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Amino acids and the kidney

Review

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Summary. The kidney has an important role in the metabolism of amino acids and control of plasma concentrations. Reabsorption by the tubules recovers about 70g/day of amino acids, derived from both the diet and metabolism in other tissues. Amino acids regulate haemodynamics and proteolysis and maintain integrity of the kidney. Abnormal plasma and muscle amino acid profiles in chronic renal failure (i.e. low essentials and tyrosine with high non-essentials) first indicated malnutrition, which can be partially corrected by supplementation. The loss of effective kidney tissue and uraemia, in addition to nutrition, have been considered in studies of phenylalanine hydroxylation used to investigate low tyrosine. Investigations in normal kidney have shown that glutamine uptake maintains acid-base homeostasis, glycine and citrulline are removed, and serine and arginine are released into the circulation. These metabolic processes are impaired in chronic renal failure. Uraemia affects most tissues and causes malnutrition, whilst acidosis activates catabolism of amino acids and proteins in muscle. Hyperinsulinaemia probably depresses plasma branched-chain amino acids and particularly valine. These abnormalities are less likely to respond to dietary supplementation.

Keywords: Amino acids – Kidney – Nutrition – Phenylalanine – Tyrosine – Uraemia

Introduction

The kidney has an important role in amino acid metabolism and in the regulation of plasma concentrations of many amino acids. This role is dependent on a supply of amino acids to maintain the physiology and integrity of the kidney, to allow the uptake, degradation, synthesis and release of amino acids, and to maintain acid-base homeostasis.

Amino acid supply

About 70g of amino acids per day, derived from the diet and metabolism in the liver, muscle and other tissues, are filtered from the arterial blood by the kidney. 97% are actively reabsorbed in the proximal tubules and after metabolism leave the kidney, in modified composition, by the renal vein: Silbernagle (1988). Amino acids reaching the kidney have several vital physiological effects depending on both the quantity and composition of the supply.

Haemodynamics

An oral protein load or infusion of amino acids induces a rise in renal haemodynamics in normal individuals: Hirschberg et al. (1988). Glomerular filtration rate and renal plasma flow are increased by mixed amino acids but mostly by arginine hydrochloride, glutamic acid and glycine. In these studies the effects were probably mediated by glucagon and prostaglandins but a direct effect of amino acids has been observed during the perfusion of isolated rat kidney: El Sayed et al. (1990). A similar mechanism may account for the effects of high protein intakes on renal haemodynamics in the acceleration of glomerulosclerosis: Brenner, Meyer, Hostetter (1982).

Proteolysis

The regulation of proteolysis is partly achieved by amino acids: Mortimore, Pösö (1987). The kidney, rich in peptidases in the proximal tubular brush border, is a major site for the catabolism of both circulating and kidney peptides and proteins: Kenny, Maroux (1982). Leucine, lysine and phenylalanine, together with insulin, have the most marked suppressive effects on proteolysis in cells derived from proximal tubular epithelium: Rabkin et al. (1989). When amino acids are not available, such as during a protein free diet, the kidney can lose about 20% of its protein in 7 days in order to provide amino acids for new proteins and also for gluconeogenesis. Consequently an adequate protein-calorie diet is required to allow for the normal daily turnover of proteins whilst maintaining the integrity of the kidney.

Plasma and muscle amino acids in renal failure

The role of nutrition in kidney metabolism was highlighted in the late 1960's from the plasma amino acid profiles in patients with chronic renal failure: Giordano (1967); Gulyassy, Aviram, Peters (1968); Young, Parsons (1969 and 1970). In our own studies of both non-dialysed and dialysed patients most plasma essential amino acids, tyrosine and arginine were low and non-essential amino acids were high (Fig. 1–3). The most severe imbalance occurred in patients undergoing intermittent peritoneal dialysis (Fig. 2) who were maintained on low protein diets and also lost appreciable amounts of protein and amino acids in their peritoneal dialysate: Young, Parsons (1969). This profile was similar to that seen in protein deficiency disorders: Holt (1963), but was also related to the

