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Renal handling of amino acids in 5/6-nephrectomized rats: Stimulation of renal amino acid reabsorption after treatment with triiodothyronine or dexamethasone under amino acid load

Ch. Fleck, K. Gräfe, and **I. Kart**

Institute of Pharmacology and Toxicology, Friedrich Schiller University of Jena, Jena, Federal Republic of Germany

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Summary. In anaesthetized adult female rats, the renal amino acid handling was measured six days after 5/6 nephrectomy (5/6NX). The distinct rise in blood urea nitrogen as well as the significant reduction in urine flow and GFR indicate an impairment of kidney function. In principle, in 5/6NX rats amino acid plasma concentrations were comparable to those of control animals with two intact kidneys, whereas the fractional excretions (FE_{AA}) of most endogenous amino acids measured were significantly enhanced. After bolus injection of leucine or taurine (each 20 mg/100 g b.wt.) or glutamine (90 mg/100 g b.wt.), dissolved in 2 ml normal saline per 100 g b.wt., the FE_{AA} of both the amino acids administered and the endogenous amino acids increased as a sign of overloaded amino acid reabsorption capacity. This effect was more pronounced in 5/6NX rats than in controls. As early as one hour after amino acid load, plasma concentrations and FE_{AA} returned to baseline values of 5/6NX rats. A pretreatment with triiodothyronine (20 μg/100 g b.wt.) or dexamethasone (60 μg/100 g b.wt.), both given intraperitoneally once daily for 3 days, stimulated the renal amino acid transport capacity in 5/6NX rats: the increase in FE_{AA} after amino acid load was significantly lower compared to non-pretreatred animals. This stimulation could be shown for the bolus amino acids and the endogenous amino acids and was more distinct in 5/6NX rats than in controls with two intact kidneys.

Keywords: Amino acids – 5/6 nephrectomy – Renal failure – Amino acid transport – Kidney – Triiodothyronine – Dexamethasone – Amino acid load – Rats

Introduction

In rats, the consequences of unilateral nephrectomy are compensated within a few days; compensatory hypertrophy of the residual kidney tissue occurred

(Fleck and Bräunlich, 1984). The removal of both kidneys (NX) was survived for about two days (Fleck and Bräunlich, 1987). 5/6 nephrectomy is followed by a long-lasting impairment of kidney function (Achtermeier et al., 1993). This surgical intervention was survived for more than 3 months, therefore this experimental approach has been applied for studies on renal insufficiency, and both morphologic changes and some functional consequences of 5/6NX were previously characterized in detail (Bräunlich et al., 1986; Gretz et al., 1988).

In the present study, the influence of 5/6NX on the renal handling of amino acids has been measured, because little is known about amino acid reabsorption in renal insufficiency. Furthermore, previously it could be shown that tubular amino acid transport capacity can be stimulated after pretreatment with triiodothyronine or dexamethasone (Fleck et al., 1997). However, this effect occurred in adult animals only after amino acid load, whereas it could be found in immature rats under physiological conditions, too (Fleck, 1992). Therefore the question arose whether or not the stimulation phenomenon can be proven in adult 5/6NX rats, whose renal transport capacity was reduced (Achtermeier et al., 1993, Fleck and Bräunlich, 1995). If it is possible to stimulate the renal amino acid transport, this approach could be of practical importance in treatment of aminoaciduria in renal failure. Glutamine, leucine, or taurine were administered as continuous infusion to overload amino acid reabsorption carriers (Silbernagl, 1992). Leucine and glutamine were chosen for the following reasons: The physiological concentrations of these amino acids are relatively high and their FE_{AA} is relatively low. Thus their renal reabsorption seems to be very effective. On the other hand, taurine, a sulfonic acid, is transported via a very effective separate carrier system in the renal tubule and its FE_{AA} is relatively high compared to the other amino acids (Chesney et al., 1990). The amino acids are nearly non toxic. Therefore they can be administered in relatively high doses. Nevertheless, using amino acid loading besides renal effects metabolic changes must also be taken into consideration in experiments *in vivo*.

Material and methods

Animals

Investigations were performed on female Wistar rats (Han:Wist) of our institute's own out-bred stock. At the beginning of the experiments the animals were 2 months old and the average body weight was 141 ± 6 g. The rats were kept under standardized conditions including standard Altromin 1316 diet and free access to tap water.

Subtotal nephrectomy

5/6 nephrectomy (5/6NX) was performed in a two-step surgical intervention under hexobarbitone anaesthesia (10 mg/100 g b.wt. i.p.). At first the cortex of the left kidney was nearly completely ablated. Bleeding was prevented using tissue adhesive (Histoacryl blau®, B. Braun, Melsungen, Germany). Three days later the right kidney was removed (see Bräunlich et al., 1986). Clearance experiments were done six days after the first operation. Control rats were sham operated: two-times narcosis and opening of the

abdominal cavity were without effect on renal functions (for details see Fleck and Bräunlich, 1987).

