Elimination of endoplasmic reticulum stress and cardiovascular, type 2 diabetic, and other metabolic diseases

Pauli V. Luoma
Institute of Biomedicine, Pharmacology, University of Helsinki, Finland

Multiple factors including unhealthy living habits influence the life-maintaining functions of the endoplasmic reticulum (ER) and induce ER stress and metabolic abnormalities. The ER responds to the disturbances by activating mechanisms that increase the capacity to eliminate ER stress. This article elucidates the effects of ER activation that eliminates both ER stress and associated cardiovascular, type 2 diabetic (DM2), and other metabolic diseases. ER-activating compounds eliminate ER stress by lowering elevated cholesterol, regressing atherosclerosis, decreasing cardiovascular mortality, reducing blood glucose and insulin, and, together with the normalization of glucose–insulin homeostasis, removing insulin resistance, pancreatic β-cell failure, and DM2. A deficient cytochrome P450 activity in hepatic ER leads to cholesterol accumulation that induces stress and xanthoma formation, whereas P450-activating therapy up-regulates apolipoprotein AI and LDLR genes, down-regulates apolipoprotein B gene, and produces an antiatherogenic plasma lipoprotein profile. The ER activation reduces the stress also by eliminating hepatic fat and converting saturated fatty acids (FAs) to unsaturated FAs. Cognitive processes require gene expression modification, and preclinical studies indicate that ER-activating therapy improves cognition. Promotion of healthy lifestyle choices and indicated therapies are key factors in the prevention and elimination of ER stress and associated global health problems.

Key messages
- The endoplasmic reticulum (ER) maintains vital cellular functions and responds to prolonged or excessive ER stress disturbing cellular homeostasis by activating mechanisms that eliminate both ER stress and associated cardiovascular, diabetic, and other metabolic disorders and diseases.
- Positive ER stress-eliminating effects of the ER-activating therapies include lowering of elevated cholesterol, prevention and regression of atherosclerosis, normalizing of glucose–insulin balance, removing of pancreatic β-cell failure, insulin resistance, and DM2, elimination of liver fat, and conversion of saturated fatty acids (FAs) to unsaturated FAs.
- The studies emphasize the importance of activities that promote healthy living habits, and therapies known to alleviate and eliminate ER stress.

Key words: Atherosclerosis, CHD, cognition, cytochrome P450, dementia, diabetes, ER activation, HDL, liver, pancreatic β-cell

Introduction
The endoplasmic reticulum (ER) is a membranous synthesis, metabolism, and transport organelle that extends throughout the cytoplasm and encompasses about half of the total membrane area in a typical eukaryotic cell (1,2). It is continuous with the nuclear envelope and encloses a single internal space called the ER lumen. The ER has vital roles in multiple processes that are required for normal cellular function, including the synthesis and processing of proteins and lipids, regulation of glucose and calcium homeostasis, and metabolism of xenobiotic compounds (1,3). It is the site for the production of proteins destined for secretion and cell membranes and membrane lipid constituents (4–7). P450 monooxygenases catalyze the biotransformation of both foreign and physiologically important substances and influence metabolic processes (3,8). The quality control mechanisms of the cell ensure that the newly made proteins are folded into their correct configuration according to the function and destination in the cell. A failure in the control leads to accumulation of unfolded proteins that are toxic to cells and, by disturbing cellular function, results in a state known as ER stress (4,5). The stress can affect the fate of proteins, lipids, and carbohydrates, cause cellular apoptosis, and promote disease processes.

The ER has capacity to adjust its functions and dimensions according to changing demands by triggering a signaling cascade called unfolded protein response (UPR) for providing new ER-folding machinery and by increasing ER proteins and membranes for restoring the metabolic balance. Clinical studies in the 1970s revealed that ER-activating compounds inducing membrane protein synthesis and proliferation, in proportion to this effect,
produce a plasma lipoprotein profile indicating a low probability of atherosclerotic vascular disease (8,9). Consequent investigations in the 1980s revealed that the compounds inducing ER function can normalize glucose-insulin homeostasis and eliminate insulin resistance and type 2 diabetes (DM2) (10,11). Recent studies have emphasized the significance of disturbed ER functions in disease processes. This review article focuses on the activation of ER functions increasing ER membrane proteins and size and eliminating ER stress and major health problems including common cardiovascular, DM2, and other metabolic diseases.

UPR and elimination of ER stress

Physiological fluctuations of unfolded protein levels may cause temporary up-regulation of protein-folding machinery, while a prolonged or excessive incorrectly folded protein load can trigger full mobilization of mechanisms for the normalization of cell function and prevention of cell death. This section is a short summary of UPR mechanisms in the elimination of ER stress; for more detailed information, see recent reviews (3–5,12,13).