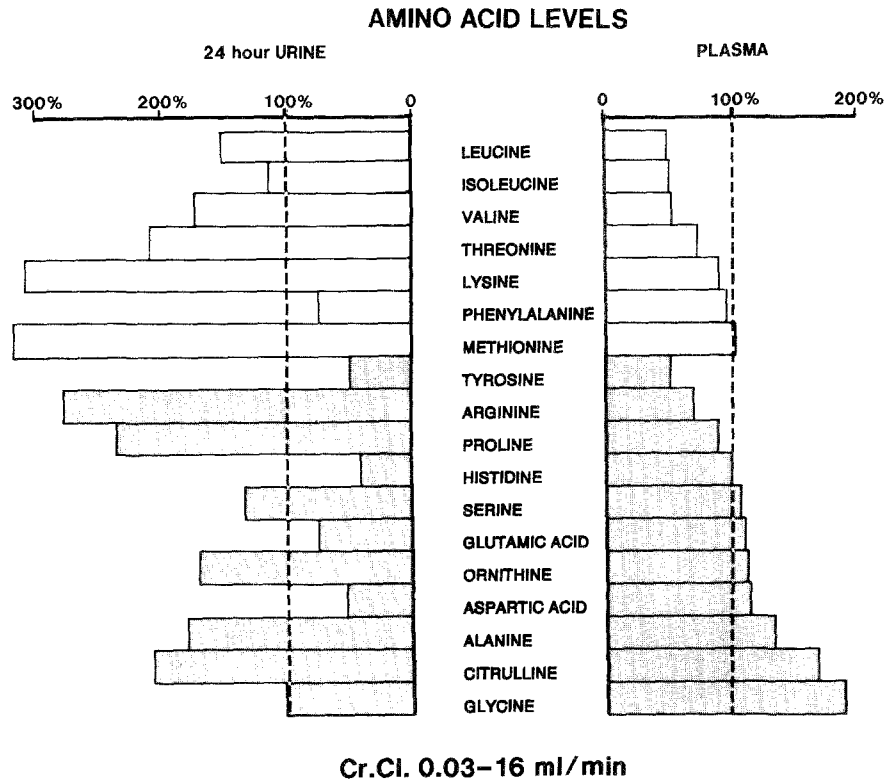

Fig. 1. 24 hour urinary excretion and plasma amino acids in non-dialysed patients ($n = 10$). Values are expressed as a percentage of normal ($n = 20$). Essential amino acids (white). Non-essential amino acids (grey)

degree of renal impairment. The relationship between the amino acid imbalance and uraemia was indicated by a significant correlation between the ratio of plasma essential to total amino acids and plasma creatinine.

Later studies have reported similar abnormalities for plasma amino acids and sometimes with low concentrations of histidine and taurine: Alvestrand, Fürst, Bergström (1982); Young, Swanepoel et al. (1982). Characteristic abnormalities for muscle intracellular free amino acids show some similarities to those in plasma. Typical changes in untreated uraemic patients are low concentrations of valine, threonine, lysine, histidine, tyrosine and taurine with high concentrations of non-essential amino acids: Alvestrand, Fürst, Bergström (1982).

Urinary amino acids in renal failure

In chronic renal failure the supply of amino acids to the kidney is further decreased by the reduced renal flow and glomerular filtration rate. However, as we observed in the 1960's, urinary amino acid clearances were often normal or increased: Young (1970), the overall losses in urine were generally similar to normal, representing about 0.5% of dietary intake (Fig. 1). Thus it was unlikely that urinary losses contributed significantly to the decrease in plasma essential amino acids. The elevated levels of some plasma non-essential amino acids,

