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Review

Endoplasmic reticulum stress, autophagy, neuroinflammation, and sigma 1 receptors as contributors to depression and its treatment

Chika Fujii[1], Charles F. Zorumski[1, 2], Yukitoshi Izumi[1, 2, *]

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From the Contents

Abstract

The etiological factors contributing to depression and other neuropsychiatric disorders are largely undefined. Endoplasmic reticulum stress pathways and autophagy are well-defined mechanisms that play critical functions in recognizing and resolving cellular stress and are possible targets for the pathophysiology and treatment of psychiatric and neurologic illnesses. An increasing number of studies indicate the involvement of endoplasmic reticulum stress and autophagy in the control of neuroinflammation, a contributing factor to multiple neuropsychiatric illnesses. Initial inflammatory triggers induce endoplasmic reticulum stress, leading to neuroinflammatory responses. Subsequently, induction of autophagy by neurosteroids and other signaling pathways that converge on autophagy induction are thought to participate in resolving neuroinflammation. The aim of this review is to summarize our current understanding of the molecular mechanisms governing the induction of endoplasmic reticulum stress, autophagy, and neuroinflammation in the central nervous system. Studies focused on innate immune factors, including neurosteroids with anti-inflammatory roles will be reviewed. In the context of depression, animal models that led to our current understanding of molecular mechanisms underlying depression will be highlighted, including the roles of sigma 1 receptors and pharmacological agents that dampen endoplasmic reticulum stress and associated neuroinflammation.

Key Words: allopregnanolone; fluvoxamine; ketamine; neurosteroids; postpartum depression; quercetin

Introduction

Major depression is a debilitating psychiatric disorder that affects 8% of the American adult population, imposing challenges in work, education, and social life (Hammen, 2005; Kessler and Bromet, 2013; Brody et al., 2018). Depression is commonly treated using selective serotonin reuptake inhibitors (SSRIs) (Carr and Lucki, 2011), including fluoxetine (Wong et al., 2005), fluvoxamine (Sukhatme et al., 2021), and sertraline (McRae and Brady, 2001). SSRIs function through inhibiting the transporter for serotonin (or 5-hydroxytryptamine) located at synaptic membranes, thereby increasing extracellular concentrations of serotonin (Ceglia et al., 2004; Carr and Lucki, 2011). While SSRIs are prescribed based on the premise that their activity primarily results from actions on serotonin concentration, SSRIs are increasingly recognized as broad-acting drugs. For example, SSRIs can bind sigma 1 receptors (S1Rs), thereby exerting anti-inflammatory effects (Ishima et al., 2014). SSRI-induced activation of the tropomyosin receptor kinase B (trkB) neurotrophin receptors (Casarotto et al., 2021) has been shown to have an anti-depressive effect by promoting brain-derived neurotrophic factor activity. Certain SSRIs have also been repurposed during the COVID-19 pandemic (Mahdi et al., 2022; Nykamp et al., 2022), based on their ability to inhibit viral replication and dampen inflammatory reactions via S1Rs (Friesland et al., 2013).

Endoplasmic reticulum (ER) stress is a critical component of neuroinflammation and the pathogenesis of depression and other neurocognitive illnesses, which requires autophagy as an anti-inflammatory program to resolve the inflammation (**Figure 1**). Inflammatory mediators can be dampened by treatment with nonsteroidal anti-inflammatory drugs, among other strategies. Using a seesaw as an analogy, autophagy and its mediators could be thought of as counterbalances to neuroinflammation (**Figure 1**). Besides the impact on serotonin, SSRIs are thought to play important roles in

[1]Department of Psychiatry, Washington University School of Medicine, St. Louis, MO, USA; [2]Taylor Family Institute for Innovative Psychiatric Research, Washington University School of Medicine, St. Louis, MO, USA

*__Correspondence to:__ Yukitoshi Izumi, MD, PhD, izumiy@wustl.edu.

https://orcid.org/0000-0002-5596-1031 (Yukitoshi Izumi)

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the induction of autophagy and preventing or reversing inflammation in the nervous system. This review will elaborate upon studies that led to our current understanding of neuroinflammatory processes involving ER stress and mechanisms induced to resolve inflammation, including autophagy.

Search Strategy and Selection Criteria

Our review of the literature used PubMed as the search engine with search terms including ER stress, autophagy, STING, SSRI, sertraline, fluvoxamine, fluoxetine, S1R, trkB, GRP78, ISRIB, quercetin, salubrinal. We also used the Google search engine for glyphosate use and history. All years were chosen in the search.

