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Research Article

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Free fatty acid, β-hydroxybutyrate, and acetoacetate increased respectively in normals to peak concentrations in plasma of 1.55 ±0.11, 2.87 ±0.23, and 0.77 ±0.09 mmoles/liter. Untreated dwarfs had significantly greater values of all three (mean maximal concentration: FFA […]

Glucose and Lipid Homeostasis in the Absence of Human Growth Hormone

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ABSTRACT To clarify the role of insulin and growth hormone (HGH) in regulating substrate production for body fuel during prolonged starvation, 6 normal subjects and 10 HGH-deficient dwarfs were fasted for 6 days. Four of these dwarfs received HGH during the fast.

Blood glucose concentration decreased a mean 15 mg/100 ml in both controls and HGH-treated dwarfs, but decreased 50 mg/100 ml in untreated dwarfs. The final level at which the blood glucose stabilized was significantly higher in the former two groups (65 ±1.0 mg/100 ml and 88 ±19 mg/100 ml, respectively, versus 39.0 ±4.0 mg/100 ml in the untreated dwarfs). The decline in plasma insulin concentration showed a comparable pattern, decreasing from a similar basal level to 7.7 ±0.4 μU/ml in controls, 8.8 ±1.1 μU/ml in dwarfs treated with HGH, and to a significantly lower level of 3.8 ±1.1 μU/ml in untreated dwarfs. When glucose concentrations were plotted against paired insulin values, the correlation in both dwarfs and normals was significant. In normals, no correlation existed at any time between plasma HGH levels and plasma concentration of either glucose or free fatty acid.

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In starvation, the relation between insulin on the one hand and glucose and free fatty acid on the other hand is maintained in the absence of HGH. However, the setting of blood glucose concentration at which this relation takes place is decreased in the absence of HGH. This results in a lower than normal insulin level and, consequently, in a higher than normal free fatty acid concentration.

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INTRODUCTION

Carbohydrate stores can provide only a small part of the body's fuel during a prolonged fast. The remainder is provided by free fatty acids (FFA) mobilized from adipose tissue and amino acids derived from protein (1–3). The role hormones play in regulating the supply of substrate to meet these metabolic needs has not been defined in detail.

Although early studies indicated a rise of plasma human growth hormone (HGH) during fasting, later ones noted the sporadic nature and lack of correlation of this response with changes of plasma FFA concentration (4–7). More recently, the importance of insulin during prolonged fasts has been emphasized (8). It was reported that in normal subjects the concentration of insulin in blood decreased as blood glucose concentration fell. FFA, whose release from adipose tissue is inhibited normally by insulin, were mobilized consequently at an accelerated rate and used directly as fuel, with glycerol being converted to glucose. Over all, this resulted in sparing nitrogen stores and maintaining the blood glucose concentration at a relatively normal level (8).

Preliminary data that we acquired in studying dwarfs with a monotropic deficiency of HGH suggested both HGH and insulin might play roles in maintaining normal homeostasis during fasting. To clarify this, the present

studies were carried out in HGH-deficient dwarfs. Our results show that in the HGH-deficient human FFA are mobilized adequately and converted to ketone bodies. Blood glucose concentration is not "adequately" maintained. Although insulin is the basic hormone regulating substrate release, the level at which the glucose-FFA-insulin mechanism operates during starvation appears to be dependent upon the presence of HGH.

METHODS

10 dwarfed subjects deficient only in human growth hormone (sexual ateliotic dwarfs) were selected for this study. Five were males and five were females with ages ranging from 18 to 68. All were in excellent health and had been on a diet containing at least 200 g of carbohydrate per day for a minimum of 2 wk before admission. Pertinent information regarding each is summarized in Table I.

