CRITICAL CARE

COMMENTARY

Does proteolysis explain glutamine release from the septic brain?

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See related research by Berg *et al.*, http://ccforum.com/content/14/1/R16

Abstract

Berg and colleagues report on amino acid exchange across the human brain during endotoxin infusion. Lipopolysaccharide infusion induced a decrease in the ratio between branched chain amino acids and aromatic amino acids, increased unidirectional phenylalanine uptake, and increased net brain glutamine release. Cerebral proteolysis is suggested to play a role, but the question is whether this is the case and why this would happen.

Berg and colleagues report on the net exchange of amino acids and ammonia across the brain in healthy volunteers before and 1 hour after a 4-hour endotoxin infusion [1]. Amino acids and ammonia were measured in arterial and venous plasma, and cerebral blood flow was measured. Lipopolysaccharide infusion induced a decrease in the ratio between branched chain amino acids (BCAA) and aromatic amino acids (AAA). This plasma BCAA/AAA ratio (Fischer ratio) was in the past also studied in patients with liver failure. In analogy to this situation, the decreased BCAA/AAA ratio was mainly the result of a decrease in BCAA and to a lesser degree an increase in phenylalanine. This led to increased arterial delivery of phenylalanine to the brain, altered its unidirectional uptake in the brain, and was accompanied by an impressive net brain glutamine release. The authors speculate that this may be related to increased cerebral protein breakdown and that these changes may adversely affect brain function (for example, sepsis-associated encephalopathy).

Berg and colleagues' study is impressive and one that may be impossible to perform outside Scandinavia. The data are interesting and important, but there are some issues that should be highlighted to put the data in context. These issues relate to the analogy with the situation in hepatic encephalopathy, the accuracy of flux measurements, and the potential role of cerebral protein breakdown.

During liver failure and associated hyperammonemia, ammonia is detoxified mainly in the brain and muscle by the formation of glutamine from ammonia and glutamate. In muscle, BCAA transaminate with α-ketoglutarate, yielding glutamate – which may lower plasma BCAA. Ammonia may then be coupled to glutamate to form glutamine. This glutamine can subsequently be exported from the brain (and muscle), which in essence means loss of glutamate, an important excitatory neurotransmitter. The increased cerebral release of glutamine during hyperammonemia could facilitate exchange of glutamine for neutral amino acids, notably the AAA, by the large neutral amino acid carrier. The increased influx of AAA in the brain would raise the availability of precursors for neurotransmitters. Phenylalanine and tyrosine may thus disturb brain neurotransmission by promoting synthesis of cerebral catecholamines and the false neurotransmitters phenylethanolamine and octopamine. The analogy between the situation during liver failure and the observations by Berg and colleagues during simulated sepsis [1] is striking.

Berg and colleagues did not observe net ammonia uptake by the brain, however, and no change in plasma ammonia was observed. Equally, no net cerebral phenylalanine uptake was observed, despite increased cerebral delivery. The authors calculated unidirectional phenylalanine uptake using a formula derived from the literature, and found this to be increased. The authors propose that the absence of net cerebral phenylalanine uptake after lipopolysaccharide infusion does not refute the hypothesis that phenylalanine has been taken up by the brain. They speculate this may be due to the establishment of a new steady state before the second measurement with elevated levels of phenylalanine in the cerebrospinal fluid. Unidirectional efflux of phenylalanine was not assessed. It should be realized that if net

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exchange remains unchanged and unidirectional phenylalanine uptake increases, then unidirectional phenylalanine efflux must increase to the same extent by definition. The question is whether these net flux measurements are sufficiently robust to pick up small changes that may play a role.

The above certainly holds true for ammonia fluxes. Lockwood and colleagues (reviewed in [2,3]) have shown in situations with relatively low ambient plasma ammonia levels that it is impossible to pick up arteriovenous differences across the brain. This may also apply to the present study.

Berg and colleagues relate the release of glutamine from the brain without concurrent ammonia uptake during sepsis to cerebral proteolysis. Cerebral proteolysis is important in both health and disease, and may play a role in controlling various processes including synaptic transmission [4-7]. At the observed magnitude of glutamine efflux, however, one wonders why a highly conserved and protected organ like the brain would exhibit such pronounced proteolysis following only a brief episode of endotoxemia. What purpose would this serve, teleologically? Would the brain not become atrophic during prolonged sepsis? Would not a more straightforward explanation be that glutamine is transported downhill following a concentration gradient resulting merely from decreased plasma glutamine during sepsis, reflecting a change in pool size of cerebral glutamine?

Future research focusing on in-depth analysis of ammonia and amino acid exchange across the brain should concentrate on three areas. First, because ammonia transport across the blood–brain barrier is both carrier mediated and pH dependent, data are required on the acid–base equilibrium that could be derived from (functional) proton nuclear magnetic resonance measurements. Second, a stable isotope methodology could be used to measure the unidirectional influx of AAA in the brain. Finally, single-photon emission computed tomography scanning may help unravel important details at the tissue level. This approach would also shed light on whether protein breakdown does actually play a role in brain glutamine release during endotoxemia.

Abbreviations

AAA, aromatic amino acids; BCAA, branched chain amino acids.

Competing interests

The authors declare that they have no competing interests.

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