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Effects of dietary carbohydrate on lipid metabolism in primates

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Since Lawes & Gilbert (1852) reported to the British Association that carbohydrates given to animals can be converted into depot fat, the knowledge that this conversion is widely present is generally accepted. Even the obese lady is aware of

the existence of the metabolic pathway between potatoes and depot fat. Until the 1950's it was widely taught that in man it was of little consequence to the metabolic processes whether the dietary carbohydrate was glucose, fructose or galactose. This knowledge was disseminated despite the fact that Togel, Brezina & Durig (1913) had found the respiratory quotient after ingestion of fructose to be above 1·0 whereas after ingestion of glucose it was persistently below 1·0. This was confirmed 3 years later by Higgins (1916) and he went so far as to state that fructose shows a tendency or preference to change to fat in the body whereas glucose tends to change to glycogen.

The flurry of research activity into dietary carbohydrates ended with the isolation and purification of insulin, and only desultory interest was shown towards the carbohydrates we eat until 1961 when it was learned that dietary carbohydrates are more likely to raise the serum triglyceride concentration than are dietary fats (Ahrens, Hirsch, Oettle, Farquhar & Stein, 1961). In 1964, further interest in the dietary carbohydrates was brought about by the hypothesis that dietary sucrose was an important aetiological factor in ischaemic heart disease. About this time it was also realized that the pattern of the carbohydrate consumed was changing both in the USA (Antar, Ohlson & Hodges, 1964) and in the UK (Hollingsworth & Greaves, 1967). The change was towards a greater consumption of refined carbohydrate (mainly as sucrose) and a reduced intake of complex carbohydrate. Thus it became apparent that some thought must be given to the question of whether the carbohydrates in the diet, which were being consumed in increasing quantities, were the metabolic nonentities that many had long considered them to be.

The major influence of dietary carbohydrate on lipid metabolism is on the triglyceride fraction, so the effect of dietary carbohydrate on cholesterol and phospholipid metabolism will not be considered further here.

If it is assumed that under normal circumstances no disaccharides pass along the portal vein, then glucose and fructose are the common monosaccharides reaching the liver. Some galactose does reach the liver from ingested lactose, but this is only a small proportion of the total monosaccharide absorbed. With the increasing consumption of sucrose, instead of complex carbohydrates which are glucose polymers, the amount and proportion of the fructose absorbed is increasing.

In primates, differences exist in the response of the serum triglycerides to glucose or fructose and this difference in response is also seen immediately after intravenous injection of the two monosaccharides (Jourdan, 1970). The fall in serum triglyceride concentration seen after consuming glucose (Albrink, Fitzgerald & Man, 1958) has been postulated to be due to the activation of lipoprotein lipase by the insulin released (Perry & Corbett, 1964) and the absence of this stimulus could account for the less marked fall in serum triglycerides after fructose ingestion. It is of interest to note that after intravenous glucose or fructose the difference in the response of the triglyceride concentration is only seen in males (Jourdan, 1970).

After several days on a diet that contains large quantities of glucose or glucose polymers the concentration of triglyceride in fasting serum is lower than that found after a diet containing fructose, usually as sucrose (Macdonald, 1967*a*). It is perhaps

worth noting, in view of the sex difference that exists in the response to intravenous fructose, that pre-menopausal women do not possess this ability to raise their serum triglyceride concentration after the ingestion of fructose (Macdonald, 1966).

In view of these alterations in the amounts of serum triglyceride, particularly after fructose ingestion, it has yet to be ascertained whether the changes are the result of an increase in triglyceride input or a decrease in output. The difficulties involved in determining this fact have recently been reviewed (Nikkila & Kekki, 1971).

