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Growth Hormone Response to Oral Glucose in Stable and Hypoglycemia-Prone Diabetics (38777)

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The diabetogenic potential of growth hormone has been well recognized since the classical studies of Houssay (1). Reports concerned with the measurement of circulating growth hormone levels and responses to provocative testing such as exercise (2) and arginine (3, 4) in diabetics have yielded seemingly conflicting results and could reflect the differences in patient population selection in these studies. We have, therefore, elected to study patterns of growth hormone response in clinically defined subgroups of diabetic patients. It is the purpose of this communication to report the growth hormone response to oral glucose in five hypoglycemia-prone, insulin-dependent diabetics in comparison to stable insulin-dependent diabetics and normal subjects.

Materials and Methods. The hypoglycemia-prone group consisted of five male, nonobese, insulin-dependent diabetics, with an age range of 33–73. The group was characterized by marked sensitivity to adjustments in their intermediate insulin dosages wherein two dosage regimens differing as little as 3–6 units/day resulted in extremes of poor control (fasting glucose > 300 mg/100 ml, 3–4 + glucosuria) or frequent hypoglycemic reactions, both early AM and during the course of the day. These observations were made while patients consumed an isocaloric American Diabetes Association type diet including mid-AM and mid-PM feedings. The amount of daily exercise was constant throughout the period of observation, which was during hospitalization on the Medical Service wards of the Wood Veterans Administration Hospital.

The stable group consisted of six male, nonobese, insulin-dependent diabetics, age and weight matched to the hypoglycemia-prone group. The stable patients had no history of ketoacidosis or hypoglycemic reactions unattended by increased exercise or decreased caloric intake. Fasting plasma glucose in this group was < 150 mg/100 ml.

Lastly, seven normal male subjects, aged 25–35, within 10% of ideal body weight were studied in a parallel fashion as controls.

All studies were performed at the Wood Veterans Administration Hospital between 7:00 and 8:00 AM after an overnight fast, and diabetic subjects withheld their AM insulin dose. All subjects had standard 100 g, 5-hr oral glucose tolerance tests with blood samples obtained at −15, 0, 30, 60, 120, 180, 240, and 300 min. Blood was obtained via a 19-gauge butterfly needle inserted in an antecubital vein through which a slow infusion of normal saline was administered. Samples were centrifuged and sera frozen until assay. Growth hormone was measured by a modified solid-phase radioimmunoassay (5) and glucose by Beckman autoanalyzer. Data were analyzed by the appropriate Student *t* test for paired and unpaired observations.

Results. Five representative days of observation with decremental insulin doses in two of the hypoglycemia-prone diabetics are depicted graphically in Figs. 1 and 2 wherein frequent hypoglycemic reactions, both at the time of arising in the morning and at other times during the day, were noted. With decreases in daily intermediate insulin dosage in both patients, periods of poor control ensued with marked glucosuria and fasting glucose levels in excess of 300 mg/100 ml. Similar observations were made in the remaining three members of the group.

The mean plasma glucose levels during glucose tolerance testing in the hypoglycemia-prone group were higher than the stable diabetic group, but the difference was not significant. The pattern of the curves, however, was identical. The glucose levels in the normal subjects were well within the normal range (Table I).

The growth hormone response to oral

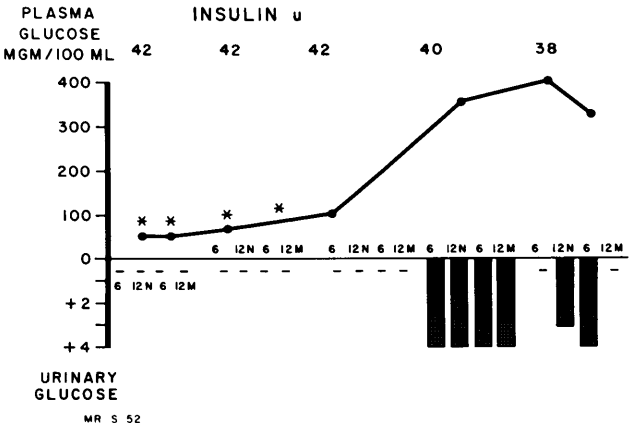

FIG. 1. Representative days (not successive) of observation with decremental insulin dosages indicating plasma glucose levels (solid line) obtained routinely and at times of hypoglycemia (asterisks). Vertical bars indicate glucosuria.

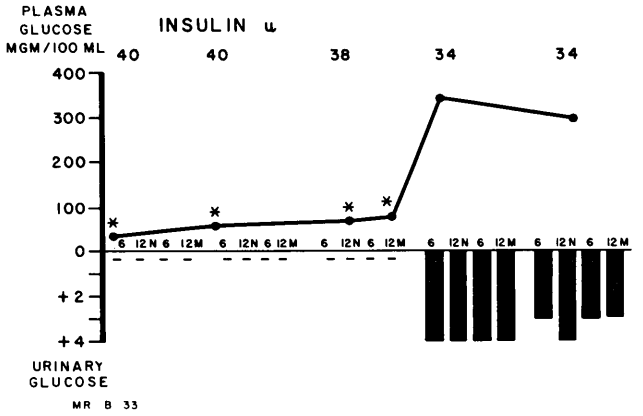

FIG. 2. Same as Fig. 1.

glucose was similar in the stable diabetic and normal groups with no significant differences except the fasting level (Fig. 3). The fasting level of 8.1 ± 2.1 μg/ml (mean ± SEM) in the stable group was significantly higher ($P < 0.01$) than observed in the normal subjects, 1.2 ± 0.3 μg/ml (mean ± SEM). Significant growth hormone suppression was noted in the diabetic group during the first 3 hr after ingestion of the glucose load. Failure to note suppression in the control group was probably related to low basal levels close to the lower limits of sensitivity of our growth hormone assay. The 4- and 5-hr growth hormone levels rose significantly above fasting levels ($P < 0.02$) in both groups. In sharp contrast was the absence of any growth hormone rise in the hypoglycemia-prone group of insulin-dependent diabetics. Mean growth hormone values at 4 and 5 hr were significantly below ($P < 0.05$) the corresponding values in normal control subjects and in stable diabetic patients (Fig. 4).

