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Taxifolin protects against cardiac hypertrophy and fibrosis during biomechanical stress of pressure overload

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ABSTRACT

Cardiac hypertrophy is a key pathophysiological component to biomechanical stress, which has been considered to be an independent and predictive risk factor for adverse cardiovascular events. Taxifolin (TAX) is a typical plant flavonoid, which has long been used clinically for treatment of cardiovascular and cerebrovascular diseases. However, very little is known about whether TAX can influence the development of cardiac hypertrophy. In vitro studies, we found that TAX concentration-dependently inhibited angiotensin II (Ang II) induced hypertrophy and protein synthesis in cardiac myocytes. Then we established a mouse model by transverse aortic constriction (TAC) to further confirm our findings. It was demonstrated that TAX prevented pressure overload induced cardiac hypertrophy in mice, as assessed by ventricular mass/body weight, echocardiographic parameters, myocyte cross-sectional area, and the expression of ANP, BNP and β-MHC. The excess production of reactive oxygen species (ROS) played critical role in the development of cardiac hypertrophy. TAX arrested oxidative stress and decreased the expression of 4-HNE induced by pressure overload. Moreover, TAX negatively modulated TAC-induced phosphorylation of ERK1/2 and JNK1/2. Further studies showed that TAX significantly attenuated left ventricular fibrosis and collagen synthesis through abrogating the phosphorylation of Smad2 and Smad2/3 nuclear translocation. These results demonstrated that TAX could inhibit cardiac hypertrophy and attenuate ventricular fibrosis after pressure overload. These beneficial effects were at least through the inhibition of the excess production of ROS, ERK1/2, JNK1/2 and Smad signaling pathways. Therefore, TAX might be a potential candidate for the treatment of cardiac hypertrophy and fibrosis.

Introduction

Cardiac hypertrophy is a cellular response to increased biomechanical stress, characterized by increased size of cardiac myocytes and accumulated extracellular matrix (Oka and Komuro, 2008). It is a common pathophysiological component of cardiac remodeling in many kinds of cardiovascular diseases, such as valvular heart disease, hypertension, and hypertrophic cardiomyopathy (Hill and Olson, 2008). Sustained pathological hypertrophy is deleterious and may lead to cardiac arrhythmias, heart failure and ultimately death (Kehat and Molkentin, 2010). Increasing evidence showed that excessive production of reactive oxygen species (ROS) played critical role in cardiac hypertrophy (Takano et al., 2003). Related signaling pathways include the mitogen activated protein kinases (MAPKs) and TGF-β/Smad pathways, could directly modulate transcriptional factors and related cardiac gene expression to induce cardiac remolding (Takeishi et al., 2001; Doetschman et al., 2012). Therefore, pharmacological interventions of

Abbreviations: TAX, taxifolin; Ang II, angiotensin II; TAC, transverse aortic constriction; ROS, reactive oxygen species; ANP, atrial natriuretic polypeptide; BNP, brain natriuretic peptide; α-MHC, α-myosin heavy chain; β-MHC, β-myosin heavy chain; 4-HNE, 4-hydroxynonenal; ERK1/2, extracellular signal regulated kinase 1/2; JNK1/2, c-Jun N-terminal kinase 1/2; MAPKs, mitogen activated protein kinases; PKC, protein kinase C; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; FCS, fetal calf serum; PSR, picrosirius red; WGA, wheat germ agglutinin; DCFH-DA, 2′,7′-dichlorofluorescein dilacerate; MDA, malondialdehyde; RV, right ventricle; LV, left ventricle; LA, left atria; LW, lung weight; BW, body weight; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; IVSD, diastolic intraventricular septum thickness; LVPWD, diastolic left ventricular posterior wall thickness; FS, fractional shortening; HCV, hepatitis C virus; L-NAME, N^G-nitro-L-arginine methyl ester; TGF-β, transforming growth factor-β; CTGF, connective tissue growth factor; MMP-9, matrix metallopeptidase-9; TIMP1, tissue inhibitor of metalloproteinases-1.