Endoplasmic Reticulum Stress, Autophagy and Neuroinflammation

Neurotoxic stress in the nervous system has been demonstrated to involve the ER stress pathway and the resulting unfolded protein response (UPR) (Fujii et al., 2021). Triggers of ER stress and the UPR have been attributed to disturbed protein homeostasis (Costa-Mattioli and Walter, 2020). In the context of neuroinflammation, ER stress could also be induced by external factors such as toxins and byproducts of the metabolism of toxins such as ethanol and acetaldehyde (Fujii et al., 2021). ER stress is a well-established phenomenon that is characterized by the induction of inositol requiring enzyme 1 (IRE1), protein kinase RNA-activated-like ER kinase (PERK), and activating transcription factor 6 (ATF6) (Costa-Mattioli and Walter, 2020), followed by downstream signaling cascades in the ER (**Figure 2**). The overall outcome of the UPR is to facilitate protein folding and downregulate protein translation. Specifically, PERK is a specialized kinase that phosphorylates the translation initiation factor eIF2α (phosphorylated-eIF2α, or p-eIF2α). IRE1α triggers translocation of XBP-1, resulting in increased expression of genes that facilitate protein folding. ATF6 resolves ER stress through promoting molecular chaperone activity (Costa-Mattioli and Walter, 2020). The dissection of the mechanisms underlying ER stress and the UPR was facilitated by the use of inhibitors of the ER stress pathway. The integrated stress response inhibitor (ISRIB) is a small molecule that blocks the ER stress pathway specifically at the PERK signaling step (Sidrauski et al., 2013).

ER stress is also linked to autophagy. Upon triggering ER stress, the resulting UPR initiates autophagy, which starts with IRE1 activation, followed by c-Jun N-terminal kinase signaling, and the formation of autophagosomes (Ogata et al., 2006). The activation of XBP1 by IRE1 results in the induction of BECLIN-1, a key contributor to autophagy (Xu and Qin, 2019) and a marker used to determine autophagy activation (Margariti et al., 2013). ATF4, one of the ER stress-induced factors, plays a role in linking ER stress to autophagy. C/EBP homologous protein (CHOP) is a molecule that acts downstream of ATF4 (Hu et al., 2019). Upon induction of ER stress or amino acid depletion, ER stress kinases PERK and general control nonderepressible 2 phosphorylate eIF2α. The activity of CHOP results in the activation of the growth arrest and DNA damage-inducible protein (GADD34), which dephosphorylates p-eIF2α (Marciniak et al., 2004). Alternatively, CHOP can trigger apoptosis mediated by caspases (Oyadomari and Mori, 2004).

Autophagy is a process by which intracellular materials are engulfed in a double-membrane structure and degraded by the lysosome, with implications for a wide range of diseases including those that affect the nervous system (Nakatogawa, 2020). As noted above, ER stress is linked to autophagy via different pathways. ATF4 and CHOP mediate the downstream alteration of the transcriptional program, which results in increased expression of autophagy genes (B'chir et al., 2013). Autophagy activation results in the formation of autophagosomes, which are membrane structures that form an enclosure around target intracellular materials. Although the detailed mechanisms of the autophagosome formation are not fully understood, the formation of the autophagosome can be determined by measuring levels of hallmark molecules such as p62/sequestosome-1 (SQSTM1) (Pankiv et al., 2007). SQSTM1 has a ubiquitin-binding domain and acts as a scaffold that recruits ubiquitinated proteins for degradation in the lysosome (Pankiv et al., 2007). Microtubule-associated protein 1A/1B-light chain 3 (LC3) is another commonly used molecule that provides a readout of autophagy activity (Tanida et al., 2008). During the formation of the autophagosome, the cytosolic form of LC3 (LC3-I) undergoes conjugation to phosphatidylethanolamine to form the engulfed form of LC3 (LC3-II) (Tanida et al., 2008). Upon fusion of the autophagosome with the lysosome and formation of the autolysosome, hydrolase enzymes degrade ubiquitinated proteins together with LC3-II (Tanida et al., 2008).

Several inflammatory processes are closely associated with neuroinflammation and neurodegeneration. NOD-, LRR- and pyrin domain-containing protein 3 is a well-established sensor of danger signals and results in the release of cytokines interleukin (IL)-1β and IL-18 (Lu et al., 2012; Swanson et al., 2019). A recent study reported on the role of the cGAS-STING pathway, a DNA-sensing mechanism, in triggering neuroinflammation and neurodegeneration (Gulen et al., 2023). Disturbances in mitochondria and the resulting release of mitochondrial DNA into the cytosol trigger cGAS activity. Initiation of cGAS in mice shifts the transcriptional program towards an aging-associated state and cognitive decline in mice (Gulen et al., 2023). A small molecule inhibitor of STING, BB-Cl-amidine, prevents activation of the STING pathway and the resulting induction of a pro-inflammatory program mediated by the transcription factor, nuclear factor-κB (Humphries et al., 2023). The cGAS-STING pathway induces type I interferons and is implicated in depression treatment (Pinto and Andrade, 2016). Furthermore, interferon treatment is associated with a 30–70% risk of treatment-emergent depression (Pinto and Andrade, 2016).

