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Increased glucose turnover and glucose cycling in acromegalic patients with normal glucose tolerance

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Summary. To characterize the diabetogenic effects of growth hormone, we simultaneously measured glucose turnover with 2-^{3}H- and 6-^{3}H-glucose in six acromegalic patients with normal fasting blood glucose and oral glucose tolerance tests. Eight healthy volunteers served as controls. All subjects were studied under both basal conditions and during glucose infusion (2 mg·kg^{-1}·min^{-1}). We determined true glucose production and irreversible glucose uptake using 6-^{3}H-glucose and glucose cycling (difference between 2-^{3}H- and 6-^{3}H-glucose). After an overnight fast, glucose production was higher than normal in the acromegalic patients (2.18±0.15 vs 1.85±0.03 mg·kg^{-1}·min^{-1}, $p<0.05$) despite hyperinsulinaemia. The metabolic clearance rate was normal. During the glucose infusion, glucose production was not suppressed as effectively in the acromegalic patients as in controls nor was glucose uptake augmented, while metabolic clearance rate was decreased. In acromegaly, basal glucose cycling was increased (0.44±0.08 vs 0.25±0.07 mg·kg^{-1}·min^{-1}, $p<0.05$). Furthermore cycling of endogenous glucose measured during glucose infusion was also augmented (0.41±0.05 vs 0.24±0.05 mg·kg^{-1}·min^{-1}, $p<0.05$). Hence the increase of glucose cycling (70%) was much more pronounced than that of glucose production (17%). In conclusion, small defects in glucose metabolism in acromegaly can be detected with sensitive tracer methods. These derangements are confined to the liver under fasting conditions, but are of both hepatic and extrahepatic origin during glucose loading.

Key words: Acromegaly, glucose turnover, glucose cycle.

It is well known that the prevalence of impaired glucose tolerance (~50%) and manifest diabetes mellitus (~10%) is higher in acromegalic patients than in the general population [1]. Since the glucose intolerance found in acromegaly is associated with increased insulin levels [2-5], it has been suggested that the impairment of carbohydrate metabolism is mainly mediated by decreased insulin sensitivity [2]. Direct support for such a view is provided by a study demonstrating reduced glucose uptake in the isolated forearm after the administration of intra-arterial insulin in acromegalic patients [6]. Furthermore, treatment for acromegaly leading to reduced plasma levels of growth hormone (GH) results in improvement in hyperglycaemia, hyperinsulinaemia and insulin sensitivity [7, 8].

The mechanisms behind insulin resistance in acromegaly are not fully understood. It is also unclear to what extent glucose intolerance is a result of increased glucose production or of decreased glucose utilization. On a cellular level acromegaly is associated with a decrease in insulin binding at high insulin concentrations [9].

The aim of the present study was to determine true and total glucose production as well as irreversible glucose uptake and total glucose phosphorylation in a group of acromegalic patients with normal oral glucose tolerance. For comparison, a group of healthy subjects and a patient with acromegaly and newly diagnosed diabetes mellitus were also included. Total glucose production and total glucose phosphorylation were determined with 2-^{3}H-glucose while true glucose production and irreversible glucose uptake were measured with 6-^{3}H-glucose. The difference in glucose production calculated using these two tracers gives a measure of glucose cycling (GC). This metabolic pathway is the main futile cycle operating in the liver. GC involves phosphorylation of glucose to glucose 6-phosphate by glucokinase and its dephosphorylation by glucose 6-phosphatase.

Subjects and methods

Subjects

Seven patients with acromegaly (Table 1) and eight healthy control subjects were studied. All patients were evaluated for severity of acromegaly at the Department of Endocrinology, Karolinska Hospital. The disease was newly diagnosed in six patients, while one patient (KOR) had significant symptomatology despite earlier transsphenoidal pituitary surgery and external irradiation. The diagnosis was based on clinical findings as well as on sustained elevation of plasma GH levels and on altered GH responses to L-DOPA [10] and thyrotropin-releasing hormone [11]. An acidophilic or basophilic pituitary

