

# Applications of heat shock proteins for Parkinson's disease

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## Abstract

*Heat shock proteins (HSPs), called molecular chaperone to help protein folding, have currently come to be a studies awareness in Parkinson's disorder (PD) due to the fact the pathogenesis of this disorder is highlighted by way of the intracellular protein misfolding and inclusion body formation. the prevailing evaluate will recognition on the features of one-of-a-kind HSPs and their defensive roles in PD. its miles postulated that HSPs may also serve as protein folding machinery and work collectively with ubiquitin-proteasome machine (UPS) to help in decomposing aberrant proteins. Failure of United States is notion to play a key role in the pathogenesis of PD. in addition, HSPs might also own anti-apoptotic results and maintain the homeostasis of dopaminergic neurons against strain conditions. The essential function of HSPs and current discovery of some novel HSPs inducers endorse that HSPs can be capacity therapeutic goals for PD and different neurodegenerative problems.*

**Key words:** Parkinson's disease (PD), heat shock proteins (HSPs), ubiquitin-proteasome system (UPS), apoptosis

## 1. Introduction

within the eukaryotic cellular, warmth surprise proteins (HSPs) offer an intrinsic mechanism to defend the cellular in opposition to outside various physiological pressure which can initiate a cascade of activities affecting cell structure and function. The high conservation of HSPs at some stage in the evolution indicates that those proteins may additionally have an important role in shielding cells from harm. HSPs are composed of various lessons of proteins in keeping with their molecular weight, which consist of high-molecular-mass HSPs ( $\geq 100\text{kD}$ ), HSP90 (81 to 99kD), HSP70 (65 to 80kD), HSP60 (55 to 64kD), HSP40 (35 to 54kD) and small HSPs ( $\leq 34\text{kD}$ ). distinct instructions of HSPs play a variety role in governing proper protein meeting, folding, and translocation. law of these HSPs synthesis creates a completely unique defense system to maintain mobile protein homeostasis and to ensure mobile survival. The cutting-edge information of HSPs' feature is based totally on fund amental strains of proof: (1) the clearance of waste proteins calls for protein folding equipment known as chaperones, and (2) HSPs chaperones bind to denatured proteins to promote their degradation. New proof indicates that HSPs may additionally actively participate in an array of mobile processes, including cyto-protection, and HSPs disorder may additionally make contributions to the pathogenesis of Parkinson's sickness (PD), a sickness characterized by way of conformational adjustments in proteins that result in misfolding, aggregation and intracellular Lewy body formation. This overview affords an update view of the cytoprotective function of HSPs in PD and the capability healing target of HSPs for the remedy of PD. Many neurodegenerative problems, together with PD, Alzheimer's sickness (ad), amyotrophic lateral sclerosis (ALS), Huntington disease (HD) and other polyglutamine enlargement issues, are related with degeneration and dying of precise neuronal populations due to accumulation of certain strange polypeptides or proteins. PD is a neurological disorder characterized by way of motion disturbance that in most cases results from progressive degeneration of dopaminergic neurons in substantia nigra pars compacta (SNpc). Several studies implicate that at least additives of cellular proteins are associated with PD: the ubiquitin proteasomal machine (UPS) and the HSPs. Transcriptional analysis of more than one mind regions in PD indicates the impairment of multiple electron delivery chain complexes and the dysfunction of united states of American PD,

together with a strong induction of numerous sorts of HSPs. Inclusion our bodies called Lewy our bodies with aberrant misfolding and aggregative proteins are commonplace pathological hallmark in PD, indicating that abnormality of protein homeostasis might also make a contribution to the pathogenesis of the disorder. Hsp70 and Torsin A, a homology to yeast Hsp104 and mutations of the gene inflicting dystonia, are colocalized with  $\alpha$ -synuclein ( $\alpha$ SN) containing Lewy our bodies. further, Dedmon et al. located that Hsp70 could inhibit  $\alpha$ SN fibril formation thru preferential binding to prefibrillar species to alternate the characteristics of toxic  $\alpha$ SN aggregates. This work therefore elucidates a particular function of Hsp70 within the pathogenesis of PD and helps a well-known concept that chaperone motion is a critical issue in protective in opposition to the in any other case unfavorable results of protein misfolding. With growing old, the extent of HSPs is decreased insufficiently to hold the cell proteins homeostasis, which may additionally supply rise to positive diseases. due to the fact the share of sufferers stricken by PD in our aging society is growing, it is urgent to locate better healing techniques to this devastating disorder.

