Suppression by Hepatectomy of Glucagon-Induced Hypertriglyceridemia in Geese[1] (35205)

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Administration of adipokinetic hormones produces elevations of plasma free fatty acids (FFA) and triglycerides (TGL), well documented in various mammalian species (1–4). There is much evidence that plasma FFA are taken up by the liver, where, after being resynthesized to TGL, they become incorporated into lipoproteins which are released into the circulating plasma (5–8). The rate of FFA mobilization is considered a major factor in the regulation of fasting plasma TGL levels in man (9).

Glucagon produces in birds elevations of plasma FFA which are followed by elevations of plasma TGL (10–12) and accumulation of liver triglycerides (11, 12). It has been demonstrated that functional hepatectomy by ligature of the liver vessels abolishes the augmentation of blood lipids produced in the fowl by administration of estrogens (13), but there is no information regarding the role of the liver in the hyperlipemia produced by administration of glucagon in birds.

The experiments reported here were designed to demonstrate the effect of hepatectomy on the plasma FFA, TGL, and blood sugar responses to continuous infusion of glucagon in geese.

Methods. Adult domestic geese (male and female of Embden and Toulouse strains), housed and fed as described in previous publications (11, 14), were used after 16–18 hr of fasting. After induction of anesthesia with sodium pentobarbital[3] (35 mg/kg; ⅔ iv, ⅓ im), PE 90 gauge catheters were inserted into the wing veins, one for infusion the other for withdrawal of blood samples. Infusions were made with a continuous infusion pump[4] at the rate of 3.06 ml/hr. Appropriate dilutions of crystalline beef–pork glucagon[5] were prepared immediately before use in 0.02 *M* glycine buffer (pH, 9.5) in saline. The dose of glucagon was 1.0 μg/kg/min for 30 minutes. Control animals received glycine buffer.

Functional hepatectomy was performed by ligature of the liver vessels as described by Ranney *et al.* (15), except that the ligatures were tied inside the abdomen of the anesthetized animal.

Blood samples were taken 30 min and just before glucagon infusion, and at various time intervals thereafter. In the hepatectomized geese the first blood sample was taken immediately after completion of the ligature of the liver vessels, and the second, 30 min later, just before starting the infusion of glucagon.

Plasma FFA and TGL were measured as described in previous reports (11, 14). Blood sugar was measured with *o*-toluidine as described by Hyvärinen and Nikkilä (16).

The data were analyzed by standard statistical methods. Unless stated otherwise, the significance of the differences reported was calculated by Student's *t* test for paired variates.

Results. Mean values of plasma FFA and TGL for 10 normal and 6 hepatectomized geese infused with glucagon are presented in Fig. 1. The figure includes also the mean

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[3] Diabutal, Diamond Laboratories Inc., Des Moines, Iowa.

[4] Model 600-910, Harvard Apparatus Co., Dover, Mass.

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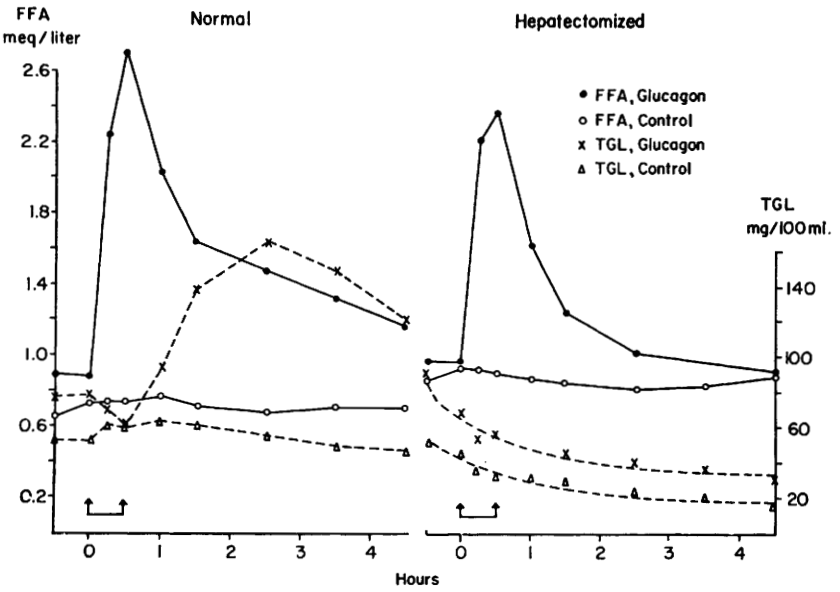

FIG. 1. Plasma FFA (meq/liter) and TGL (mg/100 ml) of 10 normal and 6 hepatectomized geese infused with glucagon (1.0 μg/kg/min for 30 min) and of 4 normal and 4 hepatectomized geese infused with glycine buffer (controls). Infusion indicated by arrows.

values for 4 normal and 4 hepatectomized control geese infused with glycine buffer.

