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Hypertriglyceridemic Effects of Glucose and Fructose Injections in Geese Infused with Oleic Acid[1] (38375)

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In the rat, oral administration of either glucose or fructose for two weeks causes elevation of plasma triglycerides (TGL), but the effect of fructose is much more striking than that of glucose (1). This effect has been related to the fact that fructose increases the concentration of glycerol phosphate in the liver which, in turn, is considered as a determinant of the synthesis of triglycerides by this organ (2). The greater formation of hepatic fatty acids, the weaker inhibition of fatty acid release by the adipose tissue and the less efficient induction of adipose tissue lipoprotein lipase by fructose, as compared to glucose, have been suggested as other factors which might be responsible for the different effects of these two sugars (3).

It was observed in this laboratory (4) that intravenous injection of glucose causes a marked elevation of plasma triglycerides when given to geese receiving a continuous infusion of oleic acid that maintains a high level of plasma free fatty acids (FFA). It was therefore of interest to determine whether fructose has a greater hypertriglyceridemic effect than glucose under these experimental conditions. The experiments reported here provide a comparison in the same animals of the hypertriglyceridemic effects of glucose and fructose, when these sugars are injected intravenously into geese receiving a continuous infusion of oleic acid.

Methods. Adult male domestic geese, housed and fed as previously described (5) were used. All the experiments were done after 16–18 hr of fasting. Throughout the experiments the geese were under anesthesia induced by the injection of sodium pentobarbital (Somnopentyl, Pitman Moore, Inc., Washington Grove, NJ) at the dose of 35 mg/kg (⅔ iv, ⅓ im). Catheters were inserted into the wing vein and artery, for infusion and withdrawal of samples, respectively. Blood samples were collected into centrifuge tubes containing heparin powder and kept in ice water. Plasma was separated by centrifugation into a refrigerated centrifuge (−2.0°). Determinations of plasma FFA and TGL were made as previously described (5). Plasma glucose was determined by the method of Hyvarinen and Nikkila (6) and plasma fructose by the method of Roe *et al.* (7).

Oleic acid emulsions (0.2 *M*) in Na oleate and gelatin were prepared as described (4). The emulsion was sonicated (Sonifer model W 185, Branson Sonic Power Co., Danbury, CN) as described by Bezman-Tarcher (8). Infusions were made with a peristaltic pump (model 1202, Harvard Apparatus Co., Inc., Millis, MA).

Glucose and fructose were injected intravenously as 50% solutions (dextrose injection, U.S.P., Travenol Laboratories, Morton Grove, IL, and 0 (—) levulose obtained from Mallinckrodt Chemical Works, St. Louis, MO).

Standard methods of statistical analysis were used. Unless stated otherwise, significance of differences was calculated by Student's *t* test for paired variates.

Results. (a) Oleic acid infusion with and without injection of glucose. Twenty-four geese were used in this experiment. Twelve of them received an infusion of oleic acid (1.6 mmole/kg/hr) for 2 hr. The other twelve received the oleic acid infusion plus an injection of glucose (0.5 g/kg) given 60 min after beginning of

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the infusion. The geese were used by pairs, both animals being infused simultaneously with oleic acid, one of them receiving, in addition, the glucose injection.

Figure 1 shows that the infusion of oleic acid produced elevations of plasma FFA and TGL. Injection of glucose caused a decrease of plasma FFA and greater elevation of TGL than the infusion of oleic acid alone. Mean TGL elevations above the mean preinfusion level were (mg/dl) 64 (SE, 7.9) and 66 (SE, 8.0) at 60 min of infusion, for the group receiving oleic acid alone and for the group receiving oleic acid and glucose injection at 60 min respectively. Both elevations were significant ($P < 0.01$). The corresponding mean TGL differences for the second hour of infusion (mean of the differences between the values at 120 and 60 min) were (mg/dl) 44 (SE, 8.4) and 131 (SE, 16.0). Both elevations were significant ($P < 0.01$). The mean TGL elevation for the geese receiving glucose was 87 mg/dl (SE, 17.9) greater than that observed in the geese receiving infusion of oleic acid alone. The difference is significant ($P < 0.01$, t test for nonpaired variates).

(b) Injection of glucose and fructose during the infusion of oleic acid. This experiment was done with eight geese. They were infused with oleic acid (1.6 mmoles/kg/hr) for 2 hr and received an injection of either glucose or fructose (0.5 g/kg), 60 min after the beginning of the infusion. Two animals were infused simultaneously with oleic acid, one receiving glucose and the other fructose. The experiment was repeated after 6 weeks with the same animals, reversing the sugar treatments. Table I shows that injection of glucose produced a sharp increase of plasma TGL, as in the previous experiment. Injection of fructose caused an elevation of plasma TGL somewhat smaller than that produced by glucose.

