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Originals

Effect of physiological elevation of plasma growth hormone levels on ketone body kinetics and lipolysis in normal and acutely insulin-deficient man

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Summary. The effect of physiological elevation of growth hormone levels on ketone body kinetics was determined using a ^{14}C-ketone body tracer technique in normal and acutely insulin-deficient man. Changes of ketone body production and metabolic clearance rates during growth hormone infusion (plasma levels of approximately 25 μg/l) were measured during basal conditions and during heparin-induced elevation of non-esterified fatty acid levels. Growth hormone administration to six subjects fasted overnight resulted in an increase in ketone body production which exceeded that observed in nine control subjects (5.5 ± 0.5 versus 3.1 ± 0.1 μmol · kg^{-1} · min^{-1}, $p < 0.025$) after elevation of plasma non-esterified fatty acids. Growth hormone infusion increased glycerol and non-esterified fatty acid concentrations indicating enhanced lipolysis. During somatostatin-induced acute insulin deficiency ($n = 7$), growth hormone enhanced the increase in total ketone body production observed in six subjects receiving somatostatin alone (8.4 ± 0.8 versus 4.1 ± 0.7 μmol · kg^{-1} · min^{-1}, $p < 0.01$). Total ketone body metabolic clearance decreased by 50% during somatostatin and remained uninfluenced by growth hormone. Non-esterified fatty acids and glycerol levels increased during somatostatin, and growth hormone failed to alter non-esterified fatty acid levels significantly. The results demonstrate a stimulatory effect of high physiological growth hormone levels on ketogenesis which is largely explained by an enhancement of lipolysis and thus increase in substrate supply for ketogenesis. Growth hormone administration during acute insulin deficiency enhanced ketogenesis in the absence of alterations in plasma non-esterified fatty acid levels, suggesting a direct hepatic ketogenic effect.

Key-words: Growth hormone, ketone bodies, ketogenesis, nonesterified fatty acids, glycerol, diabetes, insulin, glucagon, somatostatin.

Several lines of evidence suggest a role for growth hormone in the regulation of ketone body metabolism in man. Various physiological and pathological conditions are associated with elevated concentrations of ketone bodies and growth hormone such as exercise [1], poor metabolic control [2], ketoacidosis [3] and post-hypoglycaemia ketosis [4] in diabetic subjects, and alcoholic ketoacidosis [5]. Administration of pharmacological amounts of growth hormone induced ketosis in animals [6–8]. Several studies in man demonstrated lipolytic and ketogenic effects of pharmacological doses of growth hormone [9–11]. An increase in ketone body concentrations by physiological growth hormone levels has been reported in normal [12, 13] and diabetic [14, 15] man. Ketone body concentrations did not always parallel non-esterified fatty acid levels [12, 15], suggesting a direct hepatic ketogenic effect of growth hormone. However, ketone body production rates were not measured and growth hormone effects on ketone body utilization could not be excluded.

The influence of growth hormone on ketone body production and peripheral clearance has not yet been investigated. We therefore studied the effect of growth hormone levels as observed in stress conditions on ketone body kinetics and lipolysis in normal and in acutely insulin-deficient man.

Methods

Patients and procedures

Twenty-eight healthy subjects (aged 50–66 years; 20 women and 8 men) volunteered to participate. Their weight was within 15% of ideal body weight and averaged 65 ± 2 kg [16]. They were on no medication. An oral glucose tolerance test and a blood chemistry profile (SMA 12 Technicon, Tarrytown, New York) were within normal limits before the study. After their usual meal at 19.00 h the evening before the study, they remained fasted until beginning of the study at 07.30 h. A Teflon cannula was inserted into an antecubital vein for infusion, and a Butterfly needle (1.1 mm inner diameter) into a hand vein of the contralateral arm which was kept in a warming chamber at 60 °C [17].