Each of these subjects had been studied previously in detail and diagnosed as sexual ateliotic dwarfs lacking only immunoreactive HGH. Each subject had a normal hematological and urine examination as well as normal X-ray studies of the chest and bony skeleton. Electrocardiograms were normal. Tests of pituitary function included PBI, radioactive ^{131}I uptake, and 24-hr urine collections for 17-hydroxycorticoids and 17-ketosteroids before and after metapyrone. Human growth hormone was measured by immunoassay after both arginine infusion (0.25 g/lb. body weight) and insulin-induced hypoglycemia. With the exception of an absence of human growth hormone after these provocative stimuli, other tests of pituitary function were within normal limits.

Subjects 1 and 8 were type II sexual ateliotic dwarfs according to the classification of Merimee et al., showing increased insulin responses to arginine and glucose, and resistance to exogenous insulin (9, 10). The remainder of the subjects were type I sexual ateliotic dwarfs with insulinopenia after glucose and arginine, and prolonged hypoglycemia after exogenous insulin. Subjects 5 and 6 were the HGH-deficient daughters of subjects 3 and 4, both of whom were, likewise, offspring of HGH-deficient parents.

After a control period of 2 days, five of these subjects were fasted for a total of 4 days, receiving only H_2O ad lib. Four subjects were fasted for 3 days with all but one receiving 5.0 mg of HGH (Wilhelmi Lot 1-C) on days 2 and 3 of the fast. The fourth subject received one injection only. The six normal subjects have been reported previously (8).

Blood and urine collections. Blood was obtained each morning from an antecubital vein at 7:30 to 8:00 a.m. before ambulation. 30–40 ml of blood was removed in both heparinized and unheparinized syringes and divided into four aliquots. 5 ml of whole blood were injected into a centrifuge tube containing 5 ml of 30% perchloric acid. This was shaken immediately and centrifuged in the cold for 30 min. The supernatant so obtained was passed through Whatman No. 1 filter paper and frozen at −20°C for later measurement of acetoacetate, β-hydroxybutyrate, and glycerol. Plasma from 6 ml of heparinized blood was deproteinated by adding 2 ml of plasma to 1 ml of H_2O and 1 ml of 20% sulfosalicylic acid. The supernatant so obtained was decanted and frozen for amino acid determinations. The remaining plasma was either stored after centrifugation for determinations of FFA, glucose, insulin, and growth hormone or used for measurement of urea, uric acid, and CO_2.

TABLE I

Clinical Data for HGH-Deficient Dwarfs

	Age	Sex	Weight		Height	Body surface
			Initial	Final		
	yr		*kg*		*cm*	m^2
Untreated						
1. R. S.	33	M	49.2	46.0	135	1.32
2. D. T.	42	M	41.9	38.9	132	1.21
3. A. S.	42	M	41.5	40.1	139	1.25
4. M. S.	45	F	41.3	39.4	132	1.20
5. D. S.	19	F	35.0	32.9	135	1.15
6. N. S.	23	F	46.1	43.5	137	1.30
Treated*						
7. M. A.	47	F	35.4	33.2	118	1.04
8. B. A.	43	M	55.0	51.3	138	1.42
9. R. S.	68	M	45.5	42.3	135	1.28
10. F. B.	49	F	49.1	48.1	120	1.22

* Except for No. 7, each treated dwarf received 5.0 mg of HGH on days 3 and 4 (Wilhelmi Lot 1-C). Patient 7 received only one injection on day 3.

Plasma samples were stored at 4°C for periods not exceeding 1 month.

Urine was collected throughout the period in plastic containers, kept in the refrigerator during each 24 hr collection, and at the end of this period the volume was recorded and aliquots removed and frozen for later analysis of nitrogen, uric acid, urea, creatinine, β-hydroxybutyrate, and acetoacetate. Results of the latter two determinations only are given in this paper, along with total nitrogen values.

On the 2nd control day and to terminate the fast, an oral glucose tolerance test was performed with 1.5 g of glucose per kg of body weight. Samples were collected periodically for 2–3 hr and the plasma was used for determinations of glucose, FFA, and insulin.

Chemical procedures. Glucose was measured by a glucose oxidase method, all samples being determined in triplicate (11). Each value in this study represents the mean of three such determinations, with the maximum variation between duplicate samples being no greater than 2.0 mg/100 ml. Free fatty acids in plasma were measured by the Trout, Estes, and Friedberg modification of the method of Dole (12).

