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Effects of polydatin on attenuating ventricular remodeling in isoproterenol-induced mouse and pressure-overload rat models

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ABSTRACT

The study was designed to examine the effects of polydatin on ventricular remodeling induced by isoproterenol in mice and by abdominal aortic banding in rats. Polydatin reduced cardiac weight indexes in mice and rats, lowered the contents of cyclic AMP and angiotensin II in mice. It also decreased the size of cardiomyocyte, the levels of aldosterone, tumor necrosis factor-α, angiotensin II and endothelin-1, reduced ventricular collagen volume and decreased blood pressure in rats. The results demonstrate that polydatin has the beneficial effects on attenuating ventricular remodeling, which are associated with its inhibiting the activation of neurohormone, especially in rennin-angiotensin-aldosterone system.

1. Introduction

Ventricular remodeling, including myocardial hypertrophy and fibrosis, is a general process of adaptation to hemodynamic overload that is associated with hypertension or other cardiovascular abnormities. It is an independent risk factor for many cardiovascular events [1]. The degree of myocardial hypertrophy and fibrosis correlates closely with mortality of patients with heart failure [2]. Therefore, inhibiting ventricular remodeling early is an effective way to postpone heart failure for patients with hypertension, myocardial infarction or other cardiovascular diseases.

Polydatin ($C_{20}H_{22}O_8$, 3,4′,5-trihydroxystibene-3-β-mono-D-glucoside, Fig. 1) is a natural compound isolated from a traditional Chinese herb *Polygonum cuspidatum* sieb. et zucc. It is a glucoside of resveratrol, and has also been named piceid. Both polydatin and resveratrol are the main effective compounds of *Polygonum cuspidatum*. In plants, resveratrol can quickly be glycosylated into piceid [3].

It has been known that *Polygonum cuspidatum* and Polydatin have multiple activities in cardiovascular and hematological system.

Luo et al. [4] demonstrate that polydatin can protect myocardial cells injured by deprivation of oxygen and glucose. Polydatin can attenuate the damage of cardiac myocytes caused by lipopolysaccharide [5] or ischemia/reperfusion injury in rats [6]. The cardioprotection of polydatin may be related to activating cNOS, leading to an increase in NO production [6] and decrease in apoptosis [7]. It can enhance heart function, improve microcirculatory perfusion in shock [8] and survival rate in severe shock [9]. Polydatin abates the thrombosis by inhibiting the production of thromboxane A_2 [10] and raising prostaglandin I_2 level [11]. It also has prophylactic and therapeutic effects on acute lung injury with endotoxic shock in rats [12]. Polydatin markedly lowers the serum levels of total cholesterol, triglyceride, and low-density lipoprotein cholesterol in hyperlipidemic rabbits [13]. It reduces brain injury associated with stroke [14], inhibits neutrophil chemotaxis in inflammatory reactions as well [15].

Nevertheless, the effects of polydatin on ventricular remodeling have not been reported. In this study, we investigated the effects of polydatin on ventricular remodeling

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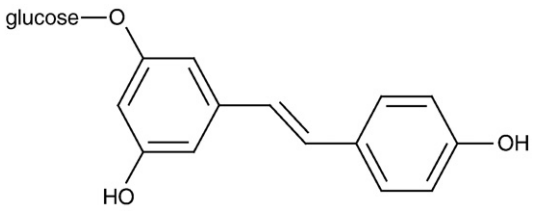

Fig. 1. Structure of polydatin.

induced by isoproterenol in mice and by abdominal aortic banding in rats.

2. Materials and methods

2.1. Animals

Male Kunming mice 20–22 g and male Sprague–Dawley rats (180–200 g) were supplied by Shanghai Experimental Animal Center, Chinese Academy of Sciences. All animals were maintained in a 12 hours light, 12 h dark cycle room with the temperature at 22–24 °C and the humidity at 40% ± 5%. These mice and rats received humane care and had free access to a standard diet and drinking water. The animal experiments were approved by the Animal Care and Use Committee of Shanghai University of Traditional Chinese Medicine.