Table 1. Basal ketone body kinetics, blood substrate and hormone levels in the four study protocols

	Saline infusion ($n = 9$)	Growth hormone infusion ($n = 6$)	Somatostatin infusion ($n = 6$)	Somatostatin + growth hormone infusion ($n = 7$)
Total ketone body concentration (μmol/l)	290 ± 79	332 ± 135	248 ± 66	233 ± 66
Acetoacetate concentration (μmol/l)	114 ± 29	130 ± 43	89 ± 22	98 ± 20
β-hydroxybutyrate concentration (μmol/l)	160 ± 50	182 ± 86	145 ± 36	120 ± 45
β-hydroxybutyrate-acetoacetate concentration ratio	1.21 ± 0.20	1.55 ± 0.41	1.64 ± 0.20	1.10 ± 0.23
Acetone concentration (μmol/l)	15 ± 5	20 ± 10	14 ± 4	15 ± 5
Total ketone body production ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	4.5 ± 1.0	4.4 ± 1.1	4.0 ± 0.9	3.8 ± 1.0
Total ketone body uptake ($\mu mol \cdot kg^{-1} \cdot min^{-1}$)	4.1 ± 0.9	4.1 ± 1.0	3.8 ± 0.9	3.7 ± 0.8
Total ketone body metabolic clearance rate ($ml \cdot kg^{-1} \cdot min^{-1}$)	15.9 ± 0.9	15.9 ± 2.4	15.6 ± 1.0	17.5 ± 1.0
Plasma growth hormone (μg/l)	1.7 ± 0.3	3.0 ± 0.7	2.0 ± 0.2	2.8 ± 0.6
Plasma insulin (mU/l)	8.9 ± 1.6	9.9 ± 1.2	10.5 ± 3.2	8.7 ± 1.0
Plasma glucagon (ng/l)	134 ± 26	145 ± 21	122 ± 19	165 ± 19
Plasma NEFA (mmol/l)	0.85 ± 0.06	0.93 ± 0.09	0.91 ± 0.09	0.76 ± 0.07
Blood glycerol (μmol/l)	82 ± 10	82 ± 8	84 ± 9	69 ± 7

Results are expressed as mean ± SEM of the average of three values

Thereafter a primed continuous infusion of 150 μCi 3-^{14}C-acetoacetate was started. The tracer was allowed to equilibrate for 60 min [18], and the first sample of the basal period was collected.

Four protocols were performed: (1) saline infusion (controls, $n = 9$); (2) growth hormone infusion at 80 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 6$); (3) somatostatin (6.5 $\mu g \cdot kg^{-1} \cdot h^{-1}$, $n = 6$) to produce insulin (and glucagon and growth hormone) deficiency; and (4) somatostatin + growth hormone at 80 $ng \cdot kg^{-1} \cdot min^{-1}$ ($n = 7$). The hormones were infused for 170 min after a basal period of 30 min. To study the effects of growth hormone on ketogenesis at basal and elevated substrate levels, non-esterified fatty acid (NEFA) concentrations were raised acutely by injecting 5000 units of heparin (Liquemine, Roche, Basal) 120 min after beginning of the growth hormone infusion. The study protocol was approved by the Ethics Committee of the Department of Medicine, University Hospital, Basal.

Infusions

Sodium 3-^{14}C-acetoacetate was prepared from 3-^{14}C-ethyl-acetoacetate as described previously [18]. The radiochemical purity of the ^{14}C-acetoacetate infusion was 80 ± 1%. Human growth hormone (Crescormon, Kabi, Stockholm) was diluted with 0.145 mol/l NaCl to which albumin (Swiss Red Cross, Berne) was added to provide a final concentration of 1% (w/v). Somatostatin (kindly provided by Serono, Freiburg i. Br., FRG) was dissolved in NaCl solution (0.145 mol/l).

Analyses and calculations

Blood concentrations of ^{14}C-acetoacetate and ^{14}C-total ketone body were determined individually by converting the ketone bodies to ^{14}C-acetone according to the method of Mayes and Felts [19] with a minor modification [20]. Blood acetone was measured by headspace analysis using gas chromatography [21]; blood acetoacetate, β-hydroxybutyrate and glycerol were determined using microfluorometric techniques as described previously [18]. Plasma NEFA were measured by a radiochemical method [22]; plasma insulin [23], growth hormone [24] and glucagon [25] by radioimmunoassay. For the latter, the pancreatic glucagon-specific antibody 4305, kindly provided by Dr. J. Holst, Copenhagen, was employed [26]. Plasma glucose concentrations were determined using a YSI glucose analyser (Yellow Springs Instruments, Yellow Springs, Ohio, USA). Recovery of ^{14}C-acetoacetate added to non-radioactive blood was 87 ± 2%, that of ^{14}C-β-hydroxybutyrate 83 ± 1%, and corrections were made accordingly.

