European Journal of Pharmacology 814 (2017) 73–80

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Cardiovascular pharmacology

Curcumin ameliorates cardiac dysfunction induced by mechanical trauma

Xintao Li[1], Tingting Cao[1], Shuo Ma, Zehao Jing, Yue Bi, Jicheng Zhou, Chong Chen, Deqin Yu, Liang Zhu*, Shuzhuang Li*

Department of Physiology, Dalian Medical University, Dalian, Liaoning 116044, China

ARTICLE INFO

Chemical compounds studied in this article:
Curcumin (PubChem CID: 969516)

Keywords:
Curcumin
Cardiac dysfunction
Mechanical trauma
Apoptosis
Reactive oxygen species

ABSTRACT

Curcumin, a phytochemical component derived from turmeric (*Carcuma longa*), has been extensively investigated because of its anti-inflammatory and anti-oxidative properties. Inflammation and oxidative stress play critical roles in posttraumatic cardiomyocyte apoptosis, which contributes to secondary cardiac dysfunction. This research was designed to identify the protective effect of curcumin on posttraumatic cardiac dysfunction and investigate its underlying mechanism. Noble–Collip drum was used to prepare a mechanical trauma (MT) model of rats, and the hemodynamic responses of traumatized rats were observed by ventricular intubation 12 h after trauma. Myocardial apoptosis was determined through terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining and caspase-3 activity assay. Tumor necrosis factor-α (TNF-α) and reactive oxygen species (ROS) generated by monocytes and myocardial cells were identified through enzyme-linked immunosorbent assay (ELISA), and the intracellular alteration of Ca^{2+} in cardiomyocytes was examined through confocal microscopy. *In vivo*, curcumin effectively ameliorated MT-induced secondary cardiac dysfunction and significantly decreased the apoptotic indices of the traumatized myocardial cells. *In vitro*, curcumin inhibited TNF-α production by monocytes and reduced the circulating TNF-α levels. With curcumin pretreatment, ROS production and Ca^{2+} overload in H9c2 cells were attenuated when these cells were incubated with traumatic plasma. Therefore, curcumin can effectively ameliorate MT-induced cardiac dysfunction mainly by inhibiting systemic inflammatory responses and by weakening oxidative stress reaction and Ca^{2+} overload in cardiomyocytes.

1. Introduction

Mechanical trauma (MT) is a common condition induced by various factors, including motor vehicle accidents and natural disasters, such as earthquakes, and this condition consequently leads to major medical and financial problems (Sauaia et al., 2014). For example, severe trauma can cause direct myocardial injury, and nonlethal-MT-induced uncontrolled systemic inflammatory responses may result in severe heart injury (Tao et al., 2005). Clinical studies have indicated that early death from multiple organ failure is correlated with a persistent low cardiac index (Laurent et al., 2002; Stoppe et al., 2011). Thus, cardiac dysfunction is a sign of progression to multiple organ dysfunction syndrome (MODS) and death from septic shock (Zanotti-Cavazzoni and Hollenberg, 2009).

Secondary heart dysfunction induced by nonlethal trauma is relevant to the overactivity of the immune system and the excessive release of inflammatory factors, such as Tumor necrosis factor-α (TNF-α) (Tao et al., 2005). Our previous research showed that the circulatory system released a large amount of TNF-α after MT, and the peak TNF-α reached after 1.5 h (Li et al., 2007a). In addition, the apoptotic climax of myocardial cells also occurred within 12 h and maintained a high level in the first 24 h after injury, and this observation indicated that TNF-α overproduction may be related to post-injury cardiac dysfunction (Li et al., 2007a). Previous evidence reported that reactive oxygen species (ROS) plays a critical role in orchestrating TNF-α-mediated inflammatory responses and cardiac injury (Feng et al., 2013). The interaction between oxidative stress and TNF-α expression is involved in the development and progression of cardiac dysfunction by depressing mitochondrial function and impairing myocardial contractility (Fernandes and Campos, 2008). Considering that ROS over-generation induced by TNF-α may participate in the pathogenesis of trauma-initiated cardiac dysfunction and MODS, we should further investigate whether inhibiting the overproduction of circulating TNF-α and alleviating the oxidative stress in cardiac myocytes can reverse posttraumatic cardiac dysfunction and attenuate MODS.

