THE VARIOUS ROLES OF HEAT SHOCK PROTEINS IN PARKINSON DISEASE

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Abstract

The present review study was conducted to bring the attention to various roles played by heat shock proteins (HSPs) in Parkinson Disease (PD). HSPs as chaperons play significant roles through offering cellular protection against multi- sources of stress. It has been suggested that HSPs could have a great potential to be involved as molecules for potential therapies in various diseases among which is PD.

Because HSPs are involved almost in all cells, and because PD involves defects in brain and skeletal muscles, any improvement in cellular response through the reactivity of HSPs should be considered significant. We have also discussed the roles of various proteins included in HSPs, since they are varying according to their molecular weight with varying functions.

We also aimed to bring more excitement to encourage researchers for conducting more studies in HSPs as targeted therapies in more details related to various proteins within the family of HSPs.

Keywords: Parkinson Disease, Heat shock proteins, chaperons

Introduction

Heat Shock Proteins

Heat shock proteins (HSPs) have been studied extensively in literature and proved to provide an intrinsic mechanism to defend the cell against external diverse physiological stress that may initiate a cascade of events affecting cell structure and function. It has been assumed that, due to the high conservation of HSPs throughout the evolution, these proteins may have a vital role in protecting cells from injury. HSPs are composed of several classes of proteins according to their molecular weight, which include high-molecular-mass HSPs (≥100kD), HSP90 (81 to 99kD), HSP70 (65 to 80kD), HSP60 (55 to 64kD), HSP40 (35 to 54kD) and small HSPs (≤34kD) (Hart, 1996).

It has been indicated that different classes of HSPs to play a diversity role in governing proper protein assembly, folding, and translocation (Hart, 1996; Hightower, 1991). Furthermore, regulation of these HSPs synthesis has been found to create a unique defense system to maintain cellular protein homeostasis and to ensure cell survival (Hightower, 1991).

The understanding of HSPs' function is based on two main lines of evidence: (1) the clearance of waste proteins requires protein folding machinery called chaperones (Hart, 1996), and (2) HSPs chaperones bind to denatured proteins to promote their degradation (Hightower, 1991). Other evidence suggests that HSPs may actively participate in an array of cellular processes, including cytoprotection (Benn, 2004) and HSPs dysfunction may contribute to the pathogenesis of PD, a disease characterized by conformational changes in proteins that result in misfolding, aggregation and intracellular Lewy Body formation (Meriin, 2005).

HSPs and PD Pathophysiology

Many neurodegenerative disorders, including PD, Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Huntington disease (HD) and other polyglutamine expansion disorders, are associated with degeneration and death of specific neuronal populations due to accumulation of certain abnormal polypeptides or proteins (Meriin, 2005). Numerous studies implicate that at least two components of cellular proteins are associated with PD: the ubiquitin proteasomal system (UPS) and the HSPs (Berke, 2003; Grunblatt, 2004). Transcriptional analysis of multiple brain regions in PD indicates the impairment of multiple electron transport chain complexes and the dysfunction of UPS in PD, along with a robust induction of several forms of HSPs (Zhang, 2005). Inclusion bodies called Lewy bodies with aberrant misfolding and aggregative proteins are common pathological hallmark in PD, indicating that abnormality of protein homeostasis may contribute to the pathogenesis of the disease (McLean, 2002). Hsp70 and Torsin A, a homology to yeast Hsp104 and mutations of the gene causing dystonia, are colocalized with α-synuclein (αSN) containing Lewy bodies. Further, Dedmon (2005) found that Hsp70 could inhibit αSN fibril formation through preferential binding to prefibrillar species to change the characteristics of toxic αSN aggregates. This work therefore elucidates a specific role of Hsp70 in the pathogenesis of PD and supports a general concept that chaperone action is a crucial aspect in protecting against the otherwise damaging consequences of protein misfolding. With ageing, the level of HSPs is decreased insufficiently to keep the cellular proteins homeostasis, which may give rise to certain diseases (Meriin, 2005; Berke; 2003).

