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LIVER GLYCOGEN, A NOVEL TARGET TO TREAT DIABETES AND OBESITY

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1. Abstract

Background: Obesity results from a prolonged imbalance between energy intake and energy expenditure. The regulation of energy intake emerges as a plausible approach to reduce the impact of this pathological condition. We proposed liver glycogen to be a key factor in the regulation of food intake.

Hypothesis: We propose that increased liver glycogen stores in diabetes and obesity contribute to decreased appetite through the maintenance of liver energy status. We hypothesize that this effect is triggered by signals from the liver that are carried to the brain by vagal sensory neurons and that the modulation of hepatic glycogen levels is a feasible strategy to target diabetes and obesity.

Methodology: We have generated transgenic mice overexpressing protein targeting to glycogen (PTG) with increasing levels of hepatic glycogen. We have crossed them with various mouse models of diabetes and obesity, and the resulting animals have been the objects of our studies. We have tested whether liver glycogen stores maintain energy status in the liver, ameliorate the diabetic state, and decrease food intake. A hepatic branch vagotomy has been performed on mice that accumulate liver glycogen.

Results: Hepatic glycogen accumulation regulates glucose homeostasis and food intake in models of diabetes and obesity. The regulation of food intake and glucose homeostasis by liver glycogen is dependent on the hepatic branch of the vagus nerve. Furthermore, increasing liver glycogen maintained hepatic energy status in diabetes, fasting and exercise.

Conclusions: We propose that hepatic glycogen content be considered a potential target for the pharmacological manipulation of diabetes and obesity.

2. Results

1. Enhanced accumulation of glycogen in the liver of mouse models of diabetes and obesity (db/db and Akita) ameliorates the diabetic state and regulates food intake.

Glycogen deposition in the liver is impaired in db/db mice compared to healthy mice. We crossed these animals with mice overexpressing PTG specifically in the liver. The db/db-PTG mice showed an increase in liver glycogen content and a lower food intake compared to db/db mice. The resulting effect was a lower body weight. The decrease in body weight in db/db-PTG animals corresponded to a decrease in fat mass. Lean mass was significantly lower in both diabetic genotypes compared to control mice. Blood glucose levels in db/db mice were significantly higher than those of healthy mice (db/+), and increasing the levels of glycogen in the liver (db/db-PTG) ameliorated the hyperglycemia. Plasma insulin was significantly increased in both diabetic genotypes. Akita mice, a genetic non-obese diabetic model, are characterized by hyperglycemia, hypoinsulinemia and hyperphagia. Akita-PTG mice showed an increased liver glycogen content, reduced food intake, increased body weight, and reduced hyperglycemia compared to Akita mice. Plasma insulin levels were similar in Akita and Akita-PTG mice. The increase in body weight in Akita-PTG mice corresponded with an increase in lean mass. Fat mass was significantly reduced in both diabetic genotypes. Akita-PTG mice showed a significant decrease in water consumption and urine output compared to Akita mice, although both variables were markedly higher than in non-diabetic mice. In conclusion, increased hepatic glycogen in two models of diabetic mice reversed hyperglycemia and decreased hyperphagia.

2. Maintenance of liver glycogen preserves energy state in mice

Liver ATP content was significantly lower in db/db and Akita mice compared to healthy mice. Strikingly db/db-PTG and Akita-PTG mice maintained a hepatic energy status similar to that of healthy animals. Fasting is a most effective way to reduce hepatic ATP and that PTG-overexpressing animals maintain higher levels of ATP in the liver under fasting condition. Control and PTG mice were fed *ad libitum* or fasted for 36 h. Upon fasting, PTG mice retained significant hepatic glycogen stores and maintained hepatic energy status. Exercise also causes a drop in hepatic ATP. Liver ATP concentration decreased and AMP concentration increased in control mice after exercise. Remarkably, the ATP and AMP levels of exercised fed and fasted PTG mice were maintained at

similar levels to those in fed sedentary mice. All together our results show that liver glycogen preserves energy state in a variety of ATP depleting conditions. Furthermore, we showed that liver glycogen controls insulin sensitivity, gluconeogenesis, lipid metabolism and ketogenesis upon nutrient deprivation.

3. Effects of hepatic glycogen are mediated by the vagus nerve

We performed hepatic branch vagotomy (HBV) or sham operation on mice overexpressing protein targeting to glycogen (PTG) in the liver. One week after the operation, the mice received a high-fat-diet (HFD) for 10 weeks. HBV did not alter liver glycogen or ATP levels, thereby indicating that this procedure does not interfere with hepatic energy balance. However, HBV reversed the effect of glycogen accumulation on food intake. In control mice, HBV led to a significant reduction in body weight without changes in food intake. Consistent with the body weight reduction, these animals showed a decrease in fat deposition, adipocyte size, and insulin and leptin levels, together with an increase in energy expenditure. PTG mice showed an increase in energy expenditure and glucose oxidation, and these differences were abolished when these animals were subjected to HBV. Moreover, PTG mice showed an improvement in HFD-induced glucose intolerance, and this effect was suppressed by HBV. These results demonstrate that the regulation of food intake and glucose homeostasis by liver glycogen is dependent on the hepatic branch of the vagus nerve.

3. Relevance

Our results highlight the importance of maintaining hepatic glycogen in controlling blood glucose and appetite. From a practical point of view, they open up the possibility of using hepatic glycogen synthase as a therapeutic target. To this end, new activators specific for this isoform should be synthesized and the corresponding clinical trials performed. Another much more immediate application would be nutritional. Extrapolating our results suggests that nutritional guidelines aimed at increasing liver glycogen levels could have positive effects on appetite and blood glucose control.

4. Publications

López-Soldado I, Fuentes-Romero R, Duran J, Guinovart JJ. Effects of hepatic glycogen on food intake and glucose homeostasis are mediated by the vagus nerve in mice. Diabetologia 2017;60(6):1076-1083.

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López-Soldado I, Guinovart JJ, Duran J. Increasing hepatic glycogen moderates the diabetic phenotype in insulin-deficient Akita mice. J.Biol.Chem. 2021. doi.org/10.1016/j.jbc.2021.100498