Serum immunoreactive insulin and HGH were measured by modifications of the methods of Berson and Yalow, and Roth, Glick, Yalow, and Berson, respectively (13, 14). To achieve maximum accuracy within the range of normal basal values of insulin, samples were run in quadruplicate with the final reported value being the mean of four determinations.

Urea, uric acid, and creatinine were measured in blood by the Technicon AutoAnalyzer procedure. Glycerol, β-hydroxybutyrate, and acetoacetate were determined by the enzymatic procedures described previously (8).

RESULTS

Basal blood values in normals. Table II summarizes the mean values of all constituents measured in plasma or serum for normal controls. Samples 1 and 2 were obtained after an overnight fast, but during the period when patients were fed a daily 200 g carbohydrate diet. The fast began after collection of the sample on the morning of day 2.

TABLE II

Serum or Plasma Concentrations of Constituents Measured in Normal Controls

	Days of study					
		Fasting*				
	1	2	3	4	5	6
Glucose, *mg/100 ml*	77.0 ±2.0	84.0 ±1.0	73.0 ±2.0	68.0 ±2.0	65.0 ±1.0	66.0 ±1.0
FFA, *mmoles/liter*	0.53 ±0.02	0.42 ±0.04	0.82 ±0.08	1.04 ±0.07	1.55 ±0.11	1.27 ±0.07
Acetoacetate, *mmoles/liter*		0.013 ±0.003	0.16 ±0.03	0.51 ±0.07	0.65 ±0.10	0.77 ±0.09
β-Hydroxybutyrate, *mmoles/liter*		0.016 ±0.001	0.39 ±0.11	1.64 ±0.14	2.24 ±0.12	2.87 ±0.23
Insulin, *μU/ml*	14.0 ±1.8	15.2 ±2.3	9.2 ±0.8	8.0 ±0.7	7.7 ±0.4	8.6 ±0.8
Glycerol, *μmoles/liter*		62.0 ±6.0	86.0 ±12.0	95.0 ±14.0	91.0 ±10.0	100.0 ±15.0

* Fast begins after the collection of sample on day 2 and terminates after collection of morning sample on day 6.

Both mean plasma glucose and mean plasma insulin concentrations decreased in normal controls to a plateau by the 3rd day of the fast, and then remained stable. All individuals showed the same pattern. The maximum decrease of plasma glucose was 15 mg/100 ml while insulin decreased during the same period to approximately half of the prefast basal value. The correlation coefficients of the paired values of insulin and glucose for each normal control had probability values of less than 0.01 in all subjects. When paired values of insulin and glucose were combined for the controls, the correlation coefficient was 0.65 ($P < 0.001$); no correlation existed between growth hormone levels and plasma levels of glucose or insulin.

In the normal controls, FFA in plasma showed a maximum threefold increase over the mean basal concentration. Acetoacetate increased from 0.013 ±0.003 mmole/liter to 0.77 ±0.09 mmole/liter, while β-hydroxybutyrate increased from 0.016 ±0.001 mmole/liter to 2.87 ±0.2 mmoles/liter.

Basal values of HGH-deficient subjects: with and without treatment. In Tables III, the same constituents measured in normal subjects are shown for the untreated dwarfs and in Table IV, for dwarfs treated with HGH.

In HGH-deficient dwarfs receiving no treatment, glucose showed a striking fall of approximately 50 mg/100 ml, contrasting with only a 15 mg/100 ml decrease in normal control subjects. The plasma glucose concentrations plateaued as in normals but at a much lower concentration. By contrast, both glucose and insulin values of the HGH-treated dwarfs failed to decrease significantly. There was a surprising lack of symptoms in the dwarfs despite their low plasma concentrations of glucose. Fig. 1 compares the mean changes of insulin and glucose in both groups of sexual ateliotics: treated and untreated. As in the normal subjects, there was a significant correlation of blood glucose and insulin values. When paired values of insulin and glucose were combined for the untreated HGH-deficient dwarfs, the coefficient of correlation was 0.82 with a P value of less than 0.001.

