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PRION PROTEINS AND DIABETES MELLITUS - A REVIEW

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ABSTRACT

The objective of this article is to provide an overview on the association between Prion proteins and diabetes mellitus which is important so as to understand the aetiology of diabetes mellitus and provide better treatment plans. Prions are misfolded proteins Which have the ability to transmit their misfolded structure to normal variants of the same protein. Prions form abnormal aggregates of protein known as amyloids. Islet amyloid polypeptide, IAPP, is a precursor protein which causes islet amyloid polypeptide amyloidosis, AIAPP, and is said to lead to type two diabetes. Prion aggregates are generally stable and resist proteolysis. Diabetes mellitus is a group of metabolic disorders characterised by high blood sugar level over a long period of time. It is mainly caused by insulin deficiency or resistance. Prion mediated diseases are generally neurodegenerative disorders such as Kuru, Parkinson's disease, Alzheimer's disease etc. There are two isoforms of prions which are PrP and PrPSc. PrPSc is the infective form and is capable of converting PrPC into infective state. In this review, we discuss the association of prion protein with diabetes mellitus, the structure and propagation of Prion proteins and the link between diabetes mellitus and other prion mediated diseases via cross seeding. A review has been done in order to understand and analyse the association between prion protein and diabetes mellitus by retrieving a minimum of 20 articles from various data search engines including pubmed, Google scholar, MESH, core, bioRXiv, Semantic scholar and so on. This review gives a clear understanding of prion proteins, their structure, propagation and disease causing abilities. It is also analyzed that diabetes mellitus could not be just a disease which is caused by insulin deficiency or resistance but could also be the consequence of protein misfolding.

Keywords: Amyloids; Cross Seeding; Diabetes Mellitus; IAPP; Prion Proteins.

INTRODUCTION

Prion proteins are misfolded proteins whose origin in humans is claimed to date back to 1966 in certain cannibalistic tribes in New Guinea who exhibited signs of Kuru due to their ritualistic activities. Prions were initially discovered due to their ability to cause scrapie and were differentiated from normal bacteria and viruses due to their extreme resistance to heat and radiation(Nunnally and Krull 2003). In the earlier days, viral infection was claimed to be the cause of scrapie. This notion was later disproved by Prusinier who did tests and experiments under the chemical, physical and enzymatic activities of the particle. He concluded that procedures that alter or decimate proteins tend to inactivate the scrapie infectivity whereas those which alter

or decimate nucleic acids do not have any activity of in activation(Aguzzi, Nuvolone, and Zhu 2013). Thus, there was the discovery of a slow acting agent which does not contain any nucleic acid. It was later termed as prion in the year 1980(Legname et al. 2004, Fevrier et al. 2004). Based on the Prion only Hypothesis, which states that the aetiology of the disease is solely based on a protein, Prion proteins have 2 isoforms(Soto 2011). This includes the normal cellular protein form-PrPC and the proteas resistance scrapie or infectious form PrPSc(Riesner 2003). PrPC is expressed in physiological states usually anchored in the lipid membrane, whereas PrPSc is expressed only in pathological states. Based on previous studies, the PrPC contains 43% α helix structure and very minimal β sheet structure, whereas, PrPSc contains 20% α helix structure and 31% β sheet structure. PrPC has an oligomeric phone whereas PrPSc has an aggregated form. The oligomeric states of the Prion proteins are preferred for biophysical states as they are more stable in the test solution. However, thermodynamically, PrPSc is more stable than PrPC . The transition between PrPC to PrPSc within the host body is a slow process as the distribution between the aqueous and liquid phase in the lipid membrane renders PrPC state more stable(Ma and Lindquist 2002). One other difference between PrPC and PrPSc is its susceptibility to proteinase k, PK. PrPSc is sensitive to PK, while PrPSc is PK resistant. Additional molecules termed as 'Chaperoning molecules' aid in the transition of the prion proteins.