The triglyceride response of any individual to dietary carbohydrate is not predictable. Some, and mainly the young, will show only slight rises as a consequence of a high carbohydrate diet, but others, who are more sensitive, will show a striking increase in the serum triglyceride concentration (Anderson, 1967). It is unlikely that the rise in triglyceride concentration seen soon after commencing carbohydrate diets, especially those containing fructose, will be maintained and it has been found that after several weeks the concentration falls towards normal (Antonis & Bersohn, 1961; Coltart & Macdonald, 1971). However, the reverse experiment has recently been done, with particular reference to sucrose. It was found that after 14 weeks on a diet where the sucrose was replaced by glucose polymers (glucose syrup) the rise in the fasting serum triglyceride concentration on resuming a normal diet was much more marked in those men whose pre-diet concentration of fasting serum triglyceride was raised (Roberts, 1971).

Evidence that fructose is more closely involved in triglyceride metabolism than is glucose is seen in the correlation found in man between the concentration of triglyceride in fasting serum and the extent of the rise in the serum fructose concentration after sucrose ingestion; this correlation is not found in young women (Crossley, 1967). It has also been shown that after 13 weeks on a high sucrose diet, baboons given a [^{14}C]sucrose meal showed a correlation between the concentration of the serum fructose and the degree to which [^{14}C]triglyceride appeared in the serum. No such correlation was found with glucose (Coltart & Crossley, 1970).

Thus, it seems that dietary fructose appears to be more intimately related to triglyceride metabolism than is dietary glucose. This being so, what are some possible explanations for this difference?

1. The insulin output after fructose ingestion is less than after glucose because fructose *per se* does not cause a very marked output of insulin. This reduced insulin output will reduce the lipoprotein lipase activity.
2. Insulin may stimulate, direct or indirect, steps in metabolism which do not favour triglyceride accumulation in the serum (Nikkila & Taskinen, 1970).
3. Fructose may follow metabolic pathways that are denied to glucose, but which favour triglyceride formation.

The hexoses, glucose and fructose, have to be split into the trioses glyceraldehyde-P or glyceraldehyde and dihydroxyacetone-P. Since glucose cannot be converted to fructose except via sorbitol (and this only in seminal vesicles (Hers, 1956) and the lens of the eye (Van Heyningen, 1959)) and since fructose can only be converted to

glucose via the trioses, it can be seen that the metabolic situation is relatively simple. (For full details of the metabolic pathways of fructose, see Herman & Zakim, 1968.)

In the formation of triglyceride the dietary carbohydrate can contribute to the triglyceride molecule either by forming fatty acid via the Embden–Meyerhof pathway and Krebs cycle or by forming, via α-glycerolphosphate, the glycerol moiety of the triglyceride molecule.

The trioses formed as a result of breakdown of fructose are dihydroxy-acetone-P and glyceraldehyde. This latter compound, not normally formed by glucose, can be converted to glycerol (Wolf & Leuthardt, 1953) and glyceric acid (Lamprecht & Heinz, 1958) as well as forming glyceraldehyde-P. If the glyceraldehyde fails to be converted to glyceraldehyde-P and instead forms α-glycerolphosphate, it is possible that this step is responsible for the difference in response between glucose and fructose. If this is so, then giving glycerol (which is converted to α-glycerolphosphate) should raise the serum triglyceride concentration in men but not in women. This has been found (Macdonald, 1970).

These results also imply that the effect of the sex hormones on the carbohydrate: lipid relationships act distal to the α-glycerolphosphate part of the pathway.

The explanation for the different lipid response to fructose in men and premenopausal women is, as might be expected, not so simple as suggested and in any full understanding of the mechanism of the difference the following fact must be taken into consideration. When fat replaces some of the carbohydrate in an experimental diet, the effect that the carbohydrate has on the serum triglyceride seems to be overruled by the type of fat consumed with the carbohydrate. For example the rise in serum triglyceride concentration found after a diet containing calcium caseinate, sucrose and cream is not seen when the cream is replaced by sunflower-seed oil (Macdonald, 1967*b*). Comparable results have been found in patients who have had a myocardial infarct (Antar, Little, Lucas, Buckley & Csima, 1970). However, though the effect of the type of fat in the diet shows marked effects generally, irrespective of the type of carbohydrate accompanying it, there seem to be subtle differences exerted by the carbohydrate. The fall in the concentration of fasting serum triglyceride after 5 d on a formula diet containing fructose is less than after a diet where the glucose replaced the fructose. This difference is seen in men but not in young women (Macdonald, unpublished).