PD-Related Gene Mutations and Possible Association with HSPs

During the last decade of discovery of several PD-associated mutant genes a remarkable progress has been made to help our understanding of the biology of PD. So far there are at least 6 genes and several loci that have been identified responsible to PD (Le, 2004; Moore, 2005). It is hypothesized that UPS dysfunction resulted from these defected genes may cause protein misfolding and aggregation, and eventually lead to nigral cell degeneration (McNaught, 2004). Polymorphisms in the 5’ promoter regions of Hsp70 gene have been found significantly associated with PD (Wu, 2004).

Alpha-synuclein (αSN)

αSN, which plays a critical role in regulating synaptic vesicle size with particular relevance to dopamine storage, was found to be the main component in the Lewy body. Stress can increase the αSN protein aggregation and inclusion body formation (Macario, 2005); misfolding αSN can change proteasome composition, impair proteasome-mediated protein degradation, alter protein synthesis, and reduce the ability of cells to withstand stationary phase ageing (Chen, 2005). Three mutations of *αSN*, which show toxic gain-of-function, have been found in association with familial PD (Le, 2004; Moore, 2005). Inducible expression of mutant *αSN* in PC12 cell lines can result in greater sensitivity to proteasomal impairment, leading to mitochondrial abnormalities and neuronal cell death (Tanaka, 2001). αSN at nanomolar concentration is able to increase Hsp70 protein level in PC12 cells, which can reduce αSN aggregation and toxicity (Kluchen, 2004). In addition, the αSN protein has a tendency to self-aggregate and the protein level of αSN is increased in SNc with ageing (Cuervo, 2004).

Parkin

Parkin is a member of E3 ligase in the UPS (Shimura, 2000). Parkin mutations are thought to result in the improper targeting of its substrates for proteasomal degradation leading to potentially neurotoxic accumulation (Kim, 2003). Thus, great emphasis has been placed on the identification of substrates of parkin and their possible role in dopaminergic neuron loss in PD (Moore, 2005). It has been shown that the bcl-2-associated athanogene 5 (BAG5) can enhance dopaminergic neuron death in a vivo model of PD through inhibiting the E3 ligase activity and the chaperone activity of Hsp70 (Liu, 2002).

Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1)

UCH-L1, a highly abundant and neuronal specific protein that belongs to a family of deubiquitinating enzymes, is responsible for hydrolyzing polymeric ubiquitin chains to free ubiquitin monomers (Le, 2004; Moore, 2005). UCH-L1 might additionally act as a dimerization-dependent ubiquitin protein ligase (Liu, 2002) and maintain ubiquitin homeostasis by promoting the stability of ubiquitin monomers in vivo (Osaka, 2003). When *UCH-L1* mutates, ubiquitin recycling is reduced, which may lead to aggregation of aberrant proteins. It is found that UCH-L1 aggresomes colocalize with Hsp70, chaperone BiP, and other ubiquitinated proteins (Ardley, 2004), suggesting that UCH-L1 may interact with HSPs in an attempt to participate in protein degradation. *DJ-1* DJ-1 is a novel oncogene and mutations in this gene can cause familial PD. It is reported that DJ-1 mutations may result in oxidative stress and mitochondrial injury, which may lead to protein aggregation and neuronal cell death (Le, 2004; Moore, 2005). Li et al (2005) reported that DJ-1 and its mutants are associated with Hsp70, CHIP and mtHsp70/Grp75, a mitochondria-resident Hsp70; and DJ-1 and its mutants are colocalized with Hsp70 and CHIP in cells. Furthermore, H2O2 treatment in cells enhances DJ-1 interaction with mtHsp70 in mitochondria (Li, 2005). These findings suggest that translocation of DJ-1 to mitochondria after oxidative stress is carried out by chaperones.

