Acta Pharmacologica Sinica (2016) 37: 425–443
 1671-4083/16
www.nature.com/aps

Review

Endoplasmic reticulum stress: a novel mechanism and therapeutic target for cardiovascular diseases

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Endoplasmic reticulum is a principal organelle responsible for folding, post-translational modifications and transport of secretory, luminal and membrane proteins, thus palys an important rale in maintaining cellular homeostasis. Endoplasmic reticulum stress (ERS) is a condition that is accelerated by accumulation of unfolded/misfolded proteins after endoplasmic reticulum environment disturbance, triggered by a variety of physiological and pathological factors, such as nutrient deprivation, altered glycosylation, calcium depletion, oxidative stress, DNA damage and energy disturbance, *etc.* ERS may initiate the unfolded protein response (UPR) to restore cellular homeostasis or lead to apoptosis. Numerous studies have clarified the link between ERS and cardiovascular diseases. This review focuses on ERS-associated molecular mechanisms that participate in physiological and pathophysiological processes of heart and blood vessels. In addition, a number of drugs that regulate ERS was introduced, which may be used to treat cardiovascular diseases. This review may open new avenues for studying the pathogenesis of cardiovascular diseases and discovering novel drugs targeting ERS.

Keywords: endoplasmic reticulum stress; unfolded protein response; ischemic cardiomyopathy; atherosclerosis; hypertension; cardiac hypertrophy; heart failure

Acta Pharmacologica Sinica (2016) 37: 425–443; doi: 10.1038/aps.2015.145; published online 1 Feb 2016

Introduction

The endoplasmic reticulum (ER) is a principal organelle responsible for folding, post-translational modifications, and transport of secretory, luminal and membrane proteins and is capable of maintaining cellular homeostasis. Newly synthesized and secretory membrane proteins transfer into the endoplasmic reticulum for modification. The modification processes include protein folding, glycosylation and disulfide bond formation[1]. The ER quality control system (ERQC) is a system that prevents protein aggregation by promoting correct folding or selective degradation of the improperly folded polypeptide[2]. This process is regulated by molecular chaperones, foldases, and lectins that maintain the ERQC. ER associates with many processes including apoptosis and autophagy[3].

Endoplasmic reticulum stress (ERS) is a condition that is accelerated by the accumulation of unfolded/misfolded proteins after a disturbance in the ERQC owing to a variety of physiological and pathological phenomena[4]. Nutrient deprivation, altered glycosylation, calcium depletion, oxidative stress, DNA damage and energy disturbance[4–6] are all the causes of ER environment disturbance, which subsequently lead to ERS[7].

Endoplasmic reticulum stress suppresses proteins synthesis at the early stages

At the early stages of ERS, the failure of molecular chaperones break the maintenance of proteostasis[8, 9]. To overcome the deleterious effects of ERS, a series of adaptive and protective strategies are initiated. For example, owing to the abundance of unfolded/misfolded proteins accumulated in the ER, especially the accumulation of unfolded proteins, new protein synthesis is inhibited. In order to clear the accumulated proteins, many chaperone genes are induced at the transcriptional level and activate the ER-associated degradation (ERAD) system, which can translocate and remove misfolded proteins through proteasomal degradation. These processes are identified as the unfolded protein response (UPR)[10, 11]. However, if unresolved, ERS is lethal to cells via what is recognized as ERS-induced apoptosis[12].

The UPR is a concerted and complex cellular response that is mediated through three ER transmembrane receptor proteins: double-stranded RNA-activated protein kinase-like endoplasmic reticulum kinase (PERK), inositol-requiring

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Received 2015-06-24 Accepted 2015-11-23

enzyme 1 (IRE1, also called ERN1) and activating transcription factor 6 (ATF6)[13, 14]. In addition, glucose-regulated protein 78 kDa (GRP78, also called Bip) also plays an essential role in the UPR.

PERK is a member of the eukaryotic translation initiation factor 2α (eIF2α) kinase subfamily, together with RNA-dependent protein kinase (PKR), general control nondepressible 2 (GCN2) kinase and heme-regulated eIF2α kinase (HRI)[15]. PERK possesses a luminal domain similar to that of IRE1 and a cytoplasmic portion that manifests protein serine/threonine kinase activity. Moreover, it has a PKR-like catalytic domain, which phosphorylates eIF2α[16]. eIF2 has three subunits: α, β, and γ. eIF2α is a translation initiation factor that functions in the early steps of protein synthesis by forming a ternary complex with GTP and initiator tRNA. This complex binds to a 40S ribosomal subunit, followed by mRNA binding to constitute a 43S preinitiation complex. Junction of the 60S ribosomal subunit to form the 80S initiation complex is preceded by hydrolysis of the GTP bound to eIF2 and release of an eIF2-GDP binary complex. In order to make eIF2 recycle and then to catalyze another round of initiation, the GDP bound to eIF2 must exchange with GTP by way of the reaction catalyzed by eIF2β. eIF2α phosphorylation stabilizes the eIF2/GDP/eIF2β complex and prevents the GDP/GTP exchange reaction; thus, it impairs the recycling of eIF2 between successive rounds of initiation and leads to global inhibition of translation at early stages of ERS.

IRE1 is an ER transmembrane protein that consists of an N-terminal luminal sensor domain, a single transmembrane domain and a C-terminal cytosolic effector region, which manifests both kinase and endoribonuclease activity[17]. In normal conditions, IRE1 forms a complex with GRP78 in the ER membrane and is inactive. ERS leads to GRP78 release from the complex, which activates IRE1. IRE1 is involved in the activation of ERAD genes via X-binding protein-1 (XBP-1) mRNA splicing and is therefore activated by self-phosphorylation[17]. XBP-1 is recognized as a transcription factor that participates in phospholipid synthesis other than ERAD and in protein quality control[6].

ATF6, which includes two isoforms ATF6α and ATF6β[18], is considered a member of a protein family associated with the regulation of genes. ATF6 contains sequences with a site referred to as the cAMP response element (CRE)[19]. This 90 kDa protein has a bZIP domain for DNA binding after homo- or heterodimerization[20].

GRP78, a member of the HSP70 family, is an ER luminal chaperone that works in an ATP-dependent manner and interacts with several ERAD substrates. GRP78 binds to the substrates to enhance the solubility of ERAD proteins and facilitates their targeting. GRP78 acts as a multifunctional modulator for the regulation of PERK, IRE1 and ATF6 in its monomeric form[21].

All the above receptor proteins are endoplasmic reticulum chaperones. These receptor proteins work together to balance the unfolded protein/chaperone system, which contributes to the homeostasis of ER at early stages of ERS. They also play very important roles in the middle stages of ERS.

Endoplasmic reticulum stress promotes ER homeostasis via the UPR during the middle stages

The processes dealing with ERS are complex. Persistent stimulus brings the UPR into focus; all the mentioned ERS sensor proteins use a unique mechanism to activate transcription factors and upregulate UPR target genes. Three pathways are activated to rescue the damaged ER during the middle stages of ERS.

First, the IRE1 pathway that is the conserved core of the UPR is activated (Figure 1). IRE1 encodes a type 1 ER resident transmembrane protein with a novel lumenal domain and a cytoplasmic portion that contains a protein kinase domain[22, 23]. In response to unfolded proteins, IRE1 activates itself[24, 25]. Trans-autophosphorylated IRE1 activates its unusual effector function, which causes the precise endonucleolytic cleavage of the only known substrate: an mRNA that encodes a transcription factor named XBP-1 in metazoans[26, 27]. IRE1 cuts the precursor XBP1 mRNA twice, excising an intervening fragment or intron. The 5′and 3′ mRNA fragments then generate a spliced mRNA that translocates to the nucleus and binds to the promoter region of the ER stress-response element (ERSE)[28, 29], contributing to the rescue of damaged cells.

PERK, the second pathway (Figure 1), inhibits protein translation, reduces protein synthesis and prevents accumulation of newly synthesized proteins[30]. PERK promotes phosphorylation of eIF2α as an immediate response[31]. Increasing unfolded proteins accumulating in the ER induces dissociation of the GRP78/PERK complex and activation of the kinase domain via autophosphorylation[32], leading to eIF2α phosphorylation and activation that decrease mRNA translation, so proteins gather in the ER[33]. However, the translation of some specific proteins, which include internal ribosomal entry sites such as ATF4, GRP94, and GRP78, is increased via PERK activation[34]. ATF4 is a bZIP transcription factor involved in the expression of survival genes such as GRP78 and GRP94[35]. Calcium-binding chaperone calnexin, calreticulin (CRT) and protein-folding enzymes such as protein disulfide isomerase (PDI) and sarco (endo) plasmic reticulum Ca^{2+} ATPase 2α (SERCA2α) are also increased. In addition, ATF4 upregulates growth arrest and DNA damage-inducible gene 34 (GADD34), promoting translational recovery of eIF2α by dephosphorylation[36].

