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# Glucoregulation of Prolactin Secretion*

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## Abstract

In order to assess the influence of glucose on prolactin secretion and differences in prolactin responses between diabetic and normal subjects, we studied a total of 18 normal and 13 stable insulin-dependent diabetic subjects. All were males and within 10% of ideal body weight. Seven of the normal subjects underwent standard insulin-induced hypoglycemia, with a significant ($P < 0.01$) prolactin response to this stimulus. Six each of the normal and diabetic groups underwent five-hour oral glucose tolerance tests. No change in prolactin levels was noted in the diabetic group, but the normal group had a suppression in prolactin levels significantly below baseline ($P < 0.001$) and significantly different from the diabetic group ($P < 0.01$). Seven of the normal and eight of the diabetic group received L-Dopa, 500 mg orally, with a resultant significant suppression of prolactin in each group ($P < 0.01$), while no difference was noted between the groups. These results suggest that hypoglycemia stimulates prolactin release and hyperglycemia inhibits prolactin release in normal subjects, while the latter response is absent in the diabetic. L-Dopa-induced suppression obtained in both the normal

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**and diabetic group, suggests that this presumed hypothalamic derived prolactin suppressing mechanism is intact in the diabetic. Possible mechanisms for the absent glucose suppression of prolactin in diabetics are discussed.**

The effects of gestation and suckling on prolactin secretion, as well as the lactogenic properties of prolactin, are well established in the human.[1,2] In addition, an osmoregulatory function of prolactin exists in lower animals,[3] and recent reports have suggested that changes in plasma osmolarity modulate prolactin secretion in man,[4] and prolactin has been shown to alter water and electrolyte metabolism in man.[5] A glucoregulatory function for prolactin has not been explored, and the effect of glucose on prolactin secretion is not clear. Furthermore, the dynamics of prolactin secretion in diabetics has not been investigated. It is the purpose of this communication to report a series of studies designed to assess the effect of glucose on prolactin secretion and to compare prolactin responses in normal and diabetic subjects.

## Materials and Methods

A total of 18 normal subjects, ages 24-35, without family history of diabetes, and a total of 13 stable insulin-dependent diabetics, ages 24-40, were studied during the course of these investigations over a 12-month period. All subjects were males and within 10% of ideal body weight. All studies were performed after an overnight fast, and blood samples were obtained through indwelling needles kept patent by a slow infusion of normal saline. Informed consent was obtained from all subjects prior to participation in the studies.

Seven of the normal subjects underwent standard insulin tolerance tests with 0.1 u/kg regular insulin administered intravenously (I.V.) at time O, and blood samples were drawn at 0, 15, 30, 60, 90, and 120 min. Six of the normal subjects had oral glucose tolerance tests with 100 g glucose at time O, and blood samples were obtained at 0, 30, 60, 120, 180, 240, and 300 min. Seven of the normal subjects received 500 mg L-Dopa orally at time O, with blood samples at 0, 30, 60, 90, 120, and 150 min.

Six of the diabetic subjects underwent oral glucose tolerance tests, and eight received oral L-Dopa as described above. The diabetics withheld their morning insulin dose on the day of study.

All blood samples were centrifuged and frozen for determination of prolactin levels by radioimmunoassay and glucose determination by Beckman autoanalyzer. Prolactin was assayed by the method of Sinha et al.[6] and the normal fasting prolactin level in our laboratory is $< 30$ ng/ml. Data were analyzed by the appropriate Student's $t$ test for paired and unpaired observations.

## Results

**Insulin-Induced Hypoglycemia.** All seven subjects had symptomatic hypoglycemia approximately 30 min after insulin injection, with a plasma glucose nadir of 21.6 $\pm$ 2.5 mg/dl (mean $\pm$ SEM). A peak prolactin response of 99 $\pm$ 20 ng/ml (mean $\pm$ SEM) occurred at 60 min, significantly ($P < 0.01$) above the baseline value of 24$\pm$3 ng/ml (mean $\pm$ SEM) (Fig. 1).