Experimental design

The rats were anaesthetized with ketamine (Ursotamin® Serumwerk Bernburg, F.R.G., 7.5 mg/100 g b.wt.) and xylazine (Ursonarkon® Serumwerk Bernburg, F.R.G., 1.2 mg/100 g b.wt.). Both substances were administered intramuscularly. A catheter was placed in a tail vein. The animals were then infused isotonic saline containing 4 g/l fluorescein isothiocyanate (FITC)-inulin (Bioflor, Uppsala, Sweden) for the remainder of the experiment. Thereafter a polyethylene catheter was inserted into the urinary bladder. Glomerular filtration rate (GFR) was determined by inulin clearance. To minimize urine collecting periods for the determination of GFR and fractional amino acid excretion (FE_{AA}), urine was collected in 30-minute intervals over a period of 3 hours. In previous experiments it could be shown that under these experimental conditions both hematocrit (Fleck et al., 1992) and blood pressure (Fleck and Bräunlich, 1986) remain nearly constant during the clearance study. In the middle of each period and at the end of the experiment 100 μl blood were collected from the retrobulbar plexus.

Amino acid load

Rats were loaded with leucine or taurine (each 20 mg/100 g b.wt.) or glutamine (90 mg/100 g b.wt.). The amino acids were dissolved in 2 ml normal saline per 100 g b.wt. Amino acid doses were determined in previous experiments. It was the goal of the experimental schedule to enhance amino acid plasma concentration about 10 fold, whereas toxic effects of amino acids should be avoided. The injection solutions of leucine, glutamine, and taurine had osmolarities of 365, 322, and 362 mosmol/l, respectively, and pH was adjusted to 7.4. The amino acids were administered as a bolus injection intravenously at the beginning of the clearance experiment. Control animals received the same volume of normal saline.

Hormone treatment Triiodothyronine (T_3; SIGMA, St. Louis, U.S.A.) was administered intraperitoneally in doses of 20 μg/100 g b.wt once daily for 3 days. In this dose range, hormone receptor sites are completely saturated (Azimova et al., 1986).

Dexamethasone (Dexa; Fortecortin® Mono, E. Merck, Darmstadt, F.R.G.): 60 μg/100 g b.wt. were given i.p. for 3 days, once daily. Following this dose, glucocorticoid receptor sites are completely saturated by dexamethasone (Rafestin-Oblin et al., 1986).

Both substances were dissolved in normal saline (1 ml/100 g b.wt). Controls received the solvent only.

Determination methods

Amino acids: The determination of amino acids by column chromatography with fluorescence detection is based on that developed by Roth and Hampai (1973) and has been described in detail elsewhere (Silbernagl, 1983). Briefly, proteins were removed from urine and plasma samples by administration of trichloroacetic acid. After centrifugation, the supernatant was neutralized by adding 0.4 N NaOH. Then the samples were diluted with citrate buffer and analyzed by HPLC on an amino acid analyzer (Knauer, Berlin, F.R.G.) with o-phthalaldehyde as a fluorescent amino ligand (Roth, 1971). Calibration runs were performed with freshly prepared amino acid solutions composed of analytical grade amino acids (Serva, Heidelberg, F.R.G.).

Glomerular filtration rate (GFR) was determined by inulin clearance. Inulin concentration was measured fluorometrically using FITC-inulin in blood and urine samples (Sohtell et al., 1983).

Blood urea nitrogen (BUN) was determined photometrically (Ceriotti and Spandrio, 1963).

Statistics

Results are given as means ± S.E.M. with n = 6 in each group. The level of significance for differences between the observations was assessed with Mann Whitney test and considered statistically significant when $p \leq 0.05$ (FE_{AA}) and $p \leq 0.001$ (plasma concentrations), respectively.

Results

As shown in Table 1, 5/6NX is followed by a distinct reduction in kidney functions: urine flow and GFR decreased significantly, and blood urea nitrogen was enhanced as a sign of uremia. Furthermore, uremia caused a marked inhibition of the normal body weight gain whereas the wet weight of the remaining kidney tissue increased during six days after ablation of renal cortex to about 42% of the weight of two kidneys despite renal tissue was removed to 83% (= 5/6). Amino acid plasma concentrations were not uniformly changed after 5/6NX: the concentrations of most amino acids were unchanged; only the levels of glutamine and glycine were slightly enhanced whereas those of aspartic acid, lysine, and isoleucine were decreased (Table 2). However, with few exceptions (phenylalanine, tyrosine, isoleucine, taurine) the fractional amino acid excretions were higher in 5/6NX rats, that means, their amino acid reabsorption capacity was reduced (Table 2).

