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Protective Effects of Butyrate Supplementation Against Inflammation and Weight Gain in C57BL/6 Mice Fed a Cafeteria Diet

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Diets rich in sugar and fat, combined with low fiber intake, have detrimental effects on gut health. The gut microbiota ferments fibers into short-chain fatty acids (SCFAs), such as butyrate, which exhibit anti-inflammatory properties and contribute to immune homeostasis. This study investigated the protective effects of butyrate supplementation in C57BL/6 mice fed a cafeteria diet, a model mimicking Western dietary patterns. Butyrate was encapsulated using ionic gelation with HEC (hydroxyethyl cellulose) in collaboration with the Nanomaterials & Nanotoxicology research group at UNIFESP-SJC. Mice were divided into four groups: (A) control (DP) fed a standard diet, (B) cafeteria diet (DC) without supplementation, (C) cafeteria diet supplemented with butyrate (BUTHEC; 8g/kg), and (D) cafeteria diet supplemented with fiber (FIBER; 9.6g/kg). Mice were monitored for weight gain and blood glucose levels over 60 days. After treatment, tissue samples (liver, intestines, adipose tissue, and feces) were collected for analysis. Gene expression was evaluated via qPCR, focusing on intestinal and hepatic markers associated with inflammation, glucose metabolism, and gut barrier integrity. Results showed that the BUTHEC group consumed more food than the other groups (BUTHEC vs. CF: $p=0.0038$, BUTHEC vs. FIBER: $p=0.00385$) but paradoxically exhibited lower weight gain compared to the FIBER group ($p=0.0326$). Gene expression analysis revealed that butyrate supplementation increased the expression of *Alpi* (intestinal alkaline phosphatase), *Tjp1* (tight junction protein), *Ffar2*, and *Ffar3* (SCFA receptors) in the ileum compared to the cafeteria diet group. Notably, *Alpi*, induced by both butyrate and fiber, likely reduced inflammation by neutralizing bacterial endotoxins. Furthermore, butyrate-specific induction of *Tjp1* suggested improved gut barrier integrity, potentially reducing intestinal permeability and systemic inflammation. In the liver, butyrate supplementation led to a significant downregulation of CD36, a gene involved in lipid uptake and metabolism, highlighting its role in modulating hepatic lipid homeostasis. The reduced expression of CD36 likely contributed to the observed attenuation in weight gain by limiting lipid accumulation and improving metabolic efficiency. Notably, while both butyrate and fiber influenced overlapping pathways, the BUTHEC group exhibited unique and pronounced metabolic advantages. These included not only protection against excessive weight gain but also enhanced regulation of inflammatory pathways and improved glycemic profiles, underscoring the specific benefits of butyrate beyond those provided by dietary fiber alone. These findings underscore the therapeutic potential of butyrate as a dietary supplement to counteract the deleterious effects of high-fat and high-sugar diets, particularly in the context of modern dietary patterns linked to metabolic disorders. By improving intestinal barrier function, modulating gene expression

related to inflammation, and reprogramming hepatic lipid metabolism, butyrate offers a multifaceted approach to addressing obesity, insulin resistance, and other metabolic dysfunctions. While these preliminary results are compelling, further investigations are essential to validate these outcomes, including detailed histological analyses of liver and intestinal tissues. Additionally, longitudinal studies exploring the long-term impact of butyrate supplementation on metabolic health are warranted. These insights could pave the way for the development of innovative functional foods and nutraceuticals aimed at preventing and managing metabolic disorders, such as obesity, type 2 diabetes, and metabolic dysfunction-associated steatohepatitis (MASH).

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