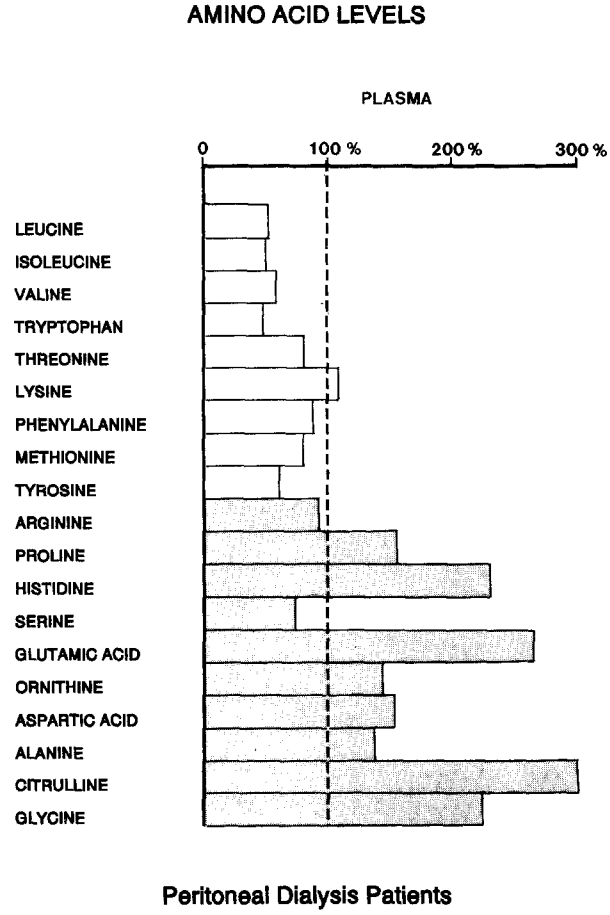

Fig. 2. Mean concentrations of plasma amino acids in peritoneal dialysis patients ($n = 7$). Values are expressed as a percentage of normal ($n = 20$)

particularly, citrulline, cystine and methyl histidines were attributed to urinary retention.

Dietary supplementation

When it was realised that malnutrition contributed to the abnormal plasma amino acid profile, attempts were made to correct the imbalance without increasing uraemia. Low protein diets were supplemented with essential amino acids within a similar total dietary nitrogen intake; and in dialysis patients, higher protein intakes were prescribed whilst ensuring adequate dialysis. In our own studies with amino acid supplements we included tyrosine, which we considered to be essential in chronic renal failure: Young, Keogh, Parsons (1969, 1973, 1975). Later, other groups, some of whom included histidine, measured nitrogen balance: Bergström et al. (1972), and extra- and intracellular free amino acids: Fürst et al. (1980). Some correction of the imbalance was usually observed both in plasma and muscle, although several amino acids, particularly valine, remained low. Many of the more recent studies have been reviewed by Fürst (1989) and improvements in composition of supplements have increased

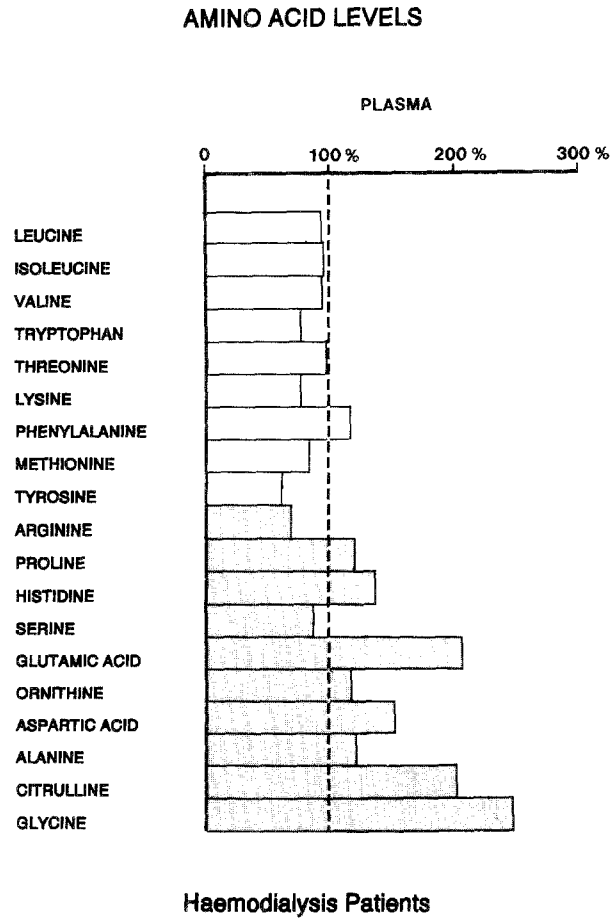

Fig. 3. Mean concentrations of plasma amino acids in haemodialysis patients ($n = 9$). Values are expressed as a percentage of normal ($n = 20$)

