Effects of Beta-Blockade on Hepatic Conversion of Amino Acid Nitrogen and on Urea Synthesis in Cirrhosis

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β-Blockers are widely used to prevent gastrointestinal hemorrhage in cirrhosis. The metabolic effects of treatment are scarcely studied: hepatic function reportedly does not change significantly, but β-adrenoceptors have been reported to regulate protein and amino acid metabolism. We studied hepatic nitrogen metabolism in response to constant alanine infusion in seven patients with cirrhosis before and 7 to 10 days after treatment with oral propranolol (60 to 100 mg/d). Beta-blockade was effective: it decreased heart rate by 25%, abolished orthostatic tachycardia, and reduced portal blood flow by 20%. Alanine-stimulated urea nitrogen synthesis rate (UNSR) was higher in patients with propranolol treatment, without any difference in aminonitrogen concentration. The kinetics of hepatic conversion of amino acid nitrogen into urea—ie, functional hepatic nitrogen clearance (FHNC)—increased by 30%, from (mean ± SD) 17.0 ± 4.1 to 22.0 ± 6.6 L/h ($P < .01$). Increased urea production during alanine infusion resulted in negative nitrogen exchange even at the peak of α-aminonitrogen concentration. Basal insulin level was only slightly reduced during propranolol treatment, whereas the insulin response to alanine was significantly blunted. No differences in glucagon and cortisol were demonstrated. Epinephrine and norepinephrine levels were high-normal and did not vary after treatment. Increased urea production and stimulation of hepatic nitrogen clearance during beta-blockade may be mediated by relative hypoinsulinemia or by direct involvement of β-adrenoceptors in the control of nitrogen metabolism, possibly by regulation of amino acid uptake and release in peripheral tissues.

THE β-BLOCKERS are widely prescribed drugs for the treatment of portal hypertension in cirrhosis. Both selective and nonselective β-blockers may be used in the prevention of recurrent variceal bleeding.[1] Many studies have been performed on the hemodynamic effects of such treatment, but only a few data are available on the metabolic implications of β-blocker therapy.

By regulating several metabolic processes in muscle tissue,[2] β-adrenergic receptors are implicated in amino acid/protein, glucose, and fat metabolism.[3] β-Adrenoceptor agonists stimulate protein deposition in striated muscle, but via a thermogenic effect, they increase energy expenditure, thereby reducing glycogen deposition and body fat content.[4] β-Adrenergic blockade by propranolol totally prevented the decrease in plasma amino acids caused by epinephrine infusion, with the effect being most pronounced for branched-chain amino acids (BCAA). This suggests that in normal man, epinephrine and insulin may exert similar rather than antagonistic effects on amino acid metabolism.[5]

The liver plays a primary role in amino acid/protein disposal. All the amino acid nitrogen that is not used for protein synthesis is converted to urea in the mitochondria and cytosol of hepatocytes. The process is dependent on both hormonal and substrate drive, with the latter being variable according to changes in peripheral amino acid disposal.[6]

The plasma amino acid profile of cirrhotic patients is almost invariably altered both quantitatively and qualitatively: total plasma α-aminonitrogen level is high-normal, BCAA concentrations are reduced, and aromatic and sulfur-containing amino acid levels are increased.[7] Eriksson and Söderman[8] suggested that β-adrenergic stimulation, expressed by high catecholamine plasma concentrations—primarily epinephrine—has a role in reduced BCAA plasma levels, as shown by the prompt increase of BCAA after short-term propranolol administration.

In the present study, we assessed the effects of nonselective beta-blockade on metabolic nitrogen exchange in patients with cirrhosis by measuring hepatic conversion of amino acids to urea. The results show that therapy with β-blockers stimulates hepatic nitrogen clearance in cirrhosis, possibly reducing the peripheral amino acid–sparing mechanism of β_2-adrenoceptor stimulation.

