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MINI REVIEW

Application of Proteostasis Regulators in $GABA_A$ Receptor Misfolding Diseases

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Abstract

Protein homeostasis (proteostasis) relies on an orchestrated balance between protein synthesis, folding, assembly, trafficking, and degradation to ensure normal physiological function. Protein misfolding diseases often arise as a result of deficient proteostasis. Proteostasis regulators enhance the proteostasis network capacity to correct the folding, thus promoting the trafficking and restoring the function of disease-associated variants. Here, we focus on the application of proteostasis regulators to promote the folding, assembly, and trafficking of pathogenic γ-aminobutyric acid type A ($GABA_A$) receptor variants. Since clinical variants in $GABA_A$ receptors often lead to neurological diseases, such as epilepsy, proteostasis regulators have the promise to be developed as novel therapeutics to target misfolding-prone $GABA_A$ receptors to treat their protein conformational diseases.

Proteostasis Maintenance

Proteostasis in human health and disease

Normal physiology depends on proteostasis maintenance in each cellular compartment, which involves a delicate balance between protein synthesis, folding, assembly, trafficking, and degradation. Many factors can compromise proteostasis, such as oxidative stress [1], environment [2], and aging [3]. The disturbance of overall proteostasis can result in loss-of-function diseases, including ion channel diseases such as cystic fibrosis and epilepsy [4,5]. This is usually caused by an accumulation of misfolding-prone variants that overwhelm the protein folding capacity. Additionally, gain-of-function diseases could arise due to protein aggregation, in the case of Alzheimer's disease and Parkinson's disease [6,7].

Two classes of small molecules can be used to repair defective proteostasis: pharmacological chaperones and proteostasis regulators [8-11]. Pharmacological chaperones directly bind to the client protein to stabilize it and correct folding and trafficking, whereas proteostasis regulators modify the organization of the proteostasis network to enhance the cellular folding capacity. In this review, we focus on the application of proteostasis regulators as a promising therapeutic strategy to treat diseases caused by $GABA_A$ receptor misfolding-prone variants.

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Proteostasis network maintains proteostasis

Proteome integrity is safeguarded by a distributed network of cellular processes (the proteostasis network), which ensures a precise control of protein synthesis, folding, and degradation to maintain homeostasis. Many factors are involved in the proteostasis network, such as molecular chaperones, degradation machineries, and trafficking networks [2]. Additionally, cellular signaling pathways respond to misfolded proteins to reduce proteotoxic stress, such as the cytosolic Heat Shock Response (HSR) [12], Endoplasmic Reticulum (ER) and mitochondria Unfolded Protein Response (UPR) [13-15], ER-Associated Degradation (ERAD) [16], and autophagy [17]. To comprehend how the proteostasis network modulates proteostasis, it is crucial to identify important network components that are involved in maintaining homeostasis. Studying protein interactomes with the aid of modern proteomics and bioinformatics tools has been shown to be valuable to acquire a comprehensive analysis of proteostasis network components. As an example, recent studies identified the interactome of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) and γ-aminobutyric acid type A ($GABA_A$) receptors in an effort to improve therapeutic efficiency [18,19]. This approach helps to elucidate novel pathways that can be targeted to restore proteostasis and mitigate related ion channel diseases.

Use of Proteostasis Regulators to Restore Proteostasis of Misfolding-Prone $GABA_A$ Receptor Variants

In this review, we focus on proteostasis regulators that modify the proteostasis network components to restore proper folding and trafficking of disease-causing variants. Instead of directly binding the client protein, proteostasis regulators target its proteostasis network components, which are involved in protein synthesis, folding, assembly, degradation, and trafficking. Proteostasis regulators have been applied to many types of diseases, such as cystic fibrosis [20], epilepsy caused by abnormal excitatory signaling [21,22], and lysosomal storage disorders [9,23]. In particular, we highlight the application of proteostasis regulators on epilepsy-associated $GABA_A$ receptors.