A bolus injection of amino acids (glutamine, leucine, taurine) induced polyuria in controls with two intact kidneys, and, more pronounced, in 5/6NX rats. On the other hand, in both experimental groups the amino acid load did not significantly influence GFR (Table 1). The plasma concentrations of the administered amino acids increased immediately after bolus injection 8–9 fold (Table 3). The concentrations of the endogenous amino acids which were not administered remained constant after amino acid load (not shown). Surprisingly, the raise in amino acid plasma concentrations was smaller in 5/6NX rats than in controls with two intact kidneys. As given in Fig. 1, the fractional

Table 1. Influence of 5/6 nephrectomy (5/6NX) on various parameters characterizing renal function in adult rats loaded with amino acid (AA) bolus (glutamine, leucine, or taurine) 6 days after 5/6 NX or sham operation. Arithmetic means ± S.E.M.; n = 6

	Two intact kidneys	5/6 NX
Body weight [g]	133 ± 5	112 ± 7*
Kidney weight [mg/100 g b.wt.]	1062 ± 40	432 ± 23*
Urine volume [ml/30min × 100 g b.wt.]		
before AA bolus	1.48 ± 0.16	0.38 ± 0.03*
after AA bolus	2.00 ± 0.20	0.70 ± 0.06*
GFR [ml/min × 100 g b.wt.]		
before AA bolus	0.79 ± 0.04	0.24 ± 0.02*
after AA bolus	0.84 ± 0.10	0.26 ± 0.03*
Blood urea nitrogen [mmol/l]	4.15 ± 0.28	9.68 ± 0.76*

Asterisks indicate significant differences between 5/6 NX and rats with two intact kidneys ($p \leq 0.05$).

Table 2. Influence of 5/6 nephrectomy (5/6NX) on amino acid plasma concentrations and fractional amino acid excretions in adult rats 6 days after 5/6 NX or sham operation. Arithmetic means ± S.E.M.; n = 6

Amino acid	Plasma concentration [μM]		Fractional excretion [%]	
	control	5/6 NX	control	5/6 NX
Acidic				
Glu	147 ± 5	115 ± 15	1,77 ± 0,34	5,16 ± 0,79*
Asp	47 ± 3	20 ± 2*	1,87 ± 0,22	6,82 ± 1,06*
Basic				
Arg	136 ± 3	126 ± 10	0,54 ± 0,04	0,73 ± 0,07
Lys	250 ± 8	134 ± 11*	0,36 ± 0,03	7,75 ± 1,46*
Neutral				
Asn	70 ± 2	49 ± 5	0,95 ± 0,09	3,36 ± 0,84*
Gln	344 ± 42	524 ± 38	0,89 ± 0,07	2,64 ± 0,41*
Ser	185 ± 5	134 ± 15	1,03 ± 0,07	4,29 ± 0,66*
Ala	302 ± 9	273 ± 20	0,73 ± 0,05	1,86 ± 0,39*
Gly	183 ± 3	318 ± 27	1,67 ± 0,12	2,92 ± 0,90
Val	250 ± 7	179 ± 4*	0,41 ± 0,04	0,55 ± 0,12
Phe	77 ± 4	64 ± 5	3,74 ± 0,66	1,96 ± 0,25
Tyr	80 ± 5	60 ± 4	1,35 ± 0,18	0,83 ± 0,19
Ile	135 ± 3	84 ± 3*	0,42 ± 0,05	0,26 ± 0,01
Leu	173 ± 22	101 ± 3	0,45 ± 0,06	1,70 ± 0,38*
Others				
Tau	115 ± 4	153 ± 11	4,37 ± 0,34	2,93 ± 0,33
β-Ala	11 ± 1	4 ± 1	2,46 ± 0,43	8,30 ± 0,29*

Asterisks indicate significant differences between 5/6 NX and rats with two intact kidneys (plasma concentrations: $p \leq 0.0001$; FE_{AA}: $p \leq 0.05$).

Table 3. Initial increase (3 minutes after bolus) of plasma amino acid concentrations in 5/6 nephrectomized rats (5/6NX) and in rats with two intact kidneys loaded with amino acid bolus (glutamine, leucine, or taurine) 6 days after 5/6 NX or sham operation. Arithmetic means ± S.E.M.; n = 6

Bolus		Plasma concentration [μM]		
		Glu	Leu	Tau
NaCl	Control	344 ± 42	173 ± 22	115 ± 4
	5/6 NX	+525 ± 38	101 ± 3	153 ± 11
Gln	Control	***5617 ± 90**	117 ± 8	92 ± 2
	5/6 NX	***3075 ± 172**	148 ± 33	102 ± 13
Leu	Control	307 ± 5	***1936 ± 87**	340 ± 2
	5/6 NX	580 ± 18	+***804 ± 37**	88 ± 10
Tau	Control	463 ± 32	177 ± 7	***1761 ± 25**
	5/6 NX	381 ± 43	76 ± 5	+***832 ± 13**

Bold print: administered amino acids: + – significant differences between 5/6 NX and rats with two intact kidneys ($p \leq 0.001$); * – significant increase in plasma concentration after bolus injection ($p \leq 0.001$).

