JCI The Journal of Clinical Investigation

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J Clin Invest. 1973;52(11):2725-2731. https://doi.org/10.1172/JCI107467.

Research Article

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These independent measures of hepatic triglyceride production changed with a similar time-course characteristic for each diet. The 75% fructose diet produced a greater increase in both determinations, reaching a maximum after 11 days.

Despite the increase in hepatic triglyceride formation by both high-sugar diets, only the 75% fructose diet resulted in a consistent and sustained increase in serum triglyceride. This results most probably from differences in the fractional rate of serum triglyceride removal between the two groups.

When serum triglyceride removal was inhibited by administration of Triton WR-1339, both high-sugar diets increased incorporation of [1,3-^{14}C]glycerol in serum triglyceride in vivo and increased serum triglyceride level above that in control rats.

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INTRODUCTION

The administration of high-carbohydrate diets to man (1–11) and experimental animals (12–19) has been associated with an increase in serum triglyceride levels. Increase in serum triglyceride level may be attributed to accelerated triglyceride production, a reduction in peripheral removal of triglyceride, or some combination of these processes. Previous studies suggest that the increased serum triglyceride observed in association with high carbohydrate intake results from enhanced hepatic triglyceride synthesis (20–23). The present experiments were designed to study and compare the effects of feeding glucose or fructose to rats for 1–14 days on *a*) the capacity for hepatic triglyceride formation as measured in liver homogenates, *b*) the rate of hepatic triglyceride formation measured in vivo with [1,3-^{14}C]glycerol, and *c*) serum and liver triglyceride concentrations. The studies demonstrate that both the high-glucose and fructose diet will increase the capacity for triglyceride formation from *sn*-glycerol-3-*P* by liver preparations and simultaneously accelerate hepatic triglyceride production as measured in vivo. However, the time-course and magnitude of these changes differ for the two sugars and only fructose results in a sustained rise in serum triglyceride levels. The discrepancy in the serum triglyceride levels is presumably related to differential effects of the two sugars on triglyceride removal mechanisms.

Received for publication 3 January 1973 and in revised form 14 May 1973.

METHODS

Groups of male Sprague-Dawley rats weighing 200–250 g were obtained from Zivic Miller, Inc., Philadelphia, and fed laboratory chow (Ralston Purina Co., St. Louis, Mo.) until the experiments began. The high-sugar diets contained by weight: 15% vitamin-free casein (Nutritional Biochemical Corporation, Cleveland, Ohio), 4% salt mixture (Hegsted), 4% vitamin mixture (Nutritional Biochemical), 2% corn oil, and 75% glucose or fructose. Rats were fed the fructose or glucose for 1–11 days and control rats were pair-fed with laboratory chow. The daily caloric intake of the rats was comparable (mean of 3.8 cal/g) in all experiments, and the weight gain was similar. Rats were killed by exsanguination from the dorsal aorta at 9 a.m. without prior starvation. Livers were removed promptly and a portion immediately frozen in liquid nitrogen. The remaining liver was weighed, diluted 1:5 (wt/vol) in 0.25 M sucrose containing 0.05 M Tris-HCl pH 7.5 and homogenized with a Teflon fitted glass homogenizer. The homogenate was centrifuged at 900*g* for 10 min, and the supernate was removed and diluted 1:2 (vol/vol) with the same buffer for further studies.

