Adiponectin during pregnancy prevents vascular dysfunction in offspring from mouse obese dams

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Maternal obesity has been associated with increased risk of metabolic and cardiovascular disease in the offspring, including impaired vasodilation. Adiponectin (ADN) is an adipokine that regulates metabolism, insulin sensitivity, and vascular function. Plasma levels of ADN are lower in obese pregnancies compared to lean controls. Moreover, ADN supplementation has been associated with improved fetal growth, metabolism, cardiac function, and placental function. We hypothesized that increasing the circulating ADN levels in obese pregnant mice could reverse the effects of maternal obesity on offsprings' vascular function. Adult female mice were fed with either control (CON, n=5) or obesogenic (OB, n=6) diet until the OB group gained 25% of their initial body weight and mated with CON males. A mini-osmotic pump was subcutaneously implanted in all pregnant dams at late pregnancy (embryonic day 14.5). CON dams received a continuous infusion of phosphate saline buffer (PBS, n=5) whereas OB females received either PBS (n=3) or ADN (0.62 μg g^{-1} day^{-1}, n=3). Dams were maintained on their respective diets during pregnancy and throughout lactation. After weaning, offspring were fed CON diet. Between seven and nine months of age, adult offspring's mesenteric arteries (MsA) were dissected and mounted in a wire myograph. Contractile responses to phenylephrine or endothelin-1 and dilator responses to acetylcholine (ACh), bradykinin (BK) or the nitric oxide donor sodium nitroprusside (SNP) were determined in the offspring of CON-PBS, OB-PBS and OB-ADN dams. Concentration-response curves were compared by one-way ANOVA. MsA responded to the vasoconstrictors phenylephrine and endothelin-1 similarly among groups. However, the vasodilatory responses to ACh were reduced in MsA from OB-PBS group (n=8) compared to CON-PBS (n=10, $p<0.01$). Furthermore, in offspring from OB-ADN dams (n=7) the ACh-evoked vasodilation was increased compared to OB-PBS ($p<0.05$). BK responses were not different among groups. SNP-evoked vasodilation was reduced in OB-ADN group (n=7) compared to both CON-PBS (n=9, $p<0.05$) and OB-PBS (n=7, $p<0.05$). These results highlight a role of the reduced levels of ADN seen during obese pregnancies in the vascular dysfunction of the offspring. The ADN supplementation during obese pregnancy showed prevention of these vascular effects on the offspring. Future studies are warranted to further explore the putative beneficial effects of ADN in pregnancies affected by obesity.

The Role of Adiponectin in Maternal Obesity and Offspring Vascular Function

Introduction

Maternal obesity has been associated with increased risk of metabolic and cardiovascular disease in the offspring, including impaired vasodilation. Adiponectin (ADN) is an adipokine that regulates metabolism, insulin sensitivity, and vascular function. Plasma levels of ADN are lower in obese pregnancies compared to lean controls, and are negatively correlated with gestational BMI. ADN supplementation has been associated with improved fetal growth, metabolism, cardiac function, and placental function. We hypothesized that increasing the circulating ADN levels in obese pregnant mice could reverse the effects of maternal obesity on offsprings' vascular function.

Methods

Adult female mice were fed with either control (CON) or obesogenic (OB) diet until the OB group gained 25% of their initial body weight and mated with CON males. A mini-osmotic pump was subcutaneously implanted in all pregnant dams at late pregnancy (embryonic day 14.5). CON dams received a continuous infusion of phosphate saline buffer (PBS) whereas OB females received either PBS or ADN (0.62 $\mu g\ g^{-1}\ day^{-1}$). Dams were maintained on their respective diets during pregnancy and throughout lactation. After weaning, offspring were fed CON diet. Between seven and nine months of age, adult offspring's mesenteric arteries (MsA) were dissected and mounted in a wire myograph. Contractile and dilator responses to phenylephrine or endothelin-1 and acetylcholine (ACh), bradykinin (BK) or an AMPK activator (A769662), respectively, were determined in the offspring of CON-PBS ($n = 7$), OB-PBS ($n = 9$) and OB-ADN ($n = 5$) dams. Concentration-response curves were compared by two-way ANOVA.

Results

*** Figure 2?

Conclusion

Acetylcholine-dependent vasodilation was found to be reduced by maternal obesity and restored by adiponectin supplementation in the mesenteric artery (MsA) from adult offspring. This research demonstrates targets for future treatment of hypertension and other cardiovascular maladies among those born to mothers with obesity during pregnancy. If adiponectin can significantly reverse the vasoconstriction of mesenteric arteries in mice whose dams were obese during gestation, this may warrant a new therapeutic intervention in pregnant humans.

Introduction

Maternal obesity increases the risk of cardiovascular and metabolic disease in the offspring both during childhood and adult life. As compared to controls with normal body mass index, pregnant women and mice that are obese have lower circulating levels of adiponectin (ADN), an adipokine involved in regulating energy metabolism, vascular function and placental function. We hypothesized that offspring of obese mice have impaired resistance artery function, which is prevented by restoration of normal circulating ADN levels in obese dams during late pregnancy.

Methods

Adult female mice were fed with either control (CON) or obesogenic (OB) diet until the OB group gained 25% of their initial body weight and mated with CON males. A mini-osmotic pump was subcutaneously implanted in all pregnant dams at late pregnancy (embryonic day 14.5). CON dams received a continuous infusion of phosphate saline buffer (PBS) whereas OB females received either PBS or ADN (0.62 μg g^{-1} day^{-1}). Dams were maintained on their respective diets during pregnancy and throughout lactation. After weaning, offspring were fed CON diet. Between seven and nine months of age, adult offspring's mesenteric arteries (MsA) were dissected and mounted in a wire myograph. Contractile and dilator responses to phenylephrine or endothelin-1 and acetylcholine (ACh), bradykinin (BK) or an AMPK activator (A769662), respectively, were determined in the offspring of CON-PBS (n = 7), OB-PBS (n = 9) and OB-ADN (n = 5) dams. Concentration-response curves were compared by two-way ANOVA.

Results

MsA vasoconstrictor responses to phenylephrine and endothelin-1 were similar among all groups. Likewise, MsA vasodilator responses to BK and A769662 were comparable among groups but offspring from OB-PBS and OB-ADN dams had 35% and 25% less ACh-evoked vasodilation ($p<0.05$ and $p=0.07$), respectively, compared to MsA from CON-PBS animals.

Conclusions

In mice, maternal obesity has a long-lasting impact on the cholinergic response of resistance vessels of the offspring. However, restoration of maternal ADN during pregnancy did not restore cholinergic responses in these vessels, suggesting they are independent of reduced ADN levels in pregnancy.