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Review

Endoplasmic Reticulum Stress: Implications for Psychiatric Disorders

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ABSTRACT

Endoplasmic reticulum (ER) is an organelle in eukaryotic cells that has specific functions and tasks. Any disruption or abnormality in these functions and tasks can lead to misfolding or inability to fold proteins, causing stress in the cell. The response of ER to overcome this stress is called the unfolded protein response (UPR). The components of the UPR, such as activating transcription factor 6, protein kinase-like ER kinase, and inositol-requiring enzyme 1 alpha, work together to mitigate or remove the stress within the ER. It has a significant role in psychiatric disorders such as bipolar disorder, schizophrenia, major depressive disorder, autism, anxiety, post-traumatic stress disorder, and depression. This role has been investigated from the past to the present, and significant clinical findings have been obtained. This review aims to provide information by addressing both the relationship between neurodegenerative disorders and ER and the relationship between psychiatric disorders and ER.

Keywords: Bipolar disorder, depression, endoplasmic reticulum, major depressive disorder, psychiatric disorders, unfolded protein response

Endoplasmic reticulum (ER) is a dynamic, large organelle present in all eukaryotic cells with a similar structure and a separate membrane from the intracellular fluid, extending into the intercellular space.[1]

It has been observed that there are differences and variations in their structures with secretory protein biogenesis, synthesis, and distribution of lipids such as phospholipids and steroids, drug metabolism, calcium signal, and balance in the cell. There are two types of ER ribosomes, depending on whether they are present or not. While the rough endoplasmic reticulum contains protein, the smooth endoplasmic reticulum does not.[2]

BASIC MECHANISM IN ENDOPLASMIC RETICULUM STRESS

Rough endoplasmic reticulum is affected by internal and external factors, resulting in deterioration in working functions.[3]

These are increased reactive oxygen species (ROS), problematic folded gene polymorphisms, insufficient calcium, viral infections, oxygen deficiency, obesity, and high blood sugar or energy depletion.[4]

In addition to these, mutations that occur in genes, cellular inadequacy, and failure to adapt are also increased factors for protein synthesis. As a result, cellular stress occurs in the ER. This stress is seen as a disruption in protein transportation and processing in the ER, accompanied by the accumulation of unfolded and misfolded proteins.[5]

Together with this accumulation, stress is released in the cell. The cell must reduce this stress. If it fails to do so, an unfolded protein response (UPR) occurs. With this response, the ER can be restored or the response can become dysfunctional, leading to cell death.[4] The responses of ER to protein accumulation are as follows: Firstly, the amount of protein entering the ER is reduced. Secondly, UPR plays an active role. In the third stage, when the cell cannot maintain homeostatic balance, it resorts to the response of cell death to avoid unfolded proteins.[6]

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When ER is not under stress, it contains inactive transmembrane proteins such as protein kinase-like ER kinase (PERK), inositol-requiring enzyme 1 alpha (IRE1α), and activating transcription factor 6 (ATF6), which are bound by glucose-regulated protein 78 (GRP78).[7]

The GRP78 is also known as a chaperone-binding immunoglobulin protein.[8] Unfolded protein response elements include ATF6, PERK, IRE1α, proapoptotic CCAAT/enhancer-binding protein homologous protein (CHOP/DDIT3), binding immunoglobulin protein (BiP), and X-box binding protein 1 (XBP1).[5] The IRE1α is a transmembrane protein that is activated by ATF6 and is important for a 26-base segment in the mRNA of XBP1, where a translational frameshift occurs. The XBP1 is also crucial for ER function.[9]

After separating from GRP78, PERK is activated through a type of homodimerization. Subsequently, eukaryotic translation initiation factor 2a (eIF2A), which is a substrate of PERK, is phosphorylated. One of the main multiple proapoptotic transcription factors is ATF4. The ATF4 has functions such as autophagy, protein folding, and metabolism.[4]

First, UPR genes involved in protein metabolism are made more permeable. Second, a protein induced by two types of deoxyribonucleic acid (DNA) damage, which are C/EBP homologous protein also known as CHOP/DDIT3 and growth arrest and DNA damage-inducible protein 34 (GADD34), is activated. These proteins are responsible for the expression of the genes. Additionally, GADD34 is involved in growth arrest. The genes of these factors are expressed. Phosphorylated eIF2A (p-eIF2A) slows down protein synthesis and translation at the beginning of ER stress, thus preventing the part where newly formed chains and unfolded proteins due to stress impair cellular function in the ER. Additionally, ATF4 activates the transcription of CHOP/DDIT3.[10]

