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Ischemic brain injury in diabetes and endoplasmic reticulum stress

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Abstract

Diabetes is a widespread disease characterized by high blood glucose levels due to abnormal insulin activity, production, or both. Chronic diabetes causes many secondary complications including cardiovascular disease: a life-threatening complication. Cerebral ischemia-related mortality, morbidity, and the extent of brain injury are high in diabetes. However, the mechanism of increase in ischemic brain injury during diabetes is not well understood. Multiple mechanisms mediate diabetic hyperglycemia and hypoglycemia-induced increase in ischemic brain injury. Endoplasmic reticulum (ER) stress mediates both brain injury as well as brain protection after ischemia-reperfusion injury. The pathways of ER stress are modulated during diabetes. Free radical generation and mitochondrial dysfunction, two of the prominent mechanisms that mediate diabetic increase in ischemic brain injury, are known to stimulate the pathways of ER stress. Increased ischemic brain injury in diabetes is accompanied by a further increase in the activation of ER stress. As there are many metabolic changes associated with diabetes, differential activation of the pathways of ER stress may mediate pronounced ischemic brain injury in subjects suffering from diabetes. We presently discuss the literature on the significance of ER stress in mediating increased ischemia-reperfusion injury in diabetes.

Graphical Abstract

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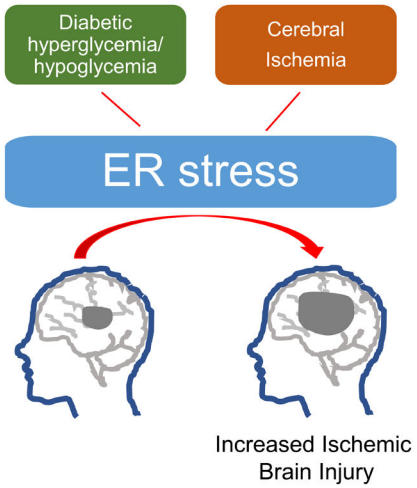

Keywords

Cell death; cerebral ischemia; hyperglycemia; hypoglycemia; unfolded protein response

1. Introduction

As defined by the American Diabetes Association “Diabetes is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both” (American Diabetes Association, 2014). More than 34 million people in the USA are presently suffering from diabetes, and the estimated cost of diagnosed diabetes was $327 billion in 2017 (Kleindorfer et al., 2010). Long-term complications associated with chronic diabetes include nephropathy, retinopathy, neuropathy, and development of cardiovascular disease (CVD) along with other secondary complications (Tracey et al., 2016; Virani et al., 2021). It is an accepted fact that diabetes causes CVD in a large subset of patients (Spencer et al., 2008). Studies have shown that the prevalence of experiencing ischemic stroke and coronary heart disease is twice that of subjects suffering from diabetes (Emerging Risk Factors Collaboration et al., 2010). Increased hypercoagulability, dyslipidemia, inflammation, and endothelial dysfunction are some of the factors that may be mediating CVD (Plutzky J ZB, 2012). Individuals suffering from diabetes show increased macrophage infiltration, atheroma, atherosclerotic plaque, and thrombus formation (Cipollone et al., 2003; Moreno et al., 2000). These factors may cause a blockage in the cerebral vasculature and result in ischemia in subjects suffering from diabetes. CVD is considered an important cause of death in patients with diabetes (Virani et al., 2021). Diabetes is associated with increased cardiovascular and cerebrovascular mortality in male and female subjects (Liu et al., 2016; Virani et al., 2021). The estimated contribution of CVD toward the total direct costs of diabetes care is 20% to 49% (Einarson et al., 2018). Diabetes enhances the risk of cerebral ischemia, and cerebral ischemia-related mortality and morbidity are also greater in individuals suffering from diabetes (Centers for Disease Control and Prevention, 2003; Ottenbacher et al., 2004).

2. Diabetes and ischemia-reperfusion injury

Cerebral ischemia results from an interruption in cerebral blood flow (CBF) due to an occlusion in the blood vessel(s) in the brain (Smith, 2015). The level of drop in CBF depends on the structure of cerebral vessels, extent of collateral circulation, site and volume of blockage, and blood pressure. The main reasons for occlusion in cerebral vasculature that results in ischemia are an embolus formed at a different location in the body circulation, thrombosis inside the cerebral vasculature, and reduced CBF because of a stenosis in a prominent blood vessel. A long episode of cerebral ischemia induces cerebral infarction due to cell death in the area affected via the activation of many signal transduction cascades.

A meta-analysis study showed that chronic diabetes leads to poor clinical outcomes following stroke (Desilles et al., 2013). Cerebral infarction is observed more frequently in people with diabetes versus those without diabetes (Lithner et al., 1988). Focal cerebral ischemia in type-2 diabetic db/db mice produces increased infarct size, neurological impairment, edema in the brain, inflammation, and mortality when compared to the non-diabetic control mice (Tureyen et al., 2011). A previous meta-analysis study showed that hyperglycemia is associated with an increased infarct size in an animal model of type 1 diabetes (T1D) (MacDougall and Muir, 2011). Our laboratory has shown that insulin treated diabetic rats experiencing previous episodes of recurrent hypoglycemia (RH) show enhanced ischemic brain injury (Dave et al., 2011; Rehni et al., 2019b; Shukla et al., 2019). However, the mechanism of increase in the ischemic brain injury during diabetes is not well understood. Studies have proposed the role of multiple mechanisms in mediating the diabetes-induced increase in ischemic brain injury. This article aims to review the scientific literature that shows the significance of endoplasmic reticulum (ER) stress in mediating increased ischemia-reperfusion injury in diabetes.

