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J Clin Invest. 1971;**50**(2):411-421. <https://doi.org/10.1172/JCI106508>.

Research Article

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Metabolic Response to Human Growth Hormone during Prolonged Starvation

PHILIP FELIG, ERROL B. MARLISS, and GEORGE F. CAHILL, JR.

From the Department of Medicine, Harvard Medical School, and the Peter Bent Brigham Hospital, and the Joslin Diabetes Foundation, Inc., Boston, Massachusetts 02215, and the Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut 06510

ABSTRACT The metabolic response to human growth hormone (HGH) was studied in five obese subjects in the fed state and during prolonged (5–6 wk) starvation. In the fed state (three subjects), HGH induced an elevation in basal serum insulin concentration, a minimal increase in blood and urine ketone levels, and a marked reduction in urinary nitrogen and potassium excretion resulting in positive nitrogen and potassium balance.

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It is concluded that in prolonged starvation (a) HGH may have a direct insulinotropic effect on the beta cell independent of alterations in blood glucose concentration, (b) persistence of the lipolytic action of HGH results in

severe exaggeration of starvation ketosis and interferes with its anticatabolic action by necessitating increased urinary ammonia loss, and (c) failure of HGH to reduce net protein catabolism in starvation suggests that this hormone does not have a prime regulatory role in conserving body protein stores during prolonged fasting.

INTRODUCTION

In recent years growth hormone has been implicated in the regulation of body fat mobilization (1) and in blood glucose homeostasis (2). With regard to protein metabolism, it has been postulated that growth hormone is not only responsible for the anabolism characteristic of young growing individuals, but also plays a role in fully grown subjects in conserving body protein stores during periods of starvation or restricted food intake (3).

Recent studies from our laboratory have demonstrated that obese subjects undergoing prolonged therapeutic starvation do, indeed, conserve body protein as indicated by a reduction in urinary nitrogen excretion from levels of 10–15 g/day in the 1st wk of fasting to levels of 3–5 g/day after 5 wk of starvation (4). Furthermore, as demonstrated by indirect calorimetry, these subjects utilize no carbohydrate stores but derive almost all their caloric requirements from dissolution of body fat (5). While this constellation of enhanced fat utilization, diminished carbohydrate consumption, and minimal protein catabolism is consistent with the known effects of exogenous growth hormone in the fed state (6), no significant elevation in serum growth hormone is demonstrable in the starved obese subjects (4). Similarly in nonobese individuals, after a transient increase in serum levels, growth hormone concentration returns to base line as fasting is extended beyond 5 days (7). The question thus arises as to whether prolonged fasting influences the tissue sensitivity to the protein-sparing effects of so-

This work was presented in part at the Fifty-first Annual Meeting of the Endocrine Society, New York, June 1969.

Dr. Felig was formerly a U. S. Public Health Service Special Postdoctoral Fellow (5-F3-AM-36-069) and is now a Teaching and Research Scholar of the American College of Physicians in the Department of Internal Medicine, Yale University School of Medicine, New Haven, Conn. 06510. Dr. Marliss was a Fellow of the Medical Research Council of Canada.

Received for publication 14 August 1970 and in revised form 5 October 1970.

TABLE I
Clinical Data

Subject	Figure symbol	Age	Sex	Height	Weight		Sequence of HGH studies	
					Initial	Final	Fed	Fasted
		yr		cm	kg			
G. M.	○	50	M	183	145	119	—	1*
M. S.	▲	23	M	191	214	183	2	1
J. C.	△	50	F	171	125	102	1	2
F. G.	●	36	F	155	81	65	—	1*
M. L.	—	26	F	168	107	—	1†	—

* Did not receive HGH in fed state.

† Not studied in fasted state.

matotropin. In addition, if growth hormone has a regulatory rather than permissive role in restricting protein catabolism in starvation, then with an excess of growth hormone it should be possible to reduce further the rate of urinary nitrogen loss. To answer these questions and to evaluate further its role in starvation, we have examined the metabolic response to human growth hormone during prolonged fasting. In addition, since very limited data are available on the effects of growth hormone in nonfasted obese individuals (8), the subjects were also studied in the fed state.

METHODS

Five obese subjects were admitted to the Clinical Research Center of the Peter Bent Brigham Hospital for study (Table I). Each had volunteered to undergo prolonged

fasting after failure of various dietary regimens. They were informed of the nature, purpose, and possible risks involved in starvation and growth hormone administration. The screening tests employed to exclude cardiopulmonary, renal, hepatic, or endocrine abnormalities have been reported previously (4).

The subjects were studied both in the fed state (three subjects) and during prolonged starvation (four subjects). Two subjects were studied in both the fed and fasted state in the sequence demonstrated in Table I. In the fed state, two of the subjects (J.C. and M.L.) received a 2000 kcal, 450 g carbohydrate, low residue, synthetic liquid diet (Vivonex-100; Vivonex Corp., Mountain View, Calif.) for 10-14 days before, during, and for 5 days after administration of growth hormone. Use of this diet eliminated the need for stool collections and analyses in performing balance studies, since these patients passed no stools (save for small amounts of mucoid material) after the 1st wk on the liquid diet. The third subject (M.S.) received a 1200 kcal conventional diet. During starvation, daily intake was

TABLE II
Blood and Urine Ketone Acid Levels during HGH Administration in Fed Subjects

