

## **HYPERGLYCEMIA-MEDIATED OVEREXPRESSION OF CYCLOOXYGENASE-2 (COX-2) PARTICIPATES IN VASCULAR HYPOREACTIVITY OF STREPTOZOTOCIN-INDUCED TYPE 1 DIABETES**

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Hyperglycemia is a well recognized trigger for endothelial dysfunction, which results from disruption of the complex balance between vascular mediators. Nitric Oxide (NO) and prostacyclin (PGI<sub>2</sub>) -respectively produced by endothelial NO synthase (NOS) and COX- are among key modulators of vascular tone. In diabetic state, overexpression of both constitutive and inducible NOS isoforms may increase NO production over physiological threshold and impair vascular function. The contribution of COX pathways to altered vascular reactivity during diabetes is still controversial. To investigate the role of COX-2 mediators on vascular changes occurring during the onset of pharmacologically induced type I diabetes, Balb/c mice were treated once with streptozotocin (STZ, 240mg/kg, i.p.) or vehicle (citrate buffer). Diabetic condition was assessed by oral glucose tolerance test. Hyperglycemia (>200mg/dl) and body weight loss progressively increased during the 8 weeks of the study. No significant change in vascular reactivity was observed in isolated mesenteric vascular arteries (MVB) up to 4-week after STZ-induced diabetes. On the other hand, 8-week STZ mice had a significant impairment in endothelial-mediated vasorelaxation induced by acetylcholine (ACh: 0.01-1 μM) (p<0.05 vs Ctrl, n=12), whereas endothelial-independent relaxation to SNP was unchanged (p>0.68, ns). Interestingly, vasoconstriction mediated by noradrenaline (NA: 0.01-100 μM) and/or thromboxane A<sub>2</sub> analogue U46619 (0.01-10 μM) was also significantly reduced in STZ-mice (p<0.01 vs Ctrl, n=15). The hyporeactivity to vasoconstrictors was reverted by pretreatment with the NOS antagonist L-NAME (100 μM/20 min) or the selective COX-2 inhibitor NS-398 (10 μM/20 min) (p<0.01 vs Ctrl, n=7, for both treatments). In addition, a significant increase in PGI<sub>2</sub> levels was observed (by ELISA assay) in aortas from STZ-8 wk under basal and NA/ACh-stimulated conditions (p<0.05 vs Ctrl, n=6). Pretreatment with NS-398 completely abolished both basal and stimulated PGI<sub>2</sub> release. Consistent with abnormal release of NO and prostacyclin, increased expression of NOS and COX-2 proteins was observed in MVB homogenates (by WB analysis), as well as in aortic sections (by immunofluorescence analysis) of 8-wk STZ-mice. These results suggest that, in addition to endothelial dysfunction with impaired vasodilation, abnormal activation of both NOS and COX-2 pathways contribute to vascular alteration characterized by progressive vascular smooth muscle dysfunction and impaired vasoconstriction in our experimental model of type I diabetes.

