Effects of probiotics and antibiotics for the treatment of chronic hepatic encephalopathy in different brain regions: a longitudinal in vivo ^{1}H MRS study.

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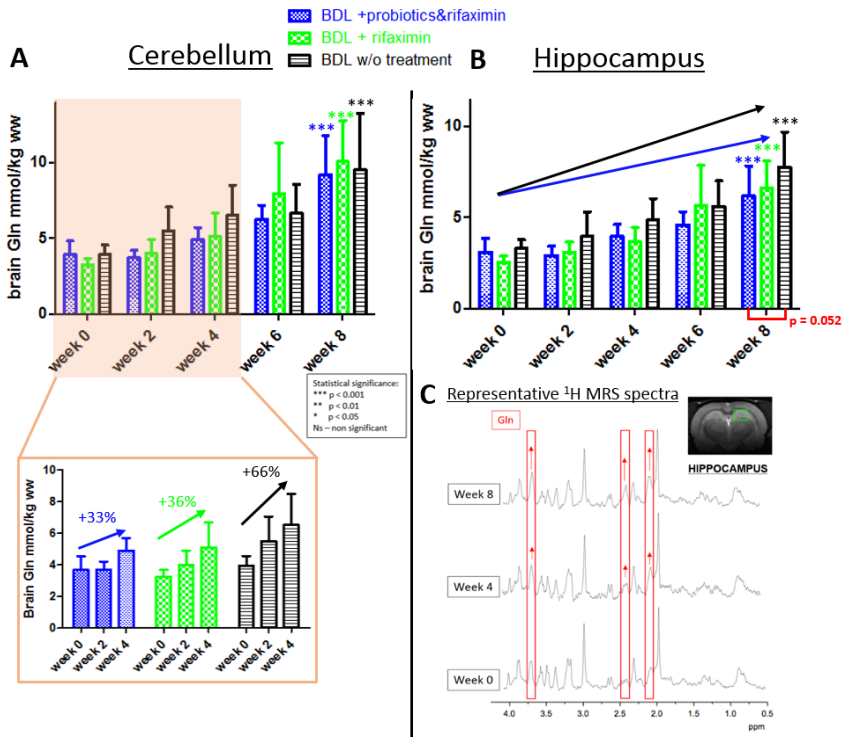
Introduction Chronic hepatic encephalopathy (HE) is a severe complication of chronic liver disease (CLD), and finding the right treatment to reduce HE episodes before liver transplant remains a challenge. Both rifaximin (non-absorbable antibiotic) and probiotics are currently used to reduce HE symptoms, but their precise effect on brain metabolites have never been studied. Our aims were first to assess *in vivo* and longitudinally the effect of the combination of probiotics and rifaximin on bile duct ligated (BDL) rats, a model of chronic HE, on different brain regions; and to compare these results to groups of non-treated/rifaximin-only treated rats[1,2].

Methods *In vivo* ^{1}H-MRS at high field (9.4T) combined with biochemical tests (plasma NH_4^+ and bilirubin) were used. Metabolites evolution was studied using the SPECIAL sequence (TE=2.8ms) in hippocampus (2x2.8x2mm^3) and cerebellum (2.5x2.5x2.5mm^3). Metabolite concentrations were estimated using LCModel and water as internal reference. Adult Wistar rats(n=9) underwent BDL[3,4]. They were scanned before BDL (week0) and at weeks 2,4,6, and 8 after surgery. Probiotics administration (VIVOMIXX® in EU, 60 billion bacteria/kg of rat) started two weeks before BDL-surgery until the end of the study. Rifaximin (15.7mg/kg/day) was administered orally twice daily starting 2 weeks after BDL-surgery.

Results & Discussion All rats displayed the characteristic rise in plasma bilirubin, regardless of treatment group, as well as a similar ammonium increase. The characteristic pattern of chronic HE is visible in the high quality spectra (**C**): a gradual increase of brain Gln as a result of ammonia detoxification by glutamine synthetase enzyme followed by a gradual decrease in the other brain osmolytes (Ins,Tau,tCho) and a later decrease of neurotransmitter Glu and of Cr. The combination of probiotics and rifaximin significantly improved some of the neuro-metabolic changes associated with chronic liver disease at early stages of HE in cerebellum: +33% increase in brain Gln in the 'probiotics+rifaximin' treated group vs + 66% in the non-treated group at week 4 (**A**). Moreover, the decrease of Cr, accepted for its role in energy metabolism, osmoregulation and potentially, neuroprotective[5], was less marked in the 'rifaximin+probiotics' treated group (-4%) compared to non-treated rats (-14%) at week 4 in the cerebellum. In the hippocampus, rats receiving both probiotics and rifaximin exhibited a smaller increase in brain Gln even at week 8 after BDL compared to non-treated rats (+99% vs +136%) (**B**). Finally, the administration of rifaximin associated with probiotics showed more beneficial effects than rifaximin only.



Conclusion Some promising changes were induced in the neurometabolic profile of rats with CLD who were treated with the probiotics VIVOMIXX and rifaximin (Gln, Cr). Cross-resistance is a major concern in long-term rifaximin administration and the combination between probiotics and antibiotics is very attractive as both could be used alternately to avoid multiresistant organisms.

References [1]Cudalbu et al, Metab Brain Dis 2012; [2]Flatt et al, ISMRM 2016, [3]Biecker et al, J Pharmacol Exp Ther 2005; [4]Butterworth et al, Liver Int 2009;[5]Braissant, MolGenetMetab 2010.

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