GASTROENTEROLOGY 1994;107:1475–1480

Proton Magnetic Resonance Spectroscopy Studies on Human Brain *Myo*-inositol in Hypo-osmolarity and Hepatic Encephalopathy

DIETER HÄUSSINGER, JÖRG LAUBENBERGER, STEPHAN VOM DAHL, THOMAS ERNST, STEPHAN BAYER, MATHIAS LANGER, WOLFGANG GEROK, and JÜRGEN HENNIG
Medizinische und Radiologische Universitätsklinik Freiburg, Freiburg, Germany

Background/Aims: **Recent in vivo studies using proton magnetic resonance (^{1}H-MR) spectroscopy showed low levels of *myo*-inositol in the brain in hepatic encephalopathy; the pathogenetic relevance of this observation is unclear.** ***Methods:*** ***Myo*-inositol and glutamine levels in the brain were studied in vivo by ^{1}H-MR spectroscopy in patients with hypo-osmolarity and hepatic encephalopathy.** ***Results:*** **A patient with severe plasma hypo-osmolarity (222 mOsm/L) had almost undetectable signals for *myo*-inositol and glutamine/glutamate in the brain. Both signals reappeared after normalization of plasma osmolarity, suggesting that both *myo*-inositol and glutamine were released as organic osmolytes from the brain. A decreased cerebral *myo*-inositol signal is also found in low-grade hepatic encephalopathy but is accompanied by an increased glutamine signal. Cirrhotics without hepatic encephalopathy have near-normal inositol signals, and patients with acquired immunodeficiency syndrome encephalopathy have increased inositol signals.** ***Conclusions:*** **The ^{1}H-MR spectroscopic *myo*-inositol signal in the human brain predominantly reflects an osmosensitive inositol pool. It is hypothesized that its depletion in latent hepatic encephalopathy points to a disturbance of cell volume homeostasis in the brain as an early pathogenetic event. This may partly be caused by a hyperammonemia-induced glutamine accumulation in the brain.**

The pathogenesis of portosystemic hepatic encephalopathy (PSE) is still unclear, although a variety of mechanisms have been implicated, such as the action of ammonia and other neurotoxins, disturbances of the blood-brain barrier, and alterations of various neurotransmitter systems and their receptors (for review, see Lockwood[1] and Ferenci et al.[2]). In PSE, no morphological abnormalities of the neurons are detectable, but astrocytes show signs of Alzheimer type II degeneration. Such Alzheimer type II changes can be induced even in cultured astrocytes in vitro by addition of ammonia.[3] In view of the increasing evidence for an important role of astrocytes in maintaining proper neuronal function,[4,5] it was hypothesized that PSE is a primary disorder of the astrocytes, with neuronal dysfunction being a secondary event.[3] Astrocytes are the only cellular compartment in the brain capable of glutamine synthesis,[6] which is the major pathway for cerebral ammonia detoxication. Whereas brain edema in hepatic encephalopathy of acute liver failure is common and eventually determines the patients' final outcome, low-grade (I–III) PSE in chronic liver disease is generally not considered to involve cell swelling in the brain. Proton magnetic resonance (^{1}H-MR) spectroscopy can be used to study metabolic abnormalities in the brain of patients with PSE in vivo. A marked decrease of *myo*-inositol signal and an increase of the glutamine signal were reported using this method.[7,8] Such alteration could also be induced in the rat after portocaval shunting.[9] However, the significance of these findings remained uncertain.

