Metabolic Encephalopathies: Liver Disease, Renal Failure, Critical Illness

Eggert Holm, Raoul Breitkreutz and Mehmet Tokus*

Department of Pathophysiology, Medical Clinic I Mannheim, University of Heidelberg, Germany

Disorders of brain function not induced by primary lesions of brain structure may become apparent as acute, chronic, or acute-on-chronic encephalopathies. Almost all of these conditions are in principle reversible upon treatment. In this brief review we will focus on those metabolic encephalopathies that are most frequently encountered in medical and surgical patients. Emphasis is placed on pathogenesis and nutritionally oriented therapy.

Liver Disease

Pathogenesis of Encephalopathy: The Dualistic Concept

In 1960, Kitani [1] proposed a novel dualistic concept in order to elucidate the basic conditions leading to HE. He distinguished between a ‘hyperammonaemic factor’ and a ‘liver insufficiency factor’. Electrophysiological findings obtained by Kitani in animal experiments suggested that ammonia per se is

*We dedicate this paper with gratitude to Prof. Dr. D.L. Heene.

Abbreviations

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<td>ARF</td>
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<td>BCAA</td>
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likely to induce predominantly mental, \textit{i.e.} intellectual, mnestic and emotional disturbances – with a normal vigilance level being maintained, whereas severe impairment of overall hepatic function would result in somnolence, sopor, and finally coma [1]. It is to Kitani’s credit that he isolated hyperammonemia as a factor operating independently of the complex biochemical deviations associated with liver failure.

According to him, hyperammonemia is attributable mainly to PSS and responsible for PSE. Forty years later there is little reason to change this view. Portacaval shunted animals of various species exhibit raised plasma levels of ammonia even in the absence of any relevant hepatic dysfunction [2]. The same is true for patients with idiopathic portal hypertension [3]. In cirrhosis, the submaximal urea synthesis capacity is mostly well preserved. Liver cell insufficiency in this condition gives rise to only a modest increase in the plasma ammonia concentration so that the collateral circulation determines the degree of hyperammonemia far more than hepatic failure does [4]. In addition, a factor analysis calculated from data obtained in 208 patients with cirrhosis failed to show a covariation of plasma ammonia with the parameters of global hepatic function, but revealed instead a negative covariation with the number of thrombocytes being an indicator of portal hypertension [2]. Considering the fact that, alternatively, acute liver failure can produce a stage 4 encephalopathy even in the absence of hyperammonemia [3], one may be forced to agree with Kitani’s dualistic concept [1]. It follows therefore that the term ‘PSE’, if used to characterize the pathogenesis of cerebral disorders in cirrhosis, can be misleading, since – by definition – it only means brain dysfunction caused by PSS, and may thus occur either without concomitant liver insufficiency or as a component of ‘HE’ which includes any neuropsychiatric derangement induced by liver disease. According to current knowledge, PSE – in contrast to most other instances of HE – is brought about predominantly (or only) by hyperammonemia [3].

Figure 1 extends the dualistic concept of Kitani [1] to the plasma concentrations of amino acids. While the levels of methionine and aromatic amino acids are known to depend primarily on the functional capacity of the liver, with protein catabolism making some contribution, the notion that PSS-induced hyperammonemia decisively mediates the deficiency of BCAA is far from being generally accepted. We hypothesize that hyperammonemia indirectly lowers the plasma concentrations of BCAA by stimulating glutamine synthesis, thus reducing the intracellular glutamate pool, which is likely to be restored, at least partly, by an intensified BCAA transamination [5]. Every clinical and experimental state of extensive PSS so far investigated is characterized by a coexistence of marked hyperammonemia and a decline in BCAA plasma levels, suggesting a causal relationship [2, 3]. Regarding the pathogenesis of HE, the decrease in the levels of BCAA plays, at most, a subordinate role, while the increased concentrations of methionine and aromatic amino acids may well be implicated.
Fig. 1. The predominant metabolic alterations associated with liver cell damage and portal-systemic shunting. The accumulation of methionine (MET) and aromatic amino acids (AAA) occurs independently of both hyperammonemia and the ammonia-induced decline in the plasma levels of branched-chain amino acids (BCAA). Synergistic neurotropic effects of liver insufficiency and hyperammonemia take place, at least in part, at the blood-brain barrier, where hepatic failure increases the entry of ammonia into the brain and hyperammonemia facilitates the transport of neutral amino acids.

The relative contributions of hepatic insufficiency and PSS to the development of encephalopathy in cirrhosis vary from patient to patient. However, the results of a factor analysis based on data from a group of 66 patients [6] clearly demonstrated that, in general, increasingly abnormal values of bilirubin, prothrombin time, methionine, phenylalanine, and tyrosine paralleled the worsening of the neuropsychiatric state from normal to grades I, II, III and IV of HE, whereas a covariation of (venous) plasma ammonia with the severity of HE was lacking (Fig. 2). A factor pattern reproduces the large amount of information given in a correlation matrix in an easily comprehensible manner, in that each factor represents a set of variables, the values of which were intercorrelated. The individual factors are independent of one another. In Figure 2, only two factors from a total of five are depicted geometrically. From these two factors the conclusion can be drawn that clinical HE in most of the patients investigated was closely related to hepatic insufficiency rather than to venous hyperammonemia. In addition, the arterial ammonia concentration measured by us in a subsequent study failed to show a covariation with the arterial amino acid levels indicative of liver cell damage. The findings presented in Figure 2 together with the arterial measurements do, of course, not rule out a pathogenetic role for ammonia; they rather emphasize a primary role of liver insufficiency in the development and progression of clinical HE.
Fig. 2. A geometrical representation of two factors from a total of five resulting from a factor analysis which was based on data obtained from 66 patients with liver cirrhosis. A factor pattern reproduces the information given in a correlation matrix in an easily comprehensible manner, in that each factor comprises a set of variables the values of which were intercorrelated. The individual factors are independent of one another. The two factors depicted show that there was a close covariation of clinical hepatic encephalopathy (HE) with the biochemical changes induced by liver insufficiency, but not with hyperammonemia. Principal component method. Varimax rotation. Only factor loadings > ± 0.60 are indicated. The first six eigenvalues of the correlation matrix were 5.0, 1.9, 1.7, 1.3, 1.2, 0.7. The five factors developed account for 78.8% of the total variance (from Greulich et al. [6]).

