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Septic encephalopathy

Etiology and management

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Septic encephalopathy is a reversible dysfunction of the central nervous system not associated with any discernible structural changes, but usually associated with general disturbances in peripheral metabolism. Irritability, agitation, disorientation, confusion, stupor, and even frank coma are common manifestations of septic encephalopathy. Other metabolic encephalopathies are those associated with hepatic dysfunction [1 – 4], renal failure, hypoglycemic coma, and respiratory failure.

It would be useful if all of these metabolic encephalopathies had as their basis a common mechanism. For the purposes of this article, we shall argue for such a universal pathogenesis (especially for septic, hepatic and uremic encephalopathy), although the available evidence is preliminary and might be easily contested.

Etiology of septic encephalopathy

There are at the present time two standard etiologies of metabolic encephalopathy which are discussed. They are: (1) effects of toxins on the central nervous system (CNS); (2) alterations in neurotransmitters.

The first, toxic encephalopathy, is a somewhat self-fulfilling prophecy because of the implication that various unidentified toxins poison the CNS in a nonspecific fashion. Myriads of toxins accumulate in organ failure and presumably, if one were to look for them, such toxins would be present in the septic patient as well. Since the CNS dysfunction which complicates severe sepsis is perhaps no different than the hepatic and renal dysfunction, one might conceivably argue for a toxic basis for the septic encephalopathy. One should point out, however, that as time goes on the various reasons for hepatic and renal malfunction in sepsis are becoming known, and it is likely that the cause for CNS malfunction will also be elucidated.

The neurotransmitter hypotheses, with or without amino acid involvement, have been especially prominent in the elucidation of hepatic encephalopathy. In this article we shall argue for a concurrence of mechanisms in septic encephalopathy. The reason for this is that the metabolic background is quite similar. Both septic and cirrhotic patients are hypercatabolic. Both manifest abnormal plasma amino acid patterns [5, 6], particularly in those amino acids which serve as monoamine precursors. Changes in the blood-brain barrier are common to the two conditions [7, 8]. Finally, changes in CNS neurotransmitters have been described in septic encephalopathy, which are somewhat different but of the same order of magnitude as seen during hepatic encephalopathy [9].

One should also note that in sepsis there is increased catabolism and decreased protein synthesis in all organs so far studied except the liver. It is entirely possible that there may be decreased synthesis of peptides or other neurotransmitters in septic encephalopathy.

Let us now examine specific changes found in septic encephalopathy in an effort to define what is known.

Plasma amino acids

The plasma amino acid pattern in sepsis is characterized by increased aromatic (phenylalanine, tyrosine, tryptophan) and sulfur-containing amino acids (taurine, cysteine, methionine), and normal or slightly reduced branced chain amino acids (BCAA: valine, leucine, isoleucine) [6], a pattern similar to that seen

in hepatic encephalopathy in which the increases in sulfur-containing amino acids are not quite as prominent [5]. The similarity between these two conditions should not be surprising, as hepatic dysfunction occurs early in sepsis and the plasma amino acid pattern may be the most sensitive clinical test of hepatic function [10]. Although interpretation of changes in plasma amino acid concentrations is difficult, since they are the result of many different factors affecting amino acid flux, some of the changes seen during sepsis are consistent with enhanced muscle proteolysis. Thus, increased release of phenylalanine and tyrosine has been demonstrated in catabolic muscle [11, 12], and in a recent study from this laboratory there was a significant positive correlation between plasma concentrations of these amino acids and proteolytic rate in incubated isolated skeletal muscles from septic rats (P. O. Hasselgren et al., unpublished data). Reduced levels of the BCAA probably in part reflect increased oxidation of these amino acids in septic muscle and perhaps fat. Varying degrees of liver failure commonly seen in sepsis also contribute to the changes in plasma amino acids.

That altered plasma amino acids may have a role in the pathophysiology of septic encephalopathy is suggested by studies demonstrating that the degree of encephalopathy could be predicted from the plasma concentrations of cysteine, methionine, phenylalanine, isoleucine, leucine and valine [13]. These amino acids gave a correct classification in 82% of patients without and in 80% of patients with septic encephalopathy. A relationship between plasma amino acids and encephalopathy has also been suggested in liver failure, and although controversial, evidence has been accumulating in support of this hypothesis [14].

Brain amino acids

A link between altered plasma amino acids and encephalopathy may be altered brain amino acids. In recent studies from this laboratory, arginine and serine were decreased while phenylalanine, tyrosine, tryptophan, methionine, cysteine, glutamine and histidine were increased in brain of septic rats [15]. The BCAA isoleucine and leucine were unchanged during early sepsis, but were elevated during late sepsis. These changes in brain amino acid concentrations are similar to those observed after portacaval anastomosis [16] and in hepatic coma [17].

The increased plasma levels of the aromatic amino acids represent one possible reason why their concentrations in brain are elevated. Another mechanism might be a decreased competition among the neutral amino acids for blood-brain transport by the reduced BCAA, which constitute the main competing group. Furthermore, the brain uptake index for neutral amino acids is elevated in sepsis. While the uptake of the basic amino acid lysine was unchanged, brain influx rates for neutral amino acids, phenylalanine in particular, were increased in both early and late sepsis [8]. Similarly, the uptake of leucine and tyrosine by isolated brain capillaries from septic rats was increased, while uptake of lysine was unchanged [8]. Blood-brain transport is also increased in uremic encephalopathy [18].

