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Oxytocin Increases Extrapancreatic Glucagon Secretion and Glucose Production in Pancreatectomized Dogs[1] (42312)

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Abstract. Infusion of oxytocin into normal dogs increases plasma levels of insulin and glucagon and glucose production and uptake. To determine whether infused oxytocin also increases glucagon secretion from extrapancreatic sites, pancreatectomized dogs, off insulin for 18 hr, were infused with oxytocin and plasma glucagon, and glucose production and uptake were measured using the [6-^{3}H]glucose primer-infusion technique. The diabetic dogs, in the control period, had elevated plasma glucose and glucagon levels, an increased rate of glucose production, and a relative decrease in glucose uptake (decreased clearance). Infusion of oxytocin (500 μU/kg/min) caused a rise in plasma glucagon and glucose levels, increased glucose production, and further decreased glucose clearance. It is concluded that oxytocin can stimulate secretion of extrapancreatic glucagon, which contributes to the increased glucose production.

Infusion of oxytocin into normal dogs increases plasma levels of glucagon and insulin and concomitantly increases rates of glucose production and overall glucose uptake by tissues (1). The effect of oxytocin on glucose production appeared to be mediated in part by the elevated levels of plasma glucagon since suppression of the hyperglucagonemia by somatostatin blocks the rise in glucose production (submitted for publication). Plasma glucagon is derived from pancreatic and extrapancreatic sites in dogs (2, 3) and it has been shown that the extrapancreatic glucagon increases hepatic glucose production (4).

The present studies were undertaken in depancreatized dogs to determine whether infused oxytocin had effects on secretion of extrapancreatic glucagon and whether such effects were associated with changes in glucose production.

Materials and Methods. *Animals.* All experiments were carried out on conscious dogs accustomed to a laboratory setting. Normal dogs of either sex, weighing 15–23 kg, were maintained on a fixed diet and were studied 18 hr following feeding. Four of the dogs were studied in the normal state and again 4–6 months after total pancreatectomy which was performed in the Department of Medicine at the Cornell University Medical College. The operated dogs were maintained on a mixture of regular and NPH insulin for at least 4 months prior to the study and their plasma glucose was monitored daily for proper dosage. Insulin was withheld 18 hr prior to an experiment.

Experimental procedure. Polyethylene catheters were inserted percutaneously into the jugular and saphenous vein for blood sampling and infusions, respectively. Urine was collected quantitatively from diabetic animals at half hour intervals for determination of glucose loss to correct glucose uptake values. Serial blood samples were collected in chilled heparinized tubes which were promptly centrifuged and aliquots of the plasma were frozen for later analysis. Plasma glucose concentration and radioactivity were determined as described before (5) and plasma insulin (6) and glucagon (7) levels were determined by radioimmunoassays.

Glucose production and overall uptake by tissues were determined by the isotope dilution technique (5). Briefly, [6-^{3}H]glucose was administered as a priming injection, followed immediately by an infusion at a constant rate for the entire period. Control samples were

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collected after 60 min. After obtaining five control blood samples, an oxytocin infusion was started at 120 min. In some experiments on the pancreatectomized dogs, only control samples were obtained over a 180-min period. The calculations of glucose production and uptake were as described before (5), with the additional correction of the latter for urinary glucose loss in the diabetic animals. The calculations for uptake during oxytocin infusion were based on 0.7 of the initial glucose pool size as the rapidly mixing compartment. Oxytocin (Syntocinon) was a gift from Sandoz, Inc.

Results. Infusion of oxytocin (500 μU/kg/min) into normal dogs resulted in hormonal and metabolic changes shown in Fig. 1. Concentrations of plasma glucose, insulin, and glucagon were increased. These changes were accompanied by significant increases in glucose production and uptake. The effects of oxytocin in pancreatectomized dogs are shown in Fig. 2. The operated animals, in the basal state and off insulin for 18 hr, had a marked hyperglycemia and high plasma glucagon levels. Plasma insulin levels ranged from 6 μU/ml to undetectable amounts (data not shown). Glucose production was higher than normal. Glucose uptake was somewhat higher than normal but glucose clearance (uptake ÷ prevailing plasma glucose) was below normal. In other experiments, extending the control period to 3 hr gave similar values as shown for the shorter control period. Specifically, there were no further changes in plasma glucose levels nor in glucose production and clearance in the third control hour compared to the preceding hour. Infusion of oxytocin resulted in a marked increase in plasma glucagon levels and in glucose production. Glucose uptake showed a transient increase, but since hyperglycemia was more severe, the glucose clearance was reduced even further. Figure 3 com-

