A review of the effects of 17 β-estradiol on endoplasmic reticulum stress: mechanisms and pathway

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ABSTRACT

The endoplasmic reticulum (ER) is an important organelle responsible for protein folding, calcium homeostasis and lipid biosynthesis. Accumulation of unfolded or misfolded proteins by hypoxia, loss of Ca^{2+} homeostasis and nutrient deprivation leads to endoplasmic reticulum stress (ERS) and then the unfolded protein response (UPR) is activated as a defense mechanism to restore endoplasmic reticulum homeostasis. It is now known that the ERS and the UPR are implicated in a variety of diseases such as diabetes, inflammatory diseases, neurodegenerative diseases and osteoporosis. Steroid hormones such as 17-βestradiol have been extensively reported to possess beneficial effects in different diseases. In this article, the concept of ERS, the underlying molecular mechanisms, and their relationship to several pathological conditions and finally, the role of 17-βestradiol and its receptors in moderating ERS and UPR are discussed to provide theoretical basis for in-depth study.

Keywords:

Endoplasmic reticulum

17 β-estradiol

Endoplasmic reticulum stress

Estrogen

Introduction

Growing evidence suggests that the endoplasmic reticulum (ER) is an important organelle responsible for several vital cellular functions, such as protein synthesis, folding and modification (Schwarz and Blower, 2016), and plays an essential role in the pathogenesis of many diseases such as neurodegenerative and metabolic diseases (Ramírez and Claret, 2015). In addition, the ER plays an important role in cell death/survival signaling mechanisms through membrane lipid biosynthesis and regulation of intracellular calcium concentration (Krebs et al., 2011; Yang and Luo, 2015). Some physiological,

biochemical and pathological stimuli such as hypoxia, inflammation, changes in calcium levels, oxidative stress, food deprivation and lipid oxidation commonly lead to the dysfunction of the ER, which can disrupt the protein folding process. All of these changes cause misfolded proteins to accumulate in the ER, resulting in endoplasmic reticulum stress (ERS) (Cominacini et al., 2015). ERS exacerbates cell dysfunction by disulfide bonding and protein glycosylation (Oakes and Papa, 2015). Recent research has shown that the incidence and severity of many diseases, such as metabolic and cardiovascular disorders and neurodegenerative diseases,

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increase in postmenopausal women (Lobo et al., 2014). Given that the positive and beneficial effects of estrogen have been shown to improve ERS under various conditions, nevertheless, the number of studies reporting estrogen ER stress modulation remains restricted. In this review, we review and discuss the current evidence about the effects of estrogen on ERS and the mechanism involved in recent years to provide ideas for relevant basic research and new therapeutic strategies in the future.

The unfolded protein response

When the misfolded or unfolded proteins accumulate in the ER and induce ERS, a homeostatic signaling network called the unfolded protein response (UPR) begins, which restores homeostasis in the ER (Lan et al., 2019; Wang and Kaufman, 2014). UPR does this by inhibiting the synthesis of new proteins in ribosomes, the breakdown of misfolded proteins and the transcription of folding chaperones (Oakes and Papa, 2015). UPR can cause restoration of homeostasis in the ER if the perturbation is moderate, but if the interference is prolonged and severe, UPR initiates cell death signaling pathways and eventually leads to various diseases (Ji et al., 2019). Protein kinase RNA-activated-like ER kinase (PERK), activating transcription factor 6 (ATF6) and inositol requiring enzyme 1 (IRE1α) are three transmembrane signaling proteins in the ER that act as ERS and UPR sensors or as initiators of upstream signals, as well as transcribing proteins associated with cell survival and maintaining ER homeostasis (Schröder and Kaufman, 2005). These three proteins are inactive as long as they bind to binding immunoglobulin (BIP), but conditions such as stress and increased misfolded and unfolded proteins cause BIP to separate from these proteins and thus activate them (Kropski and Blackwell, 2018; Lucke-Wold et al., 2016). These UPR sensor proteins, through their luminal domain, activate distinct signals and different signaling pathways and transmit them to the cytoplasm, which increases the transcription of proteins, enzymes and other substances necessary to maintain ER function (Oakes and Papa, 2015; Xu et al., 2005). So that cells can withstand conditions such as stress, the activation and function of these proteins is necessary.