SUBJECTS AND METHODS

Subjects

Seven patients (five men and two women) with histologically documented cirrhosis were studied. Patients were 46 to 70 years old (median, 61) and had cirrhosis of alcoholic (two cases) or hepatitis C virus (HCV) (five cases) origin. Patients with alcoholic cirrhosis had been abstaining from alcohol for at least 6 months before the study. Their liver-function test results are listed in Table 1. Two subjects were in fairly good condition and without nutritional defects, whereas the others had clinical evidence of reduced lean body mass. Three patients were in Child-Pugh class A,[9] three in class B, and one in class C. All patients had esophageal varices, which were small in one case (accompanied by congestive gastropathy), medium-sized in five (three with congestive gastropathy), and large in one. All had suffered ≥ one episode of variceal bleeding at least 2 months before the study. Four had mild ascites at ultrasonography examination, which was clinically undetectable. All patients were treated with diuretics (spironolactone and/or furosemide). Signs of overt hepatic encephalopathy had been previously demonstrated in a single patient, but the mental state was clinically normal under lactulose treatment.

Renal function was in the normal range, and there was no evidence of previous or actual endocrinopathies and/or complicat-

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Table 1. Clinical and Laboratory Data in Patients With Cirrhosis

Case No.	Age (yr)	Etiology of Cirrhosis	Albumin (g/dL)	Total Bilirubin (mg/dL)	Prothrombin Activity (%)	Cholesterol (mg/dL)	Esophageal Varices (grade)	Galactose Elimination (mmol/min)	Antipyrine Clearance (mL/min)
1	70	HCV	3.1	2.8	57	120	II + CG	1.81	28.1
2	70	HCV	3.7	1.5	84	184	III + CG	0.91	16.1
3	60	HCV	4.2	2.1	58	130	II	1.26	21.6
4	61	HCV	3.1	2.2	58	117	I + CG	1.61	28.5
5	46	Alcoholism	3.1	4.8	47	111	II + CG	1.33	15.2
6	62	Alcoholism	1.9	3.6	55	82	II + CG	1.62	19.7
7	54	HCV	3.0	1.0	58	157	II	2.56	28.6
Mean ± SD	—	—	3.3 ± 0.8	2.6 ± 1.3	59 ± 11	137 ± 43	—	1.59 ± 0.52	22.6 ± 5.9

Abbreviation: CG, congestive gastropathy.

ing disorders at the time of diagnosis. All medications (diuretics and lactulose) were continued unchanged throughout the study period. Before the study, all patients consumed a standard hospital diet to provide 30 to 35 kcal and 1 g protein per kilogram body weight for at least 5 days.

The effects of beta-blockade on nitrogen exchange were determined in paired experiments performed in a sequential fashion at least 1 week apart. Patients eligible for β-adrenergic treatment for secondary prophylaxis of gastrointestinal bleeding were studied before and after treatment with a nonselective β-adrenergic antagonist (propranolol 60 to 100 mg/d) in three divided doses. Adequate beta-blockade was evidenced by diminished basal heart rate, which always decreased by at least 25%, and by abolished orthostatic tachycardia. Portal vein blood velocity and flow were also measured by ultrasonography to evaluate the splanchnic effects of β-adrenoceptor blockade.

All subjects provided informed consent to take part in the study, which was approved by the Ethics Committee for Human Studies operating in our Department.

Methods

All experiments were performed on hospitalized patients over 2 consecutive days. The methods have been previously described in detail.[10] Urea nitrogen synthesis rate (UNSR) was studied in relation to intravenous alanine infusion (constant infusion rate of 2 mmol/kg/h for 4.5 hours[10]) after a 12-hour fast. Blood samples were obtained from a vein of the contralateral arm every 45 minutes, starting 90 minutes before alanine infusion. A final blood sample was obtained 90 minutes after alanine infusion was stopped. Urine was collected quantitatively by voiding in five consecutive 90-minute periods (every second blood sampling). Subjects were not fed during the course of the test.

During the experiment, urine flow was stimulated by oral water ingestion or saline infusion to keep diuresis at greater than 2 mL/min. This was attained in nearly all subjects (mean diuresis, 2.7 mL/min), and diuresis was not different in paired experiments (2.5 and 2.9 mL/min before and after propranolol treatment, respectively). The total amount of water and saline given in paired experiments was approximately the same, ie, about 2,000 mL. There were no side effects or complications during infusion of alanine; in particular, no subject complained of nausea or vomited.

