Abstract: P1618

A polymethoxy flavonoid, Nobiletin, has a therapeutic potency against the development of heart failure through NBP1 activation.

Authors:
Y Sunagawa¹, M Funamoto¹, K Shimizu¹, S Shimizu¹, Y Katayakusa¹, Y Miyazaki¹, H Wada², T Kan¹, K Hasegawa², T Morimoto¹, ¹University of Shizuoka - Shizuoka - Japan, ²Kyoto Medical Center, Clinical Research Institute - Kyoto - Japan

Topic(s):
Basic Science - Cardiac Diseases: Heart Failure

Citation:
This work was supported by JSPS KAKENHI Grant.

Introduction: Maladaptive hypertrophy is being recognized as a critical event during the development of heart failure. The control of cardiac hypertrophy may be one of the therapeutic strategies for heart failure therapy. In our previous study, we screened natural compound library and found that a natural compound, Nobiletin, could inhibit cardiomyocyte hypertrophy in culture. Nobiletin has various useful effects such as anti-cancer, anti-inflammation, and anti-oxidant and may be applicable to pharmacological therapy for heart failure.

Hypothesis: We thought that nobiletin might prevent the development of heart failure in vivo and investigated the target molecule of Nobiletin in the heart.

Methods and Results: In primary cardiomyocytes, Nobiletin significantly inhibited phenylephrine (PE)-induced hypertrophic responses such as increases in cell size and hypertrophic gene transcription, such as ANF and BNP. C57BL6 mice were subjected to sham or transrarteric constriction (TAC). Oral administrations of Nobiletin (20 mg/kg/day) or vehicle were repeated for 8 weeks. Nobiletin treatment significantly prevented TAC-induced increases in PWT and systolic dysfunction. Nobiletin also suppressed TAC-induced myocardial cell hypertrophy, perivascular fibrosis, and hypertrophic gene transcriptions. To investigate the target molecule of Nobiletin, Nobiletin-binding proteins were purified from rat heart using biotin-conjugated Nobiletin. We identified 162 novel binding protein of Nobiletin by LC/MS-MS. One of them, Nobiletin-binding protein 1 (NBP1) related to cellular metabolic pathway. Pulldown assay demonstrated that biotin-conjugated Nobiletin, but not biotin, directly interacted with recombinant NBP1. In vitro enzyme assay showed that Nobiletin enhanced NBP1 activity. Although NBP1 knockdown could not affect PE-induced hypertrophic response gene transcriptions and cardiomyocyte hypertrophy, NBP1 knockdown failed to exhibit Nobiletin-mediated anti-hypertrophic effects. NBP1-KO mice and WT mice were subjected to sham or TAC and randomly divided into two groups: Nobiletin (20 mg/kg/day) and vehicle. After 8 weeks, Nobiletin significantly improved TAC-induced cardiac hypertrophy and systolic dysfunction in WT mice but not in NBP1-KO mice. Nobiletin also prevented TAC-induced increases in HW/BW rate, myocardial cell hypertrophy, and mRNA levels of ANF and β-MHC in WT mice but not in NBP1-KO mice.

Conclusions: In this study, we demonstrate that Nobiletin inhibits cardiomyocyte hypertrophy and the development of heart failure in vivo. NBP1 activity is required to exhibit therapeutic potency of Nobiletin for heart failure. These findings suggest that a natural compound, nobiletin, might be a candidate for heart failure agent in human.