ER folding mechanisms

Several ER response mechanisms can be employed to reduce unfolded protein load and alleviate ER stress, including (14): 1) induction of ER chaperones to enhance folding activity in the luminal ER; 2) up-regulation of protein kinase-like ER kinase or PERK to inhibit translation and reduce the load of newly synthesized proteins; 3) activation of ER-associated degradation of unfolded proteins (ERAD); 4) activation of the apoptosis, a terminal death program to remove damaged cells in case the stress is too severe or prolonged for the recovery of cell function; and 5) up-regulation of phospholipid, protein, and membrane synthesis resulting in ER proliferation with increase of P450 (15–18) and size (19,20). The enlarged ER alleviates ER stress and does so also independently of an increase of ER chaperone levels (21). Transcriptional activation of the pro-apoptotic gene for CHOP (C/EBP homologous protein) and the IRE1-linked kinase pathway has been implicated in the ER stress-mediated apoptosis (14). Autophagy is a degradation pathway under ER stress conditions that is responsible for the turnover of intracellular cargo via lysosomal degradation (3).

Stress sensors and the mechanisms of UPR response

Unfolded proteins accumulated in the lumen of the ER activate three distinct ER membrane-associated stress sensors that up-regulate transcriptional and translational mechanisms to alleviate ER stress. They include inositol-requiring enzyme 1 (IRE1α), activating transcription factor (ATF6α), and PERK. Dissociation of BIP (binding protein) chaperone from the luminal domain of these sensors enables their activation.

Activated IRE1 alters the splicing of X box-binding protein 1 (XBP1), which then acts as a potent transcription factor. It up-regulates chaperones for ER protein folding and quality control, proteins involved in ER-associated protein degradation (ERAD) and in autophagy, and directs cells to construct more ER membranes for maintaining ER function (19). Activated ATF6α moves to the nucleus and via transcriptional induction of ER chaperones and ERAD genes facilitates degradation of unfolded proteins (22). The active form of ATF6α also induces membrane synthesis with resulting expansion of ER surface area and volume (6,23). Activated PERK phosphorylates translation elongation initiation factor 2α (eIF2α), which results in down-regulation of general protein synthesis. It serves as a critical effector of UPR-induced growth arrest, linking stress in the ER to control of cell cycle progression (24).

ER activators increase P450 and ER and liver size

ER-activating compounds up-regulate hepatic ER functions and increase phospholipids and proteins including P450 (15–18) and ER size (19,21), and also liver size in man (25,26). Increased production of ER-resident P450 in hepatocytes has been shown to activate a number of cellular pathways, including those acting in membrane biogenesis, affecting the fate of cholesterol, and fatty acid (FA) metabolism (Table I) (27).

Activated transcription factors influence ER structure and function. The active form of XBP1 induces CTP: phosphocholine cytidylyltransferase-α (CCTα) and the synthesis of phosphatidylcholine (PC), the primary phospholipid of the ER membranes (6,7), and co-ordinately increases membrane phospholipids and proteins, the key ingredients of ER biogenesis (19). Overexpression of active ATF6α similarly induces PC synthesis and drives ER expansion and can do so in the absence of XBP1 (23). ATF6α links membrane protein expression to ER expansion under conditions in which there is no indication of stress (20). Activated nuclear factor κB (NF-κB) up-regulates antiapoptotic genes, ensuring survival of the hepatic cells with an expanding ER compartment (27).

Activation of ER functions—effects in healthy subjects

Both endogenous and exogenous factors activate ER functions that beneficially influence lipid, protein, and carbohydrate metabolism in healthy subjects. Healthy young non-obese subjects show high plasma HDL-C, HDL₃-C, and HDL-C/total cholesterol ratio together with high P450 activity in hepatic ER in vivo (28) as indicated by enhanced antipyrine (AP) kinetics (29). Functional cross-talk of regulatory factors links lipid and xenobiotic metabolism and P450 activity (29–31). An endogenous up-regulation of apo AI synthesis raises plasma apo AI and HDL-C in familial hyper-HDL-emia which is characterized by a low death rate from coronary heart disease (CHD) and prolonged life expectancy (32), while a low apo AI synthesis rate leads to hypo-HDL-emia (33) that promotes atherosogenesis. ER-activating drug therapy similarly increases HDL-C and HDL₃-C in healthy individuals (34). The positive changes in risk factor levels could result from induction of hepatic apo AI (35), the key target for elevating HDL, and LDLR gene expression that associate with the increased production of P450 (27). Young healthy non-obese subjects show high HDL₃-C together with low plasma lipid peroxides that reflect a low level of cellular stress, and high serum glutathione peroxidase activities associate with low LDL-Cs (36). Corresponding to these associations, HDLs have been found to protect cells from ER stress and autophagic response induced by oxidized LDLs (37).

