INFLUENCE OF DIETARY SUCROSE ON GLUCOSE AND FRUCTOSE TOLERANCE AND TRIGLYCERIDE SYNTHESIS IN THE BABOON

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SUMMARY

1. Male and female baboons were fed a 75% sucrose/fat free diet for 13 weeks. At the end of this period, and when tested by a sucrose meal, the glucose tolerance was improved, but the fructose tolerance impaired.

2. There was no difference between the male and female baboons with regard to the changes observed in glucose tolerance. The impairment of fructose tolerance as a result of the sucrose diet was more marked in the males than in the females.

3. By labelling the sucrose meals uniformly with $^{14}$C, a correlation was observed between the level of peripheral blood fructose attained and the degree to which $^{14}$C-triglyceride appeared in the serum. No such correlation was found with glucose.

4. A cause-and-effect relationship between fructose tolerance and triglyceride specific activity was demonstrated by means of a high sucrose diet. The resulting impairment of fructose tolerance was reflected by a corresponding increase in triglyceride specific activity. The improvement in glucose tolerance under the same dietary conditions bore no relationship to the change in triglyceride specific activity.

5. Fructose was incorporated into serum triglyceride to a greater extent in the male baboons than in the females because of the higher levels of blood fructose attained in the male animals.

It has been shown that following a sucrose meal the level of blood fructose, but not glucose, relates to the concentration of triglyceride in the fasting serum (Crossley, 1967). Thus subjects with elevated serum triglycerides have high levels of serum fructose after a sucrose meal and vice versa. Sucrose is more hypertriglyceridaemic than glucose (Macdonald, 1965a) and $[^{14}$C]sucrose is incorporated into serum triglyceride to a greater extent than $[^{14}$C]glucose (Macdonald & Roberts, 1965, 1967). This evidence points to fructose as being more lipogenetic than glucose, the degree of lipogenesis possibly depending on the levels of blood fructose attained. In the following experiment both the fructose and glucose tolerance to a sucrose meal

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T. M. Coltart and J. N. Crossley

and the incorporation of these hexoses into serum triglyceride have been studied in baboons before and after a 13 week sucrose enriched diet.

**METHODS**

After an overnight fast twelve adult baboons (*Papio cynocephalus*, six male and six female) were each tranquilized with an intramuscular injection of phencyclidine hydrochloride (Sernylan: Parke Davies & Co., Hounslow, Middlesex) at the dose level of 1 mg/kg body weight.

Each animal was then given by stomach tube a sucrose meal, consisting of 4 g/kg body weight sucrose (as a 50% w/v solution in distilled water) to which had been added 25 μCi of uniformly labelled [14C]sucrose. Venous blood samples were obtained from each animal before the meal, and at $\frac{1}{2}$, 1, $1\frac{1}{2}$, 2, 3, 4 and 5 hr afterwards. Estimations were carried out on the serum glucose and fructose, and on the specific activity (counts/mg of lipid/100 sec) in the serum triglyceride fraction.

The animals were then started on a sucrose-enriched diet consisting on a weight basis of 75 parts sucrose, 18 parts calcium caseinate and 7 parts dried yeast. This was in contrast to the standard baboon diet which was composed of 70 parts starch, 4 parts fat and 26 parts protein. The solid constituents of the sucrose diet were mixed into an emulsion with water in the concentration of 100 g foodstuffs/500 ml water, and given to the animals to drink in sufficient amounts to keep the body weight of each animal constant. On average this amounted to 1500 ml (= 1125 calories) for a 15 kg male baboon per day, and 1000 ml (750 calories) for a 10 kg female baboon per day. While on the sucrose diet the animals were provided with salts (Hegsted *et al.*, 1941) and vitamins (Abidec: Parke Davies & Co.).

After 13 weeks on the sucrose diet each animal was given a second [14C]sucrose meal, similar to that administered before the diet. Venous blood samples were collected at the same time intervals as for the first meal, and again the serum glucose and fructose, and the specific activity in the serum triglyceride fraction estimated.

