Effect of Glucagon on Alimentary Lipemia.* (23362)

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(Introduced by Philip K. Bondy)
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Recent investigations concerning interaction of carbohydrate and fat metabolism have suggested a relationship between the magnitude of alimentary lipemia and the status of glucose metabolism. The rise of particulate serum triglycerides (neutral fat) following ingestion of a fat meal by individuals who have fasted for 15 hours can be diminished or abolished by concomitant feeding of glucose(1). The hypothesis was set forth that any factors stimulating carbohydrate metabolism would reduce the degree of alimentary lipemia. Glucagon, like glucose, causes hyperglycemia, and increased peripheral uptake of glucose as great as(2) or greater than(3,4) that caused by doses of glucose which produce comparable arterial glucose concentrations. The effect of glucagon on alimentary lipemia was therefore made the subject of the present investigation.

Methods. The subjects were 6 male medical students and staff members between the ages of 21 and 30 who were free from known disease. The subjects were requested to eat or drink nothing but water after supper. On the morning of the experiment a preliminary blood sample was drawn, and the subjects were then fed a test meal containing 22 g protein, 60 g fat, and 42 g carbohydrate. The exact composition of this meal has been reported elsewhere(1). Two or 2½ hours after breakfast another blood sample was taken, and 0.03 mg glucagon†/kg body weight (about 2 ml) diluted to 10 ml with physiological saline was injected intravenously. Glucagon was given just prior to the expected peak in concentration of serum triglycerides which usually occurs at about 3 hours with the fat meal used. In addition to glucagon, 2 subjects (RF, WA) received oral glucose in lemonade, as outlined in the next section. As a control, 3 subjects were given the same breakfast without glucagon on a separate occasion, 2 of them receiving 10 ml intravenous saline in place of the glucagon. However, an acute change in concentration of triglycerides in response to glucagon was thought to be of greater significance than a comparison of the 3-hour concentration on 2 different occasions with and without glucagon, because of variations in response of the same individual to the fat meal from time to time.

Sera obtained at intervals before and after breakfast and glucagon injection were analyzed for lipids including total fatty acids, total cholesterol, and lipid phosphorus, by methods which have been reported previously(5). Triglycerides were calculated from these data. In the sera of 2 subjects, the nonesterified fatty acids (NEFA) were analyzed by a modification(1) of the method of Dole(6). About an hour lapsed between drawing the blood and precipitating the serum in heptane and isopropyl alcohol for the NEFA determination. Blood sugar was determined by the Nelson-Somogyi method(7).

Results. Since no consistent change occurred in serum cholesterol and only an occasional slight rise occurred in the lipid phosphorus fraction after the fat meal with or without glucagon, the results reported will be confined to those fractions responding to glucagon: the triglycerides, blood sugar, and NEFA. A representative study is shown in Fig. 1. In 4 of the 6 subjects, glucagon given 2 to 2½ hours after the fat meal caused, within ½ hour, an 18 to 34 mg% increase in

* Aided in part by grants from the U. S. Public Health Service, and from the American Cancer Society.

† The glucagon kindly supplied by Dr. W. R. Kirtley, came from Lilly lot No. 208-158 B-214, containing 0.95 mg/ml of protein, and CT-800 glucagon lot No. P-60076, containing 1 mg protein/ml. Both lots were approximately 50% pure based on potency of crystalline glucagon (0.2 μg/kg of body weight injected intravenously into anesthetized cats causes a maximum blood sugar rise of 30 to 40 mg% 10 to 15 minutes following injection). Insulin content was less than 0.05 U/ml.

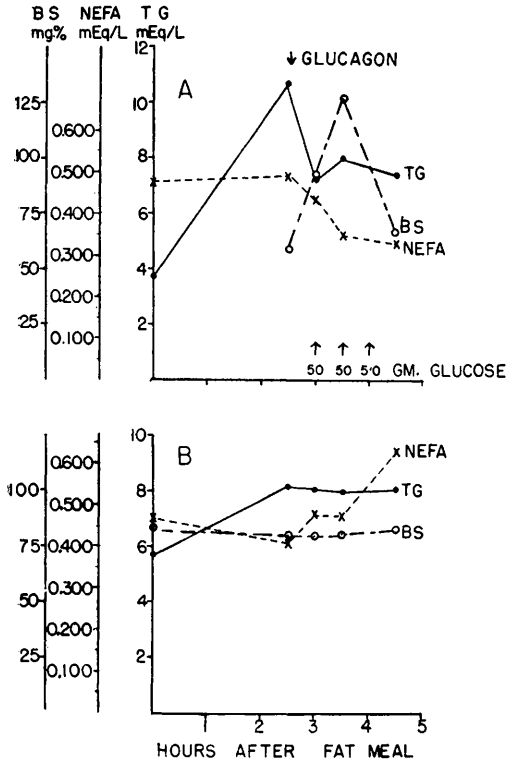

FIG. 1. Blood sugar (BS) serum nonesterified fatty acids (NEFA) and serum triglycerides (TG) of subject WA at intervals after a fat meal with (A) and without (B) glucagon.

blood sugar, and a reduction in concentration of serum triglycerides. The latter had risen from a mean fasting level of 4.1 mEq/L to 7.4 mEq/L at the time of glucagon injection, and decreased an average of 1.8 mEq/L ½ hour following glucagon. There was visible clearing of the serum at this time, when the peak of alimentary lipemia would ordinarily have occurred. Intravenous injection of saline alone instead of glucagon was followed by a further rise in triglyceride concentration in 2 control studies.

