

Metabolic interaction of dietary sugars and plasma lipids with a focus on mechanisms and *de novo* lipogenesis

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The elevation of blood lipid concentrations in response to the consumption of low-fat high-carbohydrate diets is known as carbohydrate-induced hypertriglycerolaemia (HPTG). An understanding of the mechanisms involved in the interaction between carbohydrates and plasma lipids may help determine whether carbohydrate-induced HPTG would increase cardiovascular risk. There is growing evidence to suggest that the sugar component of the diet may be largely responsible, rather than the total carbohydrate. In most studies designed to investigate the mechanisms of carbohydrate-induced HPTG, the amounts and types of sugars and starches used in the diets are not specified. Findings have been mixed and inconsistent. It is proposed that the elucidation of mechanisms from current studies could have been confounded by the different ways in which sugars are metabolized in the body. At present, there are few studies that have evaluated the independent effects of dietary sugars. Interest has been focused on *de novo* lipogenesis (DNL), as it has recently been found to be positively correlated with increases in fasting TAG levels produced on high-carbohydrate diets, indicating that DNL may contribute to carbohydrate-induced HPTG. DNL has been found to be determined by starch:sugar in a high-carbohydrate diet and affected by different types of sugars. The presence of DNL in adipose tissue is supported by emerging gene-expression studies in human subjects. In the wake of rising intakes of sugars, further research is needed to investigate the mechanisms associated with different sugars, so that appropriate therapeutic strategies can be adopted.

Carbohydrate-induced hypertriglycerolaemia: Sugars: Mechanisms: *De novo* lipogenesis

Although they belong to two different biochemical classes, carbohydrates and lipids are inextricably connected. Metabolically, the elevation of blood lipid concentrations in response to high consumption of carbohydrates, especially sugars, has been recognized since the 1960s (Hodges & Krehl, 1965; Truswell, 1994; Frayn & Kingman, 1995; Parks & Hellerstein, 2000). As macronutrients, dietary sugars appear to modulate the way in which the human body handles dietary fat. In a classic study by Jeppesen *et al.* (1995) the addition of 50 g fructose to a 5 g fat load was shown to increase the plasma TAG-rich lipoprotein fraction to a level three times greater than that with a fat load of 80 g. It has been suggested that, mechanistically, the ingestion of fat in combination with carbohydrate affects the handling of NEFA and substrate oxidation, differently from carbohydrate ingested on its own (Griffiths *et al.* 1994). This metabolic interaction forms the basis of carbohydrate-induced hypertriglycerolaemia (HPTG), a condition that occurs as a result of lowered dietary

fat and increased dietary carbohydrates. Low-fat high-carbohydrate diets have been shown to raise plasma TAG concentrations and depress HDL-cholesterol concentrations in the short term (Jeppesen *et al.* 1995), as well as becoming a long-lasting effect (Brussaard *et al.* 1982; West *et al.* 1990). This response appears to be similar to the HPTG often seen in diabetes and in the development of heart disease, which may be a common consequence of consuming diets high in fats (Karpe, 1997). It is unknown whether carbohydrate-induced HPTG confers a level of atherogenic risk similar to that in other forms of HPTG. An understanding of the mechanisms involved in the interaction between carbohydrates and plasma lipids may help determine whether carbohydrate-induced HPTG would actually increase cardiovascular risk.

The effects of carbohydrates on plasma lipids have been studied in a variety of dietary contexts. Dietary factors such as the quantity and types of total carbohydrates, fibre content and types of fat have been suggested to influence the effect

Abbreviations: DNL, *de novo* lipogenesis; HPTG, hypertriglycerolaemia.

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of carbohydrates on plasma lipids (Frayn & Kingman, 1995). For example, unsaturated fats tend to lower TAG concentrations, while saturated fats may potentiate the TAG-raising effect of sucrose (Truswell, 1994; Hodson *et al.* 2001; Vessby *et al.* 2001). The extent to which each dietary factor influences the HPTG effects of carbohydrates is still unclear. The present review will, however, focus on the effect of carbohydrates on plasma lipids, thus only studies that control for the other dietary variables will be examined.

