A Review on Protein Misfolding Diseases and therapeutics for preventing Diseases

Yogesh Kumar Singh*
Dept. of Biotechnology, Delhi Technological University (DTU) New Delhi 110042 India

Abstract

**Background:** Protein misfolding sicknesses are the gathering of irresistible lethal neuro and non-neurodegenerative infections and in ebb and flow researchers and specialists accepted that unusual folding of protein is the essential or main key of such illnesses are Alzheimer’s infections, Parkinson’s diseases, Huntington’s sickness, Creutzfeldt-Jakob infection, cystic fibrosis, Gaucher’s infection and numerous other degenerative and neurodegenerative problems. The motive of this review article is to gave a detailed of the existing structural information for prion and prion protein and also we will trying to find out their causes with respect to structural information of prions within the context of what is known about the protein misfolding diseases.

**Objective:** This article presents a brief overview of research on the use of these therapeutics for the treatment or improvement in prion diseases or protein misfolding.

**Material and Methods:** This article begins with the brief introduction about protein misfolding diseases or infections and the therapeutic materials which are used in researches or explain this article (pentosan polysulfate, Quinacrine, Doxycycline, Chaperone based therapy, Resveratrol and curcumin) etc.

**Results and Conclusions:** In this present context of prion misfolding/prion diseases diagnosis, Therapeutic approaches predicts that person infected with prion diseases prolongs the survival time of the patient and improvement in the conditions of the prion diseased infected patient which provides good result for future medicine development.

**Keywords:** Amyloid, Beta-sheet, neurodegenerative, prion, protein misfolding, therapeutics etc

Introduction

Protein misfolding infections otherwise called contagious spongiform encephalopathies (TSEs or prion sicknesses) or can says amyloid illnesses, are a gathering of lethal sicknesses that influence the cerebrum and sensory system of human and animals. Unusual folding(misfolding) of proteins currently stay mutually to form round "oligomers", whose subunits consist of the unusual folding of protein prions. The gathering of such protein oligomers in nerve cells is the basic key of neurodegenerative side effects and eventually, demise, in patients with PR(prion) illnesses. An abundance of natural and biophysical proof currently proposes that the atomic reason for prion illnesses might be encoded by protein conformation. Prions are proteinaceous irresistible particle which is created generally, if not altogether, of a strange isotype of the PrP(prion protein) assigned, on account of scrapie, prion protein scrapie ³. Prion grounds four neuro-degenerative infections of people and six of creatures, together with scrapie of sheep and ox-like spongiform encephalopathy ³. The human prion sicknesses show as irresistible, ancestral, and inconsistent problems represented a puzzler until it was found that changes in the PrP quality are hereditarily connected to advancement of neurodegeneration.

**Prion and Prion Protein**

Prion protein is present in two forms first is normal form and other one is folded protein which is a type of abnormal fold. Prion sicknesses can influence the two people and animals and are at times spread to people by contaminated meat items. The most common form of prion disease that affects humans is Creutzfeldt- Jakob disease (CJD). Typical (PrP⁰) cellular prion protein is an N-allied glycoprotein positioned on the external membranes by means of a glycoprophatidyl-inositol affix [show in fig 1], broadly spoken in a variety of tissues and enrich in the central nervous system.²

![Figure 1](http://example.com/fig1.png)
fibris are kept extracellularly in the tissues and are attention to have an infectious impact. The fibrillar congregations are characteristically steady and underlying examinations have uncovered that they are made dominantly out of β-sheets from a trade name cross-beta conformity. As of late, various instances of practical amyloid has been recognized as well as a composition of melanomases, curil and hydrophobins.

**Approaches for treatment of prion or prion disease**

Pentosan Polysulphate (PPS) is a type of polglycoside chemical compound having low heparin-like work. Pentosan polysulphate acts as a co-receptor for prion type cellular prion protein (PrP) on cell area when compared to interior heparin sulfate proteoglycans and this PPS predicts the better capacity to stop the making of newly made PrP in neuroblastoma cells or cancerous cell (tumor cell). In an experiment, the mice is taken and injects with PPS in the cerebral ventricles in prion diseased mouse, PPS shows activity of increment or increase the lag phase of diseased mice. After treatment with PPS their is no significance or no reversal of foregoing neurological deficit are experiential.

