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Endoplasmic Reticulum Stress as Therapeutic Target against Hypertension

Cheang WS*

Institute of Chinese Medical Sciences, University of Macau, China

***Corresponding author**: Wai San Cheang, Institute of Chinese Medical Sciences, State Key Laboratory of Quality Research in Chinese Medicine, University of Macau, Macao SAR, China, Tel: : +853-8822 4914; Email: AnnaCheang@um.edu.mo

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Abstract

Studies in the past decade have demonstrated that endoplasmic reticulum (ER) stress is closely associated with pathogenesis of hypertension. Signaling pathways involving AMP-activated protein kinase (AMPK) and NADPH-oxidase (Nox) have been identified to regulate ER stress; whilst ER stress contributes to the imbalance production between nitric oxide (NO) and reactive oxygen species (ROS). The present article reviews the protective effects and the potential therapeutic implication of ER stress inhibition by drugs or natural products in hypertension.

Keywords: Endoplasmic reticulum; Hypertension; Therapeutic

Abbreviations: ER: Endoplasmic Reticulum; TUDCA: Taurine-Conjugated Ursodeoxycholic Acid; FDA: Food and Drug Administration; VSMCs: Vascular Smooth Muscle Cells; SHRs: Spontaneous Hypertensive Rats; DOCA: Deoxycorticosterone-Acetate; COX: Cyclooxygenase; ACM: Angiotensin Converting Enzyme; MED: Methionine Enriched Diet; PAH: Pulmonary Arterial Hypertension; RV: Right Ventricular; DHA: Docosahexaenoic Acid.

Introduction

Endoplasmic reticulum (ER) is a crucial organelle in which protein synthesis, maturation, folding and trafficking take place. Only properly folded proteins can be destined to cellular organelles or cell surface; nevertheless, misfolded or unfolded proteins are retained in the ER to be degraded eventually [1]. Disruption of the aforementioned processes results in the accumulation of newly synthesized unfolded proteins in the ER and this condition is referred to as ER stress [2]. ER stress occurs in different pathological conditions, including ischemia, hypoxia, altered glycosylation, nutrient deprivation, oxidative stress and Ca^{2+} depletion of ER stores; and consequently activates ER membrane-associated proteins and complex downstream signaling pathways to regulate targeted gene expression [3]. Studies have demonstrated that chronic ER stress performs a role in the pathogenesis of diseases including atherosclerosis [4], hypertension [5], diabetes mellitus and obesity, as well as the associated vascular dysfunctions [6], neurological disorders [7] and cancer [8]. Moreover, several drugs and natural compounds have been identified to reduce ER stress and thereby show protective effects against ER stress-associated pathologies. The present article provides an overview of suppressing ER stress by drugs and natural products on the potential therapeutic implication against hypertension.

Suppression of ER Stress Reverses the Pathogenesis in Hypertension

Several evidence supports the implication of ER stress in hypertension and pharmacological inhibition of ER stress ameliorates the pathological conditions. Chemical

