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41

Effect in dogs of various portal vein shunts on response to insulin[1]

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STARZL, THOMAS E., GEORGE W. BUTZ, JR., WILLIAM H. MEYER, JR., ELIZABETH E. TOROK, AND RALPH E. DOLKART. *Effect in dogs of various portal vein shunts on response to insulin.* Am. J. Physiol. 203(2): 275–277. 1962.—Surgical alterations of portal drainage patterns were made in dogs in order to determine the effect of redistribution of endogenous and injected insulin. With an Eck fistula, progressive diminution of hypoglycemic response to insulin was noted. With a reverse Eck fistula, the fall in venous blood sugar was comparable whether injection was given via the portal system or systemically. With portacaval transposition, in which the pancreatic drainage is diverted from the liver, no alterations in general health, fasting blood sugars, or insulin response were noted. The results are discussed in relation to recent concepts in which insulin is thought to regulate or be regulated by the liver.

ALTHOUGH IT IS GENERALLY CONCEDED that the liver plays a major role in the regulation of blood glucose levels, there has been vigorous controversy as to whether insulin directly alters hepatic control of blood glucose or is itself altered by passage through the liver.

The present investigation was constructed to determine the effects of insulin, as measured by venous blood glucose determinations, after various types of surgical alteration of the portal venous system. The operations changed the pathway of endogenous insulin into the blood stream and also permitted measurement of the effects of exogenous insulin administration at different sites in relation to the liver.

METHODS

Nineteen mongrel adult dogs weighing 10–20 kg were used. The animals were dewormed, immunized against distemper and infectious canine hepatitis, and observed for several months before the initiation of an experiment. Diet consisted of vitamin-enriched standard kennel rations distributed in the morning, containing approximately 30% protein, 15% fat, and 55% roughage and carbohydrate. The animals were fasted for 24 hr before being tested.

Glucagon-free insulin, given intravenously, was used for testing. The dose of insulin was .07–.1 U/kg administered over a period of 10–15 sec. Venous blood sugar was determined by use of the Folin-Wu colorimetric method on Somogyi filtrates.

Eck fistulas were prepared by the technique of Freeman (1). The technique of Meyer and Starzl (2) was used for reverse Eck fistulas, with the modification that caval ligation was performed below the adrenal veins. With this method, all venous tributaries from the inguinal ligament to the site of caval ligation are removed with the exception of the renal veins, so that injections into the femoral veins pass directly to the liver without dissipation into collateral vessels (2). Portacaval transposition was done without ligation of tributary vessels of either the portal vein or vena cava (3). The pancreaticoduodenal and adrenal veins were always preserved and their contents thereby diverted into the proximal vena cava and proximal portal vein, respectively (3). The experiments were designed so each animal served as its own control for the evaluation of results.

RESULTS

Eck fistula. Seven dogs were studied in which a reproducible response to insulin could be obtained before operation. After the creation of an Eck fistula, response to insulin was determined 2 weeks after surgery and at intervals until the time of death, 4–8 weeks later. Weight loss was characteristic, averaging 40% of the preoperative weight. Despite declines in weight, the insulin dose

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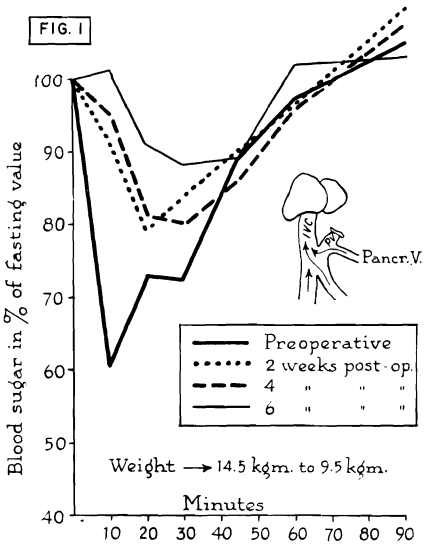

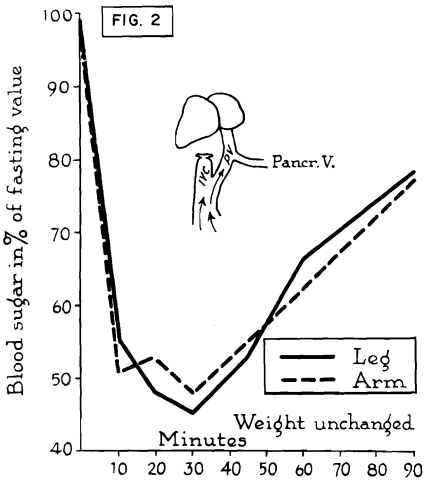

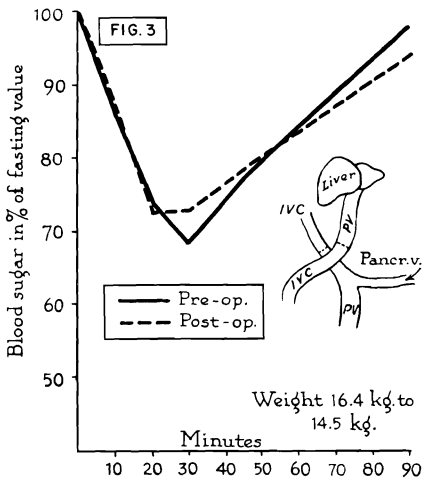

FIG. 1. Response to intravenous insulin before and at intervals after Eck fistula in representative dog. Points on preoperative curve are averages of multiple tests.

