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Alzheimer's disease pathology and the unfolded protein response: Prospective pathways and therapeutic targets

--Manuscript Draft--

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Abstract:	Many vital interdependent cellular functions including proteostasis, lipogenesis and Ca2+ homeostasis are executed by the endoplasmic reticulum (ER). Exogenous insults can impair ER performance, this must be rapidly corrected or cell death will ensue. Protective adaptations can boost the functional capacity of the ER and forms the basis of the unfolded protein response (UPR). Activated in response to the accumulation of misfolded proteins, the UPR can halt protein translation while increasing protein-handling chaperones and the degradation of erroneous proteins via a conserved three-tier molecular cascade. However, prolonged activation of the UPR can result in the maladaptation of the system, resulting in the activation of inflammatory and apoptotic effectors. Recently, UPR and its involvement in neurodegenerative disease has attracted much interest, and numerous potentially "drugable" points of crosstalk are now emerging. Here, we summarise the functions of ER and UPR, and highlight evidence for its potential role in the pathogenesis of Alzheimer's disease (AD), before discussing several key targets with therapeutic potential.

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Professor Willner
Editor-in-Chief
'Behavioural Pharmacology'

January 30th 2017

Dear Prof Willner,

We are delighted our manuscript has received positive reviews by our peers and here by submitted a revised version of our Review manuscript entitled "Alzheimer's disease pathology and the unfolded protein response: Prospective pathways and therapeutic targets" for consideration to the special issues on dementia in 'Behavioural Pharmacology'.

All comments as outlined by the reviewers have now been addressed and we have attached a itemised list stating those correction, in addition where minor alterations have been indicated we have highlighted some points in yellow to aid with reviewing this alterations.

We hope you will find our submission acceptable and look forward to hearing from you.

Yours faithfully,

Dr. David J. Koss

Reviewer Comments:

Reviewer #1: This submission BP-17-20 describes the intrinsic machinery which helps the cell during pathological events to expel abnormally folded proteins. One such proteinopathy is Alzheimer's disease, in which multiple proteins are processed and aggregated into clumps which the cell has to expel. A further corollary of this processing anomaly is the induction of inflammatory reactions. All these mechanisms provide potential targets for disease-modifying treatments of neurodegenerative diseases.
As the answer of the cell to abnormally folded proteins, the UPR provides a protective mechanism for the endoplasmic reticulum and aids in the destruction of proteinaceous aggregates. It comprises three semi-independent cellular pathways, which the authors have summarised in Fig. 1. Important not only in the context of AD is the observation that all proteinopathies are sensitive to UPR as a disease-related mechanism. So understanding the mechanist underpinnings for one disease will likely be directly translatable to the other. For AD, there is now an established link between UPR and amyloid/tau pathology.
The authors describe in great detail, how the cellular cascades interlink and how crosstalk can be established once any single or multiple UPR pathways are activated. Chronic activation of UPR is likely a reaction to any stressor which is present continuously. It follows that selective acute activation of the UPR is protective to the cell, but long-lasting UPR activity likely ends in apoptosis. Therefore, suppression of UPR (and possibly its specific components) provides a novel molecular target for disease treatment. Proof of efficacy of PERK or eIF2α blockers is provided by lowered amyloid levels and reduced tau phosphorylation, and many interactive processes (Calcium homeostasis; glutamate toxicity, etc.) are presented. This also includes early evidence for the beneficial effects of UPR suppression on cognition and behaviour in general.

While this is a welcome addition to the overall collection of papers on dementia for this issue, there are several issues here:

1. The manuscript could be improved in its language and I below list some of the spelling mistakes I found.

2. On page 4, abbreviations in paragraph 2: The abbreviation DGP is introduced as diacylglycerol phosphate. Later, DGP is combined with other terms which are not related to diacylglycerol and this is confusing.

Response:

In order to avoid confusion abbreviations relating to DGP have been removed.

3. Page 8, end of section 2.1.1. It would be quite instructive if some additional work on PERK and JNK in the context of memory formation/Learning could be added here. Specifically, I am thinking of the work of Zhu S et al., 2016, Plos One; and Ounallah-Saad et al in JNeuroscience. Both papers report on the cognitive benefits of a lowering of PERK by either genetic or pharmacological means.

Reply

We thank the reviewer for drawing our attention to the recent work of Zhu et al. On page 8, we had already discussed the findings of Ounallah-Saad et al, but have now modified the paragraph to read as follows:

"Interestingly, despite the superior performance of genetically deficient PERK mice in behavioural tasks that require protein synthesis for learning , such mice demonstrated reduced working memory in several tasks known to be independent of protein synthesis. The latter may indicate an additional role of PERK in the regulation Ca^{2+} dynamics (Zhu et al., 2016)".

4. Section 2.1.3: Recently Zhang Y et al. (Neurosci Res. 41 : 2517- 2016) provided evidence that inhibition of ATF-6 can recover deficits in spatial learning in rats. While this is not direct evidence for a potentially protective role of suppressing UPR against AD pathology, it provides indirect support for a putative treatment against the chronic expression of ATF-6 and I would think this could be added to the section.

Reply

We have now added a commentary on this interesting finding. Page 11 now reads:

"Nevertheless, at least in Parkinson's disease, the *activation* of ATF-6 has been shown to be protective in association with an increased expression of the ERAD machinery (Egawa et al., 2011) yet the deposition of α-synuclein may inhibit ATF-6 activation and ER-Golgi trafficking (Credle et al., 2015). Despite this protective role, recent work suggests that administration of taurine, may protect aged rats from isoflurane-induced hippocampal apoptosis via the reduction of CHOP in an ATF-6 dependent manor (Zhang et al., 2016[b]). These contradictory findings, highly the need for increased research into the role of ATF-6 in AD and it's pathology."

5. Page 19, second paragraph: FDA approval for Memantine (Namenda) is for moderate-to-severe AD, not as stated by the authors for mild-to-moderate AD. Please correct.

Reply

This has been amended

6. Page 19, last paragraph: the authors describe the efficiency of 'Dimebon' on mitochondrial function. However, Dimebon is the trade name and to be consistent with the previous paragraph, I suggest that the authors replace it with the compound name - Latrepirdine.

Reply

This has been amended

7. Table 1: The table could be referenced better in the main text as it contains information for multiple sections, but is only cited on page 15.

Reply

Reference to the table is now provided page 15, 16, 18 and 19 at relevant points.

Please correct: (elements to be added are underlined)

- Page 3, line of last paragraph (1.2 Protein Folding): it should read … post-translational modification …..
- Page 4, 7 from bottom: delete ultimately
- Page 5, line 2: should read …one aspect has consequences…..
- Page 5, line 18, end of line. Delete one …in in …
- Page 5, last line. End sentence after Ogata et al.
- Page 6, line 7 should read: … and hence a promising …..
- Page 8, line 5 from bottom should read: ….separated by an intronic…..
- Page 9, line 9: please add to …not only acts as a protein chaperone …..
- Page 9, line 11, please delete as indicated: …accordance with the UPR….
- Page 9, line 14: it should read …secretases …
- Page 10, line 2: overserved - not correct
- Page 10, Line 9: ..variety of growth factor deprivations … - makes no sense.
- Page 10, line 15 from bottom: …JNK activation, in particular …. been linked with the age-dep….. - please add.
- Page 10, line 10 from bottom: …the association of JNK activation …. - please add.
- Page 12, line 11: sustained pathological environment - is this correct?
- Page 12, line 15, end of sentence: … as well as apoptosis. - is this correct (I do not understand).
- Page 13, line 2: …compromise of ER physiology ….
- Page 13, line 15 from bottom: …stress led to an similar … - please delete.
- Page 14, line 9 from bottom: These include … - delete s
- Page 14, last line: … the outcome for molecular ER stress pathways remains unreported. This sentence makes no sense to me. Please reword.
- Page 15, 7: …in systemic disease models .. - delete s in diseases!
- Page 15, line 16: … rather than …
- Page 16, line 10: please correct to .. Tg2576 mice …
- Page 16, line 13: … but not their maintenance. Makes no sense, please rephrase.
- Page 16, line 10 from bottom: please correct author name to: Guthrie et al
- Page 16, line 8 from bottom: … tauopathy models and ….
- Page 16, line 2 from bottom: … limited the drug's therapeutic …

- Page 17, line 14: … whilst actually ….
- Page 18, line 16 from bottom: .. injected with 18ibrillary…. - please correct.
- Page 19, line 18: excitotoxicity.

Reply

These changes have been made and can be found highlighted in the text.

Reviewer #2:
This is an interesting review about the unfolded protein response in AD, and the prospective pathways of the unfolded protein response. This all leads to putative therapeutic targets to slow down the progression of AD. It is a timely review, and the selected papers (although it is not made clear which selection procedure was followed) seem adequate in most cases. The underlying mechanisms are well described, with substantial detail. As a consequence, though, the authors do not show much mercy to readers less familiar to the many interactions and players in this area. Nevertheless just enough concluding sentences and brief summaries are given to keep the review readable. In addition, the figure is of great help, nicely depicting the main players and interactions. All together this is a nice and valuable review. I have only some minor issues listed below.

1) End page 5: it is a long sentence; better to split it up.

Reply

Sentence has now been broken into two to read:

“In concert, all three arms of UPR also act to promote the expression/activation of pro-inflammatory mediators via the transcription factor activating protein-1 (AP-1) and nuclear factor κB (NF-κB; Garg et al., 2012). Inflammatory cells recruited to the damaged tissues may act as further contributors to cellular dysfunction and apoptosis.”

2) Not all abbreviations are introduced in the text (for example BIP), although they are listed in the legend of figure 1. Please check carefully.

Reply

The manuscript has check for these omissions.

3) There are many typo's in the manuscript, like "within in the Chinese population” (p9), "mutation have been" (p10), table instead of Table, Berridge 2009 = Berridge 2010, etc etc. Please check carefully!

Reply

The manuscript has been checked and typos corrected.