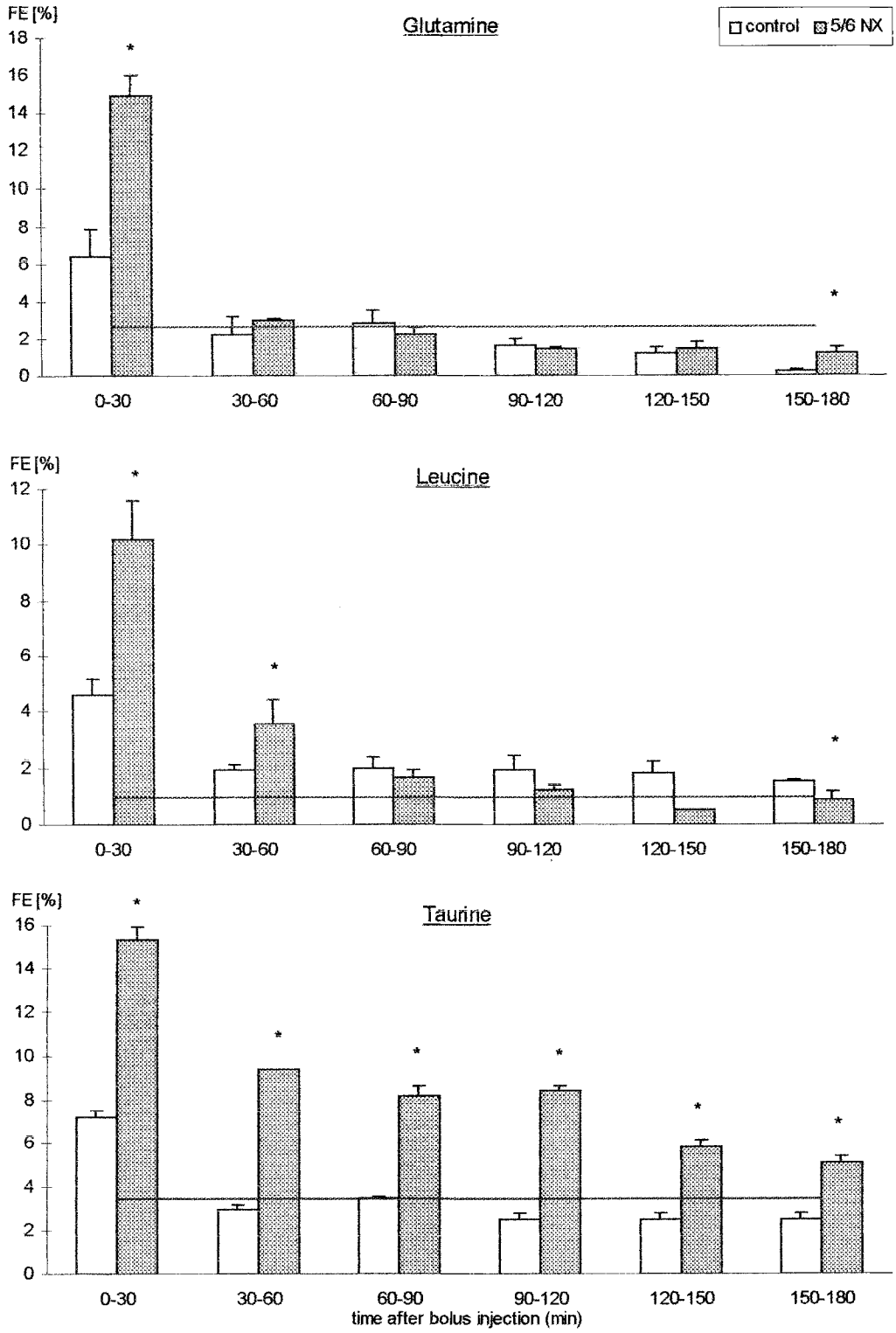

Fig. 1. Fractional excretion (*FE*) of glutamine, leucine, and taurine during 3 hours after bolus injection of the respective amino acid in controls and 5/6NX rats. Arithmetic means ± S.E.M., n = 6; continuous lines = baseline value of control rats without amino acid load. * – significantly different from rats with two intact kidneys ($p \leq 0.05$)

amino acid excretion increased after respective amino acid load, more distinct in 5/6NX rats. In controls, FE_{AA} normalized very rapidly within the first clearance period. In contrast, in 5/6NX rats the FE_{AA}-values returned to baseline (continuous lines in Fig. 1) after different times depending on the injected amino acid: glutamine within 30 min, leucine after one hour, and $FE_{taurine}$ remained significantly enhanced up to the end of the clearance experiment.

As reported previously for controls with two intact kidneys (Fleck et al., 1997), after bolus injection of amino acids the fractional excretion of the other endogenous amino acids, which were not administered, increased, too (Fig. 2).

