

Increased availability of central benzodiazepine receptors in patients with chronic hepatic encephalopathy and alcohol related cirrhosis

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Abstract

Background/aims—To measure cerebral benzodiazepine receptor binding using ^{11}C -flumazenil positron emission tomography in patients with stable chronic hepatic encephalopathy, who were also characterised by proton magnetic resonance spectroscopy.

Methods—Six abstinent patients of mean age 61 years with alcohol related cirrhosis and grade I-II hepatic encephalopathy and 11 matched healthy volunteers were studied. Each patient's encephalopathy was defined according to clinical, psychometric, electroencephalographic, and magnetic resonance spectroscopy criteria. Using positron emission tomography, the brain volume of distribution of ^{11}C -flumazenil was obtained; this reflects benzodiazepine receptor availability. Proton magnetic resonance spectra were acquired at 1.5 T using a multivoxel technique; peak area ratios were calculated for choline, glutamine/glutamate, N-acetylaspartate, and creatine resonances.

Results—The mean volume of distribution of ^{11}C -flumazenil was significantly higher in the cortex, cerebellum, and the basal ganglia in the patients compared with controls ($p < 0.001$). In the patient group, the mean glutamine/glutamate to creatine ratio was significantly increased and the mean choline to creatine ratio was significantly decreased in all brain areas, compared with healthy volunteers. However, the N-acetylaspartate to creatine ratio was unchanged compared with controls.

Conclusions—The spectroscopy results reflect the cerebral metabolic derangement associated with hepatic encephalopathy. Stable grade I-II chronic hepatic encephalopathy in alcohol related cirrhosis may be associated with increased cerebral benzodiazepine receptor availability. However, a direct effect of previous chronic exposure to alcohol cannot be excluded.

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Keywords: benzodiazepine receptors; chronic hepatic encephalopathy; ^{11}C -flumazenil; in vivo proton magnetic resonance spectroscopy; positron emission tomography

Hepatic encephalopathy is the term used to describe the neuropsychiatric abnormalities which result from liver failure and/or portosystemic shunting. It is probable that up to 80% of patients with chronic liver disease are affected, but in the majority of these patients, the syndrome is subclinical, with impairment of reaction times in activities of daily living such as driving and operating machinery.¹ In about 30% of individuals, the syndrome may become clinically overt, characterised by global depression of the central nervous system (CNS), with psychomotor retardation and reversible alterations in behaviour, mood, personality, and disturbances in consciousness.²

Patients with hepatic encephalopathy show impairment of psychometric performance and sometimes slowing of the electroencephalograph (EEG) mean cycle frequency (mcf).² In vivo proton magnetic resonance spectroscopy (^1H MRS) techniques have been used to provide objective, non-invasive biochemical information on cerebral metabolic processes in such patients.³ Previous studies have shown that an increase in the glutamine/glutamate MR resonance correlates with clinical severity of encephalopathy.⁴⁻⁶

The pathogenesis of hepatic encephalopathy is unknown, but interest has focused on the potential pathogenic role of circulating toxins and on changes in the functional state of cerebral neurotransmitter systems. γ -Aminobutyric acid (GABA) is one of the main cerebral inhibitory neurotransmitters, and alterations in the activity of the GABAergic system have been causally implicated in the genesis of the condition.^{7,8}

The GABA_A receptor is a hetero-oligomeric complex that contains a GABA binding site, a benzodiazepine binding site (BzR), and a chloride ionophore.⁹ Binding of the neurotransmitter GABA to this receptor induces opening of the chloride channel, resulting in neuronal

Abbreviations used in this paper: ARC, alcohol related cirrhosis; BGO, bismuth germanate; BzR, benzodiazepine receptor; Cho, choline containing compounds; cps, cycles per second; CNS, central nervous system; Cr, creatine; CSF, cerebrospinal fluid; CSI, chemical shift imaging; EEG, electroencephalogram; FMZ, flumazenil; GABA, γ -aminobutyric acid; Glx, glutamine/glutamate; HPLC, high pressure liquid chromatography; mcf, mean cycle frequency; MRS, magnetic resonance spectroscopy; NAA, N-acetylaspartate; NCT, number connection test; PET, positron emission tomography; ppm, parts per million; ROI, region of interest; TE, echo time; TR, repetition time; VD, volume of distribution.

