The Role of Amino Acid Changes in Septic Encephalopathy*

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Introduction

There are several factors which may be important in the altered mental state observed in patients with sepsis. These include a direct central nervous system infection [1–3], endotoxin effects on the brain [4, 5], inadequate perfusion [6, 7], altered metabolism including disturbed plasma and brain amino acid levels [8–17], deranged amino acid transport across the blood brain barrier [15], abnormal levels of neurotransmitters in the brain [8, 16, 17], metabolic disturbances [6], liver insufficiency [8], multiple organ failure [14, 18] or complications of medical therapies.

There are many metabolic causes of an altered sensorium. These include disorders of the liver, kidney, lungs, and pancreas, electrolyte disturbances including sodium, calcium, phosphorus and magnesium, acid-base alterations, hypo and hyperglycemia, hypo and hyperthermia, hypoxemia, exogenous drugs, cofactor deficiencies, and endocrine abnormalities [6, 19–21]. The large majority of these metabolic disturbances can be seen in patients with sepsis [6, 18, 22, 23]. Patients with sepsis often manifest symptoms of encephalopathy including agitation, lethargy, somnolence, disorientation, confusion, obtundation, stupor and coma [8, 12, 16]. Whether the encephalopathy of sepsis is caused by sepsis alone or is a function of other metabolic etiologies has not been determined. In addition, the exact mental changes that occur in sepsis and their etiology are unclear.

Altered Amino Acid Levels and Encephalopathy in Hepatic Failure

Before addressing the altered metabolism present in sepsis it is useful to review the altered metabolism and its relationship to encephalopathy that has been noted and more fully investigated in hepatic failure. The physiologic principles and many of the findings are similar to those found in sepsis. Patients with liver disease are highly catabolic, have few glycogen stores, are glucose resistant, have decreased ketogenesis and use of fatty acids and have extensive muscle protein

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breakdown [24, 25]. Muscle breakdown results in the release into the circulation of large amounts of various amino acids, with the exception of the branched chain amino acids (BCAA) valine, leucine, and isoleucine, which the muscle can oxidize itself [24]. The liver is the principle or exclusive site for the catabolism of the aromatic amino acids (AAA), phenylalanine, tyrosine and tryptophan and other amino acids including methionine, lysine and threonine [24]. Because the dysfunctioning liver is unable to remove these amino acids from the circulation and because of the increased catabolism of BCAA in the muscle, a characteristic amino acid pattern is found in the blood of experimental animals and patients with hepatic insufficiency and encephalopathy. The picture includes an increase in the plasma levels of tyrosine, phenylalanine and methionine, normal or slightly decreased total plasma tryptophan levels with markedly increased free tryptophan levels, and a decrease in BCAA [9, 25–30]. These changes lead to a decreased BCAA to AAA ratio which has been shown to correlate with encephalopathy [27, 28]. The increased plasma levels of AAA correlate with an increased mortality [27]. The changes in AAA levels may be of greater import in terms of encephalopathy than BCAA levels because cirrhotic patients who develop encephalopathy have changes in their CSF to plasma molar ratios of AAA but little change in the ratios of BCAA and other amino acids [31]. Fischer et al. have shown that the changes in plasma amino acid profiles noted above occur to patients with chronic liver disease when they experience acute exacerbations of encephalopathy [25, 28]. Patients with acute fulminant hepatitis have a different profile with an increase in the plasma levels of all amino acids (especially the AAA and methionine) with the exception of the BCAA which remain normal [25, 28].

The changes in plasma amino acids are believed to be important in amino acid transport, brain concentrations of amino acids, brain neurotransmitters and therefore hepatic encephalopathy [24, 32]. The distorted pattern of essential amino acids in hepatic failure results in changes in amino acid availability to the brain. Unlike capillaries in other organs, the junctions between endothelial cells in the brain are tight, so that free diffusion between cells is difficult and a blood-brain barrier is present. Since the blood-brain transport of large neutral amino acids (including the AAA and BCAA) is mediated by a single, common transport system, the brain concentrations of these amino acids as well as other substances, is closely linked to their rate of transport across the capillary membrane [24, 32, 33]. The entry of tryptophan into the brain, for instance, varies directly with total plasma tryptophan content and inversely with the concentration of the other competing amino acids, particularly the BCAA [34]. This same transport system mediates the efflux of glutamine and other neutral amino acids from the brain [32]. Consequently, increased brain glutamine concentrations may also impair the efflux of neutral amino acids from the brain because of the competition for transport sites [32]. In fact, rises in CSF glutamine levels in cirrhotic patients have been shown to correlate extremely well with the grade of encephalopathy [35]. Therefore, the high plasma concentrations of AAA and low plasma levels of BCAA together with the high brain glutamine levels act in concert to raise brain AAA concentrations [32].

In addition to the effect of competition for the transport system on brain am-