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Research Article

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Influence of Hyperthyroidism on Splanchnic Exchange of Glucose and Gluconeogenic Precursors

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ABSTRACT Arterial concentrations and splanchnic exchange of glucose, amino acids, lactate, pyruvate, and glycerol were determined in 14 hyperthyroid patients and 12 healthy controls. Seven of the patients were restudied after 5–12 mo of medical management at which time there was chemical and clinical evidence of a euthyroid state.

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Splanchnic glucose output in the patient group was 35% lower than in controls. However, total splanchnic uptake of glucogenic precursors was 100% higher than in controls and showed a direct linear correlation with serum triiodothyronine. Total precursor uptake could account for 75% of splanchnic glucose output in the patients, compared to 26% in controls. The increase in uptake of lactate, alanine, and other amino acids was due to a 35–80% rise in splanchnic fractional extraction plus a 20% rise in estimated hepatic blood flow. When the patients were restudied after medical treatment splanchnic exchange of glucose and glucose precursors had reverted to normal values.

The present findings demonstrate that in hyperthyroidism (*a*) total splanchnic glucose output is reduced in relation to controls, (*b*) splanchnic uptake of gluconeogenic precursors is accelerated, largely due to a rise in fractional extraction of precursor substrates and to a smaller extent, as a result of an increase in hepatic blood flow, and (*c*) these changes revert to normal when a euthyroid state has been achieved.

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INTRODUCTION

The metabolic effects of hyperthyroidism have been well characterized with respect to increased oxygen consumption (1, 2), augmented adipose tissue lipolysis (3, 4), and net protein catabolism (5, 6). The effects of hyperthyroidism on hepatic gluconeogenesis have been less clearly established. Studies with perfused liver have shown either increased (7) or normal rates (8) of gluconeogenesis from lactate. Increased gluconeogenesis from glycerol (9) and alanine (10) has also been reported in such studies. In rats made hyperthyroid with exogenous thyroid hormone an in vivo increase in glucose production and gluconeogenesis has been reported (11). Data in human subjects are still lacking, however, concerning the effects of thyrotoxicosis on total glucose production and on splanchnic metabolism of gluconeogenic substrates such as alanine, lactate and glycerol. Such data would be of particular interest in that thyrotoxicosis has been reported to result in depletion of muscle (12) as well as hepatic glycogen stores (13). Furthermore, changes in thyroid hormone availability (specifically a reduction in triiodothyronine) have been implicated in the regulation of gluconeogenesis and protein catabolism during starvation (14, 15). The present study was consequently undertaken to evaluate the effects of hyperthyroidism on splanchnic exchange of glucose and gluconeogenic substrate metabolism. Some of the patients were restudied after medical management had restored a euthyroid state.

METHODS

Subjects. 14 patients (13 female, 1 male) with hyperthyroidism were studied as in-patients at Huddinge Hospital,

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Sweden. The diagnosis was based on clinical symptoms and laboratory findings (Table I). All patients showed elevations of triiodothyronine and thyroxine concentrations as well as a marked rise in their basal metabolic rate. 13 patients had diffuse toxic goiter (Graves' disease). All patients showed typical clinical signs of thyrotoxicosis, such as palpitations, heat intolerance, ophthalmopathy, warm and moist skin, etc., and all but one patient had lost weight (2–15 kg). No medication was given before the study. No patient had any complicating disorder.

Seven of the patients were restudied after 5–12 mo of medical treatment. Five patients received antithyroid treatment in the form of carbimazole (30–40 mg/d), β-blocking agents and, after 4–8 wk, thyroxine, and two were given radioiodine (6–10 mCi). At the time of the second study all clinical signs of hyperthyroidism had subsided and serum thyroxine levels had fallen to normal in all patients (Table I). In two patients (Table I) serum triiodothyronine remained elevated.

12 healthy, nonobese female subjects, age 19–25 yr (mean 23), weight 52–70 kg (mean 62), and height 166–176 cm (mean 169), served as controls. The nature, purpose, and possible risks involved in the study were carefully explained to all patients and control subjects before their consent to participate was obtained. The protocol was reviewed and approved by institutional committees on human investigation.

Procedure. The studies were performed in the morning after an overnight fast (12–14 h). Teflon catheters were inserted percutaneously into a brachial artery and an antecubital vein. A Cournand catheter (No. 7 or 8) was introduced percutaneously into a femoral vein and advanced under fluoroscopic control to a right-sided, main hepatic vein. The tip of the catheter was placed 3–4 cm from the wedge position. Patency of the catheters was maintained by intermittent flushing with saline. Heparin was not employed in the study. Repeated measurements (two to four observations in each individual with 10-min intervals) were obtained in the basal state. Hepatic blood flow was estimated by the continuous infusion technique (16) using indocyanine-green dye. Expired air was collected for determination of pulmonary oxygen uptake.