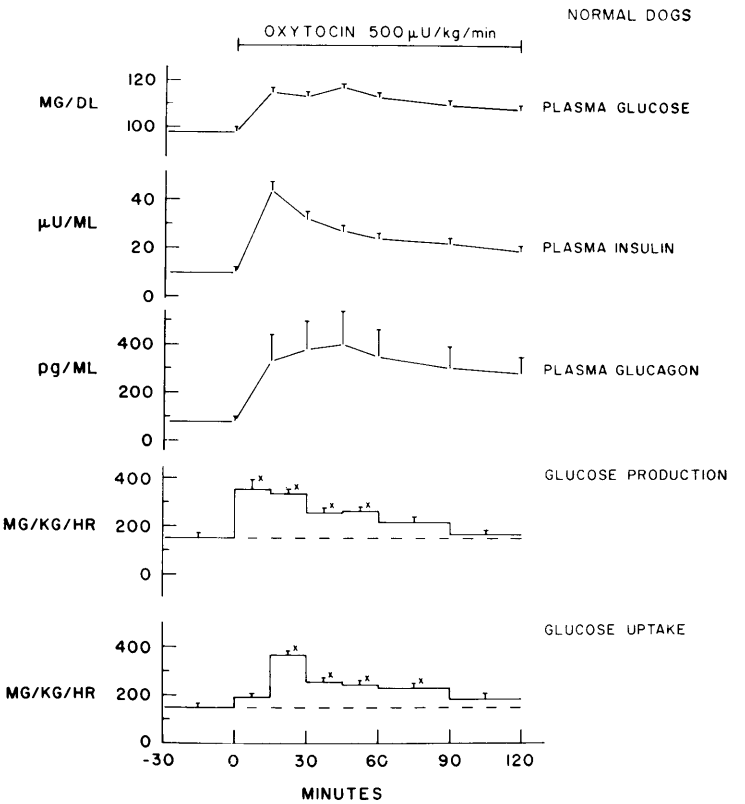

FIG. 1. Effect of oxytocin (500 μU/kg/min) infusion in normal dogs (n = 8). All increases in plasma glucose, insulin, and glucagon are statistically significant ($P < 0.01$–0.05). The significant increases in rates of glucose production and uptake are designated by ×.

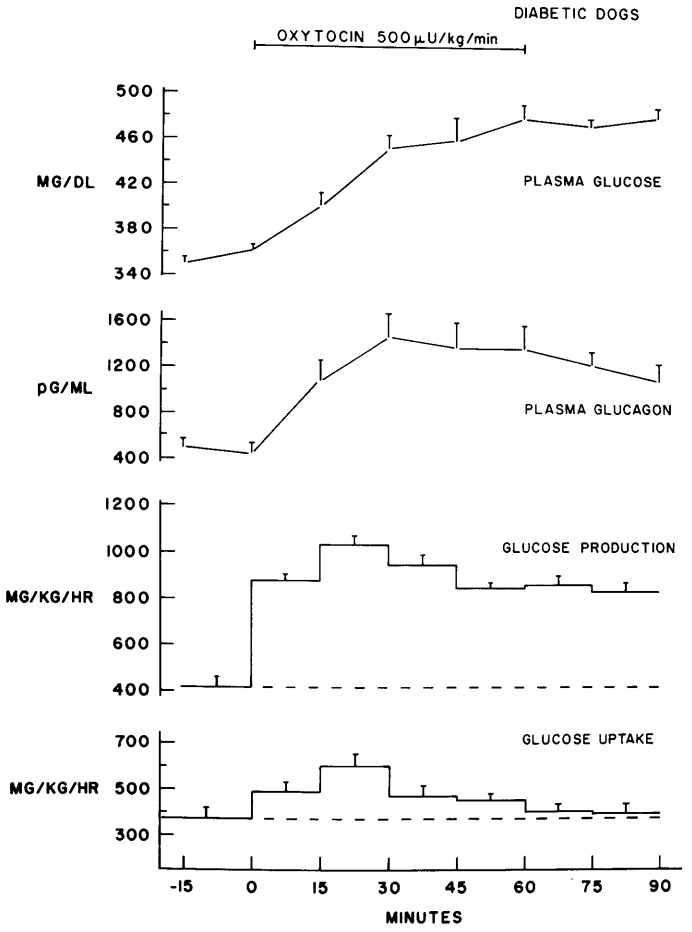

FIG. 2. Effect of oxytocin (500 μU/kg/min) infusion in pancreatectomized dogs ($n = 5$) off insulin for 18 hr. All basal values are significantly ($P < 0.01$) above normal values and all changes during oxytocin infusion are significantly ($P < 0.01$) above control values.