4) page 18: "AD rats". Please rephrase as these rats do not have AD

Reply

“AD rats” has been rephrased to a “rat model of AD”

5) Please explain what ibrillary means (ibrillaryAB1-42), as I assume not all readers will know.

Reply

We apologises for the confusion on this point, this is a result of a typo and should read fibrillary, the manuscript has been amended accordingly

6) Berridge 2010 is not the correct citation for the calcium hypothesis of AD. Please rephrase (reviewed in Berridge 2010) or cite the original papers here.

Reply

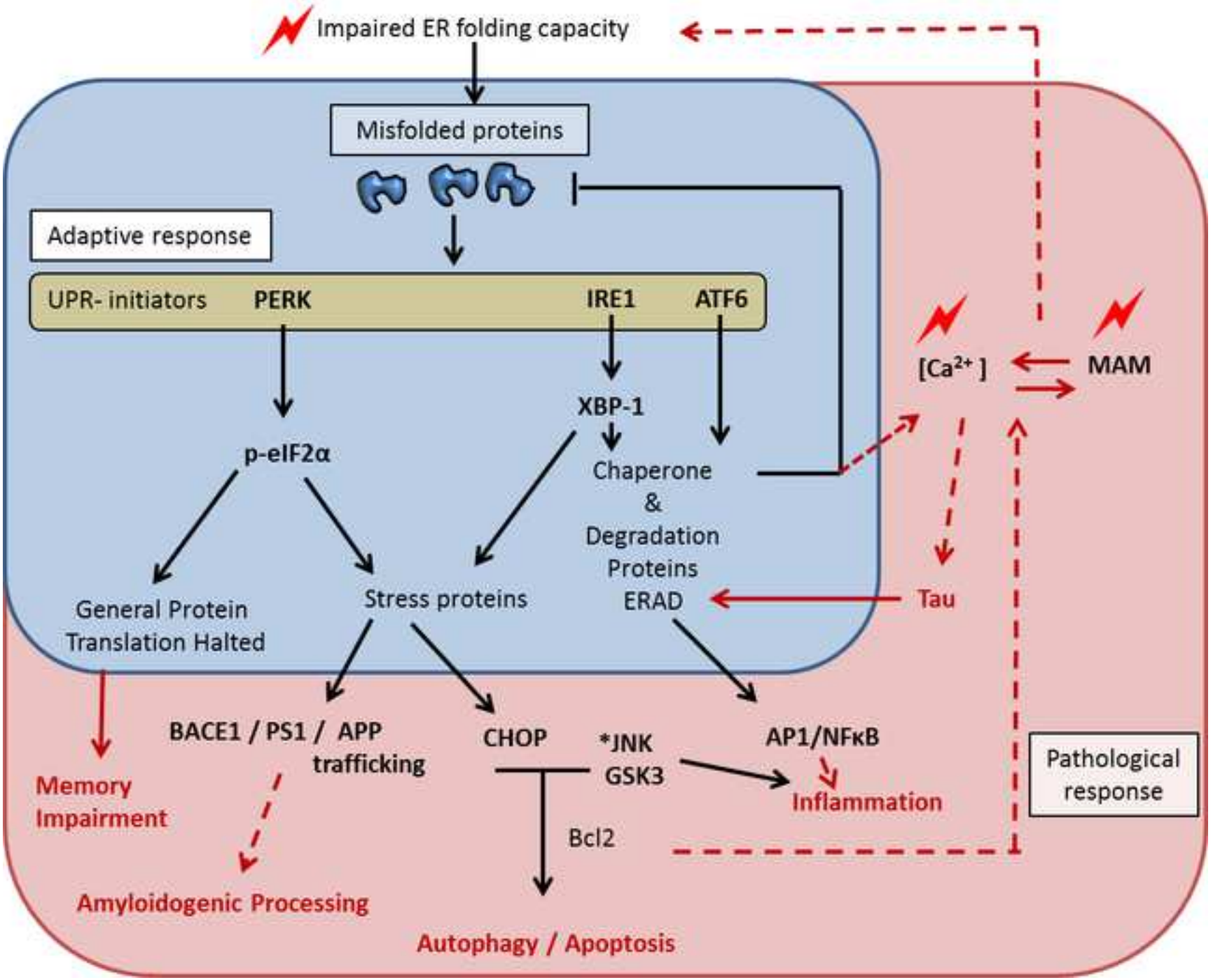
We have amended this to read “reviewed in Berridge, 2010”

7) A brief statement on how the cited papers were selected (selection criteria) would be appreciated.

In addition to key papers (largely reviews) that introduce the broader topic, we have selected papers that offer novel aspects of UPR’s role, either functionally or as drug targets.

Figure

Click here to download Figure Figure 1.tif



Table

Drug	Mode of action	*In vitro* outcomes	*In vivo* outcomes	References
Endogenous chaperone promoters				
BIX	Increase in BIP, GRP94 and calreticulin	**Chemically induced UPR** - Reduced caspase activation and apoptotic cell death	**Cerebral artery occlusion and chemical induced retinal damage** -Reduced CHOP and XBP-1 expression and neuronal death.	Inokuchi et al., 2009 Kudo et al., 2007 Oida et al., 2008+2010
MS275	HDAC Inhibition Diminished ERSRE repression	Increased BIP expression	N.R.	Baumeister et al., 2009
Trichostain A				
Valproic acid		Increased BIP expression	Increased BIP expression in rat cortex	Wang et al., 1999
Proteostasis promoters				
PBA	Undetermined. Likely indirect promotion of protein chaperone handling	**Aβ treatment** -Decreased BIP and CHOP expression, JNK activation and p-tau.*****	**Tau 35 mice** -Decreased p-tau and synaptic loss. **AD mice -** Age dependent reduction in plaque load, GSK3β activation and p-tau and maintained synaptic integrity. Improved cognitive performance.	Bondulich et al., 2016 Cuadrado-Tejedor et al., 2013. Ricobaraza et al., 2009+2012 Wiley et al., 2011 Zhang et al., 2016
TUDCA		**Chemically induced UPR** -Reduced apoptotic cell death. **Aβ treatment** - Diminished spine loss, pro-apoptotic BAX expression, p-tau and JNK and caspase activation. Reduced apoptotic cell death.*****	**AD mice** -Reduced plaque deposition, GSK3β activation, p-tau, inflammation and maintained synaptic integrity . Improved cognitive performance.	Dionísio et al., 2015 Lo et al., 2013 Nunes et al., 2012 Ramalho et al. 2004+2006+2013 Sola et al., 2003 Viana et al., 2010
JNK inhibitors				
D-JNKI 1	Substrate site	N.R.	**AD mice** - Decreased plaque load and Aβ oligomers. Improved synaptic plasticity and cognitive performance.	Sclip et al., 2011
Ginsenoside Rg1	Gensing extract - prominent JNK inhibition	N.R.	**AD rat** -Decreased BIP, GRP94 and IRE-1 expression and caspase activation. Reduced plaque and tau load.	Mu et al., 2015
SP600125	ATP site	**Aβ treatment**- Reduced Bcl-X and Bcl-W pro-apoptotic factors and cytokine release and cell death.***** **FAD gene expression** - Protective against H_2O_2 challenge	**Aβ treatment**- maintained Bcl2 expression and mitochondrial biogensis, reduced BAX expression and caspase activation. **AD mice** - Decreased plaque load, p-tau and inflammation. Improved cognitive performance.	Bamji-Mirza et al., 2014 Mahamnadi et al., 2016 Mahmoudreza et al., 2011 Marques et al., 2003 Xu et al., 2015 Yao et al.,2005 Yenki et al., 2013 Zhou et al., 2015

PERK / eIF2α pathway inhibitors				
GSK2606414	PERK inhibitor-ATP site	**Chemically induced UPR** - Decreased p-eIF2α and release of pro-inflammatory cytokines. **2DG Torpor model** –Decreased p- eIF2α and p-tau.	**rTg4510 tau mice** - Decreased p-PERK, p- eIF2α, ATF-4 expression, GSK3β activation, p-tau and neuronal loss.	Guthrie et al., 2016 Radford et al., 2015 Van der Harg et al., 2014
ISRIB	Inhibitor of downstream eIF2α pathways	**Chemically induced UPR**- Reduced ATF4, CHOP and GADD34 expression, maintained protein synthesis but increased apoptosis.	**Prion inoculated mice** - Unaltered p-eIF2α, reduced ATF4 expression, degeneration, protein synthesis recovery and increased survival.	Halliday et al., 2015 Sidrauski et al., 2013
GSK3 Inhibitors				
Lithium	Undetermined	**Chemically induced UPR** -Increased BIP and anti-apoptotic Bcl2 expression. Decreased CHOP expression and caspase activation and cell death.*****	**AD mice** – Decreased plaque load, reduced APP full length and CTFs and p-APP and p-Tau. Reduced astrocyte activation and maintained synaptic markers. Improved cognitive performance.	Avrahami et al., 2013 Chen et al., 2004 Hiroi et al., 2005 Hu et al., 2009 Meares et al., 2011 Rockenstein et al., 2007 Song et al., 2002 Serenó et al., 2009 Takadera et al., 2006 Toledo and Inestrosa, 2010 Ly et al., 2012
L803-mts	Substrate site		**AD mice** – Decreased plaque load. Improved cognitive performance	
TDZD	Non-ATP site		**AD mice** – reduced plaque load, p-tau and gliosis, Improved cognitive performance.	
BIO	ATP site		**Aβ treatment** – reduced p-tau, p-JNK, caspase activation, gliosis and neurodegeneration. **AD mice**- Reduced Aβ, reduced BACE1 expression, reduced NF- κB	
CHIR99021				
Paullone derivatives				
SB216763				
Ca^{2+} modulators				
Dantrolene	RYR antagonist	**Amyloidogenic oligomer treatment** - Decreased BIP expression and caspase activation.	**Cerebral artery occlusion model** -Decreased p-PERK and p-eIF2α, and infarct volume. **AD mouse model** - Decreased Aβ production and plaque load. Improved cognitive performance.	Li et al., 2005 Oulès et al., 2012 Teixeira et al., 2006

