Prebiotic lactulose as efficacious microbiota and metabolite modulator in cirrhosis environment

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Abstract

Gut microbiota has a fundamental role in the pathogenesis of liver cirrhosis as well as their complications as in the case of hepatic encephalopathy (HE). HE is a spectrum of neurocognitive impairments with a complex pathogenesis, where ammonia and other gut microbiota by-products have a fundamental role in its development. Current HE clinical treatment is mainly based on manipulating the gut microbiota and ammonia production/absorption using prebiotic lactulose, antibiotic rifaximin and probiotic VSL#3. Here we investigated the modulation of gut microbiota, in terms of microbial composition and metabolism, upon fermentation of lactulose, rifaximin and VSL#3, using in vitro anaerobic pH-controlled batch cultures inoculated with faecal microbiota of cirrhotic patients.

In vitro fermentations were perfomed over 24 hours. Flow cytometry (FISH/FCM) was used to accurately enumerate different bacterial species and genera, while bacterial microbiota community structure was analysed using high-throughput sequencing of the 16S rRNA gene. Modification in ammonia concentration and SCFA content were determined across the experiments.

Over time, cirrhotic microbiota responded dynamically to the treatments. In particular, significant differences (PERMANOVA Weighted/Unweighted/Bray-Curtis estimators) were observed after 24h. The main taxa associated with decompensated cirrhosis, were reduced with lactulose. At the same time, taxa associated with healthy conditions, such as Lachnospiraceae, Ruminococcaceae, Blautia, Bifidobacterium and Faecalibacterium, were promoted as confirmed by the Indicator Species Analysis. Lactulose alone or in combination with the probiotic VSL#3 led to an increase production of SCFA and decrease in ammonia production. These shifts in metabolite production are indicative of carbohydrate fermentation and are consistent with improved gut health and reduced risk of HE.

We demonstrated that lactulose is able to significantly increase the relative abundance and absolute numbers of bifidobacteria, which was associated with an increased production of SCFA and a reduction in ammonia content. Future investigations should assess the molecular pathways that are involved in the modulation of gut microbiota and its metabolic reprogramming while translational studies should examine the clinical potential of this in vitro observations.

Keywords

biochemical phenomena | brain diseases | brain diseases, metabolic | carbohydrate metabolism | carbohydrates | cell separation | central nervous system diseases | chemical phenomena | chemistry techniques, analytical | clinical laboratory techniques | cytological techniques | cytophotometry | diagnosis | diagnostic techniques and procedures | digestive system | digestive system diseases | disaccharides | fermentation | flow cytometry | fluorometry | hepatic encephalopathy | hepatic insufficiency | heterocyclic compounds | heterocyclic compounds, 4 or more rings | heterocyclic compounds, fused-ring | investigative techniques | lactams, macrocyclic | lactulose | liver | liver cirrhosis | liver diseases | liver failure | luminescent measurements | macrocyclic compounds | metabolic diseases | metabolism | nervous system diseases | nutritional and metabolic diseases | oligosaccharides | photometry | polycyclic compounds | polysaccharides | rifamycins | rifaximin | sugars