Short-Chain Fatty Acids in the Gut-Brain-Liver Axis: Implications for Hepatic Encephalopathy

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Hepatic encephalopathy (HE) is one of the serious complications of liver cirrhosis, characterized by a broad spectrum of neuropsychiatric symptoms, ranging from subtle cognitive impairment to coma, due to brain dysfunction associated with acute or chronic liver failure and/or portosystemic shunting. Globally, the prevalence of hepatic encephalopathy (HE) is reported to range from 20% to 80% in patients with liver cirrhosis, depending on whether the assessment includes minimal (MHE) or overt (OHE) forms.[1] In Indonesia, the true prevalence of HE is difficult to determine due to diagnostic challenges, with estimates ranging from 30 to 84%. At Cipto Mangunkusumo General Hospital, the prevalence of HE in 2009 was 63.2%.[2]

In recent years, evidence has highlighted the role of the gut microbiota in the pathogenesis of hepatic encephalopathy (HE), a concept now widely referred to as the "gut–liver–brain axis." Studies consistently show that patients with cirrhosis experience significant deterioration in gut function and marked alterations in microbial composition due to dysbiosis. Multiple contributing factors, including reduced intestinal motility, small intestinal bacterial overgrowth (SIBO), and impaired bile acid flow due to enterohepatic circulation, further disrupt the gut environment and promote bacterial imbalance.[3]

The gut–liver–brain axis describes the communication among the stomach, liver, and brain through interconnected pathways involving the microbiota, immune signaling, microbial toxins, and neural circuits. In HE, dysbiosis increases intestinal permeability, facilitating bacterial translocation and systemic inflammation, which worsens hepatic injury. Impaired liver detoxification leads to hyperammonemia, allowing ammonia to cross the blood–brain barrier, disrupt astrocyte function, leading to cerebral edema and cognitive impairment. Furthermore, the vagus nerve plays a role as a critical conduit for transmitting gut-derived signals to the brain, modulating neuroimmune and neuroendocrine responses that further influence HE dev elopment.[3–6]

Short-chain fatty acids (SCFAs) are gut microbial-derived metabolites that provide numerous health benefits. SCFA has been demonstrated to impact gut barrier function, immunomodulation, and glucose homeostasis. The role of SCFA in gut health is achieved through several mechanisms, including mucus production, maintenance of the intestinal barrier, and protection against inflammation.[7] SCFAs exert their effects in the gut through specific transporters on the colonic epithelium, which can be categorized into three major groups: proton-coupled transporters (MCT1, MCT4), sodium-coupled transporters that rely on two sodium ions (SMCT1), and ATP-dependent transporters such as ABCG2/BCRP. SCFA production varies across the lifespan, influenced by age-related shifts in the gut microbiota.[8]

Several studies have shown the significant association between gut dysbiosis and the development of acute decompensation of cirrhosis.[9,10] Intestinal bacterial overgrowth

and dysbiosis emerge as chronic liver disease progresses, both contributing to and worsening clinical decompensation. Cirrhosis is associated with gut dysbiosis, characterized by an increased abundance of Fusobacteria, Proteobacteria, Streptococcaceae, and Enterococcaceae, accompanied by reduced levels of Bacteroidetes, Ruminococcus, Roseburia, Veillonellaceae, and Lachnospiraceae.[11] The alterations in gut microbiota may lead to a decrease in SCFA, which has been associated with liver inflammation and steatosis.[12] As microbial metabolites, SCFAs travel from the gut to the CNS, traverse the blood-brain barrier through systemic circulation, and serve as signaling compounds that regulate host metabolic and immune functions.[13] Low levels of SCFA have been linked to the development of HE through the enhanced neurotoxin transfers, weakened gut barrier, and increased intestinal permeability, although the exact underlying mechanism remains largely unexplored.[14]

In this issue, Ferdianto et al. conducted a cross-sectional observational study comparing the amount and composition of fecal SCFA in cirrhotic patients with and without HE. The study revealed no significant difference in SFA levels between HE and non-HE groups; however, the HE groups demonstrated higher levels of total SCFA, acetate, and butyrate compared to the non-HE groups. While this study contributes valuable early evidence from an Indonesian cohort, several important limitations should be acknowledged. First, the diagnostic approach for covert or minimal HE requires clarification. The authors did not explicitly state the neuropsychological tools and specific criteria used. Clear definitions are essential, as minimal and covert HE is highly sensitive to the choice of diagnostic method and can substantially influence group classification. Second, although SCFAs represent key microbial metabolites, the study did not explore the underlying microbiome composition. Without bacterial taxonomy or species-level data, it remains difficult to determine whether differences in SCFA levels truly reflect gut dysbiosis or altered microbial diversity. SCFA concentrations may be influenced by multiple factors, and therefore, inclusion of metagenomic or sequencing data would strengthen the mechanistic interpretation and allow linking specific bacterial taxa with cognitive impairment. Future studies that include larger and more heterogeneous cohorts, alongside integrated analyses of microbiome composition and validated neurocognitive testing, will be crucial to validate the role of SCFAs in HE development.

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