**Oral Glucose Tolerance.** The mean glucose levels during the tests in six normal and six diabetic subjects are depicted in Table 1. The mean prolactin level in the normal group was significantly suppressed at 30 ($P < 0.02$), 60, 120 ($P < 0.001$), and 180 min ($P < 0.02$), and the level was significantly above baseline at 300 min ($P < 0.05$) (Fig. 2). The mean prolactin values did not significantly change throughout the test in the diabetic group (Fig. 2). Significant differences between the groups are indicated in the figure.

**L-Dopa.** A significant suppression of prolactin levels occurred at 120 ($P < 0.05$) and 150 min ($P < 0.01$) in the normal group, while prolactin was significantly suppresed at 60 ($P < 0.01$), 90, 120 ($P < 0.001$), and 150 min. ($P < 0.01$) in the diabetic group (Fig. 3). No significant differences were noted between the groups.

## Discussion

The results of these studies suggest that variations in circulating glucose levels attenuate prolactin levels in a manner similar to growth hormone.[7,8] In this regard, a brisk prolactin response was obtained with insulin-induced hypoglycemia, as has been reported by Noel et al.[9] and in abstract form by Woolf and Lee.[10] Cohen and Gala,[11] and Mendelson et al.[12] report no prolactin response to insulin-induced hypoglycemia. The reason for these conflicting reports is unclear; however, differing degrees of hypoglycemia in the various groups of

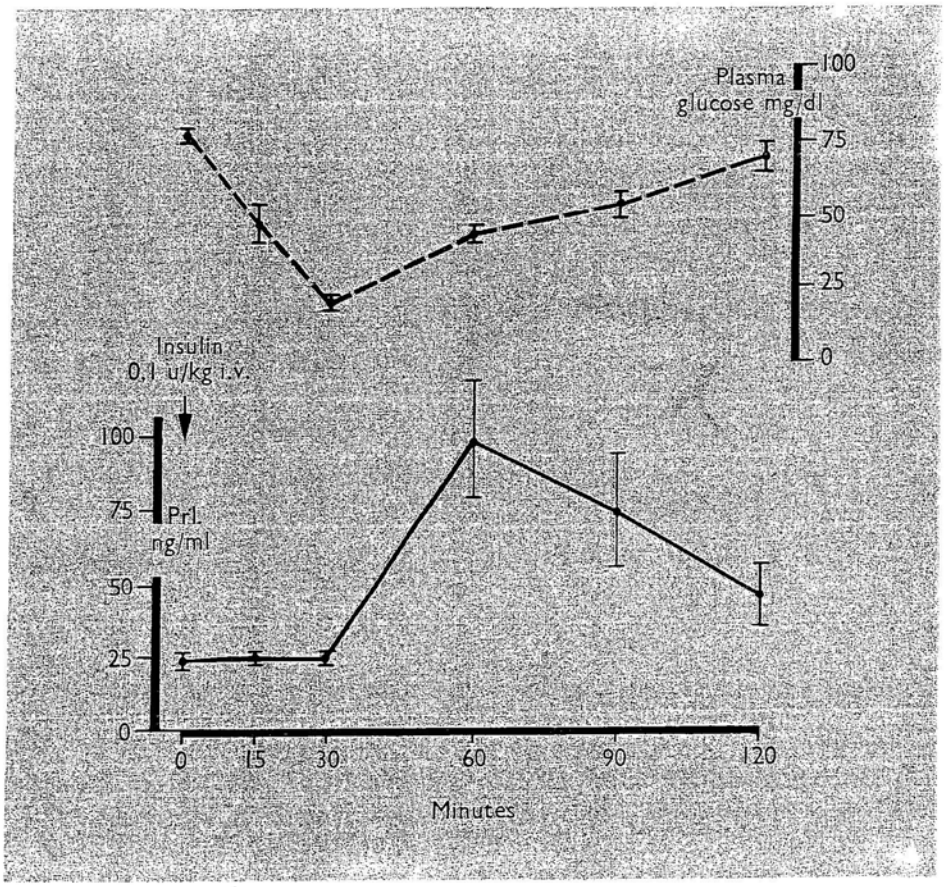


Fig. 1. The mean prolactin (lower panel, solid line) and glucose (upper panel, dashed line) response to intravenous (I.V.) insulin 0.1 u/kg in seven normal subjects. Vertical bars indicate standard error of the mean; Prl., prolactin.