Total ketone body turnover rates were determined using the combined specific activity of total ketone bodies [18]. Ketone body turnover rates of each time point were calculated by the method of moving average using the specific activity of ketones of three consecutive blood samples and regression analysis in the calculation [17]. Statistical analyses were performed using Student's two-tailed t-test for paired and for unpaired data.

Results

Basal ketone body kinetics, substrate and hormone levels in normal subjects fasted overnight

During the 30-min control period, total ketone body kinetics, and concentrations of insulin, glucagon and growth hormone, NEFA and glycerol were similar in the four study protocols (Table 1).

Effect of growth hormone on ketone body kinetics and lipolysis in normal subjects

Administration of growth hormone resulted in an increase in ketone body production which was statistically significant compared to the last pre-infusion value from 60 min onwards (Fig. 1, $p < 0.01$).

The increase in ketone body production was greater during the growth hormone than during saline infusion after heparin-induced elevation of NEFA levels from 135 min onwards. Administration of heparin resulted in a significant increase in ketogenesis; within 30 min total ketone body production increased during growth hormone by 3.6 ± 0.4 versus 2.3 ± 0.4 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ during saline ($p < 0.05$). The fact that ketone body production was already increasing at the time of heparin injection (120 min) is due to the mode of calculation of ketone body kinetics using the moving average method (see Methods). Total ketone body uptake showed a similar increase to that of production but with a slight delay, causing the increase in ketone body concentration. The metabolic clearance rate of total ketone bodies de-

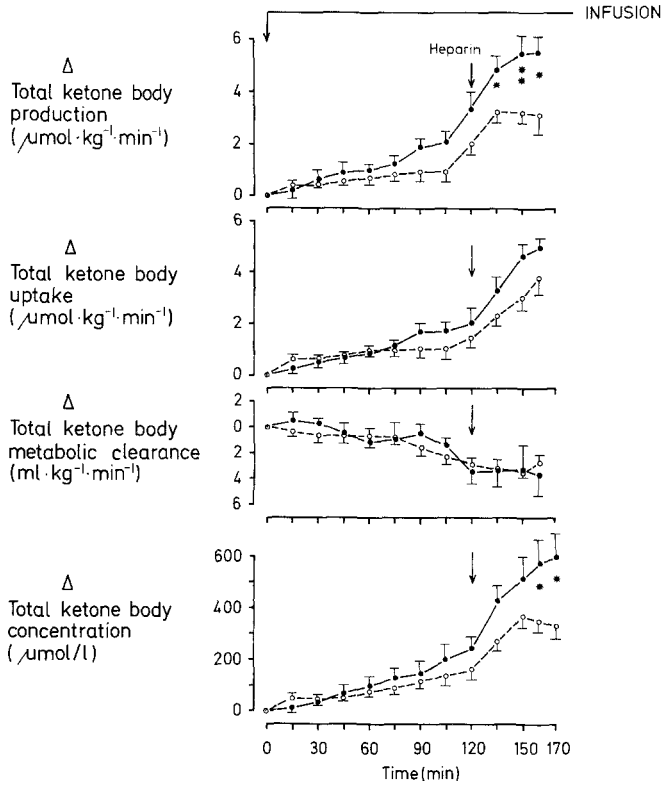

Fig. 1. Changes in total ketone body production, uptake, metabolic clearance rate and total ketone body concentration during infusion of growth hormone (80 ng·kg^{-1}·min^{-1}, solid line) or saline (dashed line) in normal subjects at 120 min, 5000 units of heparin were injected. The results are expressed as mean ± SEM. *$p<0.05$; **$p<0.025$ between groups

