

Targeted Activation of Heat Shock Proteins by Natural Bioactive Compounds to Prevent Neurodegenerative Diseases

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The predominant accumulation of aggregated proteins is observed in neurodegenerative diseases such as Alzheimer's and Parkinson's diseases. Protein misfolding and aggregation is strongly regulated by molecular chaperones known as heat shock proteins (HSPs) including Hsp90, Hsp70, Hsp27, Hsp60, and Hsp40 among others. Recent research activity indicates that expression and activation of HSPs may prevent or reduce protein aggregation in Alzheimer's disease, Parkinson's disease, Polyglutamine disease, Prion disease, and other neurodegenerative disorders. In the present review, laboratory findings that implicate the role of HSPs in the development of neurodegeneration will be discussed. Furthermore, strong experimental evidence presented here show that expression and/or increased activation of HSPs by phytochemicals may prevent various neurodegeneration through preventing protein aggregation process and reduce the toxicity of the oligomers.

Molecular consequences of altered gene products, protein, glucose and lipid oxidation due to disrupted redox homeostasis lead to accumulation of unfolded and misfolded protein in the aging brain. Neurodegenerative diseases including Alzheimer's, Parkinson's, Huntington, and Friedreich ataxia share, a common denominator, production of abnormal proteins, mitochondrial dysfunction and oxidative stress. Alzheimer's disease (AD) and Parkinson's disease (PD) are two most prevalent neurodegenerative diseases that affect the elderly population. Aggregation of β -amyloid and hyperphosphorylation and subsequent tangle formation of tau protein is believed to promote Alzheimer's disease [1,2], and tau suppression in a neurodegenerative mouse model improves memory function [3]. The exact cause of PD remains obscure, however, genes encoding α -synuclein, LRKK2, Parkin, DJ1, PINK1, ATP13A2, VPS35, FBXO7, GBA and EIF4G1 are implicated in the pathogenesis of and susceptibility to PD [4]. There is strong evidence that α -synuclein aggregation is an early step in the pathogenesis of PD [5]. α -Synuclein appears to be toxic upon overexpression and during misfolding or subsequent oligomerization [6].

In eukaryotic cells, misfolded proteins are degraded by the Ubiquitin-Proteasome System (UPS). Heat Shock Proteins (HSPs) including Hsp90 and Hsp70 along with cochaperones maintain proper folding of proteins or deliver misfolded proteins to ubiquitin-proteasome system for degradation [7]. Under conditions of stress, HSPs and their cochaperones are upregulated to help prevent misfolding of endogenous proteins. However when such quality control mechanisms fail, the resultant misfolded proteins or oligomeric species thereof may become pathogenic [8].

Classic Hsp90 inhibitors have been shown to induce the expression of heat shock proteins by activation and translocation of Heat Shock Protein Factor 1 (HSF1) to nucleus [9,10]. HSF1, a master regulator of transcription, is a highly conserved transcription factor that plays an important role in longevity as well as in maintaining proteostasis and adequate response to proteotoxic stresses [11-13]. Induction of heat shock proteins has been shown to reduce aggregated proteins in brain including tau [14].

The naturally occurring antibiotic Geldanamycin (GA) was found to selectively inhibit Hsp90. Inhibition of Hsp90 first emerged as an antiproliferative strategy in the development of cancer therapeutics

because Hsp90 stabilizes a range of proteins (clients) involved in the cell cycle progression, cell survival and oncogenesis. Hsp90 inhibition by GA has been shown to induce the expression of other HSPs and therefore attempts have been made to apply this concept to neurodegenerative diseases hoping that GA-induced HSPs expression may reduce proteotoxicity. Hsp90 inhibition by GA resulted in accelerated degradation of misfolded tau protein by activation of HSPs expression and activation of proteasome [15]. In numerous animal models, the neuronal toxicity associated with abnormally folded proteins has been successfully suppressed by HSP modulation including via the overexpression of Hsp70 and Hsp40 [16]. GA was also shown to induce heat shock response in an in vitro model of Huntington's disease [17] and PD [18,19]. Furthermore, direct expression of Hsp70 in a *Drosophila* model of polyglutamine disease was shown to suppress neurodegeneration [20], and expression of Hsp70 in a PD model of *Drosophila* supports the notion that HSPs prevent dopaminergic neuronal loss associated with expression of α -synuclein in the fly [21,22].

In this context, there is a strong impetus to study the potential use of traditional medicinal plants to prevent and reverse neurodegenerative diseases. Recent data indicates that bioactive plant compounds reduce aggregation of toxic proteins by activation and or expression of heat shock proteins. Bioactive plant compounds curcumin [23], celastrol [24,25], gambogic acid [26], and withaferin A [27] among others have been shown to induce the expression of HSPs. Additionally, curcumin has been shown to reduce soluble tau and increase HSPs in a human tau mice model [28]. These results indicate that even after tangles formation, tau-dependent behavioral and synaptic deficits can be corrected by curcumin treatment [28]. In a recent study, screening of 80 bioactive plant compounds showed that shikonin induced expression of Hsp70 in human lymphoma U937 cells [29]. Neuroprotective properties of carnosic acid was studied in neuroblastoma SK-N-SH cells and it showed that carnosic acid protected cells from rotenone-induced stress by significant induction of Hsp70 expression [30].

Similarly, plants extracts have been shown to induce expression of HSPs. Adaptogenic substances derived from *Eleutherococcus senticosus* root extract, *Schisandra chinensis* berry extract, *Rhodiola rosea* root extract induced expression of Hsp70 from isolated human neuroglia cells [31]. *Cichorium intybus* extract have recently reported to increase

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Hsp70 expression in C2C12 myoblasts [32]. Furthermore, an ethanolic leaf extract of *Jasminum sambac*, a folk medicine, has been shown to increase expression of Hsp70 in rats [33]. This data strongly suggests that medicinal plant extracts and phytochemicals have great potential to prevent neurodegenerative diseases partly through activation of HSPs.

For complete list of HSPs-induced plant extracts and bioactive compounds contact the corresponding author.

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