ER-activating therapy increasing ER P450 also influences glucose-insulin homeostasis in healthy subjects. It enhances plasma glucose disposal rate and metabolic clearance of glucose and reduces fasting immunoreactive insulin (IRI), whereas fasting blood

| Factors in membrane biogenesis | Expression of genes          |
|-------------------------------|-----------------------------|
| XBP1 ↑                        | Apo AI ↑                    |
| NF-κB ↑                       | LDLR ↑                      |
|                               | Apo B ↓                     |
|                               | Chaperones ↑                |
|                               | FA desaturase ↑             |

Table I. Up-regulation of factors in membrane biogenesis and changes in the expression of cholesterol, chaperone, and FA desaturase genes induced by microsomal P450 overproduction in hepatocytes (27).
glucose in healthy subjects remains unaltered (38). These positive effects associate with enhanced P450 activity in hepatic ER in vivo, whereas P450-inhibiting therapy reduces glucose disposal rate, glucose metabolic clearance rate, and P450 activity (38).

Healthy living habits including prudent diet and regular physical exercise influence ER functions and have positive metabolic effects. Diet constituents such as soy proteins and an optimal alcohol consumption induce apo AI expression and raise HDL-C, and vitamins, e.g. C and E, may have similar effects (39). A healthy diet also reduces insulin secretion, increases insulin sensitivity, and prevents the occurrence of metabolic syndrome (40) and also DM2 (41). The factors activating ER functions and stimulating cholesterol ef-fluxing mechanisms also prevent and regress atherosclerosis (31). Moderate alcohol consumption reduces the risk of atherosclerotic disease, dementia (42), CHD, and all-cause mortality (43).

Regular aerobic physical exercise of endurance type up-regulates factors in lipid and apolipoprotein metabolism, including receptors such as liver X receptor α (LXRα), peroxisome proliferator-activated receptor γ (PPARγ), and LDLR, enzymes such as P450 and lecithin: cholesterol acyl transferase (LCAT), and ATP-binding cassette (ABC) transporters and apo AI (reviewed in (44)). It also raises plasma apo AI, HDL-C, and HDL$_2$-C, and reduces LDL-C, cholesterol, and triglycerides, and promotes cellular cholesterol efflux (44). In addition, endurance exercise has been shown to ameliorate insulin resistance and ER stress in adipose and hepatic tissue in obese rats (45) and to reduce post-prandial hyperglycemia, improve glucose tolerance, and prevent the development of DM2 in man (41). An anaerobic exercise, e.g. weight-lifting and sprinting, lasts a short period and increases the ability to perform tasks requiring strength and speed. It does not produce positive effect on lipid, protein, and glucose metabolism comparable to that of aerobic exercise.

**ER stress in clinical disorders and diseases**

Modern lifestyle, with an excess of energy-rich foods and physical inactivity, has led to a dramatic increase of clinical disorders and diseases such as obesity, atherogenic dyslipidemia, insulin resistance, metabolic syndrome, DM2, and hypertension, all of which are independent risk factors for atherosclerotic vascular disease, including CHD, myocardial infarction, and stroke (46-47).

Atherosclerotic vascular disease has been identified as the leading cause of death in the world (47,48). One-third of US citizens are obese (BMI ≥ 30 kg/m$^2$), two-thirds overweight (BMI > 25 kg/m$^2$) (49), and nine out of ten diabetics in the US have DM2, the prevalence of which has tripled in the last 30 years (50). Studies clarifying disease mechanisms have associated ER stress with the pathogenesis of these and many other ailments including neurodegenerative diseases and cancer.

**ER stress in the liver**

The liver ER has essential functions in the biosynthesis and catabolism of lipids, proteins, and carbohydrates and metabolism of xenobiotic compounds (3,31). P450 metabolizes in addition to xenobiotics a large number of physiologically important substances including cholesterol, FAs, steroids, prostaglandins, and bile acids. The multiple functions and effects of the liver influence metabolic processes also in other tissues.

Factors affecting hepatic function such as excessive nutrient intake and alcohol abuse can induce ER stress that activates UPR mechanisms for restoring hepatocellular functions (3,22,51). If the cellular response to stress is insufficient, pathological consequences can ensue. A dysregulation of ER function can affect lipoprotein secretion and glucose-insulin homeostasis and promote lipid accumulation (52) and hyperglycemia (11), respectively. Metabolic perturbations can lead to spill-over of extra free FAs from adipose tissue and their entry to liver and other organs via the activated adipose triglyceride lipase and hormone-sensitive lipase (53), induce hepatic fatty regeneration and cholestasis, and worsen the underlying causes of liver injury, such as diabetes—obesity-related liver disease (22,51). Both plasma lipoprotein risk factor levels (18,54) and glucose disposal rate (55) vary in proportion to the amount of unaltered parenchyma in diseased liver as evaluated by morphometry.

