Effects of chronic renal insufficiency and metabolic acidosis on glutamine metabolism in man

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Summary

1. Arterial concentration and arterial–venous differences of glutamine across the kidney, forearm, hepato–splanchnic bed and brain were measured in patients with chronic renal insufficiency and in patients with normally functioning kidneys before and during chronic ammonium chloride acidosis.

2. In chronic renal insufficiency and in chronic metabolic acidosis there is a rise in glutamine release from the muscle and a suppression of glutamine uptake by the hepato–splanchnic bed and the brain.

3. In chronic renal insufficiency arterial glutamine concentration is significantly increased in comparison with subjects with normal renal function and either normal acid–base balance or chronic metabolic acidosis.

4. In patients with chronic renal insufficiency the kidney extracts negligible amounts of glutamine, which cannot account for the renal ammonia production measured in the same patients.

Key words: ammoniagenesis, chronic renal insufficiency, glutamine metabolism, metabolic acidosis.

Abbreviation: GFR, glomerular filtration rate.

Introduction

Glutamine plays a central role in nitrogen metabolism as it provides N atoms for the synthesis of other amino acids, urea, purine and pyrimidine nucleotides, some complex polysaccharides and nicotinamide–adenine dinucleotide (Meister, 1967–1968). Glutamine is also important for the storage and transport of the toxic base ammonia, which combines with glutamate to form glutamine (Meister, 1967–1968). Finally, glutamine is the major substrate utilized by the kidney for the production of ammonia, the most important buffer for fixed acid excretion (Pitts, 1973). Chronic renal insufficiency causes many alterations in nitrogen metabolism (Feldman & Singer, 1975), but glutamine metabolism in this state has not been examined. We have compared glutamine metabolism in patients with chronic renal insufficiency and in patients with normal renal function. Chronic metabolic acidosis was induced in some control subjects by ammonium chloride in order to evaluate the effect of metabolic acidosis on glutamine metabolism and to obtain a control group with an acid–base condition similar to that of patients with chronic renal insufficiency. Glutamine metabolism has been studied as arterial concentration, uptake and production in kidney, muscle, hepato–splanchnic bed and brain.

Methods

The patients were selected from the wards of the Department of Internal Medicine of the University of Genoa, during the period between 1973 and 1977. They were fully informed of the purpose, nature and procedure involved in this study, before their voluntary consent was obtained.
Patients with chronic renal insufficiency

Twenty patients between the ages of 28 and 55 years, with chronic glomerulonephritis and glomerular filtration rate (GFR) from 10 to 30 ml/min, were studied. Diagnosis was based on accepted criteria. Eight patients were on a Giovannetti diet with a daily intake of 15–25 g of protein. The other patients were on a normal diet, which provided 50–60 g of protein daily. The two diets did not give statistically significant effects on glutamine arterial–venous differences across the organs considered, and the patients were considered as a single group. The patients were actively employed up to their admission, and had no history or evidence of congestive heart failure, pulmonary or hepatic diseases or diabetes. A mild or moderate anaemia was present (haemoglobin 8.5–12.0 g/dl). Blood urea was between 10.6 and 31.6 mmol/l and serum creatinine was between 0.150 and 0.662 mmol/l. Serum sodium and potassium concentrations were normal and urine cultures were repeatedly negative. Seven patients had suspected hyperparathyroidism, and 13 were moderately or severely hypertensive, so that either an internal jugular vein catheterization for parathormone assay, or a renal vein catheterization for plasma renin activity determination was necessary as part of their diagnostic evaluation. Six patients studied in 1973–1975 received 0.6–1 mmol of NH₄Cl day⁻¹ kg⁻¹ body wt. (depending on glomerular filtration rate) administered orally during the 3 days preceding the study.

Arterial–venous differences of glutamine across the kidney were measured in six patients (three of them after NH₄Cl), across the forearm muscles in 13 patients (five of them after NH₄Cl), across the hepato–splanchnic bed in nine (four after NH₄Cl) and across the brain in seven (three after NH₄Cl). Since glutamine arterial–venous differences across the organs did not show statistically significant variations between NH₄Cl-treated and non-treated subjects, the results of both groups are considered together.