subjects might account for the variability of response. Wilson et al.[13] have reported a differential prolactin response to intravenous bolus injection of insulin and infusion of insulin, wherein the former elicited a greater decrement in plasma glucose and a significant prolactin response which was absent with insulin infusion. It would seem, therefore, that stress is the key factor rather than the fall in circulating glucose.[9] The mediation of prolactin release during hypoglycemia is unknown, and the data reported herein offer no clue; however, previous reports suggest a thyrotropin stimulating hormone (TSH) response to hypoglycemia under certain circumstances[14] in man, and a similar response in the rat is apparently mediated by thyrotropin-releasing hormone (TRH)[15] a known stimulus to prolactin release.

Table I: Plasma Glucose Concentrations (Mean ± SEM) in Normal and Diabetic Subjects during Five-Hour Glucose Tolerance Tests

| | Minutes | | | | | | |
|---|---|---|---|---|---|---|---|
| Subjects | 0 | 30 | 60 | 120 | 180 | 240 | 300 |
| Diabetic | 139±33 | 204±34 | 275±38 | 344±40 | 345±54 | 317±49 | 263±58 |
| Normal | 58±2 | 125±5 | 120±18 | 104±9 | 82±9 | 66±7 | 73±4 |

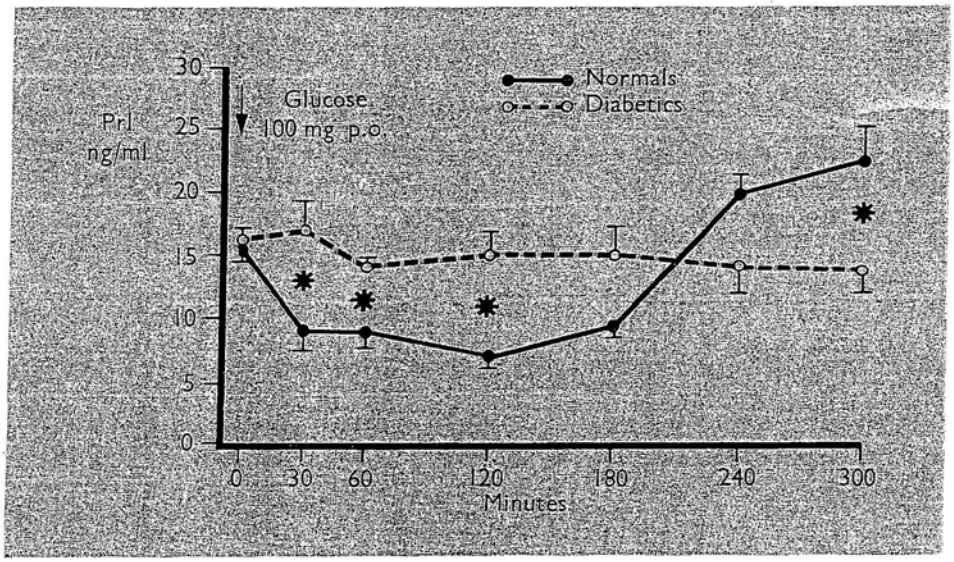


Fig. 2. The mean prolactin response to oral glucose in six diabetic and six normal subjects. Vertical bars indicate standard error of the mean. Asterisks indicate significant differences between the groups ($P < 0.01$); Prl., prolactin.