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Table 1 Patient characteristics

Patient	Age (y)	Diagnosis	Child-Pugh class	Albumin (g/l)	Urea (mmol/l)	Oesophageal varices
1	39	ARC	B ₈	41	2.3	Yes (grade 2)
2	64	ARC	C ₁₀	35	5.2	Yes (grade 2)
3	66	ARC	C ₁₀	32	3.5	Yes (eradicated)*
4	59	ARC	B ₈	30	4.3	Yes (grade 3)*
5	52	ARC	B ₈	35	5.4	Yes (eradicated)*
6	68	ARC	C ₁₀	36	5.9	Yes (eradicated)*

Albumin normal range: 35–51 g/l.

Urea normal range: 2.5–6.6 mmol/l.

*Oesophageal varices obliterated by band ligation and/or oesophageal sclerotherapy.

ARC, alcohol related cirrhosis.

membrane hyperpolarisation. BzR agonists potentiate the effects of GABA, while BzR antagonists do not possess intrinsic activity, but act by blockade of endogenous agonist.¹⁰

Postmortem studies on patients dying in hepatic coma have shown increased cerebral benzodiazepine content.¹¹ An upregulation of BzRs could explain the increased sensitivity to benzodiazepines that is characteristic of patients with hepatic encephalopathy and the improvement in arousal following administration of BzR antagonists which has been reported in some studies.^{12–13}

Positron emission tomography (PET) provides a means of studying the integrity of neurotransmitter systems in vivo.¹⁴ ¹¹C-flumazenil (¹¹C-FMZ) is a weak partial agonist that binds specifically and reversibly to the central benzodiazepine receptor site in the GABA_A complex.¹⁵ The total flumazenil (FMZ) volume of distribution (VD) represents both specific and non-specific binding in the area under study. Non-specific binding represents a small fraction in the receptor rich areas, therefore ¹¹C-FMZ VD reflects the availability of BzR binding sites.

We hypothesised that central benzodiazepine receptor binding is abnormal in patients with hepatic encephalopathy. Therefore, in this study, we used ¹¹C-flumazenil and PET to measure BzR binding in the brains of patients with stable grade I–II chronic hepatic encephalopathy. Results were related to clinical and psychometric parameters. ¹H MRS was also undertaken as an objective measure of cerebral metabolic derangements in the patient cohort.

Patients and methods

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki with a priori permission being obtained from the Ethics Committee of the Imperial College School of Medicine, London (REC 4047) and

the UK Administration of Radiation Substances Advisory Committee (ARSAC). All patients were outpatients and were studied on the morning of two consecutive days. Informed consent was obtained 24 hours prior to the study and a detailed neurological examination was performed to exclude any focal neurological signs. On day 1, the patients underwent ¹¹C-FMZ PET. On day 2, in vivo ¹H MRS of the brain was performed.

PATIENTS

Six patients with cirrhosis were studied (four men, two women; mean age 61 years, range 50–70). Table 1 summarises patient characteristics. All patients had biopsy proven alcoholic cirrhosis and had been abstinent for at least six months prior to the study. Patients were excluded from the study if they had renal failure (creatinine greater than 150 µmol/l) or if they were receiving any neurotropic medications. All patients were receiving lactulose for treatment of hepatic encephalopathy.

The baseline mental state was assessed immediately before the PET study, using the West-Haven criteria.¹⁶ Neuropsychometric evaluation involved the number connection tests (NCT) A and B,¹⁶ Digit Symbol Test of the Wechsler Adult Intelligence Scale,¹⁷ and the Digit Copying Subtest of the Kendrick battery.¹⁸ Baseline EEGs were performed using conventionally placed electrodes and the mean cycle frequency (mcf) was obtained. These tests were all performed a maximum of 24 hours before the PET study and are summarised in table 2.

Blood was also drawn for standard biochemical and haematological parameters of liver function and a Pugh's score and Child's grade (as modified by Pugh), reflecting the severity of hepatic dysfunction were calculated for each subject.¹⁹

HEALTHY VOLUNTEERS

Eleven healthy controls (eight men, three women; mean age 55 years, range 46–71) underwent ¹¹C-FMZ PET, and 10 healthy controls (six men, four women; mean age 51 years, range 40–62) underwent ¹H MRS.