Amount or type of carbohydrate

Whether it is the total amount or the type of carbohydrates that largely influences carbohydrate-induced HPTG has been an issue of much debate. A contributing problem is that the types of carbohydrates and their proportions in the high-carbohydrate diets used in studies are not always clearly specified. Often, the proportion of the macronutrients in the diet is the only information given, e.g. protein:fat:carbohydrate is 15:10:75. This problem is further compounded by the complexity of carbohydrate classification. The biochemical term 'carbohydrates' covers a wide range of compounds, from mono- and disaccharides (also known as 'simple' carbohydrates), which include sugars such as glucose, fructose and sucrose, to polysaccharides (also known as 'complex' carbohydrates), which comprise starch, resistant starch and fibres such as cellulose and lignin. The identification of carbohydrates is important, as observational and experimental studies have demonstrated that different types of carbohydrates have different effects on plasma lipids. Fructose and sucrose have been shown to raise plasma TAG concentrations to a greater extent than equal amounts of starch or glucose (Truswell, 1994; Frayn & Kingman, 1995; Abraha *et al.* 1998). Resistant starch and fibre appear to counteract the elevation of plasma lipid concentrations in high-carbohydrate diets (Anderson, 1995; Higgins, 2004).

The design of many studies is also confounded by the covariation of sugars and total carbohydrate intake (Fried & Rao, 2003), which makes it difficult to determine whether the increase in plasma TAG concentration is related to the sugar component of the diet or the total amount of carbohydrate. However, there is a growing body of evidence to suggest that the sugar component of the diet is largely responsible, rather than the total carbohydrate. For example, Vidon *et al.* (2001) have reported no effect on fasting plasma TAG concentration when the carbohydrate content of the diet is increased from 40% energy to 55% energy, with the fructose amount held constant at 18–20 g/d. Furthermore, several interventional and observational studies on the dose-dependent effect of substituting sucrose or fructose for starch (Hallfrisch *et al.* 1983; Liu *et al.* 1984; Albrink & Ullrich, 1986; Truswell, 1994) have indicated that the greater the amount of sugars in the diet, the greater the increase in plasma TAG concentrations.

Mechanisms of carbohydrate-induced hypertriglycerolaemia

The mechanisms involved in the metabolic interaction between carbohydrates and plasma lipids that results in

carbohydrate-induced HPTG have been suggested to be either TAG overproduction or decreased TAG clearance, or both. However, there have been few studies designed to investigate the mechanisms, as compared with the many observational studies. A series of studies conducted over the last 35 years that have used a range of techniques has contributed to the literature.

TAG overproduction or decreased TAG clearance

It has been proposed (Kissebah *et al.* 1976; Howard *et al.* 1987; Reaven, 1997) that carbohydrate-induced HPTG involves an impaired ability of insulin to lower adipose tissue lipolysis, which would lead to a higher NEFA flux, thus increasing the source for hepatic TAG production (mechanism 1 in Fig. 1). There is some evidence to support this hypothesis from studies involving subjects with diabetes, subjects with endogenous HPTG who consume higher-fat diets (Howard *et al.* 1987; Lewis *et al.* 1993) and rats receiving high-fructose diets (Vrana *et al.* 1974). However, no data currently exist to support this hypothesis in healthy subjects consuming high-carbohydrate diets for longer periods of time. Evidence supporting TAG overproduction has come mainly from kinetic studies in which labelled lipoproteins were injected into subjects to trace VLDL flux and calculate fractional clearance rates (for an extensive review, see Parks & Hellerstein, 2000). Some of the kinetic studies have also revealed evidence of decreased TAG clearance or the presence of both increased production and decreased clearance.