The role of IRE1, PERK and ATF6
PERK pathway
PERK is an ER transmembrane protein that is part of the serine/threonine kinase family and is responsible for detecting unfolded proteins accumulated within the ER (Ramírez and Claret, 2015). In the presence of ERS, PERK kinase activity is activated by autophosphorylation and oligomerization and eukaryotic translation initiation factor 2A (eIF2a) is inactivated by phosphorylation at the Ser-51, resulting in a general inhibition of protein production and transport to the ER (Ariyasu et al., 2017; Park and Park, 2020). In contrast, transcription of genes that have an internal ribosome entry site, such as activating transcription factor 4 (ATF4), is increased (Lu et al., 2004). Activated ATF4 has a time-dependent contrast function. In the early stages of ERS, activated ATF4 often contributes to cell survival events by increasing the genes involved in metabolism, resistance to oxidative stress and the entry of amino acids (Harding et al., 2000; Harding et al., 2003). But in the latter stages of ERS, ATF4 reduces B-cell lymphoma 2 (BCL2), adenosine triphosphate (ATP), induces oxidative stress and cell death by activating C/EBP homologous protein (CHOP), a proapoptotic transcription factor (Almanza et al., 2019; Amen et al., 2019). Overall, it is believed that PERKs play a decisive role in cell fate in ERS conditions (Liu et al., 2015). Results of a recent study have shown that this pathway is also involved in the transfer of autophagy (B'chir et al., 2013) and it is claimed that autophagy induced by the PERK pathway is a determining factor in the cell's fate (Jiang et al., 2014).

ATF6 Pathway

ATF6 is a transcription factor belonging to the basic region/leucine zipper transcription factor family and is a stimulus for the expression of ER chaperone proteins (Ariyasu et al., 2017). ATF6 has two isoforms, ATF6α and ATF6β. Detection of unfolded proteins by the ER that occurs under stress leads to the transfer of ATF6 from the ER to the Golgi apparatus by the vesicle coat protein complex II, where it is processed by two proteases, sit-1 proteases and site-2 proteases (Ye et al., 2000). This process results in the creation of a transcription activation domain and a DNA-binding domain (Almanza et al., 2019). ATF6 is then inserted into the nucleus by regulated intramembrane proteolysis and regulates transcription of genes involved in protein folding via ERS response element (Yoshida et al., 1998). Similar to the PERK signaling pathway, ATF6 is also able to increase transcription of X-box binding protein 1 (XBP1) and

CHOP (Almanza et al., 2019).

IRE1 pathway

The third sensor protein in the ER membrane is called IRE1, which is an inactive monomer (Amen et al., 2019) and has two domains, luminal and cytoplasmic. Its luminal domain is similar to PERK and is involved in the detection of unfolded proteins. Its cytoplasmic domain consists of a kinase domain and a ribonuclease (RNAse) domain. In ERS conditions, homodimerization and autophosphorylation of the RNAse domain activate IRE1 (Yoshida, 2007). IRE1 endoribonuclease activity converts XBP1 pre-mRNA to mature XBP1 pre-mRNA (XBP1s) through selective cleavage and linkage of rings within the mRNA (Amen et al., 2019). XBP1s is a potent transcription factor that enters the nucleus after formation and, through binding to the UPR element, initiates transcription from various UPR targets that are important for proper protein folding and ER biogenesis (Kimata et al., 2007; Lee et al., 2002). In addition, IRE1 ribonuclease activity is involved in a mechanism called regulated IRE1-dependent decay, which selectively breaks down mRNAs associated with the ER encoding membrane and secretory proteins, and its purpose is to eliminate the protein charge on the ER (Hollien et al., 2009; Hollien and Weissman, 2006).

Apoptosis induced by ER stress

Prolonged activation of UPR and failure to reduce ERS induce cell death in mammalian cells by activating autophagic and/or apoptotic signaling pathways. UPR-mediated apoptosis is complex and generally, three signaling cascades are involved in its induction. Activation of ERS by activating PERK and eIF2a pathways induces proapoptotic transcription factor CHOP, which is the main regulator of ERS-induced apoptosis (Rutkowski et al., 2006). Also, ATF6 and ATF4 increase CHOP expression by binding to the CHOP gene promoter (Oyadomari and Mori, 2004; Yoshida et al., 2000). Then, activated CHOP increases the expression of proapoptotic transcription factors including growth arrest DNA damage-inducible protein 34, endoplasmic reticulum oxidoreductase-1 (Campos et al., 2014; Gregor et al., 2009) and death receptor 5 (Yamaguchi and Wang, 2004). The activated IRE1 signaling pathway, by binding to tumor necrosis factor receptor-associated factor 2 and apoptosis signal-regulating kinase 1, leads

to phosphorylation and activation of the c-Jun N-terminal kinase (JNK) pathway, thereby inducing apoptosis (Nishitoh et al., 2002; Urano et al., 2000). The caspase family is considered to be one of the mediators of ERS-induced apoptosis and the JNK pathway induces apoptosis through several different mechanisms, including activation of caspase-12 in rodents and caspase-4 in humans, inhibition of the anti-apoptotic protein BCL2, activation of BCL2–associated X protein and activation of BCL2–associated death protein. Eventually, activation of mitochondrial apoptosis is occurred (Kim et al., 2006).

