Role of Insulin and Glucagon in Oxytocin Effects on Glucose Metabolism (43353)

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Abstract. **Oxytocin (OT) infusion in normal dogs increases plasma insulin and glucagon levels and increases rates of glucose production and uptake. The purpose of this study was to determine whether the effects of OT on glucose metabolism were direct or indirect. The studies were carried out in normal, unanesthetized dogs in which OT infusion was superimposed on infusion of either somatostatin, which suppresses insulin and glucagon secretion, or clonidine, which suppresses insulin secretion only. Infusion of 0.2 μg/kg/min of somatostatin suppressed basal levels of plasma insulin and glucagon and inhibited the OT-induced rise of these hormones by about 60–80% of that seen with OT alone. The rates of glucose production and uptake by tissues, measured with [6-^{3}H] glucose, were significantly lower than those seen with OT alone, and the rise in glucose clearance was completely inhibited. Clonidine (30 μg/kg, sc), given along with an insulin infusion to replace basal levels of insulin, completely prevented the OT-induced rise in plasma insulin and markedly reduced the glucose uptake seen with OT alone, but did not reduce the usual increase in plasma glucose and glucagon levels or glucose production. To determine whether the OT-induced rise in plasma insulin was in response to the concomitant increase in plasma glucose, similar plasma glucose levels were established in normal dogs by a continuous infusion of glucose and an OT infusion was superimposed. OT did not raise plasma glucose levels further, but plasma insulin levels were increased, indicating that OT can stimulate insulin secretion independently of the plasma glucose changes. Studies by others have shown that the addition of OT to pancreatic islets or intact pancreas can stimulate insulin and glucagon secretion, indicating a direct effect. Our studies agree with that and suggest that *in vivo*, OT raises plasma insulin levels, at least in part, through a direct action on the pancreas. These studies also show that OT increases glucose production by increasing glucagon secretion and, in addition, a direct effect of OT on glucose production is likely. The OT-induced increase in glucose uptake is mediated largely by increased insulin secretion.**

[P.S.E.B.M. 1992, Vol 199]

A number of recent studies have demonstrated that the administration of oxytocin (OT) causes an increase in plasma insulin and glucagon levels in dogs (1–3), rabbits (4), rats (5), and fetal and neonatal sheep (6). OT also increases secretion of insulin from rat pancreatic islets (5) and insulin and glucagon from isolated mouse islets (7) and rat pancreas (8). In humans, an injection of OT enhanced the rise of insulin secretion in response to a glucose load (9) and enhanced the arginine-induced rise in insulin and glucagon in normal men and increased glucagon secretion in diabetic men (10). In dogs, the rise in plasma insulin and glucagon levels during OT infusion was accompanied by an increase in the rate of glucose production and glucose uptake by the tissues (1).

In isolated adipocytes, the addition of OT produced several "insulin-like" effects, such as increased glucose oxidation, lipogenesis, and antilipolysis (11–13), suggesting that OT can act directly on the cells. Thus, it is unclear what role the elevated plasma levels of insulin and glucagon play in the metabolic effects of OT observed *in vivo*.

The purpose of the present study was to clarify the putative roles of insulin and glucagon in the metabolic responses to OT in normal dogs. To decrease the en-

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Received January 30, 1991. [P.S.E.B.M. 1992, Vol 199]
Accepted September 23, 1991.

0037-9727/92/1992-0236$3.00/0

hanced secretion of insulin and glucagon which occurs in response to OT infusion, dogs were infused with somatostatin, which suppresses the secretion of both insulin and glucagon (14), or with clonidine, which produces a profound decrease in insulin secretion (15).