More recently, there has been growing evidence to suggest that accumulation of atherogenic TAG-rich remnants could contribute to TAG overproduction (Mancini *et al.* 1973; Parks *et al.* 1999; mechanism 2 in Fig. 1). An increase in fasting apoB-48 concentration has been observed with chronic carbohydrate feeding (Parks *et al.* 1999). This outcome was unexpected, given that the subjects had ingested a very-low-fat meal on the previous evening. However, it is consistent with the findings of Harbis *et al.* (2001), who have shown that hyperinsulinaemia (in the absence of insulin-resistance syndrome) caused by high glycaemic index diets delays and exacerbates postprandial accumulation of intestinally-derived chylomicrons in plasma. This finding has wide implications, as numerous studies have shown that the presence of these remnant particles confers increased risk of CHD (for review, see Hodis & Mack, 1998).

Role of lipoprotein lipase

Highlighted as a potential contributor to decreased TAG clearance, the enzyme lipoprotein lipase has come under scrutiny because of its role in TAG clearance from plasma.

Lipoprotein lipase is located on the surface of capillary endothelial cells of adipose tissue and muscle tissue. Primarily, this enzyme hydrolyses TAG present in chylomicrons and VLDL, releasing NEFA into adipose tissue and muscle tissue for storage and utilization respectively. In the adipose tissue a large proportion of NEFA is delivered into the plasma, an effect known as 'spillover' (Frayn *et al.* 1997; mechanism 3 in Fig. 1). The activity of

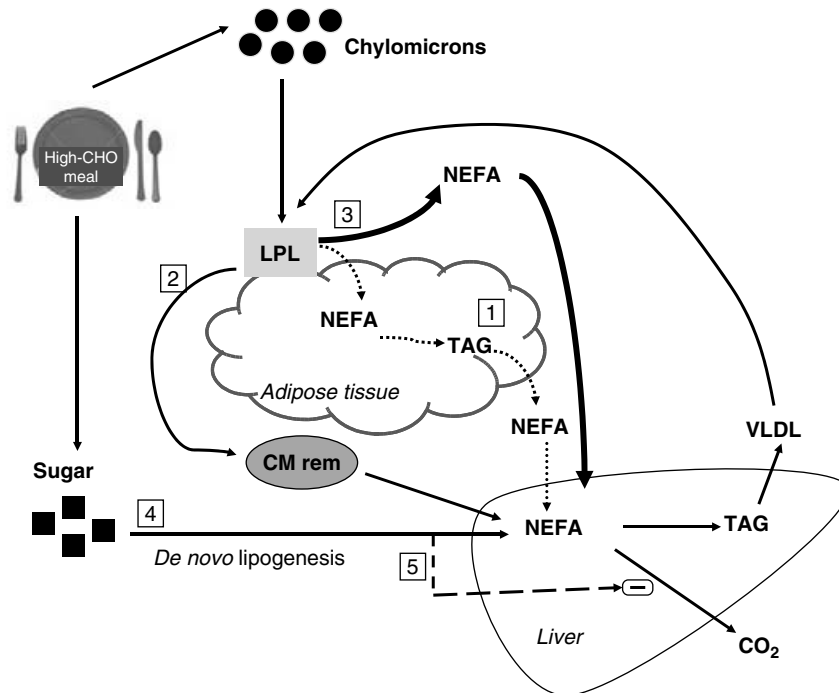


Fig. 1. Mechanisms of carbohydrate (CHO)-induced hypertriacylglycerolaemia. (1) Impaired ability of insulin to suppress lipolysis, leading to increase NEFA flux (....►); (2) accumulation of chylomicron remnants (CM rem; ►); (3) down-regulation of adipose tissue lipoprotein lipase (LPL) activity (►); (4) *de novo* lipogenesis (►); (5) less hepatic fatty acid oxidation, possibly inhibited through malonyl-CoA produced in *de novo* lipogenesis (–►).

lipoprotein lipase is known to be insulin-regulated, being up regulated in the adipose tissue and down regulated in the muscle. It is speculated that the higher affinity of lipoprotein lipase for chylomicrons than for VLDL may be a factor affecting the rate of TAG clearance in these lipoprotein fractions when these particles compete for hydrolysis by lipoprotein lipase (Brunzell *et al.* 1973). Several studies (Lithell *et al.* 1982; Campos *et al.* 1995; Yost *et al.* 1998) show conflicting results for the activity of lipoprotein lipase in both adipose tissue and muscle tissue when subjects are fed high-carbohydrate diets. This disparity is compounded by the use of heparin in the assessment of lipoprotein lipase activity *in vivo*; a commonly-used method that may not provide physiologically-relevant results (Parks & Hellerstein, 2000).

