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# Endothelin-1-Induced Endoplasmic Reticulum Stress in Parkinson's Disease

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## ABSTRACT

**Background:** ET-1 is known to be implicated in various neurodegenerative diseases, including multiple sclerosis and Alzheimer's disease. However, till date, there has been little, if any, investigation into its possible involvement in Parkinson's Disease (PD). **Results:** Recent findings implicate ET-1 in the induction of Endoplasmic Reticulum (ER) stress in disease. ER stress has also been demonstrated to be an important factor in PD pathology and recent findings also indicate increased ET-1 levels in PD. **Conclusion:** The following review attempts to highlight the potential link between ET-1-induced ER stress and PD pathology.

**Key words:** Endothelin-1, endoplasmic reticulum stress, Parkinson's disease

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## INTRODUCTION

ET-1 is a vasoactive peptide synthesized and secreted by a diverse range of cells. It acts via binding two G-protein coupled receptors, the endothelin A (ETA) and endothelin B (ETB) receptors, to initiate signaling events in a wide variety of target tissues. This includes key physiologic functions, such as maintenance of vascular tone, tissue differentiation and cell proliferation (Nelson *et al*., 2003), as well as induction of pathological processes (under elevated, pathological levels of ET-1), which includes hypertension, inflammation and oxidative stress (Dong *et al*., 2005; Fiore *et al*., 2005; Kramer *et al*., 1994; Simonson and Ismail-Beigi, 2011). A recent study by Jain *et al*. (2012) has demonstrated that ET-1 also induces Endoplasmic Reticulum (ER) stress (Jain *et al*., 2012). This was shown in the context of pregnancy disorders, where ET-1 was found to induce placental ER stress by activating the PLC-$IP_3$ pathway. The broader implications of ET-1 induced ER stress and its role in pathology have since been reviewed (De Miguel and Pollock, 2013; Jain, 2013).

Previous studies have explored the link between ER stress and neurodegeneration. Disruption of ER functioning is associated with the accumulation of misfolded proteins, which are a characteristic occurrence in many neurodegenerative diseases, including Parkinson's Disease (PD) (Gorman, 2008; Soto and Estrada, 2008; Winklhofer *et al*., 2008). Furthermore, recent studies demonstrate increased ET-1 levels in PD (Calderon-Garciduenas *et al*., 2013; Makarov *et al*., 2013), which implicates ET-1 (and associated ER stress?) in the pathology of PD. The following sections review the evidence of ER stress and associated pathology in PD, as well as the potential contribution of ET-1 to PD pathology. It is hoped that this will attract future research on this topic, which might lead to new avenues of therapeutic intervention in PD. We first begin with an explanation of the role of the ER and associated ER stress pathways.

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## ENDOPLASMIC RETICULUM STRESS

In addition to being involved in the synthesis, transport and modification of membrane and secretory proteins, the ER also serves as a reservoir of calcium ions ($Ca^{2+}$) (Zhang and Kaufman, 2008). In the ER lumen, $Ca^{2+}$ is buffered by calcium-binding proteins. Many of these proteins also serve as molecular chaperones involved in folding and quality control of ER proteins (Michalak *et al*., 1998), and their functional activity alters with changes in $Ca^{2+}$ concentration. Therefore, loss of ER $Ca^{2+}$ homeostasis leads to suppression of post-translational modifications of proteins in the ER,which leads to an accumulation of misfolded or unfolded

proteins. This induces activation of ER stress response pathways known collectively as the Unfolded Protein Response (UPR) (Brostrom and Brostrom, 2003). This is a multifaceted response, which includes suppression of non-essential protein synthesis via the PERK pathway, upregulation of ER chaperone proteins and folding enzymes, via the ATF6 (activating transcription factor 6) and IRE1α (inositol-requiring 1α) pathways and activation of ER-associated protein degradation (ERAD) machinery in order to remove any remaining unfolded or misfolded proteins. Collectively, these pathways help restore ER homeostasis. However, if this fails, then apoptosis is induced in order to eliminate the stressed cell. Malfunction of ER stress responses due to aging, genetic mutations or environmental factors can result in various diseases such as diabetes, inflammation and neurodegenerative disorders (Yoshida, 2007).