The concentrations in plasma or serum of FFA, β-hydroxybutyrate, and acetoacetate increased during the fast in all groups. Untreated HGH-deficient dwarfs had significantly greater blood concentrations of FFA, β-hydroxybutyrate, and acetoacetate during the starvation period than control subjects. The blood FFA and ketone body concentrations of untreated HGH-deficient dwarfs were also greater during the fast than that of either the dwarf group treated with HGH or the control subjects. Figs. 2 and 3 emphasize the changes of FFA, glycerol, and plasma ketones in untreated dwarfs and normal controls. Complete data for all groups are given in Tables II–IV.

Glucose tolerance before and after fasting. The five untreated dwarfs were each given 1.5 g of glucose per kg of body weight orally on a control day before fasting.

In three of these five the period of starvation could be terminated with a similar glucose load. Fig. 4 shows the glucose and insulin responses of these three subjects before and after the starvation period. Each showed, after fasting, a marked deterioration of glucose tolerance without concomitant increase of insulin secretion. Only one showed a slight augmentation of the insulin response following the fast, and that was noted only at the 2nd hour of the glucose tolerance test.

Constituents in urine: normals and HGH-deficient dwarfs. The mean excretion of urinary ketones are given for each group in Table V. In all groups, β-hydroxybutyrate and acetoacetate excretion increased as fasting progressed. Despite the higher blood ketone acid levels in the untreated dwarfs, urine β-hydroxybutyrate excretion did not differ significantly from controls, while urinary acetoacetate was significantly lower than that observed in the control group. There was considerable individual variation in ketone excretion in dwarfs treated with HGH demonstrating markedly elevated levels of urine β-hydroxybutyrate. Nitrogen excretion was similar in each group.

DISCUSSION

HGH is essential in man for reaching normal stature, but its function during adult life is difficult to determine. Although it is known to modify the hypoglycemic actions of insulin, the physiologic importance of this effect may be minor (15). Spontaneous and postprandial hypoglycemia are rare phenomena, for example, even in chronically HGH-deficient subjects. Growth hormone can also mobilize FFA from adipose tissue, an effect compatible with a function during the fasting state (16). However, studies have failed to show a consistent pattern of HGH secretion during prolonged fasts and no correlation has been noted between the increased plasma concentrations of FFA during starvation and the HGH concentrations of plasma (8).

There is evidence that plasma concentration of insulin is important in balancing blood glucose and FFA concentrations during starvation. FFA release from adipose tissue is exquisitely sensitive to small quantities of insulin. When basal insulin concentration in plasma decreases, there is a well correlated rise in plasma concen-

TABLE III

Serum or Plasma Concentrations of Constituents Measured in Untreated Sexual Ateliotic Dwarfs

	Days of study					
	1	2	3	4	5	6
Urea nitrogen, *mg/100 ml*	12.5 ±1.6	10.8 ±0.8	14.3 ±1.3	18.3 ±0.8	16.8 ±1.6	14.7 ±1.7
Uric acid, *mg/100 ml*	4.1	4.1	6.1	8.4	9.9	10.8
Glucose, *mg/100 ml*	87.0 ±5.0	91.0 ±2.0	56.0 ±11.0	39.0 ±4.0	43.0 ±5.0	46.0 ±6.0
FFA, *mmoles/liter*	0.81 ±0.17	0.56 ±0.06	1.55 ±1.25	1.74 ±0.24	2.05 ±0.16	2.16 ±0.17
Acetoacetate, *mmoles/liter*	0.051 ±0.005	0.052 ±0.006	0.46 ±0.08	0.69 ±0.07	0.99 ±0.07	1.16 ±0.10
β-Hydroxybutyrate, *mmoles/liter*	0.08 ±0.005	0.036 ±0.012	1.59 ±0.49	3.40 ±0.49	4.04 ±0.35	4.77 ±0.34
Insulin, *μU/ml*	12.4 ±1.0	12.2 ±1.4	5.2 ±1.2	4.6 ±1.2	4.9 ±1.2	3.8 ±0.3
Glycerol, *μmoles/liter*	81.0 ±22.0	94.0 ±22.0	98.0 ±23.0	111.0 ±22.0	155.0 ±23.0	159.0 ±20.0
CO_2 content, *mmoles/liter*	25.1 ±0.8	24.7 ±0.9	21.4 ±0.8	19.5 ±0.5	18.4 ±1.1	17.6 ±1.0
Human growth hormone, *mμg/ml*	1.0	1.0	1.0	1.0	1.0	1.0

