International Journal of Biophysics 2018, 8(1): 1-8
DOI: 10.5923/j.biophysics.20180801.01

Activation of Heat Shock Protein Induced by Curcumin to Prevent Huntington Disease- An Analytical Approach in the Context of Protein Vibration

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Abstract Depending on aggregate size, amino acid sequence and degree of misfolding, protein aggregates are disaggregated by Heat Shock Proteins (HSPs). Natural products can induce SHPs. Curcumin- the chemical constituent of turmeric paste/powder is now being considered as the inducer of HSPs which are able to reduce aggregates of glutamine amino acids and can also modulate the signaling pathway of small fragments of glutamine molecules. The molecular mechanism of disaggregation of aggregated glutamines has been considered from the view point of protein vibration which is expected to be happened either due to inherent electrostatic potential of the cell or due to external stimuli. Here we have discussed the current knowledge on the role of HSP induced by curcumin particularly with respect to Huntington diseases (HD) in the context of Protein Vibration Approach.

Keywords Curcumin, Heat Shock Proteins, Protein misfolding, Neurodegenerative diseases, Molecular Chaperones, Huntingtin protein (HTT), Huntington Disease

1. Introduction

Accumulation of misfolded and aggregated amyloid proteins in intra and extracellular system is a common feature in a number of neurodegenerative diseases. Most of these diseases are silent killer. These progress slowly and persist rest of life [1]. The common features of these devastating diseases constitute synaptic loss, neurobehavioral abnormalities, impairment of learning and memory. The present knowledge supports the idea that these diseases might start at early stage of life but manifest at later stage especially during aging [2]. One of the most common of these diseases is Alzheimer's diseases (AD) where amyloid beta protein ($A\beta$) is deposited in extracellular space and microtubule stabilizing protein tau as neurofibrillary tangle (NET) is deposited in intracellular space. Similarly, a number of proteins like alpha synuclein, huntingtin (HTT), prion are deposited in Parkinson's (PD), Huntington's (HD) and prion diseases respectively. In most of these devastating diseases the concerned amyloid proteins undergo conformational changes and become misfolded. These are deposited as insoluble proteinaceous aggregate inside or outside of cells. Therefore, adequate treatment requires to be started before onset of these diseases, failing which it would be hard to prevent later downstream of toxicity of these proteins. Several attempts have been undertaken to clear of these protein aggregates but no permanent solution has yet been emerged out. Recently, activation or expression of special kind of protein known as Heat Shock Protein (HSP) draws the attention of the scholar towards therapeutic strategies for removing these abnormal protein aggregates. Disaggregation of these abnormal protein aggregates has been discussed here from the view point of protein vibration –which is briefed in the methodology chapter.

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Published online at http://journal.sapub.org/biophysics

2. Characterization of Heat Shock Proteins and Their Functions

Heat Shock Proteins (HSPs) are a class of proteins that are produced by cells in response to stressful conditions. They were first identified with respect to heat shock but are now found to be expressed during other stresses like exposure to cold [3], UV Light [4] and during wound healing or tissue remodeling [5]. Many members of this group perform chaperone function to refold misfolded proteins. HSPs are thus found to act as

(i) Upregulators in stress and also as
(ii) Chaperones

HSPs are found virtually in all living organism from bacteria to human. Synthesis of increased amount of proteins in Drosophila cells following stresses were first reported in 1974 [6]. Several HSPs now function as intracellular

chaperones for other proteins. They play an important role in protein – protein interaction which aims to establish proper protein conformation and prevention of unwanted protein aggregation. Some HSPs are found to play a significant cardiovascular role [7]. On the other hand, extracellular and membrane bound HSPs are involved in binding antigens and presenting them to the immune system [8]. Thus a good number of HSPs have now been identified. They are usually named by their molecular weights and their family members are now categorized [9] as

Multiple receptors present in dendrite and other cells bind to HSPs to modulate the immune system in vivo. Protein receptors which are found to play a role in binding with HSPs are tabled [9] as

Distinct HSPs are found to posses the abilities of inducing cross – presentation of antigens. For example, it may be mentioned that four major chaperone proteins HSP – 70, HSP – 90, Grp – 94 and gp – 96 and calreticulin were identified in an extract prepared from human melanoma lines. These are functional in enhancing presentation of exogenous peptides. However, superior activity is observed in HSP-70 rich preparation that can be used in immune therapy of tumors and vaccine development [10].

