

**Increased vasoactive factors and extracellular matrix proteins in the retina and heart in type 2 diabetes are prevented by macitentan, a dual endothelin receptor antagonist**

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**Introduction:** In diabetes, hyperglycemia is known to cause alteration of endothelin (ET) system, which plays a pathogenetic role in production of vasoactive factors and extracellular matrix protein in the organs affected by chronic complications such as retina and heart. In this study, we investigated the effects of macitentan, an orally active, tissue-targeting dual ET receptor antagonist on the prevention of increased vasoactive factors and extracellular matrix proteins in the retina and heart in animals with type 2 diabetes.

**Methods:** db/db mice and there age- and sex-matched controls were examined after 2 and 4 months of diabetes. Groups of diabetic animals were treated with oral macitentan (25 mg/Kg/day) mixed with food. The animals were monitored with respect to body weight, blood glucose, urine glucose and ketones. Cardiac functions were examined. Retinal and cardiac tissues were analyzed for ET1, transforming growth factor  $\beta$ 1, vascular endothelial growth factor, fibronectin, EDB+ fibronectin and collagen 1( $\alpha$ )4 mRNA by real-time RT-PCR. Expression of molecular markers of hypertrophy such as atrial natriuretic peptide and brain natriuretic peptide were measured in the heart. Protein expressions in the cardiac tissues were measured by ELISA.

**Results:** Diabetic animals showed increased body weight, hyperglycemia and glucosuria. Diabetic animals further showed increased mRNA expression of ET1, transforming growth factor  $\beta$ 1, vascular endothelial growth factor, fibronectin, EDB+ fibronectin, Collagen 1( $\alpha$ )4 mRNA expression in the retina and heart. Augmented fibronectin protein expression was demonstrated in the cardiac tissues. Furthermore diabetes induced increased expression of atrial natriuretic peptide and brain natriuretic peptide in the heart. Such changes were pronounced after 4 months compared to 2 months of follow-up. Treatment with macitentan significantly prevented these abnormalities in all organ studied.

**Conclusion:** These experiments showed that ET system plays a significant role in the increased production of vasoactive factors and extracellular matrix proteins in the retina and heart in type 2 diabetes. We also demonstrated that, treatment with macitentan can prevent such changes, suggesting that ET blockade is a potential adjuvant treatment for chronic diabetic complications.