chaperones 4-phenyl butyric acid (4-PBA) and taurine-conjugated ursodeoxycholic acid (TUDCA) are approved by US Food and Drug Administration (FDA) for treating urea cycle disorders and biliary cirrhosis respectively. Nox (NADPH-oxidase) subcellular compartmentalization contributes to oxidative and ER stress, resulting in increased proliferation of vascular smooth muscle cells (VSMCs), protein hyperoxidation and vascular dysfunction in hypertension; and 4-PBA attenuates hypercontractility and vascular reactive oxygen species (ROS) formation in the stroke-prone spontaneous hypertensive rats (SHRs) [9]. Oral administration of 4-PBA lowers blood pressure, reduces vasoconstriction and enhances vasodilation in small mesenteric arteries from SHRs through inhibition of ER stress and oxidative stress [10]. Likewise, administration of TUDCA protects against deoxycorticosterone-acetate (DOCA) salt-induced hypertension and endothelial dysfunction in rats through reducing ER stress and apoptosis in blood vessels [11]. Similar results were obtained in hypertensive rats that ER stress inhibition by 4-PBA and TUDCA normalized blood pressure by suppressing Ca^{2+}-dependent cytosolic phospholipase A2 (cPLA2)/ cyclooxygenase (COX) pathway [12]. Diabetes mellitus and hypertension are closely related and synergistically induce kidney injury through upregulation of ER stress; whilst TUDCA treatment reverses the blood pressure and kidney injury [13]. ER stress and apoptotic markers are upregulated in the heart from SHRs, revealing that ER stress is linked to myocardial apoptosis associated with hypertension [14]. Both TUDCA and 4-PBA can ameliorate cardiac fibrosis and macrovascular endothelial function via inhibition of transforming growth factor-beta 1 (TGF-β1) pathway in angiotensin II (Ang II)-induced hypertensive mice [15]. In addition, ER stress in brain has been implicated in Ang II-induced hypertension which can be reversed by treatment with TUDCA [16].

Apart from the common ER stress alleviators 4-PBA and TUDCA, other drugs and natural products have also been demonstrated to have beneficial effects in hypertension through inhibition of ER stress. Hyperhomocysteinemia is associated with hypertension and homocysteine (Hcy) is also well-known to induce ER stress [17]. Hcy induces cell death of vascular endothelial cells by activation of JNK and ATF3 through IRE1/TRAF2 pathway [18] and by eIF2α induction of the T-cell associated gene 51 (TDAG51) [19]. Administration of enalapril, a common antihypertensive drug, reverses blood pressure and pathological changes including elevated plasma Hcy and angiotensin converting enzyme (ACE) levels, and increased contractile response and ER stress in aortas in rats on methionine-enriched diet (MED) [20]. Furthermore, black tea consumption for 2 weeks has been found to reduce ER stress and oxidative stress in aortas and thereby ameliorate vascular dysfunction and normalize plasma Hcy level and blood pressure in hypertensive rats [21].

Studies have suggested that AMP-activated protein kinase (AMPK) is a physiological suppressor of ER stress. Apart from regulating systemic energy balance and metabolism [22], AMPK activation protects endothelial function which is attributed to inhibiting proliferation of VSMCs and increasing nitric oxide (NO) production from endothelial cells [23]. Pharmacological or genetic activation of AMPK has shown to mitigate ER stress in endothelial cells and enhance the endothelial-dependent relaxation in mouse aortas [24]. A widely-used anti-diabetic drug metformin is well known to activate AMPK in different tissues in humans and rodents [25,26]. Recently, metformin has been found to decrease blood pressure by activating AMPKα2 and suppressing ER stress in VSMCs in Ang II-induced hypertensive mice [27]. Treating with JNK inhibitor SP600125 enhances neurological function and neuron survival via reduction of ER stress in hippocampal tissues from SHRs with cerebral ischemia [28].

Inhibition of ER Stress Protects against Pulmonary Arterial Hypertension

ER stress has been found to be activated in the vasculature of mice with hypoxia-induced pulmonary arterial hypertension (PAH); and administration of 4-PBA significantly reduced pulmonary hypertension, arterial remodelling and right ventricular (RV) hypertrophy [29-31]. Of note, mice with conditional deletion of GATA-6, a member of the GATA family of zinc-finger transcription factors, in endothelial cells display elevation of ER stress markers and worsening of hypoxia-induced PAH [32]. This result reveals that endothelial cells play critical role for triggering ER stress in hypoxic mice. In peripheral blood mononuclear cells isolated from patients with limited cutaneous systemic sclerosis and PAH, ER stress markers are upregulated and in positive correlation with IL-6 level and severity of pulmonary artery pressure [33]. Moreover, daily treatment of docosahexaenoic acid (DHA) [34] and exogenous H_2S [35] attenuate PAH through inhibition of ER stress. Table 1 summarizes the beneficial effects of drugs or natural products with suppression of ER stress in different hypertensive models.

