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Growth hormone administration increases glucose production by preventing the expected decrease in glycogenolysis seen with fasting in healthy volunteers☆

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Abstract

Twelve volunteers were fasted overnight and infused with [^{13}C]glucose (ul) to measure glucose production (GP), gluconeogenesis, and by subtraction, glycogenolysis. Glucose production, gluconeogenesis, and glycogenolysis were measured after a 3-hour baseline infusion and two 4-hour infusions. The first 4 hours of the pituitary-pancreatic clamp study (PPCS) with replacement insulin, cortisol, and glucagon was without growth hormone (GH) administration. The second 4 hours of the PPCS was with high-dose GH administration. Six fasting volunteers acted as controls over the 11-hour study period. Overnight 12-hour fasting measurements of hormones, glucose, GP, gluconeogenesis, and glycogenolysis were similar in both groups. The PPCS had no significant effect on GP (2.43 ± 0.19 vs 2.07 ± 0.11 mg/kg per minute, PPCS vs controls, mean ± SEM). Glycogenolysis, as a percent of GP (43%-49%), was similar between PPCS and controls (43% ± 3% vs 49% ± 4%). High-dose GH for 4 hours increased GH (20.8 ± 3.8 vs 2.0 ± 0.9 ng/mL), blood glucose (127 ± 28 vs 86 ± 4 mg/dL, $P < .05$), GP (2.21 ± 0.21 vs 1.81 ± 0.12 mg/kg per minute, $P < .05$). The increase in GP was due to sustained glycogenolysis as compared to the observed fall in glycogenolysis seen with fasting alone (0.94 ± 0.21 vs 0.53 ± 0.07 mg/kg per minute, $P < .05$). Glycogenolysis, as a percent of GP, was significantly increased with high-dose GH (43 ± 5% vs 29 ± 3%, $P < .05$). High-dose GH had no effect on gluconeogenesis (1.26 ± 0.15 vs 1.29 ± 0.12 mg/kg per minute). High-dose GH prevents the fall in glycogenolysis observed with fasting alone.

1. Introduction

Hepatic glucose production (GP) appears to be regulated in part by very small changes in insulin concentration [1,2]. Glycogenolysis is suppressed at a lower insulin concentration than gluconeogenesis [2]. Glucagon also plays an important role in its ability to increase both glycogenolysis and gluconeogenesis in human beings at a basal insulin (5 μU/mL) concentration [3].

Little is known about the effects of growth hormone (GH) on glycogenolysis or gluconeogenesis in human beings in vivo. It is well known that GP is elevated in patients with acromegaly [4,5]. In addition, acute GH administration to patients with hypopituitarism doubles the rate of GP [6]. However, acute administration of GH to normal volunteers has had mixed results: doubling GP in 2 studies [7,8] and having no effect in 2 studies [9,10]. This study was performed using 2 techniques to measure glycogenolysis [11,12] to determine the effects of a GH administration during pituitary-pancreatic clamp study (PPCS) conditions on GP and blood glucose concentration. In this project, we show that high-dose GH administration increases GP by increasing the contribution of glycogenolysis to overall GP.

2. Subjects and methods

2.1. Participants

Twelve normal volunteers gave informed consent and were admitted for 3 days into an inpatient General Clinical Research Center. The research protocol was approved by the institutional review board. After an overnight fast, 6 volunteers were studied in the fasting state and 6 were also subjected to a modified PPCS technique to control multiple plasma hormonal concentrations. The age (47 ± 5 vs 42 ± 5 years, mean ± SEM), weight (70 ± 3 vs 71 ± 2 kg), and

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body mass index (25 ± 3 vs 23 ± 3 kg/m^2) were similar between fasting and PPCS patients. On day 1, volunteers were provided a regular diet delivering energy at 1.25 × basal energy expenditure (BEE), 1 g of protein intake per kilogram of body weight per day, and a minimum of 300 g of carbohydrate intake per day. Daily food intake was recorded. The last food (snack) was provided at 9 PM on day 2.

2.2. Infusion protocol

On the morning of day 3 at 6 AM, both groups started a primed, continuous 11-hour infusion of 7 to 21 μg/kg per minute of [$^{13}C_6$]glucose (ul). The priming dose was 1 to 3 mg/kg. Baseline measurements of GP and gluconeogenesis were obtained between 8 and 9 AM (12 hours of fasting). The fasting alone group comprised 6 volunteers. They were studied during a prolonged fast (12, 16, and 20 hours). The data from the fasting group were reported earlier [13].