With increasing interests in the pharmaceutical potential of natural

* Corresponding authors.
E-mail addresses: zhuliang0210@sina.com (L. Zhu), shuzhuangli@126.com (S. Li).
[1] These authors contributed equally to this work.

http://dx.doi.org/10.1016/j.ejphar.2017.07.048
Received 29 April 2017; Received in revised form 27 July 2017; Accepted 28 July 2017
Available online 10 August 2017
0014-2999/ © 2017 Elsevier B.V. All rights reserved.

products causing minimal side effects, numerous studies have been performed to explore the use of natural phenolic compounds for biomedical purposes (Prasad et al., 2014). Our previous studies demonstrated the cardioprotective effects of proanthocyanidin in posttraumatic cardiac injury (Ma et al., 2017). Curcumin, which is a natural phenolic compound extracted from the active component of turmeric (Oliveira et al., 2015), exhibits diverse pharmacologic effects, including anti-tumor, anti-oxidative, anti-inflammatory, and low toxicity with promising clinical applications (Mahmood et al., 2015). However, the role of curcumin in protecting cardiac injury induced by nonlethal MT has been rarely reported, and the low solubility of curcumin has hindered its biological effects. Thus, we hypothesised that curcumin in a microemulsion form may effectively attenuate the secondary cardiac dysfunction of rats suffering from MT by reducing cardiomyocyte apoptosis through the suppression of inflammation and oxidative stress.

2. Materials and methods

2.1. Materials

Curcumin (purity > 98%) was purchased from Melone Pharmaceutical Company (Dalian, China). Ethyl oleate, Emulsifier OP and PEG 400 were purchased from Guangcheng chemical agent Co., Ltd. (Tianjin, China). Cremorphor EL was obtained from Sigma Chemical Co. (St. Louis, MO, USA). H9c2 cells were bought from American Type Culture Collection (ATCC , Manassas, VA, USA; CRL-1446). THP-1 cells were got from American Type Culture Collection (ATCC , Manassas, VA, USA; TIB-202). TNF-α enzyme-linked immunosorbent assay (ELISA) kits were obtained from Sangon Institute of Biotechnology (Shanghai, China). The 2′,7′-dichlorodihydro fluorescin diacetate (DCFH-DA) ROS Detection kit was purchased from Beyotime Institute of Biotechnology (Nanjing, China). The terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) apoptosis detection kit was purchased from Roche Company (Shanghai, China). The 3-(4,5-Dimethyl-2-thiazolyl)-2,5-diphenyl-2-H-tetrazolium bromide (MTT) purchased from Sigma (USA). The Noble-Collip drum was manufactured by Dalian University of Technology (Dalian, China). BL-420 biological and functional experimental system and pressure sensors were purchased from Taimeng Sciences and Technology Limited Company (Chengdu, China). The Fluorescence microscope was JEM-2000EX and was purchased from Olympus Company (Japan).

2.2. Ethics statement

This study was carried out in accordance with the National Institutes of Health guide for the care and use of laboratory animals (NIH Publications no. 8023, revised 1978). The procedure conformed to the Guide for the Care and Use of Laboratory Animals' Protocol, published by the Ministry of the People's Republic of China (issued 3 June 2004). All procedure has received approval from the Institutional Animal Care and Use Committee of Dalian Medical University. All SD rates were anesthetized with sodium pentobarbital (60 mg/kg i.p.) and efforts were made to minimize suffering and alleviate pain for the experiment.