$GABA_A$ receptors are the major inhibitory neurotransmitter-gated ion channels in the mammalian Central Nervous System (CNS) and play an essential role in maintaining the excitatory-inhibitory balance. Proteostasis maintenance is

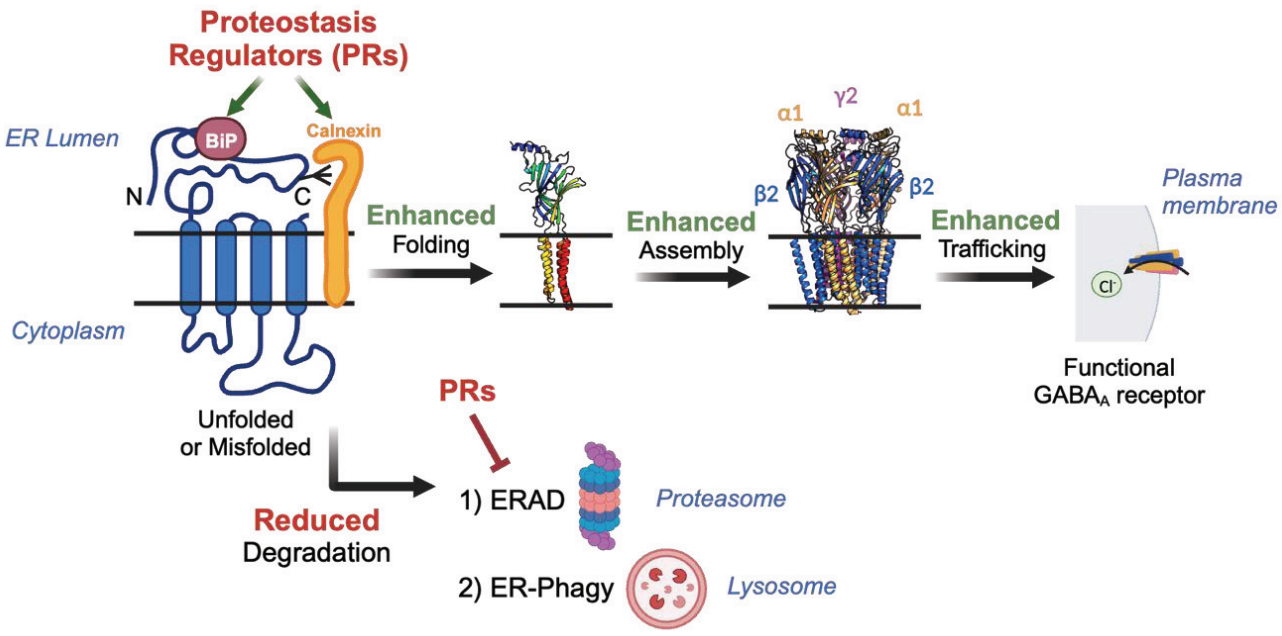

Figure 1 Proposed mechanism for Proteostasis Regulators' (PRs) effect on improving the functional surface expression of misfolding-prone $GABA_A$ receptor variant. PRs enhance the interaction between the misfolded protein and ER chaperones, such as BiP and calnexin, to promote folding, assembly, and trafficking to the plasma membrane. Additionally, they decrease excessive degradation of the misfolded protein to restore proteostasis of $GABA_A$ receptors.

critical for $GABA_A$ receptor function [24] (Figure 1). After synthesis, individual receptor subunits must first fold into their proper three-dimensional structure and then assemble with other subunits to form a pentamer in the ER. These correctly assembled heteropentamers further traffic through the Golgi apparatus to the plasma membrane to form the functional receptor.

Misfolded or unassembled subunits are remained in the ER for additional folding/assembly cycles, and terminally misfolded proteins are removed from the ER *via* cellular degradation pathways such as the ERAD pathway, being depleted by the proteasome, or the ER-phagy pathway, or being targeted to the lysosome *via* ER-phagy receptors [25,26].