The formation of neutral lipids from *sn*-[1,3-^{14}C]glycerol-3-*P* was measured with the diluted liver homogenate as an enzyme source. Homogenate (0.2 ml) was incubated with 50 mM KCl, 20 mM Tris-HCl pH 7.5, 3.2 mM $MgCl_2$, 0.7 mM dithiothreitol, 0.04 mM CoA, 3.6 mM ATP, 1.42 mM NH_4 palmitate, 2.5 mg of bovine albumin (Pentex Biochemicals, Kankakee, Ill.) and 0.12 mM *sn*-[1,3-^{14}C]-glycerol-3-*P* in a final volume of 0.7 ml. The palmitate was added to the other reagents after a 2-min preincubation at 37°C. 4 min later, the reaction was started by the addition of the *sn*-[1,3-^{14}C]glycerol-3-*P*. The mixture was shaken at 37°C for 15 min and the reaction stopped by addition of 20 vol of chloroform-methanol (2:1 vol/vol). Lipids were extracted as described by Folch, Lees, and Sloane-Stanley (24). The final lipid extract was evaporated under nitrogen, dissolved in 1.0 ml benzene, and stored at −40°C. The neutral lipids formed were separated by thin-layer chromatography on silica gel G with a solvent system of hexane:ether:acetic acid (146:50:4). Triglyceride and diglyceride were identified by comparison with known standards and the appropriate area scraped directly into liquid scintillation fluid.

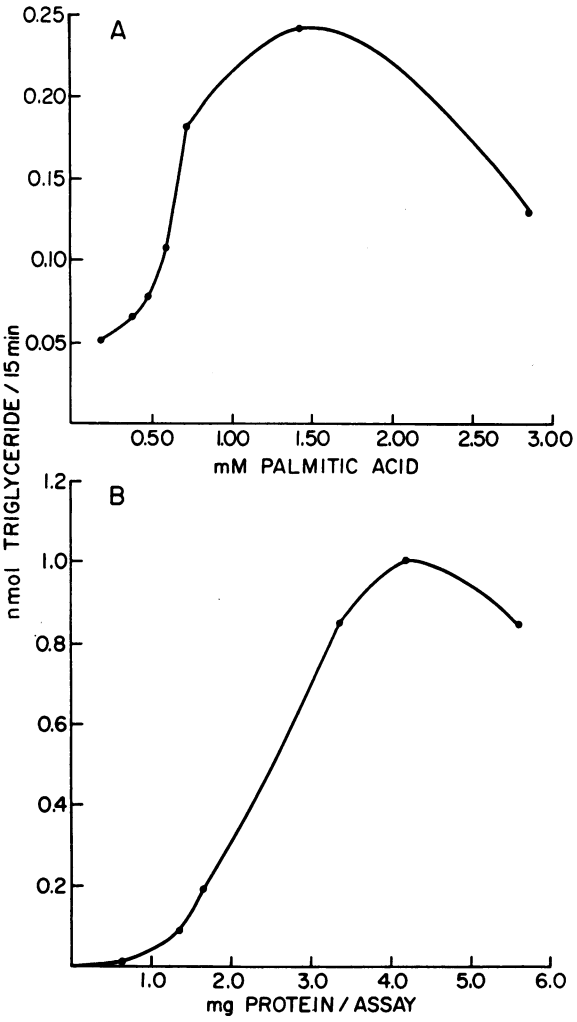

FIGURE 1 A. The formation of triglyceride from *sn*-[1,3-^{14}C]glycerol-3-*P* by rat liver homogenates at various palmitate concentrations. Values are in nanomoles of triglyceride formed in 15 minutes per milligram protein. B. The effect of increasing homogenate concentration on the rate of triglyceride formation by rat liver homogenates.

The rate of triglyceride formation from *sn*-[1,3-^{14}C]-glycerol-3-*P* by rat liver homogenate was dependent on fatty acid concentration (Fig. 1A). A concentration of 1.4 mM palmitic acid gave maximum activity with normal control homogenates and those from rats fed the high-sugar diets. This concentration was used in all studies to avoid small variations in triglyceride synthetic rate related to changes in homogenate fatty acid content. The formation of triglyceride was directly proportional to homogenate protein concentration over a limited range (Fig. 1B). The dilution of liver homogenate was adjusted to give a protein concentration of approximately 3 mg protein/assay. Reaction rate was linear for at least 20 min under these conditions.

