

FIGURE 18-6

Protein metabolism in acute renal failure (ARF): impairment of cellular amino acid transport. **A**, Amino acid transport into skeletal muscle is impaired in ARF [10]. Transmembranous uptake of the amino acid analogue methyl-amino-isobutyrate (MAIB) is reduced in uremic tissue in response to insulin (muscle tissue from uremic animals, *black circles*, and from sham-operated animals, *open circles*, respectively). Thus, insulin responsiveness is reduced in ARF tissue, but, as can be seen from the parallel shift

of the curves, insulin sensitivity is maintained (*see also* Fig. 18-14). This abnormality can be linked both to insulin resistance and to a generalized defect in ion transport in uremia; both the activity and receptor density of the sodium pump are abnormal in adipose cells and muscle tissue [11]. **B**, The impairment of rubidium uptake (Rb) as a measure of Na-K-ATPase activity is tightly correlated to the reduction in amino acid transport. (*From* [10,11]; with permission.)

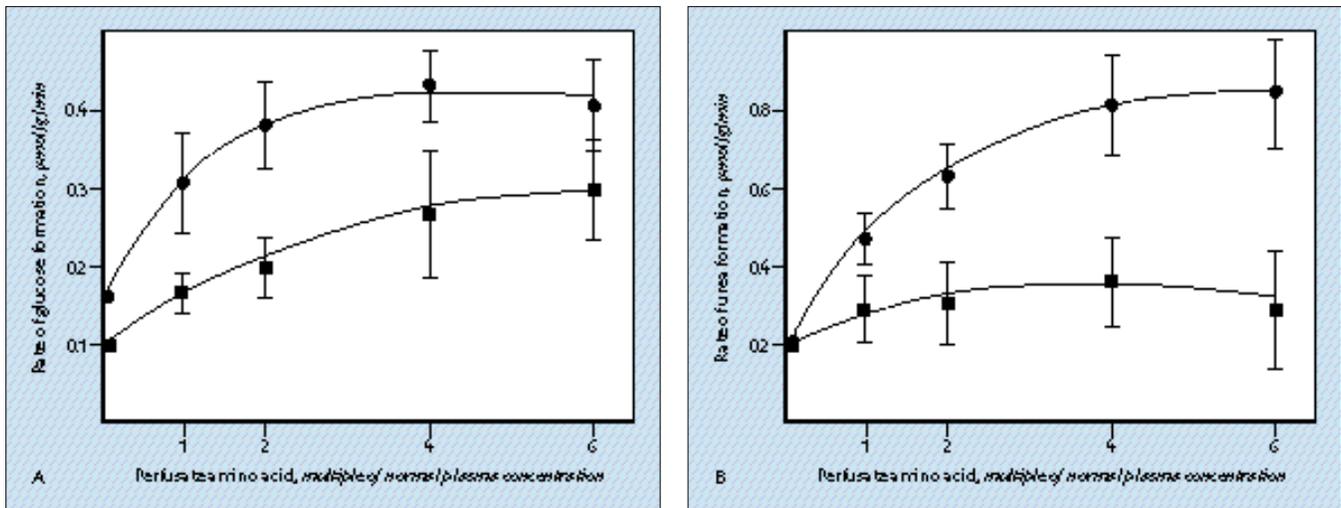


FIGURE 18-7

Protein catabolism in acute renal failure (ARF). Amino acids are redistributed from muscle tissue to the liver. Hepatic extraction of amino acids from the circulation—hepatic gluconeogenesis, **A**, and ureagenesis, **B**, from amino acids all are increased in ARF [12]. The dominant mediator of protein catabolism in ARF is this accel-

erated hepatic gluconeogenesis, which cannot be suppressed by exogenous substrate infusions (*see* Fig. 18-15). In the liver, protein synthesis and secretion of acute phase proteins are also stimulated. *Circles*—livers from acutely uremic rats; *squares*—livers from sham operated rats. (*From* Fröhlich [12]; with permission.)

CONTRIBUTING FACTORS TO PROTEIN CATABOLISM IN ACUTE RENAL FAILURE

Impairment of metabolic functions by uremia toxins
 Endocrine factors
 Insulin resistance
 Increased secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids)
 Hyperparathyroidism
 Suppression of release or resistance to growth factors
 Acidosis
 Systemic inflammatory response syndrome (activation of cytokine network)
 Release of proteases
 Inadequate supply of nutritional substrates
 Loss of nutritional substrates (renal replacement therapy)

FIGURE 18-8

Protein catabolism in acute renal failure (ARF): contributing factors. The causes of hypercatabolism in ARF are complex and multifold and present a combination of nonspecific mechanisms induced by the acute disease process and underlying illness and associated complications, specific effects induced by the acute loss of renal function, and, finally, the type and intensity of renal replacement therapy.

