Dipeptidyl peptidase-4 (DPP-4) inhibitor, linagliptin, attenuates left ventricular remodeling after myocardial infarction via DPP-4-independent pathway.

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Background: Dipeptidyl peptidase-4 (DPP-4) inhibitors not only improve impaired glucose tolerance in diabetes, but also have pleiotropic extra-pancreatic effects such as preconditioning effect for myocardial ischemia-reperfusion injury. Here, we investigated the anti-remodeling effects of linagliptin, a DPP-4 inhibitor, by use of DPP-4-deficient rats.

Methods and Results: After the induction of myocardial infarction (MI), Fischer 344 rats with inactivating mutation of DPP-4 were orally administrated with a DPP-4 inhibitor, linagliptin (5 $mg \cdot kg^{-1} \cdot day^{-1}$), or vehicle in drinking water for 4 weeks. Linagliptin did not affect hemodynamic status, body weight, and infarct size. In echocardiography, linagliptin tended to improve left ventricular (LV) systolic function, and significantly improved LV diastolic function, surprisingly. Interstitial fibrosis and macrophage infiltration were significantly lower in the linagliptin group than those in the vehicle group. Fibrosis-related gene expressions, such as collagen I and transforming growth factor-β1 (TGF-β1), and inflammation-related expressions, such as macrophage chemotactic protein 1 and matrix metalloproteinase-2 (MMP-2), were significantly suppressed in marginal area of the linagliptin-treated rats compared with the vehicle rats. The TGF-β1 and MMP-2 protein levels were attenuated by linagliptin in DPP-4-deficient cardiac fibroblasts.

Conclusions: Linagliptin can attenuate MI-induced cardiac remodeling via a DPP-4-independent pathway.