Materials and Methods

Animals and Procedures. A total of 12 normal, mongrel dogs of either sex weighing 17–22 kg were used. The dogs were used more than once, allowing at least 2 weeks between repeat use. The dogs were conditioned to accept the laboratory setting and were used without anesthesia about 18 hr after ingestion of a standard daily meal. The protocols for the experiments were approved by our Institutional Animal Care and Use Committee. Blood samples were obtained from the jugular vein via an indwelt polyethylene tube inserted percutaneously through a needle shortly before each experiment. Drugs and glucose were infused via a polyethylene tube inserted in a similar way into the saphenous vein. Rates of glucose production and overall glucose uptake were determined in the control state and during periods of changing plasma glucose, as described below. Starting at 60 min after initiation of the tracer infusion, five blood samples were taken at 15-min intervals to determine the control rates of glucose turnover and hormone levels. The various experimental protocols were initiated at 120 min, so that each experiment had its own control. Serial blood samples were collected in heparinized syringes, transferred to chilled tubes, and centrifuged. An aliquot of plasma was deproteinized with $ZnSO_4$ and $Ba(OH)_2$ and frozen for later determination of glucose and its specific activity. Aliquots of plasma for glucagon assay were placed in chilled tubes containing 0.2 ml of 2.4% Na_2-EDTA and 0.2 ml of Trasylol (Farbenfabriken Bayer, New York, NY) and frozen for later analysis. In experiments in which oxytocin was determined, plasma aliquots were placed in tubes containing 0.2 ml of 1 *N* HCl and kept frozen at −20°C until assayed. An aliquot of plasma was frozen for insulin assay.

Protocols. In the experiments in which glucose production and uptake were measured, radioactive glucose was administered by a priming injection, followed immediately by a continuous infusion that was delivered at a constant rate throughout the entire experiment. Control values were obtained during the 60- to 120-min period. At 120 min, one of three protocols was initiated: (i) OT was infused intravenously for 90 min at 500 μU/kg/min, which is the dose previously shown to produce the hormonal and metabolic effects studied here (1); (ii) somatostatin (SRIF) was infused intravenously for 105 min at 0.2 μg/kg/min, this dose having been shown previously (14) to be effective in significantly depressing the secretion of insulin and glucagon; and (iii) an OT infusion was superimposed on that of SRIF after 15 min of SRIF infusion. Each protocol was repeated on the same dog after at least 2 weeks of rest.

In other experiments, clonidine (30 μg/kg, sc), along with an intravenous infusion of insulin (100 μU/kg/min) to maintain basal plasma insulin levels, was administered at 120 min after the start of the radioactive glucose infusion. Thirty minutes were allowed for the full effect of clonidine to develop before commencing the OT infusion. This dose of clonidine was previously shown (15) to decrease plasma insulin values in the dog from 10 to 14 μU/ml in the basal state to the very low levels of 3–4 μU/ml.

In experiments in which the OT infusion was superimposed upon elevated plasma glucose levels, cold glucose was infused at 300 mg/kg/hr for 120 min in the control experiments; in other experiments, an OT infusion was superimposed at 60 min and the combined infusions were continued for another 60 min.

Measurement of Glucose Production and Uptake. Rates of glucose production and uptake were determined using [6-^{3}H]glucose, which was administered as a priming injection (55 μCi), along with a continuous infusion at a constant rate (0.5 μCi/min). Glucose turnover in the steady state was calculated as before (16). During periods of changing plasma glucose levels, the rates of glucose production and uptake were calculated based on 0.7 of the initial glucose pool as the rapidly mixing glucose compartment (16). Plasma glucose concentration was determined by the glucose oxidase technique, using the Beckman Glucose Analyzer, and the specific activity was determined as described previously (16).