The mechanisms by which hepatic failure alters brain function are less well understood than the effects of isolated hyperammonemia. An impairment of the blood-brain barrier and an accumulation of amino acid derivatives acting either as neurotoxic substances or as neurotransmitters are especially suspected. A nonspecific increase in the permeability of the blood-brain barrier is a common feature of acute HE, and exposes the brain to neuroactive compounds which normally cannot penetrate [7]. This may contribute to brain edema typical of acute HE. Alterations of specific transport systems are commonly observed in chronic HE [7]. The intensified transport of neutral amino acids such as phenylalanine, tyrosine and tryptophan has, however, been explained by hyperammonemia-induced accumulation of glutamine [8], which leaves the brain in exchange for these amino acids (Fig. 1).
What is currently known about the role of substances formed in the metabolism of methionine, phenylalanine, tyrosine and free tryptophan, which all markedly accumulate in both acute and chronic states of liver insufficiency? Among the neurotoxic compounds, methanethiol and hydrogen sulfide, metabolites of methionine, have unexpectedly been shown not to act as important mediators of HE [3]. Of the few putatively neurotoxic derivatives of phenylalanine, \( p \)-hydroxyphenolic acid was administered to cats with chronically implanted cortical and subcortical electrodes over a period of 5 days. No changes of either the spontaneous or evoked electrical activities were observed except for a decrease in the amplitudes of responses to amygdalar stimulation [9]. There are many nontransmitter metabolites of tryptophan, which could affect brain function in severe liver disease. Patients with cirrhosis and overt HE (up to grade IV) had either normal or lowered plasma levels of indican; other nontransmitter indolic compounds such as tryptamine, indoleacetic acid and indolepropionic acid were undetectable [10]. In contrast, a progressive increase of kynurenine paralleled the worsening of encephalopathy [10]. The entry of kynurenine into the brain may constitute a critical step in the cerebral formation of substances such as quinolinic acid, which is a powerful excitotoxin. At present, it remains unclear whether or not the amino acids dealt with in this context contribute to HE via neurotoxic agents. They may, however, do so via an imbalance between excitatory and inhibitory neurotransmission [7, 11, 12]. A dysfunction of the hepatic transmethylation-transsulfuration pathway for methionine degradation could be one of the reasons why the brain content of taurine is subnormal in HE. The hypothesis of false adrenergic neurotransmitters put forward by Fischer and Baldessarini [11] is still under debate. The authors suggested that high cerebral concentrations of phenylalanine may reduce the activity of tyrosine-3-hydroxylase, the key enzyme for the synthesis of dopamine and norepinephrine, a process that would result in a partial displacement of these catecholamines by weaker transmitters such as tyramine and octopamine. Many observations favor this hypothesis; however, there are also some objections [7, 9, 12]. Tryptophan is augmented in the brain of patients and animals with liver failure and, consequently, serotonin turnover is increased. PSS-induced and exogenous hyperammonemia also augments brain tryptophan because of an intensified passage across the blood-brain barrier [3]. Animal studies on the turnover and the neuronal release of serotonin yielded no convincing evidence for an involvement of this transmitter in the pathogenesis of manifest encephalopathy [3]. In patients with subclinical HE, the administration of a serotonin re-uptake inhibitor failed to worsen the mental state [13]. Alternatively to serotonin, tryptamine may mediate harmful effects of accumulated tryptophan on brain function [12]. The GABA theory of HE and the role of ‘endogenous benzodiazepines’ are not convincing [7, 12]. Apart from amino acid derivatives, short- and medium-chain fatty acids have
been implicated in the pathogenesis. Subsequent studies did not confirm this hypothesis [12, 14].

Ammonia exerts both direct and indirect effects on the brain. Concentrations of the ammonium ion equivalent to those often found in patients with cirrhosis diminish – by blocking the chloride pump – the inhibitory postsynaptic potentials, which means a disinhibition of action potentials. This is accompanied by alterations of the EEG. In addition, a postsynaptic effect on excitatory neurotransmission takes place [12]. In a study on cats with exogenous hyperammonemia, the EEG of cortical and seven subcortical areas, arousal reactions, evoked responses, and single unit discharge frequencies were analyzed. It could be shown that a clinically relevant acute rise in the arterial ammonia concentration predominantly affects cortical structures and other areas above the mesencephalic reticular formation [15]. Since almost the same pattern of modest electrical activity changes also characterizes portacaval shunted animals with chronic hyperammonemia [9], it is not surprising that only subtle behavioral alterations can be detected in such animals [3]. Likewise, the PSS-associated chronic hyperammonemic state in humans per se produces – in most cases – only subclinical encephalopathy. This is in sharp contrast to the early depression of the reticular activating system by liver insufficiency. However, in conditions of long-lasting hyperammonemia, for instance in patients given a portosystemic anastomosis, the brain is extremely sensitive to an additional ammonia load, since glutamine synthesis for ammonia detoxification already operates at its maximum capacity [16]. Thus, patients with the acute-on-chronic form of PSE, precipitated by an extra load of nitrogenous substances, often display manifest neuropsychiatric symptoms. The coexistence of an increased ammonia concentration with hepatic failure further aggravates the consequences of hyperammonemia. One of the factors responsible for the hypersensitivity to ammonia in those situations may be that (unknown) influences arising from liver dysfunction increase the entry of ammonia into the brain [17]. Furthermore, neurotropic synergisms between ammonia and metabolic deviations caused by liver insufficiency have been suggested [7, 12].

Harmful indirect, i.e. metabolically mediated neurotropic effects of ammonia require somewhat higher concentrations than the electrophysiological alterations do. The ammonia-induced accumulation of glutamine in the astrocytes is likely to be involved in cell swelling. However, there is not enough evidence in support of the hypothesis that glutamine accumulation plays a major role in the pathogenesis of clinical PSE [3]. The astrocytic lesion involves, among many other disturbances, an impairment of neurotransmission by glutamate. Since glutamate uptake into both astrocytes and neurons is inhibited by ammonia, the extracellular concentration of this transmitter substance is raised, which may explain the reduction in glutamate-binding sites [12]. Hyperammonemia also interferes with the cerebral metabolism of glucose, probably as a result of a decreased energy demand [7, 12]. Although
all of these findings are of interest, their clinical relevance has to be assessed in consideration of the fact that isolated chronic hyperammonemia usually produces only subclinical encephalopathy. The ammonia-induced depletion of energy-rich phosphates represents a final event in ammonia intoxication [7].