The serum glucose concentration was determined using an automated glucose oxidase micromethod (Faulkner, 1965), and the serum fructose by an automated Roe's method (Roe, 1934).

The specific activity in the serum triglycerides was determined using a scintillation counter after the triglyceride faction had been estimated gravimetrically (Bloor, 1926) following its separation by thin layer chromatography (Schlierf & Wood, 1965).

Each baboon was given 25 μCi of [14C]sucrose irrespective of the size of the animal. An appropriate correction factor was employed therefore, so that with each baboon the dose level of [14C]sucrose administered was proportional to body weight.

The tolerances of both glucose and fructose and the degree to which these hexoses were incorporated into serum triglyceride (specific activity tolerance) were assessed by two different methods. The first involved the use of ‘peak values’ as the sole measurement of tolerance. This was considered feasible since in all curves the peak value was representative of the magnitude of the rise. With the second method, tolerance was assessed by calculating the ‘area under the curve’. Although both methods of interpreting tolerance are open to criticism, the data when analysed by each method separately produced the same results. It was decided for the following reasons to use ‘peak values’ rather than ‘areas’.
oltart and J. N. Crossley

$P < 0.025)$. The 3, 4 and 5 hr mean values obtained before
were those observed after 13 weeks, and by 5 hr the fructose
level was 2 mg/100 ml with both sucrose meals.

![](image)

Serum fructose (mg/100 ml)

<table>
<thead>
<tr>
<th></th>
<th>1 hr</th>
<th>1½ hr</th>
<th>2 hr</th>
<th>3 hr</th>
<th>4 hr</th>
<th>5 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-3†</td>
<td>6-8†</td>
<td>6-2†</td>
<td>4-9</td>
<td>3-2</td>
<td>1-8</td>
<td></td>
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<tr>
<td>0-7</td>
<td>0-8</td>
<td>0-6</td>
<td>0-5</td>
<td>0-9</td>
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<tr>
<td>9-7†</td>
<td>10-7†</td>
<td>9-6†</td>
<td>5-6</td>
<td>3-0</td>
<td>1-6</td>
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<td>1-2</td>
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</tbody>
</table>

Values significantly different ($P < 0.025)$. 

In glucose (mg/100 ml) of twelve baboons in response to a
m e to each animal, plotted against the corresponding peak
activity (counts mg$^{-1}$ 100 sec$^{-1}$ et seq) following the same
* (●) represent the values before the 75% sucrose diet and
13 weeks on the 75% sucrose diet. On neither occasion was
meters significant ($P > 0.05$). 

: on the fructose response to a sucrose meal
Sucrose tolerance and triglyceride specific activity.

1. Peak value is an absolute value as opposed to area.
2. Owing to the time taken for hexose incorporation triglyceride specific activity were not recorded until about 1 h after [14C]sucrose (Table 4). Thus within the 5 h experimental period 50% of the specific activity curve with which to derive an area rather than the mean fasting values with both glucose meals. Within each animal before and after the sucrose diet was plotted for serum triglyceride specific activity (Fig. 1) the correlation between the two parameters. Furthermore the differences in triglyceride specific activity also showed no correlation (Fig. 1).

3. Towards the latter stages of the sucrose meal (3–5 h), when the specific activity curve with which to derive an area was probably not representative of the glucose absorbed from fructose to glucose. This necessitated manipulation of these non-contributory values from influencing the area of the specific activity curve with which to derive an area was avoided by the use of peak values.

RESULTS

Glucose

The mean serum glucose values of the twelve baboon level before the sucrose diet did not differ significantly from each other. In response to the sucrose meals, however, the 1 and 2 hr values were significantly lower after 13 weeks on the sucrose diet than the corresponding fasting values (Table 1).

