ADVANCES IN NUTRITIONAL RESEARCH

VOLUME 5

Edited by Harold H. Draper

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Preface

Volume 5 of *Advances in Nutritional Research* reflects a strong current interest in the relationship between nutrition and disease. The impact of disease on nutritional status is described for hepatic encephalopathy and cancer and for several ailments of hospitalized children. The impact of nutrition on disease is illustrated using the examples of retinol in tumorigenesis, vitamins A and E in inflammatory lung disease, fatty acids in atherogenesis and obesity, and folate in megaloblastic anemia. The contents will be of particular interest to clinicians and to students of nutritional biochemistry.

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Chapter 1

Nutritional Management of Hepatic Encephalopathy

Robert H. Bower and Josef E. Fischer

1. Introduction

Hepatic insufficiency is a common consequence of critical illness. The liver's multiplicity of processes and its position astride the portal vein, where it receives nutrients and prepares them for distribution to the periphery, make it the central organ in any metabolic scheme. It is precisely this central role which causes the derangements of these processes in hepatic insufficiency to affect all phases of body economy.

The ability of the liver to regenerate is well known. Therapy of the failing liver is aimed at support to allow time for regeneration to occur. Among the factors which are known to influence regeneration (e.g., triiodothyronine, adrenal corticosteroids, growth hormone, insulin, glucagon, "ileal factor" and nutrition), none is more easily manipulated by the physician than nutrition (Fig. 1). The provision of appropriate nutrients not only helps to sustain hepatic function but promotes regeneration as well.

Although the metabolism of all nutrients is deranged in hepatic failure, intolerance to protein most severely limits nutritional support. The provision of adequate protein for protein synthesis is necessary to keep the muscular, respiratory, metabolic, host defense, and immunologic functions of the body intact, as well as to meet the additional demands for repair of injured tissues. However, the

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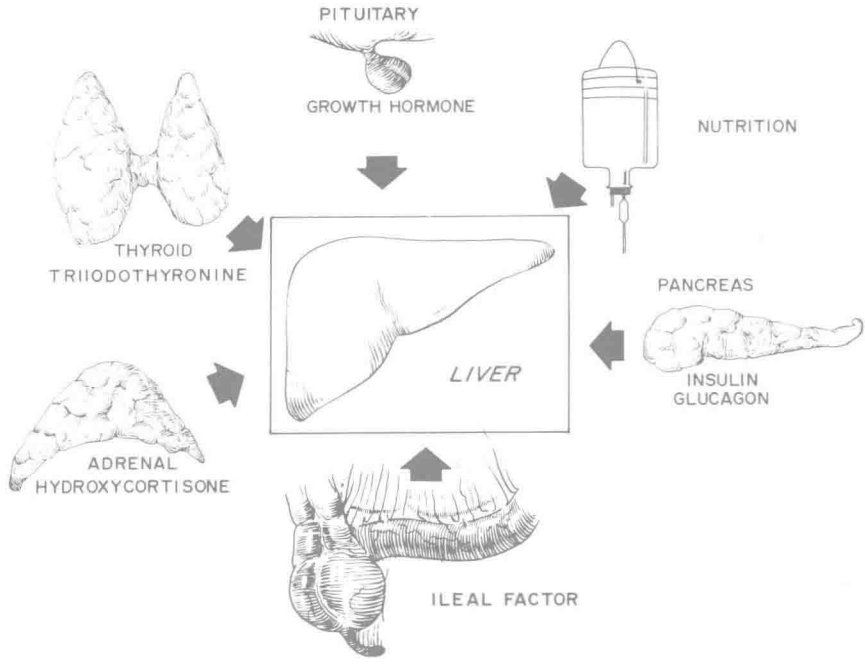

Fig. 1. Among the factors which influence hepatic regeneration, nutrition is the most easily manipulated.

administration of adequate protein to sustain these processes in the patient with hepatic failure is often accompanied by encephalopathy.

Nutritional management of hepatic encephalopathy is aimed at providing sufficient protein to the patient without precipitating encephalopathy. Such an approach requires an understanding of the cause of hepatic encephalopathy.

2. The Nature of Hepatic Encephalopathy

2.1. The Ammonia Concept

The clinical presentation of hepatic encephalopathy may be subtle and varied. Although mania and psychosis are usually prominent, associated disturbances, such as errors in judgment, reversal of day/night rhythm, and mood changes, and postural disorders, such as asterixis, may be less readily apparent. The classic explanation of hepatic encephalopathy has involved ammonia behaving as a "toxin." However, the variety of clinical presentation is unlikely to be the result of a single toxin in the presence of otherwise normal physiology. It is

equally unlikely that derangements in brain energy metabolism would produce such a varied clinical presentation.