**Nutritional Treatment of Encephalopathy**

In a recent review, the therapy of HE is discussed with special regard to the principles of ‘evidence-based medicine’ [18]. For details regarding irrigation of the small bowel after gastrointestinal bleeding, cleansing of the colon, nonabsorbable disaccharides, antibiotics, benzoate, and neuroactive drugs (L-dopa, flumazenil, bromocriptine, memantine), the reader is referred to this review and to another one that appeared in 1997 [19]. Here we will focus on some aspects of parenteral and enteral nutrition and, in particular, on the role of individual nutrients. Parenteral nutrition in acute hepatic failure has never been investigated in a controlled fashion. Thus, it remains an open question whether a lipid emulsion and an amino acid mixture (only BCAA?) should be added to the mandatory infusion of glucose, until transplantation can be carried out. The serum concentrations of glucose, lactate and triglycerides may be a useful guide in monitoring substrate utilization [20]. Patients with cirrhosis and grade II – IV encephalopathy should receive TPN including an amino acid pattern high in BCAA and low in methionine as well as aromatic amino acids [21]. This kind of therapy has been a controversial matter since 1976 up to now.

Answering the question of whether or not BCAA improve the mental state of patients with HE requires an appropriate consideration of at least two additional factors which often influence HE: clinical complications and nutrition. Ten controlled studies have addressed the topic of ‘intravenous BCAA in the treatment of HE’ [20, 22]. Our own analysis of these studies resulted in four simple statements [22]. First, BCAA do not significantly influence the clinical outcome of patients with either major complications (bleeding, infection, sepsis, renal failure) or deterioration of liver function, since major complications and even the underlying liver disease itself are superior in determining the clinical course. Second, on condition that major clinical complications do not supervene and that liver function does not deteriorate, BCAA improve the mental state of patients with HE. As a rule, this effect becomes apparent, at the latest, after 3 days of treatment. Since, at the outset, it is unknown whether, in a particular patient, a major clinical complication will occur and how liver function will develop, BCAA should be administered as a treatment for HE. Third, nutrition per se counteracts HE, and fourth, BCAA counteract HE independent of and in addition to nutrition. The evidence supporting these statements as well as answers to most of the objections that could be made are given in a brief review [22].
BCAA not only correct the abnormal plasma amino acid profile, but also compete with potentially harmful amino acids for transport across the blood-brain barrier. These effects may be more important than the decrease in plasma ammonia, which – by repletion of the intracellular glutamate pool – also occurs with BCAA treatment. Thus, in a subgroup of patients who exhibit cerebral symptoms more due to excessive hyperammonemia than to overall hepatic dysfunction, the infusion of ornithine aspartate is indicated in the sense of a ‘differential therapy’ [23, 24]. The reduction in the ammonia concentration brought about by this compound appears to be mediated by stimulation of at least three processes: urea synthesis, glutamine formation, and protein anabolism [3, 23]. In the TPN regimen, up to 50% of the nonprotein energy should be provided as fat, thus meeting both metabolic potentials and limitations in liver cirrhosis without creating neuropsychiatric problems [14]. In cirrhotic patients with grade I encephalopathy, an infusion of either the above-characterized amino acid mixture or ornithine aspartate through a peripheral line may be indicated [24]. However, both BCAA and ornithine aspartate can also be given by the oral/enteral route. As to the oral administration of BCAA, the two largest, long-term (and high-quality) studies demonstrated an effectiveness in the prevention and treatment of HE in patients with advanced cirrhosis and protein intolerance [25]. Restriction of dietary protein (to 0.8 g/kg \(\times\) day or less) should only be a transient measure and then be followed by gradual increments to assess clinical tolerance. In general, a relatively high protein intake (1.1–1.2 g/kg \(\times\) day) is desirable because of disorders in nitrogen metabolism [19]. A vegetable diet or a diet rich in fiber may help to prevent HE [19, 20]. The same applies to zinc supplementation [26]. For both parenteral and enteral nutrition one should, in addition, consider that BCAA and lipid most probably promote liver regeneration [27].

**Renal Failure**

It must be made clear at the outset of this section that patients with CRF should, whenever possible, be given early dialysis as a protective measure against both clinical complications and malnutrition.

**Mechanisms of Disease Progression**

CRF resulting from the destruction of a substantial portion of the renal tissue is characterized functionally by a steady decline in GFR with time, regardless of the initial, but eventually not persisting insult. Disease progression can appropriately be assessed by the rate of change of the reciprocal serum creatinine concentration. In most patients with CRF, a plot of this parameter against time yields a straight line [28]. Among the methods of estimating disease progression, the most reliable is to measure the rate of change in GFR.
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An increase in the intraglomerular hydrostatic pressure appears to be a decisive mechanism accounting for the development of progressive glomerular lesions and, finally, the loss of viable nephrons in CRF. To clarify the sequence of morphological changes induced by this glomerular hypertension, Kriz et al. [29] outlined a hypothesis in which the (extracapillary) podocyte is considered ‘the culprit’. The podocytes are particularly vulnerable and, once differentiated, do not replicate effectively. An increased wall tension in the glomerular capillaries puts a mechanical strain on the podocytes, which then develop various morphological changes and finally detach from the glomerular basement membrane. The denuded parts of this membrane come into contact with the parietal epithelial cells and form a tuft adhesion (synechia) to the Bowman’s capsule. Within an adhesion the tuft merges with the interstitium, a process, which is associated with misdirected filtration towards the interstitium and, thus, creates a fluid-rich paraglomerular space inducing interstitial fibrosis and global sclerosis [29].