**ER stress and atherosclerosis**

Atherosclerosis is a multifactorial disease which is characterized by the accumulation of lipids and inflammatory factors in arterial blood vessels (56–59). Accumulation of apo B-containing lipoproteins in arterial intima triggers a series of maladaptive responses which are key factors in the initiation and progression of atherosclerotic lesions. Recent studies emphasize the significance of ER stress in the pathogenesis of atherosclerotic disease.

Multiple factors can induce ER stress and promote the atherosclerotic vascular process (59). ER stress promotes hepatic lipogenesis, lipid accumulation, and dyslipidemia, and alleviation of ER stress can facilitate lipoprotein secretion (59). Disturbed ER function also affects the fate of glucose and promotes hyperglycemia through insulin resistance, stimulation of hepatic glucose production, and suppression of glucose disposal (11). The combination of stress-inducing stimuli, dyslipidemia, insulin resistance, and hyperglycemia promotes lipid accumulation, inflammation, and apoptosis and can accelerate the atherosclerotic process (60). Cholesterol accumulation in ER membranes causes ER stress (4) and can promote the progression of atherosclerosis (61) through the activation of ER stress pathways that have been detected in atherosclerotic lesions. The ER stress–CHOP pathway is activated in macrophage-derived cells at all stages of the atherosclerotic process, and apoptosis becomes prominent at the late stage of atherosclerosis (14). These processes lead to plaque formation and plaque instability and consequently to progression of atherosclerosis and possibly to infarction.

**ER stress, obesity, inflammation, insulin resistance, pancreatic β-cell failure, and DM2**

An imbalance in energy intake and expenditure leads to increase in body weight and obesity, a major health threat that increases the risk of DM2 and cardiovascular disease (CVD) (47,62,63). Obese subjects show activation of ER stress pathways in metabolic tissues including adipose tissue, liver, and pancreas (64,65). Obesity also associates with both hepatic and peripheral insulin resistance together with elevated levels of proinflammatory cytokines in blood and tissues (46,66).

Obesity-induced inflammation can be described as a chronic low-grade inflammatory response initiated by excess nutrients in metabolic cells (65). The three branches of the ERs unfolded protein response, IRE1, PERK, and ATF6, have been implicated in the cellular inflammatory process (65). The inflammation has inhibitory effects on insulin action through the inflammatory kinases c-Jun N-terminal kinase (JNK), inhibitor of k kinase (IKK), and protein kinase R (PKR) in metabolic tissues and disrupts nutrient and energy metabolism through these and other mechanisms (65). Insulin resistance, a hallmark of DM2, is linked with a metabolic and cardiovascular cluster of disorders (dyslipidemia, obesity, glucose intolerance, endothelial dysfunction, hypertension), each of which is an independent risk factor for CVD. DM2 is characterized by hyperglycemia in the context of ER stress, insulin resistance, and relative insulin deficiency by β-cell failure (66,67).
Pancreatic β-cells have an essential role in the synthesis of insulin. Type 1 DM is an autoimmune disease with absolute insulin deficiency as a result of β-cell death. DM2 patients have relative insulin deficiency as a result of β-cell dysfunction and death consequent to effects of stressors including increased circulating glucose and saturated FAs and the development of inflammation (68). Metabolic dysregulation, such as excess nutrients and insulin resistance, has been linked with the secretory burden of β-cell, leading to ER stress, severely compromising cell function (69), and contributing to β-cell apoptosis (70).

**ER stress in neurodegenerative diseases**

A common feature of neurodegenerative diseases is the accumulation of misfolded proteins in the brain (71,72). The aggregation of abnormal proteins can perturb cellular structure and function, leading to neuronal loss, and promote the pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), and many other ailments.

AD is the most common neurodegenerative disease. It also is the most common cause of dementia, the prevalence of which doubles every 5 years between 65 and 85 years of age (71,73,74). The accumulation of aggregated proteins, extracellular amyloid β (Aβ) in the senile plaques and intracellular Tau protein in neurofibrillary tangles, is a prominent hallmark of AD (74). Aβ has been considered as the main culprit in the pathogenesis of AD, resulting in synapse disruption and neuronal destruction. Several reports have indicated that UPR is activated in the neurons of AD brain (75). Increased levels of the ER chaperone BiP have been found in the temporal cortex and the hippocampus of AD cases compared to non-demented control cases (74). More direct evidence of UPR activation is the detection of activated PERK and phosphorylated eIF2α in AD neurons (74).