Over the past decade of discovery of numerous PD-associated mutant genes a fantastic progress has been made to help our information of the biology of PD. so far there are at least 6 genes and numerous loci which have been identified responsible to PD. it's far hypothesized that united states dysfunction resulted from those defected genes may reason protein misfolding and aggregation, and sooner or later cause nigral mobile degeneration. Polymorphisms within the 5' promoter regions of Hsp70 gene had been located substantially associated with PD.  $\alpha$ SN, which performs a crucial position in regulating synaptic vesicle size with specific relevance to dopamine garage, become found to be the primary thing within the Lewy frame. stress can growth the  $\alpha$ SN protein aggregation and inclusion frame formation; misfolding  $\alpha$ SN can exchange proteasome composition, impair proteasome-mediated protein degradation, regulate protein synthesis, and reduce the capability of cells to resist stationary segment growing older. Three mutations of  $\alpha$ SN, which show toxic gain-of-function, were located in affiliation with familial PD. Inducible expression of mutant  $\alpha$ SN in PC12 mobile traces can result in greater sensitivity to proteasomal impairment, leading to mitochondrial abnormalities and neuronal cell dying.  $\alpha$ SN at nanomolar awareness is capable of boom Hsp70 protein level in PC12 cells, that may lessen  $\alpha$ SN aggregation and toxicity. similarly, the  $\alpha$ SN protein has a tendency to self-combination and the protein stage of  $\alpha$ SN is increased in SNc with growing old. Parkin is a member of E3 ligase in the UPS. Parkin mutations are idea to bring about the flawed concentrated on of its substrates for proteasomal degradation main to probably neurotoxic accumulation. accordingly, top notch emphasis has been placed on the identification of substrates of parkin and their feasible position in dopaminergic neuron loss in PD. Kalia et al showed that the bcl-2-associated athanogene 5 (BAG5) can decorate dopaminergic neuron loss of life in a vivo model of PD via inhibiting the E3 ligase pastime and the chaperone hobby of Hsp70. UCH-L1, a fairly ample and neuronal unique protein that belongs to a own family of deubiquitinating enzymes, is chargeable for hydrolyzing polymeric ubiquitin chains to loose ubiquitin monomers. UCH-L1 might moreover act as a dimerization-dependent ubiquitin protein ligase and keep ubiquitin homeostasis via promoting the steadiness of ubiquitin monomers in vivo. when UCH-L1 mutates, ubiquitin recycling is reduced, which may additionally lead to aggregation of aberrant proteins. it's far discovered that UCH-L1 aggresomes colocalize with Hsp70, chaperone BiP, and different ubiquitinated proteins, suggesting that UCH-L1 may have interaction with HSPs in a try to take part in protein degradation. DJ-1 is a singular oncogene and mutations in this gene can reason familial PD. Its miles mentioned that DJ-1 mutations may bring about oxidative strain and mitochondrial harm, which may additionally cause protein aggregation and neuronal mobile loss of life. Li et al said 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, H<sub>2</sub>O<sub>2</sub> treatment in cells complements DJ-1 interaction with mtHsp70 in mitochondria. These findings endorse that translocation of DJ-1 to mitochondria after oxidative strain is completed via chaperones. it has been suggested that Hsp70 is related with  $\alpha$ SN, dopamine transporter (DAT), parkin, proteasome subunits, ubiquitin and UCH-L1.