3. Endoplasmic reticulum stress

The ER is a membranous organelle that spans across the cell and serves the vital function of making new proteins. Besides, the ER facilitates proper protein folding and transport. In addition, ER plays a role in lipid biosynthesis, transfer and signaling. Further, the ER serves the function of calcium storage and release, and detoxification of compounds (Schwarz and Blower, 2016; Thomas D Pollard William C Earnshaw Jennifer Lippincott-Schwartz Graham Johnson, 2017). ER stress results when the burden of unfolded proteins in the ER lumen exceeds its ability to facilitate proper protein folding. Unfolded protein response (UPR) is a group of physiological signal transduction mechanisms that are responsible for sensing and responding to the protein folding capacity of the ER (Ron and Walter, 2007). The UPR regulates numerous genes that either maintain ER homeostasis or induce cell death (Ron and Walter, 2007). Increase in the levels of misfolded or unfolded proteins in the ER causes activation of various UPR pathways. First pathway is the activating transcription factor-6 (ATF6) pathway. The second pathway that is activated is the double-stranded RNA-dependent protein kinase (PKR)-like eukaryotic initiation factor 2α (eIF2α) kinase (PERK) pathway. And thirdly, inositol-requiring transmembrane kinase/endoribonuclease 1 (IRE1) pathway is another pathway activated by accumulation of improperly folded proteins. Activation of these pathways conveys the information through the membrane into

the cytoplasm where several transcription factors then transmit information to the nucleus (Kadowaki and Nishitoh, 2013). Previous studies showed that ATF6, IRE1, and PERK are normally bound to the 78 kDa glucose-regulated protein or immunoglobulin heavy chain binding protein (GRP78 a.k.a BiP). BiP possesses a higher affinity for misfolded proteins in comparison to its affinity for ATF6, IRE1, and PERK (Wang and Kaufman, 2016). During conditions of stress in the ER, BiP detaches from the UPR proteins to bind to the misfolded proteins leading to the activation of the three UPR pathways (Bertolotti et al., 2000; Shen et al., 2002). Besides, the activation of IRE1 also occurs via direct binding to misfolded proteins (Gardner et al., 2013).

3.1 ATF6

ATF6 is a type II transmembrane protein with a luminal domain on the carboxy-terminal and a transcription factor domain on the amino terminal. During conditions of ER stress, ATF6 relocates from the network of the ER to the Golgi apparatus where site-1 and site-2 proteases act on them to detach its amino terminal transcription factor domain which moves to the nucleus and binds to ER stress response element (Haze et al., 1999; Shen et al., 2002). This activates the transcription of UPR target genes which corrects ER stress (Yoshida et al., 1998).

3.2 PERK

PERK is another type I transmembrane protein with a luminal stress-sensing domain and a cytosolic kinase domain. ER stress-induced-PERK trans-autophosphorylation causes phosphorylation of the eIF2α. eIF2α phosphorylation inhibits protein synthesis and thus reduces the ER protein load as discussed previously (Harding et al., 1999). However, certain mRNAs with inhibitory upstream open reading frames are preferentially translated (Jackson et al., 2010). Activating transcription factor-4 (ATF4) is upregulated resulting in increased transcription of factors like C/EBP homologous protein (CHOP) and Growth Arrest and DNA Damage-inducible 34 (GADD34) (Harding et al., 2000a; Scheuner et al., 2001). While the transcription factor GADD34 regulates a negative feedback mechanism that inhibits the PERK pathway, CHOP is known to mediate apoptotic cell death (Zinszner et al., 1998) (Wang et al., 1998; Zinszner et al., 1998). Therefore, the PERK pathway of ER stress exerts a beneficial effect on stressed cells. However, a concerted and prolonged activation of PERK pathway stimulates apoptotic cell death as reviewed previously (Walter and Ron, 2011).

3.3 IRE1

IRE1 is a type I transmembrane protein with an ER luminal domain on the amino-terminal, and cytoplasmic kinase and RNase domains on the carboxy terminal. During ER stress, IRE1 assembles into its oligomeric form by self-association of the ER luminal domains of its molecules (Kimata et al., 2007). This is followed by nucleotide binding which causes a conformational change, resulting in the activation of RNase activity of IRE1 (Papa et al., 2003). The RNase activity of IRE1 cleaves basic–leucine zipper transcription factor Hac1p mRNA (homologous to X-box binding protein 1: XBP1 in mammalian cells) (Cox and Walter, 1996) to remove introns. The resulting processed mRNA translates into an active transcription factor that up-regulates genes encoding ER quality control components

(Yamamoto et al., 2007). Moreover, the nuclease activity of IRE1 relieves the cell from the load of unfolded proteins (Hollien et al., 2009).

4 Mechanisms of ER stress

ER stress is induced in several pathophysiological processes (Nakka et al., 2016; Sozen et al., 2015). Knowledge about the mechanisms activated in disease conditions is important in designing therapeutic strategies for them. To keep this manuscript succinct, we now provide two main mechanisms of ER stress.