The ATF6 dissociates from GRP78 when under ER stress. There are two transmembrane proteins in mammals: ATF6α and ATF6β. When ATF6α dissociates from GRP78 and is activated, it undergoes processing by site 1 (S1P) and site 2 (S2P) proteases in the Golgi apparatus. Unlike the other two proteins, ATF6α plays a role in increasing ER volume and protein processing capacity, thereby protecting the cell from stress and keeping it alive.[5]

Binding immunoglobulin protein, on the other hand, is related to transmembrane proteins.[4] The relationship is as follows: unfolded proteins stimulate BiP, which is associated with transmembrane proteins, to dissociate. The dissociated BiP then activates these proteins, and this is followed by the addition of XBP1, which begins the production of UPR target genes as shown in Figure 1.

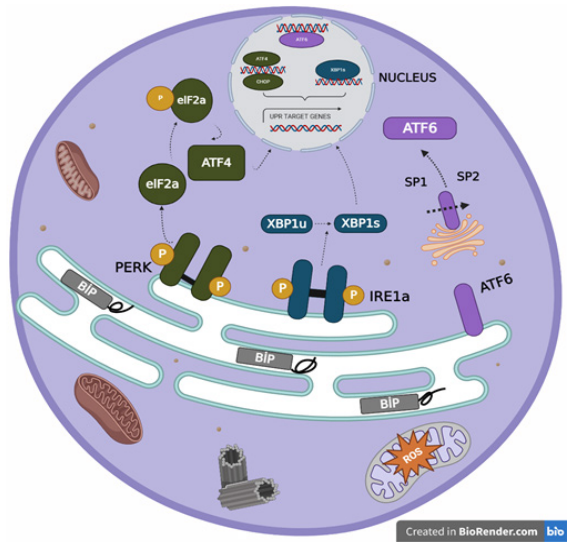

Figure 1. Endoplasmic reticulum stress mechanism. Various cellular stimuli are provided through the UPR in response to stress occurring in the ER, allowing for control of unfolded proteins.

The proteasome is a degradation mechanism for unfolded/misfolded or damaged proteins. During ER stress, molecular chaperones are involved in the disruption of proteostasis, and the ER-associated degradation (ERAD) system is responsible for regulating and eliminating misfolded proteins with the proteasomal system.[11]

ENDOPLASMIC RETICULUM STRESS IN PSYCHIATRIC DISORDERS

Our brain plays an active role in coping with and controlling the formation and progression of stress through its functional mechanisms. In significant psychiatric disorders, stress is high, but their pathophysiology is not yet fully understood, and therefore, necessary research is being conducted. Psychological stress, which affects brain functioning as well as other vital events, has been found to have significant connections with disorders such as depression and anxiety. In studies, it has been observed that rodents exposed to stress in early stages are at risk for their brain and life in terms of emotion, behavior, and consciousness. This stress can cause significant changes in our lifespan that may lead to psychiatric and neurodegenerative disorders. Early life stress caused by exposure to stress is a significant

factor in the onset of psychiatric disorders such as major depressive disorder (MDD), schizophrenia, bipolar disorder (BD), and depression.[12]

However, there are some assumptions regarding the formation of ER stress and psychiatric disorders, which are as follows:

-Increased levels of ROS and calcium intensify and persist in ER stress.

-The proapoptotic part in UPR is activated, leading to the upregulation of CHOP/DDIT3 and c-jun N-terminal kinases (JNKs).

-Malfunctioning of UPR leads to the accumulation of protein particles.

-Finally, it may cause stimulation and an increase of signals through certain pathways when inflammation occurs.[13]

Neuropsychiatric disorders such as mood (unipolar) disorders, depression, BD, and MDD, among others, can be exemplified. According to the World Health Organization, depression is seen as a leading disorder.

This can also be supported by the fact that one in every five people experiences a depressive episode at some point in their life. The role of ER stress has been found to be significant in psychiatric disorders such as BD, MDD, and schizophrenia.[8]

Studies on rodents, particularly rats and mice, have been widely conducted in psychiatric disorder research. Mildly stressed mice have increased levels of GRP78 and CHOP/DDTI3 in their short-term memory (hippocampus), while rats have higher levels of GRP78, ATF6, XBP1, and CHOP/DDIT3 expression in the striatum compared to normal rats. These differences in levels of ER transmembrane proteins and components have been observed to create a suitable environment for depression.[4]

The effects of ER stress on neurodegenerative disorders can be summarized in three ways, which are common signs of ER stress in most neurodegenerative disorders. Firstly, ER stress affects the intracellular signaling system. Secondly, it affects neuronal connections. Thirdly, it affects the ubiquitin-proteasome system (UPS) that regulates cell death. The ER stress activates the mechanism that leads the cell to death. The accumulation of misfolded proteins is associated with neuronal diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), prion diseases, and Huntington's disease (HD), as well as other disorders.[14]