Variations in genes encoding $GABA_A$ receptor subunits result in neurodevelopmental and neuropsychiatric disorders such as autism, epilepsy, schizophrenia, and bipolar disorder [4,27,28]. These diseases are often caused by an accumulation of misfolding-prone variants that disrupt proteostasis, leading to excessive degradation of the variants and loss of function of the receptor. Therefore, one promising therapeutic strategy is to improve the proteostasis capacity in the ER to restore proper folding, assembly, and forward trafficking of the pathogenic receptor. For example, Di, et al. [29], demonstrated that Suberoylanilide hydroxamic acid (SAHA), Dinoprost (DNP), and Dihydroergocristine (DHEC) reduced ERAD and improved folding and ER-to-Golgi trafficking of epilepsy-associated variant α1(A322D) subunit [30]. By enhancing the interaction between variant receptor and ER chaperones, these proteostasis regulators effectively promoted the functional surface expression of these pathogenic variants.

Additionally, verapamil, an L-type calcium channel blocker, prevented aggregation and promoted the calnexin-assisted folding, subunit assembly, and anterograde trafficking of α1(D219N)β2γ2 receptors [31]. These combined actions contributed to significantly increased surface expression and GABA-induced peak current amplitude of the α1(D219N) variant. Importantly, SAHA, DNP, DHEC, and verapamil are all FDA-approved drugs and cross the blood-brain barrier.

Proteostasis regulators that activate the UPR have also been studied in the context of $GABA_A$ receptors. The UPR consists of three signaling arms that are mediated by ER membrane proteins: IRE1 (Inositol-Requiring Enzyme 1), ATF6 (Activating Transcription Factor 6), and PERK (Protein Kinase R- like ER Kinase) [14]. An accumulation of misfolded proteins in the ER leads to subsequent activation of these pathways, causing translational and transcriptional regulation of the ER proteostasis network to restore ER homeostasis. Previous studies have shown that pharmacologically activating the ATF6 signaling arm of the UPR using AA147 and AA263 enhanced the assembly, trafficking, and surface expression of disease-causing $GABA_A$ receptor variants [32]. These UPR activators increased the activity of pro-folding machineries, such as an ER chaperone BiP (Immunoglobulin Binding Protein) and a trafficking factor LMAN1 (Lectin Mannose-Binding 1), and their interactions with variant $GABA_A$ receptors to restore receptor function. In addition, modest activation of ATF6 and IRE1 pathway with BIX (BiP activator) attenuated degradation and improved surface trafficking and function of α1(A322D) receptor variant [33]. Overall, pharmacological activation of these signaling pathways offers a promising therapeutic approach to correct receptor folding, assembly, trafficking, and function for the treatment of genetic epilepsy. Furthermore, pharmacological improvement of overall ER proteostasis has great potential to enhance trafficking and function of other pathogenic ion channels associated with various diseases.

Concluding Remarks

Proteostasis regulators are potent small molecule compounds that alter the proteostasis network to rescue misfolding-prone proteins. Their applications have been documented in various diseases, including in epilepsy that is caused by misfolding-prone $GABA_A$ receptor variants. To rescue the function of trafficking-deficient $GABA_A$ receptor variant, proteostasis regulators enhance the interaction between the variant and pro-folding factors while reducing the degradation of misfolded proteins (Figure 1). Unlike pharmacological chaperones that require direct interaction and have specificity for their client proteins, proteostasis regulators are generally applicable to different trafficking-deficient proteins because they adapt the complex network of components involved in the overall proteostasis maintenance. Due to their distinctive mechanism of action, co-application of pharmacological chaperones and proteostasis regulators could produce synergistic effect to further ameliorate proteostasis defects and treat related disorders. Future studies

on the combination of pharmacological chaperones and proteostasis regulators could provide valuable insight into developing effective treatment for many devastating protein conformational diseases.

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