PD is the second most common neurodegenerative disease which affects around 2% of individuals over 65 years of age (71). PD is a progressive disease with loss of dopaminergic neurons in the substantia nigra pars compacta, and with intracellular inclusion bodies termed Lewy bodies (71). A major component of Lewy bodies is α-synuclein (αSyn) which can be involved in the pathogenesis of PD. Cellular studies have shown that overexpression of αSyn triggers chronic ER stress and cell death (71). A mutation in the Parkin gene that induces ER stress and cell death has been linked with the pathogenesis of a juvenile-onset autosomal form of PD (74). ER stress markers have also been reported in post-mortem tissue from PD cases (71).

ALS is a motoneuron disease characterized by the degeneration of motor neurons in the spinal cord, cortex, and brain stem, leading to muscle atrophy and paralysis (71,74). Accumulating evidence suggests that ER stress contributes to ALS pathogenesis (71). Mutations in the gene coding superoxide dismutase 1 (SOD1) have been linked with the pathogenesis of the disease. A mutation in ER-resident vesicle-associated membrane protein-associated protein B (VAPB), which is involved in lipid transport, causes familial ALS through interacting and inhibiting ATF6 and XBP1 and increases ER-stress-induced motoneuron vulnerability and death (71,76). Modifications of protein disulfide isomerase (PDI), a key ER foldase, could also contribute to the pathogenesis of ALS.

Other neurodegenerative diseases with evidence of ER stress involvement in pathogenesis include Huntington's disease, prion-related diseases, lysosomal storage diseases, myelin-related disorders, and retinitis pigmentosa (71,72).

**ER stress, UPR, and cancer**

Recent research in the cancer field has revealed that ER stress and UPR are highly activated in various tumors and closely associated with cancer cell survival and resistance to anticancer treatments (for recent reviews, see (77,78)). Accumulating evidence has shown that the UPR is an important mechanism required for cancer cells to maintain malignancy and therapy resistance. The UPR pathways are activated in various human tumor cells and animal models with cancer, including breast cancer, hepatocellular cancer, gastric tumor, and esophageal carcinoma (78).

There are two main therapeutic approaches targeting the UPR components in cancer: induction of accumulation of misfolded protein in ER to overload the UPR response, and inhibition of UPR adaptive and antiapoptotic pathways to prevent cells from adapting stressful conditions leading to cell death. The UPR can respond by providing either survival signals for activating adaptive and antiapoptotic pathways, or death signals for inducing cell death programs (78). Pharmacological activation or repression of UPR may thus have beneficial and therapeutic effects against cancer. Numerous compounds are in development as agents for UPR-targeted cancer therapy, including inhibitors of ERAD, IRE1α, HSP90, GRP78, and proteasomes such as bortezomib (77,78).

**ER-activating therapy (ER-AC-TH) eliminates ER stress and diseases**

**ER-AC-TH: effects on ER, P450, liver, and risk factors, and regression of atherosclerosis**

Clinical investigations performed in the 1970s evaluated the effects of drug therapies activating hepatic ER functions on key risk factors of atherosclerotic disease (8,9). Our original observations associated drug-caused up-regulation of ER-resident P450 with the elevation of plasma HDL-C and apo AI (8,9) and lowering of LDL-C (29), and also with increase of hepatic protein and phospholipid concentrations (17,18), ER membranes (8,10), and of liver size in man (26). Plasma apo AI and HDL-C rise in proportion to liver proteins, phospholipids, and ER P450 (8,18), and subjects with high P450 activity show low LDL-C and LDL-C/HDL-C ratio (29). Corresponding to these changes, HDL-C rises and the LDL-C/HDL-C ratio (Figure 1) decreases with increasing liver size (26). The favorable elevation of HDL-C and lowering of LDL-C and the LDL-C/HDL-C ratio with the increasing liver size could be linked with the induction of membrane expansion and up-regulation of apo AI (35) and LDLR genes and the down-regulation of apo B gene (27) expression. The beneficial effects of the therapies on risk factors prevent and regress atherosclerosis (next section).
The ER-activating therapy inducing hepatic ER CYP7A1 promotes cholesterol conversion to bile acids (79) and can thus reduce cholesterol-induced ER stress (4). Similarly, drug therapy inducing phospholipid synthesis and reducing the cholesterol/phospholipid ratio alleviates cholesterol-caused stress (4).

**ER-AC-TH: antiatherogenic effects of xenobiotics on lipoproteins**

Numerous ER-activating compounds eliminate ER stress by lowering elevated cholesterol (4) and have antiatherogenic effects. They include drugs indicated for the treatment of dyslipidemias such as statins, niacin, fbrates, cholestyramine (79), and ezetimibe (80). Angioprotein receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), glitazones, anticonvulsants, retinoids, and alcohol also have antiatherogenic effects (79).