Methods

^{1}H-MR Spectroscopy and Patients

Spectra were acquired on a 2-tesla whole-body system (Bruker S 200F; Bruker Medizintechnik, Rheinstetten, Germany) equipped with actively shielded gradients (10 millitesla [mT]/m, 1-millisecond ramp time). Single-voxel spectroscopy using the point-resolved spectroscopy (PRESS) sequence[10] was used throughout. Voxels were located on coronal and transversal localizer images. An appropriate parietal location was chosen to represent signal from white matter primarily; for grey matter, a location in the occipital lobe was selected. Then 256 averages were acquired from a 2.5 × 2.5 × 2.5–cm^3 voxel. Spectra were read out with an echo time of 30 milliseconds and a repetition time of 1500 milliseconds. For postprocessing,

Abbreviations used in this paper: **AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; ^{1}H-MR, proton magnetic resonance (spectroscopy); NCT, number connecting test; PRESS, point resolved spectroscopy; PSE, portosystemic hepatic encephalopathy; TIPS, transjugular intrahepatic portosystemic shunting.**

0016-5085

Lorentzian line-broadening by 1 Hz was applied. Automated phase correction was applied using a volume-selective water signal acquired before the measurement as reference. For quantification of the spectroscopic changes, the ratio of *myo*-inositol to *N*-acetylaspartate in parietal spectra was used. The error in the individual ratio calculated from the noise of the spectra was 0.03–0.04. In seven healthy individuals, the *myo*-inositol/*N*-acetylaspartate ratio was found to be 0.39 ± 0.03 (mean ± SEM), which corresponds well with the literature value of 0.42.[11]

Informed consent for the ^{1}H-MR spectroscopic examination was obtained from all patients. The grading of hepatic encephalopathy was performed by clinical examination (consciousness, flapping tremor, or personality changes) and psychometric tests (number connection test [NCT] and trail making test).[1] Cirrhotic patients who had no overt clinical symptoms of encephalopathy but who required a time period exceeding the normal range found in an age-matched control group[12,13] to perform the NCT were considered to have latent hepatic encephalopathy. Normal values for the NCT were <37, <46, <53, and <90 seconds for the age groups <29, 30–44, 45–60, and >61 years, respectively.[12,13] In all patients with hepatic encephalopathy in the study, liver cirrhosis was proven by histological examination and was caused by chronic viral hepatitis. Acquired immunodeficiency syndrome (AIDS) encephalopathy was diagnosed from the diffuse leukoencephalopathy in nuclear MR images in patients with AIDS. Seven patients with hepatic encephalopathy and four patients with AIDS who had human immunodeficiency virus (HIV) encephalopathy were studied; representative ^{1}H-MR spectra are shown.

Results

A possible clue to the understanding of the MR spectroscopic *myo*-inositol signal in the human brain came from the ^{1}H-MR spectroscopic examination of a 49-year-old woman with severe hypo-osmolarity (222 mOsm/L) caused by autoimmune Addison's disease (Figure 1). The patient was otherwise healthy, except for asymptomatic cholecystolithiasis, and had adynamia and low serum sodium (101 mmol/L) and chloride levels (86 mmol/L). The ^{1}H-MR spectrum (Figure 1) showed almost undetectable signals for *myo*-inositol and glutamine/glutamate. After standard treatment with glucocorticoids and mineralocorticoids, plasma osmolarity slowly normalized. Repeated ^{1}H-MR spectroscopic examinations showed the reappearance of the glutamine/glutamate signal within 5 days (not shown) when plasma osmolarity was 280 mOsm/L, whereas the *myo*-inositol signal started to reappear after about 2 weeks (recording from October 22 in Figure 1) when a normal plasma osmolarity of 295 mOsm/L was reached; the signal was fully recovered after 7–8 weeks (Figure 1, recording from March 12). The ratio of *myo*-inositol to *N*-acetylaspartate increased from

