REVIEWS

The Role of the Integrated Stress Response (ISR) in Neuropsychiatric Disorders

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Abstract—The integrated stress response (ISR), a key mechanism of cellular response to various stress signals, is highly conserved across eukaryotes from yeast to humans. A central element of ISR is the phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α). This process is regulated by several kinases (PERK, GCN2, HRI and PKR) activated by different contextual cellular stressors. The ISR system plays a critical role in maintaining cell homeostasis and survival under stress. However, its chronic activation can lead to cell dysfunction and programmed cell death. Recent studies indicate that ISR is actively involved in the pathogenesis of neurodegenerative diseases, such as Alzheimer's and Parkinson's diseases, amyotrophic lateral sclerosis, and traumatic brain injury. At the same time, the contribution of ISR to common mental pathologies, including depression, schizophrenia, bipolar disorder, post-traumatic stress disorder and addiction, remains poorly understood. Here, we address current data on the role of IRS in the pathogenesis of these disorders, and discuss the possibilities of pharmacological modulation of ISR pathways in the pathological contexts.

Abbreviations: Aβ—beta-amyloid; ATF4—activating transcription factor 4; BDNF—brain-derived neurotrophic factor; AD—Alzheimer's disease; BD—bipolar disorder; CReP—constitutive repressor of eIF2α phosphorylation; CHOP—C/EBP homologous protein, also known as DNA damage-inducible transcript 3; DNA—deoxyribonucleic acid; eIF2—eukaryotic translation initiation factor 2; eIF2α—eukaryotic translation initiation factor 2 alpha; eIF2B—eukaryotic translation initiation factor 2B; GADD34—growth arrest and DNA damage-inducible protein, also known as protein phosphatase 1 regulatory subunit 15a; GCN2—general control nonderepressible 2 kinase; GDP—guanosine diphosphate; GTP—guanosine triphosphate; HRI—heme-regulated inhibitor kinase; ISR—integrated stress response; ISRIB—integrated stress response inhibitor; mRNA—messenger ribonucleic acid; MS—multiple sclerosis; NMDA—N-methyl-D-aspartate (glutamate receptor); PERK—PKR-like endoplasmic reticulum kinase; PKR—protein kinase R; PTSD—post-traumatic stress disorder; PP1—protein phosphatase 1; RNA—ribonucleic acid; SSRI—selective serotonin reuptake inhibitor; TrkB—tropomyosin receptor kinase B; TBI—traumatic brain injury; CPP—conditioned place preference; p-eIF2α—phosphorylated eukaryotic translation initiation factor 2 alpha; VTA—ventral tegmental area
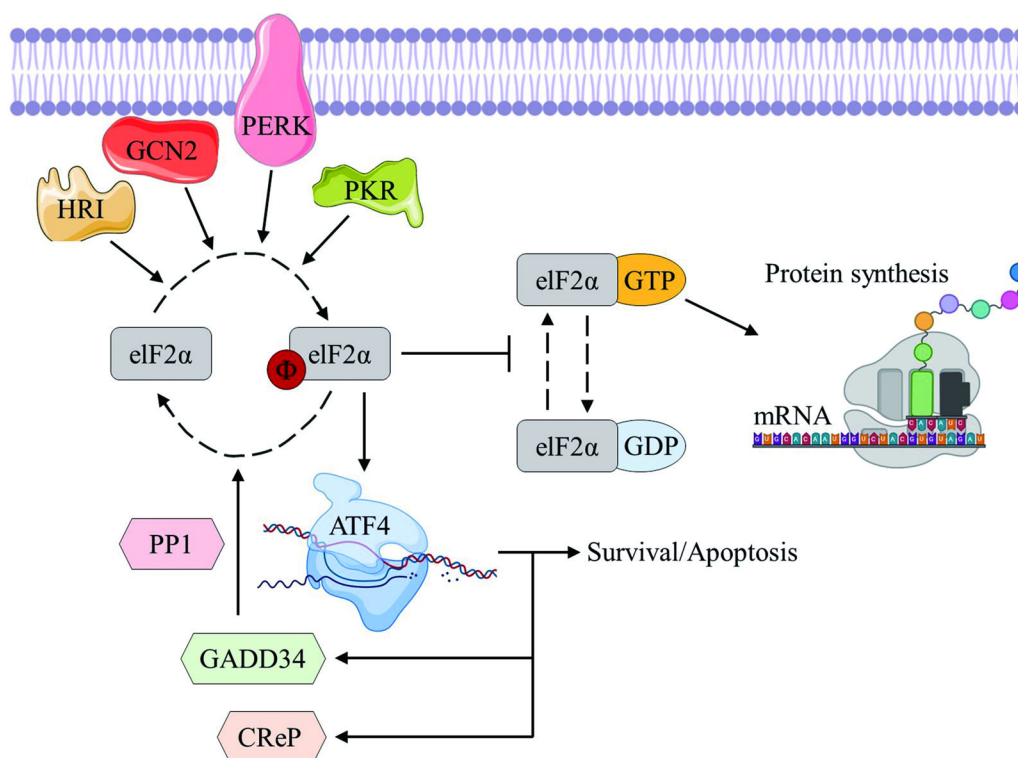
Fig. 1. The Integrated Stress Response (ISR) signaling pathway. PERK—PKR-like endoplasmic reticulum kinase; GCN2—general control nonderepressible 2 kinase; PKR—protein kinase R; HRI—heme-regulated inhibitor kinase; eIF2α—eukaryotic translation initiation factor 2α; ATF4—activating transcription factor 4; GADD34—growth arrest and DNA damage-inducible protein, also known as protein phosphatase 1 regulatory subunit 15a; PP1—protein phosphatase 1; CReP—constitutive repressor of eIF2α phosphorylation; GTP—guanosine triphosphate; GDP—guanosine diphosphate.

INTRODUCTION

The Integrated Stress Response (ISR)

The Integrated Stress Response (ISR) is a highly conserved mechanism of cellular stress response, found in all eukaryotes from yeast to humans [1]. A key event in the ISR signaling cascade is the phosphorylation of the eukaryotic translation initiation factor subunit alpha (eIF2α) (Fig. 1). Four main kinases known to catalyze this process include PKR-like endoplasmic reticulum kinase (PERK), general control nonderepressible kinase 2 (GCN2), heme-regulated inhibitor kinase (HRI), and protein kinase R (PKR) [2]. These kinases are activated in response to critical internal and external stressors, which is accompanied by the phosphorylation of appropriate sites. For example, PERK is activated in response to endoplasmic reticulum stress caused by the accumulation of misfolded proteins or impaired calcium homeostasis [3–5], HRI can be activated by iron deficiency, heat shock, or osmotic stress [6], and

GCN2 responds to amino acid deprivation, ultraviolet radiation, and several other stress signals [7, 8]. Signals for PKR activation can be viral double-stranded RNA, cytokines, heat shock proteins, and reactive oxygen species [9–11]. Thus, ISR is triggered in response to a wide range of stress exposures, the common process for which is eIF2α phosphorylation at *Ser51* by the above kinases to form the phosphorylated eIF2α (p-eIF2α).

The eIF2α is a subunit of the eukaryotic translation initiation factor 2 (eIF2) complex that also includes β- and γ-subunits. The eIF2 forms a ternary complex with GTP and initiator methionyl (mt)-tRNA, which is involved in translation initiation [12]. GTP is hydrolyzed to form GDP, after which the eIF2-GDP complex loses its connection to the 40S ribosomal subunit and diffuses into the cytoplasm. Reactivation of the complex requires yet another factor, eIF2B, which serves as a nucleotide exchanger, promoting GDP substitution for GTP to form eIF2-GTP, which is able to participate again in

translation initiation.

However, during the ISR activation, eIF2α phosphorylation at Ser51 leads to the tight and irreversible binding of eIF2 and eIF2B [13]. Under these conditions, eIF2 loses the ability to form a ternary complex with GTP and mt-tRNA, resulting in an overall inhibition of mRNA translation and protein synthesis in the cell. In parallel, translation of some mRNAs with short open reading frames in the 5'-noncoding region increases due to alternative mechanisms of translation initiation [14−16]. These mRNAs are translated into proteins that ensure the cell response to stressors.

Among these proteins, the most studied is the activating transcription factor 4 (ATF4) that regulates the expression of genes whose products are involved in the transport and biosynthesis of amino acids, carbohydrate metabolism, antioxidant defense, apoptosis, and other processes essential for the cellular response to homeostatic imbalance [17]. In addition, ATF4 is able to trigger the genetic expression of a number of proteins involved in the regulation of programmed cell death, the key one being the pro-apoptotic DNA damage inducible transcript 3, also known as the C/EBP homologous protein (CHOP) [18, 19]. In general, ISR is considered to be an adaptive reaction aimed at restoring homeostasis and ensure cell survival. However, chronic ISR activation leads to cell dysfunction and can triggerthe programmed cell death pathways [1].

Importantly, IRS activation never entails to a complete arrest of protein synthesis in the cell, due to a feedback mechanism as ATF4 induces the gene expression of the growth arrest and DNA damage-inducible protein (GADD34), also known as a protein phosphatase 1 regulatory subunit 15a, which promotes eIF2α dephosphorylation [19, 20]. Another feedback mechanism includes an ISR-induced increase in the protein level of CreP, a constitutive repressor of eIF2α phosphorylation [21]. Experimental evidence also suggests some baseline level of ISR activation, because a fraction of eIF2α molecules are always in the phosphorylated state [22−25]. Thus, stress exposures only shift the p-eIF2α/eIF2α balance toward the phosphorylated form. Moreover, ISR signaling can be involved in a number of physiological processes, independent of the presence of stressors, such as cell cycle regulation [26], glucose metabolism [27], and the maintenance of antioxidant defense [23].

eIF2α signaling plays a special role in nerve cells. For example, the shift in the p-eIF2α/eIF2α ratio serves as a mechanism for the regulation of the processes of long-term potentiation, depression, and shaping synaptic plasticity [28−30]. ISR may play a role in memory formation and the implementation of cognitive functions [29−33]. For example, a heterozygous mutation in the *eIF2α* gene at the *Ser51* phosphorylation site (rendering its phosphorylation impossible) improves long-term memory consolidation in mice [29], whereas pharmacological inhibition of eIF2α dephosphorylation in the mouse hippocampus reduces fear memories [29, 34]. Mice with a constitutive deletion in the eIF2α kinase GCN2 gene show paradoxical memory improvement during complex task execution, and impaired memory in a standard training paradigm [35]. Perhaps, stimulus-induced eIF2α phosphorylation in the dendrites and axons of neurons leads to a local suppression of protein synthesis and ATF4-mediated activity inhibition of CREB1, a transcription factor that stimulates the expression of genes involved in synaptic plasticity [36]. However, stimulus-induced reduction in ATF4 mRNA levels in the hippocampus of mice impairs synaptic plasticity and glutamatergic function, ultimately disrupting long-term memory formation [37]. Finally, the exposure of primary neuronal cultures to the brain-derived neurotrophic factor (BDNF) elevates the translation of the of protein phosphatase 1 regulatory subunit 15a (GADD34), followed by a decrease in p-eIF2α levels and an increase in *de novo* protein synthesis [38]. In addition to its involvement in animal memory formation, ISR has been linked to the regulation of eating behavior [39−41]. For example, genome editing of eIF2α at *Ser51* (making its phosphorylation impossible) in neurons expressing agouti-related peptide leads to eating disorders and increased leptin sensitivity [40].

The importance of ISR in the CNS is further supported by the fact that the brain is one of the organs most susceptible to ISR dysregulation [42]. For example, mutations in the gene encoding CReP, a constitutive eIF2α phosphatase, are associated with microcephaly and diabetes [43], mutations in the eIF2α kinase PERK gene are associated with diabetes, skeletal dysplasia, and mental retardation [44], while mutations in the genes encoding eIF2B sub-

units cause leukoencephalopathy with vanishing white matter [45]. Mounting evidence points to the involvement of ISR in CNS pathologies associated with neural tissue degeneration, such as Alzheimer's, Parkinson's and Huntington's diseases, amyotrophic lateral and multiple sclerosis, as well as traumatic brain injury [46−50]. For example, many characteristic pathological processes in these diseases, such as oxidative stress, mitochondrial dysfunction, protein misfolding, amino acid deprivation, and impaired calcium homeostasis, can trigger ISR through the activation of specific eIF2α kinases [42]. In turn, ISR hyperactivation may be one of the pathological mechanisms responsible for the dysfunction and degeneration of nerve and glial cells, and eventually for the functional impairments observed in these brain diseases. Data on ISR activation in these pathologies and its modulation in animal models are summarized in Table 1.

However, while the involvement of ISR in the above pathologies has been described in detail [42, 50, 166−168], the role of the ISR system in the most common psychiatric brain disorders, including depression, anxiety, schizophrenia, bipolar disorder (BD), posttraumatic stress disorder, and drug addiction (substance use disorder), is much less studied and hence merits further consideration. Here, a special focus will also be made on experimental data supporting the prospects for pharmacological ISR modulation in the context of these pathologies.

THE ISR CASCADE MODULATORS

The selective ISR inhibitor (ISRIB) is a relatively recently synthesized experimental small molecule (Fig. 2) that exerts an inhibitory effect on the cellular ISR pathway [169, 170] through a highly specific binding to eIF2B, thus promoting its dimerization, due to which the efficiency of eIF2B as a nucleotide exchange factor increases, while it becomes insensitive to the eIF2α phosphorylation (Fig. 2). Thus, ISRIB blocks the negative effect of eIF2α phosphorylation on translation, which prevents ISR by directly affecting the main mechanism of its activation [169].

Salubrinal (Fig. 2) is another new experimental ISR-modulating drug [171, 172] whose main mechanism of action is based on inhibiting the GADD34:PP1 complex consisting of serine/threonine protein phosphatase (PP1) and the regulatory subunit (GADD34), which acts as a PP1 regulatory subunit 15A [173−176]. This, in turn, leads to the inhibition of eIF2α dephosphorylation and, as a consequence, to indirect ISR activation. A similar mechanism of action has been observed in some other salubrinal-related drugs, specifically, Sal003 and Sephin1 [125, 177−180]. The third key class of drugs with a pronounced effect on ISR are PERK inhibitors, specifically, GSK2606414 and GSK2656157 (Fig. 2) [181−183]. In contrast to other drugs, PERK inhibitors have a stimulatory effect on ISR, and their use in experimental practice is mainly associated with the possibility of tumor growth suppression [184, 185].

ISR IN CNS PSYCHIATRIC PATHOLOGIES

Major depressive disorder (MDD) is a widespread and clinically heterogeneous mental illness with a complex etiology and high resistance to therapy. The main MDD symptoms include a prolonged decline in mood and motivation, impaired cognitive functions, and autonomic symptoms, such as sleep and appetite disorders [186]. Neuroinflammation [187], oxidative stress [188], and endoplasmic reticulum stress [189] have also been implicated in the pathogenesis of depression, and all, as already noted, can trigger ISR. Although clinical studies indicative of ISR activation in depression are rather scarce, elevated ATF4 expression has been described in post-mortem samples of the prefrontal cortex from depressed suicidal patients [190] and in peripheral blood samples of mononuclear cells from depressed patients [191, 192]. Furthermore, genome-wide association studies suggest a potential association of an intronic mutation in the *EIF2B* gene (which encodes the eIF2 complex regulatory subunit) [193], polymorphism of the transcription factor-binding domain in the *EIF2AK1* gene (which encodes the eIF2α kinase HRI) [194], as well as polymorphism of the *ATF4* regulatory region [195], with the risk of depression.

