The effect of dietary sucrose on blood lipids, serum insulin, platelet adhesiveness and body weight in human volunteers

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Summary

A study was made of the effect of high or low intake of sucrose for periods of 14 days in a group of nineteen apparently healthy men.

The high sucrose diet produced no change in blood levels of cholesterol or phospholipids, or in glucose tolerance, but it produced a significant rise in triglycerides in all nineteen men. In six of them, there was in addition a rise in serum immuno-reactive insulin, especially during the glucose tolerance test, and these same six subjects also showed a considerable increase in weight and a significant increase in platelet adhesiveness.

There was no difference between the six subjects and the remaining thirteen in any of the other measurements, or in the diets they consumed during the experiment. The changes produced by sucrose had disappeared, or nearly so, after 14 days of normal diet.

It is suggested that the effect of sucrose in producing hyperinsulinism may be more relevant to its possible role in the aetiology of ischaemic heart disease than its effect on blood lipids. It is further suggested that only some individuals are susceptible to the development of ischaemic heart disease by dietary sucrose, and that these may be identified as those that show 'sucrose-induced hyperinsulinism'.

Introduction

It is widely accepted that ischaemic heart disease (IHD) is a disease of affluence. Both longitudinal and cross-sectional studies have shown that the major dietary characteristic of affluence is a replacement of increasing amounts of starch by sugar (sucrose), so that in the United Kingdom during the last 200 years the proportion of sucrose has risen from less than 2% to about 35% of the total dietary carbohydrate (Yudkin, 1964). Relevant experiments, therefore, are those that study the effects of diets in which the relative proportion of these two major dietary carbohydrates is changed. We have conduc-

ted such an experiment on nineteen men aged 21–44 years.

Subjects and methods

The subjects were volunteers from the students and staff of two London University colleges. The purpose and design of the experiment was explained to them in detail, and they were each provided with food tables and given instruction in their use and in the recording of their food intake.

After a week's preliminary study, ten of the subjects (Group A) were asked for the next 2 weeks to take diets high in sucrose, the sucrose as far as possible substituting for starch so as not to change the caloric intake (Table 1). For the following 2 weeks—weeks 4 and 5—they reverted to their normal diets. For the next 2 weeks—weeks 6 and 7—they were asked to take diets with virtually no

TABLE 1. Experimental design

Period	No. of days	Group A	Group B
I	7	Preliminary	Preliminary
II	14	Sucrose	Starch
III	14	Rest	Rest
IV	14	Starch	Sucrose
V	14	Rest	Rest

sucrose, making up in calories by increasing their starch intake. Finally they were again allowed to eat their normal diet. The remaining nine subjects (Group B) followed a similar procedure, but took the low-sucrose diets in weeks 2 and 3, and the high-sucrose diets in weeks 6 and 7. At the end of the 1st week, and thereafter at intervals of 2 weeks, the subjects were weighed, their glucose tolerance determined, the insulin response to this test measured, and the plasma lipids assayed. In addition, we measured platelet adhesiveness, plasma fibrinogen and clot lysis time.

Blood was taken from a forearm vein after an overnight fast. Then 50 g glucose was given by mouth,

and further blood samples taken 30 and 120 min later. In all three samples, blood glucose was determined by the oxidase method of Huggett & Nixon (1957) and insulin by immunoassay (Hales & Randle, 1963). In the sample of fasting blood, cholesterol was measured by the method of Zlatkis, Zak & Boyle (1953) as modified by Henly (1957), triglyceride by the method of Handel & Zilversmit (1957), phospholipid by the method of Bartlett (1959), fibrinogen by the method of Ingram (1961) and clot lysis time by the method of Fearnley, Balmforth & Fearnley (1957).

Platelet adhesiveness was measured after 20 min rotation (Wright, 1941); no correction was made for the haematocrit values of the blood samples, since they all fell within the range 35–48%.

Each subject was given a specially prepared booklet of dietary instructions and a diary in which he recorded the foods and drinks he consumed and their quantities.

Results

We have combined the results of the different dietary treatments, so that we present them as if both groups followed the same experimental design. We feel justified in doing this because the initial values for the two groups of subjects were very similar (Table 2). Moreover, as we shall see, the effects of the high-sucrose diet had disappeared at the end of the subsequent 2-week rest period, except for a very small residual effect on serum insulin levels.