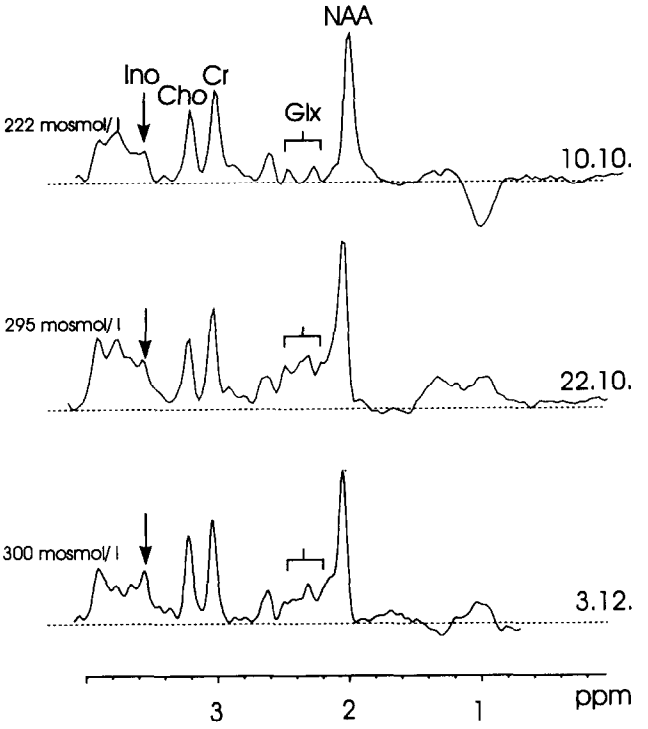

Figure 1. ^{1}H-MR spectra from a 49-year-old woman with severe hypo-osmolarity and after correction of hyponatremia. The first spectrum (October 10, 1993) was taken at a plasma osmolarity of 222 mOsm/L and the others (October 14 and October 22, 1993) during recovery with plasma osmolarities of 280 and 195 mOsm/L, respectively. Proton spectroscopy was performed using a single-voxel selective PRESS experiment[10] with a 30-millisecond echo time. Water suppression was achieved by an optimized 90-90-180 presaturation scheme.[38] Spectra were acquired at parietal and bioccipital locations with identical findings; parietal spectra are shown. Typical voxel size was 2.5 cm^3; 256 signals were averaged to increase the signal-to-noise of the final spectra. A 2-Hz exponential line-broadening was applied before Fourier transformation. All spectra were acquired on a 2-tesla whole-body system (Bruker S 200 F) using a standard head coil. Glx, glutamine/glutamate; NAA, *N*-acetylaspartate; Ino, *myo*-inositol; Cr, creatinine/phosphocreatine; Cho, choline.

0.20 (examination on October 10) to 0.26 (examination on October 22) to a nearly normal level of 0.32 (examination on March 12). Despite the marked abnormalities in the ^{1}H-MR spectrum, only minor neurological abnormalities were detectable on admission (hyporeflexia, discrete psychomotoric slowness). Also, the time required to perform the NCT (31 seconds on October 10 and 25 seconds on November 29) was within the range of the age-matched controls. A marked loss of *myo*-inositol was also observed in a 71-year-old woman with hypo-osmolarity (243 mOsm/L); only short-term follow-up of this multimorbid patient was possible, but when plasma osmolarity increased to 286 mOsm/L, a partial reappearance of the *myo*-inositol signal was observed.

For comparison, ^{1}H-MR spectra from a healthy control individual and cirrhotic patients with latent and grade I–

II PSE are shown in Figure 2*A*–*C*. In line with previous reports of latent and manifest PSE,[7,8,14] a significant decrease of the *myo*-inositol signal and an increased intensity of the glutamine/glutamate signal was consistently found in all seven patients with liver cirrhosis (of viral and alcoholic origin). On the other hand, near-normal cerebral inositol signals were found in a 48-year-old woman with cryptogenic liver cirrhosis without evidence for latent (NCT, 39 seconds) or manifest hepatic encephalopathy (data not shown). This suggests that a marked loss of cerebral *myo*-inositol levels, as detected by ^{1}H-MR spectroscopy, is not a feature accompanying cirrhosis in general but is apparently related to the presence of hepatic encephalopathy. A high sensitivity and specificity of the *myo*-inositol signal for the diagnosis of hepatic encephalopathy in cirrhotics has been reported.[14]