Serum triglyceride and liver neutral lipid were measured by the semiautomated method of Kessler and Lederer (25). Protein was measured by a variation of the Lowry, Rosebrough, Farr, and Randall method (26). Serum glycerol was measured by the fluorometric method of Laurell and Tibbling (27). Radioactive serum glucose and glycerol were separated by thin-layer chromatography on cellulose F plates in a solvent system of butanol:acetic acid:water (80:20:100). The appropriate areas were scraped directly into scintillation fluid containing 30% methanol, and counted. The rate of [1,3-^{14}C]glycerol incorporation into liver and serum lipids was determined in the intact rat from these values as described previously (28). Total liver *sn*-glycerol-3-*P* was determined by the method of Hohorst (29).

Triton WR-1339, obtained from Winthrop Laboratories (Div of Sterling Drugs, Inc., New York), was prepared in isotonic saline (200 mg/ml) and injected intravenously in a dose of 50 mg/100 g rat. 30 min after Triton injection, 5 μCi of [1,3-^{14}C]glycerol was administered intraperitoneally and the rats were killed 15 min later. The incorporation of [1,3-^{14}C]glycerol into liver and serum triglyceride during this time period was measured. Serum triton levels were measured by a modification of the method of Weber, Degner, and Bahjat (30). The serum was boiled to remove the Triton bound to the protein before analysis. Animals found to have less than 1 mg/100 ml in serum were omitted from study.

RESULTS

Changes in the capacity for triglyceride formation by liver homogenate preparations during high sugar intake are shown in Fig. 2. The rate of *sn*-[1,3-^{14}C]glycerol-3-*P* incorporation into triglyceride was increased substantially by feeding the 75% fructose diet as shown in Fig. 2A. The maximum change was achieved after 11 days of feeding fructose and was sustained for at least 15 days. In contrast, the effects of feeding 75% glucose were quantitatively less and reached a maximum by day 2. In other experiments this level of increase was maintained until day 15.

Similar high-sugar diets were fed to alloxan-diabetic rats (31, 32) maintained on 2 U neutral protemine Hagedorn insulin/100 g rat/day. Formation of triglyceride from *sn*-glycerol-3-*P* by homogenates from 10 diabetic

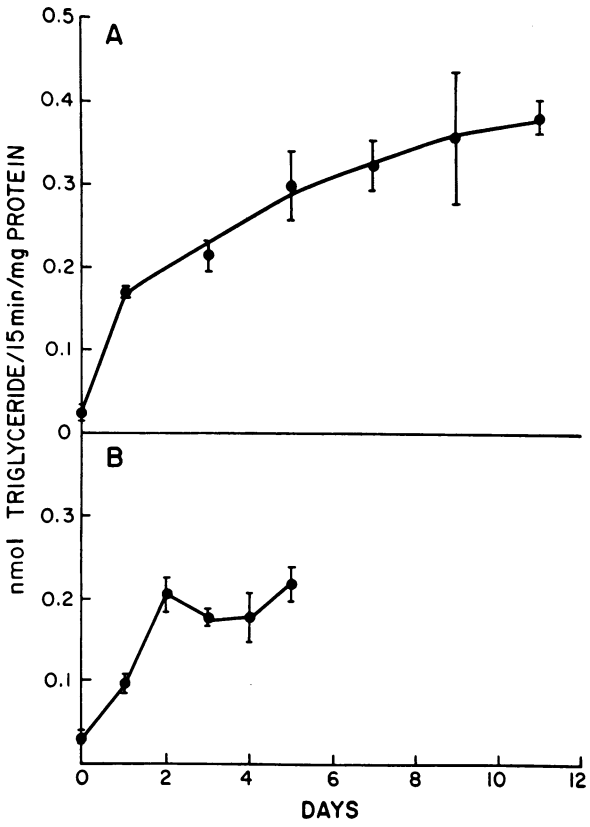

FIGURE 2 A. The rate of triglyceride formation by liver homogenates prepared from rats fed 75% fructose for 11 days. Values are means of five rats at each time point ±SEM.

B. Formation of triglyceride by homogenates prepared from rats fed 75% glucose for 5 days. In another experiment the 75% glucose diet was given for 15 days without change from the level noted at 5 days.