Another factor influencing dietary carbohydrate: lipid interrelationships to be taken into consideration is the finding that the protein consumed can affect the extent of the lipid response. When an amino acid mixture replaces the calcium caseinate in a diet containing largely sucrose, the rise in fasting triglyceride concentration was several times greater with the amino acid mixture than with the calcium caseinate (Macdonald, 1971).

What, if any, are the clinical consequences of this dietary carbohydrate: lipid interrelationship in man? The disorder most frequently associated with this relationship is obesity and it seems at the moment that the relationship is purely and simply a calorie conversion of one type of chemical to another, though there is one paper

reporting that fructose leads to a greater weight gain in baboons than does glucose (Brook & Noel, 1969).

The other disease that is associated with dietary carbohydrate, and probably related to lipid metabolism, is myocardial infarction. As dietary carbohydrates raise serum triglyceride concentrations and as raised serum triglycerides are thought to be causally related to coronary artery disease (Albrink & Man, 1959; Crowley, 1971), then it is not surprising that dietary carbohydrates have been implicated in this disorder. In fact, Yudkin (1964) goes further and postulates that one particular carbohydrate, sucrose, is more harmful in this respect than any other. Perhaps in place of generalizations it may be better to learn about an individual's sensitivity to carbohydrate as suggested by Ahrens *et al.* (1961) and classified by Levy & Fredrickson (1968), and to investigate in some detail the carbohydrate:lipid relationships in the more sensitive person.

Kwashiorkor is a state of malnutrition brought about by inadequate protein intake, the clinical picture being different from marasmus probably because of the relative excess of carbohydrate calories accompanying the inadequate protein. The large amount of fat in the liver of these children almost certainly originates from the dietary carbohydrate as there is little fat in their diet.

It was suggested some time ago in textbooks of medicine that disorders of the skin may be related to carbohydrate consumption. More recently it has been found that a high-sucrose intake raises the amount of triglyceride on the surface of the skin whereas a high-starch diet has the reverse effect (Llewellyn, 1966).

Thus, contrary to the views of 30–40 years ago, the role of dietary carbohydrates in primates is not simple, especially in lipid metabolism, and the complex metabolic interrelationships of dietary carbohydrates may have subtle and undesirable clinical consequences.

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The role of insulin in the regulation of glucose metabolism

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One of the most important routes through which the dietary availability of carbohydrate regulates metabolism is through the secretion and action of insulin. The other hormonal mechanisms which mediate metabolic adaptation to carbohydrate deficiency are much less clearly understood. This paper is limited, therefore, to the mechanism of glucose-stimulated insulin release and of insulin-regulated glucose metabolism and storage. Insulin secretion has recently been reviewed by Mayhew, Wright & Ashmore (1969) and Randle & Hales (1971).

Insulin release

A diagramatic representation of the extra-β-cell factors which may be involved in the whole process by which dietary carbohydrate regulates insulin secretion is shown in Fig. 1.

Nervous system. The effects of the autonomic nervous system and its neurotransmitters on insulin release are consistent with the known role of the system in digestion and absorption. Vagal stimulation in the baboon (Daniel & Henderson, 1968) leads to an increased release of insulin into the portal vein. Conversely, adrenaline and noradrenaline are powerful inhibitors of insulin secretion. The possibility exists, therefore, that the sight, smell and taste of food are factors capable of increasing insulin release through activation of the parasympathetic and inhibition of the sympathetic nervous systems. It has been shown that the pancreatic islets of various species are richly innervated (Lever & Findlay, 1971).

Gut factors. The route of administration of glucose has been shown to affect the size of the insulin response. When the same degree of hyperglycaemia is produced by the intravenous or intraduodenal infusion of glucose, the resulting insulinaemia is greater during the latter infusion. This has given rise to the suggestion that intraduodenal glucose or, indeed, amino acids may stimulate the release of a gut hormone