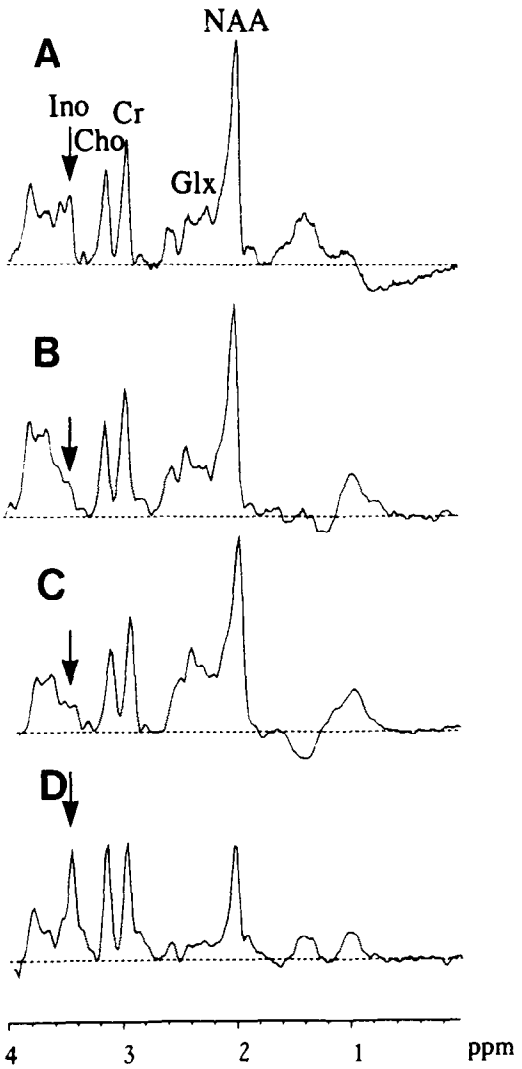

Figure 2. Parietal ^{1}H-MR spectra from (*A*) a healthy person; patients with (*B*) posthepatitic cirrhosis and latent PSE or (*C*) manifest grade I–II PSE; and (*D*) an AIDS patient with HIV encephalopathy. For experimental details, see Figure 1. Patients with HIV encephalopathy had diffuse leukoencephalopathy as detected by nuclear MR imaging, reflecting the gliosis known to be associated with the disorder.[26] Representative spectra are given. The massive increase in the *myo*-inositol signal in HIV leukoencephalopathy was consistently found in all four patients studied up to now. Likewise, the decrease of the *myo*-inositol signal and the increase in glutamine signal was a consistent finding in all patients studied with hepatic encephalopathy, in line with other reports.[8,14] All patients (*A*–*D*) were women and were 40, 71, 60, and 31 years old, respectively; in those with PSE, the cirrhosis was of viral origin.

In the rat, portocaval shunting results in a lowering of brain *myo*-inositol levels.[9] In line with this were the spectroscopic findings on a 46-year-old patient with alcoholic cirrhosis who underwent transjugular intrahepatic portosystemic shunting (TIPS). As shown in Figure 3, a normal spectrum was obtained 3 days before TIPS, whereas the spectrum recorded 1 week after the TIPS procedure showed an increased glutamine/glutamate signal and a slight lowering of the *myo*-inositol signal. The *myo*-inositol/*N*-acetylaspartate signal ratio decreased from 0.33 (3 days before TIPS) to 0.28 1 week after the TIPS procedure. No overt signs of hepatic encephalopathy, except some fatigue, developed. However, the time period required for performance of the NCT was normal (38 and 42 seconds before and after TIPS, respectively). On the other hand, a 69-year-old cirrhotic patient developed grade III hepatic encephalopathy after the TIPS procedure and showed a markedly reduced *myo*-inositol