Estrogen and its receptors

Estrogens are steroid hormones that are involved in the reproductive system and many other systems such as neuroendocrine, cardiovascular, skeletal and immune in both males and females. There are three forms of estrogen in the human body: estrone (E1), 17 β-estradiol (E2) and estriol (E3). During the reproductive years, the major circulating estrogen is E2 which is the strongest form of estrogen. E2 as a signaling molecule by regulating the expression of proteins and transcription factors affect a large number of physiological processes such as aging (Esmailidehaj et al., 2020; Farhadi et al., 2020a) and pathophysiology such as obesity, cardiovascular (Azizian et al., 2018) and metabolic disorders, cancers, osteoporosis and cerebral ischemia (Farhadi et al., 2020b) is effective. These effects of E2 are mediated through two general classes of receptors called nuclear receptors (genomic effects) and membrane receptor (non-genomic effects). There are two isoforms of classical nuclear estrogen receptors, estrogen receptor α (ERα) and estrogen receptor β (ERβ) (Hamilton et al., 2017). Genomic E2 signaling occurs as a result of estrogen receptor transport to the nucleus and their direct binding to estrogen response element, protein-protein interaction with other DNA-binding transcription factors and ligand-dependent activation (Hamilton et al., 2017). The activity of nuclear factor kappa-light-chain-enhancer of activated B cells (Kalaitzidis and Gilmore 2005), signal transducer and activator of transcription 5 (Bjornstrom and Sjoberg, 2005), ATF2, C-jun, ATF1-cAMP response element-binding protein and nuclear factor Y (O'Lone et al., 2004) is modulated by the formation of complexes with nuclear estrogen receptors. These receptors also regulate cellular processes such

as differentiation, proliferation and apoptosis by inducing the activator protein 1 transcription factor (Gaub et al., 1990). Rapid non-genomic signaling of E2 occurs through G-protein coupled estrogen receptor (GPR30) and it is involved in activating the mechanisms of production of secondary messengers into the cell, activating protein kinase signaling cascades and regulating cyclic adenosine monophosphate (cAMP), all of which lead to indirect regulation of gene expression (Lösel and Wehling, 2003). Signaling cascades of protein kinases include the Akt, MAPK/ERK (Clark et al., 2014), PKC/PLC (Garcia Dos Santos et al., 2002; Marino et al., 1998), Ras/Raf/MAPK, PI3K/Akt kinase (Marino et al., 2003) and cAMP/PKA (Gu and Moss, 1996). E2 and its receptors play an important role in the ERS process, and there is a link between unfolded protein levels and E2 signaling (Raina et al., 2014). Both ERα and ERβ can activate and regulate cell survival, growth and metabolism by modulating the expression of various genes (Xue et al., 2015). On the other hand, it has been shown that decreased expression of ERα and ERβ is associated with the activation of ERS.

The role of ER stress in disease and the effects of estrogen

The effects of estrogen on ERS in the ischemia brain injury

Cerebrovascular disorders are one of the most common diseases that cause dysfunction of the whole body, especially in the elderly. Cerebral ischemia-reperfusion causes brain damage due to changes such as acidosis, apoptosis, inflammation and increased intracellular calcium concentration (Xu et al., 2018). It has been shown that there is a strong association between ischemia-reperfusion injury and activation of ERS pathways (Han et al., 2019) so that cerebral ischemia-reperfusion induces misfolding or UPR through glycosylation of proteins and expression of mutant proteins (Xu et al., 2018) and cell apoptosis (Wang et al., 2016). As a result, it induces ERS. Therefore, inhibition of pathological mechanisms caused by ischemia-reperfusion injury is very important in the treatment of ischemic cerebrovascular diseases (Xu et al., 2018). It is now known that the severity of damage caused by cerebral ischemia-reperfusion is lower in women than in men, but after menopause, this advantage disappears, which is believed to be due to the reduced E2 effect (Herson et al., 2009). Apoptosis is

the main pathophysiological change after cerebral ischemic-reperfusion injury (Mattson et al., 2001) and the ERS pathway is a newly discovered pathway that has been shown to induce apoptosis in many brain diseases (Lee et al., 2010; Silva et al., 2005) and metabolic disorder (Sano and Reed 2013). E2 plays an important role in hypoxic-ischemia encephalopathy so that during the development of hypoxic-ischemia encephalopathy, on the one hand ERS is activated, and on the other hand, estrogen receptors are suppressed (Wang et al., 2016). In addition, estrogen receptors can regulate ERS in hypoxia-ischemic encephalopathy through the Ca^{2+}-calmodulin-dependent protein kinase II and MAPK pathways (Raval et al., 2006).

