

C-peptide Reverses Hyperglycemia-induced Mitochondrial Dysfunction in Murine Renal endothelial cells

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Renal endothelial cells are a prime target for hyperglycemic damage during diabetes because the glucose transport rate of these cells does not decline quickly enough, leading to intracellular hyperglycemia. This eventually increases the voltage gradient across the mitochondrial membrane until a threshold is reached and oxidants are generated. Numerous studies suggest a protective role for C-peptide against diabetes-induced microvascular complications. The goal of this study was to determine the effect of C-peptide on mitochondrial membrane potential ($\Delta\Psi_m$) and respiratory function, in conditionally immortalized renal microvascular endothelial cells exposed to a high glucose environment. Renal microvascular endothelial cells from H-2Kb-tsA58/mice were exposed to high glucose (HG)-25 mM or low glucose (LG)-5 mM with raffinose in the absence or presence of rat C-peptide II (6.6 nM) for 24-hours under non-permissive conditions. HG treatment resulted in significant hyperpolarization of $\Delta\Psi_m$ ($p < 0.002$) as assessed by JC-1 fluorescence. Concomitant treatment with C-peptide (6.6 nM) restored $\Delta\Psi_m$ to normal ($p < 0.002$). HG treated cells displayed significantly lower state 3 respiration rates ($p < 0.05$) compared to LG. C-peptide treatment restored state 3 rate to normal ($p < 0.05$). Respiratory control ratio (a measure of electrochemical coupling) is significantly higher in HG cells treated with C-peptide, compared to HG ($p < 0.001$). Together, these data demonstrate that rat C-peptide II protects against endothelial mitochondrial dysfunction during hyperglycemia. (Funded by NIH Grant #RO1 DK067582 to RWB)