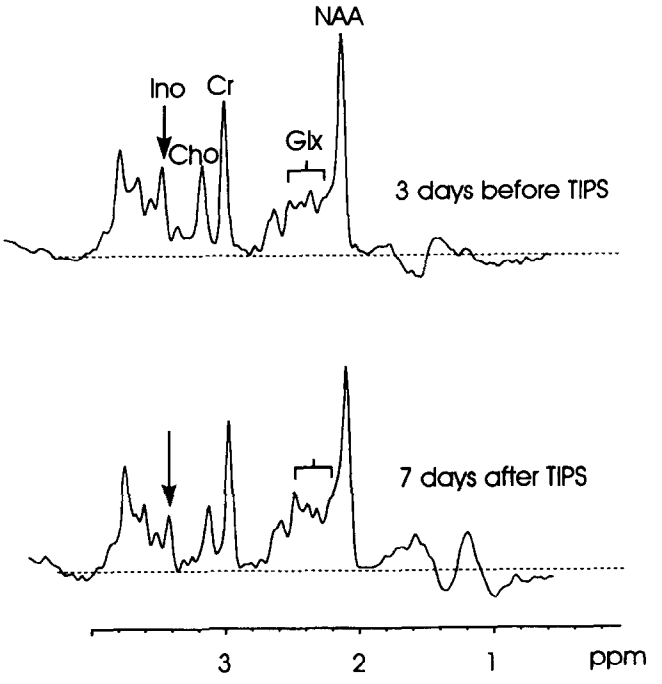

Figure 3. Parietal ^{1}H-MR spectra from a 47-year-old patient with alcoholic cirrhosis 3 days before and 7 days after implantation of TIPS showing some reduction of *myo*-inositol signal after the intervention.

signal in the brain. Reocclusion of the TIPS was followed by a rapid and complete resolution of the encephalopathic symptoms (NCT, 45 seconds) and was accompanied by a partial recovery of the *myo*-inositol signal (not shown).

In contrast to the findings in hepatic encephalopathy, the *myo*-inositol signal was found to be strongly increased in four patients with AIDS who had HIV encephalopathy and gliosis (Figure 2*D*), as evidenced by the diffuse leukoencephalopathy found in nuclear MR images (not shown). This suggests that a loss of *myo*-inositol is not a general feature of all types of encephalopathy.

Discussion

Myo-inositol As an Osmolyte in Human Brain

In general, cell swelling occurs when cells are either exposed to hypo-osmotic environments or when they accumulate osmotically active solutes (for review, see Häussinger and Lang[15]). The latter occurs under the influence of hormones, cumulative substrate uptake into the cell, or enhanced intracellular synthesis of poorly permeant metabolites. Whereas minor alterations of cellular hydration (i.e., cell volume changes below 10%) were recently recognized to act as a physiological signal, which triggers cell function,[15,16] excessive cell swelling is apparently harmful and activates counteracting volume-regulatory mechanisms.[15] In all cell types, such volume-regulatory mechanisms involve ion fluxes, but in some, such as renal medulla cells and glia cells, cell volume regulation is in addition accomplished by use of organic osmolytes, i.e., compounds that are specifically accumulated inside or released from the cells in response to cell shrinkage or swelling, respectively. *Myo*-inositol has been identified as a major osmolyte in renal medulla epithelia and astrocytes.[4,17–19] Uptake and release of *myo*-inositol by these cells as well as the expression of genes coding for *myo*-inositol transporters in the plasma membrane[18,20,21] is regulated by osmolarity. That such osmolyte mechanisms may also operate in vivo is suggested by recent animal experiments, which showed a decrease of the *myo*-inositol content in the brains removed from rats undergoing experimental short-term hyponatremia.[22] *Myo*-inositol release from brain cells in response to hypo-osmotic cell swelling may explain the loss of this osmolyte from the brain of the patient with severe hypo-osmolarity as well as the recovery of the signal after normalization of plasma osmolarity (Figure 1). The observation that also the glutamine/glutamate signal disappeared may indicate that these amino acids likewise acted as osmolytes. The role of *myo*-inositol as an osmolyte in human brain is further suggested by the observation that hypernatremia, which is expected to lead to cell shrinkage and to favor osmolyte accumulation in brain cells, is indeed associated with an increased *myo*-inositol signal as detected by ^{1}H-MR spectroscopy.[23] Thus, the findings strongly suggest that the *myo*-inositol signal picked up by ^{1}H-MR spectroscopy in human brain reflects an osmosensitive *myo*-inositol pool, which is not associated with membrane phospholipids. Our study cannot answer the question which cell types in brain contain this osmosensitive *myo*-inositol pool. However, in vitro studies have shown that astrocytes contain high amounts of *myo*-inositol in contrast to neurons.[23] In line with this, the *myo*-inositol signal is markedly enhanced in Alzheimer's disease[25] and HIV encephalopathy (Figure 2*D*), i.e., disorders known to be associated with neuronal atrophy and gliosis, astrocyte proliferation, and hyperplasia.[26,27]

