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# Plasma amino acids are highly dependent on acid-base balance in uremic rats

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**Summary.** Acidosis is a common finding in uremia. We analysed the effect of changes in acid-base balance in 42 Sprague-Dawley rats having longstanding uremia (>3 mon). The rats were treated with $CaCO_3$ or $CaCl_2$ in a random cross-over trial after being divided into two dietary groups (8% or 18% protein). At the end of each observation period parameters were assessed. The main finding was that plasma amino and keto acid concentrations varied significantly with the acid-base balance and the protein intake. Furthermore a considerable degree of catabolism and anorexia was observed. In addition other confounding variables were observed, e.g. increased corticosterone excretion, electrolyte losses, and proteinuria. Our data underline that plasma amino acid concentrations in uremic rats are highly dependent on acid-base balance and overall protein intake.

**Keywords** Amino acids – Uremia – Acid-base – Plasma amino acids – Anorexia – Glucocorticoids

## Introduction

Chronic renal failure (CRF) results in a number of changes in plasma amino acids (PAA). Flügel-Link et al. (1983), Haines et al. (1989), Kihlberg et al. (1982), Kleinknecht et al. (1980), Mannan et al. (1975), Pennisi et al. (1983), and Wang et al. (1976) described changes in uremic rats similar to those observed in humans with CRF. The most consistent findings are decreased plasma levels of valine, leucine, isoleucine, tryptophan and tyrosine, while increased concentrations of citrulline, glycine, hydroxyproline and 1- and 3-methylhistidine have been described. Currently it is not clear which factor(s) are responsible for these changes. Some of the changes might be explained by protein malnutrition either induced

by uremic anorexia or the institution of a low protein diet, by specific uremic changes in metabolism or hormonal imbalances.

Recently Hara et al. (1987) pointed out that metabolic acidosis, also a common finding in uremia, results in considerable glucocorticoid induced catabolism of branched chain amino acids (BCAA). Beside catabolism, a considerable decrease in the plasma levels of BCAA in uremic rats compared to alkali-treated CRF rats was observed. Data on the concentration of other PAAs or keto acids (KA) in severely acidotic rats, however, are missing. These findings prompted us to analyse the effect of metabolic acidosis in experimental animals with longstanding CRF (Gretz, 1988; 1990).

Thus the aim of this paper was to give an account of the PAA concentrations (PAA-C) in CRF rats with different degrees of metabolic acidosis and different dietary protein intakes.

## Materials and methods

42 male Sprague-Dawley rats of our own stock were used for the experiment. During the experiment the rats were kept in metabolic cages. The light/dark cycle was 12 hours with a constant room temperature of 22°C and a humidity of 65%. All rats were 5/6 nephrectomized as described by Gretz et al. (1988). Thereafter, all rats were kept on a 18% protein diet (C 1000, Altromin, Lage, FRG) for three months. Then, 19 rats were furtheron fed the 18% protein containing diet for another two weeks, while 23 rats were switched to an 8% protein diet (C 1003, Altromin, Lage, FRG). Thereafter, the animals of the two dietary groups were randomized to receive either calciumchloride ($CaCl_2$) or calciumcarbonate ($CaCO_3$) in the drinking water (1% solution). After two weeks, these rats were crossed over to receive the other substance in the drinking water for another fortnight. Blood and urine samples were obtained at the end of each fortnight interval.

The following parameters were determined: blood pH, serum bicarbonate, and standardised base excess (ABL, Kopenhagen); serum creatinine and urea (Reflocheque, Boehringer Mannheim GmbH, FRG); urinary sodium and potassium determined by flame photometry; urinary calcium and phosphate determined by photometry (Boehringer Mannheim GmbH, FRG). Urinary osmolarity was measured by freezing point reduction. In addition, we determined food intake, urinary volume, water intake, and body weight. Urinary urea was measured by using the Reflocheque system (Boehringer Mannheim GmbH, FRG), and urinary protein was determined by the Coomassie-Blue method. In addition, we determined PAAs and plasma KAs at the end of each interval. The method has been described in detail elsewhere by Langer et al. (1988). Urinary corticosterone was evaluated by using an RSL $^{125}$I Corticosterone RIA produced by ICN Biomedicals, Carson, CA, USA.