FIG. 2. Results of insulin administration in representative dog with reverse Eck fistula, showing comparison of effect with forelimb vein and femoral vein injection. Curves are averages of 3 determinations before and 5 after surgery.

FIG. 3. Effect of intravenous insulin administration before and after portacaval transposition in a typical dog. Preoperative curve represents average of 4 insulin tests, and postoperative curve is average of 6 tests.

in a given dog was not changed throughout the course of observation. All seven dogs developed terminal lethargy, episodic stupor, and convulsions—presumably the results of ammonia intoxication. At autopsy, the livers were small and pale.

The fasting blood sugars did not change significantly after operation. Before operation, mean fasting blood glucose of 12 determinations was 73 mg/100 ml ± 9.6 (SD). The mean of 19 postoperative determinations was 70 mg/100 ml ± 6.1. In six of the seven animals, alterations were observed in the effect of intravenous insulin. The changes were first noted at 2 weeks and in a typical animal progressed until death (Fig. 1). The hypoglycemic response was reduced, and in subsequent weeks the fall in blood sugar became less and less (Fig. 1). From 5 to 6 weeks after surgery, the maximum fall in blood glucose for the series was to a mean of 60 mg/100 ml ± 5.8. Before surgery, the same animals with identical doses of insulin dropped to 49 mg glucose/100 ml ± 5.6. In two of the seven dogs, recovery from hypoglycemia was slightly more prolonged than in the control state.

Reverse Eck fistula. Seven dogs with reverse Eck fistulas maintained their weight and appeared to be perfectly healthy. Fasting blood glucose before surgery averaged 80 mg/100 ml ± 9.8 and postoperatively averaged 78 mg/100 ml ± 8.4.

After complete recovery from surgery, 3–8 weeks after operation, multiple intravenous insulin tests were performed comparing the effect of endoportal administration (via the femoral vein) with systemic injection (via the forelimb vein). In a given week, both femoral and forelimb injections were employed in randomized order, with at least 2 days between tests. A total of 28 experiments were performed with injection 14 times by each route.

There was no significant difference in the hypoglycemic response with the two sites of injection. In four dogs the effect was essentially identical (Fig. 2). In two animals the transfemoral portal injection caused a slightly greater hypoglycemia. In the seventh dog the systemic injection by foreleg vein provoked a slightly greater hypoglycemia. The maximum reduction in blood sugar in the entire series was to 41 mg/100 ml ± 4.4 with forelimb injection and to 41 mg/100 ml ± 8.6 with femoral vein injection.

Portacaval transposition. Multiple preoperative insulin tests were performed in five dogs and repeated from 3–10 weeks after operation. All injections were given in a forelimb vein. The animals remained in good health. Weight loss occurred in only one case. The animals were kept under observation for 6 months after completion of the tests and appeared to be healthy. Preoperatively, the fasting blood sugars averaged 82 mg/100 ml ± 7. Postoperatively the mean of fasting blood sugars was 78 mg/100 ml ± 9.5.

Response to the intravenous insulin was not significantly altered after surgery in any case. The magnitude and duration of the hypoglycemic response were essentially the same (Fig. 3). In 17 tests done before surgery, the maximum hypoglycemia was 58 mg/100 ml ± 8.4. After surgery the maximum blood sugar drop was to 53 mg/100 ml ± 8.5.

DISCUSSION

In these experiments, a group of varying conditions was established for the entry of insulin into the circula-

tion. These changes involved both the mode of entry of the endogenously produced insulin as well as the mode of entry of the injected exogenous insulin. In the reverse Eck fistula preparations, the effects of endoportal and systemic venous injections of insulin were compared in the same animal. The site of injection had no influence on the venous hypoglycemic response. This observation is at variance with the results reported by a number of investigators (4–8), but it is in accord with the work of others (9–14). Failure to distinguish a difference of response in the present study with the two sites of injection conceivably could be due to the rapidity of injection in the present experiment and the long period of fasting before the tests. Both factors have been described as masking any differential effect (15, 16). The effects of smaller and more physiologic doses of insulin are currently being evaluated.

The hypoglycemic response to rapidly injected insulin was changed only in those dogs (with Eck fistula) in which impaired liver function occurred (17, 18). That this was a nonspecific effect due to partial devascularization of the liver was evident from the fact that portacaval transposition did not cause a comparable effect. With this latter preparation, splanchnic blood flow is diverted from the liver as with an Eck fistula, but the liver is revascularized by vena caval blood.

The diminished effect of insulin in dogs with an Eck fistula may have important implications in other metabolic studies in which this preparation is used. For example, the rise in insulin requirement after an Eck fistula in dogs with alloxan diabetes (19, 20) could be explained by this change. The reduction of insulin effect in dogs with an Eck fistula is probably important in the interpretation of the results of the experiments described by Madison and his associates (15), which were designed to determined the effect of insulin on hepatic glucose output. They described inhibition of hepatic glucose output by insulin in dogs with an Eck fistula and assumed that such animals respond normally to exogenous and endogenous insulin. The results in the present study indicate that this assumption is subject to some reservation.

The present data provide no basis on which to assert that insulin does or does not directly affect hepatic glucose output. They do, however, suggest that the location of entry of injected insulin into the blood stream is not of major importance with rapidly injected doses. Similarly, the site of entry into the blood stream of endogenous insulin does not affect the long-term health or the level of the fasting blood sugar of the healthy dog. The normal behavior of dogs with portacaval transposition, in which endogenous insulin is diverted from the liver, is confirmatory of older experiments by Gayet and Guillaumie (21), Houssay et al. (22), and Meythaler and Stahnke (23), who achieved similar results with other echniques of systemic transplantation of pancreatic drainage.

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