Recent evidence points to an important role of neurosteroids in exerting a neuroprotective role through inducing autophagy. Allopregnanolone (AlloP) is a neurosteroid that can protect retinal ganglion cells via effects on $GABA_A$ receptors in models of glaucoma. AlloP also reduced axonal swelling in the nerve fiber layer in a manner dependent on $GABA_A$ receptor

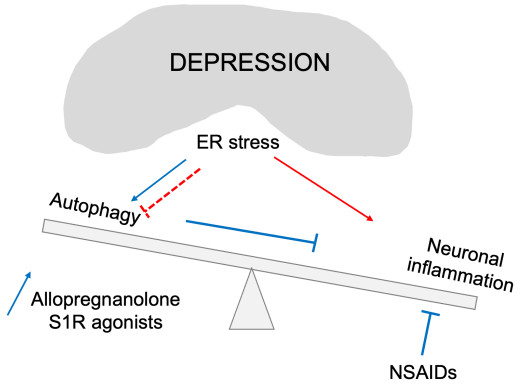

Figure 1 | Interactions among ER stress, autophagy, and neuroinflammation as contributors to depression.
Different molecular processes interact with one another in the progression and resolution of depression resulting from ER stress. Neuroinflammation could be mitigated through the use of NSAIDs and inducing autophagy by allopregnanolone and S1R agonists. Created with Microsoft PowerPoint. ER: Endoplasmic reticulum; NSAIDs: nonsteroidal anti-inflammatory drugs; S1R: sigma-1 receptor.

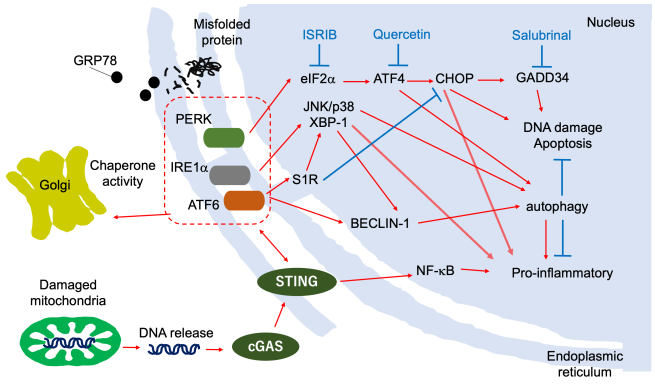

Figure 2 | Interactions among ER stress, S1R, and STING within ER to promote autophagy and neuroinflammation.
Molecular players involved in ER stress (PERK, IRE1α, ATF6) and the cGAS-STING pathways converge on S1R, BECLIN-1, and NF-κB, with different impacts on the downstream autophagy and inflammation pathways. Created with Microsoft PowerPoint. ATF4: Activating transcription factor 4; ATF6: activating transcription factor 6; cGAS: cyclic GMP-AMP synthase; CHOP: CCAAT-enhancer-binding protein homologous protein; GRP78: glucose-regulated protein 78; eIF2α: eukaryotic translation initiation factor 2 alpha; ER: endoplasmic reticulum; GADD34: growth arrest and DNA damage-inducible protein; IRE1α: inositol requiring enzyme 1 alpha; ISRIB: integrated stress response inhibitor; JNK: Jun N-terminal kinase; NF-κB: nuclear factor kappa B; PERK: protein kinase RNA-activated-like ER kinase; S1R: sigma-1 receptor; XBP-1: X-box binding protein 1.