Effects of high-carbohydrate diets v. high-sugar diets

Studies that have investigated the mechanisms of carbohydrate-induced HPTG provide contradictory findings. Decreased TAG clearance appears to be the driving mechanism when high-fibre complex carbohydrates (sucrose and monosaccharides are intentionally limited) are used (Parks *et al.* 1999). In contrast, increased VLDL production appears to be the key mechanism revealed by other studies (Stacpoole *et al.* 1991; Mittendorfer & Sidossis, 2001; Ginsberg *et al.* 1981). However, in an early study a combination of both mechanisms was indicated (Quarfordt *et al.* 1970).

The discrepancy among these findings could in part be related to differences in the subjects (i.e. healthy subjects or subjects with metabolic complications), the duration of studies (from several days to weeks), the diet composition and the diversity of methods used to measure VLDL-TAG kinetics (Mittendorfer & Sidossis, 2001). The interpretation of these findings may be further complicated by the varying amounts and types of carbohydrates (sugars and starches) used and the lack of their specification in most of the studies.

One study that has focused its investigations on the mechanisms initiated by a specific sugar is that of Nestel *et al.* (1979). In the high-carbohydrate diet (70% energy) used, sucrose comprised 55% dietary carbohydrate, and a decrease in VLDL clearance was shown to be the cause of HPTG in this study. As studies evaluating the independent effects of dietary sugars are very limited, a comparison of the acute metabolic effects of fructose *v.* glucose has been undertaken using a randomized cross-over design. Fifteen healthy lean male and post-menopausal female subjects, who were fasted overnight, were given test drinks composed of 0.75 g sugar (fructose or glucose)/kg body weight, 0.5 g oil (palm and safflower oil)/kg body weight, 500 mg [²H₂]palmitic acid and 250 mg [U¹³C]fructose or [U¹³C]glucose. The stable isotopes were used to help trace the dietary fate of the sugars and the handling of dietary fat in the body. Preliminary data indicate that plasma TAG concentrations are significantly higher after fructose compared with after glucose (Fig. 2). The lower concentrations of both plasma NEFA (data not shown) and [²H₂]palmitate

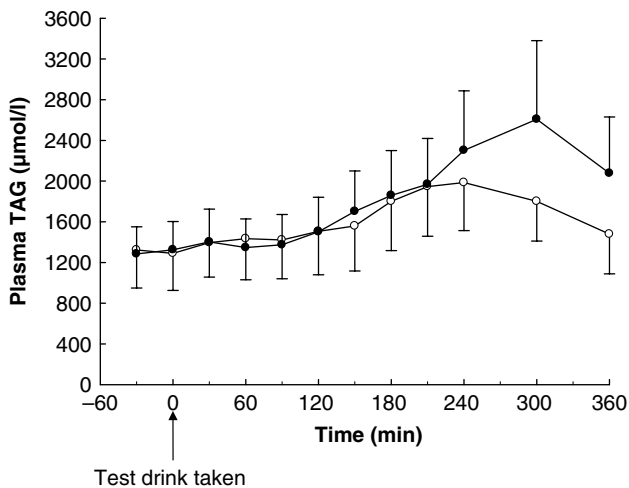


Fig. 2. Plasma TAG concentrations of healthy lean subjects before and after a test drink containing fructose (●) or glucose (○); for details of test drinks, see p. 54. Values are means with their standard errors represented by vertical bars. Values for the incremental area under the curve were significantly different between test drinks ($P = 0.008$; $n 9$).

in NEFA (Fig. 3) after fructose suggest lower insulin secretion with fructose, resulting in a lower activation of adipose-tissue lipoprotein lipase, which leads to decreased TAG clearance. There also appears to be a higher production of chylomicron remnants after fructose, which suggests that chylomicron remnants may be contributing to the overproduction of VLDL-TAG (MFF Chong, BA Fielding and KN Frayn, unpublished results).