4.1 Oxidative stress

Reactive oxygen species (ROS) are highly reactive molecules produced in low quantities during physiological conditions and quenched by intrinsic antioxidant enzymes (Moro et al., 2005). However, during various disease conditions, increased production of ROS overpowers endogenous antioxidant systems leading to oxidative stress-induced cell death (Chong et al., 2005). NADPH oxidases and mitochondrial electron transport chain are important mechanisms responsible for superoxide production (Bedard and Krause, 2007; Murphy et al., 1999). Inhibition of NADPH oxidase decreases the levels of ER stress markers like GRP78, eIF2-α1, CHOP, and caspase 12 (Al-Saleh et al., 2020). Chemical chaperones that alleviate ER stress or inhibition of oxidative stress exert a protective effect on neurons undergoing cell death (Wei et al., 2008). The signaling mechanisms of ER stress and oxidative stress have been reported to be coordinated via PERK signaling by activating nuclear factor erythroid-2-related factor and ATF4 transcription factors (Cullinan and Diehl, 2006). Superoxide free radicals participate in ER stress-induced ischemic brain injury following focal cerebral ischemia in mice (Hayashi et al., 2005). Subjects with T2D show a positive correlation between ER stress and oxidative stress (Victor et al., 2021). Therefore, the literature implicates that oxidative stress plays a role in ER stress activation and limiting oxidative stress may help lower ER stress.

4.2 Mitochondrial dysfunction

Mitochondria are vital organelles responsible for maintaining respiration and energy production (Siekevitz, 1957). Both apoptosis and necrosis-based cell death essentially depend upon the participation of mitochondria (Kroemer et al., 1998), and mitochondrial dysfunction is a key mechanism that mediates ischemic brain injury as reviewed previously (Niizuma et al., 2010). Crosstalk among UPR, autophagy, and mitochondria underlies the development of ER stress as discussed previously (Senft and Ronai, 2015). Mitochondria and ER influence each other’s functions and thus mediate apoptotic cell death (Sanges and Marigo, 2006). As discussed previously, changes in the crosstalk between the mitochondria and ER participate in the development of T2D (Rieusset, 2011). Both mitochondrial dysfunction as well as ER stress are known to participate in the pathological progression of the T2D. However, the potential role of mitochondrial dysfunction-induced activation of ER stress in diabetic increase in ischemic brain injury is not well understood and merits future investigation.

5. ER stress and cell death pathways

Normal functioning of the ER is important for the cell and its survival. Sustained stimulation of the IRE1 pathway of UPR and/or increased transcription of CHOP can initiate apoptotic cell death (Szegezdi et al., 2006). ER stress-induced apoptotic cell death aims to eliminate cells in which UPR is unable to maintain normal ER physiology, and these cells may otherwise undergo necrosis and inflammation (Szegezdi et al., 2006). However, more severe and chronic ER stress can cause widespread cell death, as seen in several chronic disease conditions (Kaufman, 2002).

Studies have established the role of CHOP in ER stress-induced cell death in diseases like diabetes (Oyadomari et al., 2002), Parkinson's disease (Silva et al., 2005), and atherosclerosis (Thorp et al., 2009). One of the mechanisms proposed to mediate the detrimental effect of CHOP include down-regulation of the anti-apoptotic protein Bcl-2 (McCullough et al., 2001). Moreover, an increase in the levels of Bim and Bax, ER oxidase 1α (ERO1α)-induced hyperoxidizing environment, and the ERO1α–inositol 1, 4, 5-trisphosphate receptor–Ca^{2+}– $Ca(^{2+})$/calmodulin-dependent protein kinase II pathway are some of the other mechanisms proposed to mediate CHOP-induced cell death (Gotoh et al., 2004; Marciniak et al., 2004; Palomeque et al., 2009; Puthalakath et al., 2007). Death receptor-5 and Tribbles-related protein 3 are other mediators proposed to cause CHOP-induced cell death (Ohoka et al., 2005; Yamaguchi and Wang, 2004).

During ER stress, IRE1 causes adaptive degradation of membrane-associated mRNAs via regulated IRE1-dependent decay (RIDD) (Hollien et al., 2009). RIDD is known to contribute to cell death (Tam et al., 2014). Besides, prolonged ER stress activates a pro-apoptotic IRE1–TRAF2–JNK pathway (Tabas and Ron, 2011). Cells that lack IRE1 and its major downstream effectors display a better survival rate than their controls (Hetz et al., 2006). Therefore, ER stress pathways, if activated in a sustained manner and to a severe extent, do possess the potential to induce cell death and play a significant role in pathogenesis of diseases.

6. ER stress and diabetes

ER stress exerts an important role in onset of diabetes by causing pancreatic β-cell death and insulin resistance.

6.1 β-cell death

β-cells are specialized cells that produce insulin and their death or impaired functioning causes T1D and some aspects of later stages of type 2 diabetes (T2D) mellitus (Eizirik et al., 2008). Translation of proinsulin takes place on ribosomes and then transits into the ER for proper folding. As the synthesis of proinsulin varies largely according to physiological requirements, β-cells use the UPR pathways to balance the variable production of proinsulin and its folding in the ER (Dodson and Steiner, 1998). In particular, the initial activation of PERK and IRE1 pathways of the UPR supports the physiological functions of pancreatic β-cells such as the biosynthesis of proinsulin and total proteins (Elouil et al., 2007). However, chronic activation of UPR impairs the functioning of β-cells and contributes to their death

leading to diabetes (Engin, 2016; Laybutt et al., 2007). Moreover, deficiency of the PERK pathway of ER stress causes β-cell death (Harding et al., 2001). Studies on human subjects demonstrated increased CHOP expression and increased ER size in the pancreatic β-cells of subjects suffering from diabetes (Marchetti et al., 2007). However, the mechanism of ER stress-mediated β-cell death is not well understood.