Now it is an established fact that most of the neurodegenerative diseases are due to abnormal protein aggregation which basically causes misfolding of the native protein with conformational changes. For example, alpha synuclein, tau isomers, huntingtin (HTT), prion proteins etc are found to be deposited in case of P.D, A.D, HD and prion diseases respectively. On the other hand, induction or expression of HSPs draws a special attention in removing the abnormal aggregates.

Table 1

Heat-shock protein (hsp) families		
Family	**Family members**	**Intrace llular location**
Small hsp	**hsp 10,** GroES, **hsp 16, ά crystallin hsp 20, hsp 25,** hsp 26, **hsp 27**	Cytosol
hsp 40	**hsp 40, DnaJ,** SIS_1	Cytosol
hsp 47	**hsp 47**	Endoplasmicreticulun
calreticulin	**Calreticulin, calnexin** Endoplasmicreticulun	
hsp 60	**hsp 60, hsp 65, GroEL**	Cytosol and mitochor
		Cytosol
hsp 72, Hsc 70 (hsp 73), hsp110 / SSE, Dnak		
hsp 70	**SSC** $_1$SSQ $_1$, ECM $_{10}$	Mitochondria
Grp 78 (BiP), Grp 170		Endoplasmic reticulun
hsp 86, HTPG		Cytosol
hsp 90	**gp 96 (Grp 94, hsp 108, endoplasmin)**	Endoplasmic reticulum
	hsp 104, **hsp 110**	Cytosol

Table 2

Heat-shock protein (hsp) receptors on cells of the immune system		
Ligand(s)	**Receptor**	**Receptors cellular**
gp 96, hsp90, hsp70,		
Calreticulin	CD91	Dendritic cell (DC), macro
hsp70	LOX-1	DC, macrophage, monocy
gp96, hsp60, hsp70, hspBS,		DC, macrophage, mast cell
Crystallin	άToll-like receptor 2/4	microglia, neutrophil
hsp70	CD 14	DC, macrophage, monocy
hsp70	CD 40	DC, macrophage, monocy
gp96, Calreticulin	Scavenger Receptor type A	DC, macrophage, microglia
mycobacterial hsp70	CCR5	DC, macrophage, T-cell, n
Calreticulin, gp96, hsp 110,	Scavenger Receptor expressed by Endothelial	
Grp170, hsp70	Cells (SREC) -I	DC, macrophage

The HSPs are highly associated with cellular defense mechanism. Now – a-days, it is found to regulate various cellular functions including protein folding, refolding of partially denatured proteins, protein transport across membrane, cytosheletal organization and apoptosis etc [11]. It acts as cytoprotective factor against deleterious environment stresses. Its activation includes also a wide range of client substrates including hormone receptor and also kinases, oncogenic proteins [12]. Different HSPs are localized in synapses and axons. These are found to regulate disposal of toxic aggregation like amyloid plaque and NFT in A.D, alpha synuclein in P.D, huntingtin (HTT) in H.D [13] and prion protein in Cretzfeldt – Jakob Diseases (CJD). Other characteristics of HSPs have also been studied by

several scholars. These include binding of HSPs in vitro or in vivo directly to tau, facilitating microtubule polymerization and limiting tau aggregation and decreasing toxicity in vitro and in vivo [14]. HSPs can also bind to mutant HTT [15], alpha synuclein or prion oligomers. HSPs can also maintain quality control and can target abnormal or inactive proteins for degradation. HSPs are absorbed in different cellular stimuli and according to molecular size or function these are categorized as

(i) The small HSPs (15 to 30 KD, HSP 10, HSP 26/27)
(ii) Larger HSPs such as HSP 40, HSP 60, HSP 70, HSP 100/104/110 [16]

These are mainly localized in cytoplasm and sometimes in nucleus. These are also found in mitochondria, endoplasmic reticulum (ER) etc. Under normal conditions, HSPs levels are properly regulated or maintained by local cellular environment but serious deterioration of HSPs defense system is observed when misfolded protein aggregates cross limit. Overproduction or over expression of certain HSPs can lead to development of some devastating diseases including cancer [17].