Patients with normal renal function

Thirty-six patients between the ages of 22 and 54 years were studied. Thirty patients had arterial hypertension and six had cardiac valvular diseases. Routine haematological tests, serum and urine electrolyte concentrations, acid–base measurements, urinanalysis and renal function tests were normal ($C_{\text{creatinine}} = 97–134$ ml min⁻¹ 1.73 m⁻²).

All patients were on a normal diet. In the hypertensive patients a renal vein catheterization was considered necessary in order to determine plasma renin activity. In the other patients a right-sided cardiac catheterization was considered necessary for diagnostic haemodynamic evaluation. Before this study 16 patients received NH₄Cl orally, 3.5 mmol day⁻¹ kg⁻¹ body wt. for 3 days (eight patients) and 6 days (eight patients). Arterial–venous differences of glutamine across the kidney were measured in 12 subjects, across the forearm muscles in 25, across the hepato–splanchnic bed in 23 and across the brain in 15.

Measurement of arterial–venous differences of glutamine across the kidney, the forearm, the hepato–splanchnic bed and the brain

All patients were studied after a 12–14 h overnight fast. A Teflon catheter was percutaneously placed into a peripheral artery in order to measure acid–base variables and arterial glutamine concentration. A Cournand no. 6 or 7 F or Cobra no. 6 or 7 S catheter was then guided under fluoroscopic control through either an antecubital or femoral vein to a renal or hepatic vein, or to the superior bulb of an internal jugular vein. For measurements of arterial–venous differences across the forearm, blood was obtained from a peripheral artery and from a deep vein of the forearm. From each subject at least two sets of simultaneous arterial and venous samples were obtained for the measurement of arterial–venous differences of glutamine concentration across the organs. Arterial blood pressure and electrocardiogram were continuously monitored during the study.

When arterial–venous differences of glutamine across the kidney had to be determined, an intravenous infusion of sodium thiosulphate and p-aminohippuric acid was started, after the administration of a priming dose of p-aminohippurate (2.5–3 mmol). The infusion was kept at a constant flow rate (thiosulphate 0.8 mmol/min and p-aminohippuric acid 0.09 mmol/min) and two or three sequential clearance periods, of 20 min each, were obtained. The correct position of the catheter in the renal vein was verified by calculating the renal extraction of p-aminohippurate and oxygen. Oxygen extraction, calculated as oxygen$\lambda$ – oxygen$\nu$/oxygen$\lambda$ × 100, was used during catheterization to verify the correct position of the catheter. Renal p-aminohippurate and oxygen extractions were particularly useful in patients with renal insufficiency, where low values of p-amino-
hippurate extraction could depend either on renal alterations or on an incorrect positioning of the catheter, but a low oxygen extraction definitely identified renal blood. At the midpoint of each clearance period blood samples were obtained simultaneously from the peripheral artery and a renal vein. During clearance periods urine was identified renal blood. At the midpoint of each renal alterations or on an incorrect positioning of measurements. An aliquot of the same sample was simultaneously from the peripheral artery and a clearance period blood samples were obtained in ice, was used for pH, $P_a$co$_2$ and ammonia concentrations. When necessary, for sodium thiosulphate and $p$-aminohippurate concentrations.

**Analysis**

Arterial and venous plasma was stored at $-25^\circ$C and the concentration of glutamine was determined within 3 days. The assay is based on hydrolysis of glutamine by glutaminase (Addae & Lotspeich, 1968). The amide N released in this reaction is then measured as ammonia. Plasma proteins were precipitated with perchloric acid (0.75 mol/l) and the supernatant was adjusted to pH 4.9 with a buffered solution. An aliquot of the supernatant was incubated at $37^\circ$C in acetate buffer (0.1 mol/l), pH 4.9, containing 0.06 unit of glutaminase (EC 3.5.1.2) (grade V, Sigma Chemical Corp., St Louis, MO, U.S.A.). After incubation for 1 h the ammonia released was measured by the method of Chaney & Marbach (1962). Each sample containing the enzyme was compared with a sample without the enzyme. Furthermore, an acetate blank and an enzyme blank were used. Blanks, samples and standards were all in triplicate. Recovery of glutamine added to plasma was determined for each assay, recovery ranging from 94 to 103%.