ATF6, the third pathway of the UPR (Figure 1), is another transcription factor that translocates to the nucleus after its cleavage under ERS conditions[18, 37]. ATF6 includes two isoforms: ATF6α and ATF6β. ATF6α has a higher transcriptional activity compared to ATF6β, which gives it a cytoprotective role in several cellular stress models[18]. After GRP78 release, ATF6 enters coat protein complex II (COPII) vesicles and is targeted to the Golgi lumen, where the cleavage processes take place at site-1 protease (S1P) and site-2 protease (S2P)[38]. Under ERS conditions, disulfide bonds in the structure of ATF6 reduce the activation and translocation of this protein out of the ER. Conversely, ATF6 could also regulate the expression of genes such as XBP1[39].

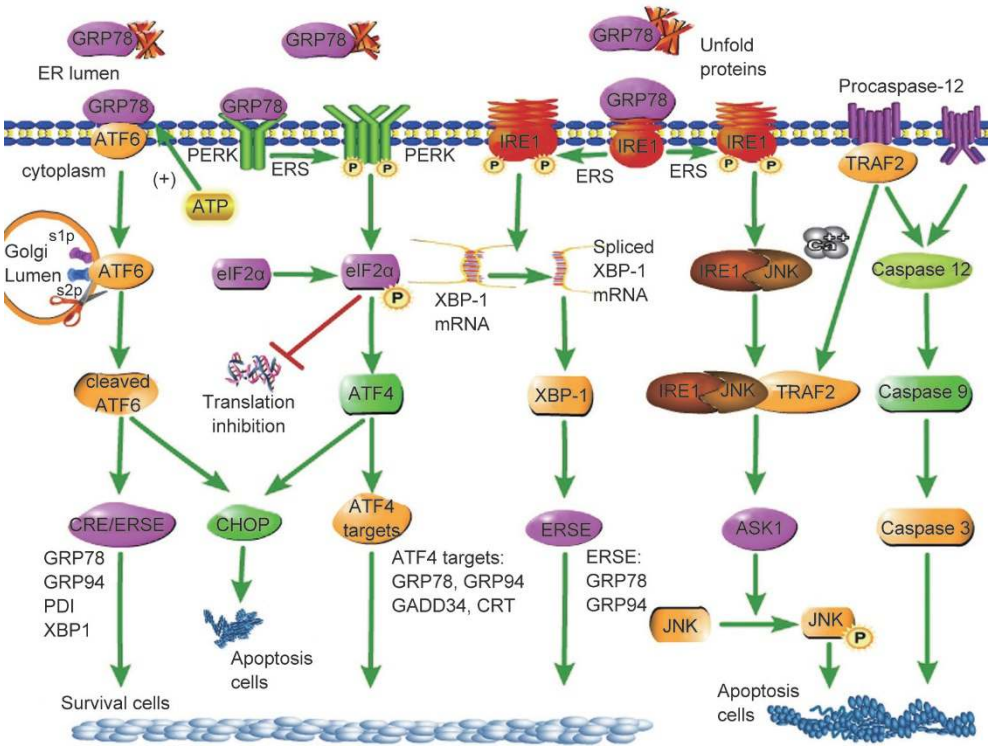


Figure 1. Signaling pathways of endoplasmic reticulum stress.

Endoplasmic reticulum stress induces cell apoptosis in the final stages

Although the UPR is primarily a pro-survival response, in the event of prolonged or severe ERS that is not resolved, the unfolded protein response switches to initiate apoptosis in either a UPR-dependent or -independent manner[40]. ERS-induced apoptosis, which participates in pathological processes of cardiovascular diseases, is mediated by GADD153, also called transcription factor CCAAT enhancer-binding protein (C/EBP), homologous protein (CHOP), IRE1 and caspase 12.

First, CHOP was initially reported as a molecule involved in ERS-induced apoptosis. The expression of CHOP is low under non-stressed conditions, but its expression markedly increases in response to ERS through IRE1-, PERK- and ATF6-dependent transcriptional induction. ATF4 is thought to play a dominant role in inducing CHOP expression in response to ERS because the expression of ATF4 is upregulated when eIF2α is phosphorylated by PERK[41]. Overexpression of CHOP promotes apoptosis in several cell lines, whereas CHOP-deficient cells are resistant to ERS-induced apoptosis[42]. CHOP leads to upregulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) receptors and thus promotes the extrinsic apoptotic pathway[43, 44]. Therefore, CHOP plays an important role in the induction of apoptosis.

In addition to CHOP, other ERS-mediated apoptosis mechanisms have been proposed[45]. For example, ERS activates IRE1, which recruits the adaptor molecule tumor necrosis factor (TNF) receptor-associated factor 2 (TRAF2) and apoptosis signal-regulating kinase 1 (ASK1); then the IRE1-JNK-TRAF2 complex forms, leading to activation of pro-apoptotic JNK signaling[46]. Interaction of IRE1–TRAF2 after ERS has also been reported to recruit pro-caspase 12, which has been proposed to be an important mediator of ERS-induced apoptosis[47, 48].

Caspase 12 is the third protein that regulates the processes of ERS-induced apoptosis[49]. Procaspase 12 localizes on the ER membrane alone or in complex with TRAF2; severe ERS induces procaspase 12 to dissociate from the ER membrane and become activated. The activated form of procaspase 12 is caspase 12[48, 50]. Two pathways lead to activation of procaspase 12. In the first pathway, elevating Ca^{2+} in the cytoplasm leads to calpain activation and translocates to the ER membrane. Caspase 12 is initially processed by calpain; active caspase 12 can initiate a positive feedback loop that activates caspase 3 through caspase 9 activation and thus potentiate apoptosis induction[51]. In the second pathway, the TRAF2-procaspase 12 complex is located on the ER membrane. ERS leads to TRAF2 dissociation from the TRAF2-procaspase 12 complex, which activates caspase 12. At the same time, IRE1-JNK recruits TRAF2 and leads to the formation of the IRE1-JNK-TRAF2 complex. The IRE1-JNK-TRAF2 complex has an effect on ASK1 activation, which may induce JNK phosphorylation and ultimately lead to cell apoptosis[52]. Signaling pathways of endoplasmic reticulum stress are summarized in Figure 1.

Endoplasmic reticulum stress regulates cardiovascular physiology function

It is knowledgeable that adhesion, proliferation[53–55], migration[56] and autophagy[57, 58] are the characteristics of cells[59–61].

ERS regulates those functions[61]. The role of ERS in regulating functions of cardiovascular physiology is still controversial. On the one hand, some researchers have reported that ERS promotes cell adhesion, proliferation, migration and autophagy. For example, Riek *et al*[62] reported that ERS induced monocyte adhesion and migration. Accordingly, suppressed ERS decreased the expression of adhesion markers integrin 1 and 2 and migration receptor chemokine (C-C motif) receptor 2 (CCR2). Nakamura *et al*[63] found that ERS promoted proliferation and migration of human retinal microvascular endothelial cells by increasing the expression of Bip at both the mRNA and protein levels and enhancing the formation of a Bip/T-cadherin immunocomplex. In an oxygen-induced retinopathy (OIR) model in mice, Bip was observed in the retinal microvascular endothelial cells; this finding has many similarities to observations of the endogenous ligand of APJ receptor apelin-13[64–66]. Yang *et al*[67] reported that hypoxia, especially intermittent hypoxia, induced endothelial cell apoptosis, possibly through ERS. Intermittent and persistent hypoxia increased the rate of endothelium apoptosis by increasing the expression of GRP78, CHOP and caspase 12. ERS promoted endothelial cell apoptosis through caspase 12 and the mitochondrial pathway[68, 69].

