Failure of Growth Hormone to Stimulate Glucagon Secretion (35925)

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About two decades ago, Bornstein *et al.* (2) and Foà *et al.* (1) noted that, under certain experimental conditions following the intravenous injection of growth hormone (GH), the blood of the pancreatoduodenal vein acquired hyperglycemic properties. Subsequently, it was reported that these properties were due to several substances, some of which, like serotonin or the catecholamines, could be blocked by dihydroergotamine (DHE) and others, like glucagon, which were unaffected by DHE (3). Further attempts to identify the materials responsible for the GH-induced hyperglycemia gave the following contradictory results: GH caused the dissociation of protein-bound circulating glucagon (4); did not modify the serotonin and catecholamine levels of pancreatoduodenal blood significantly (5), while its hyperglycemic response was almost totally prevented by adrenergic and serotonin blockers (6, 7).

Recently Farmer and collaborators (8) reported that total pancreatectomy, or the removal of the splenic lobe of the pancreas, abolished the delayed lipolytic response to GH in dogs. Since the splenic lobe is especially rich in A-cells (9), these results suggested that glucagon might act as mediator of the lipolytic action of GH. Indeed, when glucagon is infused intraportally, it can cause lipolysis without hyperglycemia (10). The objective of our experiments was to measure glucagon secretion following GH administration.

Materials and Methods. We anesthetized a number of dogs with pentobarbital sodium (35 mg/kg) and removed the entire gastrointestinal tract below the diaphragm, leaving the pancreas and its circulation intact. A polyethylene cannula (PE240) was inserted through the splenic vein to the edge of the liver and withdrawn 0.5 in. Another cannula (PE90) was inserted through the splenic artery to its intersection with the celiac artery. Porcine growth hormone, dissolved in saline (pH 9; 10 mg/ml) was infused into the splenic artery. The dogs were heparinized (500 units/kg) immediately before taking the first sample of blood.

In other experiments, the surgical trauma was reduced by dissecting the pancreas away from the gastrointestinal tract, which otherwise was left undisturbed. A polyethylene cannula (PE240) was inserted through the splenic vein to within 0.5 in. of the portal vein to collect blood from the splenic portion of the pancreas. The splenic vessels were ligated and the spleen was removed immediately before the injection of a single dose of porcine growth hormone (1 mg/kg; 10 mg/ml) and of heparin (500 units/kg) into the jugular vein.

In one eviscerated dog, ganglionic blockade was achieved by a priming injection of hexamethonium chloride (50 mg/kg) given immediately after termination of surgery, and was maintained by subsequent hourly injection of 1 mg/kg. Blood pressure was monitored by means of a cannula inserted into a femoral artery. All blood samples were collected by letting it flow freely. The samples were chilled immediately after withdrawal and centrifuged. The plasma was transferred to another tube containing Trasylol (10,000 units/ml), frozen immediately, and kept at $-20°$. When enough samples had been collected they were packed in Dry Ice and shipped to Detroit for glucagon radioimmunoassay (11).

Glucagon was measured using an antiglucagon serum that does not discriminate between pancreatic and gut glucagon. However, in

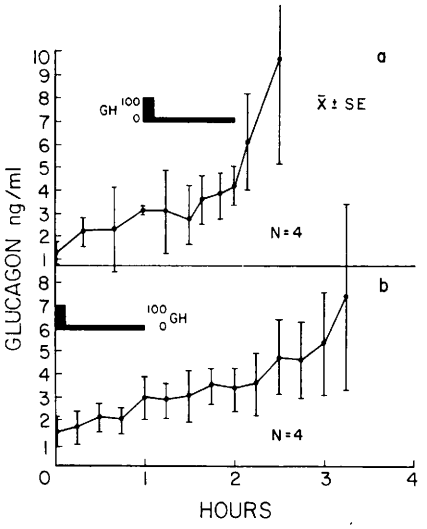

FIG. 1. Pancreatic venous glucagon in partially eviscerated dogs following infusion of growth hormone into the pancreatic artery after a control period (a); and immediately upon termination of surgery (b).

our preparation, no gut glucagon could have contaminated the samples.