¹¹C-FMZ POSITRON EMISSION TOMOGRAPHY

¹¹C-FMZ PET studies were performed in 3D mode using a 953b Siemens/CTI camera. The reconstructed spatial resolution of this scanner, for 31 simultaneously acquired slices, is 8.5 × 8.5 × 5.2 mm at full width half maximum.²⁰

Table 2 Neuropsychological status of the patients studied prior to positron emission tomography

Patient	Mental grade	Asterixis	NCT A	NCT B	Digit copying	Digit symbol	EEG mcf
1	1+	1+	35	85	133	65	6 cps
2	2+	1+	105	240	91	30	6.5cps
3	1+	0	107	195	70	43	7.5cps
4	1+	0	90	180	133	65	9 cps
5	1+	2+	46	190	95	46	8 cps
6	2+	2+	115	250	98	66	8.5cps

Mental grade according to West Haven criteria: 0, no abnormality; 1+, trivial lack of awareness; 2+, lethargy and disorientation.¹⁶Asterixis grades: 0, none; 1+, rare flapping motion; 2+, occasional, irregular flapping motion.¹⁶

NCT, number connection test A and B. Normal range for NCT A: up to 35 seconds; NCT B: up to 81 seconds.

EEG mcf, mean cycle frequency (normal range more than 8.9 cycles per second).

Digit copying and digit symbol tests. Normal range for digit copying: score in two minutes, more than 95; digit symbol: number completed in two minutes, more than 55.

Each patient's head was immobilised while in the scanner using a comfortable moulded head holder and was aligned with the glabella-inion line parallel to the detector rings using a laser beam. Correct positioning of the patient in the scanner was verified with a two minute transmission scan. A 10 minute transmission scan was collected using a retractable external source of $^{68}\text{Ga}/^{68}\text{Ge}$ to correct for attenuation of 511 Kev γ radiation by the brain and skull. Before scanning, a 22 gauge cannula was inserted into the radial artery after subcutaneous infiltration with 0.5% bupivacaine. High specific activity ^{11}C -FMZ (370 MBq, EDE 2.6 mSv) was injected intravenously in tracer doses. The tracer was prepared by a modification of the method of Maziere *et al.*¹⁵ Arterial blood was continuously sampled for determination of the metabolite corrected arterial input function. Radioactivity in arterial blood was assayed continuously using an online bismuth germanate (BGO) detection system.²¹ Discrete samples taken at 2, 3, 4, 5, 10, 20, 35, 60, and 90 minutes after injection were used to calibrate the BGO detector and to derive the metabolite corrected plasma curve from the measured whole curve. Fractional concentrations of hydrophilic metabolites and of unchanged, lipophilic ^{11}C -FMZ were determined by solid phase extraction of plasma followed by high pressure liquid chromatography (HPLC).²² The derivation of a plasma input function from the data obtained from arterial blood was carried out as described previously.²³ Scanning began 30 seconds before tracer injection, collecting 20 serial time frames, over a 90 minute study period.

Data analysis

The 20 frames of the dynamic images were realigned with one another by an automated "least square" technique which reduced any movement artefact during the scan.²⁴ The data were then processed with spectral analysis to generate pixel by pixel parametric images of the volume of distribution (VD) of ^{11}C -FMZ from the brain uptake and plasma input functions.²⁵ Cerebral ^{11}C -FMZ binding is 90% specific and FMZ VD reflects the binding of available BzR (Bmax).²⁶