Table 1: UPR-targeting pharmacological agents. Drug categories are listed based on the primary mode of action, and major outcomes reported *in vitro* and *in vivo*. Phosphorylation is indicated by a "p-" prefix . Where drugs have been evaluated for protective abilities in disease models / or cellular stress the description is given in bold. ***** denotes where *in vitro* studies have been conducted in primary neuronal cultures as oppose to cell lines. Abbreviations: **Aβ** = beta amyloid, **AD**= Alzheimer's disease, **ATF-4** = Activating transcription factor 4, **ATP**= adenosine triphosphate, **BACE1**= β secretase, **BAX**= Bcl2 associated X, **Bcl** = B-cell lymphoma, **BIO**= 6-bromoindirubin-3'-oxime, **BIP** = binding immunoglobulin protein, **BIX**= BIP inducer X, **CHOP**= CCAAT enhancer binding protein homologous protein, **eIF2α** = eukaryotic initiation factor 2α kinase, **ERSRE**= endoplasmic reticulum stress response element, **GADD34** = growth arrest and DNA damage inducible protein 34, **GRP94** = glucose regulated protein 94 , **GSK3β**, Glycogen syntheses kinase 3β, **HDAC** = histone deacetylates, **IRE-1** = inositol-requiring enzyme 1, **ISRIB** = integrated stress response inhibitor, **JNK**= Jun-N-Kinase, **NF-κB**= Nuclear factor κB, **N.R.** = not reported, **PBA**= 4-phenyl butyric acid, **PERK** = PRK-like ER kinase , **RYR** = ryanodine receptor, **TDZD**= thiadiazolidinone, **TUDCA** = tauroursodeoxycholic acid, **UPR**= Unfolded Protein Response, **XBP-1** = Xbox protein 1 and **2DG** = 2-deoxy-D-glucose.

Full Title: **Alzheimer's disease pathology and the unfolded protein response: Prospective pathways and therapeutic targets**

Running head: **Alzheimer's disease pathology and the UPR**

Authors: **David J. Koss[1*] and Bettina Platt[1]**

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Abstract

Many vital interdependent cellular functions including proteostasis, lipogenesis and Ca^{2+} homeostasis are executed by the endoplasmic reticulum (ER). Exogenous insults can impair ER performance; this must be rapidly corrected or cell death will ensue. Protective adaptations can boost the functional capacity of the ER and forms the basis of the unfolded protein response (UPR). Activated in response to the accumulation of misfolded proteins, the UPR can halt protein translation while increasing protein-handling chaperones and the degradation of erroneous proteins via a conserved three-tier molecular cascade. However, prolonged activation of the UPR can result in the maladaptation of the system, resulting in the activation of inflammatory and apoptotic effectors. Recently, UPR and its involvement in neurodegenerative disease has attracted much interest, and numerous potentially "drugable" points of crosstalk are now emerging.

Here, we summarise the functions of ER and UPR, and highlight evidence for its potential role in the pathogenesis of Alzheimer's disease (AD), before discussing several key targets with therapeutic potential.

Keywords: Amyloid, Alzheimer's disease, apoptosis, endoplasmic reticulum, ER stress, tau, neurodegeneration, homeostasis, proteostasis, drug discovery.

~~1.~~ The endoplasmic reticulum and its role in age-related disease

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The endoplasmic reticulum (ER) is central to an array of cellular processes, including protein translation and modification (Schwarz and Blower, 2016), lipogenesis (Fagone and Jackowski et al., 2009) and Ca^{2+} homeostasis (Berridge et al., 2003); the disturbance of such functions is implicated in a wide range of disease processes. Here, we briefly summarise aspects of ER stress associated with neurodegenerative processes.

~~1.1.~~ *Ca^{2+} homeostasis*

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The ER (in concert with mitochondria) is the cellular organelle responsible for Ca^{2+} homeostasis, and maintains a high Ca^{2+} gradient (0.1mM ER lumen vs 10nm cytoplasmic; Moore et al., 1975). This gradient is crucial particularly for excitable cells such as neurons, as it forms the basis for intra- and inter-cellular communication, and must be maintained despite the high associated energy demand. ER stores are regulated by the Sarco/endoplasmic Ca^{2+} ATPase pump (SERCA ATPase)~~,~~; which scavenges passive Ca^{2+} leaks and recaptures Ca^{2+} released by inositol triphosphate (IP_3) signalling, or via Ca^{2+} induced Ca^{2+} release due to ryanodine receptor (RyR) stimulation (Berridge et al., 2003).

Both ionotropic and metabotropic signalling can trigger Ca^{2+} release from ER stores, which in turn causes extracellular Ca^{2+} influx via the activation of ~~store~~ store-operated Ca^{2+} channels (SOCC~~;~~; Koss et al., 2009~~, &~~ 2013), ensuring refilling of ER stores ~~refilling~~, strengthening Ca^{2+} dependent signalling as well as activating distinct signalling pathways (Bobe et al., 2011, Zou et al., 2011~~, and~~ Selvaraj et al., 2012). The importance of Ca^{2+} homeostasis and excitotoxicity in neurodegenerative diseases has been acknowledged for many years; respective reviews on the topic have been published previously (see for example Berridge, 2010).

~~1.2.~~ *Protein folding*

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The ER is the cellular centre for post-translational modification of newly synthesised proteins leading to the adoption of the correct tertiary structure. Those mRNA sequences containing an ER recognition sequence encode proteins destined for either membrane integration or secretion, and contain a sequence recognition particle (SRP). The SRP-guided translocation process feeds polypetides into the ER via a highly conserved heterotrimeric transmembrane protein channel translocon complex. Once inside, proteins undergo sequential post-translational modifications via e.g. N-linked glycosylation, signal peptide cleavage, disulphide bond formation, pro-isomerization and oligomerization, each of which prompt, facilitate and stabilise proper protein folding. Critical to this process are numerous ~~ER~~ ER-resident protein chaperones, including members of the heat shock protein (HSP) family, BIP (binding immunoglobulin protein) and GRP94 (glucose regulated protein 94), as well as carbohydrate-selective chaperones such as c~~C~~alnexin and ~~C~~calreticulin (Schwarz and Blower, 2016). Many of these chaperones are multifaceted i.e. they carry out a variety of functions dependent on their interaction with adaptor proteins and the hydrolysis of ATP. For example, the protein-

binding chaperone BIP requires nucleotide exchange factors such as Sil1 to regulate activity-dependent substrate binding whilst the association of ER J-domain protein (ERDJ) family members assists in localising a variety of different substrates and thus exerts a degree of functional control. Such functions include the association of BIP's association with the translocon pore that recruits emerging polypeptides into the ER lumen, whilst also preventing ionic flow mediated by ERDJ1/2. Additionally, the binding of unfolded proteins via ERDJ 3/6 and ERDJ 4/5 promotes binding of BIP's binding to misfolded proteins and hence their subsequent degradation (Braakman and Hebert, 2013). Only successfully chaperoned proteins are correctly presented for enzymatic modification and ultimately available for transport to the Golgi apparatus.

1.3. *Lipid biosynthesis*

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In concert with its roles in protein translation, the ER is the main site for lipid synthesis. High levels of glycerol-3-phosphate, O-aclytransferase and 1-acyl-sn-glycerol-3-phosphate O-acyltransferase, needed for the production of diacyl-glycerol phosphate, are present in the ER, alongside phosphatidic acid phosphatase enzymes which convert diacyl-glycerol phosphate to diacylglycerol, the basis of all phospholipids. As such the ER is the primary site for production of most gylcerophospholipids, phosphatidylcholine and phosphatidylethanolamine, and also the storage of lipids in the form of triacylglycerol (Fagone and Jackowski et al., 2009). In contrast to the self-contained production of gylcerophospholipids, the production of ceramide-containing sphingolipids is only initiated in the ER, which generates ceramides prior to trafficking to the Golgi apparatus where sphingolipid synthesis is completed (Futerman and Riezman, 2005).

1.4. *Cross-talk between ER functions*

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A number of studies have demonstrated a high degree of interdependence of ER functions: Many protein chaperones that ensure proper protein folding, such as calrecticulin and calnexin, not only bind Ca^{2+} t, thus regulating both basal ER Ca^{2+} and releasable Ca^{2+}, but also limit SOCC activation (Fasolato et al., 1998). Reciprocally, ER Ca^{2+} oscillations modulate chaperone interactions with target proteins, which enable protein folding (Corbett et al., 1999,). Similarly, balanced lipogenesis, which requires properly folded enzymes, is essential for SERCA ATPase modulation. Moreover, lipogenesis itself is regulated by ER luminal Ca^{2+} (Fu et al, 2011). This complementary balance of ER functionality and integrity is exemplified by the three principle means of inducing ER stress: Tunicamycintunicamycin, an inhibitor of N-link protein glycosylation (Agouni et al., 2011; and Bassik and Kampmann, 2011), Thapisgargin thapisgargin, an irreversible inhibitor of the SERCA ATPase pump which induces ER Ca^{2+} store depletion (Rogers et al., 1995;, Koss et al., 2009, 2013), and palmitic acid, a saturated fatty acid that in, which integrates into the ER membrane and causes a stress response independent of luminal protein folding (Volmer et al., 2013).

The inter-dependence between ER regulatory pathways has wide-ranging implications, as modifications or disruptions of one aspect has consequences on others. During aging, essential protein chaperones such as calnexin and BIP (Brown and Naidoo, 2012), together with SOCC (Vanterpool et al., 2005; Zhao et al., 2008; Brotto, 2011) and SERCA ATPase activity (Toescu and Verkhratsky, 2000; Puzianowska-Kuznicka and Kuznicki, 2009), are downregulated, lowering ER Ca^{2+} levels whilst raising cytoplasmic Ca^{2+} levels, thus priming the aged ER for dysfunction. This predisposition of ER to malfunction may be further exacerbated by numerous environmental stresses, such as toxic metals, infections, thermal stress and hypoxia (Kitamura, 2013), and shows obvious links between neurodegenerative disease and metabolic conditions, such as Type 2 diabetes and obesity (T2D, Chakrabarti et al., 2011).