Notoginsenoside R1 (NGR1) is a phytoestrogen used to treat heart disorders (Sun et al., 2013) and acute liver failure (Zhou et al., 2014). In pathological conditions such as ischemia-induced encephalopathy, this phytoestrogen can regulate Akt/Nrf2 or tumor necrosis factor α (Meng et al., 2014; Zhong et al., 2015), NF-kB (Zhong et al., 2015) and autophagy pathways (Lu et al., 2011; Zhou et al., 2014) through estrogen receptors, and since there is a direct link between activation of inflammatory pathways (Oyadomari and Mori, 2004) and autophagy (Rashid et al., 2015) with ERS, therefore, NGR1 may be able to attenuate apoptosis and ERS. NGR1 also reduces the activation of ERS by estrogen receptors and improves the dysfunction of primary cortical neurons. For example, the use of classical estrogen receptor blockers such as ICI eliminates the protective effects of NGR1 against ERS and apoptosis, suggesting that the therapeutic effects of this phytoestrogen on ERS-mediated brain damage are mediated by classical estrogen receptors (Wang et al., 2016). Furthermore, E2 can regulate cellular apoptosis and inflammatory responses through rapid signaling responses mediated by GPR30 (Prossnitz and Barton, 2014). Several studies have shown that E2 may protect the brain by inhibiting the ERS and apoptosis (Jia et al., 2009; Shughrue and Merchenthaler, 2003). Both *in vivo* and *in vitro* studies have shown that E2 inhibits ERS with its secondary effects and plays a key role in reducing ischemic-reperfusion injury (Han et al., 2019; Raval et al., 2006; Xu et al., 2018). For example, a study by Han et al. (2019) showed that treatment with E2 and GPR30 agonist reduced ischemia-reperfusion damage in the hippocampus by reducing the expression of genes and proteins such as 78-kDa glucose-regulat-
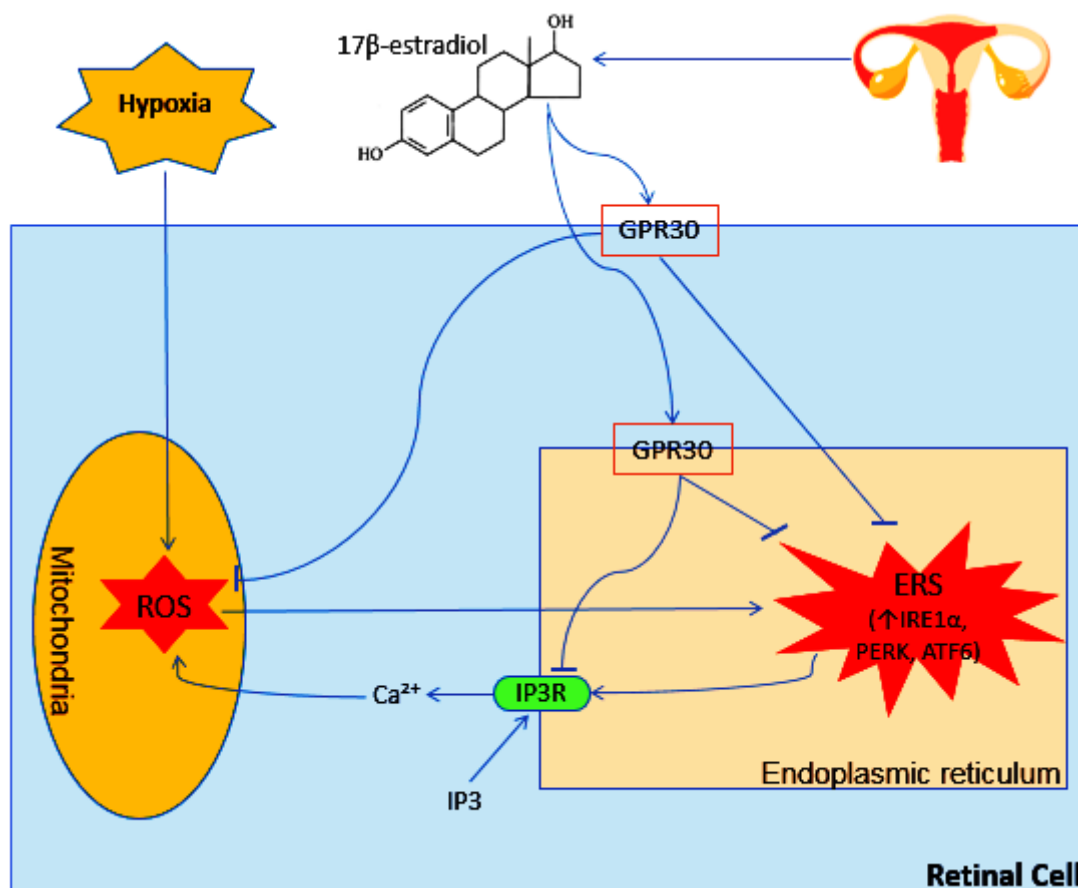
FIGURE 1. Summary of effects of 17β-estradiol on ERS in the retinal cells.