Table 1. Clinical and metabolic data on the acromegalic patients

Patient	Sex	Age (years)	Body mass index (kg/m^2)	Plasma glucose (OGTT)		Basal plasma growth hormone[a] (μg/l)	Basal serum prolactin[a] (μg/l)
				Fasting	2 h-value		
				(mg/dl)			
KOR	M	38	32.7	79	130	6	5
OR	M	23	23.6	94	86	232	21
RK	F	47	28.3	79	126	6	4
HG	F	65	19.9	83	94	12	6
AS	F	45	23.5	86	137	92	16
BT	M	59	27.4	90	149	5	3
BA	M	51	27.8	198	-	188	6

[a] mean of 4–6 values for each patient

adenoma was found during transsphenoidal surgery in all patients. There was no significant hyperprolactinaemia in any patient (Table 1). Type 2 (non-insulin-dependent) diabetes mellitus was discovered in one patient (BA), while in the remaining patients fasting plasma glucose levels as well as an oral glucose tolerance test (OGTT) were normal [12]. None of the patients were taking any medication except KOR, who was receiving appropriate hormonal replacement therapy consisting of cortisone acetate, thyroxine and testosterone. With the exception of one patient (AS) who had secondary amenorrhoea of a few years duration and who regained normal menses after transsphenoidal surgery, there was no evidence of pituitary insufficiency.

The control group consisted of five male and three female healthy volunteers aged 43.8 ± 2.3 years (mean ± SEM). The average body mass index was $23.0 \pm 0.8\ kg/m^2$. All subjects had normal OGTT [12] with fasting and 2 h glucose values being 77 ± 1 and 90 ± 7 mg/dl respectively.

Infusions

All subjects were studied in the recumbent position at 08.00 hours after a 12–14 h overnight fast. An indwelling catheter was placed in an antecubital vein in each arm, one for infusion of unlabeled and isotopically labeled glucose and the other for blood sampling.

After cannulation a primed constant infusion of sterile and non-pyrogenic 2-^{3}H-glucose and 6-^{3}H-glucose (New England Nuclear, Boston, Mass, USA) in isotonic saline was begun and continued throughout the experiment (240 min). The priming dose of labeled glucose was 24–30 μCi (1 Ci = 3.7×10^{10} bequerels) and the rate of infusion was 0.20–0.25 μCi/min. After an equilibration period of 120 min an infusion of unlabeled glucose was begun as well. It was given at a rate of $2\ mg \cdot kg^{-1} \cdot min^{-1}$ by means of a Tecmar pump. The concentration of glucose in the infusate was measured in each experiment with the same assay as the plasma samples.

Blood sampling

During the equilibration period blood samples were drawn at 0, 90, 100, 110 and 120 min. At the start of the infusion of unlabeled glucose, the clock was reset to zero and samples were drawn every 10 min thereafter.

Analytical procedures

Heparinized blood was kept on ice until centrifuged at 4 °C. A plasma sample was used for determination of plasma glucose in triplicate while the rest was frozen at −20 °C for later analysis of C-peptide, insulin, glucagon and GH as well as for specific activity of glucose. Plasma glucose was determined by the glucose oxidase method [13]. C-peptide and GH were measured by radioimmunoassay with commercially available kits (Novo Research, Bagsvaerd, Denmark and Phadebas hGH Prist, Pharmacia, Sweden, respectively). Insulin was measured by radioimmunoassay using antibodies raised in guinea pigs against porcine insulin. Human insulin served as a standard [14]. Blood samples for analysis of glucagon were collected in prechilled tubes containing Trasylol and EDTA. The radioimmunoassay was based on the method of Faloona and Unger [15] using the 30K antibody.

Tracer methods and calculations

Measurements of specific activity of glucose were performed after deproteinization with Ba $(OH)_2$ and $ZnSO_4$. The supernatant was passed through ion-exchange chromatography to remove labeled metabolites. An aliquot of the eluate was evaporated to dryness under reduced pressure at 40 °C. After addition of water and liquid scintillation solution the total radioactivity from 2-^{3}H-glucose and 6-^{3}H-glucose was measured in a beta scintillation counter. An external standard was used for quenching. All samples and standards were counted for 50 min and the counts for the samples were at least 4 times higher than for the background.