As HSPs are induced by stressful conditions, two distinct conditions of induction may be mentioned like (i) auto induction in cells under any stress condition and (ii) induction due to administration of external stimuli that may be considered as stressful condition. Among these external stimuli, some Indian medicinal herbs are found to play vital role in this respect. There in are a good number of medicinal plants in India. These include (i) Bacopa Monnieri, (ii) Ashwaganda and (iii) Turmeric plant. HSPs induced by these plants are found to be suitable to disaggregate the aggregated parts of concerned proteins like alpha synuclein, A β amyloid or tau protein and HTT protein with respect to P.D, A.D and H.D respectively. A brief note on certain characteristics of Turmeric plant (Curcumina Longa) - the source of curcumin is mentioned here for the interest of the present work.

3. Curcumin – A Natural Polyphenol to Activate H.S. Response

The scholars of the day are found to be interested to investigate natural polyphenol as HSP inducer to prevent neurodegenaration. This is because of the fact that these are basically nontoxic, safe, easily available, cost effective and also can be administreated orally. A good number of phenolic compounds derived from traditional medicinal plants have antioxidant, anti – inflammatory properties. But only few of these have been identified as HSPs inducers / modulators. Likewise curcumin derived from yellow powder / paste of turmeric – a product of the plant curcumina longa has recently been identified as HSPs inducers / modulators.

Turmeric is used as an essential spice of Indian food item. On the other hand, it is being used as an item of therapeutic necessities in a number of diseases in Indian Ayurvedic system of medicine since more than five thousand years. It is used not only in India but also in China, Vietnam and other South – East Asian States. Practically, it is used as a therapeutic agent due to the presence of polyphenol in curcumin. But its use as therapeutic agent due to its pleotropic beneficial effects has started in Western World since last two decades only.

From pharmacological point of view curcumin is anti inflammatory, anti oxidant and it also stimulates neurogenesis [18]. It has got anti – amyloid properties which reflect on its capability to be a potent drug for treatment of neurological diseases including A.D, P.D, depression, epilepsy, cerebral ischemia, brain tumor and different neuropathic pain. Due to its anti – amyloid properties, it can prevent aggregation of related protein (Aβ amyloid and tau isomers). Recently, it was shown by Maiti and Manna [19] that curcumin reduced HTT aggregation in CAG 140 KI mouse model of H.D. It was shown also by Yang et al [20] that curcumin reduced Aβ and tau aggregates from 3 x T_g rat. In vitro data, it is shown that out of 214 – anti oxidant compounds, curcumin got strongest inhibitory effect on the formation of A β fibrils [21]. It reveals from recent experimental data that oral administration of curcumin could inhibit Aβ oligomerization and tau phosphorylation and thereby could improve impairment of AD – animal models [22]. It was also shown by other groups that tau vain injection of curcumin for one week had marked with 30% amyloid plaque size reduction in AD patients [23]. It can stimulate phagocytosis of Aβ in rat AD models [24]. It can decrease Aβproduction by inhibiting GSK - 3β(the enzyme responsible for phosphorylation of tau). Further, curcumin is also found to bind with neurofibrillary tangles (NFT) in human AD and in animals too [25]. Moreover, it reveals from the studies of different group of scholars that curcumin can also bind with other amyloid proteins like β - pleated sheet structure including alpha synuclein protein [26], HTT [27] and also prion protein.

