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The role of the endoplasmic reticulum stress in depression

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Summary

Depression is an important health problem around the world. There are several effective methods for its treatment, but it is estimated that one-third of patients with depression do not respond adequately to conventional antidepressants. There is, therefore, an urgent need to identify the biological mechanism of depression and the pharmacological action of antidepressants. The participation of broadly understood inflammatory factors in the etiology of depressive disorders no longer raises doubts. In recent years, a lot of attention has also been devoted to changes in the endoplasmic reticulum, suggesting that the so-called endoplasmic reticulum stress gives rise to many diseases. The endoplasmic reticulum stress is activated in response to the increasing amount of unfolded or improperly folded proteins in the ER. Research on the so-called endoplasmic reticulum stress inspire hope not only in the context of a more thorough understanding of the pathophysiology of diseases, but it can also be an inspiration to search for new, more effective drugs. This paper presents the connections between changes of the endoplasmic reticulum and inflammatory states and oxidative-reduction balance. Both the occurrence of inflammation and so-called oxidative stress have been confirmed in depressive disorders.

Key words: depression, endoplasmic reticulum stress, inflammation, oxidative stress

Introduction

Depression is an important health problem around the world. Millions of people suffer from this illness and it will probably have been considered the second leading cause of disability by 2020 [1]. There are several effective treatments for depression, but it is estimated that one-third of patients with depression do not respond adequately to conventional antidepressants [2–4]. There is, therefore, an urgent need to identify the biological mechanism of depression and the pharmacological action of antidepressants. Several studies suggest that there are structural abnormalities in the brain of

people with depression. One of the well-documented phenomena is the shrinkage and atrophy of the hippocampus. This phenomenon has been noticed by many researchers [5, 6]. Among the dominant theories of this phenomenon, a hyperactive hypothalamic-pituitary-adrenal axis [7] is mentioned and, among others, dysregulation of growth factor and disorders in the endoplasmic reticulum (ER) [8–10]. More and more research on humans and animal models suggests that stress of the endoplasmic reticulum may play an important role in psychiatric disorders [11, 12].

Stress of the endoplasmic reticulum

The endoplasmic reticulum is an intracellular organelle responsible, inter alia, for rolling and folding proteins, calcium storage and biosynthesis of lipids and sterols [13, 14]. The stress of the endoplasmic reticulum is activated in response to the increasing amount of unfolded or improperly folded proteins in the ER. These disorders lead to the activation of three major receptors: PERK (Protein kinase RNA-like Endoplasmic Reticulum Kinase), IRE1 (Inositol-Requiring-Enzyme 1) and ATF6 (Activating Transcription Factor 6). These receptors are responsible for activating the mechanism of adaptive response to stress of the endoplasmic reticulum (unfolded protein response – UPR). The result of it is the restoration of balance to cells (cellular homeostasis). On the other hand, excessive, long-lasting ER stress can contribute to cell death through apoptosis.

In homeostatic conditions, these three proteins are associated with a chaperone protein – BiP (binding protein), located in the ER. BiP prevents the activation of the above-mentioned enzymes, the major signal transducers of the UPR pathway by preventing their homodimerization [15, 16]. Under stress conditions, BiP as a chaperone binds to misfolded proteins, releasing IRE1, PERK and ATF6. The initiation of the signaling pathway for UPR, which is dependent on the autophosphorylation of the IRE1 enzyme, triggers its activity as RNases, enabling the excision of a 26-nucleotide intron from mRNA for XBP1 protein (X-box DNA binding protein). mRNA for XBP1 encodes a transcription factor, and its cleavage by IRE1 enables the formation of mature mRNA followed by XBP1 translation [17]. The XBP1 protein binds to the ERSE regions (ER stress elements) within the DNA [CCAAT(N9)CCACG] present in the promoters of many UPR pathway genes, activating, among others, gene transcription for the family of heat shock proteins and other reticular chaperones as well as XBP1 itself [15, 17].