In experimental animals and humans, the infusion of amino acid mixtures and the ingestion of protein can augment the GFR [30]. This hemodynamic response was shown to be due to an increase of both the glomerular blood flow and the transcapillary hydrostatic pressure gradient as a consequence of a predominant dilatation of the preglomerular arterioles [30]. The changes in renal hemodynamics occurred when a mixture of many amino acids was infused, while the GFR remained almost unaffected with BCAA [30]. Also, a meat meal enhanced the GFR, whereas eggwhite, cheese, or soya-protein had no or only moderate effects. The mechanisms by which amino acids and protein elicit the hemodynamic alterations certainly include an increase in glucagon secretion but may additionally involve a liver-derived factor other than glucagon. This putative factor is called glomerulopressin and is probably a glucuronide, which causes afferent vasodilatation [30]. Furthermore, the hemodynamic changes could also be dependent on intrinsic renal effects, i.e. on tubular sodium cotransport with amino acids [30]. In patients with CRF, the percentage protein-induced rise in GFR is not diminished [28, 30]. Dietary protein may thus – via an increased glomerular pressure – contribute to disease progression, which means a shortened interval until the onset of encephalopathy.

Pathogenesis of Uremic Encephalopathy

Although the uremic syndrome involves multiple organ systems, most of the clinical manifestations arise from a disordered function of the nervous system. The symptoms of encephalopathy in both CRF and ARF patients who have not yet received dialysis range from mild mental disturbances to delirium and coma [31]. In ARF, the clinical symptoms as well as alterations of the EEG are
usually more severe than in CRF, and tend to develop at lower serum concentrations of urea [32]. Since patients with marginal but stable renal function may become uremic, when they either ingest a high protein diet or undergo a period of massive degradation of body protein stores, uremia is attributed to toxic influences of protein-derived waste products [31]. The ‘urea appearance rate’, i.e. the sum of urea excreted plus accumulated, varies directly with protein intake and is augmented by acidosis, which accelerates muscle protein breakdown. Urea accumulation is a representative substitute for an index of the accumulation of all waste products of protein metabolism. Among these waste products, many compounds are preferentially considered to act as ‘uremic toxins’ (or false neurotransmitters): phenols, indoles, skatoles, aliphatic and aromatic amines, sulfate, serum proteinases and others. Urea itself seems to be clinically important only at extreme concentrations. Methylguanidine and guanidinosuccinic acid being synthesized in the metabolism of both arginine and creatinine have also been implicated in the pathogenesis. Apart from intermediary nitrogen metabolism, protein degradation by intestinal bacteria, the density of which in the small intestine of uremic patients is increased, yields the products under debate [31]. For none of these products could a role as uremic toxin satisfactorily be ascertained. This is also true for solutes of middle molecular mass [31], with the remarkable exception of PTH [32].

Raised concentrations of PTH may well be causally related to many of the cerebral symptoms observed in uremic individuals [32, 33]. PTH adversely affects brain function in both normal subjects and patients with primary hyperparathyroidism. In patients with ARF, abnormalities of the EEG are present within 18 h after onset and persist – despite dialysis – as long as the PTH levels are raised [32]. EEG changes as well as mental dysfunction improved in uremic patients after either parathyroidectomy or pharmacological lowering of the PTH concentration [32, 33]. Likewise, the increase in EEG slow-wave activity induced by experimental uremia could be prevented by prior thyroid parathyroidectomy [33]. The mechanism behind the neurotoxic potential of PTH is still controversial, but may be related to the increased calcium content of the cerebral cortex in humans and animals with renal failure [32, 33]. In particular, the calcium content of brain nerve terminals in acutely uremic animal was found to be elevated due to an intensified calcium inflow [32, 33]. This phenomenon was prevented by parathyroidectomy. There may also be a connection between the increase in intracellular calcium and the reasonably consistent observation that (red blood) cells of patients with renal failure show a high sodium content [31], because the energy needed for calcium export is derived from sodium export. As a consequence of the decline in sodium pump activity, a significant fall in the resting membrane potential of muscle could be documented by the working group of Knochel [31, 34] in uremic patients. The abnormality of the membrane potential associated with clinical symptoms of uremia only occurred with a less than sufficient dialysis
Fig. 3. Resting transmembrane potential of skeletal muscle cells in 6 patients with uremia. Phase I: measurements when all patients were on conventional hemodialysis for periods of 6 h three times per week. Phase II: measurements after the dialysis time had been decreased. Phase III: measurements after the dialysis had been continued at the same decreased rate, but dietary protein had been reduced from 0.1 to 0.5 g/kg \times \text{day}, with a supplement of essential amino acids being added. In 5 patients, the membrane potential returned to normal; the remaining patient did not comply with the diet (adapted from Cotton et al. [34], with permission).

regimen (Fig. 3). When, at this stage, dietary protein was reduced from 1.0 to 0.5 g/kg \times \text{day} (supplemented with an amino acid mixture), the membrane potential returned to normal and the clinical state improved, although the reduced frequency of dialysis treatment was not changed; in one patient who did not comply with the diet, the membrane potential remained abnormal (Fig. 3). In summary, waste products of protein metabolism, PTH, and disorders of transmembrane ion transport as well as of intracellular ion content are involved in the pathogenesis of uremia.

**Nutritional Treatment**

There are two goals to the use of nutritional therapy: slowing down the progression of chronic renal disease and ameliorating the uremic symptoms. Both of these goals can be achieved to an appreciable extent by protein restriction. In a recent meta-analysis of the efficacy of protein restriction in delaying disease progression, five studies on nondiabetic renal disease and five on type 1 diabetes-associated nephropathy were considered, including the ‘Modification of Diet in Renal Disease Study’ [35]. A low-protein diet (0.7–0.8 g of protein/kg \times \text{day}) was demonstrated to reduce the risk of either renal failure or death in nondiabetic renal disease, as well as to slow the increase in urinary albumin, or the decline in GFR, or creatinine clearance in diabetic nephropathy [35]. However, the results obtained in the diabetic
population were viewed only as a strong indication but not as a conclusive proof that the low-protein diet is beneficial. Assuming that the GFR declines by about 12 ml/min per year and based on the meta-analysis’ results, Gretz [36] calculated that for a nondiabetic ‘standard patient’ starting with a GFR of 90 ml/min, the time interval elapsing until a GFR of zero is reached will be prolonged by a low-protein diet from 7.5 to 11.1 years; the benefit for patients with GFR values of 60 and 30 ml/min at start will be a delay from 5.0 to 7.4 and from 2.5 to 3.7 years, respectively. Diabetic patients would – at each of the three GFR values as starting points – profit from the diet of approximately another 2 years [36]. Dialysis can thus be forestalled considerably. In practice, a prescription of 0.8 g of protein/kg \( \times \) day appears reasonable in the early stages of CRF, followed by 0.6 g/kg \( \times \) day in advanced stages. As a rule, low-protein diets contain relatively low amounts of phosphate and may thereby antagonize calcium-phosphate deposition in the kidney.

