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Probiotic *Lactobacillus rhamnosus GG* culture supernatant improves energy expenditure and glucose tolerance in high-fat-high-fructose fed mice exposed to chronic intermittent hypoxia through regulation of intestinal microbiota and bile acid homeostasis

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Background Obstructive sleep apnea syndrome (OSAS) has been recently connected to metabolic disorders such as nonalcoholic fatty liver disease (NAFLD) and type 2 diabetes, which is characterized by gut dysbiosis in recent studies. Our previous studies have demonstrated that the probiotic *Lactobacillus rhamnosus* GG cultural supernatant (LGGs) prevents alcoholic liver disease (ALD) and fructose-induced NAFLD. In the current study, we aimed to examine the effects of LGGs on glucose metabolisms and body energy expenditure in mice fed a high-fat-high-fructose (HFHF) diet and exposed to chronic intermittent hypoxia in order to understand the underlying mechanisms.

Methods C57BL/6 mice were fed HFHF diet or normal liquid diet (NLD) respectively for 15 weeks. After 3 weeks feeding, two groups of mice were exposed to chronic intermittent hypoxia (CIH) for 12 weeks, and one of the groups was supplemented with LGGs at a dose equivalent to 10^9 CFU bacteria/day. The effects of LGGs on body fat composition and energy expenditure were assessed by dual-energy X-ray absorptiometry (DEXA) using a GE Lunar PIXI and by indirect calorimetry using metabolic chamber system, respectively. Glucose tolerance and insulin tolerance were also evaluated. Hepatic and adipose tissue was examined by histological staining. Circulating adiponectin concentration was determined using an ELISA, and adipose tissue adiponectin protein expression was determined by Western blot. Hepatic and circulating bile acid composition were determined by LC-MS-based metabolomics analysis, and intestinal microbiota were analyzed by pyrosequencing.

Results HFHF diet feeding significantly increased body fat mass, hepatic steatosis, glucose tolerance, and liver injury, and decreased energy expenditure. These indices of metabolic disorders were worsened in mice exposed to CIH, indicating that CIH has an additive effect on HFHF diet feeding. The HFHF-fed mice supplemented with LGGs showed marked improvements in indices of metabolic disorder including fat mass, energy expenditure and glucose and insulin tolerance. LGGs treatment decreased hepatic fat content and adipocyte size. Adipose expression of HIF-1α, a marker of tissue hypoxia, was increased in HFHF-CIH mice, which was reduced by LGGs treatment. The reduction of adipose tissue hypoxia was associated with decreased inflammatory cytokines such as TNFα, IL-1β and IL-6. HFHF-CIH mice had a markedly reduced circulating adiponectin, which is critical in the regulation of insulin sensitivity and was significantly elevated by LGGs treatment. Metabolomic analysis showed that LGGs supplementation significantly changed hepatic and fecal bile acid composition. Fecal concentrations of TαMCA and TβMCA, which are known FXR antagonists, were decreased in HFHF-CIH mice but were significantly increased by LGGs treatment.

Conclusion LGGs treatment prevents metabolic abnormalities induced by diet and hypoxia in HFHF-CIH mice. The beneficial effects of LGGs are mediated by multiple mechanisms. LGGs modulates intestinal bile acid regulation and intestinal specific FXR inactivation, which has been shown to be a strategy in the prevention of NAFLD-associated metabolic derangement. LGGs treatment decreases adipose hypoxia-associated inflammation leading to improved adiponectin production, which plays an important role in insulin sensitivity. LGGs may be a potential prevention/treatment strategy in subjects with sleep disorder and metabolic syndrome.

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