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The Molecular Chaperone GRP78/BiP as a Therapeutic Target for Neurodegenerative Disorders: A Mini Review

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Abstract

The glucose regulated protein 78 (GRP78), also known as BiP, is the endoplasmatic reticulum (ER) homologue of HSP70, which plays a dual role in the ER by controlling protein folding, in order to prevent aggregation, and by regulating the signaling of the unfolded protein response (UPR). Most neurodegenerative disorders including Parkinson's, Alzheimer's diseases and progressive retinal degeneration are characterized by activation of the UPR and modified expression of GRP78. The expression levels and activity of GRP78 are altered with age raising the question of whether the lack of GRP78 could be a predisposing factor for many neurodegenerative disorders associated with age including PD, Alzheimer and Age-related macular degeneration. Attempts to induce or upregulate GRP78 in animal models of neurodegeneration have recently been made with the help of pharmacological BiP protein Inducer X (BIX) and GRP78 cDNA delivery via adeno-associated virus (AAV) vectors. The results of these studies validate GRP78 as a new therapeutic target for treatments of forebrain ischemia, Parkinson disease and retinal degeneration. These data, together with the results from age-related studies, highlight the importance for developing drugs to induce elevation of endogenous GRP78 in order to increase cellular survival and extend functional longevity.

Keywords: Molecular chaperone GRP78/BiP; Neurodegenerative disorders

Introduction

Neurodegeneration refers to the processes whereby damaged neuronal cells deteriorate and eventually die. Most neurodegenerative disorders including Parkinson's, Alzheimer's diseases and progressive retinal degeneration (RD) are characterized by activation of the Unfolded Protein Response (UPR) and the accumulation of the intracellular or extracellular aggregations of misfolded proteins or mutated gene products [1-6]. Glucose regulated protein 78 (GRP78), also known as BiP, is a key mediator of the UPR. Accumulation of unfolded proteins within the ER leads to dissociation of GRP78 from three "stress sensor" proteins, including Activating Transcription Factor 6 (ATF6), Inositol Requiring protein 1 (IRE1) and PKR-like Endoplasmic Reticulum Kinase (PERK), thereby inducing their activation. Once activated, the UPR can proceed through two phases: pro-survival (early) and pro-apoptotic UPR (late). If the original stress is not resolved, apoptotic responses are activated involving a subsequent crosstalk between the ER and mitochondria leading to apoptosis [7,8]. For this reason, ER stress is considered to be a common mediator of apoptosis in neurodegenerative disorders.

Apoptosis is known to be a common feature of degenerative neurons. Activation of apoptotic pathways leads to accelerated neuronal loss and to the progression of disease symptoms [9-12]. Therefore, identification of mechanisms that either promote or prevent neuronal apoptosis may provide a new therapeutic approach for averting and/or treating neurodegenerative disorders.

Structure and Function of GRP78/BiP

GRP78 is the ER homologue of HSP70 proteins and contains a KDEL ER-retention signal, as well as a conserved ATPase domain and a peptide-binding domain [13]. It plays a dual role in the ER, functioning as a resident chaperone regulating protein folding and preventing aggregation while also regulating signaling within the UPR. As a chaperone, GRP78 recognizes and binds hydrophobic residues in the unfolded regions of proteins [14].

GRP78 belongs to the large ER chaperone network along with other molecular chaperones including GRP94, PDI, ERp72, GRP170/ORP150, CaBP1 (calcium binding protein), cyclophilin B and SDF2-L1, which processes unfolded protein substrates [15]. GRP78 doesn't localize exclusively to the ER and under specific circumstances, such as development of drug resistance and cell transformation, it has been shown to re-locate to the cell membrane [16]. In addition GRP78 has recently been shown to exist as a splice variant (GRP78va) that is specific to cancer cells and which lacks the N-terminal ER localization sequence. It has been shown that the GRP78va localizes to the cytoplasm, where it can potentially interact with many other client proteins [17]. Finally GRP78 has been reported to translocate to the mitochondria [18], where it can potentially regulate mitochondrial functions such as energy balance and help maintain mitochondrial homoeostasis, especially under conditions of ER stress [17].