As to uremia, diets poor in protein have for more than 100 years been recognized to result in a decrease of both the serum urea concentration and the severity of clinical symptoms. In the ‘National Cooperative Dialysis Study’, a time-averaged urea concentration <80 mg/dl was associated with fewer EEG abnormalities and a better neurobehavioral state than was a urea level >100 mg/dl [31]. Nitrogen economy is optimized by diets relatively low in protein by minimizing amino acid oxidation (and thus urea production) in favor of protein synthesis, a metabolic response called ‘adaptation’ [28]. A further positive effect on nitrogen economy can be achieved by administering supplements of either essential amino acids or even better – their ketoanalogues [28]; this, however, is not widely accepted. Metabolic acidosis in CRF contributes markedly to uremia by stimulating muscle protein breakdown and amino acid oxidation [28]. A low-protein diet counteracts acidosis [28]. It is very important to note that patients undergoing protein-restricted dietary regimens run the risk of malnutrition. To prevent such a development, sufficient energy as well as vitamins and trace minerals have to be provided [28]. Regarding protein metabolism and nutritional measures in ARF, the reader is referred to one of the excellent reviews by Druml [37].

**Critical Illness**

This term applies to those life-threatening conditions that are treated in intensive care units. Apart from severe acute HE and uremic complications, disorders in the metabolism of glucose, sodium and phosphate deserve particular consideration in the context of nutritional influences on brain function. Septic encephalopathy is left aside in this article, because its pathogenesis involves not only metabolic abnormalities but also a multitude of other factors such as increased procoagulant activity, ischemia and small areas of infarction.
Hyperglycemia

DKA and HHNS should not be viewed as separate nosological entities, because they are the extremes of a continuum of emergencies caused by an insufficient secretion and/or action of insulin (Fig. 4). They differ only in the extent of metabolic acidosis and hyperglycemia-induced dehydration [38, 39]. DKA, which occurs much more frequently in type I than type II diabetes, is characterized by an acute onset, severe acidosis and modest hyperglycemia (usually not exceeding 300 mg/dl). In contrast, HHNS, mostly a complication in older patients with type II diabetes, develops gradually over days to weeks and becomes apparent with no or only mild acidosis, but with blood glucose levels >400 mg/dl [38, 39]. Although metabolic acidosis may alter the mental state to some degree, it is the hyperosmolarity which causes brain dysfunction.

Fig. 4. Pathogenesis of acute metabolic decompensation in diabetes mellitus. Diabetic ketoacidosis is characterized by an acute onset, severe acidosis and modest hyperglycemia. In contrast, the hyperglycemic hyperosmolar nonketotic syndrome develops gradually and shows no or only mild acidosis, but excessively high blood glucose levels.
ranging from disorientation to stupor, to coma, and convulsions (Fig. 4). A patient admitted to hospital with DKA and coma has as a rule a total osmolarity of at least 340 mosm/l [38].

The deficiency of insulin in DKA is associated with a marked rise in the concentrations of the counterregulatory hormones glucagon, catecholamines and cortisol (Fig. 4). This hormonal milieu combined with insulin resistance results in an increase of both gluconeogenesis and glycogenolysis, as well as in decreased peripheral glucose utilization. The enhanced glucose production by the liver represents the predominant factor in determining the glucose level. Hyperglycemia remains, however, limited, as long as glucosuria – in the presence of an adequate GFR – prevents excessive glucose concentrations. In adipose tissue, the hormone-sensitive lipase is activated. The extent of ketone body production in the liver is not only dependent on the amount of lipolysis-derived fatty acids, but also on a resetting of hepatic metabolism particularly by glucagon, which disinhibits fatty acid oxidation by lowering the level of malonyl coenzyme A. Acidosis occurs, when the ketone bodies can no longer be buffered by body bases [39].

At least three hypothetical mechanisms have been invoked to explain the development of HHNS instead of DKA. First, the insulin secretion, although not sufficient to prevent the abnormalities in glucose metabolism, may be high enough to limit lipolysis. Second, patients may have glucagon and catecholamine levels lower than those found in DKA, but if this is not the case, the insulin/glucagon ratio still remains an important determinant. Third, hyperosmolarity per se could play a part, for instance, by allowing sufficient malonyl-CoA to be formed (perhaps from glucose-derived lactate) and/or by inhibiting insulin secretion as well as insulin-mediated glucose uptake [39]. During the slow development of HHNS, a gradual decrease in both relative water intake and the capacity to excrete glucose contribute decisively to hyperosmolarity, with a multitude of precipitating factors operating additionally [38–40]. Once a patient is hyperglycemic, ‘glucose toxicity’ may establish a vicious cycle by reducing insulin secretion and insulin-mediated glucose uptake. While these processes undoubtedly take place in normal subjects [41], their occurrence in diabetics has, to the best of our knowledge, not yet been demonstrated with certainty. Hyperglycemia causes osmotic diuresis with loss of more water than sodium. Hyperosmolality-induced cellular dehydration is crucial in producing the severe neurological symptoms of HHNS [38].

Of the various therapeutic procedures [38–40], intravenous fluid replacement by using isotonic saline is the first measure to be undertaken and needs to be adjusted to the effective osmolality. Patients with DKA also require insulin immediately, but in those with HHNS correcting the water deficit should precede insulin administration. Otherwise, glucose and water move from the extracellular space into the cells leading to a deleterious reduction in circulating volume. While potassium administration is indispensable in connection with insulin treatment, the routine use of phosphate in DKA is
no longer recommended [38, 39, 47]. Bicarbonate is not required unless the arterial pH equals 7.0 or less [38, 39]. In patients with HHNS, major whole-body deficits of several electrolytes as well as B-complex vitamins should be addressed [40].

Nondiabetic patients in intensive care units often display significant deviations in carbohydrate metabolism, but usually do not develop a neurologically relevant degree of hyperglycemia.

