

The Butyrate-Producing Microbiome in Murine Models of Insulin Resistance: Time for Translational Research

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Introduction

Significant among the 21st century's global health challenges is the growing prevalence of obesity and insulin resistance, particularly type 2 diabetes mellitus (T2DM) [1-3]. Type 2 diabetes mellitus is characterized by obesity and insulin resistance and is associated with cardiovascular disease, renal disease, neuropathy, nonalcoholic fatty liver disease, blindness and malignancy, making it a significant global cause of morbidity and mortality [2,3]. Research increasingly indicates that obesity, metabolic derangement and T2DM could be interrelated through the gut Microbiome, as studies have found that obese individuals possess a Microbiome that diverges significantly from that found in lean individuals [1].

The gut Microbiome refers to the ecosystem of >10¹⁴ bacteria that reside in the human gastrointestinal tract in a symbiotic relationship with the human host [2,3]. It is well documented that the gut Microbiome plays a role in host health by synthesizing vitamins and altering bile acid solubility. The Microbiome also contributes to daily caloric intake via the breakdown of insoluble dietary components into the short chain fatty acids (SCFA) acetate, propionate and butyrate. Without the gut Microbiome, these dietary elements would be indigestible by the human enterocyte [2]. Additionally, the Microbiome influences disease states -deviations from normal gut flora impact numerous inflammatory and metabolic conditions such as inflammatory bowel disease, irritable bowel syndrome, nonalcoholic fatty liver disease, T2DM and obesity [1-4].

Current hypotheses regarding mechanisms of Microbiome impact on obesity and insulin resistance include enhanced absorption of nutrients, enhanced SCFA production and lipogenesis, decreased activity of fasting-induced adipose factor, increased inflammation and intestinal permeability and altered bile acid circulation [2]. The focus of much research in recent years has been the SCFA butyrate and its relationship to obesity and T2DM. A preliminary search of PubMed reveals that

the number of papers published on “butyrate and obesity” or “butyrate and diabetes” has almost doubled in the last decade. Specific research that focuses on the role of SCFAs in obesity and T2DM indicates that butyrate may promote insulin sensitivity in peripheral tissues, contribute to glucose homeostasis and may even prevent and treat diet-induced insulin resistance in obesity [1,5]. However, the majority of studies have been performed in rodents and there is still a great deal of knowledge to be elucidated on the subject of human gut Microbiome interactions with obesity and T2DM, as well as the impact of specific SCFAs and microbial products on insulin resistance and glucose tolerance [2].

The obese Microbiome exhibits decreased bacterial species diversity and altered species -to-species ratios, both of which are associated with increased insulin resistance. Specifically, in T2DM, the populations of the phyla Firmicutes is increased, while Bacteroides is decreased [3]. Studies indicate, albeit with varying levels of certainty, that these derangements in bacterial ratios correlate with decreased numbers of butyrate-producing bacteria and increased numbers of Lactobacillus, a Firmicute. Butyrate then appears significant in the relationship between insulin resistance and the Microbiome. In fact, insulin-resistant individuals treated with vancomycin were noted to have a decrease in the number of butyrate-producing gut microbiota and an associated increase in insulin resistance. Additionally, fecal transfer of lean individuals into obese recipients results in increased insulin sensitivity and increased numbers of butyrate-producing bacteria in the Microbiome of obese recipients [4].

Studies in mice have attempted to characterize the impact of butyrate on insulin resistance and obesity, however such studies are lacking in humans. A study of mice that underwent Roux-en-Y gastric bypass (RYGB) indicates that the microbiome of post-RYGB mice is modified compared to that found in the native gut. Indeed, diabetic mice that received a fecal transplant

from the gut of post-RYGB mice were noted to have weight loss, improved glucose and lipid metabolism, and an increase in butyrate-producing organisms in their gut microbiota [3]. This data, in conjunction with a study by [5] continues to lend significance to butyrate's role in modulating insulin sensitivity. In this study, obese mice received dietary supplementation with butyrate and were noted to have increased insulin sensitivity and decreased body fat content. In addition, mice receiving a high fat diet supplemented with butyrate did not develop insulin resistance and obesity. In comparison with mice not receiving butyrate supplementation, these mice had decreased adiposity, increased energy expenditure, and increased fatty acid oxidation [5] This indicates that dietary supplementation with butyrate can prevent insulin resistance in susceptible animals and halt further development of obesity in already obese mice [5].

Although some promising research has been conducted to untangle the mechanistic relationships between obesity, insulin resistance, and the function of the gut Microbiome in mice, there is a dearth of information on these subjects in humans. In order to more fully investigate etiology and treatments for T2DM, obesity and insulin resistance, research on the Microbiome and its role in these conditions needs to shift its focus into human subjects. Future studies could investigate the effect of dietary supplementation with butyrate in humans, as well as attempt to characterize the mechanism of action of SCFAs in inducing insulin-sensitivity, should that be a benefit of human butyrate

supplementation. Moreover, studies could investigate the impact of diet upon the gut microbiome and attempt to characterize the relationship between changes in diet and changes in microbial populations. Mechanistic studies could characterize the most representative places in the gastrointestinal tract from which to sample the Microbiome, and still other studies could investigate the role of individual species as opposed to the "cocktail" of the entire Microbiome in inducing insulin sensitivity.

We look forward to developments in translational research in the relationship between the gut Microbiome and obesity and T2DM.

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