Normal values of the PAA-C for our stock of Sprague-Dawley rats are given in Table 1. The data were obtained while the rats were fed an 18% protein containing chow. The 8% and 18% chows were made isocaloric by adding maltodextrin and differed only with respect to the amino acid composition.

The data analysis was performed by using the SAS system (1985). The data are expressed as mean $\pm$SD. Differences between the $CaCO_3$ and $CaCl_2$ periods were evaluated by using a paired t-test. A p-value less than 0.05 is referred to as statistically significant.

## Results

In the study a considerable degree of acidosis could be achieved in both dietary groups by giving $CaCl_2$ (blood pH: 18 %: 7.18 in the $CaCO_3$ period, 7.11 in the $CaCl_2$ period, $p = 0.0675$; 8%: 7.26 in the $CaCO_3$ period, 7.09 in the $CaCl_2$

**Table 1.** Normal (mean ± SD) plasma amino and keto acid concentrations (μmol/l) of our Sprague-Dawley rats on an 18% protein containing chow

| | |
|---|---|
| keto-Ile | 8.9 ± 4.7 |
| keto-Leu | 16.4 ± 9.5 |
| keto-Val | 10.2 ± 3.9 |
| Ala | 678.9 ± 142.3 |
| Arg | 172.4 ± 35.2 |
| Asn | 86.9 ± 20.8 |
| Asp | 21.4 ± 8.4 |
| Cys | 6.4 ± 4.9 |
| Glu | 145.5 ± 50.6 |
| Gln | 690.8 ± 118.5 |
| Gly | 286.0 ± 59.8 |
| His | 86.7 ± 12.9 |
| Ile | 95.2 ± 16.7 |
| Leu | 147.1 ± 42.6 |
| Lys | 588.5 ± 113.5 |
| Met | 84.2 ± 19.4 |
| Orn | 56.5 ± 15.6 |
| Phe | 79.0 ± 9.5 |
| Pro | 260.8 ± 90.7 |
| Ser | 329.4 ± 67.0 |
| Tau | 341.1 ± 189.9 |
| Thr | 451.6 ± 105.8 |
| Trp | 95.7 ± 23.5 |
| Tyr | 115.8 ± 32.9 |
| Val | 200.0 ± 37.6 |

*keto-Ile* keto-isoleucine; *keto-Leu* keto-leucine; *keto-Val* keto-valine; *Ala* alanine; *Arg* arginine; *Asn* asparagine; *Asp* aspartic acid; *Cys* cystein; *Glu* glutamic acid; *Gln* glutamine; *Gly* glycine; *His* histidine; *Ile* isoleucine; *Leu* leucine; *Lys* lysine; *Met* methionine; *Orn* ornithine; *Phe* phenyl-alanine; *Pro* proline; *Ser* serine; *Tau* taurine; *Thr* threonine; *Trp* tryptophan; *Tyr* tyrosine; *Val* valine

period, $p = 0{,}001$; standardised base-excess: 18%: −5.9 in the $CaCO_3$ period, −9.7 in the $CaCl_2$ period, $p = 0.0482$; 8%: −3.6 in the $CaCO_3$ period, −12.6 in the $CaCl_2$ period, $p = 0.0001$). The difference between the $CaCl_2$ and $CaCO_3$ periods was significant in each dietary group with respect to serum bicarbonate. No neutral acid-base balance, however, occurred by applying $CaCO_3$. Only a less acidotic state could be induced. During the two periods, food intake was not different in the group with an 8% protein containing chow ($CaCO_3$: 16.9 g/24 h; $CaCl_2$: 14.0 g/24 h; $p = 0.1372$), while a lower one was observed in the $CaCl_2$ period with the 18% protein containing chow ($CaCO_3$: 15.3 g/24 h; $CaCl_2$: 10.6g/24h; $p = 0.0016$).The same was true for body weight and urinary urea

excretion corrected for food intake (Gretz, 1990). Further laboratory data have been reported elsewhere in detail (Gretz, 1990; Lasserre, 1990).