The mean TGL elevations at 1 hr of infusion (mg/dl) were 61 (SE, 5.7) and 60 (SE, 13.3) for the experiments with glucose and fructose, respectively. Both elevations were significant ($P < 0.01$) and comparable to those observed in the previous experiment. The TGL elevations for the second hour of infusion were (mg/dl) 151 (SE, 19.5) and 99 (SE, 22.3) for the glucose and fructose injections respectively. Both elevations are significant ($P < 0.01$). The TGL elevation after glucose was 52 mg/dl (SE, 16.7) greater than that observed after fructose injection ($0.01 < P < 0.02$). Oleic acid infusion caused a small decrease of plasma glucose. The mean plasma sugar for the eight geese (each on two occasions) was (mg/dl) 172 (SE, 2.7) before infusion, and 159 (SE, 2.6) at 1 hr of infusion. The difference (13 mg/dl, SE, 2.3) is significant ($P < 0.01$).

(c) Injection of glucose and fructose in fasting, anesthetized geese. Six geese were injected with glucose and the other six with fructose. Each sugar was injected at the dose of 0.5 g/kg.

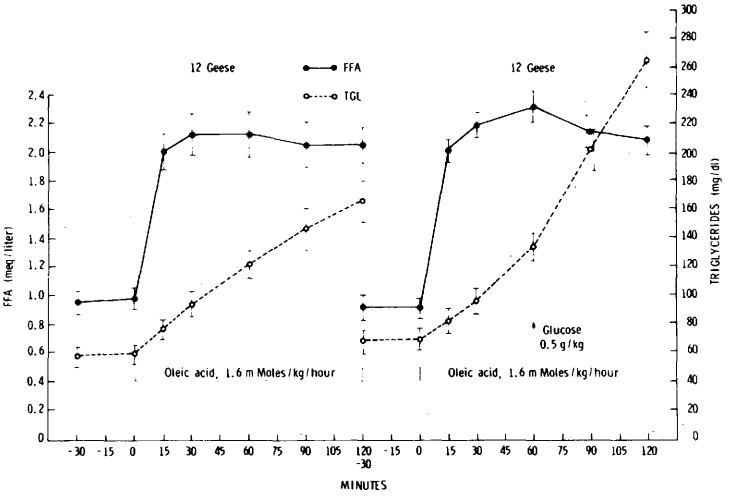

FIG. 1. The effect of oleic acid infusion and glucose injection on plasma FFA and TGL of fasting anesthetized geese. Left Hand: Means (± SE) for 12 geese infused with oleic acid (1.6 mmole/kg/hr) for 2 hr. Right Hand: Means (± SE) for 12 geese infused with oleic acid (1.6 mmoles/kg/hr) for 2 hr, and injected with 0.5 g of glucose/kg (iv) 60 min after beginning the infusion of oleic acid.

The experiment was run with two geese at the time, one receiving glucose and the other fructose. As shown in Table II, both glucose and fructose caused a decrease of plasma FFA and TGL.

Compared with the mean preinjection level the mean FFA decrease was 0.35 meq/liter (SE, 0.06, $P < 0.01$), 30 min after glucose injection. Corresponding value after fructose was 0.34 meq/liter (SE, 0.04, $P < 0.01$). The mean decreases of plasma TGL were (mg/dl), 15 (SE, 3.2, $P < 0.01$) and 13 (SE, 3.2, $P < 0.01$), 1 hour after the injections of glucose and fructose, respectively.

Plasma glucose rose from a mean of 182 mg/dl (SE, 2.5) before the injection, to 475 (SE, 28.9), 5 min after the injection of glucose, and was 202 (SE, 3.8) 1 hr after the injection.

Mean plasma fructose for four geese was (mg/dl) 151 (SE, 11.2), 10 (SE, 5.2), and 4 (SE, 2.7) 5, 30 and 60 min after fructose injection, respective y.

Discussion. In agreement with our previous observation (4), the present results demonstrate that injection of glucose, superimposed on the infusion of oleic acid, causes an elevation of plasma TGL significantly greater than that produced by the infusion of oleic acid alone. By contrast, the injection of the same amount of glucose in the absence of oleic acid infusion caused a small but significant decrease of plasma TGL, somewhat less pronounced than that observed in man and various animals after acute oral or intravenous administration of glucose (9–11). It is clear therefore that, as previously noted (4), the acute hypertriglyceridemic effect of glucose depends on the availability of FFA.

Injection of fructose in the absence of oleic acid infusion also caused decreases of plasma TGL and FFA which were not significantly different from those produced by glucose. It is unlikely that the FFA decrease is explained by insulin release, because insulin does not decrease plasma FFA in the goose (12) and because fructose is considered to be a weaker stimulant of the beta cells than glucose (3).

Fructose had a significant hypertriglyceridemic effect when injected during the infusion of oleic acid but the effect was smaller than that of glucose at variance with the results of feeding experiments in the rat (1).

