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Original Article

Mitochondrial adaptations during myocardial hypertrophy induced by abdominal aortic constriction

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ABSTRACT

Introduction: Myocardial hypertrophy is an adaptive response of the heart to work overload. Pathological cardiac hypertrophy is usually associated with the ultimate development of cardiac dysfunction and heart failure. The mitochondria have an important function in the development of cardiac hypertrophy. However, mitochondrial adaptations to hypertrophic stimulus remain ambiguous.
Methods: A rat model of myocardial hypertrophy was established using abdominal aortic constriction. The expression of mitochondrial complexes was evaluated through electrophoresis using blue native and blue native/sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). The enzyme activity of mitochondrial complexes was detected through in-gel activity.
Results: Mitochondrial function and biogenesis decreased in hypertrophied myocardium. The content and activity of mitochondrial Complex V dimers and Complex I significantly decreased during hypertrophy, as well as those of the α, β, B, and D chains of the Complex V dimers. However, the content and activity of mitochondrial Complex V oligomers and Complexes II, III, and IV did not change.
Conclusions: The decreased content and activity of Complex V dimers and Complex I caused the decline in mitochondrial function and biogenesis during cardiac hypertrophy.

1. Introduction

Various stimuli may cause different types of myocardial hypertrophy, which is an adaptive response of the heart to work overload. The mitochondria have important functions in all types of cardiac hypertrophy because of their involvement in energy generation. During cardiac hypertrophy, the expression of mitochondrial proteins is significantly changed, which then affects the proteome phenotype and function of the mitochondria [1,2]. Mitochondrial dysfunction decreases energy generation and increases cellular reactive oxygen species (ROS) levels, as well as stimulates the myocardium to undergo hypertrophy and contribute to the transformation from pathological hypertrophy to heart failure [2,3]. Although the mitochondria have important functions in the development of cardiac hypertrophy, their adaptations to hypertrophic stimulus remain ambiguous.

Oxidative phosphorylation (OXPHOS) is the major metabolic pathway in which the mitochondria generate adenosine triphosphate (ATP). OXPHOS is carried out by the electron transport chain, which consists of a series of protein complexes located in the mitochondrial inner membrane. This research aimed to determine the mitochondrial adaptations and investigate their associated mitochondrial complexes during abdominal aortic constriction (AAC)-induced myocardial hypertrophy.

2. Methods

2.1. Construction of the rat model of myocardial hypertrophy

AAC was performed as previously described [4]. Young male Wistar rats weighing 180 g to 200 g were anaesthetized. After opening the abdomen, the suprarenal abdominal aorta was released from the connective tissue, and a bent 7-gauge needle was placed next to the abdominal aorta. The suture was securely tied around the needle and the aorta. After ligation, the needle was quickly removed. Sham-operated rats underwent the same intervention, except that the aorta was not ligated. After echocardiographic analysis at 6 weeks after AAC, the rats were sacrificed through cervical dislocation, and the hearts were removed and weighed promptly. The experimental procedures performed in the rats conformed to the principles of the Laboratory Animal Care published by the US National Institutes of Health (NIH publication No. 86-23, revised 1985) and approved by the Animal Subjects Committee of Beijing Institute of Basic Medical Sciences, Beijing, China (Approval No. 2013-D-2312).

