Butyrate And Its Derivative N-(1-Carbamoyl-2-Phenylethyl) Butyramide (FBA) Improve The Obese Phenotype And Reduce Liver Steatosis In A Mouse Model Of Diet-Induced Obesity (DIO)

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The pathogenesis of obesity is characterized by an alteration in energy balance between caloric intake and energy expenditure. Evidence shows that obesity increases the risk of cardiovascular diseases, type 2 diabetes, dyslipidemia and hepatic steatosis, contributing to the prevalence and incidence of the metabolic syndrome (MS). Insulin resistance, hyperleptinaemia and low plasma levels of adiponectin has been widely related to features of the MS (Aguilera et al., 2008). There is a close correlation between MS and liver steatosis (den Boer et al., 2004); it is known that the IR, oxidative stress and inflammation promote its development (Tarantino et al., 2007). Experimental studies show that butyrate, a short chain fatty acid (SCFA), is able to reduce serum glucose and lipids, inflammation and insulin resistance (Mattace Raso et al., 2013). Moreover, sodium butyrate, administered through diet supplementation in the high-fat diet can prevent and treat diet-induced insulin resistance in mouse, promoting energy expenditure (Gao et al., 2009).

The aim of this study was the evaluation of the therapeutic efficacy of sodium butyrate (BuNa) and its derivative N-(1-carbamoyl-2-phenylethyl) butyramide (FBA) in an animal model of diet-induced obesity (DIO), characterized by insulin resistance and steatosis.

Young male C57BL/6J mice were divided into 4 groups: 1) control group (STD diet, 17% of fat); 2) DIO group (DIO, 45% of fat); 3) DIO group treated with sodium butyrate (DIO+BuNa, 100 mg/kg/die per os) and 4) DIO mice receiving equimolecular dose of FBA (DIO+FBA, 212.5 mg/Kg/die per os). The treatments started after 12 weeks of DIO feeding and continued for 6 weeks; then animals were sacrificed, blood samples and tissues were collected for following determinations. At 5th week of treatment oral glucose tolerance test (OGTT) was performed at 8:00 a.m. and after 12 h fast. BuNa and FBA reduced body weight and fat mass, increased in DIO-fed mice. Both drugs significantly increased glucose disposal and restored insulin sensitivity, as shown by OGTT and HOMA index. Consistently, both treatments increased protein expression of GLUT-2, the glucose transporter in liver. Moreover, we demonstrated that BuNa and FBA significantly lowered serum metabolic parameters (i.e. ALT, cholesterol and triglycerides), markedly modified in DIO mice. The concentration of pro-inflammatory mediators (TNFα, IL-1, MCP-1 and lipopolysaccharide) were assessed in serum by ELISA. Their levels, increased in DIO mice compared with STD, were significantly reduced by BuNa or FBA. Both drugs also normalized serum levels of pro- and anti-inflammatory adipokines, such as leptin and adiponectin respectively, improving inflammation and adipose tissue function. In liver lysates western blot analysis showed that both treatments significantly modified the activity of key enzymes of fatty acid metabolism, AMPK and ACC, increasing their phosphorylation reduced in obese mice.

In conclusion, our data clearly demonstrate the beneficial effects of BuNa and FBA in reducing obesity associated to non alcoholic fatty liver disease and IR. The efficacy of BuNa and its palatable derivative FBA suggests their clinical potential therapy for the treatment of obesity and closely related complications.

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