Results. Figure 1a shows that a marked increase in portal venous glucagon concentration occurred approximately 1 hr after the beginning of GH infusion and approximately 2 to 2.5 hr after the end of surgery. When the infusion of GH started immediately upon the termination of surgery (Fig. 1b), the overall shape of the curve was not markedly different and the sharpest rise in glucagon concentration occurred at approximately the same time after surgery as in the preceding experiment. These results suggest that surgery rather than the infusion of GH may have caused the observed release of glucagon. Figure 2a and b shows that when the surgical shock was reduced by separation of the pancreas from the gastrointestinal tract rather than by partial evisceration, the concentration of glucagon in the portal blood rose in two of the three dogs that were treated with saline, but only in one of the four dogs that had received GH. Figure 3 shows that following ganglionic blockage with hexamethonium in a dog in which the entire gastrointestinal tract had been removed, the concentration of glucagon in the plasma remained stable for the duration of the experiment.

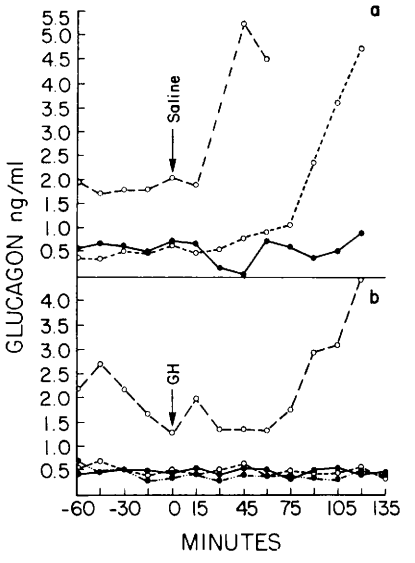

FIG. 2. Pancreatic venous glucagon following a single intrajugular injection of saline (1 mg/kg (a); or of growth hormone (1 mg/kg) in dogs with pancreas dissected free of the gastrointestinal tract (b).

Discussion. The results of our experiments provide evidence that GH does not stimulate glucagon secretion. The progressive increase in glucagon concentration noted in partially eviscerated dogs, but not in animals pretreated with hexamethonium, may have been the result of progressive increase in autonomic nervous system activity caused by blood loss or by anesthesia, and resulting in a change in blood supply to the pancreas. This hypothesis is supported by the following observation: hemorrhagic shock is associated with a rise in serum glucagon in dogs and sheep (12), surgery (13), and barbiturate anesthesia (14) may cause epinephrine release, hyperglycemia (15), and an increase in serum fatty acid level (16) and there is morphologic and functional evidence that autonomic nervous impulses may regulate glucagon secretion [for references, see (17)].

Summary. Experiments in partially eviscerated dogs failed to provide evidence that growth hormone stimulates glucagon secretion. The results suggest that the rise in plasma glucagon level observed in a variety of

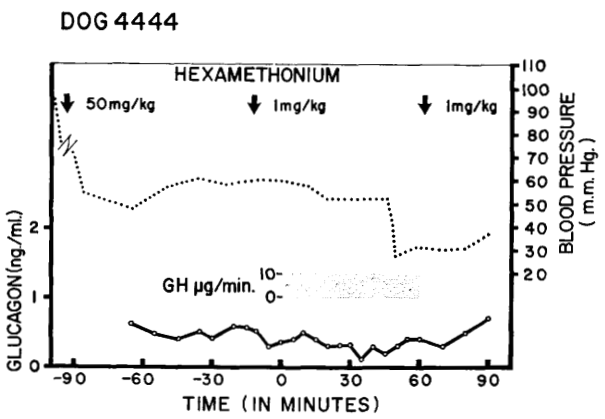

FIG. 3. Pancreatic venous glucagon during growth hormone infusion in a partially eviscerated dog treated with hexamethonium chloride (50 mg/kg, followed by hourly injections of 1 mg/kg).

experimental conditions may have been caused by surgical trauma, perhaps resulting in changes in the blood supply or in the autonomic impulses to the pancreas.

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