Hsp70 is assumed not simplest to shield cells from rotenone-mediated cytotoxicity but additionally to lower soluble  $\alpha$ SN aggregation. furthermore, Hsp70 can work as a putative anti-apoptotic factor to defend against neuronal cellular loss of life in PD. these results highlight the opportunity of the usage of Hsp70 as a capacity therapy for PD. latest research of characteristic and inducer of Hsp90 also imply its capability therapy for PD. Hsp90 is the main component of the cytosolic molecular chaperone complex that has been implicated inside the bad regulation of the warmth shock issue 1 (HSF1). HSF1 is chargeable for the transcriptional activation of the warmth surprise genes including Hsp40, Hsp70, and Hsp90, suggesting a regulatory position in Hsp90 synthesis on the transcriptional stage. Hsp90 paperwork a multichaperone complicated with Hsp70 and Hsp40 to modify several regulatory proteins, together with steroid hormone receptors and transcription factors, and to modulate the protein translocation from peroxisomal to organelle. The interplay between these chaperones is of vital importance for cellular feature and survival. lately, Uryu et al. proven that Hsp90 become predominantly multiplied in PD brains, which became in correlation with the extended level of insoluble  $\alpha$ SN. these changes of Hsp90 in PD mind had been recapitulated by neuropathological findings in  $\alpha$ SN mutant transgenic mouse model of PD. furthermore, publicity of cells to proteasome inhibitors led to elevated degrees of Hsp90. Microglia, which performs a major function of inflammation in mind, explicit excessive degrees of Hsp90 following excitotoxic lesion within the mouse hippocampus. the protective feature of Hsp90 may be very crucial since inflammation evoked by microglia may additionally growth the risk of PD. recently, we have proven that (-)-Epigallocatechin gallate EGCG, a primary monomer of inexperienced tea polyphenols, isa robust inhibitor of microglial activation. EGCG could immediately bind to Hsp90 and stabilize the complex of Hsp90. as a consequence, EGCG may be used to alleviate microglia-mediated dopaminergic neuronal injury in Auluck et al. pronounced that software of Hsp70 can save you dopaminergic neuronal loss in  $\alpha$ SN transgenic Drosophila and interference with endogenous chaperone pastime can accelerate toxicity. furthermore, Lewy our bodies in human postmortem tissues have been usually immunoassayed high quality for molecular chaperones, suggesting that chaperones may additionally play a function in PD progression. it has been stated that Hsp70 can decorate parkin binding and ubiquitinating of increased polyglutamine protein in vitro, suggesting that Hsp70 might also assist recruit misfolded proteins as substrates for parkin E3 ubiquitin ligase pastime. This finding affords immediate evidence to expose the Hsp70 can sell the interest of E3 ligase to degrade aberrant  $\alpha$ SN. its miles postulated that Hsp70 itself or cooperating with other factors can defend the neurons from cytotoxicity due to aberrant proteins. The crosstalk among the Hsp70 and USA may also provide a clue for the intrinsic mechanism of protein aggregation and degradation. furthermore, Hsp70 exerts anti-apoptotic hobby with the aid of blockading the feature of several key proapoptotic factors. lately, several studies have established that Hsp70 may also play a role in neuroprotection towards rotenone-mediated apoptosis in human dopaminergic cell line SH-SY5Y in vitro and against MPTP-prompted nigral injury in vivo by using inhibiting the proapoptotic elements as well as activating the survival pathway. Chaperone Hsp25/27(Hsp25 in mice and Hsp27 in human beings), is an inhibitor of actin polymerization, which has been confirmed to play a main position in actin filament dynamics in diverse mobile sorts. In human endothelial cells, inhibition of p38-MAPK activation can abolish Hsp27 phosphorylation, actin polymerization, and cell migration. p38-MAPK can also act as an upstream activator of strain-inducible Hsp25/27 phosphorylation. it has been tested that Hsp27 should bind to the microtubule associated protein tau and result in reduced stage of hyperphosphorylated tau and consequently enhance cellular survival in ad. another crucial characteristic of Hsp27 is its shielding consequences on mitochondria pathway leading to inhibition of apoptosis. It has been located that Hsp27 can block the tBID getting into the mitochondria and reduce SMAC and Cytochrome C liberating from mitochondria with the intention to block the apoptotic manner.  $\alpha$ B-crystallin Chaperone (Hsp22): increased expression and strange aggregation of small HSPs  $\alpha$ B-crystallin has been detected in Lewy our bodies and reactive astrocytes in diverse neurodegenerative diseases. Rekas et al. validated that  $\alpha$ B-crystallin was an amazing inhibitor of  $\alpha$ SN fibrillization in vitro.  $\alpha$ B-crystallin may additionally redi  $\alpha$ SN from a fibril-formation pathway closer to an