Of considerable interest is the prolactin suppression in response to oral glucose in normal subjects which was absent in diabetics. The normal group, furthermore, had a significant rise in prolactin levels at the fifth hour, possibly owing to the falling plasma glucose levels, as is noted with the growth hormone response to oral glucose,[8] although, as noted above, it appears that prolactin responds only to decrements in plasma glucose associated with stress. The inverse relationship between circulating glucose and prolactin levels would be consistent with a glucoregulatory role for this hormone; however, no such properties have been ascribed to prolactin. In this regard, Berle et al.[16] reported that human prolactin is lipolytic, with no discernible difference in its effect in comparison to growth hormone, and

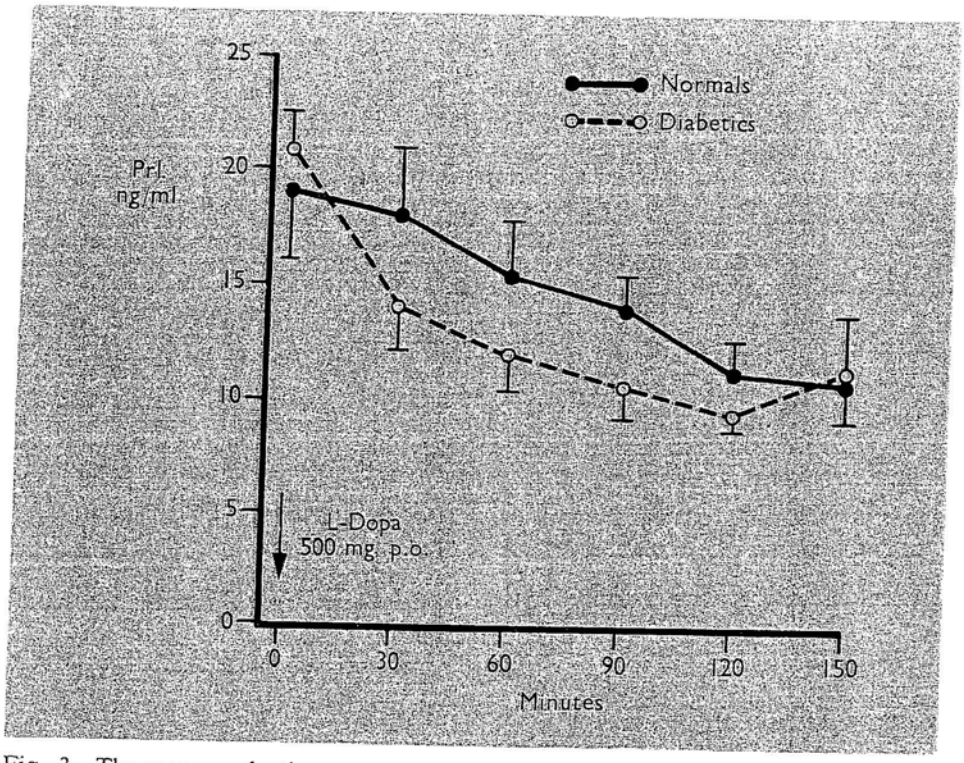


Fig. 3. The mean prolactin response to oral L-Dopa in six diabetic and eight normal subjects. Vertical bars indicate standard error of the mean; Prl., prolactin.

furthermore, these investigators suggested that the common somatotrophic loci of these two peptide hormones exert this effect, rather than the lactotrophic loci. Thus, it is conceivable that prolactin affects carbohydrate metabolism, as does growth hormone. The lack of suppression following oral glucose in the diabetics might be due to a cancelling effect of the greater increase in serum osmolarity in this group in comparison to the normal subjects, as increases in serum osmolarity have been reported to stimulate prolactin release.[4] A more likely explanation would be a relative insensitivity to glucose at the hypothalamic-pituitary level in the diabetics, as appears to be operative with growth hormone, wherein hyperglycemia fails to inhibit growth hormone responsiveness in diabetics in contrast to normal individuals.[17,18] Clearly, a role of insulin in permitting this central effect of glucose might well explain the observed differences between normal and diabetic subjects.

The indistinguishable responses to L-Dopa in diabetic and normal

subjects indicate that prolactin is suppressible in diabetics via an established dopaminergic hypothalamic mechanism, presumably via prolactin inhibitory factor.[19] Thus, a deficiency at some level of this pathway in the diabetic is unlikely.

These data suggest that circulating glucose levels might be operative in the attenuation of prolactin secretion and, furthermore, that diabetic subjects differ in terms of prolactin responsiveness to glucose. Further studies on the role of prolactin in intermediary carbohydrate metabolism, as well as confirmation of our data, are necessary to establish this concept.

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