TABLE 1. Effect of diet on the glucose response

<table>
<thead>
<tr>
<th>Time after meal</th>
<th>Before Mean ± SEM</th>
<th>After Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 hr*</td>
<td>72.8 ± 1.8</td>
<td>68.8 ± 2.6</td>
</tr>
<tr>
<td>½ hr</td>
<td>110.0 ± 5.8</td>
<td>101.4 ± 4.5</td>
</tr>
<tr>
<td>1 hr</td>
<td>113.7 ± 8.9</td>
<td>88.1 ± 6.2</td>
</tr>
<tr>
<td>1½ hr</td>
<td>99.1 ± 8.2</td>
<td>74.9 ± 6.0</td>
</tr>
</tbody>
</table>

* Time after meal.
† Corresponding mean values significantly different from fasting value.
Sucrose tolerance and triglyceride synthesis

Fig. 2. Individual differences between peak values of serum glucose (mg/100 ml) of twelve baboons in response to a 4 g/kg body weight sucrose meal given to each animal before and after 13 weeks on the 75% sucrose diet, plotted against the corresponding individual differences between peak values of serum triglyceride specific activity (counts mg⁻¹ 100 sec⁻¹) following the same sucrose meals. The correlation between the two parameters is not significant (P>0.05).

Table 3. Changes in fructose tolerance in male and female baboons

<table>
<thead>
<tr>
<th>Time after meal</th>
<th>Serum fructose (mg/100 ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 hr*</td>
</tr>
<tr>
<td>Males</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>+0.1 ± 0.1</td>
</tr>
<tr>
<td>Females</td>
<td>Mean ± SEM</td>
</tr>
<tr>
<td>(n = 6)</td>
<td>−0.3 ± 0.1</td>
</tr>
</tbody>
</table>

* Time after meal.
† Mean value significantly greater than zero (P<0.025).
‡ Mean value significantly greater than zero (P<0.05).
Table 3 shows the mean changes in fructose tolerance of the male and female baboons separately. The results are expressed as 'within animal' differences. Before the sucrose diet, the mean levels of blood fructose following a sucrose meal were the same in both male and female baboons. After 13 weeks on the sucrose diet the 1, 1½ and 2 hr fructose values in the male baboons were all significantly greater than zero ($P<0.05$). In the females, however, on no occasion did the mean level of serum fructose differ significantly from zero. Fig. 3 shows the peak values for serum fructose in each animal following the first sucrose meal, plotted against the corresponding peak values for triglyceride specific activity. A regression line fitted by the method of least squares confirmed that the slope was significant ($b = 10.1$, SE 3.8, $0.025>P>0.01$). In Fig. 3 also, peak fructose is plotted against peak triglyceride specific activity following the second sucrose meal, and again a fitted regression line indicated the slope to be statistically significant ($b = 10.5$, SE 3.9, $0.025>P>0.01$). When as a result of the sucrose diet, the difference in peak serum fructose was plotted against the corresponding difference in peak triglyceride specific activity (Fig. 4) the slope of the fitted line was again significant ($b = 12.1$, SE 3.7, $0.01>P>0.005$).
When the results of the male and female baboons were considered separately, significant correlations with triglyceride specific activity were found in both sexes with fructose \((P < 0.05)\),

\[
\begin{align*}
\text{TABLE 4. Effect of diet on triglyceride specific activity response to a sucrose meal} \\
\hline \\
\text{Serum triglyceride specific activity (counts mg}^{-1}\text{100 sec}^{-1}) & 0 \text{ hr}^* & \frac{1}{2} \text{ hr} & 1 \text{ hr} & 1\frac{1}{2} \text{ hr} & 2 \text{ hr} & 3 \text{ hr} & 4 \text{ hr} & 5 \text{ hr} \\
\hline \\
\text{Before diet} & \text{Mean} & 0 & 3 & 11 & 21 & 32 & 41 & 32 & 35 \\
& \pm \text{SEM} & 0 & 1.7 & 4.0 & 4.2 & 10.4 & 11.8 & 7.7 & 6.2 \\
\text{After diet} & \text{Mean} & 0 & 3 & 18 & 39 & 70 & 88 & 87 & 80 \\
& \pm \text{SEM} & 0 & 1.2 & 6.0 & 9.0 & 13.9 & 15.3 & 15.1 & 17.6 \\
\hline \\
\end{align*}
\]

