**Nutritional aspects of the management of chronic hepatic encephalopathy**

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**Introduction**

Hepatobiliary diseases include all disorders affecting the parenchyma of the liver, the efferent and afferent vascular system, and the biliary tree and may be primary or secondary.

Patients with hepatobiliary disease are encountered frequently in companion animal practice. It is estimated that 2-3% of all animals presented at the University Clinic for Companion Animals in Utrecht have some kind of hepatobiliary disease. Hereditary portosystemic shunts and chronic active hepatitis, which account for the major portion of the patients with hepatobiliary diseases, occur in 2-3% of investigated breeds (Meyer and others 1995), and 0.1-1% of all clinical cases in dogs (Strombeck 1991), respectively. Since the liver plays an essential role in the homeostasis of the metabolism of protein, carbohydrate, and fat, nutritional support plays an essential role for many patients with long standing liver disease.

Irrespective of its initial cause, severe and long standing hepatic dysfunction often leads to just a few syndromes with potentially serious metabolic consequences, i.e., hepatic encephalopathy and cholestasis. The pathophysiology of hepatic encephalopathy and its nutritional support will be discussed.

**Hepatic encephalopathy**

Hepatic encephalopathy (HE) is a commonly occurring syndrome in dogs and cats with liver disease. It is defined as a metabolic dysfunction of the brain resulting from impaired liver function (Conn 1989). HE can be separated into an acute form due to fulminant hepatitis and a chronic form in which abnormal liver perfusion by portal blood is the essential pathogenetic factor. Fulminant hepatitis is rare in the dog and cat. Hence in these species almost all cases of HE are of the chronic form. Therefore, this discussion will only deal with chronic HE which differs pathogenically from acute HE.

The essential factors that must coexist in liver disease in order to develop chronic HE are portosystemic collateral circulation and damage to or atrophy of the liver parenchyma itself. The impaired liver function may be primary, i.e., the cause of the portosystemic shunting, or it may be secondary. In the former there is always portal hypertension leading to the formation of multiple collateral vessels between the vena porta and the vena cava or azygos. In the latter the primary disease is a single congenital portosystemic shunt. Congenital portosystemic shunts (PSS) are inherited and may occur in 2-3% of the population (Meyer and others 1994). They may be either intrahepatic (large and giant breeds, such as the Irish wolfhound and Bernese mountain dog) or extrahepatic (medium and toy breeds, such as the Yorkshire terrier, Cairn terrier, and dachshund) (Rothuizen and others 1982, Maddison 1988 & 1991). In hereditary PSS there is a complete diversion of portal blood via the shunts (Meyer and others 1994), thus bypassing the liver from birth onward and depriving the liver of growth factors, oxygen, and essential nutrients. Consequently, affected animals have a severely underdeveloped liver.

Brain dysfunction in HE is essentially a neurotransmitter dysfunction. The main transmitter systems involved are glutamate, γ-aminobutyric acid and benzodiazepines (GABA/BZ), and dopamine. The complexity of all these changes may be the main reason for the still unresolved pathogenesis of HE (Tab. 1).
Hyperammonemia and glutamate neurotransmission

Ammonia, which is a product of intestinal nitrogen metabolism, normally enters the liver via the portal vein. The hepatic clearance of ammonia is very efficient and under physiological conditions only minute amounts of ammonia enter the systemic circulation and thus reach the astrocytes which form a barrier between the circulation and the neurons in the brain. In the astrocytes, ammonia is incorporated into glutamate to form glutamine, which is catalyzed by glutamine synthetase.

Portosystemic shunting leads to a high concentration of systemic ammonia and the reserve capacity of astrocytic glutamine synthetase is exceeded (Bosman 1991). The excess ammonia then diffuses into the neurons, where it inhibits the enzyme glutaminase which converts glutamine into glutamate. This results in depletion of the neuronal glutamate pool and increase in the cerebral glutamine concentration.

Glutamate is one of the most abundant excitatory neurotransmitters in the brain. The compromised availability of glutamate as a result of hyperammonemia has long been thought to be an important factor in the deranged neurotransmission in HE (Hamberger 1981). However, a whole body of evidence has emerged as to the increased availability of glutamate in the extracellular space and CSF in acute and chronic HE, which could indicate increased glutamatergic neurotransmission (Bosman and others 1992, de Knegt and others 1994). A decreased neuronal reuptake of glutamate has been shown by in vitro studies resembling acute HE (Oppong 1995) and exposure of cultured astrocytes to high ammonia concentrations resulted in a decreased glutamate uptake (Norenberg and others 1992). There is also evidence of decreased hippocampal uptake of glutamate in humans who died in hepatic coma (Schmidt and others 1990).

