News Release

Title

Chronic psychological stress accelerates vascular senescence and impairs ischemia-induced neovascularization: The role of dipeptidyl peptidase-4/glucagon-like peptide-1-adiponectin axis

Key Points

- Present findings show a critical role of the interaction between DPP4-related GLP-1/GLP-1R and APN/AdiopR1 signaling pathways in ischemic vascular regeneration under chronic stress conditions.
- This novel biological function of the cross-talk may be exploited for the therapeutic management of chronic psychosocial stress-related vascular aging and cardiovascular disease.

Summary

Limei Piao (the first author; 3rd PhD student, Department of Community Health & Geriatrics), Xian-Wu Cheng (Associate Professor, Institute of Innovation for Future Society and Department of Community Health & Geriatrics), Masafumi Kuzuya (Professor, Institute of Innovation for Future Society and Department of Community Health & Geriatrics), Rei Shibata (Associate Professor, Department of Cardiology, Nagoya University Graduate School of Medicine), Toyoaki Murohara (Professor, Department of Cardiology, Nagoya University Graduate School of Medicine) and both team from Nagoya University Graduate School of Medicine (Dean: Kenji Kadomatsu, MD, PhD) found that DPP4/GLP-1-APN axis is novel therapeutic target for the treatment of vascular aging and cardiovascular disease under chronic stress conditions.

Here we report that increased DPP4 activity may negatively modulate ischemic neovascularization via an APN-PPARγ/PGC-1α-dependent mechanism that is mediated by the reduction of GLP-1 in mice under chronic stress.

Research Background

Exposure to chronic psychosocial stress is a risk factor for many diseases, including vascular aging and cardiovascular disease. It is established that there is close-linking between chronic psychological stress and atherosclerosis-based cardiovascular disease. It was also reported that endothelial cells (ECs) and endothelial progenitor cells (EPCs) are sensitive to various pathological stressors. However, the changes in vascular aging and regenerative capacity under chronic stress conditions remain largely unknown.

Dipeptidyl peptidase 4 (DPP4) is a complex enzyme that acts as a membrane-anchored cell surface exopeptidase that transmits intracellular signals through a small intracellular tail. DPP4 has gained considerable interest as a therapeutic target, and a variety of DPP4 inhibitors that prolong the insulinotropic effects of glucagon-like peptide-1 (GLP-1) are widely used in clinical settings as a new class of antidiabetic drugs. Recent study reported a close link between increased plasma DPP4 activities and inflammatory and metabolic disorders. Moreover, chronic stress increased plasma and tissue DPP4 activities in mice and rats.

The peroxisome proliferator-activated receptor-γ (PPAR-γ) is a member of the typical nuclear receptor superfamily of ligand-inducible transcription factors. Adiponectin (APN) is an important adipocytokine that is down-regulated in obesity-related metabolic and cardiovascular disorders. Many studies suggested that APN as well as PPAR-γ ligands have beneficial effects on cardiac and muscle injuries and angiogenesis. In *vitro* experiments, the activation of APN-mediated PPAR-γ/its coactivator 1α (PGC-1α) pathway has been implicated in the regulation of a variety of cellular biological events such as cell differentiation, migration, apoptosis and proliferation. Accordingly, we first investigated whether the interaction between DPP4-related GLP-1/GLP-1R and APN/AdiopR1 signaling pathways are involved in the process of ischemia-induced neovascularization in mice under chronic stress.

Research Results

- Stress impaired the recovery of the ischemic/normal blood-flow ratio throughout the follow-up period and capillary formation.
- Here, at the molecular and cellular levels, stressed mice showed the following: increased levels of plasma and ischemic muscle DPP4 and decreased levels of GLP-1 and APN in plasma and phospho-AMP-activated protein kinase α (p-AMPKα), vascular endothelial growth factor, PPAR-γ, PGC-1α, and Sirt1 proteins and insulin receptor 1 (IRS-1) and glucose transporter 4 (GLUT4) genes in the ischemic tissues, vessels, and/or adipose tissues and numbers of circulating $CD31^{+}$/$c\text{-}Kit^{+}$ endothelial progenitor cells (EPCs).
- Chronic stress accelerated aortic senescence and impaired aortic endothelial sprouting.
- DPP4 inhibition with anagliptin increased plasma and/or tissues GLP-1 and APN levels. Anagliptin also improved the targeted molecular levels (including p-AMPKα, PPAR-γ, PGC-1α, Sirt1, IRS-1, and GLUT4) proteins and genes in the ischemic tissues, vessels, and/or adipose tissues and peripheral blood EPC numbers. DPP4 inhibition restores impaired ischemia-induced blood flow recovery and capillary formation in stressed mice.
- GLP-1 analogue exenatide supplementation ameliorated ischemia-induced neovascularization under our experimental conditions.

- APN deficiency diminished DPP4 inhibition-mediated vasculoprotective actions in mice under chronic stress.
- Thus, these findings indicate that DPP4/GLP-1-APN axis is novel therapeutic target for the treatment of vascular aging and cardiovascular disease under chronic stress conditions.

Research Summary and Future Perspective

Taken together, the previous and present findings show a critical role of the interaction between DPP4-related GLP-1/GLP-1R and APN/AdiopR1 signaling pathways in ischemic vascular regeneration under chronic stress conditions. This novel biological function of the cross-talk may be exploited for the therapeutic management of chronic psychosocial stress-related vascular aging and cardiovascular disease.

Publication

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Chronic psychological stress accelerates vascular senescence and impairs ischemia-induced neovascularization: The role of dipeptidyl peptidase-4/glucagon-like peptide-1-adiponectin axis. The paper on the above result will be published online (before print) in an English journal Journal of the American Heart Association on September 28, 2017.

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