UNSR during each 90-minute period was measured as the sum of urea N excretion rate in urine and accumulation of urea N in the urea space, assumed to equal total body water, corrected for gut urea hydrolysi[6]: UNSR = (E + A)/(1 − L), where E is urine flow in liters per hour times urinary urea N in millimolars, A is change in blood urea N in millimolars per hour times total body water in liters, and L is fractional loss of newly formed urea in the gut.

In each patient, total body water was considered to be equal to the distribution space of antipyrine,[11] calculated in both conditions in the course of the antipyrine clearance test. Intestinal loss of urea N due to bacterial hydrolysis was taken to be 0.26.[12]

Functional hepatic nitrogen clearance (FHNC) was calculated as the slope of the linear regression analysis of UNSR during each period on the corresponding average α-amino-N concentrations (mean of α-amino-N values measured at the beginning and end of each period of urine collection).

The stoichiometric balance between infused amino acid nitrogen and urea nitrogen appearance rate (nitrogen exchange in millimoles per hour) was calculated as the difference between alanine N infusion rate, corrected for urinary α-amino-N excretion and α-amino-N accumulation, and urea N appearance (urea N excretion + urea N accumulation in total body water, not corrected for intestinal hydrolysis).[13] The volume of distribution of α-amino-N was also taken to equal total body water.

The echo-Doppler investigation was performed using equipment that combines a mechanical sector scanner and a pulsed Doppler unit (Hitachi Esaote, Tokyo, Japan). Portal flow was calculated by multiplying the estimated blood velocity by the cross-sectional area of the vessel, as reported in detail elsewhere.[14]

In all cases, galactose elimination capacity was measured according to Tygstrup's technique,[15] and antipyrine clearance was measured using a two-sample procedure.[16]

In our laboratory, values of galactose elimination capacity in healthy subjects aged 26 to 68 years vary from 5.87 to 8.03 mg/kg/min (median, 6.98; N = 30[17]), antipyrine clearance varies from 26.5 and 48.8 mL/min (median, 36.2; N = 9; age range, 30 to 64 years), and FHNC varies from 22.3 to 44.6 L/h (median, 31.4; N = 9; age range, 32 to 69). Repeated measurements of the three tests in the same subject vary within ±10%, ±8%, and ±15%, respectively.[10]

Substrate and hormone levels measured in previous experiments in normal subjects were considered as control values.[10]

Laboratory Procedures

Urea N concentration in plasma and urine was measured by the urease Berthelot method.[18] Alanine level was measured enzymatically,[19] and total α-amino-N was assayed by the dinitrofluorobenzene method.[20] All analyses were performed in batches in duplicate or triplicate to minimize analytical error. Intraassay coefficients of variation are as follows: urea, ± 1.5%; α-amino-N, ± 2%; and alanine, ± 3%. The plasma amino acid profile was measured by ninhydrin reaction after ion-exchange chromatography at baseline and at the end of alanine infusion,[21] with a coefficient of variation less than 5%. Plasma glucagon, insulin, and cortisol levels were measured by radioimmunoassay (Glucagon and Insulin kits; Biodata-Serono, Guidonia, Italy; and Coat-A-Count Cortisol; DPC, Los Angeles, CA). Glucose level was measured enzymatically.

Catecholamine levels were measured by a high-performance liquid chromatography technique.[22] Galactose level was determined enzymatically (Test Combination Galactose; Boehringer, Mannheim, Germany). Antipyrine level was measured by a high-performance liquid chromatography technique.[23]

Statistical Analysis

Linear correlation analysis between variables was performed by the least-square method. Differences between paired data were analyzed by paired *t* test. Differences in substrate and hormone concentrations between paired experiments were also tested by ANOVA for repeated measurements. Data in the text are shown as the mean ± SD.

RESULTS

In the fasting preinfusion state, α-amino-N and glucose concentrations were in the normal range and did not significantly change with propranolol treatment (Table 2). Basal glucagon and ammonia levels were increased approximately 50% in comparison to control values, and did not change in paired experiments. Also, insulin was in the normal range, and was reduced by 30% by propranolol administration.

