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Anti-apoptotic and pro-survival effect of protocatechuic acid on hypertensive hearts

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ABSTRACT

Cardiac apoptosis was found in hearts from hypertensive animals, therefore in this study we aimed to evaluate the anti-apoptotic and pro-survival effects of protocatechuic acid (PCA) on hypertensive hearts. At first we found that, sedentary group (SHR)-PCA group's decreased TUNEL-positive apoptotic cells than SHR group alone. Protein levels of Fas ligand, Fas death receptor, Fas-associated death domain (FADD), Bid, t-Bid, Bax, cytochrome *c*, activated caspase-8, activated caspase 9 and activated caspase-3 were decreased in SHR-PCA group compared with SHR group. Moreover, SHR-PCA groups increased pro-survival pathway proteins like IGF1, pIGF1R, pPI3K, p-Akt, Bcl-xL, and Bcl-2 than SHR and sedentary normotensive group (WKY). All these finding suggest us that, Protocatechuic acid prevented hypertension-enhanced cardiac Fas-dependent and mitochondria-dependent apoptotic pathways and enhanced cardiac pro-survival pathway in rat models.

1. Introduction

The major reason behind Heart failure (HF) is hypertensive heart disease (HHD), ischemic heart disease associated with prior myocardial infarction(s), and idiopathic dilated cardiomyopathy. HF is viewed today as one of the major health care problems worldwide [4], in which arterial hypertension is the most common cause for HF [14]. Whereas, left ventricular hypertrophy and alterations in diastolic and/or systolic cardiac function was found in hypertensive patients [2]. This could be overcome by using antihypertensive drugs [8], though there are several antihypertensive strategies to reduce the incidence of HF, no conclusive evidence about the optimal antihypertensive therapy has been reported so far [25]. Therefore to develop therapeutic approaches to overcome hypertension in failing heart is important.

Previous studies have showed that, during myocardial ischemia and heart failure; cardiac myocyte could use an alternative apoptotic pathway by death receptors (Fas, tumor necrosis factor receptor and caspase-8) [30]. Contrarily, cardiac myocytes also uses a mitochondria-dependent apoptotic pathway [17]. The mitochondria-dependent apoptotic pathway involves the release of cytochrome c from mitochondria to cytosol. Cytochrome c further binds to apoptotic protease activating factor 1 and then induces caspase-9 to form apoptosome complex. This complex further results in activation of caspase-3 and executes cell death [10]. This are firmly regulated by antiapoptotic proteins, such as Bcl-2, and proapoptotic proteins, such as Bax [1,12].

Insulin-like growth factor 1 (IGF1) via the IGF1R triggers activates various signaling cascades that regulate cell growth, development related to cardiac biology [22]. This, IGF1 was considered as a potential candidates for the treatment of heart failure [23]. Previous studies by McMullen JR, et al. have found that, targeting IGF1R-PI3K(p110α) pathway could be a potential therapeutic strategy for promoting physiological cardiac growth and improving contractile function [22]. However, the relationships between

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Table 1
Cardiac characteristics of WKY, SHR group and SHR with feeding protocatechuic acid.

	WKY	SHR	SHR-PCA
Number of animals	10	8	10
Body weight (BW), g	317 ± 0.01	347 ± 0.01	354 ± 0.01
Whole heart weight (WHW), g	1.04 ± 0.05	1.22 ± 0.19*	1.20 ± 0.01**
Left ventricular weight(LVW), g	0.75 ± 0.04	0.94 ± 0.17*	0.93 ± 0.02**
WHW/BW (×104)	33.51 ± 1.78	34.93 ± 3.72	33.39 ± 1.60
LVW/BW (×104)	24.24 ± 1.27	27.08 ± 2.43	25.74 ± 4.94
LVW/WHW	0.72 ± 0.03	0.78 ± 0.02**	0.77 ± 0.01**
WHW/Tibia, g/mm	0.024 ± 0.001	0.028 ± 0.002**	0.029 ± 0.001**
LVW/Tibia, g/mm	0.017 ± 0.001	0.022 ± 0.001**	0.023 ± 0.001**
Systolic blood pressure, mmHg	136 ± 32.8	190 ± 5.0**	172 ± 10.0$^{*,\#}$
Diastolic blood pressure, mmHg	84 ± 12.2	141 ± 11.1***	135 ± 10.7**
Mean blood pressure, mmHg	90 ± 6.1	161 ± 5.7**	144 ± 6.2$^{**,\#\#}$

Values are means ± SEM amount the Wistar Kyoto rat (WKY) and spontaneously hypertensive rat with or without feeding protocatechuic acid (SHR and SHR-PCA). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ Significant differences between WKY and SHR or between WKY and SHR-PCA group. $^{\#}P < 0.05$, $^{\#\#}P < 0.01$ significant differences between SHR group and SHR-PCA group.

