Commentary

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Benzodiazepines in hepatic encephalopathy: sleeping with the enemy

This issue of the journal contains an article on the sometimes controversial area of the pathogenesis of hepatic encephalopathy (see page 861). There is little consensus in the field but most accept that failure of hepatic clearance of toxic compounds originating in the gut causes hepatic encephalopathy. Most evidence suggests that ammonia is the key gut derived toxin mediating hepatic encephalopathy.[1] Initially there was doubt whether ammonia was truly present in blood in vivo. Once this issue was resolved, many studies were undertaken to establish whether the level of hyperammonaemia correlated with the clinical severity of hepatic encephalopathy. The result of these efforts has largely been negative. To quote Stahl's classic study published in 1963, "A considerable overlap still persists amongst the ammonia values of the different degrees of coma."[2] Other gut derived compounds have been proposed as possible mediators of hepatic encephalopathy and include gamma amino butyric acid and benzodiazepines.[3] These benzodiazepines refer to a group of largely lipophillic compounds of low molecular weight, which bind to specific benzodiazepine receptors. Since the discovery of central nervous system (CNS) benzodiazepine receptors in 1977, a vigorous search has been made to identify endogenous ligands that bind to these receptors.[4 5] Unlike the analogous situation with opiate receptors where endogenously synthesised ligands were identified (for example, endorphins and enkephalins) the benzodiazepine receptor ligands may be xenobiotic in origin. That is, these receptors exist in mammalian brain because of exposure to natural benzodiazepines present in food or generated in the gut.[6–8] The endogenous benzodiazepine hypothesis should probably therefore be renamed the "natural benzodiazepine hypothesis" unless subsequently evidence of endogenous synthesis of these compounds becomes available.

The natural benzodiazepine hypothesis simply states that hepatic encephalopathy may arise in a proportion of patients as a result of accumulation of natural benzodiazepines. These are either derived from the diet or arise from in vivo synthesis in the gut (for example, from bacteria or fungi). In the presence of significant liver disease, these compounds escape hepatic clearance, accumulate in the systemic circulation and contribute to hepatic encephalopathy by simulating the action of prescription benzodiazepines like diazepam. Technical issues involved in the extraction and detection of these compounds are substantial. Like ammonia in the past, some laboratories have had great difficulty in finding these benzodiazepines,[9] whereas others have experienced no difficulty.[10] Adding enormously to the complexity in this area, natural benzodiazepines have now been shown to be identical to a number of benzodiazepines formerly thought to be only synthetically manufactured. Distinguishing surreptitious prescription benzodiazepine intake from natural benzodiazepine accumulation may only be feasible when the factors involved in the generation and absorption of natural benzodiazepines are better understood.

This interesting paper by Avallone *et al* has evaluated the presence of endogenous benzodiazepines in patients with liver cirrhosis with and without clinically overt encephalopathy. A novel aspect of the study was the inclusion of a group of subjects who were regular users of commercial benzodiazepines, possibly for insomnia. This places in perspective the benzodiazepine concentrations observed in cirrhotics. Formerly, there has been considerable debate as to whether benzodiazepine concentrations in cirrhotic patients with hepatic encephalopathy are high enough to have any CNS effect.[4] A comparison was made of three groups which included, in addition to the above groups, a healthy control group who were not taking medication. The results are complicated and hence a brief summary is warranted. The authors report detection of benzodiazepines at low concentrations in 44/99 healthy controls. These low levels have been known to be present in normal subjects for years.[4] In cirrhotic patients, analysis of the subgroup without encephalopathy showed detectable benzodiazepines in 49/59 patients. Of the cirrhotic patients with encephalopathy, 49/54 had detectable serum concentrations of benzodiazepines. In cirrhotic patients without hepatic encephalopathy who had detectable benzodiazepines, the concentrations were low and similar to those in the normal controls. In the former, however, the concentrations were much higher and were similar to levels detected in commercial benzodiazepine users. The authors claim no correlation between the grade of hepatic encephalopathy and the presence or concentrations of benzodiazepines detected. A correlation was reported between hepatic function (Child's score) and the level of benzodiazepine. Assays were done for the presence of diazepam and desmethyl diazepam in a sample of healthy controls and cirrhotic patients. Diazepam and desmethyl diazepam were not detected in any of the 12 healthy controls nor in 34 of the 37 cirrhotic patients without hepatic encephalopathy. However, these compounds were detected in 12 of 16 cirrhotic patients with overt hepatic encephalopathy. Finally, diazepam binding inhibitor (DBI), another endogenous benzodiazepine receptor ligand, was assayed in all subjects and similar concentrations were observed in patients with or without hepatic encephalopathy and in the commercial benzodiazepine users. Higher concentrations were detected in the control subjects.