Hormone Assays and Drugs. Hormones were assayed by radioimmunoassay. In the insulin assay, dextran-coated charcoal was used to separate the bound insulin from the free (17). For insulin, the coefficient of variation was ±7% for intraassay and ±10% for interassay, and the limits of detection were 1.0 μU/ml. The glucagon assay (18) used the Unger 30-kDa antibody and the coefficient of variation was ±8% for intraassay and ±11% for interassay; the limits of detection were 35 pg/ml. The OT antibody (19) was a gift from Dr. Mariana Morris, Bowman Gray School of Medicine, Winston Salem, NC; the OT standard used in the assay was the fourth international standard received from the National Burma of Standards, United Kingdom. The detection limits of the OT assay were 0.25 μU/ml, the variation for intraassay were ±7% and for interassay ±16%. [6-^{3}H]Glucose was purchased from ICN Corp., Irvine, CA. Oxytocin (Syntocinon) was a gift from Sandoz, Inc., Hanover, NJ, insulin and glucagon were gifts from Eli Lilly & Co., Indianapolis, IN, and clonidine was from Boehringer Ingelheim, Ltd, Ridgefield, CT. Linear somatostatin was purchased from Bachem, Inc., Torrance, CA.

Statistical Analysis. The data were analyzed using two-factor mixed analysis of variance (20). When any

of the factors were significant in the analysis of variance, differences between individual pairs of means were analyzed using Tukey's test for comparison between treatment groups and Dunnett's test for differences within each treatment group (21). All data are presented as means ± SE. All computations were done using the SAS/STAT User's Guide (22).

Results

Effects of Oxytocin Infusion. As shown in Table I, infusion of OT at 500 μU/kg/min produced statistically significant increases in plasma levels of glucose, insulin, and glucagon ($P < 0.01$ by Dunnett's test). Likewise, the rates of glucose production and uptake, as well as those of glucose clearance, were significantly increased during the infusion.

Effect of Concomitant Somatostatin Infusion. Infusion of SRIF alone, as shown in Table I, decreased the plasma levels of glucose, insulin, and glucagon ($P < 0.01$–0.05, Dunnett's test). The rate of glucose production decreased during the first 60 min, but returned to basal rates by 105 min, despite continuous infusion of SRIF. Glucose uptake by tissues was significantly depressed at 75 min and beyond, and there were no significant changes in glucose clearance. Infusion of OT superimposed upon that of SRIF resulted in increases in plasma insulin levels that were 60–80% lower than those produced by OT alone (Table I). Glucagon levels in response to the superimposed OT infusion did not increase significantly and the levels were 60–80% lower than those produced by OT alone. Glucose production was still increased significantly by the superimposed OT infusion and the increase was about 15–35% lower than that produced by OT alone. Glucose uptake too was increased during the SRIF-OT infusion and was also about 15–35% lower than that seen with OT alone. There was no rise in glucose clearance.

Inhibition of Insulin Secretion by Clonidine. To prevent the OT-induced rise in plasma insulin levels more effectively than was possible with SRIF, clonidine was administered subcutaneously at 30 μg/kg, along with insulin infusion, to restore the basal levels of plasma insulin. As reported previously (15), this regimen of clonidine plus insulin did not alter any of the basal parameters studied here. As shown in Figure 1, infusion of clonidine prevented the increase in plasma insulin seen with OT alone. The glucagon response was not impaired and plasma glucose levels rose much higher than with OT alone, probably because insulin secretion was inhibited. The effectiveness of OT in increasing glucose production was not impaired by the clonidine infusion, but glucose uptake was significantly less than that seen with only OT infusion.

Effect of Hyperglycemia. The above experiments suggested that some of the effects of OT, notably on glucose uptake, were mediated partly by the increased plasma insulin levels, but it was not clear whether the rise in insulin levels was due to OT per se or resulted from the rise in plasma glucose. Since some of the responses to OT might have been influenced by the concomitant hyperglycemia, a similar rise in plasma glucose levels was induced in normal dogs by infusion of glucose (300 mg/kg/hr), and then an OT infusion was superimposed. As seen in Table II, infusion of glucose alone for 2 hr resulted in a prompt rise in plasma glucose and insulin levels, which tended to decline somewhat during the infusion period, but still remained well above control levels until 105 min into the infusion. Superimposing an OT infusion at 60 min caused no further increase in plasma glucose levels and, in fact, the glucose values were not significantly different (by Tukey's test) from those seen during infusion of glucose alone. Nevertheless, the OT infusion resulted in a further increase in plasma insulin secretion at 15 and 30 min. Plasma glucagon levels have been shown previously to increase in response to OT during similar combined glucose and OT infusions (3).