In turn, PERK protein kinase dimerizes after being released from the connection with BiP and similarly to IRE1 undergoes trans-autophosphorylation. Active PERK phosphorylates the subunit a of the second factor initiating translation – eIF2a (eukaryotic translation initiation factor 2) [16]. The phosphorylated form of eIF2a poorly recognizes the translation initiation codon of AUG, which causes the inhibition of protein synthesis dependent on the presence of the cap, i.e., 7-methylguanosine [15]. Such translation control helps to reduce the number of misfolded proteins in a cell of the endoplasmic reticulum exposed to stress and enables its survival.

Paradoxically, the translation of some mRNA molecules that have reduced requirements for the availability of the active form of the translational initiator is enhanced.

Molecules having special regulatory sequences, so-called IRES (internal ribosome entry site), may bypass the PERK-dependent block of translation. An example of such a molecule is the transcription factor ATF4 (activating transcription factor 4) [15, 16]. ATF4 has been shown to influence cell survival by inducing genes related to amino acid metabolism or the alteration of the oxidoreductive potential [18]. On the other hand, ATF4 is considered to be the strongest signal for the transcription of pro-apoptotic factor CHOP (CEBP homologous protein) [19].

The ATF6 transcription factor is another receptor activated by misfolded proteins. After detaching from the BiP protein, it passes into the Golgi apparatus where it is activated by protease cleavage S1P (site 1 protease; first protease to cleave the SREBP transcription factor) and S2P (site 2 protease; second protease to cleave SREBP) [15–17]. The resulting protein has a leucine zipper structure that, like XBP1, binds to the ERSE regions within the DNA, but only in the conjunction with the transcription factor CBF (CCAAT binding factor). ATF6 increases the transcription of XBP1, BiP, calreticulin, protein disulfide isomerase – PDI and CHOP [15–17].

The dysregulation or hyperactivation of the UPR pathway is involved in the initiation and development of various diseases such as cardiovascular disease, metabolic disease, neurodegenerative disease and cancer [20]. Some studies also point to the role of UPR in mood disorders. Hayashi et al. [21] reported a compromised ER stress response in peripheral leukocytes from patients with bipolar disorder. Grunebaum et al. [22] described the association of XBP1 with cortisol levels in patients with major depressive disorders (MDD). Recently, Nevell et al. [23] found a stable activation of ER stress response in peripheral tissues of patients with MDD, in turn, studies in rats suggest that stress related to ER is associated with the damage to the hippocampus and cognitive impairment [5].

Some pharmacological interventions used in the treatment of affective disorders interact with the UPR pathways. For example, valproate and carbamazepine are mood stabilizing drugs that increase the expression of 78-kilodalton glucose-regulated protein (GRP78), also known as the binding immunoglobulin protein (BiP) [24]. BiP/GRP78 is a member of the ER stress gene family that is believed to inhibit ER stress response and inhibit UPR-induced apoptosis [25].

According to Gałecki and Talarowska [4], anti-inflammatory preparations will be used more widely in the treatment of depressive disorders. The work of Souza et al. [26] indicates that an effective alternative to the treatment of depression could be not only non-steroidal anti-inflammatory drugs (NSAIDs), but also cytokine preparations with anti-inflammatory effects.

Endoplasmic reticulum stress – inflammation – depression

The presence of the inflammatory process as well as the activation of the immune system in depression is observed on the periphery and in the central nervous system (CNS). Data regarding the above changes come from studies on the animal model of depression, postmortem study and from patient studies [27]. Raison et al. [28] reported increased levels of proinflammatory cytokines in people with depression: interleukin

1 b (IL-1b), IL-2, IL-4, IL-6. In depressed patients, changes in tumor necrosis factor alpha (TNF-α, tumor necrosis factor alpha) and interferon gamma (INF-g) levels are also observed [29]. The significance of changes in the concentration of proinflammatory cytokines in depression is also indicated by the correlation between the use of antidepressants and the decrease in the concentration of cytokines with simultaneous improvement of the patient's clinical status [30].