Hyperammonemia and glutamate neurotransmission

<table>
<thead>
<tr>
<th>Derangement</th>
<th>Cerebral effect</th>
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<tbody>
<tr>
<td>Hyperammonaemia (possibly synergism with mercaptans &amp; fatty acids?)</td>
<td>Decreased glutamate, increased synaptic glutamate, increased glutamine, increased GABAergic tone</td>
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<tr>
<td>Decreased BCAA/AAA ratio</td>
<td>Deranged dopaminergic neurotransmission</td>
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<td>Increased endogenous benzodiazepines</td>
<td>Increased GABA-ergic tone</td>
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The GABA/bz receptor complex

GABA and the GABA/benzodiazepine (BZ) receptor complex are the most abundant inhibitory neurotransmitter system throughout the central nervous system. In the neuron GABA is formed from glutamate. An increased activity of GABA-containing pathways may contribute to the manifestations of HE.

Whether the increased GABA-ergic tone is actually due to an increase in GABA concentration (formed locally or derived from the gut) is disputed (Maddison and others 1987). This has led to the hypothesis that naturally occurring benzodiazepines may play a role in the pathogenesis of HE through positive modulation of the GABAergic tone (Mullen and others 1988). This idea was based on clinical and electrophysiological improvement of acute HE in rats and rabbits with a BZ antagonist and an inverse agonist (Bassett and others 1988, Gammal and others 1990), as well as the discovery of substances that could displace benzodiazepine ligands from its receptor in CSF from rabbits and humans with HE (Mullen and others 1986 & 1989). This concept has resulted in extensive research into the presence and nature of naturally-occurring BZ receptor ligands (also referred to as endogenous benzodiazepines, although their endogenous nature remains obscure (Mullen and others 1996)) in HE during the past decade. Radioreceptor-binding studies have revealed significant BZ receptor binding activity in CSF and/or plasma of patients with various stages of HE and animal models with acute HE (Mullen and others 1989, Basile and others 1990). BZ receptor-binding activity has also been shown in portal and systemic blood of dogs with congenital portosystemic shunts (Aronson and others 1997).

The structure of these naturally occurring BZ receptor ligands remains obscure. They may be related to halogenated 1,4 benzodiazepines, such as diazepam and N-desmethyldiazepam (Basile and others 1991) or to the polypeptide diazepam binding in-
hibitor (DBI) or its metabolic product octodecan europoptide (Rothstein and others 1989). Naturally occurring benzodiazepines may be derived from the diet (Wildmann and others 1987) or from the enteric flora (Yurdaydin and others 1995). Although many studies have shown increased BZ receptor binding activity in HE, there is still considerable debate about the role of benzodiazepines in the genesis of the increased GABAergic tone (Butterworth 1996), since the concentration of these ligands may be too low to play a pathogenetic role (Widler and others 1993). However, irrespective of the role natural benzodiazepines in the increased GABA-ergic tone in HE, avoidance of the intake of benzodiazepines (both dietary or medicinal) is essential to prevent aggravation of the increased GABA-ergic tone.

**Amino acid metabolism and dopaminergic neurotransmission**

Impaired liver function may result in a disturbed metabolism of amino acids and carbohydrates. In health, the neutral aromatic amino acids (AAA) tyrosine, tryptophan, and phenylalanine are efficiently cleared from the portal blood by the liver. In the presence of PSS, these amino acids bypass the liver and hence systemic concentrations are high. Because of a decrease in carbohydrate metabolism and subsequent hypoglycaemia, muscles and other tissues utilize the ketogenic neutral branched chain amino acids (BCAA) leucine, isoleucine, and valine. This leads to a decreased molar ratio BCAA/AAA in the circulation (Iob and others 1970, Fischer and Baldessarini 1971, Aguirre and others 1974, Soeters 1979). Increased concentrations of both insulin and glucagon, together with a low insulin/glucagon ratio, aggravate the decrease in plasma BCAA/AAA (Soeters and Fischer 1986, Fiaccadori and others 1991). In both humans and dogs the normal BCAA/AAA ratio of 3-3.5 decreases to 0.6-1.2 in subjects with HE (Soeters 1979).

Since both AAA and BCAA use the same carrier for neutral amino acids (NAA) to enter the brain (Orlowski and others 1974), a decreased availability of BCAA will lead to an increased uptake of AAA, resulting in a high concentration of AAA in the brain.

In the brain, phenylalanine (phe) can be converted to tyrosine (tyr), which is precursor for the catecholamines (dopamine, norepinephrine). In the several conversion steps from tyr to the catecholamines, the enzyme tyrosine-3-hydroxylase is the rate-limiting step. When there is an excess of AAA, the precursors accumulate and phe and tyr are abnormally decarboxylated to form β-phenylethanolamine and octopamine, respectively. These two abnormal metabolites have been postulated to be “false” neurotransmitters, inertly occupying the catecholamine (preferentially dopamine) receptors and thus preventing catecholaminergic neurotransmission.