According to the classical toxin hypothesis, ammonia, liberated by bacteria in the gut, exerts its toxic influence on the central nervous system (CNS) due to lack of inactivation by the liver. It is often overlooked that ammonia is a metabolite which may arise from protein catabolism, deamination of amino acids by muscle, and endogenous production in the gut, not necessarily from gut bacteria (Hoyumpa *et al.*, 1979). Moreover, there is dissociation of blood ammonia level and the grade of hepatic encephalopathy. Rationalization of this lack of correlation is based on imperfections in measurement. Nonetheless, neither arterial nor venous ammonia levels correlate well with the grade of encephalopathy. Furthermore, the toxicity of ammonia does not correlate with its concentration. Methionine sulfoximine increases the concentration of ammonia in the CNS through inhibition of glutamine synthesis but decreases its toxicity (Warren and Schenker, 1964). In contrast, monoamine oxidase inhibitors decrease blood ammonia concentration but increase its toxicity and the grade of encephalopathy (Dawson and Sherlock, 1957). These observations suggest that ammonia is unlikely to be the sole etiologic agent of hepatic encephalopathy.

Zieve has proposed a synergism hypothesis. According to this theory, in the presence of underlying liver disease, encephalopathy and coma are the result of the synergistic effects of coma-producing toxins and endogenous metabolic abnormalities. Ammonia is considered to be central to the pathogenesis with mercaptans, fatty acids, and endogenous metabolic abnormalities creating an environment in which smaller accumulations of any single substance may produce encephalopathy. Although isolated experiments have implicated some of these pathogenetic factors individually, direct evidence that these biochemical abnormalities are responsible for the abnormalities is lacking (Zieve, 1981).

2.2. The Amino Acid Neurotransmitter Concept

A decade ago, Fischer and Baldessarini proposed that under conditions of decreased hepatic function and shunting of blood around the liver, amines or their amino acid precursors escape inactivation by the liver and flood the central and peripheral aminergic nervous system. In the CNS, these compounds produce the symptoms of hepatic encephalopathy and basal ganglia postural disorders such as asterixis (Fischer and Baldessarini, 1971). Cardiovascular effects such as the high output–low peripheral resistance congestive failure syndrome and the hepatorenal syndrome associated with redistribution of renal blood flow are secondary to loss of catecholaminergic tone in the peripheral autonomic nervous system (Fischer and Baldessarini, 1971; Fischer and James, 1972). This hypothesis was based on observations on experimental animals in hepatic encephalopathy, which displayed imbalances in the central, primitive, and generally midline aminergic system. Norepinephrine and striatal dopamine were decreased while

increases were noted in β-hydroxyphenylethanolamine neuromodulators or neuroregulators, octopamine and phenylethanolamine, and indoleamines, including serotonin (Baldessarini and Fischer, 1973; Dodsworth *et al.*, 1974).

The aminergic nervous system is not arranged in classical anatomic fashion. Rather than ending in classic synaptic relationships, its axons and dendrites end free in the matrix, yet no neuron seems to be more than 30 Å from a nerve ending of the aminergic system. This system has feedback circuits which ramify throughout the CNS (Dismukes, 1977). These extensive ramifications and feedback circuits suggest a neuromodulatory or neuroregulatory role for this system rather than a classical action (Dismukes, 1977).

The monoamine imbalance in the aminergic nervous system in hepatic encephalopathy is due not to the amines themselves entering the brain but to disorders in the metabolism of their precursor amino acids, including phenylalanine, tyrosine, and tryptophan. These aromatic amino acids, along with the branched-chain amino acids (BCAA) valine, leucine, and isoleucine, as well as histidine and methionine, are members of the large neutral amino group. Members of this group compete for a single transport system (System L) which mediates their entry across the blood–brain barrier (Wade and Katzman, 1975). Neutral amino acid disturbances in plasma during encephalopathy include increased aromatic amino acids (phenylalanine, tyrosine, free tryptophan, and methionine) with decreased BCAA (Iber *et al.*, 1957; Svec and Freeman, 1949; Fischer *et al.*, 1974). The deranged pattern of plasma amino acids is the result of hormonal imbalances including a relative lack of insulin and a relative excess of glucagon. Increased levels of epinephrine and adrenocortical steroids, due to their decreased catabolism, augment the hyperglucagonemia to cause sustained gluconeogenesis (Eigler *et al.*, 1979). In addition, failure of energy production in the form of decreased glucose and ketone body production from the failing liver results in further catabolism. The BCAA tend to be consumed locally by muscle and fat for energy production. The aromatic amino acids, which are catabolized primarily by the liver, accumulate in plasma. The resultant excess of aromatic amino acids and scarcity of BCAA in plasma give rise to excessive concentrations of aromatic amino acids within the brain (Rosen *et al.*, 1977; Soeters and Fischer, 1976).