Fasting begins after collection of sample on day 2 and terminates after collection of the sample on day 6.

TABLE IV

Serum or Plasma Concentrations of Constituents in Treated Sexual Ateliotic Dwarfs

	Days of study				
	1	2	3	4	5
Urea nitrogen, *mg/100 ml*	19.2 ±1.65	18.3 ±2.01	9.5 ±1.55	14.5 ±3.66	15.7 ±2.93
Uric acid, *mg/100 ml*	7.9 ±0.04	6.7 ±0.43	8.7 ±0.62	11.9 ±0.33	11.4 ±1.17
Creatinine, *mg/100 ml*	0.82 ±1.05	0.675 ±1.06	1.03 ±0.15	1.22 ±0.25	1.18 ±0.16
Glucose, *mg/100 ml*	104.5 ±14.6	101.0 ±13.8	88.0 ±19.0	96.0 ±8.75	105.0 ±3.60
FFA, *mmoles/liter*	0.879 ±0.159	0.696 ±0.140	1.630 ±0.236	1.647 ±0.107	1.439 ±1.090
Acetoacetate, *mmoles/liter*	0.053 ±0.004	— —	0.99 ±0.40	1.38 ±0.31	0.91 ±0.23
β-Hydroxybutyrate, *mmoles/liter*	0.083 ±0.025	— —	2.87 ±0.77	6.03 ±1.70	2.71 ±0.60
Insulin, *μU/ml*	11.0 ±2.1	11.2 ±1.4	7.6 ±4.8	12.6 ±1.7	8.8 ±1.1
Glycerol, *μmoles/liter*	86.7 ±10.7	— —	118.5 ±19.2	127.8 ±18.2	8.6 ±8.6
CO_2 content, *mmoles/liter*	29.5 ±0.87	— —	— —	— —	25.5 ±1.32

Fasting begins after collection of sample on day 2 and terminates after collection of the sample on day 5. Subjects received 2.5 mg of HGH (Wilhelmi Lot 1-C) on days 3 and 4 immediately after collection of the morning blood sample at 6 a.m.

tration of FFA; when basal concentration of insulin increases, FFA release quickly decreases (8).

During our initial studies of HGH-deficient sexual ateliotic dwarfs, we were struck by two facts: (*a*) an apparent increased propensity of these individuals to develop ketosis during a very short-term fast (2 days), and (*b*) a more profound decrease of plasma glucose than in normal controls. There observations were limited, however, to only three patients.

When these findings were placed in juxtaposition with the previous report on the effects of fasting in normals (8), it seemed to us that the role of HGH during periods of prolonged food deprivation might be more subtle than expected. We postulated that the glucose-insulin-FFA mechanism was, indeed, the major control mechanism for regulating substrate availability during starvation, but that the homeostatic setting of this mechanism depended upon concomitant or prior exposure of tissues and organs to HGH.

The results of the present study, in general, support this conclusion. The dwarfs deficient only in HGH differed strikingly in several respects when fasted from normals. The first difference noted was an inability of the HGH-deficient subjects to stabilize blood glucose concentrations at a level similar to that seen in controls. Whereas normal subjects showed, during a 6 day fast, a mean decrease of plasma glucose of 15 mg/100 ml, HGH-deficient dwarfs had a mean decrease of plasma glucose of 50 mg/100 ml. Associated with the profound decrease of glucose was a greater than normal decrease of plasma insulin and an increase of FFA to significantly higher concentration. β-Hydroxybutyrate, acetoacetate, and glycerol concentration in blood were likewise increased to a greater than normal degree in the HGH-deficient group during practically all phases of the starvation period.