A major stimulus of muscle protein catabolism in ARF is insulin resistance. In muscle, the maximal rate of insulin-stimulated protein synthesis is depressed by ARF and protein degradation is increased even in the presence of insulin [9].

Acidosis was identified as an important factor in muscle protein breakdown. Metabolic acidosis activates the catabolism of protein and oxidation of amino acids independently of azotemia, and nitrogen balance can be improved by correcting the metabolic acidosis [13]. These findings were not uniformly confirmed for ARF in animal experiments [14].

Several additional catabolic factors are operative in ARF. The secretion of catabolic hormones (catecholamines, glucagon, glucocorticoids), hyperparathyroidism which is also present in ARF (see Fig. 18-22), suppression of or decreased sensitivity to growth factors, the release of proteases from activated leukocytes—all can stimulate protein breakdown. Moreover, the release of inflammatory mediators such as tumor necrosis factor and interleukins have been shown to mediate hypercatabolism in acute disease [1, 2].

The type and frequency of renal replacement therapy can also affect protein balance. Aggravation of protein catabolism, certainly, is mediated in part by the loss of nutritional substrates, but some findings suggest that, in addition, both activation of protein breakdown and inhibition of muscular protein synthesis are induced by hemodialysis [15].

Last (but not least), of major relevance for the clinical situation is the fact that inadequate nutrition contributes to the loss of lean body mass in ARF. In experimental animals, starvation potentiates the catabolic response of ARF [7].

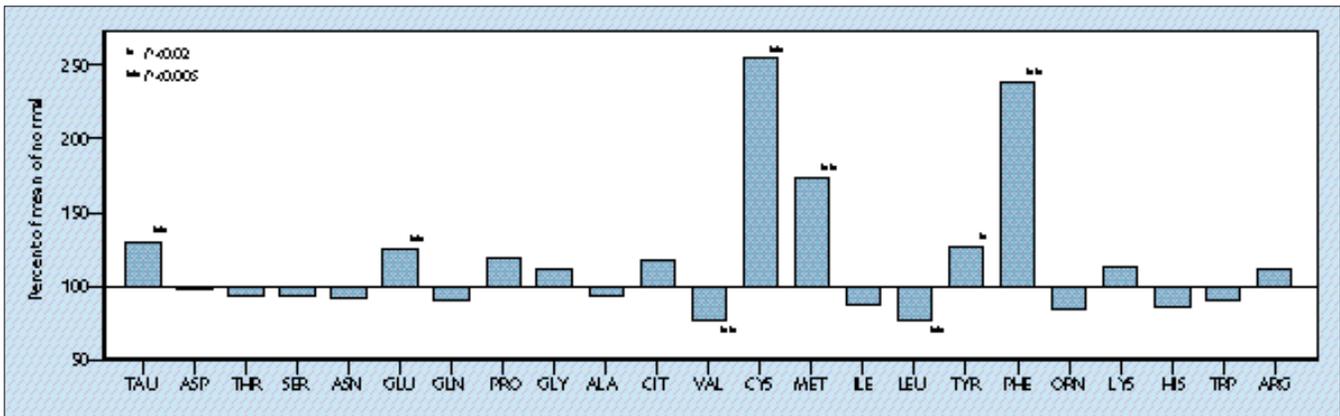


FIGURE 18-9

Amino acid pools and amino acid utilization in acute renal failure (ARF). As a consequence of these metabolic alterations, imbalances in amino acid pools in plasma and in the intracellular compartment occur in ARF. A typical plasma amino acid pattern is seen [16]. Plasma concentrations of cysteine (CYS), taurine (TAU), methionine (MET), and phenylalanine (PHE) are elevated, whereas plasma levels of valine (VAL) and leucine (LEU) are decreased.

Moreover, elimination of amino acids from the intravascular space is altered. As expected from the stimulation of hepatic

extraction of amino acids observed in animal experiments, overall amino acid clearance and clearance of most glucoplastic amino acids is enhanced. In contrast, clearances of PHE, proline (PRO), and, remarkably, VAL are decreased [16, 17]. ALA—alanine; ARG—arginine; ASN—asparagine; ASP—aspartate; CIT—citrulline; GLN—glutamine; GLU—glutamate; GLY—glycine; HIS—histidine; ORN—ornithine; PRO—proline; SER—serine; THR—threonine; TRP—tryptophan; TYR—tyrosine. (From Druml *et al.* [16]; with permission.)