The radioactivity of 6-^{3}H-glucose was determined as described by Dunn et al. [16]. In short, 10.0 mg of glucose was added as a carrier to 2 ml of the eluate from ion-exchange chromatography. Glucose was then oxidized with periodate to 5 molecules of formic acid (derived from carbons 1–5) and 1 molecule of formaldehyde, derived from carbon 6. After addition of dimedon, formaldehyde precipitates as formaldemethone. The radioactivity of the precipitate was determined after filtering, drying and weighing.

The radioactivity of 2-^{3}H-glucose was calculated as the difference between total radioactivity and that of 6-^{3}H-glucose as measured with the dimedon procedure. Aliquots of the infused mixture of 2-^{3}H-glucose and 6-^{3}H-glucose were run along with the plasma samples to determine the exact rate of the tracer infusion and to estimate possible losses of 6-^{3}H-glucose relative to 2-^{3}H-glucose during the dimedon procedure. On average, 6-^{3}H-glucose accounted for 50% of total radioactivity in the infusate in acromegalics and controls. Aliquots of 2-^{3}H-glucose did not display any radioactivity above background after being passed through the dimedon procedure.

The rates of glucose production (Ra, rate of appearance) and of glucose uptake (Rd, rate of disappearance) were determined using the method of primed constant tracer infusion [17]. This method is based on modified single compartment analysis of glucose turnover, in which it is assumed that rapid changes in the specific activity and concentration of glucose do not occur uniformly within the entire glucose pool. To compensate for this non-uniform mixing, a term of the non-steady-state equation was multiplied by a correction factor (pool fraction) of 0.65 [18, 19]. A sliding fit technique employing three consecutive values of glucose concentration and specific activity was also used in the calculations as described previously [20]. This approach for calculating non-steady-state kinetics of glucose turnover has been validated and confirmed in vivo [19].

During glucose infusions the endogenous rate of glucose production was calculated by subtracting the rate of infusion of exogenous glucose from the tracer-determined total rate of glucose appearance. An integrated value of Ra during the glucose infusion was calculated

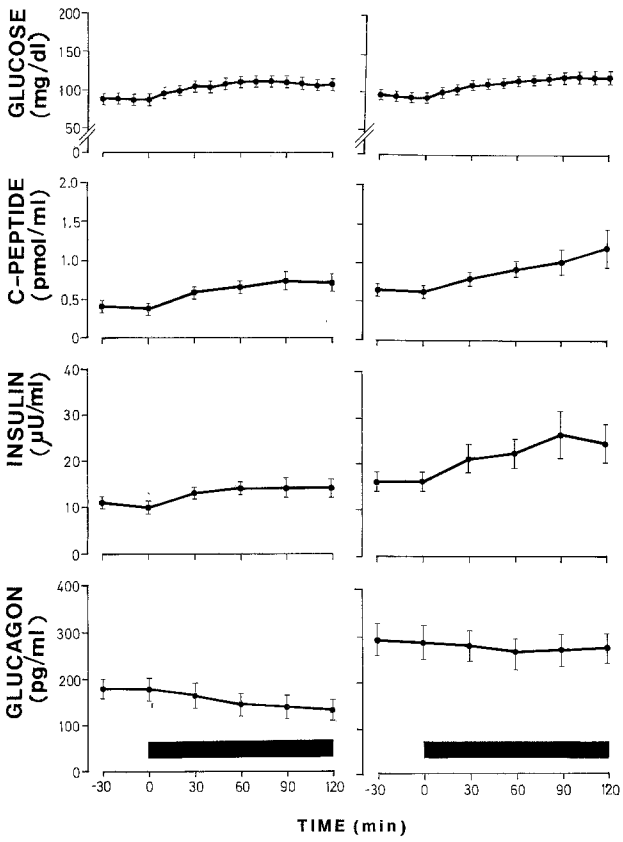

Fig. 1. Effect of glucose infusion (black bar) on plasma concentrations of glucose, C-peptide, insulin, and glucagon in eight control subjects (left) and in six patients with acromegaly (right). Data are shown as the mean ± SEM