4. Role of Huntingtin in Huntington

It has been mentioned that like P.D, A.D etc, H.D is also caused due to aggregation of a protein called huntingtin abbreviated as HTT. Huntingtin gene is an “interesting transcript 15” gene symbol as IT 15 [28]. It is suggested by a number of scholars [28] that HTT plays vital role in long – term memory storage. It has got variable structure due to the presence of variable [28 i] number of glutamine residue (amino acid) - one of the basic constituents of the amino acid sequence of the protein HTT. In its normal form it contains 6 – 35 glutamine residues. But when an individual gets affected by H.D, the number of glutamine residue is increased from 36 residues to more than 100 based on which magnitude of HD attack may also be increased. The status of HD due to CAG repeats [28 ii] is described as

Repeat count	Classification	Disease status
<26	Normal	Unaffected
27-35	Intermediate	Unaffected
36-40	Reduced penetrance	+/- Affected
>40	Full penetrance	Affected

(Courtesy: Wikipedia under the Title Huntingtin.)

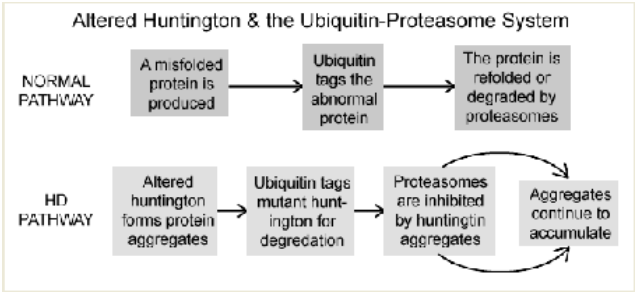
Figure 1. Classification of the trinucleotide repeat, and resulting disease status, depends on the number of CAG repeats

The mass of HTT depends on the number of glutamine residues. The projected mass is 340 kD with 3144 amino acids. The exact function of HTT is still not clear. However, it is found to play an important role in nerve cells. HTT is expected to be involved in signaling, transporting materials, binding proteins and protecting programmed cell death (apoptosis). It is required for normal development before birth [29]. It is expressed in many tissues with highest level of expression in the brain.

Normally, no case of HD is reported with a count less than 36 glutamine repeats. However, the altered gene is passed from one generation to the next with CAG repeat expansion. People with 28 to 35 CAG repeats have not been reported to be affected with the disorder, but their children have the chance of attacking with the diseases with increase of CAG repeat. After several biochemical process, increases of CAG repeat lead to HTT aggregation. Now the simple question arises whether these aggregates are a cause or a consequence of neurodegenerative diseases such as HD? Are aggregates harmful, cause nerve cell dysfunction or death?

It reveals from recent studies that "the translation of irregular HTT protein with expanded poly glutamine domains signals to the cell that these aggregated proteins are abnormal. For this, recruitment of proteases such as caspase – 3 and caspase – 6 is essential by the cell for cutting these proteins into small fragments that can be recycled and digested by the cell"! Some of these fragments belonging particularly to N- terminal domain of HTT protein are harmful to the cell and cause protein aggregation. These aggregates in turn disrupt the function of the cell carried out by the nucleus normally called transcription. This kind of aggregation of HTT protein is not only due to small cutting by proteins but also due to alternative splicing of the HTT mRNA into very small fragments that can enter the nucleus. This has been found to occur in all H.D mouse models with wide range of CAG repeat normally from fifty to hundred. This kind of aberrant splicing is also found to occur in human mutant HTT proteins. This is evidenced in fibroblasts and blood cells of HD patients. This splicing is mediated by SRSF -6 proteins. This is found to bind to the beginning of the mutant HTT transcript leading to the generation of these small protein fragments. From another study namely nuclear export sequence- a specific sequence of amino acid encoded in the first seventeen amino acids of the HTT protein when mutated in HD, the protein will aggregate and accumulate in the nucleus similarly. The excess glutamine in HTT can also constitute a type of bundling formally known as neuronal inclusion (NI). NI_S [29 i] are usually formed at the axons and dendrites of the nerve cells in specific regions of the human brain where damaged neuron characteristics of HD are produced. Subsequently, protease cuts HTT into smaller fragments which on entering the nerve cell nuclei form more clumps at the centrosomes. Thus NI causes problems to the cell and also brings significant change in the cell structure and also interferes with the normal production of other proteins. This leads to the fact that the formation of NI and outburst of neurodegenerative symptoms are found to be linked.