For blood ammonia determination, blood was deproteinized at $+4^\circ$C with sodium tungstate and sulphuric acid immediately after the withdrawal. The protein-free supernatant was stored at $-25^\circ$C and the assay was carried out according to Chaney & Marbach (1962) within 12 h. An eightfold concentration of phenol and hypochlorite reagents was used. The same method was followed for the measurement of ammonia in urine.

Sodium thiosulphate concentration in plasma and urine was determined according to Brun (1950). The concentration of $p$-aminohippurate in plasma and urine was measured as suggested by Smith, Goldring & Chasis (1938). Renal arterial plasma flow was calculated from clearance and extraction of $p$-aminohippurate acid from the equation of Wolf (1941). Renal blood flow was calculated from renal plasma flow and packed cell volume.

Creatinine in plasma and urine was determined after absorption with Lloyd’s reagent (Hare, 1950). Blood urea was measured enzymatically with the method of Chaney & Marbach (1962).

Blood and urine pH and $P_a$co$_2$ were estimated at $37^\circ$C with a PHM 72/BMS 3 apparatus (Radiometer, Copenhagen). Blood [HCO$_3^-$] was calculated by using the Henderson–Hasselbalch equation. $S_a$O$_2$ was measured with an Hellige Oximeter (American Optical Corp., Buffalo, NY, U.S.A.).

Statistical significance was examined by analysis of variance by using a completely randomized design or a randomized block design (Dixon & Massey, 1957). Values are given as mean ± 1 SEM.

**Results**

In 20 patients with chronic renal insufficiency (pH 7.333 ± 0.0180; $P_a$co$_2$ 3.99 ± 0.185 kPa; [HCO$_3^-$]$_a$ 15.7 ± 0.95 mmol/l), glutamine arterial concentration was 627 ± 23.9 μmol/l. This concentration is significantly higher ($P < 0.01$) than that measured in 20 patients with normally functioning kidneys under normal acid–base balance (pH 7.402 ± 0.0066; $P_a$co$_2$ 4.96 ± 0.086 kPa; [HCO$_3^-$]$_a$ 22.8 ± 0.44 mmol/l; [Gln]$_a$ 534 ± 26.2 μmol/l) or that observed in 16 patients with NH$_4$Cl acidosis (pH 7.291 ± 0.0165; $P_a$co$_2$ 3.94 ± 0.192 kPa; [HCO$_3^-$]$_a$ 14.2 ± 1.10 mmol/l; [Gln]$_a$ 473 ± 18.2 μmol/l).

In subjects with normal renal function, renal glutamine extraction was 34.8 ± 2.23 μmol/min (Table 1). After a 6 days NH$_4$Cl acidosis, renal glutamine extraction increased markedly (109.6 ± 16.47 μmol/min). On the contrary, in six patients with chronic renal insufficiency and GFR between 10 and 30 ml/min, the kidney extracted only negligible amounts of glutamine (2.7 ± 1.30 μmol/min). In these patients total renal ammonia production (i.e. ammonia excreted with urine plus ammonia added to the renal veins) was 22.4 ± 3.91 μmol/min.

In patients with chronic renal insufficiency arterial–venous difference across the forearm was $-66 ± 9.5$ μmol/l, indicating a net glutamine release into the circulation (Table 2). This difference is the same as that detected in subjects with
TABLE 1. Renal metabolism of glutamine (Gln) and NH\textsuperscript{+} production in patients with chronic renal insufficiency and in subjects with normal renal function with or without metabolic acidosis

\[ [\text{HCO}_3^-] = \text{arterial bicarbonate concentration; [Gln]} = \text{arterial glutamine concentration; [Gln]}_v = \text{venous glutamine concentration; glutamine extracted} = (\text{renal plasma flow} \times [\text{Gln]}_v) - ([\text{Gln}] \times (\text{renal plasma flow} - \text{urine flow})); \]
\[ \text{NH}_\text{\textsuperscript{+}} \text{produced} = \text{NH}_\text{\textsuperscript{+}} \text{excreted with urine} + \text{NH}_\text{\textsuperscript{+}} \text{added to the renal veins. Values are given as mean \pm SEM.} \]
\*P < 0.001 compared with normal subjects and with NH\textsubscript{4}Cl acidosis.