Evidence from experimental animal models of depression also indicates a possible activation of ISR in affective pathogenesis. For example, in a mouse model of chronic social defeat, hippocampal levels of PERK and eIF2α phosphorylated forms increase, and activation of the PERK-eIF2α pathway can

Table 1. Evidence for the Integrated Stress Response (ISR) activation in neurodegenerative pathologies

Findings	References
Alzheimer's Disease (AD)	
↑ p-eIF2α in various brain regions of AD patients	[51−58]
↑ p-PKR in the brains of AD patients	[53]
↑ p-PERK in the olfactory bulbs of AD patients	[56]
↓ eIF2B in the brains of AD patients	[51]
↓ p-eIF2α in the brains of AD patients at late stages of the disease	[59]
Distribution of p-PERK correlates with abnormally phosphorylated tau protein in the brains of AD patients	[60]
↑ p-eIF2α, p-PERK, ATF4, and other UPR markers in mouse and rat models of AD	[51, 53−55, 61−72]
↓ p-eIF2α in the brain of rats after injection of Aβ oligomers into the brain ventricles	[73]
↓ p-eIF2α at early stages of the disease in Tg2576 transgenic mouse model	[74]
Aβ peptide causes PKR-mediated increase in p-eIF2α in primary mouse neurons and in the brains of monkeys	[34]
PERK-independent ↑ p-eIF2α, ↓ GADD34, and reduced protein synthesis in astrocytes of 3xTg-AD mice	[75]
↑ p-eIF2α in cells overexpressing mutant Aβ precursor protein	[55]
↑ p-eIF2α in human neuroblastoma cells exposed to Aβ oligomers	[76, 77]
↑ p-eIF2α in a cell line overexpressing mutant Aβ precursor protein	[55]
Deletion of PERK gene improves synaptic plasticity and spatial memory in mouse models of AD	[61]
Deletion of eIF2α phosphorylation site in 5xFAD transgenic mice did not lead to improved behavioral performance	[78]
PERK haploinsufficiency reduced UPR activation and cognitive impairment in 5XFAD transgenic mice	[62]
Conditional PERK knockout in the forebrain reduces p-eIF2α and restores long-term potentiation in the APP/PS1 mouse model of AD	[79]
GCN2 gene deletion leads to hyperactivation of the PERK-eIF2α pathway and increased amyloidosis in the brain of 5XFAD transgenic mice	[80]
Salubrinal increases beta-secretase levels and Aβ synthesis in primary neurons	[54]
Salubrinal reduced oxidative stress and apoptosis markers caused by Aβ injections into the brain ventricles of rats	[73]
Salubrinal reduced AD-like symptoms at early stages of pathology in Tg2576 transgenic mouse model	[74]
GSK2606414 reduces p-eIF2α and restores long-term potentiation in the APP/PS1 mouse model of AD	[79]
PKR inhibitor SAR439883 showed neuroprotective effect in several mouse models of AD	[72]
GADD34 injections into the hippocampus reduced ↑ p-eIF2α and improved cognitive performance in APP23 mouse model of AD	[64]
ISRIB prevents p-eIF2α-mediated long-term memory impairment in an acute AD mouse model	[51]
ISRIB restores synaptic function and memory in a transgenic mouse model of AD	[51]
ISRIB reduces Aβ-induced markers of endoplasmic reticulum stress, neurodegeneration, and neuroinflammation in a rat model of Aβ brain injection	[71]
ISRIB could not restore memory impairment in APP/PS1 and APP J20 mouse models of AD	[81, 82]

Table 1. (Contd.)

Findings	References
Parkinson's Disease (PD)	
↑ p-eIF2α and p-PERK in the brains of people with PD	[83−85]
↑ p-eIF2α in mononuclear blood cells of patients with familial and sporadic forms of PD	[86]
↑ p-eIF2α, p-PERK, and ATF4 in genetic and pharmacological rodent models of PD	[83, 87−89]
↑ p-eIF2α in pink1- and parkin-mutant Drosophila	[90]
↑ p-eIF2α and ↑ p-PERK in rat astrocyte culture overexpressing α-synuclein	[91]
↑ p-eIF2α and ↑ CHOP in a cell model of PD overexpressing α-synuclein	[92]
Guanabenz (inhibits eIF2α phosphatase) promotes neuronal survival in various PD models	[93]
GSK2606414 showed neuroprotective effect in several mouse models of PD	[83]
Neuroprotective effect of salubrinal in a rotenone-induced rat model of PD	[88]
PKR inhibitor C-16 reduces ATF4 activation and dopaminergic neuron death in mouse models of PD	[89]
Huntington's Disease (HD)	
↑ p-eIF2α in the striatum in the N171-82Q transgenic mouse model	[94]
↑ p-eIF2α in a cell model of HD	[95, 96]
↑ ATF4 mRNA and protein levels in a cell model of HD	[97]
ISRIB reduces cell death in striatal cell cultures of STHdhQ111 transgenic mice	[98]
GSK2606414 restores spatial memory and recognition memory and restores dendritic spine density in CA1 pyramidal neurons in R6/1 mouse model	[99]
PERK activator MK-28 restores motor and executive functions and extends lifespan in R6/2 mouse model	[100]
eIF2α phosphatase inhibitor salubrinal shows neuroprotection in a cell model of HD	[96]
Amyotrophic Lateral Sclerosis (ALS)	
↑ p-eIF2α in spinal cord samples from people with ALS	[101]
↑ p-eIF2α and p-PKR in cortex samples from patients with C9ORF72-associated ALS	[102]
↑ ATF4 in the spinal cord of patients with sporadic and familial ALS	[103]
UPR pathway contributes to the translation of intron repeats involved in ALS pathogenesis	[104]
↑ ATF4 mRNA in the spinal cord in the SOD1-mutant mouse model	[105]
PERK activation in motor neurons of SOD1-mutant mice	[106]
↑ p-eIF2α and p-PERK in SOD1-mutant neuroblastoma cells	[107]
GSK2606414 reduced cell death in an ALS neuron culture model	[108]
Heterozygous PERK gene knockout worsens disease progression in the mtSOD1 transgenic mouse model	[109]
ATF4 gene knockout increases lifespan in SOD1-mutant mice	[110]
Sephin1 (eIF2α phosphatase inhibitor) mitigated behavioral, morphological, and molecular changes in SOD1-mutant mice	[111]
Guanabenz showed neuroprotection in the mtSOD1 transgenic mouse model via eIF2α phosphatase inhibition	[112]
Salubrinal improved disease progression in SOD1-mutant mice	[113]
ISRIB improved survival of SOD1-G93A transgenic neurons	[114]
ISRIB-like compounds 2BAct and PRXS571 worsen disease progression in SOD1-G93A transgenic mice	[115]

Table 1. (Contd.)

Findings	References
Multiple Sclerosis (MS)	
↑ p-eIF2α in affected brain regions of people with MS	[116]
↑ ATF4, CHOP, and markers of endoplasmic reticulum stress in the brains of people with MS	[117−119]
↑ p-eIF2α, ATF4, and CHOP in human oligodendrocyte culture under MS-relevant stress conditions	[120]
PERK-eIF2α-CHOP pathway activation in neurons of optic nerves in a mouse model of autoimmune encephalomyelitis	[121]
↑ p-eIF2α, p-PERK, and markers in mouse dorsal root ganglia in a model of autoimmune encephalopathy	[122]
↑ p-eIF2α in oligodendrocytes in a mouse model of CNS-specific interferon-γ overexpression	[123]
↑ GADD34 in oligodendrocytes in a mouse model of CNS-specific interferon-γ overexpression	[124]
↑ p-eIF2α in oligodendrocyte culture under inflammatory stress conditions	[125]
Interferon-γ induces p-eIF2α phosphorylation and increases apoptosis markers in oligodendrocyte culture	[123]
Neuroprotective effect of interferon-γ-mediated increases in p-PERK and p-eIF2α in oligodendrocytes in a mouse model of autoimmune encephalopathy	[126, 127]
Neuroprotective effect of GADD34 gene inactivation in a model of interferon-γ-mediated demyelination	[124]
Deletion of the eIF2α phosphatase gene GADD34 alleviates pathology in a mouse model of autoimmune encephalopathy	[125]
PERK gene inactivation in oligodendrocytes reduces p-eIF2α, oligodendrocyte loss, demyelination, and axon degradation in a mouse model of autoimmune encephalopathy	[128]
Induced PERK hyperactivation in oligodendrocytes promotes neuroprotection and remyelination in cell cultures and mouse models of MS	[129]
Heterozygous PERK gene knockout worsens pathology in a model of CNS-specific interferon-γ overexpression	[123, 130]
ISRIB restores process growth and reduces oligodendrocyte cell death under MS-relevant stress conditions	[120]
Sephin1 inhibited oligodendrocyte process formation under stress conditions	[120]
Sephin1 increased p-eIF2α in oligodendrocyte culture under inflammatory stress conditions and showed neuroprotective effect in a mouse model of autoimmune encephalopathy	[125]
Salubrinal increased p-eIF2α, reduced hypomyelination, and oligodendrocyte loss in hippocampal slices exposed to interferon-γ	[124]
Guanabenz increases p-eIF2α, reduces interferon-γ-induced oligodendrocyte loss and demyelination in cell culture and mouse models of MS	[131]
Traumatic Brain Injury (TBI)	
↑ p-eIF2α, p-PERK, ATF4, and other UPR markers in various brain regions in mouse and rat models of TBI	[46, 132−158]
↓ p-eIF2α and ATF4 in a mild TBI model in mice	[159]
Conditional PERK gene knockout in oligodendrocytes leads to UPR hyperactivation and greater white matter damage following spinal cord injury	[160]
Salubrinal reduced neuronal apoptosis in a fluid percussion injury model in rats	[134]
Salubrinal improved behavioral outcomes in a contusion-induced TBI model in rats	[138]
Salubrinal reduced markers of endoplasmic reticulum stress, autophagy, and apoptosis in a cortical impact model in mice	[142]

Table 1. (Contd.)

| Findings	References
Salubrinal improved cognitive performance and reduced neuronal death in a mild TBI model in mice	[159]
Salubrinal reduced apoptosis markers and normalized impulsive behavior in a blast-induced TBI model	[152]
Guanabenz increased p-eIF2α and improved behavioral parameters in a controlled cortical impact model	[135]
GSK2606414 reduced neuron loss and improved contextual discrimination in a controlled cortical impact model in mice	[140]
GSK2606414 reduced expression of UPR markers and neuronal apoptosis in a surgical brain injury model in rats	[145]
GSK2656157 prevents dendritic spine loss and normalizes memory impairment in a controlled cortical impact model in mice	[161]
ISRIB restored long-term memory function and normalized long-term potentiation impairment in a focal contusion model in mice	[46]
ISRIB reduced neuronal apoptosis and contributed to the normalization of locomotor function in a spinal cord injury model in mice	[151]
ISRIB reduced neuroinflammation and normalized behavioral impairments in a spinal cord injury model	[162]
ISRIB reduced ferroptosis and white matter damage in a controlled cortical impact model in rats	[163]
ISRIB normalized impulsive behavior and synaptic function in a multiple TBI model in mice	[164]
ISRIB normalized motor and cognitive impairments in the stab-wound injury model in zebrafish (*Danio rerio*)	[165]
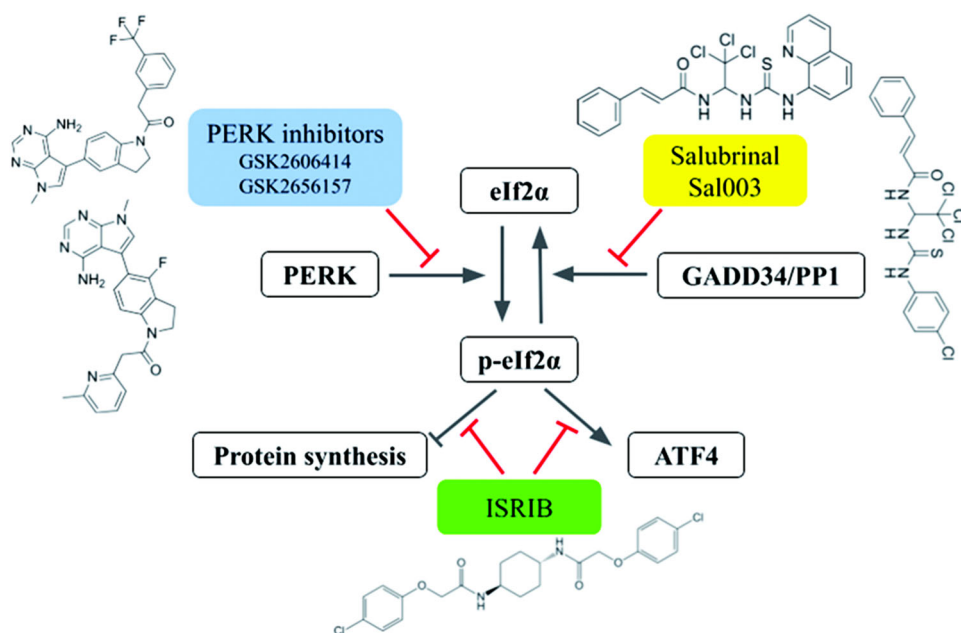
Fig. 2. Mechanisms of action of the Integrated Stress Response (ISR) modulators. PERK—PKR-like endoplasmic reticulum kinase; eIF2α—eukaryotic translation initiation factor 2α; ATF4—activating transcription factor 4; GADD34—protein phosphatase 1 regulatory subunit 15a; PP1—protein phosphatase 1.

inhibit CREB, leading to the suppression of BDNF expression [196]. Likewise, ISR activation is also found in rat models of depression based on moderate unpredictable stress, leading to increased PERK and

eIF2α phosphorylation in the hippocampus, as well as increased protein levels of ATF4 and eIF2α phosphorylated form in the prefrontal cortex [192], with depression-like behavior in the sucrose preference and the forced swim tests. In male Wistar rats exposed to mild stressors (e.g., white noise, bright light, immobilization, swimming in hot and cold water) for 6 weeks [197], depression-like behavior parallels an increase in PERK and eIF2α phosphorylated forms in hippocampal samples, while the serotonergic antidepressant fluoxetine, a selective serotonin reuptake inhibitor (SSRI), normalizes these changes. Lastly, in female Wistar rats, a 6-week chronic unpredictable stress protocol evokes an increase in *ATF4* gene expression in the prefrontal cortex, which is abolished by another SSRI, sertraline [198], suggesting that the suppression of eIF2α signaling activity may be somehow linked to mechanisms underlying the therapeutic effect of SSRI antidepressants.