## ENDOPLASMIC RETICULUM STRESS IN PARKINSON'S DISEASE

PD is a progressive neurodegenerative disease characterized by a loss of dopaminergic neurons in the Substantia Nigra Pars Compacta (SNPC) and the presence of intracytoplasmatic inclusions known as Lewy bodies (Thomas and Beal, 2007). Within the Lewy bodies, diffuse deposits of misfolded α-synuclein form the core in association with other proteins, including components of the ubiquitin-proteasome system (Gorman, 2008). Neurotoxins, such as 6-hydroxydopamine (6-OHDA) and N-methyl-4-phenyl-1, 2,3,6-tetra-hydroyridine are used as model compounds to mimic the disease process. Recent studies with cultured neuronal cells, including dopaminergic neurons, showed that these compounds trigger ER stress and induce a number of UPR target genes (Holtz and O'Malley, 2003; Ryu *et al*., 2002). Gene profiling revealed that both ER chaperones (GRP78 and GRP94) and other components of the UPR, such as the transcription factor, CHOP/Gadd153 were upregulated in exposed cells, in addition to increased phosphorylation of the ER stress kinases, IRE1α and PERK. Furthermore, neurons from PERK-/-embryos display increased sensitivity to 6-OHDA (Ryu *et al*., 2002) suggesting that at least some neurotoxins of relevance to PD kill dopaminergic neurons through mechanisms modulated by or involving ER stress and UPR signalling components (Fig. 1).

Hereditary mutations in the ER-associated E3 ubiquitin ligase, Parkin, have also been associated with ER-stress-induced cell death and are found in patients with juvenile-onset PD (Dawson and Dawson, 2003; Takahashi *et al*., 2003). Overexpression of wild-type Parkin suppresses ER stress-mediated cell death induced by α-synuclein, the principal component of Lewy bodies that represent the hallmark lesions of PD (Imai *et al*., 2000; Petrucelli *et al*., 2002; Takahashi *et al*., 2003). α-synuclein is normally enriched in nerve terminals and is involved in synaptic function. There is an increase in the levels of natively folded α-synuclein in the cytoplasm of substantia nigra neurons during normal aging and in PD (Chu and Kordower, 2007). In addition,