Neither the increase nor the decrease in sugar intake produced a significant change in the level of serum cholesterol or phospholipid, in glucose tolerance, in level of fibrinogen or in fibrinolytic activity (Table 3). On the other hand, the 14 days on the high-sugar diet produced a significant increase in the level of plasma triglycerides, in insulin response and in body weight, effects that were

TABLE 2. Initial findings in nineteen male subjects (mean and range)

	Group A (ten subjects)	Group B (nine subjects)
Age (years)	28 (23–44)	28 (22–41)
Height (cm)	175 (165–188)	174 (163–183)
Weight (kg)	73·7 (58·3–81·5)	72·4 (61·0–74·9)
Daily kCal	3420 (2520–4150)	3370 (3070–3640)
Diet (g/day)		
Protein	85 (72–108)	83 (71–96)
Fat	112 (98–182)	116 (100–149)
Carbohydrate	509 (301–599)	480 (402–656)
Sucrose	167 (98–209)	163 (93–248)
Serum lipids (mg/100 ml)		
Cholesterol	240 (199–272)	258 (213–281)
Phospholipid	222 (187–261)	238 (199–274)
Triglyceride	137 (98–168)	149 (122–176)
Blood glucose (mg/100 ml)		
0 min	68 (64–72)	70 (61–81)
30 min	94 (91–104)	104 (94–108)
120 min	66 (59–72)	70 (59–82)
Serum insulin (μU/ml)		
0 min	23 (17–26)	21 (14–25)
30 min	64 (49–86)	62 (53–75)
120 min	35 (29–46)	32 (23–41)
Platelet adhesiveness (%)	67 (59–81)	68 (59–82)
Fibrinogen (mg/100 ml)	231 (193–278)	283 (260–300)
Clot lysis time (hr)	5¾ (3½–7½)	5¼ (3½–7¼)

TABLE 3. Effect of dietary sucrose in nineteen male subjects (mean)

	Preliminary	Sucrose	Rest	Starch	Rest
kCal/day	3390	3350	—	3370	—
Weight (kg)	73·0	74·0*	73·4	73·6	73·5
Sucrose (g/day)	164	438	—	10	—
Lipids (mg/100 ml)					
Cholesterol	249	248	250	243	248
Phospholipid	230	231	231	230	230
Triglyceride	143	150*	142	140	142
Blood glucose (mg/100 ml)					
0 min	69	69	68	69	70
30 min	99	99	98	99	100
120 min	68	68	68	67	68
Serum insulin (μU/ml)					
0 min	22	28†	23	22	21
30 min	63	86†	67	64	64
120 min	34	49†	36	32	32
Platelet adhesiveness (%)	67	65	69	67	67
Fibrinogen (mg/100 ml)	255	256	259	257	255
Clot lysis time (hr)	5¾	5	5	5¼	5¼

* or † Significant differences between these values and those for preceding and subsequent period.
*P < 0.05. †P < 0.01.

Stephen Szanto and John Yudkin

completely or almost completely reversed at the end of the next 14 days of the normal diet.

A more detailed analysis of these changes shows that the effect on serum insulin levels was confined to six of the subjects (Table 4). These same six subjects also showed an increase in platelet adhesive-

TABLE 4. Effect of dietary sucrose on insulin response (mean, μU/ml)

	Period					
	Thirteen subjects			Six subjects		
	0 min	30 min	120 min	0 min	30 min	120 min
Preliminary	22	63	33	23	64	34
Sucrose	23	65	33	39*	131*	84*
Rest	22	65	34	25	72	40
Starch	22	64	33	22	64	32
Rest	21	64	31	23	63	34

*Significant difference between these values and those for preceding and subsequent period ($P < 0.01$).

ness, as well as a much greater increase in body weight than did the other thirteen subjects (Tables 5 and 6, Fig. 1). The weight, platelet adhesiveness and insulin levels returned to their previous values during the next 14 days when the subjects were eating their normal diet. The changes in these three parameters were confined to six out of the nineteen subjects, whereas the change in triglyceride levels, with a rise during the high-sucrose diet and subsequent fall, were the same in the six subjects as

TABLE 6. Changes in platelet adhesiveness (%) in six subjects who developed hyperinsulinism and thirteen who did not (see Table 4)

	Period				
	Prelimi-nary	Sucrose	Rest	Starch	Rest
Thirteen subjects	67	67	68	69	66
Six subjects	68	60*	71	65	68

*Significant difference between this value and those for preceding and subsequent period ($P < 0.05$).

in the remaining thirteen. Moreover, there was nothing in the experimental diets or in the original measurements—age, weight, height, blood pressure, smoking habits, blood lipids, diet, glucose tolerance or insulin response—that distinguished these six subjects from the other thirteen (Table 7).