Protective Role of HSPs in PD

It has been reported that Hsp70 is associated with αSN, dopamine transporter (DAT), parkin, proteasome subunits, ubiquitin and UCH-L1 (Cuervo, 2004). Hsp70 is believed not only to protect cells from rotenone-mediated cytotoxicity but also to decrease soluble αSN aggregation (Zhou, 2004). Furthermore, Hsp70 can work as a putative anti-apoptotic factor to protect against neuronal cell death in PD (Benn, 2004; Meriin, 2005). These results highlight the possibility of using Hsp70 as a potential therapy for PD. Recent studies of function and inducer of Hsp90 also indicate its potential therapy for PD (Uryu, 2006; Waza, 2006).

Hsp90

Hsp90 is the main component of the cytosolic molecular chaperone complex that has been implicated in the negative regulation of the heat shock factor 1 (HSF1). HSF1 is responsible for the transcriptional activation of the heat shock genes including Hsp40, Hsp70, and Hsp90 (Bharadwaj, 1999), suggesting a regulatory role in Hsp90 synthesis at the transcriptional level. Hsp90 forms a multichaperone complex with Hsp70 and Hsp40 to regulate several regulatory proteins, such as steroid hormone receptors (Sabbah, 1996) and transcription factors (Zhang, 2006), and to modulate the protein translocation from peroxisomal to organelle (Crookes, 1998). The interplay between these chaperones is of crucial importance for cell function and survival. Recently, Uryu *et al*. demonstrated that Hsp90 was predominantly increased in PD brains, which was in correlation with the elevated level of insoluble αSN. These alterations of Hsp90 in PD brain were recapitulated by neuropathological findings in αSN mutant transgenic mouse model of PD (Uryu, 2006). Furthermore, exposure of cells to proteasome inhibitors resulted in increased levels of Hsp90 (Uryu, 2006).

Microglia, which plays a principal role of inflammation in brain (Mor, 1999), express high levels of Hsp90 following excitotoxic lesion in the mouse hippocampus (Jeon, 2004). The protective function of Hsp90 can be very important since inflammation evoked by microglia may increase the risk of PD. Recently, we have demonstrated that (-)-Epigallocatechin gallate EGCG, a major monomer of green tea polyphenols, is a potent inhibitor of microglial activation (Li, 2004). EGCG could directly bind to Hsp90 and stabilize the complex of Hsp90 (Palermo, 2005).Thus EGCG could be used to alleviate microglia-mediated dopaminergic neuronal injury in PD.

Hsp70

Auluck *et al*. (2002) reported that application of Hsp70 can prevent dopaminergic neuronal loss in αSN transgenic Drosophila and interference with endogenous chaperone activity can accelerate αSN toxicity. Furthermore, Lewy bodies in human postmortem tissues were usually immunostained positive for molecular chaperones, suggesting that chaperones may play a role in PD progression (Auluck, 2002). It has been reported that Hsp70 can enhance parkin binding and ubiquitinating of expanded polyglutamine protein *in vitro*, suggesting that Hsp70 may help recruit misfolded proteins as substrates for parkin E3 ubiquitin ligase activity (Tsai, 2003). This finding provides a direct evidence to show the Hsp70 can promote the activity of E3 ligase to degrade aberrant αSN.

It is postulated that Hsp70 itself or cooperating with other factors can protect the neurons from cytotoxicity caused by aberrant proteins. The crosstalk between the Hsp70 and UPS may provide a clue for the intrinsic mechanism of protein aggregation and degradation. Moreover, Hsp70 exerts anti-apoptotic activity by blocking the function of several key proapoptotic factors (Benn, 2004). Several studies have demonstrated that Hsp70 may play a role in neuroprotection against rotenone-mediated apoptosis in human dopaminergic cell line SH-SY5Y *in vitro* and against MPTP-induced nigral injury *in vivo* by inhibiting the proapoptotic factors as well as activating the survival pathway (Pan, 2005; Shen, 2005).