Plasma Oxytocin Levels. To ascertain that the doses of OT used here did not produce unphysiologic plasma levels of OT, measurements of plasma OT were made during infusion of OT at 500 μU/kg/min. The basal plasma levels of OT in our untreated normal dogs were 2.09 ± 0.21 μU/ml and, by 15 min, increased to the steady state levels of 28.3 ± 2.3 μU/ml.

Discussion

The present study confirms and expands the earlier findings that OT infusion increases plasma insulin and glucagon levels in several species, including humans. The effects reported here were seen with doses of OT that produce plasma levels seen under various physiologic or pathologic conditions, e.g., feeding (23), lactation (23), labor and parturition (24, 25), hypovolemic shock (26), and other stressful conditions (27, 28).

The present studies also provide *in vivo* evidence that is in harmony with *in vitro* data that indicate that OT can have a direct effect on insulin and glucagon secretion. As noted above, the addition of OT to islets isolated from mouse pancreas (7) or injected via a microdialysis probe into the splenic portion of the rat pancreas (8) was shown to stimulate insulin secretion. In the present experiments, administration of OT in the glucose-infused dogs increased insulin secretion in the absence of an increase in plasma glucose levels, which indicates that an increase in plasma glucose is not a prerequisite for the OT-induced insulin secretion and which most likely reflects a direct effect of OT on insulin secretion. *In vitro* experiments have also clearly shown that OT can stimulate directly the secretion of glucagon when added to isolated rat (5) or mouse (7) islet cells or injected into the splenic portion of the rat pancreas (8). The present study was not designed to investigate a direct effect of OT on glucagon secretion *in vivo*.

Table I. Metabolic Effects of Oxytocin Infused Alone and During Somatostatin Infusion in Normal Dogs[a]