Experimental period	Subject	Pre-HGH*	HGH treatment		Post-HGH*
			Day 3	Day 5	
Blood β -hydroxybutyrate, mmoles/liter	M. S.	0.10	0.50	0.38	0.10
	J. C.	0.08	0.10	0.13	0.06
	M. L.	0.02	0.09	0.24	0.09
Blood acetoacetate, mmoles/liter	M. S.	0.07	0.44	0.23	0.10
	J. C.	0.04	0.08	0.08	0.04
	M. L.	0.06	0.08	0.06	0.04
Urine β -hydroxybutyrate, mmoles/24 hr	M. S.	0.17	0.98	0.88	0.14
	J. C.	0.06	0.41	0.35	0.09
	M. L.	0.10	0.53	0.11	0.11
Urine acetoacetate, mmoles/24 hr	M. S.	0.13	0.29	0.34	0.10
	J. C.	0.03	0.10	0.04	0.04
	M. L.	0.08	0.17	—	0.04

* Values for urine β -hydroxybutyrate and acetoacetate in the pre- and post-HGH periods represent the mean of two to five consecutive daily observations immediately preceding and after HGH treatment.

restricted to 1500 ml of water, 17 mEq of NaCl (sugar-free tablets), one multivitamin tablet (Theragran; E. R. Squibb & Sons, New York), and intermittently, 17 mEq of KCl (gelatin capsules).

Human growth hormone (HGH), prepared (9) and provided in generous quantities by Dr. M. S. Raben, was administered intramuscularly in a dose of 5 mg every 12 hr. In the studies performed in the fed state, the growth hormone was injected for 5 days after a 10-14 day control period. During starvation, growth hormone administration was initiated on the morning of the 35th day of the fast and was continued for 3 days. The fast was extended for 4-5 days after injection of the last dose of growth hormone.

Blood samples were obtained between 8:00 and 8:30 a.m. from an antecubital vein after the subjects had been resting in the recumbent position for at least 30 min. In the studies performed while the subjects were receiving the 2000 or 1200 kcal diet (fed state), specimens were drawn daily for 3 days before growth hormone administration, on each day

of injection, and for 3 days thereafter. For collection of all of these specimens the subjects were in the postabsorptive state (overnight fast). During starvation, samples were obtained on the day fasting was initiated, after 3, 5, and 10 days of fasting, and daily for 3-6 days before HGH treatment (fore-control, days 30-35 of fast), during HGH treatment (days 36-38), and for 5-6 days after completion of growth hormone therapy (postcontrol, days 39-43 of the fast). In both the fed and fasted states, the morning dose of growth hormone was administered immediately after blood was drawn. Thus the blood specimens obtained on day 35 of the fast were drawn immediately before institution of therapy, while the samples for days 36, 37, and 38 represent those obtained 12 hr after the previous or final dose of growth hormone.

Urine was collected in refrigerated plastic containers for 24-hr periods beginning at 7:30 a.m. The urine specimens for days 35, 36, and 37 of the fast represent those obtained during growth hormone administration.