Alanine infusion increased α-amino-N concentrations fourfold (Table 2), without differences between groups (repeated-measures ANOVA: time × treatment, $P = .48$). In response to amino acid infusion, glucose level did not change in the pretreatment experiment and decreased by 10% after therapy, whereas glucagon and ammonia levels doubled, without any difference between experiments (ANOVA: time × treatment, NS). Insulin level increased in both experiments, but the insulin response to alanine was markedly blunted by propranolol (ANOVA: time × treatment, $P = .03$).

Total body water as estimated by antipyrine distribution space was, on average, 43.5 ± 4.0 L in cirrhotic patients (corresponding to 56% of body weight) and did not change after propranolol treatment. During alanine infusion, mild fluid retention was observed in a few experiments, but never exceeded 1 L (< 2.5% of body water).

Table 2. Glucose, α-Amino-N, Insulin, Glucagon, Ammonia, and Cortisol Concentrations at the Beginning and End of Alanine Infusion in Paired Experiments in Cirrhotic Patients Before and After Propranolol Therapy (mean ± SD)

	Before Infusion	End of Infusion	*P*
Pretreatment			
Glucose	5.1 ± 0.9	5.2 ± 0.5	NS
α-Amino-N	2.1 ± 0.3	8.6 ± 1.2	<.001
Insulin	72.8 ± 15.7	112.7 ± 26.7	<.05
Glucagon	57.2 ± 16.4	120.0 ± 24.6	<.001
Ammonia	49.1 ± 27.0	97.3 ± 41.1	NS
Cortisol	184.8 ± 86.8		
Posttreatment			
Glucose	5.2 ± 0.6	4.7 ± 0.3*	NS
α-Amino-N	2.2 ± 0.3	9.5 ± 1.5	<.001
Insulin	54.3 ± 15.8	80.0 ± 18.3*	<.05
Glucagon	57.4 ± 11.0	123.4 ± 22.3	<.001
Ammonia	41.7 ± 25.9	82.9 ± 51.5	NS
Cortisol	175.3 ± 74.7		

NOTE. Glucose and α-amino-N concentrations are in mmol/L, ammonia is in μmol/L, glucagon and insulin are in pmol/L, and cortisol is in ng/mL.

*Significantly different from corresponding value in experiment performed before beta-blockade.

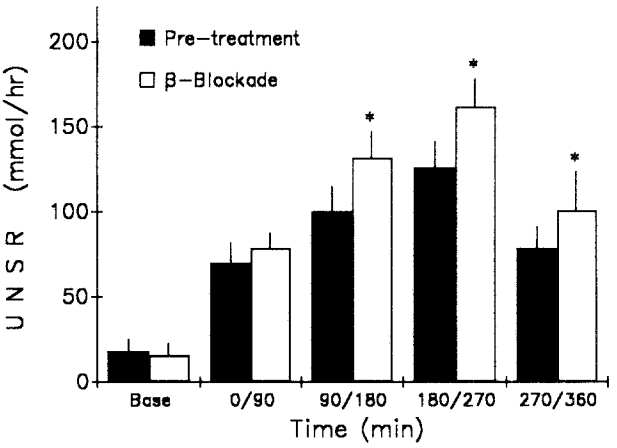

Fig 1. UNSR in the basal state, in response to alanine infusion (in 3 separate periods from time 0 to time 270 minutes), and after infusion (270 to 360 minutes) in cirrhotic patients before (■) and after (□) therapy with β-blockers (mean ± 2 SE). *Significantly different from corresponding pretreatment value, $P < .05$.

Basal UNSR was normal in both experiments. In the course of alanine infusion, UNSR increased linearly with increasing α-amino-N concentrations in each group. Under propranolol treatment, more urea was produced during each time period (ANOVA: time × treatment, $P = .0013$) and UNSR was greater by 40 to 50 mmol/h at the peak of α-amino-N concentrations (Fig 1). FHNC markedly varied in cirrhosis (mean ± SD: 17.0 ± 4.1 L/h; range, 12.3 to 24.4; normal value, > 25) and increased by 30% in response to propranolol treatment (22.0 ± 6.6; range, 16.7 to 35.7; $P < .01$; Fig 2). When related to body surface area, FHNC was 9.2 ± 2.7 L/h/m^2 and 12.2 ± 4.3 before and after propranol, respectively.

