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

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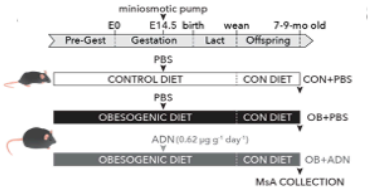
BACKGROUND

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.

METHODS

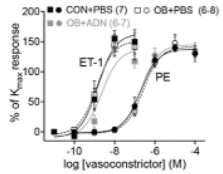
Adult female mice were fed with either control (CON, n=5) or obesogenic (OB, n=6) diet until the OB group gained 25% of their initial body weight and mated with CON males. A mini-osmotic pump was subcutaneously implanted in all pregnant dams at late pregnancy (embryonic day 14.5). CON dams received a 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.

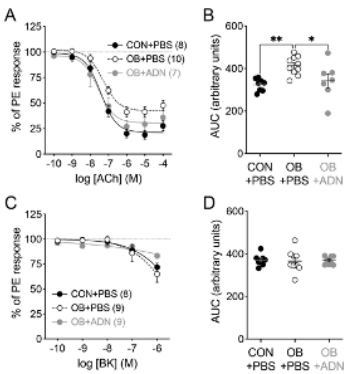
RESULTS

1 Mesenteric artery (MsA) responses to vasoconstrictors.



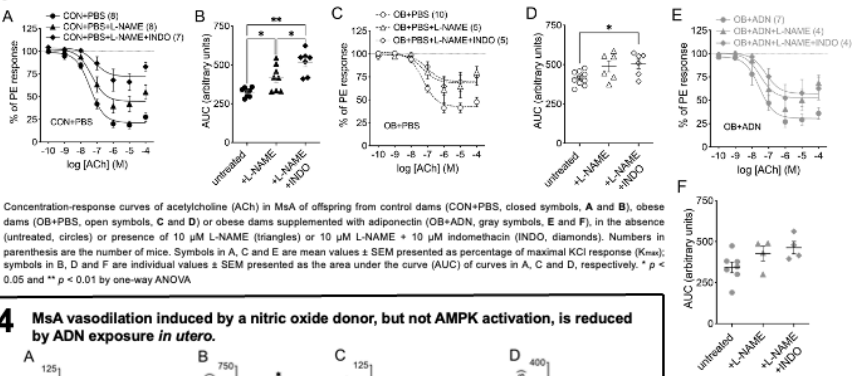
Concentration-response curves of endothelin-1 (ET-1, squares) or phenylephrine (PE, circles) in MsA of offspring from control dams (CON+PBS, closed symbols), obese dams (OB+PBS, open symbols) or obese dams supplemented with adiponectin (OB+ADN, gray symbols), presented as percentage of maximal KCl response (K_{max}). Numbers in parenthesis are the number of mice, symbols are mean values ± SEM

2 Acetylcholine-dependent vasodilation is reduced by maternal obesity and restored by adiponectin supplementation in MsA from adult offspring.



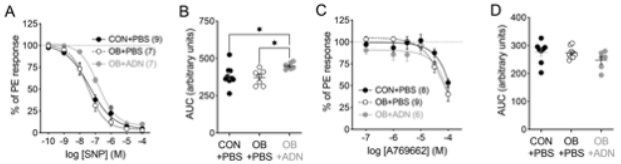
Concentration-response curves of acetylcholine (ACh, **A**) or bradykinin (BK, **C**) in MsA of offspring from control dams (CON+PBS, closed symbols), obese dams (OB+PBS, open symbols) or obese dams supplemented with adiponectin (OB+ADN, gray symbols), presented as percentage of maximal KCl response (K_{max}). Numbers in parenthesis are the number of mice, symbols are mean values ± SEM. **B** and **D** show the area under the curve (AUC) analysis of curves in A and C, respectively. * $p < 0.05$ and ** $p < 0.01$ by one-way ANOVA.

3 ACh-dependent vasodilation is partially mediated by prostaglandin signaling in MsA from adult offspring.



Concentration-response curves of acetylcholine (ACh) in MsA of offspring from control dams (CON+PBS, closed symbols, **A** and **B**), obese dams (OB+PBS, open symbols, **C** and **D**) or obese dams supplemented with adiponectin (OB+ADN, gray symbols, **E** and **F**), in the absence (untreated, circles) or presence of 10 µM L-NAME (triangles) or 10 µM L-NAME + 10 µM indomethacin (INDO, diamonds). Numbers in parenthesis are the number of mice. Symbols in A, C and E are mean values ± SEM presented as percentage of maximal KCl response (K_{max}); symbols in B, D and F are individual values ± SEM presented as the area under the curve (AUC) of curves in A, C and D, respectively. * $p < 0.05$ and ** $p < 0.01$ by one-way ANOVA

4 MsA vasodilation induced by a nitric oxide donor, but not AMPK activation, is reduced by ADN exposure *in utero*.



Concentration-response curves of sodium nitroprusside (SNP, **A**) or A769662 (**C**) in MsA of offspring from control dams (CON+PBS, closed symbols), obese dams (OB+PBS, open symbols) or obese dams supplemented with adiponectin (OB+ADN, gray symbols), presented as percentage of maximal KCl response (K_{max}). Numbers in parenthesis are the number of mice, symbols are mean values ± SEM. **B** and **D** show the area under the curve (AUC) analysis of curves in A and C, respectively. * $p < 0.05$ by one-way ANOVA

SUMMARY & CONCLUSIONS

- MsA responded to the vasoconstrictors phenylephrine and endothelin-1 similarly among groups.
- MsA vasodilatory responses to ACh were reduced by maternal obesity and restored in offspring from obese dams supplemented with ADN.
- BK responses were not different among groups.
- SNP-evoked vasodilation was reduced in offspring from obese dams supplemented with ADN.
- 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.

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