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Renal Amino Acid Excretion and Aging

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Summary

The urinary excretion and serum concentration of amino acids were studied in 62 healthy individuals aged 15 to 70 years. In elderly subjects (61–70 years), it was found that renal amino acid clearance per 100 ml GFR (fractional excretion, FE) rose significantly in the following amino acids: CYS, VAL, MET, ILE and LEU. Since the serum concentrations of these amino acids showed no significant changes, but the GFR was reduced, it can be concluded that the raised FE of these amino acids was due to a decrease in their effective tubular reabsorption. A significant correlation was found between FE_{Na} and FE of most amino acids including those mentioned above. The findings support the assumption that changes in tubular Na^+ transport probably participate in the changes of tubular amino acid transport in elderly individuals.

Key words:
Renal amino acid clearance – Aging – Cotransport of Na^+ and amino acids

Introduction

A number of renal functions change in the course of aging. It has been demonstrated that the glomerular filtration rate (GFR) and renal plasma and blood flow fall during aging (Shock 1946). These changes are interpreted as the outcome of vascular changes in the renal vascular bed (Oliver 1942). In addition to these haemodynamic changes, various tubular functions have likewise been shown to alter

Abbreviations of Amino Acids:

ASP	Aspartate	SER	Serine
PRO	Proline	GLU	Glutamate
GLY	Glycine	ALA	Alanine
CYS	Cystine	TYR	Tyrosine
HIS	Histidine	ARG	Arginine
THR	Threonine	VAL	Valine
MET	Methionine	ILE	Isoleucine
LEU	Leucine	PHE	Phenylalanine
LYS	Lysine	TRP	Tryptophane
TAU	Taurine	CIT	Citrulline
ORN	Ornithine	ASN	Asparagine
GLN	Glutamine		

during aging. The concentrating (Nádvorníková 1983) and acidification ability of the kidneys (Schück *et al.* 1989) decreases. Davies and Shock (1950) demonstrated a decrease in the maximum secretory capacity for diodrast and in maximum reabsorptive capacity for glucose. Changes in the tubular transport of these substances were proportional to the decrease of inulin clearance, however, and need not be caused by primary changes in tubular transport.

The mechanism of changes in tubular transport processes in the residual nephrons of elderly healthy subjects is still obscure. The observed changes are open to several explanations. In the first place, they might be due to haemodynamic changes caused by atherosclerotic changes in the renal bed (Oliver 1942). There is also a possibility of adaptive changes in the tubular functions caused by a decrease in the GFR (Bricker 1972). Theoretically, the participation of age-related metabolic changes in tubular transport processes cannot be ruled out. Lastly, changes in the tubular transport of some substances might be the outcome of age-dependent changes in regulatory mechanisms, e.g. altered antidiuretic hormone production (Pacovský *et al.* 1959).

In this study we have tried to study the changes in tubular amino acid transport during aging. According to present knowledge, after being filtrated in the glomeruli the individual amino acids are reabsorbed in the tubules at a very high rate and the process is probably not influenced by regulatory mechanisms, since the organism makes every effort to prevent urinary loss of these substances. It has, however, been demonstrated that the tubular transport of some amino acids is dependent on the tubular transport of sodium (Fox *et al.* 1964, Sactor 1980, Silbernagl 1976, Ullrich *et al.* 1974, Ullrich 1979). In consequence, it could be assumed that changes of tubular Na^+ transport induced by reduction in the number of functioning nephrons during aging might also influence tubular amino acid transport. Since sodium balance is still maintained in elderly subjects even when the number of functioning nephrons has been reduced, one must presume that the reabsorption of Na^+ in the residual nephrons of these subjects is also relatively reduced as in patients with chronic kidney disease (Bricker 1972). The question is thus whether tubular amino acid transport, which is dependent on tubular Na^+ transport, is also influenced by these adaptive changes.

Our aim in this study was to investigate how far changes in the tubular Na^+ transport (in the presence of the age- determined GFR reduction) influence the tubular transport of amino acids.

Material and Methods

Sixty-two healthy individuals aged 15 – 70 years were examined (Tab. 1).

Table 1

Basic data of the group of healthy volunteers

Age (years)	15-20	21-30	31-40	41-50	51-60	61-70
n	10	11	10	11	10	10
males/females	6/4	5/6	3/7	4/7	1/9	4/6

The probands were given a diet with a normal protein content (1–1.5 g/kg/24 h) and sodium and water *ad libitum*. The investigations were always carried out in the morning before breakfast in a separate quiet room where the examination started with a drink of 500 ml water. After blood had been withdrawn from the cubital vein, the subjects were given a single dose of polyfructosan S (Inutest) (50 mg/kg body weight), followed by its further administration using a microinfusion pump (0.2 ml/min) until its plasma level was stabilized. Urine was collected for one hour (for details see Schück 1984).