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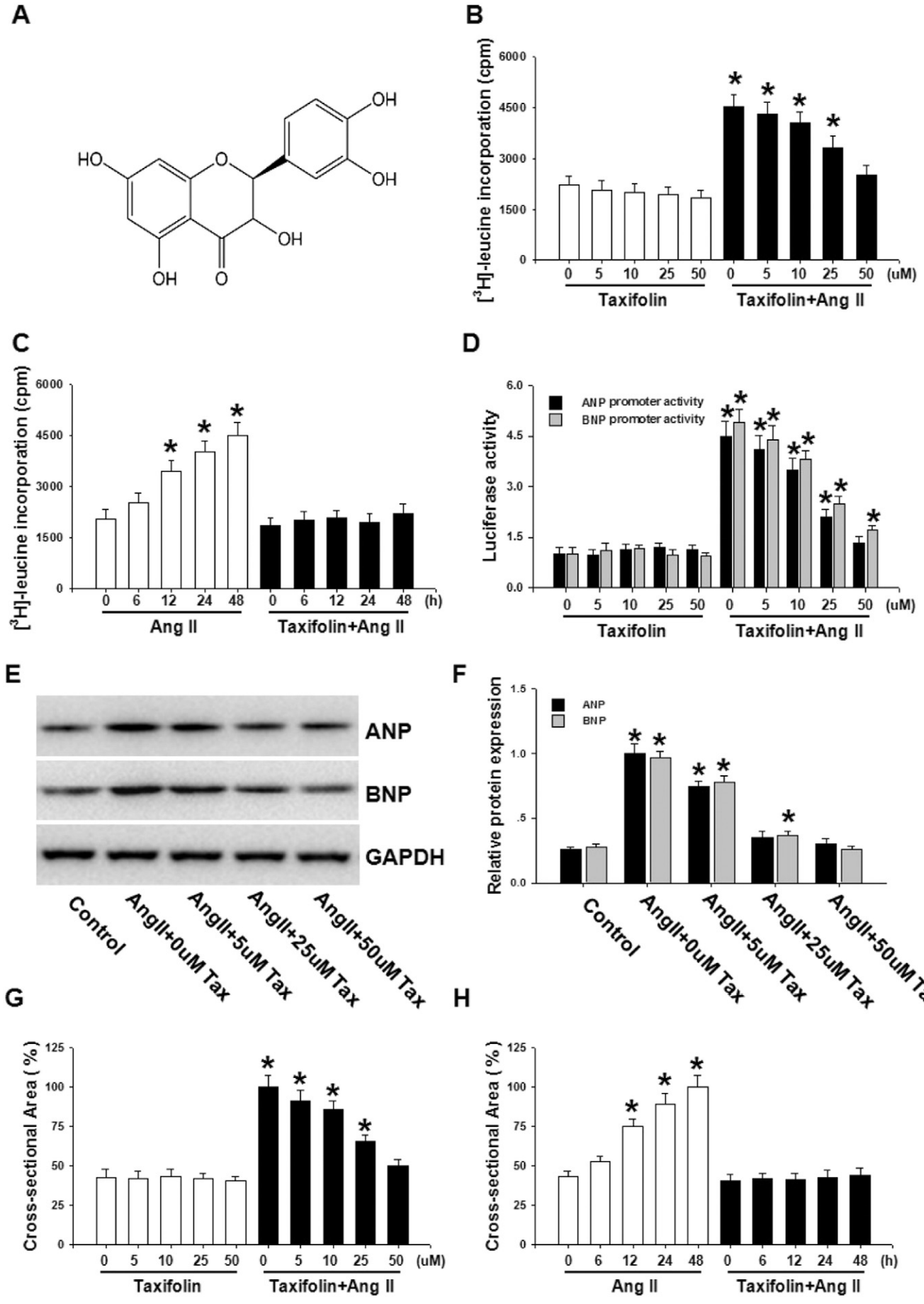
A
HO
OH
OH
OH
OH
O
O
B
[3H]-leucine incorporation (cpm)
6000
4500
3000
1500
0
0 5 10 25 50 0 5 10 25 50 (uM)
Taxifolin
Taxifolin+Ang II
C
[3H]-leucine incorporation (cpm)
6000
4500
3000
1500
0
0 6 12 24 48 0 6 12 24 48 (h)
Ang II
Taxifolin+Ang II
D
Luciferase activity
6.0
4.5
3.0
1.5
0.0
ANP promoter activity
BNP promoter activity
0 5 10 25 50 0 5 10 25 50 (uM)
Taxifolin
Taxifolin+Ang II
E
ANP
BNP
GAPDH
Control
AngII+0uM Tax
AngII+5uM Tax
AngII+25uM Tax
AngII+50uM Tax
F
Relative protein expression
1.5
1.0
.5
0.0
ANP
BNP
Control
AngII+0uM Tax
AngII+5uM Tax
AngII+25uM Tax
AngII+50uM Tax
G
Cross-sectional Area (%)
125
100
75
50
25
0
0 5 10 25 50 0 5 10 25 50 (uM)
Taxifolin
Taxifolin+Ang II
H
Cross-sectional Area (%)
125
100
75
50
25
0
0 6 12 24 48 0 6 12 24 48 (h)
Ang II
Taxifolin+Ang II