Brain *myo*-inositol in hepatic encephalopathy. The observations on the patients undergoing TIPS as well as morphological studies in hepatic encephalopathy[1,3] may argue against the possibility that the loss of *myo*-inositol in PSE is caused by a marked reduction of the number of brain cells containing this sugar. In view of the data shown in Figure 1, a more likely explanation is that the markedly decreased *myo*-inositol signals in patients with PSE (Figure 2*B* and *C*) reflect a disturbance of cell volume homeostasis in brain, which may occur already at preclinical stages of PSE in vivo. This disturbance of brain cell volume homeostasis in PSE may at least in part be attributed to an intracellular accumulation of glutamine in response to hyperammonemia. The ^{1}H-MR signal for glutamine is increased with a compensatory loss of *myo*-inositol content in both latent and manifest PSE, with the alterations being less pronounced in the latent stage (Figure 2*B* and *C* and Figure 3). If this interpretation of a volume-regulatory *myo*-inositol release in response to ammonia-induced glutamine accumulation in the brain is correct, and considering the fact that glutamine formation from ammonia is a glial but not a neuronal process,[6] glial cell swelling could be involved. Indeed, cultured astrocytes swell under the influence of ammonia.[28] Because no significant neuropsychiatric abnormalities were observed in the patient with severe plasma hypo-osmolarity (Figure 1) in contrast to the patients with PSE (Figure 2*B* and *C*), it seems that a "deficiency" of cerebral *myo*-inositol per se does not predict major encephalopathy symptoms. However, the *myo*-inositol loss, which likely indicates glial swelling, may, when persistent, lead to sustained disturbances of cell function, with yet unknown consequences for glial-neuronal communication.[5] As a matter of fact, in other

cell types (e.g., hepatocytes), cell swelling, even when <10%, leads to marked alterations of carbohydrate and protein metabolism,[15,16,29–31] gene expression,[32,31] transport processes,[15,16,30,33] protein phosphorylation and intracellular signaling,[30,31] and cytoskeletal organization.[15,30,32] It is not yet clear whether such findings can be extrapolated to brain cells; however, recent in vitro studies suggest that swelling of astrocytes affects transmembrane ion fluxes,[19] acidification of intracellular vesicular compartments,[33] protein phosphorylation,[34] and other intracellular signaling pathways.[19,35] Thus, the hypothesized cell swelling in PSE, as indicated by inositol release, could have important functional consequences despite the absence of clinically overt increases of intracranial pressure. Indeed, effects of cell swelling could explain several established phenomena in PSE, such as disturbances of cerebral glucose metabolism and alterations of blood-brain barrier permeability and glial cytoskeletal proteins. Because astrocyte volume changes may not only be triggered by ammonia but also by hormones, excitatory amino acids,[19] peripheral type benzodiazepines,[36] and mediators of inflammation,[19,37] the hypothesized role of glial swelling in the pathogenesis of PSE would also explain why many investigators have failed to show a correlation between plasma ammonia levels and the severity of PSE.

