyl-CoA mutase) and it has been found that, in congenitally-deranged metabolism of the vitamin in man (Kishimoto, Williams, Moser, Hignite & Biemann, 1973) and in vitamin B_{12}-depleted baboons (G. A. Garton, J. R. Scaife, A. Smith & R. C. Siddons, unpublished results), unusual monomethyl-branched FA similar to those found in cereal-fed lambs are produced in small amounts.

The fact that it may be desirable for man to consume less 'saturated' fat (particularly that of ruminant origin) has prompted research to 'protect' the dietary unsaturated FA of ruminants against hydrogenation in the rumen. Studies such as those by Scott, Cook, Ferguson, McDonald, Buchanan & Hills (1970) and Scott, Cook & Mills (1971) led to the production of preparations of casein and unsaturated vegetable oils which, when treated with formaldehyde, resist microbial modification in the rumen, but which are digested in the small intestine. The feeding of such material to lactating goats and cows results in milk fat which has a

high content of polyunsaturated FA and which resembles modern soft margarine; depot lipids of the animals are similarly affected.

Effects on enzymes involved in the biosynthesis of FA

Saturated FA. The biosynthesis of saturated FA depends essentially on the co-ordinated activities of: (1) an acyl-CoA carboxylase (principally acetyl-CoA carboxylase (*EC* 6.4.1.2)); and (2) FA synthetase which, in animal tissues, is a multi-enzyme complex (see Wakil, 1970; Vagelos, 1974). A supply of ATP and of reducing equivalents (NADPH) is required and the major end-product is usually palmitic acid, from which all the long-chain saturated, hydroxy- and unsaturated FA (except linoleic acid and its metabolites) can be derived. Synthesis takes place mainly in liver and in adipose tissue and the extent to which each of these two sites normally contributes to the over-all production of FA varies from species to species and can, as already mentioned, vary within a species, depending in the rat, for example, on whether glucose or fructose is the precursor of the necessary acetate (Chevalier *et al.* 1972).

Dietary conditions which influence the supply of the short-chain acyl-CoA derivatives required for FA synthesis or which affect the provision of NADPH are clearly of great importance in regulating this synthesis and thus many of the enzymes concerned with glucose metabolism (notably some of those of the glycolytic and pentose phosphate pathways) can be considered to be 'lipogenic' enzymes. However, as Romsos & Leveille (1974) point out, the activities of these enzymes respond to, rather than effect, changes in the rate or extent of FA synthesis which itself is governed, except in starved animals (Numa & Yamashita, 1974), by the rates of synthesis of the key enzymes involved in acyl-CoA carboxylation and in the synthetase complex. It is noteworthy that Leveille (1966) found that the increased hepatic synthesis of FA which takes place when rats are changed from being 'nibblers' to being 'meal-eaters' is not dependent on increased activity of the NADPH-generating enzymes of the pentose phosphate pathway, enhanced activity of which was not observed until about 2 d after increased lipogenesis had begun to take place (cf. Taketa, Kaneshige, Tanaka & Kosaka, 1970).

The formation of malonyl-CoA from acetyl-CoA by acetyl-CoA carboxylase is normally the rate-limiting step in FA synthesis (Ganguly, 1960) and changes in the rate of synthesis of this enzyme have been shown to be influenced by diet. In rats the hepatic content of acetyl-CoA carboxylase was found to be markedly elevated when the animals were fed on a lipid-free diet and depressed when they were fasted, fed on a high-fat diet, or made diabetic, as is exemplified by studies such as those of Allman, Hubbard & Gibson (1965), Majerus & Kilburn (1969) and Nakanishi & Numa (1970).

Though long-term adaptations to dietary conditions are reflected in changes in the amounts of acetyl-CoA carboxylase per unit weight of tissue, short-term allosteric control can also be involved, as was demonstrated in a recent study by Nishikori, Iritani & Numa (1973). Liver slices from previously-fasted rats which had been refed on a fat-free diet showed an increased rate of FA synthesis several

hours before the amounts of acetyl-CoA carboxylase began to increase, and this was attributed in part to activation of the enzyme by citrate, enhanced production of which accompanied the initial increase in FA synthesis.

The amounts of FA synthetase also change markedly in response to dietary manipulation, as has been shown, for example, in the liver of pigeons (Butterworth, Guchwait, Baum, Olson, Margolis & Porter, 1966) and rats (Burton, Collins, Kennan & Porter, 1969) when they were given a fat-free diet after having been fasted. In the young rat (Volpe & Kishimoto, 1972) and young mouse (Smith & Abraham, 1970) hepatic activity of FA synthetase increases greatly when they are weaned on to a normal diet which has a lower fat content than milk. There is evidence (Lakshmanan, Nepokroeff & Porter, 1972) which suggests that changes in the FA synthetase content of liver may be mediated by the relative concentrations of insulin and glucagon. However, these hormones do not apparently influence the synthetase in brain which reaches its highest level of activity in late foetal life (Volpe & Kishimoto, 1972) and thereafter gradually declines and is unaffected by the dietary changes which so markedly affect the hepatic synthetase (see Vagelos, 1974). It has, however, been reported (Frenkel, Kitchens & Johnston, 1973) that FA synthetase activity is increased in both brain and liver of rats deficient in vitamin B_{12} and this appears to be a compensatory effect related to the increased tissue concentrations of methylmalonate which characterize this deficiency condition. Methylmalonyl-CoA inhibits both acetyl-CoA carboxylase and FA synthetase though, as noted previously, it can be incorporated into long-chain FA, thereby giving rise to branched chains.