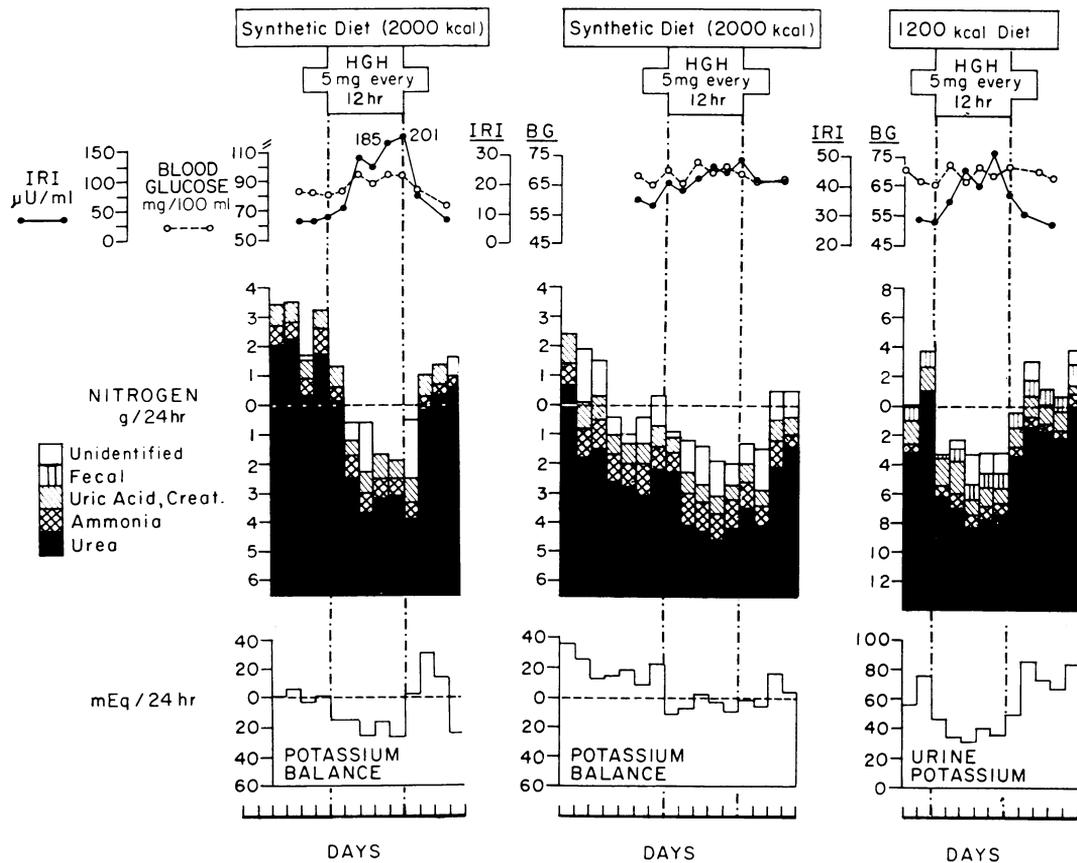


FIGURE 1 Influence of human growth hormone (HGH) on nitrogen and potassium balance and blood glucose and serum immunoreactive insulin levels in fed obese subjects. IRI = immunoreactive insulin, BG = blood glucose. Unidentified is that component of total nitrogen in urine not accounted for as urea, ammonia, creatinine, and uric acid. In the nitrogen and potassium balance diagrams, intake is plotted downward from the dashed zero line, and excretion is charted up from this intake line. Positive balance is indicated by a clear area below the zero line. Nitrogen and potassium excretion in the subjects on the synthetic diet represents loss in urine only since no stools were passed. In the subject on the 1200 kcal conventional diet, net potassium balance was not determined because fecal potassium was not measured. For this subject total urine potassium excretion is shown.

TABLE III
Influence of HGH Administration on Circulating Hormone and Substrate Concentrations during Prolonged Fasting*

Experimental period Days fasted	Precontrol‡	HGH treatment				Postcontrol			
	30-35	36	37	38	39	40	41	42	
Serum growth hormone, m μ g/ml	0.8 ±0.2	4.7 ±0.8	6.5 ±2.1	4.9 ±1.8	1.1 ±0.4	0.8 ±0.6	0.7 ±0.1	0.9 ±0.3	
Serum insulin, μ U/ml	22.3 ±3.6	53.3 ±21.6	45.8 ±3.3	60.3 ±7.6	50.8 ±6.4	41.3 ±6.7	53.0 ±7.5	46.0 ±7.9	
Blood glucose, mg/100 ml	64 ±1	62 ±2	67 ±3	81 ±5	91 ±8	80 ±6	82 ±8	79 ±6	
Plasma free fatty acids, mmole/liter	1.29 ±0.06	1.83 ±0.08	1.94 ±0.23	2.10 ±0.15	1.63 ±0.09	1.65 ±0.17	1.63 ±0.11	1.70 ±0.70	
Blood glycerol, mmole/liter	0.145 ±0.012	0.258 ±0.060	0.240 ±0.045	0.263 ±0.070	0.182 ±0.022	0.168 ±0.041	0.225 ±0.023	0.182 ±0.043	
Blood β -hydroxybutyrate, mmole/liter	5.75 ±0.48	7.95 ±0.65	7.98 ±0.83	7.38 ±0.90	4.75 ±0.52	4.31 ±0.28	4.34 ±0.57	4.28 ±0.72	
Blood acetoacetate, mmole/liter	1.76 ±0.12	2.00 ±0.19	2.13 ±0.22	2.06 ±0.23	1.69 ±0.23	1.52 ±0.15	1.54 ±0.22	1.49 ±0.24	

* Data presented as mean \pm SEM.

‡ Precontrol values represent the mean of three to six observations on each subject during the week preceding HGH administration.

The methods employed for measurement of blood glucose, serum insulin and growth hormone, plasma free fatty acids, total serum CO₂, blood glycerol, blood and urinary acetoacetate and β -hydroxybutyrate, and total nitrogen, urea nitrogen, ammonia nitrogen, and potassium in urine have been described (4, 10). The paired *t* test and calculation of the coefficient of correlation were employed in the statistical analyses (11).

RESULTS

Fed state. The response to growth hormone in the fed state is shown in Fig. 1 and Table II. In all subjects positive nitrogen balance amounting to 2-5 g/day and positive potassium balance were observed (Fig. 1). Noteworthy is the fact that the decrease in nitrogen loss was

due to a reduction in urea excretion with urine ammonia remaining unchanged.

In agreement with previous studies in nonobese individuals (12), HGH administration resulted in an elevation in postabsorptive serum insulin levels in each of the obese subjects. On the other hand, blood glucose levels failed to show a consistent increment. The small but measurable increases observed in blood and urine ketone acids (Table II) are consistent with previous reports in nonfasted subjects (13).

Starvation. The mean concentrations of circulating hormones and substrates before, during, and after growth hormone administration in prolonged starvation are shown in Table III. Before HGH treatment each of the

TABLE IV
Influence of HGH Administration on Urinary Excretion of Ketone Acids, Potassium, and Nitrogen during Prolonged Starvation*

Experimental period Days fasted	24 hr urinary excretion							
	Precontrol‡	HGH treatment			Postcontrol			
	30-34	35	36	37	38	39	40	41
β -Hydroxybutyrate, mmoles	90 ±5	155 ±13	234 ±40	238 ±31	130 ±10	35 ±12	22 ±9	18 ±7
Acetoacetate, mmoles	12 ±3	14 ±4	18 ±5	16 ±4	10 ±2	6 ±2	7 ±2	6 ±2
Potassium, mEq	16 ±2	19 ±2	37 ±9	52 ±11	27 ±4	16 ±6	15 ±4	14 ±4
Total nitrogen, g	4.3 ±0.5	4.3 ±0.4	4.4 ±0.3	4.9 ±0.4	4.4 ±0.5	3.5 ±0.6	4.1 ±0.8	4.1 ±0.8
Urea nitrogen, g	1.4 ±0.3	1.5 ±0.2	1.0 ±0.3	0.9 ±0.2	0.6 ±0.1	0.6 ±0.1	1.1 ±0.3	1.5 ±0.5
Ammonia nitrogen, g	1.9 ±0.1	2.0 ±0.2	2.5 ±0.2	3.0 ±0.3	2.5 ±0.1	1.6 ±0.4	1.8 ±0.4	1.3 ±0.3

* Data presented as mean \pm SEM.