Thus it reveals that the characteristics of HTT protein particularly with respect to aggregation, configuration etc is very complicated. Formation of aggregation in HTT protein is not as that of alpha synuclein protein or tau protein which get β aggregated with different segments of alpha synuclein protein and different isomers of tau protein particularly with respect to P.D and A.D respectively. The role of HTT in HD may be described as



(Courtesy: Huntington's outreach project for Education at Stanford, quoted from Wikipedia)

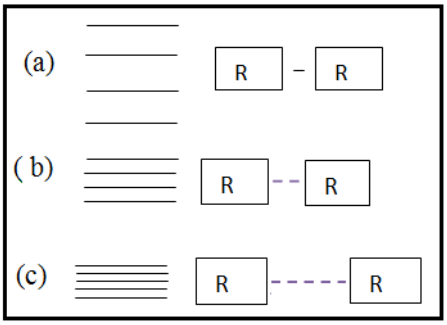
Figure 2

However, a good number of experiments conducted by different group of Scholars observed positive role with respect to disaggregation of aggregated proteins and hence improvement in memory of mice model. But the molecular mechanism of curcumin therapeutic effects is not clear till to- date.

5. Methodology

In view of the above discussions, it requires an in-depth study to explore the complicacy of functioning of HTT protein particularly with respect to therapeutic aspects of H.D, based on which an alternative mechanism namely "protein vibration Approach" may be suggested for combating the problem with HSP induced by Indian Medicinal herb namely Turmeric plant. It is an established fact that protein vibrates due to either electrostatic force (potential) or due to external stimuli. The authors in a paper [30] suggested that the vibration characteristics of protein depend on the magnitudes of molecular weights of the concerned protein. It was also held by the authors that more the molecular weight of protein, the less is the number of vibration frequency. On the other hand, less the value of molecular weight of protein is, the more is the number of

frequency. Thus the vibration pattern of protein may be described as



Vibration energy spacing of protein molecules

Figure 3

The vibration frequency and vibration energy of the concerned protein can be evaluated by using one dimensional Schrodinger's Equation. The reason of considering one dimensional Schrodinger's Equation lies in the fact that an electrostatic force can control atomic motion in a protein.

The vibration energy and vibration frequency of concerned proteins may be evaluated by using the solution of one dimensional Schrodinger's Equation

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + \nu\,(r)\psi = \varepsilon\,\psi \qquad (1)$$

which turns to

$$\frac{-h^2}{8\pi^2 m}\frac{d^2\psi}{dr^2} + \frac{1}{2}\,\mathrm{kr}^2\psi = \varepsilon\psi \qquad (2)$$

with potential energy $V = \frac{1}{2}\,\mathrm{kr}^2$,

while other symbols stand for usual meaning.

The energy of the allowed vibration states derived from the solutions of the Schrodinger's Equation are

$$\varepsilon_{vib} = (\nu + \frac{1}{2})\,\frac{h}{2\pi}\sqrt{\frac{k}{m}},\ \nu = 0,1,2 \qquad (3)$$

while the expression for vibration frequency stands as

$$\nu_{vib} = \frac{1}{2\pi}\sqrt{\frac{k}{m}} \qquad (4)$$

Now – a – day's curcumin has been identified as HSP modulator / activator like withaferin – A [31], celastrol [32] and gambogic acid [33]. In addition a good number of other adaptogens extracted from roots of Eleutherococcus senticosus, Rhodiola rosea etc are reported to increase HSP – 70. These were observed when tested in isolated human neuroglia cells [30]. But as our present interest is concerned with curcumin, we like to concentrate our attention to disaggregation of HTT protein by HSP – 70, 90, induced by curcumin in the context of Protein Vibration Approach [30].

6. Result and Discussions

Recently, a detailed study on the mechanism of functioning of the extract of Bacop Morrieri (B.M) and of Ashwagandha which are able to induce HSP – 70, 90 was undertaken from the view point of "Protein Vibration Approach" by the author [34] with respect to P.D and A.D respectively.