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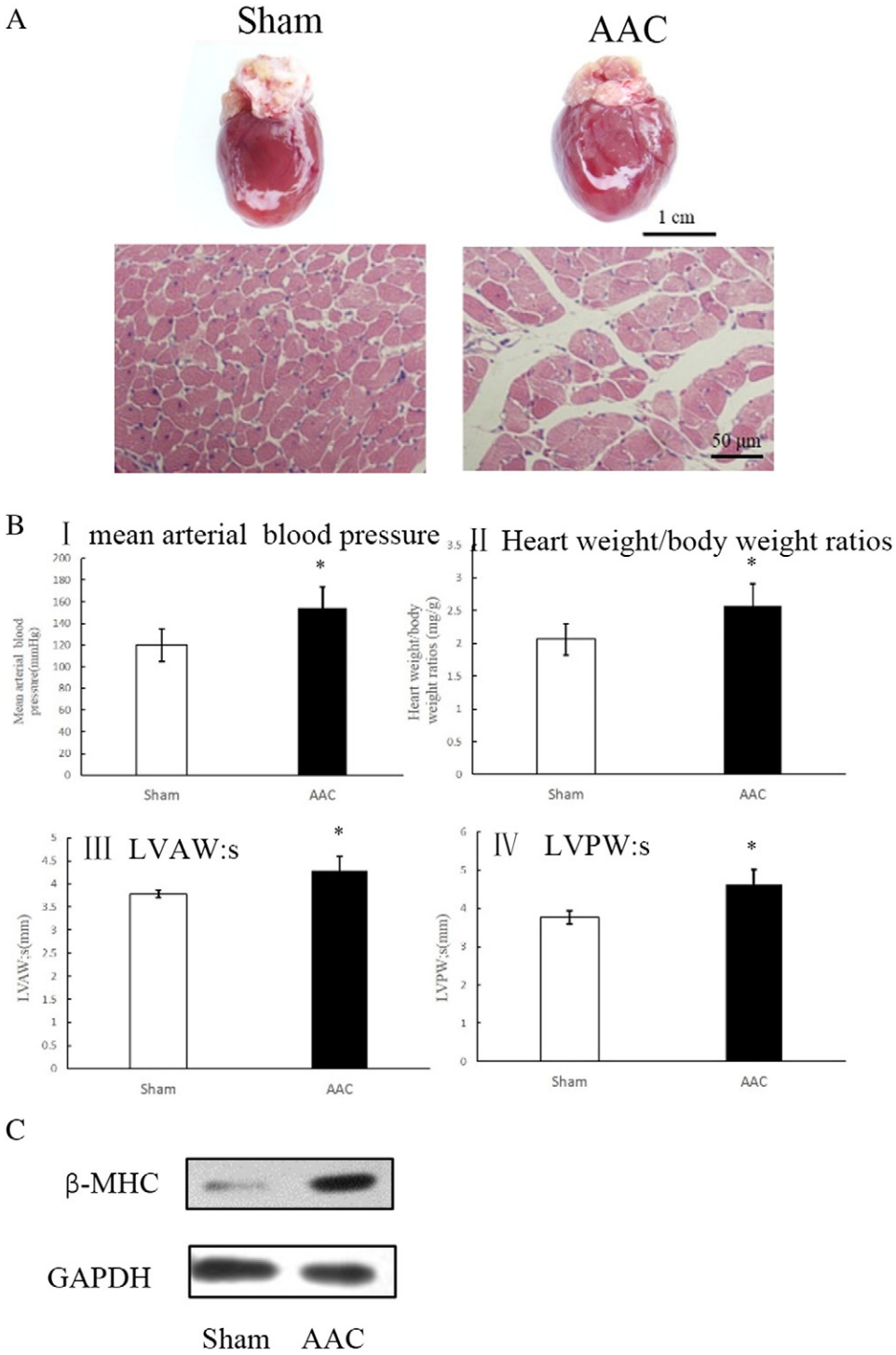

Fig. 1. Biological characteristics of AAC-induced myocardial hypertrophy. (A) Gross morphology of the whole heart and left ventricular (LV) transverse sections (HE staining) showing cardiac enlargement in the rats after AAC; (B) (I) and (II) Heart weight/body weight ratios and mean arterial blood pressure of the rats subjected to AAC or sham operation; (III) and (IV) Echocardiographic evaluation of the rats subjected to AAC or sham operation. $n=8$, $^{*}P\leq 0.05$ versus same-time sham operation; (C) Western blot analysis of the β-MHC expression levels of the rats subjected to AAC or sham procedure.

2.2. Mitochondrial function analysis

The mitochondria were isolated as previously described [5]. Intracellular ATP level and H^{+}-ATPase activity were detected using an ATP assay Kit (Beyotime). Mitochondrial membrane potential was determined using Rhodamine123 (Beyotime). All assays were performed according to the manufacturer's instructions. The details are provided as supplementary data.

2.3. Measurement of mitochondrial DNA (mtDNA) content by real-time polymerase chain reaction (PCR)

Total heart DNA was isolated using a DNeasy tissue kit (Qiagen 69504). DNA Master SYBR green (Roche, Palo Alto, CA) was used for real-time PCR. The content of mtDNA was determined by coamplifying the mt D-loop and the nuclear-encoded β-actin gene through real-time PCR. The primers and cycling conditions used were previously described by Branda et al. [6].