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TRPV4 Dysfunction in Both Endothelial and Smooth Muscle Cells From Diabetic Rat Aorta

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Diabetes mellitus (DM) is a pandemic metabolic disease characterized by chronically elevated blood glucose concentration (hyperglycaemia) and accounts for approximately a death every 7 seconds (1). Diabetic vascular dysfunction is a major complication where vasodilation is compromised rendering the diabetic prone to elevated blood pressure and limb infections (1). Numerous vasodilation pathways are found in the vasculature including transient receptor potential channels (TRPs). Human transient receptor potential channels (hTRPs) are mainly categorised into 6 subfamilies of distinct activation profile (2). Among these is the vanilloid TRP (TRPV) comprised of 6 members including TRPV4 which is found to be expressed in the vasculature, endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) according to western blotting, RT-PCR and immunohistochemistry studies (3, 4). As a cation channel, TRPV4 mediates Ca+2 influx that plays a major role in endothelium-dependent vasodilation (VD) and VSMCs hyperpolarization and hence VD (5, 6). Accordingly, in this study the role of TRPV4 in diabetic vascular dysfunction was investigated.

Two groups of male Wistar rats (N= 4-5/group) were studied, the first group was injected i.p. with 65mg/kg streptozotocin (STZ) while the second was injected with 20mM citrate buffer (Control). Thoracic aortic and mesenteric arterial rings from rats that had been euthanized, were isolated and suspended in organ baths attached to a transducer allowing quantitative isometric tension measurement. Arterial rings were pre-contracted with noradrenaline (300nM) followed by TRPV4-agonist, RN-1747 (3nM-3µM) to evoke relaxation dose response curves. Moreover, primary VSMCs were isolated from thoracic aorta. The cells were then lysed and studied through western blotting. TRPV4 protein was probed with rabbit Anti-TRPV4 antibody and visualized through enhanced chemiluminescence (ECL).

Thoracic aortic rings from diabetic rats showed compromised TRPV4-induced VD compared to control (Diabetic: 24.3±5.3% max. relaxation **p□0.01 vs control; 62.4±8.7% max. relaxation). Mesenteric arteries also showed significant suppressed VD (diabetic: 38.9±6.5% max. relaxation *p□0.05 vs control; 58.5±4.6% max. relaxation). Moreover, primary VSMCs showed significant reduction in expressed TRPV4 (61.8±3.5% vs control 100±10.7%, *p□0.05) which was accompanied with reduced iNOS expression (32.7±10.3% vs control 100±16.2%, *p□0.05) and significant difference in total nitrite production (29.9.3±9.4% vs control 100±12.8%, **p□0.01).

These results showed the TRPV4 function is compromised in both endothelial and VSMC and is in part due to reduction in channel number. Diabetes-induced lipolysis might accelerate the degradation of caveolae, a cone shaped pocket of proteins and lipids serves as a docking site for channels and receptors in endothelium and hence reduce levels of caveolin-associated TRPV4 so compromising vascular function (7).

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