6.2 Insulin resistance

Insulin resistance is a situation when insulin is not able to mediate utilization of blood glucose in the body cells (https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/prediabetes-insulin-resistance (accessed April 15 2021)). Some of the subjects suffering from obesity have insulin resistance which makes the affected individuals vulnerable to T2D (Permutt et al., 2005). Studies have shown the role of ER stress in the pathogenesis of insulin resistance (Nakatani et al., 2005). The treatment of diabetic animals with chemical chaperones decreases ER stress, normalizes hyperglycemia and insulin sensitivity, and increases insulin activity in the liver, adipose tissues, and muscles (Ozcan et al., 2006). An *in vitro* study demonstrated that thapsigargin-induced ER stress in human hippocampal neurons leads to impaired insulin signaling (Sims-Robinson et al., 2016). The literature thus suggests a potential role for ER stress in insulin resistance.

6.3 Advanced glycation end products (AGEs)

AGEs are proteins, lipids and nucleic acids, which are progressively glycated because of chronic hyperglycemia in diabetes (Cho et al., 2007). They are a heterogeneous group of highly reactive molecules produced by a non-enzymatic reaction between reducing sugars and proteins, lipids, or nucleic acids (Cho et al., 2007). AGEs cause changes in the functions of extracellular proteins. Moreover, AGEs modulate certain signal transduction cascades by binding to their receptors (called receptor for AGEs) leading to free radical formation, cytokine secretion, and modulation of hormonal activity (Brownlee, 1995). A cell culture based *in vitro* study has shown that treatment with AGEs elicit ER stress (Adamopoulos et al., 2014). Moreover, chronic administration of AGEs causes ER stress activation in the brain, kidney, liver, and pancreas (Adamopoulos et al., 2016). An earlier study demonstrated that a precursor of AGEs causes ER stress-mediated activation of the caspase-3 cell death pathway potentially via NADPH oxidase 4 upregulation (Loughlin and Artlett, 2010). Additionally, ER stress inhibition decreases AGE-induced apoptotic cell death (Chen et al., 2008). These studies suggest the role of AGEs in the induction of ER stress in diabetes.

7. ER stress, diabetes, and the brain

Chronic hyperglycemia during diabetes affects the central nervous system leading to cognitive dysfunction, enhanced risk of dementia and cognitive impairment, and cerebrovascular diseases (Selvarajah and Tesfaye, 2006). ER stress mediates hippocampal neuronal apoptosis in diabetes and thus may be involved in cognitive impairment in diabetes (Zhang et al., 2013). Pharmacological modification of ER stress in animal models of T1D and T2D leads to alleviation of cognitive deficit (Ye et al., 2018; Zou et al., 2017). Metformin, an antidiabetic drug, inhibits ER stress in rat astrocytes (Wang et al., 2021). Moreover, hyperglycemia-induced ER stress activation and neuronal cell death

occurs via the activation of transient receptor potential melastatin 7 channels (Huang et al., 2018). Hyperglycemia exacerbates oxygen-glucose deprivation-induced neuronal injury by activating the ER stress pathway (Lin et al., 2019). Therefore, the literature shows that chronic diabetes produces detrimental effects on the brain, possibly via activation of the ER stress pathway.

Studies have also evaluated ER stress in different brain cell types. Endothelial cells play an important role in various long-term complications of diabetes. Endothelial cells are continuously exposed to fluctuations in blood glucose levels during diabetes. Earlier studies have identified activation of all three pathways of ER stress in endothelial cells under hyperglycemic/diabetic conditions (Maamoun et al., 2019; Yao et al., 2021). Besides hyperglycemia, exposure to hypoglycemia also activates ER stress in endothelial cells (Soejima et al., 2018). Exposure to hyperglycemia is shown to activate ER stress in primary hippocampal neurons, NS20Y cells (cholinergic neuronal cell line obtained from mouse neuroblastoma), and dorsal root ganglion neurons (Huang et al., 2018; Liu et al., 2021; Sharma et al., 2016; Zhang et al., 2013). Moreover, glucose deprivation also activates ER stress in neurons (de la Cadena et al., 2014; Gomora-Garcia et al., 2021). Streptozotocin-induced diabetes is shown to activate ER stress in Müller cells: a type of retinal glial cells (Zhong et al., 2012). Exposure of rat primary astrocytes to high glucose results in increased phospho-PERK levels without any change in levels of total PERK (Wang et al., 2021). Moreover, primary human astrocytes exposed to an acute episode of hypoglycemia had increased levels of ER stress-related genes. However, ER stress was diminished in these astrocytes when they were exposed to recurrent low glucose conditions (Weightman Potter et al., 2021). On the other hand, recurrent low glucose exposure of mouse Schwann cells resulted in increased CHOP levels (Kato et al., 2019). The same study also reported that exposure to constant low, constant high, as well as intermittent high glucose increased CHOP levels in mouse Schwann cells. However, the role of various degrees of ER stress observed in different brain cell types, under hyperglycemic or hypoglycemic conditions, in brain-related long-term complications observed in diabetic patients requires further in-depth studies. Overall, the literature shows that chronic diabetes produces detrimental effects on the brain, possibly via activation of the ER stress pathway.