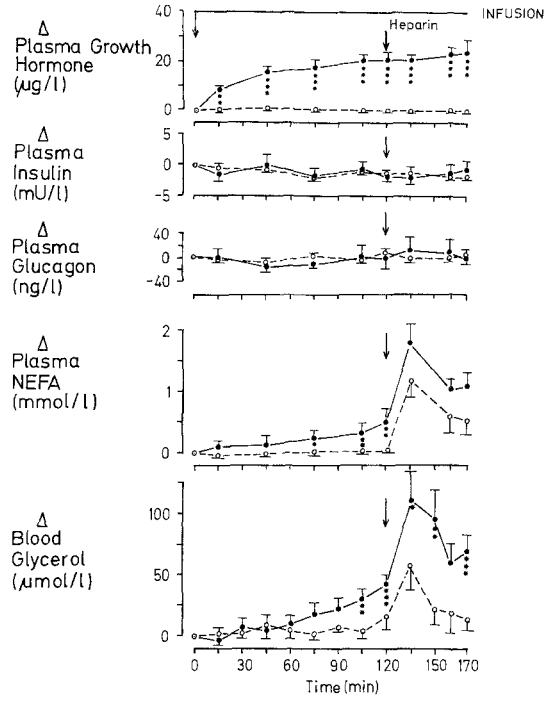

Fig. 2. Changes in the concentrations of growth hormone, insulin, glucagon, NEFA and glycerol during growth hormone infusion (solid line) or saline (dashed line). See legend to Figure 1. Results are expressed as mean ± SEM. *$p<0,05$; **$p<0.02$; ***$p<0.01$ between groups

creased slightly but significantly (−17 ± 3%) during saline ($p<0.01$), and similarly during growth hormone (−22 ± 7%). Blood β-hydroxybutyrate concentrations increased during 170 min of growth hormone infusion by 419 ± 69 μmol/l ($p<0.001$), and acetoacetate by 161 ± 23 μmol/l ($p<0.001$). In comparison, blood β-hydroxybutyrate concentrations increased less in the control subjects by 240 ± 49 μmol/l, and acetoacetate by 86 ± 11 μmol/l ($p<0.05$ and $p<0.01$ respectively, compared with the growth hormone infusion study). Blood acetone concentrations increased similarly in both protocols (by 14 ± 5 and 18 ± 6 μmol/l, $p<0.01$, respectively). Figure 2 demonstrates that growth hormone infusion resulted in an elevation of plasma growth hormone levels by 20 ± 2 μg/l, while plasma insulin and glucagon remained unchanged. Plasma concentrations of NEFA increased gradually during growth hormone, the increase was significantly higher than in control subjects receiving saline from 75 min onwards. After heparin injection, mean plasma NEFA increased briskly and similarly in both protocols, within 15 min by 1.1 and 1.2 mmol/l, respectively. The course of blood glycerol concentrations was similar to that of NEFA. Elevation of growth hormone levels resulted in a higher increase in blood glycerol concentrations than in controls, indicating enhanced lipolysis. After heparin, blood glycerol concentrations increased in a spike-decline pattern in both protocols.

Effect of elevated growth hormone levels on ketone body kinetics and lipolysis during somatostatin-induced insulin deficiency

Administration of somatostatin alone resulted in a significant elevation of ketone body production after 30 min ($p<0.001$ compared to the last pre-infusion value, Fig. 3). The increase in ketone body production was significantly greater during growth hormone than during infusion of somatostatin alone from 90 min onwards. Heparin-induced elevation of plasma NEFA levels resulted in a further acceleration of ketogenesis in both protocols. At the end of the infusions, ketone body production rates during combined infusion of growth hormone and somatostatin had increased more than threefold. Total ketone body uptake increased during both protocols, but the rates were always slightly lower than the concurrent production rates. The metabolic clearance rate of ketone bodies declined similarly in both protocols by approximately 50%. Total ketone body concentrations increased continuously during both protocols as a result of the positive balance between production and uptake. The β-hydroxybutyrate/