Hyper- and Hyponatremia

Abnormal serum sodium concentrations result primarily from disorders of the water balance and may occur independently of total body sodium content. The associated cerebral symptoms are mediated by changes in the ‘effective osmolarity’; they vary from mild lethargy to unconsciousness and seizures. In hospitalized patients, the incidence figures of relevant hyper- and hyponatremia are 0.2–2.5 and 1–2%, respectively, with 5- to 10-fold higher occurrence rates being reported for patients in intensive care units [42, 43]. At the present time, there is an ongoing debate regarding some of the treatment modalities for both hyper- and hyponatremic patients [42, 44, 45].

Patients with hypernatremia may display either a severe, a moderate or only minimal dehydration; overhydration is rare. A further stratification can be made on the basis of urine concentration. In instances of moderate to severe dehydration, urine concentration may be (1) increased (water deprivation, extrarenal loss of more water than sodium), (2) normal to decreased (osmotic diuresis), or (3) clearly decreased (DKA, HHNS, CRF, loop diuretics). Likewise, if dehydration is absent or only minimal, urine concentration may be (1) increased (hypertonic saline infusion, seawater ingestion), (2) normal (essential hypernatremia), or (3) decreased (diabetes insipidus). Soon after the onset of an acute extracellular hyperosmolarity, the reduction in brain volume is not proportional to the degree of hyperosmolarity [44]. Instead, a three-step cerebral response, the so-called ‘regulatory volume increase’, takes place (Fig. 5). First, there is cell shrinking which leads to a decline in intracranial pressure, and an inflow of cerebrospinal fluid into the interstitium of the brain, thus counteracting the rise in pressure and creating a medium for cellular uptake of solutes. Second, an enhanced permeability of the blood-brain barrier allows for potassium accumulation in the brain. Due to changes in cell membrane transporters, potassium, sodium and chloride are taken up by the neurons, a process that markedly reduces cellular water loss. Third, other osmolytes are produced in the neurons: amino acids, methylamines, polyols and further substances (‘idiogenic osmoles’). The increase in cell solute content can establish an almost normal cell volume [44].

It is critical to consider the cerebral response to hyperosmolarity, when treating this condition. Whereas acute hypernatremia needs rapid correction, chronic hypernatremia, the development of which has taken many hours or days, requires a treatment period of approximately 48 h, because a shorter
Fig. 5. Regulatory volume increase of brain cells in states of hypernatremia. First, the exposure to the hypertonic environment causes acute cell shrinking. Later, the cells regain their original volume by accumulating solutes (from Ayus and Brennan [44], with permission).

The period of restoring isotonicity carries the risk of cerebral edema. The hydration state is the next crucial aspect. For patients with advanced extracellular volume depletion, therapy may start with the infusion of isotonic saline (0.9% NaCl). However, particularly in symptomatic patients, a hypotonic saline solution (0.45% NaCl) is preferable. Such a solution is also adequate for patients who are not dehydrated. In cases of extracellular volume overload, the administration of any sodium should be avoided, and 5% dextrose in water should be used together with diuretics. If the enteral route is chosen for therapy, hypotonic electrolyte solutions may yield satisfactory results [44].

Hyponatremia is sometimes associated with serum osmolality values >285 mosm/kg. Examples are hyperglycemia, uremia in ARF, factitious hyponatremia and lithium therapy [42, 45]. When serum osmolality ranges <285 mosm/kg – the condition of interest in our context – a urine sodium concentration <20 mmol/l mostly points to a disorder not primarily involving the kidney, while urine sodium >20 mmol/l is indicative of either renal disease or an alteration of renal function due to hormonal influences, diuretics, or other factors [45]. In the hyponatremic states associated with urine sodium <20 mmol/l, the extracellular fluid may be (1) decreased (extrarenal loss of more sodium than water), (2) normal (polydipsia, transurethral resection of the prostate gland), or (3) increased (cirrhosis, nephrosis, congestive heart failure). Similarly, hyponatremia associated with urine sodium >20 mmol/l may be combined with (1) extracellular volume depletion (renal loss of more sodium than water caused by diuretics, aldosterone deficiency, cerebral salt wasting syndrome), (2) a normal extracellular volume (syndrome of inappropriate antidiuretic hormone secretion, other endocrine perturbances), 298
or (3) an expansion of the extracellular space (ARF, CRF). For details the reader is referred to recent reviews [42, 45]. In the presence of serum hypotonicity, water shifts into the cells and causes brain swelling. However, hyponatremia evokes a cerebral regulatory response, as does hypernatremia. There is a cellular loss of sodium followed by a loss of potassium. After about 24 h of hyponatremia, the extrusion of substances such as taurine, glutamine, methylamines and myoinositol may contribute to the ‘regulatory volume decrease’ [42]. Consequently, chronic hyponatremia is often better tolerated than acute hyponatremia.

In the treatment of hyponatremia, the first point to be considered is the rapidity of the development of this state [45]. Acute hyponatremia requires an immediate correction. For patients with a contracted extracellular fluid volume, an isotonic (0.9%) NaCl solution is indicated. If the extracellular volume appears to be normal, a hypertonic (3%) NaCl solution is preferred and should be combined with a loop diuretic in order to minimize volume expansion. Patients with chronic, asymptomatic hyponatremia and a decreased extracellular volume should receive isotonic saline. The same measure may be taken if the extracellular volume is normal. In these cases, fluid restriction is the alternative option. Patients presenting with the syndrome of inappropriate antidiuretic hormone secretion are, in addition, treated with demeclocycline. For those suffering from polydipsia, an infusion of 3% saline may be necessary. Chronic hypernatremia associated with an increased extracellular volume needs both water restriction and a loop diuretic [42, 45].

Special attention has to be paid to the presence of hyponatremic encephalopathy, which first causes headache, nausea, emesis and weakness, and may then progress to respiratory insufficiency, seizures and death. In hyponatremic encephalopathy, the morbidity is in excess of 20% [42]. Active intervention, i.e. the infusion of hypertonic (3%) NaCl raising serum sodium at a rate of about 1 mmol/l per hour is therefore mandatory. However, this infusion must be discontinued when either of three endpoints has been reached: reversal of encephalopathy, increase in serum sodium by 25 mmol/l (the maximum not to be exceeded within the initial 48 h of therapy), a serum sodium value of 125–132 mmol/l [42]. If circulatory congestion is a possible complication of this treatment, the infusion should be combined with a loop diuretic. The danger of inducing demyelinating lesions and, in particular, central pontine myelinolysis appears to be extremely small compared to the risk of hyponatremic permanent brain damage which results from the failure of starting a timely and active therapy [42].