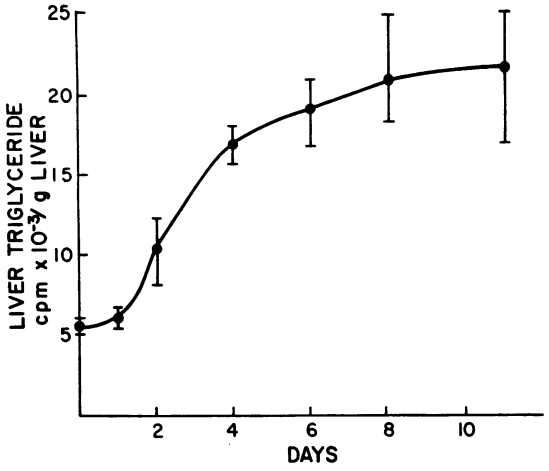

FIGURE 3 The incorporation of [1,3-^{14}C]glycerol into liver triglyceride in rats fed 75% fructose for 10 days. The [1,3-^{14}C]glycerol was given intraperitoneally and the rats killed 17 min later when liver triglyceride radioactivity was maximum. Values shown are the mean of five rats at each time period with the SEM indicated by brackets.

rats fed chow was 0.202±0.045 nmol/15 min/mg protein and was increased to 0.340±0.086 nmol/15 min/mg protein in homogenates from 9 diabetic rats fed 75% fructose for 4 days and 0.498±0.052 nmol/15 min/mg protein in 9 rats fed 75% glucose. These changes were highly significant ($P < 0.01$).

The alterations in triglyceride synthesis by liver homogenates may be compared with estimates of triglyceride formation in vivo as shown in Table I and Fig. 3. The rate of [1,3-^{14}C]glycerol incorporation into hepatic triglyceride in the intact animal was increased fourfold in rats fed 75% fructose for 10 days, as shown in Fig. 3, and two-fold in rats fed 75% glucose for 4 days (Table I). Therefore, the effect of high sugar intake on the capacity for triglyceride formation by liver homogenates was accompanied by changes in triglyceride synthesis as estimated in vivo. The time-course of these changes followed a similar pattern.

TABLE I

The Effect of Feeding 75% Fructose or 75% Glucose for 4 days on the Incorporation of [1,3-^{14}C]Glycerol into Liver Triglyceride in vivo, *and the Hepatic Content of Triglyceride and sn-Glycerol-3-P*

	Triglyceride	P§ value	Liver triglyceride	P§ value	*sn*-Glycerol-3-*P*	*P* value
	mg/g liver		*cpm* × 10^{-3}*/g liver*		*μmol/g liver*	
Chow (7)*	5.55‡		3.45‡		0.293‡	
	±0.49		±0.74		±0.019	
75% Fructose (7)	25.32	<0.001	15.08	<0.001	0.315	NS
	±2.82		±1.58		±0.041	
75% Glucose (7)	13.98	<0.001	10.51	<0.001	0.489	<0.01
	±1.36		±1.04		±0.043	

* Number in parentheses indicates number of animals in each group.

‡ All values are means±SEM.

§ *P* value, significance of difference from chow group.