Nitrogen exchange during the whole period of alanine infusion was +7.8 ± 17.6 mmol/h before therapy and became negative after propranolol treatment (−20.0 ± 19.3, $P < .05$). The difference was entirely due to increased urea production during beta-blockade (92.5 ± 13.3 *v* 74.4 ± 10.9, $P < .001$) (Fig 3).

Both at baseline and at the end of alanine infusion, individual plasma amino acid concentrations did not significantly differ in relation to values obtained after propranolol therapy (Table 3), with the notable exception of the sum of BCAA (valine, isoleucine, and leucine), which markedly increased during alanine infusion under propranolol treatment (basal experiment: before infusion, 328 ± 48 μmol/L; after infusion, 325 ± 41; beta-blockade: 317 ± 65 and 371 ± 70, respectively; repeated-measures ANOVA, $P = .037$).

Propranolol treatment was effective in all cases. It significantly decreased basal heart rate (by ≥ 20%), abolished orthostatic tachycardia, and reduced systolic blood pressure in orthostatism (by 15%) and portal blood flow (by

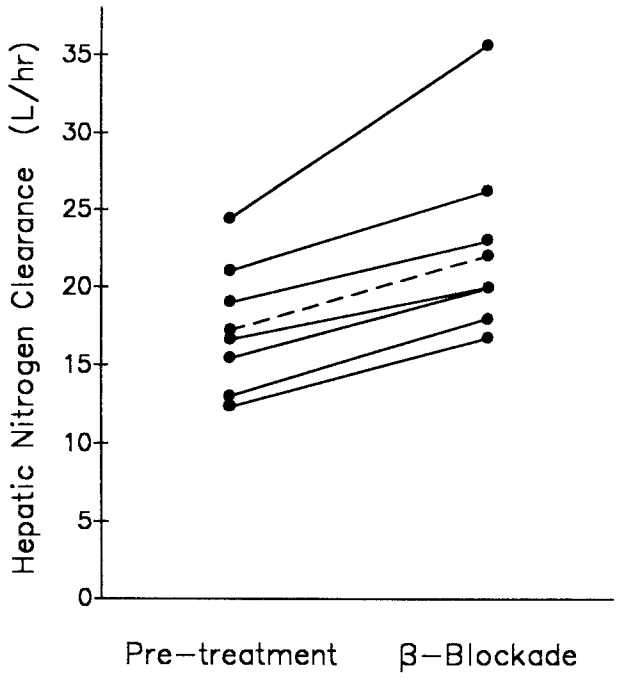

Fig 2. FHNC in cirrhotic patients before and after therapy with propranolol. (——) Values measured in individual subjects in paired experiments; (----) average values.

20%) (Table 4). Epinephrine and norepinephrine levels were high-normal or increased, and increased further in orthostatism before propranolol. After beta-blockade, no remarkable changes were observed (Table 4).