their effectiveness. The benefits of using ketoacids have yet to be established. Supplementation studies have highlighted both the difficulties of regulating amino acid metabolism and the existence of several specific abnormalities in chronic renal failure.

Studies on specific amino acids

During the past thirty years many groups have investigated the metabolic roles of the normal kidney and the effects of renal failure. Some abnormalities associated with impairment of renal haemodynamics, the inability to synthesise or catabolise certain amino acids, and urinary retention, can be attributed directly to loss of functional kidney. However, other effects of renal failure, such as uraemia, particularly acidosis and hormonal imbalance also affect amino acid metabolism in kidney and other tissues, and consequently contribute to the abnormal plasma amino acid profile.

One of the first specific amino acids to be investigated was tyrosine and this will be considered in some detail. Several amino acids have been studied exten-

sively by measurement of arteriovenous differences in humans, dogs and rats to establish the net removal of amino acids from, or the addition to the circulation in the normal kidney and these have been well documented: Brosnan (1987), Kuhlmann, Kopple (1990). These studies have shown that the kidney removes glycine and produces serine and also removes citrulline and produces arginine. Studies on rats have shown a large uptake of glutamine in diabetes, and after high protein feeding and in those given NH_4Cl in their drinking water. These specific amino acids and the effects of chronic renal failure will be considered in relation to the plasma amino acid profile. The renal metabolism of several other amino acids that are decreased in chronic renal failure have been reviewed elsewhere, and these include histidine and taurine: Kuhlmann, Kopple (1990).

Phenylalanine and tyrosine

Interest in phenylalanine hydroxylation in chronic renal failure was first stimulated by low tyrosine concentrations in plasma, muscle and lymphocytes, which in the presence of normal phenylalanine caused a low tyrosine to phenylalanine ratio: Giordano et al. (1967); Young, Parsons (1969); Gulyassy, Aviram, Peters (1970). Later studies with oral phenylalanine loading indicated decreased clearance and impaired oxidation, although metabolism of tyrosine was normal: Pickford, McGale, Aber (1973); Letteri, Scipione (1974); Jones, Kopple, Swenseid (1978). An enhanced post prandial release of phenylalanine and a lack of a significant release of tyrosine was also observed: Tizianello et al. (1987). In non-dialysed and dialysed patients some metabolic products of phenylalanine may be increased, including phenylacetylglutamine: Frimpter, Thompson, Luckey (1961); Young, Parsons (1969), phenylpyruvic acid: Giordano et al. (1967), phenyllactic acid, *p*-hydroxyphenylacetic acid and *p*-hydroxybenzoic acid: Jones, Kopple, Swenseid (1978).

A possible role for dietary protein in the impairment of phenylalanine hydroxylation was indicated by a similar abnormality in protein deficiency disorders: Whitehead, Milburn (1964). We also observed that the tyrosine to phenylalanine ratio correlated with the essential to total amino acid ratio, both in patients with chronic renal failure and in partially nephrectomised rats: Young, Parsons (1970 and 1973). Phenylalanine hydroxylase activity in liver was unaffected in rats with moderate renal insufficiency who were receiving normal diets but when protein intake was decreased, synthesis of enzyme and plasma tyrosine fell in consequence. This relationship between hydroxylation and protein intake was later confirmed using pair-fed rats: Wang et al. (1975), and also in normal man using [^{14}C]-phenylalanine: Jones, Kopple, Swenseid (1978).

