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Rapamycin prevents apoptosis of myocardial cells in heart failure rats through up-regulating Akt.

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Abstract

Objectives: Heart Failure (HF) progression could be prevented by an inhibitor of the mTOR and an autophagy enhancer rapamycin. This study aimed to investigate the effect of rapamycin on HF progression and myocardial cells apoptosis.

Methods: HF rats were injected with low-, middle-, and high-dose rapamycin. Echocardiography, HE staining, plasma Brain Natriuretic Peptide (BNP), myocardial cells apoptosis and Akt activation in rapamycin treated rats were detected.

Results: HF rats showed reduced cardiac functions, destructive pathological changes in myocardium, enhanced Akt activation and myocardial cells apoptosis. However, rapamycin reversed all the changes in a dose-dependent manner. Cardiac functions were enhanced by rapamycin. Myocardial cells apoptotic percentage, Akt expression, and pathological changes in HF rats myocardium were inhibited by rapamycin administration.

Conclusions: Rapamycin protected against myocardial hypertrophy and myocardial cells apoptosis in HF rats in a dose-dependent manner.

Keywords: Heart failure, Rapamycin, Akt, Apoptosis

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Introduction

Heart Failure (HF) is a clinical syndrome with inability of heart pumping blood of which the derived metabolic dysfunction contributes to high rates of disability [1]. Though numerous studies focus on HF, the mechanisms of heart failure are still unclear and the treatment of HF still needs to be improved.

The well-known phosphatidylinositol 3-phosphate kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathway involves in the regulation of autophagy and apoptosis in mammal cells [2]. PI3K pathway plays an essential role in cell, organ, and body size determination [3]. Despite of Akt's beneficial effects on contractility, prolonged Akt activation could result in contractile dysfunction, including heart failure [4]. The excessive cardiac growth induced by Akt or others, rather than long-term Akt activation itself, is detrimental for the HF or myocardial hypertrophy [4]. On contrary, reports showed that Akt activation inversely preserved cardiac function and prevented injury after transient cardiac ischemia [5]. The overexpressed Akt in mesenchymal stem cells dramatically repaired infarcted myocardium and improved cardiac function [6].

Rapamycin is a lipophilic, macrolide antibiotic. Rapamycin can effectively attenuate myocytes hypertrophy induced by growth factors *in vitro* [3]. Moreover, HF progression and the associated long-term Akt activation could be prevented by rapamycin [4,7]. The effect of rapamycin on cell apoptosis is duality too. Rapamycin exhibits apoptotic effect on cancer cells, or protects against apoptotic neuronal death [8,9]. In cancer cells, rapamycin administration induced cancer cell apoptosis and blocked cell proliferation [10-14]. In male germ cells, rapamycin could inhibit chemicals induced apoptosis *via* impairing ROS-derived dysfunction in mitochondria [15]. In human neuronal SH-SY5Y cells, rapamycin showed neuroprotective against rotenone-induced apoptosis through enhancing autophagy to clear damaged mitochondria [16]. As reported by Shioi et al. rapamycin could attenuate load-induced compensated hypertrophy *via* an mTOR-dependent mechanism [3].

Studies also showed that rapamycin is an inhibitor of the mTOR and an autophagy enhancer [7,16-18]. mTOR negatively regulates autophagy, and rapamycin could induce autophagy by inactivating mTOR [17]. However, the effect of rapamycin on myocardial cells apoptosis in HF progression had not been well reported.