8. ER stress modulation and brain injury

To understand the role of ER stress in mediating pathological changes in the brain in many neurological conditions, studies have evaluated the effect of ER stress inhibition on such conditions. Inhibiting ER stress using salubrinal protects neurons from excitotoxic injury (Sokka et al., 2007). ER stress inhibition using either salubrinal or guanabenz exerts an ameliorative effect on trauma-induced brain injury (Hood et al., 2018; Tan et al., 2018). Similarly, treatment with a chemical chaperone that reduces unfolded protein loss also produces a beneficial effect on the brain during Alzheimer's disease by preventing aging-associated deficits in memory (Ricobaraza et al., 2011; Ricobaraza et al., 2012). Lowering unfolded protein response in Parkinson's disease using various pharmacological strategies may be prosurvival for dopaminergic neurons as reviewed previously (Kovaleva and Saarma, 2021). Moreover, ER stress inhibition improves learning and memory and synaptic plasticity damage in aged rats (Carvajal-Flores et al., 2020). Treatment with 4-phenylbutyric acid

(4-PBA), an ER stress inhibitor, lowers the detrimental effect of diabetes on spinal cord injury in rats (He et al., 2017). Therefore, there is a sizable amount of published data showing the significance of ER stress activation on brain injury.

9. ER stress and ischemic brain injury

Cerebral ischemia is one of the pathological events that activates ER stress. A severe episode of cerebral ischemia causes a sudden increase in misfolded proteins. Brain cells tend to correct the overload of misfolded proteins by decreasing protein synthesis, enhancing the expression of chaperones that facilitate proper folding of misfolded proteins, and activating protein degradation mechanisms for eliminating damaged organelles (Kristian and Hu, 2018). Recovery of protein synthesis in vulnerable neurons is not complete even after a brief period of ischemia (Thilmann et al., 1986), showing that their failure to revive protein synthesis is associated with cell death. Inhibition of protein translation initiated by the activation of eIF2α kinase causes cell death (Srivastava et al., 1998). A 10 min period of global cerebral ischemia activates the PERK pathway of ER stress along with an increase in eIF2α phosphorylation, leading to the inhibition of protein translation in the cerebral cortex, brain stem, and hippocampus when quantified after 4 h of reperfusion in rats (Kumar et al., 2003). Other studies confirmed that global cerebral ischemia and reperfusion inhibit protein synthesis (Krause and Tiffany, 1993) via a PERK-dependent acute increase in the levels eIF2α phosphorylation (Kumar et al., 2001). A study by Hayashi et al. (Hayashi et al., 2003) showed that the cerebral ischemia-induced increased phosphorylation of eIF2α and PERK is lower in transgenic rats overexpressing copper/zinc superoxide dismutase when compared to their wild-type counterparts. This study implicates the role of oxidative stress in ischemic activation of PERK and further proposes that ischemia reduces PERK-GRP78 binding resulting in PERK activation.

Aspirin is shown to limit cerebral infarction along with downregulation of toll-like receptor 4/nuclear factor kappa light chain enhancer of activated B cells-mediated ER stress measured in terms of PERK, eIF2α, and CHOP levels (Wang et al., 2018). Moreover, diazoxide exerts a marked neuroprotective effect on ER-stress-induced apoptotic cell death in an in vitro and in vivo model of cerebral ischemia (Lei et al., 2018). Another study showed that dexmedetomidine decreases ischemia-reperfusion injury in the brain by inhibiting ER stress-dependent apoptosis via modulation of the PERK pathway (Liu et al., 2018). Melatonin treatment exerts a protective effect on ischemic brain injury. The protective effect of melatonin occurs via decrease in autophagy. Activation of PERK- and IRE1-dependent pathways of UPR mediate the effect of melatonin on ischemic brain injury (Feng et al., 2017). Although a study showed that global cerebral ischemia did not activate IRE1 and ATF6 pathways, another study showed that xbp1 mRNA splicing is facilitated after transient focal as well as global cerebral ischemia, suggesting that ischemia may activate the IRE1-pathway of ER stress (Kumar et al., 2003; Paschen et al., 2003).

Treatment with salubrinal, a potent inhibitor of dephosphorylation of phosphorylated-eIF2α, has been shown to restore the ischemia-induced increase in phosphorylated eIF2α in these mice and improve functional recovery after focal (Wang et al., 2020) and global cerebral ischemia (Font-Belmonte et al., 2019). Concomitant treatment with robenacoxib and

salubrinal post-ischemia reduces ischemic neuronal damage (Anuncibay-Soto et al., 2018). A recent study showed that neuron-specific inducible PERK knockout mice display larger infarcts and worse neurological outcomes when compared to control mice, showing that PERK activation-induced eIF2α phosphorylation and resulting suppression of translation exerts a protective effect on ischemic neurons (Wang et al., 2020). Yu et al demonstrated that the activation of the ATF6 pathway of ER stress in an inducible sATF6 knock-in mice reduced infarct size and improved functional outcome 24 h after stroke (Yu et al., 2017b). While the deletion of XBP1 exerted a detrimental effect on outcomes following experimental stroke, pharmacological activation of O-GlcNAcylation exerted a beneficial effect on stroke outcomes (Jiang et al., 2017).

The literature cited presents conflicting views that both strategies that lower activation of ER stress pathways as well as preservation of ER stress pathways results in protection against ischemic brain injury. It is plausible that suppressing activation of ER stress during the early period after ischemia, when cellular energy levels are not yet normalized, may have beneficial effects. On the contrary, during the late/recovery stage, when protein synthesis is required for recovery, preservation of ER stress pathways can have protective effects against cerebral ischemic damage.