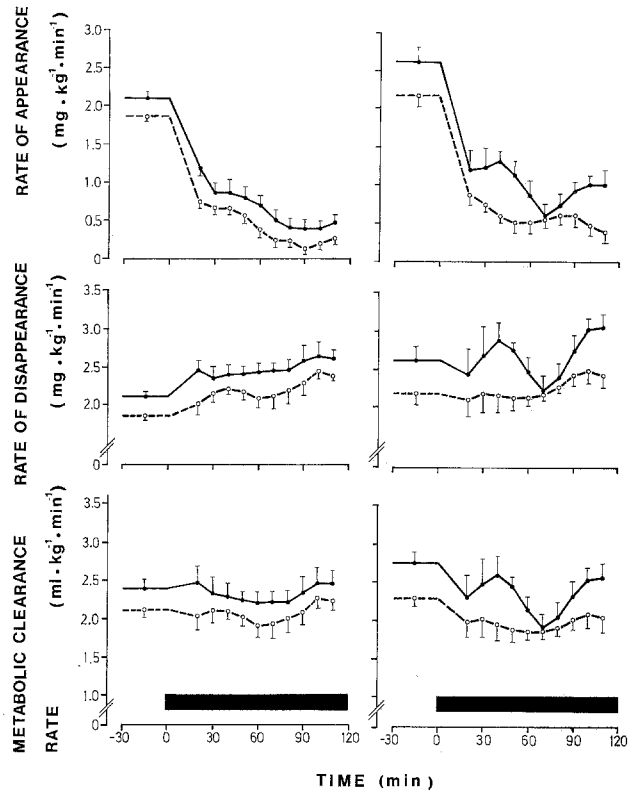

Fig. 2. Effect of glucose infusion (black bar) on rates of appearance (Ra), disappearance (Rd) and metabolic clearance (MCR) of glucose in eight control subjects (left) and in six patients with acromegaly (right). Data are shown as the mean ± SEM, for 2-^{3}H-glucose (●—●) and for 6-^{3}H-glucose (○-----○)

as the area under the Ra curve between 20 and 110 min. This value was divided by 90 to obtain the average value during this 90 min period. In a similar way the average Ra during 90–110 min was calculated. Using the same technique the average Rd was obtained for both time periods during the glucose infusion. In addition, the metabolic clearance rate of glucose (MCR) was calculated as Rd/C, where C is the glucose concentration.

The activity of GC was determined as the difference in Ra measured with 2-^{3}H-glucose and with 6-^{3}H-glucose in the basal state as well as between 20 and 110 min and between 90 and 110 min of the glucose infusion. In postabsorptive state the difference between 2-^{3}H-glucose and 6-^{3}H-glucose measures substrate cycling that corresponds the activity of glucokinase, the enzyme that catalyzes a reaction opposite to the net flux. During glucose infusion 2-^{3}H-glucose measures all endogenously released glucose, including glucose that recycles back, while 6-^{3}H-glucose measures endogenously released glucose that does not recycle back. Thus the difference between 2-^{3}H and 6-^{3}H-glucose measures the rate at which endogenous glucose cycles back, but it does not measure the cycling that results from exogenous glucose infusion.

Statistical analysis

Results are expressed as the mean ± SEM. Student's t-test was performed for paired and unpaired data after logarithmic transformation. Correlation analysis was undertaken using the Spearman rank correlation coefficient.

Results

In both control subjects and acromegalic patients an isotopic plateau was reached during the last 30 min of the equilibration period. The mean coefficient of variation (CV) was below 6% for both isotopes. Plasma glucose was also stable during this period (Fig. 1), with an average CV of 2.1% in the acromegalic patients and 0.6% in the control subjects. This implies that steady state conditions were obtained for labeled and unlabeled glucose by the end of the equilibration period.

Plasma glucose levels are shown in Figure 1. During the last 30 min of the equilibration period plasma glucose tended to be higher in the acromegalic patients than in the control subjects (95 ± 3 vs 89 ± 3 mg/dl, NS). During the glucose infusion, plasma glucose reached a plateau of about 120 mg/dl in the acromegalic patients and 110 mg/dl in the control subjects. Neither the plateau levels nor the incremental areas under the glucose curves were significantly different. Mean plasma C-peptide was higher in acromegalic patients than in control subjects in the basal state (0.64 ± 0.03 vs 0.40 ± 0.05 pmol/ml, $p < 0.01$), whereas the plateau levels did not differ significantly (1.11 ± 0.20 vs 0.73 ± 0.10 pmol/ml, NS). Plasma insulin levels were higher in the acromegalic patients than in the control subjects in the basal state (16 ± 2 vs 11 ± 1 μU/ml, $p < 0.025$) and at the end of the infusion period (25 ± 4 vs 14 ± 2 μU/ml, $p < 0.025$). The increments of plasma C-peptide and insulin did not differ between the groups during the glucose infusion. Plasma glucagon concentrations were

