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ADIPONECTIN DEFICIENCY LEADS TO HEPATIC STEATOSIS AND GESTATIONAL DIABETES IN PREGNANT MICE

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Background:

Gestational diabetes mellitus (GDM) is a common pregnancy-related condition with implications for both maternal and neonatal health. Factors such as diet and genetics can contribute to development GDM, but evidence suggests that low levels of adiponectin are correlated with elevated risk. Adiponectin is a fat derived hormone that improves insulin sensitivity.

Objective:

We hypothesize that adiponectin deficiency causes fatty liver during pregnancy that induces GDM.

Methods:

We compared the insulin insensitivity of low fat and high fat and sucrose diet fed pregnant (3rd trimester) adiponectin$^{-/-}$ (strain B6;129-*Adipoq*^{tm1Chan}/J) and wild-type mice. We assessed parameters of hepatic metabolism, mitochondrial function and fatty acid metabolism. Adiponectin was added back to pregnant dams at the end of the second trimester by administering adenovirus expressing full-length adiponectin .

Results:

In the third trimester, fasting pregnant adiponectin$^{-/-}$ are hyperglycemic even on a low-fat diet (9.2mmol/L vs. 7.7mmol/L in controls, $p<0.05$); they also display impaired glucose and insulin intolerance relative to wild-type controls. Pregnant adiponectin$^{-/-}$ mice developed hepatic steatosis, including a 3-fold elevation in hepatic triglycerides ($p<0.05$) relative to wild-type. In addition, a 2.5-fold increase in hepatic fatty acid synthase and increased beta-hydroxybutyrate dehydrogenase expression ($p<0.05$) and a 2-fold increase in circulating ketones ($p<0.05$) was observed. A 2-fold reduction ($p<0.05$) in maximal mitochondrial respiration was measured in hepatocytes of pregnant adiponectin$^{-/-}$ mice. Despite increased fatty acid uptake, hepatocytes of adiponectin$^{-/-}$ mice exhibit elevated synthesis and secretion of triglycerides and cholesterol. Adiponectin supplementation to pregnant adiponectin$^{-/-}$ mice improved glucose tolerance, prevented fasting hyperglycemia, and attenuated fatty liver.

Conclusion:

Adiponectin deficiency is associated with altered hepatic lipid metabolism and hepatic steatosis during the period of pregnancy associated with increased fat oxidation. Consequently, adiponectin deficiency dysregulated maternal insulin sensitivity and resulted in hyperglycemia that is characteristic of GDM. Adiponectin supplementation rescues the effects of adiponectin deficiency on insulin sensitivity and hepatic lipid metabolism