Analytical methods. Glucose was analyzed in whole blood by the glucose oxidase reaction (17). Lactate (18), pyruvate (19), and glycerol (20) were determined enzymatically in whole blood. Individual acidic and neutral amino acids were measured in plasma by the automated ion-exchange chromatographic technique (21). Insulin, glucagon, triiodothyronine, and thyroxine were analyzed by radioimmunoassay (22–25). Indocyanine-green dye was determined spectrophotometrically at 805 nm in serum samples. Oxygen saturation was measured spectrophotometrically and hemoglobin concentration was determined by the cyanmethemoglobin technique. Hematocrit was measured using a microcapillary centrifuge and corrected for trapped plasma. Expired air was analyzed by the Scholander microtechnique. In 2 of the 14 patients splanchnic exchange of glucose precursors was not measured. Splanchnic exchange was calculated from arterial-venous differences and blood flow determinations. Consequently, all values for splanchnic exchange given in the text and tables refer to net output or uptake. Splanchnic fractional extraction of alanine was calculated as A-HV/A, where A = arterial concentration and HV = hepatic venous concentration.

RESULTS

Before treatment

Arterial concentrations. Arterial concentrations of substrates and hormones are shown in Table II. The blood glucose level was slightly (+10%) higher in the patients ($P < 0.005$), while arterial lactate and pyruvate concentrations were similar to those of the controls. The glycerol concentration was almost threefold greater in the patients ($P < 0.005$). Insulin levels were similar in

TABLE I

Age, Body Dimensions, Clinical, and Laboratory Findings in Hyperthyroid Patients before and during Treatment

	Age	Height	Weight	Duration of symptoms	Triiodothyronine*		Thyroxine‡		Basal metabolic rate	
					Before therapy	During therapy	Before therapy	During therapy	Before therapy	During therapy
	yr	*cm*	*kg*	*mo*	*nmol/liter*		*nmol/liter*		*%*	
1	51	167	70	11	4.2	3.2	245	149	+54	+33
2	51	158	43	5	8.4	4.9	296	149	+84	+29
3	40	175	69	5	7.3	2.0	196	119	+64	±0
4	31	167	57	4	6.6	2.5	281	152	+59	+17
5	49	161	55	5	16.4	1.7	373	132	+98	+5
6	35	172	54	6	5.5	2.5	267	133	+79	+18
7	46	158	47	7	5.9	2.1	244	154	+45	−3
8	41	162	54	6	6.7		216		—	
9	38	154	61	8	14.8		280		+86	
10	24	164	61	4	8.0		278		+36	
11	47	165	76	10	10.0		224		+32	
12	47	181	65	4	12.3		238		—	
13	42	165	50	4	8.4		243		+16	
14	42	160	55	4	11.6		259		+18	

* Normal range 1.7–3.1 nmol/liter.

‡ Normal range 58–167 nmol/liter.

TABLE II

*Arterial Concentrations and Splanchnic Exchange of Substrates and Hormones in Hyperthyroid Patients and Controls in the Postabsorptive State**

	Hyperthyroid patients	Controls	P‡
		mmol/liter	
Arterial concentrations			
Glucose	4.69±0.14	4.18±0.07	<0.005
Lactate	0.48±0.02	0.44±0.02	NS
Pyruvate	0.043±0.003	0.044±0.003	NS
Glycerol	0.114±0.010	0.042±0.009	<0.005
Insulin	15±2	14±3	NS
Glucagon	96±12	62±14	NS
		mmol/min	
Splanchnic exchange			
Glucose	0.52±0.04	0.78±0.12	<0.025
Lactate	0.35±0.01	0.21±0.03	<0.01
Pyruvate	0.031±0.004	0.008±0.007	<0.05
Glycerol	0.135±0.018	0.041±0.009	<0.001
Oxygen	3.75±0.30	2.46±0.13	<0.01

* Data represent the mean of two to four observations in each individual with 10–15-min intervals and are given as mean±SE.

‡ *P* values denote the probability that the differences between patient and control groups are caused by random factors.

patients and controls. Mean glucagon levels were higher than in controls but this difference was not significant ($P > 0.1$).