Statins are effective antiatherogenic agents. They inhibit cholesterol synthesis, reduce hepatic cholesterol, up-regulate LDLR pathway, and reduce plasma LDL-C (81). The drugs also induce apo AI synthesis in liver cells and raise plasma apo AI, HDL-C, and HDL₂-C (82). Statins stimulate P450 enzymes which generate PPAR-activating eicosanoids (83,84) and via PPAR activation up-regulate LXR, ABCA1, and ABCG1 genes in cholesterol-loaded macrophages and hepatocytes, and promote cholesterol efflux to apo AI and HDL (79).

Niacin reduces cholesterol and triglycerides and raisesapo AI and particularly HDL₂-C (85). It stimulates apo AI production, up-regulates PPARγ, LXRα, and ABCA1 genes, and promotes HDL-dependent cholesterol efflux (79). Fibrates, PPARα agonists, reduce LDL-C and triglycerides and raise HDL-C and apo AI and HDL (86). Fibrate-caused PPARα activation up-regulates P450-FA desaturase (27,87) and LXR and ABCA1 genes, and promotes cellular cholesterol efflux (79). Cholestyramine binds bile acids, induces CYP7A1, and reduces cholesterol in hepatocytes, increases LDL-C elimination via the up-regulated LDLR pathway, and also induces apo AI synthesis and raises plasma apo AI and the HDL₂-C subfraction (88). Ezetimibe, an effective inhibitor of cholesterol absorption, reduces plasma cholesterol and apo B and raises HDL-C (80). It has also been shown to decrease hepatic cholesterol, triglycerides, and steatosis, improve insulin signaling in rats, and reduce reactive oxygen species generation and ER stress in steatotic hepatocytes (89).

**ER-AC-TH targeting the UPR and atherosclerosis**

Different kinds of molecules act on ER stress and UPR and have potential to influence the atherosclerotic vascular process. Studies on animal models of obesity, DM2, and atherosclerosis have indicated that chemical chaperones can alleviate disease symptoms by reducing ER stress (90). Chemical chaperones such as 4-phenylbutyrate (PBA) and taurosodesoxycholic acid (TUDCA) have been shown to reduce ER stress both *in vitro* and *in vivo* in rodent models (91). PBA has been shown to reduce macrophage ER stress and vascular disease progression *in vivo*, and the reducing of the stress through macrophage lipid chaperone alleviates atherosclerosis (91). Statins have also recently been shown to activate UPR and ameliorate ER stress. They up-regulate UPR target genes such as GRP78 and transcription factors XBP1 and ATF6 (92). Other molecules that enhance the UPR include BiP inducer X (BIX), a small molecule inducer of endogenous GRP78 expression, and salubrinal which confers protection from the accumulation of unfolded proteins in the ER (60). Valproate, an ER chaperone inducer, has been found to attenuate accelerated atherosclerosis in mice *in vivo* (60).

**ER-AC-TH eliminates pancreatic ER stress, β-cell failure, insulin resistance, and DM2**

Drug therapy up-regulating ER functions in DM2 patients reduces both blood glucose and plasma IRI levels (10,11). Consequently, the therapy that normalizes glucose-insulin homeostasis eliminates the stress-linked glucose intolerance, insulin resistance, and DM2 (10,11). The normalization of glucose and IRI levels also indicates the elimination of the DM2-associated pancreatic ER stress and β-cell failure. Changes in hepatic ER function influence lipid, protein, and glucose metabolism, and, correspondingly, DM2 patients show improvement of both glucose tolerance and plasma lipoprotein profile with increasing liver phospholipid and P450 (93). All three UPR transducers (IRE1α, ATF6α, PERK) responses are crucial in β-cell to alleviate ER stress and restore ER homeostasis (68).

TUDCA has been shown to alleviate ER stress in obese and diabetic mouse models, normalize hyperglycemia, increase insulin sensitivity, resolve the fatty liver disease, and enhance insulin action in liver, muscle, and adipose tissues (91). Studies testing TUDCA in obese subjects with insulin resistance also have produced positive results: an increase in hepatic and muscle insulin sensitivity (94). Weight loss has beneficial effects. It reduces ER stress in man, together with a decrease of triglycerides in adipose tissue and liver, and blood glucose and insulin concentrations (64). The activation of nuclear receptors could also modify the effect of the diet on lipids and glucose. Recent studies revealed that an agonist of the constitutive androstane receptor (CAR), which is highly expressed in the liver, reversed diet-induced obesity, reduced hepatic steatosis, improved insulin sensitivity (95), and ameliorated diabetes and fatty liver disease in mice (96).