Schonfeld and Pfleger (13) reported increased production of very low density lipoprotein triglycerides (VLDLP, TGL) by the perfused liver of fructose-fed rats, when fatty acids were added to the perfusate, and concluded that the increased secretion of TGL was accomplished by enhanced formation of VLDLP, TGL from exogenous fatty acids. Presumably, a similar mechanism may be responsible for the hypertriglyceridemic effects of glucose and fructose described here. Insulin is believed to stimulate TGL and lipoprotein formation in the liver (14). It is therefore possible that the hypertriglyceridemic effects of glucose and fructose reported here are mediated by insulin release. Our results, in this respect, are consistent with the view that fructose is a weaker stimulant of insulin secre-

TABLE I. Effect of Oleic Acid Infusion (1.6 mmole/kg/hr, for 2 hr) and Intravenous Injection of Either Glucose or Fructose (0.5 g/kg) on Plasma Free Fatty Acids (FFA) and Triglycerides (TGL) in Fasting, Anesthetized Geese. Means and SE for 8 Geese (the Same Geese on Both Experimental Situations).

	Time (min)						
	−30	0[a]	15	30	60[b]	90	120
Glucose injection							
FFA, meq/liter	1.20	1.21	2.14	2.41	2.60	2.21	2.12
	±0.14	±0.11	±0.13	±0.14	±0.09	±0.14	±0.14
TGL, mg/dl.	96	99	110	129	159	230	310
	±11.6	±12.4	±13.6	c15.8	±12.5	±20.1	±23.4
Fructose injection							
FFA, meq/liter	1.09	1.13	1.97	2.42	2.42	2.15	2.02
	±0.08	±0.08	±0.20	±0.25	±0.27	±0.24	±0.19
TGL, mg/dl	84	86	99	121	145	188	244
	±9.5	±9.3	±9.8	±15.9	±20.4	±26.9	±38.9

[a] Beginning of oleic acid infusion.

[b] Injection of either glucose or fructose.

TABLE II. Effect of Intravenous Injection of Glucose or Fructose (0.5 g/kg at 0 time) on Plasma Free Fatty Acids (FFA) and Triglycerides (TGL) in Fasting Anesthetized Geese. Means and SE for Six Geese Injected with Glucose and Six Geese Injected with Fructose.

	Time (min)							
	−90	−60	−30	0[a]	30	60	90	120
Glucose injection								
FFA, meq/liter	0.93 ±0.09	0.95 ±0.07	0.93 ±0.11	0.96 ±0.09	0.60 ±0.06	0.70 ±0.06	0.75 ±0.05	0.74 ±0.05
TGL, mg/dl	55 ±6.7	54 ±6.2	53 ±5.9	53 ±6.8	46 ±6.4	39 ±4.7	39 ±5.4	40 ±6.1
Fructose injection								
FFA, meq/liter	0.83 ±0.12	0.91 ±0.09	0.85 ±0.08	0.81 ±0.09	0.51 ±0.08	0.64 ±0.07	0.68 ±0.06	0.74 ±0.06
TGL, mg/dl	60 ±7.1	60 ±7.0	60 ±7.3	60 ±7.1	52 ±7.3	47 ±5.8	44 ±5.4	42 ±5.2

[a] Injection.

tion than glucose (3).

Although our results give convincing evidence of the hypertriglyceridemic effects of glucose and fructose under the conditions of our experiments, the relevance of such effects for the mechanism of the hypertriglyceridemia induced by feeding carbohydrates is doubtful. On the one hand, as already noted, the effect depends on the elevated plasma FFA concentration maintained by the infusion of oleic acid; on the other, Den Besten *et al.*(15) have demonstrated in man that a diet made up of glucose and a protein hydrolizate, in amounts corresponding respectively to 80 and 20% of its energy value, causes marked hypertriglyceridemia when given orally, but not when intravenously infused. This observation strongly suggests a key role of the intestinal mucosa in the mechanism of the hypertriglyceridemia induced by carbohydrate feeding.

The infusion of oleic acid caused a small but significant decrease of plasma sugar. This result compares with observations in dogs using a different technique for the infusion of fatty acids (16, 17) and using the emulsion of oleic acid described here (18).

Summary. Injections of either glucose or fructose (0.5 g/kg, iv) given during a continuous infusion of oleic acid, produced elevations of plasma TGL in fasting geese significantly greater than those produced by infusion of oleic acid alone. The elevation of plasma TGL produced by injection of fructose is smaller than that produced by the injection of glucose. The same doses of glucose or fructose injected into fasting geese, in the absence of oleic acid infusion, caused small but significant decreases of plasma FFA and TGL. No significant difference between glucose and fructose was found in this respect. Infusion of oleic acid caused a small but significant decrease of plasma glucose concentration.

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