In chronic renal failure, loss of effective kidney tissue could be a potential cause of reduced enzyme activity. However, phenylalanine hydroxylase activity in rats: Young, Parsons (1973) and in humans: Ayling, Helfand, Pirson (1975), Murthy, Berry (1968), is probably less than 10% of that in liver and it has yet to be shown whether such a small proportion alone could impair hydroxylation.

An effect of kidney failure on hydroxylation may be attributable to uraemia. Rat liver hydroxylase was inhibited by 15% when incubated with uraemic plasma or ultrafiltrate: Young, Parsons (1973). We were unable to identify a

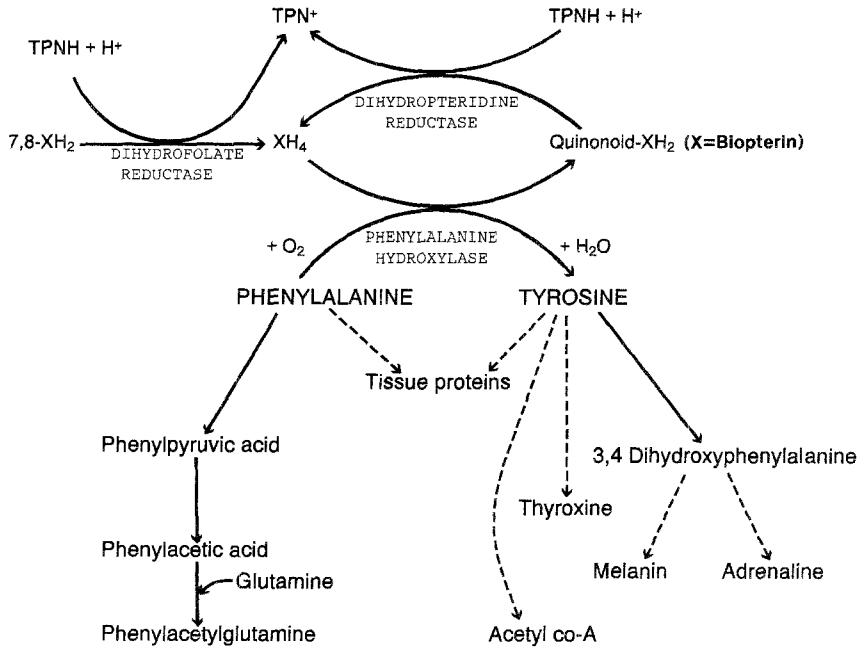

Fig. 4. Scheme for phenylalanine hydroxylation with 7, 8-dihydrobiopterin (7, 8-XH_2) as the cofactor: Kaufman (1971)

single component but there was a cumulative effect of urea, creatinine and other dialysable components. In 1984 Stoner et al. confirmed the presence of a dialysable inhibitor and part of the inhibiting effect was due to a substance of molecular mass of 800.

Consequently, the information currently available, suggests that impairment of phenylalanine hydroxylation is probably due to an inhibitory effect of one or more dialysable uraemic compounds combined with a decrease in enzyme activity due to malnutrition. It is uncertain whether loss of functional kidney tissue could contribute to low tyrosine.

Glutamine

Glutamine has the highest concentration in blood of all amino acids and is the major source of ammonia generated by the kidney. Extraction is linked to acid-base balance and is increased in metabolic acidosis. Glutamine is metabolised in the mitochondria by deamination to form glutamate and ammonia and the reaction is catalysed by glutaminase: Brosnan (1987). Glutamate can be transaminated or deaminated. Transamination with pyruvate is catalysed by alanine amino tranferase to form alanine and α-ketoglutarate. This is the usual pathway in the normal state. α-ketoglutarate is reconverted to pyruvate yielding bicarbonate which is excreted into renal venous blood. Deamination of glutamate is catalysed by glutamate dehydrogenase and is important in acidosis forming α-ketoglutarate and ammonia. The α-ketoglutarate is converted to pyruvate and then to glucose in rat kidney or to carbon dioxide in the dog kidney.

Increased glutamine extraction during acidosis releases ammonium and bicarbonate into the renal vein and increases urinary excretion of ammonium. In chronic renal insufficiency renal glutamine uptake accounts for only about 35% of ammonia production and other amino acids may contribute the rest: Stone, Pitts (1967).