~~2.~~ The Unfolded Protein Response (UPR)

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During impaired ER function, the UPR cascade is activated, initially as a physiological adaptive response to ER stress, which is initiated when the demand for protein translation exceeds the ~~ER's~~ protein folding capacity of the ER, and hence is caused either by inefficiencies in the ER machinery or by excessive protein demand. Errors within the folding process lead to an accumulation of mis/unfolded proteins, resulting in the sequestration of BIP, removing the inhibitory influence of the chaperone over key ER resident initiators of UPR, which in turn activate the stress response.

An adaptive UPR promotes cell survival via three convergent pathways (see Figure 1) that lead to:

1) The inhibition of general protein synthesis, promoting only the translation of key stress genes, via PKR-like ER kinase (PERK~~)~~)-mediated phosphorylation of eukaryotic initiation factor 2α (eIF2α), and thus selective translation of key transcription factors such as Activating Transcription Factor 4 (ATF-4).

2) Increased expression of ~~ER-~~ER-folding proteins via downstream signalling regulated by Activating Transcription Factor 6 (ATF-6) and by inositol-requiring enzyme 1 (IRE1).

3) Increased protein degradation to remove misfolded proteins, via the up regulation of the ~~endoplasmic reticulum~~ER-associated protein degradation (ERAD) machinery, via IRE1.

The ultimate function of acute UPR is to enhance the ~~ER's~~ capacity of the ER for protein folding, i.e. once the production capacity meets demand and misfolded proteins are removed, UPR is deactivated and normal proteostasis resumed (Chakrabarti et al., 2011). However, under conditions of chronic cellular stress a sustained UPR activation ultimately results in maladaptation and enters a pathological phase. This is signalled via the activation of Jun-N-Kinase (JNK), downstream of IRE1, and the selective translation of the pro-apoptotic mediator CCAAT enhancer binding protein homologous protein (CHOP), promoted by ATF-4 and ATF-6 (Fig. 1). These secondary UPR mediators converge upon the B-cell lymphoma-2 (Bcl2) protein family, hence differentially regulating their activity to induce autophagy and/or apoptosis (Bassik et al., 2004; Ogata et al., 2006). The former predicts cell survival by assisting in the degradation of misfolded proteins, whilst the latter results in cell death via caspase activation.

In concert, all three UPR arms also act to promote the expression/activation of pro-inflammatory mediators via the transcription factor activating protein-1 (AP-1) and nuclear factor κB (NF-κB; Garg et al., 2012). Inflammatory cells recruited to the damaged tissues may further contribute to cellular dysfunction and apoptosis.

Many connections between UPR and traditional AD pathology have recently emerged. This has led to the suggestion that ~~it~~ UPR may be a central pathological pathway, and hence offer promising therapeutic targets for a range of neurodegenerative diseases (for an overview, see Figure 1).

~~2.1.~~ *UPR and Neurodegeneration*

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Neurodegenerative disorders are also classed as 'proteinopathies', immediately recognising the central relevance of ER- and UPR-related functions. Moreover, the vast majority of neurodegenerative cases are idiopathic, which suggest a major impact of age, environment, and lifestyle factors. Over the last decade or so, a number of post-mortem investigations have identified elevated UPR markers as present in the tissue most severely affected as a result of many neurodegenerative diseases, including AD (Hoozemans et al., 2005, 2009), tauopathies (Nijholt et al., 2012), Parkinson's disease (Hoozemans et al., 2007), Lewy body dementia (Baek et al., 2016) and amyotrophic lateral sclerosis (ALS; Atkin et al., 2008; for a recent overview, see Scheper and Hoozemans, 2015).

Specific to AD, investigations have centred on the hippocampus, and demonstrated an increase in several key markers of UPR, such as BIP, phosphorylated (p-)PERK, p-IRE and p-eIF2α (Hoozemans et al., 2005, ~~+~~ 2009; Unterberger et al., 2006). Immunohistological investigations frequently report a close association of elevated UPR markers and neurons containing pre-tangle phospho-tau pathology. The correlation between the presence of tau pathology and ER stress is further corroborated by neuropathological investigations into tauopathy cases (Nijholt et al., 2012) and from mixed-dementia cases where tau as well as α-synuclein may cause an additive burden (Baek et al., 2016). Despite this evidence, there are several studies which failed to find conclusive evidence for the induction of UPR across affected brain regions. Notably, a decline in total and phosphorylated PERK and eIF2α has been detected despite the upregulation of downstream mediators such as ATF-4, CHOP and the pro-apoptotic Bcl2 associated X (BAX) protein (de la Monte et al., 2012). Overall, the evidence appears weaker in temporal and frontal cortices than the robust detection of these UPR mediators in the hippocampus (see de la Monte et al, 2012; Baek et al., 2016). Critically, it must be considered that many negative findings stem from lysed tissues and thus prominent activation of signalling cascades restricted to specific neuronal populations may be masked. Equally, given that these principle activators of UPR are dependent on protein phosphorylation, post-mortem dephosphorylation of substrates must be considered as a factor.

~~2.1.1.~~ PERK

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The most widely studied arm of the UPR response is the PERK- eIF2α axis. This key component is central to and overlapping with the 'integrated stress response (ISR)', which is triggered by a wide range of cellular stressors. eIF2α phosphorylation regulates protein translation, cell survival and apoptosis via stress-responsive kinases. So far, these kinases comprise PERK, protein kinase double-stranded RNA-dependent (PKR), general control non-depressible-2 (GCN2) and Heme-regulated inhibitor (HRI). All are regulated by dimerization and autophosphorylation; however, signal specificity specificities arise due to each kinase having differing sensitivity to varying cellular stressors, differential subcellular locations and additional substrates beyond eIF2α. Whilst HRI is restricted to cells of the erythroid cell linage and reactive to iron deficiency, PERK, PKR and GCN2 are widely expressed and prominent within the CNS. PERK is the principle kinase for eIF2α phosphorylation in response to ER stress, yet PKR activation also occurs in response to inflammatory, oxidative and ER stress as well as viral infection. Similarly, GCN2 demonstrates overlapping activation stimuli and responds towards viral infection, amino-acid and glucose depletion, as well as UV irradiation (Donnelly et al., 2013).

The rate-limiting step in de-novo protein synthesis is translational initiation via presentation of Met-tRNA^{Met} by eIF2 complex to the ribosomes. This association of Met-tRNA^{MET} with eIF2 is regulated by the binding of GTP, which, after hydrolysis to GDP, requires replacement with GTP by the nucleotide exchange factor eIF2B. The phosphorylation of eIF2α at Ser^{51} induced by ISR kinases effectively inhibits the association of eIF2B, preventing GTP exchange. Thus, the levels of eIF2α bound to GTP required for the presentation of Met-tRNA^{MET} fall, effectively preventing ribosomes from initiating translation (reviewed in Donnelly et al., 2013). Even though overall translation is heavily reduced as a consequence, translation of mRNA with inhibitory upstream open reading frames (ORF) is paradoxically increased, as altered ribosomal engagement can bypass this region, promoting their translation. It is by this mechanism that ER stress and thus eIF2α phosphorylation can lead to increased expression of activating transcription factors such as ATF-4 and consequently CHOP (Vattem and Wek, 2004 and Palam et al., 2011).

Of notable relevance for AD is the enhanced expression of ATF-4 and CHOP, but also β-secretase (BACE1), all derived from mRNA mRNA-containing inhibitory ORFs (Lammich et al., 2004; Zhou and Song, 2006). As BACE1 is the rate-limiting secretase for the cleavage of amyloid precursor protein (APP), several studies have demonstrated that eIF2α phosphorylation, induced either by PERK (O'Connor et al., 2008) or PKR (Mouton-Liger et al., 2012), can ultimately facilitate BACE expression and thus β-amyloid (Aβ) production. Recent work suggests a further mechanism of eIF2α phosphorylation to modulate Aβ production, as ATF-4 regulates both BACE1 as well as α-secretase–/–ADAM10 (Reinhardt et al., 2014). However, the overall impact of such regulations remains to be fully determined.

In addition to the modulation of Aβ production, the PERK-eIF2α axis is critically involved in the regulation of synaptic plasticity, and thus mechanisms involved in memory formation,

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likely via direct actions as opposed to actions downstream from amyloid β (Aβ) production. Protein translation is required for memory formation, and recent evidence has highlighted eIF2α as the limiting factor. Hence, the prolonged phosphorylation of eIF2α could essentially deny neurons the de-novo proteins required for structural adaptations such as synaptic remodelling, essential for learning and memory. Indeed, wild-type mice treated acutely with a p-eIF2α inhibitor (ISRIB, see below for more details) demonstrated enhanced memory performance in both hippocampus-dependent and -independent learning tasks (Sidrauski et al., 2013), and the transient inhibition of PERK was associated with enhanced cortex-dependent taste learning (Ounallah-Saad et al., 2014). Interestingly, despite the superior performance of genetically deficient PERK mice in behavioural tasks that require protein synthesis for learning, such mice demonstrated reduced working memory in several tasks known to be independent of protein synthesis. The latter may indicate an additional role of PERK in the regulation Ca^{2+} dynamics (Zhu et al., 2016). Nevertheless, the regulation of protein synthesis dependent memory via p-eIF2α is likely to be multifaceted, as ATF-4 (aka CREB-2) is widely accepted to be a repressor of cAMP-responsive element (CREB~~))~~-mediated gene expression, required for the conversion of short- to long-term memory (Kida and Serita, 2014). Although a variety of consequences for memory and long-term potentiation have been observed following inhibition of each of the eIF2α kinases (Trinh and Klann, 2013), Aβ-mediated inhibition of LTP in hippocampal slices was dependent on PERK. Conversely, the deletion of PERK prevented the elevation of p-eIF2α levels, inhibition of protein translation ~~as well as~~and memory deficits in a variety of behavioural paradigms, in a familial AD (APPswe/PS1ΔE9) mouse model (Ma et al., 2013). Similar results have been observed in 5xFAD mice where PERK but not GCN2 haplo-insuffciency blocked the age-dependent increase in BACE1 expression, alongside memory deficits and cholinergic degeneration (Devi and Ohno, 2013 + 2014).