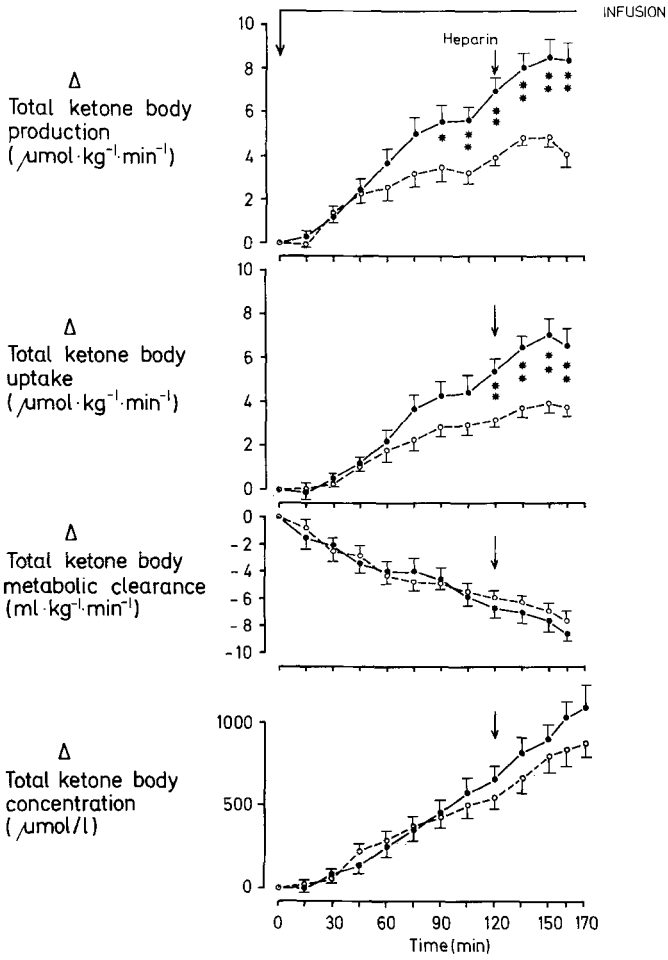

Fig. 3. Changes in total ketone body production, uptake, metabolic clearance rate and total ketone body concentration during infusion of somatostatin (6.5 μg·kg^{-1}·h^{-1}) alone (dashed line) or in combination with growth hormone (80 ng·kg^{-1}·min^{-1}, solid line) in normal subjects. At 120 min, 5000 units of heparin were injected. Results are expressed as mean ± SEM. *$p<0.05$; **$p<0.01$ between groups

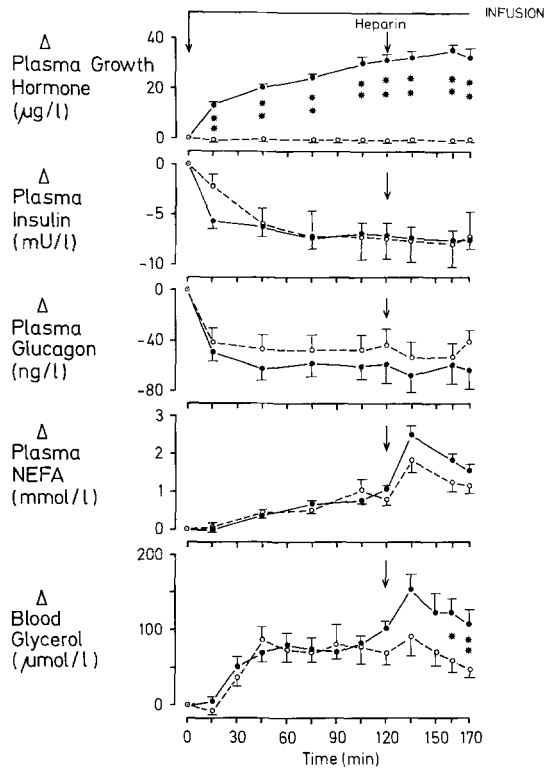

Fig. 4. Changes in concentrations of growth hormone, insulin, glucagon, NEFA and glycerol during infusion of somatostatin alone (dashed line) or in combination with growth hormone (solid line). See legend to Figure 3. Results are expressed as mean ± SEM. *$p<0.02$; **$p<0.01$ between groups

acetoacetate concentration ratio increased similarly during somatostatin with and without growth hormone infusion (from 1.1 ± 0.2 to 3.3 ± 0.3 in the growth hormone study, $p<0.001$).

Figure 4 demonstrates that plasma growth hormone concentration increased during growth hormone infusion by approximately 30 μg/l. Infusion of somatostatin alone decreased basal growth hormone levels modestly but significantly (−0.4 ± 0.1 μg/l at 45 min, $p<0{,}025$). Infusion of somatostatin lowered plasma concentrations of insulin and glucagon, and increased plasma NEFA and blood glycerol levels significantly in both protocols. Heparin injection resulted in a significant increase in plasma NEFA and blood glycerol concentrations. Growth hormone did not influence plasma NEFA levels but enhanced the heparin-induced increase in blood glycerol concentrations at the last two time points of the study.

Plasma glucose levels

Plasma glucose levels did not change significantly during 170 min of growth hormone or saline infusion. Plasma glucose concentrations decreased during somatostatin infusion, with and without addition of growth hormone (from 5.3 ± 0.2 and 5.3 ± 0.2 mmol/l to nadirs at 90 min of 3.8 ± 0.3 and 3.6 ± 0.3 mmol/l, respectively). Thereafter, plasma glucose levels increased gradually reaching values of 4.7 ± 0.4 and 4.0 ± 0.3 mmol/l at the end of the infusions (NS).