<table>
<thead>
<tr>
<th></th>
<th>No. of subjects</th>
<th>[\text{HCO}_3^-] (mmol/l)</th>
<th>[Gln] (\mu mol/l)</th>
<th>[Gln]v (\mu mol/l)</th>
<th>Glutamine extracted (\mu mol/min)</th>
<th>NH\textsubscript{+} produced (\mu mol/min)</th>
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<tr>
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<td>23.1 ± 0.83</td>
<td>510 ± 37.2</td>
<td>451 ± 27.1</td>
<td>34.8 ± 2.23</td>
<td>50.3 ± 1.83</td>
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<tr>
<td>6 days NH\textsubscript{4}Cl acidosis</td>
<td>6</td>
<td>12.3 ± 1.96</td>
<td>453 ± 22.4</td>
<td>279 ± 11.2</td>
<td>109.6 ± 16.4</td>
<td>149.0 ± 21.77</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>6</td>
<td>14.6* ± 1.13</td>
<td>615* ± 38.4</td>
<td>598* ± 29.9</td>
<td>2.7* ± 1.30</td>
<td>22.4* ± 3.91</td>
</tr>
</tbody>
</table>

TABLE 2. Forearm muscle, hepato–splanchnic and cerebral metabolism of glutamine (Gln) in patients with chronic renal insufficiency and in subjects with normal renal function with or without metabolic acidosis

For abbreviations, see Table 1. Values are given as mean ± SEM. *P < 0.05 compared with normal subjects. †P < 0.01 compared with normal subjects. ‡P < 0.01 compared with NH\textsubscript{4}Cl acidosis. §P < 0.005 compared with 3 days NH\textsubscript{4}Cl acidosis. ||P < 0.001 compared with 6 days NH\textsubscript{4}Cl acidosis.

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<th></th>
<th>No. of subjects</th>
<th>[\text{HCO}_3^-] (mmol/l)</th>
<th>[Gln] (\mu mol/l)</th>
<th>[Gln]v (\mu mol/l)</th>
<th>[Gln]v - [Gln] (\mu mol/l)</th>
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<td>22.4 ± 0.58</td>
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<td>601 ± 40.6</td>
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<td>491 ± 33.5</td>
<td>555 ± 29.3</td>
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<tr>
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<td>16.0* ± 1.11</td>
<td>658* ± 29.5</td>
<td>724* ± 32.8</td>
<td>-66 ± 9.5</td>
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<tr>
<td>Hepato–splanchnic metabolism</td>
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<td>Normal subjects</td>
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<td>511 ± 25.8</td>
<td>447 ± 27.8</td>
<td>+64 ± 7.1</td>
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<td>3 days NH\textsubscript{4}Cl acidosis</td>
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<td>430 ± 42.1</td>
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<td>430 ± 23.9</td>
<td>+11 ± 12.1</td>
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<tr>
<td>Chronic renal insufficiency</td>
<td>9</td>
<td>15.2†± 0.95</td>
<td>608‡± 19.1</td>
<td>623‡± 25.4</td>
<td>-15‡± 5.4</td>
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<td>Cerebral metabolism</td>
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<tr>
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<td>23.6 ± 0.56</td>
<td>533 ± 26.0</td>
<td>486 ± 28.8</td>
<td>+47 ± 8.8</td>
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<tr>
<td>3-6 days NH\textsubscript{4}Cl acidosis</td>
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<td>12.9 ± 1.97</td>
<td>430 ± 16.2</td>
<td>434 ± 18.4</td>
<td>-4 ± 3.2</td>
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<tr>
<td>Chronic renal insufficiency</td>
<td>7</td>
<td>13.1†± 1.50</td>
<td>546‡± 11.2</td>
<td>571‡± 26.0</td>
<td>-25†± 6.3</td>
</tr>
</tbody>
</table>

normally functioning kidneys and NH\textsubscript{4}Cl acidosis (−64 ± 7.9 \mu mol/l). Both these values are higher than arterial–venous difference found in control subjects in normal acid–base balance (−46 ± 5.5 \mu mol/l), but only at the borderline of significance (P < 0.1). Since the patients with 3 and 6 days NH\textsubscript{4}Cl acidosis did not show significant differences in glutamine release they are reported as a single group.