Evidence for the activation of PERK in response to exogenous Aβ is weak, as only aggregated, fibrillar Aβ and not oligomeric Aβ increased PERK phosphorylation (Lee et al., 2010). On the other hand, accumulation of pathological tau reportedly resulted in PERK activation (Abisambra et al., 2013; Radford et al., 2015). Hence, Aβ may act indirectly via tau pathology, or alternatively via inflammatory stressors such as Tumour Necrosis Factor α (TNFα), which activates PKR and hence the p-eIF2α mediated inhibition of protein translation. This would also result in the activation of the additional arms of UPR (Lourenco et al., 2013; Clarke et al., 2015).

~~2.1.2~~ IRE1

Distinct from the PERK axis of the UPR, ~~IRE1~~ IRE1-mediated pathways are also closely associated with AD pathology. IRE1 is a trans-ER-membrane protein containing both endoribonuclease and serine/theronine kinase domains within the cytoplasmic domain (Tirasophon et al., 1998). Once unbound from BIP, IRE1 oligomerises and autophosphorylates,

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which activates ~~IRE1's~~ the endoribonuclease domain of IRE1 and generates X-box-protein-1 (XBP-1) mRNA (Yoshida et al., 2001). At rest, XBP-1 mRNA exists in an unspliced form (XBP-1u), i.e. the DNA-binding domain and the activation domain are separated by an intronic sequence. The translation of XBP-1u mRNA results in a protein deficient for gene activation, which is rapidly degraded. In contrast, upon activation of IRE1's nuclease activity, the intronic sequence of XBP-1u is excised, inducing a frame shift which allows for full translation of XBP-1s, a competent transcription factor (Yoshida et al., 2007).

Although a degree of cell ~~type~~ type-specific gene activation has been reported, approximately ~~~95 core genes are upregulated as a result of XBP-1 splicing, ~~these~~ which include ER co-chaperones for BIP, ERDJ4 as well as $P58^{IPK}$ and modestly BIP itself, but also calrecticulin and calnexin, as well as components of ERAD such as ER degradation-enhancing α mannosidase-like protein, but also core UPR mediators such as PERK, ATF-4 and XBP-1 (Lee et al., 2003; Acosta-Alvear et al., 2007). Together, this profile likely enhances the ~~protein~~ protein-folding capacity of the ER and facilitates protein clearance. It may also provide a feedback loop to modulate the ongoing UPR by increasing key UPR mediators, but also via the elevation of $P58^{IPK}$ ~~w~~, which not only acts as a protein chaperone but is also associated with the inhibition of eIF2α kinases, PERK and PKR (Yan et al., 2002; van Huizen et al., 2003).

The activation of IRE1 is acutely associated with cell survival, yet during sustained ER stress is linked with apoptosis. In addition to classic ER ~~stress~~ stress-related transcription, a number of AD-relevant gene transcripts may also be regulated, for example the γ-secretase components presenilin 1 (PS1) and ~~Nicastrin~~ nicastrin as well as APP trafficking proteins and the tau kinase cyclin dependent kinase 5 (Acosta-Alvear et al., 2007). However, such observations were based on the ectopic expression of XBP-1s in muscle and secretory cells. In contrast, overexpression of XBP-1 in cells of a neuronal lineage strongly enhanced the expression of ADAM10, which was recapitulated following pharmacological induction of UPR (Reinhardt et al., 2014).

Across the spectrum of neurodegenerative conditions, the involvement of XBP-1 appears inconsistent. *In vitro* evidence has suggested strong activation by both α-synuclein and Aβ oligomers, yet XBP-1 appears relatively insensitive to other toxic aggregates, e.g. prion protein or the familial British dementia amyloid protein (Castillo-Carranza et al., 2012). In mouse models of ALS (Hetz et al., 2009) and Huntington's disease (Vidal et al., 2012), the genetic removal of XBP-1 protected against the onset of disease, while *increasing* XBP-1 expression appeared protective against Aβ toxicity in cultured neurons (Casas-Tinto et al., 2011). This protective potential is supported by observations in both the 5xFAD and an APP/PS1 AD mouse model, where early, pre-symptomatic upregulation of spliced XPB-1 coincided with an increased ADAM10 expression, followed by a late stage collapse of XBP-1 associated with disease progression (Reinhardt et al., 2014). Again, post mortem data report either an increase of IRE1 mediated activation of XBP-1 (Lee et al., 2010), or conversely a

decrease of spliced XBP-1 mRNA levels despite a prevalence of increased IRE1 activation (Reinhardt et al., 2014).

Together, the data imply that prolonged UPR signalling may lead to XBP-1 downregulation. Certainly, downregulation of XBP-1 would mimic the mechanistic consequences of the XBP-$1^{116C/G}$ polymorphism, which disrupts the XBP-1 binding motif and results in lower level of transcription (Kakiuchi et al., 2003). This has recently been identified as an AD risk gene within the Chinese population (Liu et al., 2013). Similarly, a disruption of XBP-1 signalling may also affect the cellular pathology of familial AD, where PS1 mutations have been observed to downregulate IRE1 signalling (Katayama et al., 1999 and 2001).

With respect to Aβ-mediated toxicity, the nuclease activity of IRE1 may appear neuroprotective. H~~,~~ ~~h~~owever, IRE1 also interacts with numerous additional substrates via its kinase domain, including TNF associated factor 2 (TRAF2) leading to the activation of the well-established stress activated JUN N-terminal kinase, JNK (Urano et al., 2000). Additional connections between IRE1 and JNK comprise numerous cellular stimuli capable of JNK activation, including inflammatory signalling via TNFα and interleukin-1 (IL-1), oxidative stress, UV irradiation and growth factor deprivations (Cui et al., 2007). Various stimuli engage mitogen activated kinase kinase kinases (MAPKKK) which in turn targets MAPK kinases, specifically MAKK4 and MAKK7, ultimately phosphorylating JNK. This induces nuclear responses (including the canonical c-Jun substrate and nuclear hormone receptors) as well as several cytoplasmic changes in ubiquitination-mediated protein degradation, insulin receptor substrate 1 and Bcl2 proteins (Bogoyevitch and Kobe, 2006) and pro-inflammatory AP-1 (Garg et al., 2012, see below). JNK signalling undoubtedly plays important physiological roles, e.g. in brain development, synaptic plasticity and neuronal regeneration, but prolonged activation of JNK is prominently associated with apoptosis (Mehan et al., 2011).

In addition, JNK is capable of phosphorylating tau (Reynolds et al., 1997; Anderton et al., 2001), but also targets a number of substrates relevant for the Aβ cascade. Upstream from the Aβ, APP is an effective substrate of JNK and its phosphorylation at Thr668 effectively promotes amyloidogenic cleavage (Standen et al., 2001~~, and~~ Sclip et al., 2011), potentially via modulation of intracellular APP trafficking (Triaca et al., 2016). Downstream signalling links JNK with apoptotic pathways, likely via the modulation of apoptotic Bcl2 proteins (Troy et al., 2001). Consequently, elevated JNK activation, in particular of the p54 forms, has been linked with the age-dependent production of Aβ in murine APP/PS1 (Shoji et al., 2000; Savage et al., 2002), but also in FTD models (Allen et al., 2002). As oligomeric Aβ may trigger tau hyper-phosphorylation in a JNK dependent manner (Ma et al., 2009; Zhang et al., 2016a[a]), JNK emerges as a potential link and common denominator for stress responses activated by both Aβ and tau pathologies. Post-mortem studies further support ~~the~~ this association~~, of~~ with progression of tau pathology in human AD, i.e. high cytoplasmic levels are found in neurofibrillary tangle~~s~~-bearing neurons, but also in a substantial number of tau-positive

neurons without mature aggregates (Pei et al., 2001; Lagalwar et al., 2006). Corresponding findings have also been observed in cases of human FTD (Lagalwar et al., 2007).

Recently, IRE1 has also been linked to the activation of another principle tau kinase, glycogen synthase 3β (GSK3β;; Kim et al., 2015). At least in peripheral tissues the activation of GSK3β by IRE1 has been observed, alongside changes in pro-inflammatory cytokines, IL-1 and XBP-1 splicing, leading to a reduction in TNFα (Kim et al., 2015). In neuronal cell lines a similar increase in GSK3 activity has also been reported following pharmacological UPR induction, yet this shift in activation was attributed to the selective degradation of inhibited GSK3 as opposed to enhanced tyrosine phosphorylation, in accordance with post-mortem investigation (Nijholt et al., 2013).

GSK3β has demonstrated a striking efficiency in phosphorylating tau and a close association with AD pathology (Maqbool et al., 2016). Contributions specifically linked with UPR were identified in neuronal cell lines and primary hippocampal neurons (but not fibroblasts or astrocytes), where GSK3 activation appeared to contribute to ~~UPR~~ UPR-induced apoptosis, either by caspase-3 activation induced by CHOP (Meares et al., 2011) and/or the regulation of key ~~ER~~ ER-resident proteins, γ-taxilin and α nascent polypeptide-associated complex subunit, two proteins which are downregulated in AD (Hotokezaka et al., 2015). In an APP/PS1 mouse model, GSK3β activation appeared to facilitate ~~UPR~~ UPR-mediated cell death following a series of sub-threshold hypoxic events, as well as exacerbating tau phosphorylation (Wang et al., 2013).

Therefore, both JNK and GSK3β provide mechanistic links between key AD pathologies and UPR.

