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Macronutrient Metabolism Group Symposium on 'Dietary fat: how low should we go?'

Changes in fat synthesis influenced by dietary macronutrient content

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De novo lipogenesis is the biological process by which C₂ precursors of acetyl-CoA are synthesized into fatty acids. In human subjects consuming diets higher in fat (>30 % energy), lipogenesis is down regulated and extremely low; typically <10 % of the fatty acids secreted by the liver. This percentage will increase when dietary fat is reduced and replaced by carbohydrate, although the extent of carbohydrate-induced lipogenesis is dependent on the type of carbohydrate (monosaccharide *v.* polysaccharide) and the form in which the carbohydrate is fed (liquid meals, solid less-processed food). Clearly, massive overconsumption of carbohydrate can also increase lipogenesis. A second related phenomenon that occurs when dietary fat is reduced is hypertriacylglycerolaemia. This rise in blood triacylglycerol concentration could be due to increased *de novo* lipogenesis or to reduced clearance of lipid from the blood. The present paper will review the metabolic mechanisms leading to the elevations in blood triacylglycerol concentration that occur with dietary fat reduction. Studies considered will be those investigating fatty acid synthesis in subjects chronically fed low-fat high-carbohydrate diets and studies in which data were obtained in both the fasted and fed states. Also summarized will be data from subjects who had consumed diets of different carbohydrate types, as well as the most recent data from postprandial studies investigating factors that affect the magnitude of the rise in blood lipids following a meal. Given the changing availability of carbohydrate in the food supply, it will be important to understand how the balance of fat and carbohydrate in the diet influences lipogenesis, and the relative contribution of the process of *de novo* lipogenesis to the escalating incidence of obesity observed around the world.

Dietary carbohydrate: Triacylglycerol: Lipogenesis: Human feeding study

The number of human studies of the effect of dietary intake on blood triacylglycerol (TAG) concentration is large, as reviewed elsewhere (Parks & Hellerstein, 2000). When individuals are advised for health reasons to lower their dietary fat intake, three events typically occur: (1) new food choices result in the energy previously derived from fat being replaced by carbohydrate; (2) the cholesterol content of the diet is reduced; (3) the subject loses weight (Gambera *et al.* 1995; Ortega & Andres, 1996; Parks & Hellerstein, 2000). As has been well demonstrated, blood cholesterol concentrations fall, although another consequence of these diets is that blood concentrations of blood TAG rise. As hypertriacylglycerolaemia on *ad libitum* diets has been found to be an independent risk

factor for CHD (Austin, 1998; Miller, 1999), the phenomenon of carbohydrate-induced hypertriacylglycerolaemia has led some scientists to conclude that these diets may not provide net benefit to health (Lichtenstein & Van Horn, 1998; Rudel, 1998; Strain, 1998) and may be potentially atherogenic (Liu *et al.* 2000). Determination of the role of lipogenesis in carbohydrate-induced hypertriacylglycerolaemia will be aided by an understanding of how dietary intake changes fasting and postprandial lipaemia, elucidation of the metabolic mechanisms underlying the phenomenon (overproduction or reduced clearance of TAG) and knowledge of how fatty acid synthesis may act as a signal in fatty acid partitioning either to tissue oxidation or re-esterification.

Abbreviations: apo, apolipoprotein; TAG, triacylglycerol.

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In the blood the majority of TAG are carried in two types of TAG-rich lipoprotein particles. The first type of lipoprotein is the chylomicron, which is made in the intestine and transports dietary lipid to the tissues; this particle is present in the blood primarily after meals. The second TAG-rich lipoprotein is the VLDL, which is made in the liver and transports endogenous lipids. Although most fasting TAG are carried in VLDL, elevations in postprandial blood TAG can be a result of greater TAG carried in both chylomicrons and VLDL (as described on p. 283). The present paper will review how changes in dietary macronutrient composition (specifically the replacement of dietary fat with carbohydrate) has been studied previously (in both the fasted and fed states), what is currently known about the metabolic mechanisms that cause blood TAG elevation and how dietary carbohydrate may increase lipogenesis.

