eISSN 2255-0569

SPECIAL ARTICLE

Protein misfolding and medicinal strategies in neurodegenerative disorders

Mal plegamiento de proteínas y estrategias medicinales en los trastornos neurodegenerativos

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Received: 8 - VI - 2022
Accepted: 21 - VI - 2022

doi: 10.3306/AJHS.2022.37.04.166

Abstract

Proteins that misfold may accumulate and cause disorders like Alzheimer's and Parkinson's. New medicines are also explored to forecast and even cure these illnesses' severe symptoms. Because they were misfolded during creation or maintenance, rogue proteins may harm a biological system. This causes over twenty human illnesses, including Alzheimer's, Huntington's, Parkinson's, and other neurodegenerative diseases. To create new therapies and medications, researchers will need to understand protein misfolding and aggregation formation. To summarize, protein misfolding causes aggregation and neurodegeneration. This suggests that nature employs protein aggregation to execute unique physiological activities in various biological conditions.

Key words: Protein misfolding, Alzheimer's disease, Huntington's disease, Parkinson's disease.

Resumen

Las proteínas que se pliegan mal pueden acumularse y causar trastornos como el Alzheimer y el Parkinson. También se exploran nuevos medicamentos para prever e incluso curar los graves síntomas de estas enfermedades. Las proteínas mal plegadas durante su creación o mantenimiento pueden dañar un sistema biológico. Esto provoca más de veinte enfermedades humanas, como el Alzheimer, el Huntington, el Parkinson y otras enfermedades neurodegenerativas. Para crear nuevas terapias y medicamentos, los investigadores deberán comprender el mal plegamiento de las proteínas y la formación de agregados. En resumen, el mal plegamiento de las proteínas causa agregación y neurodegeneración. Esto sugiere que la naturaleza emplea la agregación de proteínas para ejecutar actividades fisiológicas únicas en diversas condiciones biológicas.

Palabras clave: Mal plegamiento de proteínas, enfermedad de Alzheimer, enfermedad de Huntington, enfermedad de Parkinson.

Introduction

At several stages of the biological process, the ability of proteins to function properly depends on their coordinated interactions. The normal number of cell proteins is 30,000 and the linear chain of a protein consists of amino acids[1]. This linear chain can be used in its natural form. After translation, proteins begin to fold due to the interactions between amino acids. Proteins that fold themselves after production are more prone to misfolding and The crowded cell environment increases misfolding[2,3]. Also, the PQC mechanism ensures that proteins are folded, transported, and eliminated correctly in live creatures. Even when the original structure of a protein is present, misfolding occurs because numerous proteins do not have access to it. After partial unfolding of the protein, some critical intermediates are formed, which can then self-organise into oligomeric aggregates that eventually form amyloid fibrils. Protein degradation and lysosomal degradation are triggered when molecular chaperones fail to refold misfolded proteins. It can happen because of somatic or genetic mutations, age, changes in the cell environment (like temperature, pH, oxidative stress, and the presence of metal ions), and because of alterations in the cell environment. Diabetes type II, which occurs when amyloid fibrils accumulate in the pancreas, Alzheimer's

disease (AD), which occurs when the aggregates accumulate in brain cells, and other systemic diseases, which occur when amyloid fibrils accumulate in multiple organs such as the liver and heart, are all examples of human diseases associated with amyloid fibrils[4].

Alzheimer's, Parkinson's, Huntington's, and TSE are all induced by improper protein folding and aggregation[5-8]. The buildup of misfolded proteins in diverse brain areas causes CNS amyloidosis; researchers have found a pathogenic pathway connected with these disorders[9]. Proteins, which are very soluble in water, progressively convert into cruciform sheet filamentous polymers. In the cytoplasm and nucleus of afflicted brain cells, as well as in the extracellular space[10], amyloid fibrils develop. A robust quality control mechanism prevents misfolded and aggregated proteins from forming. Molecular chaperones prevent misfolding and aggregation of non-native proteins[11].

This article discusses protein misfolding and aggregation in neurodegenerative disorders. Protein misfolding causes neurodegeneration. To investigate the clinical and biological consequences of recent research supporting these concepts[12].