Image analysis was performed using Analyze software (version 7.5.4 BRU, Mayo Foundation, Rochester, Minnesota) on SUN SPARCstations (Sun Microsystems, Inc., Mountain View, California). Regions of interest (ROIs) were defined with Gaussian clustering using the multispectral voxel classification feature of Analyze, version 7.5.²⁷ Two different FMZ images of the same dynamic ^{11}C -FMZ PET scan (an early blood flow weighted and a late receptor weighted image of ^{11}C -FMZ binding), were used as "multispectral" images and segmented using Gaussian clustering. This automated algorithm allocates each voxel into three different clusters: (1) high blood flow and high FMZ VD; (2) high blood flow and moderate FMZ VD; and (3) low blood flow and low FMZ VD. These clusters correspond to: (1) cerebral cortex; (2) cerebellar cortex, thalamus, and basal ganglia; and (3) white

matter and CSF, respectively. The Gaussian clustering technique calculates means and standard deviations for each cluster, and then models probability distribution of the clusters as a Gaussian function with these parameters. Each voxel is then classified by calculating the probability that it belongs to a particular cluster. A voxel is included in one cluster if it lies within five standard deviations from the cluster's centre. An automated postprocessing iterative relaxation technique smoothes the segmentation, so that classification of voxels which are of uncertain cluster membership will be influenced by adjoining voxels and no voxel is left unclassified. Cerebral cortex was defined over 17 consecutive axial planes in each subject, thalamus over seven planes, and cerebellum over six planes.

Statistical analysis

Mean values for ^{11}C -FMZ VD of the cerebral cortex, thalamic, and cerebellar voxels were calculated from the ^{11}C -FMZ VD image. The results of ^{11}C -FMZ VD obtained from the patients were compared with those of controls using Student's unpaired two tailed *t* test.

IN VIVO ^1H MRS

Cerebral ^1H MR spectra were acquired using a 1.5 T Picker magnet (Picker International, Cleveland, Ohio). An enveloping quadrature transmit/receive coil tuned to 64 MHz was used for all the examinations. Details of methodology used are described elsewhere.⁵ Briefly, a T_1 weighted image was acquired to position a transverse 2 cm slice at the level of the basal ganglia. In the selected slice a 2D CSI technique was used to acquire spectra (TR 1500 ms, TE 130 ms) from contiguous voxels from all brain areas with a nominal voxel size of 4 cc.

Data analysis

All data were analysed by an observer who was unaware of the clinical status of the patient. All spectra were manually phased and processed with an exponential filter of 120 ms in the time domain. Spectra localised to the cortex, cerebellum, and basal ganglia were analysed in each patient. A knowledge based algorithm was used for removal of the water peak and also for baseline flattening.⁵ Cerebral creatine (Cr) was taken as the internal reference. Peak area ratios of N-acetyl aspartate (NAA), choline (Cho), and glutamine/glutamate (Glx) were measured relative to the Cr resonance using the NMR1 spectral processing program (New Methods Research, Inc., E Syracuse, New York) on a SUN SPARCstation 10 (Sun Microsystems, Inc., Mountain View, California).

Statistical analysis

All the data were expressed as mean and standard deviation unless otherwise stated. Differences between groups were tested using the Mann-Whitney U test for the spectroscopy data. Correlations were measured using Pearson analysis. In all cases, a *p* value of less than 0.05 was considered statistically significant.

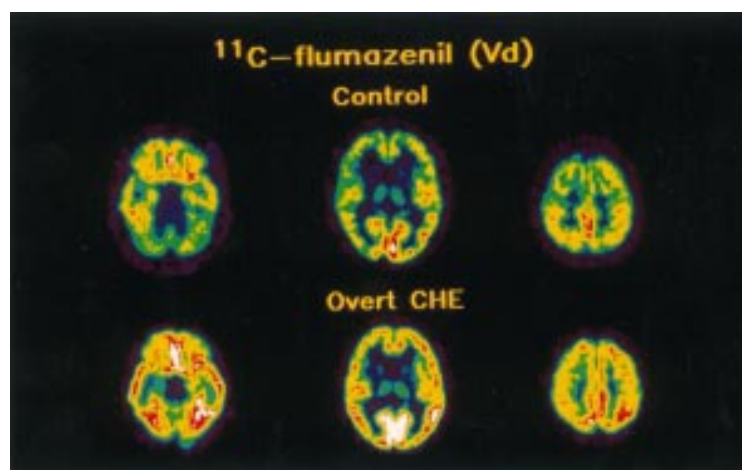


Figure 1 PET images with ¹¹C-flumazenil, showing a significantly higher uptake of the ligand in all brain areas in a patient with grade I hepatic encephalopathy compared with a healthy volunteer ($p < 0.0001$).

