Oxytocin Infusion Increases Plasma Insulin and Glucagon Levels and Glucose Production and Uptake in the Normal Dog

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SUMMARY

Infusion of oxytocin (50–500 μU/kg/min) into normal conscious dogs produces a rise in plasma glucose, insulin, and glucagon levels. These changes are accompanied by a prompt increase in glucose production followed by an increase in overall glucose uptake, as determined using 6-^{3}H-glucose infusion. DIABETES *30*: 112–114, February 1981.

In the course of studying the effects of vasopressin and oxytocin infusion on growth hormone secretion it was noted that oxytocin produced a mild hyperglycemia. The metabolic and hormonal changes associated with this hyperglycemia were explored and are reported here.

MATERIALS AND METHODS

All experiments were performed on trained, normal, conscious dogs about 18 h after feeding. Blood samples were obtained from the jugular vein, through a polyethylene tube inserted percutaneously through a needle shortly before the start of the experiment. Drugs were administered into the saphenous vein via an indwelling polyethylene cannula. Blood samples were drawn into heparinized syringes, transferred into chilled tests tubes, and centrifuged. Aliquots of plasma were deproteinized by the Somogyi method[1] and the remainder frozen for hormone assays. Blood (2 ml) for glucagon assay was collected in tubes containing 0.1 ml of Trasylol and 0.1 ml of 2.4% Na_2 EDTA (1.2 mg/ml blood), centrifuged, and the plasma frozen for later analysis. Rates of glucose production and utilization were determined using the priming injection-constant infusion of 6-^{3}H-glucose.[2] Rates of glucose production and utilization in the steady state were calculated as before.[3] During periods of oxytocin infusion and consequent changes in plasma glucose, 0.7 of the initial glucose pool size was used for calculating the rapidly mixing glucose compartment.[4,5]

Glucose concentration was determined by the glucose-oxidase method[6] on a Beckman glucose analyzer, plasma insulin by radioimmunoassay,[7] and glucagon by radioimmunoassay,[8] using antiserum 30K obtained from Dr. Roger Unger and ^{125}I-glucagon from Nuclear Medical Laboratories, Dallas, Texas. Oxytocin (Syntocinon) was kindly provided by Sandoz, Inc., East Hanover, New Jersey

RESULTS

As seen in Figure 1, infusion of oxytocin, 500 μU/kg/min, into normal dogs produced a prompt, statistically significant ($P < 0.01-0.05$) increase in plasma glucose concentration that persisted throughout the infusion period. Plasma glucagon levels were increased at the first 15 min sampling ($P < 0.01$) and remained elevated during infusion period. Similarly, plasma insulin levels increased promptly ($P < 0.01$) and remained significantly above control levels throughout the infusion. Similar changes, although of a lesser magnitude, were observed when oxytocin was infused at 50 μU/kg/min as shown in Table 1.

The prompt rise in plasma glucose and plasma glucagon levels during oxytocin infusion was associated with an increase in glucose production, as shown in Table 2. Glucose production increased from basal values of 3.81 g/m^2/h to 8.74 at 15 min and remained significantly elevated during the 120-min infusion period. Likewise, overall removal of glucose from the plasma (glucose uptake) was significantly increased during the entire infusion period.

DISCUSSION

The oxytocic and milk-ejection effects of oxytocin are well established but little is known about possible other effects. Pharmacologic doses of oxytocin have been reported to cause a brief decrease in systolic and diastolic pressure[9] and to have an antidiuretic effect.[10] Metabolic effects of oxytocin have been cited in several reports. Injection of oxytocin (10 mU/kg, i.v.) into nonpregnant women had no immediate effect on plasma glucose during first 30 min, but a

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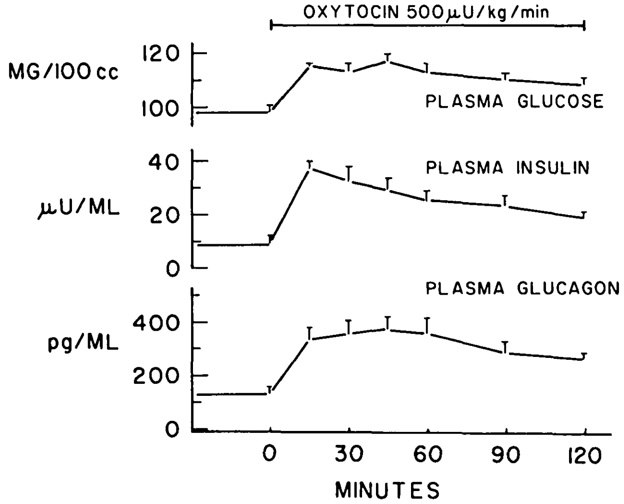

FIGURE 1. Plasma glucose, insulin, and glucagon concentration in 8 normal dogs during infusion of oxytocin, 500 µU/kg/min. All changes are statistically significant, P < 0.01, and for glucose and glucagon values at 120 min, P < 0.05.