On the other hand, other researchers hold the opposite view: that ERS inhibits proliferation and migration of cells. For instance, Nakamura *et al*[63] found that severe ERS induced by 10 μmol/L of the ERS inducers tunicamycin (Tm) and thapsigargin (TG) led to HRMEC apoptosis; however, HRMEC proliferation and migration was inhibited by Tm. Yi *et al*[70] found that pretreatment with Tm significantly inhibited platelet-derived growth factor (PDGF)-BB-induced VSMC proliferation and migration without causing significant apoptosis. Tm increased the expression of the antioxidant heme oxygenase-1 (HO-1) gene at both the transcriptional and translational levels, while reducing phosphorylation and activation of mitogen-activated protein kinases (MAPK).

ERS also has effects on cardiovascular function *in vivo*. Nakamura *et al*[63] reported that in OIR model mice, ERS accelerated retinal neovascularization. Bip was observed in the pathological vasculature. Yang *et al*[71] showed that ERS led to a compromise of echocardiographic and cardiomyocyte contractile function by increasing intracellular Ca^{2+}. ERS increased the left ventricular end systolic and diastolic diameter and suppressed fractional shortening and whole-heart contractility[72]. The research on ERS in cardiovascular physiology function is summarized in Table 1.

Endoplasmic reticulum stress is a major case of cardiovascular diseases

Endoplasmic reticulum stress regulates the processes of atherosclerosis

Animal models of atherosclerosis and human atherosclerotic lesions have provided unmistakable evidence that ERS occurred in atherosclerotic plaques, particularly in the advanced stages[73]. The number of apoptotic cells depends on the plaque stage; it is generally high in advanced plaques. In this section we briefly elucidate the role of ERS in three major types of cells in atherosclerosis: smooth muscle cells (SMCs)[74], macrophages and endothelial cells. The role of sterol regulatory element-binding proteins (SREBPs) in regulating ERS to control atherosclerosis is also discussed.

SMCs within the vascular wall exist in predominantly two phenotypes: a contractile phenotype and a synthetic phenotype. Transformation from the quiescent contractile phenotype to the active synthetic phenotype can be stimulated by numerous growth factors, including PDGF-BB[75]. The synthetic SMCs phenotype is actively involved in *de novo* protein synthesis and as such may experience ERS if the protein-folding machinery of the ER is overwhelmed by the demand of newly synthesized proteins[76]. Generally, in the case of mild ERS, the UPR is responsible for activating molecular chaperones to attenuate cellular dysfunction or damage. However, if ERS is prolonged or too severe, the UPR may result in the activation of apoptosis[77]. SMCs synthesize most of the inter-

Table 1. Studies of endoplasmic reticulum stress in cardiovascular physiology function.

Reference	Protein level	Experiment cell	Effect	Mild ERS	Severe ERS	ERS inducer
Riek *et al* [62]	β1, β2 integrin	Monocyte	Enhance adhesion; enhance proliferation	Yes	No	Thapsigargin
Nakamura *et al* [63]	Bip/T-cadherin	Human retinal microvascular endothelial cells (HRMEC)	Enhance proliferation; enhance migration	Yes	No	Tunicamycin Thapsigargin
	Bip/T-cadherin	Human retinal microvascular endothelial cells (HRMEC)	Suppress proliferation; suppress migration	No	Yes	Tunicamycin Thapsigargin
	Bip/T-cadherin	OIR model mice	Enhance neovascularization	Yes	No	Tunicamycin Thapsigargin
Yang *et al* [67]	GRP78, CHOP, caspase 12	Human umbilical vein endothelial cells (HUVECs)	Induce cells apoptosis	No	Yes	Intermittent/ persistent hypoxia
Yi *et al* [70]	XBP1, GRP94, ATF6	Vascular smooth muscle cells (VSMC); SD rats aortic endothelialcell cells	Suppress abnormal proliferation and migration	No	Yes	Tunicamycin

stitial collagen, which stabilizes the fibrous cap of a plaque. Therefore, excessive apoptosis of SMCs in the fibrous cap may break plaque integrity and render it vulnerable to proteolytic attack by inflammatory cells, subsequently leading to plaque rupture[78]. Pedruzzi *et al*[79] reported that the 7-ketocholesterol (7-Kchol)-activating pathway induced an early triggering of ERS in SMCs, as assessed by transient intracellular Ca^{2+} oscillations and IRE-1, JNK, and AP-1 expression. The IRE-1/JNK/AP-1 signaling pathway has likewise been shown to promote the expression of NADPH oxidase 4 (Nox-4) and subsequently cause SMC death. Furthermore, 7-ketocholesterol-induced ERS caused macrophage apoptosis. ERS also promoted oxidative stress and enhanced calcification of vascular smooth muscle cells[80].

ERS is a prominent mechanism of macrophage apoptosis in advanced atherosclerotic lesions. Solanki *et al*[81] shown that the number of ERS-related apoptotic macrophages was increased by a deficiency of calcium-permeable channel transient receptor potential canonical 3 (TRPC3). TRPC3 reduced scavenging of apoptotic SMCs and macrophages and then allowed cells to undergo secondary necrosis, thereby increasing the thrombogenicity of the plaque[82]. Suppression of ERS decreased the number of apoptotic macrophages[83]. Yao *et al*[84] showed that ERS was involved in regulating oxidized low-density lipoprotein (ox-LDL) induced scavenger receptor A1 (SR-A1) upregulation in macrophages. Ox-LDL caused significant SR-A1 upregulation with concomitant activation of ERS as assessed by upregulation of GRP78. Ryan *et al*[85] also detected an increased level of ERS in macrophages. ERS induced by asbestos caused disruption of calcium homeostasis. ERS-induced apoptosis in macrophages may be due to neutral cholesterol ester hydrolase 1 (Nceh1). Sekiya *et al*[86] reported that Nceh1-deficient thioglycollate-elicited peritoneal macrophages (TGEMs) were susceptible to apoptosis induced by oxysterols, particularly 25-hydroxycholesterol (25-HC). Incubation with 25-HC caused massive accumulation of 25-HC ester in the ER due to its defective hydrolysis function, thereby activating ERS signaling proteins such as CHOP. Fatty acid-binding protein-4 (FABP-4), also known as adipocyte FABP (A-FABP)/-adipocyte P2 (aP2), is a cytosolic lipid chaperone that regulates cellular lipid metabolism, receives lipid signals, and promotes atherosclerosis development. FABP-4 links to atherosclerosis also have something to do with ERS. Gao *et al*[87] reported that FABP-4 induced ERS in macrophages. In addition, FABP-4 mediated ERS takes part in the progression of interleukin 17A (IL-17A)-induced atherosclerosis. Erbay *et al*[88] reported that FABP-4 is required in lipid-induced ERS and apoptosis in macrophages from atherosclerotic lesions. Deletion of FABP4 in macrophages increased *de novo* lipogenesis pathways through LXRα-mediated SCD-1 activation, resulting in production of palmitoleate and resistance to ERS. However, Xu *et al*[89] reported that FABP4/aP2 indirectly controlled macrophage ERS by regulating the expression of uncoupling protein 2 (UCP2).

ERS has also been detected in endothelial cells subjected to atherosclerosis-prone shear stress[90]. Increased levels of GRP78 were observed in atherosclerotic regions from C57BL6 mice[91]. Dong *et al*[91] reported that in human umbilical vein endothelial cells and aortic endothelial cells from 5′ adenosine monophosphate-activated protein kinase 2 (AMPK2)-deficient C57BL6 mice, the level of ERS increased. Reduction of AMPK2 expression significantly increased ERS levels in human umbilical vein endothelial cells. In addition, mouse aortic endothelial cells from AMPK2 knockout mice showed higher expression of ERS markers such as XBP1, ATF6, GRP78, p-eIF2α, p-PERK, p-JNK and an increased level of intracellular Ca^{2+}. Li *et al*[92] reported that heat stress activated UPR signaling through the PERK-eIF2α-ATF4, IRE1-XBP1s and ATF6 pathways in human umbilical vein endothelial cells. ERS also mediated aldosterone (Aldo)-induced apoptosis in vascular endothelial cells, as evidenced by increasing expression of GRP78 and CHOP. When CHOP was knocked down, Aldo-mediated apoptosis was attenuated[93].