Glucagon infusion (1.0 μg/kg/min for 30 min) in the normal geese produced a sharp elevation of plasma FFA concentration. The mean elevation above the preinfusion level at the end of infusion, was 1.83 meq/liter (SE ± 0.14, $p<0.0001$). Plasma TGL decreased during glucagon infusion. The mean decrease at the end of infusion was 16 mg/100 ml (SE ± 3.28, $p = 0.001$). After discontinuing glucagon infusion plasma TGL rose to a peak 88 mg/100 ml (SE ± 19.2, $p = 0.0015$) above the preinfusion level two hours after end of infusion. Plasma TGL returned to the preinfusion value 3 hr later (not given in Fig. 1). No significant changes of FFA or TGL were noted in the control geese.

Glucagon produced an elevation of plasma FFA in the hepatectomized geese. The mean elevation at the end of infusion (1.40 meq/liter ± 0.17, $p<0.001$) was somewhat smaller than that observed in the normal geese, but the difference between these two mean elevations was not significant (0.43 ± 0.22, $p = 0.07$, t test for nonpaired variates). The curves in Fig. 1. indicate, however, that FFA concentration of hepatectomized geese returned to the preinfusion value faster than that of the normal animals.

Hepatectomy abolished the elevation of plasma TGL observed in the normal geese infused with glucagon. The ligature of the liver vessels was followed by a continuous decrease of plasma TGL concentration which was not affected by glucagon, as shown by the parallelism of the TGL concentration curves for the glucagon infused and the control animals. Since the plasma TGL values for the first 90 min after hepatectomy tended to describe a straight line on a semilogarithmic plot, the constant k in the equation $\ln y_t = \ln y_0 - kt$, was calculated by least squares for each of the hepatectomized animals. The mean value for the 6 geese infused with glucagon was — 0.0072 (SE ± 0.0006), that for the 4 control geese was —0.0071 (± 0.0019). This indicates that glucagon did not modify the rate of decrease of plasma TGL concentration in the hepatectomized geese.

Blood sugar rose in the 10 normal geese infused with glucagon from a mean preinfusion level of 126 mg/100 ml (SE ± 4.7) to a maximum level of 257 mg/100 ml (SE ± 21.0), 30 min after the end of glucagon infu-

sion. The mean blood sugar elevation (131 ± 19.6) was highly significant ($p = 0.0001$). In the hepatectomized geese infused with glucagon there was only a small and nonsignificant blood sugar elevation (11 mg/100 ml, SE ± 6.0, $p = 0.12$) at the end of infusion. In these animals the blood sugar showed a slow and continuous decrease to a level 36 mg/100 ml below control (SE ± 11.2, $p = 0.023$), 5 hr after hepatectomy.

Discussion. Our experiments show that functional hepatectomy suppresses the elevation of plasma TGL which follows the infusion of glucagon in the normal geese. This result compares with the suppression by hepatectomy of the hyperlipemia produced in the fowl by administration of estrogens (13). The effect of hepatectomy reported here is consistent with the concept that hyperlipemias associated with elevated plasma FFA concentrations are the consequence of increased release by the liver of TGL-carrying lipoproteins (2, 6–8, 17–20). The continuous decrease of plasma TGL observed in the hepatectomized geese suggests that the liver is the main, and perhaps only, site of lipoprotein formation in the fasting bird.

Glucagon infusion in normal geese caused a small, but significant, decrease of plasma TGL at a time when the concentration of plasma FFA reached its highest level. On the other hand plasma TGL rose after discontinuing glucagon infusion, reaching a peak 2 hr after the end of infusion, when the level of plasma FFA showed a marked decrease from its peak value. A similar observation has been reported previously (11).

Glucagon infusion, on the other hand, caused no apparent change in the rate of decrease of plasma TGL concentration after hepatectomy. This suggests that the decrease of plasma TGL produced during glucagon infusion in the normal geese is due to an interference with the ability of the liver to release into the circulation the TGL formed in this organ from the plasma FFA, thus delaying the development of hyperlipemia. Because of the speed with which TGL accumulate in the liver of birds infused with glucagon (11), it seems unlikely that the delay in the release of TGL discussed here is due to an impairment of TGL synthesis in that organ.

Hepatectomy abolished the hyperglycemic response to glucagon observed in the normal geese. This result compares with the absence of hyperglycemic effect of glucagon reported in eviscerated dogs and rats (21, 22).

Summary. Continuous infusion of glucagon (1.0 μg/kg/min for 30 min) in normal geese caused an elevation of plasma FFA and blood sugar and a decrease of plasma TGL concentration. Upon discontinuing glucagon infusion, plasma TGL rose significantly to a peak level 2 hr after the end of infusion.

Functional hepatectomy suppressed the elevations of plasma TGL and blood sugar observed in normal geese infused with glucagon, and produced a continuous decrease of plasma TGL which was not affected by the administration of glucagon.

These results indicate that the elevation of plasma TGL after glucagon infusion is due to increased release of lipoproteins by the liver, induced by the elevation of plasma FFA. The decrease of plasma TGL during the infusion of glucagon and the delay between the elevations of plasma FFA and plasma TGL suggest that glucagon, in addition to its adipokinetic effect, decreases the release of TGL by the liver into the circulation.

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