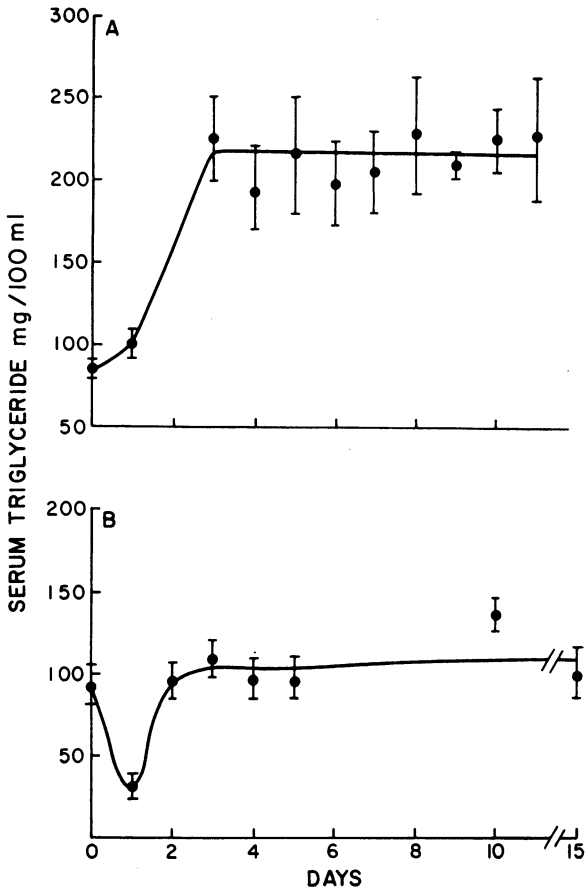

FIGURE 4 A. Serum triglyceride levels in rats fed 75% fructose for 11 days. Values are means±SEM for five rats at each time period.
B. Serum triglyceride levels in rats fed 75% glucose for five days.

The response of serum and liver triglyceride concentration to the increased liver triglyceride formation was studied. A rise in serum triglyceride level was observed in rats fed 75% fructose, reaching a maximum at 3 days as shown in Fig. 4A. The rise was sustained until the end of the study. However, the serum triglyceride level in rats fed 75% glucose decreased during the first 24 h, returning to the control level by day 2–3, as shown in Fig. 4B. The same pattern was repeated in several independent experiments.

The liver triglyceride content was increased by both high-carbohydrate diets and reached a maximum by day 5 in rats fed 75% fructose (Fig. 5A). Liver triglyceride level in the rats fed 75% glucose rose until day 4 and then declined toward the control value (Fig. 5B). Serum free fatty acid levels fell from 0.588±0.141 μmol/ml to 0.133±0.020 μmol/ml 1 day after the start of the 75% glucose diet, but returned to the original level by day 5. The 75% fructose diet did not alter serum free fatty acid level significantly. The hepatic concentration of *sn*-glycerol-3-*P* was raised in rats fed 75% glucose but not in those fed 75% fructose (Table I).

Under these experimental conditions the increased capacity for hepatic triglyceride formation produced by 75% glucose or fructose diets results in a sustained increase in serum and liver triglyceride only during 75% fructose feeding. In the steady state, achieved after 4 days of the 75% glucose diet and 11 days of 75% fructose, the net formation of serum triglyceride must be equal to net serum triglyceride removal. Since the 75% glucose diet does not result in an increased serum triglyceride level, an enhanced fractional rate of triglyceride removal apparently compensates during the change to a new steady state. In contrast, the 75% fructose diet does cause a substantial rise in serum triglyceride, indicating a less than equivalent increase in the fractional rate of serum triglyceride removal under these conditions. Presumably, net serum triglyceride removal in the rats fed 75% fructose increases to balance the higher level of the triglyceride production only after a higher serum triglyceride concentration is achieved.