activation (Ishikawa et al., 2014, 2021). In addition, AlloP was also shown to induce autophagy, as evidenced by changes in the autophagy markers LC3B-II and SQSTM1, and autophagy contributed significantly to retinoprotective effects. How AlloP stimulates autophagy remains uncertain. Surprisingly, the enantiomer of AlloP (ent-AlloP) was also found to protect the retina from pressure-mediated degeneration via autophagy (Ishikawa et al., 2022). Similar to AlloP, ent-AlloP attenuated granule cell damage and axonal swelling in the nerve fiber layer. However, a distinguishing feature of ent-AlloP is that it does not modulate $GABA_A$ receptors (Wittmer et al., 1996; Covey et al., 2023). Consistent with this, treatment with a $GABA_A$ receptor antagonist did not affect the impact of ent-AlloP, in contrast to natural AlloP (Ishikawa et al., 2022). These observations strongly suggest that the effects of the neurosteroids on autophagy can be independent of GABA receptors. Similar to AlloP, ent-AlloP can induce the formation of autophagosomes and degenerative autophagic vacuoles. Interestingly, ent-AlloP induced a greater number of autophagosomes and degenerative autophagic vacuoles than natural AlloP, suggesting that ent-AlloP may be a more effective autophagy inducer than AlloP. The ability of ent-AlloP to induce autophagy was further confirmed by treatment with methyladenine, which inhibits autophagic flux, where treating with ent-AlloP and methyladenine simultaneously resulted in increased damage to cells in the ganglion cell layer. The study on the neuroprotective role of AlloP and ent-AlloP was further extended to an *in vivo* model of ocular hypertension. Although intravitreal injection of AlloP and ent-AlloP did not reduce intraocular pressure, both steroids were still able to reduce apoptosis, loss of retinal ganglion cells, and axonal loss. Induction of autophagy, as indicated by the increase in autophagosomes and degenerative autophagic vacuoles, was also confirmed upon increasing the intraocular pressure. Furthermore, a single injection of either AlloP or ent-AlloP prevented pressure-induced changes in the scotopic threshold response, indicating preservation of retinal function as well as structure (Ishikawa et al., 2022). Autophagy has also been implicated in providing an anti-inflammatory function in other neurodegenerative disease models. In the case of Alzheimer's disease, reduction in autophagy resulted in stimulation of microglia, resulting in increased release of pro-inflammatory cytokines, IL-1β, and IL-18 (Houtman et al., 2019). Inhibition of autophagy in microglia also resulted in exacerbation of neuroinflammation in a Parkinson's disease mouse model (Tu et al., 2021).

Although autophagy often has an anti-inflammatory function, it could also be harmful depending on the context. For example, ATG5 reduction increases the interferon response upon viral infection (Jounai et al., 2007), thereby promoting an anti-inflammatory state in the host cell. However, viruses can hijack the double-membraned autophagosome and employ it as a site for replication, as a mechanism to protect themselves from the host's antiviral molecules (Choi et al., 2018). This could make autophagy detrimental for the host, since viruses replicate more effectively with the help of autophagy.

Endoplasmic Reticulum Stress-Derived Neuroinflammation in the Context of Major Depressive Disorder

Historically, a diagnosis of major depressive disorder (MDD) depends on an assessment of patients' physiological disturbances in sleep and appetite as well as mood changes including sadness, irritability, and suicidal thoughts (Belmaker and Agam, 2008). The molecular mechanisms that lead to the development and progression of MDD remain to be determined, but recent evidence suggests that ER stress could be linked to MDD, both in studies involving post-mortem analysis of patient samples and in animal models of MDD. Patients who died by suicide have been shown to have increased expression of the ER stress proteins, including GRP78 (Bown et al., 2000). Importantly, the expression of

ER stress factors is increased in the dorsolateral prefrontal cortex in patients experiencing MDD (Yoshino and Dwivedi, 2020). Not only are ER stress genes upregulated in the brains of MDD patients, but also immune cells. For example, MDD patients in a community-based health study have been shown to have increased ER stress gene expression by real-time polymerase chain reaction in leukocyte samples (Nevell et al., 2014). A genome-wide association study also found increased expression levels of ER stress-associated genes in MDD patients' immune cells, including macrophages and monocytes (Zhang et al., 2022).

Animal models have also been used to investigate inflammatory processes and ER stress in the context of MDD. The chronic restraint stress model is a well-established system for inducing depression-like symptoms in rats (Wang et al., 2017). In the hippocampus of restrained rats, expression of UPR genes and toll-like receptors 2, 4, 7, and 9, which are mediators of innate immunity, are significantly elevated. This suggests that UPR is an integrated part of neuroinflammation in depression (Timberlake et al., 2018). Hippocampal apoptosis and cognitive impairment resulting from restraint stress have also been shown to mediate ER stress, and the neurodegenerative effect of ER stress was reversed upon treatment with salubrinal, an ER stress inhibitor (Zhang et al., 2014). Furthermore, an increase in ER stress markers, including GRP78 and CHOP, were observed, implicating the involvement of the ER stress pathway (Zhang et al., 2014). In the mouse restraint stress model, serum and hippocampal caspase-1-IL-1β levels were increased with a negative correlation between caspase-1 levels and symptoms, suggesting the involvement of neuroinflammation in the hippocampus in the development of depression-like behavior (Li et al., 2023a). Physical pain is often associated with depression and pain induced by nerve ligation in rats has been shown to induce ER stress markers, including ATF-6 (Seo et al., 2023). Besides MDD, a research model for post-traumatic stress disorder has also been reported to show increases in ER stress gene induction (Li et al., 2015; Kong et al., 2017). These findings imply that ER stress responses might be a common response mechanism shared between different types of stressful events.