Alzheimer's Disease

Alzheimer's disease is a fatal condition characterized by advanced dementia and decline. The neuropathology of AD is characterized by the accumulation of amyloid plaques and intracellular neurofibrillary tangles (I-NFTs) in the brain. In addition to these factors, stress, nutrition, sleep patterns, and age are also contributing factors in the development of the disease.[15,16]

Tau proteins, which are the main component of I-NFTs, are associated with microtubules. Although tau proteins are soluble, they are responsible for bringing together and stabilizing microtubules involved in vesicle transport.[17]

Amyloid beta (Aβ) is a part of amyloid precursor protein (APP) and accumulates in the cell by the breakdown of APP, leading to the formation of amyloid plaques and damage to structures that facilitate intercellular communication.[18]

When considering the association between ER stress and AD, it has been observed that APP is involved in the subcellular trafficking of amyloid, intracellular Aβ pathology, maturation and processing, intracellular calcium release, and activation of caspase-12 and JNKs. Amyloid precursor protein is a transmembrane protein synthesized in the ER, folded, and transported towards the Golgi apparatus, and then moved to the outer plasma membrane.[16]

It has been concluded that ER stress triggers Aβ formation, and Aβ formation triggers ER stress, resulting in a feedback loop.[19]

In general, an increase in UPR activation and p-eIF2A is observed in neurodegenerative disorders.[16]

In AD, the accumulation of tau protein leads to the phosphorylation of PERK and eIF2A, resulting in an increase in the hippocampal pyramidal cells and frontal cortex in AD brains.[20]

Hoozemans et al.[21] examined the pathophysiology of AD at different times and stages, acquiring information about UPR activation of ER. As a result, it was observed that BiP, GRP78, and phosphorylation of PERK placement and expression increased in the neurons of the hippocampus and temporal cortex regions of the brain after death, compared to the control group.

Parkinson's Disease

There are around seven million PD patients

worldwide, and only 5-10% of this number is genetically inherited. The disease was first described by James Parkinson in 1817 in his book "An Essay on the Shaking Palsy," summarizing the motor symptoms that are a significant part of PD.[22,23]

This condition is a neurodegenerative disorder that occurs with the accumulation of Lewy bodies in the substantia nigra (SN) in the basal ganglia. Abnormal accumulation of Lewy bodies leads to the loss of dopaminergic neurons, and as a result, dopamine cannot be released. Parkinson's disease progresses, and its symptoms become more pronounced when dopamine cannot be released.[24]

Although the cause-and-effect relationship between them is not yet fully understood, it has been shown that ER stress is related to PD pathology.[23]

Proteins associated with this disease, which is inherited as autosomal recessive, are α-synuclein (SNCA) some proteas, DJ-1/PARK7 redox sensor, parkin (PARK2) E3 ligase, phosphatase and tensin homolog-induced putative kinase 1 (PINK-1) protein stability, ubiquitin and ubiquitin carboxyl-terminal hydrolase-1 (UCHL-1). The main component of Lewy bodies is SNCA. Accumulation of parkin and UCHL-1 leads to unfolded protein response.[25]

In post-mortem brain tissues of SN in PD patients, p-EIF2A and phosphorylation of PERK were found to be high compared to the control group, and phosphorylation of PERK was found only in proteins containing SNCA. Moreover, an increase in ATF4 was observed in the neuromelanin-positive neurons of SN in patients. Additionally, ER stress was found to lead to a decrease in caspase-12, which protects cells from apoptosis.[14]

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis is a motor neuron disorder that results from the degeneration of upper and lower motor neurons, leading to symptoms such as muscle weakness, paralysis, fasciculations, atrophy, and spasticity.[26,27]

It is common in the adult population. Its discovery began with Aran Duchenne and was subsequently described by the French neurologist Dr. Jean-Martin Charcot, which is why the disease is also known as Charcot's disease. [28]

10% of this disease is familial, while the remaining 90% is sporadic. The most important pathophysiology is the misfolding of superoxide dismutase 1 (SOD1), which leads to the formation of cytoplasmic inclusions. Errors in the SOD1 gene account for 20% of familial cases and 2% of sporadic cases.[29]

Genetic alterations that occur in specific proteins in ALS, such as SOD1 and transactivation-responsive DNA-binding protein 43 (TDP-43), occupy the folding order.[30]