The uniform increase in FE_{AA} indicates an overloading of tubular amino acid reabsorption capacity. Under these conditions the effects of a pretreatment with triiodothyronine and dexamethasone on renal amino acid handling in 5/6NX rats should be characterized in detail. The well-known hormone effects on basic parameters describing renal function could be reproduced in 5/6NX rats, too (Table 4): urine flow was higher in dexamethasone pretreated rats and glomerular filtration rates was enhanced after pretretment with the two hormones. After amino acid bolus injection (glutamine, leucine, or taurine), GFR was increased additionally about 1.5-fold. Furthermore, both hormones seem to improve the compensation after 5/6NX because the kidney weight was higher than in non hormone-pretreated animals. As could be shown pereviously for rats with two intact kidneys (Fleck et al., 1997), without amino acid load the fractional amino acid excretion was enhanced in T3 pretreated 5/6NX rats whereas it was nearly unchanged after dexamethasone pretreatment (not shown). However, after amino acid bolus injection the increase in FE_{AA} of the administered amino acids in the first clearance period after loading (see Fig. 1) was prevented with one exception: glutamine after dexamethasone treatment (Fig. 3). Under leucine load, the $FE_{leucine}$ of both T3 and dexamethasone pretreated rats was not significantly different from that of non AA-loaded animals. Interestingly, the hormone effect on the urinary taurine excretion was only moderate: at the end of the clearance study the $FE_{taurine}$ was even higher in hormone pretreated 5/6NX rats compared to the saline treated group. The $FE_{taurine}$ values of non AA-loaded rats were not reached during the whole experiment.

As shown in the synopsis of Table 5, the FE_{AA} of the endogenous amino acids which were not administered as amino acid bolus, were influenced by T3 and dexamethasone, respectively, in 5/6NX rats, too: in 76% of all amino acids the FE_{AA} was decreased, whereas it was enhanced in 4% only. The decrease in FE_{AA} compared to those of non hormone-pretreated 5/6NX animals indicates an improved amino acid reabsorption capacity and was significant for 32% of the amino acids. This effect was more pronounced after taurine bolus than after leucine or glutamine load. An increase in FE_{AA} after hormone pretreatment occurred only in 4 of altogether 102 cases and can be neglected for the following interpretations.

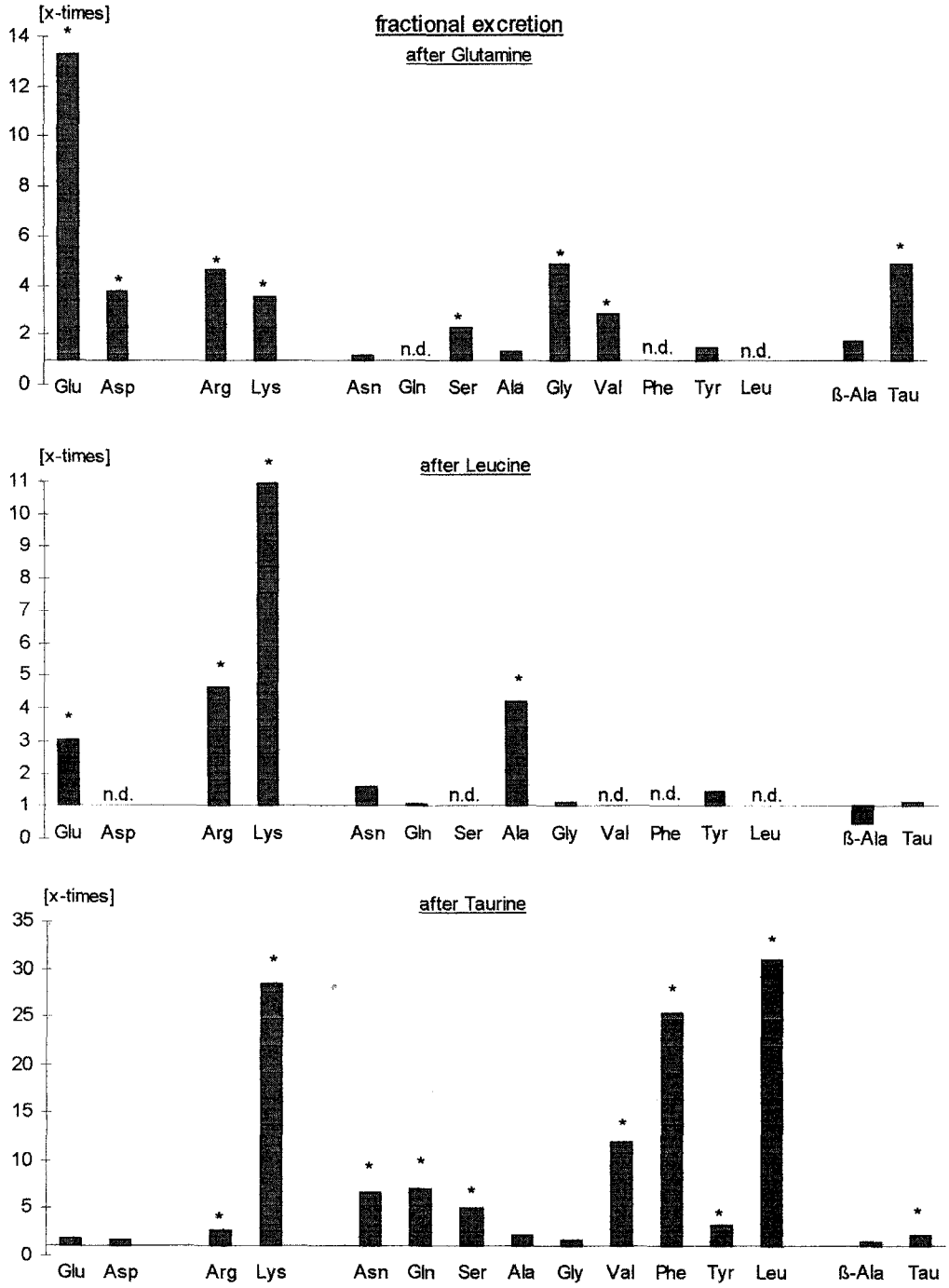

Fig. 2. Changes in the fractional amino acid excretion (*x-times*) of *endogenous* amino acids in the first 30-minutes clearance period after the administration of a bolus injection of glutamine, leucine, or taurine, respectively, in 5/6NX rats. Arithmetic means are given, n = 5–6; n.d. = not determined. * – significantly different from rats (= 1) with two intact kidneys ($p \leq 0.05$)

