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Differences in the metabolism of dietary carbohydrates studied in the rat

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In the British diet, approximately one-half of the total calories are derived from carbohydrates, of which starch and sucrose together make up more than 90%

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(Yudkin, 1971). Diets in less-developed countries contain an even higher proportion of carbohydrate, most of it in the form of starch, but with sucrose again second in order of importance. The study of carbohydrate metabolism in man, therefore, is concerned primarily with two carbohydrates only—the polysaccharide, starch and the disaccharide, sucrose.

Until comparatively recently it was presumed that starch and sucrose followed the same metabolic pathways leading to the production of energy and the synthesis of body fat. MacDonald & Braithwaite (1964) were the first to show that differences existed in the metabolism of the two carbohydrates, as revealed by differences in the concentrations of lipids in the plasma of men consuming diets rich in sucrose or in starch. The sucrose-containing diet induced a rise in the plasma lipid fraction containing the glycerides, free sterols and free fatty acids. Similar changes in the triglyceride concentration in the plasma were subsequently noted in the rat when dietary starch was replaced with sucrose (MacDonald, 1965; Allen & Leahy, 1966; Taylor, Conway, Schuster & Adams, 1967; Akinyanju & Yudkin, 1967). The rat appeared, therefore, to be a suitable experimental animal for the detailed biochemical investigation of this problem.

The endogenous plasma triglycerides originate in the liver, the fatty acids being obtained from the hydrolysis of chylomicron triglycerides, or by synthesis from carbohydrates (Havel & Goldfien, 1961). While both glucose and fructose may act as precursors of fatty acids in the liver, fructose is metabolized to a very limited extent outside the liver (Wick, Sherrill & Drury, 1953; Herman & Zakim, 1968). It seemed likely, therefore, that the rise in the plasma triglyceride concentration induced by feeding sucrose might result from increased hepatic lipogenesis from fructose, a constituent monosaccharide of sucrose but not of starch. By the same argument, it might be expected that fat synthesis in the adipose tissue would be reduced in the sucrose-fed animal.

Table 1. *Effect of different carbohydrates and fats on the plasma triglyceride concentration and on the activities of pyruvate kinase (PK) and glucose-6-phosphate dehydrogenase (G-6-PD) in liver and adipose tissue of rats*

Diet	Plasma triglycerides (mg/100 ml)	Liver (i.u./liver)		Adipose tissue (i.u./g)	
		PK	G-6-PD	PK	G-6-PD
Starch	42·5	154	23·6	2·0	0·33
Sucrose	60·1*	312*	37·8*	1·8	0·24*
Sunflower-seed oil	27·0*	39*	3·3*	1·0*	0·11*
Dripping	31·6*	56*	4·3*	0·7*	0·10*

*Value differs significantly from that for starch.

In order to test this hypothesis (Naismith, 1971), rats were given, for 50 d, diets in which most of the energy was derived from sucrose, starch or two kinds of fat. The aim of the experiment was to relate the fasting lipid concentrations in the plasma at the end of the feeding period to the rate of fatty acid synthesis in the liver

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and adipose tissue. As an index of lipogenesis, the activities of pyruvate kinase (PK) (*EC* 2.7.1.40) and glucose-6-phosphate dehydrogenase (G–6–PD) (*EC* 1.1.1.49) were measured; these two enzymes play an important part in regulating the rate of biosynthesis of the fatty acids.

The results of the analyses are given in Table 1. In these and subsequent experiments, the starch-fed animals have been regarded as a control group. Feeding sucrose caused a substantial rise in the plasma triglycerides. In the liver, the activities of the two enzymes were almost doubled, whereas in the adipose tissue G–6–PD activity was depressed. Both fats lowered the plasma triglyceride concentration and, as expected, greatly reduced the activities of both PK and G–6–PD in the liver and adipose tissue.

This experiment clearly demonstrated that a rise in blood triglycerides is associated with increased hepatic lipogenesis and, conversely, that a fall in the plasma concentration accompanies depressed hepatic lipogenesis.

The following experiments were designed to clarify the role of fructose in the altered pattern of fat synthesis in the tissues which results from the exchange of sucrose for dietary starch.