In another experimental model, a depressive-like state in rats was induced by lipopolysaccharide (LPS) injections, which also led to the activation of PERK kinase in the hippocampus, but not in the prefrontal cortex [199]. In contrast, ISRIB administration to rats reduced both LPS-induced neuroinflammation and depression-like behavior [199]. Finally, two mouse models of depression, LPS-induced neuroinflammation and corticosterone-induced stress, showed elevated eIF2α phosphorylation in serotonergic raphe neurons, decreased BDNF levels, increased content of endoplasmic reticulum stress-related proteins, as well as anxiety- and depression-like behavior [200]. Injections of tunicamycin, a compound that induces endoplasmic reticulum stress and consequent ISR activation, into the mouse dorsal raphe nuclei also increased p-eIF2α levels in these nuclei and depression-like behavior. Local tunicamycin injections into the raphe nuclei altered the expression of genes encoding neuroplasticity-related proteins (e.g., BDNF and its receptor TrkB, neuritin, and others), and decreased serotonin-mediated neurotransmission in other brain regions [200].

In contrast, ISRIB injections block tunicamycin-induced changes in gene expression of synaptic proteins and prevent depressive-like behavior of animals [200]. At the same time, the administration of salubrinal, an eIF2α inhibitor and ISRIB activator,

enhances tunicamycin effects on the above parameters [200]. Interestingly, ketamine, an inhibitor of N-methyl-D-aspartate (NMDA) glutamate receptors, considered as a fast-acting antidepressant, also normalizes tunicamycin-induced changes in p-eIF2α levels and behavior, assuming that increased eIF2α phosphorylation and the activation of p-eIF2α-mediated signaling in the dorsal raphe nuclei may be responsible for the impairments in neurotransmission, neuroplasticity and behavior, observed in experimental models [200]. Overall, despite the paucity of clinical data, animal model studies indicate that ISR and especially PERK-eIF2α signaling may play an important role in the pathogenesis of depression, opening up new avenues for the use of drugs targeting the ISR system as possible antidepressants.

Schizophrenia is a prevalent heterogeneous disorder with an intricate etiology, resulting due to a combination of genetic predisposition and environmental factors [201]. The symptoms of schizophrenia are categorized into the positive (delusions and hallucinations) and negative (a lack of motivation, social isolation, and cognitive impairments) [202]. Although the role of ISR in the pathogenesis of this disease remains poorly understood, evidence of ISR involvement in schizophrenia can be found in genetic studies, clinical reports, as well as in experimental models of the disease. For example, certain single nucleotide mutations in the *ATF4* gene are associated with schizophrenia in males, but not in females, in China [203]. A genome-wide association study of >13000 cases links schizophrenia to *EIF2AK2* encoding the eIF2α kinase HRI [204]. Proteomic analysis of the prefrontal cortex in schizophrenia patients shows elevated level of another eIF2α kinase, GCN2 [205]. The neurospheres derived from olfactory epithelial cells of schizophrenia patients also demonstrate lower both global protein synthesis and ribosomal protein content. A subsequent pathway analysis of differentially expressed proteins and mRNA transcripts in neurospheres showed the enrichment of the pathway associated with eIF2α signaling. Studies of blood cells from schizophrenia patients demonstrate elevated eIF2α phosphorylation in lymphocytes [206] the fraction of peripheral blood mononuclear cells [207], suggesting a possible systemic activation of ISR.

Evidence of ISR activation has also been

described in mouse models of schizophrenia. For example, in a model of prenatal exposure to the viral mimetic polyriboinosinic-polyribocytidylic acid (poly I:C, an immunostimulant causing schizophrenia-like changes in offspring), there is increased p-eIF2α/eIF2α ratio in the hippocampus and prefrontal cortex [206]. In another model, mice with a conditional knockout of the *CACNA1C* gene (which encodes the L-type Cav1.2 calcium channel associated with schizophrenia and BD) in the excitatory glutamatergic neurons of the prefrontal cortex [208] exhibit increased anxiety and social behavior disorder, as well as decreased protein synthesis and increased p-eIF2α level in the prefrontal cortex, whereas ISRIB restores protein synthesis and normalizes behavioral impairment in this model [208]. Using a culture of cortical neurons with a mutant *DISC1* (disrupted in schizophrenia 1) gene associated with schizophrenia, there were observed ATF4 accumulation in the cell nuclei and ATF4-induced changes in the expression of a number of genes leading to synaptic dysfunction [209]. A structural analysis showed that mutations in the *DISC1* gene prevent DISC1-ATF4 complex formation, resulting in the impaired DISC1-mediated suppression of ATF4 activity [209]. Genetic suppression of ATF4 expression (by a heterozygous *ATF4* mutation) normalizes synaptic function, restoring the density of synaptic contacts, as well as increasing the average frequency of spontaneous discharges and the number of active neuronal gap junctions. In contrast, the enhancement of ATF4 expression in a culture of non-mutant neurons leads to transcriptomic changes and decreased synaptic excitability, similar to those observed in *DISC1*-mutant cells. This suggests a key role of ATF4 in the pathogenesis of *DISC1*-mediated schizophrenia, and raises the question of the role of ISR-mediated ATF4 activation in other forms of this disease (e.g., an analysis of brain cortex samples from patients with schizophrenia shows a decrease in the pivotal ISR components, PERK and ATF4 [210]).

Moreover, mice with a conditional *PERK* knockout in the cerebral cortex exhibit several schizophrenia-like behavioral abnormalities related to information processing and behavioral flexibility, as well lower p-eIF2α and ATF4 levels in the prefrontal cortex [210]. The content of p-eIF2α and ATF4 in the prefrontal cortex of older adults with schizophrenia is indistinguishable from controls [211]. In general, the inconsistency of these data may be due to the great clinical heterogeneity of schizophrenia, as well as the differences in animal models employed. Therefore, despite the growing body of evidence of ISR involvement in schizophrenia, the specific role of this pathway in its pathogenesis remains obscure and warrants further investigation.

Bipolar disorder (BD) is characterized by recurrent swings of mood and various specific cognitive, physiological and behavioral symptoms [212]. To date, there is only indirect evidence for a possible role of ISR in the pathogenesis of BD. For example, in a human lymphocyte culture model, tunicamycin (as an endoplasmic reticulum stress activator) stimulates eIF2α phosphorylation in controls, but not in lymphocytes of BD patients [213]. The lack of a normal response to tunicamycin is accompanied by increased cell mortality, and this effect is only observed for lymphocytes from patients at the late stage of the disease. These data suggest the role of ISR dysfunctions in BD.

Peripheral blood cells from BD patients show elevated endoplasmic reticulum stress markers [213–216], although it remains unclear whether these changes are associated with eIF2α phosphorylation and ISR activation per se. Lastly, a recent genetic analysis of public genomic databases of BD patients using Mendelian randomization to link the genes encoding ISR pathway components to BD [217] revealed significant BD associations with the *EIF2B5* gene encoding the eIF2B factor subunit (a molecular target of ISRIB), as well as with *EIF2AK4* encoding GCN2, an eIF2α kinase.

Post-traumatic stress disorder (PTSD) results from a severe traumatic event and is accompanied by long-term psychiatric, neuroendocrine, and neurophysiological disturbances [218]. Data on the involvement of ISR in the pathogenesis of PTSD are currently limited to animal models using single prolonged stress in rats, which elevates p-eIF2α and p-PERK levels and the content of several endoplasmic reticulum stress markers in the prefrontal cortex [219, 220], as well as evokes the accumulation of ATF4 and CHOP proteins in the nuclei of prefrontal cortical neurons, paralleled by increased apoptosis and behavioral disorders related to the rat learning abilities and memory [219]. Interestingly, the PERK inhibitor GSK2606414 restores both changes in protein levels and behavioral abnormalities, observed in

this model of PTSD [219]. Overall, these data suggest a PERK-dependent ISR hyperactivation in this model, yet calling for further studies using alternative models, as well as more extensive and systematic clinical data, to draw a definite conclusion on the role of ISR in PTSD.

Drug addiction. The dependence on the use of diverse psychoactive substances (substance use disorder) is also based on long-term molecular and cellular alterations in neurons of the mesolimbic and dopaminergic systems [221], in which ISR has recently been implicated. For example, in rat conditioned place preference (CPP), as well as cocaine and morphine self-stimulation studies, exposure to a drug-associated stimulus evokes a decrease in p-eIF2α and ATF4 levels in the basolateral amygdala [222], whereas injections of Sal003 (an eIF2α phosphatase inhibitor) into this brain region suppresses drug-directed behavior, while decreased *ATF4* expression via RNA interference blocks the effect of Sal003. Injection of the latter into the rat nucleus accumbens suppresses drug-seeking behavior in the rodent model of cocaine withdrawal [223]. In mice, cocaine [224, 225], nicotine [226], alcohol and methamphetamine [224] reduce eIF2α phosphorylation level in the ventral tegmental area (VTA), a key brain region involved in the formation of drug addiction [227]. Interestingly, young adolescent mice with reduced p-eIF2α/eIF2α ratio in the VTA show a greater predisposition to cocaine and nicotine addiction [224, 226]. Moreover, in young mice, cocaine and nicotine are able to induce long-term potentiation in VTA neurons (one of the mechanisms behind the formation of addiction) at lower doses compared to adults [224, 226].

Genetic suppression of eIF2α phosphorylation in the VTA (Ser51 substitution for alanine in one of the *EFf2s1* gene alleles) lowers the threshold of nicotine- and cocaine-induced long-term potentiation in the VTA neurons of adult mice to a level comparable to that observed in adolescents [224, 226]. At the same time, the administration of the ISR activator Sal003 into the VTA inhibits the effect of cocaine on long-term potentiation, and additionally, reduces the indices of addictive behavior in adolescent mice [224].

In contrast, ISRIB enhances the effects of cocaine and nicotine on long-term potentiation and, additionally, contributed to the formation of addictive behavior [225]. The administration of the cannabinoid receptor agonist WIN 55,212-2 to rats also decreases eIF2α phosphorylation in the nucleus accumbens of adolescent, but not adult, individuals [228], whereas WIN 55,212-2 and cocaine enhance each other's behavioral effects (cross-sensitization) in adolescent rats [228]. The involvement of eIF2α signaling in the pathogenesis of drug addiction is further supported by the fact that in humans, the genetic predisposition to smoking is associated with a polymorphism of *EFf2s1* that encodes eIF2α [226]. Thus, ISR inhibition in the neurons of the mesolimbic system plays an important role in the formation of addiction to a wide variety of drugs, while the suppression of p-eIF2α signaling may be a key factor determining a greater predisposition of young individuals to drugs.

Chronic morphine exposures increases p-eIF2α content in the rat cerebral cortex, which is accompanied by apoptotic changes in cell morphology [229], while systemic morphine injections elevate p-eIF2α levels in the rat spinal cord and increase the expression of endoplasmic reticulum stress and apoptosis markers [230]. Repeated amphetamine administration increases p-eIF2α phosphorylation and decreases total protein synthesis in the mouse striatum [231], while a single exposure to a high dose of methamphetamine and amphetamine increases p-eIF2α levels in the mouse hippocampus [232] and rat striatum [233]. Taken together, these observations indicate that pathological changes in the brain caused by drugs of abise (including opiates and amphetamine), are associated with the activation of the ISR system.

GENERAL DISCUSSION

ISR is an important protective mechanism aimed at maintaining cellular homeostasis under stress conditions. At the same time, altered eIF2α signaling can have both adaptive and pathogenic effects, depending on the context and the degree of ISR activation. In the short term, this mechanism promotes cell survival by reducing the total level of protein synthesis and redistributing homeostasis restorative resources. However, a chronic activation of the ISR pathway can induce programmed cell death via mediators, such as ATF4 and CHOP, which may lead to neuronal dysfunction and cell death, as described in Alzheimer's and Parkinson's diseases, as well as in other neurodegenerative disorders.

However, the functional significance of ISR signaling cascades for mental diseases remains unclear. On the one hand, the above data attest to the involvement of ISR components in the pathogenesis of depression, schizophrenia, BD, addiction, and PTSD. Furthermore, ISR modulators, such as ISRIB and salubrinal, show therapeutic efficacy in some models of these diseases. On the other hand, the possibility for the changes in eIF2α signaling to be not causative but consequential for general cellular dysregulation in pathology cannot be ruled out.

Notably, most of the data discussed here are obtained using animal models, and this introduces certain limitations into their interpretation. Firstly, such models do not always fully capture the complexity and multicomponent nature of mental illness in humans. Secondly, the pathogenesis of depression or schizophrenia in humans often involves a wide range of factors, such as genetic, social, and biochemical components that are difficult to reproduce in animal experiments. Thirdly, the significance of ISR in rodent models of neurodegeneration and mental disorders may vary depending on the methods used and experimental conditions. For example, ISR activation in the rat hippocampus in a model of chronic unpredictable stress may represent a response to chronic stress, but not necessarily mean that this cascade is the first cause of the disease.

Furthermore, the issue of the advisability of artificial modulation of eIF2α signaling activity under conditions of pathology remains open. On the one hand, such drugs as ISRIB and salubrinal show a potential to improve behavioral and neurophysiological parameters in some models of the above pathologies. On the other hand, artificial inhibition or stimulation of eIF2α signaling may have unpredictable consequences toward general cellular homeostasis, especially in the context of complex multicomponent CNS pathologies. Finally, biological effects of ISR modulators (e.g., ISRIB) with vs. without CNS pathology merit further scrutiny. Overall, despite the potential importance of ISR in the pathogenesis of mental disorders, current data remain fragmentary, and it remains unclear whether ISR is a pivotal mechanism or a collateral link in a broader network of pathophysiological systemic changes in the brain. Future research should focus on integrating the knowledge of the role of ISR and other signaling cascades and on developing therapeutic strategies aimed at precise and controlled intervention in this pathway.

CONCLUSION

ISR in the brain is an important mechanism of cellular adaptation to biological stress, affects neuronal activity and is involved in the pathogenesis of multiple CNS diseases. Both ISR activation (e.g., in depression and PTSD) and inhibition (e.g., in some models of BD, schizophrenia, and addiction) can correlate with the development of mental disorders. Thus, pharmacological agents (e.g., ISRIB and salubrinal) that target diverse components of the ISR system represent promising therapeutic tools to minimize negative effects of ISR activation or inhibition in the brain by modulating the symptoms of mental illness. In general, future studies can further elucidate the specific roles of the ISR pathways in mental disorders and develop targeted therapies mitigating their deleterious effects and preventing the development of undesirable side effects associated with ISR deregulation. The deeper insight into the complex interplay between cellular stress responses and the pathogenesis of mental disorders will advance treatment strategies for these conditions.

AUTHORS' CONTRIBUTION

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This work does not contain experimental animal or human studies.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflict of interest.