References

1. Lockwood AH. Hepatic encephalopathy. Boston: Butterworth–Heinemann, 1992.
2. Ferenci P, Püspök A, Steindl P. Current concepts in the pathogenesis of hepatic encephalopathy. Eur J Clin Invest 1992;22:573–581.
3. Norenberg MD, Neary JT, Bender AS, Dombro RS. Hepatic encephalopathy: a disorder in glial-neuronal communication. In: Yu ACH, Hertz L, Norenberg MD, Sykova E, Waxman SG, eds. Progress in brain research. New York: Elsevier, 1992:261–269.
4. Murphy S, eds. Astrocytes—pharmacology and function. San Diego: Academic, 1993.
5. Nedergaard M. Direct signalling from astrocytes to neurons in cultures of mammalian brain cells. Science 1994;263:1768–1771.
6. Martinez-Hernandez A, Bell KP, Norenberg MD. Glutamine synthetase: glial localization in brain. Science 1977;195:1356–1358.
7. Kreis R, Farrow NA, Ross BD. Diagnosis of hepatic encephalopathy by proton magnetic resonance spectroscopy. Lancet 1990;336:635–636.
8. Kreis R, Ross BD, Farrow NA, Ackerman Z. Metabolic disorders of the brain in chronic hepatic encephalopathy detected with ^{1}H-MR spectroscopy. Radiology 1992;182:19–27.
9. Moats RA, Lien YHH, Filippi D, Ross BD. Decrease in cerebral inositols in rats and humans. Biochem J 1993;295:15–18.
10. Bottomley PA. Spatial localization in NMR-spectroscopy in vivo. Proc NY Acad Sci 1987;508:333–348.
11. Kreis R, Farrow N, Ross BD. Localized ^{1}H-NMR spectroscopy in patients with chronic hepatic encephalopathy. Analysis of changes in cerebral glutamine, choline and inositols. NMR Biomed 1991;4:109–116.
12. Schomerus H, Schreiegg J. Prevalence of latent portasystemic encephalopathy in an unselected population of patients with liver cirrhosis in general practice. Z Gastroenterol 1993;31:231–234.
13. Schönleber R. Standardisierung eines psychometrischen Tests zur Erfassung der hepatischen Enzephalopathie. Thesis, University of Tübingen, 1988.
14. Ross B, Shonk T, Moats RA, Jacobson S, Draguescu J, Ernst T, Lee JH, Kreis R. ^{1}H MRS for the diagnosis of subclinical hepatic encephalopathy. Abstr Commun 12th Ann Meet Soc MR Med 1993;131.
15. Häussinger D, Lang F. Cell volume in the regulation of hepatic function: a mechanism for metabolic control. Biochem Biophys Acta 1991;1071:331–350.
16. Häussinger D, Lang F. Cell volume and hormone action. Trends Pharmacol Sci 1992;13:371–373.
17. Lien YHH, Shapiro JL, Chan L. Effects of hypernatremia on organic brain osmoles. J Clin Invest 1990;85:1427–1435.
18. Graf J, Guggino WB, Turnheim K. Volume regulation in transporting epithelia. In: Lang F, Häussinger D, eds. Interactions in cell volume and cell function. Heidelberg, Germany: Springer-Verlag, 1993:67–117.
19. Kimelberg HK, O'Connor ER, Kettenmann H. Effects of swelling on glial cell function. In: Lang F, Häussinger D, eds. Interactions in cell volume and cell function. Heidelberg, Germany: Springer-Verlag, 1993:158–186.
20. Paredes A, McManus M, Kwon HM, Strange K. Osmoregulation of Na^+-inositol cotransporter activity and mRNA levels in brain glial cells. Am J Physiol 1992;263:C1282–C1288.
21. Yamauchi A, Uchida S, Preston AS, Kwon HM, Handler JS. Hypertonicity stimulated transcription of gene for Na^+-myo inositol transporter in MDCK cells. Am J Physiol 1993;264:F20–F23.
22. Sterns RH, Baer J, Ebersol S, Thomas D, Lohr JW, Kamm DE. Organic osmolytes in acute hyponatremia. Am J Physiol 1993;264:F833–F836.
23. Lee JH, Ross BD. Quantitation of idiogenic osmoles in human brain. Abstr Commun 12th Ann Meet Soc MR Med 1993;1553.
24. Brand A, Leibfritz D. Metabolic markers in glial cells for differentiation of brain tissue. Abstr Commun 11th Ann Meet Soc MR Med 1992;649.
25. Miller BL, Moats RA, Shonk T, Ernst T, Woolley S, Ross BD. Alzheimer disease: depiction of increased cerebral *myo*-inositol with proton magnetic resonance spectroscopy. Radiology 1993;187:433–437.
26. Gelman BB. Diffuse microgliosis associated with cerebral atrophy in the acquired immune deficiency syndrome. Ann Neurol 1993;34:65–70.
27. Schipper HM, Liang JJ, Wang E. Quiescent and cycling cell compartments in the senescent and Alzheimer diseased human brain. Neurology 1993;43:87–94.
28. Norenberg MD, Baker L, Norenberg LOB, Blicharska J, Bruce-Gregorius JH, Neary JT. Ammonia-induced astrocyte swelling in primary culture. Neurochem Res 1991;16:833–836.
29. Häussinger D, Roth E, Lang F, Gerok W. The cellular hydration state: an important determinant for protein catabolism in health and disease. Lancet 1993;341:1330–1332.
30. Häussinger D, Lang F, Gerok W. Regulation of cell function by the cellular hydration state. Am J Physiol 1994;267:E343–E355.
31. Meijer AJ, Baquet A, Gustafson L, van Woerkom GM, Hue L. Mechanism of activation of liver glycogen synthase by swelling. J Biol Chem 1992;267:5823–5828.
32. Theodoropoulos PA, Stournaras C, Stoll B, Markogiannakis E, Lang F, Gravanis A, Häussinger D. Hepatocyte swelling leads to rapid decrease of the G-/total actin ratio and increases actin mRNA levels. FEBS Lett 1992;311:241–245.
33. Lang F, Busch G, Völkl H, Häussinger D. Lysosomal pH—a link

