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### **P300/CBP-HISTONE ACETYLTRANSFERASE MEDIATES THE UP-REGULATION OF NADPH OXIDASE EXPRESSION AND OXIDATIVE STRESS IN THE AORTA OF DIABETIC MICE**

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**Purpose:** NADPH oxidase (Nox)-derived reactive oxygen species (ROS) play a major role in the pathoetiology of diabetes-associated cardiovascular disorders. The mechanisms of vascular Nox up-regulation in diabetes are not entirely elucidated. P300/CBP-histone acetyltransferase (HAT) is an important co-transcriptional activator for numerous pro-inflammatory transcription factors. In this study we aimed at elucidating the role of p300/CBP in the modulation vascular Nox expression and oxidative stress in experimental diabetes. **Methods:** Non-diabetic and streptozotocin-induced diabetic C57BL/6J mice were randomized to receive vehicle or C646 (10 mg/kg, 4 weeks), a selective p300/CBP pharmacological inhibitor. Luciferase reporter gene assays were employed to measure the activation of NF- $\kappa$ B, C/EBP, and STAT transcription factors (regulators of Nox) in a human endothelial cell (EC) line (EA.hy926). The gene/protein expression levels were determined by real-time PCR/western blot. **Results:** Significant increases in p300/CBP (type A HAT) and HAT1 (type B HAT) along with NADPH oxidase subtypes (Nox1, Nox2, Nox4), and nitrotyrosine (NT)-modified proteins were detected in the aorta of diabetic mice compared to non-diabetic animals. Treatment of diabetic mice with C646 significantly reduced the gene and protein expression levels of Nox1, Nox2, Nox4, and NT-protein adducts. C646 reduced the activation of NF- $\kappa$ B, C/EBP, and STAT in cultured EC.

**Conclusions:** Pharmacological inhibition of p300/CBP reduces oxidative stress in the aorta of diabetic mice, possibly by a mechanism involving negative regulation of Nox expression. The novel data of this study point to p300/CBP as potential therapeutic target in diabetes-related vascular complications. **Financial Disclosure:** No

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