However, abnormalities in the observed concentrations of neutral amino acids within the brain cannot be explained on the basis of plasma competitor ratios alone. Using the technique of Fernstrom and Faller (1978), the brain concentration of amino acids could be predicted by calculating the plasma competitor ratios. The equation accurately predicted the concentration of brain aromatic amino acids in control animals. However, in animals with portacaval anastomosis (PCA), the neutral amino acid concentration exceeded the predicted values in an orderly way (Fig. 2). There is recent evidence to suggest a derangement in the blood–brain barrier and that transport of the neutral amino acids is selectively increased (Cremer *et al.*, 1977). From experiments on animals fol-

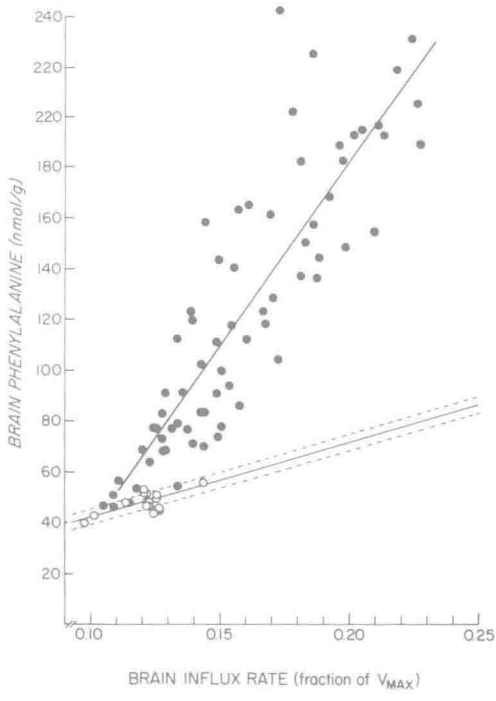

Fig. 2. The observed brain concentration of neutral amino acids, using phenylalanine as an example, is compared with the predicted brain concentration of phenylalanine as calculated from the brain influx rate from the equation of Fernstrom and Faller (1978). The open circles represent sham-operated animals, and the closed circles represent animals which have undergone PCA. Note that the sham-operated animals fall within 1 standard deviation of the predicted brain concentration of phenylalanine as calculated from the brain influx rate. The shunted animals are all above the line but follow another linear function far above that which holds true for the sham-operated animals.

lowing end-to-side PCA and on isolated brain capillaries from normal animals and those with PCA, it appears that ammonia and its intracerebral metabolite, glutamine, are involved in the blood–brain transport abnormality (James *et al.*, 1978; Cardelli-Cangiano *et al.*, 1981). Exchange for glutamine appears to be responsible for the increased velocity of transport of the neutral amino acids into the brain. Ammonia appears to contribute to encephalopathy indirectly by raising the brain concentration of neutral amino acids and altering neurotransmitter metabolism, rather than by exerting any direct toxic effect (James *et al.*, 1979; Jeppsson *et al.*, 1980).

In clinical practice, catabolism, sepsis, starvation, gastrointestinal bleeding, or overdiuresis may result in an increase in aromatic amino acids, a decrease in BCAA or both. The cirrhotic patient is thus sensitized so that any stress will increase the neurotransmitter disorder and increase the tendency toward encepha-

lopathy. The nutritional therapy of hepatic encephalopathy should attempt to decrease the level of aromatic amino acids and to increase BCAA in plasma in order that the patient may tolerate increased amounts of protein without an exacerbation of hepatic encephalopathy.

3. Nutritional Support in Hepatic Insufficiency

3.1. Therapeutic Implications

As has been mentioned earlier, the provision of adequate nutrition is the most easily manipulated of the factors which influence hepatic regeneration. Protein is the most important component of nutrition, not only for repair of the failing liver but for the maintenance of nonspecific host resistance (Alexander *et al.*, 1980). Unfortunately, administration of adequate protein results in encephalopathy. Therefore, despite abnormalities in the metabolism of all nutrients, it is encephalopathy which most severely limits nutritional support of the patient in hepatic failure.

Paradoxically, a diet devoid of protein mimics the amino acid imbalanaces which are seen with a high-protein diet. Gluconeogenesis results in the release of amino acids from muscle and the resultant accumulation of aromatic amino acids. In rats which had undergone PCA, an inverse relationship between the amount of protein infused and the concentration of aromatic amino acids in plasma and brain was observed. Plasma phenylalanine and tyrosine as well as brain octopamine, a false neurotransmitter, decreased as nitrogen balance became positive (Rosen *et al.*, 1978). Even small amounts of protein may be sufficient to stimulate anabolism and to incorporate the aromatic amino acids into protein.

3.2. Therapeutic Options

It becomes apparent that modest amounts of protein are preferable to a protein-free diet. Nearly 50% of patients with impaired but stable hepatic function with little or no encephalopathy may tolerate up to 60–80 g of oral protein or the equivalent of one of the commercially available amino acid solutions. Those patients who are intolerant of protein and become encephalopathic are candidates for special amino acid mixtures.

BCAA-enriched mixtures offer a number of theoretical advantages. Provision of BCAA may decrease the efflux of amino acids across the muscle–plasma membrane (Buse and and Reid, 1975). BCAA may be utilized directly for energy by the periphery. Although they normally provide only 5 to 8% of the total energy output, they may provide a greater percentage under conditions of energy deficit, such as decreased production of glucose and ketone bodies in hepatic failure. The BCAA are the principle competitors of the aromatic amino acids for