‡ Precontrol values represent the mean of five consecutive observations on each subject on the 5 days preceding initiation of HGH treatment.

subjects demonstrated the characteristic metabolic response to prolonged fasting (4), manifested by low levels of growth hormone and a reduction in serum insulin and blood glucose (Fig. 2). After initiation of treatment, circulating HGH levels were 5- to 10-fold above base line 12 hr after hormone injection. Presumably much higher levels would have been observed had samples been obtained at shorter intervals after hormone injection (14). A significant elevation in serum insulin ($P < 0.025$) was observed within 24-48 hr of initiation of HGH injection and persisted for 4 days after cessation of treatment. While blood glucose levels also rose to levels significantly above base line ($P < 0.025$), this elevation clearly lagged behind the insulin response, becoming apparent only after 72 hr of treatment.

Plasma free fatty acids exhibited a progressive rise during growth hormone administration which reached

its peak after 72 hr of treatment (day 38, $P < 0.01$). That this increase in fatty acid concentration was due to augmented lipolysis in adipose tissue is supported by the parallel rise in blood glycerol. Coincident with the increase in fat mobilization, growth hormone treatment resulted in a marked augmentation in starvation ketosis. Blood β -hydroxybutyrate levels, which had stabilized before HGH, rose by 40-50% during hormone treatment ($P < 0.02$), while in three of four subjects, acetoacetate levels rose by 20-30% ($P < 0.05$) (Fig. 3). As expected, this increase in organic acids (ketone acids and free fatty acids) was accompanied by a corresponding decrease in serum $[\text{HCO}_3^-]$ and blood pH (Fig. 4). Interestingly, after cessation of HGH injection, blood β -hydroxybutyrate fell significantly below base line (pre-control) levels ($P < 0.01$).

The components measured in urine are shown in Table IV. β -Hydroxybutyrate excretion increased 2- to

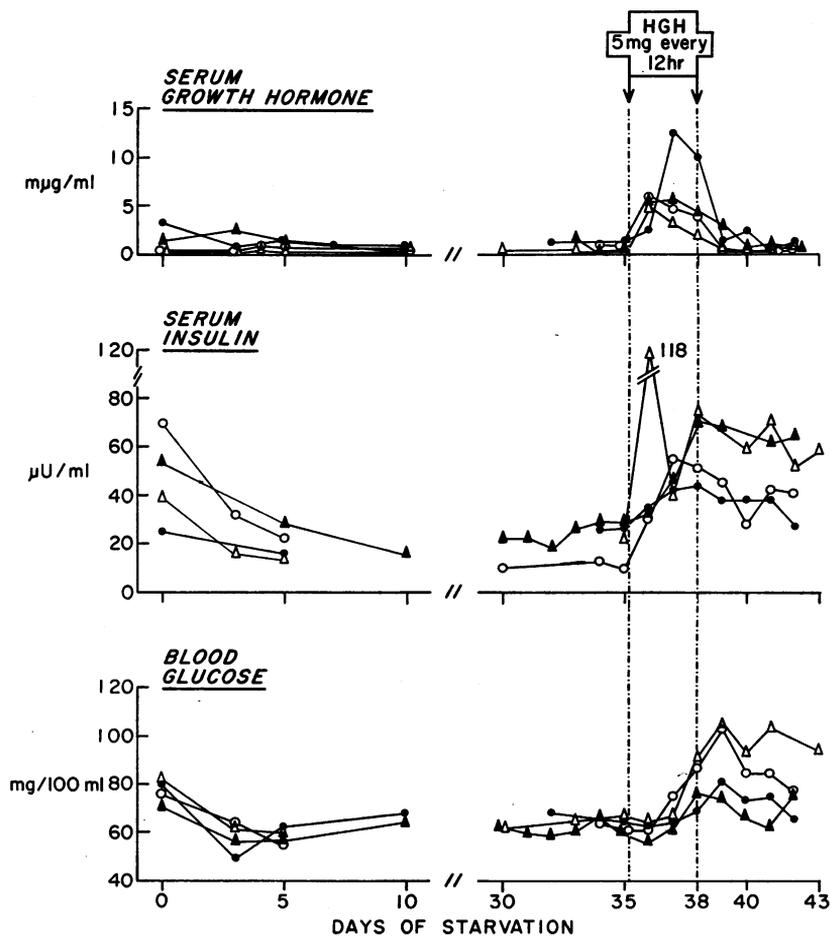


FIGURE 2 Individual values for serum growth hormone, serum insulin, and blood glucose before, during, and after human growth hormone (HGH) administration in prolonged starvation. Blood samples were taken at the end of the 12 hr period between injections of HGH.