Unsaturated FA. Double bonds can be introduced stereospecifically into saturated FA and into preformed unsaturated FA by desaturase enzyme systems which are present in the endoplasmic reticulum (microsomes) of most animal tissues, particularly liver and adipose tissue (see Brenner, 1971; Gurr, 1974). These desaturase systems involve molecular oxygen and NADPH in association with an electron transport chain which includes a flavoprotein, cytochrome b_5 and a terminal enzyme (the so-called 'cyanide-sensitive factor') which, in the reduced state, activates molecular oxygen and effects the removal of two hydrogen atoms from a long-chain FA esterified to coenzyme A (see Oshino & Sato, 1972; Gurr, 1974; Strittmatter, Spatz, Corcoran, Rogers, Setlow & Redline, 1974). Double bonds can thus be introduced into saturated FA between C atoms 9 and 10 ($\Delta 9$ desaturation) or between C atoms 6 and 7 of oleic, linoleic and linolenic acids ($\Delta 6$ desaturation) and further desaturation ($\Delta 4$ and $\Delta 5$) can follow chain lengthening.

Activity of desaturase enzyme systems is affected by the nature of the diet. With respect to $\Delta 9$ desaturation of stearyl-CoA to oleyl-CoA, Oshino & Sato (1972) found that enzyme activity of rat liver microsomes decreased in starvation and increased rapidly when the animals were given food. Evidence was adduced which indicated that the changes in enzyme activity reflected changes in the amounts of 'cyanide-sensitive factor'. The enzyme system which is responsible for the desaturation of saturated FA is apparently different from that which effects $\Delta 6$ desaturation of preformed unsaturated acids. Whereas the feeding to rats of carbohydrate-rich diets occasions a notable increase in hepatic $\Delta 9$-desaturase

activity, the effect on Δ6 (and Δ5) desaturation is much less marked (Inkpen, Harris & Quackenbush, 1969). On the other hand, when rats are fed on a high-protein diet, Δ6-desaturase activity (and, to a lesser extent, that of Δ5-desaturase) is increased though Δ9 desaturation is unaffected (Inkpen *et al.* 1969; Castuma, Catala & Brenner, 1972; Peluffo & Brenner, 1974). Additional evidence which indicates that Δ9 and Δ5 desaturation result from the activities of different enzymes was obtained by Lee & Sprecher (1971) who observed that the rate of Δ9 desaturation by rat liver microsomes was depressed when the animals were fasted after having been fed on a fat-free diet, whereas Δ5 desaturation was relatively unaffected. As has been noted above with respect to FA synthetase activity of brain, Δ9 desaturation of saturated FA by brain tissue is relatively unaffected by dietary changes which have a marked effect on liver enzyme activity (Cook & Spence, 1973).

Dietary unsaturated FA also seem to play a part in the regulation of desaturase activity. Uchiyama, Nakagawa & Okui (1967) and Bickerstaffe & Annison (1970) reported that oleic acid, linoleic acid and polyunsaturated acids inhibited Δ9 desaturation and Holloway & Holloway (1975) observed that liver microsomes from rats fed on a fat-free diet showed much higher Δ9-desaturase activity than did similar preparations from animals fed on a diet containing safflower oil (cf. Wahle & Radcliffe, 1975).

It is not yet certain whether the responses of desaturase enzyme systems to different dietary conditions reflect differences in amounts of terminal enzyme (i.e. 'cyanide-sensitive factor'), though it seems a likely possibility (see Holloway & Holloway, 1975). However, apparently regardless of amounts of terminal enzyme, there is evidence which indicates that the copper status of an animal can influence hepatic Δ9-desaturase activity. Following the observations of Elliot & Bowland (1968) and Moore, Christie, Braude & Mitchell (1969) that the soft back fats of pigs given supplementary Cu to improve their growth rate were, in part, due to the presence of more oleic and palmitoleic acids than are normally present, Ho & Elliot (1973) and Thompson, Allen & Meade (1973) reported that this effect was accompanied by enhanced activity of the Δ9-desaturase system in liver. Subsequently, Wahle & Davies (1974) found that Δ9-desaturase activity was markedly decreased in liver microsomes from Cu-deficient rats and that the activity was restored when deficient animals were given Cu in their diet or by injection. As discussed by Wahle & Davies (1975), Cu may play a part in the redox system associated with the terminal enzyme of the Δ9-desaturase system.

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