2.2. Drugs

Polydatin (with a purity of 98.87%) was supplied by the Traditional Chinese Medicine Modernization Engineering Center of Tianjin Zhongxin Pharmaceutical Group Co., Ltd. (Tianjin, China). Isoproterenol was from Shanghai Harvest Pharmaceutical Co., Ltd (Shanghai, China). Metoprolol was from AstraZeneca Pharmaceutical Co., Ltd. (Wuxi, China). Captopril was obtained from Shanghai Hengshan Pharmaceutical Co., Ltd. (Shanghai, China).

2.3. Effects of polydatin on ventricular remodeling induced by Isoproterenol in mice

2.3.1. Experimental protocols

Mice were randomly divided into 5 groups: normal control, isoproterenol control, isoproterenol plus low dose polydatin (100 mg/kg/day), isoproterenol plus high dose polydatin (200 mg/kg/day), and isoproterenol plus metoprolol (60 mg/kg/day). Mice in normal control group were subcutaneously administered with 0.9% NaCl injection and the model mice were subcutaneously injected with isoproterenol daily at a dose of 2 mg/kg/day for 7 days. Mice in the treatment groups were administrated with polydatin, or metoprolol, as positive control drug intragastrically for 7 days, while the mice in normal and isoproterenol control groups were treated with the same volume drinking water.

2.3.2. Measurement of plasma cyclic AMP concentration

At the end of the experiment, mouse body weight (BW) was recorded after fasting for 16 h. Blood sample was collected from carotid artery into cuvette containing anticoagulant ethylene diamine tetraacetic acid, centrifuged (4 °C, 2325 g, 10 min) to get plasma. The cyclic AMP (cAMP) concentration in plasma was determined by radioimmunological assay.

2.3.3. Assessment of cardiac weight indexes

After blood sample collection, all animals were sacrificed by cervical dislocation. Heart was taken out and then the left ventricle was separated from the atria, aorta and adipose tissue. Heart weight (HW) and left ventricle weight (LVW) were measured, then left ventricular weight index (LVWI) and heart weight index (HWI) were estimated by calculating HW/BW and LVW/BW ratio. The myocardial tissue was rapidly frozen in liquid nitrogen and then stored at −70 °C until assay.

2.3.4. Measurement of angiotensin (Ang) II concentration of left ventricular tissue

Ventricular tissue (40 mg) was homogenized with 2 ml cool 0.9% NaCl and centrifuged (4 °C, 1780 g, 15 min). The supernates were analyzed with an [^{125}I] Ang II Radioimmunoassay Kit (Beijing Puerweiye Biology and Technology Co. Ltd., Beijing, China).

2.4. Effects of polydatin on ventricular remodeling induced by abdominal aortic banding in rats

2.4.1. Experimental protocols

Rats were anaesthetized with intra-peritoneal injection of amobarbital sodium (35 mg/kg). The abdominal aorta between the left and right renal artery of the model rat was constricted with a silver ring to a diameter of 0.6 mm, and the sham-operated rats underwent the identical surgical procedure as described above except for artery constriction. After surgical operation, each rat was given benzyl-penicillin by intramuscular injection for 3 days to prevent infection. On the third day after operation, the surviving abdominal aortic banding (AAB) rats were divided randomly into 4 groups: AAB control, AAB plus low dose polydatin (60 mg/kg/day), AAB plus high dose polydatin (120 mg/kg/day), and AAB plus captopril (40 mg/kg/day). Those rats in the treatment groups were intragastrically administered with polydatin or captopril once a day. Drinking water was administered for the sham-operated and AAB control groups. Treatment started from the third day after operation and continued for one month.

2.4.2. Recording blood pressure

One month after treatment, BW of rat was recorded after fasting for 16 h and rats were anesthetized with intraperitoneal injection of urethane (1.0 g/kg). Then a polypropylene catheter was inserted into the right carotid artery. The arterial catheter was filled with heparinized saline solution and connected to a pressure transducer. After equilibrium of about 5 min, systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP) were recorded with a multi-channel biological signal analysis system.

2.4.3. Cardiac weight indexes and morphological examinations

After collection of blood sample, the heart was taken out, and the left ventricle was separated from the atria, aorta, and