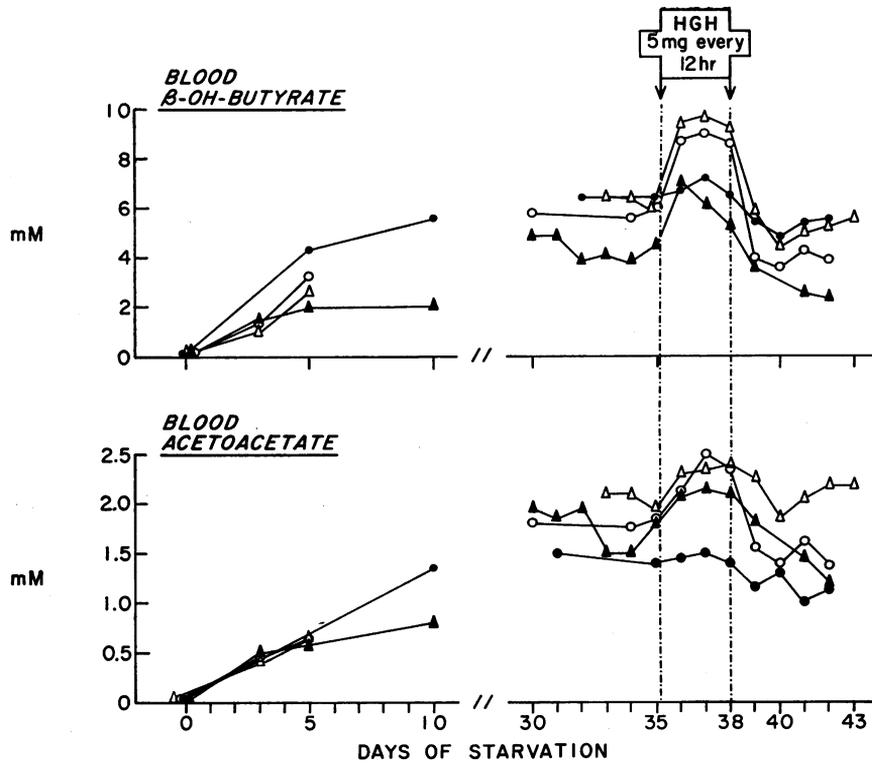


FIGURE 3 Individual concentrations of blood ketone acids in four subjects receiving human growth hormone (HGH) during prolonged fasting.

3-fold above pretreatment levels to 150–320 mmoles/24 hr (Fig. 5). That the heightened ketonemia was responsible for the augmented ketonuria is suggested by

the direct linear correlation between urine and serum β -hydroxybutyrate levels ($r = 0.535$, $P = 0.05$). In marked contrast to the reduction in urine potassium noted

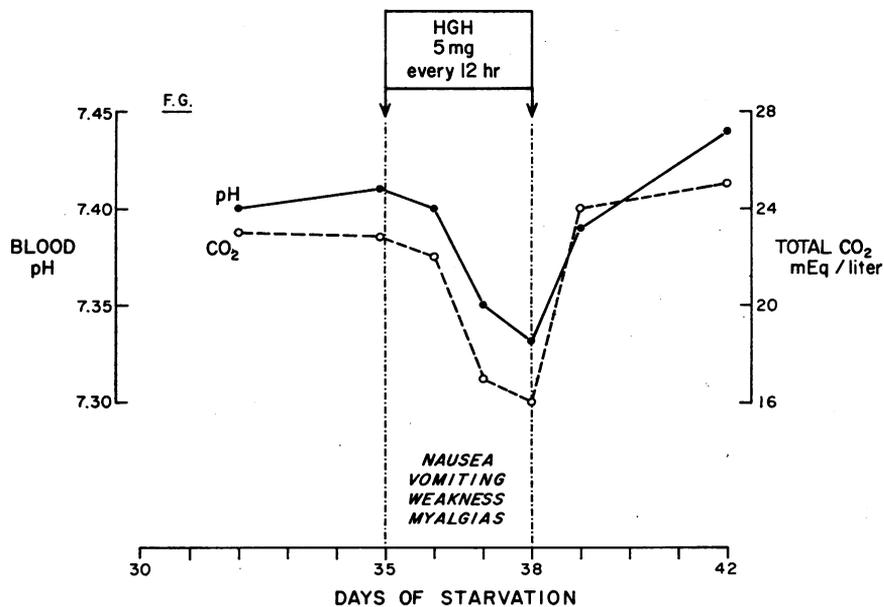


FIGURE 4 Arterial blood pH and serum total CO_2 in a subject receiving human growth hormone (HGH) during prolonged starvation. The symptoms noted during HGH administration are shown at the bottom of the figure.

in the fed state, growth hormone treatment in starvation resulted in a 2- to 4-fold increase in urine potassium excretion (Fig. 5).

The contrast with the fed state is also evident from the data on urinary excretion of total nitrogen. Unlike the fed state in which HGH induced a marked diminution in total nitrogen loss in urine (Fig. 1), no significant decrease in total nitrogen excretion was demonstrable during HGH treatment in starvation (Fig. 6). The diminution observed in two patients after cessation of HGH injection (day 39) was not statistically significant ($P > 0.2$). That exogenous growth hormone was nevertheless not devoid of effects on protein metabolism during starvation is apparent from the response of urinary urea and ammonia, the primary nitrogenous components of urine. As shown in Fig. 7, before HGH administration urea

and ammonia excretion had plateaued at 1.3–1.5 and 1.6–2.2 g/day, respectively. Injection of growth hormone resulted in a 50% decrease in urea excretion which was maximal 24–48 hr after cessation of hormone administration. In contrast, urine ammonia excretion rose by 50% to a maximal level of 3 g/day and correlated directly with urine β -hydroxybutyrate excretion ($r = 0.728$, $P < 0.01$, Fig. 8). These simultaneous yet oppositely directed effects on urea and ammonia excretion thus served to obliterate any net effect on total nitrogen loss.