Results

¹¹C-FMZ PET

The mean volume of distribution of ¹¹C-FMZ in the cerebral cortex was 5.4 (0.3) in the patients and 4.3 (0.5) ($p < 0.001$) in the healthy volunteers (fig 1). In the cerebellum, ¹¹C-FMZ VD was 4.7 (0.4) in the patients and 3.7 (0.4) in the controls ($p < 0.001$); in the basal ganglia, ¹¹C-FMZ VD was 3.3 (0.4) in the patients and 2.2 (0.3) in the controls ($p < 0.001$). In two patients the cerebellum was only partially in the field of view, preventing calculation of the cerebellar ¹¹C-FMZ VD. Table 3 shows individual patient values for ¹¹C-FMZ VD. Metabolism of the parent ¹¹C-FMZ in the plasma was significantly slower in patients compared with controls (fig 2).

There was no significant correlation between the concentration of plasma albumin and cortical or basal ganglia ¹¹C-FMZ VD.

IN VIVO ¹H MRS

Figure 3 shows ¹H MR spectra from a patient and a healthy volunteer. Table 4 summarises mean values of NAA/Cr, Cho/Cr, and Glx/Cr ratios obtained from the patients and the controls. There was no difference in the mean value of the NAA/Cr ratio in the patient and volunteer populations. The mean Cho/Cr ratio was significantly lower in the cortex, cerebellum, and the basal ganglia in the patients compared with the controls ($p < 0.05$, $p < 0.05$, and $p < 0.05$ respectively). The mean Glx/Cr ratio was significantly higher in the cortex, cerebellum, and the basal ganglia in the patients compared with the controls ($p < 0.01$, $p < 0.01$, and $p < 0.001$ respectively).

Table 3 Volume of distribution of ¹¹C-flumazenil (ml plasma/ml brain)

Subject	Cortex	Cerebellum	Basal ganglia
Patient 1	5.9	4.5	3.6
Patient 2	5.2	5.1	3.1
Patient 3	6.2	—	3.9
Patient 4	5.5	—	3.5
Patient 5	4.8	4.3	2.8
Patient 6	5.0	5.1	2.8
Controls: mean (SEM)	4.3 (0.5)	3.7 (0.4)	2.2 (0.3)

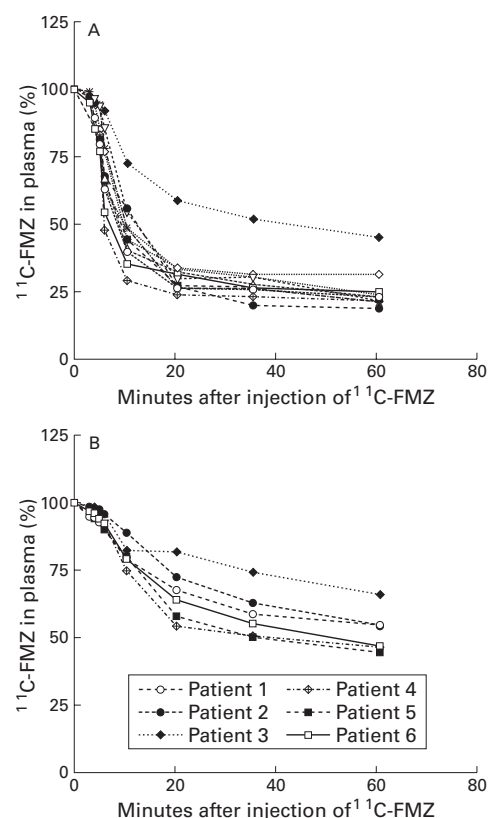


Figure 2 Percentage of unchanged ¹¹C-flumazenil in the plasma of (A) healthy volunteers and (B) patients with hepatic encephalopathy during the PET study (¹¹C decay corrected curve).