Increased carbohydrate intake and fasting hypertriacylglycerolaemia

The phenomenon of carbohydrate-induced hypertriacylglycerolaemia was first noted in the early 1950s (Watkin *et al.* 1950). Most studies investigating the phenomenon have tracked fasting TAG concentration during carbohydrate feeding, and it is now clear that some elevation in fasting TAG will occur in almost all subjects who lower their dietary fat by as little as 5 % energy, replacing it with carbohydrate-rich foods. Preliminary data suggest that individual characteristics make some subjects more sensitive to replacement of dietary fat by carbohydrate. These characteristics include a higher fasting TAG concentration on the habitual higher-fat diet (Retzlaff *et al.* 1995; Parks *et al.* 2001), fasting insulin concentrations >10 mU/l and higher body weight, as denoted by a BMI >27 kg/m² (Parks *et al.* 2001). Hormone-replacement therapy (Kasim-Karakas *et al.* 2000) and genetic factors (Dreon *et al.* 2000) have also been shown to affect the magnitude of the increase in fasting TAG seen with low-fat high-carbohydrate diets.

The postprandial state: differences between glucose and triacylglycerol metabolism

Human subjects are in the fed state for an average of 16–18 h/d. Representative postprandial glucose and TAG concentration curves, shown in Fig. 1, demonstrate the responses of healthy hyperlipidaemic subjects whose blood glucose and TAG were monitored while they consumed three high-fat meals (45 % energy as fat) in a single day. Fig. 1 illustrates two important points. First, human subjects are in the postprandial state for approximately 16 h/d, and this state is a dynamic one. Given that the postprandial state is the habitual condition of daylight hours for most individuals, it is probable that the activity of digestion and metabolism of dietary substrates governs the evolution of diseases more than has been appreciated previously. The practical use of an oral glucose tolerance test to predict insulin resistance demonstrates how observing the body respond to an oral challenge of substrate (glucose in this case) in real time reveals more about where the patient is in the progression of diabetes than a fasting glucose concentration does. Even though fasting values of metabolites are

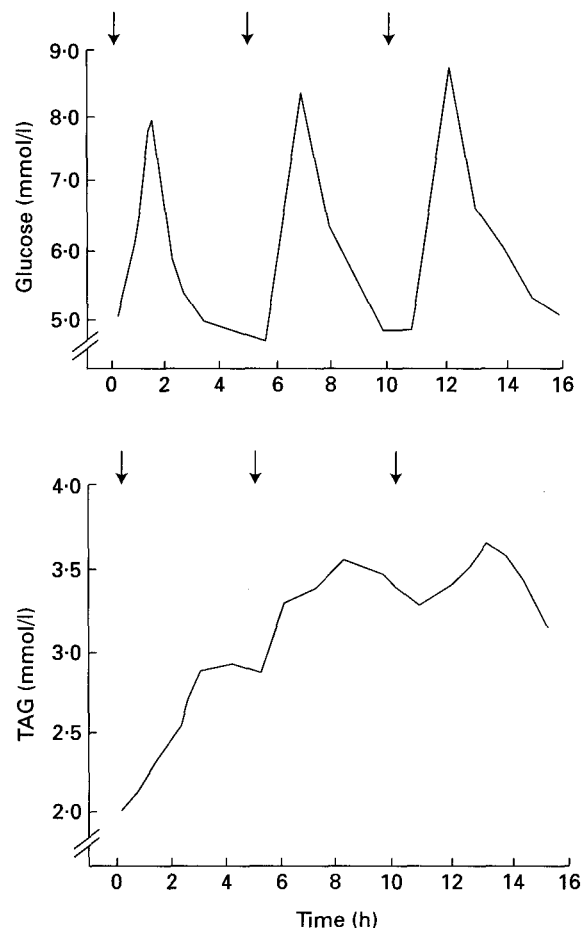


Fig. 1. Representative data of the change in blood glucose and triacylglycerol (TAG) concentrations following three meals (↓) consumed in 1 d. (Data modified from Anderson *et al.* 1995.)

used as the standard in clinical medicine to predict future disease risk (i.e. fasting glucose and insulin are used to predict diabetes risk, cholesterol for heart disease, etc.), it may not be long before standardized postprandial measurements of lipids will be used for this purpose. In clinical studies delayed clearance of postprandial TAG (i.e. elevated concentration >4 h after a meal has been eaten) has been found to be predictive of CHD (Braun *et al.* 1997; Otto *et al.* 1997; Cohn, 1998) and the availability of an enzymic kit used in clinical medicine to quantify remnant lipoproteins is on the horizon (Devaraj *et al.* 1998; McNamara *et al.* 1998; Marcoux *et al.* 2000).

