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13 ABSTRACT

Insulin release during alpha-adrenergic receptor blockade in a variety of experimental animals has raised the possibility of a direct effect of alpha-blockade on insulin secretion. However, in 7 unanesthetized baboons, an increase in the serum insulin concentration during phentolamine-induced alpha-adrenergic receptor blockade occurred only in hyperglycemic animals and the magnitude of the increase in serum insulin was significantly correlated with the serum glucose concentration immediately prior to phentolamine. These findings are consistent with observations showing no effect of alpha-adrenergic inhibitors on basal insulin concentration in (normoglycemic) man and indicate that insulin secretion during alpha-adrenergic receptor blockade occurs only in the presence of an appropriate glycemic stimulus. (Endocrinology 89:918, 1971)

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INSULIN RELEASE DURING ALPHA-ADRENERGIC RECEPTOR BLOCKADE: PRIMACY OF THE GLYCEMIC STIMULUS

BY

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Insulin Release During Alpha-Adrenergic Receptor Blockade: Primacy of the Glycemic Stimulus[1]

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ABSTRACT. Insulin release during alpha adrenergic receptor blockade in a variety of experimental animals has raised the possibility of a direct effect of alpha-blockade on insulin secretion. However, in 7 unanesthetized baboons, an increase in the serum insulin concentration during phentolamine-induced alpha-adrenergic receptor blockade occurred only in hyperglycemic animals and the magnitude of the increase in serum insulin was significantly correlated with the serum glucose concentration immediately prior to phentolamine. These findings are consistent with observations showing no effect of alpha-adrenergic inhibitors on basal insulin concentration in (normoglycemic) man and indicate that insulin secretion during alpha-adrenergic receptor blockade occurs only in the presence of an appropriate glycemic stimulus. (*Endocrinology* **89:** 918, 1971)

HYPERINSULINEMIA during phentolamine-induced alpha-adrenergic receptor blockade has been observed in rats (1), dogs (2) and baboons (3). In contrast, an increase in the serum insulin concentration has not been seen during phentolamine infusion in fasting human subjects (4–6). Our measurements of serum glucose and insulin during alpha-adrenergic receptor blockade in fasting baboons permit reconciliation of these conflicting observations.

Materials and Methods

Serum insulin was measured by radioimmunoassay using dextran-coated charcoal to separate antibody-bound from unbound insulin (7). Porcine insulin standards were used. Dilution experiments with a high-insulin baboon serum demonstrated an adequate degree of cross-reactivity between baboon and porcine insulin with respect to our antiserum. All insulin values reported in this paper were determined in a single assay; the intra-assay coefficient of variation of replicate determinations on a normal serum in our laboratory was 6.8%. Serum glucose was measured by the ferricyanide method with a Technicon dual-channel AutoAnalyzer.

All studies were performed on unanesthetized male baboons (*Papio doguera*) weighing between 23 and 28 kg. Four hr after tranquilization with 1-(1-phenylcyclohexyl)-piperidine hydrochloride (Sernylan), 1.0 mg/kg, for insertion of arterial and venous catheters and placement in a primate chair, base-line observations were begun. Ninety min later, a rapid iv injection of 5.0 mg of phentolamine (Regitine, Ciba) was given and an infusion of phentolamine, 25 μg/min, was begun and continued for the following 30 min. Arterial samples for serum glucose and insulin determinations were drawn at 0, 60, 90, 105 and 120 min.

The adequacy of the alpha-adrenergic receptor blockade produced by these doses of phentolamine was established in control baboons given iv epinephrine (in preparation). In the absence of phentolamine, the diastolic pressure response to 0.1 μg/kg of epinephrine iv exceeded 20 mm Hg in all instances whereas during phentolamine infusion this response was reduced to 0–5 mm Hg. In a single animal, iv epinephrine, 2.5 μg/kg, produced the expected fall in serum insulin concentration, whereas this dose caused an increase in the serum insulin level in animals receiving phentolamine, indicating that effective alpha-receptor blockade had unmasked the beta-receptor stimulating effect of epinephrine.

As a group, these baboons are clearly stressed, as evidenced by the elevated mean base-line catecholamine excretion measured in other similarly prepared animals in our own laboratory (8).

Standard statistical methods were used (9). Correlation was determined by a least squares analysis; the coefficient of variation was defined as the standard deviation divided by the mean, expressed as a percentage.

Results

The serum glucose and insulin values prior to and during phentolamine administration are shown in Fig. 1. No increase in the serum insulin

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[1] The opinions or assertions contained herein are the private ones of the authors and are not to be construed as official or reflecting the views of the Navy Department or the Naval service at large. The experiments reported herein were conducted according to the principles enunciated in "Guide for Laboratory Animal Facilities and Care."

