Effect of Glucose on the Growth Hormone Response to L-dopa in Normal and Diabetic Subjects

Kamel Ajlouni, M.D., Donald R. Martinson, M.S., and Thad C. Hagen, M.D., Milwaukee

SUMMARY

The effect of hyperglycemia on the growth hormone response to oral L-dopa (500 mg.) was assessed in eight normal and eight insulin-dependent diabetic subjects. A peak growth hormone response of 21.0 ± 4.0 ng./ml. (mean ± S.E.M.), significantly above baseline ($p < 0.01$), was achieved in the normal group following oral L-dopa. Glucose concentrations did not change and were approximately 80 mg./100 ml. throughout. Administration of 100 gm. oral glucose with the L-dopa, or thirty minutes thereafter, totally suppressed the growth hormone response in all eight and six of the subjects, respectively.

A peak growth hormone response of 20.0 ± 1.7 ng./ml. (mean ± S.E.M.), significantly above baseline ($p < 0.001$), was obtained in eight nonobese, insulin-dependent diabetics, in spite of prevailing hyperglycemia (mean plasma glucose 243-258 mg./100 ml.) throughout the test. Endogenous hyperglycemia was achieved in these patients by lessening the usual strict adherence to plasma glucose control for the purpose of the study.

These results suggest an abnormality in the hypothalamus or pituitary of diabetic subjects allowing growth hormone responsiveness in spite of hyperglycemia. DIABETES *24* :633-36, July, 1975.

The growth-hormone-releasing effect of the catecholamine precursor L-3, 4-dihydroxyphenylalanine (L-dopa) has been well established by recent investigations.[1-3] The potential of glucose in attenuating this effect in normals is unclear, and studies to date have yielded conflicting results,[4-6] as have been noted in studies of the effect of glucose on arginine-induced growth hormone release.[7,8] Furthermore, the utility of L-dopa as a provocative agent in the measurement of growth hormone reserve in diabetics is not established, and studies in this regard are limited.[4] We have studied the growth hormone response to L-dopa in a group of insulin-dependent diabetics and in a normal group that was rechallenged with L-dopa while hyperglycemic. It is the purpose of this communication to report the results of these studies.

Presented at the Midwest Section, American Federation for Clinical Research, Chicago, Illinois, October 1974 (Clin. Res. 21:616, 1974/Abstr.)

From the Department of Medicine, Wood Veterans Administration Center and the Medical College of Wisconsin, Milwaukee, Wisconsin.

Accepted for publication March 17, 1975.

MATERIALS AND METHODS

Eight normal male subjects, ages 24 to 32, within 10 per cent of ideal body weight and without family history of diabetes,were studied on an outpatient basis following an overnight fast. Studies were performed with subjects at bed rest, and blood samples were obtained through an indwelling needle in an antecubital vein that was kept patent with normal saline. Following needle insertion, subjects rested thirty minutes before zero-time samples were obtained. Following this sample, 500 mg. of L-dopa was administered orally and samples were obtained at thirty-minute intervals for three hours. All of the subjects underwent identical testing with the addition of a 100-gm. oral glucose dose at time zero. Six of these subjects were studied with the L-dopa dose given at zero time and the oral glucose at thirty minutes. For all studies incorporating oral glucose, subjects had received high-carbohydrate preparatory diets. Eight male, insulin-dependent diabetics, ages 24 to 40, within 10 per cent of ideal body weight, were also studied. This group was well controlled (fasting plasma glucose <150 mg./100 ml.) on single daily injections of intermediate-acting insulins, and, to the best of our knowledge, all subjects had no history of ketoacidosis or spontaneous hypoglycemic reactions unattended by caloric deprivation or exercise. For the purpose of this study, the subjects underwent a three- to-five-day period of decreased daily insulin dose to induce moderate endogenous fasting hyperglycemia (150-300 mg./100 ml.). When this was achieved, the subjects received 500 mg. of L-dopa orally following an overnight fast and with omission of the morning insulin

dose. Samples were obtained in the manner described above at zero time and at thirty-minute intervals following the administration of L-dopa. Informed consent was obtained from all participating subjects.