SREBPs, a small family of lipogenic transcription factors, control cholesterol and lipid metabolism and play critical roles during atherosclerosis development. SREBPs are expressed as inactive precursors and reside as integral trans-membrane proteins within the ER membrane, where they bind to the SREBP cleavage-activating protein (SCAP)[94]. Three SREBP isoforms: SREBP-1a, SREBP-1c and SREBP-2, have been identified in mammalian cells[95, 96]. Usually, SREBPs are activated in response to cholesterol deprivation and control lipid metabolism. ATF6 processing required for S1P and S2P, the enzymes that process SREBPs in response to cholesterol deprivation, demonstrated an important relationship between ERS and SREBPs[97]. Zeng *et al*[98] reported that ATF6 antagonized SREBP-2 to regulate the homeostasis of lipid and glucose. Hyperhomocysteinemia-induced ERS accompanied by upregulation of SREBP-2 and increased lipid deposits in VSMCs[99]. Glucosamine accumulated in vascular cells in diabetes. Its accumulation has a primary responsibility for ERS induction in VSMCs from diabetic patients through GRP78 upregulation, and this process may accelerate atherosclerosis[100]. Increasing evidence indicates that non-alcoholic fatty liver disease (NAFLD) is a major cause of atherosclerosis[101]. ERS triggered NAFLD by dramatically increasing SREBP-1a and SREBP-1c *in vivo*[102]. Fang *et al*[103] demonstrated that ERS may promote lipid synthesis through SREBP-1c in L02 and HepG2 hepatocytes.

In summary, ERS is a key regulator of atherosclerosis, controlling the whole process of atherosclerosis. ERS regulates the progression of atherosclerosis together with several other factors, such as Nox4, TRPC3, SR-A1, and AMPK2. Thus, ERS is a potential target for therapeutic drug design.

Endoplasmic reticulum stress and ischemic cardiomyopathy

ERS mediates the progression of ischemic cardiomyopathy. Ischemia/reperfusion (I/R) injury and myocardial infarction are two major types of ischemic cardiomyopathy. I/R injury is accompanied by contractile dysfunction and cellular damage, contributing to cardiovascular diseases[104]. I/R injury activates ERS, causing apoptosis by promoting the expression of GRP78,

cleaved caspase 3[105] and CHOP[106]. Tao *et al*[107] reported that I/R injury was associated with a time-related increase in ERS-dependent apoptosis through activation of CHOP, caspase 12, and JNK. Liu *et al*[108] reported that myocardial I/R caused ERS and perturbed ER function by increasing the expression of calreticulin, JNK and caspase 12. Ischemic postconditioning (I-postC) is a newly discovered endogenous protective phenomenon. It has the ability to protect myocardium from I/R injury by suppressing ERS through the p38 MAPK and JNK pathways. These reports present the view that I/R injury activates ERS, and, at the same time, ERS exacerbates injury of I/R myocardium. Martindale *et al* obtained results inconsistent with the above opinions. They suggested that the UPR is activated in the heart during I/R, and as a result, the ATF6 branch of UPR-induced expression of proteins, including GRP78 and GRP94, can reduce I/R injury[109]. I/R injury rats are accompanied by myocardial infarction (MI), and increased myocardial infarct size and myocardial enzyme activity were observed[106]. Luo *et al*[110] reported that MI induced ERS and provoked cardiac apoptosis and fibrosis by increasing the expression of ERS markers GRP78 and CHOP, pro-apoptotic proteins Bax and caspase 3, and pro-fibrotic proteins transforming growth factor-beta 1 (TGF-β1) and Smad 2/3, culminating in cardiac rupture and remodeling. Li *et al*[111] reported that ERS contributed to MI through the activation of NADPH oxidase. NADPH oxidase inhibition attenuated an increase in ERS in the remote non-infarcted myocardium and LV remodeling after MI by preventing the increase of GRP78, CHOP and cleaved caspase 12 protein expression in rabbits.

Endoplasmic reticulum stress and hypertension

Hypertension is a major modifiable risk factor for cardiovascular diseases[112, 113]. An increasing amount of evidence indicates that ERS has links to hypertension. Young *et al*[114] first reported that ERS, notably brain ERS, played a key role in chronic hypertension (HTN). The C57BL/6 mouse model of HTN was induced by angiotensin II (Ang II); the circumventricular subfornical organ (SFO), which is a brain region, revealed a robust increase of ERS biomarkers such as $p58^{IPK}$ mRNA, p-PERK, GRP78, CHOP. In addition, ultrastructural abnormalities of the rough ER (RER) are another classic hallmark of ERS. Young *et al* also detected abnormal RER morphology in SFO neurons in this article. ERS mediated Ang II-dependent hypertension in SFO through nuclear factor (NF)-κB activation[115]. ERS also contributed to neurogenic hypertension[116]. Severe hypertension caused neuronal injury through neuronal ERS and apoptosis[117]. ERS is a key player in endothelial dysfunction during hypertension[118]. Reactive oxygen species (ROS) overproduction or the increase of oxidative stress impaired endothelial function in hypertension[119]. ERS may induce oxidative stress to impair endothelial function in the development of hypertension. Liu *et al*[120] reported that carotid arteries exhibited exaggerated acetylcholine-triggered endothelium-dependent contractions (EDCs) and elevated ROS accumulation compared with WKY arteries isolated from spontaneously hypertensive rats (SHRs). In addition, Western blot analysis revealed decreased levels of p-AMPK, and elevated levels of p-eIF2α, ATF3, ATF6, XBP1 and cyclooxygenase 2 (COX-2) in SHR carotid arteries. Chao *et al*[121] found that ERS promoted oxidative stress associated with hypertension in the rostral ventrolateral medulla (RVLM) by increasing the expression of GRP78 and p-eIF2α. ERS also promoted vasoconstriction. Spitler *et al*[122] reported that ERS played a key role in endothelium derived contracting factors (EDCFs), which mediated responses via activation of the cytosolic phospholipase A2 (cPLA2)/COX pathway in the aorta of the SHRs. Suppressed ERS normalized EDCFs-mediated contractions due to reduced cPLA2 phosphorylation, COX-1 expression, and oxidative stress. Kassan *et al*[123] observed that Ang II led mice to develop an increase in blood pressure, cardiac hypertrophy and fibrosis. ERS markers such as ATF4 mRNA, ATF6 mRNA, CHOP mRNA, GRP78, p-eIF2α and caspase 3 increased in the myocardium, dysfunctional aorta and mesenteric resistance arteries (MRA). Hypertension-induced ERS in the aorta and MRA reduced endothelial NO synthase phosphorylation and endothelium-dependent relaxation (EDR) in the aorta and MRA[124]. Guo *et al*[125] reported that in spontaneously hypertensive rats, MI/R increased the level of ERS via the PERK-eIF2α-ATF4 pathway.

Endoplasmic reticulum stress is involved in the development of cardiac hypertrophy

Cardiac hypertrophy is an adaptive response that is triggered by a series of physiological and pathological conditions. Evidences have shown that several factors, including calcium dysregulation which is characterized by Ca^{2+} overload, abnormal protein synthesis and apoptosis, are involved in the development of cardiac hypertrophy[126, 127]. However, the potential role of ERS in pathophysiological hearts remains unclear. Park *et al*[128] demonstrated that pressure overload caused by transverse aortic constriction (TAC) induced prolonged ERS, which was performed in the upregulation of ERS chaperones GRP78, p-PERK, p-elF2α, CHOP, caspase 12 and p-JNK, and then contributed to cardiac myocyte apoptosis in hypertrophy. Apart from these changes in TAC model, ERS chaperones GRP78, caspase 12 and JNK increased abdominal aortic constriction (AAC) in rats[129].

The ERS contribution to hypertrophy may result from the high level of cytosolic Ca^{2+} in cardiac myocytes[130]. Ca^{2+} mobilizing agents, such as Ang II and phenylephrine, which induced an increase of cytosolic Ca^{2+} in cardiac myocytes, led to cardiac hypertrophy. These effects appeared to be mediated by calcineurin (CaN) through dephosphorylating the nuclear factor of activated T cells 3 (NF-AT3); CaN translocates to the nucleus and subsequently interacts with promoters of hypertrophic response genes[130]. Indeed, experiments have shown that a constitutively active NF-AT3 mutant in the hearts of transgenic mice produced ventricular wall fibrosis and cardiac myocytes enlargement *in vivo*[130], which demonstrated the importance of Ca^{2+}, CaN, NF-AT3 pathway in cardiac hypertrophy. In cardiac myocytes, thapsigargin, tunicamycin and Ang II induced rat cardiac hypertrophy by increasing the

expression of atrial natriuretic peptide (ANP) or B-type natriuretic peptide (BNP) mRNA, promoting total protein synthesis and enlarging the cell surface area; they have also been shown to induce ERS through increasing ER chaperone expression[130]. Researchers found that cyclosporine A (CsA) inhibited the development of cardiac hypertrophy. CaN and the transcription factors from the NF-AT family are potential targets for new anti-hypertrophic agents[131]. Further studies are required to determine the effect of ERS on cardiac hypertrophy.