Discussion

Our primary object in carrying out this experiment was to discover a further link between the ingestion of sucrose and the production of ischaemic heart disease. The great difficulty that has been encountered in producing in experimental animals an exact parallel to human ischaemic heart disease, and to a lesser extent its precursor atherosclerosis, has directed research towards the discovery of factors that produce what are usually accepted as concomitants to the disease. This is the reason why

TABLE 5. Weight changes in six subjects who developed hyperinsulinism and thirteen who did not (see Table 4) [mean, kg (and range)]

	Average change during each week of experiment	After high-sucrose diet for 14 days	After reversion to normal diet for 14 days
Thirteen subjects	+0·1 (−0·5 — +0·4)	+0·4 (0 — +0·9)	+0·05 (−1·8 — +2·8)
Six subjects	0 (−0·1 — +0·05)	+2·1* (+1·4 — +2·7)	−2·0 (−3·2 — −1·4)

*Significant difference between this value and those for preceding and subsequent period ($P < 0.01$).

TABLE 7. Findings in six subjects who developed hyperinsulinism and thirteen subjects who did not (see Table 4)

	Age (years)	Height (cm)	Weight (kg)	Daily diet			Serum triglyceride (mg/100 ml)	
				kCal	Pr.g.	Suc.g.	Mean	Range
Initial findings								
Thirteen subjects	27·5	175	72·5	3360	84	163	139	(98–169)
Six subjects	29·5	174	74·5	3460	84	166	151	(132–176)
High-sucrose diet								
Thirteen subjects	27·5	175	72·5	3330	83	431	146	(115–159)
Six subjects	29·5	174	74·5	3400	81	452	158	(139–179)

such a great deal of attention has been paid to raised levels of blood lipids, and why it is now common to ascribe aetiological significance in IHD, or therapeutic effect, to agents simply on the basis that they affect blood lipids.

That dietary sucrose can cause an increase in serum triglycerides in man is now well established, though most of the experiments hitherto reported have used diets that are quite different from those normally consumed (Macdonald & Braithwaite, 1964; Akinyanju *et al.*, 1968). Although the amounts of sugar eaten by our subjects during the high-sucrose period were three or more times as much as the average intake in this country, there are at least a few people who normally consume amounts of this order (Salter & Yudkin, unpublished).

It has been suggested that sucrose produces an increase in level of triglyceride because it produces an increase of weight (*Nutr. Rev.*, 1966). We have previously shown, with men consuming an 'atherogenic' diet, that the increase in the lipid can occur without weight gain (Akinyanju *et al.*, 1968). In our present experiment, thirteen subjects showed
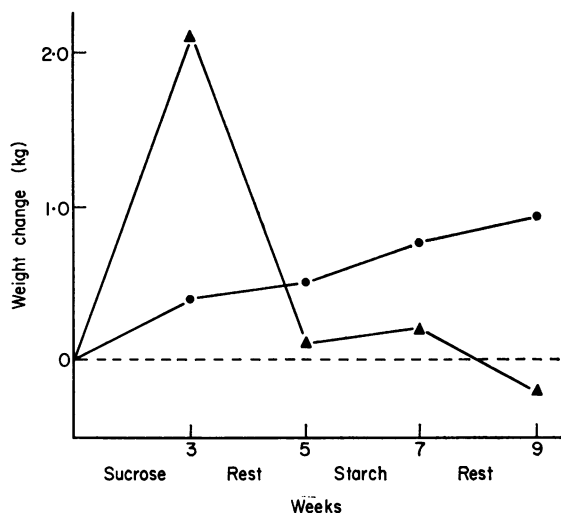

FIG. 1. Change in weight of the six subjects (▲) that showed hyperinsulinism, and of the thirteen subjects (●) that did not.

variable, small and usually insignificant changes of weight during the 9 weeks, while six subjects showed a considerable increase after 2 weeks on the high-sucrose diet, and a decrease to the previous value in the following 2 weeks. Nevertheless, in both sets of subjects there was a very similar rise in triglycerides induced by the high sucrose diet, and a fall to the previous level when the subjects reverted to their normal diet.

Much more striking, however, than the rise in serum lipids observed in all of our subjects was the

great increase in levels of serum insulin in six of them —the same six that showed a large increase in weight and an increase in platelet adhesiveness— during the 2 weeks of high-sucrose diet. In these subjects, the level of insulin was raised both in the fasting state and after the ingestion of glucose. Since the level of insulin rose to more than 100 µU/ml serum, these subjects can be said to have shown hyperinsulinism according to the definition of Grodsky *et al.* (1965). The high levels of insulin caused by the high sucrose diet were not associated with any change in the levels of blood glucose which remained within normal limits. It is likely that a decrease in glucose tolerance would have occurred if the high-sucrose diet had been continued for a longer time, as shown in the experiments of Cohen *et al.* (1966).

Although we do not yet know how much of the increase in weight was due to water retention and how much to fat synthesis, the association between the two features of weight gain and hyperinsulinism recalls the association between obesity and hyperinsulinism (Rabinovitz & Zierler, 1962; Samaan *et al.*, 1965).