Table 2. Rate of appearance (Ra) of glucose in patients with acromegaly and in healthy controls. During the glucose infusion Ra was averaged during 20–110 min and during 90–110 min. Values are mean ± SEM

Experimental condition	Tritium label	Ra ($mg \cdot kg^{-1} \cdot min^{-1}$)		
		Healthy controls	Acromegalic patients	
			Normal glucose tolerance	Diabetes
Basal state	6-^{3}H-glucose	1.85 ± 0.03	2.18 ± 0.15[a]	4.85
		**	**	
	2-^{3}H-glucose	2.10 ± 0.07	2.62 ± 0.19[a]	5.95
Glucose infusion (20–110 min)	6-^{3}H-glucose	0.40 ± 0.04	0.58 ± 0.07[a]	2.33
		***	**	
	2-^{3}H-glucose	0.64 ± 0.08	0.99 ± 0.04[b]	3.83
Glucose infusion (90–110 min)	6-^{3}H-glucose	0.20 ± 0.04	0.49 ± 0.12[a]	1.95
		*	*	
	2-^{3}H-glucose	0.42 ± 0.08	0.98 ± 0.09[c]	4.20

[a] $p < 0.05$, [b] $p < 0.01$, and [c] $p < 0.001$ acromegalic patients vs control subjects
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ 2-^{3}H-glucose vs 6-^{3}H-glucose

Table 3. Rate of disappearance (Rd) of glucose in patients with acromegaly and in healthy controls. During the glucose infusion Rd was averaged during 20–110 min and during 90–110 min. Values are mean ± SEM

Experimental condition	Tritium label	Ra ($mg \cdot kg^{-1} \cdot min^{-1}$)		
		Healthy controls	Acromegalic patients	
			Normal glucose tolerance	Diabetes
Basal state	6-^{3}H-glucose	1.85 ± 0.03	2.18 ± 0.15[a]	4.85
		**	**	
	2-^{3}H-glucose	2.10 ± 0.07	2.62 ± 0.19[a]	5.95
Glucose infusion (20–110 min)	6-^{3}H-glucose	2.20 ± 0.08	2.25 ± 0.12	4.35
		**	***	
	2-^{3}H-glucose	2.47 ± 0.09	2.67 ± 0.14	5.93
Glucose infusion (90–110 min)	6-^{3}H-glucose	2.37 ± 0.10	2.45 ± 0.15	4.10
		*	**	
	2-^{3}H-glucose	2.61 ± 0.16	2.95 ± 0.12	6.28

[a] $p < 0.05$ acromegalic patients vs control subjects
*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ 2-^{3}H-glucose vs 6-^{3}H-glucose

higher in acromegalic patients than in control subjects in the basal state and at the end of the glucose infusion ($p < 0.025$). Within both groups hyperglycaemia resulted in decreased glucagon concentrations ($p < 0.05$). In acromegalic patients basal plasma GH averaged 47 ± 24 ng/ml. There was a slight but not significant increase in GH during the glucose infusion. The correlation between basal levels of GH and glucagon was not significant ($r = 0.829$).

As summarized in Table 2 and Figure 2, Ra measured after an overnight fast was significantly higher in the acromegalic patients than in the control subjects with both isotopes. The basal Ra determined with 6-^{3}H-glucose was lower than with 2-^{3}H-glucose in acromegalic patients and control subjects. The glucose infusion caused a prompt suppression of Ra irrespective of the isotope used. During the last 20 min of glucose infusion the suppression of Ra was less pronounced in the acromegalic patients than in the control subjects with 6-^{3}H-glucose (77 ± 6% vs 90 ± 2%, $p < 0.05$) and with 2-^{3}H-glucose (62 ± 4% vs 81 ± 4%, $p < 0.005$). Thus, also during glucose infusion (Table 2) Ra remained higher in the acromegalic patients than in the control subjects.