At each time interval, serum was obtained for growth hormone determinations by a modified solid-phase radioimmunoassay,[9] and plasma was obtained for glucose determination by the glucose oxidase method in an AutoAnalyzer.

Data were analyzed statistically using the Student's *t* test for paired observations.

RESULTS

The administration of L-dopa orally resulted in a peak growth hormone release of 21.0 ± 4.0 ng./ml. (mean ± S.E.M.), significantly ($p < 0.01$) above the baseline level of 1.5 ± 0.3 (mean ± S.E.M.), in the eight normal subjects (figure 1). Plasma glucose levels did not change during the test but remained at approximately 80 mg./100 ml. throughout.

The administration of oral glucose suppressed totally the growth hormone response to L-dopa whether given simultaneously or thirty minutes after the L-dopa dose (figure 1). Glucose levels during these studies were well within the normal limits of oral glucose tolerance (table 1).

The eight stable diabetic subjects achieved a significant ($p < 0.001$) growth hormone response of 20.0 ± 1.7 ng./ml. (mean ± S.E.M.) at sixty minutes in spite of hyperglycemia throughout the test (figure 2). Glucose levels were between 243 and 258 mg./100 ml. (mean values).

All of the normal subjects noted mild nausea, without vomiting, during L-dopa testing, which interestingly did not occur during testing with combined oral glucose and L-dopa. None of the diabetic subjects complained of nausea.

DISCUSSION

The data reported herein confirm previous observations indicating the utility of L-dopa as a provocative testing agent for pituitary growth hormone reserve.[1-3]

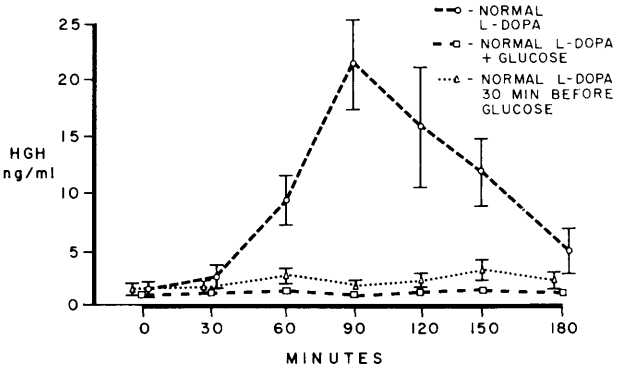

FIG. 1. Growth hormone response to 500 mg. L-dopa p.o. in eight normal subjects (open circles), during simultaneous glucose administration (100 gm. p.o.) in the same group (open squares), and with glucose administered thirty minutes after L-dopa in six of the subjects (open triangles). (Vertical bars indicate standard error.)

The mean growth hormone increment in our normal group was 19.5 ng./ml. at ninety minutes, and each individual had an increment greater than 10 ng./ml. In addition, the administration of oral glucose uniformly suppressed the growth hormone response in the normals regardless of the timing of the dose, i.e. with L-dopa or thirty minutes following the L-dopa dose. Mims et al. have reported a similar suppression

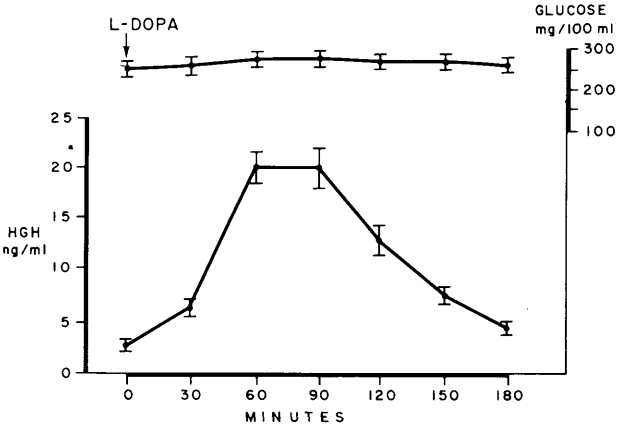

FIG. 2. Growth hormone response (lower panel) and glucose concentrations (upper panel) following 500 mg. L-dopa p.o. in eight hyperglycemic (see text) diabetics. (Vertical bars indicate standard error.)