A second fact illustrated by Fig. 1 is the dramatically different mechanisms of absorption and transport of glucose and TAG. As is well known, following a morning meal consumed by a healthy subject glucose concentrations abruptly increase, peak and can return to basal levels within 2–3 h. By contrast, TAG concentrations progressively rise throughout the day, peak about midnight, and then slowly return to basal levels between 04.00 and 07.00 hours. These differences in the postprandial fluctuation of glucose and TAG result in their fasting values being respectively more and less representative of an individual's daily metabolism. Since the fasting value of glucose is re-established three or

four times during the day (between meals), it is more likely that the fasting glucose concentration will more closely represent the postprandial metabolism of glucose. By contrast, since TAG concentrations rise steadily during the day and do not come back down to fasting levels until about 02.00 or 03.00 hours, the TAG concentration in the fasting state is a poor surrogate for the postprandial concentration. In essence, the fasting concentration of TAG reveals very little about concentrations that may have been present in the individual in the fed state the day before the test. This fact may be one reason why it has taken so long to identify TAG concentration as an independent risk factor for CHD (Austin *et al.* 1998). Confirmation of the atherogenicity of elevated TAG has been strengthened by recent advances in the measurement of postprandial lipaemia. Furthermore, acknowledgement that postprandial hypertriacylglycerolaemia contributes to atherosclerosis has strengthened the belief that carbohydrate-induced hypertriacylglycerolaemia is atherogenic because chronic consumption of higher-carbohydrate diets increases blood TAG concentration after meals, as will now be described.

We (Parks *et al.* 1999) performed a metabolic study in which healthy normolipidaemic and hypertriacylglycerolaemic males consumed a diet containing 15 % energy as fat and 68 % energy as carbohydrate for 5 weeks. Low-fat high-carbohydrate feeding significantly doubled the fasting concentrations of both TAG-rich lipoproteins apolipoproteins (apo) B100 and B48 ($P < 0.05$ in both cases). The elevation in fasting chylomicron concentration (as evidenced by increased apoB48 concentrations) was a bit surprising, since the high-carbohydrate meal fed the night before the fasting blood sampling had very little fat in it, and would presumably be associated with low levels of chylomicron TAG secretion postprandially. Elevated apoB48 concentration in the fasting state could result from either prolonged chylomicron secretion following the previous meal, or from reduced clearance of chylomicrons made immediately after a meal that, for some reason, did not clear normally and continued to circulate for >8 h. Future research goals should be to determine how replacement of dietary fat with carbohydrate leads to this effect, and to elucidate factors that control these events.

Not only does carbohydrate feeding elevate apoB48 in the fasting state, but it also appears to increase the concentration of chylomicrons postprandially. A study recently reported by Hyson and colleagues (Kasim-Karakas *et al.* 1997; Hyson *et al.* 1999) confirmed the elevation in fasting apoB48, and also showed that lowering dietary fat and replacing it with carbohydrate was associated with elevations in postprandial TAG-rich lipoprotein particles in proportion to their fasting level. Thus, against this higher load of blood TAG in the fasting state, the potential reduction in clearance of TAG-rich lipoprotein-TAG following a meal leads to significantly higher postprandial TAG concentrations ($P < 0.05$). Reduced TAG-rich lipoprotein-TAG clearance could be due to a reduction in postprandial lipoprotein lipase activity, or from reduced remnant uptake into the liver by receptor-mediated processes.