ed protein (GRP78), CCAAT-enhancer-binding proteins (C/EBP) and caspase-12. Also, this study showed that inhibition of GPR30 with G15 reverses the effects of E2 on ischemia-reperfusion injury. These results confirm that E2, through its membrane receptor, inhibits the expression of ERS-related proteins and apoptosis in the hippocampus and therefore can reduce the disorder caused by ischemia-reperfusion injury.

The effects of estrogen on ERS in the retinopathy

Abnormal growth of retinal arteries due to hypoxia causes retinal detachment and retinopathy, which eventually leads to blindness. In premature infants, E2 levels decline rapidly after birth, which is associated with increased retinal vascular growth and oxidative stress, both of which increase the incidence of retinopathy (Li et al., 2020b). It has been shown that E2 is able to reduce oxidative stress and regulates ERS in retinal ganglion cells (RGCs) through GPR30 (Li et al., 2020b). GPR30 is also expressed in the ER of the RGCs (Molina et al., 2017) and regulates the functions of the ER under normal, physiological, and E2-related conditions (Prossnitz

and Barton, 2011; Revankar et al., 2005).

In hypoxia, the GPR30 agonist reduces UPR directly by reducing the expression of proteins such as IRE1α, PERK, ATF6 (Li et al., 2020a;b) and indirectly by reducing oxidative stress levels in RGCs, which ultimately reduces the damage caused by retinopathy (Prossnitz and Barton, 2011; Revankar et al., 2005). The mechanism for this function of GPR30 in retinopathy is activated by reducing the time-dependent activity of inositol 1, 4,5 triphosphate receptor (IP3R) and increasing the calcium concentration in the ER of RGCs (Li et al., 2020a;b). IP3R is located on the surface of the ER and is responsible for regulating calcium release from the ER and there is a close interaction for the exchange of calcium between the ER and the mitochondria (Vannuvel et al., 2013). IP3 as a secondary messenger binds to IP3R on the ER and stimulates calcium release. On the other hand, calcium accumulation in mitochondria also increases oxidative stress and increases unfolded/misfolded proteins and UPR in the ER. As a result, an increase in these proteins stimulates calcium leakage from the ER, triggering a vicious cycle (Chaudhari et al.,

2014). In contrast, activation of GPR30 reduces IP3R activity and subsequently reduces calcium leakage into the mitochondria, which normalizes calcium concentrations in the ER. Overall, activation of GPR30 helps maintain calcium homeostasis in the ER and reduces ERS in hypoxia-induced retinopathy, which increases the survival of retinal ganglion cells (Li et al., 2020a;b). A schematic representation of the potential role of E2 in ERS-induced retinopathy is shown in Figure 1.

The effects of estrogen on ERS in energy balance

The mechanisms that control energy balance are the same in both males and females, but high levels of female steroids, especially E2, can affect this balance (Mauvais-Jarvis, 2015; Mauvais-Jarvis et al., 2017; Mauvais-Jarvis et al., 2013). Menopausal E2 depletion is associated with hyperphagia, decreased energy expenditure, weight gain and E2 replacement therapy reverses these effects (Mauvais-Jarvis, 2015; Mauvais-Jarvis et al., 2017; Mauvais-Jarvis et al., 2013). Evidence suggests that ERS in the hypothalamus is one of the central pathophysiological mechanisms that induce obesity and energy imbalance by inducing insulin and leptin resistance (Ozcan et al., 2009; Schneeberger et al., 2013; Zhang et al., 2008). For example, increasing the concentration of ceramide in the hypothalamus induces ERS and consequently obesity, insulin resistance, decreased sympathetic activity and these ceramide actions are reversed by inhibiting ERS, which improves obesity and energy balance (Contreras et al., 2014; Contreras et al., 2017). E2 has been reported to be able to reduce the serum concentration of ceramide (Vinayavekhin et al., 2016) and if injected centrally, leads to decreased ceramide levels in the hypothalamus and consequently a decrease in ERS (González-García et al., 2018). This central action of E2 is mediated by increased sympathetic beta-3 adrenoceptor signaling, which increases brown fat thermogenesis and improves lipotoxicity (González-García et al., 2018).