Drugs or natural products	Dosages	Effects	Animal models	References
4-PBA	1 g/kg/day, 5 weeks, orally	• ↓blood pressure • ↓contractility and ↑endothelium-dependent relaxation in small mesenteric arteries • ↓ER stress	SHRs	[10]
4-PBA	500 mg/kg/day, 4 weeks, orally	• ↓pulmonary artery pressure, pulmonary vascular resistance, pulmonary artery remodeling, and RV hypertrophy and ↑ functional capacity • ↓ER stress • ↓proliferation and ↑apoptosis in pulmonary artery SMCs	hypoxia-induced pulmonary hypertensive mice and monocrotaline (MCT)-induced pulmonary hypertensive rats	[29]
4-PBA	350–550 mg/kg/day, 4 weeks, orally	• ↓RV systolic pressure, RV hypertrophy and pulmonary arterial muscularization • ↓ER stress and inflammation in lungs	hypoxia-induced pulmonary hypertensive mice	[30]
4-PBA	500 mg/kg/day, 4 weeks, orally	• ↓mean pulmonary artery pressure and RV systolic pressure • ↓RV hypertrophy and remodeling • ↓ER stress and cardiomyocyte apoptosis in RV	MCT-induced pulmonary hypertensive rats	[31]
TUDCA	150 mg/kg/day, 4 weeks, i.p.	• ↓systolic blood pressure and endothelial dysfunction • ↑plasma nitric oxide (NO) level • ↓ER stress in aortas	DOCA salt-induced hypertensive rats	[11]
TUDCA	200 mg/kg/day, 6 weeks, s.c.	• ↓blood pressure, albumin excretion, ER and oxidative stress, and glomerular injury • ↑ glomerular filtration rate	Diabetic-hypertensive rats	[13]
enalapril	15 mg/kg/day, 30 days	• ↓systolic blood pressure • ↓Ang II-induced contractile response and ER stress in aortas • ↓plasma Hcy and ACE levels	MED-induced hypertensive rats	[20]
metformin	300 mg/kg/day, 2 weeks, orally	• ↓systolic and diastolic blood pressures • ↑phospholamban phosphorylation and ↓ER stress in human VSMCs	Ang II-induced hypertensive mice	[27]
Black tea extract	15 mg/kg/day, 2 weeks, orally	• ↓blood pressure • ↓plasma Hcy level • ↑relaxations in aortas, carotid arteries, mesenteric resistance arteries, and renal arteries • ↓ER stress, ROS level and Hcy metabolic enzymes in aortas	Ang II-induced hypertensive rats	[21]
DHA	100 mg/kg/day, 4 weeks, orally	• ↓mean pulmonary arterial pressure, pulmonary vascular remodeling and RV hypertrophy • ↓ER stress	MCT-induced pulmonary hypertensive rats	[34]

		• ↓inflammation in lung and adventitia of resistance pulmonary arteries		
GYY4137 (H_2S donor)	4 weeks, i.p.	• ↓mean pulmonary artery pressure and total pulmonary resistance • ↓pulmonary artery remodeling and RV hypertrophy • ↑functional capacity • ↓ER stress in pulmonary arteries • ↓mitochondrial ROS and Nox4 levels in pulmonary artery SMCs	hypoxia-induced pulmonary hypertensive rats	[35]

Table 1: beneficial effects of drugs or natural products with suppression of ER stress in different hypertensive models.

Conclusions

Taken all together, increasing evidence proves the crucial role of ER stress in pathogenesis of hypertension. ER stress alleviators 4-PBA and TUDCA and drugs such as metformin and enalapril as well as natural products including DHA and black tea alleviate hypertension through suppression of ER stress. A better understanding of the cellular interactions of ER stress and other specific pathways in different vascular beds contributing to pathogenic condition will enhance the developing therapies to prevent or reverse hypertension.

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