Diets containing a variety of carbohydrates were given to rats for 50 d. Three of the carbohydrates used (starch, maltose and glucose) supplied only glucose to the tissues, whereas two (sucrose and fructose) supplied fructose as well as glucose. Fructose is partly converted into glucose in the intestinal mucosa and in the liver (Miller, Burke & Haft, 1955; Kiyasu & Chaikoff, 1957). Blood was analysed for lipids, and the activities of PK and G–6–PD were measured in the liver. The results of these determinations are summarized in Table 2 and in Fig. 1.

Table 2. *Plasma lipid concentrations (mg/100 ml) in rats given different carbohydrates*

Diet	Triglycerides	Total cholesterol
Starch	51	111
Sucrose	88*	124*
Maltose	81*	128*
Fructose	78*	135*
Glucose	77*	118

*Value differs significantly from that for starch.

All the sugars promoted an increase in the plasma triglyceride concentration of roughly the same order and all but glucose significantly raised the cholesterol value. The rise in plasma cholesterol was later shown to be confined to the esterified fraction (Naismith & Khan, 1971*a*). Likewise, all the sugars raised the activities of both enzymes in the liver (Fig. 1*a*,*b*). Maltose gave values identical with those found for sucrose, but fructose gave the highest values of all.

Changes in enzyme activity reflect, quantitatively, changes in throughput in the metabolic pathway in which the enzyme participates. It was nevertheless thought

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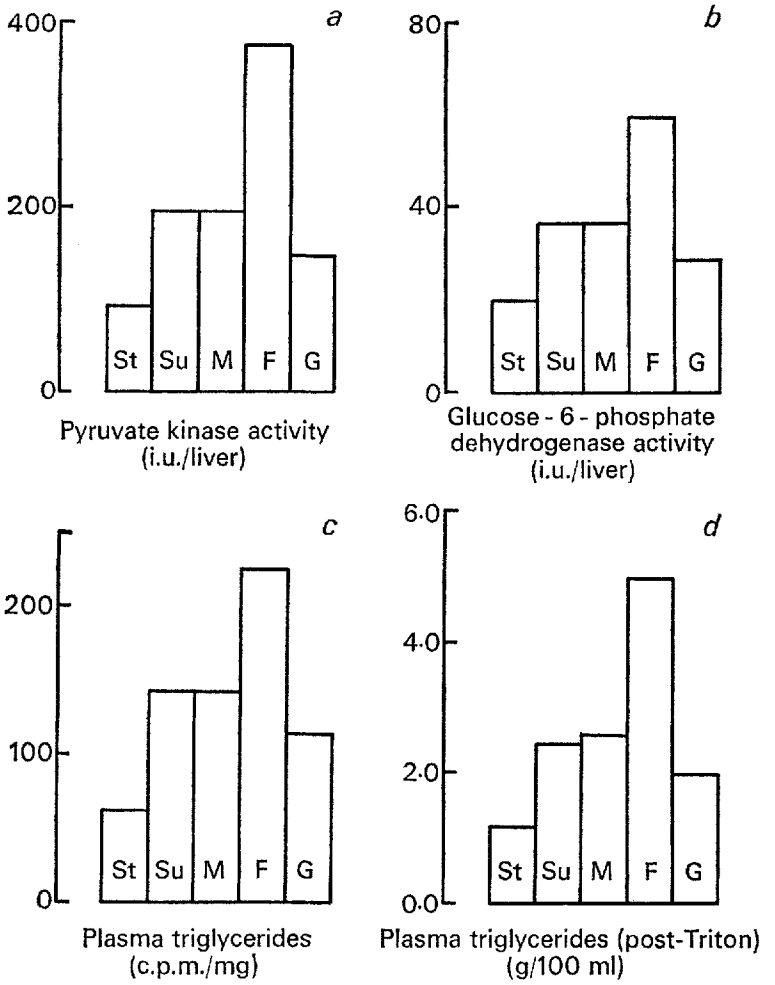

Fig. 1. The effect in rats of prolonged ingestion of starch (St), sucrose (Su), maltose (M), fructose (F) or glucose (G) on (a), the activity of hepatic pyruvate kinase; (b), the activity of hepatic glucose-6-phosphate dehydrogenase; (c), the specific activity of plasma triglycerides following the injection of [^{14}C]glucose and (d), the throughput of triglycerides in the plasma.

desirable to confirm the findings of the enzyme studies using isotopic tracers (Naismith & Khan, 1970*a*).