amorphous aggregation pathway, thus reducing the amount of physiologically stable amyloid deposits in prefer of without problems degradable amorphous aggregates. it has been pronounced that treatment with proteasomal inhibitors MG-132 or lactacystin in cultured rat mind oligodendrocytes can motive apoptotic cell death and induction of heat surprise proteins in a time- and awareness-dependent way. specifically, in this observe,  $\alpha$ B-crystallin was up-regulated, and ubiquitinated proteins have been accumulated. meanwhile, the tau became dephosphorylated, which more desirable its microtubule-binding ability. those findings imply that  $\alpha$ B-crystallin may match collectively with different HSPs, ubiquitin and microtubule related proteins (MAPs) to address stressed conditions.

Dong et al. said that Hsp70 gene transferred to dopaminergic neurons through a recombinant adeno-related virus significantly covered the mouse towards MPTP-prompted nigral dopaminergic neuron loss and striatal dopamine levels decline. Hsp70 attenuated MPTP brought on apoptosis within the SNpc, and increased amphetamine-triggered rotation. together, these results exhibit that increasing chaperone pastime can be useful for the treatment of PD. HSPs may additionally exert shielding characteristic thru two principal pathways besides their very own chaperon hobby: reducing mitochondrial disorder and oxidative pressure, and preventing us impairment. Mitochondrial disorder is probably the main motive of extended oxidative strain and apoptosis in PD. Dopaminergic neurons are more at risk of oxidative pressure than other neurons because of the special substrate dopamine. In fashionable, apoptotic manner can be divided into the three phases: induction (or triggering), transduction of sign, and execution. Theoretically, HSPs may also modulate any of those apoptotic levels to rescue the cells. in addition, it's been reported that stable expression of wild-type  $\alpha$ B-crystallin protects cancer cells from caspase-three activation in vitro, indicating that small HSPs  $\alpha$ B-crystallin is a singular inhibitor of the activation of apoptosis. other gene products connected to monogenic sorts of PD also seem like implicated in mitochondrial dysfunction. Parkin can have interaction with leucine-wealthy repeat kinase 2 (Lrrk2) that's a part of the mitochondrial outer membrane. for that reason, Parkin may additionally have an sudden position within the regulation of everyday mitochondrial characteristic in an oblique way. The USA plays a pivotal position in the degradation of short-lived regulatory proteins which can be additives of mobile cycle regulation, cell floor receptors, ion channels modulation, and antigen presentation. (parent 2) it's miles believed that once the disposal machine fails to paintings, the materials, inclusive of regulatory molecules p53, NF $\kappa$ B, and Bax that promote apoptosis, may additionally collect to an excessive degree that is dangerous to the cellular. A speculation for the etiology of PD is that subsets of neurons are vulnerable to a failure in proteasome-mediated protein turnover. Accumulation of ubiquitin conjugates has been stated inside the pathologic lesions of many chronic neurodegenerative sicknesses, including the neurofibrillary tangles in ad and brainstem Lewy bodies in PD. Inhibition of proteasome interest will sensitize dopaminergic neurons to protein alterations and oxidative pressure. Hsp90, collectively with Hsc70, Hsp40 and 20S proteasome subunit are the powerful additives to seize firefly luciferase all through thermal inactiveness and to prevent it from present process an irreversible off-pathway. The 20S proteasome has been found in tight affiliation with the molecular chaperone Hsp90. Composed inside 26S proteasome subunit, they form a complex worried in a mess of intracellular procedures. similarly, Kim et al has proven that the inhibition of proteasome can growth the expression of Hsp27 and Hsp70, implying that HSPs may also act as reimbursement of UPS or work collectively to alter the intracellular protein degree. Robertson et al. supported the hypothesis by using demonstrating that Hsp70 antisense oligomers enhanced proteasome inhibitor-induced apoptosis.