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GRP78/BiP in Parkinson's Disease and Retinal Degeneration

A growing body of evidence now indicates that the level and localization of GRP78 is altered in different models of Parkinson's disease (PD). For example, in a rabbit model of PD it has been demonstrated that GRP78 translocates from the ER to the nucleus and cytosol in response to treatment with 400 nm of MPP^+. This treatment also leads to a marked reduction in TH-positive cells in the substantia nigra pars compacta (SNc) [19]. Similarly, in the SH-SY5Y cell model, treatment with MPP^+ leads to a down-regulation of GRP78 mRNA [20], while treatment of the same cells with 6-OHDA has the opposite effect [20,21].

Retinitis pigmentosa (RP) is considered to be a progressive neurodegenerative disorder [22]. As already mentioned, there have been reports of GRP78 perturbations in animal models of RD. For example, in the RP mouse model affected by expression of mutant rhodopsins we have demonstrated an increase in both GRP78 mRNA and protein [5,6,23]. Recently in a mouse model of light-induced RD it has been revealed that the induction of GRP78 mRNA is divided into two phases: early UPR and late UPR [4]. This suggests that the early UPR signaling can suppress ER stress and restore ER homeostasis, but that prolonged ER stress may be so severe that the UPR cannot restore ER homeostasis, thus instead leading to apoptotic cell death [4]. In rd1 mice carrying a nonsense mutation in the gene coding for the β subunit of the rod photoreceptor-specific cGMP phosphodiesterase 6 (PDE6-β), expression of the GRP78 protein was shown to be modulated in a time-dependent manner and peak GRP78 induction corresponded with its localization to the outer or inner layer of the photoreceptors [24].

GRP78/BiP and Aging

As a consequence of aging, the balance between the protective and pro-apoptotic signaling in the UPR shifts. The protective, pro-survival arm of the UPR is thus significantly reduced, while the pro-apoptotic arm becomes more prominent with age [25-27]. Such changes are accompanied by structural alteration in the ER. One such change is seen in the rough ER, where young neurons are characterized by highly ordered parallel cisternae which become gradually more dispersed with age [28]. The age-related declines in important UPR chaperones, enzymes and the changes in the ER structure significantly affect the ability of the ER to maintain proper protein folding and ultimately control ER homeostasis. This age-related breakdown in ER function is believe to occur at least in part due to the impairment of key ER resident chaperones and enzymes such as BiP, PDI, calnexin and GRP94, through oxidative "wear" during the aging process [29].

In old (20-24 months) mice a 20% decrease in BiP ATPase activity, as compared to young (3-5 month) mice, has been demonstrated and is consistent with a 2-fold increase in the carbonylation of GRP78. This observation supports the hypothesis that the loss of ER chaperone activity to oxidative damage is in turn responsible for the decline of tissue function that occurs in normal aging and in age-related diseases [29]. In another study by Erickson et al. a marked decline of up to 73% in GRP78 mRNA is described in old (900 day-old) vs. young (21day-old) Sprague-Dawley rats suggesting that the loss of GRP78 activity and the associated (age-related) physiological declines occur at both the protein and transcript levels [30].

Examination of the existing literature highlights the fact that both the expression levels and activity of molecular chaperones as well as the ER structure are modified with age and raises the question of whether the loss of GRP78 function could be a predisposing factor for many neurodegenerative disorders associated with age including PD, Alzheimer, Age-related macular degeneration and other forms of RD. This opens up a possible future, in which pharmacological manipulation of GRP78 in elderly patients could result in a slowdown of aging and it's associated neurocognitive declines, and an extension of functional life span through the elimination of neurodegenerative diseases.

Therapeutic Modulation of GRP78/BiP in Animal Models of Neurodegenerative Disorders

There is a long history of attempts to validate GRP78 as a therapeutic target for the treatment of neurodegenerative diseases. In the MPTP mouse model of PD it has been demonstrated that administration of 2-deoxy-D-glucose (2-DG; a nonmetabolizable analogue of glucose) leads to reduction in the damage to dopaminergic neurons in the SN and improvement of behavioral outcomes [31]. The 2-DG treatment has been found to suppress oxidative stress, preserve mitochondrial function, and attenuate cell death in cultured dopaminergic cells exposed to the complex I inhibitor rotenone or Fe^{2+} [31]. Interestingly, the mechanism by which 2-DG acts as a therapeutic agent in dopaminergic cells has been found to be associated with induction of GRP78, suggesting the involvement of this cytoprotective protein in the neuroprotective actions of 2-DG.