**Hypophosphatemia**

Severe hypophosphatemia (serum phosphate <1.5 mg/dl) occurs in about 2% of hospitalized patients [46] and is not recognized or adequately treated in as many as 42% of the cases [47]. In intensive care units, the incidence of the phosphate depletion syndrome may reach about 10% [46]. These
figures are highly alarming, since hypophosphatemia potentially impairs the function of almost all organ systems, with brain dysfunction being a prominent feature. Subnormal phosphate levels may cause weakness, sensory as well as motor disorders, confusion, coma, seizures, and even death. In patients with moderate hypophosphatemia (serum phosphate <2.5 mg/dl), clinical symptoms are either absent or less pronounced [47].

There are three possible mechanisms of hypophosphatemia: (1) either a decreased phosphate intake or a decreased intestinal absorption (vitamin D deficiency, phosphate-binding antacids); (2) increased renal excretion (mostly brought about by either acidosis or volume expansion), and (3) a shift of phosphate from the extracellular space into the cells (respiratory alkalosis, artificial nutrition and/or insulin). Two or all of these mechanisms often operate synergistically. This is especially true for those conditions in which hypophosphatemia is very common, i.e. chronic alcoholism and alcohol withdrawal, the so-called refeeding syndrome, and the patient’s status after major surgery [47]. The refeeding syndrome, characterized by various electrolyte derangements and heart failure, develops preferentially in malnourished or starved patients undergoing either a parenteral or an enteral nutrition regimen with inadequate phosphate supply [47]. It is essentially an anabolic response with a considerable influx of phosphate into the cells.

The metabolic disturbances and cerebral symptoms associated with severe hypophosphatemia are mediated by an increased phosphorylation potential with a decay of ATP production, together with a critical diminution of the entire adenine nucleotide pool, and probably – in addition – by a reduction in the 2,3-diphosphoglycerate content of red blood cells with impaired oxygen delivery to tissues. Glycolysis in erythrocytes does not yield sufficient amounts of 2,3-diphosphoglycerate because of an inhibition of glyceraldehyde-3-phosphate dehydrogenase due to phosphate depletion. In contrast, the reduction in erythrocyte glycolysis observed in DKA is caused by a decrease in the activity of phosphofructokinase due to acidosis and is less pronounced.

Severe and sustained hypophosphatemia requires replacement of phosphate. This can easily be achieved by offering skim or low-fat milk (0.9 mg phosphate per ml). The average patient needs 1–2 g of phosphate orally to have body stores repleted within 7–10 days [47]. With intravenous administration, 10 mmol (0.3 g) of phosphate infused in a 70-kg adult over 4–6 h would raise the phosphate concentration by about 1–2 mg/dl [47]. Provision of much higher amounts (Fig. 6) may be necessary in depleted patients receiving enteral nutrition [48]. In patients with DKA, routine replacement of phosphate is no longer recommended [47]. Considering the harmful effects of hypophosphatemia especially on brain function, this condition should no longer be a poor cousin of clinical medicine.
Fig. 6. Time course of serum phosphate concentration and phosphate intake in a patient with chronic alcoholism, pancreatitis, malabsorption and malnutrition. The oral diet (mixed meals) contained 20–30 mmol, and the artificial enteral nutrition (nasogastric tube) 37.4 mmol of phosphate daily. On the fifth day, 60 mmol of glucose-1-phosphate were given intravenously, and subsequently 40 mmol/day (adapted from Maier-Dobersberger and Lochs [48], with permission).

References

Metabolic Encephalopathies: Liver Disease, Renal Failure, Critical Illness


**Discussion**

*Dr. Bunout:* I would like to comment on protein catabolism in cirrhosis. We had the same idea that cirrhotic patients were catabolic and we documented their loss of lean body mass. But when we studied protein catabolism objectively we couldn’t find any difference between patients with cirrhosis and normal individuals. The only cirrhotic patients who really were catabolic were those who had subclinical infections, specifically spontaneous bacterial peritonitis. So we got to the idea that most of the protein catabolism that we see in cirrhosis is not due to cirrhosis itself, but to the complications and infections that are often undiagnosed in these patients.
My second point relates to what happens with protein restriction and the progression of renal failure. Under conditions of reduced glomerular filtration rate, angiotensin-converting enzyme inhibitors obtain the same result as protein restriction and the patients are likely to comply better with the treatment. Do you know of any argument that it is better to use protein restriction than to give this type of drug?

Dr. Holm: As to your first question, protein kinetics have been investigated by O'Keefe [1] in cirrhotic patients. He showed that there was an increase in both the protein breakdown and synthesis, and the protein balance was negative, but I don’t know the clinical characteristics of his patients. The Dutch workers Swart et al. [2] showed that at least 0.8 g of protein per kg per day are necessary to maintain nitrogen equilibrium. You are right, it is quite possible that many cirrhotic patients are not in a protein catabolic state, but there is a danger of this occurring, since protein intake is often too low and the amino acid utilization may be deranged. For instance the branched chain amino acids are oxidized to a greater degree than normally, maybe because of hyperammonemia. Under these conditions the normal protein intake may be insufficient for cirrhotic patients. They need at least 1 g of protein/kg per day. If they achieve this intake they may preserve their muscle mass.

I cannot answer your second question as I have no experience with ACE inhibitors under these circumstances. Are there controlled studies on this? Even protein restriction has been a subject of disagreement for several decades, and it was only quite recently that a meta-analysis showed that the progression of chronic renal failure can be slowed down by protein restriction [3].

Dr. Bunout: There are several prospective studies in diuretic patients showing that they come to hemodialysis later when they are on ACE inhibitors.

Dr. Pasquetti: When you treat patients with liver failure with total parenteral nutrition you risk precipitating encephalopathy. This has been attributed to the type of lipid used. For example, free fatty acids may displace tryptophan from the albumin-binding sites. And short chain fatty acids, maybe even medium chain fatty acids, may interfere with brain function. What is known about this?