Endoplasmic reticulum stress and heart failure

Various stimuli, such as hypoxia[132, 133], Ang II stimulation[134], oxidative stress[135] and inflammatory factors[136], have been proposed to trigger ERS during heart failure (HF). However, the role of ERS in heart failure is still in dispute.

Some researchers reported that ERS promoted heart failure; others hold a contrary view. In heart failure, the crosstalk between the endoplasmic sarcoplasmic reticulum (ER/SR) and juxtaposed mitochondria is altered, leading to malfunction of cardiomyocytes and decline of cardiac function. Ca^{2+} may be a key regulator between ERS and heart failure. Chaanine *et al*[137] reported that in a rat model of pressure overload-induced heart failure, calcium shifted from the ER to mitochondrial compartments, leading to a decrease in ER calcium content, mitochondrial damage, cells apoptosis and LV interstitial fibrosis, hence contributing to both systolic and diastolic myocardial dysfunction. In systolic heart failure, SERCA2α downregulation, along with Bcl-2/adenovirus E1B19 kd-interacting protein 3 (BNIP3) upregulation, exacerbate myocardial diastolic and systolic dysfunction. Dysregulation of intracellular Ca^{2+} cycling is crucial to the pathogenesis of heart failure and central to the decrease of myocyte contractile function. George *et al*[138] also provided some evidence of the importance of Ca^{2+} in heart failure. When heart failure was induced by daily coronary embolization in chronically instrumented dogs, SERCA, ryanodine receptor (RyR2), Na^{+}-Ca^{2+} exchanger (NCX1), and Ca^{2+} storage protein calreticulin (CRT) were disordered. However, when those calcium-handling proteins were restored, heart failure was alleviated. ERS and ERS-induced apoptosis were also observed in a model of acute myocardial infarction[139] and chronic myocardial ischemia-induced HF[140]. Okada *et al*[141] demonstrated that the number of apoptosic cells in cultured cardiac myocytes was significantly increased in mouse hearts 4 weeks after TAC, and CHOP was induced concurrently. ERS may have promoted heart failure via the NF-κB pathway[142]. NF-κB p65 activity is a nodal point in the transformation of the ERS response from adaptation to cell death in failing myocytes.

Pro-survival and pro-apoptotic are two different effects of ERS on cells. The UPR may rescue patients from heart failure by promoting unfolded or misfolded proteins to fold properly and then decreasing the proteins stored in the cells of heart failure patients. Ling *et al*[143] demonstrated that when the UPR was activated in patients with heart failure, ERS markers XBP-1s and GRP78 mRNA increased. UPR increased the expression of BNP[144, 145]. BNP is mainly secreted in response to stress in the ventricular wall of ventricular hypertrophy. It is detectable at high concentrations in certain circumstances, which often occur in cardiac ischemia and severe heart failure. XBP-1 regulated BNP expression in cultured cardiomyocytes. Thus, UPR increased the expression of BNP to regulate the plasma volume of the heart and kidney, finally rescuing patients from heart failure[145]. The effects of ERS on diseases are summarized in Table 2 and Figure 2.

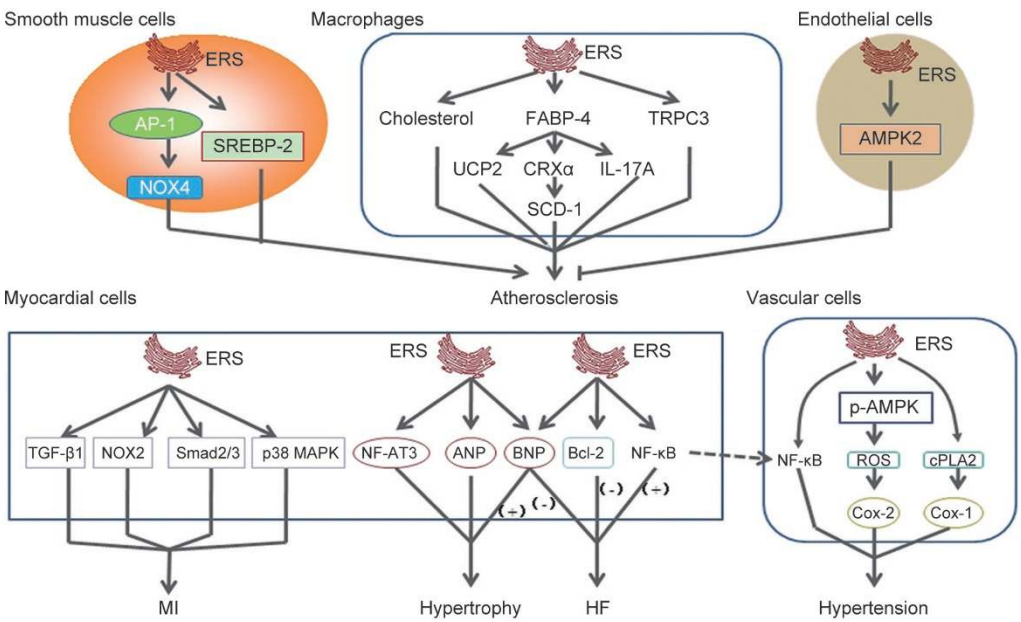


Figure 2. The relationship between endoplasmic reticulum stress and cardiovascular diseases.

Table 2. Endoplasmic reticulum stress is involved in the development of cardiovascular diseases.

Diseases	Experiment models	Levels	Disease inducer	ERS Lesion	Disease⇄ERS	References
Atherosclerosis	SMCs	IRE-1, JNK, Ca^{2+}	7-ketocholesterol		Atherosclerosis⇢ERS	[79]
Atherosclerosis	SMCs	GRP78/Bip, CHOP, Ca^{2+}			Atherosclerosis⇢ERS	[80]
Atherosclerosis	J774A1 murine macrophages	XBP1	Tunicamycin		Atherosclerosis⇢ERS	[81]
Atherosclerosis	RAW264.7 cells	GRP78	Tunicamycin, thapsigagin		ERS⇄atherosclerosis	[84]
Atherosclerosis	Macrophages	Ca^{2+}	Asbestos		ERS⇄atherosclerosis	[85]
Atherosclerosis	Macrophages	CHOP	Oxysterols		ERS⇄atherosclerosis	[86]
Atherosclerosis	Macrophages	p-PERK, p-eIF2α, XBP-1, CHOP	FABP4		ERS⇄atherosclerosis	[88]
Atherosclerosis	Macrophages	Bip, CHOP, XBP1			ERS⇄atherosclerosis	[89]
Atherosclerosis	HUVEC, MAEC	p-PERK, p-eIF2α, XBP-1, p-JNK, GRP78, ATF6			Atherosclerosis⇢ERS	[91]
Atherosclerosis	Endothelial cells	PERK, eIF2α, ATF4, IRE1, XBP1, ATF6			ERS⇄atherosclerosis	[92]
Atherosclerosis	HUVECs	GRP78, CHOP	Aldosterone (Aldo)		ERS→atherosclerosis	[93]
Atherosclerosis	SMCs	ATF6	Hyperhomocysteinemia		ERS→atherosclerosis	[98]
Atherosclerosis	SMCs	GRP78	Glucosamine		ERS→atherosclerosis	[100]
I/R injury	Wistar rats with I/R injury	GRP78, cleaved caspase 3	Surgery	Myocardium	I/R injury→ERS	[105]
I/R injury	Rats	GRP78, CHOP, caspase 12, SERCA	Surgery and TG	Myocardium	I/R injury→ERS	[106]
I/R injury	Rats	CHOP, caspase 12, JNK	Surgery	Myocardium	I/R injury→ERS	[107]
I/R injury	Rats	Calreticulin, JNK and caspase 12	Surgery	Cardiomyocyte	I/R injury⇄ERS	[108]
I/R injury	Mice	GRP78, GRP94	Surgery	Myocardium	UPR⊣ I/R injury	[109]
Myocardial infarction (MI)	Mice	GRP78, CHOP, Bax, caspase 3, TGF-β1, Smad 2/3	LCA ligated	Heart	MI⇄ERS	[110]
Myocardial infarction (MI)	Rabbits	GRP78, CHOP, cleaved caspase 12	Surgery	Heart	MI⇄ERS	[111]
Chronic hypertension (HTN)	HTN in C57BL/6 mice	$p58^{IPK}$ mRNA, p-PERK, GRP78, CHOP	Angiotensin II	Subfornical organ (SFO)	Chronic hypertension⇄ERS	[114]
Hypotension	SHR	p-AMPK, p-eIF2α, ATF3, ATF6, XBP1 and COX-2	Surgery	Carotid arteries	ERS→hypotension	[120]
Hypertension	Wistar-Kyoto rats	GRP78, p-eIF2α	Angiotensin II, tunicamycin	RVLM		[121]
Hypertension	Wistar-Kyoto rats with SHR	ATF4 mRNA, ATF6 mRNA, CHOP mRNA, p-eIF2α, caspase-3	Angiotensin II	Aorta, MRA	Hypertension⇢ERS	[123]
Hypertension	SHR	PERK, eIF2α, ATF4	MI/R	Heart tissues	Hypertension⇄ERS	[125]
Hypertrophy	C57BL/6 mice model of TAC	GRP78, p-PERK, p-eIF2α, CHOP, caspase-12, p-JNK	TAC	Left ventricular	Hypertrophy⇄ERS	[128]
Hypertrophy	Rats model of AAC	GRP78, caspase-12, JNK		Left ventricular	Hypertrophy⇄ERS	[129]
Hypertrophy	Transgenic mice	Ca^{2+}, CaN, NF-AT3	Ang II, phenylephrine	Cardiac myocytes	Hypertrophy⇄ERS	[130]
Hypertrophy	Cardiac myocytes	ANP, BNP, CHOP	Thapsigargin, tunicamycin, Ang II	Cell	Hypertrophy⇄ERS	[130]
Heart failure	Rat model HF	SERCA2a, Ca^{2+}	Pressure overload	Left ventricular	Heart failure⇄ERS	[137]
Heart failure	Dogs model of coronary embolization induced CHF	SERCA, RyR2, NCX1, CRT	Coronary embolization	Heart	Heart failure⇄ERS	[138]
Heart failure	Mouse subject to TAC	CHOP	TAC	Heart	Heart failure⇄ERS	[141]
Heart failure	Patients	XBP1s, GRP78 mRNA		Cardiomyocytes	UPR⊣ heart failure	[143]
Heart failure	Cardiomyocytes	ANP, BNP		Heart	UPR⊣ heart failure	[144, 145]