Recently, the application of a selective inducer of BiP, BiP Inducer X (BIX), was tested in animals [4,32-34]. It was shown that in gerbils with global transient forebrain ischemia BIX significantly induced GRP78 expression. Furthermore pretreatment with BIX via intracerebraventricular injection at 10 or 40 mg protected from cell death and significantly reduced the number of TUNEL-positive cells in the hippocampus. This study also demonstrated that BIX could be used to prevent a wide spectrum of neuronal damage associated with apoptosis and pointed to GRP78 as a potentially potent therapeutic target for pharmacological manipulation of neuronal cell damage in the brain. A subsequent study by the same group [32] demonstrated that intracerebroventrical injection of 20 μg of BIX administered at either 5 min or 3 h post- middle cerebral artery occlusion (MCAO) reduced both infarct volume and brain swelling. Additionally, BIX was also demonstrated to have anti-apoptotic and neuroprotective effects against acute ischemic neuronal damage [32]. The same study however showed that BIX injection at 6 h post-occlusion did not have a protective effect, suggesting a limited, early window for therapeutic intervention via GRP78-inducing drugs.

The BIX molecule was also recently tested in mouse models of RD [4,34]. In the RD mouse model induced by intravitreal injection of tunicamycin or NMDA, intravitreal injection of BIX (5 nmol) was demonstrated to significantly induce GRP78 expression, and was found to reduce both retinal cell death and CHOP protein expression in retinal ganglia cells. The same group [4] later proposed that treatment with the ER stress inhibitor BIX, also results in the induction of GRP78 mRNA, and a reduction of both pro-apoptotic CHOP expression and photoreceptor cell death in the mouse model of light-induced RD. This indicates that excessive ER stress may induce photoreceptor cell death in light-exposed retina via activation of the CHOP-dependent apoptotic pathway and also implies that ER stress may play a pivotal role in light-induced retinal damage [4].

Attempts to find regulators of ER stress have been ongoing and recently methoxyflavones, a family of flavonoids, have been revealed to

have a strong protective effect against enhanced ER stress [35]. It has been demonstrated that pre-treatment with tangeretin in MPTP-treated mice enhanced the expression of GRP78 in the SNc and protected dopaminergic neurons against MPTP; a neurotoxin that induces both oxidative and ER stress. These results suggest that methoxyflavones could be used as regulators of ER stress thus further identifying this cellular process as a therapeutic target for the treatment of a wide range of associated pathologies including PD and RD [35].

In the past we have also made attempts to validate GRP78s' potential as a therapeutic target for the prevention of neuronal cell death. We first demonstrated that the visual function of degenerative photoreceptors could be restored by over-expression of GRP78 in RD photoreceptors [36].

Initially we found that rats with autosomal dominant RP (ADRP) arising from the P23H mutation in rhodopsin experienced UPR activation during RD progression. This mutation is known to cause misfolding of opsin and decreased association of 11-cis retinal, leading to an aberrant visual cycle and retinal degeneration. This process is accompanied by UPR activation and up-regulation of all three branches of UPR signaling. We observed that the level of the 50 kDa cleavage product of pATF6 is nearly 2.7-fold higher in ADRP rats as compared to wild-type animals. Another ER stress marker, peIF2α, was also elevated by 50% in transgenic retinas, suggesting persistent PERK signaling in the retinas of postnatal day P30 rats. This observed activation of the PERK and ATF6 pathways might in turn be responsible for the 26% elevation in pro-apoptotic CHOP protein levels resulting in a 4-fold increase of cleaved caspase-7. Additionally we also found splicing of the XBP1 mRNA in transgenic retinas.