~~2.1.3.~~ ATF-6

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The third arm of UPR involves ATF-6, an ~~ER~~ ER-resident transmembrane protein. It is inactive in the BIP-bound form, but following the loss of BIP association is trafficked to the Golgi apparatus, where proteolysis (via site 1 and 2 proteases) activates the protein and enables nuclear transcription of key ER proteins, including chaperones (e.g. BIP, GRP94 and Calreticulin) and ERAD components (Shen et al., 2002). ATF-6 also regulates enzymes for disulphide-bond formation related to the Ca^{2+} homeostasis, including SERCA2 gene (Okada et al., 2002). Notab~~ilit~~y, there is some functional redundancy with XBP-1 in relation to BIP and other protein chaperones and ERAD proteins (Lee et al., 2003, Yamamoto et al., 2004), but also with ATF-4 in relation to the expression of CHOP (Okada et al., 2002). The ATF-6 pathway is arguably the least investigated in relation to neurodegeneration, with few studies conducted to establish its role in human diseases or engagement of pathological cascades. Nevertheless, at least in Parkinson's disease, the *activation* of ATF-6 has been shown to be protective, in association with an increased expression of the ERAD machinery (Egawa et al., 2011) yet the deposition of α-synuclein may inhibit ATF-6 activation and ER-Golgi trafficking (Credle et al., 2015). Despite this protective role, recent work suggests that administration of

taurine, may protect aged rats from isoflurane-induced hippocampal apoptosis via the reduction of CHOP in an ATF-6 dependent manor (Zhang et al., 2016b[b]). These contradictory findings~~,~~ highlight~~ly~~ the need for increased research into the role of ATF-6 in AD and it~~'~~s pathology.

~~3.~~ Secondary AD pathologies

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Beyond the primary AD pathologies and their implications for neuronal plasticity, UPR likely plays an additional role in other degenerative processes. ER stress is closely associated with autophagy, inflammation and Ca^{2+} dyshomeostasis, each of which is implicated in the exacerbation of AD.

~~3.1~~ *UPR & Autophagy*

Macroautophagy is heavily implicated in the clearance of toxic protein species, including tau and Aβ (Kim et al., 2011; Salminen et al., 2013), yet in AD, key autophagic proteins such as Beclin-1 are progressively reduced, sequestered or cleaved, which correlates with cognitive decline (Pickford et al., 2008, Jaeger et al., 2010; Ma et al., 2010). Despite the protective role of autophagy as an outcome of UPR, deregulated autophagic processes in AD may facilitate disease progression and favour apoptosis. Outcomes are dependent on the balance, expression and activity of key Bcl2 proteins, controlled by CHOP (Galehdar et al., 2010) and JNK phosphorylation (Bassik et al. 2004), respectively, which modulate autophagy via interactions with Beclin-1 (Pattingre et al., 2005, Maiuri et al., 2007; Luo et al., 2012).

~~3.2.~~ *UPR & Inflammation*

Neuroinflammation is mediated by multi-protein inflammasomes against exogenous pathogens and metabolic by-products and involves pro-inflammatory caspases which activate cytokines (e.g. IL-1β, IL-18, and IL-33). At present, the nucleotide-binding oligomerization domain-like receptor family, pyrin domain-containing-3 (NLRP3) is the best characterized inflammasome in AD (Pennisi et al., 2016). Cytokine- and chemokine-expressing microglia surround Aβ plaques; and overall levels of these pro-inflammatory agents are elevated in AD brain tissue (Akiyama et al., 2000). The recruitment of activated glia via pro-inflammatory agents is regulated by AP-1 and NF-κB (Glass et al., 2010). Of interest here is that PERK and IRE1 converge to promote the activation of these transcription factors: PERK via the eIF2α-mediated downregulation of the NK-κB inhibitor IκB (Jiang et al., 2003) and IRE1 via the promotion of IκB degradation and activation of AP-1 via JNK phosphorylation (Hu et al., 2006;

Kaneko et al., 2003). Thus, UPR activation has the potential to exacerbate pro-inflammatory signalling and ultimately immune-driven cellular damage and neuronal death.

~~3.3~~ *UPR, Ca^{2+} homeostasis and mitochondrial function*

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Cellular dysfunctions and impaired homeostatic UPR has wide-ranging consequences on protein translation, but also affects other aspects of cellular physiology such as Ca^{2+} homeostasis and mitochondrial ATP production. ~~UPR~~ UPR-mediated adaptations have a clear potential to compromise ER physiology and Ca^{2+} homeostasis, for example via altered IP_3 receptor activation (Nutt et al., 2002), Ca^{2+} binding protein chaperones, such as calreticulin, and ~~as well as~~ regulatory enzymes, including various kinases and phosphatases such as PTP1B (Agouni et al., 2011), which we have identified as a key regulator of SOCC (Koss et al., 2013). Consequently, altered Ca^{2+} buffering can increase ER luminal Ca^{2+} uptake, facilitate agonist-mediated Ca^{2+} release, affect ER-mitochondria tethering and Ca^{2+} exchange, and suppress SOCC. These changes are key hallmarks of excitotoxicity and lead to enhanced tau phosphorylation, as reported for example after experimental depletion of ER Ca^{2+} stores (Hartigan and Johnson., 1999). ER stress-induced Ca^{2+} dysregulation, as well as changes in Bcl2 proteins (Adams and Cory, 1998) can disrupt mitochondrial activity, leading to the collapse of ATP production and apoptotic processes (Vannuvel et al., 2013). Recently, "mitochondrial association membranes" (MAM) have emerged as substrates for ER-mitochondria interactions. MAM are specialised areas for lipid metabolism and Ca^{2+} transfer (Paillusson et al., 2016) but also for Aβ production (Schreiner et al., 2015). Interestingly, several key ER chaperones, including BIP, calreticulin and calnexin are enriched in MAM (Hayashi et al., 2009). MAMs are reportedly decreased in ALS, Parkinson's disease, and ~~as well as~~ TDP-43 variants of fronto-temporal dementia (Paillusson et al., 2016), but evidence from post-mortem studies as well as rodent AD models suggest an actual increase in ER-mitochondria associations (Hedskog et al., 2013). Similar findings have been reported in fibroblasts isolated from both sporadic and familial AD cases (Area-Gomez et al., 2012), and nanomolar Aβ concentrations also appeared to promote ER-mitochondria associations as well as Ca^{2+} transfer in neuronal cultures (Hedskog et al., 2013). Additionally, chemically induced ER stress led to similar changes, but these were followed by a collapse of ATP production and apoptotic activation ~~followed~~ (Bravo et al., 2011; Vannuvel et al., 2013). Clearly, these studies imply that mitochondrial pathology and disrupted Ca^{2+} handling ~~lay~~ lie downstream of the UPR.

~~4.~~ Emerging therapeutic targets

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The cellular cascades engaged by UPR activation offer numerous molecular sites and pathways for pharmacological intervention. However, the diverse signalling components involved and their upstream-/-downstream pathways paint a complex picture that presents challenges, as a complete mechanistic understanding is at present missing.

~~4.1.~~ *Chaperones*

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A key concern when therapeutically targeting UPR components is that the ER stress response is, at least acutely, protective and essential for normal cellular physiology, and therefore caution must be taken when targeting this cascade. One potential strategy is to promote chaperones in support of the capacity of the ER~~'s capacity~~ for protein handling (proteostasis) and prevent the induction of chronic UPR, instead of attempting selective downstream inhibition.

In line with this strategy several avenues have been explored in models of neurodegeneration (see Table 1). However, many compounds exert a range of cellular actions, which makes interpretation of data difficult. Of note, a recent review suggests that a clearer distinction should be made between genuine endogenous chaperons (such as HSPs) and other chemical chaperones and 'proteostasis promoters', as the actions of the latter compounds are likely indirect (Vega et al., 2016).

~~4.1.1.~~ ER chaperones

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Drugs promoting the expression of ~~ER~~ ER-specific HSP chaperones may offer a mode of intervention, but limited candidate molecules are available at present. To date, only one such drug has been identified, i.e. BIP inducer X (BIX), identified via a high throughput BIP reporter assay. BIX (1-(-3,4-dihyrdoxy-phenyl)-2-thiocyanate-ethanone) induces a transient increase in BIP expression at low micromolar concentrations, as well as modest increases in GRP94, calreticulin, ~~but~~ and also CHOP (Kudo et al., 2008). The induction of these ER stress components is observed in the absence of PERK or IRE1 activation, yet appears dependent on ATF-6 signalling. It protects against chemically induced ER stress and resultant apoptosis, as well as ~~the~~ cerebral infarcts, where notably an overall decrease in CHOP expression was observed (Kudo et al., 2008; Oida et al., 2008). These results have been largely confirmed in response to NMDA and ~~Tunicamycin~~ tunicamycin-induced retinal damage (Inokuchi et al., 2009). Although *in vivo* data indicate a narrow therapeutic window in relation to vessel ~~occlusion~~ occlusion-induced cerebral infarct (effective at 3h~~r~~ but not 6h~~r~~ post insult~~;~~ Oida et al., 2010), such limitations may not be of concern when dealing with a progressive neurodegenerative disorder. There are at present no reports on the potential of BIX ~~'s potential~~ to perturb the neuropathology or cognitive decline associated with dementia, although the genetic overexpression of BIP has proven protective in models of Parkinson's disease (Gorbatyuk et al., 2012).

Several other compounds show potential to induce increased BIP expression, which appears linked to the inhibition of histone deacetylates (HDAC). These include the pan-HDAC inhibitor ~~Trichostatin~~ trichostatin A and the class ~~I~~ I-specific HDAC inhibitor MS275 (Baumeister et al., 2009), but also the mood-stabilising drug valproic acid, which also promotes BIP expression dependent on HDAC inhibition (Wang et al., 1999; Shi et al., 2007). Mechanistically, these drugs appear to inhibit the endogenous repression of HDAC upon the ER stress response

element (ERSRE), in turn promoting BIP expression. Although numerous HDAC inhibitors have been tested in AD models *in vivo*, and beneficial outcomes reported, i.e. successful modification of neuropathology and preservation of cognition (Yang et al., 2014; Bang et al., 2015; Klein et al., 2015), the modulation of ER stress pathways in these models remains to be determined.