We used the modified PPCS technique by administering somatostatin and replacement doses of insulin, GH, cortisol, and glucagon by intravenous administration [14]. Metyrapone was not administered under the traditional PPCS protocol because of the tendency to decrease liver glycogen stores [15], which may alter glycogenolysis. The PPCS (hormone infusion study) began at 9 AM or 3 hours after the start of the isotope infusion. During the 8-hour infusion period, somatostatin (0.1 μg/kg per minute), insulin (0.14 mU/kg per minute), glucagon infusion (0.8 ng/kg per minute), and hydrocortisone (0.6 μg/kg per minute) were administered. High-dose human GH was administered over the last 4 hours of the study at a rate of 40 ng/kg per minute (Fig. 1).

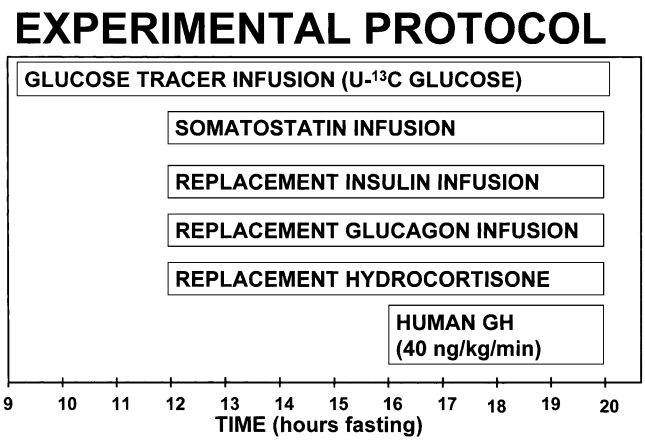

Fig. 1. This figure demonstrates the infusion protocol for the 11-hour isotope, 4 to 8 hours of hormone infusion period. The 3-hour baseline [^{13}C]glucose (ul) infusion period started at 6 AM. The PPCS started after 3 hours of a baseline stable glucose infusion or at 9 AM. At 9 AM, a 4-hour PPCS was performed without GH to determine the effects of the PPCS on glucose metabolism. At 1 PM, a 4-hour PPCS with high GH (40 ng/kg per minute) was administered until 5 PM. Both 4-hour infusions had equal amounts of insulin, cortisol, glucagon, and somatostatin. Six volunteers were infused with glucose tracer only and acted as 12-, 16-, and 20-hour fasting alone controls. The PPCS patients were also studied in the fasting state.

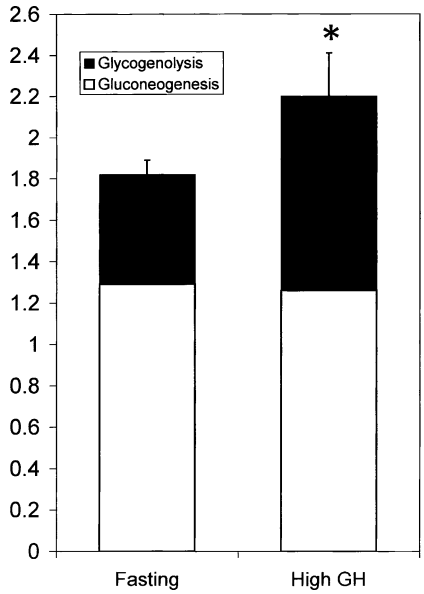

Fig. 2. The total bar represents net GP with the open bar representing gluconeogenesis and the black tone representing glycogenolysis (GP minus gluconeogenesis). High-dose GH infusion increased GP. High-dose GH infusion did not stimulate gluconeogenesis, but there was a significant increase glycogenolysis.

No GH was administered to 6 of the volunteers for the first 4 hours of the 8-hour PPCS. These 6 volunteers were given high-dose GH for their second 4 hours of the PPCS. These 6 volunteers therefore have two 4-hour PPCS (first 4 hours with no GH and second 4 hours with high-dose GH infusion, Fig. 1). The first 4-hour period was to determine if PPCS conditions were different from just fasting alone (1 PM). The second 4-hour PPCS with high GH infusion was to determine the effect of GH on glycogenolysis and gluconeogenesis, and it was completed at 20 hours of fasting (5 PM) (Fig. 2). The comparisons were made with fasting controls that would have lost a similar amount of liver glycogen depending upon the length of the fast (12, 16, and 20 hours of fasting). Comparison among different periods of fasting was not performed because liver glycogen content decreases rapidly over the first 20 hours of fasting and glycogen content may influence the rate of glycogenolysis.