In general, these results are in agreement with most published literature on benzodiazepines in hepatic encephalopathy. The impact of the results may be reduced because of some of the unorthodox approaches in the design of the study and analysis of the data. A major concern is the unusual selection of the subjects in each of the groups studied. It is not clear whether these were randomly selected patients or consecutive patients with liver cirrhosis. Subgroups of patients were studied without clarification of the selection criteria. The use of electroencephalography (EEG) alone for grading the degree of hepatic encephalopathy is unconventional. The study quoted by Avallone *et al* used EEG for grading encephalopathy in patients with acute liver failure and not hepatic encephalopathy in chronic liver disease.[11] The authors'

conclusion that there is no relation between the presence of overt hepatic encephalopathy and benzodiazepines is perhaps not an appropriate interpretation of the data presented. It is clear from the data that benzodiazepine concentrations are higher in patients with hepatic encephalopathy than in those without or in healthy controls. It is also perhaps difficult to conclude that a correlation between the Child's score and benzodiazepine concentrations was present without running a valid statistical test. One may conclude on the basis of the data presented that benzodiazepine concentrations are raised in cirrhotic patients with hepatic encephalopathy to levels similar to those in non-cirrhotic subjects consuming commercial benzodiazepines. Finally the observations by the authors on the lower levels of DBI in commercial benzodiazepine consumers and cirrhotic patients compared with the healthy controls is at variance with other publications on this interesting natural ligand.[5 12] The exact role played by DBI in normal neurotransmission or in disease states is unclear.

One of the limitations of publications on the pathogenic agents in hepatic encephalopathy has been the expectation that the compound evaluated will be the only perpetrator of the change in mental status. A more realistic expectation should be that the factor may be one of many involved in or responsible for the encephalopathy in certain patients but may not be in all. This has been the problem that has plagued the various putative toxins evaluated to date in the pathogenesis of hepatic encephalopathy.[1] Another issue that needs to be noted is that correlation of the levels of an agent with the grade of hepatic encephalopathy may implicate the agent in the pathogenesis and progression of encephalopathy. The reverse may not be true—that is, lack of a correlation does not automatically eliminate the agent being evaluated. The time of sampling, treatment given, and control of precipitating factors may be some of the reasons for an inability to find a correlation between the grade of hepatic encephalopathy and the toxin. In Avallone *et al*'s study no correlation was claimed between benzodiazepine concentrations and the severity of hepatic encephalopathy. The unusual grading of hepatic encephalopathy by EEG without consideration of clinical characteristics may explain this lack. This lack of correlation between clinical grade and toxin level has plagued the ammonia hypothesis too since its description some four decades ago. Explanations for this deficiency may also hold true for benzodiazepines.

Returning to the issue of the source of these benzodiazepines, surreptitious ingestion has been the traditional explanation for the presence of these compounds in blood and at other sites. Avallone *et al*'s study does not resolve the issue of the origin of the benzodiazepines detected in the blood of patients with overt hepatic encephalopathy. The authors have attempted to exclude dietary and surreptitious sources of benzodiazepines but the difficulties with these exclusion methods are enormous. Regardless, one may continue to harbour suspicions that there is surreptitious ingestion of drugs. The higher concentrations of benzodiazepines in cirrhotic patients with hepatic encephalopathy seem to be accounted for by diazepam and desmethyl diazepam. Unfortunately the data presented do not allow calculation of the contribution of these two compounds to total benzodiazepine activity. Accordingly the proportion of benzodiazepine activity due to other compounds in not known. In any event, even the known compounds could have arisen from natural sources or prescription drugs. Some may still consider exogenous ingestion of benzodiazepines to be the major cause of hepatic encephalopathy in cirrhotics and for finding benzodiazepines in their blood. If that were true, then possibly the validity of the results of every study on the pathogenesis of hepatic encephalopathy since 1959, when benzodiazepines became available, would need to be questioned.

Regardless of some of our reservations about this study, a simple fact remains: serum concentrations of benzodiazepines are raised in most patients with hepatic encephalopathy. Until the source and identity of these compounds are fully clarified, their role in hepatic encephalopathy will remain uncertain. Based on the therapeutic response of hepatic encephalopathy to flumazenil, it can be surmised that only 20–30% of patients have hepatic encephalopathy from accumulation of benzodiazepines.[14] As we proceed to investigate the role of benzodiazepines in hepatic encephalopathy, the interaction of these compounds with some of the other known gut derived toxins such as ammonia must be explored too.

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