Measurements	R_x	SRIF (0.2 μg/kg/min)						
		Control	15 (min)	30 (min)	45 (min)	60 (min)	75 (min)	105 (min)
				Oxytocin (500 μU/kg/min)				
				15 (min)	30 (min)	45 (min)	60 (min)	90 (min)
Plasma glucose (mg/dl)	OT	95 ± 1	—	N< 109 ± 2	N< 113 ± 3	N< 112 ± 2	N< 110 ± 2	N< 105 ± 3
	SRIF + OT	98 ± 2	95 ± 2	107 ± 1 >b	112 ± 3 >b	115 ± 2 >b	115 ± 2 >b	113 ± 4 >b
	SRIF	102 ± 0.5	94 ± 0.4	91 ± 1	90 ± 1	86 ± 2	91 ± 2	98 ± 3
Plasma insulin (μU/ml)	OT	9 ± 1	—	b< 43 ± 4	b< 31 ± 3	b< 27 ±3	b< 24 ± 2	b< 21 ± 3
	SRIF + OT	8 ± 1	4 ± 1	13 ± 3 >d	13 ± 3 >d	13 ± 3 >d	13 ± 4 >d	10 ± 2 >N
	SRIF	11 ± 1	7 ± 1	5 ± 1	5 ± 1	5 ± 1	5 ± 1	6 ± 1
Plasma glucagon (pg/ml)	OT	93 ± 8	—	d< 325 ± 42	b< 390 ± 49	b< 393 ± 62	c< 355 ± 67	d< 308 ± 85
	SRIF + OT	98 ± 7	68 ± 12	157 ± 27 >N	130 ± 17 >N	138 ± 18 >N	153 ± 9 >N	150 ± 10 >N
	SRIF	105 ± 6	80 ± 4	80 ± 6	80 ± 5	77 ± 7	76 ± 6	75 ± 5
Glucose production ($g/m^2/HR$)	OT	3.8 ± 0.3	—	b< 8.9 ± 1.1	b< 8.8 ± 0.6	d< 6.1 ± 0.4	d< 6.5 ± 0.2	N< 5.5 ± 0.2
	SRIF + OT	3.5 ± 0.2	2.3 ± 0.3	5.7 ± 0.6 >b	5.8 ± 0.6 >b	5.2 ± 0.4 >b	5.0 ± 0.5 >b	4.5 ± 0.4 >N
	SRIF	3.6 ± 0.2	2.7 ± 0.4	2.5 ± 0.3	2.4 ± 0.2	3.1 ± 0.3	3.0 ± 0.2	3.5 ± 0.2
Glucose uptake ($g/m^2/HR$)	OT	3.8 ± 0.3	—	b< 4.6 ± 0.6	b< 8.9 ± 0.3	b< 7.3 ± 0.2	N< 5.6 ± 0.3	N< 5.8 ± 0.6
	SRIF + OT	3.5 ± 0.2	3.0 ± 0.4	2.9 ± 0.2 >N	4.3 ± 0.5 >N	4.8 ± 0.3 >b	4.9 ± 0.4 >b	4.7 ± 0.3 >b
	SRIF	3.6 ± 0.2	3.4 ± 0.2	3.3 ± 0.3	3.4 ± 0.3	3.1 ± 0.2	2.8 ± 0.2	27 ± 0.3
Glucose clearance (ml/kg/min)	OT	2.6 ± 0.3	—	c< 3.0 ± 0.5	b< 5.0 ± 0.5	b< 4.5 ± 0.2	b< 4.3 ± 0.3	N< 3.5 ± 0.3
	SRIF ± OT	2.4 ± 0.2	2.5 ± 0.3	2.0 ± 0.1 >N	2.6 ± 0.3 >N	2.8 ± 0.3 >N	2.8 ± 0.1 >N	2.8 ± 0.1 >N
	SRIF	24 ± 0.2	2.3 ± 0.3	2.3 ± 0.2	2.5 ± 0.2	2.6 ± 0.3	2.4 ± 0.2	2.5 ± 0.2

[a] Differences between treatments were adjusted for total number of comparisons in the experiments (Tukey's test). Values represent mean ± SE; $n = 8$. N, not significant.
[b] $P < 0.001$.
[c] $P < 0.01$.
[d] $P < 0.05$.