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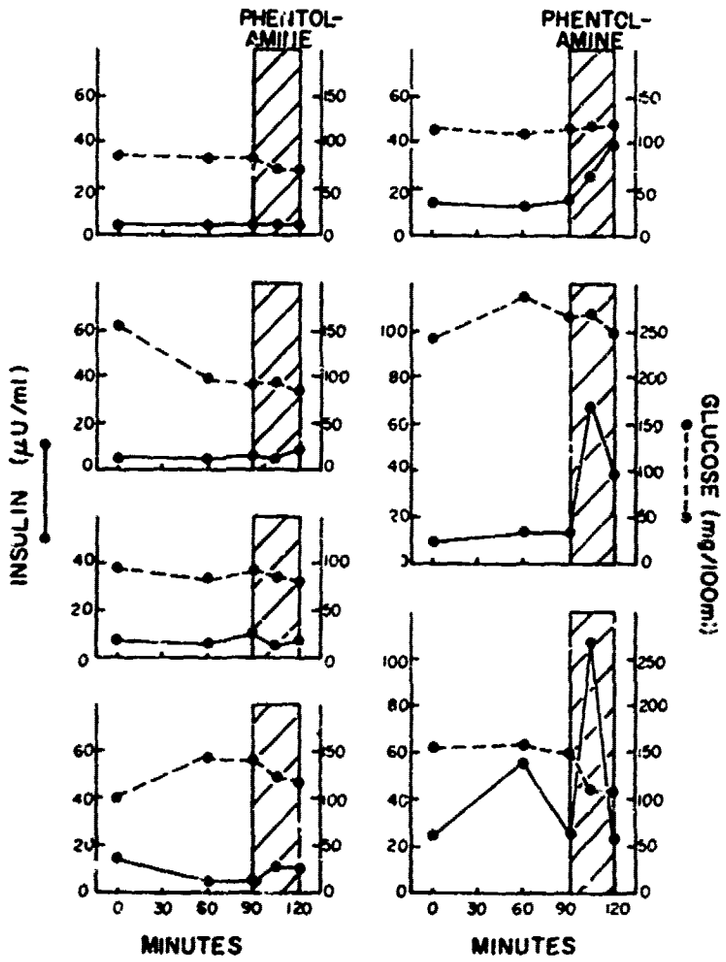

FIG. 1. Serum glucose (interrupted lines) and insulin (solid lines) concentrations in 7 unanesthetized baboons prior to and during phentolamine-induced alpha-adrenergic receptor blockade.

concentration occurred during phentolamine infusion in the 3 baboons with serum glucose values of 84–92 mg/100 ml immediately prior to phentolamine, whereas increments ranging from 6 to 83 μU/ml in the serum insulin concentration occurred during phentolamine infusion in the 4 animals with serum glucose values 114–266 mg/100 ml immediately before phentolamine. Furthermore, in the 7 animals the per cent increase in serum insulin concentration during phentolamine infusion was significantly correlated with the serum glucose concentration immediately prior to phentolamine ($r = 0.879$; $p < .01$).

Discussion

Despite the occurrence of an augmented serum insulin response to a glucose load during phentolamine infusion in man (5, 6), basal insulin levels do not rise during alpha-adrenergic receptor blockade (4–6). These observations suggest that, while sympathetic inhibition of insulin secretion may modulate the insulin secretory response to a glucose load, it does not tonically limit insulin secretion in the basal state. In contrast, the development of hyperinsulinemia during alpha-adrenergic receptor blockade has been observed in fasting rats (1), dogs (2) and baboons (3). It is implicit in the latter reports that insulin release in these experimental animals is a function of alpha-adrenergic receptor blockade *per se*, a mechanism inconsistent with the cited findings in man.

In the present study, insulin secretion during phentolamine-induced alpha-adrenergic receptor blockade in fasting baboons was a function of the serum glucose concentration at the time of initiation of phentolamine. The serum insulin concentration did not increase during phentolamine infusion in 3 baboons with serum glucose

concentrations of less than 100 mg/100 ml, whereas increments in the serum insulin concentration (ranging from 120 to 500%) occurred in 4 baboons with serum glucose concentrations of greater than 100 mg/100 ml (Fig. 1). Furthermore, in the 7 animals studied, the per cent increase in the serum insulin concentration during alpha-adrenergic receptor blockade was significantly correlated ($p < .01$) with the serum glucose concentration at the initiation of phentolamine infusion. Thus, alpha-adrenergic receptor blockade permitted the insulin response appropriate to the glycemic stimulus but did not trigger insulin release in the absence of a glycemic stimulus. As a corollary, the relative hypoinsulinemia and hyperglycemia in some baboons prior to phentoalmine may have been due to stress-initiated sympathetic activation, which thus set the scene for glucose-stimulated insulin secretion with the induction of alpha-adrenergic receptor blockade.

In conclusion, insulin secretion during alpha-adrenergic receptor blockade in our animals, as in man, occurred only in the presence of an appropriate glycemic stimulus to insulin secretion.

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