The increased level of brain glutamine, probably in part reflecting hyperammonemia, contributes to elevated levels of the other neutral amino acids since the carrier system mediating the efflux of glutamine from brain also mediates influx of the other neutral amino acids [2]. The accelerated blood-brain neutral amino acid transport activity in sepsis corresponds well with results in rats after portocaval anastomosis [16].

Brain neurotransmitters

Several amino acids (e.g, tryptophan, tyrosine and phenylalanine) serve as precursors of brain neurotransmitters. Consequently, it is not surprising that altered brain amino acid concentrations give rise to disturbances of central nervous system neurotransmitter profile, both in hepatic [17] and septic [9, 19] encephalopathy. When neurotransmitters were measured in six different brain regions (cortex, diencephalon, hippocampus, striatum, mesencephalon and pons-medulla) of septic rats, evidence of increased indoleamine turnover was found in all regions studied [15, 19]. Thus, the concentrations of tryptophan and 5-hydroxyindoleacetic acid (5-HIAA) were elevated and the serotonin: 5-HIAA ratio was increased, indicating an increased serotonin turnover. Enhanced activity of the serotoninergic pathway is probably one of the mechanisms of inhibited behavioral and motor activity in septic encephalopathy.

Concomitant with the activation of the inhibitory, serotoninergic line of neurotransmitters, the levels of the catecholaminergic neurotransmitters norepinephrine (NE), 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) are reduced [15, 19]. The changes in brain serotoninergic and catecholaminergic neurotransmitters during sepsis are consistent with findings in hepatic [17] and uremic encephalopathy [18].

The high concentrations of tyrosine and phenylalanine in septic brain can give rise to increased amounts of their decarboxylation products, tyramine and phenylethylamine. The β-hydroxylated products of these substances, i.e., β-phenylethanolamine and

octopamine, are weak or "false" neurotransmitters which displace norepinephrine as well as dopamine and epinephrine from neural synaptosomes [20]. This disturbance in neurotransmission is probably one of the mechanisms of hepatic encephalopathy [1]. Interestingly, elevated plasma levels of octopamine and phenylethanolamine have been observed in septic patients [13, 21], suggesting an involvement of these false neurotransmitters also in the pathogenesis of septic encephalopathy.

Although much experimental data indicate that septic encephalopathy is associated with altered brain neurotransmitter profile, especially an increase in the inhibitory, serotoninergic line of neurotransmitters, and the occurrence of false neurotransmitters, other mechanisms may be operational as well. Thus, changes in the number and activity of receptors for inhibitory or excitatory neurotransmitters might take place in sepsis. Energy deficit during sepsis may also result in central nervous system manifestations since the maintenance of membrane potential and many metabolic processes, including peptide and protein synthesis, in the brain are energy requiring.

Management of septic encephalopathy

In a number of previous studies, infusion of BCAA-enriched solutions proved beneficial in hepatic encephalopathy [22–26]. Thus, several of the changes in plasma and brain amino acids and neurotransmitter profile were normalized and clinical improvement was reported following infusion of high-BCAA formulations [22–27]. One of the mechanisms by which BCAA exert their beneficial effect in hepatic encephalopathy is probably to increase competition for neutral amino acid blood-brain transport system, thereby reducing the brain levels of several of the other neutral amino acids, especially phenylalanine. Another mechanism of BCAA may be to reduce muscle proteolysis by which the derangement of plasma amino acids can be lessened.

Since many of the amino acid and neurotransmitter disturbances are similar in hepatic and septic encephalopathy, infusion of BCAA-enriched solutions has been tested in sepsis as well. In septic rats this treatment resulted in reduced brain levels of tryptophan, tyrosine, 5-HIAA and serotonin: 5-HIAA ratio, while norepinephrine was increased in the mesencephalon and pons-medulla [15, 19]. Similar results were observed following the administration of a BCAA-enriched solution to septic guinea pigs (C. A. Nachbauer et al., unpublished data). In that study, reduced level of brain glutamine was also observed with BCAA treatment.

In a previous study, in which a BCAA-enriched solution was administered to a group of septic patients, normalization of the plasma amino acid pattern and reversal of encephalopathy were observed, although other treatments such as antibiotics and abscess drainage were also utilized [6]. These results are in line with recent controlled, clinical studies in which improved nitrogen balance, short turnover plasma protein concentrations and immune function were found in septic patients receiving a high-BCAA formulation [28, 29]. Treatment of patients in renal failure with essential amino acids and hypertonic dextrose also improved CNS status [Abel, unpublished data].

Summary

There are widespread disturbances in hepatic and peripheral metabolism in sepsis. Prominent effects include elevated plasma concentrations of aromatic and sulfur-containing amino acids during sepsis, while BCAA are normal or reduced. These alterations probably in part reflect accelerated muscle protein breakdown and hepatic dysfunction. Concomitant with changes in plasma amino acids, altered brain levels of amino acids and neurotransmitters are observed. Increased brain concentrations of the serotoninergic and reduced levels of the catecholaminergic neurotransmitters, along with the occurrence of false neurotransmitters, may be important factors in the pathophysiology of septic encephalopathy. Although the main objective in the treatment of septic patients, of course, is to remove or drain the septic focus, recent studies have shown that administration of BCAA-enriched solutions may be beneficial in the improvement of metabolic derangements and septic encephalopathy.

It should be emphasized that not a great deal of work has been done in this area, and the above results are preliminary and fragmentary. However, they do at least provide a working hypothesis for testing of another form of metabolic encephalopathy.

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