* Time after meal.
but not with glucose. No sex difference could be demonstrated with either hexose apart from higher blood levels of fructose after 13 weeks on the sucrose diet in the males than in the females, an observation reflected in the serum triglyceride specific activities. It would appear, therefore, that there was no sex difference with regard to the incorporation of either glucose or fructose into serum triglyceride, the extent of incorporation depending only on the level of blood fructose attained in both males and females.

**DISCUSSION**

The results of the investigation indicate that in baboons a high sucrose diet for 13 weeks had the effect of improving the glucose tolerance when tested by a sucrose meal. However, under the same dietary conditions, fructose tolerance to the same sucrose meal was impaired.

By labelling the sucrose uniformly with $^{14}$C, a correlation was observed between the level of blood fructose and the degree to which $[^{14}$C]sucrose was incorporated into serum triglyceride. A cause-and-effect relationship between these two parameters was demonstrated by means of the sucrose diet, following which an alteration in fructose tolerance resulted in a corresponding alteration in triglyceride specific activity. With glucose, however, this was not apparent, and the blood glucose levels that resulted from the sucrose meals bore no relationship to the triglyceride specific activities either before the diet or afterwards. Furthermore, when the glucose tolerance improved during the course of the sucrose diet, there was no corresponding decrease in triglyceride specific activity.

The rates of absorption of glucose and fructose from the intestine would appear to increase under the stimulus of high sucrose diet. Blair, Yakimets & Tuba (1963) showed that rats fed a sucrose rich (70%) diet had twice as much intestinal sucrase activity compared with animals fed a sucrose free/high casein diet. Deren, Broitman & Zamcheck (1967) also in rats, confirmed the observation of Blair et al., and by using a gut perfusion technique were able to demonstrate that the increased intestinal sucrase activity was associated with a significant increase in the absorption rate of fructose. Crossley (unpublished observations) showed that the same adaptation to sucrose probably occurred in baboons, since with chronic portal catheterization a 75% sucrose diet in these animals led to increased porto-arterial differences in the concentration of both glucose and fructose following a sucrose meal.

It would seem, therefore, that since a sucrose diet may lead to an increased rate of entry of glucose and fructose from the gut, the improved tolerance to glucose after sucrose feeding in the male and female baboons would need to be explained by a greater rate of uptake of glucose by the tissues. As the rate of glucose uptake by the cells is dependent upon the action of insulin, it is probable that in the baboons the sucrose diet may have had the effect of increasing the secretion of insulin. In man there is some evidence to support the possibility of this occurring (Szanto, 1967) although in rats, Cohen & Teitelbaum (1964) found that sucrose diets led to impaired glucose tolerance and a diminished insulin-like activity in the serum.

Fructose is thought to be metabolized in the liver rather than in the peripheral tissues (Butterfield, Sargeant & Whichelow, 1964) the metabolism occurring more quickly if the fructose passes via the portal vein rather than a systemic artery (Cori & Cori, 1927; Peters & Van Slyke, 1946). Following the administration of fructose there is a greater rise in the plasma pyruvate than is found with an equivalent intake of glucose regardless of whether the route of administration is oral (Root, Stoltz & Carpenter, 1946) or intravenous (Miller et al.,
Sucrose tolerance and triglyceride synthesis

1952; Beal & Smith, 1954). These observations suggest that in the liver fructose is metabolized differently from glucose. Also, unlike glucose, the uptake of fructose by the cells appears to be largely independent of insulin (Cori et al., 1951; Stuhlauth, 1958; Froesch & Ginsberg, 1962), and pyruvate levels in the blood after intravenous fructose are the same in normal and diabetic patients (Miller et al., 1952). Furthermore, fructose tolerance is unimpaired in long-standing diabetics (Miller et al., 1952) whereas glucose tolerance in the same patients is typically abnormal.