The fact that all our subjects responded to dietary sucrose by a rise in triglyceride, but only some of them responded by a rise in insulin, supports the view of Nikkilä and his colleagues (1965) that 'disordered insulin–glucose homeostasis operates through a mechanism different from that of hyperlipidaemia'. That only about one-third of our subjects showed hyperinsulinism after the high-sucrose diet may be because only these were specially susceptible. This recalls the suggestion that only some people have a defect in one or other part of the insulin mechanism, which makes them susceptible to diabetes mellitus (Vallance-Owen & Ashton, 1963) or to obesity (Butterfield, 1967). It recalls also the experiments that demonstrate that sucrose may produce its effects upon enzymes and upon blood lipids through different mechanisms (Aitken, Robinson & Yudkin, 1967; Akinyanju & Yudkin, 1967).

Evidence is growing that hyperinsulinism may be a more relevant factor in the production of IHD than an increase in particular blood lipids. The injection of insulin into rats increases the incorporation of labelled glucose or acetate into aortic lipid (Stout, 1968), and oral administration of carbutamide to cockerels increases the degree of spontaneous atherosclerosis (Härtel, Punsar & Louhija, 1968). These facts support the view of Mahler (1965) that insulin may be an important factor in the development of atherosclerosis; it may indeed turn out that insulin is the beginning of the final common path to the production of IHD. If we accept the view that an increase in platelet adhesiveness is an im-

portant factor in the production of occlusive arterial disease, it would be relevant that sucrose produced in our experiment an increase both in insulin and in platelet adhesiveness in the same susceptible subjects.

One can now begin to explain the effects of the various factors known to be associated with IHD in terms of an association with levels of circulating insulin. Peripheral vascular disease, maturity-onset diabetes, obesity, smoking and hypertension all predispose to IHD, and all are associated with hyper-insulinism (Yalow & Berson, 1960; Rabinovitz & Zierler, 1962; Welborn *et al.,* 1966; Kingsbury & Jarrett, 1967; Szanto, 1967). Conversely physical exercise and weight reduction, which reduce the risk of IHD, are associated with a reduction in circulating insulin (Devlin, 1963; Szanto, 1968). Low levels of insulin are also found in the diabetes of chronic pancreatitis, in which vascular complications are said to be relatively uncommon (Joffe *et al.,* 1968).

We may now add sucrose to the list of agents—diabetes, obesity, smoking and hypertension—that produce hyperinsulinism. This is further evidence for the hypothesis that, like these other agents, sucrose increases an individual's proneness to occlusive arterial disease.

The hyperinsulinism caused by dietary sucrose may be responsible for many of the biochemical changes that this substance has increasingly been found to induce (see for example Yudkin, 1967). It will be useful we believe to bear this possibility in mind in future studies of the biochemical changes produced by sucrose. Similarly, if hyperinsulinism is a factor closely related to the underlying abnormality in IHD, we must not expect other changes—secondary and more remote—to be equally uniform in subjects with the disease.

In the light of this discussion, we suggest that only a proportion of the population is susceptible to the development of occlusive atherosclerotic disease following an habitual high consumption of sucrose. We believe that the sucrose leads, after many years, to an increase in insulin levels in those people that are susceptible. If these suggestions prove correct, such individuals might be identified before they develop overt disease by determining the effect upon their insulin levels of the challenge of a high consumption of sucrose for a few days; they might show what we may call 'sucrose-induced hyper-insulinism'. We would then have a relatively simple predictive test for the identification of susceptible persons who will develop IHD if they habitually consume large amounts of sucrose. We do not yet know whether these are the same persons as are susceptible because of cigarette smoking or some other predisposing factor.

There is a further consequence that we can derive from our hypothesis. It is that men with overt occlusive arterial disease should include those whose insulin levels have been increased by a high continuing intake of sucrose. Although it will also include those whose insulin levels have been increased by cigarette smoking or hypertension, we should nevertheless expect that persons with a high sucrose intake will tend to congregate among those with high serum insulin levels; those with low sucrose intake will be more likely to congregate among those with low insulin levels. In general, that is, men with occlusive arterial disease should show a correlation between serum insulin level and sucrose intake. On the other hand, men who by middle age have developed no symptoms or signs of athero-sclerosis will be composed largely of the non-susceptible part of the population. Whatever their intake of sugar, this would not affect their serum insulin levels, so that we would expect this group to show little or no relationship between the insulin level and sucrose intake. This prediction of the presence or absence of a relationship between insulin and sucrose intake in these two groups has already been tested, and the results are reported in the following paper (Yudkin, Szanto & Kakkar, 1969).

Acknowledgments

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