Discussion. The growth hormone response to oral glucose in our stable diabetic group closely paralleled the response in normals. Two exceptions were noted, namely, the fasting level and the timing of the peak response. The mean fasting level in the con-

TABLE I. PLASMA GLUCOSE LEVELS DURING ORAL GLUCOSE TOLERANCE TESTING MG/100 ML (MEAN ± SEM).

	0 (min)	30 (min)	60 (min)	120 (min)	180 (min)	240 (min)	300 (min)
Hypoglycemia-prone diabetics	223 ± 53	235 ± 59	326 ± 60	403 ± 66	450 ± 63	422 ± 52	405 ± 53
Stable diabetics	138 ± 38	193 ± 38	261 ± 39	325 ± 39	329 ± 39	296 ± 36	244 ± 51
Normals	61 ± 2	125 ± 7	118 ± 15	105 ± 8	81 ± 8	64 ± 6	71 ± 3

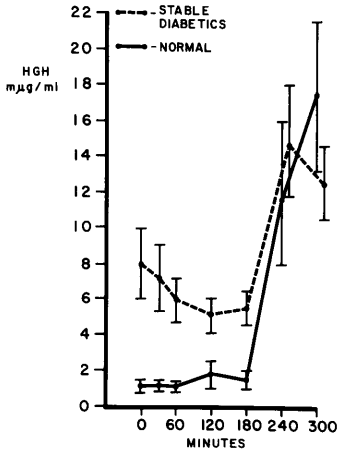

FIG. 3. Growth hormone response to 100 g oral glucose administered at time 0 in normal subjects (solid line) and stable diabetics (dashed line). Vertical bars indicate SEM.

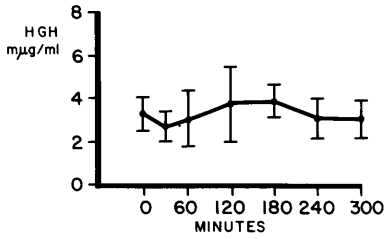

FIG. 4. Growth hormone response to 100 g oral glucose administered at time 0 in hypoglycemia-prone diabetics. Vertical bars indicate SEM.

trol group was lower than the stable diabetic group; however, growth hormone levels were suppressed to within the normal range at the second and third hour in our subjects, as is noted in normals (6). The earliest peak in growth hormone response to oral glucose in our stable diabetic group, which occurred at the fourth hour with a fall in the fifth hour, might indicate a decreased growth hormone secretory reserve, or alternatively, an essentially normal pattern occurring 1 hr closer to the time of glucose ingestion. Yde has reported an earlier peak growth hormone in response to oral glucose occurring at 2-½ hr (7), and Baird *et al.* reported multiple peaks in growth hormone secretion over a 6-hr period after glucose ingestion (8); however, both of these studies involved newly diagnosed, untreated diabetics who subsequently required insulin therapy. Our data would suggest that the growth hormone response to oral glucose is essentially normal in established, well-controlled insulin-dependent diabetics. The data of Hansen, where a given exercise challenge resulted in growth hormone secretion in insulin-dependent diabetics but failed to elicit such a response after improvement in blood glucose control, would lend support to this hypothesis (2, 9).

Our five hypoglycemia-prone diabetics represent a very unusual subpopulation of insulin-dependent diabetics manifesting an extreme sensitivity to minor alterations in insulin dosage with resultant swings from poor control to frequent hypoglycemic reactions. Their growth hormone response to oral glucose is of considerable interest, in that no significant change occurred during the 5-hr testing period. It could be argued that a 6- or 7-hr determination may have yielded a significant response; however, the glucose curve was identical to the stable diabetic group in terms of the time of peak and subsequent descent. This terminal descent in the glucose level during the glucose tolerance test successfully elicited a growth hormone response in the normal and stable diabetic groups reported herein. Falling blood glucose levels induced by insulin infusion are well known to be associated with growth hormone secretion in normals (10) and diabetics (11). Furthermore, decreasing blood glucose levels far above symptomatic hypo-

glycemic levels elicit growth hormone responses in diabetics, particularly during the treatment of ketoacidosis (12, 13). The underlying reasons for the absence of a growth hormone response following oral glucose in these unique diabetics are unclear.

We feel that the data reported herein suggest that a variety of secretory patterns exist in diabetic patients with regard to growth hormone. The confusion about the role of growth hormone in diabetes or, conversely, the effect of diabetes upon growth hormone secretion may be lessened by careful attention to the clinical status of the diabetic patients. Additional reports of clinically defined diabetics with growth hormone hyperresponsiveness are limited; however, Hagen *et al.* have reported heightened growth hormone responses to arginine infusion in a ketosis-prone group (14).

Summary. The growth hormone response during standard 5-hr oral glucose tolerance tests was studied in three groups: normals, hypoglycemia-prone diabetics, and an age–weight-matched stable diabetic group. The stable diabetic and normal groups had significant ($P < 0.02$) growth hormone responses at the 4-hr and 5-hr determinations during the tests, while the hypoglycemia-prone diabetic group failed to respond. The 4-hr and 5-hr growth hormone levels in this group were significantly ($P < 0.05$) below the levels in the stable diabetics and normals. These data suggest that growth hormone responses differ in subgroups within the diabetic population.

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