Zhang and Kaufman [31] believe that the stress of the endoplasmic reticulum is closely related to the onset of inflammation. In response to ER stress, the autophosphorylation of IRE1α induces a conformational change in its cytosolic domain, which may then bind with tumor necrosis factor alpha (TNF-α) binding agent – bound to receptor 2 (TRAF2) [32]. The IRE1α-TRAF2 complex can recruit IκB kinase (IKK) that phosphorylates IκB, which leads to IκB degradation and NF-κB nuclear translocation [33]. Translocation into the NF-κB cell nucleus causes it to act as a transcription factor and regulate the transcription of multiple target genes encoding pro-inflammatory cytokines, chemokines, cell adhesion molecules and enzymes producing pro-inflammatory factors, such as nitric oxide or prostaglandins [34]. ER-stress-induced NF-κB activation and the production of inflammatory TNF-α cytokine is impaired in murine embryonic fibroblasts that do not have IRE1α. The above observation is to confirm the contribution of ER stress in the onset of inflammation [33].

The IRE1α-TRAF2 complex can also recruit JNK protein kinase, which leads to the activation of JNK. Activated JNK induces the expression of inflammatory genes by phosphorylation of the activator protein of transcription factor 1 (AP1) [35]. The formation of the IRE1α-TRAF2 complex, therefore, appears to be crucial for the activation of both JNK and NF-κB in response to ER stress. JNK kinase (c-Jun; c-Jun N-terminal kinase) is a group of MAP kinases (mitogen-activated protein kinases – MAPK), referred to as stress-activated protein kinases (SAPK). JNK kinase is activated in response to environmental stress, such as inflammatory stimuli, cytokine-induced stress, stress induced by Toll-like receptor ligands (TLR), oxidative stress, osmotic shock, ultraviolet (UV) irradiation, chemotherapy drugs [36]. JNK is a factor in the apoptosis of neurons and oligodendrocytes, which makes this kinase important in the development of various CNS diseases [37, 38].

A growing body of evidence suggests that ER stress and inflammation are also interconnected by other mechanisms, including the production of reactive oxygen species (ROS), calcium release from ER and the induction of acute phase response [39, 40]. Considering the "cytokine theory of depression" by Maes [41], the results of research carried out by Zou et al. [42] seem to be interesting. The authors compared MDD patents, who had significantly higher levels of IL-1β, IL-10 and TNF-α but significantly lower levels of IL-8, with healthy individuals. There were no significant differences in IL-6 or TGF-β1 levels. The linear correlations between IL-1β, TNF-α and IL-8 and the severity of depression as well as between IL-8 and anxiety level in patients with concomitant anxiety disorder were found. In addition, higher levels of IL-1β and TNF-α were associated with a higher results on *the Hamilton Depression Rating Scale* (HAMD), while higher IL-8 levels were associated with lower HAMD results and results on *the Hamilton Anxiety Rating Scale*.

The changes described above have their consequences. It has been proved that IL-1β can lead to over-activation of the HPA axis [43]. TNF-α may increase the levels of the adrenocorticotropic hormone and cortisol, which may also lead to the hyperactivity of the HPA axis. The hyperactivity of the HPA axis may in turn interfere with the normal function of the glucocorticoid receptor (GR). According to Zhang et al. [44] and Smith [45], the level of proinflammatory cytokine regulation is interwoven at various levels with UPR. UPR influences paths that detect pathogens and activates the cytokine regulatory transcription factors such as the nuclear factor (NF-κB), activator protein 1 (AP-1) and interferon regulatory factors (IRF). This interaction between UPR and inflammation seems to be 'bidirectional' because inflammatory cytokines induce ER stress in turn.

Stress of the endoplasmatic reticulum – oxidative-reduction balance – depression

Reactive oxygen species (ROS) are molecules derived from oxygen, possessing unpaired electrons that easily oxidize and modify the functions of RNA, DNA, proteins, and lipids [46]. Under normal conditions, ROS levels are balanced by an antioxidant defense system, but when there is an imbalance between oxidants and antioxidants, the state of oxidative stress is achieved. Cells in the brain are particularly susceptible to ROS. The fact that oxidative stress takes part in depression has been confirmed in many studies [47, 48]. The increased level of biomarkers of oxidative damage to lipids, proteins and DNA, as well as low levels of antioxidant compounds such as coenzyme Q-10, glutathione, ascorbic acid, vitamin E, and polyunsaturated fatty acids are regularly detected in the blood of depressed patients. [49]. According to Yanik et al. [50], the level of oxidative stress is correlated with the severity of depression.