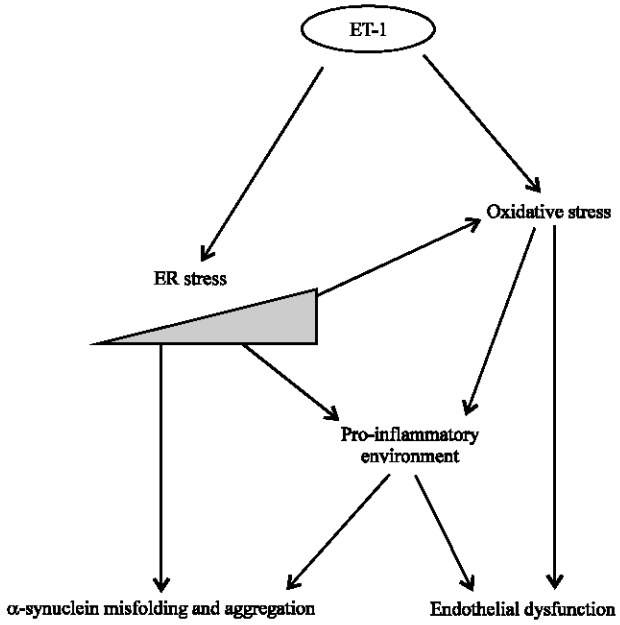


Fig. 1: ET-1 induced biochemical pathways of relevance to PD pathology

α-synuclein in Lewy bodies of PD is misfolded and aggregates accumulate (Uversky, 2007). The precise cause of the misfolding of α-synuclein is unknown but various factors are associated with aggregation of α-synuclein (Uversky, 2007). Indeed, there is also evidence of activation of the UPR with aggregation of α-synuclein. This includes increased expression of GRP78 and CHOP, as well as increased p-eIF2α levels (Doyle *et al*., 2011; Smith *et al*., 2005). ET-1-induced loss of ER $Ca^{2+}$ (Jain *et al*., 2012) would be a cause of the α-synuclein misfolding and induction of ER stress response pathways (Fig. 1). Furthermore, the Parkin-associated endothelin receptor-like receptor (Pael-R) has been shown to induce UPR-mediated cell death in models of PD (Imai *et al*., 2001). Pael-R is a putative G protein-coupled transmembrane polypeptide, which was originally identified as an ETB receptor homologue (Donohue *et al*., 1998). When over expressed in cells, this receptor tends to become unfolded, insoluble and ubiquitinated *in vivo* and insoluble Pael-R leads to UPR-mediated cell death. Parkin specifically ubiquitinates this receptor in the presence of ubiquitin-conjugating enzymes resident in the ER and promotes the degradation of insoluble Pael-R, resulting in suppression of cell death induced by Pael-R overexpression (Imai *et al*., 2001). Although this endothelin receptor-like receptor (Pael-R) has been shown to induce UPR-mediated cell death in PD (Imai *et al*., 2001), the detailed mechanisms underlying ET-1's neurodegenerative effects in PD remain to be elucidated. Previous work suggests that the ETB receptor is the key mediator of ET-1's neurodegenerative effects following intravitreal administration of ET-1 (Krishnamoorthy *et al*., 2008). This finding, together with the fact that Pael-R is an ETB receptor homolog, further supports a role in neurodegeneration for ET-1 induced ER stress (via the ETB receptor), which has been recently demonstrated by Jain *et al*. (2012) for pregnancy disorders.

## FURTHER PATHOLOGICAL PROCESSES INDUCED BY ET-1 AND RELATED ER STRESS

In addition to ER stress, both inflammation and oxidative stress are also closely associated with PD pathology (Bartels and Leenders, 2007; Block and Hong, 2005; Dauer and Przedborski, 2003; Gao and Hong, 2008; Jenner, 2003; Shukla *et al*., 2011). It is well established that inflammation is ongoing in the PD brain. It is believed that the progressive nature of PD is characterized by chronic inflammation-induced neurodegeneration of dopamine-producing neurons within the substantia nigra and striatum (Bartels and Leenders, 2007; Block and Hong, 2005; Dauer and Przedborski, 2003; Gao and Hong, 2008). There is evidence for increased levels of pro-inflammatory factors, such as tumour necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and IL-6 in the striatum and substantia nigra (Whitton, 2007). Inflammatory mediators can promote upregulation of α-synuclein and α-synuclein aggregation (Fig. 1). ET-1 has previously been shown to induce an inflammatory response in different pathologies, including pregnancy disorders and cardiovascular disease. A recent review by De Miguel and Pollock (2013) reviews the contribution of ET-1 induced ER stress to inflammation. Indeed, previous work has suggested that the ET-1 induced ER stress response can induce an inflammatory response (Jain, 2012; Jain *et al*., 2012). ER stress can stimulate the activation of pro-inflammatory responses through a number of different pathways. For instance, the ER produces ROS as a by-product of protein folding, which would be increased under conditions of ER stress during repeated attempts to refold misfolded proteins, as would also be the case under the stress response induced by ET-1 (Jain *et al*., 2012). ROS produced under conditions of ER stress initiates an inflammatory response through phosphorylation and subsequent degradation of the inhibitory subunit of NF-κB. NF-κB is a transcriptional regulator that plays a key role in the induction of inflammation (Rius *et al*., 2008). A number of factors are released upon activation of the NF-κB pathway, which includes pro-inflammatory cytokines, such as TNF-α and IL-1β, which as described above are known to be implicated in PD pathology.

Apart from stimulating an inflammatory response, ROS produced during ER stress can also contribute to oxidative stress. A large body of evidence from post-mortem studies implicates oxidative stress in the pathology of the PD brain (Jenner, 2003; Shukla *et al*., 2011). Oxidative stress can promote protein modifications, such as nitrosylation, which can cause α-synuclein misfolding and aggregation (Uversky, 2007). It has also been found that neurons exposed to such insults can develop increased α-synuclein levels (Takahashi *et al*., 2007; Vila *et al*., 2000). In addition to via ER stress pathways, ET-1 can directly induce oxidative stress, which has been demonstrated in different diseases, including neurodegenerative disorders (Briyal *et al*., 2011; Fiore *et al*., 2005; Kalani, 2008; Mi *et al*., 2012; Pollock, 2006; Potenza *et al*., 2009). The study by Briyal *et al*. (2011) demonstrated that ETA receptor antagonists block oxidative stress and associated cognitive impairment in Alzheimer's disease. Another study found that in the brain, as part of the oxidative stress and inflammatory response, activated microglia secrete pro-inflammatory factors, such as nitric oxide (NO) that induce astrocytosis and exacerbate neuronal damage (Barbeito *et al*., 2004). Several other studies have also