between cell volume and metabolism. Biochem Soc Trans 1994;22:504–507.

34. Bender AS, Neary JT, Norenberg MD. Role of phosphoinositide hydrolysis in astrocyte volume regulation. J Neurochem 1993; 61:1506–1514.
35. Bender AS, Neary JT, Norenberg MD. Involvement of second messengers and protein phosphorylation in astrocyte swelling. Can J Physiol Pharmacol 1992;70:S632–S636.
36. Norenberg MD, Bender AS. Astrocyte swelling in liver failure: role of glutamine and benzodiazepines. In: Ito U, ed. Brain edema IX. Vienna: Springer-Verlag 1994:24–27.
37. Bender AS, Rivera IV, Norenberg MD. Tumor necrosis factor α induces astrocyte swelling. Trans Am Soc Neurochem 1992; 23:113.
38. Ernst T. Optimization of water suppression for localized in vivo proton spectroscopy. Magn Reson Med (in press).

Received March 24, 1994. Accepted July 8, 1994.

Address requests for reprints to: Dieter Häussinger, M.D., Medizinische Universitätsklinik Düsseldorf, Moorenstrasse 5, D-40225 Düsseldorf, Germany. Fax: (49) 211 311 8752.

Supported by Deutsche Forschungsgemeinschaft through Sonderforschungsbereich 154, the Gottfried Wilhelm Leibniz-Programm, the Schilling Stiftung, and the Fonds der Chemischen Industrie.