The FFA response in the HGH-deficient group is par-

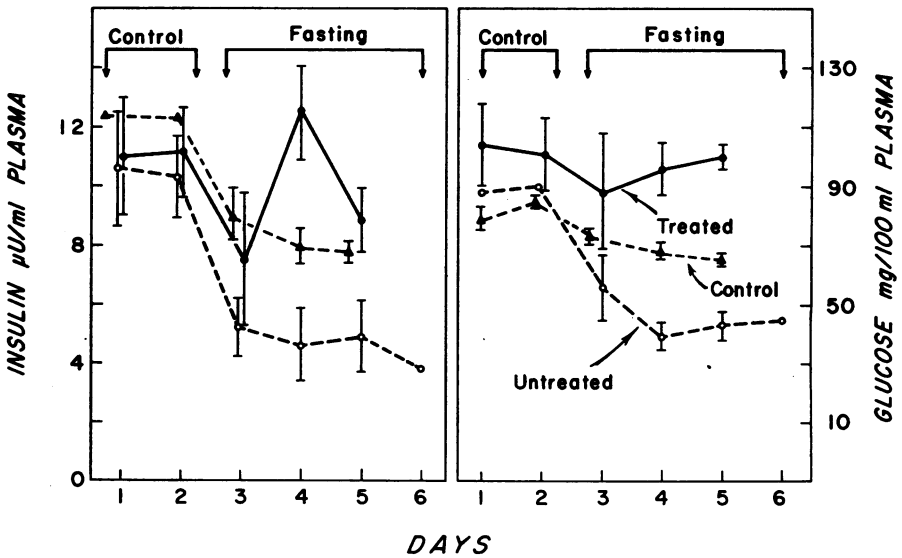

FIGURE 1 Plasma concentrations of insulin and glucose are shown during control days and while fasting. The fast begins after collection of the blood sample on day 2. All points are means ±SEM.

ticularly noteworthy in view of the known lipolytic actions of HGH and the postulated role of FFA in blood glucose homeostasis (17). It is clear from the foregoing data that lipolysis in starvation is not mediated principally by growth hormone. The greater than normal increase of FFA and ketones in the untreated dwarfs is probably secondary to the lower insulin levels observed in this group. The accelerated lipolysis could result also from a compensatory increase in activity of other lipolytic stimuli, but we are not aware of any data supporting this view. To the extent that FFA levels were greater while glucose concentrations were lower in the untreated dwarfs, it is also evident that the action of HGH in mitigating the decline in plasma glucose con-

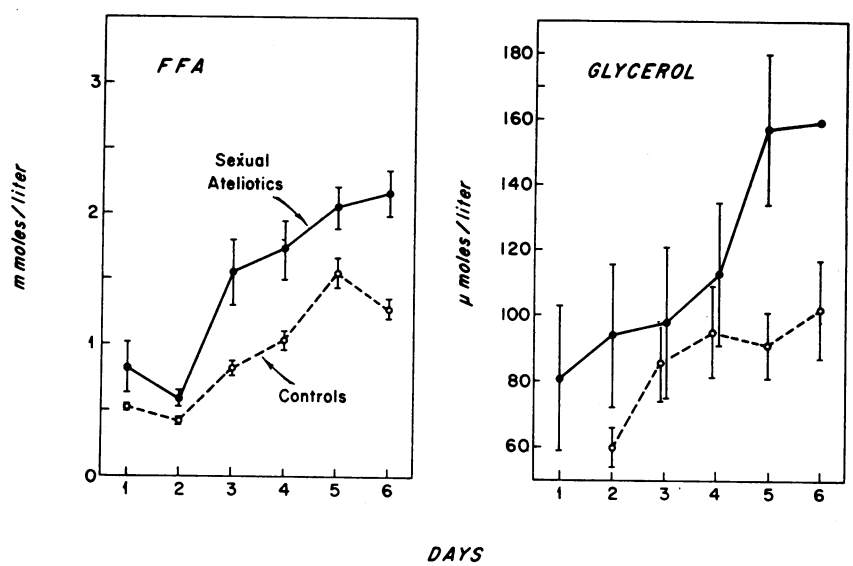

FIGURE 2 Plasma concentrations of glycerol and FFA are shown during control days and while fasting. Sexual ateliotics are untreated. The fast begins after collection of the blood sample on day 2.

