Metabolic Clearance Rate of Growth Hormone in Juvenile Diabetes Mellitus

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SUMMARY

The metabolic clearance rate (MCR) of radio-labeled growth hormone (GH) was measured in eleven recently diagnosed patients with juvenile-onset diabetes mellitus and in seven healthy nonhospitalized healthy children. The patients with diabetes mellitus demonstrated a significant reduction in MCR of GH as compared to the contrast group. Peripheral GH levels did not reach steady state conditions in the patients with diabetes, thus pituitary production rates of GH could not be evaluated in these patients. It is suggested that diabetes mellitus, even in its earliest clinically apparent stages is associated with a defect in the metabolic clearance of GH. Since the liver has been demonstrated to be the major organ responsible for GH clearance in man, it is evident that diabetes mellitus may be associated with a defect in the hepatic clearance mechanisms for growth hormone. DIABETES *21*:175-77, March, 1972.

Although the diabetogenic effects of growth hormone (GH) in man have been clearly demonstrated, the role of this hormone in the pathogenesis and complications of human diabetes mellitus remains unclear. Plasma concentrations of GH have been extensively evaluated in patients with diabetes. The basal plasma GH concentrations and the responses following provocative testing in adult diabetics do not generally differ from control subjects.[1-4] In contrast, studies in the prediabetic and juvenile diabetic patient have suggested the presence of elevated GH levels following tolbutamide adminstration,[5] during the twenty-four-hour day[6] and in response to exercise.[7] These observations have been interpreted to indicate that pituitary GH release is increased in diabetes mellitus. Elevated plasma GH levels alone do not permit distinction, however, between enhanced pituitary GH release and decreased clearance of the hormone from the blood. In an attempt to resolve this question, the metabolic clearance rate (MCR) of GH was directly measured in children with the recent onset of insulin-dependent diabetes mellitus.

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METHODS

After informed consent was obtained from the parents, eleven children with insulin-dependent diabetes mellitus were studied. Seven healthy, nonhospitalized children with a negative family history of diabetes mellitus served as a contrast group. The diabetic children had clinically evident diabetes for two days to six years (table 1). All were within one standard deviation of the normal height and weight for their age. Laboratory studies revealed normal renal and hepatic function in all of the children. The metabolic clearance rate of GH was measured in the supine position after fourteen to seventeen hours of fasting by a constant infusion to equilibrium technic previously described.[8] Insulin injections were withheld on the day of the study in the diabetic patients. Several modifications were used in the present study: highly purified GH (gift of Dr. W. Peckam, University of Pittsburgh) was isotopically labeled to a specific activity of approximately 350 $\mu c/\mu g$ with I-131 (Union Carbide, Tuxedo, New York) rather than I-125 as in the previous study. After injection of approximately 1 μc as a priming dose, 4 to 5 μc of I-131-labeled GH in a 1 per cent serum albumin-0.85 per cent sodium chloride solution was infused at a constant rate of 1 ml./min. for ninety to 120 minutes. Heparinized blood samples were obtained before and every ten minutes beginning sixty minutes after the start of the infusion. The concentration of immunoprecipitable GH-I-131 was measured in the plasma and in the infusate according to the previous method.

The MCR of GH was calculated from four or more plasma samples at equilibrium according to the general procedure of Tait[9] using the following formula:

TABLE 1

Results of constant infusion of GH-I-131 in normals and diabetic children

	Age (yr.)	Sex	Surface area (m^2)	Duration of diabetes	FBS (mg./100 ml.)	MCR (ml./min.)	MCR/m^2 (ml./min./m^2)	Endogenous GH Mean±SEM‡ (ng./ml.)	Increment in GH† (ng./ml.)
Normals									
PS	12	F	1.50	—	100	144	96	0.7 ± 0.1	+ 8.8
MV	12	F	1.47	—	88	191	130	7.8 ± 0.6	+ 2.6
LS	13	F	1.08	—	96	151	140	1.0 ± 0.1	+ 0.7
VV	13	F	1.04	—	78	149	143	3.6 ± 0.1	+ 3.2
IB	13	M	1.49	—	97	255	171	0.8 ± 0.1	+ 0.7
ES	16	M	1.78	—	102	172	97	7.6 ± 1.7	+ 8.4
GV	11	M	1.40	—	88	201	194	6.4 ± 0.5	+ 7.3
Mean ± SEM			1.39 ± 0.10			180.4 ± 14.9	138.7 ± 13.6	3.9 ± 0.6	4.5 ± 1.3
Diabetics									
EL	11	F	1.05	6 mos.	238	51	49	6.7 ± 1.4	+ 16.7
IP	15	F	1.44	6 mos.	500	145	100	5.5 ± 1.1	+ 7.0
MR	9	F	1.17	2 mos.	106	99	85	1.2 ± 0.2	+ 0.6
TW	13	F	1.36	18 mos.	117	113	83	2.1 ± 0.4	+ 14.8
ET	14	F	1.48	5 days	340	131	89	2.2 ± 0.2	+ 3.5
JI	14	F	1.35	3 days	268	86	55	8.0 ± 0.7	+ 9.5
SM	12	M	1.57	14 days	402	71	87	4.0 ± 1.4	+ 16.7
TR	6	M	0.82	5 days	184	206	118	1.4 ± 0.2	+ 5.0
RR	13	M	1.75	3 mos.	230	91	101	5.1 ± 1.0	+ 6.1
ES	8	M	0.90	6 yrs.	175	126	79	3.0 ± 0.1	+ 5.0
CS	13	M	1.60	3 mos.	250	129	96	13.4 ± 3.0	+ 19.0
Mean ± SEM			1.32 ± .09			113.5 ± 12.6*	86.0 ± 6.0*	4.5 ± 0.5	9.5 ± 1.9*

* Significantly different from control ($p < .01$).
† Rise in GH above lowest value during study.
‡ Mean concentration during equilibrium of GH-I-131 infusion.