Cohen & Schall (1988) have compared the effects of glucose, sucrose and fructose ingestion on the responses of plasma TAG to test drinks containing 40 g fat in twenty-one normolipidaemic non-obese medical students. Postprandial lipaemia was not found to be significantly different after the ingestion of test drinks containing 50 g glucose with 40 g fat *v.* test drinks containing 40 g fat alone. Ingestion of 50 g fructose with 40 g fat and 100 g sucrose with 40 g fat were found to augment postprandial lipaemia compared with the ingestion of fat alone. It was suggested that because the increment in postprandial lipaemia induced by the ingestion of 100 g sucrose was quantitatively similar to that induced by 50 g fructose the effect of sucrose was probably related to its fructose component.

Taken together, the results of these two studies inevitably lead to the following questions: (1) if postprandial lipaemia induced by high fructose consumption is indeed regulated by insulin, how does that explain the mechanisms that occur when sucrose is consumed, bearing in mind that sucrose causes a larger insulin excursion; (2) as a low dose of fructose added to a glucose load has been shown to improve glucose tolerance without affecting the TAG response, even in the presence of marked insulin resistance (Moore *et al.* 2000; McGuinness & Cherrington, 2003), what mechanism is occurring here.

A study conducted by Daly *et al.* (2000) may provide some insight. Using [^{13}C]fructose and [^{13}C]glucose it was shown that fructose is preferentially oxidized after a high-sucrose meal, while glucose is oxidized more slowly

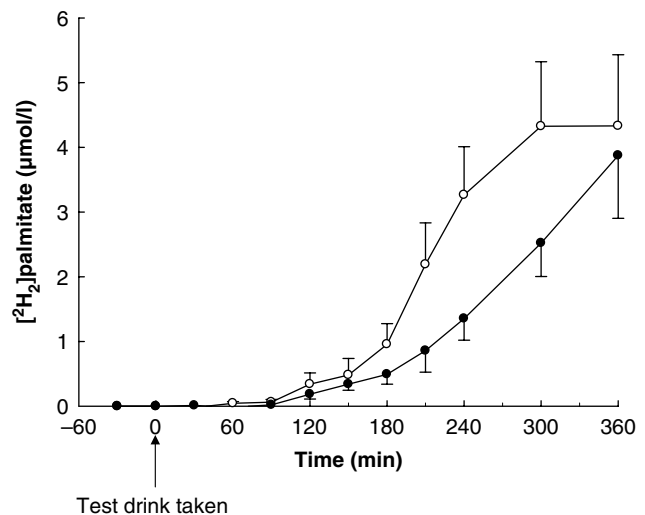


Fig. 3. Concentration of [$^2\text{H}_2$]palmitate in plasma NEFA in healthy lean subjects before and after test drinks containing fructose (●) or glucose (○) with [$^2\text{H}_2$]palmitate (for details of test drinks, see p. 54). Values are means with their standard errors represented by vertical bars. Values for the incremental area under the curve were significantly different between test drinks ($P = 0.038$; $n 9$).

after a high-sucrose meal than after a high-starch meal. It can be inferred that monosaccharides such as glucose and fructose are metabolized differently when consumed together as the disaccharide sucrose and when consumed with other carbohydrates, such as starch. It is therefore proposed that a number of possible mechanisms can arise from the differing metabolic responses the body has to various sugars. The elucidation of mechanisms from published studies could have been confounded by the different ways in which sugars are metabolized in the body. When mixed in varying quantities and types in diets the combined effects appear to give different mechanistic results.

Similarly, the role of insulin in determining hepatic TAG production has been controversial, appearing to be inhibitory in some studies and stimulatory in others (Daly, 2003; Fried & Rao, 2003). Recently, there has been a suggestion that high-glycaemic index foods increase TAG concentrations as a result of their effects on glycaemia and insulinaemia (Fried & Rao, 2003). Thus, a clear conclusion on the mechanisms of different sugars needs to be drawn before the relationship between the glycaemic effects of sugars and starches and plasma lipids can be clarified.