Gluconeogenesis was measured by 2 techniques [11,12]. The equations for the reciprocal pool model for the measurement of gluconeogenesis and GP were recently published [12]. The M in the equations refers to the isotopomer fraction (enrichment) of glucose. Glucose production is determined by the infused dose of glucose divided by the enrichment of uniformly labeled glucose (M_6) in plasma (Eq. 1). Fractional gluconeogenesis is $\sum_1^5$ E Mn in the 5 carbons of glucose (M_1 to M_5) divided by the $\sum_1^6$ E Mn of glucose in the entire molecule (M_1 to M_6). This is then multiplied by the ratio of the entry rates of carbon 12 (^{12}C) and carbon 13 (^{13}C). The ratio of the sums of the entry rate of ^{12}C and ^{13}C in M_1 to M_5 is listed as $\sum_1^5$ E ^{12}C Mn divided by $\sum_1^5$ E ^{13}C Mn (Eq. 3). In the Tayek-Katz

Table 1
Hormone concentrations during a 4-hour PPCS, no or high GH infusion study

	Insulin (μU/mL)	Cortisol (μg/dL)	Glucagon (ng/mL)	GH (ng/mL)
12-h fasting controls (6)	9.4 ± 3.3	8.5 ± 1.0	49 ± 10	1.0 ± 0.3
12-h fasting no GH (6)	10.2 ± 2.4	9.6 ± 2.0	64 ± 7	1.3 ± 0.6
16-h fasting controls (6)	6.7 ± 1.0	9.0 ± 1.0	45 ± 6	1.3 ± 0.3
PPCS group no GH (6)	7.9 ± 1.5	13.1 ± 4.1	65 ± 10	1.7 ± 0.3
20-h fasting controls (6)	3.9 ± 0.7	6.6 ± 0.8	53 ± 10	2.0 ± 0.9
PPCS group high GH (6)	7.3 ± 1.9	11.2 ± 5.0	60 ± 9	20.8 ± 3.8*

Mean ± SEM. There was no difference in the 12-, 16-, or 20-hour values for the 2 groups.
* $P < .05$ vs 20 hours of fasting alone.

equation, fraction rate of gluconeogenesis is the product of the Cori cycle and the dilution of hepatic lactate (Eq. 2). Note that the little m is the enrichment in lactate and the big M is the glucose. The absolute gluconeogenesis is the product of the percent gluconeogenesis multiplied by GP. Nongluconeogenic glucose release (glycogenolysis) is the subtraction of gluconeogenesis from GP.

$$\text{Glucose Production} = \text{Infused Dose } (\mu\text{mol/kg/minute})/\text{Plasma } M_6 \text{ Enrichment} \quad (1)$$

$$\text{Tayek and Katz's Percent (\%) Gluconeogenesis} = \frac{\sum_1^3 M}{\sum_1^6 M} \times \frac{\sum_1^6 Mn}{2 \times \sum_1^3 mn} \quad (2)$$

(Ref. [3])

$$\text{Reciprocal Pool Fractional (\%) Gluconeogenesis} = \frac{\sum_1^6 E\ Mn \times \sum_1^5\ ^{12}C\ Mn}{\sum_1^6 E\ Mn \times \sum_1^5\ ^{13}C\ Mn} \quad (3)$$

(Haymond-Sunehag method [12])

Plasma glucose and lactate enrichment, as well as plasma insulin, C-peptide, glucose, glucagon, GH, cortisol, catecholamines (epinephrine and norepinephrine), and free fatty acids (FFAs), were determined every 20 minutes over the final 60 minutes of each infusion period (hours 2-3 [baseline], 6-7, and 10-11). Indirect calorimetry was performed over a 30-minute period between 8 and 9 AM, noon and 1 PM, and 3 and 4 PM using the delta track (Sensor Medics, Yorba Linda, Calif). Glucose oxidation was measured by collecting $^{13}CO_2$ every 20 minutes over the same periods as the blood sampling mentioned above. Percent CO_2 due to glucose oxidation was determined by percent $^{13}CO_2$ in expired air divided by the enrichment of the glucose in the blood, then corrected for loss of CO_2 into the bicarbonate pool by dividing by 0.81 [16]. Glucose oxidation was determined by the percent CO_2 due to glucose oxidation multiplied by the VCO_2 divided by 6 (all 6 carbons are labeled using [$^{13}C_6$]glucose [ul]).