The disease progression occurs by transition of normal PrPC molecules into PrPSc molecules. The PrPSc aggregates recruits PrPC proteins and Conforms into its own misfolded structure(Zhang et al. 2008). This procedure is similar to formation and chipping off of ice(Derkatch et al. 2001, Castilla et al. 2005). Prions can evade the immune reaction of the host, colonise their immune system and take over the immune components. This is done by the mechanism called peripheral resistance. The infective prion aggregates then take over the cns and cause life threatening conditions. Several other proteins termed as prionoids contain the self perpetuating property akin to prion proteins but generally transmit within a person and not between individuals. PrPC has many physiological functions(Bhavani 2015). It aids in myelin maintenance and causes activation of myelin repair wherein absence of PrPC can lead to demyelination of the Cells. It is also associated with T cell development, activation and involvement of dendritic cells, inhibition of it's phagocytosis by macrophages, pluripotency differentiation of embryonic stem cells and and Self renewal of the haematopoietic pluripotent stem cells. Adversely, it is also linked with the internalisation of Brucella abortus in the macrophages. However, There are conflicts of interest in these studies and contradicting studies indicate the misattribution of the function of inhibition of phagocytosis to PrPC(Haritha and Brundha 2019).

Prions can lead to the formation of abnormal protein aggregates known as amyloids. Toxic aggregates of amylin is said to lead to β cell dysfunction and loss in the islets of langerhans(Bosco et al. 2010). Islet amyloid polypeptide (IAPP), also known as amylin is a precursor protein which causes islet amyloid polypeptide amyloidosis (AIAPP)(Westermark, Andersson, and Westermark 2011). It is secreted by the islet β cells and stored in the secretory granules along with insulin. IAPP amyloids have been discovered in the pancreas of diabetic patients. Islet amyloids are also present in healthy individuals albeit in a lesser amount(Venkatanarayan et al. 2015). The propagation of the IAPP aggregates depend on their release extracellularly and their internalisation by neighbouring cells. The internalisation can be achieved through Endocytosis, pinocytosis, or simple diffusion(Soto 2012). IAPP also known as diabetes associated polypeptide is a 37 amino acid residue peptide which is primarily expressed as part of an 82aa residue Pre-proprotein containing 22 amino acid signal peptide and two short adjacent peptides. The adjacent polypeptide is later cleaved off, akin to proinsulin. IAPP aggregates tend to accumulate in the kidney before the appearance of clinical symptoms of T2D. This can indicate elevated plasma IAPP level in pathological conditions such as diabetes(Timothy, Samyuktha, and Brundha 2019). IAPP is stored along with insulin in a 1:2.50 molar ratio. IAPP mediated β cell dysfunction and death can result from membrane permeabilisation, cal pain hyper activation, ER stress induction, improper regulation of clearance pathways And induction of inflammation.

Type 2 diabetes is a common disorder which affects around 8.3% of the population of the United States. It is estimated that around 285 million people have diabetes worldwide and the figure is increasing(Matthews and Matthews 2011). India ranks highest in diabetes prevalence With 51 million cases throughout. People with diabetes type 2 display insulin resistance wherein the insulin is not completely utilised as it should be. Islet

amyloid proteins are found in more than 90% of the patients affected with diabetes type 2. Cell's ending is the interaction point of protein aggregates. Oligomeric, misfolded protein seeds are claimed to be produced during the nucleation or lag phase which is a thermodynamically unfavorable process(Mukherjee et al. 2015, Bokadia et al. 2018). Seeding can be of 2 types, homologous seeding and heterologous seeding. Cross seeding or heterologous seeding takes place when oligomers composed of one misfolded protein can induce and promote the polymerization of a different protein(Morales, Moreno-Gonzalez, and Soto 2013). Cross seeding may affect an individual and be the reason for the simultaneous presence of more than 1 misfolded proteins in one disease coexistence of more than one prion mediated disease in the same individual, Occurance of 1 PMD in presence of an underlying other and the worsening of clinical features when various misfolded protein aggregates accumulate simultaneously(Ono et al. 2014). Cross-seeding with functional amyloids might have played an important and yet unidentified role in the origin of prion mediated diseases(Mukherjee and Soto 2017). Previously our team had conducted numerous clinical trials(Priya 2010, Prashaanthi and Brundha 2018), lab animal and in-vitro studies(Ravichandran and Brundha 2016)(Brundha 2015) over the past 5 years. Now, we are focussing on surveys and reviews. The idea for this review stemmed from the current interest in our community.