The results of the PAA determinations are presented according to dietary protein intake (18% protein: Table 2; 8% protein: Table 3). In comparison to the 'normal' values for rats (Table 1) considerable changes were observed within each study period. Total PAA-C were highest with the 8% protein containing chow during the $CaCl_2$ period (18%: 4683 mmol/l in the $CaCO_3$ period, 4721 mmol/l in the $CaCl_2$ period; 8%: 4620 mmol/l in the $CaCO_3$ period, 5135 mmol/l in the $CaCl_2$ period). During all other periods, the total PAA-C was roughly the same. A common finding for both dietary groups is that histidine increases significantly during the $CaCl_2$ period. All other statistically significant changes in PAA-C occurred into different directions. This phenomenon becomes even more obvious when expressing the changes as percentage changes when the animals were switched from $CaCO_3$ to $CaCl_2$ (Fig. 1). This figure underlines that the PAA-C are highly dependent on acid-base balance and the protein content of the diet. The same tendency, though not statistically significant, can be detected in the respective KA concentrations.

**Table 2.** Amino/keto acid concentrations ($\mu$mol/l) obtained with the 18% protein containing diet and the use of $CaCO_3$ and $CaCl_2$ (for legends see Table 1)

| | $CaCO_3$ MEAN ± SD | $CaCl_2$ MEAN ± SD | p-values |
|---|---|---|---|
| keto-Ile | 4.2 ± 2.0 | 3.3 ± 1.6 | 0.1578 |
| keto-Leu | 6.8 ± 3.0 | 5.9 ± 3.0 | 0.2675 |
| keto-Val | 6.2 ± 2.6 | 5.1 ± 2.3 | 0.1640 |
| Ala | 687 ± 115 | 575 ± 181 | 0.7050 |
| Arg | 139 ± 24 | 122 ± 19 | 0.0283 |
| Asn | 77 ± 15 | 75 ± 27 | 0.8173 |
| Asp | 19 ± 3 | 18 ± 7 | 0.5671 |
| Cys | 6 ± 4 | 2 ± 3 | 0.1778 |
| Glu | 116 ± 22 | 106 ± 29 | 0.5359 |
| Gln | 662 ± 67 | 671 ± 167 | 0.8806 |
| Gly | 378 ± 97 | 419 ± 139 | 0.3613 |
| His | 91 ± 6 | 115 ± 28 | 0.0107 |
| Ile | 95 ± 14 | 80 ± 9 | 0.0003 |
| Leu | 129 ± 50 | 140 ± 11 | 0.2213 |
| Lys | 559 ± 79 | 512 ± 146 | 0.2470 |
| Met | 107 ± 26 | 90 ± 26 | 0.1747 |
| Orn | 50 ± 10 | 45 ± 12 | 0.3141 |
| Phe | 78 ± 8 | 76 ± 7 | 0.5418 |
| Pro | 289 ± 77 | 191 ± 74 | 0.0229 |
| Ser | 289 ± 50 | 289 ± 98 | 0.7751 |
| Tau | 320 ± 87 | 339 ± 59 | 0.1079 |
| Thr | 491 ± 99 | 513 ± 175 | 0.7667 |
| Trp | 86 ± 19 | 80 ± 21 | 0.3237 |
| Tyr | 108 ± 28 | 95 ± 32 | 0.5033 |
| Val | 196 ± 36 | 168 ± 21 | 0.0039 |

**Table 3.** Amino/keto acid concentrations ($\mu$mol/l) obtained with the 8% protein containing diet and the use of $CaCO_3$ and $CaCl_2$ (for legends see Table 1)

| | $CaCO_3$ MEAN ± SD | $CaCl_2$ MEAN ± SD | p-values |
|---|---|---|---|
| keto-Ile | 4.1 ± 2.0 | 4.3 ± 2.2 | 0.8646 |
| keto-Leu | 7.2 ± 2.3 | 8.7 ± 3.7 | 0.1511 |
| keto-Val | 6.0 ± 1.9 | 6.4 ± 2.4 | 0.5185 |
| Ala | 780 ± 150 | 748 ± 229 | 0.5194 |
| Arg | 133 ± 17 | 145 ± 61 | 0.3459 |
| Asn | 71 ± 11 | 99 ± 26 | 0.0001 |
| Asp | 23 ± 5 | 26 ± 6 | 0.3534 |
| Cys | 5 ± 4 | 7 ± 4 | 0.0076 |
| Glu | 90 ± 19 | 94 ± 27 | 0.2655 |
| Gln | 680 ± 118 | 702 ± 129 | 0.5408 |
| Gly | 481 ± 153 | 453 ± 151 | 0.3873 |
| His | 74 ± 8 | 97 ± 24 | 0.0003 |
| Ile | 68 ± 6 | 93 ± 20 | 0.0001 |
| Leu | 117 ± 9 | 158 ± 34 | 0.0001 |
| Lys | 487 ± 48 | 557 ± 139 | 0.0306 |
| Met | 100 ± 46 | 104 ± 41 | 0.5861 |
| Orn | 46 ± 9 | 53 ± 29 | 0.2371 |
| Phe | 64 ± 7 | 78 ± 15 | 0.0004 |
| Pro | 304 ± 96 | 336 ± 154 | 0.4133 |
| Ser | 330 ± 41 | 342 ± 140 | 0.6212 |
| Tau | 210 ± 52 | 183 ± 64 | 0.1379 |
| Thr | 278 ± 55 | 480 ± 127 | 0.0001 |
| Trp | 58 ± 14 | 86 ± 29 | 0.0005 |
| Tyr | 88 ± 20 | 109 ± 36 | 0.0178 |
| Val | 133 ± 14 | 185 ± 43 | 0.0001 |