Discussion

Research to date has focused on the neurotoxic or neuroactive effects of circulating gut derived toxins and on disturbances in the activity of certain neurotransmitter systems, including the GABAergic system.²⁸ It is of note that no increase in BzR density has been observed in the brains of animals with fulminant liver failure and hepatic encephalopathy,²⁸ but in this study we have shown that ¹¹C-FMZ VD is increased in the cortex, cerebellum, and the basal ganglia of a relatively uniform population of patients with alcohol related cirrhosis, portal hypertension (indicated by presence of oesophageal varices), and stable chronic grade I–II hepatic encephalopathy. This observed change in ¹¹C-FMZ VD is probably related to an increase in availability of BzR receptors. The differences between our study and previous animal data are likely to be owing to the fact that we studied patients with chronic liver disease and stable chronic hepatic encephalopathy, whereas the animal studies were performed with models of acute hepatic decompensation.²⁸

The peripheral metabolism of FMZ was slower in our patient population than in healthy volunteers (fig 2). However, the input function for the calculation of brain VD is the arterial plasma concentration of the parent tracer (¹¹C-FMZ). This calculation therefore, takes into account the metabolic fraction and also the partition of counts between red cells and plasma, but it does not account for protein

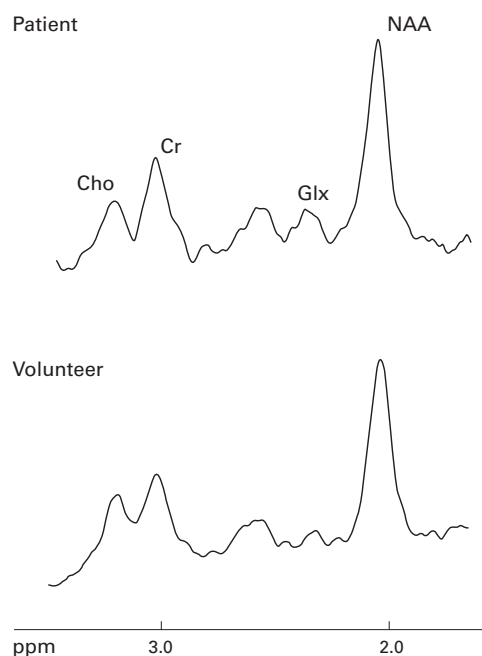


Figure 3 Proton magnetic resonance spectrum from a healthy volunteer and a patient with grade I hepatic encephalopathy. Cho, choline; Cr, creatine; Glx, glutamine and glutamate; NAA, N-acetylaspartate.

binding of the tracer to plasma proteins.²³ Plasma albumin was measured for the six patients with hepatic encephalopathy on the day of the PET scan. Values were within the normal range for four patients and reduced by up to 3 g/l in the other two individuals. There was no significant correlation between the concentration of plasma albumin and cortical or basal ganglia ¹¹C-FMZ VD. Additionally, the majority of circulating ¹¹C-FMZ is unbound, the binding of ¹¹C-FMZ to plasma albumin being only of the order of 40% (S Osman, MRC Clinical Sciences Centre, London; personal communication). Therefore, the increase in mean brain ¹¹C-FMZ VD observed in patients with hepatic encephalopathy does not seem to result from an increase in the plasma concentration of the parent tracer (either as a consequence of slower metabolism or reduced plasma protein binding). It may reflect an increase in BzR availability or a reduction in endogenous BzR agonists. There is evidence for an increase in BzR agonist ligands in the brain in animal models of fulminant hepatic failure (FHF) and humans with FHF and for

an increase in BzR agonist ligands in the body fluids of patients with decompensated cirrhosis.^{11 29 30} Although a secondary effect of binding to free fatty acids cannot be excluded, it is likely that our findings represent an increase in BzR availability.

There is some controversy in the PET literature regarding the concentration of BzR binding in patients with hepatic encephalopathy. Samson *et al* studied four patients with hepatic encephalopathy (and underlying cirrhosis) and showed a significant increase in the cortical uptake of ¹¹C-FMZ.³¹ In their study, these authors did not correct for the plasma metabolite fraction of ¹¹C-FMZ. On the other hand, using the same method of analysis of ¹¹C-FMZ VD as we have used in our study, MacDonald *et al* found a trend towards increased global binding of ¹¹C-FMZ in nine patients with liver disease.³² These results did not reach statistical significance, except in the cerebellum and the thalamus. However, their data are broadly supportive of our findings. The cohort studied by MacDonald *et al* had liver disease of varying severity and differing aetiologies. One of the patients they studied had glycogen storage disease, five patients had a transjugular intrahepatic portosystemic stent shunt insertion, and one patient had a distal splenorenal shunt. Our study was performed on a more homogenous group of patients with alcohol related cirrhosis and well characterised grade I–II hepatic encephalopathy. These differences may account for the more significant increases in BzR binding which we have observed.