Table 4. Influence of pretreatment with dexamethasone (Dexa) or triiodothyronine (T3) on various parameters characterizing renal function in 5/6 nephrectomized rats (5/6NX) loaded with amino acid (AA) bolus (glutamine, leucine, or taurine). Arithmetic means ± S.E.M.; n = 6

	5/6NX	5/6NX + Dexa	5/6NX + T3
Body weight [g]	112 ± 7	106 ± 4	105 ± 5
Kidney weight [mg/100g b.wt.]	440 ± 20	515 ± 10	507 ± 20
Urine volume [ml/30min × 100g b.wt.]			
before AA bolus	0,55 ± 0,03	*1,17 ± 0,15	0,54 ± 0,10
after AA bolus	0,78 ± 0,11	0.71 ± 0.15	0.63 ± 0.16
GFR [ml/min × 100g b.wt]			
before AA bolus	0,24 ± 0,04	*0,37 ± 0,03	*0,33 ± 0,04
after AA bolus	0,27 ± 0,05	+*0,52 ± 0,03	+*0,44 ± 0,03

* – significant hormone effect ($p \leq 0.05$); + – significant influence of AA bolus injection ($p \leq 0.05$).

Table 5. Influence of pretreatment with dexamethasone or triiodothyronine on fractional excretions of amino acids (↓ – reduction; ↑ – increase; = unchanged) in 5/6 nephrectomized rats loaded with amino acid bolus (glutamine, leucine, or taurine). n = 6

Fractional excretion	Triiodothyronine			Dexamethasone		
	Gln bolus	Leu bolus	Tau bolus	Gln bolus	Leu bolus	Tau bolus
Acidic						
Glu	↓*	↓	↓*	=	↓	↓
Asp	n.d.	↑	↓*	n.d.	=	↓
Basic						
Arg	↓*	↓	↓*	↓*	↓	↓*
Lys	↓	=	↓*	=	↓	↓*
Neutral						
Asn	↓	↓	↓	=	=	↓*
Gln	↓*	↑	↓	=	=	↓
Ser	↓*	=	↓*	↓	↓*	↓*
Ala	↓	↓*	=	↓	↓*	=
Gly	↓	=	↓	↓	↓	↓
Val	↓	↓	↓*	↓	↓	↓*
Phe	↓*	=	=	=	↓	↑
Thr	↓	=	↓	=	↓*	↓
Tyr	↓	↓*	↓	↓	↓	↓
Ile	↓	↑	↓	↓	↓	↓
Leu	↓	↓*	↓*	↓	↓*	↓*
Others						
β-Ala	↓*	↓*	↓	↓	↓	↓
Tau	↓*	=	↓*	↓*	↓	↓*

n.d. – not determined. Asterisks indicate significant hormone effects ($p \leq 0.05$).

