

[gw22-e0397]

**METFORMIN MAY INHIBIT CARDIOVASCULAR
REMODELING THROUGH SUPPRESSING
UROTENSIN II AND ANGIOTENSIN II SYSTEM**

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10.1136/heartnl-2011-300867.182

Background Cardiovascular complications of diabetes always affect the prognosis of patients. Cardiovascular remodeling

characterised by proliferation and collagen synthesis of cardiovascular cells is the key stones of cardiovascular complications. Urotensin II and angiotensin II are two most important vascular peptides involved in cardiovascular remodeling. Previous studies have shown that metformin has cardiovascular protective effect. However, its mechanism is still not fully understood. It is not clear whether metformin could exert its cardiovascular protective effect through its action on urotensin II and angiotensin II system.

Objective To explore the mechanism of the cardiovascular protective effect of metformin, to determine whether metformin could inhibit the expression of urotensin II and its receptor GPR14 as well as angiotensin II receptor-AT₁R and proliferation and collagen synthesis of cardiovascular cells including cardiac fibroblast, vascular smooth muscle cells and adventitial fibroblasts induced by urotensin II and angiotensin II.

Methods In OLETF rats, we detected the expression of urotensin II, GPR14 and AT₁R in the left ventricle and aorta and the effect of metformin on their expression with real-time PCR. In cultured cardiovascular cells, we investigated the effect of metformin on the proliferation and collagen synthesis induced by urotensin II and angiotensin II using MTT and ELISA.

Results (1) Compared with control (OLETF) rats, the expression of urotensin II, GPR14 and AT₁R in left ventricle and aorta was increase to 3.26 and 4.2 times (3.26 ± 0.08 vs 1.00 ± 0.09 , $p < 0.01$; 4.20 ± 0.55 vs 1.00 ± 0.09 , $p < 0.01$), 3.81 and 3.26 times (3.81 ± 0.52 vs 1.00 ± 0.10 , $p < 0.01$; 3.26 ± 0.36 vs 1.01 ± 0.14 , $p < 0.01$), 3.99 and 3.80 times (3.99 ± 0.66 vs 1.02 ± 0.21 , $p < 0.01$; 3.80 ± 0.43 vs 1.01 ± 0.19 , $p < 0.01$). (2) Metformin could significantly down-regulate the mRNA expression of urotensin II, GPR14 and AT₁R in the ventricle and aorta of OLETF rats by 60.4% and 73.3%, 66.1% and 60.4%, 65.9% and 59.7%. (3) Metformin could significantly inhibit the proliferation of cardiac fibroblasts, vascular smooth muscle cells and adventitial fibroblasts induced by urotensin II and angiotensin II. (4) Metformin could significantly inhibit collagen I secretion of cardiac fibroblasts and adventitial fibroblasts.

Conclusion Metformin could significantly down-regulate the expression of urotensin II, GPR 14 and AT₁R which are involved in cardiovascular remodeling and inhibit the proliferation and collagen synthesis of cardiovascular cells induced by urotensin II and angiotensin II. Our results suggested that metformin could exert its cardiovascular protective effect partly through inhibiting urotensin II and angiotensin II along with their induction of proliferation and collagen synthesis of cardiovascular cells. Thus, our study provided new evidence for the use of metformin in the prevention and treatment of cardiovascular complication in diabetes.