The effects of estrogen on ERS in the endothelial cells

Increased oxidative stress and ERS are involved in many vascular pathological processes such as atherosclerosis (Araki et al., 2003; Özcan et al., 2004). Although these two pathways can occur simultaneously (Nardai et al., 2003; Sheikh-Ali et al., 2010b), they are not always related to each other and can be activat-

separately (Sheikh-Ali et al., 2010b). Excessive ERS and high apoptosis in endothelial cells also play a role in the development of cardiovascular disease and may play a major role in premature rupture of atherosclerotic plaques (Hetz, 2012). Studies have been shown that ERS which induced hyperglycemia play a potential role in metabolic damage of endothelial cells (Sheikh-Ali et al., 2010a;b) and smooth muscle cells in cardiovascular disease and diabetes (Hansson, 2005). Given the interrelationship between oxidative stress and ERS (Sheikh-Ali et al., 2010b) and also the known antioxidant activity of some sex steroids (Rifici and Khachadurian, 1992; Strehlow et al., 2003), it can be speculated that sex steroids play an important moderating role in ERS. E2 can reduce oxidative stress and subsequently ERS, via reduction in GRP78 expression and JNK phosphorylation which leads to decrease in UPR in cells (Haas et al., 2012). Alternatively, E2 may also have independent effects in reducing ERS (Haas et al., 2012). In addition, it has been observed that E2 and testosterone can suppress ketosis-dependent oxidative stress and inhibit dextrose-induced ERS in a dose-dependent manner. These beneficial effects are seen in physiological plasma concentrations of E2 and testosterone, and even the effects of testosterone are due to its aromatization to E2 (Mooradian, 1993). Induction of ERS in the *in vivo* with tunicamycin and dithiothreitol stimulates all three major ERS signaling pathways, p-PERK/PERK, IRE1/IRE1 and ATF6, and E2 can inhibit all three signaling pathways. On the other hand, these inhibitory effects of E2 disappear in the presence of estrogen receptor inhibitors such as ICI and G15. Furthermore post-estrogen receptor signaling pathway inhibitors such as phosphoinositide 3-kinase (PI3K) inhibitor, p38-MAPK inhibitor, JNK inhibitor, and ERK1/2 inhibitor eliminate E2 inhibitory effects (Su et al., 2017). In general, E2 inhibits ERS in endothelial cells by inhibiting apoptotic initiators, and the main mechanism responsible for this action of E2 is through the activation of estrogen receptors (Su et al., 2017).

The effects of estrogen on ERS in the uterus

ERS-causing agents such as lipopolysaccharides and pro-inflammatory cytokines such as TNF-α and interleukin 6 can alter immune responses and hormone secretion in the female reproductive system (Iwawaki et al., 2009; Lin et al., 2012; Park et al., 2014) by activat-

ing the toll-like receptor 4 signaling pathway (Mehta et al., 2015; Price et al., 2013). These factors inhibit the production of steroids by immune responses in granulosa cells and reduce E2 production in granulosa cells (Lei et al., 2019). As a result of these changes, the female reproductive system is more disrupted (Bromfield and Sheldon, 2011; Herath et al., 2007; Price et al., 2013). In contrast, inhibition of ERS leads to decreased production of pro-inflammatory cytokines and reversal of E2 production. Thus, ERS plays an important role in reducing E2 production induced by lipopolysaccharide in granulosa cells, indicating a cross-talk between inflammatory responses and ERS in uterine tissue (Lei et al., 2019).