Plasma amino acid concentrations are shown in Table III. Significant reductions were seen in the levels of alanine (−20%, $P < 0.005$), glycine (−25%, $P < 0.001$), serine (−35%, $P < 0.001$), and citrulline (−50%, $P < 0.001$). The arterial level of tyrosine was increased

TABLE III

*Arterial Concentrations and Splanchnic Exchange of Amino Acids in Hyperthyroid Patients and Healthy Controls in the Postabsorptive State**

	Arterial concentrations			Splanchnic exchange			Fractional extraction		
	Hyperthyroid patients	Controls	P‡	Hyperthyroid patients	Controls	P‡	Hyperthyroid patients	Controls	P‡
	μmol/liter			*μmol/min*			%		
Taurine	45±4	46±2	NS	1±2	2±1	NS	—	—	—
Threonine	102±8	112±5	NS	23±4	9±1	<0.001	23±3	11±2	<0.01
Serine	79±5	120±4	<0.001	19±2	13±2	<0.02	25±3	18±3	NS
Proline	144±12	156±9	NS	23±10	1±2	<0.005	16±7	1±2	<0.05
Citrulline	18±1	38±2	<0.001	−2±2	−10±1	<0.005	—	—	—
Glycine	156±12	214±8	<0.001	34±6	9±3	<0.001	23±4	3±2	<0.001
Alanine	178±11	225±9	<0.005	115±11	62±6	<0.001	64±2	36±3	<0.001
NH_4-but.	24±4	27±2	NS	1±1	−1±1	NS	—	—	—
Valine	251±19	226±5	NS	19±8	−1±2	<0.01	—	—	—
Cysteine	101±11	99±4	NS	10±6	3±1	NS	12±7	4±3	NS
Methionine	17±1	17±1	NS	4±1	3±1	NS	25±3	22±4	NS
Isoleucine	68±2	54±1	<0.001	5±3	−1±1	<0.02	—	—	—
Leucine	142±5	121±3	<0.005	11±6	−2±1	<0.02	—	—	—
Tyrosine	77±8	43±2	<0.005	15±3	5±1	<0.001	19±3	17±2	NS
Phenylalanine	52±4	46±1	NS	10±3	3±1	<0.005	17±4	9±2	<0.05

Data represent the mean of two observations at 10–15-min intervals in each subject and presented as mean±SE. Probability that the differences between the patient and control groups are caused by random factors.

(+80%, $P < 0.005$) as were the levels of isoleucine (+25%, $P < 0.001$) and leucine (+20%, $P < 0.005$).

Splanchnic exchange. Splanchnic glucose output was 35% lower in the patient group (0.52±0.04 mmol/min) compared to the controls (0.78±0.12 mmol/min, $P < 0.025$, Table II). In contrast, splanchnic uptake of gluconeogenic precursors was augmented in the patients. The uptake of lactate was increased by 35% ($P < 0.01$), primarily as a consequence of increased splanchnic fractional extraction (patients: 46±2%, controls: 35±5%, $P < 0.05$). In the case of glycerol the augmented splanchnic uptake (+230%) resulted from increased availability rather than from augmented splanchnic fractional extraction.

Splanchnic uptake of amino acids was increased in the patient group (Table III). Marked increments were found for the splanchnic uptakes of alanine ($P < 0.001$), glycine ($P < 0.001$), proline ($P < 0.005$), threonine ($P < 0.001$), serine ($P < 0.02$), tyrosine ($P < 0.001$), and phenylalanine ($P < 0.005$). Moreover, splanchnic exchange of the branched-chain amino acids, leucine and isoleucine differed between patients and controls ($P < 0.02$) in the direction of an uptake in the patient group. Splanchnic fractional extraction of the amino acids (Table III) was increased in the case of alanine ($P < 0.001$), glycine ($P < 0.001$), proline ($P < 0.05$), threonine ($P < 0.01$), and phenylalanine ($P < 0.05$).

A direct linear relationship was observed between the total splanchnic uptake of glucose precursors (sum of lactate, pyruvate, glycerol, and gluconeogenic amino acid uptake) and the triiodothyronine levels (Fig. 1, $r = 0.76, P < 0.01$). Likewise, there was a direct relationship between splanchnic uptake of alanine and serum triiodothyronine levels (Fig. 2, $r = 0.65, P < 0.05$).

