Exposure to Maternal Diabetes Is Associated With Early Abnormal Vascular Structure in Offspring

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Résumé en anglais	Aim/hypothesis: In utero exposure to maternal diabetes increases the risk of developing hypertension and cardiovascular disorders during adulthood. We have previously shown that this is associated with changes in vascular tone in favor of a vasoconstrictor profile, which is involved in the development of hypertension. This excessive constrictor tone has also a strong impact on vascular structure. Our objective was to study the impact of in utero exposure to maternal diabetes on vascular structure and remodeling induced by chronic changes in hemodynamic parameters. Methods and Results: We used an animal model of rats exposed in utero to maternal hyperglycemia (DMO), which developed hypertension at 6 months of age. At a pre-hypertensive stage (3 months of age), we observed deep structural modifications of the vascular wall without any hemodynamic perturbations. Indeed, in basal conditions, resistance arteries of DMO rats are smaller than those of control mother offspring (CMO) rats; in addition, large arteries like thoracic aorta of DMO rats have an increase of smooth muscle cell attachments to elastic lamellae. In an isolated perfused kidney, we also observed a leftward shift of the flow/pressure relationship, suggesting a rise in renal peripheral vascular resistance in DMO compared to CMO rats. In this context, we studied vascular remodeling in response to reduced blood flow by in vivo mesenteric arteries ligation. In DMO rats, inward remodeling induced by a chronic reduction in blood flow (1 or 3 weeks after ligation) did not occur by contrast to CMO rats in which arterial diameter decreased from 428 ± 17 µm to 331 ± 20 µm (at 125 mmHg, p = 0.001). In these animals, the transglutaminase 2 (TG2) pathway, essential for inward remodeling development in case of flow perturbations, was not activated in low-flow (LF) mesenteric arteries. Finally, in old hypertensive DMO rats (18 months of age), we were not able to detect a pressure-induced remodeling in thoracic aorta. Conclusions: Our results demonstrate for the first time that in utero exposure to maternal diabetes induces deep changes in the vascular structure. Indeed, the early narrowing of the microvasculature and the structural modifications of conductance arteries could be a pre-emptive adaptation to fetal programming of hypertension.
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