Besides physically induced stressors, inflammatory processes could also contribute to the development of depressive symptoms. For example, cytokines have been thought to contribute to depressive symptoms in patients receiving cytokine therapy as a treatment (Capuron and Dantzer, 2003). Furthermore, the severity of depression in COVID-19 survivors has been found to be proportional to the level of systemic inflammation (Mazza et al., 2020, 2021). Lipopolysaccharide (LPS), a potent stimulator of the innate immune system, has been linked to the induction of depression-like symptoms in rodents (Yirmiya, 1996; O'Connor et al., 2009; Ali et al., 2020). LPS-induced depressive symptoms are characterized by a reduction in the consumption of saccharine, a rewarding stimulus (Yirmiya, 1996), as well as increased inactivity during the forced swim test and tail suspension test (O'Connor et al., 2009). LPS treatment increased levels of the ER stress marker, PERK, in the hippocampus of mice exhibiting depression symptoms. The depression symptoms could be reversed upon inhibiting the PERK-mediated ER stress through treatment with ISRIB, which resulted in a reduction in pro-inflammatory cytokine release from microglia (Xu et al., 2022).

In recent studies, we examined the effects of LPS on synaptic function and plasticity in the CA1 region of the rat hippocampus and observed that brief (10–15 minutes) exposures of hippocampal slices to 1–10 μg/mL LPS had little effect on basal synaptic transmission but prevented the induction of long-term potentiation (LTP), a cellular model of learning and memory. LPS-induced LTP inhibition involves microglia (York et al., 2021), and we found that the inhibition of LTP by LPS was overcome by preincubation of slices with minocycline, an inhibitor of microglial activation. Effects of LPS on LTP were mimicked by exogenous 25-hydroxycholesterol and absent in mice deficient in cholesterol 25 hydroxylase, the key enzyme in 25-hydroxycholesterol synthesis, indicating the involvement of cholesterol metabolism in LPS-mediated neuronal impairment (Izumi et al., 2021). LTP inhibition by LPS also involved a form of metaplasticity resulting from untimely activation of N-methyl-D-aspartate receptors that triggers neuronal stress responses (Zorumski and Izumi, 2012). In humans, injection of LPS in healthy volunteers alters long-term memory performance, decreases mood, and raises cytokines in plasma (Grigoleit et al., 2011). Moreover, several lines of evidence suggest that LPS-mediated microglial activation and cytokine release in animal experiments are overcome by antidepressants including fluoxetine, paroxetine, and citalopram (Mariani et al., 2022). Additionally, neuroinflammation induced by LPS is ameliorated by rapamycin, an autophagy inducer (Ye et al., 2020).

Besides binding toll-like receptor 4, LPS has other mechanisms of action that could contribute to depressive-like behaviors. LPS can stimulate indoleamine 2,3-dioxygenase (IDO), which leads to the degradation of tryptophan and changes in serotonin levels (O'Connor et al., 2009). Either inhibition of cytokine release or antagonizing IDO could ameliorate depressive symptoms. It is thought that increased IDO enzymatic activity results in a decrease in tryptophan concentration, thereby interfering with the synthesis of serotonin (Booij et al., 2003; O'Connor et al., 2009).

In addition to the triggers of inflammation described above, studies show the involvement of the metabotropic glutamate receptor subtype 5 (mGluR5), which is a G-protein coupled receptor that regulates neuronal cell excitability in the central nervous system (Niswender and Conn, 2010). mGluR5 has been shown to reduce anxiety-like behavior induced by the restraint stress model (Li et al., 2023b). Conversely, knocking down mGluR5 resulted in the exacerbation of anxiety-like behavior in mice (Li et al., 2023b). mGluR5 in non-neuronal cells has also been associated with depression in animal models. For example, removing mGluR5 in astrocytes has been shown to result in depressive-like symptoms in mice (Liu et al., 2022). Inhibiting mGluR5 in BV-2 microglia cells results in the upregulation of ER stress genes (Chantong et al., 2014). In contrast to the protective role of mGluR5 reported in several studies, others show that mGluR5 stimulation can have a pro-inflammatory effect. For example, Gu et al. (2022)

observed an increase in ER stress and DNA damage upon stimulating mGluR5, an effect that is mediated by the NMDA receptor. In the context of MDD, stimulating mGluR5 resulted in the induction of PERK signaling, leading to the development of depression-like behavior in mice (Li et al., 2019). In a rat model of post-traumatic stress disorder, inhibition of mGluR5 was found to alleviate stress behavior (Cheng et al., 2023).