Uniformly labelled [^{14}C]glucose (10 μCi) were administered intraperitoneally to rats maintained for 50 d on the diets previously used. The animals were in the fed state, and specific activities of the tissue lipids were measured after 2 h. The rate of incorporation of labelled glucose into the plasma triglycerides of rats given sucrose or maltose was double that found in rats given starch, whereas the feeding of fructose caused a fourfold increase in specific activity (Fig. 1*c*). In the adipose tissue of rats consuming sucrose or fructose the picture was reversed; both these sugars brought about a striking reduction in the uptake of glucose into the triglycerides in this tissue.

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The degrees by which the plasma lipids are elevated by the different carbohydrates do not correspond to the rates of fatty acid synthesis in the liver. It should be borne in mind, however, that the plasma concentration represents a state of equilibrium between input of triglycerides from the liver and their removal by the adipose tissue, which is catalysed by the plasma-clearing enzyme, lipoprotein lipase. The discovery that the detergent Triton WR 1339 acts as an inhibitor to this enzyme (Byers & Friedman, 1960) offered a means of estimating the throughput of triglycerides in the plasma during the ingestion of the different carbohydrates (Naismith & Khan, 1970*b*).

Triton was injected intraperitoneally into rats that had been reared for 50 d on diets containing the five carbohydrates that had previously been used and blood was drawn 24 h later for analysis for lipids. Food intakes were very similar for all dietary groups and were not affected by the administration of Triton. All the simple sugars greatly increased the flow of triglycerides from the liver to the adipose tissue (Fig. 1d) in amounts which reflected precisely the rates of fat synthesis in the liver.

It follows from this observation that the rate of clearing of the triglycerides from the plasma must vary very considerably within the different groups in order to maintain a plasma triglyceride concentration that is similar for diets containing the monosaccharides and disaccharides. Pawar & Tidwell (1968), using diets containing saturated or polyunsaturated fat, have claimed that a negative correlation exists between the plasma triglyceride level and lipoprotein lipase activity. In their experiments, however, the variable factor was a qualitative one, the degree of unsaturation of exogenous and endogenous triglycerides in the plasma; there was clearly no difference in throughput. It seemed to us that the hyperlipidaemia associated with feeding simple sugars should be accompanied by a rise, rather than a fall, in the activity of the enzyme in adipose tissue. This hypothesis was put to the test in two groups of rats given diets containing starch or sucrose (Naismith & Khan, 1971*b*). Blood was analysed for lipids and samples of epididymal adipose tissue were taken for estimation of lipoprotein lipase activity after the animals had been on diet for 50 d. The high-sucrose diet raised the plasma triglyceride concentration by 60% and induced a large (64%) increase in the activity of lipoprotein lipase.

The ingestion of fructose manifestly provides the most potent stimulus to hepatic lipogenesis but, since maltose, a disaccharide devoid of fructose, proved to be as effective as sucrose, an alternative explanation for the hyperlipidaemic property of sucrose had to be found.

If sucrose were more rapidly digested and absorbed than starch, monosaccharides entering the liver at a higher concentration might lead to adaptive changes in the activities of the enzymes involved in their metabolism. This idea was examined in an experiment (Naismith and Rana, unpublished results) in which rats were given a single 2 g meal of the diets to which they had been accustomed for 50 d. The meals were consumed in less than 1 min. Blood was then taken at 5 min intervals

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for the estimation of total reducing sugars. The 'meal tolerance' curves are shown in Fig. 2.