In mouse models of ALS, it has been observed that ER stress is associated with the SOD1 gene and leads to the formation of UPR, which follows a path of initiating and progressive disease. Vesicle-associated membrane protein-associated protein B is a transmembrane protein located in the ER and is involved in regulating ER stress. Endoplasmic reticulum stress cases in ALS are seen in the spinal cord tissues of sporadic patients in humans. Recent evidence has shown that TDP-43 and fused in sarcoma occur due to ER dysfunction in ALS cases.[31]

Huntington's Disease

Huntington's disease is a neurodegenerative disorder with an autosomal dominant specific phenotype, which includes balance disorders, consciousness decline, and difficulty in behavior. The symptoms are seen in middle-aged groups after birth from parents carrying the disease. The disease arises from the excessive repetition of the CAG sequence at the N-terminal end of the mutant protein called huntingtin (mHTT), resulting in the formation of a polyglutamine (polyQ) helix.[32]

Polyglutamine's abnormally elongates and folds. This pathological length, estimated to be up to 35 repetitions, is transmitted through generations. Misfolded proteins accumulate and become insoluble in the cell, forming amyloid-like structures. This situation, which is present in the brain and sperm cells, makes the disease permanent.[18]

The relationship between ER stress and HD occurs through mHTT protein. Mutated mHTT accumulates in the cytosol and causes ER stress. The presence of accumulated mHTT with apoptosis signal-regulating kinase 1 (ASK1) protein leads to an increase in GRP78 (BiP), IRE1α, PERK, CHOP, and Caspase 12, which are elements responsible for ER stress. Additionally, mHTT inhibits calcium channels, causing an imbalance in calcium levels in the ER, and abnormal chaperone activation in the lumen.[33]

Mutated mHTT protein and ASK1 together initiate ER stress and activate the UPR through the mammalian ERAD, which is non-functional due to polyQ expansion in mammals. Disruption in the pathway of ERAD outflow has caused ERAD substrate damage,

leading to the accumulation of misfolded proteins in the lumen. Ongoing research is investigating how signal pathways responsible for reducing toxicity by eliminating the accumulation of misfolded proteins can be used as a treatment for HD.[34]

Bipolar Manic-Depressive Disorder

Bipolar disorder is a psychiatric disorder with similar symptoms to depression and schizophrenia and has a high risk of suicide.[9]

It is characterized by cycling between manic and depressive states, with symptoms being more pronounced during the manic phase, making diagnosis easier. However, early diagnosis of BD may not be accurate as it may present initially as symptoms of depression.[35]

The role of ER stress in BD has been debated, but not fully understood. In studies on humans, peripheral blood samples were analyzed using real-time quantitative polymerase chain reaction (RQ-PCR) to examine the gene expression of BiP and CHOP. [4]

The association between bipolar disorder and single nucleotide polymorphisms in the promoter region of XBP1 has been identified. The gene expression of BiP is higher in bipolar disorder, but there is no significant difference in the gene expression of CHOP and XBP1 between bipolar disorder patients and healthy individuals.[4]

Depression

Depression is a common psychiatric disorder characterized by symptoms such as lack of interest in daily life, depressed mood, and lack of appetite, and it can cause anomalies in the brain, although its mechanism is not yet fully understood.[9]

It is important not to confuse a person's daily lack of motivation, distress, and stress with depression. Its diagnosis becomes more apparent when the symptoms persist for at least two weeks, with the individual's complaints disrupting their daily routine.[36]

With the increasing frequency of research on ER stress, the idea of whether it underlies many diseases is also being considered.[37]

Unfolded protein response has been analyzed in terms of gene expression in general psychological disorders. When looking at the research, it is observed that the expressions of BiP, CHOP, and XBP1 do not change within mania, depression, and hypomania.[4]

Major Depressive Disorder

Major depressive disorder is a common mood disorder that causes difficulties in learning, memory and lasts for at least two weeks.[35]

The causes of MDD include inflammation in the communication mechanisms of the brain, leading to disruptions in neuron production.[12]

It has been repeatedly shown in sources that ER stress plays an active role in the development of MDD. According to various research groups, the levels of GRP78, CHOP, and XBP1 are higher than normal.[7]

In another study on MDD, the expression of GRP78, GRP94, ATF6, and XBP1 in rats exposed to extreme shock and rats that did not learn helplessness were examined, and it was found that XBP1 was more prevalent in rats that did not learn helplessness.[9]

The circadian rhythm and sleep patterns in living organisms are concepts that play an effective role in this disorder as well as in other psychiatric disorders.[38]

Schizophrenia

In terms of its Greek origins, schizophrenia is derived from the words "schizo" and "phrenos". These patients have two different perceptions of reality and do not believe in dual personalities. It affects approximately 0.5-1% of the population when looking at the general population.[39]