pares the responses to oxytocin of a group of normal dogs to that of the pancreatectomized dogs; the percentage change relates to their respective individual control values immediately prior to oxytocin infusion. Plasma glucagon levels showed a greater percentage rise in the normal animals but the depancreatized animals had much higher basal values and the picogram per milliliter increments were greater than in the normal animals. The increase in glucose production in the pancreatectomized dogs was greater and persisted for a longer time than it did in the normal dogs. Glucose uptake showed lesser increases in the diabetic animals than in normals.

Discussion. A rise in plasma glucagon concentrations in response to administration of oxytocin has been demonstrated in the rat (8), rabbit (9), and dog (1, 10, 11). Direct effects of oxytocin to stimulate glucagon secretion have also been demonstrated in the perfused rat pancreas (11). The rise in plasma glucagon in the dog has been associated with an increase in glucose production (1). Subsequent studies, using SRIF to inhibit glucagon secretion, have shown that the rise in plasma glucagon levels is implicated in the increased glucose production (submitted for publication). Although both pancreatic and extrapancreatic sources presumably contribute to the circulating plasma glucagon levels (4), it has not previously been determined whether oxytocin indeed acts at the extrapancreatic sites.

The present study demonstrates that infu-

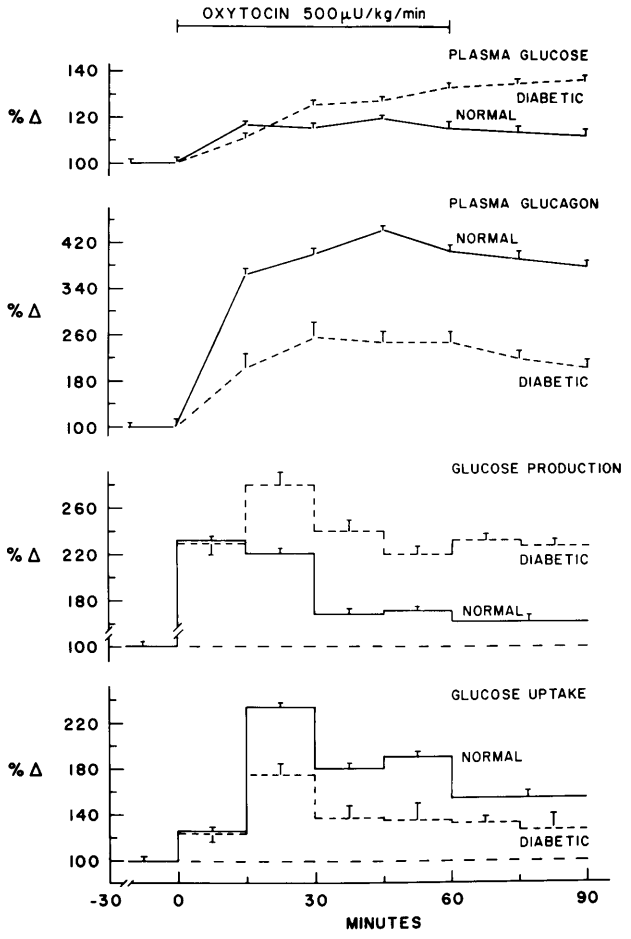

FIG. 3. Changes in the various parameters during oxytocin infusion (500 μU/kg/min) presented in percentage relative to their respective individual controls (shown as 100%). Calculations based on data from preceding figures.

sion of oxytocin in pancreatectomized dogs causes a marked increase in plasma glucagon levels, evidently arising from extrapancreatic sites. Furthermore, the concomitant increase in glucose production suggests a causal relationship between the two responses. This is supported by the fact that SRIF infusion in the pancreatectomized animals results in a decrease in plasma glucagon levels and in glucose production [(4), unpublished observations].

Although the present study suggests that extra pancreatic glucagon may be a mediator of the stimulatory effect of oxytocin on glucose production in dogs, it is not possible to assess its contribution relative to that of pancreatic glucagon. Thus based on the present findings it may be concluded that oxytocin can increase secretion of glucagon from extrapancreatic sites and that such secreted glucagon can contribute to the observed increase in glucose production. The contribution of the extrapancreatic glucagon to the effects of oxytocin in normal dogs remains to be determined.

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