Rd was by definition identical to Ra in the basal state (Table 3 and Fig. 2). During the glucose infusion there was no significant change in Rd in the acromegalic patients. In controls, however, Rd determined with 6-^{3}H-glucose and with 2-^{3}H-glucose increased significantly ($p < 0.005$).

The basal MCR tended to be higher in the acromegalic patients than in the control subjects but the difference was not significant (Table 4 and Fig. 2). The glucose infusion decreased MCR in acromegalic patients with both 6-^{3}H-glucose ($p < 0.01$) and with 2-^{3}H-glucose ($p < 0.005$) while MCR did not change in control subjects.

In the basal state a significant amount of glucose was metabolized through GC in acromegalic patients and control subjects (Table 5, $p < 0.05$). The cycling of endogenous glucose remained unchanged during the glucose infusion. Interestingly, the basal GC activity as well as cycling of endogenous glucose during glucose infusion were higher in acromegalic patients than in control subjects ($p < 0.05$). In the acromegalic patients there was a correlation between basal GH and GC ($r = 0.943$, $p < 0.05$), while basal glucagon levels were not significantly related to GC ($r = 0.800$).

The acromegalic patient with manifest diabetes (BA) had a basal plasma glucose level of 198 mg/dl, which did not change during the glucose infusion. Plasma C-peptide was 1.8 pmol/ml throughout the experiment while plasma insulin levels increased from 35 to 45 μU/ml. Basal Ra was about twice that of acromegalic patients with normal glucose tolerance. During the glucose infusion the degree of suppression of Ra was similar to that found in the nondiabetic acromegalic group. The activity of basal GC as well as the endogenous glucose cycling measured during glucose infusion were considerably increased and amounted to 1.10 and 1.50 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively.

Discussion

In order to characterize defects which can lead to glucose intolerance in acromegaly we investigated glucose turnover, and in particular glucose cycling, in patients with normal glucose tolerance. Once diabetes is established it is difficult to dissociate metabolic defects due to GH hypersecretion from the effects of hyperglycaem-

Table 4. Metabolic clearance rate (MCR) of glucose in patients with acromegaly and in healthy controls. During the glucose infusion MCR was averaged during 20–110 min and during 90–110 min. Values are mean ± SEM

Experimental condition	Tritium label	MCR ($ml \cdot kg^{-1} \cdot min^{-1}$)		
		Healthy controls	Acromegalic patients	
			Normal glucose tolerance	Diabetes
Basal state	6-^{3}H-glucose	2.11 ± 0.09	2.30 ± 0.11	2.46
		**	***	
	2-^{3}H-glucose	2.39 ± 0.12	2.76 ± 0.13	3.02
Glucose infusion (20–110 min)	6-^{3}H-glucose	2.06 ± 0.13	1.96 ± 0.15	2.17
		**	***	
	2-^{3}H-glucose	2.31 ± 0.14	2.33 ± 0.17	2.96
Glucose infusion (90–110 min)	6-^{3}H-glucose	2.18 ± 0.13	2.05 ± 0.17	2.08
		*	**	
	2-^{3}H-glucose	2.40 ± 0.19	2.46 ± 0.17	3.19

*$p < 0.05$, **$p < 0.01$, and ***$p < 0.001$ 2-^{3}H-glucose vs 6-^{3}H-glucose

Table 5. Activity of glucose cycling (GC) in patients with acromegaly and in healthy controls. During the glucose infusion GC was calculated during 20–110 min and during 90–110 min. Values are mean ± SEM

Experimental condition	GC ($mg \cdot kg^{-1} \cdot min^{-1}$)		
	Healthy controls	Acromegalic patients	
		Normal glucose tolerance	Diabetes
Basal state	0.25 ± 0.07	0.44 ± 0.08[a]	1.10
Glucose infusion (20–110 min)	0.24 ± 0.05	0.41 ± 0.05[a]	1.50
Glucose infusion (90–110 min)	0.22 ± 0.09	0.49 ± 0.11	2.25

[a] $p < 0.05$ acromegalic patients vs control subjects

ia and other metabolic derangements which accompany it. After an overnight fast in acromegalic patients Ra was significantly elevated despite hyperinsulinaemia, while MCR was normal. During glucose infusion, Ra was not suppressed as effectively in the acromegalic patients as in control subjects although the prevailing insulin levels were higher. Moreover, in the acromegalic patients glucose administration did not augment glucose uptake, resulting in a decreased MCR.