Although sucrose diets in rats have been shown to impair glucose tolerance (Cohen & Teitelbaum, 1964), evidence as to the influence of diet on fructose tolerance appears to be sparse. However, Craig et al., (1958) have found that unlike glucose, fructose tolerance is unaltered by restricting the carbohydrate intake, an observation that could be accounted for by fructose being independent of insulin.

Since there is reason to suppose that the sucrose diet had the effect of increasing the rate of absorption of fructose from the gut, the impaired tolerance to fructose in the baboons while on the sucrose diet therefore indicated a proportionately smaller increase in fructose uptake by the tissues. This would seem to have occurred in the presence of an improved tolerance to glucose, a finding that suggested enhanced tissue utilization of glucose over and above the already increased rate of absorption.

Liver lipid has been shown to accumulate more with diets containing sucrose than with isocaloric diets of starch or glucose (Litwack et al., 1952; Macdonald, 1962; Allen & Leahy, 1966). Kuo et al. (1967), using radioisotopes, found that both normolipaemic and hyperlipaemic subjects incorporated more $[^{14}\text{C}]$fructose than $[^{14}\text{C}]$glucose into mixed liver lipids. At the metabolic level, Tzur, Tal & Shapiro (1964) suggested that in the rat liver, glycerol phosphate was the rate-limiting product in triglyceride synthesis. Zakim & Herman (1968), also in rats, showed that intravenous fructose produced higher levels of hepatic glycerol phosphate than intravenous glucose, an observation that could explain why after intraportal $[^{14}\text{C}]$fructose in rats Kupke & Lamprecht (1967) found nearly all the recoverable radioactivity of the liver glycerides in the glycerol moiety, and only a small proportion in the fatty acids. Macdonald (1968) showed that in man there was nearly four times the specific activity in the serum triglycerides following a $[^{14}\text{C}]$fructose meal as there was after an equivalent meal of $[^{14}\text{C}]$glucose. These observations, in conjunction with our results, suggest that in the liver the fructose pathway primarily involved in triglyceride synthesis is that via dihydroxyacetone phosphate to glycerol. Glucose, on the other hand, is metabolized either in the peripheral tissues (Butterfield et al., 1964), or in the liver via glycolysis to fatty acids (Masoro, Chaikoff & Dauben, 1949; Masoro et al., 1950), a pathway which would appear to stimulate less triglyceride formation.

Fructose incorporation into serum triglyceride was observed in both sexes following a $[^{14}\text{C}]$sucrose meal, the extent of incorporation depending on the level of blood fructose attained. Before the sucrose diet the levels of blood fructose following a $[^{14}\text{C}]$sucrose meal were the same in both male and female baboons, an observation similar to that found in man (Macdonald & Turner, 1968). After 13 weeks on the sucrose diet, a $[^{14}\text{C}]$sucrose meal led to higher levels of blood fructose in the male baboons than in the females, and therefore resulted in a proportionately greater extent of incorporation of fructose into triglyceride in the male animals. This finding would seem to provide one explanation for the higher levels of triglyceride found in men than premenopausal women on fructose containing diets.
(Macdonald, 1965b; Klugh & Irwin, 1966) and suggests that this sex difference operates at a level of absorption rather than at one of metabolism. Although there is no direct evidence that an increase in endogenous triglyceride synthesis necessarily predisposes to higher levels of triglyceride in the fasting serum, the results of our study would suggest that in man as in the baboon, the level of blood fructose is a factor influencing lipogenesis.

ACKNOWLEDGMENT

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Sucrose tolerance and triglyceride synthesis


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