Interestingly, we have shown that GRP78 over-expression reprograms the UPR in the transgenic retina. The over-expression of GRP78 was achieved by subretinal injection of adeno-associated viral (AAV) vectors encoding the human GRP78 cDNA. We determined that elevating levels of GRP78 in photoreceptors could be therapeutic for ADRP. This led us to hypothesize that elevating levels of GRP78 could restore vision in P23H-3 RHO transgenic rats. Our hypothesis was based on the assumption that GRP78 was responsible for the primary chaperone activity in our model and that its overexpression would potentially promote the correct folding of opsin, alleviate ER stress signaling, and ultimately prevent apoptosis of photoreceptors in the ADRP rat model. Our subsequent experiments found that GRP78 overexpression did indeed alleviate ER stress and reduced signaling from both the ATF6 and PERK branches of the UPR. Most importantly, overexpression prevented ER stress-induced apoptosis in ADRP photoreceptors. We also demonstrated that moderate elevation of GRP78 preserved the function of P23H RHO photoreceptors for up to 3 months with subsequent trials showing retinal structure and function preservation for up to 9 months post-treatment.

Findings from the studies with BIX in MCOA mice and GRP78-overexpression in degenerative P23H RHO photoreceptors encouraged us to test GRP78 as a therapeutic target in the rat model of PD [37]. PD has been induced by direct injection of AAV vector encoding human α-synuclein (α-syn) cDNA into the rat SNc. This model has become widely accepted due to its mimicking of human PD features such as robust overexpression of α-syn in the nigrostriatal pathway and dystrophy of dopaminergic neurons.

Thus, we have investigated the involvement of ER stress signaling in the degeneration of nigral DA cells caused by α-syn-induced pathology and have demonstrated that overexpression of GRP78 diminished α-syn cytotoxicity by reprogramming ER stress signaling pathways and eliminating apoptosis. First, we found that the mechanism of α-syn neurotoxicity in nigral DA neurons was associated with an activation of the ER stress response. This increase in α-syn correlated with an increase in markers for two of the three pathways in the UPR at 4 weeks post-injection when α-syn expression reached maximum levels but significant neurodegeneration had not yet occurred. We observed a 23% elevation of peIf2α protein levels, a nine-fold induction in ATF4 (PERK pathway), and a greater than two-fold elevation of cleaved pATF6 protein levels (ATF6 pathway). These increases were also accompanied by a three-fold elevation of pro-apoptotic CHOP protein that is known to be a downstream marker of the ATF6 and PERK pathways. Elevation of this protein is known to directly promote apoptosis [38] and is thus perhaps responsible for DA cell death.

After demonstrating the involvement of the UPR in DA neuron degeneration, we next found that AAV delivery of GRP78 cDNA leads to a significant reduction in the α-syn-induced loss of TH-positive neurons in the SNc. This effect was also seen as a reduction of striatal DA loss, and amelioration of behavioral deficits in the amphetamine induced rotation test at 8 and 16 weeks post-injection. In addition, we have found that AAV-mediated overexpression of GRP78 reduced the levels of both cleaved pATF6 and ATF4 proteins by 42% and 41%, respectively and significantly attenuated the levels of CHOP protein at 4 and 8 weeks post AAV injection (by 42% and 46% respectively). Finally we were also able to demonstrate that while α-syn over-expression alone in SH-SY5Y cells leads to the elevation of nucleosome release mediated by DNA fragmentation, a telltale sign of apoptosis, GRP78 over-expression with α-syn was able to reduce this effect.

Concluding Remarks

GRP78 is a key protein in ER stress signaling, whose expression is modulated in degenerative cells depending on their stage of ER stress and UPR. Expression of GRP78 has been demonstrated to decrease with age raising the question of whether the lack of GRP78 could be a predisposing factor for most degenerative disorders associated with age. BIX has been shown to selectively induce the GRP78 mRNA and to modulate the ER stress response in cells, thus promoting the survival of neuronal cells undergoing degeneration associated with activation of the UPR. This has further implied that augmentation of GRP78 is a feasible therapeutic approach for the treatment of neurodegeneration. This hypothesis is supported by the fact that sustained over-expression of human GRP78 (via AAV vectors) in neuronal cells reprograms the UPR by halting ATF6 and PERK signaling and significantly reduces the level of pro-apoptotic CHOP protein, thus leading to a reduction of apoptosis. The presented studies highlight the importance of controlling UPR signaling as a means for curtailing the progression of neurodegenerative disorders associated with ER stress. These same studies also validate GRP78 as a prospective new and key therapeutic target for future treatment of a potentially wide spectrum of neurodegenerative diseases.

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