REFERENCES

1. Pakos-Zebrucka K, Koryga I, Mnich K, Ljujic M, Samali A, Gorman AM (2016) The integrated stress response. EMBO Rep 17(10): 1374–1395.
https://doi.org/10.15252/embr.201642195

2. Boye E, Grallert B (2020) eIF2α phosphorylation and the regulation of translation. Curr Genet 66(2): 293–297.
https://doi.org/10.1007/s00294-019-01026-1

3. Liang S-H, Zhang W, Mcgrath BC, Zhang P, Cavener DR (2006) PERK (eIF2α kinase) is required to activate the stress-activated MAPKs and induce the expression of immediate-early genes upon disruption of ER calcium homoeostasis. Biochem J 393(1): 201–209.
https://doi.org/10.1042/BJ20050374

4. Wang P, Li J, Tao J, Sha B (2018) The luminal domain of the ER stress sensor protein PERK binds misfolded proteins and thereby triggers PERK oligomerization. J Biol Chem 293(11): 4110–4121.
https://doi.org/10.1074/jbc.RA117.001294

5. Almeida LM, Pinho BR, Duchen MR, Oliveira JM (2022) The PERKs of mitochondria protection during stress: insights for PERK modulation in neurodegenerative and metabolic diseases. Biol Revs 97(5): 1737–1748.
https://doi.org/10.1111/brv.12860

6. Girardin SE, Cuziol C, Philpott DJ, Arnoult D (2021) The eIF2α kinase HRI in innate immunity, proteostasis, and mitochondrial stress. FEBS J 288(10): 3094–3107.
https://doi.org/10.1111/febs.15553

7. Hinnebusch AG (2005) Translational regulation of GCN4 and the general amino acid control of yeast. Ann Rev Microbiol 59: 407–450.
https://doi.org/10.1146/annurev.micro.59.031805.133833

8. Marbach I, Licht R, Frohnmeyer H, Engelberg D (2001) Gcn2 mediates Gcn4 activation in response to glucose stimulation or UV radiation not via GCN4 translation. J Biol Chem 276(20): 16944–16951.
https://doi.org/10.1074/jbc.M100383200

9. Lemaire PA, Anderson E, Lary J, Cole JL (2008) Mechanism of PKR Activation by dsRNA. J Mol Biol 381(2): 351–360.
https://doi.org/10.1016/j.jmb.2008.05.056

10. Gal-Ben-Ari S, Barrera I, Ehrlich M, Rosenblum K (2019) PKR: a kinase to remember. Front Mol Neurosci 11: 480.
https://doi.org/10.3389/fnmol.2018.00480

11. Chukwurah E, Farabaugh KT, Guan BJ, Ramakrishnan P, Hatzoglou M (2021) A tale of two proteins: PACT and PKR and their roles in inflammation. FEBS J 288(22): 6365–6391.
https://doi.org/10.1111/febs.15691

12. Hinnebusch AG, Ivanov IP, Sonenberg N (2016) Translational control by 5′-untranslated regions of eukaryotic mRNAs. Science 352(6292): 1413–1416.
https://doi.org/10.1126/science.aad9868

13. Kashiwagi K, Yokoyama T, Nishimoto M, Takahashi M, Sakamoto A, Yonemochi M, Shirouzu M, Ito T (2019) Structural basis for eIF2B inhibition in integrated stress response. Science 364(6439): 495–459.
https://doi.org/10.1126/science.aaw4104

14. Lu PD, Harding HP, Ron D (2004) Translation reinitiation at alternative open reading frames regulates gene expression in an integrated stress response. J Cell Biol 167(1): 27–33.
https://doi.org/10.1083/jcb.200408003

15. Zhang J, Shi Y (2024) An upstream open reading frame (5′-uORF) links oxidative stress to translational control of ALCAT1 through phosphorylation of eIF2α. Free Rad Biol Med 214: 129–136.
https://doi.org/10.1016/j.freeradbiomed.2024.02.015

16. Silva J, Fernandes R, Romão L (2019) Translational regulation by upstream open reading frames and human diseases. In: mRNA Metab Hum Dis. 99–116.
https://doi.org/10.1007/978-3-030-19966-1_5

17. Neill G, Masson GR (2023) A stay of execution: ATF4 regulation and potential outcomes for the integrated stress response. Front Mol Neurosci 16: 1112253.
https://doi.org/10.3389/fnmol.2023.1112253

18. Rozpedek W, Pytel D, Mucha B, Leszczynska H, Diehl JA, Majsterek I (2016) The role of the PERK/eIF2α/ATF4/CHOP signaling pathway in tumor progression during endoplasmic reticulum stress. Curr Mol Med 16(6): 533–544.
https://doi.org/10.2174/1566524016666160523143937

19. Márton M, Bánhegyi G, Gyöngyösi N, Kálmán EÉ, Pettkó-Szandtner A, Káldi K, Kapuy O (2022) A systems biological analysis of the ATF4-GADD34-CHOP regulatory triangle upon endoplasmic reticulum stress. FEBS Open Biol 12(11): 2065–2082.
https://doi.org/10.1002/2211-5463.13484

20. Novoa I, Zeng H, Harding HP, Ron D (2001) Feedback inhibition of the unfolded protein response by GADD34-mediated dephosphorylation of eIF2α. J Cell Biol 153(5): 1011–1022.
https://doi.org/10.1083/jcb.153.5.1011

21. Kastan JP, Dobrikova EY, Bryant JD, Gromeier M (2020) CReP mediates selective translation initiation at the endoplasmic reticulum. Sci Adv 6(23): eaba0745.
https://doi.org/10.1126/sciadv.aba0745

22. Jimenez-Diaz A, Remacha M, Ballesta JP, Berlanga JJ (2013) Phosphorylation of initiation factor eIF2 in response to stress conditions is mediated by acidic ribosomal P1/P2 proteins in Saccharomyces cerevisiae. PLoS One 8(12): e84219.
https://doi.org/10.1371/journal.pone.0084219

23. Lewerenz J, Maher P (2009) Basal levels of eIF2α phosphorylation determine cellular antioxidant status by regulating ATF4 and xCT expression. J Biol Chem 284(2): 1106−1115.
https://doi.org/10.1074/jbc.M807325200

24. Wek RC (2018) Role of eIF2α kinases in translational control and adaptation to cellular stress. Cold Spring Harb Persp Biology 10(7): a032870.
https://doi.org/10.1101/cshperspect.a032870

25. Zeng N, Li Y, He L, Xu X, Galicia V, Deng C, Stiles BL (2011) Adaptive Basal Phosphorylation of eIF2α Is Responsible for Resistance to Cellular Stress-Induced Cell Death in Pten-Null Hepatocytes. Mol Cancer Res 9(12): 1708−1717.
https://doi.org/10.1158/1541-7786.MCR-11-0299

26. Grallert B, Boye E (2007) The Gcn2 kinase as a cell cycle regulator. Cell Cycle 6(22): 2768−2772.
https://doi.org/10.4161/cc.6.22.4933

27. Scheuner D, Song B, McEwen E, Liu C, Laybutt R, Gillespie P, Saunders T, Bonner-Weir S, Kaufman RJ (2001) Translational control is required for the unfolded protein response and in vivo glucose homeostasis. Mol Cell 7(6): 1165−1176.
https://doi.org/10.1016/S1097-2765(01)00265-9

28. Di Prisco GV, Huang W, Buffington SA, Hsu C-C, Bonnen PE, Placzek AN, Sidrauski C, Krnjević K, Kaufman RJ, Walter P (2014) Translational control of mGluR-dependent long-term depression and object-place learning by eIF2α. Nat Neurosci 17(8): 1073−1082.
https://doi.org/10.1038/nn.3754

29. Costa-Mattioli M, Gobert D, Stern E, Gamache K, Colina R, Cuello C, Sossin W, Kaufman R, Pelletier J, Rosenblum K (2007) eIF2α phosphorylation bidirectionally regulates the switch from short-to long-term synaptic plasticity and memory. Cell 129(1): 195−206.
https://doi.org/10.1016/j.cell.2007.01.050

30. Trinh MA, Klann E (2013) Translational control by eIF2α kinases in long-lasting synaptic plasticity and long-term memory. Neurobiol Learn Mem 105: 93−99.
https://doi.org/10.1016/j.nlm.2013.04.013

31. Zhang Q, Bestard-Lorigados I, Song W (2021) Cell-type-specific memory consolidation driven by translational control. Sign Transduct Targ Ther 6(1): 40.
https://doi.org/10.1038/s41392-021-00471-0

32. Ma T, Trinh MA, Wexler AJ, Bourbon C, Gatti E, Pierre P, Cavener DR, Klann E (2013) Suppression of eIF2α kinases alleviates AD-related synaptic plasticity and spatial memory deficits. Nat Neurosci 16(9): 1299.
https://doi.org/10.1038/nn.3486

33. Sharma V, Sood R, Khlaifia A, Eslamizade MJ, Hung T-Y, Lou D, Asgarihafshejani A, Lalzar M, Kiniry SJ, Stokes MP (2020) eIF2α controls memory consolidation via excitatory and somatostatin neurons. Nature 586(7829): 412−416.
https://doi.org/10.1038/s41586-020-2805-8

34. Lourenco MV, Clarke JR, Frozza RL, Bomfim TR, Forny-Germano L, Batista AF, Sathler LB, Brito-Moreira J, Amaral OB, Silva CA (2013) TNF-α mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's β-amyloid oligomers in mice and monkeys. Cell Metabol 18(6): 831−843.
https://doi.org/10.1016/j.cmet.2013.11.002

35. Costa-Mattioli M, Gobert D, Harding H, Herdy B, Azzi M, Bruno M, Bidinosti M, Ben Mamou C, Marcinkiewicz E, Yoshida M (2005) Translational control of hippocampal synaptic plasticity and memory by the eIF2α kinase GCN2. Nature 436(7054): 1166−1170.
https://doi.org/10.1038/nature03897

36. Oliveira MM, Klann E (2022) eIF2-dependent translation initiation: Memory consolidation and disruption in Alzheimer's disease. Sem Cell Devel Biology 125: 101−109.
https://doi.org/10.1016/j.semcdb.2021.07.009

37. Pasini S, Corona C, Liu J, Greene LA, Shelanski ML (2015) Specific downregulation of hippocampal ATF4 reveals a necessary role in synaptic plasticity and memory. Cell Rep 11(2): 183−191.
https://doi.org/10.1016/j.celrep.2015.03.025

38. Oliveira MM, Mohamed M, Elder MK, Banegas-Morales K, Mamcarz M, Lu EH, Golhan EA, Navrange N, Chatterjee S, Abel T (2024) The integrated stress response effector GADD34 is repurposed by neurons to promote stimulus-induced translation. Cell Rep 43(2): 113670.
https://doi.org/10.1016/j.celrep.2023.113670

39. Maurin A-C, Benani A, Lorsignol A, Brenachot X, Parry L, Carraro V, Guissard C, Averous J, Jousse C, Bruhat A (2014) Hypothalamic eIF2α signaling regulates food intake. Cell Rep 6(3): 438-444.
https://doi.org/10.1016/j.celrep.2014.01.006

40. Kim KK, Lee TH, Park BS, Kang D, Kim DH, Jeong B, Kim JW, Yang HR, Kim HR, Jin S, Back SH, Park JW, Kim JG, Lee BJ (2023) Bridging Energy Need and Feeding Behavior: The Impact of eIF2α Phosphorylation in AgRP Neurons. Diabetes 72(10): 1384−1396.
https://doi.org/10.2337/db23-0004

41. Anderson R, Agarwal A, Ghosh A, Guan BJ, Casteel J, Dvorina N, Baldwin WM, Mazumder B, Nazarko TY, Merrick WC, Buchner DA, Hatzoglou M, Kondratov RV, Komar AA (2021) eIF2A-knockout mice reveal decreased life span and metabolic syndrome. FASEB J 35(11): e21990.
https://doi.org/10.1096/fj.202101105R

42. Costa-Mattioli M, Walter P (2020) The integrated stress response: From mechanism to disease. Science 368(6489): eaat5314.
https://doi.org/10.1126/science.aat5314

43. Kernohan KD, Tétreault M, Liwak-Muir U, Geraghty MT, Qin W, Venkateswaran S, Davila J, Consortium CRC, Holcik M, Majewski J, Richer J, Boycott KM (2015) Homozygous mutation in the eukaryotic translation initiation factor 2alpha phosphatase gene, PPP1R15B, is associated with severe microcephaly, short stature and intellectual disability. Hum Mol Genet 24(22): 6293−6300.
https://doi.org/10.1093/hmg/ddv337

44. Julier C, Nicolino M (2010) Wolcott-Rallison syndrome. Orphanet J Rare Dis 5(1): 29.
https://doi.org/10.1186/1750-1172-5-29

45. Elroy-Stein O, Schiffmann R (2020) Chapter 19—Vanishing white matter disease. In: Rosenberg RN, Pascual JM (eds) Rosenberg's Molecular and Genetic Basis of Neurological and Psychiatric Disease (Sixth Edition). Academic Press p. 301−317.
https://doi.org/10.1016/B978-0-12-813866-3.00019-9

46. Chou A, Krukowski K, Jopson T, Zhu PJ, Costa-Mattioli M, Walter P, Rosi S (2017) Inhibition of the integrated stress response reverses cognitive deficits after traumatic brain injury. Proc Natl Acad Sci USA 114(31): E6420−E6426.
https://doi.org/10.1073/pnas.1707661114

47. Marlin E, Viu-Idocin C, Arrasate M, Aragón T (2022) The Role and Therapeutic Potential of the Integrated Stress Response in Amyotrophic Lateral Sclerosis. Intl J Mol Sci 23(14): 7823.
https://doi.org/10.3390/ijms23147823

48. Way SW, Popko B (2016) Harnessing the integrated stress response for the treatment of multiple sclerosis. Lancet Neurol 15(4): 434−443.
https://doi.org/10.1016/S1474-4422(15)00381-6

49. Mercado G, Castillo V, Soto P, Sidhu A (2016) ER stress and Parkinson's disease: Pathological inputs that converge into the secretory pathway. Brain Res 1648: 626−632.
https://doi.org/10.1016/j.brainres.2016.04.042

50. Oliveira MM, Lourenco MV (2016) Integrated Stress Response: Connecting ApoE4 to Memory Impairment in Alzheimer's Disease. J Neurosci 36(4): 1053−1055.
https://doi.org/10.1523/JNEUROSCI.4110-15.2016

51. Oliveira MM, Lourenco MV, Longo F, Kasica NP, Yang W, Ureta G, Ferreira DD, Mendonça PH, Bernales S, Ma T (2021) Correction of eIF2-dependent defects in brain protein synthesis, synaptic plasticity, and memory in mouse models of Alzheimer's disease. Sci Signal 14(668): eabc5429.
https://doi.org/10.1126/scisignal.abc5429

52. Chang RC, Wong AK, Ng H-K, Hugon J (2002) Phosphorylation of eukaryotic initiation factor-2α (eIF2α) is associated with neuronal degeneration in Alzheimer's disease. Neuroreport 13(18): 2429−2432.
https://doi.org/10.1097/00001756-200212200-00011

53. Mouton-Liger F, Paquet C, Dumurgier J, Bouras C, Pradier L, Gray F, Hugon J (2012) Oxidative stress increases BACE1 protein levels through activation of the PKR-eIF2α pathway. Biochim Biophys Acta Mol Basis Dis 1822(6): 885−896.
https://doi.org/10.1016/j.bbadis.2012.01.009

54. O'Connor T, Sadleir KR, Maus E, Velliquette RA, Zhao J, Cole SL, Eimer WA, Hitt B, Bembinster LA, Lammich S (2008) Phosphorylation of the translation initiation factor eIF2α increases BACE1 levels and promotes amyloidogenesis. Neuron 60(6): 988−1009.
https://doi.org/10.1016/j.neuron.2008.10.047