A review of scientific literature was done in preparation of the manuscript. The relevant articles were collected from databases such as pubmed, Google scholar, MESH, core, bioRXiv, Semantic scholar and so on. The timeframe of the articles are from the year 2000 to 2020. Around 30 articles were collected, analysed and reviewed. The articles were collected on the basis of containing keywords such as prion proteins, amyloids, IAPP, Diabetes mellitus, cross seeding etc. All topics irrelevant to the topic were excluded. The results of this review are based on previous studies done by other esteemed authors.

THE ROLE OF PROTEIN MISFOLDING AND PROPAGATION IN DIABETES MELLITUS

Diabetes mellitus is a compound metabolic disorder distinguished by chronic insulin resistance and loss of β-cell function and mass(Shenoy and Brundha 2016). This loss leads to reduced insulin release and thus results in hypoglycemia. Generally, glucolipotoxicity toxicity is claimed to be the reason for the dysfunction and loss of β cell mass(Ferdioz and Brundha 2016). Other causes such as islet cholesterol accumulation and islet inflammation are also considered as aetiology For diabetes mellitus. However newer evidences and researchers suggest that toxic oligomeric aggregates of IAPP may result in β-cell dysfunction and thus, diabetes type 2(Seino and on behalf of The Study Group of Comprehensive Analysis of Genetic Factors in Diabetes Mellitus 2001). Such accumulation of IAPP associated with type 2 diabetes was first termed in 1901 as islet hyalinization(Balaji and Brundha 2016). However, non-diabetic people also exhibited the presence of such aggregates in a smaller amount(Hannah et al. 2019). But, such expression is also seen in other prion mediated diseases as when an individual gets older, presence of such deposits are common(Brundha and Nallaswamy 2019). Several studies and researches have been performed which link IAPP aggregation with loss of β cells and thus, progression of diabetes mellitus. Post-mortem studies done on diabetes patients support the notion that IAPP aggregates are associated with the loss of β-cell mass.

In clinically transplanted islets, IAPP aggregation was seen to be one of the major causes of β-cell dysfunction(Carey et al. 2012). Early onset of diabetes mellitus is associated with the mutation in the IAPP gene which leads to the increase of its aggregative property(Kaarthikeyan et al. 2009). Parallel studies in animal models indicates that IAPP aggregation and deposition precedes β cell dysfunction and expression of clinical symptoms(Sekar 2019). Animal studies in transgenic mice and rats which over expressed human IAPP was seen to spontaneously develop hallmarks of type 2 diabetes(Matveyenko and Butler 2006). However, even though many researches have been done, the course and initial origin of IAPP aggregation and its mechanism of toxicity is not completely understood(Brundha, Pathmashri, and Sundari 2019).

TOXIC OLIGOMERS IN DIABETES MELLITUS

An oligomer is generally a polymer with a relatively few repeating units. Oligomers exert their toxicity through a variety of mechanisms including receptor and direct membrane interactions. IAPP toxic Oligomers are formed within the cell's secretory pathway in presence of type 2 diabetes and in obesity conditions(Shamseddeen et al. 2011). Proteotoxicity of the toxic Oligomers is found to play an important role in neuro degenerative diseases(Gurlo et al. 2010). Toxic Oligomers may be associated with cellular dysfunction and apoptosis of β cells as seen in diabetes mellitus due to membrane damage(Prashaanthi and Brundha 2018). Many factors primarily related to the formation of membrane permeable Oligomers may contribute to the dysfunction of the pancreatic β cells in diabetic mellitus(Atlas 2015). One of the related factors is calcium homoeostasis. Calcium homoeostasis is important, both for survival of the cell and preventing intra cellular trafficking(Shreya and Brundha 2017). It also regulates the discharge of secretory and synaptic vesicles at the level of the cell membrane. Unregulated remodelling of the tubulin cytoskeleton results in the hyperactivation of Calpain, which is a protein which belongs to the family of calcium dependent, non-lysosomal Cysteine protease, leads to impaired intracellular movements and functions. Such impaired movements can be seen within the islet cells of pancreas in diabetes mellitus(Kumar and Brundha 2016). The disruption of the mitochondrial membrane by these Oligomers provides a novel mechanism for the mitochondrial dysfunction leading to β cell dysfunction as a whole in diabetic patients.