De novo lipogenesis

A potential contributor to increased TAG production is the conversion of carbohydrates to fat in the liver and/or adipose tissue through the *de novo* lipogenesis (DNL) pathway (mechanism 4 in Fig. 1). As there is a limit to the amount of glucose or glycogen that can accumulate in the body, DNL provides a physiological pathway for the synthesis of lipids from carbohydrate when a human subject or an animal is overfed carbohydrate (Frayn & Langin, 2004). However, net whole-body lipogenesis is only seen in human subjects in extreme conditions, e.g. during

overfeeding with a carbohydrate-rich diet (Schwarz *et al.* 1995) or during total parenteral nutrition with glucose as the main energy substrate (Aarsland *et al.* 1997). Under these conditions, based on absolute (hepatic) DNL calculations, only a few grams total fat are synthesized (Neese *et al.* 1994; Schwarz *et al.* 1995). As DNL does not appear to be a main route for storage of excess energy, it has not been widely investigated until recently.

Recent developments in techniques for measuring DNL, i.e. the stable-isotope tracer method using mass isotopomer distribution analysis and the non-isotopic linoleate-dilution method, have been used to establish that fatty acid synthesis can also be stimulated in the isoenergetic state by very-low-fat high-carbohydrate diets (Hudgins *et al.* 1996, 2000). In the study of Hudgins *et al.* (1996) a group of subjects were fed, for 25 d, a liquid diet in which 75% energy was carbohydrate in the form of glucose polymers. It was found that 40% of the VLDL-TAG is produced by DNL. Growing evidence also indicates that DNL is positively correlated with increases in fasting TAG levels produced on high-carbohydrate diets, indicating that DNL does contribute to TAG overproduction during carbohydrate-induced HPTG (Hudgins *et al.* 2000; Schwarz *et al.* 2003), albeit to a small extent. It has been suggested that hepatic DNL may increase VLDL-TAG secretion by causing inhibition of fatty acid oxidation as a result of increased concentrations of malonyl-CoA (produced by DNL), which is an inhibitor of carnitine-palmitoyl transferase-1, the enzyme involved in the transport of long-chain fatty acids into the mitochondria (Schwarz *et al.* 2003). This hypothesis is supported by studies showing that high-carbohydrate diets alter the partitioning of fatty acids in the liver by decreasing hepatic fatty acid oxidation and channelling them towards esterification instead (Sidossis *et al.* 1996; Mittendorfer & Sidossis, 2001; mechanism 5 in Fig. 1).

More importantly, changes in plasma fatty acid composition have been observed to accompany fatty acid synthesis. The composition of plasma TAG has been shown to be enriched in palmitate, the saturated fatty acid preferentially formed by mammalian fatty acid synthase, and depleted in essential PUFA that cannot be synthesized *de novo*, e.g. linoleic acid (18:2n-6). This increase in plasma TAG and the reduced plasma PUFA have both been associated with increased risk of CVD (Hudgins *et al.* 1996).

Starch:sugar

Starch:sugar of the carbohydrate component of dietary energy has been found to be critical in determining the amount of DNL. In a subsequent study Hudgins *et al.* (1998) have compared the effects of different forms of carbohydrate (solid food *v.* liquid formula), the presence of starch and the type of carbohydrates (mono-, di- or polysaccharides) in diets containing 75% energy as carbohydrate. As in the previous study (Hudgins *et al.* 1996), ingestion of the liquid formula, which contained glucose polymers, was found to result in marked VLDL-TAG production by DNL. In contrast, the liquid diet containing equal amounts of starch and sugar, and the solid food diet

in which starch:sugar was 60:40 were both found to show no stimulation of DNL. This finding was replicated in the study of Parks *et al.* (1999), in which it was shown that DNL is minimal when the carbohydrate in a high-carbohydrate diet has a starch:sugar of >50:50. Subsequent studies (Hudgins *et al.* 2000; Schwarz *et al.* 2003) have confirmed that the elevation of DNL appears to be more pronounced when more than half the carbohydrate is consumed as sugars.