Discussion

The results of the present study demonstrate that high physiological plasma growth hormone levels exert lipolytic and ketogenic effects in subjects fasted overnight. They explain the previously noted increase in ketone body concentrations during physiological elevation of growth hormone levels as a result of increased ketone body production [12–15]. The concomitant elevation of plasma NEFA levels in normal subjects suggests that the ketogenic effect was secondary to lipolysis and thus to increased substrate supply for ketogenesis. This conclusion is supported by the observation that substrate elevation per se, as observed after heparin injection, resulted in a parallel increase in plasma NEFA levels and

ketone body production. The effect of growth hormone effect was significant in normal subjects after ketogenesis was supported by increased NEFA concentrations induced by heparin injection.

It was of interest to note that growth hormone infusion during insulin deficiency failed to increase plasma NEFA levels, whereas ketogenesis was significantly enhanced. In addition, the ketogenic response to heparin-induced elevation of plasma NEFA levels was significantly greater during growth hormone than during saline administration. This dissociation between plasma NEFA levels and ketogenesis agrees with previous findings of increased ketone body concentrations without concomitant changes in plasma NEFA levels during growth hormone administration in normal [12] and in diabetic [14] subjects. It suggests a direct hepatic ketogenic effect of growth hormone independent of substrate uptake since plasma NEFA levels and, thus presumably, hepatic NEFA uptake [27, 28] were unaffected. The issue of the effects of growth hormone on hepatic ketogenesis in vitro is controversial; ketogenic effects were observed in rat liver slices [29] but not in perfused rat liver [30].

The present study employed a tracer technique to determine growth hormone effects on ketone body production and on peripheral uptake. This turned out to be of importance since changes in ketone body production were apparent before significant alterations in ketone body concentrations were observed.

Growth hormone effects on ketone body clearance, and thus on utilisation, were not detected in the present study, in agreement with previous findings in vitro [31]. Thereby we excluded the possibility that early insulin-like [32, 33] or late anti-insulin [34] effects of growth hormone affected ketone body utilisation. This was of significance since insulin has been shown to enhance ketone body utilisation in dogs [35]. The same effect may also be the explanation for the decrease of ketone body clearance during somatostatin-induced insulin deficiency in the present study. However it is possible that hyperketonaemia contributed to the decrease in ketone body clearance, since a fall in clearance has previously been observed when ketone body concentrations were raised by ketone body infusions [18]. On the other hand, insulin-like effects of growth hormone on lipolysis, ketone body production or clearance were not detectable in the present study, suggesting that the recently reported early insulin-like effect on hepatic glucose production affected this process selectively [33].

It was of interest to note that during the initial 120 min of growth hormone infusion, lipolytic effects were detectable in normal subjects but not during acute insulin deficiency. This suggests that the lipolytic effect of growth hormone resulted from its anti-insulin properties [34] which was not apparent in acutely insulin-deficient subjects.

Infusion of somatostatin was used to produce acute insulin deficiency. The validity of this model is supported by the fact that direct metabolic effects of somatostatin in liver cells and adipocytes were absent in a previous study in vitro [36]. Additionally, insulin replacement during somatostatin infusion in vivo prevented the somatostatin-induced increase in lipolysis and ketogenesis in normal subjects [37]. Moreover the same study demonstrated that glucagon deficiency during somatostatin infusion did not influence ketogenesis [37].

The elevated growth hormone concentrations achieved during infusion in the present studies resemble those observed during surgical stress [38], exercise [1, 39], poorly controlled diabetes mellitus [2, 3], and alcoholic ketoacidosis [5]. Since in these situations lipolysis and ketone body concentrations are frequently increased, the present results suggest that growth hormone contributes to the development of hyperketonaemia during these conditions. The findings of the present study provide evidence that elevated growth hormone levels during insulin deficiency may accelerate hepatic ketogenesis directly, in addition to a stimulatory effect on lipolysis and substrate-induced enhancement of ketogenesis. Increased rates of ketogenesis during insulin lack result in a further elevation of ketone body levels due to a decrease of the metabolic clearance rate of ketone bodies.

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