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RESISTANCE TO DIET INDUCED DIABETES DUE TO REDUCED HEPATIC GLUCOSE PRODUCTION IN MICE LACKING PHOSPHATIDYLCHOLINE TRANSFER PROTEIN (PC-TP)

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Background: PC-TP is a specific lipid binding protein that is highly expressed in liver and extrahepatic oxidative tissues. When fed a chow diet, *Pctp*$^{-/-}$ mice exhibit increased hepatic insulin sensitivity that is associated with increased body fat and reduced lean muscle mass. Aim: The current study was designed to examine whether mice lacking PC-TP expression are protected against type 2 diabetes, which is characterized by elevated rates of hepatic glucose production. Methods: Male *Pctp*$^{-/-}$ and WT control mice were fed a high fat diet (HF; 60% kcal from fat) for 8 to 18 weeks. Percentages of body fat and lean muscle mass were determined by magnetic resonance imaging. Fasting plasma glucose concentrations were monitored as mice became diabetic. Rates of hepatic glucose production and glucose clearance from the plasma were quantified in hyperinsulinemic euglycemic clamp studies. To reconstitute hepatic PC-TP expression in *Pctp*$^{-/-}$ mice, recombinant adenovirus for PC-TP or a control green fluorescent protein (GFP) adenovirus was administered intravenously. WT mice administered GFP adenovirus also served as controls. The influence of liver-only PC-TP expression on hepatic glucose production rates was determined using pyruvate tolerance tests, which were validated against the clamp studies. Results: Both genotypes of mice consumed the same amounts of food, gained weight equally, and became obese. After 18 weeks of HF feeding, body fat and lean muscle mass did not differ in *Pctp*$^{-/-}$ and WT mice. In WT mice, fasting plasma glucose concentrations increased 1.9 fold between 8 and 12 weeks of HF feeding and then leveled off. The absence of PC-TP expression was associated with 25%, 46%, and 17% reductions in plasma glucose at 8, 12, and 18 weeks respectively. Clamp studies performed at 18 weeks of HF feeding revealed a 46% decrease in hepatic glucose production rates, but no difference in rates of glucose clearance. Reconstitution of hepatic PC-TP expression to WT levels did not increase hepatic glucose production rates in *Pctp*$^{-/-}$ mice infected with PC-TP compared with GFP adenovirus, both of which exhibited reduced hepatic glucose production compared with WT mice infected with GFP adenovirus. Conclusions: Despite obesity, mice lacking PC-TP are resistant to developing type 2 diabetes. Because this effect was not reversed by acute reconstitution of PC-TP expression in liver, extrahepatic expression likely plays an important role in hepatic glucose homeostasis. Taken together, our findings suggest that recently developed small molecule inhibitors of PC-TP could provide a novel approach to the management of type 2 diabetes.

Disclosures:

The following people have nothing to disclose: Janis M. Stoll, Sudeep Shrestha, Erez F. Scapa, Yingxia Li, Ya Su, Michele W. Niepel, Linda A. Jelicks, Roger Gutierrez-Juarez, David E. Cohen

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SPP1 CONTRIBUTES TO NON-ALCOHOLIC STEATOHEPATITIS IN MICE FED A METHIONINE-CHOLINE DEFICIENT DIET

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Background: Non-alcoholic steatohepatitis (NASH) is one of the major chronic liver diseases. NASH is characterized by significant inflammation with concurrent hepatic fat accumulation. Many patients with NASH may progress to cirrhosis. SPP1 is a secreted cytokine that promotes cell adhesion, T cell activation, and mediates the immune response in both physiological and pathophysiological settings. **Objective**: Recent studies from our laboratory have shown that SPP1 plays a significant role in the development of liver fibrosis by regulating collagen I expression; however, the role of SSP1 in NASH is still to be defined. We hypothesized that SPP1 could play a significant role in the development of NASH and in its progression to liver fibrosis. **Methods**: C57BL/6 WT, *Spp1*$^{-/-}$, and *Spp1* transgenic mice were fed either a methionine-choline sufficient (MCS) or a methionine-choline deficient (MCD) diet for 6 wks. The MCD diet is known to increase fatty acid uptake, decrease VLDL secretion, and lower glutathione levels; thus, resulting in liver injury similar to human NASH. Blood and liver samples were collected for biochemical analysis and pathology evaluation. Samples were scored by an experienced hepatopathologist using the Brunt classification. **Results**: Mice fed with the MCD diet did not show any change in the liver-to-body weight ratio in any of the groups. However, there was significant hepatic steatosis in all the MCD-fed mice. The *Spp1* Tg mice showed the highest steatosis score while the *Spp1*$^{-/-}$ mice showed the lowest. The *Spp1* Tg mice also presented the highest score for hepatocyte ballooning degeneration and lobular inflammation, when compared with WT and *Spp1*$^{-/-}$ mice fed the MCD diet. The *Spp1*$^{-/-}$ mice fed the MCD diet had only mild inflammation when compared with WT and *Spp1* Tg mice. Signs of fibrosis were already present in the *Spp1* Tg mice. **Conclusion**: SPP1 enhances liver damage in NASH by promoting steatosis and inflammation. Thus, a role for Spp1 in the progression of NASH to fibrosis is likely.

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TRANS-FATTY ACID INDUCES APOPTOSIS OF HEPATOCYTES BY ENHANCEMENT OF OXIDATIVE STRESS IN STEATOTIC LIVER OF KK-A^{Y} MICE

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Background: Apoptosis of hepatocytes is a critical event in non-alcoholic fatty liver disease (NAFLD); however, the pathogenic factors of apoptosis in NAFLD are not fully understood. *Trans*-fatty acid causes hypercholesteremia and results in atherosclerosis, but the role of *trans*-fat diet in pathogenesis of NAFLD has not been elucidated. Therefore, the aim of this study was to compare the impact of *trans*-, and *cis*-fatty acid on fructose-