10. ER stress and ischemic brain injury in diabetes

Diabetes is another pathological event that activates ER stress (Fig. 1). ER stress plays an important role in ischemia/reperfusion injury in various organ systems including brain in diabetes. For example, ischemia-reperfusion injury in the liver causes excessive inflammation and exacerbated ischemic injury in diabetic and hyperglycemic animals, possibly via increased CHOP levels (Rao et al., 2017). However, treatment with diallyl trisulfide, an inhibitor of ER stress, exerts an ameliorative effect on ischemic myocardium in T1D rats possibly via inhibition of PERK pathway of ER stress (Yu et al., 2017a). Further, tauroursodeoxycholic acid-induced in vivo inhibition of ER stress exerts a significant protective effect against ischemic damage in the myocardium of db−/db− mice with T2D (Mali et al., 2018). Moreover, chronic treatment with tauroursodeoxycholic acid for 4 weeks attenuated ER stress, inflammation, and neovascularization and resulted in recovered blood flow following hind-limb ischemia in db/db mouse model of T2D (Amin et al., 2012). Preconditioning with tunicamycin, a selective ER stress inducer, exerts an ameliorative effect on ischemic injury in the myocardium in streptozotocin-diabetic rats (Yan et al., 2019). ER stress decreases erythropoietin-induced cardioprotective effect on ischemic myocardium in a rat model of T2D (Miki et al., 2009).

The role of ER stress has also been explored in models of cerebral ischemia. An earlier study using streptozotocin-induced diabetes showed that infarct volume as well as the levels of GRP78 and CHOP were significantly higher in diabetic animals subjected to focal cerebral ischemia (Srinivasan and Sharma, 2011a). Using transient focal cerebral ischemia in diabetic rats as a model system the group further showed the beneficial effect of sodium 4-phenylbutyrate, a chemical chaperone, in terms of a decrease in cerebral infarct size and improvement in functional outcomes (Srinivasan and Sharma, 2011b). Therefore, some studies have implicated the role of ER stress in diabetic exacerbation of ischemic brain

injury (Srinivasan and Sharma, 2011a, b, 2012; Su et al., 2017). A recent study showed that glucagon-like peptide-1 / glucose-dependent insulinotropic polypeptide dual agonist DA3-CH reduces ER stress as well as reduces both the infarct size and the neurological deficit score in streptozotocin-diabetic rats exposed to cerebral ischemia-reperfusion injury (Bai et al., 2021). A neuroprotective agent monosialotetrahexosy-1 ganglioside (GM1) is observed to reduce cerebral infarct size, and neuronal apoptosis and improve the neurological behavior in streptozotocin-diabetic rats (Su et al., 2017). The beneficial effect of GM1 on ischemic brain is accompanied by an increase in the level of GRP78 and a decrease in the level of CHOP. Nonetheless, there are a limited number of studies that show the role of ER stress pathways in cerebral ischemia-induced injury in animal models of diabetes. Therefore, the literature indicates that increased ER stress seen during diabetes may cause an exacerbated activation of ER stress following cerebral ischemia in diabetes, and a corresponding increase in ischemic damage (Fig. 2).

11. ER stress and hypoglycemia in diabetes

Chronic drug therapy of diabetes is known to elicit episodes of iatrogenic hypoglycemia (Dagogo-Jack, 2004). Repeated episodes of such transient hypoglycemia inhibit the mechanisms of glucose counter-regulation (Dagogo-Jack et al., 1993), increase hypoglycemia unawareness (Cryer, 2004), and thus enhance the risk of hypoglycemia (Cryer, 2013). Continuous glucose monitoring studies have shown that patients suffering from T1D experience hypoglycemia for 30 to 90 mins every day (Battelino et al., 2011; Heinemann et al., 2018; Oliver et al., 2020). Patients with T2D experience approximately 2 episodes of hypoglycemia every 5 days (McNally et al., 2007).

PERK pathway of ER stress is an adaptive mechanism of the cell (Harding et al., 2000b; Harding et al., 1999), but a prolonged severe activation of this pathway activates cell death mechanisms (Rutkowski et al., 2006; Wang and Kaufman, 2016). ER stress mediates cell death in glucose-deprived neurons via PERK activation (de la Cadena et al., 2014) and acute hypoglycemia increases CHOP levels (Gonzales et al., 2008). The upstream mechanism by which hypoglycemia causes ER stress is however not well understood. As discussed above, cerebral ischemia stimulates PERK activation and increases ATF4 and CHOP levels (Hadley et al., 2018; Paschen et al., 1998), and CHOP mediates ischemic neuronal death in the brain (Tajiri et al., 2004). We have reported that prior RH exposure in treated diabetic rats causes increased cerebral ischemic damage in comparison to the normoglycemic treated diabetic control rats (Dave et al., 2011; Rehni et al., 2019b; Shukla et al., 2019). Our previous data showed that the exposure to RH alone or cerebral ischemia in animals exposed to prior RH causes an increase in free radical production (Dave et al., 2011; Rehni et al., 2019a). Oxidative stress activates ER calcium release channels like ryanodine receptors (Bull et al., 2003) and IP3 receptors (Bansaghi et al., 2014). ER calcium depletion/increased calcium release causes ER stress (Doutheil et al., 1997; Farrukh et al., 2014; Luciani et al., 2009; Paschen and Doutheil, 1999). Cerebral ischemia-induced oxidative stress activates the PERK pathway (Hayashi et al., 2005; Hayashi et al., 2003). Dantrolene, a ryanodine receptor inhibitor (Zhao et al., 2001), inhibits ischemic activation of the PERK pathway of ER stress (Li et al., 2005). Therefore, it may be hypothesized that RH-induced activation of the PERK pathway of ER stress is dependent on free radical production and renders the brain of

RH-exposed insulin-treated diabetic rats susceptible to increased ischemic injury. However, future studies are warranted to test such a hypothesis.