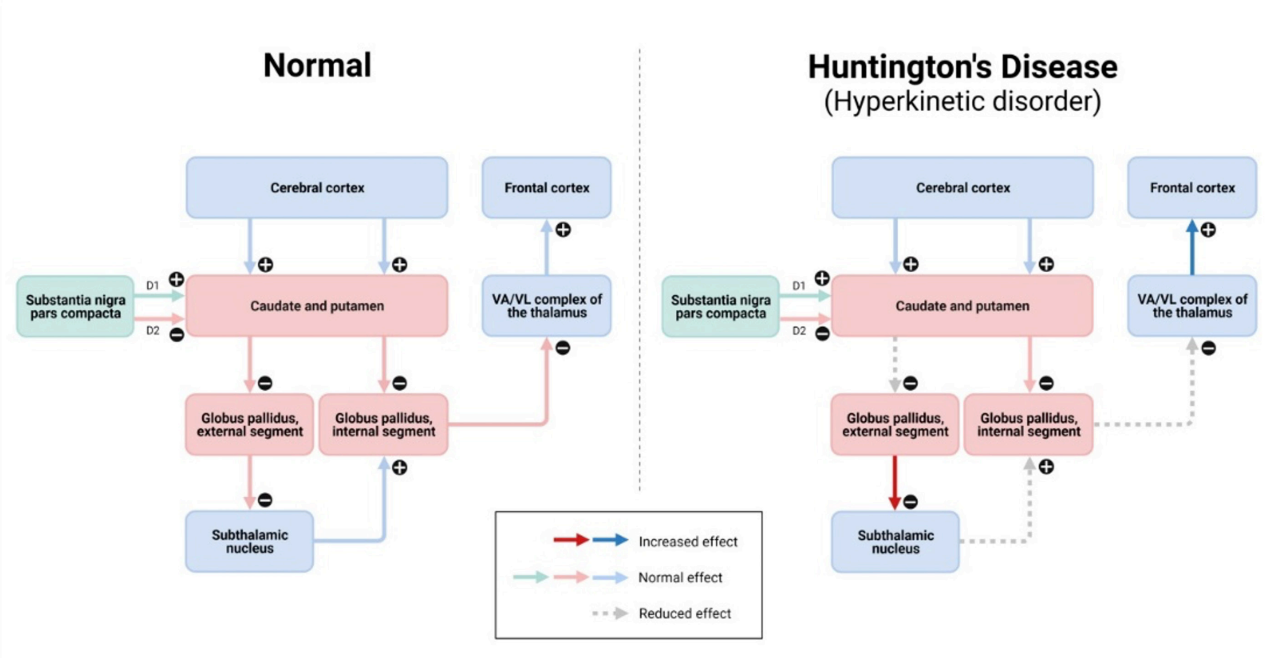
Cells Protein Folding

During folding, several aspects of the process are affected by the environment in which it occurs. After release from the ribosome, polypeptides are folded either in the cytoplasm or in other subcellular compartments such as the endoplasmic reticulum (ER) or mitochondria after being transported across membranes during cellular synthesis[13]. The carboxy-terminal region of a developing chain may also initiate the cotranslational folding of proteins, whereas the exit channel of the ribosome contains the carboxy-terminal segment[14]. Prior to folding, proteins face unique obstacles in the manufacturing process due to the tightly packed macromolecules in cells[15]. Due to the exposed hydrophobic surfaces of incompletely folded chains, they are more likely to bind with other molecules than fully folded chains. The accumulation is due to the fact that their concentration increases[15] and exceeds the first-order folding process that normally occurs in the concentrated environment of cells[16], making the situation even more difficult[17], Complex methods have been developed to prevent proteins from aggregating before folding. Molecular chaperones and the ubiquitin-proteasome system are two examples of systems that are not only independent but also work together in living cells. One of the best known neurodegenerative diseases will be briefly reviewed in this part to provide insight into the pathology that distinguishes it from other diseases[18].

Huntington's disease (HD)

Huntington's disease is a well-known hyperkinetic movement disorder defined by chorea-like movements. This hereditary disorder usually affects people between the ages of 30 and 50. Alzheimer's disease progresses to fatality. Children of Huntington's disease patients have a 50% probability of developing the illness. Frequent repeated actions include hand flapping, swaying, hitting the head, mouthing and choosing objects. Dependence to drugs or alcohol is not the cause of these unpredictable behavior[19]. Dementia and mortality occur within 15 to 20 years after the onset of this condition20 (**Figure 1**).