The relationship between postprandial glucose and insulin and TAG concentrations has been investigated in

two recent publications. Harbis *et al.* (2001) compared the effects of carbohydrate-rich meals that had different glycaemic indices. In healthy subjects chylomicron apoB48 concentrations were significantly elevated after high-glycaemic-index meals compared with the low-glycaemic-index meals ($P < 0.05$; Harbis *et al.* 2001). One interpretation of these data is that higher postprandial glucose and insulin concentrations may act directly on the liver to increase VLDL-TAG synthesis. However, in data from four studies analysed no such positive relationship between fatty acid synthesis and either blood insulin or glucose concentrations could be found among subjects on high-carbohydrate diets (Parks, 2002). On the contrary, a positive association was found between fasting insulin concentration and *de novo* lipogenesis (fatty acid synthesis) among subjects on a high-fat diet, but the correlation was not present when these subjects were switched to the low-fat high-carbohydrate diet. Indeed, insulin has been shown *in vitro* (Gibbons 1990, 1994; Gibbons & Burnham, 1991; Gibbons *et al.* 1992) and in human studies using infusion of insulin at high concentration (Lewis *et al.* 1993, 1995) to reduce VLDL-apoB secretion. Much of the inhibitory effect of insulin may be due to its anti-lipolytic effect, producing a reduction in fatty acid flux to the liver. These data suggest that in healthy subjects some other variable besides glucose or insulin is directly related to increased lipogenesis, and the stimulation of fatty acid synthesis by dietary carbohydrate may be highly variable in the population.

Marques-Lopez *et al.* (2001) have used stable-isotope infusion and meal feeding to investigate the effect of a single, low-fat (4 % energy) high-carbohydrate (80 % energy) meal on lipogenesis in six lean and seven overweight men. Compared with the lean men, overweight men had higher postprandial concentrations of insulin, free fatty acids and plasma TAG. Compared with the fasting state, *de novo* lipogenesis was higher in the fed-state in both lean and overweight men, and postprandial lipogenesis was significantly higher ($P < 0.05$) in the overweight men (8.28 (SE 1.04) v. 3.16 (SE 0.75) % VLDL-TAG-fatty acids derived from the *de novo* pathway in the lean men). These data suggest that the connection between lipogenesis, postprandial triacylglycerolaemia and obesity is a research question worthy of further study. A clear relationship between the glycaemic index of a meal and its ability to stimulate lipogenesis awaits further study.

Studies of triacylglycerol turnover and lipogenesis

The effect of carbohydrate intake and VLDL and fatty acid synthesis has been the subject of numerous studies, as reviewed recently (Parks & Hellerstein, 2000). Feeding a high-carbohydrate diet has been shown to both increase the production rate and reduce the clearance rate of VLDL particles and VLDL-TAG. Hudgins *et al.* (2000) have shown that both lean and obese subjects experienced similar increases in fatty acid synthesis when switched to diets high in monosaccharides, and for the group as a whole the magnitude of *de novo* lipogenesis was significantly correlated with the increase in blood TAG concentration ($P < 0.05$). We (Parks *et al.* 1999) have measured the contribution of *de novo* lipogenesis to VLDL-TAG-fatty acids in

healthy normolipidaemic and hypertriacylglycerolaemic men before and after 5 weeks of isoenergetic low-fat (15 % energy) high-carbohydrate feeding (68 % energy). Consumption of a high-carbohydrate diet, rich in polysaccharides and high in fibre, was not associated with an increase in *de novo* lipogenesis. This diet did induce hypertriacylglycerolaemia, which was explained by a 37 % reduction in TAG clearance from the blood. By contrast, in a 2-week study of six subjects consuming very-high-fat (55 % energy) and very-low-fat (10 % energy) high-carbohydrate (75 % energy) diets, carbohydrate-induced hypertriacylglycerolaemia was attributed to elevated VLDL-TAG secretion (Mittendorfer & Sidosis, 2001). Thus, increasing the carbohydrate content of the diet has been shown to increase blood TAG concentration through many mechanisms, including elevations in fatty acid synthesis and VLDL-TAG secretion, and also through reduced VLDL-TAG clearance. There exists large variability between subjects, and an interesting difference in diurnal pattern among subjects (Hudgins *et al.* 2000). Understanding the role of dietary macronutrient content in controlling lipogenesis will be better understood in the future as a result of the recent development of accurate methods for quantifying fatty acid and TAG synthesis and VLDL secretion *in vivo* in human subjects.