Psychosis, hallucinations, delusions, or disturbances in thought processes have become the central aspect of the definition of schizophrenia.[40]

Schizophrenia is a psychiatric disorder that causes certain damage in the psychosocial field due to a decrease in reality perception.[12]

Recently, there has been a frequent focus on the improper folding of proteins and the subsequent UPR response in the ER in studies on schizophrenia. Looking at the research and its results, the levels in BiP and the three transmembrane proteins mentioned, PERK, ATF6, and IRE1α, are as follows: an increase in the expression of proteins is observed in BiP, while a decrease in PERK and a decrease in the phosphorylation of IRE1α are observed. In addition, no difference was observed in the levels of eIF2A and ATF4 compared to normal subjects.[41]

Autism Spectrum Disorder

The term autism spectrum disorder (ASD) was first defined by Leo Karner in 1943 along with a syndrome of 11 symptoms. Children with autism are often compared to those with attention

deficit hyperactivity disorder due to symptoms of hyperactivity, inattention, and impulsivity.[42]

Common symptoms of ASDs include repetitive and stereotyped behaviors, social interaction difficulties, and intellectual disability in verbal development. The likelihood of occurrence is four times higher in males than in females, and the prevalence in the community is around 10-20%, which is quite common.[43]

Although there are many results in ASDs, its pathogenic mechanisms are not clear. However, it has been seen that a genetic defect and chromosomal duplication are the cause of this disorder. Some information is available on mutations that occur in several genes encoding adhesion molecules such as neuroligin, neurexin, contactin-associated protein-like 2 gene (CNTNAP2), and cell adhesion molecule 1 (CADM1), as well as the pathogenesis caused by a few mutations. It has also been reported that ASD is caused by duplications in the 15q11-q13 arms encoding gamma-aminobutyric acid (GABA) subreceptors in the neuroligin-neurexin-shank complex and genetic defects such as ubiquitin ligase. An increase in the level of expression of the ubiquitin protein ligase HRD1 was observed in response to ER stress.[44-46]

In another study, the prefrontal cortex, hippocampus, and cerebellum regions of the brain were studied, and it was observed that there was a change in ER stress in autistic individuals. It has been observed that IRE1α is activated in the cerebellum and prefrontal cortex and ATF6 is activated in the hippocampus. No change was observed for PERK in all three regions. Thus, ER stress has been shown to play an important role in the pathogenesis of autism, mostly due to the downregulation of ER chaperones.[47]

Anxiety

Generalized anxiety disorder was first described by Freud in 1894. Symptoms such as irritability, tension, threat, sleep disturbance, dry mouth, and sweating have been observed.[48] These symptoms have been found to largely overlap with those of other disorders. It has been determined that it is twice as common in women as in men. Despite its association with many psychiatric and medical conditions, it is generally seen as chronic.[49] There is no evidence for genetic transmission of anxiety when viewed from a genetic perspective. Although the amygdala is the center of fear and learning, it also plays an important role in regulating stress. Stress occurring here has been shown to cause many disorders, including anxiety.[50]

An increase in ATF4 and CHOP protein expression levels and a decrease in GRP78 were observed in immunohistochemistry.[51]

Post-Traumatic Stress Disorder

Post-traumatic stress disorder (PTSD), is commonly seen as a psychopathological consequence of exposure to a traumatic event. Specific features of PTSD include triggering events that remind of the experience, increased duration of distressing responses, the feeling of widespread threat, insomnia, and irregular sleep, changes in consciousness and mood. When looking at the rate of PTSD, 70% of adults experience a traumatic event once in their lifetime, while the remaining 30% experience four or more traumatic events.[52] The limbic system in the brain has a part called the amygdala, which is more related to emotional memory. The amygdala consists of three subgroups: the cortical nucleus, the basolateral nucleus, and the central nucleus. It has been found that the basolateral nucleus is associated with anxiety and studies have focused more on this part. In studies of long-term stress, it has been observed that GRP78 and caspase-12 increase in the basolateral amygdala. Morphological changes were observed in the structures of the ERs in the neurons of the amygdala due to long-term stress.[53-55]

In conclusion, as with most organelles, disruptions in ER function due to external or internal stimuli can lead to cellular stress. This stress is manifested as an accumulation of proteins. The ER is responsible for the proper folding of proteins as part of its normal function, but under stress, these proteins exhibit abnormal folding. Based on research and studies, understanding the UPR response to ER stress and the pathways that contribute to many psychiatric disorders and neurodegenerative disorders will provide valuable insights for clinical studies.

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