Association between Depression and Autophagy

Postpartum depression is characterized by emotional instability and irritability among women following child birth (Miller, 2002). Extracellular RNA communication mediated by RNA enclosed in extracellular vesicles plays a critical role throughout pregnancy. A study that surveyed extracellular vesicles before and after pregnancy revealed that women who went on to develop postpartum depression also had an altered gene expression profile in their RNA in extracellular vesicles (Osborne et al., 2022). Among the genes that were differentially expressed, autophagy-related genes were found to be depressed whereas the expression of other genes known to be negatively regulated by autophagy was upregulated (Osborne et al., 2022). Interestingly, the sources of the extracellular vesicles were shown to be derived from monocytes and macrophages (Osborne et al., 2022). Antidepressants including fluoxetine accumulate ceramide in the ER, which then activates phosphatase 2A to promote autophagy (Gulbins et al., 2018). The reversal of depression-like behaviors in stressed mice by fluoxetine is accompanied by the upregulation of autophagy-associated proteins (Tan et al., 2018). Social defeat stress in mice results in depressive-like symptoms. Repeated social stress induces the initial activation of autophagy in the prefrontal cortex. Furthermore, enhanced autophagic flux was only observed in resilient mice, implying a relationship between autophagy and the symptoms (Sakai et al., 2022).

Pharmacological Agents with an Anti-Inflammatory Function in the Context of Depression-Like Symptoms

An increasing number of studies have described synthetic and naturally occurring pharmacological agents that could reduce LPS-induced inflammation linked to depression-like symptoms. Sodium phenylbutyrate and edaravone have been shown to reduce LPS-induced behavioral abnormalities such as anxiety and depression-like symptoms in mice (Jangra et al., 2016, 2017). Additionally, mice that were administered with sodium phenylbutyrate or edaravone experienced improvements in spatial learning tasks and memory formation (Jangra et al., 2017). Ketamine, a dissociative anesthetic and rapidly acting antidepressant, has been shown to reduce inflammation in a depression model induced by LPS, through facilitating autophagic flux (Wu et al., 2022). Esketamine, the more active enantiomer of ketamine at N-methyl-D-aspartate receptors, is approved for therapeutic use against depression (Kaur et al., 2021) and has been found to dampen inflammation in an LPS-induced model of MDD (Jiang et al., 2022). Similarly, melatonin has been shown to alleviate MDD symptoms through inducing autophagy in a mouse model of MDD induced by LPS (Ali et al., 2020). In the context of cognitive decline associated with aging, growth differentiation factor 11 has been demonstrated to reduce depression-like symptoms in aged mice through promoting autophagy in the hippocampus (Moigneu et al., 2023).

Besides synthetic agents, quercetin is a naturally occurring flavonoid that is present at high levels in certain foods, including onions and red-leaf lettuce (Nishimuro et al., 2015). The molecular mechanism of quercetin involves inhibition of the ER stress factor, ATF4 (Ohta et al., 2011). It is important to note the complexity of the effects of quercetin, as other ER stress molecules including XBP-1 and GADD34 are increased in the presence of quercetin (Ohta et al., 2011). In addition to its neuroprotective role in neurocognitive diseases such as Alzheimer's disease (Nakagawa and Ohta, 2019), quercetin has also been shown to reverse the effects of sepsis induced by intraperitoneal injection of LPS in mice (Liao and Lin, 2015). While LPS-induced sepsis involves triggering systemic inflammation, administering quercetin either prophylactically or therapeutically resulted in an increase in the production of the anti-inflammatory cytokine, IL-10, by macrophages residing in the peritoneum (Liao and Lin, 2015). Importantly, quercetin has been shown to have antidepressant-like activity in various animal models (Herrera-Ruiz et al., 2011; Mehta et al., 2017; Guan et al., 2021; Ma et al., 2021; Wang et al., 2021) in both mice (Samad et al., 2018) and rats (Şahin et al., 2020). The antidepressant effect of quercetin could be attributed to the reduction in inflammatory markers (Khan et al., 2019) and restoration of protein expression in the hippocampus (Fang et al., 2020).