TABLE 1

Plasma glucose concentrations (mean ± S.E.M.) in normal subjects during administration of oral glucose and L-dopa

Minutes	0	30	60	90	120	150	180
100 gm. oral glucose with L-dopa: 8 subjects	81 ± 2	112 ± 8	129 ± 7	110 ± 6	91 ± 5	83 ± 5	81 ± 3
100 gm. oral glucose 30′ after L-dopa: 6 subjects	79 ± 1	78 ± 3	103 ± 7	126 ± 8	107 ± 8	95 ± 5	85 ± 5

of the growth hormone response to L-dopa in normals during simultaneous intravenous glucose administration.[4] Of interest in their study was the prevailing glucose concentration of approximately 180 mg./100 ml. during the sixty- to-ninety-minute period following L-dopa administration. Previous reports have suggested that significant L-dopa concentrations are first achieved at sixty to ninety minutes after oral administration.[10] In the two sets of data herein reported with glucose and L-dopa, the maximal mean glucose levels achieved during the sixty- to-ninety-minute period were 126-129 mg./100 ml. Our data suggest that very minimal hyperglycemia inhibits growth hormone responsiveness to L-dopa in normals when comparing our maximal glucose levels to those of Mims et al. In contrast to our results, Boyd et al. reported no suppression of the growth hormone response to oral L-dopa in parkinsonians when glucose was administered orally thirty minutes after the L-dopa dose.[11] Their data suggested that oral glucose given thirty minutes after L-dopa failed to induce hyperglycemia at a time appropriate for attenuating the growth hormone response to L-dopa; however, in our study there was no difference in the suppressive effect of glucose when given simultaneous to or thirty minutes after L-dopa. It must be reiterated that the studies of Boyd et al. were conducted in parkinsonian subjects in whom L-dopa was a chronic form of therapy, making exact comparison between our study group and theirs virtually impossible.

The role of L-dopa as a provocative agent for growth hormone release in the diabetic has not been examined, with the exception of the aforementioned study by Mims et al., wherein five adult-onset diabetics failed to respond to oral L-dopa.[4] These five subjects were treated by diet, with the addition of sulfonylurea therapy in two of the five. We have studied eight nonobese, stable insulin-dependent diabetics and have clearly demonstrated the presence of a significant growth hormone response to L-dopa in spite of moderate endogenous hyperglycemia throughout the test. These results suggest that the sensitive glucoreceptor mechanisms within the normal hypothalamic-pituitary apparatus fail to function normally in insulin-dependent diabetics. The nature of this abnormality is as yet unclear; however, at least two possibilities seem likely. First, episodic hyperglycemia as is found in this type of diabetic might alter an otherwise normal glucoreceptor, allowing continued growth hormone response to L-dopa in spite of simultaneous hyperglycemia, as has also been reported with arginine infusion.[7] Similarly, in a previous study from our laboratory, stable insulin-dependent diabetics had a brisk growth hormone response during the terminal phase of standard five-hour oral glucose tolerance tests even though their plasma glucose levels were significantly above those of a normal control group.[12] The data of Mims et al. would additionally seem to favor this possibility as their early adult-onset diabetic group not requiring insulin therapy had suppressed growth hormone responses in the face of mild hyperglycemia. Second, one might consider the possibility that the genetic syndrome of diabetes mellitus is accompanied by abnormal glucoreceptors within the hypothalamus and/or pituitary. In support of this are the interesting data of Hansen, wherein optimally controlled insulin-dependent diabetics with near normal fasting plasma glucose levels had normal-appearing growth hormone responses to an exercise stimulus,[13] yet the same group had greater responses when studied during a period of poor control.[14] Thus, his group seemed to have heightened growth hormone responsiveness when hyperglycemic.