Based on the literature and our own findings (Fischer and Baldessarini 1971, Rothuizen and Mol 1987, Meyer and Rothuizen 1994), we hypothesize that in HE there is a blockade of the catecholaminergic and especially dopaminergic neurotransmission due to “false” neurotransmitters, and that this blockade can be reversed by the administration of an excess of branched chain amino acids. In this light, the hypothalamo-pituitary-adrenocortical axis (HPA axis) in the dog may serve as a good indicator for dopaminergic dysfunction, since the pars intermedia (PI) of the pituitary is mainly under dopaminergic control (Kempainen and Sartin 1988). In dogs with HE due to congenital portosystemic shunts or multiple collaterals as a result of cirrhosis, several derangements in the HPA axis have been described. The basal activity of the HPA axis in these dogs was increased, as reflected by increased basal ACTH and cortisol levels in plasma and increased urinary excretion of cortisol (expressed as the urinary cortisol: creatinine (C/C) ratio) (Rothuizen and Mol 1987, Rothuizen and others 1995 & 1996). In addition basal plasma α-MSH levels in these dogs were increased, suggesting higher activity of the PI (Rothuizen and Mol 1987). The normal release of ACTH, αMSH and cortisol after the IV administration of the dopamine antagonist haloperidol was completely abolished in these dogs, which is indicative for a lack of dopaminergic inhibition of the PI, and possibly also the anterior pituitary (Rothuizen and Mol 1987). Thus, these data suggest chronic hypercortisolism due to dopaminergic disinhibition in dogs with chronic HE. It is tempting to suggest a role herein for the increased availability of AAA leading to “false” dopaminergic neurotransmitters. The resulting hyperadrenocorticism may further aggravate the catabolic situation, which is frequently present in subjects with chronic liver disease (Latifi 1991). Thus, we hypothesise that normalisation of the deranged BCAA/AAA ratio may lead to decreased catabolism in chronic liver disease through normalization of the hypercortisolemic state, which is the result of reconstitution of the inhibitory dopaminergic tone in the pituitary.

**Dietary strategy in hepatic encephalopathy**

From the involvement of ammonia in the pathogenesis of HE it can be deduced that protein restric-
tion is a cornerstone in the treatment of HE (de Bruijn 1986, Uribe 1989). However, chronic excessive protein restriction is undesirable, because patients with HE are already in a catabolic state (Rosen and others 1978, Uribe 1989). Apart from the total protein intake, the source and quality of proteins may also affect HE. Meat and blood have long been known to worsen the state of HE, whereas vegetable and milk proteins have been shown to be beneficial (Fenton and others 1966). On the other hand, the use of the latter proteins can be disputed, since they may be a source of benzodiazepines (Bosman, 1991). Therefore, in view of the present state of knowledge, moderate protein restriction (Bosman, 1991). Therefore, in view of the present state of knowledge, moderate protein restriction (protein content not below 11% (D.M. base)) at a rate of 2.1 g crude protein/kg body weight/day seems most desirable (Laflamme and others 1994) for chronic treatment of patients with HE.

The possible involvement of “false” neurotransmitters as a result of excess aromatic amino acids gives another clue for an active dietary strategy. By avoiding AAA and instead feeding protein containing high concentrations of BCAA one could possibly restore the formation of the normal catecholaminergic neurotransmitters and prevent the further production of “false” neurotransmitters. Several studies using high concentrations of BCAA have been performed in humans and experimental animals (Soeters, 1979) with HE, both chronic and acute. Oral or intravenous administration of BCAA normalized the molar ratio BCAA/AAA in serum and cerebrospinal fluid, but the effect on the degree of HE was variable. Of four reviews of clinical trials in humans, one showed a decreased mortality rate and improved mental performance during administration of BCAA (Naylor and others 1989), but the other three reported no detectable influence (Wahren and others 1983, Eriksson and Conn 1989, Morgan 1990). A study in dogs with HE has shown a detrimental effect of the use of a high BCAA diet (Laflamme and others 1993). Further research on the applicability of this concept has to be done to establish the role of BCAA in the diet for HE.

If portal hypertension as a consequence of hepatic disease is a clinical problem, a diet with low sodium and high potassium content is advisable (Laflamme 1988).

We do not recommend the use of homemade diets in such cases, because of the inconvenience and risk for introducing deficiencies in various constituents. Therefore, a low-protein diet containing at least the minimum requirements of the National Research Council (NRC 1985 & 1986) for all macro- and trace elements is the best we can offer to dogs and cats with chronic liver disease at the moment.

Summary

This paper reviews the common pathogenetic mechanisms of chronic hepatic encephalopathy, the neurological syndrome resulting from chronic liver disease with portosystemic shunting. The involvement of several neurotransmitter systems, including the glutamate, *γ*-aminobutyric acid and benzodiazepines (GABA/BZ), and dopamine systems in the pathogenesis of HE is outlined.

From its pathogenesis it can be deduced that moderate protein restriction is the cornerstone of the dietary management of HE. Thus, prevent further accumulation of ammonia, which plays a pivotal role in the derangement in several neurotransmitters can be prevented.

References


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Regional Enteritis in a dog

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