All hormones and substrates, except for glucagon, were measured as previously described [17]. Glucagon was assayed by radioimmunoassay (Linco Res Inc, St Charles, Mo) with an antibody that reports much lower glucagon concentrations than those previously reported using the Unger method [13].

2.3. Data analysis

Both methods were used to calculate gluconeogenesis [11,12]. Data were compared by analysis of variance at 3 different time points. This is because glycogen stores decrease over time and the rate of gluconeogenesis and glycogenolysis changes. The first comparison was between both groups fasting alone for 12 hours. The second comparison was between PPCS conditions without GH and fasting alone (16 hours of fasting). The third comparison was between the PPCS condition with high GH and fasting alone (20 hours of fasting for both groups). Simple linear and multiple-step linear regression analysis was determined by the method of least squares. Significance was defined as $P < .05$. Data are represented by both methods for gluconeogenesis, glycogenolysis, and GP as mean ± SEM.

3. Results

Plasma GH concentrations increased 10-fold in the high GH infusion group. Plasma insulin and other hormones were unchanged (Table 1). Glucose and FFA concentrations were similar in the 2 groups at 12 hours of fasting. Plasma glucose increased in no GH and high-dose GH infusion periods (Table 2). Free fatty acids increased during the high GH infusion period only (Table 2).

Rates of GP, gluconeogenesis, glycogenolysis, and glycogenolysis as a percent of GP were similar between

Table 2
Substrate and hormone concentrations during a 4-hour PPCS, no or high GH infusion study

	Glucose (mg/dL)	FFA (mmol/L)	Epinephrine (ng/mL)	Norepinephrine (ng/mL)
12-h fasting controls (6)	93 ± 3	0.580 ± 0.020	25 ± 3	184 ± 60
12-h no GH group (6)	92 ± 5	0.578 ± 0.076	29 ± 3	180 ± 20
16-h fasting controls (6)	88 ± 3	0.626 ± 0.086	32 ± 4	196 ± 54
PPCS group no GH (6)	142 ± 31*	0.749 ± 0.120	30 ± 5	180 ± 20
20-h fasting controls (6)	86 ± 4	0.847 ± 0.107	32 ± 9	205 ± 33
PPCS group high GH (6)	127 ± 28*	1.335 ± 0.087*	30 ± 5	190 ± 20

Mean ± SEM. There was no difference in the 12-hour values for 2 groups.
* $P < .05$ vs fasting.

Table 3
Effects of high-dose GH on GP, gluconeogenesis, and glycogenolysis

	Glucose production	Gluconeogenesis (mg/kg per min)	Glycogenolysis	
			(mg/kg per min)	(% of GP)
12-h fasting controls (6)	2.33 ± 0.11	0.96 ± 0.05	1.37 ± 0.07	59 ± 3
12-h no GH group (6)	2.26 ± 0.19	0.84 ± 0.19	1.40 ± 0.06	62 ± 3
16-h fasting controls (6)	2.07 ± 0.11	1.19 ± 0.15	0.88 ± 0.09	43 ± 3
PPCS group no GH (6)	2.43 ± 0.19	1.24 ± 0.11	1.19 ± 0.15*	49 ± 4
20-h fasting controls (6)	1.81 ± 0.12	1.29 ± 0.12	0.53 ± 0.07	29 ± 3
PPCS group high GH (6)	2.21 ± 0.21**	1.26 ± 0.15	0.94 ± 0.21**	43 ± 5**

Mean ± SEM.
* $P < .05$ vs 16 hours of fasting.
** $P < .05$ vs 20 hours of fasting.

the 2 groups at 12 hours of fasting (Table 3). Between 12 and 16 of hours fasting, glucose concentration and GP decreased by 9% to 10% ($P < .05$). Glycogenolysis decreased by 36% under fasting conditions (1.37 ± 0.07 to 0.88 ± 0.09 mg/kg per minute). In contrast, glycogenolysis decreased by only 15% under the PPCS conditions (Table 3). The PPCS condition resulted in a higher blood glucose concentration (Table 2) because of an increase in glycogenolysis ($P < .05$, Table 3). Despite the effects of the PPCS conditions, the rates of glycogenolysis as a percent of GP were similar in the controls and the PPCS groups at baseline hour 16 (43%-49% of overall GP). The PPCS condition had no effect on gluconeogenesis.