Estimated hepatic blood flow in the patient group (1,590±70 ml/min) was increased compared with the control subjects (1,310±70 ml/min, $P < 0.01$). A significant relationship was observed between estimated hepatic blood flow and pulmonary oxygen uptake (Fig. 3, $r = 0.82, P < 0.001$). Splanchnic oxygen uptake, estimated as the product of estimated hepatic blood flow and the arterial-hepatic venous oxygen difference, was increased by 50% in the patients as compared to the controls (Table II).

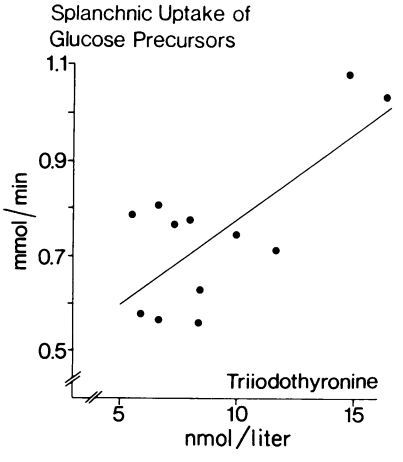

FIGURE 1 Relationship between total splanchnic uptake of glucose precursors (lactate, pyruvate, glycerol, and amino acids) and triiodothyronine levels in hyperthyroid patients ($r = 0.76, P < 0.01$).

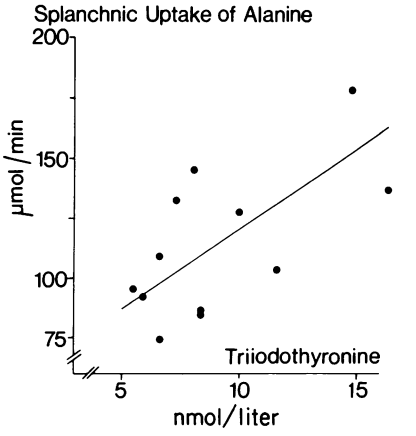

FIGURE 2 Relationship between splanchnic uptake of alanine and triiodothyronine levels in hyperthyroid patients ($r = 0.65, P < 0.05$).

After treatment

Seven patients were restudied after 5–12 mo of medical management. At the time of the second study all clinical symptoms of hyperthyroidism had subsided and triiodothyronine and thyroxine levels had been essentially normal (Table I) for at least 1 mo.

Arterial concentrations. Arterial concentrations of substrates and hormones before and during therapy are shown in Table IV. The arterial glycerol level fell by 50% during treatment ($P < 0.005$), while the arterial

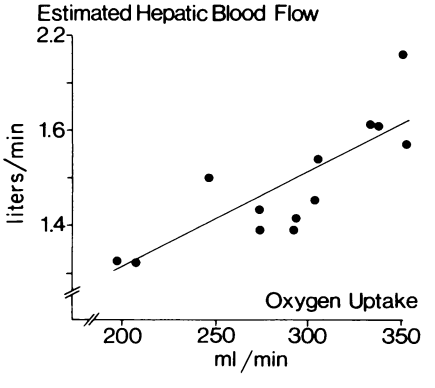

FIGURE 3 Relationship between estimated hepatic blood flow and pulmonary oxygen uptake in hyperthyroid patients ($r = 0.82, P < 0.01$).

TABLE IV

*Arterial Concentrations and Splanchnic Exchange of Substrates and Hormones in Postabsorptive Hyperthyroid Patients before and after Treatment**

	Before treatment	After treatment	P‡
		mmol/liter	
Arterial concentrations			
Glucose	4.51±0.24	4.54±0.20	NS
Lactate	0.48±0.02	0.54±0.10	NS
Pyruvate	0.038±0.002	0.049±0.009	NS
Glycerol	0.124±0.015	0.061±0.004	<0.005
Insulin	13±3	13±1	NS
Glucagon	88±12	58±15	NS
		mmol/min	
Splanchnic exchange			
Glucose	0.51±0.05	0.66±0.12	$0.05 < P < 0.1$
Lactate	0.35±0.02	0.26±0.02	<0.05
Pyruvate	0.038±0.008	0.022±0.002	NS
Glycerol	0.157±0.026	0.064±0.004	<0.02
Oxygen	4.01±0.32	2.89±0.21	<0.05

* Data represent the mean of two to four observations in each individual with 10–15-min intervals and are given as mean±SE.

‡ *P* values denote the probability that the differences before and after treatment are caused by random factors.

concentrations of glucose, lactate, pyruvate, insulin, and glucagon were unchanged.