Although none of the subjects complained of any untoward symptoms when receiving growth hormone in the fed state, all developed nausea, mild vomiting, weakness, and myalgias after 24–48 hr of HGH administration in starvation. The symptoms cleared without specific therapy within 24 hr of cessation of hormone injection.

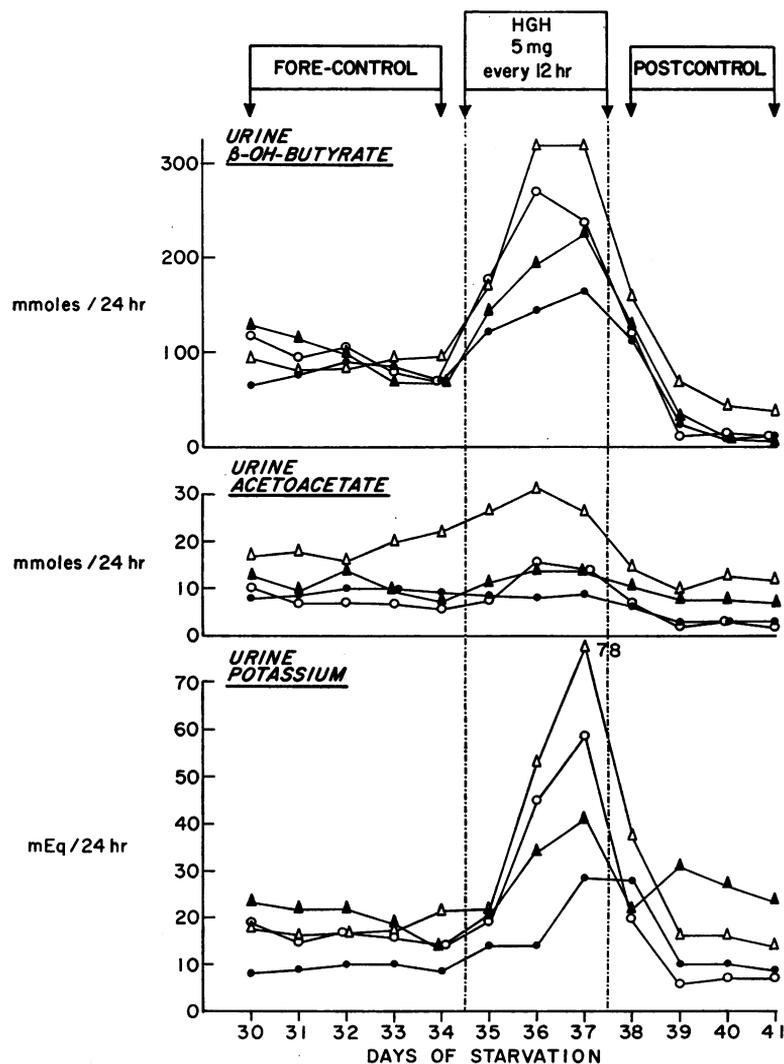


FIGURE 5 Influence of human growth hormone (HGH) on urinary excretion of β -hydroxybutyrate, acetoacetate, and potassium during starvation.

DISCUSSION

Although the metabolic response to exogenous growth hormone has been well characterized in fed subjects (8, 15, 16), the present study provides information on the influence of prolonged fasting on this response. As in the fed state, the effects of growth hormone in starvation may be considered in terms of alterations in carbohydrate and insulin metabolism, fatty acid mobilization, and net protein balance.

Persistence of the insulinotropic effect of growth hormone in prolonged fasted man is evident from the marked increment observed in serum insulin levels. Comparable findings have recently been reported in fasted dogs (17). Since blood glucose levels did not fall in association with the hyperinsulinemia, a concomitant increase in peripheral insulin resistance may be inferred. With respect to the mechanism whereby somatotropin elevates insulin levels, the clear lag in the increase in blood glucose concentration militates against hyperglycemia acting as the mediator of the hyperinsulinemia. Since neither ketones nor free fatty acids

have been demonstrated to have a consistent insulinogenic effect in man (18) and since, if anything, growth hormone lowers plasma amino acid levels (19), the possibility of a direct insulinotropic action on the pancreatic beta cell must be considered. Such an action would be consistent with the *in vitro* stimulating effects of growth hormone on isolated islets (20).

The elevations demonstrated in free fatty acid and glycerol concentrations indicate that the lipolytic or adipokinetic effects of growth hormone are well preserved in starvation. The consequences of this increase in fat mobilization are, however, far different in the fasted than in the fed state. Whereas only minimal elevations in blood and urine ketone levels were observed in the fed state, ketonemia amounting to 10–12 mmoles/liter was demonstrated in the fasted subjects. Such elevations in blood ketone acids are comparable with those observed in patients with moderate diabetic ketoacidosis (21). Furthermore, it is likely that the symptoms reported by the fasted subjects resulted from the severe ketoacidosis and potassium loss induced by somatotropin.