A recent study showed that acute glucose deprivation activates PERK and IRE1α pathways of ER stress (Gomora-Garcia et al., 2021), a pathway also known to mediate ischemic brain injury (Sanderson et al., 2015). Although direct studies conclusively showing the role of ER stress in diabetic exaggeration of ischemic brain injury are still required, the above literature shows that hypoglycemia-induced ER stress activation may play an important role in diabetic increase in ischemic brain injury.

12. Summary and Future Directions

Studies have shown that the PERK, ATF6, and IRE1 pathways of ER stress play an adaptive role in cerebral ischemia injury. The literature shows that ER stress plays a central role in diabetes by mediating pancreatic β-cell death and insulin resistance (Eizirik et al., 2008). The literature reviewed above demonstrates that diabetes activates ER stress pathways as well as increases ischemic brain injury. Because several metabolic changes are associated with diabetes, the effect of ER stress on ischemic brain injury in diabetic subjects is expected to produce a differential effect in comparison to normal subjects. However, experimental evaluation is required to characterize the effect of diabetes on ischemic activation of the signal transduction cascades of ER stress. Additionally, studies aimed to better understand the upstream pathways that cause the ischemic activation of ER stress pathways in diabetes (both hyperglycemia and hypoglycemia) are also needed. Moreover, studies are also required to identify the downstream mechanisms that potentially cause ER stress-induced changes in ischemic brain injury in diabetes. Given the multifarious pathogenesis of cerebral ischemia and diabetes, it is important to conduct studies using an experimental design that allows evaluating the impact of both cerebral ischemia and diabetes separately as well as together. Such detailed studies may also help confirm, if any, the therapeutic relevance of the role of ER stress in diabetes-induced increase in ischemic brain injury.

13. Conclusion

In conclusion, only a few studies have demonstrated the role of activation of the ER stress pathway in ischemia-reperfusion injury in the brain of diabetic animals. We expect that diabetes-induced ER stress activation plays a major role in mediating diabetes-induced exacerbation of ischemic brain injury, possibly via modulating multiple cell death mechanisms associated with the pathway. A complete understanding of these pathways in diabetes-induced exacerbation of ischemic brain injury may help develop new therapies to treat ischemic brain damage in patients with diabetes.

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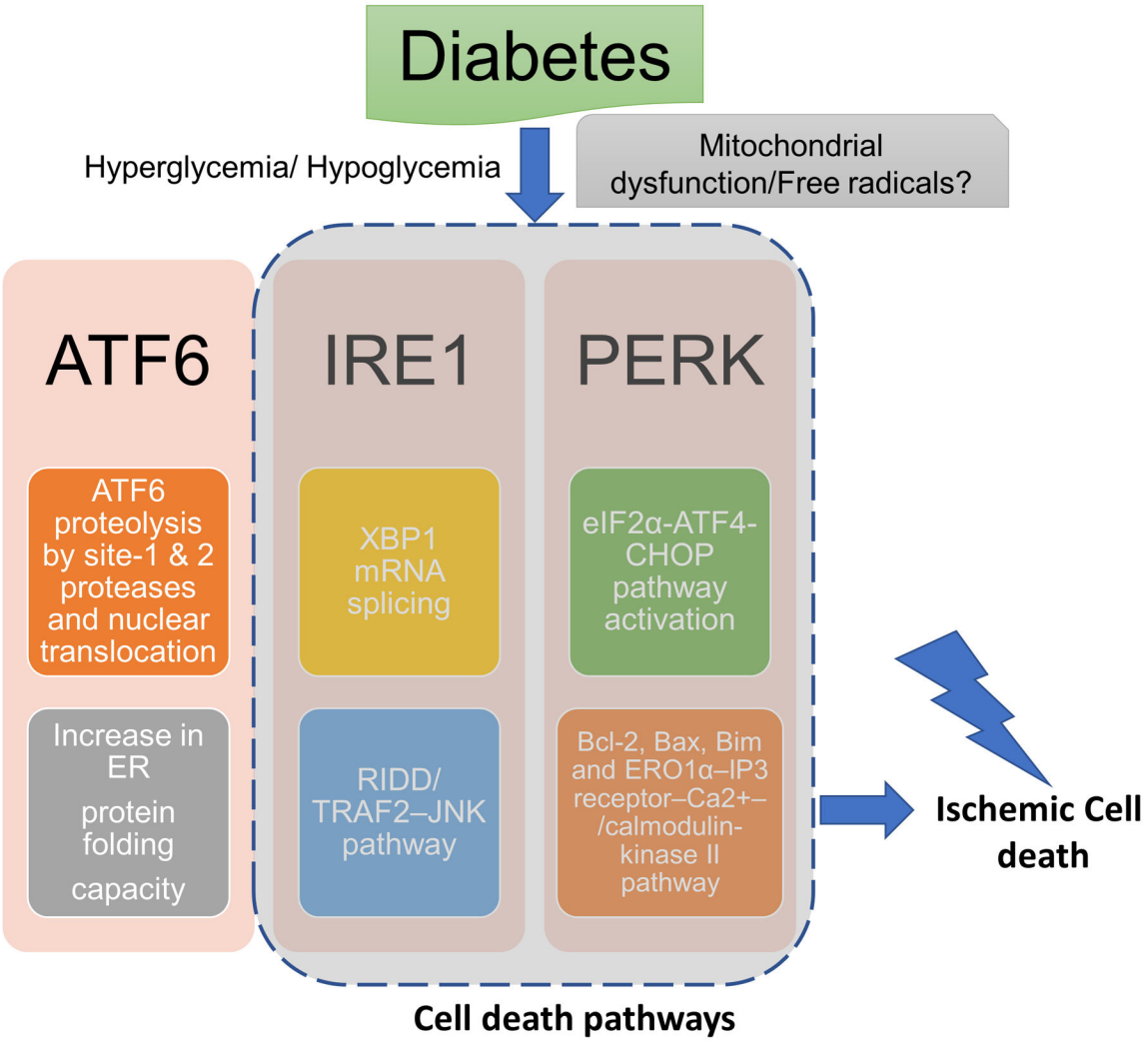