Function and Mechanism of Sigma-1 Receptors in the Context of Neuronal Cell Physiology

While different pharmacological agents can ameliorate inflammation by directly acting on autophagy as described earlier, other studies highlight the important role of modulation of intracellular mechanisms such as S1R signaling in reducing inflammation and cell stress. The S1R is a chaperone protein that is situated at the interface of the ER and mitochondria and regulates signaling mediated by calcium ions (Hayashi and Su, 2007). S1Rs are expressed in cells comprising the nervous system and have been linked to neurodegenerative diseases such as Alzheimer's disease and amyotrophic lateral sclerosis (Ryskamp et al., 2019). At the molecular level, S1Rs are involved in the transfer of calcium ions from the ER to the mitochondria (Hayashi et al., 2000). Mechanistically, S1Rs stabilize IRE1 upon induction of ER stress (Mori et al., 2013). In cardiomyocytes, S1R ablation decreases IRE-1 phosphorylation and induces CHOP expression for cellular toxicity, suggesting a pivotal role of S1Rs in controlling ER stress (Alam et al., 2017). In ER stress, S1Rs are upregulated by ATF4 (Mitsuda et al., 2011). The *atf4* gene overexpression is reported in the retina of S1R knockout mice, and S1R knockout results in blindness in mice (Ha et al., 2014). Several studies have shown that S1R signaling plays a critical role in controlling ER stress (Omi et al., 2014; Morihara et al., 2018; Zhao et al., 2019).

Several studies have investigated the role of S1Rs during autophagy. Yang et al. (2019) focused on mitophagy, a form of autophagy specific to mitochondria. Retinal tissue isolated from mice with genetic ablation of the S1R was found to have impaired mitochondrial clearance (Yang et al., 2019). This result was further confirmed in NSC34 cells that were genetically modified by CRISPR-Cas9 at the locus encoding S1R. To determine the substage of autophagy affected by the lack of S1R, the level of SQSTM1 was measured in S1R-deficient versus wild-type cells, and no difference in SQSTM1 levels were observed. This implies that SQSTM1, which is found in autophagosomes, is not degraded and that the enclosure of the autophagosome is not disrupted in the absence of S1R. Upon measuring the levels of LC3-II in the presence or absence of a lysosome blocker, the authors observed a reduction in the turnover rate of the LC3-II, which suggests that the lysosomal degradation step is likely affected in S1R-deficient cells (Yang et al., 2019).

While S1Rs may be important for lysosomal degradation, they also may play a role in initiating autophagy. Christ et al. investigated the impact of an agonist of the S1R, tetrahydro-N,N-dimethyl-2,2-diphenyl-3-furanmethanamine hydrochloride (ANAVEX2-73), in human cell line cells, HeLa and HEK293, or *C. elegans* with a mutation that results in flaccid paralysis (Christ et al., 2019; Moerman et al., 1982). Upon treatment with ANAVEX2-73, autophagic flux was enhanced in both human cells and *C. elegans*. Furthermore, a lower fraction of mutant *C. elegans* animals experienced paralysis (Christ et al., 2019). Pericytes are cells situated within the capillaries throughout the body and play an important role in establishing the blood-brain barrier and the blood vasculature supporting the brain (Brown et al., 2019). To study the impact of the S1R in the context of ischemic stroke, Zhang et al. (2020) developed a model for ischemic stroke by photothrombotic middle cerebral artery occlusion. The S1R has been shown to play a role in maintaining pericyte integrity, since mice deficient in S1R were found to experience pericyte loss. The mechanism leading to the loss of pericytes is speculated to involve cross-talk between autophagy and apoptosis.

