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Review Article

A Review on Protein Misfolding Diseases and therapeutics for preventing Diseases

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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 preventing root 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 protein misfolding/prion diseases diagonsis.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.

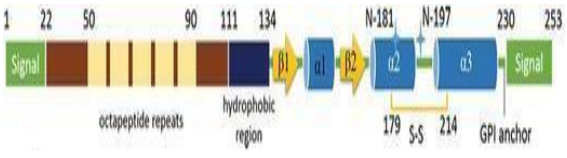
Keywords: Amyloid, Beta-sheet, neurodegenerative, prion, protein misfolding, therapeutics etc

Introduction

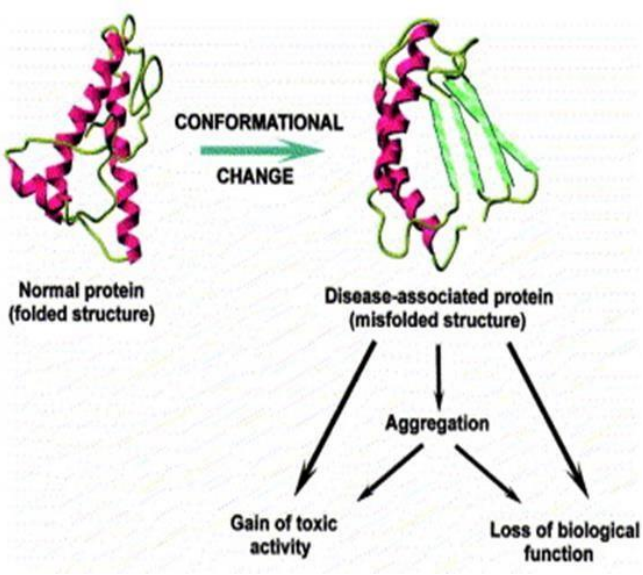
Protein misfolding infections otherwise called contagious spongiform encephalopathies (TSEs or prion sicknesses) or can says amyloid illnesses, are a gathering of lethal sicknesses that influence the cerebrum and sensory system of human and animals. unusual folding(misfolding) of proteins currently stay mutually to form round "oligomers", whose subunits consist of the unusual folding(misfolding) 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 scarpie [1]. Prion grounds four neuro-degenerative infections of people and six of creatures, together with scrapie of sheep and ox-like *spongiform encephalopathy* [1]. The human prions 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 (PrP^C) cellular prion protein is an N-allied glycoprotein positioned on the external membranes by means of a glycophosphatidyl-inositol affix [**show in fig-1]**, broadly spoken in a variety of tissues and enrich in the central nervous system [2]



(Fig-1) [1]



(Fig-2) [3]

Conformational Change in Prion Protein (PRP^{C} TO PRP^{SC} Conversion)

PrP^{c}(cellular prion protein) is a dispersible monomeric protein that is eagerly degraded by proteinase K, in comparison, prion protein scarpie (PrP^{Sc}) form unsolvable aggregate that predicts property of resistance to proteinase K absorption. Conformational change of α-helix loaded prion protein scarpie to unusual folded(misfolded) β-sheet-loaded prion protein scarpie, account for the growth of prion infections [2]. Prion protein scarpie is synthesize from the typical cellular isotype cellular prion protein by a post-translational method that most likely occur in endosomes [1]. Endeavors to recognize a post-translational compound change that highlights in the transformation of cellular prion protein into prion protein scarpie have been ineffective.[1]All discoveries raise the likelihood that prion protein scarpie contrasts from cellular prion protein just concerning adaptation [1]. As per Fourier-change infrared spectroscopy (FTIR) showed that cellular prion protein has a elevated α-helix content 42% and no β-sheet (3%only), discoveries that were affirmed by round about dichroism estimations. In difference, the β-sheetcontent of prion protein scarpie was 43% and the α-helix 30% as calculated by fourier-change infrared spectroscopy [1].