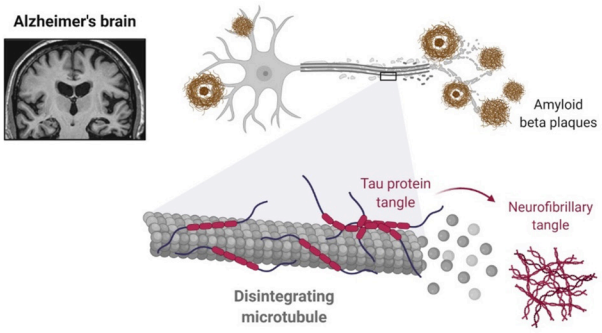
Figure 1: Schematic diagrams display Normal state and hyperkinetic disease (e.g. Huntington disease).



Alzheimer's disease (AD)

Alzheimer's disease (AD) is a neurodegenerative condition that progresses over time (**figure 2**)[21]. Age is a significant risk factor for neurodegenerative disorders such as Alzheimer's, which are characterized by aberrant protein aggregation. As a result, amyloid-beta plaques in the extracellular space and tau neurofibrillary tangles in the medial temporal region and cortex of afflicted neuronal tissues reflect two separate illnesses[22].

Figure 2: Alzheimer's disease is a degenerative neurological condition caused by extracellular amyloid-beta plaques and tau neurofibrillary tangles in the medial temporal region and brain.



Prion disease

Neurodegenerative illnesses induced by prion infection are known as transmissible spongiform encephalopathies (TSE)[23]. The condition is hypothesized to be caused by structural changes to the PrPc protein in the brain, which leads in the compulsive form of PrPTSE. The pathogenesis and emergence of an infectious prion are dependent on this change. Predatory prion infections have been proven to impact the central nervous system (CNS) of a wide range of species[24].

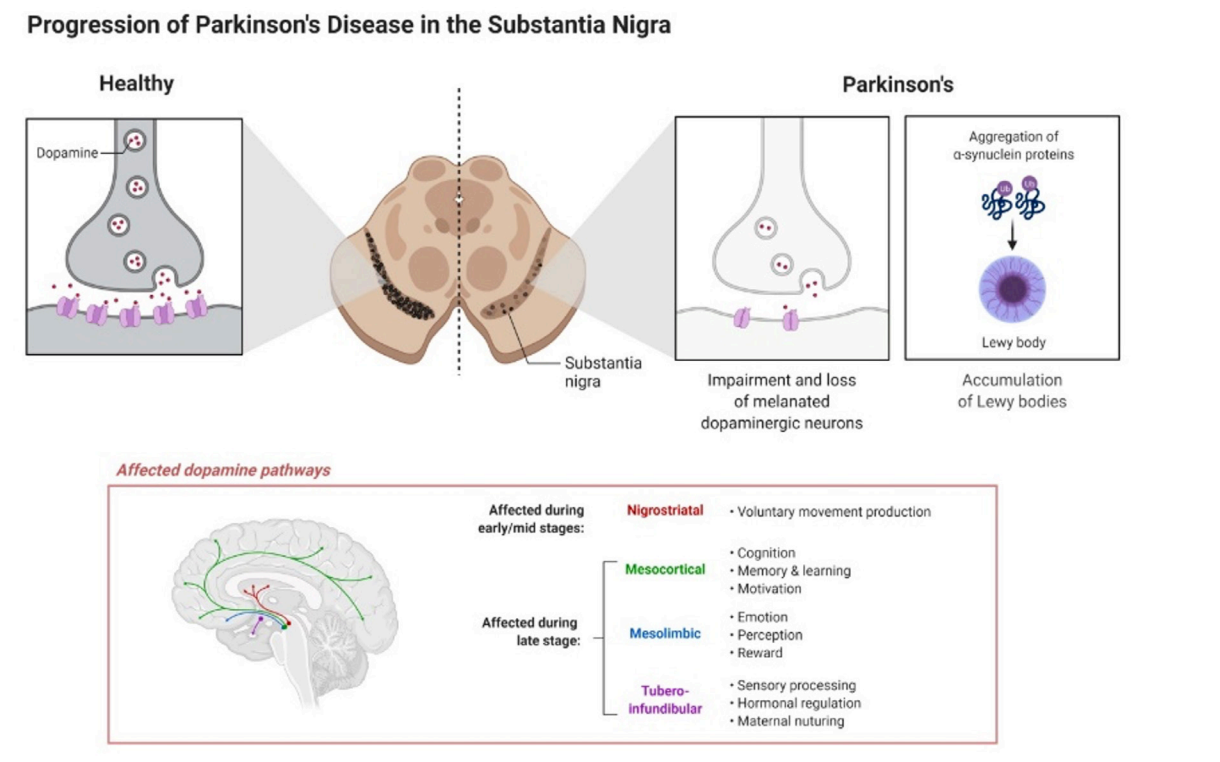
Amyotrophic lateral sclerosis (ALS)

