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Young Investigator Award

Topic: 3. Heart Failure and Cardiomyopathy

Nobiletin a Citrus Flavonoid, Exerts Additional Effects with Angiotensin II Receptor Blocker on Systolic Function in Salt-sensitive Dahl Rats

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Introduction and Objectives

Maladaptive hypertrophy is being recognized as a critical event during the development of heart failure. We screened natural compounds purified from fruits library and found that Nobiletin, contained in the peel of *Citrus depressa*, represses phenylephrine-induced hypertrophic responses in cardiomyocytes. Nobiletin has various useful effects such as anti-cancer, anti-inflammation, and anti-oxidant. In previous study, we demonstrated that Nobiletin suppresses phenylephrine-induced hypertrophic responses in cardiomyocytes in a dose-dependent manner in cultured cardiomyocytes and oral administration of Nobiletin prevented systolic dysfunction and development of heart failure after myocardial infarction in rats. Thus, Nobiletin is expected as an effective agent for heart failure. To clinically apply this novel therapy to humans, it should be clarified whether or not Nobiletin exhibits additional effects on conventional heart failure therapy, such as Candesartan, an angiotensin II receptor antagonist (ARB). Thus, we examined the effects of Nobiletin / Candesartan combination therapy on heart failure *in vivo*.

Materials and Methods

Six week-old salt-sensitive Dahl (DS) rats and salt-resistant Dahl (DR) rats were fed with a high salt diet for 5 weeks. Eleven week-old DS rats were randomly assigned to 4 groups. Group I: DR rats with vehicle treatment (1 % gum arabic, n=5) as control. Groups II: DS rats with vehicle (n=8). Group III: Nobiletin (20 mg/kg/day, n=9). Group IV: Candesartan (1 mg/kg/day, n=8). Group V: Nobiletin and Candesartan combination (n=8). This dose of Candesartan has therapeutic potency

for heart failure without affecting blood pressure. Oral administrations were repeated everyday for 7 weeks. At 18 week-old, echocardiography were performed. The mRNA were extracted from left ventricle of these rats and the expression levels of the hypertrophic markers, such as ANF and BNP, were measured with quantified RT-PCR. Finally, left ventricle of these rats were stained with hematoxylin-eosin and myocardial cell diameter was measured.

Results

There were no differences among the 4 groups of DS rats in any LV geometric and functional parameters at 11 weeks-old. At 18 weeks-old, both Nobiletin and Candesartan did not affect increases in systolic and diastolic blood pressures. Left ventricular fractional shortening (LVFS) was significantly higher in Nobiletin (50.1 %; p<0.05) and Candesartan (49.7 %; p<0.05) groups than in the DS vehicle group (38.9 %). Notably, LVFS additionally increased in Nobiletin / Candesartan combination treatment (58.3 %; p<0.05) compared to Nobiletin or Candesartan alone. The DS vehicle group had increased hypertrophy-response gene activation, and this increase was significantly inhibited by all of treatments. Finally, the results of the quantitative analyses were that DS vehicle group had increased myocardial cell diameter, and that this increase was significantly inhibited by all the treatments.

Conclusions

A polymethoxy flavonoid, Nobiletin prevents hypertension-induced systolic dysfunction addition to ARB *in vivo*. This compound might be applicable for heart failure patients in clinical setting. ■