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Intranasal Instillation of Oxytocin Increases Insulin and Glucagon Secretion (41245)

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Abstract. Intravenously administered oxytocin was found to increase plasma insulin and glucagon levels. To explore if the same effects could be obtained by nonparenteral routes of administration, oxytocin was given by nasal instillation in normal conscious dogs. Plasma glucose, insulin, and glucagon levels all increased to levels which previously were shown to cause increased glucose production and utilization. Vasopressin infusion had no effect on these measurements. This is the first report of the effectiveness of oxytocin to evoke insulin and glucagon secretion by the nasal route of administration.

The polypeptide nature of insulin has precluded its administration by routes other than by injection. Stimulation of endogenous insulin secretion can be induced by ingestion of various carbohydrates and protein which are the normal physiologic stimuli for insulin secretion. For therapeutic purposes in the treatment of maturity-onset type of diabetes mellitus the only orally effective agents are the so-called oral hypoglycemics, namely, the sulfonylurea compounds. However, these agents have untoward side effects and furthermore their ability to lower plasma glucose may not involve increased insulin secretion (1).

Recently we have observed that intravenously administered oxytocin causes significant increases in plasma insulin and glucagon levels (2). It was of interest to determine if other routes of administration, and specifically the nasal route, might also affect insulin and glucagon secretion.

Materials and Methods. Normal, conscious dogs (eight) were used about 18 hr after ingestion of food. Serial blood samples were obtained from the jugular vein with the aid of an indwelling polyethylene tubing inserted percutaneously through a needle shortly prior to each experiment. A similar technique was used on the saphenous vein to administer oxytocin (50 and 500 μU/kg/min) or vasopressin (250 μU/kg/min). Oxytocin was given intranasally (1.5–2 U/kg) by dropper administered in 0.2 ml from stock solution of 180 U/ml. The same volumes of saline were administered in control experiments. Blood samples were collected in heparinized syringes, placed in chilled tubes, and centrifuged. The plasma was frozen for later analysis of glucose (3), insulin (4), and glucagon (5).

Results and Discussion. Intravenous infusion of oxytocin produced a prompt modest rise in plasma glucose and significant rises in plasma insulin and glucagon (Fig. 1). Vasopressin, which produces antidiuretic effects and stimulates growth hormone secretion at the dose given, had no effects on glucose, insulin, or glucagon (not shown). Intranasal instillation of oxytocin produced a prompt and striking increase in all three measurements (Fig. 2), whereas similar instillation of saline had no effects.

Although blood levels of oxytocin following intranasal instillation were not determined, it is evident that the effects on plasma glucose, insulin, and glucagon were somewhat greater than those seen when oxytocin was infused at 500 μU/kg/min. Since the latter dosage results in increased glucose production and utilization (2) it suggests that the hormonal changes following intranasal instillation also produce meta-

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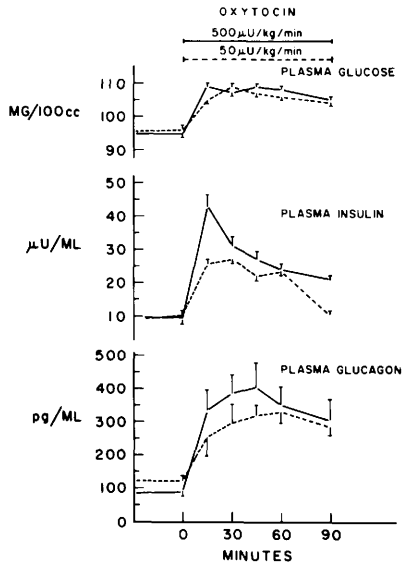

FIG. 1. Plasma concentrations of glucose, insulin, and glucagon during administration of oxytocin in eight normal dogs. Oxytocin was infused at 50 and 500 μU/kg/min. Bars represent standard error of mean (SEM). All values, except insulin at 90 min (50 μU/kg) were significantly elevated ($P = <0.05-0.01$).

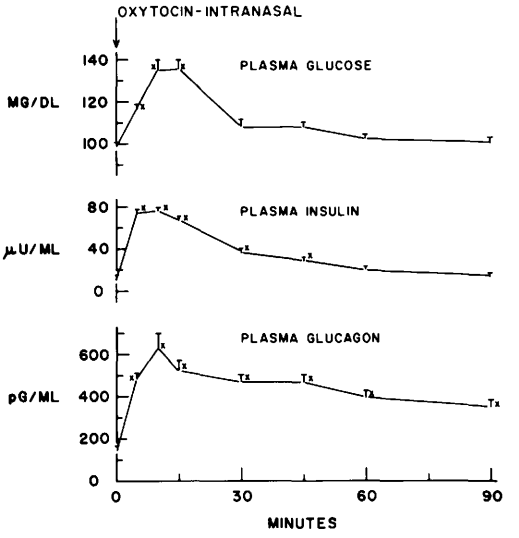

FIG. 2. Plasma concentrations of glucose, insulin, and glucagon following intranasal instillation of 1.5–2 U/kg in eight normal dogs. Statistically significant increases occurred at most times as indicated by x next to SEM bars. Instillation of saline had no effect on any of the measurements.

bolic effects. No untoward effects of oxytocin administration by either route were evident.

To our knowledge this is the first demonstration that the intranasal route of administration can be used to stimulate the secretion of insulin and glucagon. The usefulness of this route for the treatment of maturity-onset diabetes would depend on the separation of the two effects. Studies are in progress using analogs of oxytocin with the expectation of obtaining one preparation which stimulates only insulin secretion.

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