A 3 d cross-over design study with healthy lean subjects has been conducted using the non-isotopic linoleate-dilution method to determine whether DNL would occur in this short time span (other studies have measured fasting DNL after 5–25 d of dietary intervention). Eight subjects followed a low-fat high-carbohydrate diet and a high-fat low-carbohydrate diet (starch:sugar 40:60 for both diets), each for 3 d, and were investigated after an overnight fast. All subjects were found to have higher fasting plasma TAG after the high-carbohydrate diet, and DNL (measured by the linoleate-dilution method) was detected in half the subjects. More importantly, depletion of 18:2n-6 and an increase in 16:0 in plasma VLDL was observed in all subjects on the high-carbohydrate diet ($P < 0.01$; MFF Chong, A Bickerton, R Roberts, F Karpe, L Hodson, B Fielding and K Frayn, unpublished results).

To further support these findings, the expression of lipogenic genes in adipose tissue has been determined. Using real-time PCR, levels of selected mRNA transcripts were measured in adipose-tissue biopsies taken from the subjects after the 3 d on the diets. Preliminary data have revealed a trend of increased adipose tissue stearoyl-CoA desaturase mRNA when subjects were on the high-carbohydrate diet compared with the low-carbohydrate diet (data from five subjects). Using the palmitoleic:palmitic acid index (Risérus *et al.* 2005; calculated from plasma VLDL), stearoyl-CoA desaturase activity was also estimated to be higher with the high-carbohydrate diet ($P = 0.012$), thus strengthening the evidence that DNL occurs after 3 d on the high-carbohydrate diet (L Hodson, MFF Chong, BA Fielding and KN Frayn, unpublished results). Whether this finding actually indicates the occurrence of DNL in the liver warrants further investigation.

The site of DNL is classically thought to be mainly the liver, and there is no clear evidence to indicate that adipose tissue is actively involved in carbohydrate-induced DNL (Schutz, 2004). For example, Minehira *et al.* (2004) have reported that the lipogenic enzymes fatty acid synthase and sterol regulatory element binding protein 1c are expressed in adipose tissue after carbohydrate overfeeding, while two other studies (Diraison *et al.* 2002; Letexier *et al.* 2003) indicate that the same genes are unaffected by high-carbohydrate diets. Further research is needed in this area to understand the regulation of DNL in the adipose tissue.

Differential effects of sugars

Different sugars have been found to have different effects on DNL. In a study of the effects of glucose and sucrose on DNL during overfeeding (McDevitt *et al.* 2001), eight lean and five obese subjects were subjected to two overfeeding