2.3. Animal groups design

Male Sprague Dawley (SD) rats (200 ± 30 g) supplied by the Animal Center of Dalian Medical University were acclimated to their surroundings for 3 days before experimentation. The animals were fed a standard laboratory diet and were maintained under 12-h light-night circle with 20–26 °C temperature and 60–80% humidity. SD rats were randomly divided into four groups namely sham group, trauma group, trauma + curcumin group (curcumin, 100 mg/kg intragastric administration, 12 h before MT), and trauma + vehicle group (microemulsion without effective components, the same volume as curcumin, intragastric administration, 12 h before MT). Activity space for each rat weight at 200 g was around 110 cm2*20 cm (2–3 rats per cage).

2.4. The preparation of curcumin microemulsion

The self-microemulsifying drug delivery system was used to prepare curcumin microemulsion as previously described (Cui et al., 2009). Briefly, excessive curcumin was added into the oily mixtures of 57.5% surfactant (emulsifier OP: Cremorphor EL = 1:1), 30.0% co-surfactant (PEG 400) and 12.5% oil (ethyl oleate). Then the mixture was continuously shaken at 37 °C for 72 h. After centrifuged at 12000r for 10 min, supernatant were taken to remove the remaining insoluble curcumin and diluted with methanol.

The morphology of curcumin microemulsion was observed under transmission electron microscopy (TEM) after putting a drop of suspension onto copper grids and staining with phosphotungstic acid. The diameter was conformed to microemulsion standard with mean droplet size less than 50 nm.

2.5. Nonlethal mechanical trauma (MT) model in rats

Noble-Collip drum was well-accepted model to trigger nonlethal whole body trauma (Jing et al., 2016; Tao et al., 2005). Briefly, after anesthetization, rats were individually traumatized in Noble-Collip drum as the wheel rotated at a rate of 40 rpm for 200 revolutions. As for sham group, rats were subjected to the identical procedure but taped on the inner wall to avoid traumatic injury. After trauma process, rats were laid in cage in a lateral position to maintain airway unobstructed until recovery. Nonlethal MT was characterized by the lack of circulatory shock, no direct cardiac injury. The post-trauma rats were normally active in their cages within 2 h and the 12-h survival rate was 100%.

2.6. Determination of cardiac function

All manipulations were performed on anesthetized male SD rats. Carotid artery cannulation was performed 12 h after trauma as previous described (Ma et al., 2017). A polyethylene catheter connecting to BL-420S Biological Signal Analytical System was inserted through the right carotid artery into the left ventricular for cardiac hemodynamic measurements. The left ventricular (LV) systolic pressure (LVSP), LV end-diastolic pressure (LVEDP), LV developed pressure (LVDP = LVSP − LVEDP), and the maximal positive and negative values of the instantaneous first derivative of LVP (+ dP/dt_{max} and − dP/dt_{max}) were obtained by the BL-420S system.

2.7. Determination of myocardial apoptosis

Myocardial apoptosis was determined by TUNEL staining and caspase-3 activity. The tissues of left ventricular sham or traumatized mice (5 each group) were harvested 12 h after trauma and were perfused first with 0.9% NaCl for 5 min and then with 4% paraformaldehyde in PBS (pH 7.4) for 20 min. Four longitudinal sections from the free wall of the left ventricle were cut and further fixed in 4% paraformaldehyde in PBS for 24 h at room temperature, then dehydrated with sucrose, embedded in OCT and made into 4–5 μm thickness frozen section.

Following the manufacturer's instructions, TUNEL positive cells were observed by Olympus BX51 fluorescence microscope. Total nuclei (DAPI staining, blue) and TUNEL positive nuclei (green) in each field were calculated in five randomly chosen fields. The index of apoptosis (number of TUNEL-positive nuclei/total number of nuclei × 100%) was calculated.

The caspase-3 activity was determined by measuring the generation of the fluorogenic cleavage product methylcoumarylamide (AMC) from the fluorogenic substrate Ac-DEVD-AMC at 360 nM excitation wavelength and 460 nM emission wavelength (5 each group). AMC was measured to represent caspase-3 activity levels and the results of each

Download English Version:

https://daneshyari.com/en/article/5554354

Download Persian Version:

https://daneshyari.com/article/5554354

Daneshyari.com