Vibration frequencies and vibration energies of alpha synuclein protein (native) and its aggregated form responsible for P.D and those of tau (native) and it aggregated form with six isomers responsible for A.D were evaluated by using Equations (4) and (3) with electro static potential in the range of 0.8 mv to 1 mv and these are tabled in Tables 3, 4, 5 and 6.

Table 3

Electrostatic potential	Molecular weights of			
	Alpha Synuclien protein	Aggregated form (segments) of alpha synuclien protein		
	m=144.76	m=152	m=162.50	m=175
0.8 mv	1.32	1.32	1.32	1.15
1.0 mv	1.66	1.65	1.44	1.44

Table 4

Electrostatic potential	Energy of native proteins	Vibration energy of aggregated alpha synuclein protein with different fragments		
	Mol. Weights			
	m=144.76	m=152	m=162.50	m=175
0.8 mv	0.04	0.04	0.03	0.03
1.0 mv	0.05	0.05	0.04	0.04

Table 5

Electrostatic potential	Molecular weights of aggregated tau					
	45+48 =93	93+52 =145	145+54 =199	199+59 =199	199+59 =258	320+67 =397
0.8 mv	1.94	1.53	1.33	1.33	1.16	0.96
1.0 mv	2.17	1.73	1.48	1.48	1.30	1.07

Table 6

Electrostatic potential	Molecular weights of aggregated tau					
	93	140	199	250	320	387
0.8 mv	.383	.340	.258	.231	.205	.185
1.0 mv	.430	.334	.292	.258	.231	.211

On the other hand, vibration frequency and vibration energy of HSP – 70 and 90 with the same magnitude of electrostatic potential responsible for disaggregation of aggregated proteins were also calculated and these are tabled in Table 7 and 8.

Table 7

Electrostatic potential	Molecular weights of HSPs in kD		Molecular weights of receptor protein in kD
	HSP – 70	HSP – 90	RLP receptor 18.8
0.8 mv	2.23	1.97	4.32
1.0 mv	2.49	2.21	4.83

Table 8

Electrostatic potential	Molecular weights of HSPs in kD		Molecular weights of receptor protein in kD
	HSP – 70	HSP – 90	RLP receptor 18.8
0.8 mv	.47	.39	.853
1.0 mv	.49	.43	.959

It was analyzed by the author [34] that HSP – 70 is capable to disaggregate different segments of aggregated alpha synuclein protein responsible for P.D and also different isomers of tau protein responsible for A.D due to higher frequency of vibration generated by HSP – 70 in comparison with those frequencies generated by aggregated alpha synuclein protein and tau protein.

Keeping in view the outcomes of these analyses, an attempt has been taken here to examine the role of HSP – 70 and 90 induced by curcumin in combating the complicated functions of HTT responsible for H.D. For these, vibration frequencies and vibration energies of HTT – 340 (projected molecular weights), Caspase – 3 and Caspase – 6 or 9 having different molecular weightsare also evaluated by using Equations (4) and (3) respectively and these are tabled in Tables 9 and 10.

Table 9. Vibration frequencies and vibration energies of HTT Protein

Electrostatic potential	Molecular weights of HTT Protein	Vibration frequency (m^{-1})	Vibration energy in 10^{-22} ergs
0.8 mv	340 kD	0.99	0.0019
1.0 mv	340 kD	1.13	0.0025

Table 10. Vibration frequencies of caspases in (m^{-1})

Electrostatic potential	Molecular weights of different caspases in kD				
	12 kD	17 kD	25 kD	35 kD	37 kD
0.8 mv	5.39	4.55	3.75	3.17	3.08
1.0 mv	6.05	5.08	4.19	3.54	3.44