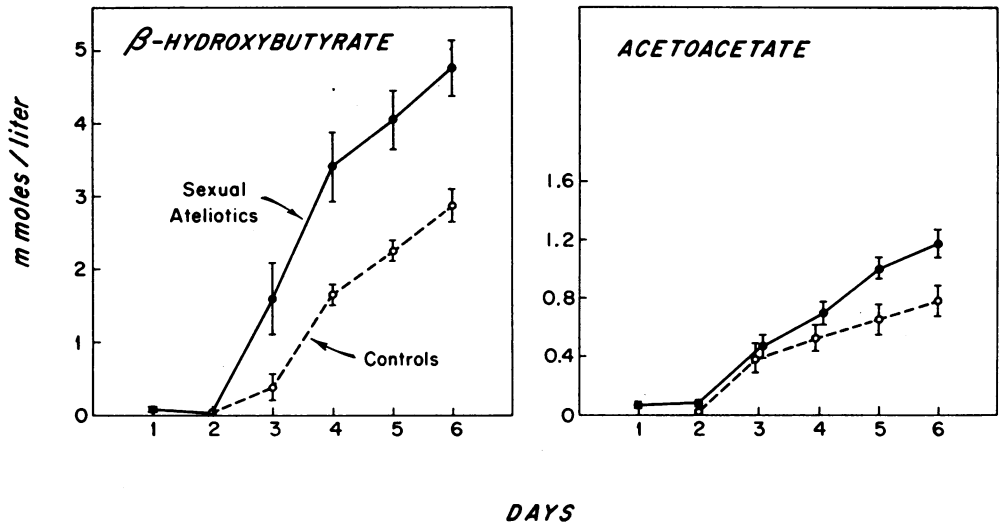

FIGURE 3 Plasma concentrations of β-hydroxybutyrate and acetoacetate are shown during control days and while fasting. Sexual ateliotics are untreated. The fast begins after collection of the blood sample on day 2.

centrations is not mediated via alterations in plasma FFA levels.

The data supported the conclusion that growth hormone is of importance in blood glucose homeostasis during starvation. The greater than normal decline in blood glucose concentration which occurs in the absence of HGH could be attributed to over-utilization of glucose, underproduction of glucose from endogenous precursors, or both. In view of the known anticatabolic action of growth hormone, it is unlikely that HGH has a stimulatory effect on gluconeogenic mechanisms; in fact, the reverse has been postulated. Moreover, the levels of urinary nitrogen suggest normal states of protein dissolution. Studies on amino acid metabolism likewise support this view.[1]

[1] Felig, P., and T. J. Merimee. Amino acid metabolism in the growth hormone deficient state. Unpublished data.