Small HSPs

Chaperone *Hsp25/27*(Hsp25 in mice and Hsp27 in humans), is an inhibitor of actin polymerization (Miron, 1991), which has been demonstrated to play a major role in actin filament dynamics in diverse cell types (Benn, 2004). In human endothelial cells, inhibition of p38-MAPK activation can abolish Hsp27phosphorylation, actin polymerization, and cell migration (Huot, 1997). p38-MAPK may act as an upstream activator of stress-inducible Hsp25/27 phosphorylation. It has been demonstrated that Hsp27 could bind to the microtubule associated protein tau and lead to decreased level of hyperphosphorylated tau and therefore enhance cell survival in AD (Shimura, 2004). Another important function of Hsp27 is its protective effects on mitochondria pathway leading to inhibition of apoptosis (Concannon, 2003). It has been found that Hsp27 can block the tBID entering the mitochondria and reduce SMAC and Cytochrome C releasing from mitochondria so as to block the apoptotic process (Benn, 2004).

αB-crystallin Chaperone (Hsp22)*:* Increased expression and abnormal aggregation of small HSPs αB-crystallin has been detected in Lewy bodies and reactive astrocytes in various neurodegenerative diseases (Yun, 2002).. Rekas *et al* (2004*)* demonstrated that αB-crystallin was a potent inhibitor of αSN fibrillization *in vitro*. αB-crystallin may redirect αSN from a fibril-formation pathway towards an amorphous aggregation pathway, thus reducing the amount of physiologically stable amyloid deposits in favor of easily degradable amorphous aggregates (Rekas, et al, 2004). It has been reported that treatment with proteasomal inhibitors MG-132 or lactacystin in cultured rat brain oligodendrocytes can cause apoptotic cell death and induction of heat shock proteins in a time- and concentration-dependent manner (Goldbaum, 2004). Specifically in this study, αB-crystallin was up-regulated, and ubiquitinated proteins were accumulated. Meanwhile, the tau was dephosphorylated, which enhanced its microtubule-binding capacity (Goldbaum, 2004). These findings imply that αB-crystallin may work together with other HSPs, ubiquitin and microtubule associated proteins (MAPs) to cope with stressed conditions.

Potential Target for the Treatment of PD

Dong *et al*. (2005) reported that Hsp70 gene transferred to dopaminergic neurons by a recombinant adeno-associated virus significantly protected the mouse against MPTP-induced nigral dopaminergic neuron loss and striatal dopamine levels decline (Dong et al, 2005). Hsp70 attenuated MPTP induced apoptosis in the SNpc, and increased amphetamine-induced rotation (Dong et al, 2005). Collectively, these results demonstrate that increasing chaperone activity may be beneficial for the treatment of PD. HSPs may exert protective function through two major pathways besides their own chaperon activity: reducing mitochondrial dysfunction and oxidative stress, and preventing UPS impairment.

Anti-apoptotic effects of HSPs in PD

Mitochondrial dysfunction is probably the leading cause of increased oxidative stress and apoptosis in PD. Dopaminergic neurons are more vulnerable to oxidative stress than other neurons because of the special substrate dopamine (Jenner, 2003). In general, apoptotic process can be divided into the three phases: induction (or triggering), transduction of signal, and execution. Theoretically, HSPs may modulate any of these apoptotic phases to rescue the cells (Beere, 2001). In addition, it has been reported that stable expression of wild-type αB-crystallin protects cancer cells from caspase-3 activation *in vitro*, indicating that small HSPs αB-crystallin is a novel inhibitor of the activation of apoptosis (Kamradt, 2005). Other gene products linked to monogenic forms of PD also appear to be implicated in mitochondrial dysfunction. Parkin can interact with leucine-rich repeat kinase 2 (Lrrk2) which is part of the mitochondrial outer membrane (Smith, 2005; West, 2005). Thus, Parkin may have an unexpected role in the regulation of normal mitochondrial function in an indirect way (Palacino, 2004; Winklhofer, 2003).