## Discussion

Our findings demonstrate that PAA-C are highly dependent on acid base balance (Fig. 1) and the overall protein intake of longterm uremic animals. Therefore it seems to be difficult to assume that there is a uremia specific pattern of PAA-C. With respect to humans the same might be true, as uremic patients are often quite acidotic and suffer from anorexia, which in turn might influence the protein intake. Thus it may also be concluded that PAA-C are not helpful in assessing nutritional adequacy of dietary measures in uremia, as long as acid-base balance and food intake are not taken into account. The same seems to be true for the plasma KA of valine, leucine, and isoleucine.

The overall protein intake in our animals was not only determined by the two levels of protein content in the rat chow, but also by the overall food intake. In the rats on the 8% containing diet this intake was not significantly different during the two experimental periods, while on the 18% protein containing diet a significant decrease in intake was induced (Gretz, 1990). Thus in this group a significant degree of anorexia occurred. As we wanted, however, to

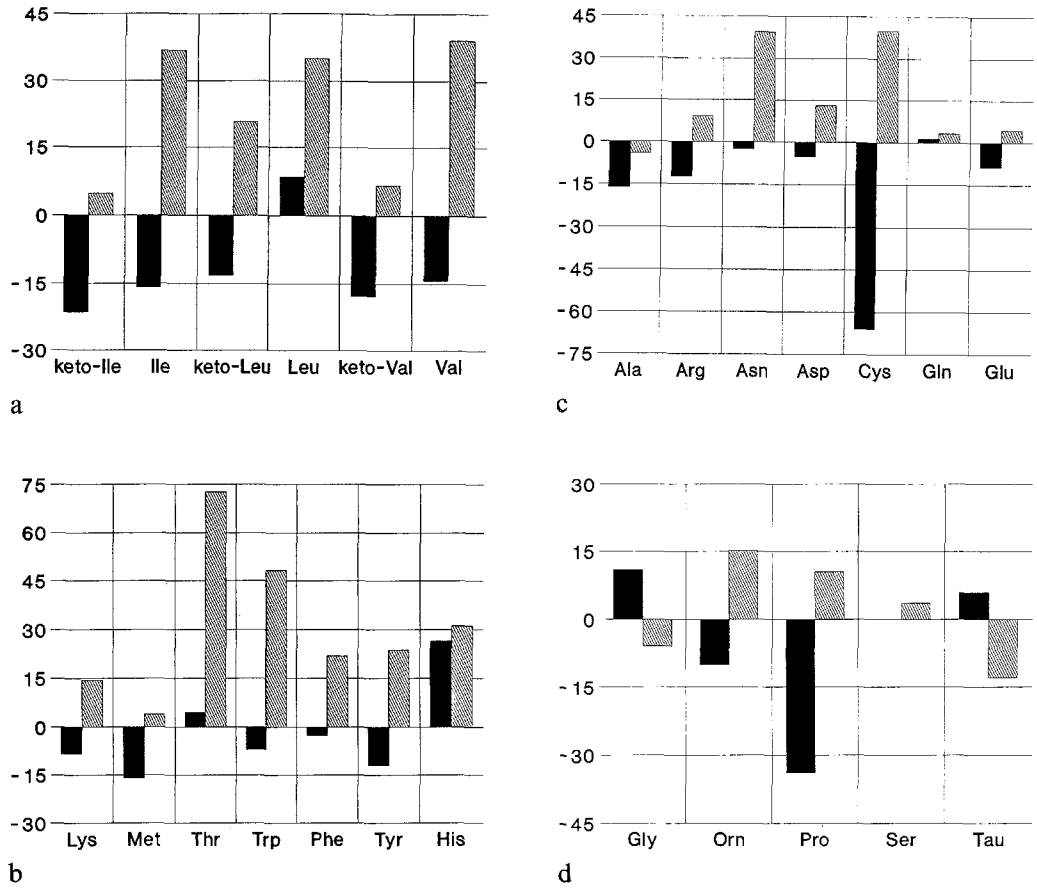


**Fig. 1.** Percentage changes in PAA and KA concentrations according to dietary protein when the animals were changed from $CaCO_3$ to $CaCl_2$: **a** changes in BCAA and KA, **b** changes in other 'essential' amino acids including Tyr and His, which can be regarded as essential in uremia, **c** and **d** changes in non-essential amino acids (for abbreviations see table 1, solid bars: 18% protein, hatched bars: 8% protein)

analyse the overall impact of acidosis in uremic rats, pair feeding was not performed deliberately.

Acidosis induced anorexia is a well known phenomenon (Brodsky, 1952; Kaye, 1974; Oster, 1975). There are several factors, which might contribute to this anorexia. One is that due to changes in the amino acid metabolism and a competitive amino acid transport across the blood-brain barrier false neurotransmitters occur in the brain resulting in a reduced food intake (Tackman, 1990). Other causes might be changes in the electrolyte balance in the brain leading to anorexia (Badgaiyan, 1990). Furthermore the membrane potential of hepatocytes changes with alterations in the acid-base balance which results in changes of the vagal activity (Sawchenko, 1979). This in turn could reduce food intake.

Thus, our data are in good agreement with the literature and support the notion that acidosis induced anorexia occurs independently of uremia. It is, however, difficult to explain why the rats on the 8% protein containing chow