During high GH administration, glucose concentration remained increasing (Table 2). The increase in fasting glucose was due to a sustained rate of GP and glycogenolysis when compared to the observed fall in GP and glycogenolysis seen with fasting alone (Table 3). At the 20-hour time point, the percent glycogenolysis was significantly increased in the high-dose GH group (43 ± 5% vs 29 ± 3%, $P < .05$, see Table 3). Between 16 and 20 hours of fasting, glycogenolysis decreased by 40% in the controls and the contribution of glycogenolysis to GP decreased from 43% to 29%. In contrast, glycogenolysis only decreased by 21% in the high-dose GH group between 16 and 20 hours, and the contribution of glycogenolysis failed to decrease (49 ± 3% to 43 ± 5%, Table 3).

Table 4
Effects of GH on glucose oxidation

	Glucose oxidation (mg/kg per min)
12-h fasting controls (6)	1.20 ± 0.10
12-h no GH group (6)	1.14 ± 0.08
16-h fasting controls (6)	1.59 ± 0.10
PPCS group no GH (6)	1.51 ± 0.11
20-h fasting controls (6)	1.56 ± 0.07
PPCS group high GH (6)	1.34 ± 0.09*

Mean ± SEM.
Glucose oxidation was determined by measuring the ^{13}C enrichment in the breath; Rates of CO_2 production were measured by calorimetry measurements.
* $P < .05$ vs 20 hours of fasting.

Despite a blunted fall in the rate of glycogenolysis in the PPCS group at 16 hours, the PPCS conditions had no effect on glucose oxidation (Table 4). In comparison, high-dose GH administration (hour-20) reduced glucose oxidation by 14% compared to controls (Table 4).

4. Discussion

Administration of GH is known to increase blood glucose concentrations. Extreme elevations in GH concentrations as seen in acromegalics coincide with an elevated rate of fasting GP [4,5]. Growth hormone administration to patients with GH deficiency increased GP [6]. However, acute administration of GH has had mixed results, increasing GP in 3 studies [7,8,18] and having no effect in 2 studies [9,10]. The dose of GH may have been inadequate in one of these studies because GH was only elevated to 7 ng/mL [9]. The other study was performed under conditions of an elevated insulin concentration, which may have prevented GH's effect at the liver [10]. Therefore, it is likely that the elevated GH concentration obtained in this study resulted in the prevention of the expected decline in rate of glycogenolysis seen with fasting alone.

This study controlled for all hormone profiles by administration of somatostatin to normalize the effect of several hormones. By matching hormone concentrations under fasting conditions, the effect of the GH can be isolated from small changes in other hormone concentrations. Small increases in glucagon (20 nL/mL) have been shown to increase glycogenolysis and GP [3]. A 20-ng/mL (nonsignificant) increase was seen in the 16-hour PPCS group that may have been responsible for the observed greater GP and glycogenolysis seen at hour 16. The small increase in the cortisol concentration during the PPCS (Table 1) may have also contributed to the observed increase in GP at hour 16. However, an increase in cortisol concentration would be unlikely to alter glycogenolysis because cortisol's major effect is on gluconeogenesis [13,18].

Growth hormone has an ability to inhibit insulin's action at the liver, but not in muscle tissue [19-21]. The blunted fall in GP and glycogenolysis observed was likely due to either a primary or secondary effect of GH. A direct effect is unlikely because GH fails to mobilize liver

glycogen in rats [22]. However, there are data that GH has an indirect effect on the liver by inhibiting the effect of insulin at the liver [21-23]. Insulin receptor substrate-1 (IRS-1) in liver is decreased in rats given GH [23]. It is interesting to note that there was no effect of GH on IRS-1 in skeletal muscle [23]. In our study, the slightly higher insulin concentration in the high GH group may have reduced GH's effect on liver (Table 2). It is well known that a small increase in insulin concentration has recently been demonstrated to reduced glycogenolysis by 30% or greater [1].

