Maternal Hyperleptinemia Increases Arterial Stiffening and Alters Vasodilatoy Responses to Insulin in Adult Male Mice Offspring

Francisco I Ramirez-Perez[1,2], Kathleen A Pennington[3], Kelly E Pollock[3], Omonseigho O Esangbedo[3,4], Christopher A Foote[1], Constantino C Reyes-Aldasoro[7], Ho-Hsiang Wu[5], Tieming Ji[5], Luis A Martinez-Lemus[1,2,6] and Laura C Schulz[3,4]

Author Affiliations

1 Dalton Cardiovascular Research Center, University of Missouri, Columbia, MO
2 Biological Engineering, University of Missouri, Columbia, MO
3 Obstetrics, Gynecology, and Women's Health, University of Missouri, Columbia, MO
4 Biological Sciences, University of Missouri, Columbia, MO
5 Statistics, University of Missouri, Columbia, MO
6 Medical Pharmacology and Physiology, University of Missouri, Columbia, MO
7 School of Engineering and Mathematical Sciences, City University London, London, United Kingdom

Abstract

Cardiovascular disease (CVD) is the number one cause of death in the U.S., and exposure to adverse maternal environments has been associated with the development of CVD including hypertension. Gestational diabetes mellitus (GDM) is an adverse maternal environment that has been associated with metabolic and CVD outcomes in the offspring. Key features of GDM and CVD are maternal hyperleptinemia and vascular disfunction/remodeling, respectively. Yet, there is limited information on the effects of maternal hyperleptinemia has on the function and structure of the offspring's resistance vasculature. We hypothesize that alterations in offspring's resistance artery structure and function underlie programming mechanisms for cardiovascular disease that are associated with maternal hyperleptinemia and GDM. To test this hypothesis, we used Leprdb/+ mice dams, which exhibit maternal hyperleptinemia and wildtype (WT) as controls. Vascular function was assessed in WT male offspring of control and hyperleptinemic dams at 31 weeks of age, after half the offspring had been fed a high fat diet (HFD) for 6 weeks. On a standard diet (SD), offspring of hyperleptinemic dams had mesenteric arteries with larger internal diameters than those of WT dams (258.36±14.99 vs 233.65±9.36 μm, $p<0.05$) indicative of outwardly remodeled, and enhanced maximal vasodilatory responses to insulin (39.97±6.71 vs 32.23±5.07 %, $p<0.05$). In offspring of WT, but not hyperleptinemic dams, HFD increased vessel wall cross-sectional area (18590.01±1251.16 vs 12807.20±1060.70 μm2, $p<0.05$), and enhanced the maximal vasodilatory response to acetylcholine (33.74±4.92 vs 21.86±2.73 %, $p<0.05$). HFD reduced the maximal response to insulin in offspring of hyperleptinemic dams compared to their WT and lean controls (21.88±3.80 vs

37.42±7.84 and 39.97±6.71 % respectively, $p<0.05$). Offspring of hyperleptinemic dams fed a HFD had increased elastic moduli normalized as a function of the percolation of the internal elastic lamina compared to their WT and lean controls (0.53±0.038 vs 0.34±0.023 and 0.38±0.032 ×106 dynes/cm2 respectively, $p<0.05$). Offspring of hyperleptinemic dams also had stiffer arteries at high pressure under both dietary conditions (2.36±0.35 vs 1.45±0.11 ×106 dynes/cm2, $p<0.05$). We conclude that when mice were fed a SD, maternal hyperleptinemia had beneficial effects to offspring's vascular health, but did not protect offspring fed a HFD. Furthermore, maternal hyperleptinemia induced arterial stiffness in offspring regardless of diet. These results suggest that GDM programs offspring vascular function and structure through mechanisms that may be in part dependent on circulating maternal leptin levels and are differentially affected by postnatal developmental exposures.

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