→, promote; ⊣, supress; ⇄, mutually induced.

Drugs regulating endoplasmic reticulum stress may be a new choice for cardiovascular disease treatment

Because ERS plays an essential role in cardiovascular diseases, drugs targeting ERS should be studied. Several drugs are briefly described in the following section.

Endoplasmic reticulum stress may be a pathway for metformin to reduce cardiovascular risks

Metformin, a common antidiabetic drug, improves insulin sensitivity and glucose homeostasis and has been demonstrated to activate AMPK in tissues from humans and rodents[146, 147]. AMPK controls systemic energy balance and metabolism and has been found to improve endothelial function and reduce cardiovascular risk in diabetic patients[148]. Its activation suppresses ERS in endothelial cells[149], which is associated with several diseases, including atherosclerosis and obesity. Peroxisome proliferator-activated receptor δ (PPARδ) is ubiquitously expressed, for example, in adipose and endothelial cells. PPARδ protects against atherosclerosis and endothelial dysfunction, in addition to depleting lipid accumulation and reducing obesity[150]. PPARβ/δ suppress ERS in the heart[151]. Notably, AMPK is shown to form a transcriptional complex with PPAR and act cooperatively *in vivo*. Drugs targeting the AMPK/PPAR complex may be a new option for treating obesity-associated cardiovascular diseases. Cheang *et al*[147] reported that metformin restored endothelial function through inhibiting ERS and oxidative stress and increasing NO bioavailability in activation of the AMPK/PPARδ pathway in obese diabetic mice. Thus, metformin may be a novel drug to treat obesity- and diabetes-induced atherosclerosis and other cardiovascular diseases.

Endoplasmic reticulum stress is a pathway for nuclear receptor agonists to ease injury of myocardial ischemia/reperfusion

The vitamin D receptor (VDR), also known as NR1I1 (nuclear receptor subfamily 1, group I, member 1), and liver-X-receptors (LXRs) are members of the nuclear receptor superfamily. VDR has also been reported to regulate a variety of metabolic pathways, such as those involved in kidney diseases, immune responses and cancers. Moreover, recent evidence has demonstrated that VDR has a protective role in cardiac hypertrophy[152], heart failure after cardiac remodeling[153] and MI/R injury[154]. LXRs have two receptor subtypes–LXRα (NR1H3) and LXRβ (NR1H2)—that exhibit different expression patterns and perform different functions[155]. Recent evidence suggested that LXRα/LXRβ are both expressed in the cardiovascular system. However, the two subtypes function differently in the pathogenesis of vascular diseases, such as MI/R injury[156], hypertrophy and fibrosis[157]. Nuclear receptors are major targets for drug discovery, and their modulators regulate ERS to control cardiovascular diseases. Calcitriol and paricalcitol (PC) are natural or synthetic agonists of VDR that are used to treat kidney diseases clinically. Recently, Yao *et al*[154] reported that calcitriol and PC activate VDR to protect against MI/R injury by reducing ERS-induced apoptosis via inhibition of caspase 12 and CHOP expression in mice. 22(*R*)-hydroxycholesterol [22(*R*)-HC] and GW3965 are two endogenous or synthetic agonists of LXRs. He *et al*[156] demonstrated that 22(*R*)-HC and GW3965 activated LXRα, but not the LXRβ subtype, to reduce myocardial infarction and improve contractile function after MI/R by attenuating ERS and the ERS-mediated apoptosis pathway by inhibiting caspase 12 and CHOP expression. ERS may be a novel pathway of nuclear receptor agonists, such as calcitriol, paricalcitol, 22(*R*)-HC and GW3965, to treat MI/R injury.

Salubrinal blocks endoplasmic reticulum stress to relieve hypertension and myocardial infarction

Salubrinal acts as a specific inhibitor of eIF2α phosphatase and is used in experiments primarily to study stress responses in eukaryotic cells associated with the action of eIF2α. Salubrinal indirectly inhibited eIF2α to suppress the activation of the stress response triggered by oxidative stress or the buildup of unfolded proteins in the ER. Salubrinal currently has a new therapeutic value. Chao *et al*[121] reported that in the RVLM of spontaneously hypertensive rats, salubrinal-mediated ERS stability relieved hypertension. Furthermore, induction of oxidative stress by Ang II induced ERS in the RVLM; induction of ERS by tunicamycin in the RVLM induced the pressor response in normotensive Wistar-Kyoto rats. Autophagy, as reflected by the expression of lysosome-associated membrane protein-2 and microtubule-associated protein 1 light chain 3-II (LC3-II), was significantly increased in the RVLM of spontaneously hypertensive rats and abrogated by salubrinal. Li *et al*[158] reported that salubrinal protected against ERS-induced rat cardiomyocyte apoptosis by suppressing the dephosphorylation of eIF2α in a rat myocardial infarction model. Thus, salubrinal may prove to be a new drug to remedy hypertension and alleviate the damage of myocardial infarction.

Black tea alleviates endoplasmic reticulum stress to protect against hypertension-associated endothelial dysfunction

Hyperhomocysteinemia is a principal complication of hypertension, which has been found to be associated with elevated levels of homocysteine (Hcy) in hypertensive patients. Homocysteine can induce ERS in endothelial cells and result in endothelial dysfunction. Cheang *et al* observed impaired vasodilatation, upregulated levels of plasma Hcy, reduced Hcy metabolic enzymes and increased ERS markers in aortae from rats with chronic Ang II-induced hypertension. Black tea (BT) extracts and the major theaflavin-3, 3′-digallate (TF3) reversed Hcy-induced endothelial dysfunction and Hcy-elevated ERS in rat aortae. In addition, BT extract treatment normalized plasma Hcy levels; reversed attenuated endothelium-dependent relaxations in aortae, carotid and renal arteries as well as flow-mediated dilatations (FMD) in third-order mesenteric resistance arteries, inhibited ERS, and upregulated the Hcy metabolic enzymes cystathionine-β-synthase (CBS) and cystathionine gamma-lyase (CSE) in the Ang II-infused rats. Moreover, BT mitigated high blood pressure[118]. BT may not just be a drink anymore, it may become a drug to treat hypertension and hypertension-associated endothelial dysfunction.