55. Kim HS, Choi Y, Shin KY, Joo Y, Lee YK, Jung SY, Suh YH, Kim JH (2007) Swedish amyloid precursor protein mutation increases phosphorylation of eIF2α in vitro and in vivo. J Neurosci Res 85(7): 1528−1537.
https://doi.org/10.1002/jnr.21267

56. Murray HC, Dieriks BV, Swanson ME, Anekal PV, Turner C, Faull RL, Belluscio L, Koretsky A, Curtis MA (2020) The unfolded protein response is activated in the olfactory system in Alzheimer's disease. Acta Neuropathol Commun 8: 1−15.
https://doi.org/10.1186/s40478-020-00986-7

57. Ferrer I (2002) Differential expression of phosphorylated translation initiation factor 2 alpha in Alzheimer's disease and Creutzfeldt-Jakob's disease. Neuropathol Appl Neurobiol 28(6): 441−451.
https://doi.org/10.1046/j.1365-2990.2002.t01-1-00410.x

58. Stutzbach LD, Xie SX, Naj AC, Albin R, Gilman S, Group PGS, Lee VM, Trojanowski JQ, Devlin B, Schellenberg GD (2013) The unfolded protein response is activated in disease-affected brain regions in progressive supranuclear palsy and Alzheimer's disease. Acta Neuropathol Commun 1: 1−13.
https://doi.org/10.1186/2051-5960-1-31

59. de la Monte SM, Re E, Longato L, Tong M (2012) Dysfunctional pro-ceramide, ER stress, and insulin/ IGF signaling networks with progression of Alzheimer's disease. J Alzheim Dis 30(s2): S217−S229.
https://doi.org/10.3233/JAD-2012-111728

60. Unterberger U, Höftberger R, Gelpi E, Flicker H, Budka H, Voigtländer T (2006) Endoplasmic reticulum stress features are prominent in Alzheimer disease but not in prion diseases in vivo. J Neuropathol Exper Neurol 65(4): 348−357.
https://doi.org/10.1097/01.jnen.0000218445.30535.6f

61. Ma T, Trinh MA, Wexler AJ, Bourbon C, Gatti E, Pierre P, Cavener DR, Klann E (2013) Suppression of eIF2α kinases alleviates Alzheimer's disease-related plasticity and memory deficits. Nat Neurosci 16(9): 1299−1305.
https://doi.org/10.1038/nn.3486

62. Devi L, Ohno M (2014) PERK mediates eIF2α phosphorylation responsible for BACE1 elevation, CREB dysfunction and neurodegeneration in a mouse model of Alzheimer's disease. Neurobiol Aging 35(10): 2272−2281.
https://doi.org/10.1016/ j.neurobiolaging.2014.04.031

63. Zhang J-S, Zhou S-F, Wang Q, Guo J-N, Liang H-M, Deng J-B, He W-Y (2016) Gastrodin suppresses BACE1 expression under oxidative stress condition via inhibition of the PKR/eIF2α pathway in Alzheimer's disease. Neuroscience 325: 1−9.
https://doi.org/10.1016/j.neuroscience.2016.03.024

64. Hayakawa-Ogura M, Nakagawa T, Itoh M (2023) GADD34 suppresses eIF2α phosphorylation and improves cognitive function in Alzheimer's disease-model mice. Biochem Biophys Res Commun 654: 112−129.
https://doi.org/10.1016/j.bbrc.2023.02.077

65. Devi L, Ohno M (2010) Phospho-eIF2α level is important for determining abilities of BACE1 reduction to rescue cholinergic neurodegeneration and memory defects in 5XFAD mice. PLoS One 5(9): e12974.
https://doi.org/10.1371/journal.pone.0012974

66. Segev Y, Michaelson DM, Rosenblum K (2013) ApoE ε4 is associated with eIF2α phosphorylation and impaired learning in young mice. Neurobiol Aging 34(3): 863−872.

https://doi.org/10.1016/j.neurobiolaging.2012.06.020

67. Liang Y, Ye C, Chen Y, Chen Y, Diao S, Huang M. (2021) Berberine improves behavioral and cognitive deficits in a mouse model of Alzheimer's disease via regulation of β-amyloid production and endoplasmic reticulum stress. ACS Chem Neurosci 12(11): 1894−1904.
https://doi.org/10.1021/acschemneuro.0c00808

68. Hayakawa M, Itoh M, Ohta K, Li S, Ueda M, Wang M-x, Nishida E, Islam S, Suzuki C, Ohzawa K (2015) Quercetin reduces eIF2α phosphorylation by GADD34 induction. Neurobiol Aging 36(9): 2509−2518.
https://doi.org/10.1016/ j.neurobiolaging.2015.05.006

69. Lizarazo S, Yook Y, Tsai NP (2022) Amyloid beta induces Fmr1-dependent translational suppression and hyposynchrony of neural activity via phosphorylation of eIF2α and eEF2. J Cell Physiol 237(7): 2929−2942.
https://doi.org/10.1002/jcp.30754

70. Devi L, Ohno M (2013) Mechanisms that lessen benefits of β-secretase reduction in a mouse model of Alzheimer's disease. Transl Psychiatry 3(7): e284.
https://doi.org/10.1038/tp.2013.59

71. Goswami P, Akhter J, Mangla A, Suramya S, Jindal G, Ahmad S, Raisuddin S (2023) Downregulation of ATF-4 Attenuates the Endoplasmic Reticulum Stress-Mediated Neuroinflammation and Cognitive Impairment in Experimentally Induced Alzheimer's Disease Model. Mol Neurobiol 61: 5071−5082.
https://doi.org/10.1007/s12035-023-03861-3

72. Lopez-Grancha M, Bernardelli P, Moindrot N, Genet E, Vincent C, Roudieres V, Krick A, Sabuco J-F, Machnik D, Ibghi D (2021) A novel selective PKR inhibitor restores cognitive deficits and neurodegeneration in Alzheimer disease experimental models. J Pharmacol Exper Ther 378(3): 262−275.
https://doi.org/10.1124/jpet.121.000590

73. Goswami P, Afjal MA, Akhter J, Mangla A, Khan J, Parvez S, Raisuddin S (2020) Involvement of endoplasmic reticulum stress in amyloid β (1-42)-induced Alzheimer's like neuropathological process in rat brain. Brain Res Bull 165: 108−117.
https://doi.org/10.1016/j.brainresbull.2020.09.022

74. Borreca A, Valeri F, De Luca M, Ernst L, Russo A, Nobili A, Cordella A, Corsetti V, Amadoro G, Mercuri NB (2020) Transient upregulation of translational efficiency in prodromal and early symptomatic Tg2576 mice contributes to Aβ pathology. Neurobiol Dis 139: 104787.
https://doi.org/10.1016/j.nbd.2020.104787

75. Tapella L, Dematteis G, Moro M, Pistolato B, Tonelli E, Vanella VV, Giustina D, La Forgia A, Restelli E, Barberis E (2022) Protein synthesis inhibition and loss of homeostatic functions in astrocytes from an Alzheimer's disease mouse model: a role for ER-mitochondria interaction. Cell Death Dis 13(10): 878.
https://doi.org/10.1038/s41419-022-05324-4

76. Chang RCC, Suen KC, Ma CH, Elyaman W, Ng HK, Hugon J (2002) Involvement of double-stranded RNA-dependent protein kinase and phosphorylation of eukaryotic initiation factor-2α in neuronal degeneration. J Neurochem 83(5): 1215−1225.
https://doi.org/10.1046/j.1471-4159.2002.01237.x

77. Picón-Pagès P, Gutiérrez DA, Barranco-Almohalla A, Crepin G, Tajes M, Ill-Raga G, Guix FX, Menéndez S, Arumí-Uría M, Vicente R (2020) Amyloid Beta-Peptide Increases BACE1 Translation through the Phosphorylation of the Eukaryotic Initiation Factor-2α. Oxid Med Cell Longevity 2020(1): 2739459.
https://doi.org/10.1155/2020/2739459

78. Paesler K, Xie K, Hettich MM, Siwek ME, Ryan DP, Schröder S, Papazoglou A, Broich K, Müller R, Trog A (2015) Limited effects of an eIF2αS51A allele on neurological impairments in the 5xFAD mouse model of Alzheimer's disease. Neural Plasticity 2015(1): 825157.
https://doi.org/10.1155/2015/825157

79. Yang W, Zhou X, Zimmermann HR, Cavener DR, Klann E, Ma T (2016) Repression of the eIF2α kinase PERK alleviates mGluR-LTD impairments in a mouse model of Alzheimer's disease. Neurobiol Aging 41: 19−24.
https://doi.org/10.1016/j.neurobiolaging.2016.02.005

80. Devi L, Ohno M (2013) Deletion of the eIF2. PLoS One 8(10): 77335.

81. Briggs DI, Defensor E, Ardestani PM, Yi B, Halpain M, Seabrook G, Shamloo M (2017) Role of endoplasmic reticulum stress in learning and memory impairment and Alzheimer's disease-like neuropathology in the PS19 and APPSwe mouse models of tauopathy and amyloidosis. ENeuro 4(4): 0025.
https://doi.org/10.1523/ENEURO.0025-17.2017

82. Johnson EC, Kang J (2016) A small molecule targeting protein translation does not rescue spatial learning and memory deficits in the hAPP-J20 mouse model of Alzheimer's disease. PeerJ 4: e2565.
https://doi.org/10.7717/peerj.2565

83. Mercado G, Castillo V, Soto P, López N, Axten JM, Sardi SP, Hoozemans JJ, Hetz C (2018) Targeting PERK signaling with the small molecule GSK2606414 prevents neurodegeneration in a model of Parkinson's disease. Neurobiol Dis 112: 136−148.
https://doi.org/10.1016/j.nbd.2018.01.004

84. Hoozemans J, Van Haastert E, Eikelenboom P, De Vos R, Rozemuller J, Scheper W (2007) Activation of the unfolded protein response in Parkinson's disease. Biochem Biophys Res Commun 354(3): 707−711.
https://doi.org/10.1016/j.bbrc.2007.01.043

85. Baek J, Mamula D, Tingstam B, Pereira M, He Y, Svenningsson P (2019) GRP78 level is altered in the brain, but not in plasma or cerebrospinal fluid in Parkinson's disease patients. Front Neurosci 13: 697.
https://doi.org/10.3389/fnins.2019.00697

86. Mutez E, Nkiliza A, Belarbi K, de Broucker A, Vanbesien-Mailliot C, Bleuse S, Duflot A, Comptdaer T, Semaille P, Blervaque R (2014) Involvement of the immune system, endocytosis and EIF2 signaling in both genetically determined and sporadic forms of Parkinson's disease. Neurobiol Dis 63: 165−170.
https://doi.org/10.1016/j.nbd.2013.11.007

87. Motawi TK, Al-Kady RH, Abdelraouf SM, Senousy MA (2022) Empagliflozin alleviates endoplasmic reticulum stress and augments autophagy in rotenone-induced Parkinson's disease in rats: Targeting the GRP78/PERK/eIF2α/CHOP pathway and miR-211-5p. Chem-Biol Interact 362: 110002.
https://doi.org/10.1016/j.cbi.2022.110002

88. Gupta S, Mishra A, Singh S (2021) Cardinal role of eukaryotic initiation factor 2 (eIF2α) in progressive dopaminergic neuronal death and DNA fragmentation: Implication of PERK: IRE1α: ATF6 axis in Parkinson's pathology. Cell Signal 81: 109922.
https://doi.org/10.1016/j.cellsig.2021.109922

89. Demmings MD, Tennyson EC, Petroff GN, Tarnowski-Garner HE, Cregan SP (2021) Activating transcription factor-4 promotes neuronal death induced by Parkinson's disease neurotoxins and α-synuclein aggregates. Cell Death Different 28(5): 1627−1643.
https://doi.org/10.1038/s41418-020-00688-6

90. Celardo I, Costa AC, Lehmann S, Jones C, Wood N, Mencacci NE, Mallucci GR, Loh SH, Martins LM (2016) Mitofusin-mediated ER stress triggers neurodegeneration in pink1/parkin models of Parkinson's disease. Cell death Dis 7(6): e2271.
https://doi.org/10.1038/cddis.2016.173

91. Liu M, Qin L, Wang L, Tan J, Zhang H, Tang J, Shen X, Tan L, Wang C (2018) α-synuclein induces

apoptosis of astrocytes by causing dysfunction of the endoplasmic reticulum-Golgi compartment. Mol Med Rep 18(1): 322−332.
https://doi.org/10.3892/mmr.2018.9002

92. Jiang P, Gan M, Ebrahim AS, Lin W-L, Melrose HL, Yen S-HC (2010) ER stress response plays an important role in aggregation of α-synuclein. Mol Neurodegen 5: 1−15.
https://doi.org/10.1186/1750-1326-5-56

93. Sun X, Aimé P, Dai D, Ramalingam N, Crary JF, Burke RE, Greene LA, Levy OA (2018) Guanabenz promotes neuronal survival via enhancement of ATF4 and parkin expression in models of Parkinson disease. Exp Neurol 303: 95−107.
https://doi.org/10.1016/j.expneurol.2018.01.015

94. Leitman J, Barak B, Benyair R, Shenkman M, Ashery U, Hartl FU, Lederkremer GZ (2014) ER stress-induced eIF2-alpha phosphorylation underlies sensitivity of striatal neurons to pathogenic huntingtin. PLoS One 9(3): e90803.
https://doi.org/10.1371/journal.pone.0090803

95. Almeida LM, Oliveira Â, Oliveira JM, Pinho BR (2023) Stress response mechanisms in protein misfolding diseases: Profiling a cellular model of Huntington's disease. Arch Biochem Biophys 745: 109711.
https://doi.org/10.1016/j.abb.2023.109711

96. Reijonen S, Putkonen N, Nørremølle A, Lindholm D, Korhonen L (2008) Inhibition of endoplasmic reticulum stress counteracts neuronal cell death and protein aggregation caused by N-terminal mutant huntingtin proteins. Exp Cell Res 314(5): 950−960.
https://doi.org/10.1016/j.yexcr.2007.12.025

97. Sbodio JI, Snyder SH, Paul BD (2016) Transcriptional control of amino acid homeostasis is disrupted in Huntington's disease. Proc Natl Acad Sci USA 113(31): 8843−8888.
https://doi.org/10.1073/pnas.1608264113

98. Xu H, Bensalel J, Capobianco E, Lu ML, Wei J (2022) Impaired restoration of global protein synthesis contributes to increased vulnerability to acute ER stress recovery in Huntington's disease. Cell Mol Neurobiol 42(8): 2757−2771.
https://doi.org/10.1007/s10571-021-01137-9

99. Espina M, Di Franco N, Brañas-Navarro M, Navarro IR, Brito V, Lopez-Molina L, Costas-Insua C, Guzmán M, Ginés S (2023) The GRP78-PERK axis contributes to memory and synaptic impairments in Huntington's disease R6/1 mice. Neurobiol Dis 184: 106225.
https://doi.org/10.1016/j.nbd.2023.106225

100. Ganz J, Shacham T, Kramer M, Shenkman M, Eiger H, Weinberg N, Iancovici O, Roy S, Simhaev L, Da'adoosh B (2020) A novel specific PERK activator reduces toxicity and extends survival in Huntington's disease models. Sci Rep 10(1): 6875.
https://doi.org/10.1038/s41598-020-63899-4

