Effect of Growth Hormone Deficiency on Glucagon Secretion (37466)

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Hypoinsulinism is a well-recognized accompaniment of growth hormone deficiency (1–3). With the recent availability of sensitive and specific assays for determination of plasma glucagon, the effect of growth hormone deficiency on glucagon secretion can now also be assessed. In this report, four growth hormone deficient subjects were studied to determine the arginine-induced glucagon response before and after 5 days of HGH administration. Three of these subjects had panhypopituitarism and were receiving replacement therapy with cortisone and thyroid and the fourth subject had isolated growth hormone deficiency.

Materials and Methods. All four subjects were males between the ages of 12 and 40. Two teenage subjects (both age 16) had had curative surgery for a craniopharyngioma at least 5 yr previously while a third subject (age 40) had a chromophobe adenoma which had not been treated at the time of study. The fourth subject (age 12 yr) had isolated growth hormone deficiency. The three subjects with pituitary tumors were taking cortisone and thyroid replacement therapy. All four subjects demonstrated plasma human growth hormone (HGH) concentrations less than 1.5 ng/ml (range 0–1.4 ng/ml) after either insulin or arginine. All were well below the third percentile in height for their ages except for the 40 year old subject with a chromophobe adenoma.

Arginine infusion tests were administered to the four subjects prior to growth hormone therapy and again after five daily injections of 10 units HGH. After an overnight fast two base line blood samples were obtained followed by an infusion of 10% arginine (0.5 g/kg) over 30 min. Additional blood specimens were obtained every 15 min for 90 min following the commencement of arginine administration. Blood samples were placed in heparinized tubes or in tubes specially prepared for glucagon preservation containing 1.2 mg Na_2 EDTA and 500 units Trasylol/ml of blood to be collected.

Blood glucose, plasma immunoreactive insulin (IRI), HGH, and immunoreactive glucagon (IRG) were determined on all specimens. Blood glucose was measured by the glucose oxidase method (4). Plasma IRI was determined by a double antibody radioimmunoassay method utilizing ^{125}I as tracer (5). Plasma HGH was determined by a modification of the double antibody radioimmunoassay method of Schalch and Parker (6) utilizing ^{125}I labeled hormone. Tracer and standards were prepared from highly purified human growth hormone supplied to us by Dr. A. E. Wilhelmi. Plasma glucagon was assayed by the radioimmunoassay method described by Aguilar-Parada, Eisentraut and Unger (7) using their pancreatic specific antibody 30-K.

HGH (lot C-13) was supplied to us for use in this study by the National Pituitary Agency of the University of Maryland, and the National Institute of Arthritis, Metabolism, and Digestive Diseases.

Results. Figure 1 shows the arginine-induced glucagon responses in normal subjects and in the four growth hormone deficient subjects studied. No significant difference was noted in the glucagon response of HGH deficient subjects compared to that of normals. The arginine-induced glucagon response appeared slightly less after HGH treatment, but the differences were not significant. The base line plasma IRG concentrations in the

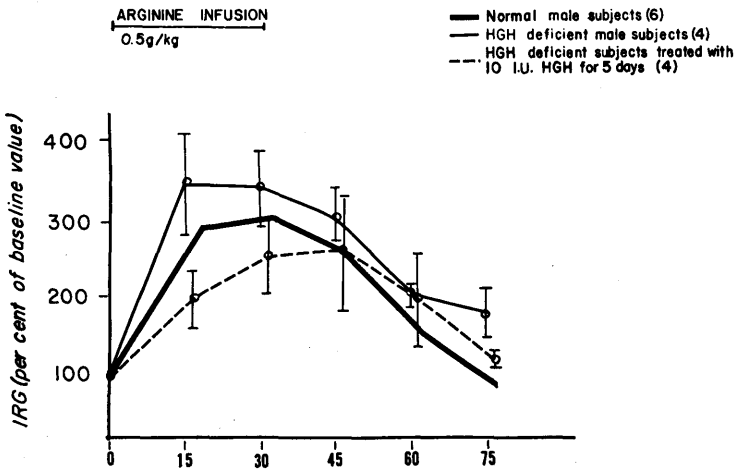

FIG. 1. Effect of HGH deficiency on plasma glucagon response to arginine. Means ± SEM shown. Base line plasma IRG concentrations in the HGH deficient subjects were 250 ± 163 pg/ml prior to HGH treatment and 235 ± 63 pg/ml after HGH treatment. Base line IRG values in normal subjects were 193 ± 46 pg/ml. Number of observations in parentheses.

