

News Release

Title

Dipeptidyl Peptidase 4 Inhibition Alleviates Shortage of Circulating Glucagon-like Peptide-1 in Heart Failure and Mitigates Myocardial Remodeling and Apoptosis via the EPAC1/Rap1 Axis

Key Points

#1 GLP-1 may play a pivotal role in neurohormonal regulation in heart failure.

#2 The cAMP signaling protects heart from apoptosis exclusively via Rap1/EPAC axis independently of PKA.

Summary

Professor Toyoaki Murohara, Associate Professor Yasuko K. Bando (corresponding author), and Haruya Kawase and Morihiko Aoyama (first authors) at Department of Cardiology of the Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) demonstrated in collaboration with their colleagues that the incretin hormone glucagon-like Peptide-1 (GLP-1) plays a pivotal role in neurohormonal regulation in heart failure. GLP-1 modulates cyclic AMP signaling that protects heart from apoptosis exclusively via Rap1/EPAC axis. These data also implicates that the cAMP/Rap1/EPAC1 axis may be expected as new drug discovery target.

The present study was conducted to address the impact of DPP4i/GLP-1/cAMP axis on cardiac dysfunction and remodeling induced by pressure overload (TAC) independently of diabetes. DPP4i (alogliptin, ALO; 10 mg/kg/day for 4 weeks) prevented TAC-induced contractile dysfunction, remodeling, and apoptosis of myocardium in a GLP-1 receptor antagonist [exendin(9-39)]-sensitive fashion. In TAC, circulating level of GLP-1 (in pM; 0.86 ± 0.10 for TAC versus 2.13 ± 0.54 for sham control) unexpectedly declined and so did the myocardial cyclic AMP (cAMP) concentration (in pmole/mg protein; 33.0 ± 1.4 for TAC versus 42.2 ± 1.5 for sham). ALO restored the decline in the GLP-1/cAMP levels observed in TAC thereby augmented cAMP signaling effectors [protein kinase A (PKA) and exchange protein directly activated by cAMP (EPAC1)]. In vitro assay revealed that distinct roles of PKA and EPAC1 in cardiac apoptosis. EPAC1 promoted cardiomyocyte survival via concomitant increase in B-cell lymphoma-2 (Bcl-2) expression and activation of small G protein Rap1 in a cAMP-dose-dependent and PKA-independent fashion.

Research Background

Ample evidence demonstrates cardiovascular protection by incretin-based therapy using dipeptidyl peptidase inhibitors (DPP4i) and glucagon-like peptide-1 (GLP-1) under either diabetic or nondiabetic condition. Their action on myocardium is mediated by cAMP signal, however, the pathway remains uncertain.

Research Results

Unexpectedly, the circulating GLP-1 level exhibited pathological decline in heart failure, which caused cardiac remodeling and apoptosis via the cAMP/Rap1/EPAC1 pathway independently of PKA.

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Research Summary and Future Perspective

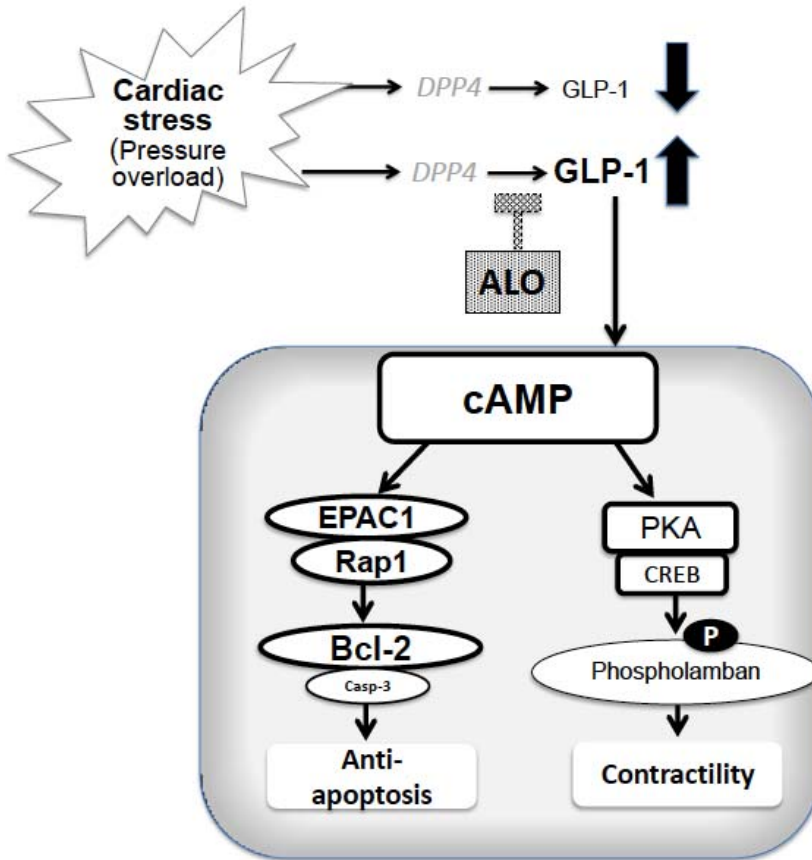
GLP-1 may play a pivotal role in neurohormonal regulation in heart failure. The cAMP signaling protects heart from apoptosis exclusively via Rap1/EPAC axis that may be expected as new drug discovery target.

Article

Morihiko Aoyama, Haruya Kawase, Yasuko K Bando, Akio Monji, Toyooki Murohara. Dipeptidyl Peptidase 4 Inhibition Alleviates Shortage of Circulating Glucagon-like Peptide-1 in Heart Failure and Mitigates Myocardial Remodeling and Apoptosis via the EPAC1/Rap1 Axis. *Circulation Heart Failure*; Jan.1,2016.

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http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2015/GLP_1_20160104jp.pdf



Suggested mechanism
Heart failure and cAMP-signal pathway

GLP-1 activates Rap1 independently of PKA activity in cardiomyocytes