Quinacrine is a derivative of acridine that shows the activity of inhibition in PrPsc occurrence in scarpie-infected neuroblastoma cells. Many studies predicts that use of quinacrine results in increase the incubation time and survival time of the infected mice, which are infected with different scarpie strains, but, there is no specific reason for this, the particular mechanism is controversial. Quinacrine stabilizes the PrPsc that prevent PrPsc polymerization and then reduces the conversion to PrPc to PrPsc. Practically in a experiment with a patient having CJD, the 300mg quinacrine is administered in patient; after 300mg dose of quinacrine the symptoms of disease slowly deteriorated. Then, again some quantity of quinacrine is given to patient continuously for 3 weeks. However, subsequent testing of quinacrine and observational data has predict changes in the survival of patient with CJD.

In CJD brains PrPsc is extracted then, Doxycycline is treated with CJD, which shows the activity of Uptown of protease resistance of PrPsc which then, prolongs the survival time when experimentally done in animals which are infected with prions. Doxycycline shows the property of positive kinetics, good ability to eliminate the blood brain barriers and low deadly property when administered. Many researches describe that patients with CJD received the doxycycline, which results that, exhibit longer survival time, when compared to other patient which are not receive doxycycline. But, during doxycycline is orally administer in patients (100mg) does not predicts or predict the continued existence of patient with creutzfeld-jakob disease.

Iron Tetrapyrole Derivative Fe(III) – TMPyP interact with the PrPc and Fe(II) - TMPyP works just like therapeutic chaperone for prion protein cellular; that reduces the ground state of the occupant confinement and shows the activity of inhibition in prion-induced unusual folding in vitro. Whereas, iron tetrapyrole derivative Fe(III) and its strongly same type of porphyrins predicts the increase in survival activity in prion-diseased mice. Fe(II)-TMPyP combines to PrPc produces the two type of effects (Blocks the prion duplication and also stops the activity of PrP intervened toxicity).

Another approach for stops or reduces the fibrils formation and aggregation in prion diseases or neurodegenerative diseases are developing chaperone based therapeutics. In an...
experimental setup, this is found that the Yeast Disaggregation HsP104 contains a activity of fibrils formed dissolve type of activity from a different type of neurodegenerative disease proteins, and it also predicts the same activity in other type of fibrils or aggregation compounds; such as tau, polyglutamine, A-beta42, alpha-synuclein and prion protein, in another case high level or high concentration of HsP104 is required to liquefy these proteins; some change in HsP104 series shows high level of disaggregation activity and shows the toxicity level. Other chaperone which are used as a good approach for this type of neurodegenerative diseases (Le A-beta42,tau). This chaperone approach include yeast chaperone Tric, which shows protective activity against Htt toxicity and another one chaperone is metazoan chaperone which has the property of disaggregation (eg HsP110.Hsp70 and Hsp40).

Some of the naturally occurring plant based compounds shows promising effect to reduce/eliminate the prion diseases. Resveratrol a type of polyphenol compound that found naturally in foods/fruits, such as blueberries, peanuts, grapes and red wine. Resveratrol shows many potential activities such as antioxidant, anti-allergic and neuro-protective activities, and in some researches it is predict/discover that resveratrol reduces prion duplication and prion disease in vivo. Also it shows that they clears/eliminate PrPSc by reducing endogenous sirtuin levels in brain. In different researches it is showed that resveratrol act together with prion and disruption of prion fibrils formation, it too steady the prion protein peptide during pi-pi stacking interaction amid resveratrol and Tyr128. And the bonding linkage of hydrogen of resveratrol and prion protein peptide additionally reduces the supleness of the peptide and its vulnerability to the aggregates.

Curcumin yellowish coloured present or draw out from turmeric rhizomes, this plant belongs to the family of ginger. More studies set up that curcumin stop the anti-inflammatory work, antioxidant and antitumor properties, also curcumin shows the neuro safety property by altering themicotrichonial assimilation and ease unusual free-radical stress. Curcumin in less quantity of doses effectively enhance the free-radicle stress reaction in cells, it also exert antiprion property by stopping of amyloid occurred by prion. Curcumin increment the quantity of oligomer and holdup the occurrence time of the birth of fibers, also affects the change of prion protein cellular to prion protein scrapie by reduces the birth rate also yields of aggregation in prions.