Polyfructosan S (PFS) concentration was determined in blood and urine samples (White and Samson 1954). This polysaccharide furnishes the same information as inulin as regards the determination of GFR (Mertz 1963). The endogenous creatinine concentration was determined with a Hitachi automatic analyser, the serum electrolyte concentration with an ion-selective electrode (NOVA) and the urinary electrolyte concentration by flame photometry (Eppendorf). The concentrations of twenty two amino acids were determined using a Beckman automatic analyser. Clearance values (C) and fractional excretion (FE) values were computed in the usual way.

The results were evaluated statistically by correlation analysis and the U-Mann-Whitney test.

Results

In agreement with a number of earlier studies, we demonstrated a drop in GFR with aging in our healthy volunteers. A decrease was demonstrated both in polyfructosan clearance (C_{PFS}) and in endogenous creatinine clearance (C_{cr}) (Tab. 2). The mean clearance values in the oldest age group (61–70 years) were significantly lower than in the youngest individuals (21–30 years). A decrease of these values was also demonstrated by correlation analysis. Urea clearance (C_{urea}) showed similar changes. The drop in the GFR was not associated with an increase in the plasma concentration of endogenous creatinine (P_{cr}) although the plasma urea concentration (P_{urea}) rose significantly from 5.3 ± 1.75 mmol/l in young subjects (21–30 years) to 6.5 ± 0.93 mmol/l in old subjects (61–70 years) ($p < 0.05$).

Table 2

Endogenous creatinine clearance (C_{cr}), polyfructosan S clearance (C_{PFS}) and urea clearance (C_{urea}) in individual age groups

Age (years)	15-20	21-30	31-40	41-50	51-60	61-70
C_{cr} (ml/min)	135 ±25	123 ±45	122 ±32 r=-0.395**	116 ±34	113 ±33	87** ±19
C_{PFS} (ml/min)	110 ±20	112 ±23	107 ±55 r=-0.389**	98 ±21	103 ±26	86** ±15
C_{urea} (ml/min)	65 ±16	64 ±12	60 ±17 r=-0.403**	62 ±25	49 ±14	46** ±8

*Means ± S.D.; ** $p < 0.01$*

The fractional excretion of sodium (FE_{Na}) and of all osmotically active substances (FE_{osm}) rose significantly during aging. The increase was demonstrated as a significant elevation of mean values in old subjects (61–70 years) and also on the basis of correlation analysis (Tab. 3). An increase was also demonstrated in the

plasma concentration of all osmotically active substances (P_{osm}), from 278.0 ± 5.0 mmol/kg H_2O in young subjects (21–30 years) to 287.9 ± 7.7 mmol/kg H_2O in old subjects (61–70 years) ($p < 0.05$).

Table 3

Fractional excretion of sodium (FE_{Na}) and of all osmotically active substances (FE_{osm}) in individual age groups

Age (years)	15-20	21-30	31-40	41-50	51-60	61-70
FE_{Na} (%)	1.40 ±0.37	1.32 ±0.58	1.31 ±0.78 r = 0.400**	1.66 ±0.95	1.90 ±1.00	2.44* ±1.03
FE_{osm} (%)	2.96 ±0.44	2.79 ±1.04	2.68 ±0.94 r = 0.321**	3.12 ±1.24	3.66 ±1.92	3.85* ±0.79

*Means ±S.D.; * $p < 0.05$, ** $p < 0.01$*

Table 4

Serum amino acid concentrations in individuals aged 21-30 and 61-70 years.

Age (years)	21-30	61-70		21-30	61-70		21-30	61-70
ASP	5.4 ±2.2	6.5 ±1.9	HIS	96.0 ±14.1	75.9 ±17.0	PHE	47.1 ±4.9	40.9* ±8.4
SER	134.6 ±36.2	103.1* ±19.0	ARG	61.5 ±23.2	84.7 ±33.7	LYS	173.1 ±20.2	146.1 ±23.7
PRO	180.7 ±67.1	176.1* ±39.6	THR	107.8 ±25.7	81.6* ±9.8	TRP	62.3 ±11.9	62.6 ±23.7
GLU	62.6 ±31.6	62.0 ±11.4	VAL	194.0 ±38.5	195.8 ±47.3	TAU	52.6 ±14.8	61.8 ±14.1
GLY	214.9 ±70.3	253.3 ±92.1	MET	21.8 ±3.9	15.8 ±6.9	CIT	40.2 ±9.1	35.8 ±10.6
ALA	304.4 ±90.9	354.5 ±49.4	ILE	52.4 ±12.7	49.3 ±11.3	ORN	106.4 ±37.8	90.5 ±14.0
CYS	86.6 ±22.4	76.0 ±10.5	LEU	111.7 ±20.2	113.3 ±22.3	ASN+ GLN	629.2 ±86.3	702.7 ±268.8
			TYR	40.9 ±11.8	46.2 ±11.50			