Motor neuron degeneration in the brain stroma, motor cortex, and anterior horn of the spinal cord is a hallmark of ALS, which is lethal and occurs in the latter stages of the illness[25].

Parkinson's disease (PD)

Parkinson's disease is a progressive neurological illness. This second highest frequent neurological illness is caused by dopaminergic cell loss in the substantia nigra. Lewy bodies are a neurodegenerative characteristic of Parkinson's disease[26]. Recently, exosomes, extracellular nanovesicles, have been shown to transport aggregated proteins from one cell to another (**Figure 3**)[27].

Figure 3: Parkinson's disease is a progressive neurological disease. This second most frequent neurodegenerative illness is caused by dopaminergic cell loss in the substantia nigra. Lewy bodies are a neuropathological characteristic of Parkinson's disease.



Exosomes have long been thought to clear cells of waste products and thus play an active role in intercellular communication. In addition, these vesicles contain a variety of inflammatory and signalling substances as well as short RNAs. Prevention of Parkinson's disease could be as simple as targeting molecules such as these vesicles[28].

Medication strategies

The increasing prevalence of neurodegenerative diseases in the general population worldwide is a cause for concern[29]. As described above, neurodegeneration is exacerbated by protein misfolding and aggregation. Extensive research on potential treatments and countermeasures is needed[30-32].

Proteins Stabilization

It is possible to avoid protein misfolding and aggregation by using compounds that bind to the native protein. Examples of this strategy include transthyretin, PrP, and Ab. In the blood and cerebrospinal fluid (CSF), transthyretin (TTR) predominates[33]. T4 and RBP are transported by this transporter[34]. Stabilization of the tetramer by thyroxine could limit TTR fibril formation in vitro[34,35]. Preventing PrPTSE may need the study of chemicals that stabilize PrP c and alter its structure.

Protein aggregation disruption

Neurodegeneration progresses due in part to protein aggregation, which serves a key function. This pathway may also be stopped after protein misfolding has occurred[36]. Amyloid abnormalities are linked to an unique molecule that inhibits the spread of fibrils by binding to the end of a filament. There is one end of these molecules that binds to the fibril, while the other end has no apparent binding surface. Studies conducted in the laboratory using -leaf breakers have shown promising outcomes. It is possible to stop polypeptide chains from forming by using a blocker[37,38].

The self-recognition motif of a misfolded protein is included in these short synthetic peptides, which make use of foldable sheet structure. Synuclein, IAPP, Ab, PrP, and insulin have been found to alter the structure and aggregation of these proteins[39]. However, these inhibitors themselves form amyloid fibrils, which is a drawback to this technique. To avoid amyloid formation, hydrogen bonds may be disrupted in the backbone of the protein. N-methylation and other structural modifications, like streric hindrances to amyloid growth, decrease the stranding capacity of amyloids.

Conclusion

Conformational alterations in proteins are the primary cause of protein aggregation. When these alterations are made, the amyloidogenic amino acids become more accessible to the environment. Protein folding, misfolding, aggregation, and related disorders were the primary emphasis of this review in order to acquire a complete picture of neurodegenerative disease, as well as associated diseases and medicines. Aggregation is a key cause of many neurodegenerative illnesses, and it has to be explored more thoroughly in the future. For amyloids, hydrophobic interaction is an essential mechanism for stabilization, based to a research published in the journal ACS Nano. Despite the prevalence of neurodegenerative illnesses, there is presently no cure for them. Hydrophobic bonds between aromatic and hydrophobic amino acid residues, according to the study, may be weakened. Protein self-aggregation inhibitors might be developed using the findings of this study. A function for protein misfolding and aggregation is well-known in these disorders' underlying pathogenesis. Furthermore, new treatments for these incurable illnesses are very certain to be identified in the future.

Conflict of interest

Authors do not have any conflict of interest to declare.

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