The brain uses more than 20% of the oxygen consumed by the body, and although oxygen is essential, in the case of neurons, some of its products may be neurotoxic. Higher ROS levels cause mitochondrial dysfunction [51]. The lesions of the structure of mitochondria in mice with depression were observed by, among others, Gong et al. [52] and Czarny et al. [12]. Interestingly, ROS are also produced as a by-product of monoamine oxidase activity, which is necessary to inactivate monoaminergic neurotransmitters of serotonin, dopamine, noradrenaline, and adrenaline, which are involved in the pathophysiology of depression [51].

CNC protein (the family of cap'n'collar proteins), located in the cytoplasm in the form of inactive complexes with their inhibitors, is the factor regulating the oxidative-reduction balance of cells. Proteins after activation move to the cell nucleus. This is where heterodimers are formed with other proteins containing a sequence homologous to the leucine zipper sequence. The complexes formed in this way attach to the DNA molecule in the ARE (antioxidant responsive element) sequence, also called EpRE (electrophile response elements), with a characteristic sequence 5'-TGACnnnGCA-3', and initiate gene transcription [53].

One of the most researched and described components of the CNC family is the Nrf2 (nuclear erythroid 2-related factor) protein, also known as NFE2L2 factor

(nuclear factor erythroid-derived 2-like 2). It is an intracellular transcription factor responsible for the transcription of antioxidant enzyme genes, such as catalase or heme oxygenase 1 [54]. According to Kimura et al. [53], Nrf2 adheres to the DNA in the ARE regions and stimulates the transcription of genes coding for antioxidant proteins (mainly phase II enzymes) such as: glutathione S-transferase (GST), NAD(P)H oxidoreductase: ubiquinone 1 (NQO1), UDP-glucuronyltransferase (UGT), epoxide hydrolase (EPHX), γ-glutamylcysteine ligase (GCL), heme oxygenase 1 (HO-1), glutathione reductase (GR), thioredoxin reductase (TrxR), catalase (CAT), and superoxide dismutase (SOD) [54].

It is also assumed that Nrf2 activates the transcription of other antioxidant protein genes that contain the ARE sequence in their structure (e.g., thioredoxin, ferritin) [55, 56]. In addition to the transcription of antioxidant proteins, Nrf2 acts cytoprotectively, stimulating the level and activity of anti-apoptotic proteins from the Bcl-2 family [57]. In stress-free cells, Nrf2 is maintained in the inactive cytoplasmic complex by association with the Keap 1 protein. The PERK kinase receives a signal of oxidative stress from the cytoplasmic reticulum and consequently inhibits the cell cycle and Nrf2 phosphorylation results in dissociation of Nrf2 from Keap1. PERK kinase phosphorylation enhances Nrf2 transport to the cell nucleus [58]. The importance of Nrf2 for gene transcription regulation is demonstrated by the results of studies carried out on animals with muted genes or overexpression of Nrf2 proteins. Overexpression has been shown to reduce the body's resistance to oxidative stress [59]. Martín-de-Saavedra et al. [60], in turn, prove the hypothesis that Nrf2 can play a role in depressive disorders. The Nrf2 deletion in mice leads to depression-like behavior, reduces the level of dopamine and serotonin as well as increases the level of glutamate in the prefrontal cortex, changes levels of proteins associated with depression such as VEGF (vascular endothelial growth factor), synaptophysin and microglia.

Recapitulation

Despite the significant progress made over the last decades, there is still a lack of clear understanding of the etiology of depression, in particular the complex interactions between genetic, immune-inflammatory and environmental factors that dictate the relative susceptibility of individuals to this disorder. Depression hypotheses include, inter alia, the dysregulation of serotonergic, noradrenergic and dopaminergic signaling, pituitary, adrenal cortex and other endocrine glands function disorders, dysregulation of neurogenesis, immunological disorders, and recently much attention has been paid to the endoplasmic reticulum stress. Research on this issue raises hope not only in the context of a more thorough understanding of the pathophysiology of depression, but it can be an inspiration to search for new, more effective drugs. Patients and doctors are looking forward to the latter**.**

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