Berberine improves hypertension-associated endothelial function by inhibiting endoplasmic reticulum stress

Berberine ($[C_{20}H_{18}NO_4]^+$), an isoquinoline alkaloid isolated from many medicinal herbs, such as the Chinese herbs *Huanglian, berberis aquifolium, and berberis vulgaris,* has long been employed in traditional Chinese medicine to treat various infectious disorders. Recently, its cardiovascular benefits have been investigated[159]. Berberine has been reported to ameliorate proinflammatory cytokine-induced ERS in human intestinal epithelial cells[160], reduce hypoxia/reoxygenation-induced human renal proximal tubular cell injury[161], and inhibit the human immunodeficiency virus protease inhibitor-induced inflammatory response in murine macrophages[162]. Berberine has also been suggested to have an anti-hypertensive property[163]. Liu *et al* also reported that berberine improved endothelial function by inhibiting ERS in the carotid arteries of spontaneously hypertensive rats[120]. Treating hypertension-associated endothelial dysfunction may be another function of berberine.

Apelin-13 may be a new peptide to treat ischemia-reperfusion injury through inhibition of endoplasmic reticulum stress

Apelin-13 is an endogenous ligand of angiotensin receptor-like 1 (APJ), a new G protein-coupled receptor with the typical seven transmembrane domains. It was discovered in 1993 via homology cloning[164, 165]. Apelin-13/APJ system has been identified as a potential therapeutic target for hypertension[166] and atherosclerosis[167]. Our laboratory has demonstrated that apelin-13 induced proliferation of vascular smooth muscle cells[66, 168] and rat bone marrow-derived mesenchymal stem cells[169] through the Jagged-1/Notch3, cyclin D1 and AKT/GSK3β/cyclin D1 pathways. However, other researchers demonstrated that apelin-13 is no longer merely a potential therapeutic target; it may serve as a new peptide to treat I/R injury. Tao *et al*[107] reported that apelin-13 protected against I/R injury by inhibiting ERS-dependent apoptosis activation via the PI3K/Akt, AMPK and ERK pathways.

4-Phenylbutyric acid (PBA) reduces endoplasmic reticulum stress to rescue cardiac hypertrophy and fibrosis

4-Phenylbutyric acid (PBA) was approved by the US Food and Drug Administration (FDA) for use in humans[170]. PBA is a low molecular weight fatty acid and a non-toxic pharmacological compound that has been found to have a chaperone-like activity. Its physiochemical properties make it possible to stabilize peptide structures and improve luminal folding capacity and traffic of aberrant proteins[171]. Park *et al*[128] reported that oral administration of PBA to TAC mice reduced the expression of GRP78, p-PERK and p-elF2α. PBA also severely downregulated hypertrophy and fibrosis related genes (TGF-β1, phospho-smad2, and pro-collagen isoforms). Thus, PBA may be a novel therapeutic agent for cardiac hypertrophy and fibrosis through inhibition of ERS.

Cyclosporine A normalizes Ca^{2+} to regulate hypertrophy through endoplasmic reticulum stress

Cyclosporine A is a CaN inhibitor. High levels of CaN induced ERS in hypertrophy. Fu *et al*[172] found that cyclosporine A decreased ERS by inhibiting CaN activity and reducing protein synthesis in Ang II-stimulated cardiomyocytes. It also downregulated DNA synthesis in Ang II-reated fibroblasts in a dose-dependent manner. At the same time, the mRNA level of hypertrophy genes also decreased. Thus, cyclosporine A may be a new therapeutic agent for cardiac hypertrophy through inhibiting ERS.

Metoprolol and propranolol mediate heart failure through endoplasmic reticulum stress

Metoprolol and propranolol are two major β adrenergic receptor (β-AR) blockers. Several clinical studies have demonstrated that metoprolol and propranolol belong to one of the few classes of drugs that improve cardiac function and reduce mortality in patients with heart failure. However, the mechanisms underlying the therapeutic effects of β-AR blockers on failing hearts is poorly understood. Zhou *et al*[42] found that metoprolol and propranolol suppressed ERS and ERS-mediated apoptosis by decreasing the expression of ERS chaperones GRP78, XBP-1, and calmodulin kinase II (CaMKII) and apoptosis maker CHOP in hypertrophic and failing hearts of rats. Metoprolol also normalized the level of calcium and decreased the expression of p-eIF2α in dogs with heart failure[138]. So, the mechanism underlying the therapeutic effects of β-AR blockers on failing hearts may be ERS.

Telmisartan and olmesartan have been found to have a novel value related to endoplasmic reticulum stress in hypertrophy and heart failure

Selective Ang II type 1 (AT1) receptor antagonists such as telmisartan and olmesartan are commonly used to treat hypertension clinically. Their new effects were identified recently. For example, Guan *et al*[53] discovered that telmisartan reduced ERS and thereby attenuated both apoptosis and cardiac hypertrophy. Telmisartan significantly reduced LVH and interstitial fibrosis, thus improving left ventricular function compared with AAC alone. ERS markers in the myocardial, such as GRP78, CHOP, caspase 12 and p-JNK, significantly increased in rats with AAC; telmisartan significantly dampened these changes. Sukumaran *et al*[173] reported that olmesartan decreased ERS in rats with heart failure and downregulated the expression of GRP78, caspase 12 and p-JNK in the myocardium. These novel findings improved the therapeutic value of these two drugs.

Heart failure may be another indication of atorvastatin via inhibiting endoplasmic reticulum stress

Atorvastatin, a reductase inhibitor, has the capacity to effectively decrease blood lipids and may provide some advantages compared with other statins[174]. Sola *et al*[175] found that administration of atorvastatin improved left ventricular ejection fraction and attenuated adverse left ventricular remodeling in patients with nonischemic heart failure. Atorvastatin also dampened the inflammatory process in patients with heart failure[176]. In a rat model of post-myocardial infarction-

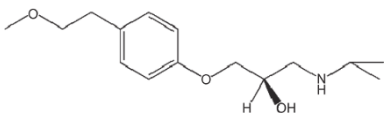
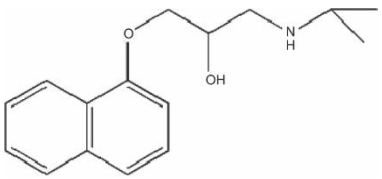
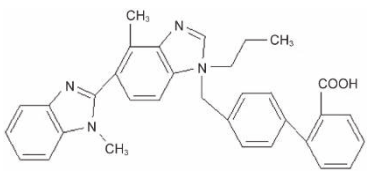
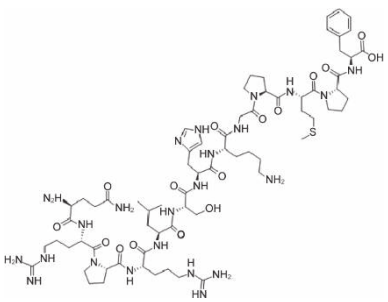
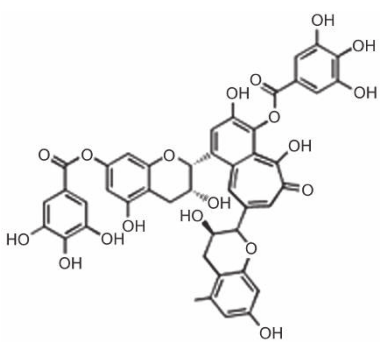
induced heart failure, expression of GRP78, caspase 12, and CHOP in myocardial cells increased. Apoptosis was verified in myocardial cells. Atorvastatin down regulated GRP78, caspase 12 and CHOP expression and decreased apoptosis of myocardial cells, suggesting that atorvastatin protected against heart failure through ERS[177].

Qi deficiency and blood stasis are the main causes of heart failure according to the traditional Chinese medicine system. Li *et al*[178, 179] reported that the Yiqi Huoxue recipe is useful in treating heart failure in laboratory and clinical studies. However, the mechanism of action is not clear. Lou *et al*[180] reported that the Yiqi Huoxue recipe may have improved injured heart function through inhibition of the ERS response pathway by inhibiting the expression of GRP78 and caspase 12 in a rat MI model. ERS may be a pathway targeted by the Yiqi Huoxue recipe to protect the heart from failure. Drugs regulating ERS to treat cardiovascular diseases are summarized in Table 3.