The role of S1Rs in inducing autophagy has also been demonstrated in models of Wolfram syndrome. Wolfram syndrome is a complex neurodegenerative disorder caused by a mutation in the Wolfram syndrome 1 (*WFS1*) gene encoding Wolframin, a transmembrane protein in the ER membrane (Crouzier et al., 2022). Wolfram syndrome is also associated with high psychiatric co-morbidity including anxiety and depression. The S1R could be selectively activated using the agonist PRE-084 (Su et al., 1991; Skuza and Rogóz, 2009; Motawe et al., 2020; Borbély et al., 2022). Upon enhancing S1R activity with PRE-084, or S1R overexpression, Crouzier et al. (2022) found improvements in defects observed in behavioral tests performed on *WFS1* mutant mice and zebrafish. Since *WFS1* has been associated with alterations in autophagy (Cagalinec et al., 2016), Crouzier et al. (2022) interrogated the impact of S1R on autophagy and found accumulation of LC3-II in neuronal cells in the hippocampus and cortex in mice, implying that the autophagy process is impaired in mice deficient in *WFS1*. The involvement of S1R in mediating the protective effect of autophagy was confirmed by treating fibroblasts derived from Wolfram syndrome patients with the PRE-084 agonist and observing increased autophagic flux measured by the levels of LC3-II (Crouzier et al., 2022). Improvements in behavioral defects in animal model experiments demonstrate that the impact of S1R agonist occurs at therapeutic levels (Crouzier et al., 2022). Ligands for the S1R include antipsychotic medications such as chlorpromazine and haloperidol (Milenina et al., 2022), gonadal and adrenal steroids (Su et al., 1988), as well as certain drugs of abuse such as cocaine (Sharkey et al., 1988). Importantly, S1R ligands can impact neuronal cells, since S1R agonists and antagonists have been shown to modulate GABAA receptors (Voronin et al., 2023). NMDA receptors are even more affected by S1R than GABARs. S1R enhances NMDA receptor functions with bell-shaped dose-response curves (Bergeron et al., 1995; Liang and Wang, 1998) and enhances NMDA receptor-mediated LTP (Martina et al., 2007), but also prevents calcium-induced toxicity by perturbing interactions between NMDA receptors and neuronal nitric oxide synthase (Aarts et al., 2002; Yang et al., 2010). The importance of S1R interactors in the context of neurocognitive disease is supported by animal model experiments in the studies described above.

As described earlier, some SSRIs bind S1Rs and promote anti-inflammatory responses. We investigated the impact of SSRIs in the context of neuroinflammation and LTP (Izumi et al., 2023). Inhibitory actions of LPS on LTP are prevented by pretreatment with fluvoxamine and fluoxetine via overlapping but distinct mechanisms that result in local synthesis of 5α-reduced neurosteroids including AlloP. AlloP has anti-inflammatory properties via effects on Toll-like receptors (including toll-like receptor 4) and is an effective treatment for post-partum depression (Balan et al., 2021, 2023). In addition to brexanolone, an intravenous form of alloP, zuranolone is an orally active neuroactive steroid that is now approved by FDA for treating post-partum depression (Rubin, 2023). While the effects of both SSRIs involve neurosteroid synthesis, only fluvoxamine requires activation of S1Rs. How fluoxetine promotes neurosteroid synthesis is not certain, but fluoxetine is a weak S1R agonist and S1Rs appear to promote neurosteroidogenesis by interacting with voltage-dependent anion channel 2 and steroidogenic acute regulatory protein, resulting in the movement of cholesterol from ER to mitochondria for synthesis of pregnenolone, the first step in neurosteroid synthesis (Marriott et al., 2012). Among SSRIs, fluvoxamine is the most potent S1R ligand (Ishima et al., 2014) and activates the receptor triggering downstream effects, including neurosteroidogenesis. To further test the hypothesis that prevention of LTP inhibition is mediated by triggering the S1R, we used the S1R antagonist, NE-100, which blocked the protective effect of fluvoxamine, but did not alter the protective effects of fluoxetine. Sertraline is another SSRI, but acts as an inverse agonist (Ishima et al., 2014; Hashimoto, 2015; Matsushima et al., 2019), in contrast to fluvoxamine or fluoxetine. Sertraline exhibited markedly different effects than fluvoxamine and fluoxetine. When administered alone at a low micromolar concentration, sertraline inhibited LTP induction by a mechanism that was reversed by either the selective S1R

agonist PRE-084 or S1R antagonist NE-100 (Izumi et al., 2023). These latter results are consistent with prior observations indicating that sertraline functions as an S1R inverse agonist (Ishima et al., 2014; Hashimoto, 2015; Matsushima et al., 2019). The inhibitory actions of LPS on LTP are overcome by sertraline when it is combined with the S1R agonist, PRE-084.

Conclusions and Future Directions

While the detailed molecular mechanisms underlying the clinical syndrome of major depression and other psychiatric disorders remain to be defined, findings from recent studies indicate the involvement of ER stress as an important mechanism in the development of neuroinflammation and progression of mental illnesses. Although SSRIs have traditionally been thought to exert their therapeutic effect through modulating serotonin levels, more recent studies indicate that SSRIs can alleviate inflammation by previously under-appreciated mechanisms, including a critical role of autophagy in mediating anti-inflammatory and anti-stress effects. In addition to serotonin transporters, other receptors, such as S1Rs, are being recognized as a link between neuroinflammation and autophagy. It is expected that future studies will elucidate further mediators of neuroinflammation that could be used as therapeutic targets against neurocognitive diseases.

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P-Reviewers: Andersen N, Ishikawa M; C-Editors: Zhao M, Sun Y, Qiu Y;
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