101. Ilieva EV, Ayala V, Jové M, Dalfó E, Cacabelos D, Povedano M, Bellmunt MJ, Ferrer I, Pamplona R, Portero-Otín M (2007) Oxidative and endoplasmic reticulum stress interplay in sporadic amyotrophic lateral sclerosis. Brain 130(12): 3111−3123.
https://doi.org/10.1093/brain/awm190

102. Parameswaran J, Zhang N, Braems E, Tilahun K, Pant DC, Yin K, Asress S, Heeren K, Banerjee A, Davis E (2023) Antisense, but not sense, repeat expanded RNAs activate PKR/eIF2α-dependent ISR in C9ORF72 FTD/ALS. Elife 12: e85902.
https://doi.org/10.7554/eLife.85902.sa2

103. Hetz C, Thielen P, Matus S, Nassif M, Kiffin R, Martinez G, Cuervo AM, Brown RH, Glimcher LH (2009) XBP-1 deficiency in the nervous system protects against amyotrophic lateral sclerosis by increasing autophagy. Gen Devel 23(19): 2294−2306.
https://doi.org/10.1101/gad.1830709

104. Cheng W, Wang S, Mestre AA, Fu C, Makarem A, Xian F, Hayes LR, Lopez-Gonzalez R, Drenner K, Jiang J (2018) C9ORF72 GGGGCC repeat-associated non-AUG translation is upregulated by stress through eIF2α phosphorylation. Nat Commun 9(1): 51.
https://doi.org/10.1038/s41467-017-02495-z

105. Kikuchi H, Almer G, Yamashita S, Guégan C, Nagai M, Xu Z, Sosunov AA, McKhann GM, Przedborski S (2006) Spinal cord endoplasmic reticulum stress associated with a microsomal accumulation of mutant superoxide dismutase-1 in an ALS model. Proc Natl Acad USA 103(15): 6025−6030.
https://doi.org/10.1073/pnas.0509227103

106. Sun S, Sun Y, Ling S-C, Ferraiuolo L, McAlonis-Downes M, Zou Y, Drenner K, Wang Y, Ditsworth D, Tokunaga S (2015) Translational profiling identifies a cascade of damage initiated in motor neurons and spreading to glia in mutant SOD1-mediated ALS. Proc Natl Acad USA 112(50): E6993−E7002.
https://doi.org/10.1073/pnas.1520639112

107. Oh YK, Shin KS, Yuan J, Kang SJ (2008) Superoxide dismutase 1 mutants related to amyotrophic lateral sclerosis induce endoplasmic stress in neuro2a cells. J Neurochem 104(4): 993−1005.
https://doi.org/10.1111/j.1471-4159.2007.05053.x

108. Kim H-J, Raphael AR, LaDow ES, McGurk L, Weber RA, Trojanowski JQ, Lee VM, Finkbeiner S,

Gitler AD, Bonini NM (2014) Therapeutic modulation of eIF2α phosphorylation rescues TDP-43 toxicity in amyotrophic lateral sclerosis disease models. Nat Genet 46(2): 152−160.
https://doi.org/10.1038/ng.2853

109. Wang L, Popko B, Roos RP (2011) The unfolded protein response in familial amyotrophic lateral sclerosis. Hum Mol Genet 20(5): 1008−1015.
https://doi.org/10.1093/hmg/ddq546

110. Matus S, Lopez E, Valenzuela V, Nassif M, Hetz C (2013) Functional contribution of the transcription factor ATF4 to the pathogenesis of amyotrophic lateral sclerosis. PLoS One 8(7): e66672.
https://doi.org/10.1371/journal.pone.0066672

111. Das I, Krzyzosiak A, Schneider K, Wrabetz L, D'Antonio M, Barry N, Sigurdardottir A, Bertolotti A (2015) Preventing proteostasis diseases by selective inhibition of a phosphatase regulatory subunit. Science 348(6231): 239−242.
https://doi.org/10.1126/science.aaa4484

112. Wang L, Popko B, Tixier E, Roos RP (2014) Guanabenz, which enhances the unfolded protein response, ameliorates mutant SOD1-induced amyotrophic lateral sclerosis. Neurobiol Dis 71: 317−324.
https://doi.org/10.1016/j.nbd.2014.08.010

113. Saxena S, Cabuy E, Caroni P (2009) A role for motoneuron subtype-selective ER stress in disease manifestations of FALS mice. Nat Neurosci 12(5): 627−636.
https://doi.org/10.1038/nn.2297

114. Medinas DB, González JV, Falcon P, Hetz C (2017) Fine-tuning ER stress signal transducers to treat amyotrophic lateral sclerosis. Front Mol Neurosci 10: 216.
https://doi.org/10.3389/fnmol.2017.00216

115. Marlin E, Valencia M, Peregrín N, Ferrero R, Nicolás MJ, Vinueza-Gavilanes R, Pineda-Lucena A, Artieda J, Arrasate M, Aragón T (2024) Pharmacological inhibition of the integrated stress response accelerates disease progression in an amyotrophic lateral sclerosis mouse model. Br J Pharmacol 181(3): 495−508.
https://doi.org/10.1111/bph.16260

116. Ní Fhlathartaigh M, McMahon J, Reynolds R, Connolly D, Higgins E, Counihan T, FitzGerald U (2013) Calreticulin and other components of endoplasmic reticulum stress in rat and human inflammatory demyelination. Acta Neuropathol Commun 1: 1−15.
https://doi.org/10.1186/2051-5960-1-37

117. Mháille AN, McQuaid S, Windebank A, Cunnea P, McMahon J, Samali A, FitzGerald U (2008) Increased expression of endoplasmic reticulum stress-related signaling pathway molecules in multiple sclerosis lesions. J Neuropathol Exp Neurol 67(3): 200−211.
https://doi.org/10.1097/NEN.0b013e318165b239

118. McMahon J, McQuaid S, Reynolds R, FitzGerald U (2012) Increased expression of ER stress-and hypoxia-associated molecules in grey matter lesions in multiple sclerosis. Mult Sclerosis J 18(10): 1437−1447.
https://doi.org/10.1177/1352458512438455

119. Cunnea P, Mháille AN, McQuaid S, Farrell M, McMahon J, FitzGerald U (2011) Expression profiles of endoplasmic reticulum stress-related molecules in demyelinating lesions and multiple sclerosis. Mult Sclerosis J 17(7): 808−818.
https://doi.org/10.1177/1352458511399114

120. Pernin F, Luo JXX, Cui Q-L, Blain M, Fernandes MG, Yaqubi M, Srour M, Hall J, Dudley R, Jamann H (2022) Diverse injury responses of human oligodendrocyte to mediators implicated in multiple sclerosis. Brain 145(12): 4320−4333.
https://doi.org/10.1093/brain/awac075

121. Huang H, Miao L, Liang F, Liu X, Xu L, Teng X, Wang Q, Ridder WH, Shindler KS, Sun Y (2017) Neuroprotection by eIF2α-CHOP inhibition and XBP-1 activation in EAE/optic neuritiss. Cell Death Dis 8(7): e2936.
https://doi.org/10.1038/cddis.2017.329

122. Yousuf MS, Samtleben S, Lamothe SM, Friedman TN, Catuneanu A, Thorburn K, Desai M, Tenorio G, Schenk GJ, Ballanyi K, Kurata HT, Simmen T, Kerr BJ (2020) Endoplasmic reticulum stress in the dorsal root ganglia regulates large-conductance potassium channels and contributes to pain in a model of multiple sclerosis. FASEB J 34(9): 12577−12598.
https://doi.org/10.1096/fj.202001163R

123. Lin W, Harding HP, Ron D, Popko B (2005) Endoplasmic reticulum stress modulates the response of myelinating oligodendrocytes to the immune cytokine interferon-γ. J Cell Biol 169(4): 603−612.
https://doi.org/10.1083/jcb.200502086

124. Lin W, Kunkler PE, Harding HP, Ron D, Kraig RP, Popko B (2008) Enhanced integrated stress response promotes myelinating oligodendrocyte survival in response to interferon-γ. Am J Pathol 173(5): 1508−1517.
https://doi.org/10.2353/ajpath.2008.080449

125. Chen Y, Podojil JR, Kunjamma RB, Jones J, Weiner M, Lin W, Miller SD, Popko B (2019) Sephin1, which prolongs the integrated stress response, is a promising therapeutic for multiple

sclerosis. Brain 142(2): 344−361.
https://doi.org/10.1093/brain/awy322

126. Lin W, Bailey SL, Ho H, Harding HP, Ron D, Miller SD, Popko B (2007) The integrated stress response prevents demyelination by protecting oligodendrocytes against immune-mediated damage. J Clin Invest 117(2): 448−456.
https://doi.org/10.1172/JCI29571

127. Lin W, Lin Y, Li J, Fenstermaker AG, Way SW, Clayton B, Jamison S, Harding HP, Ron D, Popko B (2013) Oligodendrocyte-specific activation of PERK signaling protects mice against experimental autoimmune encephalomyelitis. J Neurosci 33(14): 5980−5991.
https://doi.org/10.1523/JNEUROSCI.1636-12.2013

128. Hussien Y, Cavener DR, Popko B (2014) Genetic inactivation of PERK signaling in mouse oligodendrocytes: normal developmental myelination with increased susceptibility to inflammatory demyelination. Glia 62(5): 680−691.
https://doi.org/10.1002/glia.22634

129. Lin Y, Huang G, Jamison S, Li J, Harding HP, Ron D, Lin W (2014) PERK Activation Preserves the Viability and Function of Remyelinating Oligodendrocytes in Immune-Mediated Demyelinating Diseases. Am J Pathol 184(2): 507−519.
https://doi.org/10.1016/j.ajpath.2013.10.009

130. Lin W, Kemper A, Dupree JL, Harding HP, Ron D, Popko B (2006) Interferon-γ inhibits central nervous system remyelination through a process modulated by endoplasmic reticulum stress. Brain 129(5): 1306−1318.
https://doi.org/10.1093/brain/awl044

131. Way SW, Podojil JR, Clayton BL, Zaremba A, Collins TL, Kunjamma RB, Robinson AP, Brugarolas P, Miller RH, Miller SD (2015) Pharmaceutical integrated stress response enhancement protects oligodendrocytes and provides a potential multiple sclerosis therapeutic. Nat Commun 6(1): 6532.
https://doi.org/10.1038/ncomms7532

132. Zhao J, Zhao G, Lang J, Sun B, Feng S, Li D, Sun G (2024) EXPRESS: Astragaloside IV ameliorated neuroinflammation and improved neurological functions in mice exposed to traumatic brain injury by modulating the PERK-eIF2α-ATF4 signaling pathway. J Invest Med 72(7): 747-762.
https://doi.org/10.1177/10815589241261293

133. Petrov T, Underwood BD, Braun B, Alousi SS, Rafols JA (2001) Upregulation of iNOS expression and phosphorylation of eIF-2 α are paralleled by suppression of protein synthesis in rat hypothalamus in a closed head trauma model. J Neurotrauma 18(8): 799−812.
https://doi.org/10.1089/089771501316919166

134. Tan H-P, Guo Q, Hua G, Chen J-X, Liang J-C (2018) Inhibition of endoplasmic reticulum stress alleviates secondary injury after traumatic brain injury. Neur Regener Res 13(5): 827−836.
https://doi.org/10.4103/1673-5374.232477

135. Dash PK, Hylin MJ, Hood KN, Orsi SA, Zhao J, Redell JB, Tsvetkov AS, Moore AN (2015) Inhibition of eukaryotic initiation factor 2 alpha phosphatase reduces tissue damage and improves learning and memory after experimental traumatic brain injury. J Neurotrauma 32(20): 1608−1620.
https://doi.org/10.1089/neu.2014.3772

136. Sun D, Wang J, Liu X, Fan Y, Yang M, Zhang J (2020) Dexmedetomidine attenuates endoplasmic reticulum stress-induced apoptosis and improves neuronal function after traumatic brain injury in mice. Brain Res 1732: 146682.
https://doi.org/10.1016/j.brainres.2020.146682

137. Begum G, Yan HQ, Li L, Singh A, Dixon CE, Sun D (2014) Docosahexaenoic acid reduces ER stress and abnormal protein accumulation and improves neuronal function following traumatic brain injury. J Neurosci 34(10): 3743−3755.
https://doi.org/10.1523/JNEUROSCI.2872-13.2014

138. Lucke-Wold BP, Logsdon AF, Turner RC, Huber JD, Rosen CL (2017) Endoplasmic reticulum stress modulation as a target for ameliorating effects of blast induced traumatic brain injury. J Neurotrauma 34(S1): S62−S70.
https://doi.org/10.1089/neu.2016.4680

139. Liu S, Jin R, Xiao AY, Chen R, Li J, Zhong W, Feng X, Li G (2019) Induction of neuronal PI3Kγ contributes to endoplasmic reticulum stress and long-term functional impairment in a murine model of traumatic brain injury. Neurotherapeutics 16(4): 1320−1334.
https://doi.org/10.1007/s13311-019-00748-x

140. Hood KN, Zhao J, Redell JB, Hylin MJ, Harris B, Perez A, Moore AN, Dash PK (2018) Endoplasmic reticulum stress contributes to the loss of newborn hippocampal neurons after traumatic brain injury. J Neurosci 38(9): 2372−2384.
https://doi.org/10.1523/JNEUROSCI.1756-17.2018

141. Wang CF, Zhao CC, He Y, Li ZY, Liu WL, Huang XJ, Deng YF, Li WP (2019) Mild hypothermia reduces endoplasmic reticulum stress-induced apoptosis and improves neuronal functions after severe traumatic brain injury. Brain Behav 9(4): e01248.
https://doi.org/10.1002/brb3.1248

142. Wang Z-f, Gao C, Chen W, Gao Y, Wang H-c, Meng Y, Luo C-l, Zhang M-y, Chen G, Chen X-p (2019) Salubrinal offers neuroprotection through suppressing endoplasmic reticulum stress, autophagy and apoptosis in a mouse traumatic brain injury model. Neurobiol Learn Mem 161: 12−25. https://doi.org/10.1016/j.nlm.2019.03.002

143. Underwood BD (2001) Phosphorylation of eukaryotic initiation factor 2 alpha and release of cytochrome c following traumatic brain injury in the rat. Wayne State University.

144. Chen X, Mi L, Gu G, Gao X, Gao X, Shi M, Chai Y, Chen F, Yang W, Zhang J (2022) Dysfunctional endoplasmic reticulum-mitochondrion coupling is associated with endoplasmic reticulum stress-induced apoptosis and neurological deficits in a rodent model of severe head injury. J Neurotrauma 39(7−8): 560−576. https://doi.org/10.1089/neu.2021.0347

145. Wu M-Y, Gao F, Tang J-F, Shen J-C, Gao R, Dang B-Q, Chen G (2021) Possible mechanisms of the PERK pathway on neuronal apoptosis in a rat model of surgical brain injury. Am J Transl Res 13(2): 732.