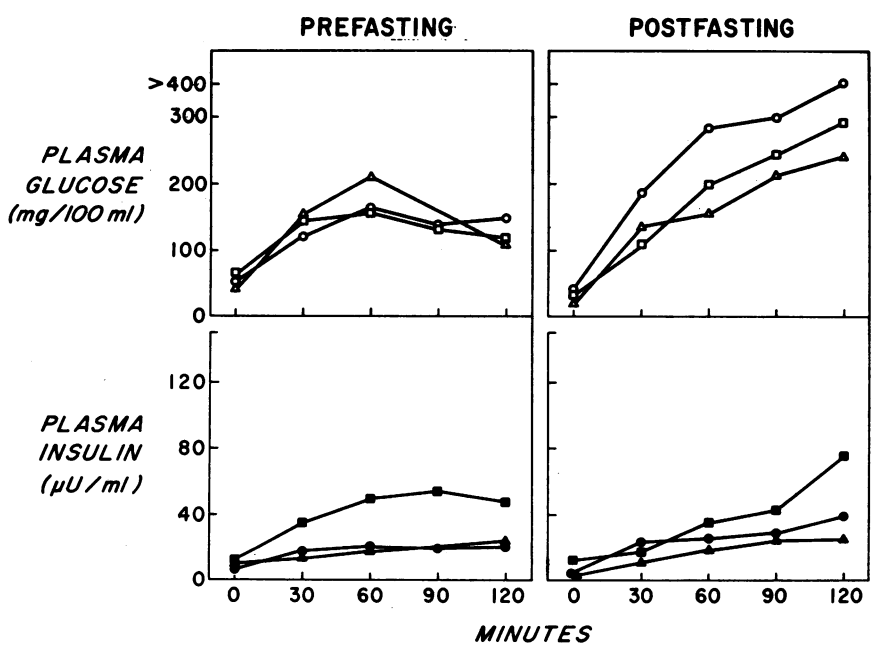

FIGURE 4 Plasma glucose and insulin concentration are shown after ingestion of 1.5 g of glucose per kg of body weight. All three subjects are HGH-deficient dwarfs.

TABLE V

Urinary Ketone Acid and Nitrogen Excretion

	Days of study				
	1	2	3	4	5
β-Hydroxybutyrate, *mmoles/m² per day*					
Control	0.014 ±0.01	0.12 ±0.07	6.6 ±2.5	19.3 ±4.9	30.2 ±6.7
Untreated dwarfs	0.05 ±0.01	0.47 ±0.02	8.21 ±1.35	11.69 ±3.59	21.47 ±3.8
Treated dwarfs	0.05 ±0.01	8.31 ±3.6	73.98 ±30.63	32.25 ±15.51	
Acetoacetate, *mmoles/m² per day*					
Control	0.025 ±0.0	0.27 ±0.09	1.76 ±0.28	5.4 ±0.97	5.4 ±0.80
Untreated dwarfs	0.03 ±0.01	0.16 ±0.05	1.87 ±0.25	2.09 ±0.26	2.49 ±0.28
Treated dwarfs	0.03 ±0.01	0.94	1.63 ±0.39	1.92 ±0.39	
Nitrogen, *g/m² per day*					
Control	6.4 ±0.32	5.9 ±0.25	6.1 ±0.43	7.2 ±0.28	6.6 ±0.37
Untreated dwarfs	5.2 ±0.52	4.3 ±0.26	5.9 ±0.43	7.2 ±0.28	6.6 ±0.35
Treated dwarfs ($n = 4$)	7.6 ±0.28	5.4 ±0.99	4.2 ±0.68	4.1 ±0.48	5.0 ±1.08

Although the data are consistent with the conclusion that HGH is important in the control of blood glucose during starvation, other explanations are possible. It may be that another agent, such as glucagon, is also deficient in these subjects. This could account for a decrease in plasma glucose concentration, and an associated decrease in plasma insulin concentration. Accelerated lipolysis would then follow. We have no data allowing us to comment on such a role for glucagon.

Alternatively, the explanation for the greater degree of ketosis and the lower glucose concentration in the HGH-deficient dwarf, may be the quantitative distortion of body tissues in the dwarf compared to the adult. The principle site of ketoacid metabolism is muscle, and the site of its production is liver; its rate of production usually appears to parallel the rate of gluconeogenesis. Since brain size in these dwarfs is near to that of the adult, its glucose consumption must approximate that of the adult. Thus, the dwarf, like a child, may have tissue "imbalance" with a relative ketoacid under-utilization, resulting in a predisposition to ketosis during fasting.

In summary, it can be stated that in fasting, the mobilization of FFA and the production of β-hydroxybutyrate and acetoacetate occur in the complete absence of HGH. The relation between insulin, glucose, and FFA is maintained, but the setting of blood glucose concentration at which this relation takes place is decreased in the growth hormone–deficient dwarf.

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