Of the 2 exceptions, one (RM) had displayed no alimentary lipemia 2½ hours after the fat meal at the time of glucagon injection, and although his blood sugar concentration increased ½ hour after glucagon, there was no decrease in his serum triglyceride concentration (Fig. 2). The other exceptional subject failed to respond to glucagon with either a rise in blood sugar or a fall in triglyceride concentration. The latter subject was given the test meal on another occasion, but instead of glucagon he received 150 g glucose in divided doses 1 hour, and ½ hour before, and ½ hour after breakfast, treatment known to abolish alimentary lipemia in most individuals(1), but despite this his serum triglyceride concentration rose 3 hours after the fat meal. On a third occasion he was fed the fat meal with the same amount of added glucose as on the second occasion, this time followed also by injection of glucagon 2 hours after the meal. This combination of glucose and glucagon effectively abolished the 3-hour peak in triglyceride concentration, although glucagon still caused no rise in blood sugar.

The NEFA measured in 2 of the subjects are shown graphically in Fig. 1 and 2 together with the triglyceride and blood sugar concentrations. Glucagon produced a rise in blood sugar and a fall in concentration of NEFA of both subjects. One normal subject (WA) was given oral glucose beginning one-half hour after the glucagon injection, in quantities indicated in Fig. 1. This prolonged the effect of glucagon on serum triglycerides and NEFA.

Discussion. The physiological influence of glucagon on carbohydrate metabolism is similar to that of glucose administration: by mobilization of liver glycogen it causes a temporary rise in blood sugar concentration. Although glucagon has been thought by some to decrease peripheral uptake of glucose (reviewed by Cardillo and Bondy(8)) recent experiments indicate that it does not interfere

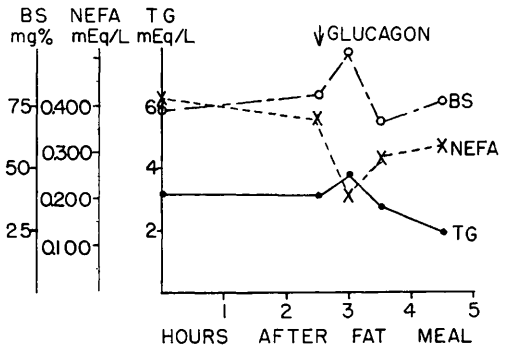

FIG. 2. Effect of glucagon on blood sugar, serum nonesterified fatty acids, and serum triglycerides of subject RM at intervals after a fat meal. Symbols same as in Fig. 1.

with peripheral uptake of glucose(2) and may even cause a greater peripheral uptake of glucose than does a hyperglycemia of similar degree evoked by intravenous glucose(3,4). Our study demonstrates that glucagon also has an effect on lipid metabolism: it diminishes alimentary lipemia and causes a fall in concentration of plasma NEFA. These effects are identical with the effects of glucose administration on alimentary lipemia(1) and on NEFA during fasting(6,9) or after a fat meal(1). The similarity of action of glucose and glucagon on lipid metabolism strengthens the view that glucagon increases rather than inhibits peripheral glucose utilization.

The effectiveness of glucagon would seem to depend on availability of glucose. One subject who experienced no rise in blood sugar also displayed no fall in serum triglycerides following glucagon. When he was prefed glucose his alimentary lipemia was then abolished by glucagon although both glucagon and glucose alone were ineffective. Availability of liver glycogen is a limiting factor in ability of glucagon to induce hyperglycemia(3).

Experimental(10,11) and clinical(12) observations suggest that the pancreas has a role in removal of triglyceride particles from the blood stream. The possible significance of the present study to those observations is not clear. At present it can be concluded only that glucagon, like glucose, causes an acute reduction of particulate triglycerides and of NEFA of plasma. Although other mechanisms must be considered, this action of glucagon may be entirely secondary to the large amount of glucose mobilized or diverted from the liver and thus made available to stimulate peripheral carbohydrate metabolism.

Summary. 1. In 4 of 6 normal subjects, the intravenous injections of 0.03 mg of glucagon per kg body weight 2½ hours after the ingestion of a standard fat breakfast caused a reduction of serum triglyceride concentration either toward or to the postabsorptive levels within half an hour. Of the 2 exceptions one failed to display any rise in concentration of triglycerides following the fat meal, prior to glucagon injection. The second failed to have a hyperglycemic response to glucagon. The rise in concentration of his serum triglycerides could be prevented by glucagon only when he was fed additional glucose with the fat meal. 2. Concentration of nonesterified fatty acids, measured in the sera of 2 subjects decreased following glucagon administration. 3. It was concluded that the effect of glucagon on serum lipids is secondary to its hyperglycemic effect.

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Received May 15, 1957. P.S.E.B.M., 1957, v95.