The effects of estrogen on ERS in the bone

An imbalance between bone formation and reabsorption is the major mechanism for osteoporosis (Karsenty and Wagner, 2002; Rodan and Martin, 2000). ERS is well controlled in secretory cells such as collagen-secreting osteoblasts (Guo et al., 2014), and factors that act by increasing apoptosis in osteoblasts, such as ERS, can cause osteoporosis (Cui et al., 2013; Hamamura and Yokota, 2007). Some ERS-related proteins play an important role in bone formation. For example, factors such as old astrocyte specifically induced substance through transcription of collagen type I alpha 1 chain and secretion of bone matrix proteins (Murakami et al., 2009), transcription factor XBP1 by increasing runt-related transcription factor 2 expression, (Liu et al., 2012) and ATF4 by facilitating collagen production and the entry of amino acids into osteoblast (Elefteriou et al., 2006) all increase bone formation. Postmenopausal E2 deficiency is a major cause of osteoporosis (Guo et al., 2014) and many studies have shown that in postmenopausal women with osteoporosis, apoptosis is high in osteoblasts (Kousteni et al., 2002). Because E2 increases the survival of cell types by activating cell survival signaling pathways such as MAPK (Song et al., 2002). For example, E2 increases the production of GRP78 through the Ras-ERK1/2 pathway and thus prevents the activation of caspase 12 and 3, which ultimately leads to a decrease in ERS-induced cell apoptosis in osteoblast cells (Guo et al., 2014).
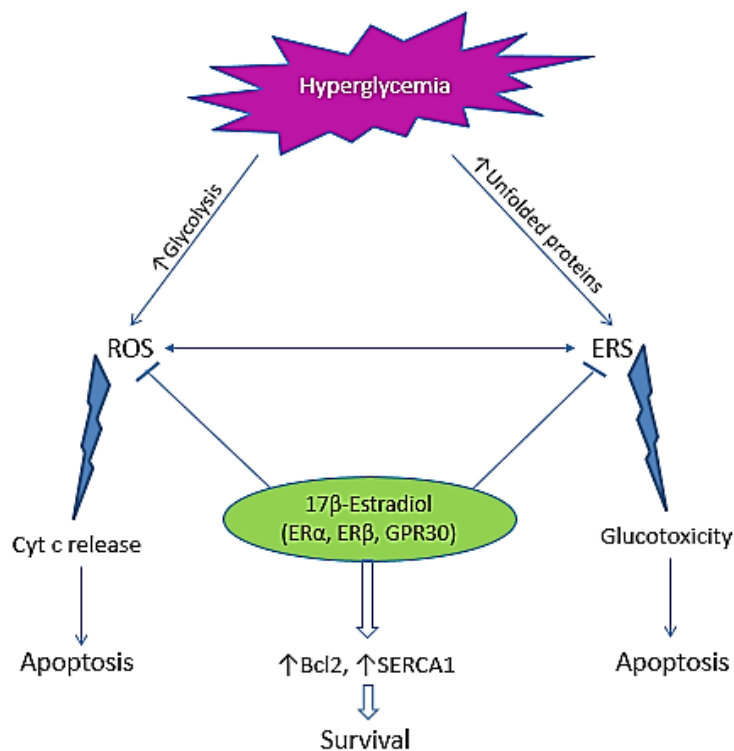
The effects of estrogen on ERS in the heart

Various conditions such as ischemia, hypoxia, redox disorder and gene mutation cause the production of unfolded proteins and induction of ERS (Szegezdi et al., 2006; Xu et al., 2005), which are involved in the pathogenesis of a number of diseases, including diabetic cardiomyopathy (Li et al., 2008) and pressure overload cardiac hypertrophy (Okada et al., 2004). Excessive pressure induces ERS in the heart (Okada et al., 2004; Zhang et al., 2009), and males are more sensitive so that GRP78 expression is increased in males more than females (Sari et al., 2011). One of the reasons for this gender difference is the difference in the regulation of intracellular calcium during hypertension Because it has been shown that changing the level of calcium sarcoplasmic/endoplasmic below the acceptable functional range leads to increased ERS and altered regulation of calcium-binding proteins, such as sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA2) (Guo et al., 2014). Given that the expression of SERCA2 and phospholamban in the heart are sex-dependent (Chu et al., 2005; Pavlovic et al., 2005), a decrease in SERCA2 levels in male rather than female hearts under conditions of pressure overload is justified (Weinberg et al., 1999). Another reason for this gender difference could be due to differences in apoptotic-inducing proteins such as CHOP, since it has been shown that E2 can directly suppress CHOP under conditions of excessive stress in in vivo (Park et al., 2009).

The effects of estrogen on ERS in the pancreas

Due to the high secretory function of the islets of Langerhans, pancreatic beta cells have an extensive ER (Lipson et al., 2006) and the production of appropriate proteins by the ER is essential for the survival of beta cells (Zhou et al., 2018). Prolonged hyperglycemia causes glucotoxicity (Robertson et al., 2003) and the results of other studies show that ERS plays an important role in this glucotoxicity (Marchetti et al., 2007; Robertson et al., 2003; Wang et al., 2005). In hyperglycemia or insulin resistance, increased ER performance increases insulin secretion. This increase in ER overactivity is accompanied by the production of large amounts of unfolded proteins and eventually leads to ERS (Harding et al., 2001; Scheuner et al., 2005). It has been shown that in beta cells, where proteases consume a lot of energy, there is a strong link between the ER and mitochondria. ERS activates a set of UPRs that release cytochrome C from mitochondria and initiate apoptosis in beta cells

FIGURE 2. The interplay of ERS, oxidative stress and apoptosis in 17βestradiol-mediated protection in pancreatic β-cells

TABLE 1: Summary of effects of estrogen on ERS in diverse disease models.

