Curcumin: A Natural Modulator against PolyQ Diseases

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Abstract

Misfolding of proteins in the neuronal tissue causes aggregation of amyloid proteins, induces oxidative stress leading to synaptic damage and impairment of neural communication in several poly glutamine (polyQ) neurodegenerative diseases. Dietary intake of polyphenols moderates the oxidative stress caused by aggregates in these diseases. Curcumin, which belongs to the family of polyphenols has protective and preventive effects against these neurological disorders. Curcumin can pass blood brain barrier and therefore is a promising natural polyphenol for age onset polyQ disorders.

Keywords: Curcumin, Aggregates; PolyQ; Neurodegeneration; Polyphenols; Huntington Diseases

Introduction

The polyglutamine (polyQ) diseases are an assembly of inborn neurodegenerative diseases categorized with the genomic abnormalities in the expansion of cytosine-adenine-guanine (CAG) triplet repeats in coding regions of specific genes [1-3]. The CAG triplet codon codes for glutamine (one-letter code, Q) and its expansion in the disease-causative genes cause the formation of amyloid proteins with a peculiar pathogenic extension of polyQ tract. Fischbeck and coworkers in 1991 for the first time observed the extension of CAG repeats in exon 1 of the androgen receptor gene of spinal and bulbar muscular atrophy (SBMA) affected patients [4], after which it has been discovered in other different inherited neurodegenerative problems [5]. There are so far, 9 disorders mentioned that make up a group of these type of diseases, which include Huntington’s ailment (HD), spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7 and 17 and dentatorubralpallidoluysian atrophy (DRPLA) [2]. A common characteristic of the polyQ ailments is deterioration of neurons in specific regions of the brain, which causes impairment in the basic functioning like motor disturbance that depend on the part of the brain that is affected. Effective treatment plans against the polyQ diseases to extend or stop the onset and development of this disease are rare and have not yet been deciphered and mostly treatment is symptomatic.

Curcumin is a known anti-oxidant having a wide spectrum of apparent pharmacological effects including anti-carcinogenic, anti-inflammatory, Alzheimer’s prevention and has medicinal benefits against diseases such as cardiovascular diseases, neurodegenerative diseases, inflammatory bowel diseases, multiple sclerosis, arthritis, asthma and more. Curcumin, is the major curcuminoid (2 - 8%) in the dried ground rhizome of the perennial herb, *Curcuma longa*, family Zingiberaceae and known as turmeric [6]. New research in cell culture show that curcumin prevent aggregation of amyloid proteins [7], which has opened a new dimension in studying the altering effect of curcumin in polyQ diseases in animal models and humans.

PolyQ diseases and polyphenols

The pathological hallmark of polyQ diseases [2] is the formation of amyloid aggregates, which is the target of therapeutics. As these aggregates are an easy marker for neuropathology and neurodegeneration in different cell models but exact role of aggregates is still under debate. In different polyQ diseases, it was observed that there was formation of intranuclear inclusions like in Huntington disease model of mouse and it was also confirmed in patients suffering from HD [8]. These aggregates affect various pathways, like mitochondrial

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Respiration and antioxidants NAC and cytochrome c resist the reduction of mitochondrial respiration caused by aggregates. Thus it was proposed that polyQ aggregates reduces mitochondrial respiration by increasing oxidative stress via production of ROS [9]. These misfolded proteins can also impair cellular protein clearance pathways, including dysfunction of molecular chaperones, proteasome system and autophagy pathway [10]. Dictyostelium discoideum a new invertebrate model system that used now to study polyQ diseases [11] established that autophagy pathway get dysregulated in presence of aggregates (unpublished data).

No specific drugs are available in the market against these polyQ aggregates pathology and chemical based drugs used for treatment of these diseases have multiple side effects. There is a need to find natural modulators, which have neuro protective effects against polyQ diseases. The most promising candidates which has neuroprotective activity are polyphenols [12].