CROSS SEEDING BETWEEN ALZHEIMER'S DISEASE AND DIABETES MELLITUS

Amyloid formation and deposition leads to a wide variety of prion mediated diseases. While diabetes mellitus is a metabolic disorder, Alzheimer's disease is a form of dementia. The plaques formed extra cellularly in the brain tissue (Saivignesh and Brundha 2019)by the amyloid β, Aβ protein and neuro fibrillary tangles, NFT, can lead to Alzeimer's disease(Arya et al. 2019). Similarly diabetes mellitus is linked with the aggregation of IAPP residues in the pancreas. IAPP aggregation also occurs in non-pancreatic issues such as kidney, heart and sensory neurons(Kalaiselvi and Brundha 2016). Studies show that people suffering from diabetes are more likely to be diagnosed with dementia than non-diabetic individuals(Steen, Terry, and Rivera 2005, Luchsinger et al. 2001). Around 80% of the AD patients seem to have diabetes or impaired tolerance of glucose. There is also presence of Aβ deposits and TAU protein in the pancreatic tissue of diabetes mellitus patients while IAPP deposits have been observed in the brain tissues of AD patients(Martande et al. 2014). The simultaneous expression and existence of the Aβ, TAU and IAPP amyloids in the brain, pancreas and other organs indicate heterologous seeding or cross seeding and leads to amyloid accumulation, deposition and cellular dysfunction in both neurons and pancreatic β cells(Oskarsson et al. 2015).

ASSOCIATION OF DIABETES MELLITUS AND PARKINSON'S DISEASE

New researches indicate the Association of diabetes mellitus with Parkinson's disease. Of the total percentage of Type 2 diabetes patients, 38% of patients suffer from Parkinson's disease(Horvath and Wittung-Stafshede 2016). Parkinson's disease is mainly caused due to α-Synuclein accumulation in the brain tissues. In diabetes mellitus patients, α-Synuclein is also seen expressed in the pancreatic β cells(Martinez-Valbuena et al. 2018). The role of α-Synuclein is yet unclear, but a few researches point out that activity of α-Synuclein in inhibiting insulin secretion by binding to potassium ATP channels(Sun et al. 2020). IAPP can accelerate the aggregation of α-Synuclein in vitro. Interaction between IAPP and α-Synuclein has also been detected in the islet β cells(Hu et al. 2007, Xu et al. 2011). Diabetic patients exhibit a greater risk of developing Parkinson's disease, while patients with Parkinson's disease display abnormally disturbed sugar metabolism which leads to diabetes mellitus. Antidiabetic drugs have also been proved effective against Parkinson's disease in some cases(Kahn, Cooper, and Del Prato 2014).

LIMITATIONS AND FUTURE DIRECTIONS OF STUDYING THE ASSOCIATION BETWEEN PRION PROTEINS AND DIABETES MELLITUS

Even though many researches have been performed previously, the structure of the infectious prions form PrPSc is not yet clear due to their instability in test solutions. The time required to sequence the events is also longer(Harsha and Brundha 2017). The biochemical and biophysical characterization of prions is yet to be performed. As prion diseases are not very prevalent, the availability of samples pose a barrier(Preethikaa and Brundha 2018).