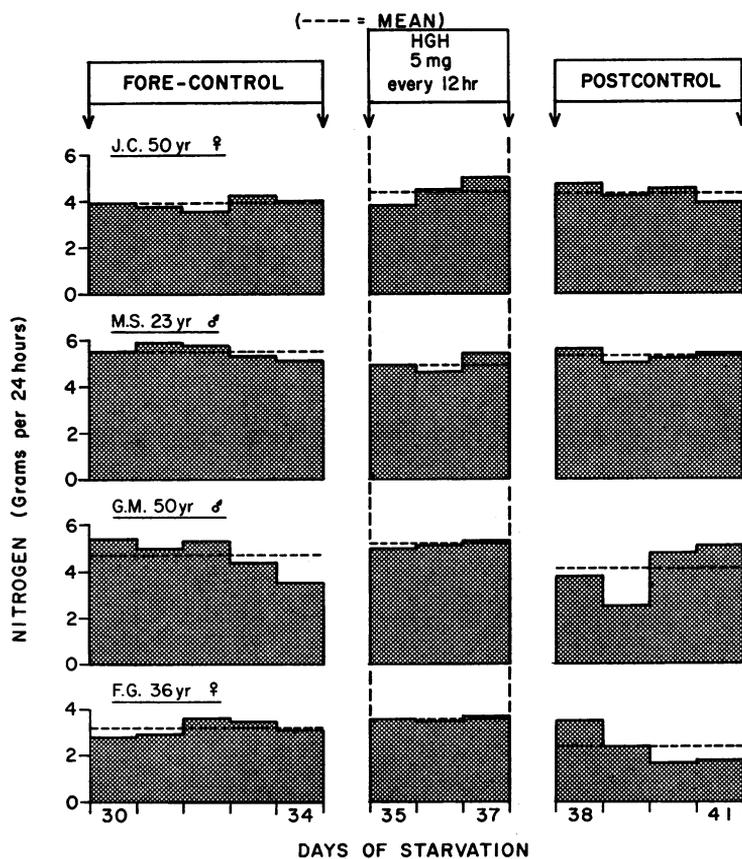


FIGURE 6 Individual values for total urinary nitrogen excretion in four subjects treated with human growth hormone (HGH) during prolonged fasting. The dashed horizontal lines represent the mean values in each subject for each experimental period.

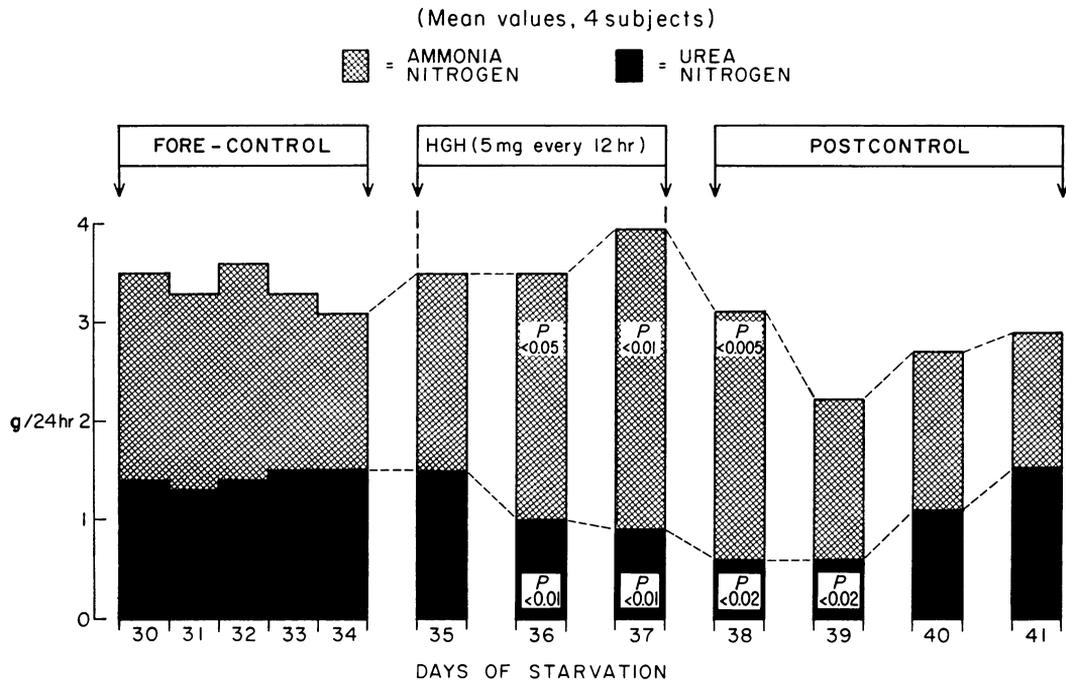


FIGURE 7 Influence of human growth hormone (HGH) on urinary excretion of ammonia and urea nitrogen during prolonged starvation. The height of the bars represents the mean value for four subjects. *P* values represent significance of difference from fore-control values (paired *t* test).