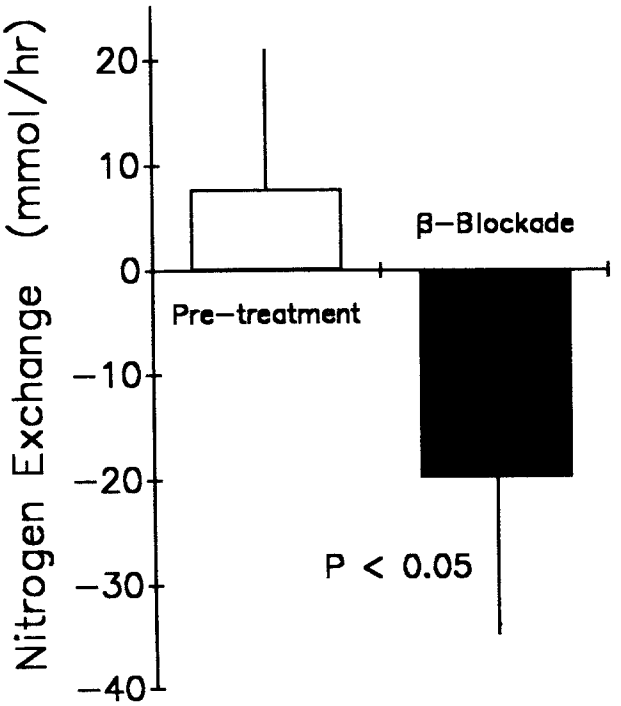

Fig 3. Nitrogen exchange in the whole period of alanine infusion before propranolol treatment and after beta-blockade in cirrhosis (mean ± 2 SE).

Table 3. Individual Plasma Amino Acid Concentrations at the Beginning and End of Alanine Infusion in Paired Experiments in Cirrhotic Patients Before and After Propranolol Therapy (mean ± SD, μmol/L)

	Before Infusion	End of Infusion
Taurine		
Before	88 ± 67	94 ± 68
After	69 ± 22	106 ± 72*
Asparagine		
Before	17 ± 11	63 ± 61*
After	17 ± 7	60 ± 38*
Threonine		
Before	156 ± 38	243 ± 82*
After	134 ± 70	217 ± 102*
Serine		
Before	116 ± 25	212 ± 66*
After	115 ± 57	176 ± 81*
Glutamate		
Before	114 ± 52	236 ± 116*
After	98 ± 66	258 ± 129*
Glutamine		
Before	434 ± 136	677 ± 234*
After	489 ± 177	645 ± 275*
Proline		
Before	211 ± 70	293 ± 46*
After	216 ± 82	414 ± 251*
Glycine		
Before	269 ± 44	338 ± 69*
After	252 ± 63	348 ± 93*
Alanine		
Before	327 ± 76	5,502 ± 1,653*
After	310 ± 94	6,127 ± 1,455*
Citrulline		
Before	45 ± 33	77 ± 25*
After	33 ± 21	62 ± 34*
Valine		
Before	155 ± 15	151 ± 10
After	154 ± 25	183 ± 33*†
Cystine		
Before	18 ± 17	22 ± 18
After	19 ± 15	33 ± 14
Methionine		
Before	46 ± 17	42 ± 8
After	58 ± 40	64 ± 33†
Ileucine		
Before	62 ± 20	63 ± 20
After	64 ± 27	72 ± 33
Leucine		
Before	111 ± 24	110 ± 28
After	100 ± 23	117 ± 24*
Tyrosine		
Before	118 ± 16	98 ± 11*
After	115 ± 24	122 ± 32
Phenylalanine		
Before	78 ± 20	52 ± 18*
After	80 ± 32	67 ± 32*
Ornithine		
Before	94 ± 30	100 ± 36
After	89 ± 29	83 ± 40
Lysine		
Before	165 ± 43	188 ± 52
After	146 ± 35	158 ± 45
Histidine		
Before	70 ± 16	71 ± 12
After	77 ± 26	81 ± 20
Arginine		
Before	106 ± 30	125 ± 46
After	93 ± 35	93 ± 36

*Significantly different from preinfusion values.

†Significantly different from corresponding value in experiment performed before beta-blockade.

Table 4. Epinephrine and Norepinephrine Concentrations, Systolic and Diastolic Blood Pressure, and Heart Rate in Clinostatism and Orthostatism, and Portal Blood Flow in Paired Experiments in Cirrhotic Patients Before and After Propranolol Treatment (mean ± SD)

	Clinostatism	Orthostatism	P
Pretreatment			
Epinephrine*	85 ± 39	94 ± 42	NS
Norepinephrine*	349 ± 201	528 ± 307	NS
Systolic blood pressure	118 ± 7	120 ± 9	NS
Diastolic blood pressure	77 ± 11	77 ± 9	NS
Heart rate	76 ± 3	86 ± 8	<.001
Portal flow	1,166 ± 238		
Posttreatment			
Epinephrine	52 ± 10	123 ± 95	NS
Norepinephrine	390 ± 248	625 ± 368	NS
Systolic blood pressure	110 ± 5†	104 ± 14†	NS
Diastolic blood pressure	71 ± 9	68 ± 11	NS
Heart rate	60 ± 6†	59 ± 5†	NS
Portal flow	938 ± 188†		

NOTE. Epinephrine and norepinephrine are in pg/mL, systolic and diastolic blood pressure are in mm Hg, heart rate is in beats per minute, and portal flow is in mL/min.