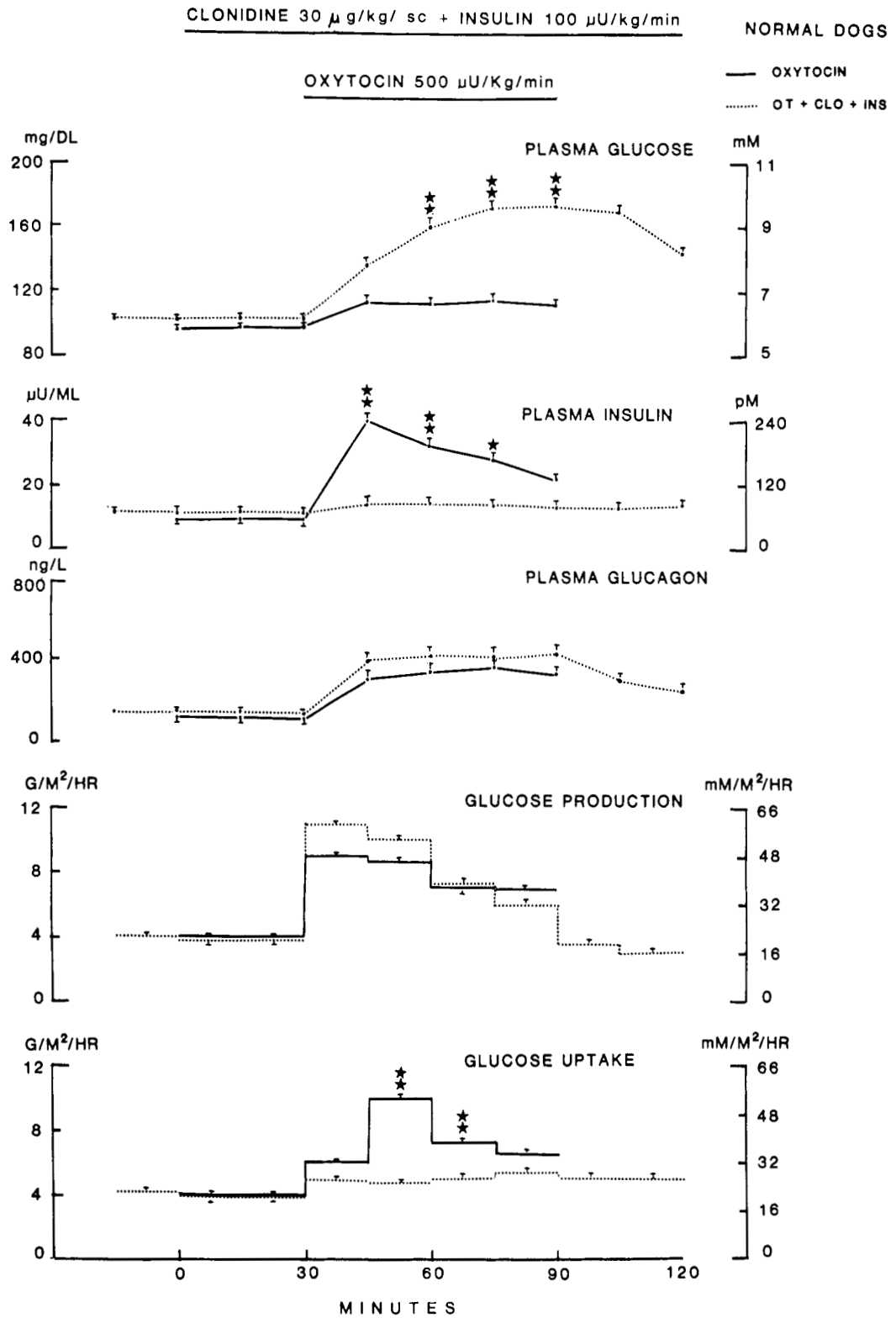

Figure 1. Effect of oxytocin infusion (500 μU/kg/min) in normal dogs (n = 6) on glucose metabolism when increased secretion of insulin was prevented by injection of clonidine (30 μg/kg, sc) given along with insulin replacement (OT + CLO + INS). Clonidine plus insulin was administered at 120 min after start of the radioactive glucose infusion and had no effects on any of the measurements. Statistically significant differences (Tukey's test) between treatments are indicated by asterisks. ** $P < 0.001$; and * $P < 0.05$.

Table II. Effect of Superimposing Infusion of Oxytocin on Plasma Glucose and Insulin Levels in Normal Dogs Infused with Glucose

	Control (min)	15	30	45	60	75	90	105	120
	Glucose (300 mg/kg/hr)								
Glucose[a] (mg/dl)	101 ± 2[b]	126 ± 4	126 ± 7	123 ± 6	120 ± 6	127 ± 6	116 ± 4	118 ± 4	121 ± 5
Insulin[a] (μU/ml)	11 ± 1	31 ± 8	32 ± 4	29 ± 2	26 ± 3	22 ± 3	23 ± 2	20 ± 3	17 ± 2
					Oxytocin (500 μU/kg/min)				
	Glucose (300 mg/kg/hr)								
Glucose (mg/dl)	100 ± 2	132 ± 4	137 ± 5	136 ± 6	127 ± 5	123 ± 4	110 ± 4	106 ± 3[b]	107 ± 2[b]
Insulin (μU/ml)	7 ± 1	25 ± 4	28 ± 7	37 ± 7	28 ± 4	50 ± 4[c]	44 ± 6[c]	28 ± 2	24 ± 1

[a] All values significantly greater ($P < 0.01$–0.05) than control values.
[b] Mean ± SE; $n = 8$.
[c] Significantly higher than values at corresponding time during infusion of glucose only; $P < 0.01$ by Tukey's test.