Plasma amino acid concentrations changed during treatment in the direction of a return to normal (Table V). A rise was observed in the levels of glycine (+20%, $P < 0.05$) and serine (+45%, $P < 0.02$), while decreases were noted in the levels of leucine (−40%, $P < 0.005$), isoleucine (−35%, $P < 0.005$), and tyrosine (−30%, $P < 0.05$).

Splanchnic exchange. Splanchnic glucose production (Table IV) tended to rise during treatment (+30%, $0.05 < P < 0.1$), reaching a value that was not significantly different from that observed in healthy controls (Table II). Splanchnic uptake of lactate and glycerol decreased by 28 and 60%, respectively, in response to treatment ($P < 0.02$–0.05) (Table IV). Amino acid uptake by the splanchnic bed is shown in Fig. 4. Significant decreases in splanchnic uptake were observed for alanine ($P < 0.01$), threonine ($P < 0.05$), glycine ($P < 0.05$), methionine ($P < 0.05$), tyrosine ($P < 0.05$), and phenylalanine ($P < 0.05$). The splanchnic uptake of each of these amino acids after treatment (Fig. 4), was not significantly different from that of healthy controls (Table IV).

Estimated hepatic blood flow fell to 1,320±90 ml/min after treatment (−25%, $P < 0.05$), a value similar to healthy controls (1,310±70). Likewise, splanchnic oxygen uptake (Table IV) fell by 30% ($P < 0.05$) during therapy and was not significantly different from controls (Table II) ($P > 0.1$).

DISCUSSION

The current data demonstrate that in hyperthyroid patients a decrease in splanchnic glucose output is associated with an increase in splanchnic uptake of gluconeogenic precursors. These changes returned toward

TABLE V

*Arterial Concentrations of Plasma Amino Acids in Hyperthyroid Patients Before and After Treatment**

	Arterial concentration		
	Before treatment	After treatment	P‡
	μmol/liter		
Threonine	86±4	80±12	NS
Serine	70±6	102±7	<0.02
Glycine	186±12	219±13	<0.05
Alanine	154±9	190±21	NS
Valine	249±33	193±16	NS
Methionine	16±2	15±2	NS
Isoleucine	68±4	41±3	<0.005
Leucine	146±10	92±7	<0.005
Tyrosine	66±8	49±5	<0.005
Phenylalanine	54±8	41±4	NS

* Data represent mean±SE in seven patients studied before and after treatment.

‡ *P* values denote the probability that the differences before and after treatment are caused by random factors (paired *t* test).

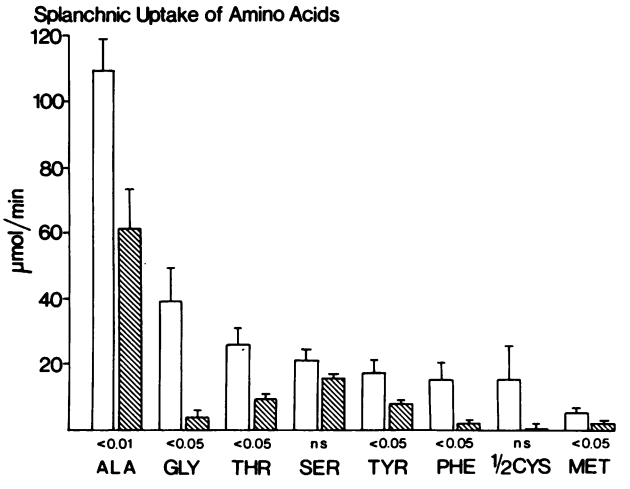

FIGURE 4 Splanchnic amino acid uptake before (open columns) and during (hatched columns) treatment of hyperthyroidism (mean±SE). *P* values indicate the probability that the differences are caused by chance alone.

normal after restoration of a euthyroid state. Although the control subjects were younger than the patient group, they were closely matched with respect to height and weight. Furthermore, the values for splanchnic exchange of glucose and alanine reported for the control group in the present study are in agreement with previous studies from our laboratory in which control subjects up to age 32–52 yr were studied (26–34).

The decrease in splanchnic output of glucose in hyperthyroid patients could reflect a reduction in hepatic glycogenolysis, a decrease in gluconeogenesis or a combination of the two. In normal subjects in the postabsorptive state ~ 75% of total hepatic glucose output is derived from glycogenolysis, the remainder being accounted for by gluconeogenesis (26, 27). The present finding that splanchnic glucose output is reduced by 35% suggests that this fall is due, at least in part, to decreased hepatic glycogenolysis. In keeping with this conclusion, liver biopsy studies have revealed a depletion of hepatic glycogen stores in thyrotoxic patients (13).

