**THYROID HORMONE INDUCES VASCULAR RELAXATION THROUGH VASP PHOSPHORYLATION AT SERINE 239: A POTENTIAL THERAPEUTIC APPROACH TO TREAT DIABETIC VASCULAR DYSFUNCTION**

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Vascular complications are the major problem faced by diabetic patients. Impairment of vasorelaxation is the earliest manifestation of diabetic vascular dysfunction. Anti-hyperglycemic drugs have improved the life quality of these patients; however it still does not prevent the onset of vascular complications. Alternative therapeutic strategies are clearly needed. Studies have indicated that triiodothyronine (T3) has anti-diabetic effects. T3 is known to rapidly relax vascular smooth muscle cells (VSMCs) via mechanisms that involve nitric oxide (NO). Recently, a correlation between VASP phosphorylation at serine 239, a substrate for cGMP-dependent protein kinase (PKG), and VSMC relaxation has been demonstrated. We hypothesized that a signaling pathway through NO/cGMP/PKG/VASP is involved in T3-induced vasorelaxation. Human endothelial cells (EC) treated with 0.1uM T3 for short-time increased NO levels. Additionally, T3 stimulated VASP phosphorylation at serine 239 in human VSMCs (2.0 ± 0.2 fold of increase), which was diminished with 1uM KT5823, a selective PKG inhibitor. Rat aortas incubated with T3 showed a significant increase in PKG expression (1.8±0.1 fold of increase). Endothelium-dependent and –independent relaxation was assessed in rat aortas treated with T3 for 20 minutes. Aortas treated with T3 exhibited greater sensitivity (EC50) to acetylcholine (EC50 value: 7.80±0.07 vs. 7.10±0.05 control, p<0.0001) and sodium nitroprusside (EC50 value: 8.12±0.03 vs. 7.6±0.02, p<0.0001). T3-induced vasorelaxation independent of endothelium was partially reduced in the presence of 1uM KT5823 (EC50 value: 7.8±0.02, p<0.05). Aortas from male db/db mice, a model of type 2 diabetes, displayed decreased levels of VASP phosphorylated at serine 239 (2.7 ± 0.1 fold of decrease). Moreover, impaired relaxation response to Ach observed in db/db aortas was improved with T3 incubation. Our results suggest a novel NO/PKG/VASP molecular mechanism underlying T3-induced vascular relaxation. Strategies utilizing T3 in safe dose pose a promising approach as an adjunct therapy to treat vascular dysfunction in diabetes.