HSPs may promote the UPS in protein degradation

The UPS plays a pivotal role in the degradation of short-lived regulatory proteins which are components of cell cycle regulation, cell surface receptors, ion channels modulation, and antigen presentation (Schwartz, 1999). It is believed that once the disposal system fails to work, the substances, such as regulatory molecules p53, NFκB, and Bax that promote apoptosis, may accumulate to a high level that is harmful to the cell (Hernandez, 2004). A hypothesis for the etiology of PD is that subsets of neurons are vulnerable to a failure in proteasome-mediated protein turnover (Schwartz, 1999). Accumulation of ubiquitin conjugates has been reported in the pathologic lesions of many chronic neurodegenerative diseases, such as the neurofibrillary tangles in AD and brainstem Lewy bodies in PD (Winklhofer, 2003; Schwartz, 1999). Inhibition of proteasome activity will sensitize dopaminergic neurons to protein alterations and oxidative stress (Mytilineou, 2004). Hsp90, together with Hsc70, Hsp40 and 20S proteasome subunit are the effective components to capture firefly luciferase during thermal inactiveness and to prevent it from undergoing an irreversible off-pathway (Minami, 2000). The 20S proteasome has been found in tight association with the molecular chaperone Hsp90 (Whittier, 2004). Composed within 26S proteasome subunit, they form a complex involved in a multitude of intracellular processes (Schwartz, 1999). In addition, Kim *et al*(1999) has demonstrated that the inhibition of proteasome can increase the expression of Hsp27 and Hsp70, implying that HSPs may act as compensation of UPS or work together to regulate the intracellular protein level. Robertson *et al.* supported the hypothesis by demonstrating that Hsp70 antisense oligomers enhanced proteasome inhibitor-induced apoptosis (Robertson, 1999).

All evidences above implicate that HSPs and UPS are participants in keeping proteins folding correctly. They provide an effective protein quality control system that is essential for cellular functions and survival in many tissues. Dysfunction of these systems leads to protein aggregation and inclusion body formation in dopaminergic neurons.

HSPs inducers and their potential application in PD

It is proposed that up-regulation of protective factors may benefit our cells, but overload of some proteins may be a burden for cells or even cause cancer. So we need to find better way to keep cells in delicate balance with maximal protective effects and minimal side effects. Cyclopentenone prostaglandin A1 (PGA1), an inducer of HSPs, has been shown to inhibit SH-SY5Y neuron apoptosis. PGA1 can protect against rotenone-induced neuronal degeneration by promoting the expression of HSPs as well as attenuating nuclear translocation of NF-kappaB and caspase-3 activation (Wang, 2002). Geldanamycin (GA) binds to an ATP site on HSP90 and blocks its interaction with HSF1 to promote HSF1 activation (Zou, 1998). GA also sensitizes the stress response within normal physiological parameters to enhance chaperone activation and offerprotection against αSN neurotoxicity (Auluck, 2005). Furthermore, GA uncouples neuronal toxicity from Lewy body and Lewy neurite formation so that dopaminergic neurons are protected from the effects of αSN expression despite the continued presence of or even increased inclusion pathology (Auluck, 2005). Significantly, GA does not alter the basal level of HSP70, suggesting that GA acts only to elevate chaperone levels in stressed cells and does not alter chaperone activity in neighboring, healthier cells (Auluck, 2005). Because αSN expression leads to a local elevation of inducible HSP70 in dopaminergic neurons (Auluck, 2002), these neurons should be preferentially targeted by GA treatment (Auluck, 2005). Its new derivative 17-Allylamino-17-demethoxygeldanamycin 17-AAG shares its important biological activities with less toxicity (Waza et al, 2006), which gives us a much bright perspective to use GA to induce specific HSPs expression and to attenuate the side effect.

There is feasibility to use Hsp70 as a pretreatment therapy because there are many nontoxic or low toxic Hsp70 inducers available, such as paeoniflorin (Yan, 2004), bimoclomol (co-inducer to increase the activity) (Nanasi and Jednakovits, 2001; Hargitai et al., 2003), radicicol, and valproic acid (VPA) (Pan, 2005). These Hsp70 inducers can up-regulate Hsp70 effectively for reconfirmation of the cellular homeostasis. Thus, it is hope that modulates the stress response by inducers can be a promising target for treatment of PD.

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