found excessive generation of NO and NO-derived reactive nitrogen species is implicated in the pathogenesis of neurodegenerative disorders, including PD (Calabrese *et al*., 2000; Dehmer *et al*., 2000; Uehara *et al*., 2006; Wang *et al*., 2011). Glial cells, including astrocytes, are considered the major sources of NO production from iNOS in inflammatory neurodegeneration (Bal-Price and Brown, 2001; Weldon *et al*., 1998). ET-1 is actually found to induce iNOS expression in rat brain astrocytes via the ETB receptor-dependent activation of PI3K, MAPK and NF-κB pathways (Wang *et al*., 2011). As described earlier, NF-κB would also be stimulated under the ET-1 induced ER stress response. It has also previously been found that ET-1 significantly enhances the synthesis of NO in glial cells through activation of PLC (Filipovich and Fleisher-Berkovich, 2008). The study by Jain *et al*. (2012) demonstrated that ET-1 induces ER stress via activation of the PLC-IP3 pathway. Therefore, there are several overlaps in the signaling pathways already known to be activated by ET-1 that can contribute to neurodegeneration with those demonstrated to be stimulated by the ET-1-induced ER stress response and it would be worth investigating to what extent ET-1 triggers ER stress response pathways that could contribute to PD pathology.

Further to the above, oxidative stress can also induce a plethora of different factors that cause endothelial cell dysfunction (Haorah *et al*., 2007; Heitzer *et al*., 2001; Yachie *et al*., 1999). The pro-inflammatory factors stimulated under conditions of ER stress would further compound this effect and contribute to endothelial cell injury (Fig. 1). Endothelial dysfunction is a systemic pathological state of the endothelium that is broadly defined as an imbalance between vasodilating and vasoconstricting substances produced by (or acting on) the endothelium (Deanfield *et al*., 2005). Increasing evidence implicates dysfunction of brain endothelial cells in the pathogenesis of neurodegenerative diseases, including PD (Lauwers *et al*., 2003). Furthermore, a recent study by Makarov *et al*. (2013) has identified markers of endothelial damage in PD that include increased ET-1 levels which further implicates ET-1 (and associated ER stress) in the pathology of PD. The potential importance of ET-1 in PD is also suggested by another recent study that found flavonol-rich cocoa intervention significantly decreases plasma ET-1 in test subjects, which is correlated to improved cognition and reduced development of some of the neuropathological hallmarks of PD, such as endothelial dysfunction and neuroinflammation (Calderon-Garciduenas *et al*., 2013).

## THERAPEUTIC INTERVENTION BASED AROUND ET-1 IN PARKINSON'S DISEASE

Given the evidence at hand, it would be useful to investigate the potential role of ET-1 in the pathology of PD. If implicated, future research can then investigate the efficacy of blocking ET-1 induced pathology as a therapeutic tool. Recent work has described the use of ET-1 traps as a potential therapeutic tool (Jain, 2013). The application of such a tool has the advantage of blocking the action of ET-1 through both the ETA and ETB receptors. This would have the benefit of potentially targeting all different pathological processes induced by ET-1, including ER stress, oxidative stress and inflammation that might be induced from ET-1 binding the ETA or ETB receptor. The design of ET-1 traps would require constructing a fusion molecule encompassing the different domains of interaction between ET-1 and each of its receptors. As previously described, this would then need to be fused to the Fc portion of human IgG1, which would direct formation of disulfide-linked dimers (Economides *et al*., 2003; Jain, 2013). Transfection of these expression constructs into mammalian cells would result in secretion of the desired dimeric inline trap, which would act as a soluble receptor that binds ET-1 and therefore prevents it binding the target cell surface receptors. Another approach would be to design therapeutic antibodies against ET-1. There have been recent advances in the design of therapeutic antibodies (Chames *et al*., 2009), which may be exploited in the development of therapeutic antibodies against ET-1. These would again have the advantage of potentially blocking the pathological actions of ET-1 through both receptors.

## CONCLUSION

It is hoped that this review has highlighted the potential pathological role of ET-1 in PD. ET-1 could be a key mediator of ER stress, inflammation, as well as oxidative stress, which are all important pathological processes in PD. Needless to say, the primary objective would be to first verify the role of ET-1 in PD pathology. Subsequent investigation into potential therapeutic strategies for circumventing potential ET-1-induced pathology might lead to the development of new strategies for therapeutic intervention that ameliorate PD pathology.

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