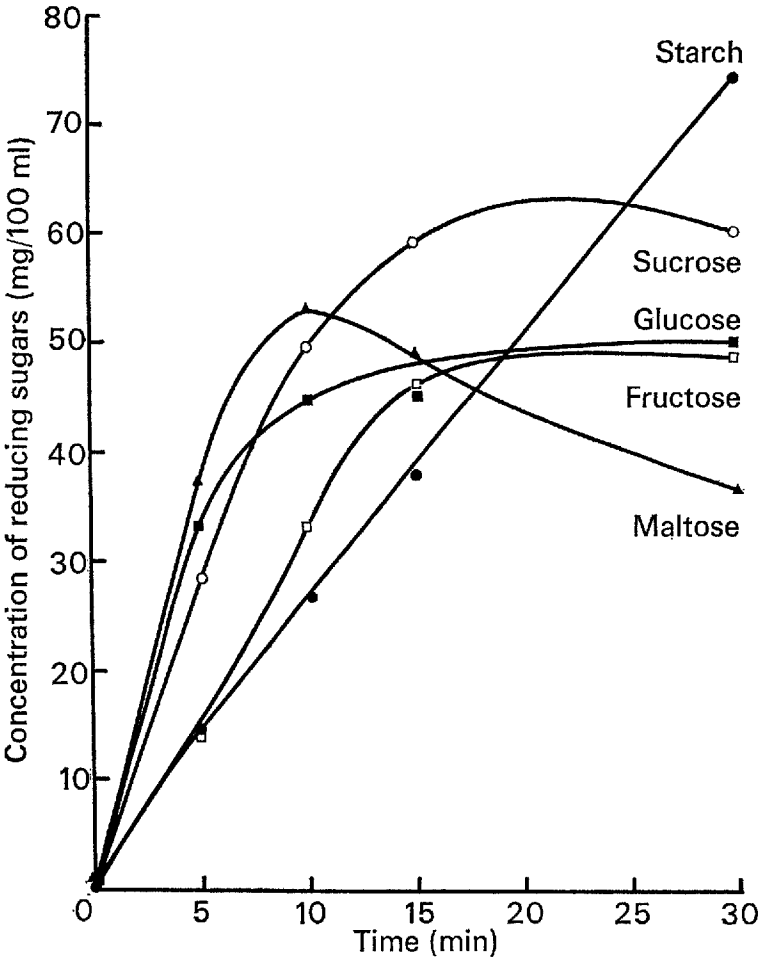

Fig. 2. Rise in the concentration of reducing sugars in the blood of rats after meals of 2 g containing starch, sucrose, maltose, fructose or glucose.

The rise in the blood sugar level was much more rapid after the ingestion of meals containing sucrose, maltose or glucose than it was after a starch meal. The lower blood concentrations of sugar after the fructose meal can be attributed to the greater proportion of this sugar that is diverted by the liver for fatty acid synthesis as evidenced by the threefold to fourfold rise in the activities of hepatic PK and G–6–PD. In animals accustomed to eating starch and, therefore, not adapted to metabolizing fructose, a single meal containing fructose produces a rate of entry of monosaccharides into the systemic blood more than twice as great as that observed after a meal containing starch (Naismith and Karikari, unpublished results).

These findings suggest that the primary stimulus to enhanced hepatic lipogenesis is a recurrent flooding of the liver cells with high concentrations of monosaccharides,

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with the consequent induction of enzymes involved in fatty acid synthesis, and that any difference between the metabolism of fructose and glucose is comparatively unimportant as a factor determining the hyperlipidaemic effect of sucrose.

To conclude, I will return to the species with which I began. The few sucrose or fructose tolerance tests that have been conducted on human volunteers (Butterfield, Sargeant & Whichelow, 1964; Swann, Davidson & Albrink, 1966) have shown that neither of these sugars, given by mouth, produced as great a rise in blood reducing sugars as did glucose or 'liquid glucose' (partially hydrolysed starch); the increase in hexose sugars in the blood after fructose administration was less than half that found with glucose or 'liquid glucose', and approximately half of this increase was due to fructose. Furthermore, a significant rise in blood pyruvate was observed with both sucrose and fructose, which may be taken as an indication of augmented throughput of sugars in the Embden–Meyerhof pathway in the liver.

It appears, therefore, that in man, as in the rat, a substantial part of ingested sucrose does not reach the systemic blood as monosaccharides but is diverted by the liver, presumably for fat synthesis, and that the hyperlipidaemia encountered in human volunteers consuming sucrose-rich diets may also be explained on this basis.

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Glucose metabolism in the ruminant

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The metabolism of the tissues of the ruminant, in general, has been the subject of an excellent review by Ballard, Hanson & Kronfeld (1968). In this paper particular attention will be paid to the glucose metabolism of the lactating udder, since the

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