

Prion Proteins and Sleep Disturbances

Edward T Chang^{*}, Camilo Fernandez-Salvador, Justin M Wei and Macario Camacho

Division of Otolaryngology, Tripler Army Medical Center, 1 Jarrett White Road, Tripler AMC, HI, USA

^{*}**Corresponding author:** Edward T Chang, Division of Otolaryngology, Tripler Army Medical Center, 1 Jarrett White Road, Tripler AMC, HI 96859, USA, Tel: 808-433-3181; E-mail: etchan78@gmail.com

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Abstract

Prions normally exist as cellular membrane proteins. In humans, 209 amino acids with one disulfide bond form a primarily alpha-helical prion protein structure with a molecular mass of 35 to 36 kDa. The specific role and function of the prion protein elude research efforts and remains a controversial topic. Misfolding of the native prion protein leads to a protein structure with increased proportion of alpha-helices to beta-sheets. Advancing our understanding of the role of the prion protein as it relates to sleep and sleep disturbances presents an appealing avenue into diagnosing and more effectively treating a devastating and debilitating disease. New research into multiple system atrophy further validates evidence of a direct association between the prion protein and sleep. This reinforces previous observations regarding changes in sleep patterns noted with patients affected by Creutzfeldt-Jakob Disease and Fatal Familial Insomnia. From these earlier studies, a more focused approach to identifying and defining the role of the prion protein appears possible. A clearer understanding of the functional prion protein in its native role within the cell membrane allows identification of the potential signaling pathways and the aberration that likely occurs that leads to misfolding at the thermodynamic level. This discovery holds the greater, global potential of elucidating the mystery of proteopathies.

Keywords: Prion; Obstructive sleep apnea; Central sleep apnea; Insomnia

Editorial

Prions normally exist as cellular membrane proteins. In humans, 209 amino acids with one disulfide bond form a primarily alpha-helical prion protein structure with a molecular mass of 35 to 36 kDa [1]. The native prion protein exists in this state and appears likely to play a role in cell-cell adhesion and intracellular signaling leading to cell-cell communication within the brain [1,2]. The specific role and function of the prion protein elude research efforts and remains a controversial topic. In addition, early and definitive diagnosis of the infection remains difficult. According to the protein only theory, variations in the protein structure and resistance to proteases may cause infectious diseases leading to encephalopathy [1-3]. Misfolding of the native prion protein leads to a protein's structure that increases the proportion of alpha-helices to beta-sheets [1-5].

From in-depth evaluations of patients suffering from these types of diseases, a relationship between prion proteins and sleep disturbances appears likely [6]. Patients infected with the sporadic variant of Creutzfeldt-Jakob Disease (CJD) experience alterations in sleep with excessive daytime fatigue [6,7]. More specifically, patients affected by Fatal Familial Insomnia (FFI) attributed to a mutation in the prion protein amino acid sequence (codon 178) display loss of slow-wave sleep, abnormalities during REM, and arrhythmic circadian cycles [6-8]. Recently, continuing research implicates a potential role in development of sleep apnea as related to Multiple System Atrophy (MSA) due to aggregation of alpha-synuclein as a direct consequence of misfolded prion proteins [9,10]. Previous studies using the animal model also implicate a role of the prion protein in sleep and sleep regulation [6].

With difficulty in diagnosing a patient affected by prion disease, an association with sleep and prion appears likely to provide a more effective means for assessment and planning. Currently, definitive diagnosis requires pathologic evaluation of brain tissue and/or genetic testing [3,11]. By identifying definitive abnormalities assessed through current diagnostic techniques and criteria, such as multi-channel polysomnography, accurate diagnosis of prion infection with high sensitivity and specificity appears feasible [11]. This association promises a significant advancement in diagnosis and development of more effective treatments.

Further, identification of a clear association with physiologic mechanisms such as sleep provides a means for focusing research efforts to more effectively identify the role of the prion protein. A more lucid identification of the potential signaling pathway(s) involving the prion promotes development of greater insight into cellular and protein signaling in general. Misfolded proteins are implicated in various diseases to include, but not limited to Alzheimer's, Parkinson's, type 2 diabetes and amyloidosis grouped under "proteopathies" [12]. Misfolding of the protein appears likely due to abnormal signaling from protein-protein interaction; however, the specific mechanism remains elusive and currently exists only as a theory.

Advancing our understanding of the role of the prion protein as it relates to sleep and sleep disturbances presents an appealing avenue into diagnosing and more effectively treating a devastating and debilitating disease. New research into MSA further validates evidence of a direct association between the prion protein and sleep. This reinforces previous observations regarding changes in sleep patterns noted with patients affected by CJD and FFI. From these earlier studies, a more focused approach to identifying and defining the role of the prion protein appears possible. A clearer understanding of the functional prion protein in its native role within the cell membrane allows identification of the potential signaling pathways and the

aberration that likely occurs that leads to misfolding at the thermodynamic level. This discovery holds the greater, global potential of elucidating the mystery of proteopathies.

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