It reveals from the tables that the magnitudes of vibration frequencies (m^{-1}) and vibration energies kof HTT proteins with projected mass 340 kD are lower than those of HSP – 70 and 90. In this context, it is held by the author that the vibration frequency of HSP – 70 and 90 is comparatively more frequent and also higher than HTT protein of mass 340 kD. As a result these will be able to disaggregate different molecules of aggregated glutamine amino acids. This many continue with administration of curcumin present in turmeric powder or paste till native (original) state of HTT comes out and gets rid of aggregation of glutamine molecule. But pulling out of disaggregated parts (individual glutamine molecules) by any process or by any biochemical agency as in the case of aggregated isomers of tau protein responsible for A.D is not reported by any scholar till the date. Moreover, it has been mentioned by the scholars that aggregated protein molecules on cutting by enzyme caspase – 3 and caspase –6 or 9 into small fragments are recycled and digested by the cell. Hence, on getting into nucleus these once again cause protein aggregation resulting in a continuous process of aggregation of HTT. As a result, the process of cutting aggregated HTT protein by enzyme caspase – 3 or caspase –6 or 9, whatever it may be, continues and fails to serve the purpose of disaggregated of HTT. Based on these difficulties of disaggregation the author attempts to look into the problem differently.

In a recent paper [35] it was suggested that HSP – 70, 90 and gp – 96 are able to modulate the signaling pathway of certain cancer causing proteins and receptor proteins like MYC, P_{53}, Mdm – 2, CD – 47 having molecular weights 49, 53, 55, 50 kDs respectively which are smaller than that of HSP – 70 and 90. This is due to the fact that the wavelengths of the vibrations generated by HSPs are higher than those generated by cancer causing proteins and protein receptors. In view of this the author suggests that the vibrations (viz. vibration frequencies) generated by HSP – 70 and 90 may also modulate the signaling pathway of concerned molecules having smaller molecular weight, since the magnitude of wavelength of the vibrations generated by HSP – 70, and 90 are higher than those of small wavelength of vibrations caused by glutamine amino acids. Thus the process of frequency modulation practically stands for changing signaling pathway of disturbing amino acid molecules and caspases responsible for aggregation of HTT. However, the possibilities of cutting glutamine by enzyme caspases of the aggregated glutamine molecules may not arise if all molecules are disaggregated by the vibration frequencies of HSP – 70 and 90 as suggested by us. This is because of the fact that caspases are synthesized as inactive zymogens (pro-caspases) which are activated by appropriate condition and this may not be possible if the glutamine molecules are disaggregated by higher frequencies of vibrations caused by HSP – 70 or HSP – 90. Thus the author based on different aspects of analytical approaches suggest for two fold possibilities of disaggregation of HTT protein.

(i) Disaggregation of glutamine molecule wise aggregated HTT protein by HSP -70 and 90.
(ii) Modulation of signaling pathway of small fragments of glutamine molecules even before cutting by caspase – 3 and caspase –6 or 9.

7. Conclusions

Our analytical approaches of disaggregation of aggregated HTT due to glutamine amino acids may be compatible to the experimental findings of Panchanan Maiti and others [19] where the scholars observed slow but progressing neurobehavioral improvements and reduction in HTT neuropil aggregates with curcumin administration to certain varieties of mice like CAG 140 KI (140 – glutamine codon) animal model HD. Further, our approaches with modulating effect of HSP – 70 and 90 are also found to be in parity with the investigated results of minimum dose (0’01 μ M) of curcumin which was able to increase significantly HSP – 70 and HSP – 90 even after 24 hours of incubation in SH-SY5Y

cells by the same group of scholars (unpublished). Thus curcumin might slow down amyloid formation and eventually will reduce neuronal death in neurodegenerative diseases.

From the above observations, it may be held that out "Protein Vibration Approach" is on the one hand able to explain disaggregation of glutamine amino acid molecules from aggregated HTT responsible for HD and on the other hand is able also to modulate HSP in slowing down amyloid formation. Thus our analytical approaches are found to be in reasonable proximity with the experimental findings conducted by Panchanan Maiti and others [19].

ACKNOWLEDGEMENTS

The author expresses his thanks to Dr. U.C. De, Asst. Professor, Department of Chemistry, Tripura University, Agartala, Tripura, for helpful discussion. He is thankful to Miss Joysree Sutradhar for under taking the Computer work of the Paper.

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