In vivo longitudinal ^{1}H MRS Study of hippocampal, cerebral and striatal metabolic changes in BDL rats

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Introduction

Chronic hepatic encephalopathy (CHE) is a severe neuropsychiatric disorder associated with chronic liver disease (CLD). Previous studies showed that glutamine synthesis and ammonia uptake rates differ in various brain regions leading to a conclusion that spectral information from multiple voxels may be useful for assessment of patients with CHE. To our knowledge, there are no published studies in animal models with CLD and no *in vivo* ^{1}H MRS longitudinal studies assessing the potential brain regional differences. Thus, the aim of this study is to investigate metabolic differences between hippocampus, cerebellum and striatum as key brain regions involved in manifestation of CHE.

Methods

Hippocampus (2×2.8×2mm^3), cerebellum (2.5×2.5×2.5mm^3) and striatum (2.5×2×2.5mm^3) of Wistar male adult rats were scanned longitudinally using *in vivo* ^{1}H-MRS on 9.4 T system (Varian/Magnex Scientific) before and after bile duct ligation (BDL, accepted model of CHE) (**Fig 1A**). Scans as well as blood tests were performed before BDL (scan0) and every two weeks (scan2, 4, 6, 8). MR experiments were performed using the SPECIAL sequence (TE=2.8ms). Metabolite concentrations were calculated by LCModel using water as a reference.

Results and Discussion

All BDL rats showed significant increase in plasma bilirubin proving the presence of CLD. Increase of blood ammonia was observed and it correlated significantly with brain glutamine (Gln) for all three mentioned brain regions (**Fig 1D**). Increase in brain Gln concentration was observed in all brain regions reaching significance already at week4 (**Fig 1B**). Gln increase in cerebellum was the most pronounced (reaching 142% increase at week8) (**Fig 1B-C**). As expected, the main brain organic osmolytes followed a similar trend of decrease in concentration as a response to Gln increase (osmoregulation): taurine (Tau), creatine (Cr) and myo-inositol (Ins) displayed the decreasing trend for all mentioned brain regions, being the most significant for cerebellum (**Fig 1C**).

Conclusion

This is the first study showing *in vivo* longitudinal analysis of metabolic response in three different brain regions to CHE. Although, the same tendency in metabolite changes was measured for the three brain regions, we demonstrated that cerebellum shows the strongest metabolite changes followed by hippocampus and finally by striatum where the changes were minor. Our results prove a different susceptibility of brain regions to CHE.

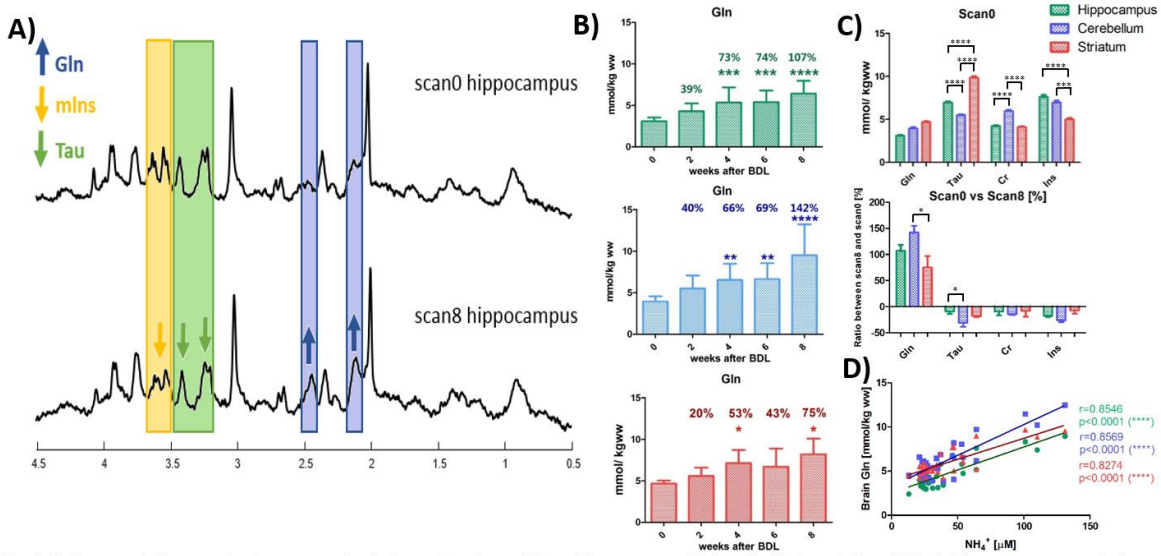

Fig. 1 A) Representative spectra from one animal at scan0 and scan8 from hippocampus. B) Longitudinal evolution of Gln in hippocampus, cerebellum and striatum (One-way ANOVA, Bonferroni correction). C) Graphs represent the evolution of main metabolites in different brain regions at scan0 (known brain regional differences) and scan8 vs scan0 (previously unknown brain regional response to CHE) (Two-way ANOVA). D) Positive correlation between increase of blood NH_4^+ and brain Gln during evolution of CLD in BDL rats.

Acknowledgements: *SNSF project no 310030_173222/1 and the CIBM (UNIL, UNIGE, HUG, CHUV, EPFL, the Leenaards and Jeantet Foundations*