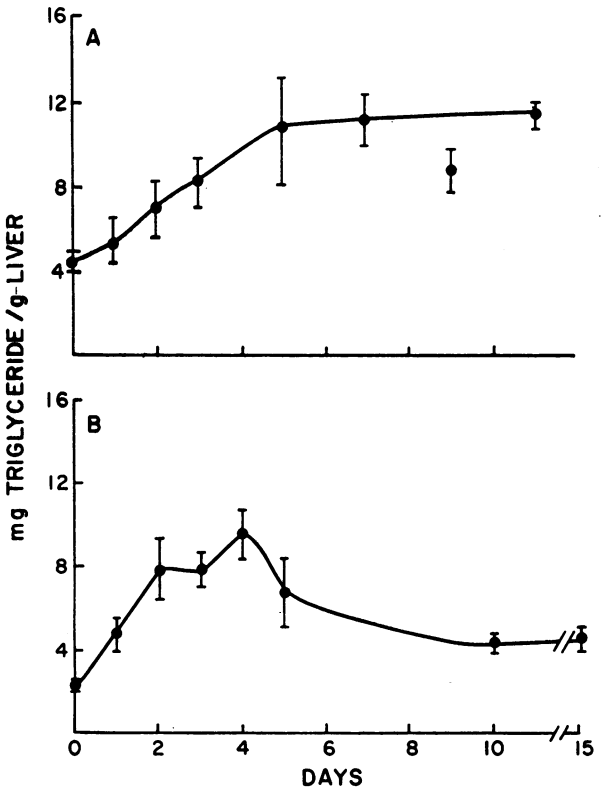

FIGURE 5 A. The level of liver triglyceride in rats fed 75% fructose for 11 days. Values are means±SEM at each time point.
B. Liver triglyceride concentration in rats fed 75% glucose for 11 days.

These differential effects on the rate of serum triglyceride removal were reduced by studying the rise in serum triglyceride and rate of [1,3-^{14}C]glycerol incorporation into serum triglyceride after administration of Triton WR-1339 as described by Otway and Robinson. Triton substantially retards the removal of serum triglyceride, probably by inhibition of lipoprotein lipase (35). After the injection of Triton, the rise in serum triglyceride in rats fed either 75% fructose or 75% glucose for 4 days was greater than in rats fed chow, as seen in Table II. This result supports the other findings, which show enhanced triglyceride production in rats fed either of these diets. Furthermore, they indicate that triglyceride release into the serum also is increased in rats fed either high-sugar diet when compared to rats fed chow. This is shown by the finding of an increased incorporation of [1,3-^{14}C]glycerol into serum triglyceride in the rats fed either 75% glucose or fructose.

TABLE II

The Effect of Triton Administration on Serum Triglyceride and Incorporation of [1,3-^{14}C]Glycerol into Serum Triglyceride in Rats Fed Chow, 75% Fructose, or 75% glucose for 4 Days

	Serum Triglyceride	P§ value	Serum Triglyceride	P§ value
	mg/100 ml		*cpm × 10^{-3}/ml serum*	
Chow (7)*	465‡ ±29		7.07‡ ±0.39	
75% Fructose (7)	694 ±108	<0.05	13.50 ±2.64	<0.01
75% Glucose (7)	643 ±35	<0.01	12.59 ±1.59	<0.01

The [1,3-^{14}C]glycerol was given intraperitoneally 30 min after Triton administration as described under Methods. Incorporation of [1,3-^{14}C]glycerol into liver triglyceride was increased by both high-sugar diets as shown in Table I.

* Number in parentheses indicates the number of rats in each group.

‡ All values are means ±SEM.

§ *P* value, significance of difference from chow groups.

DISCUSSION

Previous studies in man have shown that high carbohydrate intake increases serum triglyceride level (6, 9), especially in patients with endogenous hyperprebetalipoproteinemia (1, 3). Several investigators report that this effect is more marked when fructose is the main source of dietary carbohydrate (7, 16, 17). The rat will tolerate up to 80% of calories as either glucose or fructose (36), providing an opportunity to study the individual effects of these sugars in the experimental animal. Bar-On and Stein (16) have shown an increase in serum triglyceride level in rats given 10% fructose in their drinking water, whereas a similar amount of glucose did not produce this effect. In contrast, Eaton and Kipnis (37) reported an increase in serum triglyceride in rats fed 10% glucose in drinking water. In the present experiments, in which solid diets containing either 75% fructose or glucose were used, only the fructose produced a sustained rise in serum triglyceride.

The present studies examined the possibility that diets of high sugar content accelerate hepatic triglyceride production in part by increasing the capacity for fatty acid esterification. Earlier results from this laboratory suggested that a high-glucose diet would increase the rate of triglyceride formation by liver homogenates (38). It is now shown that this effect reaches a maximum after 48 h of the high-glucose diet and results in a three- to fourfold increase in triglyceride formation. The increase is not related to detectable changes in substrate levels but is best explained by enhanced activity of one or more enzymes in neutral lipid biosynthesis (39). This in vitro change is accompanied by a corresponding increase in hepatic triglyceride formation, as measured by [^{14}C]glycerol incorporation in vivo, thus indicating its possible physiological significance.