Polyphenols are referred to as secondary metabolites produced by plants and protect against different harmful agents like ultraviolet radiation, pathogens and physical damage [13]. Broadly they are divided into two categories based on their complex structure (no. of phenol rings and chemical groups attached): flavonoid and non-flavonoid polyphenols [14].

Curcuminoids (curcumin) share its space in the list of non-flavonoid polyphenols with other members like phenolic acids (e.g. caffeic acid, gallic acid), lignans (e.g. secoisolariciresinol) and stilbenes (e.g. resveratrol).

The antioxidant properties of these polyphenols [15], is the most beneficial pharmacological property to fight against polyQ diseases. Resveratol, which is a polyphenol purified from grapes, now proven as an anti-aging agent and is neuroprotective in transgenic mouse model of Huntington’s disease [16]. Epigallocatechin gallate (EGCG), a polyphenol delayed and extended the life span in mice model of amyotrophic lateral sclerosis (ALS) [17]. In invertebrate system like Drosophila melanogaster model of Parkinson disease, EGCG showed beneficial effect by reverting back its movement disability [18].

It has been reported that curcumin has multifaceted effect over the cellular homeostasis and has been reported to be effective against a wide variety of diseases like cancer [19], neurodegenerative diseases, cardiovascular disease [20], obesity [21], liver disease [22], inflammatory disease [23] and even aging [24].

Therapeutic role of curcumin in polyQ diseases

Curcumin is a diarylheptanoids represent ((1E, 6E)-1,7-Bis (4-hydroxy-3-methoxyphenyl)-1, 6-heptadiene-3,5-dione) the major component of C. longa, generically known as turmeric [25]. Curcumin has neuroprotective effect as it modulates different pathways like it promote neurogenesis, activates molecular chaperones, acts as imaging probe, improve cerebral circulation, chelates metal, acts as antioxidant, anti-inflammatory and limits the tau and IRS lesion [26]. In polyQ diseases there is an increase in protein misfolding, which cause aggregates formation, which get accumulated in intra and extra cellular spaces of cells [27].

Aggregation of misfolded proteins and amyloid-β (Aβ) get inhibited by binding with curcumin [28]. Curcumin also inhibit tau [29], α-synuclein [30], huntingtin [31] and prion proteins [32] in tauopathies, Parkinson diseases (PD), Huntington diseases (HD) and prion diseases respectively. Curcumin act as an activator of molecular chaperones in polyQ diseases [33] and molecular chaperone facilitates correct folding, assembly and degradation of proteins [34] and is one of the members of post-translational quality control system for the prevention of aggregation [35].

Curcumin binds with Aβ-plaques in retina [28], act as a potent inhibitor of the metabolic pathway for amyloid precursor protein (APP) and reduce Aβ level [36]. It also control Aβ production by inhibiting GSK-3β-mediated PS1 activation [37]. It also enhance the clearance of Aβ-plaques by up surging the association of phagocytic cells around amyloid plaques [29].

α-synuclein fibrillation observed in Parkinson disease (second most common neurodegenerative disorders) was inhibited in the presence of curcumin, solubilization of fibrils get more pronounced and thus aggregation propensity of misfolded proteins gets reduced [38]. Curcumin can dramatically reduce existing amyloid plaques and associated neurotoxicity in a mouse model of Alzheimer’s [39].

Further studies are needed to understand the pharmacological and therapeutic roles of curcumin in relation to amyloidogenic properties of aggregates.
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Conclusion

Misfolding of proteins is the pathological feature of polyQ diseases like Alzheimer’s, Parkinson’s, Huntington and prion diseases. The beneficial effects of polyphenols may prove to be a valuable asset in the quest to develop a new generation of drugs capable of counteracting neuroinflammation and associated neurodegenerative diseases, however, the research in this field is still incomplete. Natural polyphenol, curcumin has multifaceted effect, as its binding ability with aggregates, enhances its clearance and reduction in toxicity make curcumin a promising candidate which may fight against neurodegeneration at various front. More research is needed to make this polyphenol or its derivative to work against neurodegeneration.

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