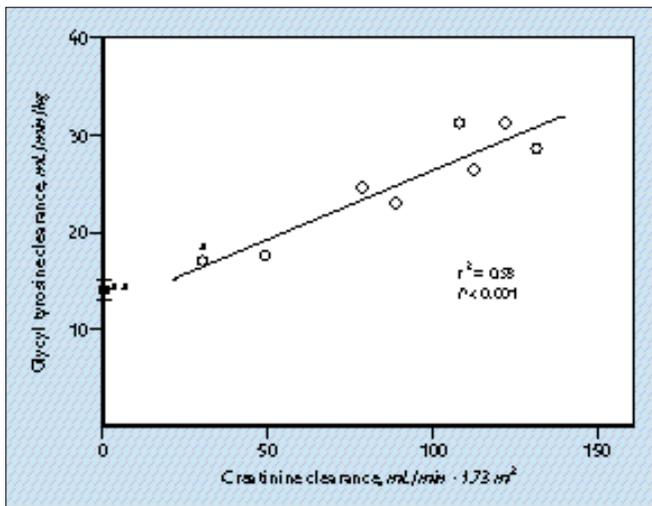


FIGURE 18-10

Metabolic functions of the kidney and protein and amino acid metabolism in acute renal failure (ARF). Protein and amino acid metabolism in ARF are also affected by impairment of the metabolic functions of the kidney itself. Various amino acids are synthe-

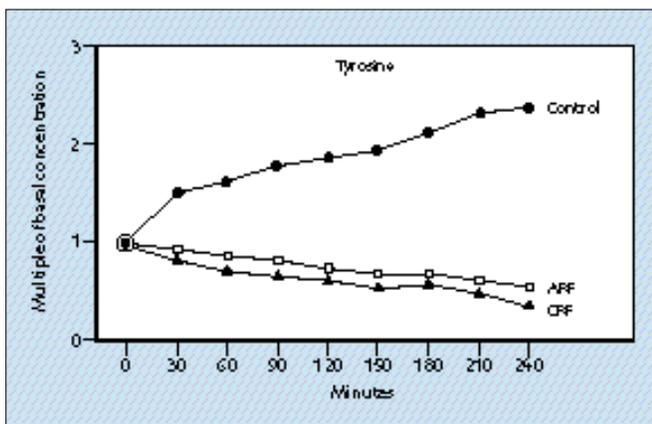


FIGURE 18-11

Amino acids in nutrition of acute renal failure (ARF): Conditionally essential amino acids. Because of the altered metabolic environment of uremic patients certain amino acids designated as nonessential for healthy subjects may become conditionally indispensable to ARF

sized or converted by the kidneys and released into the circulation: cysteine, methionine (from homocysteine), tyrosine, arginine, and serine [18]. Thus, loss of renal function can contribute to the altered amino acid pools in ARF and to the fact that several amino acids, such as arginine or tyrosine, which conventionally are termed nonessential, might become conditionally indispensable in ARF (see Fig. 18-11) [19].

In addition, the kidney is an important organ of protein degradation. Multiple peptides are filtered and catabolized at the tubular brush border, with the constituent amino acids being reabsorbed and recycled into the metabolic pool. In renal failure, catabolism of peptides such as peptide hormones is retarded. This is also true for acute uremia: insulin requirements decrease in diabetic patients who develop of ARF [20].

With the increased use of dipeptides in artificial nutrition as a source of amino acids (such as tyrosine and glutamine) which are not soluble or stable in aqueous solutions, this metabolic function of the kidney may also gain importance for utilization of these novel nutritional substrates. In the case of glycyl-tyrosine, metabolic clearance progressively decreases with falling creatinine clearance (*open circles*, 7 healthy subjects and a patient with unilateral nephrectomy*) but extrarenal clearance in the absence of renal function (*black circles*) is sufficient for rapid utilization of the dipeptide and release of tyrosine [21]. (From Druml *et al.* [21]; with permission.)

patients: histidine, arginine, tyrosine, serine, cysteine [19]. Infusion of arginine-free amino acid solutions can cause life-threatening complications such as hyperammonemia, coma, and acidosis.

Healthy subjects readily form tyrosine from phenylalanine in the liver: During infusion of amino acid solutions containing phenylalanine, plasma tyrosine concentration rises (*circles*) [22]. In contrast, in patients with ARF (*triangles*) and chronic renal failure (CRF, *squares*) phenylalanine infusion does not increase plasma tyrosine, indicating inadequate interconversion.

Recently, it was suggested that glutamine, an amino acid that traditionally was designated non-essential exerts important metabolic functions in regulating nitrogen metabolism, supporting immune functions, and preserving the gastrointestinal barrier. Thus, it can become conditionally indispensable in catabolic illness [23]. Because free glutamine is not stable in aqueous solutions, dipeptides containing glutamine are used as a glutamine source in parenteral nutrition. The utilization of dipeptides in part depends on intact renal function, and renal failure can impair hydrolysis (see Fig. 18-10) [24]. No systematic studies have been published on the use of glutamine in patients with ARF, and it must be noted that glutamine supplementation increases nitrogen intake considerably.