Extended Abstract Journal of Diabetes Research and Endocrinology 2019
Vol.3 No.2

Euro Diabetes 2019: The international debate on the effect of Butyric acid on Insulin signaling genes in preadipocytes and hepatocyte- Lisa R Manes- Winston-Salem State University

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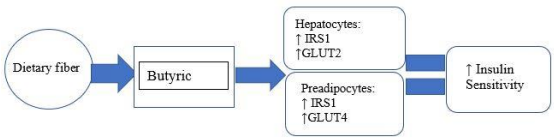
Type 2 diabetes mellitus (T2DM) affects millions globally and costs billions of dollars annually. A greater understanding of dietary components that prevent or ease the symptoms of the disease would help the growing number of people who suffer its effects. Butyric acid is a fatty acid that can be fermented from fiber by encouraging the growth of beneficial intestinal bacteria. In mice and intestinal cell culture studies, butyric acid has been shown to increase insulin sensitivity at the level of gene expression. Since little or no work has been done to show the effects of butyric acid on gene expression in human cells, our lab determined the effects on hepatocytes or preadipocytes in vitro. Using quantitative PCR, we determined the changes in expression of insulin receptor substrate-1 (IRS1) and glucose transporter 2 (GLUT2) on insulin-shocked THLE-2 human liver cells exposed in vitro to 0.05, 0.1, and 1.0 mg/ml butyric acid. We also determined the effects of this fatty acid on IRS1 and GLUT4 in human preadipocytes at the same concentrations. In human hepatocytes, IRS1 and GLUT2 were increased in expression by levels of butyric acid similar levels found to be nontoxic in humans while IRS1 and GLUT4 were both upregulated in preadipocytes. Results suggest that altering the human diet to encourage the fermentation of butyric acid could increase insulin sensitivity in those with T2DM or aid in the prevention of the disease.

Image



Discussion: This study indicates that butyric acid increases the expression of GLUT4 and IRS1 in human preadipocytes in vitro. All concentrations of butyric acid used in the study resulted in upregulations in expression of these genes. While the greatest increase coincided with 0.1 mg/ml butyric acid for GLUT4, the lowest concentration of butyric acid resulted in the greatest change in expression of IRS1. Interestingly, the lowest concentration tested is close to the level that has been shown to be nontoxic in plasma of human subjects. Conley et al., (1998) showed that 0.04 mg/ml butyric acid in the plasma was safe for humans. This means that a level of butyric acid that is safe in humans is likely to upregulate genes that are important to insulin sensitivity. This fatty acid holds great promise in the prevention of DMT2 for patients at risk and for treatment of those already suffering from it. The effect on the expression of these genes is not as marked on human preadipocytes in vitro as the effect on human hepatocytes. THLE-2 human hepatocytes exhibited a 9.1-fold upregulation of GLUT2 using 1.0 mg/ml of butyric acid and a 15.8-fold upregulation of IRS1 using 0.05 mg/ml butyric acid. The lowest level of butyric acid tested (0.05 mg/ml) resulted in a 3.0-fold upregulation of GLUT2, indicating that both genes are affected by the level that is close to that deemed by Conley et al. to be safe for humans. Altogether, human hepatocytes and preadipocytes have genes in the insulin pathway, glucose transporter genes and IRS1, which are increased in the presence of butyric acid. In other words, cells that are direct targets of insulin have increased sensitivity to insulin in the presence of safe levels of butyric acid. Educating patients at risk for DMT2 on the best foods to Advances in Diabetes and Metabolism 4(3): 45-48, 2016 47 eat to prevent the disease, along with increasing physical activity, is the best philosophy for prevention. Diets that include high fiber will increase butyric acid levels, which has been shown to ease symptoms in mice and rats with diabetes. Butyric acid has also been shown to increase genes involved in the insulin pathway and thereby increase insulin sensitivity of cells that are insulin resistant in vitro. Collectively, these findings highlight the use of butyric acid in the prevention and treatment of DMT2.

Conclusion: This study showed that butyric acid increases the levels of the expression of GLUT4 and IRS1 in human preadipocytes in vitro. This research coincides with studies in rodents in vivo and in human intestinal and liver cells in vitro and supports the claim that this carboxylic acid increases insulin sensitivity. Boosting dietary fiber, and thereby the production of butyric acid, in the intestines can aid in the prevention and treatment of DMT2.

This work is partly presented at 28th European Diabetes Congress June on 10-11, 2019 held at Edinburgh, Scotland