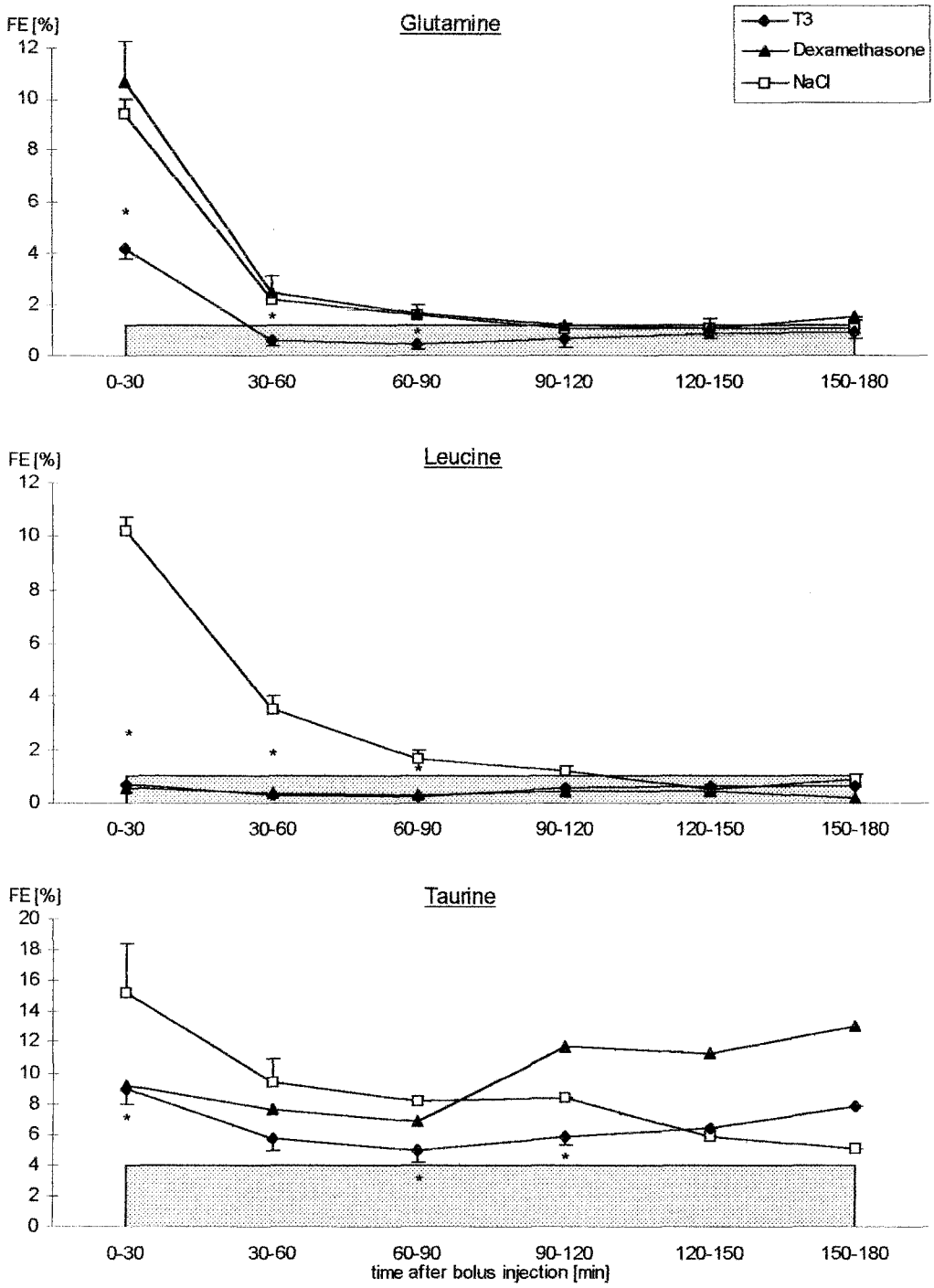

Fig. 3. Fractional excretion (*FE*) of glutamine, leucine, and taurine during 3 hours after bolus injection of the respective amino acid in 5/6NX rats pretreated with triiodothyronine or dexamethasone(cf. method). Controls received normal saline. Arithmetic means ± S.E.M., n = 6; continuous bands = baseline value of 5/6NX rats without amino acid load. * – significantly different from saline treated 5/6NX rats ($p \leq 0.05$)

Discussion

5/6NX is a suitable method to produce an acute renal failure with reduced GFR and enhanced BUN concentration. This type of reduction in renal mass is furthermore reported to induce a significant increase in systolic blood pressure, total urinary protein excretion, and plasma creatinine concentration (Ikeda et al., 1989; Faraj and Morley, 1992; Nabokov et al., 1996). It could be confirmed in our study that rat kidney is able to compensate rapidly the loss of renal tissue: within 6 days after renal ablation, kidney weight reached 41% of controls with two intact kidneys, despite kidney mass was removed to 83% (=5/6). The same is true for GFR: filtration capacity reached about 30% of controls after removal of 83% of the kidney. This compensatory increase in GFR has been described by other authors, too (Haylor et al., 1996). Interestingly, calculated to 1 g kidney weight, in our controls GFR accounts for 0.74 ml/min whereas in 5/6NX rats only 0.55 ml/min were filtered. That means, there is a discrepancy between kidney mass increase and filtering capacity.

In the present study attention was focused on renal transport of amino acids in 5/6NX rats because in the literature only little information exists concerning this field. After 5/6NX the concentrations of aspartic acid, lysine, valine and isoleucine were decreased whereas those of glutamine and glycine were increased. Quite comparable changes were found in plasma of children with renal failure for serine, threonine, glutamic acid, tyrosine, arginine, and glycine. These children excreted up to 40% of the filtered load of amino acids in the urine (Betts and Green, 1977). Michalk et al. (1983) reported that immediately after 5/6NX, taurine concentration in plasma increases two to three times the normal levels, but in chronic renal failure taurine was unchanged in plasma as a consequence of increased hepatic elimination. The kidney regulates taurine balance by modulating proximal tubular reabsorption (Trachtman et al., 1993). In uremic dogs, there was evidence for preservation of glomerular-tubular balance between the filtered load of amino acids and tubular reabsorption (Kopple and Fukuda, 1980). But in our 5/6NX rats the fractional excretion of most amino acids was enhanced up to 2- to 5-fold as a sign of exhausted amino acid reabsorption capacity. In animals and patients with acute renal failure accelerated protein catabolism occurs. Metabolic acidosis in uremia stimulates amino acid breakdown (Mitch et al., 1989; Schaefer et al., 1989; Greiber and Mitch, 1992). Maroni et al. (1990) found that acute renal failure depresses maximal transport velocity of the amino acid transport system in muscle.