146. Sun D, Gu G, Wang J, Chai Y, Fan Y, Yang M, Xu X, Gao W, Li F, Yin D (2017) Administration of tauroursodeoxycholic acid attenuates early brain injury via Akt pathway activation. Front Cell Neurosci 11: 193. https://doi.org/10.3389/fncel.2017.00193

147. Liu H, He S, Li C, Wang J, Zou Q, Liao Y, Chen R (2022) Tetrandrine alleviates inflammation and neuron apoptosis in experimental traumatic brain injury by regulating the IRE1α/JNK/CHOP signal pathway. Brain Behav 12(12): e2786. https://doi.org/10.1002/brb3.2786

148. Li L, Luo Q, Shang B, Yang X, Zhang Y, Pan Q, Wu N, Tang W, Du D, Sun X (2022) Selective activation of cannabinoid receptor-2 reduces white matter injury via PERK signaling in a rat model of traumatic brain injury. Exper Neurol 347: 113899. https://doi.org/10.1016/j.expneurol.2021.113899

149. Deng C, Yi R, Fei M, Li T, Han Y, Wang H (2021) Naringenin attenuates endoplasmic reticulum stress, reduces apoptosis, and improves functional recovery in experimental traumatic brain injury. Brain Res 1769: 147591. https://doi.org/10.1016/j.brainres.2021.147591

150. Faulkner MB, Rizk M, Bazzi Z, Dysko RC, Zhang Z (2023) Sex-Specific Effects of Buprenorphine on Endoplasmic Reticulum Stress, Abnormal Protein Accumulation, and Cell Loss After Pediatric Mild Traumatic Brain Injury in Mice. Neurotrauma Rep 4(1): 573−585.

https://doi.org/10.1089/neur.2023.0051

151. Chang L, Liu X, Chen J, Liu H, Wang G, Wang G, Liao X, Shen X (2022) Attenuation of activated eIF2α signaling by ISRIB treatment after spinal cord injury improves locomotor function. J Mol Neurosci 72: 585−597. https://doi.org/10.1007/s12031-021-01920-9

152. Logsdon AF, Turner RC, Lucke-Wold BP, Robson MJ, Naser ZJ, Smith KE, Matsumoto RR, Huber JD, Rosen CL (2014) Altering endoplasmic reticulum stress in a model of blast-induced traumatic brain injury controls cellular fate and ameliorates neuropsychiatric symptoms. Front Cell Neurosci 8: 421. https://doi.org/10.3389/fncel.2014.00421

153. Ling Y, Ramalingam M, Lv X, Niu D, Zeng Y, Qiu Y, Si Y, Guo T, Ni Y, Zhang J (2024) Human neural stem cell secretome relieves endoplasmic reticulum stress-induced apoptosis and improves neuronal functions after traumatic brain injury in a rat model. J Mol Histol 55: 329−348. https://doi.org/10.1007/s10735-024-10192-7

154. Li L, Tan H-P, Liu C-Y, Yu L-T, Wei D-N, Zhang Z-C, Lu K, Zhao K-S, Maegele M, Cai D-Z (2019) Polydatin prevents the induction of secondary brain injury after traumatic brain injury by protecting neuronal mitochondria. Neur Reg Res 14(9): 1573−1582. https://doi.org/10.4103/1673-5374.255972

155. Wang F, Zhang C, Zhang Q, Li J, Xue Y, He X, Li F (2023) Lithium ameliorates spinal cord injury through endoplasmic reticulum stress-regulated autophagy and alleviated apoptosis through IRE1 and PERK/eIF2α signaling pathways. J Neurorestoratol 11(4): 100081. https://doi.org/10.1016/j.jnrt.2023.100081

156. Lucke-Wold BP, Turner RC, Logsdon AF, Nguyen L, Bailes JE, Lee JM, Robson MJ, Omalu BI, Huber JD, Rosen CL (2016) Endoplasmic reticulum stress implicated in chronic traumatic encephalopathy. J Neurosurg 124(3): 687−702. https://doi.org/10.3171/2015.3.JNS141802

157. Kwon SK, Ahn M, Song H-J, Kang SK, Jung S-B, Harsha N, Jee S, Moon JY, Suh K-S, Do Lee S. (2015) Nafamostat mesilate attenuates transient focal ischemia/reperfusion-induced brain injury via the inhibition of endoplasmic reticulum stress. Brain Res 1627: 12−20. https://doi.org/10.1016/j.brainres.2015.09.013

158. Huang T, Zhao J, Guo D, Pang H, Zhao Y, Song J (2018) Curcumin mitigates axonal injury and neuronal cell apoptosis through the PERK/Nrf2 signaling pathway following diffuse axonal injury.

Neuroreport 29(8): 661−677.
https://doi.org/10.1097/WNR.0000000000001015

159. Rubovitch V, Barak S, Rachmany L, Goldstein RB, Zilberstein Y, Pick CG (2015) The neuroprotective effect of salubrinal in a mouse model of traumatic brain injury. Neuromol Med 17: 58−70.
https://doi.org/10.1007/s12017-015-8340-3

160. Saraswat Ohri S, Forston MD, Myers SA, Brown BL, Andres KR, Howard RM, Gao Y, Liu Y, Cavener DR, Hetman M (2024) Oligodendrocyte-selective deletion of the eIF2α kinase Perk/Eif2ak3 limits functional recovery after spinal cord injury. Glia 72(7): 1259−1272.
https://doi.org/10.1002/glia.24525

161. Sen T, Gupta R, Kaiser H, Sen N (2017) Activation of PERK elicits memory impairment through inactivation of CREB and downregulation of PSD95 after traumatic brain injury. J Neurosci 37(24): 5900−5911.
https://doi.org/10.1523/JNEUROSCI.2343-16.2017

162. Huang T-c, Luo L, Jiang S-h, Chen C, He H-y, Liang C-f, Li W-s, Wang H, Zhu L, Wang K (2021) Targeting integrated stress response regulates microglial M1/M2 polarization and attenuates neuroinflammation following surgical brain injury in rat. Cell Signal 85: 110048.
https://doi.org/10.1016/j.cellsig.2021.110048

163. Zhou W, Liang Y, Liao X, Tong L, Du W, Fu W, Tian S, Deng Y, Jiang X (2024) ISRIB improves white matter injury following TBI by inhibiting NCOA4-mediated ferritinophagy. Neurochem Intl 177: 105744.
https://doi.org/10.1016/j.neuint.2024.105744

164. Krukowski K, Nolan A, Frias ES, Grue K, Becker M, Ureta G, Delgado L, Bernales S, Sohal VS, Walter P (2020) Integrated stress response inhibitor reverses sex-dependent behavioral and cell-specific deficits after mild repetitive head trauma. J Neurotrauma 37(11): 1370−1380.
https://doi.org/10.1089/neu.2019.6827

165. Ilyin NP, Galstyan DS, Demin KA, Kalueff AV (2023) Behavioral, Genomic and Neurochemical Deficits Evoked by Neurotrauma in Adult Zebrafish (*Danio rerio*). J Evol Biochem Physiol 59(6): 2179−2195.
https://doi.org/10.1134/S0022093023060224

166. Bond S, Lopez-Lloreda C, Gannon PJ, Akay-Espinoza C, Jordan-Sciutto KL (2020) The integrated stress response and phosphorylated eukaryotic initiation factor 2α in neurodegeneration. J Neuropathol Exper Neurol 79(2): 123−143.
https://doi.org/10.1093/jnen/nlz129

167. Korneeva NL (2022) Integrated stress response in neuronal pathology and in health. Biochemistry (Moscow) 87(Suppl 1): S111−S127.
https://doi.org/10.1134/S0006297922140103

168. Romero-Ramírez L, Nieto-Sampedro M, Barreda-Manso MA (2017) Integrated stress response as a therapeutic target for CNS injuries. BioMed Res Intl 2017(1): 6953156.
https://doi.org/10.1155/2017/6953156

169. Rabouw HH, Langereis MA, Anand AA, Visser LJ, de Groot RJ, Walter P, van Kuppeveld FJ (2019) Small molecule ISRIB suppresses the integrated stress response within a defined window of activation. Proc Natl Acad Sci USA 116(6): 2097−2102.
https://doi.org/10.1073/pnas.1815767116

170. Sidrauski C, McGeachy AM, Ingolia NT, Walter P (2015) The small molecule ISRIB reverses the effects of eIF2α phosphorylation on translation and stress granule assembly. Elife 4: e05033.
https://doi.org/10.7554/eLife.05033.016

171. Cnop M, Ladriere L, Hekerman P, Ortis F, Cardozo AK, Dogusan Z, Flamez D, Boyce M, Yuan J, Eizirik DL (2007) Selective inhibition of eukaryotic translation initiation factor 2α dephosphorylation potentiates fatty acid-induced endoplasmic reticulum stress and causes pancreatic β-cell dysfunction and apoptosis. J Biol Chem 282(6): 3989−3997.
https://doi.org/10.1074/jbc.M607627200

172. Zadorozhnii PV, Kiselev VV, Kharchenko AV (2022) In Silico ADME Profiling of Salubrinal and Its Analogues. Fut Pharmacol 2(2): 160−197.
https://doi.org/10.3390/futurepharmacol2020013

173. Matsuoka M, Komoike Y (2015) Experimental evidence shows salubrinal, an eIF2α dephosphorylation inhibitor, reduces xenotoxicant-induced cellular damage. Intl J Mol Sci 16(7): 16275−16287.
https://doi.org/10.3390/ijms160716275

174. Boyce M, Bryant KF, Jousse C, Long K, Harding HP, Scheuner D, Kaufman RJ, Ma D, Coen DM, Ron D (2005) A selective inhibitor of eIF2α dephosphorylation protects cells from ER stress. Science 307(5711): 935−939.
https://doi.org/10.1126/science.1101902

175. Jeon Y-J, Kim JH, Shin J-I, Jeong M, Cho J, Lee K (2016) Salubrinal-mediated upregulation of eIF2α phosphorylation increases doxorubicin sensitivity in MCF-7/ADR cells. Mol Cells 39(2): 129−135.
https://doi.org/10.14348/molcells.2016.2243

176. Cankara FN, Kuş MS, Günaydın C, Şafak S, Bilge SS, Ozmen O, Tural E, Kortholt A (2022) The beneficial effect of salubrinal on neuroinflammation and neuronal loss in intranigral LPS-induced hemi-

Parkinson disease model in rats. Immunopharmacol Immunotoxicol 44(2): 168−177.
https://doi.org/10.1080/08923973.2021.2023174

177. Chen Y, Li B, Xu Y, Zhou T, Zhao C, Zhao J (2023) Sal003 alleviated intervertebral disc degeneration by inhibiting apoptosis and extracellular matrix degradation through suppressing endoplasmic reticulum stress pathway in rats. Front Pharmacol 14: 1095307.
https://doi.org/10.3389/fphar.2023.1095307

178. Fujita R, Ono Y (2016) eIF2α, a potential target for stem cell-based therapies. Stem Cell Invest 3: 1.
https://doi.org/10.21037/sci.2016.07.01

179. Lean G, Halloran M, Mariscal O, Jamet S, Lumb J-P, Crist C (2019) Ex vivo expansion of skeletal muscle stem cells with a novel small compound inhibitor of eIF2α dephosphorylation. bioRxiv:567461.
https://doi.org/10.1101/567461

180. Wu Y, Zhang H, Wang Y, Zhang Y, Hong Z, Wang D (2024) Sephin1 enhances integrated stress response and autophagy to alleviate myocardial ischemia-reperfusion injury in mice. Biomed Pharmacother 176: 116869.
https://doi.org/10.1016/j.biopha.2024.116869

181. Axten JM, Romeril SP, Shu A, Ralph J, Medina JR, Feng Y, Li WHH, Grant SW, Heerding DA, Minthorn E (2013) Discovery of GSK2656157: an optimized PERK inhibitor selected for preclinical development. ACS Med Chem Lett 4(10): 964−968.
https://doi.org/10.1021/ml400228e

182. Krishnamoorthy J, Rajesh K, Mirzajani F, Kesoglidou P, Papadakis A, Koromilas AE (2014) Evidence for eIF2α phosphorylation-independent effects of GSK2656157, a novel catalytic inhibitor of PERK with clinical implications. Cell Cycle 13(5): 801−816.
https://doi.org/10.4161/cc.27726

183. Dhir N, Jain A, Sharma AR, Prakash A, Radotra BD, Medhi B (2023) PERK inhibitor, GSK2606414, ameliorates neuropathological damage, memory and motor functional impairments in cerebral ischemia via PERK/p-eIF2α/ATF4/CHOP signaling. Metab Brain Dis 38(4): 1177−1792.
https://doi.org/10.1007/s11011-023-01183-w

184. Axten JM (2017) Protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK) inhibitors: a patent review (2010-2015). Exp Opin Ther Patents 27(1): 37−48.
https://doi.org/10.1080/13543776.2017.1238072

185. Yu Z-Z, Xu B-Q, Wang Y-Y, Zhang P-W, Shu Y-B, Shi Z (2023) GSK2606414 Sensitizes ABCG2-Overexpressing Multidrug-Resistant Colorectal Cancer Cells to Chemotherapeutic Drugs.