All evidences above implicate that HSPs and u.s.a. are participants in retaining proteins folding correctly. They offer an effective protein exceptional manage machine this is essential for cellular capabilities and survival in many tissues. disorder of these systems results in protein aggregation and inclusion body formation in dopaminergic neurons. it's far proposed that up-regulation of protecting factors might also benefit our cells, but overload of some proteins may be a burden for cells or maybe reason cancer. So, we want to find higher way to preserve cells in delicate balance with maximal



protective outcomes and minimum aspect effects. Cyclopentenone prostaglandin A1 (PGA1), an inducer of HSPs, has been shown to inhibit SH-SY5Y neuron apoptosis. PGA1 can guard in opposition to rotenone-brought about neuronal degeneration by using selling the expression of HSPs as well as attenuating nuclear translocation of NF-kappa B and caspase-3 activation. Geldanamycin (GA) binds to an ATP web site on HSP90 and blocks its interaction with HSF1 to sell HSF1 activation. GA also sensitizes the strain reaction inside normal physiological parameters to decorate chaperone activation and provide safety in opposition to  $\alpha$ SN neurotoxicity. furthermore, GA uncouples neuronal toxicity from Lewy body and Lewy neurite formation in order that dopaminergic neurons are protected from the outcomes of  $\alpha$ SN expression no matter the ongoing presence of or even expanded inclusion pathology. extensively, GA does now not alter the basal stage of HSP70, suggesting that GA acts handiest to elevate chaperone tiers in burdened cells and does not regulate chaperone hobby in neighboring, healthier cells. due to the fact  $\alpha$ SN expression leads to a neighborhood elevation of inducible HSP70 in dopaminergic neurons, these neurons need to be preferentially centered by GA treatment. Its new derivative 17-Allylamino-17-demethoxygeldanamycin 17-AAG stocks its essential biological activities with much less toxicity, which gives us a much bright attitude to apply GA to result in particular HSPs expression and to attenuate the side impact. there is feasibility to use Hsp70 as a pretreatment remedy due to the fact there are numerous riskless or low toxic Hsp70 inducers available, such as paeoniflorin, bimoclomol (co-inducer to boom the activity), radicicol, and valproic acid (VPA) those Hsp70 inducers can up-adjust Hsp70 efficiently for reconfirmation of the cellular homeostasis. therefore, it's miles hope that modulates the pressure reaction by means of inducers can be a promising target for treatment of PD.

## 2. Conclusion

HSPs have most important cell capabilities aimed at promoting the America function and inhibiting the apoptotic hobby. But the distinctive molecular mechanisms underlying their organic functions are still unclear. it is believed that HSPs, UPS, mitochondria and other organelles may go coordinately to hold the cellular in a solid and nicely-operated nation. HSPs are specifically critical in PD and different neurodegenerative issues due to the fact aberrant protein aggregation and neuron degeneration are the not unusual pathophysiology of these disorders. Several research in vitro and in vivo version of PD have demonstrated that boom in the expression of HSPs particularly Hsp70 via gene switch or HSPs inducers can reduce the aberrant protein misfolding and inhibit the proapoptotic pathway to attenuate dopaminergic neuron degeneration. Hence such intervention provides a promising remedy for PD. enhance within the studies of HSPs objectives will shed a mild at the feasibility of clinical application of HSPs in PD. The future study will focus on finding the mechanisms of aberrant protein aggregation and trying to find the selective HSPs inducers for the remedy of PD.

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