Type of disease	Estrogen action	Type of estrogen receptor	Mechanism	Reference
Ischemia brain injury	↓ ERS	ERα, ERβ, GPR30	↓Apoptosis, ↓Autophagy ↓GRP78, ↓C/EBP, ↓Caspase 12, ↓TNFα, ↓NFkB	(Han et al., 2019; Meng et al., 2014; Zhong et al., 2015)
Retinopathy	↓ ERS	GPR30	↓ROS ↓IRE1α, ↓PERK, ↓ATF6	(Lei et al., 2019; Li et al., 2020a; Prossnitz and Barton 2011)
Obesity	↓ ERS	?	↓Ceramid, ↑β3-AR, ↑Thermogenesis	(González-García et al., 2018; Vinayavekhin et al., 2016)
Atherosclerosis	↓ ERS	ERα, ERβ, GPR30	↓ROS, ↓Apoptosis ↓GRP78, ↓p-JNK, ↓IRE1α, ↓PERK, ↓ATF6	(Haas et al., 2012; Su et al., 2017)
Osteoporosis	↓ ERS	?	↓Apoptosis ↑MAPK, ↑Ras-ERK1/2, ↓GRP78, ↓Caspase 12, ↓Caspase 3	(Guo et al., 2014; Song et al., 2002)
Cardiac hypertrophy	↓ ERS	?	↓CHOP, ↑SERCA2	(Park et al., 2009; Weinberg et al., 1999)
Diabetes	↓ ERS	ERα, ERβ, GPR30	↓ROS ↓GRP78, ↓CHOP, ↓ATF6, ↓UXBP1, ↑ Bcl2, ↑P-p38, ↑SERCA2	(Kooptiwut et al., 2014; Zhou et al., 2018)

(Zhou et al., 2018). Pancreatic beta cells have all three estrogen receptors, ERα, ERβ and GPR30 (Liu et al., 2009) and studies have shown that E2, through three of its receptors, can reduce pancreatic beta-cell death via reducing oxidative stress and ERS markers due to high glucose concentrations such as GRP78, CHOP, ATF6 and XBP1. On the other hand, E2 increases the survival of INS-1 cells (a rat insulinoma cell line) by increasing survival proteins such as BCL2, P-p38, and SERCA2 (Kooptiwut et al., 2014) (Figure 2).

In general, the anti-apoptotic and anti-ERS effects of E2 are mediated by activating the PI3k-Akt signaling pathway and inactivating p38 (Kooptiwut et al., 2014). Classical and non-classical estrogen receptor antagonists attenuate these estrogenic effects (Azizian et al., 2018; Kooptiwut et al., 2014). It has been shown that ERα increases insulin secretion and beta-cell survival by regulating mitochondrial-ER function (Kooptiwut et al., 2014). Knocking out the estrogen receptor 1 gene, which encodes ERα, increases the expression of CHOP and in contrast, activating and over-expressing ERα by binding to estrogen response element reduces the expression of CHOP (Zhou et al., 2018).

Conclusion and perspective
E2 has been reported to exert many biological effects through several mechanisms. Among these mechanisms, affecting ERS is considered as a therapeutic candidate for several diseases, including brain ischemia and metabolic and neurodegenerative disorders (Table 1). This review provided information on the specific function of E2 by targeting ERS, which suggests E2 has a potential therapeutic ability to prevent disease or at least slow the progression of such diseases. On the other hand, due to the diversity of estrogen receptors in the body, the effects of E2 on the ERS in different organs are mediated with distinct mechanisms. Although it was reported that E2 can prevent ERS-induced apoptosis and autophagy, the associated molecular mechanism(s) remains unclear. Based on the available evidence, it is clear that complex mechanisms are involved in the ERS process which leads to cell death and E2 and its receptor agonists can largely inhibit these mechanisms. Additional research is needed to establish the role of ERS in the development of disease because of its apparent dualistic response. In addition, despite the growth of preclinical evidence, there is still no adequate clinical support for the use of E2 as part of the therapeutic arsenal for the treatment of such diseases. Future studies should provide details of the functional mechanisms of E2 in ERS, suggesting that E2-inhibition of ERS may be a therapeutic goal.

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Conflict of interests
Authors declare no conflict of interest.

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