Inherent in both of the possibilities discussed above is the equal likelihood that prevailing insulin concentrations in the circulation might well be important in modulating the effect of glucose on the centers responsible for controlling growth hormone secretion. Accordingly, insulin-deficient subjects might lack a suppressive influence of glucose on growth hormone release. Exactly what mechanisms might underlie the intact growth hormone responsiveness in hyperglycemic diabetics remain to be elucidated; however, it seems quite clear that L-dopa is a valuable tool in assessing growth hormone reserve in diabetic subjects, even when poorly controlled.

ACKNOWLEDGMENT

The authors wish to thank the National Pituitary Agency and the National Institute of Arthritis and Metabolic Diseases for provision of human growth hormone for the radioimmunoassay.

REFERENCES

[1]Eddy, R.L., Jones, A.L., Chakmakjian, Z.H., and Silverthorne, M.C.: The effect of levodopa (L-dopa) on human hypophyseal trophic hormone release. J. Clin. Endocrinol. Metab. *33*:709-12, 1971.

[2]Kansal, P.C., Buse, J., Talbert, O.R., and Buse, M.G.: The effect of L-dopa on plasma growth hormone, insulin, and thyroxine. J. Clin. Endocrinol. Metab. *34*:99-105, 1972.

[3]Porter, B.A., Rosenfield, R.L., and Lawrence, A.M.: The levodopa test of growth hormone reserve in children. Am. J. Dis. Child. *126*:589-92, 1973.

[4]Mims, R.B., Scott, C.L., Modebe, O.M., and Bethune, J.E.: Prevention of L-dopa-induced growth hormone stimulation by hyperglycemia. J. Clin. Endocrinol. Metab. *37*:660-63, 1973.

[5]Boyd, A.E., Lebovitz, H.E., and Pfeiffer, J.B.: Stimulation of human growth hormone secretion by L-dopa. N. Engl. J. Med. *283*:1425-29, 1970.

[6]Johansen, K.: Glucose-suppressible growth hormone release after L-dopa administration to normal subjects. Metabolism *22*:773-78, 1973.

[7]Burday, S.Z., Fine, P.H., and Schalch, D.S.: Growth hormone secretion in response to arginine infusion in normal and diabetic subjects: relationship to blood glucose levels. J. Lab. Clin. Med. *71*:897-911, 1968.

[8]Rabinowitz, D., Merimee, T.J., Burgess, J.A., and Riggs, L.: Growth hormone and insulin release after arginine: indifference to hyperglycemia and epinephrine. J. Clin. Endocrinol. Metab. *26*:1170-72, 1966.

[9]Catt, K., and Tregear, G.W.: Solid-phase radioimmunoassay in antibody-coated tubes. Science *158*:1570-72, 1967.

[10]Tyce, G.M., Muenster, M.D., and Owen, C.A.: Dihydroxyphenylalanine (dopa) in plasma during dopa treatment of patients with Parkinson's disease. Mayo Clin. Proc. *45*:438-43, 1970.

[11]Boyd, A.E., Lebovitz, H.E., and Feldman, J.M.: Endocrine function and glucose metabolism in patients with Parkinson's disease and their alteration by L-dopa. J. Clin. Endocrinol. Metab. *33*:829-37, 1971.

[12]Hagen, T.C., and Ajlouni, K.: Growth hormone response to oral glucose in stable and hypoglycemia-prone diabetics. Proc. Soc. Exp. Biol. Med. *149*:223-26, 1975.

[13]Hansen, A.P.: Normalization of growth hormone hyperresponse to exercise in juvenile diabetics after "normalization" of blood sugar. J. Clin. Invest. *50*:1806-11, 1971.

[14]Hansen, A.P.: Abnormal serum growth hormone response to exercise in juvenile diabetics. J. Clin. Invest. *49*:1467-78, 1970.