In subjects with normal renal function a large glutamine uptake by the hepato–splanchnic bed was observed (+64 ± 7.1 \mu mol/l) (Table 2). The uptake was not changed by a 3 days NH\textsubscript{4}Cl load, whereas it was suppressed by a 6 days NH\textsubscript{4}Cl load (+11 ± 12.1 \mu mol/l). In patients with chronic renal insufficiency glutamine arterial–venous difference became negative (−15 ± 5.4 \mu mol/l). This value is statistically different (P < 0.005) from that found in subjects in normal acid–base balance and in 3 days NH\textsubscript{4}Cl acidosis, but not from that observed in acidosis lasting for 6 days.

In subjects with normally functioning kidneys a significant cerebral uptake of glutamine was observed (+47 ± 8.8 \mu mol/l) (Table 2). In patients with chronic renal insufficiency the arterial–venous difference of glutamine became negative (−25 ± 6.3 \mu mol/l). This value is different from that obtained in normal control subjects (P < 0.01), but not from that found in chronic acidosis (−4 ± 3.2 \mu mol/l). Since no significant difference in cerebral glutamine metabolism was detected between patients with 3 and 6 days NH\textsubscript{4}Cl acidosis, they are reported as a single group. Arterial glutamine concentration in patients with chronic renal insufficiency and in acidotic control subjects studied for cerebral arterial–venous differences are lower,
but not significantly different (0.05 > P < 0.1) from the respective values in all other cases. This may depend on a casual presence of subjects within this group with unusual low glutamine concentrations.

Discussion

This study demonstrates that chronic renal insufficiency is associated with significant alterations in glutamine metabolism. Such alterations are observed even in patients with a relatively high GFR, in good general health, eating a normal protein diet. In this study blood flow was measured only in the kidney. Consequently, the absolute rates of glutamine release or uptake by muscle, hepato-splanchic bed and brain could not be calculated. Nevertheless, the reversal of arterial-venous differences across the hepato-splanchic bed and brain, observed in chronic renal insufficiency, cannot be due to changes in blood flow.

The normally functioning kidney is an important site for glutamine utilization in subjects in normal acid-base balance and even more important in chronic metabolic acidosis, where renal ammonia production is markedly enhanced (Owen & Robinson, 1963; Shalhoub, Webber, Glabman, Canessa-Fisher, Klein, De Haas & Pitts, 1963; Tizianello, De Ferrari, Gurreri & Acquarone, 1975). In chronic renal insufficiency renal ammonia excretion decreases in relation to the reduction of GFR (Wrong & Davies, 1959); renal ammonia production also decreases (Tizianello et al., 1975). The patients with chronic renal insufficiency in this study had relatively high GFR and ammonia production, and a significant extraction of glutamine by the kidney would have been expected. However, the results showed that only a negligible extraction of glutamine occurs in this clinical state. These findings confirm a preliminary report (Tizianello et al., 1975) and indicate a derangement of glutamine metabolism in the kidney in chronic renal insufficiency so that glutamine is not the major substrate utilized by the kidney for ammonia production. One can speculate that an 'Uraemic toxin' inhibits glutaminases or the transport of glutamine into the mitochondria, where phosphate-dependent glutaminase (EC 3.5.1.2) is located. It has been recently shown that methylguanidine significantly depresses ammonia production from glutamine by rat renal cortical slices and inhibits renal phosphate-independent glutaminase activity in the same animal (Acquarone, Tizianello, De Ferrari, Bruzzone, Papio & Garibotto, 1977).

