Title: Endothelium-dependent impairments to cerebral vascular reactivity with type 2 diabetes mellitus in the Goto-Kakizaki rat

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Structured Abstract:

Introduction: Type II diabetes mellitus (T2DM) is characterized by hyperglycemia and insulin resistance. It is both a widespread and growing public health concern affecting nearly 400 million people worldwide. T2DM is associated with the development of cerebrovascular disease largely due to impairments in vascular tone regulation leading to inappropriate cerebral blood flow. This study tested the hypothesis that the diabetic environment in the Goto-Kakizaki (GK) rat, in the absence of obesity and other comorbidities, leads to endothelial dysfunction and impaired vascular tone regulation.

Methods: We determined wall mechanics and vascular reactivity in ex vivo middle cerebral arteries (MCA) from 17-18-wk-old male Wistar Kyoto (WKY) and GK (n=12) after isolating and cannulating with glass micropipettes. Mechanical responses following challenge with logarithmically increasing dosages of an agonist were fit with a three-parameter logistic equation to determine the upper bound of the change in diameter with agonist concentration.

Results: Dilation of MCA following challenge with acetylcholine and hypoxia was blunted in MCA from GK versus WKY, due to lower nitric oxide bioavailability and altered arachidonic acid metabolism, whereas myogenic activation and constrictor responses to serotonin were unchanged. MCA wall distensibility and cross-sectional area were not different between GK and WKY, suggesting that wall mechanics were unchanged at this age, supported by the determination that MCA dilation to sodium nitroprusside was also intact. With the use of ex vivo aortic rings as a bioassay, altered vascular reactivity determined in MCA was paralleled by relaxation responses in artery segments from GK, whereas measurements of vasoactive metabolite production indicated a loss of nitric oxide and prostacyclin bioavailability and an increased thromboxane A2 production with both methacholine challenge and hypoxia.

Discussion: These results suggest that endothelium-dependent dilator reactivity of MCA in GK is impaired with T2DM, and that this impairment is associated with the genesis of a prooxidant/pro-inflammatory condition with diabetes mellitus. The restriction of vascular impairments to endothelial function only, at this age and development, provide insight into the severity of multimorbid conditions of which T2DM is only one constituent. Given the extensive correlations between the incidence and prevalence of T2DM and negative cerebrovascular outcomes associated with the progression of the diabetic condition, this study provides a framework for additional investigation into mechanistic pathways and potential therapeutic options for restoring function in the cerebral circulation and improving current negative outcomes associated with T2DM.