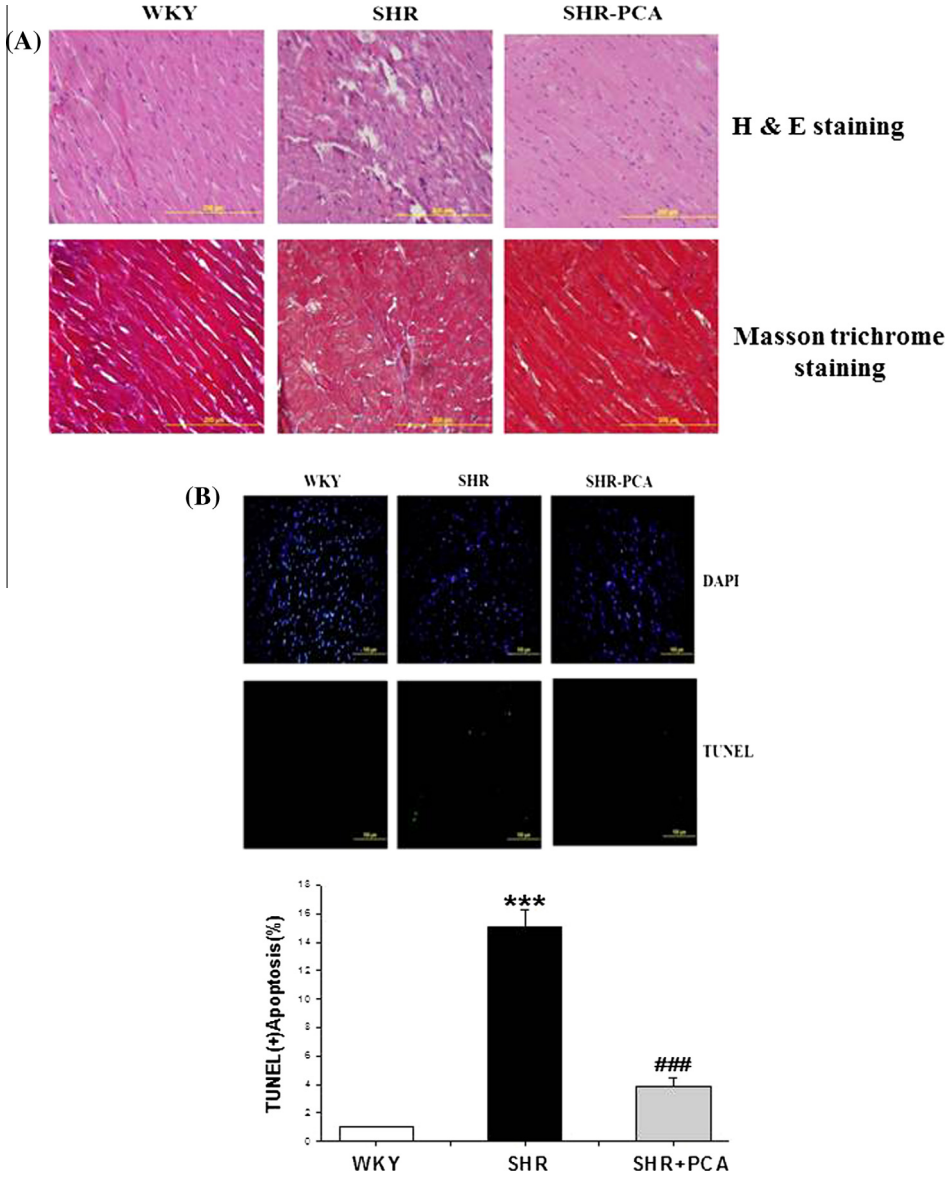

Fig. 1. Histopathological analysis reveals that PCA decreased myocardial hypertrophy in spontaneously hypertensive rats. (A) H & E staining, Masson trichrome staining (fibrosis: blue color) was performed in cardiac tissue sections obtained from all the three groups. (B) Apoptotic cells of cardiac sections from left ventricles in WKY, SHR, and SHR-PCA were measured by 4,6-diamidino-2-phenylindole (DAPI) staining (*top*, blue spots) and terminal deoxynucleotidyl transferase dUTP-mediated nick-end labeling (TUNEL) assay (*bottom*, green spots). Bars represent the percentage of TUNEL positive cells relative to total cells ($n = 11$ each group). All the images of cardiac architecture were magnified by 400 times. $^{***}P < 0.001$ significantly different from WKY group. $^{\#\#\#}P < 0.001$ significant differences between SHR group and SHR-PCA group. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)