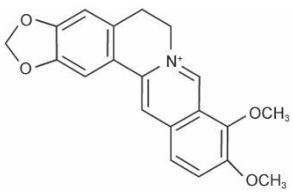
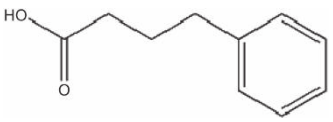
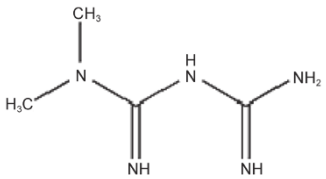
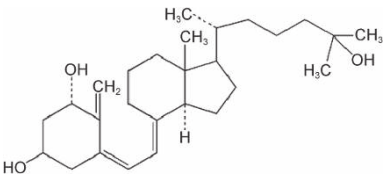
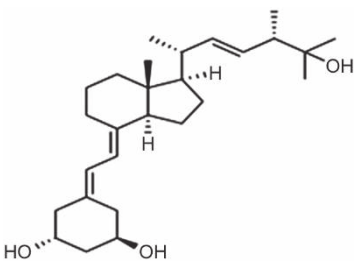
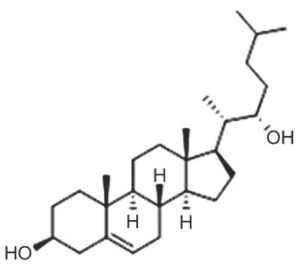
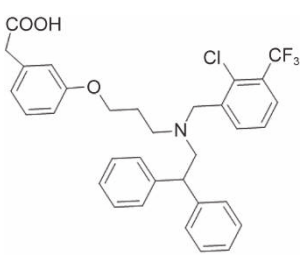
Outlook

ERS-related accumulation of unfolded/misfolded proteins

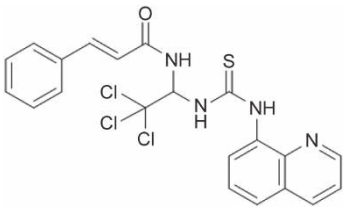
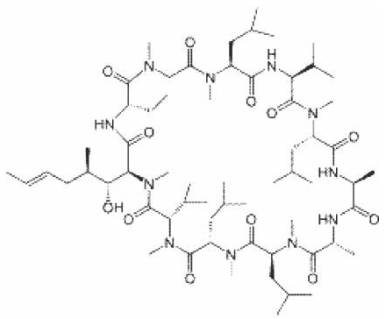
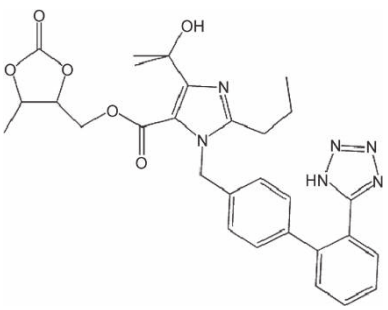
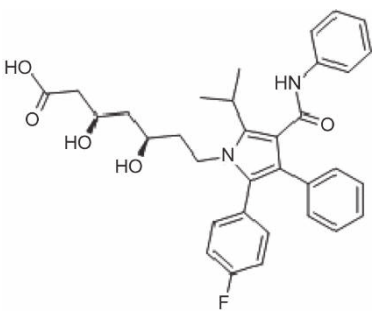
Table 3. Drugs that regulate endoplasmic reticulum stress to treat cardiovascular diseases.

Name	Molecular formula	Chemical structure	Targets	Target diseases	Reference
Metoprolol	$C_{15}H_{25}NO_3$		GRP78 XBP-1, CaMKII, CHOP, p-eIF2α	Heart failure	[43]
Propranolol	$C_{16}H_{21}NO_2$		GRP78 XBP-1, CaMKII, CHOP	Heart failure	[43]
Telmisartan	$C_{33}H_{30}N_4O_2$		GRP78 CHOP Caspase-12 p-JNK	Hypertrophy	[53]
Apelin-13	$C_{69}H_{111}N_{23}O_{16}S$		CHOP Caspase-12 JNK	Ischemia-reperfusion injury	[107]
Theaflavin-3, 3'-digallate (TF3)	$C_{43}H_{32}O_{20}$		ATF3 ATF6 p-eIF2α	Hypertension	[118]

(To be continued)

Name	Molecular formula	Chemical structure	Targets	Target diseases	Reference
Berberine	$C_{20}H_{18}NO_4^+$		ATF3 ATF6 p-eIF2α XBP-1	Hypertension	[120]
4-Phenylbutyric acid (PBA)	$C_{10}H_{12}O_2$		GRP78, p-PERK, p-eIF2α	Hypertrophy	[128]
Metformin	$C_4H_{11}N_5$		ATF6 ATF3 eIF2α	Atherosclerosis	[147]
Calcitriol	$C_{27}H_{44}O_3$		Caspase-12, CHOP	Ischemia-reperfusion injury	[154]
Paricalcitol (PC)	$C_{27}H_{44}O_3$		Caspase-12 CHOP	Ischemia-reperfusion injury	[154]
22(*R*)-hydroxy cholesterol [22(*R*)-HC]	$C_{27}H_{46}O_2$		Caspase-12, CHOP	Ischemia-reperfusion injury	[156]
GW3965	$C_{33}H_{31}ClF_3NO_3$		Caspase-12, CHOP	Ischemia-reperfusion injury	[156]

(To be continued)

Name	Molecular formula	Chemical structure	Targets	Target diseases	Reference
Salubrinal	$C_{21}H_{17}Cl_3N_4OS$		eIF2α	Hypertension	[158]
Cyclosporine A	$C_{62}H_{111}N_{11}O_{12}$		CaN Ca^{2+}	Hypertrophy	[172]
Olmesartan	$C_{24}H_{26}N_6O_3$		GRP78, Caspase-12 p-JNK	Heart failure	[173]
Atorvastatin	$C_{33}H_{35}FN_2O_5$		GRP78, Caspase-12 CHOP	Heart failure	[177]
Yiqi Huoxue Recipe	NO		GRP78, Caspase-12	Heart failure	[178, 179]

and the unfolded protein response are important signals for the progression of many diseases. Cardiovascular disorders lead to disturbance in the ER. Cardiovascular disorders related to the mechanisms of ERS have been identified, and attention has been paid to them by basic and clinical scientists in recent years. Although many detailed studies have highlighted the mechanisms of ERS in cardiovascular diseases, they have yielded conflicting results and additional studies should be conducted to elucidate these mechanisms. Other factors associated with ERS have also been searched, such as the apelin/APJ system[181, 182], in which both apelin-13 and ERS can regulate cardiomyocyte proliferation, migration and adhesion[183, 184]. ERS induced ATF4 expression, regulating apelin-13 transcription via a p38 AMPK-dependent pathway. In addition, nuclear receptors that can be activated by ERS are also worthy of attention. Selective nuclear receptor modulators have been reported to regulate ERS to control cardiovascular diseases. Thus, if the relationship between ERS and nuclear receptors in cardiovascular diseases can be understood clearly, it would support more efficient drug discovery.

In this article, we have summarized the relationship between ERS and cardiovascular diseases and discussed drugs that regulate ERS to control these diseases. However, there are several limitations of previous studies. First, although many studies have been conducted on the relationship between ERS and cardiovascular diseases, it is still a controversial topic. Second, because most of the studies were performed in animal models, they do not fully represent human patients. Finally, despite the discovery of drugs that regulate ERS to control cardiovascular diseases, additional studies are needed to determine whether ERS could be an accurate pathway for treating cardiovascular diseases. Therefore, an improved understanding of ERS proteins and pathways involved in cardiovascular diseases is necessary and may lead to identification of potential targets for new therapies.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No 81270420, 81470434, and 81503074), the Hunan Provincial Natural Science Foundation of China (No 14JJ3102), the Construct Program of the Key Discipline in Human Province, the Hunan Province Cooperative Innovation Center for Molecular Target New Drugs Study (Hunan Provincial Education Department, No 2014-405), and the China Postdoctoral Science Foundation (No 2014M560647 and 2015T80875). We especially thank Bing-bing WANG (Assistant Professor, Perinatal Biology Laboratory, Division of Maternal-Fetal Medicine, Rutgers University–Robert Wood Johnson Medical School, USA) for helping with English language correction.

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