**ER-AC-TH eliminates hepatic steatosis and cholestasis**

A dysregulation of cell function inducing ER stress and affecting lipoprotein metabolism can lead to fat accumulation in the liver, and ER-activating factors including living habits and drugs promote fat elimination. The compounds induce reparation of cell membranes and ER proliferation, reduce liver fat (10) and triglycerides in man (17), and can eliminate the stress-associated steatosis. The chemical chaperones, PBA and TUDCA, and molecular chaperone BiP/GRP78 have been shown to reduce hepatic steatosis in obese mice (97).

The compounds inducing ER CYP7A1, the rate-limiting hepatic P450 enzyme in the synthesis of bile acids, enhance cholesterol conversion into bile acids (79) and can by normalizing impaired bile acid synthesis and bile flow eliminate the ER stress-associated cholestasis.

**Effects of FAs and ER-AC-TH-induced FA desaturation**

Saturated and unsaturated FAs differ significantly in their effects on cellular functions. Saturated FAs including palmitate and stearate, but not their monounsaturated counterparts, are known to induce ER stress (90) and contribute to the pathogenesis of obesity, the metabolic syndrome, and CVD (98). FA-binding proteins (FABPs) influence the effects of FAs (90). While saturated FAs are proinflammatory, unsaturated omega-3 FAs including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) have opposite effects. A recent study identified GRP120 as an omega-3 FA receptor mediating potent anti-inflammatory, insulin-sensitizing, and antidiabetic effects of DHA and EPA (99). C16:1n7 palmitoleate, a lipokine, has been identified as a potential adipose tissue-derived lipid hormone that stimulates muscle insulin action and suppresses hepatosteatosis (100).

The ER-AC-TH increasing P450-desaturase activity (27,87) induces the conversion of saturated FAs into unsaturated FAs and
thus reduces FA-induced ER stress and has beneficial eliminating effects on associated metabolic abnormalities.

**ER-AC-TH in neurodegenerative diseases**

Different kinds of compounds act on neuronal function and have potential as therapeutic agents in neurodegenerative diseases. Several mechanisms could be involved including activation of nuclear receptors, reducing ER stress, enhancing the UPR, and stimulation of protein degradation.

LXRs have an important function in lipid homeostasis in the brain, and the loss of the receptors leads to neurodegenerative processes (101). LXR-activating compounds reduce amyloid load and improve cognitive function in mouse models of AD (102). Pregnenolone-16α-carbonitrile (PCN), a pregnane X receptor (PXR) agonist, has also been shown to reduce brain Aβ levels (103), and PBA to reduce AD-linked Tau protein and ameliorate cognitive deficit in a mouse model of AD (104). PBA also restored the folding of acetylcholine receptors in a cell culture (74). Arimoclomol, an inducer of molecular chaperone, has been shown to reduce neuronal loss and improve motor function in mutant SOD1 mice (74). Valproate, a drug used for the treatment of epilepsy and bipolar disorder, has been found to increase BiP and other ER chaperones (74) and could be effective in AD by reducing ER stress and Tau phosphorylation. An inducer of BiP, BIX, protects against ER stress and neuronal loss in an animal model, suggesting a beneficial effect in neurodegenerative disorders (74). Lithium, which promotes the activation of autophagy, has been found to be effective in delaying disease progression in ALS patients, and salubrinal to act against ER stress and be protective in a PD cell model and in ischemia-induced stress in mice (74).

**Discussion**

Advanced methods in molecular biology have identified diverse biological and clinical roles for ER in maintaining cellular homeostasis. It responds to both endogenous and exogenous stimuli and generates new signaling molecules acting in metabolic processes. ER-activating compounds induce membrane synthesis and increase ER size and also liver size in man. The liver is of critical importance in the metabolism and elimination of endogenous and exogenous compounds, and changes in hepatic structure and function influence metabolic balance also in other tissues. The ER size control has an important function in maintaining cellular homeostasis. The enlargement of ER volume and luminal space through membrane synthesis increases the ER capacity to respond to changing demands, and it is an integral yet distinct part of the cellular program to overcome ER stress (21). Table II gives a summary of the effects of ER activation presented in this article and earlier studies.

The clinical studies reviewed show that the compounds activating ER functions alleviate and eliminate major global health problems. They prevent and regress atherosclerosis, reduce cardiovascular morbidity and mortality, and remove insulin resistance and DM2 together with the elimination of the DM2-linked pancreatic β-cell failure. The ER activation could also influence cognitive processes. They require gene expression modification to consolidate information, and disturbed transcriptional regulation could perturb neuronal function and cognitive performance (104). Healthy living habits prevent cognitive decline and dementia in man, and preclinical studies show that ER-activating therapy improves cognition. Low HDL has been identified as a risk factor for deficit and decline in memory in midlife (105), and, correspondingly, high HDL-C and apo AI concentrations associate with good cognitive performance in advanced age (106). Hyperinsulinemia similarly promotes cognitive impairment and increases the risk of AD (73), and removing modifiable risk factors of DM has a great reducing impact on the incidence of dementia (107).