*Normal values in our laboratory are as follows: epinephrine, 10 to 80 pg/mL in clinostatism and 40 to 200 in orthostatism; norepinephrine, 40 to 400 and 200 to 600 pg/mL, respectively.[22]

†Significantly different from corresponding value in experiment performed before β-blocker therapy.

DISCUSSION

Our study shows that amino acid–induced ureagenesis is increased in cirrhosis after therapy with a nonselective β-blocker, suggesting that the drug may significantly affect hepatic nitrogen homeostasis. Increased urea production was not matched by a concomitant decrease in α-amino-N concentrations. Since the amount of amino acid nitrogen infused in paired experiments was the same, the increased hepatic urea formation is likely to be dependent on substrates derived from altered peripheral turnover of amino acids, mediated by hormonal changes or β-adrenoceptor blockade.

The methodology of the present study is the same previously used,[10] ie, study of the dynamics of hepatic urea formation during standardized conditions of substrate availability.[6,10] Also, the assumptions underlying the technique have been extensively dealt with in previous reports.[6,10] In the calculation of UNSR, intestinal hydrolysis was considered a fixed fraction of total urea nitrogen excretion on the basis of average values derived from the literature.[12] In our study, all patients were on long-term lactulose treatment, which is likely to reduce gut hydrolysis.[24] This may lead to overestimation of urea synthesis rate, but is not likely to be of any relevance in paired experiments, since there is no evidence of possible effects of β-adrenoceptor blockade on bacterial intestinal urea hydrolysis.

The observation period between paired experiments was short; all subjects were in stable condition, had not recently suffered gastrointestinal bleeding, had a controlled diet, and had no changes in drug treatment (apart from propranolol). Under our experimental conditions of standardized substrate supply, FHNC depends strictly on liver function.[10] There is conflicting evidence as to the effects of treatment with β-blockers on the functional capacity of the liver. Studies using galactose elimination capacity failed to detect abnormalities after propranolol treatment, and elimination of flow-dependent substrates seemed to be variably affected. In accordance with the kinetic characteristics of urea formation, it can be calculated that changes in splanchnic perfusion may affect FHNC by less than 5%.[25] In any case, decreased liver function and/or decreased hepatic perfusion would lead to decreased FHNC, and we found it to be increased after propranolol.

Also, antecedent protein intake contributes to FHNC. An increase in dietary proteins was shown to activate urea cycle enzymes[26] and the in vivo capacity of urea synthesis in rats.[27] Also, in man an increase in protein intake augments conversion of α-amino-N to urea.[28] In our patients, antecedent protein intake was controlled, and changes in urea synthesis were observed in the absence of any difference in basal and stimulated glucagon, which is known to mediate diet-induced changes in hepatic nitrogen conversion.[28]

The observed changes in FHNC were greater than the intrinsic variability of repeated tests[10] and were present in all patients, ranging from +2.4 to +11.3 L/h, corresponding to an increase of +15% to +46% due to the large variability of pretreatment values. Such variability probably reflects the different degree of hepatocellular failure,[10] confirmed by the wide range of galactose elimination capacity and antipyrine clearance.

