Conducted Dilation Of The Resistance Vasculature In A Mouse Model Of Chronic Hyperglycaemia

Stimulation of proteinase-activated receptor 2 (PAR2) on endothelial cells (ECs) leads to an increase in intracellular Ca^{2+} stimulating endothelium-derived hyperpolarization (EDH), which spreads to 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 dilation. Previously, mouse models of diabetes mellitus have been reported to exhibit diminished EC Ca^{2+} signalling and EDH (1). However, the effect of prolonged hyperglycaemia, the hallmark of diabetes mellitus, on conducted dilation has not been characterised. The present investigation studied EDH-dependent local and conducted vasodilation induced by the PAR2-selective agonist SLIGRL in resistance arteries during acute and chronic exposure to high glucose.

Diabetic (db/db) mice were used as a model of chronic hyperglycaemia, and wild type C57BL/6 (WT) and heterozygote (db/+) mice were used as controls. Double or triple cannulated mesenteric arteries were pressurised to assess SLIGRL-induced local and conducted dilation, respectively. Confocal microscopy enabled visualisation of changes in vessel diameter and EC Ca^{2+} using the Ca^{2+}-sensitive dye fluo-8-AM.

Localised intraluminal perfusion into the bifurcation of triple cannulated arteries from WT mice with 10μM SLIGRL induced conducted dilation 2.5mm away from the initial site of local dilation (11.1±1.50%; n=5). This conducted response was reduced during an acute exposure to a high glucose (40mM) (0.00±0.00%; n=4; $p \leq 0.001$ vs control) or hyperosmolar (29mM mannitol) (4.80±0.55%; n=5; $p \leq 0.01$ vs control) solution. However, arteries isolated from the chronically hyperglycaemic db/db mice did not exhibit diminished conducted dilation. Furthermore, no differences in SLIGRL-induced local dilation or EC Ca^{2+} activity were observed between arteries isolated from each genotype. Together, these findings suggest Ca^{2+} signalling and EDH production leading to conducted dilation is preserved in the resistance vasculature of db/db mice, and may represent a possible adaptation to maintain vascular function during chronic hyperglycaemia.

(1) Chen H *et al.* (2015). *Eur J Pharmacol* **767**: 17-23.