Hyperglycaemia disrupts conducted vasodilation in the resistance vasculature of db/db mice

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Stimulation of proteinase-activated receptor 2 (PAR2) on endothelial cells (ECs) leads to an increase in intracellular calcium activating endothelium-derived hyperpolarization (EDH), which then spreads to the adjacent vascular smooth muscle (VSM) causing vasodilation. In the resistance vasculature, EDH can also rapidly spread to neighbouring ECs to trigger VSM relaxation along the length of the artery in a process termed conducted vasodilation. Previously, mouse models of diabetes mellitus have been reported to exhibit diminished EC calcium signalling and EDH. However, whether or not chronic hyperglycaemia, the hallmark of diabetes mellitus, alters conducted vasodilation has not been reported.

Small mesenteric arteries were isolated from healthy and diabetic db/db mice, which were used as a model of chronic hyperglycaemia. Endothelium-dependent vasodilation via the Gq/11-coupled proteinase-activated receptor 2 (PAR2) was stimulated with the selective agonist SLIGRL. The calcium-sensitive fluorescent indicator fluo-8 reported changes in intracellular endothelial cell (EC) calcium concentration, and triple-cannulated bifurcating mesenteric arteries were used to study conducted vasodilation.

Localized intraluminal perfusion of SLIGRL into the bifurcation of triple-cannulated arteries from WT mice induced conducted vasodilation 2.5 mm away from the initial site of local vasodilation. This conducted response to regions not exposed to SLIGRL was reduced during acute exposure to a high glucose (40 mM) or hyperosmolar (29 mM mannitol) solution. Furthermore, arteries isolated from db/db mice also exhibited diminished conducted vasodilation compared with WT. However, in db/db arteries chronic hyperglycaemia did not modify either EC calcium mobilization or EDH-dependent vasodilation stimulated by SLIGRL.

The current investigation demonstrates for the first time that the spread of a hyperpolarizing current along the endothelium of the resistance vasculature is attenuated in a mouse model of chronic hyperglycaemia. In addition, diminished conducted vasodilation was also observed during acute exposure to a hypertonic solution containing glucose or mannitol in WT arteries. Our findings reiterate the importance of studying the effects of hyperglycaemia in the vasculature, and provide the basis for further studies regarding the modulation of junctional proteins involved in cell to cell communication by diseases such as diabetes.