MCR (ml./min.) = rate of infused GH (cpm/min.)/plasma immunoreactive GH-I-131 in cpm/ml.

After allowance for radioactive decay of the infused I-131, endogenous GH concentrations were measured in the same plasma sample by a modification of the dextran coated charcoal immunoassay method of Herbert et al.[10] The reproducibility of the assay system was determined by measuring two different GH standards in each assay. The results were: 1.58 ± 0.59 (S.D.) ng./ml. and 10.61 ± 1.49 ng./ml., respectively.

The effect of acute hyperglycemia on the MCR of GH was studied in two normal subjects. A 20 per cent glucose solution was infused at an initial rate of 1 gm./min. This was then increased by 0.5 gm./min. every twenty minutes for sixty minutes in order to produce increasing degrees of hyperglycemia during the GH-I-131 infusion.

Results between the diabetic and contrast group were compared by the Student "t" test for unpaired samples. Probabilities at the 5 per cent level or less were accepted as significant.

RESULTS

The mean MCR of the diabetic patients was 113.5 ± 12.6 ml./min. (mean ± S.E.M.) which was significantly lower than the mean value in the contrast group (180.4 ± 14.9 ml./min.; table 1). The mean surface area of the two groups did not differ significantly. There was no correlation between sex, fasting blood glucose or duration of the diabetes mellitus and the MCR. The mean endogenous GH concentrations in the diabetic patients (4.5 ± 0.5 ng./ml.) during the equilibrium period of the GH-I-131 infusion was not statistically different from the mean GH concentration during the similar period in the control subjects (3.9 ± 0.6 ng./ml.). Ten of the eleven diabetic patients had spontaneous elevations in endogenous GH concentrations of 4 ng./ml. or greater above the lowest value obtained during the infusion. In contrast in the control group only three out of the seven patients had spontaneous rises in GH levels of 3 ng./ml. or greater.

The effect of acute hyperglycemia on the MCR of GH is illustrated in table 2. Induction of hyperglycemia for sixty minutes did not appear to significantly change the metabolic clearance rate.

DISCUSSION

Recent studies from this laboratory[8] have demonstrated that the constant infusion to equilibrium technic[9] employing radioisotopically labeled GH is a valid

TABLE 2

Effect of acute hyperglycemia on metabolic clearance rate of growth hormone

	Plasma glucose (mg./100 ml.)	MCR (ml./min.)
W.M.	87	160
	92	153
	96	157
	88	149
	225	149
	320	164
	400	164
A.G.	89	161
	99	149
	102	164
	88	164
	220	155
	230	151
	380	156

method to evaluate the MCR of endogenous GH. The determination of the production rate (PR) of GH, utilizing the MCR, depends upon obtaining steady state GH levels or obtaining continuous measurements during the experimental procedure. In the present study mean endogenous GH concentrations were not statistically different on comparison of the diabetic patients and the contrast group. In the diabetic patients use of the mean plasma endogenous GH value obscures the marked instability in GH concentrations observed in these patients. The instability in plasma GH concentrations in insulin-dependent juvenile diabetic patients has been noted by others.[6] Although this variation in endogenous GH concentrations does not affect the determination of the MCR of GH,[8] the calculation of PR of GH could vary several-fold depending upon which endogenous GH value is used (PR = MCR x endogenous GH concentration). Therefore, the data do not permit the evaluation of the possibility of an alteration in pituitary PR of GH in diabetes mellitus.

The data do indicate, however, that diabetes mellitus even in its earliest clinical stages is associated with significant alterations in the MCR of GH. The reduction in MCR of GH described herein is similar to the results of previous studies in adult insulin-dependent and independent diabetic patients.[8] This abnormality in the metabolism of GH could not be attributed to alterations in circulatory, hepatic or renal function in the patients in the past study[8] nor in the patients in the present study. It is unlikely that the reduction of MCR observed in the children with clinically evident diabetes mellitus of such short duration is a complication of the disease.

Recent studies from this laboratory have demonstrated that the liver is the major organ responsible for the clearance of GH from the plasma in man;[11] hepatic metabolism accounted for over 90 per cent of the total metabolic clearance of GH. It is apparent, therefore, that a defect in the hepatic GH clearance may be present in diabetes mellitus. At present, the nature of this hepatic defect is unclear.

ACKNOWLEDGMENT

This study was supported in part by the Clinical Research Center's Grant (No. RR261), V.A. Training Grant (No. TR-177), and NIH Grant (No. 5 R01 AM14106-02).

Dr. Taylor is a recipient of a Research Associate Award from the Veteran's Administration.

We are indebted to Dr. Douglas Sandberg for his help in this study; and for the technical assistance of Mrs. Antoinette Schenk, Mrs. Argelia Novoa, and the staff of the Clinical Research Unit for their excellent technical assistance.

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