

## News Release

### Title

A dipeptidyl peptidase-4 inhibitor ameliorates hypertensive cardiac remodeling via angiotensin-II/sodium-proton pump exchanger-1 axis.

### Key Points

- Distinct action of dipeptidyl peptidase-4 inhibitors on hypertension
- BP lowering mechanism induced by teneligliptin via non-canonical angiotensinII (AngII) pathway.
- Novel mechanisms that modulate hypertensive cardiac hypertrophy via NHE-1.
- Regulatory role of intracellular acidification via NHE-1 in cardiac hypertrophy.

### Summary

Professor Toyooki Murohara, Associate Professor Yasuko K. Bando (corresponding author), and Haruya Kawase (first author) at Department of Cardiology of the Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) tested the impact of dipeptidyl peptidase-4 (DPP4) inhibitors on hypertension and comorbid cardiac remodeling in preclinical settings by use of rat hypertensive model and cultured caridomyocytes. They found that some of DPP-4 inhibitor ameliorated hypertension and hypertensive cardiac remodeling via AngII/ sodium-proton pump exchanger type 1 (NHE-1)-dependent fashion.

### Research Background

To address the impact of antidiabetic drugs on cardiovascular safety is a matter of clinical concern. Preclinical studies revealed that the various protective effects of dipeptidyl peptidase-4 inhibitor (DPP4i) on cardiovascular disease; however, its impact of on hypertension remains controversial.

The present study was conducted to address the impact of DPP4 inhibitors on hypertensive cardiac remodeling independently of diabetes.

### Research Results

The anti-hypertensive action of DPP4i was presumably drug-specific effects in hypertensive rat model. The DPP-4i-induced amelioration of hypertension was

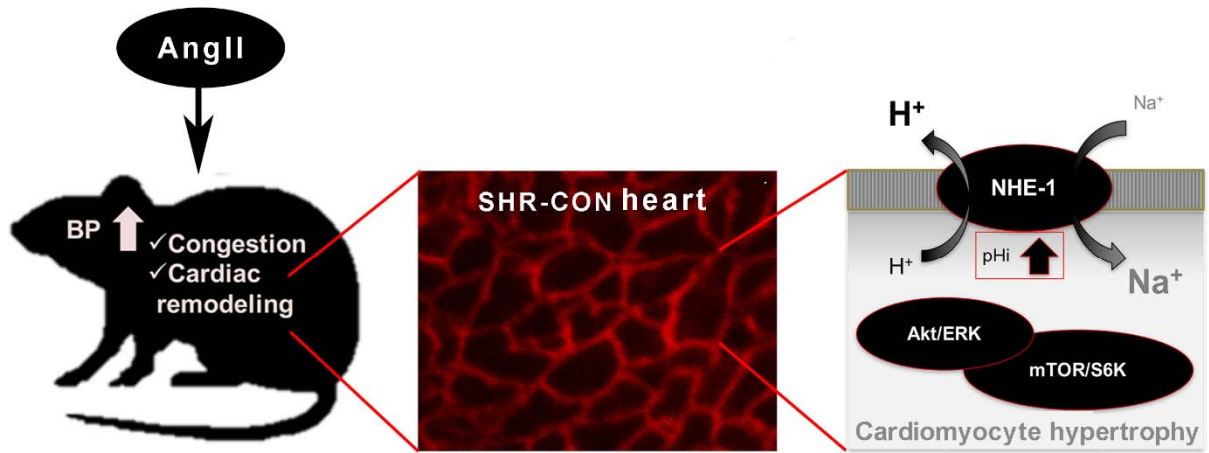
mediated by normalizing a rise of angiotensin-II (AngII) that specifically observed in spontaneously hypertensive rats (SHR). The abnormal rise of AngII in hypertension promotes cardiac remodeling and congestive heart failure. AngII directly affects cardiomyocytes by upregulation of Sodium-proton pump exchanger type 1 (NHE-1), a regulator of intracellular acidity (pHi) that has been previously implicated pathophysiological role in cardiac remodeling occurred in diseased myocardium. Cardiac NHE-1 expression level was increased in SHR and this was restored in reduction of AngII induced by DPP4i. In vitro analysis by using cardiomyocytes revealed that the AngII induced cardiac hypertrophy via upregulation of NHE-1 both in mRNA and protein levels. Loss of NHE-1 activity by specific inhibitor or RNA silencing attenuated the AngII-mediated cardiac hypertrophy in vitro. Thus, we provide the evidences regarding not only the drug action of DPP4i but also the novel pathophysiological role(s) of the AngII/NHE-1 axis in hypertensive cardiac remodeling. The present study reinforces the primary role of AngII pathway in cardiac remodeling particularly in hypertensive population.

### **Research Summary and Future Perspective**

It is unique characteristics of DPP4i that the chemical structure of this drug class is quite distinct from each other. The present study demonstrated a clue for new drug discovery that might contribute to an anti-hypertrophic remedy targeting NHE-1.

### **Publication**

Kawase H, Bando YK, Nishimura K, Aoyama M, Monji A, Murohara T. A dipeptidyl peptidase-4 inhibitor ameliorates hypertensive cardiac remodeling via angiotensin-II/sodium-proton pump exchanger-1 axis. *Journal of Molecular and Cellular Cardiology* 2016 Jun 30. pii: S0022-2828(16)30218-8. doi: 10.1016/j.yjmcc.2016.06.066. [Epub ahead of print]



Japanese ver.

[http://www.med.nagoya-u.ac.jp/medical/dbps\\_data/material/nu\\_medical/res/topix/2016/dpp4\\_20160713jp.pdf](http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2016/dpp4_20160713jp.pdf)