Another explanation for the slight differences in the results between our study and that of MacDonald *et al* may be related to the chronic effects of alcohol on benzodiazepine-GABA_A receptor complex function. All our patients were abstinent for a minimum of six months prior to the study, but all had a previous long term history of excess alcohol consumption. Animal studies have shown an increased number (Bmax) of receptor sites in the cortex and cerebellum when rats are subjected to chronic alcohol administration.³³ More recent studies have shown that chronic alcohol consumption may lead to modulation of the GABA_A receptor complex with decreased GABA_A receptor α_1 and increased α_4 subunit gene expression.³⁴ Changes in the GABA_A receptor conformation and function may be responsible for alcohol tolerance, dependence, and withdrawal syndromes,³⁵ but the long term effects on BzR function following prolonged abstinence from alcohol and the confounding effects of hepatic encephalopathy are not known. However, acute alcohol ingestion did not change ¹¹C-FMZ binding in cerebral PET studies of healthy volunteers.^{36 37} Furthermore, in a single photon emission tomography study (SPET), Lingford-Hughes *et al* showed that compared with subjects without a history of alcohol dependence, there was reduced GABA_A-benzodiazepine receptor binding in abstinent alcohol dependent subjects (none of whom had hepatic encephalopathy or a history of it).³⁸ It would therefore seem

Table 4 Comparison of metabolite ratios in patients and controls

Regional metabolite ratios	Controls	Patients	p Value
Cortex			
NAA/Cr	2.2 (0.4)	2.4 (0.5)	NS
Cho/Cr	0.7 (0.3)	0.4 (0.3)	<0.05
Glx/Cr	0.1 (0.1)	0.5 (0.4)	<0.01
Cerebellum			
NAA/Cr	2.1 (0.5)	2.2 (1.0)	NS
Cho/Cr	0.9 (0.3)	0.6 (0.1)	<0.05
Glx/Cr	0.1 (0.1)	0.5 (0.4)	<0.01
Basal ganglia			
NAA/Cr	2.1 (0.5)	2.0 (0.5)	NS
Cho/Cr	0.9 (0.3)	0.6 (0.2)	<0.05
Glx/Cr	0.1 (0.3)	0.6 (0.2)	<0.001

Results expressed as mean (SEM).

Cho, choline containing compounds; Cr, creatine; Glx, glutamine/glutamate; NAA, N-acetylaspartate.

unlikely that the increased ¹¹C-FMZ VD that we observed in our abstinent patients with hepatic encephalopathy is directly related to a sustained effect of alcohol or the effects of abstinence causing increased receptor availability. Further studies should be performed in other homogeneous groups of patients with hepatic encephalopathy, such as primary biliary cirrhosis.

In line with our previous publications, we have also shown in this study that in this group of patients there is a significant increase in the mean Glx/Cr ratio.^{5 39 40} Other investigators have previously shown an elevation in this multi-component glutamine/glutamate resonance, which in patients with hepatic encephalopathy, reflects an increase in cerebral glutamine.^{3 4 41 42} Glutamate is also the substrate for GABA synthesis catalysed by the enzyme glutamic acid decarboxylase. However, direct linkage of glutamine and GABA metabolism is unlikely, because the former is synthesised in astrocytes, whereas the latter is formed in a neuronal pool.⁴³

In conclusion, we have shown that in a relatively homogeneous population of abstinent patients with alcohol related cirrhosis and stable grade I–II hepatic encephalopathy, the ¹¹C-FMZ VD and Glx/Cr ratio are significantly increased, while the Cho/Cr ratio is decreased in the cerebral cortex, cerebellum, and basal ganglia. Although an effect of chronic alcohol consumption cannot be completely excluded, these results suggest that in patients with hepatic encephalopathy and MRS proven metabolic derangement, there is a brain GABAergic system dysfunction as reflected by increased brain BzR availability. Further confirmatory studies must be performed in patients with cirrhosis who do not have a previous history of alcohol excess.

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