suffered less from anorexia. One might speculate that rats on the 18% diet experienced anorexia due to a suddenly more pronounced pH difference when digesting the chow compared to the rats on the 8% diet. This difference might be due to the higher protein content per gram food of the former chow resulting in the production of more $H^+$-ions. Thus also this finding might be explained by the above mechanisms.

In addition, acidosis induced anorexia could have precipitated a nutritional state in these animals comparable to starvation. This might, in part, explain why body weight dropped and urinary urea excretion (Table 4) rose sharply. Furthermore this notion would be compatible with the decrease in BCAA and KA in the 18% group as starvation is known to decrease protein synthesis and increase protein degradation (Mitch, 1984). A further protein degradation has been induced by acidosis in stimulating branched chain KA dehydrogenase resulting in a more pronounced catabolism of BCAAs as pointed out by Mitch (1988).

An additional catabolic stimulus might have been added by an increased corticosterone production. This is reflected by the rise in daily urinary corticosterone excretion during $CaCl_2$ periods especially in the 18% group. Thus, this observation is in agreement with the findings of Hara et al. (1987). The mechanism by which acidosis stimulates glucocorticoid production, however, is still unclear.

Concerning the overall importance of the glucocorticoid mechanism our data provide little explanatory help, as the daily urinary corticosterone excretion during $CaCl_2$ periods factored for the food intake is increased by a factor of 3

**Table 4.** Changes in serum creatinine, food and water intake, body weight and daily urinary excretion of urea, corticosterone, protein and electrolytes expressed as ratio: $CaCl_2/CaCO_3$ (/f = per gram food intake). These data are summarised from previous publications (Gretz, 1990; Lasserre, 1990).

| protein content | 18% | 8% |
|---|---|---|
| creatinine | 1.2 | 1.3 |
| food intake | 0.7 | 0.8 |
| water intake | 0.8 | 1.0 |
| body weight | 0.8 | 1.0 |
| urea | 9.7 | 1.1 |
| urea/f | 14.0 | 1.1 |
| corticosterone | 2.7 | 1.1 |
| corticosterone/f | 3.0 | 1.5 |
| protein | 0.8 | 1.5 |
| protein/f | 1.4 | 3.2 |
| calcium | 4.5 | 4.5 |
| phosphate | 2.2 | 0.8 |
| sodium | 2.0 | 3.0 |
| potassium | 2.2 | 2.6 |
| osmolarity | 2.5 | 2.6 |

(18% group), while the respective urinary urea excretion is raised by 14. The glucocorticoid effect, however, might be non-linear with respect to catabolism. Then this effect might explain this increased catabolism. Furthermore it is of note that a 'high' protein intake increases the size of the adrenal gland (Tepperman, 1943) and thus probably the glucocorticoid production.