A hormone a type Neuroendocrine hormone called as Melatonin which is excreted by pineal gland. When melatonin directly combine with free radicals it shows the antioxidant effect and also this blocks the sequence of chain reaction of superoxide oxidation and also by enhancing the property of antioxidant macromolecules. Melatonin shows effective property for patients with fatal familiar insomnia, in different words it is beneficial in case of insomnia.

Gallic Acid (polyphenol) in green tea extracts gallocathecin gallate, it shows the clear activity of reducing or clears the PrPSc from ScNza cells. But, in another case it hinders with simple PrPSc utterance in undiseased cells.

Flupirtine Maleate acts centrally, monopiod analogic that exhibits cytoprotective action in opposition to apoptotic assistant in brain neuron in vivo or in artificial environment. It is occured by PrP106-126 type of different piece like structure which guide toxicity in neurons, increasingly slows the neurotoxicity in the availability of this fragment, in double blind placebo prohibited study of CJD, this chemical molecule shows well organized against cognitive degradation. In another words it does not show any other significant effecton other neurological symptoms, or survival.

Ubiquitin-Specific Protease 14 recent research work predicts that UPS are concerned in quality assurance of PrPSc, we expose the implication of PrP ubiquitination, so firstly paying attention on ubiquitin-specific protease 14 (USP14), a type of de-ubiquitinating enzyme which catalyze adornment of polyubiquitin sequence and play as a function in direction of proteasomal progress. Overexpressed of the leading negative deviant forms of USP14 reduces PrPSc whereas in case of wild type USP14 increases PrPSc in prion-diseased cells. All datas propose that USP14 stops the detoration of simple and abnormal forms of Prion protein, jointly a well-organized considerate about the directive of PrPSc clearance occurred by USP14 may gave highly to the expansion of therapeutic approach for prion’s type of infections.

Conclusion

In this review we are suggested some types of chemical compounds and enzyme which degrade or reduces the prion protein scrapie formation which causes amyloid fibril formation in neurons. But, no promising treatment provides for prion diseases. some chemical compounds or enzymes shows some type of prevention property for prion diseases, they can reduce or decrease the level of PrPSc formation at some levels. so, we can suggest that by use of these compounds which we are explain in this review shows promising results to prevent many prion disease or misfolding of proteins which leads to amyloid formation.

References

1. Zhou, Z., & Xiao, G. Conformational conversion of prion protein in prion diseases. Acta Biochim Biophys Sin, 2013; 45(6):465-476. https://doi.org/10.1093/abbs/gmt027
2. Pan, K. M., Baldwin, M., Nguyen, J., Gasset, M., Serban, A. N. A., Groth, D., & Cohen, F. E. Conversion of alpha-helices into beta-sheets features in the formation of the scrapie prion proteins. Proceedings of the National Academy of Sciences, 1993; 90(23):10962-10966. https://doi.org/10.1073/pnas.90.23.10962
3. Scheinost, J. C., Boldt, G. E., & Wentworth, P. Protein Misfolding and Disease: Chemical Biology: Approaches to Drug Discovery and Development to Targeting Disease, 2012; 579-400. https://doi.org/10.1002/9781118357622.ch19
4. Rambaran, R. N., & Serpell, L. C. Amyloid fibrils: abnormal protein assembly. Prion, 2008; 2(3):112-117. https://doi.org/10.4161/prion.2.3.7488
5. Chen, C., & Dong, X. Therapeutic implications of prion diseases. Biosafety and Health, 2020.
6. Sweeney, P., Park, H., Baumann, M., Dunlop, J., Frydman, J., Kopito, R., Hodgson, R. Protein misfolding in neurodegenerative diseases: implications and strategies. Translational neurodegeneration, 2017; 6(1)-1.3. https://doi.org/10.1186/s40035-017-0077-5
7. Nargeh, H., Aliabadi, F., Ajami, M., & Pazok-Torioudi, H. Role of Polyphenols on Gut Microbiota and the Ubiquitin-Proteasome System in Neurodegenerative Diseases. Journal of Agricultural and Food Chemistry. 2021. https://doi.org/10.1021/acs.jafc.1c00923