In subjects fasted for prolonged periods, loss of nitrogen by nonurinary routes is quantitatively insignificant (22). Urinary nitrogen excretion in this circumstance serves as a reliable index of net protein catabolism. The failure to demonstrate a reduction in urinary nitrogen excretion with growth hormone treatment in starvation thus is particularly noteworthy since it is indicative of the lack of an anticatabolic effect. Obesity per se cannot be implicated as interfering with the protein-conserving effects of somatotropin since a reduction in urinary nitrogen excretion and positive nitrogen balance were observed in the fed state. A more reasonable explanation is provided by the data on the individual components of urinary nitrogen. The significant reduction in urinary urea suggests that somatotropin does have an effect in reducing protein catabolic processes, primarily at the liver. As suggested on the basis of data in the fed state (23), the insulinotropic action of HGH may be of some importance in mediating this response. A net effect on total protein balance is obliterated, however, by the concomitant increase in urinary ammonia excretion. The direct correlation between urinary levels of β -hydroxybutyrate and ammonia (Fig. 8) suggests that the heightened ketonemia and ketonuria induced by growth hormone are responsible for the increased loss of nitrogen in urine as ammonia. Thus in starvation, the adipokinetic effect of HGH interferes with its anti-

catabolic action, resulting in no net conservation of body protein stores (Fig. 9). In this respect, the current findings support the concept that the dual effects of

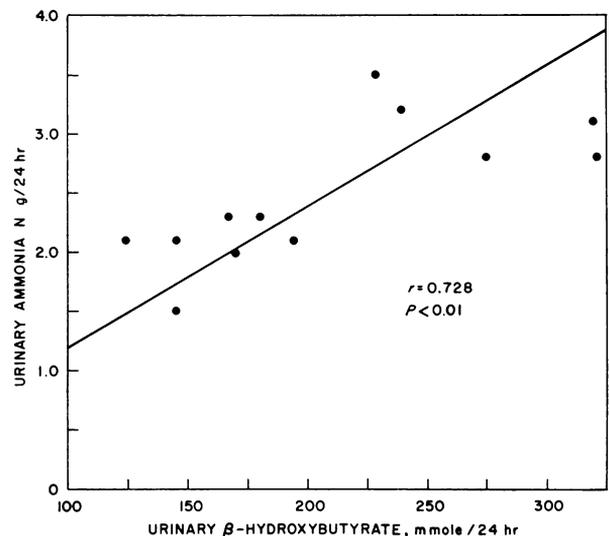


FIGURE 8 Relation between urinary ammonia nitrogen and β -hydroxybutyrate excretion during growth hormone administration in prolonged fasting. The values plotted are those observed on days 35-37 of the fast for each of four subjects (Table IV).

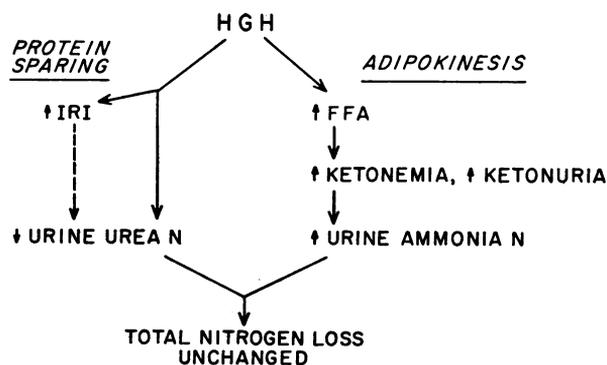


FIGURE 9 Postulated interaction of adipokinetic and protein sparing effects of human growth hormone (HGH) in prolonged starvation. The dashed arrow indicates that the insulinotropic action of HGH may be of some importance in mediating the reduction in urea nitrogen excretion. IRI, immunoreactive insulin; FFA, free fatty acids.

growth hormone on fat and protein metabolism are mutually antagonistic (24) rather than synergistic (6).

The notion that somatotropin is of physiologic importance in reducing protein catabolism in situations of caloric deprivation is derived primarily from short-term studies in hypophysectomized rats (3). The failure to observe a diminution in urinary nitrogen loss with an excess of HGH in the present study, suggests that growth hormone is not the prime regulatory factor responsible for conservation of body protein stores in man during prolonged fasting. Supporting this conclusion are the low levels of circulating HGH and the demonstration that dwarfs with an isolated deficiency of growth hormone have no greater nitrogen loss during starvation than normal controls.¹

The longstanding interest in growth hormone as a diabetogenic factor (25) raises the question as to whether the observations described in the current study are manifestations of a transient HGH-induced diabetic state (idiophyphyseal diabetes). The latter, however, has been produced in man only in the case of hypophysectomized subjects and is characterized by hyperglycemia and a reduction in urine nitrogen excretion (26), neither of which was observed in the present study. Furthermore, it has long been recognized that fasting reduces rather than enhances the diabetogenic effects of growth hormone (25).

Finally, the figures and tables show significant differences in insulin and glucose levels persisting 1 or more days after cessation of growth hormone administration. Urea nitrogen depression also continues, and there appears to be a reversal in the severity of the base line

¹Merimee, T. J., P. Felig, E. B. Marliss, S. E. Fineberg, and G. F. Cahill, Jr. 1971. Glucose and lipid homeostasis in the absence of human growth hormone. *J. Clin. Invest.* In press.

ketoacidosis as evidenced by decreased serum and urinary levels of β -hydroxybutyrate and acetoacetate. At present only speculation can be given to the meaning of these observations but a physiological basis may be present in view of the sporadic nature of growth hormone release and its induction of "secondary" factors which in turn exert metabolic effects or its initiation of altered enzyme levels with longtime constants.

ACKNOWLEDGMENTS

We wish to express our appreciation to Dzidra Rumba, Adacie Allen, Velta Ramolins, and Anna Karras for their expert technical assistance and to the nurses and staff of the Clinical Center at the Peter Bent Brigham Hospital.

This work was supported in part by U. S. Public Health Service Grants AM-05077, AM-09584, AM-09748, AM-13-526, and FR-31, and the John A. Hartford Foundation, Inc., New York.

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