Amyloid Fibrills

Amyloid refers to the irregular fibrous, extracellular, proteinaceous deposit originates in organs and tissues. Amyloid is unsolvable and is fundamentally overwhelmed by β-sheet form. Dissimilar to further fibrous proteins it doesn't usually have an underlying, strong or motility job however is related with the pathology found in a scope of infections called as the *amyloidosis*. Many researchers finding and recommended that amyloid is fibrillous in[4] structure this means it consist of linear biopolymer, and are characterize by rod-like form with high length-to-diameter ratios. Oftentimes, they suddenly position into helical forms. Amyloid fibrills are occurred by usually dissolvable proteins, which bring together to form unsolvable fibres that are opposed to proteinase K degrade [4]. Their arrangement can go with illness and every sickness is described by a particular protein or peptide that totals (prion protein) [4]. Notable instances of amyloid sicknesses incorporate alzheimer's infection, diabetes type 2 and the spongiform encephalopathies (e.g., frantic cow illness) [4]. His amyloid fibrills are kept extracellularly in the tissues and are attention to have [4] an infectious impact. The fibrillar congregations are characteristically steady and underlying examinations have uncovered that they are made dominatingly out of β-sheet from in a trade name cross-beta [4] conformity. As of late, various instances of practical amyloid has been recognized as well as a composition of melanosomes, curli and hydrophobins[4].

Approaches for treatment of prion or *prion disease*

Pentosan Polysulphate(PPS) is a type of polyglycoside [5] chemical compound having low heparin-like [5] work. Pentosan polysulphate acts as a co-receptor for prion type of protein(PrP) on cell area [5] when compared to interior heparin sulfate proteoglycans and this PPS predicts the better capacity to stop the making of newly maked PrP^{sc} in neuroblastoma cells [5] 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 [5] 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 [5].

Quinacrine is a derivative of acridine that shows the activity of inhibition in PrP^{sc} occurance 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 PrP^{c} that prevent PrP^{sc} polymerization and then reduces the conversion to PrP^{c} to PrP^{sc}. Practically in a experiment with a patienthaving 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 PrP^{sc} is extracted then, **Doxycycline** is treated with CJD, which shows the activity of U-turn of protease resistance of PrP^{sc} 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 [5], 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 profit the continued existence of patient with creutzfeldt-jakob disease [5].

Iron Tetrapyrole Derivative Fe(III) – TMPyP interact with the PrP^{c} and Fe(III0- TMPyP works just like therapeutic chaperone for prion protein cellular,that reduces the ground state of the occupant conformation and [5] 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 [5]. Fe(III)- TMPyP combines to PrP^{c} produces the two type of effects [5].(Blocks the prion duplication and also stops the activity of PrP intervened toxicity) [5].

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 [6] 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 [6] shows high level of disaggregation activity and slows the toxicity level. Other chaperone which are used as a good approach for this type of neurodegerative diseases (i.e A-beta42,tau). This chaperone approach include yeast chaperone Tric, which shows protectiveactivity against Htt toxicity and another one chaperone is metazoan chaperone which has the property of disaggregation(e.g 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 [5] 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 [5]. Also it shows that they clears/eliminate PrP^{sc} by reducing endogenous sirtuin 1levels 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 suppleness of the peptide and its vulnerability to the aggregates [5].

Curcumin yellowish coloured present or draw out from turmeric rhizomes, this plant belongs to the family of ginger [5]. More studies set up that curcumin stop the anti-inflammatory work, antioxidant and antitumor properties, also curcumin shows the neuro safety property by altering themitochondrial assimilation and ease unusual free-radical stress [5]. 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 [5]. 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 scarpie by reduces the birth rate also yields of aggregation in prions [5].

A hormone a type Neuroendocrine hormone [5] 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 [5] reaction of superoxide oxidiation and also by enhancing the property of antioxidant macromolecules [5]. 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 gallocathechin gallate, it shows the clear activity of reducing or clears the PrP^{sc} from ScNza cells. But, in another case it hinders with simple PrP^{c} utterance in undiseased cells [5].

Flupirtine Maleate acts centrally, monopioid analgesic that exhibits cytoprotective action in opposition to apoptotic assistant in brain neuron in vivo or in artificial environment [5]. 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 [7] PrP^{c}. we expose the implication of PrP ubiqitination, so firstly paying attention on ubiquitin-specific protease 14 (USP14), a type of de-ubiqutinating enzyme [7]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 PrP^{sc}, whereas in case of wild type USP14 increases PrP^{sc} in prion-diseased cells. All datas propose that USP14 stops the detoriation of simple and abnormal forms of Prion protein. jointly a well-organized considerate about the directive of PrP^{sc} clearance occured by USP14 may gave highly to the expansion of therapeutic approach for prion's type of infections [7].

Conclusion

In this review we are suggested some types of chemical compounds and enzyme which degrade or reduces the prion protein scarpie 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 PrP^{sc} 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.

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