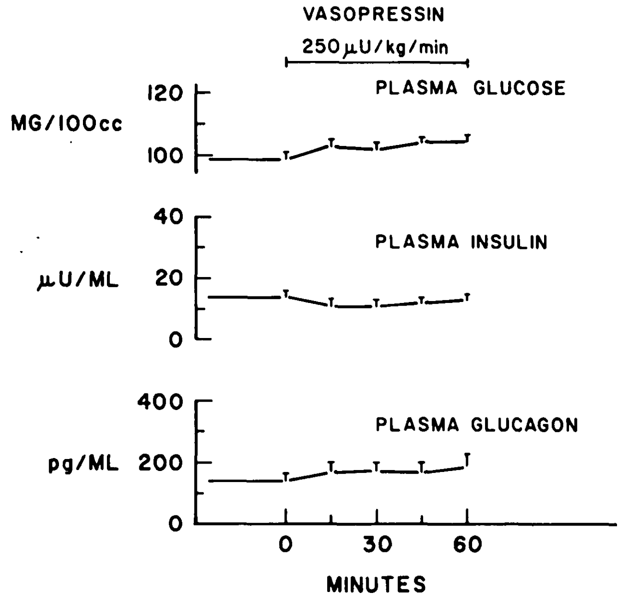

FIGURE 2. Plasma glucose, insulin, and glucagon concentration in 8 normal dogs during infusion of arginine vasopressin (Sigma) 250 µU/kg/min. There were no significant effects on any of the above measurements.

progressive hypoglycemia began at 60 min, reaching about 40% of control values at 3 h.[11] In normal dogs, injection of 1 U/kg i.v. produced a prompt rise of 33% in blood glucose concentration.[12] A lesser increase in blood glucose was noted when oxytocin was infused at 1 U/kg for 1 h. In both instances plasma free fatty acids levels decreased markedly. The rises in blood glucose in these studies were attributed to impaired glucose utilization, since large doses of oxytocin (10–40 U) failed to induce any changes in glucose concentration in the hepatic vein.[13]

The present studies used much smaller doses of oxytocin (50–500 µU/kg/min) than those used in the above studies or those used clinically for oxytocic effects. Although blood levels of oxytocin were not measured, infusion of 250 µU/kg/min of vasopressin in these dogs resulted in plasma vasopressin levels of 20–30 µU/ml. Plasma levels of oxytocin of 5–15 µU/ml have been reported in women during infants' suckling,[15] thus the lower doses of oxytocin (50 µU) would give plasma levels within physiologic range.

As shown here, infusion of oxytocin causes a rise in plasma glucagon and a concomitant increase in glucose

TABLE 1
Effect of oxytocin infusion on plasma glucose, insulin, and glucagon in normal dogs

		Oxytocin 50 µU/kg/min				
Measurement	Control	15 min.	30 min.	45 min.	60 min.	90 min.
Glucose (mg/dl)	96 ± 1*	105 ± 2†	109 ± 2†	107 ± 3†	106 ± 3†	104 ± 2†
Insulin (µU/ml)	9 ± 1	28 ± 7†	27 ± 5†	22 ± 4†	24 ± 5†	12 ± 2
Glucagon (pg/ml)	130 ± 30	260 ± 27‡	300 ± 51‡	323 ± 40‡	328 ± 40‡	280 ± 2‡

* Mean ± SEM; N = 6 dogs.
† P < 0.02–0.01.
‡ P < 0.05.

TABLE 2
Effect of oxytocin infusion on glucose production and uptake in normal dogs

		Oxytocin 500 µU/kg/min					
Measurement	Control	15 min.	30 min.	45 min.	60 min.	90 min.	120 min.
Plasma glucose mg/dl	98 ± 1*	115 ± 1†	113 ± 4†	117 ± 3†	113 ± 3†	110 ± 2†	108 ± 2†
Glucose production g/m²/h	3.8 ± 0.3	8.7 ± 1†	8.4 ± 0.7†	6.4 ± 0.5†	6.5 ± 0.2†	5.4 ± 0.7†	4.6 ± 0.2†
Glucose uptake g/m²/h	3.8 ± 0.3	4.6 ± 0.6	8.9 ± 0.3†	5.6 ± 0.3†	7.3 ± 0.2†	5.8 ± 0.6†	4.9 ± 0.3‡

* Mean ± SEM; N = 4 dogs.
† P < 0.02–0.01.
‡ P < 0.05.

production. This is followed by increased glucose utilization, which is accompanied by elevated plasma insulin levels. Although it would appear that stimulation of glucagon secretion might be an initiating step in the sequence of events, this remains to be determined. Arginine vasopressin, which differs in its chemical composition by two amino acids, does not alter plasma glucagon and insulin levels (Figure 2) nor glucose production and utilization (not shown).

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