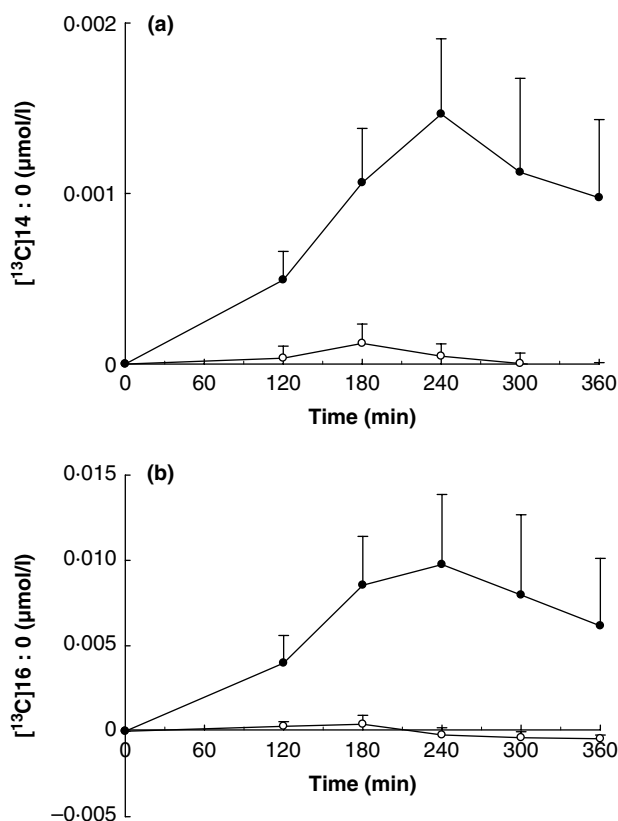


Fig. 4. Concentration of [^{13}C]myristic acid (a) and [^{13}C]palmitic acid (b) in plasma VLDL in healthy lean subjects after test drink containing [^{13}C]fructose (●) or [^{13}C]glucose (○); for details of test drinks, see p. 54. Values are means with their standard errors represented by vertical bars. The values for incremental area under the curve were significantly different between test drinks for [^{13}C]myristic acid ($P = 0.046$; $n = 6$) and for [^{13}C]palmitic acid ($P = 0.008$; $n = 9$).

treatments (diets providing 50% more energy than the control diet, with either glucose or sucrose as the carbohydrate component of the extra energy) and a control treatment, each for 4 d. DNL was found to be 2–3-fold higher after the overfeeding treatment than after the control diet. Correspondingly, the rate of DNL was observed to increase with increasing concentrations of plasma TAG. However, DNL and plasma TAG concentrations were not found to be different between the two types of carbohydrate overfeeding.

Schwarz *et al.* (1993) have demonstrated that oral administration of fructose for 6 h (at 10 mg/kg lean body mass per min) increases fractional DNL substantially (to >30%) compared with an isoenergetic load of glucose, which fails to increase DNL (2–4%). This finding is consistent with preliminary data from the acute metabolic study comparing fructose and glucose described earlier (p. 54). Significantly higher levels of ^{13}C -labelled myristic acid (14:0; $P = 0.046$; Fig. 4(a)) and palmitic acid (16:0; $P = 0.008$; Fig. 4(b)) were found in the plasma VLDL after the fructose drink compared with after the glucose drink, indicating that a higher level of DNL (i.e. [^{13}C]fructose converted to ^{13}C -labelled fatty acids) after fructose

consumption (MFF Chong, BA Fielding and KN Frayn, unpublished results).

It has been speculated that fructose is more lipogenic than glucose because it bypasses the enzyme phosphofructokinase, which is a major rate-determining step in glycolysis as well as an important feature of glucose metabolism. A greater flux of fructose is allowed through the rest of the glycolytic pathway, thus facilitating hepatic TAG production (Frayn & Kingman, 1995). Whether the same effect is retained in sucrose is unknown. Although increases in DNL appear to be associated with increases in TAG production, the question of whether the DNL is linked to the other mechanisms of carbohydrate-induced HPTG still remains open. Factors such as BMI, insulin and glucagon levels do not appear to be associated with DNL (Hudgins *et al.* 1996, 2000); instead, inter-individual variations in DNL appear to be considerable.

Conclusions

In conclusion, possible mechanisms involved in the metabolic interaction between dietary sugars and plasma lipids include: stimulation of hepatic secretion and DNL, leading to TAG overproduction; impairment of the activation of adipose tissue LPL by insulin, leading to decreased TAG clearance. Further research is needed to investigate how specific sugars differ in their mechanisms, so that appropriate therapeutic strategies can be implemented. For example, reduced clearance of VLDL can be ameliorated by exercise training (Koutsari *et al.* 2001; Mittendorfer & Sidossis, 2001). Dietary modifications, e.g. an appropriate proportionate intake of complex carbohydrates *v.* simple carbohydrates, can be made to prevent the accumulation of VLDL. Dietary advice has often focused on the fat component of the diet, while the carbohydrate component has been neglected. Increased knowledge in this area could lead to improved dietary advice for individuals, particularly those at risk of CVD. It has been postulated that dietary sugars may alter the kinetics of lipid metabolism in a way that accentuates the changes characteristic of insulin resistance (Frayn & Kingman, 1995). In the wake of rising intakes of sugars, and with speculation about its association with the increasing rate of obesity and diabetes, this issue becomes even more pressing (Murphy & Johnson, 2003; British Broadcasting Corporation, 2004).

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