This research is important so as to stop the notion that only insulin deficiency causes diabetes and inoculation of extra insulin will cure the disorder. Further research can aid in discovering crucial therapeutic targets to inhibit the IAPP amyloid propagation. Better treatments can be administered. Better understanding and knowledge about the Association of diabetes mellitus with Prion proteins can be obtained and this can open up many fields of interest in the medical industry.

CONCLUSION

This review gives a clear understanding of prion proteins, their structure, propagation and disease causing abilities. Since, prion diseases are a developing field of interest in the medicinal field, researches in this area can aid in better understanding of their ways of action, propagation and transmission. Researches based on analysing the fact that diabetes mellitus could not be just a disease which is caused by insulin deficiency or resistance but could also be the consequence of protein misfolding are being undertaken. This fact can change the way of diagnosing diabetes mellitus and can provide a more contemporary way of treatment.

AUTHOR CONTRIBUTIONS

S.Vidyashri, contributed to the data acquisition and drafting of manuscript. Dr.M.P.Brundha, contributed to the design, editing and critical revision of the manuscript. Dr.Jayalakshmi Somasundaram, contributed to the supervision and proof reading of the manuscript.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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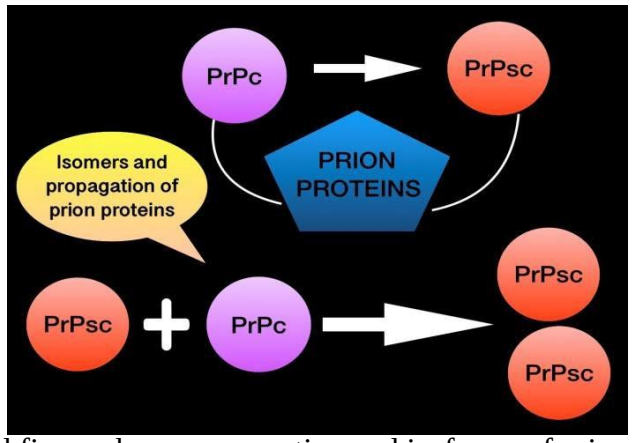

Figure 1: Self illustrated figure shows propagation and isoforms of prion proteins, namely, PrPc(Cellular prion proteins) and PrPSc(Mutated Scrapie isoform). PrPC is generally observed when the body is in a physiological state whereas PrPSc, an infectious form, tends to occur majorly during pathological conditions. The propagation of prions occurs by recruitment of the normal PrPc proteins and their conformation into a misfolded structure by the PrPSc isomers.

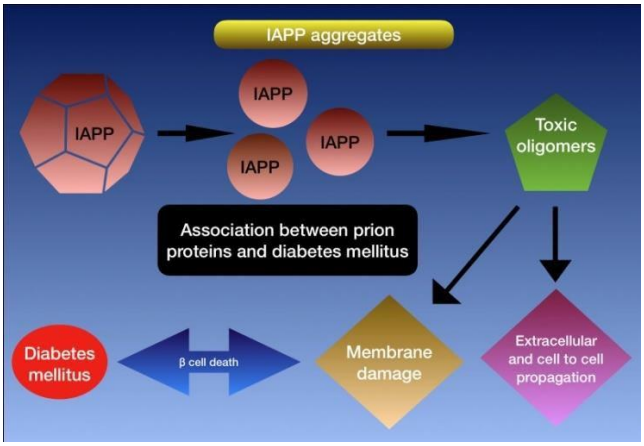

Figure 2: Self illustrated figure shows association between prion proteins and Diabetes Mellitus. Islet amyloid polypeptide(IAPP), also known as amylin is a precursor protein which causes islet amyloid polypeptide amyloidosis. IAPP residues tend to propagate by conformation of normal proteins into its own misfolded structure. IAPP toxic Oligomers are formed within the cell's secretory pathway. These toxic Oligomers can either progress extracellularly or cause membrane damage in the mitochondria by various mechanisms including disrupted calcium homeostasis. Disruption of the mitochondrial membrane by these Oligomers leads to β cell dysfunction, resulting in diabetes type 2.