Nitroxyl-mediated relaxation is preserved in the diabetic mesenteric artery despite endothelial dysfunction and increased axial stiffness

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Streptozotocin-induced type 1 diabetes is characterized by hyperglycaemia (~30mM), which causes endothelial dysfunction, vascular hypertrophy and arterial wall stiffness. In diabetic mesenteric arteries, endothelial dysfunction is attributed to a reduction in nitric oxide ($NO^{\cdot}$) and endothelium-derived hyperpolarization (EDH). The redox sibling of $NO^{\cdot}$, nitroxyl (HNO), has recently emerged as an important endogenous vasodilator that has distinct pharmacological actions to $NO^{\cdot}$. However the effect of diabetes on the contribution of HNO to relaxation in mesenteric arteries remains unknown. Therefore the aims of this study were to examine the effects of different levels of hyperglycaemia on vascular structure and function and to determine the effect of diabetes on HNO-mediated relaxation in the mesenteric artery.

Methods: Diabetes was induced with streptozotocin (STZ; 55mg/kg). Moderate hyperglycaemia (20 mM) and hyperglycaemia (30 mM) were maintained with 1-2 and 6-7 daily units of insulin, respectively. 8 weeks after STZ, endothelial function was assessed with wire myography. Concentration response curves to endothelium-dependent vasodilator acetylcholine (ACh) were assessed. Pharmacological tools, hydroxycobalamin (HXC; $NO^{\cdot}$ scavenger) and L-Cysteine (HNO scavenger) were used to distinguish between $NO^{\cdot}$ and HNO. Pressure myography was used to assess passive mechanical wall properties (wall thickness (WT), inner diameter (ID) and outer diameter (OD)).

Results: Hyperglycaemic, but not moderate hyperglycaemic arteries, had a significantly reduced sensitivity to ACh compared to control (pEC_{50} - control 7.88±0.09 *vs* 7.20±0.06 for hyperglycaemic, n=15-17, $P<0.05$), indicating endothelial dysfunction. Basal levels of $NO^{\cdot}$ synthase activity were significantly reduced in moderate and hyperglycaemic. This was accompanied by a significant reduction in basal levels of $NO^{\cdot}$, but not HNO. Interestingly, ACh-evoked $NO^{\cdot}$-mediated relaxation was significantly reduced only in mesenteric arteries from hyperglycaemic but not moderate hyperglycaemic rats. However, the component of relaxation attributed to HNO in the mesenteric arteries was unaffected by different levels of hyperglycaemia. Both moderate hyperglycaemic and hyperglycaemic mesenteric arteries had significantly increased WT, ID and OD compared to control, indicating outward hypertrophic remodelling. Under physiological pressures (50-120mmHg), both hyperglycaemic and moderate hyperglycaemic mesenteric arteries had significantly reduced volume distensibility compared to control, indicating an increase in axial stiffness.

Conclusion: Mesenteric arteries in moderate hyperglycaemic and hyperglycaemic rats undergo vascular remodelling that causes an increase in axial stiffness, however hyperglycaemia (~30mM), is required to cause endothelial dysfunction. Furthermore the contribution of HNO to endothelium-dependent relaxation is preserved in moderate hyperglycaemia and hyperglycaemia, which demonstrates its role as a potential treatment target in diabetes.