FHNC directly depends on hormone concentrations, too. Glucagon is the most potent stimulator of hepatic nitrogen metabolism,[29,30] but hepatic unresponsiveness to glucagon has been demonstrated in cirrhosis.[31] Cortisol is relevant in the hepatic response to surgical stress,[32] and acts either directly[33] or through glucagon stimulation.[34] Finally, increased plasma levels of catecholamines were shown to promote the catabolic effects of other hormones in experimental animals[35] and in surgical stress in man.[36] However, in the present study, plasma levels of glucagon, cortisol, and catecholamines did not change significantly with propranolol treatment. Only insulin concentrations differed in paired experiments, and the amino acid–induced increase of plasma insulin was nearly halved after propranolol. Both selective and nonselective β-blockers may inhibit insulin release after glucose challenge in diabetes.[37] Insulin is not generally considered a major drive for hepatic nitrogen metabolism. However, there is evidence that insulin concentrations may exert modest but significant effects on hepatic nitrogen metabolism, mediated by the peripheral action of insulin on amino acid metabolism in muscle, and decreased substrate availability for urea synthesis.[38] Also, the relative increase in the sum of BCAA after propranolol is in keeping with this hypothesis. BCAA are scarcely ureogenetic,[21] but their circulating levels are strictly regulated by insulin levels.[39]

The change in the kinetics of amino N to urea N might also be mediated by regulation of β-adrenoceptors, either in the liver or in peripheral tissues, via regulation of amino acid release. The effects of beta-blockade in the liver have

long been debated: both β_1- and β_2-receptor blockade have been shown to influence splanchnic hemodynamics,[40] as confirmed in the present series, but no metabolic effects have ever been described.

In muscle tissue, β-adrenoceptor stimulation influences several metabolic processes,[2] including amino acid, glucose, and fat disposal.[3,41] Fatty acid release from adipocytes depends on β-adrenergic stimulation,[42] and blockade results in blunted fatty acid mobilization and decreased oxidation.[43] Also, muscle glycogenolysis may be reduced after beta-blockade,[44] and in our patients, glucose levels attained at the end of alanine infusion were decreased after propranolol.

In experimental animals, long-term treatment with clenbuterol, a β_2-adrenoceptor agonist, had protein anabolic and thermogenic properties. It caused hypertrophy of skeletal muscle fibers, whereas butoxamine, a β_2-receptor antagonist, reduced fiber size, with a change in fast-twitch fiber growth.[41] Also, in man, clenbuterol can affect muscle mass and function[3] by increasing the rate of protein synthesis during the first 3 to 4 days of treatment and subsequently reducing the rate of protein degradation.[44] These results are indicative that β-adrenoceptor agonists and insulin may have similar rather than antagonistic effects on plasma amino acid metabolism. It is conceivable that β-adrenoceptor blockade may counteract the nitrogen-sparing mechanism of elevated β-adrenoceptor agonist concentrations found in cirrhosis, finally giving rise to increased catabolism.

Increased nitrogen conversion in the liver, expressed by a counterclockwise shift of the relation of UNSR to α-amino-N concentrations, is indicative of a metabolic condition prone to catabolism, in which more amino acid N is converted to urea at each α-amino-N concentration. Amino acid–derived urea cannot be further reused, but is irreversibly lost in urine. The calculation of nitrogen exchange in the course of the experiment, ie, the total amount of nitrogen irreversibly transferred from α-amino-N to urea, although limited by a non–steady-state condition, may give an idea of total body nitrogen losses. According to data obtained in other physiologic and pathologic conditions (glucagon infusion[31] and hyperthyroidism[45]) associated with increased catabolism, the finding of negative nitrogen exchange after beta-blockade indicates a defect in the retention of amino-nitrogen derived either from infused alanine or from endogenous amino acid release.

It might be argued from the present data that long-term propranolol treatment in cirrhosis that presents a risk of bleeding might lead to a remarkable nitrogen loss and lean body mass wasting. This has never been reported in clinical studies. As suggested earlier, β-adrenoceptor regulation of protein metabolism changes with time, and a resetting of metabolism is expected after long-term treatment. Unfortunately, long-term studies are potentially biased by changes in other conditions that affect hepatic nitrogen clearance (liver function, hormones, and acute events).

In conclusion, short-term propranolol treatment in cirrhosis leads to increased aminonitrogen to urea nitrogen conversion in response to amino acid infusion. Increased hepatic nitrogen conversion and negative nitrogen exchange may derive from enhanced peripheral substrate release induced by β-adrenoceptor blockade and relative hypoinsulinemia, or from the synergistic action of both events on amino acid metabolism.

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