Growth hormone ability to increase GP is greater in obese compared to nonobese women [17], which may be due to hepatic hyperresponsiveness in women with central obesity and increased liver fat. In patients with HIV, GP is increased after 1 month of GH treatment because of an increase in gluconeogenesis and glycogenolysis [24]. Glycogenolysis was increased to a lesser degree, which may have been due to the greater insulin concentration (31 vs 22 μU/mL, $P < .05$). Likewise, the slightly higher insulin concentration in the GH-treated group may have blunted the GH effect on glycogenolysis seen in the current study because small increases in insulin concentration have been shown to reduce glycogenolysis compared to gluconeogenesis [1].

A small increase in GH concentration reduces glucose oxidation in healthy volunteers [9]. Likewise, in the current study, high-dose GH administration also reduced glucose oxidation by 14% when compared to controls (Table 4). Growth hormone increased gene expression for glucose oxidation in the muscle including pyruvate kinase, glycerol-3-phosphate dehydrogenase, and glucose-6-phosphate isomerase [25]. This may explain why glucose oxidation was increased in those in the GH-treated group.

4.1. Effects of GH on FFA concentrations

Serum FFA concentrations increased over time in both groups. The high GH infusion demonstrated a significant increase in FFA greater than that seen at 20 hours fasting alone. Of note is the direct correlation of FFA concentrations with the percent gluconeogenesis ($r = 0.64$, $P < .05$). Earlier unpublished observations demonstrate a direct correlation between FFA and gluconeogenesis in normals ($r = 0.665$, $P < .05$, n = 14b [17]), type 2 diabetes ($r = 0.616$, $P < .05$, n = 9 [26]), and patients with cancer ($r = 0.599$, $P < .05$, n = 13 [27]). Recent work has demonstrated that FFAs prevent the fall in both gluconeogenesis and glycogenolysis in type 1 diabetic patients [28]. The elevated FFA concentrations in our GH-treated group may have contributed to the failure of glycogenolysis to decrease as seen in the 20-hour fasting controls.

4.2. Comparison of 2 methods for gluconeogenesis

Data in Table 5 demonstrate that at 12 hours of fasting, the Haymond-Sunehag method underestimates the Tayek-Katz method by as much as 11 percentage points (26% vs 37%, $P < .05$). Haymond-Sunehag calculated gluconeogenesis in several groups by comparing their method and the Tayek-Katz method [12]. The mean rate of gluconeogenesis was similar to that obtained in the current experiment and it averaged 52% ± 7% by the Haymond-Sunehag method and 52% ± 6% by the Tayek-Katz method. The current study demonstrated the similar comparisons between the 2 methods (Table 5). The advantage of the Haymond-Sunehag method is that there is no need to measure the lactate enrichment. This reduces the costs and workload. The use of the reciprocal model (Haymond-Sunehag method) provides similar estimates of gluconeogenesis as the Tayek-Katz method. The lower results obtained in the 12-hour fasted volunteers may be due to the lower enrichment obtained.

Table 5
Percent gluconeogenesis by the Tayek-Katz and Haymond-Sunehag methods

	Gluconeogenesis (Haymond-Sunehag) (%)	Gluconeogenesis (Tayek-Katz) (%)
12-h fasting controls (6)	35 ± 4	41 ± 2
12-h no GH group (6)	26 ± 4	37 ± 1
16-h fasting controls (6)	57 ± 5	57 ± 5
PPCS group no GH (6)	52 ± 5	51 ± 4
20-h fasting controls (6)	70 ± 4	71 ± 4
PPCS group high GH (6)	69 ± 9	57 ± 6
Overall mean ± SEM	52 ± 7	52 ± 6

4.3. Conclusion

In summary, using a PPCS protocol, high-dose GH infusion prevents the expected fall in glycogenolysis seen over 16 to 20 hours fasting in normal volunteers. The percent glycogenolysis contribution to GP was greater in the high GH group (43% ± 5% vs 29% ± 3%). Glucose oxidation was also reduced when GH is administered, as has been demonstrated earlier [9]. The sustained glycogenolysis was likely due to GH's effect on GP via an indirect route of inhibiting insulin's action.

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