To further characterize the amino acid transport in acute renal failure, 5/6NX rats were loaded with amino acids. Under these experimental conditions, in control rats with two intact kidneys the amino acid reabsorption mechanisms are exhausted to capacity and changes in the transport ratio can be investigated (Fleck et al., 1997). In 5/6NX rats this effect is much more pronounced: the bolus injection of amino acids is followed by a significant increase in FE_{AA}. Similar findings were reported for men: in patients having

dialysation treatment FE_{AA} of all amino acids with the exception of taurine was increased, due to a rise of their serum concentrations (Fischerova, 1992). As shown for control rats (Fleck et al., 1997), in 5/6NX rats the administration of an amino acid bolus increased the FE_{AA} of endogenous amino acids, which were not administered, too. The reason for this phenomenon could be

- a direct competition at the amino acid carrier sites in the kidney between leucine, taurine, or glutamine and endogenous amino acids using the same carrier (Christensen, 1990),
- a loss of ATP, and, therefore, a reduction of the Na^+-gradient in the renal tubuli (Gutmann et al., 1993),
- the reduced contact time in the nephron because of the increased urine flow.

Furthermore, uremia following 5/6NX seems to be responsible for a couple of transport disturbances at various membranes: in renal failure the basal sodium pump activity was decreased in sceletal muscle and adipocytes. The sodium-dependent amino acid transport in adipocytes closely paralleled diminished Na^+ pump acitivity (Druml et al., 1988). The lysine transport capacity was reported to be increased in erythrocytes from patients with renal failure (Fervenza et al., 1989). In uremic rats, the acceleration of amino acid transport seems to represent an additional component of amino acid utilization (Fröhlich et al., 1977). Altogether, aminoaciduria is an early marker of renal tubular damage: the amino acid excretion increased dramatically within 24 hours after the onset of acute renal failure caused by gentamycin (Mac Person et al., 1991). Further transports seemed to be reduced in uremia, too, e.g. the renal clearance of oxalate was decreased by 50% (Hatch et al., 1994).

The last aspect of this study was to characterize the hormonal regulation of renal amino acid transport. In control rats with two intact kidneys, loaded with amino acid bolus, it could be shown that pretreatment with dexamethasone or T3 stimulates the renal amino acid reabsorption (Fleck et al., 1997). This phenomenon was investigated in 5/6NX rats because in human renal failure it could be beneficial to find a sufficient therapy preventing aminoaciduria. Summarizing our results it can be stated that the stimulation of the renal transport of amino acids occurred in uremic rats, too. The following reasons might be responsible for the hormonal stimulation of renal amino acid reabsorption in 5/6NX rats:

- Dexamethasone induces the gene expression and might enhance the content of carrier molecules in the tubular cells (Yamamoto, 1985)
- T3 is reported to increase the synthesis of proteins in the kidney in general (Capasso et al., 1987). This de-novo protein synthesis could include amino acid carrier proteins followed by an enhanced amino acid transport capacity in the tubular cell.
- Dexamethasone (Baum and Quigley, 1993) and T3 (Guernsey and Edelmann, 1984) enhance the activity of the Na^+/K^+-ATPase and increase the sodium gradient between tubular lumen and tubular cell. This might

increase the highly sodium dependent amino acid reabsorption (Yao et al., 1994).

- Patients and/or experimental animals with chronic renal failure have decreased serum levels of T3 (Anagnostou et al., 1988). T3 is assumed to facilitate recovery of renal function following ischemic acute renal failure (Rogers et al., 1996).
- On the other hand, corticosterone replacement after adrenalectomy has no beneficial efects on renal recovery after 5/6NX in rats (Quan et al., 1992).
- The potassium permeability at the basolateral membrane of the tubular cells is increased after T3 administration (De Nayer, 1987) and might cause an enhanced Na^+/K^+-ATPase activity, too. Interestingly, potassium depletion causes a greater increase in renal mass and RNA content after 5/6NX (Peterson et al., 1987).

The effectiveness of hormone pretreatment on renal amino acid transport seems to be more distinct in 5/6NX rats than in controls. This indicates an overlapping of compensatory processes after 5/6NX and stimulation phenomena as described previously for renal tubular transport of xenobiotics (Fleck and Bräunlich, 1990). The two processes cause an increase in transport capacities of the tubular cells, but some of these reasons for this rise are identical, others are different (increase in kidney mass, enhanced renal perfusion, improved energy supply, increase in carrier protein synthesis) (for review see Fleck and Bräunlich, 1995). It should be clarified in further studies whether or not a hormone pretreatment can diminish or prevent amino acid loss in patients with kidney insufficiency, if physiological compensation is exhausted to capacity.

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Authors' address: Prof. Dr. Christian Fleck, Institut für Pharmakologie und Toxikologie, Klinikum der Friedrich-Schiller-Universität Jena, D-07740 Jena, Federal Republic of Germany, Fax ++49+3641+938702, E-mail: <CFLE@mti-n.uni-jena.de>

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