Another factor possibly influencing PAA-C is the change in electrolyte excretion (Table 4), as this affects the $Na^+/K^+$, $Na^+/H^+$ antiporter system. In turn protease activity is increased by ion/electrolyte changes in the cell. These changes in activity could subsequently affect PAA-C. In addition amino acid transport seems to depend on electrolyte dependent carriers. Thus any substantial change in intra- and extracellular electrolyte concentrations would affect amino acid transport and thus PAA-C. Any of these factors could also compromise intracellular amino acid concentrations. Thus intracellular amino acid measurements are probably not more 'reliable' than PAA-C.

In our animals, a further loss of amino acids/protein occurred during the $CaCl_2$ periods as proteinuria corrected per gram of food intake was always higher during this period than during the $CaCO_3$ period (Table 4). Proteinuria was lower in the 8% group than in the 18% group. This is probably due to hyperfiltration (Brenner, 1982) in the 18% group. As in the 8% group no such stimulus occurs, the percentage increase in proteinuria was more pronounced during the $CaCl_2$ period. In the 18% group the animals had a higher protein excretion already during the $CaCO_3$ period, and the percentage increase during the $CaCl_2$ period was not that pronounced as in the 8% group. Thus our data provide evidence that acidosis per se increases proteinuria. The increase in proteinuria during the $CaCl_2$ period can easily be explained by changes in permselectivity of the basal membrane of the glomerulus (Brenner, 1977). Anyway proteinuria results in a protein/amino acid depletion and thus adds another catabolic stimulus.

Insulin causes protein synthesis. During acidosis as well as during severe uremic intoxication insulin resistance occurs. At the same time, uremic intoxication increases, as demonstrated in the rise of serum urea in our animals (18%: 58 mg/dl in the $CaCO_3$ period, 82 mg/dl in the $CaCl_2$ period, $p = 0.1285$; 8%: 40 mg/dl in the $CaCO_3$ period, 52 mg/dl in the $CaCl_2$ period, $p = 0.0608$). As urea rises, the animals become more acidotic. Thus, a vicious cycle starts. When reducing or abolishing acidosis, uremic intoxication improves, as do insulin resistance and protein synthesis.

The BCAA concentrations reported by us differ from what has been found by Hara et al. (1987). In their study the plasma concentrations of BCAAs are roughly three times higher during the bicarbonate supplemented period in the CRF rats than in our study. This might be explained by the animal model used, as their rats exhibited a less longstanding CRF in comparison to ours. Furthermore, the amino acid composition of the chow was quite different as was the degree of acidosis/alkalosis. It should be stressed, however, that the sham operated and the CRF animals exhibited a contrasting BCAA concentration when given bicarbonate. The former group showed a decrease, while in the latter an increase occurred. This increase, however, is quite different from what we found in the 8% group.

The overall PAA-C found in our study are only partly comparable to previous studies performed by Wang et al. (1976), Kihlberg et al. (1982) and Haines et al. (1989), using about the same animal model. As neither of the studies reported on the degree of acidosis a comparison might be misleading. Furthermore, in these studies the amino acid composition of the diets was quite variable. Additionally, PAA-C are influenced by food restriction prior to blood sampling and the duration of the fasting state. In severely uremic animals, food restriction is another catabolic stress factor for the animals. Thus, we performed blood sampling between 10 and 11 o'clock in the postabsorptive state.

In summary: Our PAA data demonstrate that PAA-C in uremic rats are highly dependent on the acid-base balance, the overall protein intake, the total energy intake, and indirectly on glucocorticoid production. Due to the high degree of dependency on all these variables no really uremia specific PAA pattern can be determined. In the future standardised conditions in this model have to be used, e.g. 3 mon duration, akali treatment, minimum pH of 7.32 and defined food intake (defined with respect to total protein and energy intake).

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