A 75% fructose diet also increases triglyceride formation by liver homogenates but the total rise is greater (five- to tenfold) and is not maximum until day 11. The increasing rate of [^{14}C]glycerol incorporation into hepatic triglyceride, as measured in vivo, also corresponds to this slower time-course. The significant quantitative differences between the effects of glucose and fructose on triglyceride formation indicate that the latter is not substantially converted to glucose during absorption. This has been shown previously (40) and explained by the low activity of intestinal fructokinase (41) and glucose-6-phosphatase (42) in rat intestine.

Despite the evidence that both fructose and glucose increase hepatic triglyceride formation as determined in vitro and in vivo, only fructose produces a substantial and sustained rise in serum triglyceride. In fact, the initial response to glucose is a fall in serum triglyceride level, an effect noted previously after starvation (14) and attributed to the abrupt fall in serum fatty acid levels. A similar mechanism may occur during the first 24 h of feeding glucose in the present experiments.

It is well known that the rate of triglyceride formation is not the only determinant of serum triglyceride level. The rate of triglyceride release from liver, its formation by intestine, and most importantly, the net rate of serum triglyceride removal may also influence the final serum concentration (22, 43). Measurements of hepatic triglyceride content (Table I, Fig. 5) and the increased rate of [^{14}C]glycerol incorporation into serum triglyceride in the intact rat fed a 75% glucose or fructose diet (Table II) do not suggest that variations in hepatic triglyceride

release account for the markedly different effects of the two sugars on serum triglyceride levels. The contribution of intestinal triglyceride formation under these conditions is as yet unknown but is unlikely to explain the discrepancy in serum triglyceride levels fully.

Therefore, it is concluded that high-glucose and high-fructose diets probably alter net serum triglyceride removal but by different means. At the new steady state, the increased production of triglyceride must be balanced by an accelerated net triglyceride removal. For example, the rise in serum triglyceride level in rats fed 75% fructose would permit an increase in net or total triglyceride removal without requiring a rise in the fractional rate of clearance. On the other hand, high glucose intake most likely produces an early acceleration in the fractional rate of triglyceride removal that fully compensates for any increased production. This effect may be related to threefold increases in adipose tissue lipoprotein lipase activity (16) and accelerated adipose tissue lipogenesis (14, 44), mediated by stimulation of insulin release (45). The latter is not reported to follow fructose administration.

A portion of the difference in ultimate serum triglyceride level between the fructose and glucose groups also may be attributed to the lesser increase in hepatic triglyceride production in the rats given glucose. Nonetheless, a major factor must involve the rate of serum triglyceride removal. Identification of the exact mechanisms by which differences in the removal processes occur will require further study.

It is important to note that the changes observed in hepatic triglyceride production in these studies developed slowly, requiring 2–11 days to reach a maximum. Such changes, apparently dependent upon gradual alterations in enzyme levels or activities, could not explain any abrupt fluctuations in triglyceride production in vivo. Other factors, including variations in serum fatty acid composition and concentration (14, 46) or the rate of fatty acid oxidation (47) probably contribute to rapid changes in the rate of triglyceride biosynthesis. However, the increased capacity for esterification of fatty acid to triglyceride noted under conditions of high sugar intake should markedly enhance the effects of other stimuli to hepatic triglyceride production. A reported rise in liver fatty acid synthetase activity may increase the availability of fatty acids for esterification during high carbohydrate intake (48). Other studies indicate that glucose administration to rats also induces a gradual increase in prebeta lipoprotein biosynthesis (37), thus facilitating an accelerated delivery of lipoprotein triglyceride to the serum. These several biochemical alterations may explain the observation that high carbohydrate intake increases net triglyceride production in both normal and hyperlipemic man (22, 43, 49).

ACKNOWLEDGMENTS

The technical assistance of Judith Schuster, Jesse Bright, and Joyce Barwich is acknowledged. The help of Dr. Robert Lamb in the preparation of this manuscript is appreciated.

This work was supported by U.S.P.H.S. grants AM-09000 and ES0129.

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