Our findings resemble, in several respects, those seen during short-term administration of GH to healthy human volunteers [21, 22]. A 12 h infusion of GH, which gave rise to increments of plasma GH within the physiological range, decreased both insulin-mediated suppression of Ra and the stimulatory effect of insulin on Rd. In these studies, however, basal Ra was not increased. In contrast, when pharmacological doses of GH were infused into normal dogs over a 3–8 day period, not only were the Ra and Rd response to insulin altered but there was also a clear increase in basal Ra [23, 24].

A novel finding in the present study is that acromegaly augmented the activity of GC. This means that a large amount of glucose that has been taken up by the liver and phosphorylated is promptly dephosphorylated and released to the blood stream instead of being polymerized to glycogen or oxidized. We have determined GC by subtracting glucose turnover measured with 6-^{3}H-glucose from that measured using 2-^{3}H-glucose. This technique is based on two assumptions: 1) 6-^{3}H-glucose provides a true measure of hepatic glucose production, and 2) there are no isotope effects. With respect to the first assumption, tritium from 6-^{3}H-glucose is retained through the whole glycolytic process [25] and is lost to a large extent by carboxylation-decarboxylation reactions between pyruvate and dicarboxylic acids as well as by the action of glutamate-pyruvate transaminase. The measurement of hepatic glucose production with 6-^{3}H-glucose is thus not influenced by activity of the Cori cycle and reflects the true rate of hepatic glucose production in vivo [26, 27] and in vitro [28]. The second assumption implies that tritium loss from 2-^{3}H-glucose is representative of hydrogen loss in the hexose isomerase reaction. This, however, has not been completely ascertained. The possibility that there is an isotope effect cannot be fully excluded [28]. Such an effect could result in retention of tritium in position 2 of glucose 6-phosphate, leading to underestimation of glucose cycle activity.

All four disturbances of glucose metabolism appearing in our acromegalic patients with normal OGTT (increased basal Ra, impaired action of insulin on Ra and Rd, and increased GC) are also characteristic features of patients with Type 2 diabetes [29–31]. In the latter patients, however, these defects are more pronounced and in addition the B cell capacity to release insulin is impaired (for review see 32), leading to overt hyperglycaemia.

Interestingly, in our patient who had both acromegaly and Type 2 diabetes, basal Ra and GC were as high as 4.85 and 1.10 $mg \cdot kg^{-1} \cdot min^{-1}$, respectively. This single experiment cannot constitute the basis for major conclusions and has to be extended to include more patients with acromegaly and diabetes.

In acromegaly basal GC activity was correlated with plasma GH levels, suggesting that the hormone may be directly involved in regulation of this metabolic pathway. Since glucagon is known to increase the activity of glucose 6-phosphatase [33] and the activity of GC [27], it is possible that hyperglucagonaemia found in our acromegalic patients at least partially contributes to increased GC. Similar to glucagon, other hormones known to augment GC activity, such as cortisone and thyroid hormone, have also been shown to increase the activity of glucose 6-phosphatase [33]. The interaction between GH and this enzyme has not been studied.

The cellular mechanisms behind the effects of GH on carbohydrate metabolism in liver and extrahepatic tissues are not clear. Several experimental studies have suggested that a short-term GH excess has no or little

effect on the binding of insulin to its receptor [21, 22]. In monocytes from acromegalic patients with normal OGTT the number of insulin binding sites is reduced only in patients with plasma GH levels >30 ng/ml [9]. Hence, the GH-induced insulin resistance may involve post-receptor events to a large extent.

In conclusion, it appears that in acromegalic patients defects in glucose metabolism can be detected with sensitive tracer methods, even when fasting plasma glucose is near normal and when OGTT is not impaired. Interestingly the major defect in the postabsorptive state was a 70% increase in glucose cycling, while the increment in glucose production was much less pronounced (17%).

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