*Means ± S.D.; * $p < 0.05$*

Table 5

Fractional amino acid excretion (%) in the individual age groups

Age (years)	15-20	21-30	31-40	41-50	51-60	61-70
ASP	4.88	4.52	2.79	4.25	4.68	1.74*
	±3.50	±3.30	±1.44	±2.14	±3.54	±1.56
SER	1.77	2.27	1.98	1.76	2.40	2.37
	±0.74	±1.48	±1.16	±0.70	±1.34	±2.90
PRO	0.05	0.04	0.03	0.03	0.05	0.10
	±0.07	±0.04	±0.03	±0.03	±0.03	±0.14
GLU	1.04	2.16	1.22	1.20	2.30	1.84
	±0.67	±3.01	±0.75	±0.69	±2.11	±1.41
GLY	4.08	4.44	5.17	4.31	4.41	6.80
	±2.43	±2.70	±2.29	±1.87	±2.43	±9.24
ALA	0.52	0.55	0.64	0.82	0.58	0.70
	±1.16	±0.27	±0.47	±0.57	±0.37	±0.52
CYS	1.62	1.62	1.27	1.38	0.79	4.55*
	±1.56	±1.56	±1.35	±0.99	±0.35	±4.12
TYR	1.51	1.62	1.44	1.55	1.90	2.20
	±0.94	±0.61	±0.85	±0.79	±0.67	±2.63
HIS	5.46	6.12	5.81	7.24	5.25	5.94
	±2.99	±1.69	±3.15	±4.07	±3.08	±3.26
ARG	0.22	0.34	0.13	0.25	0.26	0.38
	±0.15	±0.54	±0.08	±0.18	±0.29	±0.81
THR	0.93	0.90	0.96	0.91	0.84	2.41*
	±0.42	±0.34	±0.59	±0.44	±0.40	±2.80
VAL	0.17	0.21	0.24	0.26	0.31	0.69**
	±0.10	±0.126	±0.12	±0.17	±0.20	±0.69
MET	0.83	0.71	0.70	0.73	0.69	2.95**
	±0.44	±0.34	±0.51	±0.33	±0.39	±1.62
ILE	0.31	0.33	0.30	0.29	0.22	1.23*
	±0.12	±0.16	±0.20	±0.22	±0.10	±1.36
LEU	0.35	0.33	0.30	0.37	0.38	0.98*
	±0.12	±0.19	±0.13	±0.11	±0.28	±0.77
PHE	0.83	0.95	0.88	0.92	1.39	1.22
	±0.28	±0.38	±0.49	±0.42	±0.87	±1.19
LYS	0.98	0.73	0.57*	0.91	0.92	0.88
	±0.65	±0.39	±0.39	±0.54	±0.83	±0.61
TRP	0.94	1.35	2.00	2.05	1.47	0.52
	±0.67	±0.71	±1.66	±1.62	±1.18	±0.32
TAU	6.49	10.36	8.04	11.40	6.30	10.40
	±3.87	±5.45	±8.01	±11.28	±4.03	±8.79
CIT	0.59	0.32	0.29	0.45	0.50	1.20
	±0.49	±0.28	±0.26	±0.46	±0.40	±0.78
ORN	0.31	0.40	0.29	0.61	0.37	0.53
	±0.23	±0.38	±0.16	±0.39	±0.23	±0.37
ASN+GLN	0.43	0.38	0.46	0.47	0.29	0.52
	±0.28	±0.16	±0.24	±0.37	±0.17	±0.38

*Means ± S.D.; * $p<0.05$, ** $p<0.01$*

The serum concentrations of most amino acids did not show any significant changes during aging except of a slight decrease of SER, PRO, THR and PHE levels (Tab. 4). Renal amino acid excretion was evaluated on the basis of their clearance calculated per 100 ml C_{PFS}. The values of amino acid fractional excretion in the individual age groups are given in Table 5 which shows a significant increase in the fractional excretion of following amino acids: ASP, THR, CYS, VAL, MET, ILE and LEU in old subjects (61–70 years). In last five of these seven amino acids a significant correlation with age was observed (Fig. 1).