Glycine and serine

The kidney removes glycine and releases serine into the renal vein in many species including rats: Pitts, Damian, Macleod (1970), dogs: Fukudo, Kopple (1980) and humans: Owen, Robinson (1963). The synthesis of serine is maintained independently of nutritional intake and in a 70 kg man the kidneys produce about 4 g daily which is equivalent to the normal dietary supply: Lowry, Hall, Brosnan (1986). Three metabolic pathways have been identified.

Glycine is extracted from arterial blood but may also be derived from peptides, hydroxyproline and glutathione. Conversion to serine via a glycine cleavage complex and serine hydroxymethyl transferase occurs in the mitochondria of the proximal tubules. Over half of renal serine is derived from gluconeogenic precursors. Two pathways, involving phosphorylated or non-phosphorylated intermediates of the triose phosphates of substrates such as glutamine, glutamate, proline and aspartate, occur mainly in the cytoplasm of the proximal tubule. Some synthesis of serine from sarcosine occurs in cortical tubules involving sarcosine dehydrogenase.

Glycine, in addition to a role in serine synthesis, is involved in the production of guanodinoacetic acid and creatine. It also serves as a source of ammonia and is an important ammoniagenic precursor in metabolic acidosis: Tizianello (1987). Clearly the kidney has a role in the metabolism of glycine and is an important source of serine. In chronic renal failure renal serine falls but a marked decrease in plasma serine may be prevented by synthesis in other tissues. Increase in plasma glycine may be less during metabolic acidosis.

Citrulline and arginine

The kidney removes citrulline, which is produced from glutamine in the intestine: Windmueller, Spaeth (1981), and is the main site for conversion to arginine: Featherstone, Rogers, Freedland (1973). Additional arginine may be formed from dimethylarginines produced during protein degradation.

In chronic renal failure both citrulline uptake and arginine release are decreased: Fikudo, Kopple (1980), although conversion may be preserved or even increased in residual nephrons: Tizianello (1980). Plasma, red cell and muscle citrulline concentrations are increased two to threefold by impaired uptake, whereas arginine concentrations are usually maintained at normal levels unless dietary intake is inadequate.

Effects of uraemia

Uraemic toxicity, metabolic acidosis and hormonal imbalance have an adverse effect on protein and amino acid metabolism, not only in the kidney, but also

in other tissues. Consequently, the supply and composition of amino acids to the kidney may be affected and contribute to the abnormal plasma amino acid profile.

Uraemia is the main cause of malnutrition in chronic renal failure and in a recent study all patients with severe malnutrition were uraemic and had no residual function: Young, Kopple, Lindholm et al. (1991). Loss of appetite, inadequate protein-calorie intake, impaired anabolic response and wasting are commonly found in chronic uraemic patients: Kopple (1976).

The catabolic effect of uraemia increases muscle protein degeneration and this can be eliminated by correcting the metabolic acidosis: Mitch (1987). These authors conclude that metabolic acidosis activates the catabolism of protein and amino acids in muscle independently of azotaemia. Studies with acidotic rats indicated an accelerated decarboxylation of both valine and leucine: Hara, May et al. (1987).

The persistence of low concentrations of branched-chain amino acids in plasma, and in particular, low valine in muscle, even after supplementation, is not fully understood and has been reviewed by Fürst (1989). The sustained hyperinsulinaemia of chronic renal failure may contribute to reduced amino acid concentrations. An increased splanchnic uptake of valine in uraemic patients is consistent with selective valine depletion: Alverstrand, Defronzo et al. (1988).

The regulation of amino acid and protein metabolism in chonic renal failure remains a problem. The provision of a correctly balanced diet, with supplements where appropriate may help to correct those abnormalities due to malnutrition or deficiencies of amino acids due to loss of functional kidney. However, abnormalities associated with uraemia, acidosis or hormonal imbalance are less likely to be corrected unless more efficient dialysis or more specific treatment can be used.

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