HGH deficient subjects were 250 ± 163 pg/ml prior to HGH treatment and 235 ± 63 pg/ml after HGH treatment. The base line IRG values in the normal subjects were 193 ± 46 pg/ml.

The expected increase in blood glucose and improved insulin response to arginine were observed following 5 days of HGH administration to the growth hormone deficient subjects (Fig. 2).

Plasma HGH levels prior to treatment were less than 1.5 ng/ml (range 0–1.4 ng/ml) at all times during arginine testing. After 5 days of HGH treatment, mean fasting plasma HGH in the treated hypopituitary patients was 8.1 ± 1.5.

Discussion. Several studies have indicated an impaired insulin response to glucose in growth hormone deficient subjects (1–3). In addition Merimee and Fineberg (8) have re-

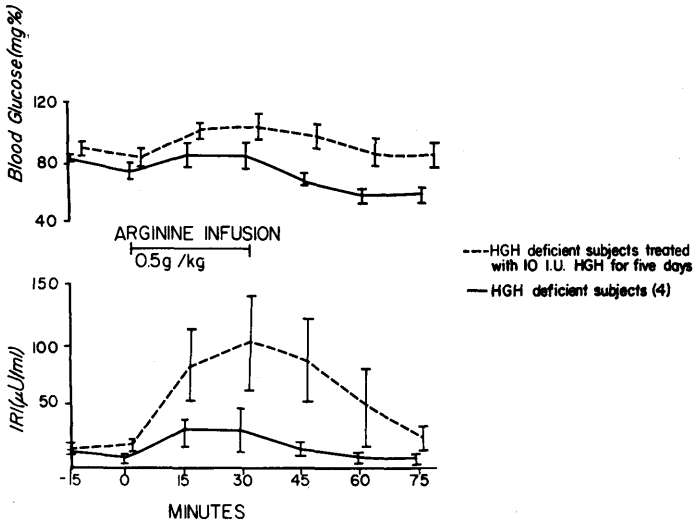

FIG. 2. Blood glucose and plasma IRI response to arginine in HGH deficient subjects before and after HGH treatment. Means ± SEM shown.

ported diminished insulin responsiveness to amino acids in growth hormone deficient states. Our results confirm this latter finding.

Although abundant reports on plasma insulin in growth hormone deficient states are available, assessment of the effect of growth hormone deficiency on plasma glucagon has not been systematically studied. The present studies indicate that growth hormone deficiency does not cause an impaired glucagon response to an amino acid infusion. In addition, the administration of growth hormone to HGH deficient patients does not increase glucagon secretion. These findings are in contrast to those of Lawrence (9) who observed enhanced glucagon responses in acromegalic subjects and impaired, virtually flat glucagon responses in acromegalic subjects. The glucagon secretory response after growth hormone supplementation was not tested in these latter subjects. The depressed glucagon response to arginine in their hypopituitary subjects may have been due to a deficiency other than growth hormone as no statement was made concerning replacement therapy for these patients.

The possibility that our radioimmunoassay might be nonspecific and measure some substance other than pancreatic glucagon is unlikely on the basis of Dr. Unger's prior experience with the antibody. In addition, negligible plasma glucagon levels after an arginine infusion were observed by us in a totally pancreatectomized patient using this antibody.

The preservation of the early hyperglycemic response in states of growth hormone deficiency support our findings of a normal glucagon response in these subjects. The early hyperglycemic response to arginine is thought to be due to glucagon-induced glycogenolysis since conversion of labeled amino acids to glucose does not occur until after 30 min (10).

Our observations on the failure of HGH to enhance glucagon secretion in man are in agreement with studies in dogs reported by Farmer and co-workers (11). These findings in no way exclude a stimulatory effect of acromegaly on glucagon secretion. Pancreatic hypertrophy (similar to hypertrophy of other organs in this condition) as a result of chronically elevated growth hormone levels might result in enhanced glucagon responses and indeed some histologic evidence exists for this (12). On the other hand, our findings would deny a role of glucagon deficiency in the fasting hypoglycemia observed in growth hormone deficient subjects.

Conclusions. Growth hormone deficiency does not result in impaired glucagon responses to arginine nor does HGH administration to HGH deficient subjects enhance their glucagon response to this stimulus. The insulinopenic response to arginine of HGH deficient subjects is confirmed.

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