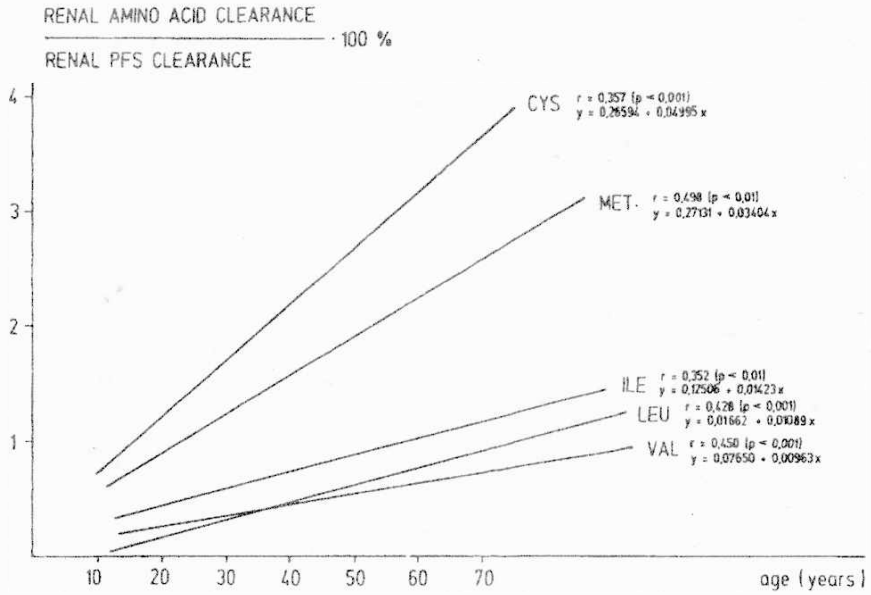

Fig. 1
Relationship between age and renal amino acid clearance per 100 ml polyfructosan S (PFS) clearance.

From the results given in Table 6 it is evident that there was a significant correlation between the FE of the most amino acids and FE_{Na}, except of PRO, ARG, TRP and ASN + GLN.

Table 6
Correlation coefficients of the relationship between fractional amino acid excretion and fractional sodium excretion.

	r		r		r
ASP	0.250*	HIS	0.314*	PHE	0.467***
SER	0.417***	ARG	0.052	LYS	0.343**
PRO	0.021	THR	0.399**	TRP	0.107
GLU	0.462***	VAL	0.385**	TAU	0.303*
GLY	0.397**	MET	0.395**	CIT	0.497***
ALA	0.317*	ILE	0.343**	ORN	0.275*
CYS	0.288*	LEU	0.495***	ASN+	0.197
TYR	0.494***			GLN	

*$p<0.05$, ** $p<0.01$, *** $p<0.001$*

Discussion

The finding of a drop in the GFR during aging is in agreement with earlier observations. Since serum concentration of most amino acids did not fall significantly, it can be concluded that the amount of amino acids which is filtered is decreased in elderly subjects. It is therefore remarkable that, despite the reduced filtered amount of amino acids, the fractional excretion of CYS, VAL, MET, ILE and LEU showed a significant increase. This can be caused by the reduced tubular reabsorption of the amino acids in question. These amino acids are handled by different tubular transport systems (Silbernagl 1985). CYS is known to be reabsorbed both separately and together with dibasic amino acids, while MET, VAL, ILE and LEU belong to a different transport system (Silbernagl 1976).

We investigated whether the changes found in amino acid tubular transport might have been influenced by changes in tubular Na^+ transport. The reason for the analysis of these relationships was the finding of a significant increase in FE_{Na} in elderly subjects (Tab. 3). This increase is probably a manifestation of adaptive changes in functioning nephrons allowing the maintenance of an equilibrated external Na^+ balance in older individuals, even in the presence of a decreased GFR. Similarly, it was demonstrated in patients suffering from various chronic renal diseases.

It is evident from our findings that the increase in FE_{Na} during aging was associated with an increase in the FE of most amino acids. Since the cotransport of a number of amino acids with Na^+ has been demonstrated (Fox *et al.* 1964, Sactor 1980, Silbernagl 1976, Ullrich *et al.* 1974, Ullrich 1979), it could be supposed that the decrease of tubular Na^+ reabsorption in the functioning nephrons is also responsible for the decrease in tubular amino acid reabsorption. Aminoaciduria in the newborn has lately also been attributed to the changes in Na^+ transport (Zelikovic and Chesney 1989). Our findings support the assumption that changes in tubular amino acid transport in elderly individuals are associated with changes in tubular Na^+ transport.

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