The other question of interest in this study was whether infused OT has direct or indirect effects in glucose production and uptake. This would require a complete suppression of secretion of both insulin and glucagon which has not been possible with the currently available tools. With regard to glucagon, SRIF is the best available agent to inhibit glucagon secretion, but doses that we found to be effective in maximally inhibiting glucagon secretion in the steady state did not prevent small increases in glucagon secretion during OT infusion (Table I). However, it is noteworthy that the greatly reduced glucagon responses to OT during SRIF infusions were accompanied by increases in glucose production that were significantly less than those evoked by OT in the absence of SRIF. Thus, increased glucagon secretion is clearly involved in the increased glucose production seen with OT infusion in the normal animals. This is in agreement with the studies of Vilhardt *et al.* (3), who used a 10-fold higher dose of SRIF, along with very large doses of insulin (1 mU/kg/min), and attributed the hyperglycemic effect of OT in their dogs to the secretion of glucagon. Whether the entire response to OT can be attributed to glucagon, as claimed by Vilhardt *et al.*, is open to question, since they did not measure glucose production or uptake and they used very large doses of insulin, which have potent inhibitory effects on glucose production. Also, the finding that the addition of OT to isolated rat liver slices increases glycogenolysis (29) supports a direct effect of OT on glucose production.

The question regarding the role of insulin in the OT-induced increase in glucose uptake is somewhat easier to answer, as evident from the experiments in which clonidine administration effectively prevented insulin secretion during OT infusion (Fig. 1). The insulin response to OT infusion was completely suppressed and glucose uptake was very markedly decreased. The small increases in glucose uptake seen during the combined clonidine-OT treatments were most likely due to the mass action effect of the elevated plasma glucose levels. Thus, the data strongly suggest that the OT-induced increase in glucose uptake is due mainly to the increased secretion of insulin. This conclusion is not necessarily at variance with the insulin-like effects of OT found *in vitro*. These effects include increased glucose oxidation, glycogen synthesis, and lipogenesis, but not glucose uptake (12, 13), and it is the latter that is being measured in our *in vivo* experiments. Also much larger doses of oxytocin (n*M*) range were used in the *in vitro* studies whereas the tissues in our experiments were exposed to plasma levels in the 50-p*M* range.

While our studies, as well as those of Vilhardt *et al.* (3), have clearly implicated insulin and glucagon in the metabolic responses to OT, they do not preclude the possibility that other mediators may be involved. The participation of adrenergic neurotransmitters seems unlikely, since neither propranolol (15) nor phentolamine (unpublished data) prevented a rise in glucose production in response to oxytocin. It has been shown that infusion of OT elevated plasma levels of vasoactive intestinal polypeptide in the dog (30) and vasoactive intestinal polypeptide stimulated secretion of insulin and glucagon in the dog (31). It is also of interest that OT has recently (32) been shown to have direct effects on phosphoinositide metabolism in adipocytes that are different from those produced by insulin.

Lastly, our understanding of the physiologic role of OT warrants reexamination, as new data reveal the occurrence of OT and its receptors in tissues other than its main target sites, namely the myometrium and mammary gland. Thus, the findings on the hormonal and metabolic effects of OT gain further importance from the recent evidence of OT binding sites within the

pancreatic islets (8) and the immunohistochemical localization of OT in pancreatic islets in normal and diabetic rats (33). Also, the presence of OT receptors in adipose tissues (13), kidney (34), and brain (35, 36) of rats suggests a broader physiologic role for OT.

This work was supported in part by grants from the UPS Foundation (N. A.), Warner Lambert Foundation (A. R. F.), and Obesity Care Center, and Grant DK-26687 from the National Institute of Health (F. X. P. S.). We wish to thank Yim Dam for her excellent assistance in these studies.

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