In normal man the muscle is the major site for glutamine synthesis (Marliss, Aoki, Pozefsky. Most & Cahill, 1971; Tizianello, De Ferrari, Gurreri, Bertocchi & Acquarone, 1973). Although glutamine synthetase (EC 6.3.1.2) content and glutamine production per tissue weight unit in muscle are low (Lund, 1970), the total amount of glutamine produced by this tissue is considerable, as the whole mass must be taken into account. The findings reported here suggest that glutamine release from muscle is increased both in patients with chronic renal insufficiency and in chronic metabolic acidosis. A possible role of metabolic acidosis in increasing glutamine production by the muscle is supported by the enhanced muscular release of glutamine recently shown in acidotic rats (Oliver, Koelz, Costello & Bourke, 1977). However, other possibilities must be considered since rats with experimental chronic renal insufficiency exhibit an increased muscular glutamine production consequent to an enhanced muscle proteolysis (Garber, 1977).

The results in the patients with normal renal function confirm the glutamine hepato-splanchic uptake previously reported by Marliss et al. (1971) and Tizianello et al. (1973). The intestines utilize glutamine in mammals (Addae & Lotspeich, 1968; Felig, Wahren, Karl, Cerasi, Luft & Kipnis, 1973), so that the portal blood, which represents 75% of the liver blood flow, is depleted of glutamine. As the glutamine concentration in hepatic veins reflects both liver and intestinal metabolism of this amino acid, net hepato-splanchic uptake does not rule out hepatic synthesis. Addae & Lotspeich (1968) suggested from studies on dogs that the liver was the major source of glutamine under metabolic acidosis. However, our subjects with NH4Cl acidosis and normal renal function did not show glutamine release into the hepatic veins, although, after a 6 days NH4Cl load hepato-splanchic glutamine uptake disappears. The lack of hepato-splanchic glutamine uptake in chronic renal insufficiency may therefore be in some way dependent on chronic metabolic acidosis.

In contrast to the other animal species so far studied in vivo (Addae & Lotspeich, 1968; Lund, 1971) the human brain does not release glutamine into the circulation in normal conditions but, on the contrary, significantly extracts this amino acid (Tizianello, De Ferrari, Garibotto, Gurreri & Barberis, 1976), as it does many other amino acids (Felig, Wahren & Ahlborg, 1973). Cerebral glutamine uptake is suppressed in chronic metabolic acidosis. It is possible that chronic metabolic acidosis.
acidosis is responsible for the suppression of cerebral glutamine uptake observed in chronic renal insufficiency.

In chronic renal insufficiency alterations of glutamine metabolism across many organs contribute to the rise in glutamine arterial concentration. It should be emphasized that the arterial concentration is the most representative index of the overall balance between synthesis and utilization of glutamine by the various organs, whereas the local venous concentration reflects also the metabolic effects induced by each circulatory bed. Therefore values of glutamine concentration in peripheral venous blood previously reported (Müting & Dishuk, 1967; Peters, Gulyassy, Lin, Ryan, Berridge, Chao & Cummings, 1968) cannot be compared with the arterial concentration reported here. A significant rise of arterial glutamine concentration is reported by Ganda, Aoki, Soeldner, Morrison & Cahill (1976) in uremic patients who underwent periodic haemodialysis for more than 1 year. These data also cannot be strictly compared with our findings, as their patients had a more severe renal insufficiency, and required periodic haemodialysis.

In conclusion, striking changes in the pattern of glutamine metabolism across many organs take place in patients with chronic renal insufficiency studied in the post-absorptive state: the renal glutamine utilization disappears, the muscular production seems increased, the net utilization by the hepato-splanchnic bed and by the brain is suppressed and arterial glutamine concentration rises. The fate of excess of glutamine due to its defective utilization is unclear. One can speculate that other sites for utilization come into play in chronic renal insufficiency. Since one of the major physiological roles of glutamine is the transport of ammonia to renal and intestinal sites where ammonia is then released, the lack of renal and hepato-splanchnic glutamine extraction observed in chronic renal insufficiency suggests that the normal pattern of ammonia transport by glutamine is changed in this pathological condition.

The mechanisms which alter glutamine metabolism in chronic renal insufficiency are unclear. However, at least acidosis and perhaps guanidines affect glutamine metabolism across many organs, by modifying the synthesis or utilization of this amino acid.

Acknowledgments

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References


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