Biomedicines 11(11): 3103.
https://doi.org/10.3390/biomedicines11113103

186. Otte C, Gold SM, Penninx BW, Pariante CM, Etkin A, Fava M, Mohr DC, Schatzberg AF (2016) Major depressive disorder. Nat Revs Dis Primers 2(1): 1−20.
https://doi.org/10.1038/nrdp.2016.65

187. Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C (2021) Neuroinflammation and depression: A review. Eur J Neurosci 53(1): 151−171.
https://doi.org/10.1111/ejn.14720

188. Bhatt S, Nagappa AN, Patil CR (2020) Role of oxidative stress in depression. Drug Discov Today 25(7): 1270−1276.
https://doi.org/10.1016/j.drudis.2020.05.001

189. Mao J, Hu Y, Ruan L, Ji Y, Lou Z (2019) Role of endoplasmic reticulum stress in depression. Mol med Rep 20(6): 4774−4780.
https://doi.org/10.3892/mmr.2019.10789

190. Yoshino Y, Dwivedi Y (2020) Elevated expression of unfolded protein response genes in the prefrontal cortex of depressed subjects: Effect of suicide. J Affect Disord 262: 229−236.
https://doi.org/10.1016/j.jad.2019.11.001

191. Munshi S, Alarbi A, Zheng H, Kuplicki R, Burrows K, Figueroa-Hall L, Victor T, Aupperle R, Khalsa S, Paulus M (2024) Increased expression of ER stress, inflammasome activation, and mitochondrial biogenesis-related genes in peripheral blood mononuclear cells in major depressive disorder. Res Square (in press).
https://doi.org/10.21203/rs.3.rs-3564760/v1

192. Tang M, Liu T, Shen Y, Wang L, Xue Y, Zhao T, Xie K, Gong Z, Yin T (2023) Potential antidepressant-like effects of N-3 polyunsaturated fatty acids through inhibition of endoplasmic reticulum stress. Psychopharmacology 240(9): 1877−1889.
https://doi.org/10.1007/s00213-023-06377-9

193. Ripke S, Wray NR, Lewis CM, Hamilton SP, Weissman MM, Breen G, Byrne EM, Blackwood DH, Boomsma DI, Cichon S, Heath AC, Holsboer F, Lucae S, Madden PA, Martin NG, McGuffin P, Muglia P, Noethen MM, Penninx BP, Pergadia ML, Potash JB, Rietschel M, Lin D, Müller-Myhsok B, Shi J, Steinberg S, Grabe HJ, Lichtenstein P, Magnusson P, Perlis RH, Preisig M, Smoller JW, Stefansson K, Uher R, Kutalik Z, Tansey KE, Teumer A, Viktorin A, Barnes MR, Bettecken T, Binder EB, Breuer R, Castro VM, Churchill SE, Coryell WH, Craddock N, Craig IW, Czamara D, De Geus EJ,

Degenhardt F, Farmer AE, Fava M, Frank J, Gainer VS, Gallagher PJ, Gordon SD, Goryachev S, Gross M, Guipponi M, Henders AK, Herms S, Hickie IB, Hoefels S, Hoogendijk W, Hottenga JJ, Iosifescu DV, Ising M, Jones I, Jones L, Jung-Ying T, Knowles JA, Kohane IS, Kohli MA, Korszun A, Landen M, Lawson WB, Lewis G, Macintyre D, Maier W, Mattheisen M, McGrath PJ, McIntosh A, McLean A, Middeldorp CM, Middleton L, Montgomery GM, Murphy SN, Nauck M, Nolen WA, Nyholt DR, O'Donovan M, Oskarsson H, Pedersen N, Scheftner WA, Schulz A, Schulze TG, Shyn SI, Sigurdsson E, Slager SL, Smit JH, Stefansson H, Steffens M, Thorgeirsson T, Tozzi F, Treutlein J, Uhr M, van den Oord EJ, Van Grootheest G, Völzke H, Weilburg JB, Willemsen G, Zitman FG, Neale B, Daly M, Levinson DF, Sullivan PF (2013) A mega-analysis of genome-wide association studies for major depressive disorder. Mol Psychiatry 18(4): 497−511.
https://doi.org/10.1038/mp.2012.21

194. Mei L, Gao Y, Chen M, Zhang X, Yue W, Zhang D, Yu H (2022) Overlapping common genetic architecture between major depressive disorders and anxiety and stress-related disorders. Prog Neuro-Psychopharmacol Biol Psychiatry 113: 110450.
https://doi.org/10.1016/j.pnpbp.2021.110450

195. Lee PH, Anttila V, Won H, Feng Y-CA, Rosenthal J, Zhu Z, Tucker-Drob EM, Nivard MG, Grotzinger AD, Posthuma D (2019) Genomic relationships, novel loci, and pleiotropic mechanisms across eight psychiatric disorders. Cell 179(7): 1469−1482.
https://doi.org/10.1016/j.cell.2019.11.020

196. Li M-X, Li Q, Sun X-J, Luo C, Li Y, Wang Y-N, Chen J, Gong C-Z, Li Y-J, Shi L-P (2019) Increased Homer1-mGluR5 mediates chronic stress-induced depressive-like behaviors and glutamatergic dysregulation via activation of PERK-eIF2α. Prog Neuro-Psychopharmacol Biol Psychiatry 95: 109682.
https://doi.org/10.1016/j.pnpbp.2019.109682

197. Liu K, Qu Y, Li B, Zeng N, Yao G, Wu X, Xu H, Yan C, Wu L (2024) GRP94 in cerebrospinal fluid may contribute to a potential biomarker of depression: Based on proteomics. J Psychiatr Res 169: 328−340.
https://doi.org/10.1016/j.jpsychires.2023.11.028

198. Karaağaç M, Ak M, Kurar E, Uguz F, Kutlu S (2023) Investigation of the effects of antidepressant treatment on hippocampus and hypothalamus endoplasmic reticulum stress in chronic mild stress induced depression in rats. Turk J Clin Psychiatry 26(4): 238−247.
https://doi.org/10.5505/kpd.2023.43410

199. Xu XF, meng Shi M, ying Luo M, dan Liu D, ming Guo D, Ling C, Zhong XL, Xu Y, Cao WY (2022) Targeting perk mediated endoplasmic reticulum stress attenuates neuroinflammation and alleviates lipopolysaccharide-induced depressive-like behavior in male mice. Intl Immunopharmacol 111: 109092.
https://doi.org/10.1016/j.intimp.2022.109092

200. Miquel-Rio L, Sarriés-Serrano U, Sancho-Alonso M, Florensa-Zanuy E, Paz V, Ruiz-Bronchal E, Manashirov S, Campa L, Pilar-Cuéllar F, Bortolozzi A (2024) ER stress in mouse serotonin neurons triggers a depressive phenotype alleviated by ketamine targeting eIF2α signaling. Iscience 27(5): 109787.
https://doi.org/10.1016/j.isci.2024.109787

201. Hosak L, Hosakova J (2015) The complex etiology of schizophrenia-general state of the art. Neuroendocrinol Lett 36(7): 631−637.

202. McCutcheon RA, Marques TR, Howes OD. (2020) Schizophrenia-an overview. JAMA Psychiatry 77(2): 201−210.
https://doi.org/10.1001/jamapsychiatry.2019.3360

203. Qu M, Tang F, Wang L, Yan H, Han Y, Yan J, Yue W, Zhang D (2008) Associations of ATF4 gene polymorphisms with schizophrenia in male patients. Am J Med Genet Part B: Neuropsychiatric Genet 147(6): 732−736.
https://doi.org/10.1002/ajmg.b.30675

204. Carter CJ (2007) eIF2B and oligodendrocyte survival: where nature and nurture meet in bipolar disorder and schizophrenia? Schiz Bull 33(6): 1343−1353.
https://doi.org/10.1093/schbul/sbm007

205. Aryal S, Bonanno K, Song B, Mani D, Keshishian H, Carr SA, Sheng M, Dejanovic B (2023) Deep proteomics identifies shared molecular pathway alterations in synapses of patients with schizophrenia and bipolar disorder and mouse model. Cell Rep 42(5): 112497.
https://doi.org/10.1016/j.celrep.2023.112497

206. Ifhar LS, Ene HM, Ben-Shachar D (2019) Impaired heme metabolism in schizophrenia-derived cell lines and in a rat model of the disorder: Possible involvement of mitochondrial complex I. Eur Neuropsychopharmacol 29(5): 577−589.
https://doi.org/10.1016/j.euroneuro.2019.03.011

207. Menéndez-Valle I, Cachán-Vega C, Boga JA, González-Blanco L, Antuña E, Potes Y, Caballero B, Vega-Naredo I, Saiz P, Bobes J (2023) Differential Cellular Interactome in Schizophrenia and Bipolar Disorder-Discriminatory Biomarker Role. Antioxidants 12(11): 1948.

https://doi.org/10.3390/antiox12111948

208. Kabir Z, Che A, Fischer D, Rice R, Rizzo B, Byrne M, Glass M, De Marco Garcia N, Rajadhyaksha A (2017) Rescue of impaired sociability and anxiety-like behavior in adult cacna1c-deficient mice by pharmacologically targeting eIF2α. Mol Psychiatry 22(8): 1096−1109.
https://doi.org/10.1038/mp.2017.124

209. Wang X, Ye F, Wen Z, Guo Z, Yu C, Huang W-K, Rojas Ringeling F, Su Y, Zheng W, Zhou G (2021) Structural interaction between DISC1 and ATF4 underlying transcriptional and synaptic dysregulation in an iPSC model of mental disorders. Mol Psychiatry 26(4): 1346−1360.
https://doi.org/10.1038/s41380-019-0485-2

210. Trinh MA, Kaphzan H, Wek RC, Pierre P, Cavener DR, Klann E (2012) Brain-specific disruption of the eIF2α kinase PERK decreases ATF4 expression and impairs behavioral flexibility. Cell Rep 1(6): 676−688.
https://doi.org/10.1016/j.celrep.2012.04.010

211. Kim P, Scott MR, Meador-Woodruff JH (2021) Dysregulation of the unfolded protein response (UPR) in the dorsolateral prefrontal cortex in elderly patients with schizophrenia. Mol Psychiatry 26(4): 1321−1331.
https://doi.org/10.1038/s41380-019-0537-7

212. Anderson IM, Haddad PM, Scott J (2012) Bipol Disordr. BMJ 345: e8508.
https://doi.org/10.1136/bmj.e8508

213. Pfaffenseller B, Wollenhaupt-Aguiar B, Fries GR, Colpo GD, Burque RK, Bristot G, Ferrari P, C“esér KMM, Rosa AR, Klamt F, Kapczinski F (2014) Impaired endoplasmic reticulum stress response in bipolar disorder: cellular evidence of illness progression. Intl J Neuropsychopharmacol 17(9): 1453−1463.
https://doi.org/10.1017/S1461145714000443

214. Hayashi A, Kasahara T, Kametani M, Toyota T, Yoshikawa T, Kato T (2009) Aberrant endoplasmic reticulum stress response in lymphoblastoid cells from patients with bipolar disorder. Intl J Neuropsychopharmacol 12(1): 33−43.
https://doi.org/10.1017/S1461145708009358

215. Bengesser SA, Reininghaus EZ, Lackner N, Birner A, Fellendorf FT, Platzer M, Kainzbauer N, Tropper B, Hörmanseder C, Queissner R, Kapfhammer H-P, Wallner-Liebmann SJ, Fuchs R, Petek E, Windpassinger C, Schnalzenberger M, Reininghaus B, Evert B, Waha A (2018) Is the molecular clock ticking differently in bipolar disorder? Methylation analysis of the clock gene ARNTL. World J Biol Psychiatry 19 (Suppl 2): S21S9.

216. So J, Warsh JJ, Li PP (2007) Impaired Endoplasmic Reticulum Stress Response in B-Lymphoblasts From Patients With Bipolar-I Disorder. Biol Psychiatry 62(2): 141−147.
https://doi.org/10.1016/j.biopsych.2006.10.014

217. Ting Z (2023) Druggable causal genes of bipolar disorder identified through Mendelian Randomization analysis offer a route to intervention in integrated stress response. medRxiv: 2023.12.20.23300345.
https://doi.org/10.1101/2023.12.20.23300345

218. Asalgoo S, Jahromi G, Meftahi G, Sahraei H (2015) Posttraumatic stress disorder (ptsd): Mechanisms and possible treatments. Neurophysiology 47: 482−489.
https://doi.org/10.1007/s11062-016-9559-9

219. Wen L, Xiao B, Shi Y, Han F (2017) PERK signalling pathway mediates single prolonged stress-induced dysfunction of medial prefrontal cortex neurons. Apoptosis 22: 753−768.
https://doi.org/10.1007/s10495-017-1371-5

220. Wen L, Han F, Shi Y, Li X (2016) Role of the endoplasmic reticulum pathway in the medial prefrontal cortex in post-traumatic stress disorder model rats. J Mol Neurosci 59: 471−482.
https://doi.org/10.1007/s12031-016-0755-2

221. Koob GF, Volkow ND (2010) Neurocircuitry of addiction. Neuropsychopharmacology 35(1): 217−238.
https://doi.org/10.1038/npp.2009.110

222. Jian M, Luo Y-X, Xue Y-X, Han Y, Shi H-S, Liu J-F, Yan W, Wu P, Meng S-Q, Deng J-H (2014) eIF2α dephosphorylation in basolateral amygdala mediates reconsolidation of drug memory. J Neurosci 34(30): 10010−10021.
https://doi.org/10.1523/JNEUROSCI.0934-14.2014

223. Werner CT, Stefanik MT, Milovanovic M, Caccamise A, Wolf ME (2018) Protein translation in the nucleus accumbens is dysregulated during cocaine withdrawal and required for expression of incubation of cocaine craving. J Neurosci 38(11): 2683−2697.
https://doi.org/10.1523/JNEUROSCI.2412-17.2018

224. Huang W, Placzek AN, Viana Di Prisco G, Khatiwada S, Sidrauski C, Krnjević K, Walter P, Dani JA, Costa-Mattioli M (2016) Translational control by eIF2α phosphorylation regulates vulnerability to the synaptic and behavioral effects of cocaine. Elife 5: e12052.
https://doi.org/10.7554/eLife.12052

225. Placzek AN, Prisco GVD, Khatiwada S, Sgritta M, Huang W, Krnjević K, Kaufman RJ, Dani JA, Walter P, Costa-Mattioli M (2016) eIF2α-mediated translational control regulates the persistence of

cocaine-induced LTP in midbrain dopamine neurons. Elife 5: e17517.
https://doi.org/10.7554/eLife.17517.011

226. Placzek AN, Molfese DL, Khatiwada S, Viana Di Prisco G, Huang W, Sidrauski C, Krnjević K, Amos CL, Ray R, Dani JA (2016) Translational control of nicotine-evoked synaptic potentiation in mice and neuronal responses in human smokers by eIF2α. Elife 5: e12056.
https://doi.org/10.7554/eLife.12056.010

227. Kauer JA (2004) Learning mechanisms in addiction: synaptic plasticity in the ventral tegmental area as a result of exposure to drugs of abuse. Annu Rev Physiol 66: 447−475.
https://doi.org/10.1146/annurev.physiol.66.032102.112534

228. Melas P, Qvist J, Deidda M, Upreti C, Wei Y, Sanna F, Fratta W, Scherma M, Fadda P, Kandel D (2018) Cannabinoid modulation of eukaryotic initiation factors (eIF2α and eIF2B1) and behavioral cross-sensitization to cocaine in adolescent rats. Cell Rep 22: 2909−2923.
https://doi.org/10.1016/j.celrep.2018.02.065

229. Liu J, Yi S, Shi W, Zhang G, Wang S, Qi Q, Cong B, Li Y (2021) The pathology of morphine-inhibited nerve repair and morphine-induced nerve damage is mediated via endoplasmic reticulum stress. Front Neurosci 15: 618190.
https://doi.org/10.3389/fnins.2021.618190

230. Lin T-T, Qu J, Wang C-Y, Yang X, Hu F, Hu L, Wu X-F, Jiang C-Y, Liu W-T, Han Y (2020) Rescue of HSP70 in spinal neurons alleviates opioids-induced hyperalgesia via the suppression of endoplasmic reticulum stress in rodents. Front Cell Devel Biol 8: 269.
https://doi.org/10.3389/fcell.2020.00269

231. Biever A, Boubaker-Vitre J, Cutando L, Gracia-Rubio I, Costa-Mattioli M, Puighermanal E, Valjent E (2017) Repeated exposure to D-amphetamine decreases global protein synthesis and regulates the translation of a subset of mRNAs in the striatum. Front Mol Neurosci 9: 165.
https://doi.org/10.3389/fnmol.2016.00165

232. Chen G, Yu G, Yong Z, Yan H, Su R, Wang H (2021) A large dose of methamphetamine inhibits drug-evoked synaptic plasticity via ER stress in the hippocampus. Mol Med Rep 23(4): 278.
https://doi.org/10.3892/mmr.2021.11917

233. Xue B, Fitzgerald CA, Jin D-Z, Mao L-M, Wang JQ (2016) Amphetamine elevates phosphorylation of eukaryotic initiation factor 2α (eIF2α) in the rat forebrain via activating dopamine D1 and D2 receptors. Brain Res 1646: 459−466.
https://doi.org/10.1016/j.brainres.2016.06.027

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