Dr. Holm: We have to differentiate between acute and chronic liver failure. In acute liver failure we know we must give glucose because there’s hypoglycemia, but we know nothing else. There are no studies on the administration of amino acids or fat. Many studies have been done in chronic liver failure. In cirrhosis, the use of fat emulsions is justified and necessary, because there is glucose intolerance, and if you want to give enough energy you must use fat emulsions. We evaluated EEG power spectra, did psychometric tests, and measured levels of many metabolites and toxins, and showed no harmful effect of fat emulsions [4]. You mentioned that free fatty acids may displace tryptophan from the albumin-binding sites. That is correct. You also mentioned that short chain fatty acids might interfere with brain function. However, Smit and coworkers showed that short chain fatty acids have no pathogenetic role in hepatic encephalopathy [5]. Secondly, if you administer octanoate included in an MCT/LCT emulsion, there is no deterioration in encephalopathy. So there is no reason to worry about the administration of fat to cirrhotic patients.

Dr. Fernstrom: What happened to the idea that the hyperinsulinemia associated with chronic liver cirrhosis accounts for some of the fall in branched chain amino acids? You’re attributing it to the branched chain amino acid transaminase making more glutamine.

Dr. Holm: There are many papers claiming that hyperinsulinemia is the main cause of the decrease in branched chain amino acids. There are also many arguments against this. First, in pancreatetectomized dogs which underwent ammonia infusions, there was lowering of the branched chain amino acids in spite of the absence of insulin. Furthermore, there is also no correlation between the amount of insulin present in the
plasma and the branched chain amino acid levels. And there are states like idiopathic portal hypertension where the branched chain amino acids are lowered in the presence of hyperammonemia but insulin levels are normal. I would not say that insulin plays no role at all, because it has been pointed out that there may be a long-term control of the branched chain amino acid concentrations [6]. However, I think ammonia has a part to play as well.

**Dr. Fernstrom:** My other question has to do with glutamine. There is a hypothesis in the glutamate/glutamine cycle in brain between glia and neurons that when glutamate is released from a nerve terminal it is taken into a glial cell, turned into glutamine, and then the glutamine goes back to the glutamatergic neuron, where it’s turned back into glutamate. It’s thought that branched chain amino acids from the periphery serve as a source of nitrogen for the glutamine synthesis. I wonder whether in this particular situation, where you have so much ammonia in brain, the ammonia can have an impact on glutamine synthesis, and in general what glutamine levels might be like in the brains of these patients.

**Dr. Holm:** I think you have to differentiate between what happens in whole brain and in the synaptic cleft. In the whole brain, of course, glutamine is increased and glutamate is decreased, as it is in muscle, but in the synaptic cleft there’s an increase of glutamate because ammonia inhibits the uptake of glutamate into both the neurons and the astrocytes. Nobody knows what this kind of glutaminergic transmission derangement means clinically. If you look at the action of infused branched chain amino acids you have to consider three points. First, the branched chain amino acids contribute to the lowering of ammonia, because more glutamine is formed in muscle. Second, and more important, the branched chain amino acids correct the plasma amino acid levels. Third, they act at the blood-brain barrier, competing for the entry into the brain. These are the mechanisms of action we know about. I think that there is a special therapeutic role for branched chain amino acids in patients in whom liver insufficiency is predominant over hyperammonemia. But in cases where liver insufficiency is not so pronounced, it may be better to give ornithine aspartate, which is an ammonia-lowering substance, or you can also give sodium benzoate which combines with glycine to form hippurate which is excreted in the urine.

**Dr. Bunout:** I want to insert a note of caution about therapeutic trials in acute hepatic encephalopathy. Our work is mostly with alcoholic cirrhotic patients, and maybe that’s different from your experience. However, what normally happens when you admit a patient with cirrhosis and encephalopathy is that you treat the causes of the encephalopathy – usually infection or acute gastrointestinal bleeding or whatever – and not the encephalopathy per se. The encephalopathy resolves because of the treatment of its precipitating cause. This is the problem of all the trials on acute hepatic encephalopathy: you cannot distinguish between what’s done to treat the patient or his complications and the treatment of encephalopathy itself. If you study chronic hepatic encephalopathy, where there is no precipitating event, you find that in those cases therapeutic measures such as branched chain amino acids have no clinical effect on the encephalopathy. I think we have to be very cautious about interpreting the results of treatment trials for this reason.

**Dr. Holm:** I would like to refer you to a monograph that has recently appeared [7]. It contains a contribution by Ferenci on evidence-based gastroenterology, and he emphasizes that conventional treatment is very important, as you said. But that does not mean that there are no additional effects of special measures. For instance, there are controlled studies on the branched chain amino acids, there are controlled studies on flumazenil, and there are studies on bowel cleansing, all giving positive results. There are also controlled studies of sodium benzoate vs. placebo with positive results. So we cannot say that these additional measures are not effective. They are indeed
effective, in addition to the conventional treatment, and this holds true for acute and chronic encephalopathy. If you look specifically at chronic encephalopathy, there are about 25 studies and an attempt was made by Fabbri and co-workers to perform a meta-analysis [8]. However, they came to the conclusion that only two of these studies had an acceptable quality score and fulfilled all the criteria necessary for these kinds of study. These were the studies by Horst et al. and by Marchesini et al. The Horst study pertains to the prevention of encephalopathy. The authors increased the protein intake every 7 days by 20 g. When they gave branched chain amino acids instead of normal protein, almost all of the patients did not develop encephalopathy, but with normal protein many more of them did. This study is recognized worldwide as a good study. The second one, by Marchesini et al., is a study about treatment. In that study the patients had chronic encephalopathy with increased ammonia levels, decreased performance in the number connection test and so on, and there was a significant improvement with branched chain amino acids. This has been acknowledged by all hepatologists.

**Dr. Uauy:** Could you comment on muscle weakness? You mentioned decreased ATP, but magnetic resonance spectroscopy shows that unless you have hypoxia it’s very difficult to reduce the ATP peaks. What is not unusual is a fall in phosphocreatine, so that you have a decreased reserve and fatigability, but ATP is very hard to reduce unless you compromise oxygenation.

**Dr. Holm:** To the best of my knowledge, the deficit of 2,3-diphosphoglycerate in particular has been more clearly demonstrated as a cause of muscle weakness than the decrease in cellular ATP.

**References**