Despite the overall fall in splanchnic glucose output, net uptake of glucose precursors (lactate, pyruvate, glycerol, and alanine) by the splanchnic bed was increased by ~100%. It is noteworthy that in the case of alanine and other glycogenic amino acids as well as lactate (but not glycerol), the rise in splanchnic uptake was due to an increase in fractional extraction rather than a rise in arterial concentration (Tables II and III). The increase in fractional extraction of alanine and lactate was in fact comparable to that observed in known circumstances of increased gluconeogenesis, such as insulin-withdrawn diabetes (29) and prolonged exercise (30). In keeping with the current findings in intact humans, studies with perfused liver from thyroxine-treated animals have shown an increased conversion of alanine (10), glycerol (9), and lactate (7) to glucose. Furthermore, in the perfused liver both the transport of amino acids into liver and the enzymatic conversion of pyruvate to phosphoenolpyruvate are stimulated by thyroxine (10). The data thus suggest that augmented gluconeogenesis from alanine and other amino acids in hyperthyroidism is initiated as a consequence of altered hepatic events (uptake and/or conversion to glucose) rather than via increased substrate delivery.

With regard to the mechanism for the increased splanchnic fractional extraction of gluconeogenic amino acids and lactate, it is noteworthy that plasma insulin concentrations were not different from control values. Although the differences were not statistically significant, mean plasma glucagon levels were higher in the patients with thyrotoxicosis than in controls, raising the possibility that glucagon contributes to the changes in gluconeogenic substrate exchange. On the other hand, the possibility that increased gluconeogenic substrate uptake is a result of increases in thyroid hormone levels per se or is due to alterations in sensitivity to catecholamines (35) cannot be answered from the present data.

In addition to the changes in splanchnic fractional extraction of amino acid substrates mentioned above, a rise in substrate supply contributed to the increased splanchnic uptake of glycerol, lactate, and pyruvate in the thyrotoxic patients. Thus, augmented blood flow (+20%) in association with unchanged (lactate, pyruvate) or elevated (glycerol) arterial concentrations of substrates resulted in an increased availability of these precursors to the liver. Taken together with the data on amino acids, the findings indicate that delivery to, as well as extraction by, the splanchnic bed contribute to the rise in gluconeogenic precursor utilization in thyrotoxicosis. Further evidence supporting a rise in hepatic gluconeogenesis in hyperthyroidism is provided by the finding that splanchnic oxygen uptake is substantially increased in this condition (Table II), as reported (36).

The effects of hyperthyroidism on amino acid metabolism are of interest not only with respect to the splanchnic uptake of alanine and other glycogenic amino acids, but also with regard to changes in arterial amino acid concentrations. The thyrotoxic patients demonstrated a reduction in arterial levels of alanine and other glycogenic amino acids, while an increase was observed in the arterial levels of the branched-chain amino acids. A similar pattern of circulating amino acids has been demonstrated in diabetes (37) and in normal subjects after a 3-d fast (38). In fact, the coexistence of this pattern of arterial amino acid concentrations, an increase in splanchnic uptake of amino acids and a reduction in splanchnic output of glucose is virtually identical to the metabolic pattern observed in normal subjects after a 3-d fast (38, 39). Thyrotoxic patients thus may be

described as demonstrating accelerated starvation not only with regard to lipolysis (3, 4, 40) and ketogenesis (41), but also with respect to amino acid metabolism and splanchnic glucose exchange.

It should be noted that the technique employed in the present study (net splanchnic exchange) does not measure the intrahepatic disposal of gluconeogenic precursors. The possibility that substrates extracted by the splanchnic bed are utilized along nonglucogenic pathways cannot be excluded. For example, altered gluconeogenesis induced by glucagon may be due to changes in the intrahepatic disposal of amino acids rather than alterations in net splanchnic uptake (39, 42). Furthermore, changes in gut metabolism could conceivably contribute to the observed differences in net splanchnic balances.

Finally, in a recent report Okajima and Ui (11) examined the effects of administration of thyroxine on glucose metabolism in rats. Whereas their findings showed evidence of increased gluconeogenesis and decreased liver glycogen in animals made hyperthyroid, in contrast to the present findings, they noted an increase (rather than a decrease) in total glucose turnover in the hyperthyroid state (11). The basis for these differences may relate to species differences, the duration of hyperthyroidism (8–12 d in the rat study as compared to 4–11 mo in the human study) or possibly differing metabolic responses in spontaneous (endogenous) hyperthyroidism as opposed to experimental (induced) hyperthyroidism.

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