Figure 1: Schematic representation of the possible ER stress mechanisms that mediate diabetes-induced increase in ischemic cell death:

Diabetic hypoglycemia/ hyperglycemia may activate endoplasmic reticulum (ER) stress via mitochondrial dysfunction-induced free radical generation. The major possible pathways of ER stress that may mediate pronounced ischemic brain injury in diabetes: (1) activating transcription factor-6 (ATF6) translocates from the ER compartment of the cell to the Golgi apparatus where it is activated by site-1 and site-2 proteases via proteolysis. The activated ATF6 then moves to the nucleus and stimulates the production of UPR proteins via ER stress response element dependent changes in gene transcription. This binds to the ER stress response element and activates the transcription of UPR target genes which corrects ER stress. (2) inositol-requiring transmembrane kinase/endoribonuclease 1 (IRE1α) splices X-box protein 1 mRNA resulting in the activation of regulated IRE1-dependent decay (RIDD) and the IRE1α cytosolic domain activates tumor necrosis factor receptor-associated factor (TRAF)-TRAF2–JUN N-terminal kinase (JNK) signaling. (2) PERK causes phosphorylation of eukaryotic translation initiation factor 2 subunit-α (eIF2α) resulting in inhibition of protein synthesis by reducing mRNA translation initiation. Nevertheless, PERK-eIF2α

pathway causes increase in the levels of ATF4 and C/EBP homologous protein (CHOP) and associated cell death pathways.

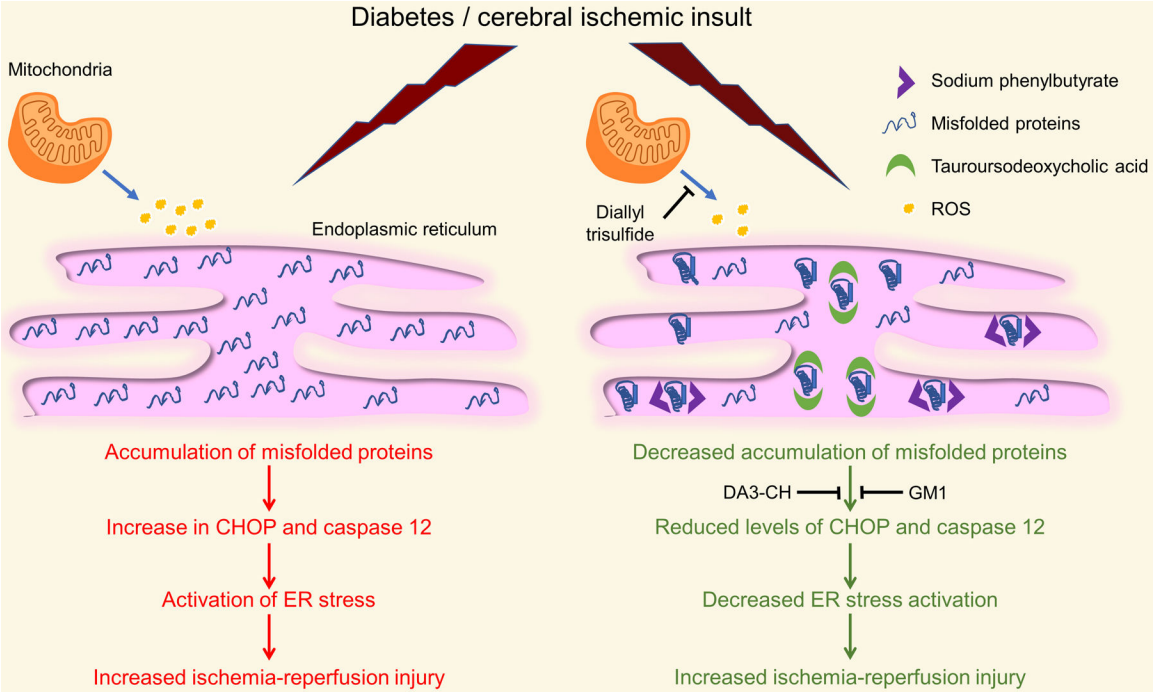

Figure 2: Representation of the tested ER stress interventions that exerts a protective effect on ischemic damage during diabetes:

Treatment with chemical chaperones like sodium phenylbutyrate and tauroursodeoxycholic acid and modulators of ER stress like DA3-CH (glucagon-like peptide-1/ glucose-dependent insulinotropic polypeptide dual agonist), diallyl trisulfide, and monosialotetrahexosy-1 ganglioside (GM1) decreases diabetic exacerbation of ischemic injury. CHOP: C/EBP homologous protein; ROS: Reactive oxygen species.