The Aortic function of Male UC Davis Type 2 Diabetes Mellitus (UCD-T2DM) Rats: Possible Involvement of Intermediate Conductance Potassium Channels (IKCa)

Farjana Akther¹, Md Rahatullah Razan¹, James L. Graham², Kimber L. Stanhope², Peter J. Havel², Rosahnak Rahimian¹

¹*Physiology and Pharmacology, University of the Pacific, USA,* ²*Department of Molecular Biosciences, School of Veterinary Medicine, and Department of Nutrition, University of California, Davis, USA*

Background: UC Davis type 2 diabetes mellitus (UCD-T2DM) rat is a novel and validated model of type 2 diabetes mellitus. UCD-T2DM rats are characterized by polygenic, adult-onset obesity and spontaneous beta-cell failure and, as a result, more closely models the pathophysiology of type 2 diabetes in humans than other rodent models. The objectives of this study were to determine whether the aortic function is altered in male UCD-T2DM rats, and to test the hypothesis that potassium (K⁺) channels contribute in modulating vascular reactivity of aorta in this model.

Method: Endothelium-dependent vasodilation (EDV) to acetylcholine (ACh, 10⁻⁸ to 10⁻⁵M) was measured in intact aortic rings pre-contracted with phenylephrine (PE, 2μM) before and after pretreatment with tetraethylammonium (TEA, 2 mM), a non-selective K⁺ channel blocker or TRAM-34 (1μM), a selective blocker of the intermediate-conductance Ca²⁺ + activated K⁺ (IKCa) channel or apamin (1μM), a small-conductance Ca²⁺ activated K⁺ (SKCa) channel inhibitor. Vasodilation to sodium nitroprusside (SNP, 10⁻⁹ to 10⁻⁵ M) was assessed in endothelium-denuded aortic rings. Furthermore, constrictor response curves to PE (10⁻⁸ to 10⁻⁵ M) were generated. Expression of K⁺ channels were also evaluated in aortic tissues.

Results: Both maximal relaxation and sensitivity to ACh were significantly enhanced in aortic rings from male UCD-T2DM rats compared to controls. Incubation of aortic rings with TEA or TRAM 34 blunted the relaxation responses to ACh in both groups. However, the inhibitory effects of TEA or TRAM 34 on the ACh-induced relaxation in UCD-T2DM group was greater than those in controls. By contrast, ACh responses were not affected following incubation with Apamin in either group. Accordingly, the level of expression of IKCa channels was significantly higher in diabetic group than in the controls, but SKCa expression did not differ between the groups. The responsiveness to PE was significantly enhanced, while smooth muscle sensitivity to NO, as measured by SNP-induced relaxation, was not altered in UCD-T2DM group.

Conclusion: These data, for the first time, show that the vascular function is altered in male UCD-T2DM rats, and an elevation of IKCa channels may partially contribute to the potentiated ACh responses in this disease model (supported by NIH).