~~4.1.2.~~ Proteostasis promoters

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Two well-described compounds in this category are tauroursodeoxycholic acid (TUDCA), a taurinated form of the endogenous bile acid ursodeoxycholic acid (UDCA), and 4-phenyl butyric acid (PBA). These have long been part of health supplements and traditional medicines, and are currently used for e.g. liver and muscle support, or urea cycle disorders, respectively. They are well established protectants against excess UPR, either when induced pharmacologically (Malo et al., 2010; ~~+~~ 2013) or in systemic disease models, such as T2D (Özcan et al., 2006).

Although commonly referred to as chemical chaperones, it remains unclear if these two principle compounds behave as such. TUDCA has demonstrated only limited inhibition of protein aggregation. It acted primarily indirectly to enhance the properties of endogenous chaperones, e.g. by facilitating anti-aggregate capabilities of α-crystallin in retinal lens extracts (Song et al., 2011). Equally, TUDCA failed to alter the aggregation of synthetic $A\beta_{1\text{-}42}$, despite inhibiting apoptosis induced by similar Aβ application to endothelial cells (Viana et al., 2009). Given the nature of aggregation assays, these findings are in line with the potential of TUDCA to moderate endogenous protein handling rather that direct interaction with the aggregating proteins, though the exact mechanisms remain to be determined. Somewhat more robustly, PBA directly inhibits aggregation when tested against α-lactalbumin and bovine serum albumin (Kubota et al., 2006). However, lacking evidence for its ability to inhibit Aβ or indeed tau aggregation, it remains plausible that PBA may regulate ~~AD~~ AD-relevant protein aggregation, or indeed ~~more generally~~ AD pathology more generally, by other means (see below).

Despite this uncertainty, both TUDCA and PBA have been well established as neuroprotective agents against synthetic Aβ and in APP/~~PS1~~ PS1-expressing cell lines and primary cultures (Ramalho et al., 2006; Dionisio et al., 2015; ~~and~~ Zhang et al., 2016a~~6~~[a]). Although most studies have not specifically investigated alterations in the ER stress machinery, neuroprotection can rather consistently be attributed to the blocking of mitochondria-dependent apoptotic pathways via Bcl2 proteins, the reduction of several caspases and the inhibition of JNK signalling cascades, at least when tested *in vitro* (for examples and details, see Table 1). This is consistent with the involvement of mitochondria in Aβ-induced apoptosis and the recent

finding that PBA reduces the expression of CHOP and BIP, as well as tau phosphorylation following Aβ oligomer treatment of PC12 and primary neuronal cultures (Zhang et al., 2016a).

In accordance with the *in vitro* work, several groups have identified an effective reduction in Aβ load, restoration of cognitive function and a preservation of neuronal integrity in AD mouse models following various treatment regimes with TUDCA or PBA (see Table 1). Best outcomes were often achieved following pre-symptomatic treatment. Long-term treatments commonly perturbed Aβ plaque deposition, reduced GSK3β activation along with tau phosphorylation, and increased glutamatergic receptor subunit expression as well as ~~maintained~~ maintaining synaptic integrity (Wiley et al., 2011; Ricobaraza et al., 2012). Similar findings have recently also been reported in an FTD model that expresses an aggregate-prone tau fragment (Bondulich et al., 2016). In many studies, the amelioration of AD-relevant neuropathology occurred alongside improvements in cognition. Shorter treatments given post-symptomatically also improved cognition and reduced tau phosphorylation, while Aβ profiles were inconsistent. An effective decrease of cortical Aβ plaques following a 6 months TUDCA treatment of APP/PS1 mice was reported when given prior to plaque deposition (Nunes et al., 2012; Lo et al., 2013) yet when given following frontal plaque formation failed to diminish the load and only reduced the late-stage hippocampal plaque pathology (Dionísio et al., 2015). Similarly, treatment of aged Tg2576 mice with PBA did not reduce plaque load and even Aβ production, yet cognition and synaptic integrity improved alongside a decreased tau phosphorylation (Ricobaraza et al., 2009).

Therefore, proteostasis promoters may fail to aid plaque clearance and only prevent plaque formation. This is also supported by the reduced neuronal loss observed in $hAPP_{WT}$ overexpressing mice in the absence of plaques and Aβ over-production (Cuadrado-Tejedor et al., 2013), which is indicative of alternative mechanisms of action such as the noted HDAC inhibition activity (Kubota et al., 2006). However, comparative studies with PBA and other HDAC inhibitors that do not affect the ER's chaperone system have demonstrated ~~PBA's~~ selective effects of PBA, both for ER-stress induced neuronal toxicity *in vitro* (Mimori et al., 2013) and in AD models (Cuadrado-Tejedor et al., 2013).

~~4.2.~~ *PERK & eIF2α inhibitors*

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Despite the evidence provided by genetic manipulation of PERK or its immediate downstream substrate eIF2α in models of AD, there are surprisingly few studies utilising pharmacological inhibitors of PERK (See Table 1). Two such compounds are GSK2606414 (Axten et al., 2012) and the inhibitor of the downstream targets of eIF2α, the so called 'integrated stress response inhibitor' ISRIB (Sidrauski et al., 2013). *In vitro*, GSK2606414 was effective at inhibiting UPR-mediated tau phosphorylation in SH-SY5Y cells (Van der Harg et al., 2014) and has demonstrated a dose-dependent inhibition of p-eIF2α activation without altered CHOP or ATF-4 levels in isolated astrocytes, leading to a decrease in the expression of pro-inflammatory cytokines (Guthrie et al., 2016). Currently, there are no reports of this neuroprotective potential of GSK2606414 following either AD gene expression or Aβ

challenge. GSK2606414 has only been tested in prion and tauopathy models and although a promising reduction of neuronal loss, decreased tau phosphorylation and GSK3β expression ~~was~~ were reported, cognitive performance was not assessed (Radford et al., 2015). Upon its initial use *in vivo*, GSK2606414 showed impressive neuroprotective properties, drastically reducing any neurodegeneration in response to prion protein inoculation and substantially reducing attrition rates. However, systemic inhibition of PERK caused pancreatic toxicity, leading to weight loss and high attrition rates, which has severely limited the drug's therapeutic potential (Moreno et al., 2013). More recently, a follow up study using ISRIB, which appears devoid of pancreatic toxicity, achieved similar degrees of neuroprotection against prion protein inoculation. ISRIB reportedly acts via an as yet unresolved mechanism that inhibits downstream signalling of eIF2α, partially restoring protein translation without altering eIF2α phosphorylation levels (Halliday et al., 2015). Although examination of pancreatic tissue has demonstrated no signs of toxicity or tissue loss, significant weight loss was still apparent, the cause of which remains to be determined. Currently, no reports have emerged on the use of ISRIB within AD or FTD models.

~~4.3.~~ *IRE1 modulators*

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Few small molecule modulators of IRE1 have been developed thus far. The best characterised is 4-methylumbelliferone 8-carbaldehyde (4μ8C), which targets and inhibits the endoribonuclease function of IRE1 (Cross et al., 2012), in a similar manner to STF-083010 (Papandreou et al., 2011); ~~;~~ hence, such drugs fail to address the potentially diminished XBP-1 splicing in AD. Equally, several other compounds identified as IRE1α modulators block XBP-1 splicing whilst actually increasing IRE1 kinase activation and thus autophosphorylation (Volkmann et al., 2011). Thus, the dual functional domains of IRE1 in AD and the apparently divergent kinase activation (increased) and endoribonuclease function (reduced) means that pharmacological targeting of this enzyme is at present problematic.

Despite these issues, some progress towards pharmacological manipulations specific for one functional domain of IRE1 have been made. A comparative study of novel compounds related to PBA (see above) has demonstrated potent inhibition of both kinase and endoribonuclease functions of IRE1 and as well as the ATF-6 pathway, which may be independent from HDAC (Zhang et al., 2013). However, further structural refinement may be needed to offer specific inhibition of the ~~IRE1's~~ kinase function of IRE1, as some analogues favoured the inhibition of JNK over XBP-1 splicing (Zhang et al., 2013). Indeed, genetic manipulation of the IRE1 kinase domain can produce a kinase-dead IRE1 variant, which still maintained intact RNase functionality (Rubio et al, 2011). This work essentially demonstrated that the two functional domains can operate in isolation, and thus the selective targeting of each is theoretically possibly. Targeting the RNase domain whilst inhibiting ~~-~~/~~-~~blocking the kinase activity may be possible, although no such reports exist for mammalian cells (Korennykh et al., 2009; Wiseman et al., 2010). Also, the activation of the IRE1 kinase domain may be required for UPR

deactivation~~;~~, therefore, kinase-dead IRE1 variants may be more vulnerable to ER stress. Nevertheless, several small molecule activators of IRE1 RNase activity have now been developed, but cell toxicity remains an issue (Mendez et al., 2015). Interestingly, a significant reduction in toxicity could be achieved by co-administration of the PERK inhibitor GSK2606414.

Ultimately, the complexity of targeting IRE1 directly suggests that selective inhibition of downstream effector kinases involved in the propagation of the apoptotic cascade may be a more promising approach to interrupt chronic UPR and establish protection.

~~4.4~~ *JNK*

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In comparison to many of the other ~~UPR~~ UPR=related targets, there have been more thorough investigations into the development of effective JNK inhibitors and characterisation of the resulting neuroprotective outcomes in multiple models of AD and other neurodegenerative disease (see Table 1). An excellent review has recently been published covering the subject extensively (Yarza et al., 2016). Here, particular attention will be given to the direct ATP-competitive inhibitor SP600125, which has been investigated in relation to UPR and AD neurodegeneration.