The relation of lipoprotein metabolism and glucose-insulin homeostasis to ER function has been evaluated in studies including different patient groups and also healthy individuals. The up-regulation of ER-resident P450 has been linked with the expression of genes positively affecting the fate of cholesterol, and, correspondingly, individuals with high P450-activity in hepatic ER show high HDL-C, HDL-C/T-C, LDL-C/HDL-C, apo AI decrease—LDL-C, cholesterol, triglycerides, LDL-C/HDL-C, apo B increase/normalization Glucose tolerance, metabolic clearance rate of glucose Insulin sensitivity, glucose disposal rate Lowering/normalization/elimination Fasting blood glucose, insulin secretion, plasma IRI Insulin resistance, hyperinsulinemia Liver triglycerides, liver fat Amyloid β, Tau protein

| Table II. Effects of ER activation (this review, references (8,27,44)). |
| Up-regulation | Synthesis—proteins, phospholipids, membranes |
| | IRE1α, ATF6α, PERK, XBP1, NF-κB |
| | Chaperones |
| | Apo AI gene, LDLR gene |
| | Cholesterol metabolism, o xoyster, and bile acid synthesis |
| | Receptors—LXRs, PPARs, PXR, CAR, LDLR |
| | Enzymes—P450s, LCAT, CCTα, glucokinase, FA desaturase |
| | Transporters—ABCA1, ABCG1, apo AI |
| | HDL-apo AI—anti-inflammatory, antioxidative, vasodilatative, anti-thrombotic activity |
| | Cholesterol efflux |
| | Down-regulation/prevention |
| | Enzymes—HMGCoAR |
| | Apo B gene |
| | Reparation |
| | Effects of inflammation and cellular stress, cell membranes |
| Change in risk factor | Increase—HDL-C, HDL-C/T-C, HDL-C/HDL-C, apo AI |
| | Decrease—LDL-C, cholesterol, triglycerides, LDL-C/HDL-C, apo B |
| | Increase/normalization |
| | Glucose tolerance, metabolic clearance rate of glucose |
| | Insulin sensitivity, glucose disposal rate |
| | Lowering/normalization/elimination |
| | Fasting blood glucose, insulin secretion, plasma IRI |
| | Insulin resistance, hyperinsulinemia |
| | Liver triglycerides, liver fat |
| | Amyloid β, Tau protein |

Dietary factors influence disease processes, and different kinds of dietary supplements have been marketed for health promotion. Leicithin or phosphatidylcholine (PC) is a commonly recommended supplement to reduce the risk of CVD. PC has important physiological functions, but no favorable effect of dietary PC on the risk of heart disease has been documented. Hence, it is of interest that a recent study reported potentially harmful, ER stress-linked effects of the metabolites of this supplement (114). Gut flora converted PC to metabolites that were found to augment cholesterol accumulation in macrophages, promote the atherosclerotic process in mice, and predict the risk
for CHD in a large clinical cohort. The discovery of a relationship between gut flora-dependent metabolism of dietary PC and CVD pathogenesis also implicated some therapeutic approaches to prevent and treat atherosclerosis, including the use of probiotics to modulate gut flora and reduce the production of harmful metabolites.

Studies clarifying the effect of age on ER function indicate that there is impairment of the adaptive ER stress response and increase in pro-apoptotic signaling (115). Many key components of the UPR could display reduced activity with aging, resulting in a dysfunctional ER (115) and thus increasing the risk of cardiovascular and metabolic disease and cognitive impairment. Elderly healthy individuals have had capacity to maintain adequate ER function. Very old people possess a lipoprotein profile that is typical for a low risk of atherosclerotic disease and good cognitive health (106). The subtraction HDL2, which increases with aging is the most common phenotype among people in the advanced decades of life (116) and associates with low plasma insulin levels and good glucose tolerance (117).

In conclusion, this article elucidates the effects of ER functions on cellular homeostasis and regulation of metabolic processes. It clarifies how ER stress leads to cellular malfunction and disease processes and how ER activation eliminates both ER stress and associated cardiovascular, diabetic, and other metabolic diseases. ER-activating compounds induce reparation of altered cellular structures consequent to ER stress and normalize and improve metabolic functions. Lifestyle factors and appropriate therapies are central in the prevention and elimination of ER stress and promotion and maintaining well-being.

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