Effects of increasing dietary protein

As described earlier, most studies of the effect of change in dietary macronutrient content on *de novo* lipogenesis have investigated the replacement of dietary fat with carbohydrate. However, a few important research questions pertaining to dietary protein should be mentioned. The first question is: why, when an individual is counselled to reduce dietary fat intake, he or she will typically increase the consumption of carbohydrate as opposed to adding additional protein to the diet? Is it because carbohydrate is already the primary source of energy in the diet and, therefore, provides the most variety of foods to choose from when making a substitution? Or, is it because some of the most popular protein-rich foods are also naturally high in fat (meats) and are therefore avoided? Dietary protein can be increased without increasing fat intake, but the options for consumers are fewer and involve increasing the consumption of beans and items such as textured vegetable protein and other less-accepted foods. Concerns about the potential negative consequences of eating a high-carbohydrate high-glycaemic-index diet have led to the popular consumption of diets with higher levels of energy from protein. Whether such diets are merely a fad or will influence the intake of individuals for longer periods of time is unknown, but research studies investigating the effects of high-protein diets on blood concentrations of insulin, glucose and lipids are amassing (Baba *et al.* 1999; Wolfe & Piche, 1999). Higher-protein diets also have the potential to facilitate weight loss by increasing satiety. As interest in these diets increases, so too will the commercial availability of protein-rich, low-fat foods. The effect of replacing dietary carbohydrate with protein on *de novo* lipogenesis will be of interest. Another potential area of interest relates to overfeeding. In healthy subjects massive amounts of carbo-

hydrate must be overfed to stimulate *de novo* lipogenesis (Aarsland *et al.* 1997). Overfeeding carbohydrate increases total body lipogenesis, with the majority (approximately two-thirds) of whole-body fat synthesis occurring in the liver (Lammert *et al.* 2000). Subjects overfed an extra 5MJ (1200 kcal)/d gained 1.5 kg (3.3 lbs) in 21 d, regardless of whether they were overfed carbohydrate or fat (Lammert *et al.* 2000). Schwarz *et al.* (1995) have shown similar results. However, individuals who are overweight or have insulin resistance may be more sensitive to overfeeding carbohydrate. If this were the case, it would be of interest to determine whether the relative 'lipogenic potential' of feeding excess protein is less than that of excess carbohydrate. No studies investigating the effect of excess dietary protein on *de novo* lipogenesis have been performed in human subjects.

Summary and future research priorities

The investigation of how dietary macronutrient content affects fatty acid synthesis has been primarily studied in human subjects by reducing dietary fat and replacing it with carbohydrate. Both fasting and postprandial research has shown that elevations in blood TAG concentration occur when the carbohydrate content of the diet is increased above 50 % energy. In general, lipogenesis studies conducted in healthy individuals consuming higher-fat *ad libitum* diets have shown that *de novo* lipogenesis is normally quite low, representing <5–10 % of the fatty acids in VLDL-TAG secreted by the liver. So far, no lipogenesis studies have been conducted in which dietary fat or carbohydrate has been replaced by increasing energy from protein or by overfeeding protein. A number of key research questions regarding lipogenesis remain to be addressed (Table 1). These include: which subject characteristics are related to elevations in lipogenesis, and which hormones or genes control the diurnal pattern of fatty acid synthesis? If an individual has a higher level of hepatic lipogenesis, can this process be changed by weight loss or treatment of insulin resistance? Another area of need is that of method development, which will be necessary to quantify *de novo* lipogenesis in human adipose tissue *in vivo* and the factors which influence adipose lipogenesis in obesity. Last, dietary studies of individuals with genetic forms of hypertriacylglycerolaemia, such as familial-combined hyperlipidaemia,

Table 1. Priority research areas for the future

Priority areas of research
1. Determine the factors (subject characteristics, hormones, metabolites, the amount of dietary fat etc.) that govern hepatic fatty acid synthesis in human subjects
2. Determine whether insulin resistance is associated with elevations in hepatic lipogenesis and whether insulinizing agents will lower lipogenesis
3. Determine how weight loss may affect carbohydrate-induced hypertriacylglycerolaemia and <i>de novo</i> lipogenesis
4. Develop methods to determine the role of adipose tissue <i>de novo</i> lipogenesis in body-weight gain
5. Determine how hepatic lipogenesis and cholesterol synthesis may be linked metabolically

may clarify the relationship between diet, TAG synthesis and cholesterol synthesis, and may give clues as to whether diet-induced elevations in TAG concentration due to elevations in *de novo* lipogenesis may be atherogenic.

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