SP600125 has relatively high specificity for JNK1-3 over other related kinases (Han et al., 2001). A number of studies have demonstrated substantial neuroprotection with SP600125 towards Aβ mediated apoptosis *in vitro* (Yao et al., 2005; Bamji-Mirza et al., 2014; Xu et al., 2015). SP600125 when given prior to or in combination with oligomeric Aβ mediated a number of UPR relevant signalling pathways, such as the inhibition of Aβ mediated suppression of anti-apoptotic Bcl2 proteins Bcl-XI and Bcl-W (Yao et al., 2005) as well as the prevention of a key downstream apoptotic effector of CHOP, GADD43 (Xu et al., 2015). Similar protective effects have been observed *in vivo* following acute application of SP600125, e.g. in rats intra-hippocampally injected with fibrillary $A\beta_{1\text{-}42}$ (Ramin et al., 2011; Yenki et al., 2013; Mahammadi et al., 2016). These studies report preservation of cognitive abilities alongside a lower pro-apoptotic expression ratio between Bcl2 and BAX, decreased caspase expression and reduction of autophagic markers. Unfortunately, no direct quantification of the principa~~l~~~~e~~ activators of UPR, nor its modulation by JNK inhibition, was reported. Similarly, promising effects have been described following chronic SP600125 treatment or the application of the D-~~JNKI1~~ JNKI1-inhibiting peptide in AD mouse models, but a direct investigation of UPR aspects remain unexplored (Sclip et al., 2011; Zhou et al,. 2015). However, the treatment of a rat model of AD with the ginsenoside Rg1, an extract known to inhibit JNK (Zhang et al., 2015), led to reduced AD pathology and apoptosis via the down-regulation of IRE1 (Mu et al., 2015).

~~4.5~~ *Other ER / UPR relevant therapeutics: GSK3 inhibitors & Ca^{2+} stabilisers*

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The central role of GSK3 in tau phosphorylation and Aβ production and its involvement in both sporadic and familial cases originally led to the GSK3 hypothesis of AD (Hooper et al., 2008). A range of inhibitors (natural, inorganic metal ions, organo-synthetic, and peptide-like) are available and have been probed in models of AD (reviewed in: King et al., 2015, see Table 1). Lithium is arguably the best-studied inhibitor, and despite its questionable specificity, was recently acknowledged as offering dementia protection in adults treated for bipolar disorders (Gerhard et al., 2015). Indeed, lithium, but also the synthetic inhibitors, alsteropaullone, 1-azakenpaullone, SB216763 and TDZD-8 as well as the GSK3-specific inhibitor peptide L803-mts, inhibits ER ~~stress~~ stress-mediated apoptosis in several neuronal models of neurodegeneration (Song et al., 2002; Chen et al., 2004; Hiroi et al., 2005; Takadera et al., 2006). Mechanistically, the protective effect of GSK3β inhibition would appear to be downstream of UPR induction, reducing CHOP expression independent of ATF-4, and leading to a reduction in caspase 3 activation and subsequent apoptosis (Meares et al., 2011). Notably, the inhibition of GSK3β, may also promote neuronal survival via the increased expression of anti-apoptotic Bcl2 proteins and BIP (Hiroi et al., 2005). Despite promising protective outcomes *in vitro* and in an *in vivo* model of acute liver failure (Chen et al., 2012), the exploitation of GSK3β inhibitors for the repression of ER stress in AD models remains to be fully investigated.

A Ca^{2+} hypothesis of AD has also been proposed (reviewed in Berridge, 2010), and as outlined before, identifies the crucial role of ER function, mitochondria and UPR for neuronal physiology and homeostatic control. A range of Ca^{2+} channel blockers specifically targeting various Ca^{2+} permeable channels, including L, P/N type voltage gated channels and the NMDA receptor have been trialled against neurodegeneration-related excitotoxicity (Nimmrich and Eckert, 2012). Of note, memantine, currently prescribed for AD patients at moderate to severe stages, has been marketed based on its NMDA antagonistic actions and the suggested prevention of Ca^{2+} overload, though it should be noted that its cholinergic properties are likely more crucial to its temporary benefits (Drever et al, 2007). Nevertheless, further meta-analysis has demonstrated beneficial outcomes following the treatment of AD sufferers with the L-type Ca^{2+} blocker nimodipine (López-Arrieta and Birks, 2002). In comparison, less work has been conducted evaluating drugs targeting ER Ca^{2+} release mechanisms via IP_3 receptors and RyR, which may more directly target ER Ca^{2+} homeostasis and impact on ER stress. Interestingly, the RyR antagonist dantrolene reduced neuronal cell death associated with UPR activation in a model of cerebral artery occlusion (Li et al., 2005) and inhibited UPR induction and subsequent cell death in a model of a rare peripheral amyloidosis (Teixeira et al., 2006). Similarly, dantrolene reduced Aβ levels, deficits in synaptic plasticity and memory impairments in several AD models (Oulès et al., 2012; Chakroborty et al., 2012; Wu et al., 2015), although varying protective mechanisms were proposed (Del Prete et al., 2014).

Crucially, changes in energy metabolism and impaired glucose handling due to failing mitochondria are central to ageing, the primary risk factor for all dementias (Bhatti et al., 2016). Latrepirdine (tradename: dimebon), an anti-histamine repurposed for treatment of AD and Huntington's disease, showed promise in experimental models and early trials largely linked with mitochondrial actions but later failed in phase III clinical trials (Bezprozyanny, 2010). Other attempts to target mitochondria directly are now under way. For example, natural polyphenols such as resveratrol, an anti-oxidant and anti-inflammatory agent found in grapes and berries, potentially offers some neuroprotection (Ahmed et al., 2016), while other inhibitors of mitochondrial fission are also being developed (Reddy, 2014), but implications for UPR pathways remain to be confirmed.

5. Conclusions

Complex signalling pathways related to neuronal homeostasis and proteostasis are currently being unravelled and provide a better understanding of cellular physiology and pathology. Regulatory mechanisms link UPR not only with protein handling, but also with Ca^{2+} homeostasis and mitochondrial function, metabolics, inflammation, autophagy and synaptic plasticity, and a number of promising therapeutic targets are now emerging. However, comprehensive investigations into these targets are still required and it is essential to identify not just opportunities but also potential pitfalls, so as to avoid failures of future clinical trials.

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Figure legend

Figure 1: Molecular pathways of UPR and potential mechanisms of cellular damage promoting AD-relevant pathology. Damaging factors such as age, environment and lifestyle (↗) affect cellular organelles and hence ER protein folding and cellular homeostasis. Impairments result in increased misfolded proteins, which accumulate in the ER lumen. These sequester protein chaperones such as BIP, and lead to the activation of three UPR-arms via PERK, IRE1 and ATF-6. The initially ***adaptive phase*** of UPR requires phosphorylation of eIF2α, halting general protein translation, whilst favouring the translation of protective stress proteins. In parallel, IRE1 activates XBP-1 alongside the cleavage and activation of ATF-6, which together promote~~s~~ the expression of key ER protein chaperones and enhance the ER protein degrading machinery (ERAD) to clear misfolded proteins. If this adaptive response can restore ER functionality the stress response is terminated. However, if the ~~ER's~~ protein~~-~~ handling capacity of the ER remains impaired and UPR persists, it enters a ***pathological phase***: the prolonged blockade of protein translation prevents structural changes essential for plasticity~~;~~ it increases amyloidogenic processing via BACE1 and PS1, alongside APP trafficking proteins as well as the induction of the pro-apoptotic mediator CHOP, which in turn increases expression of pro-apoptotic Bcl2 proteins. Supported by the activation of JNK stress kinase and GSK3, Bcl2 proteins cause mitochondrial damage as well as autophagy. In conjunction with elevated levels of JNK as well as GSK3, IRE1-mediated degradation of anti-inflammatory factors leads to the upregulation of AP-1/NFκB, promoting the production of chemokines and cytokines and hence inflammation. The continued alteration of Ca^{2+}-binding chaperones impairs Ca^{2+} homeostasis, this promotes tau phosphorylation and further impairs binding of newly translated proteins. *= Kinases activated downstream from IRE kinase domain. For abbreviations, see text.

Table legend

Table 1: UPR-targeting pharmacological agents. Drug categories are listed based on the primary mode of action, and major outcomes reported *in vitro* and *in vivo*. Phosphorylation is indicated by a "p-" prefix . Where drugs have been evaluated for protective abilities in disease models / or cellular stress the description is given in bold. ***** denotes where *in vitro* studies have been conducted in primary neuronal cultures as oppose to cell lines. Abbreviations: **Aβ** = beta amyloid, **AD**= Alzheimer's disease, **ATF-4** = Activating transcription factor 4, **ATP**= adenosine triphosphate, **BACE1**= β secretase, **BAX**= Bcl2 associated X, **Bcl** = B-cell lymphoma, **BIO**= 6-bromoindirubin-3'-oxime, **BIP** = binding immunoglobulin protein, **BIX**= BIP inducer X, **CHOP**= CCAAT enhancer binding protein homologous protein, **eIF2α** = eukaryotic initiation factor 2α kinase, **ERSRE**= endoplasmic reticulum stress response element, **GADD34** = growth arrest and DNA damage inducible protein 34, **GRP94** = glucose regulated protein 94 , **GSK3β**, Glycogen syntheses kinase 3β, **HDAC** = histone deacetylates, **IRE-1** = inositol-requiring enzyme 1, **ISRIB** = integrated stress response inhibitor, **JNK**= Jun-N-Kinase, **NF-κB**= Nuclear factor κB, **N.R.** = not reported, **PBA**= 4-phenyl butyric acid, **PERK** = PRK-like ER kinase , **RYR** = ryanodine receptor, **TDZD**= thiadiazolidinone, **TUDCA** = tauroursodeoxycholic acid, **UPR**= Unfolded Protein Response, **XBP-1** = Xbox protein 1 and **2DG** = 2-deoxy-D-glucose.