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Protein Misfolding in Alzheimer's Disease and Sleep Related Disorders

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Abstract

Some studies have indicated a relationship between the development of Alzheimers Disease (AD) and having obstructive sleep apnea (OSA), while others argue that AD itself leads to sleep disturbances and sleep disordered breathing. Whether peripheral due to the direct effects of abnormal protein aggregation or central due to the systemic effects of Beta - A aggregation in functionally important areas of the central nervous system, there seems to be an association between misfolded protein and sleep disordered breathing. These findings from studies into another proteopathy lends further credence to the revelations reported from the prion related research and brings us closer to understanding the disease mechanism behind both OSA and protein misfolding. The conglomeration of findings from studies into proteopathies clearly provides significant impetus into continuing research in proteopathies to improve our understanding of not only sleep disordered breathing but the enigma that is proteopathy.

Keywords: Sleep; Alzheimer's disease

Introduction

Recently, an editorial highlighted an association between sleep disturbances and abnormal protein related diseases termed proteopathies [1]. More specifically, the paper commented on the relationship between prion disease and sleep related disorders [1]. Developing studies such as those pursued by Dr. Prusiner reveal a possible correlation between the misfolded native prion protein and obstructive sleep apnea (OSA) as it relates to Multi-System atrophy (MSA) [2]. The mechanism(s) and/or signaling pathway(s) implicated in the conversion from endogenous non-infection protein to the infectious pathologic forms remain elusive [3,4]. In addition, compelling evidence suggests a direct connection between abnormally folded proteins and sleep related disorders [4]. This correlation between misfolded proteins, sleep disturbances and possibly even more specifically OSA has been further elucidated with the burgeoning research efforts into furthering our understanding of a more prevalent yet just as enigmatic affliction of protein misfolding, Alzheimer's Disease (AD) [5-8].

Though the mechanism behind development of AD remains unknown, pathologic evaluation of neural tissue identified evidence of abnormally folded Beta amyloid protein (Beta-A). The Beta-A protein is an abnormally short proteolytic peptide byproduct of the Beta amyloid precursor protein (Beta–APP). The Beta-APP is a transmembrane protein that appears to play a role in neural growth and repair. The misfolded Beta–A protein exhibits characteristically more thermodynamically unstable protein with the greater presence of Beta sheets versus the endogenous form characterized by more alpha helices [9]. Unlike prion disease, the misfolded protein in AD is not infectious and it is the abnormal aggregation of these abnormally folded proteins that have a direct causality to development of AD. Like prion disease, however, the mechanism behind irregular misfolding remains a mystery [10].

Discussion

As research continues into the various facets of AD, a direct correlation between sleep disordered breathing and AD has emerged [11]. More specifically, subsequent morbidity associated with OSA appears to include AD. One theory suggests the effects of inflammatory by-products contributing directly to possibly both protein misfolding and aggregation [12]. Inflammation and inflammatory effects appear directly related to hypoxia from apneic and hypopneic events of sleep disordered breathing. Other studies suggest that these hypoxic events lead to development of oxygen free radicals that cause direct cellular damage and again induce both the protein misfolding and subsequent abnormal protein aggregation [13]. A similar mechanism has been proposed by some in prion research to explain the conversion of the native, benign prion protein to the infections form. This then raises the compelling question as to a possible association between all proteopathies and a single causal signaling pathway/mechanism.

Some studies have indicated a relationship between the development of Alzheimers Disease and having obstructive sleep apnea (OSA), while others argue that AD itself leads to sleep disturbances and sleep disordered breathing [8,11,12]. These researchers suggest that sleep apnea is in fact a direct consequence of AD. Whether peripheral (obstructive) due to the direct effects of abnormal protein aggregation or central due to the systemic effects of Beta-A aggregation in functionally important areas of the central nervous system, there seems to be an association between misfolded protein and sleep disordered breathing [14]. Additional studies into abnormal protein misfolding dementia involving Lewy Body aggregation such as Parkinson's Disease (PD) reveal further evidence of correlation between proteopathy and sleep disturbances. Rapid eye movement (REM) Sleep Behavior Disorder (RBD) characterized by loss of atonia during REM has emerged as a potential prodromal stage of PD [15]. In addition, RBD appears to correlate directly with OSA or at a minimum exist as a co-morbidity in those with OSA and PD [16].

Conclusion

These findings from studies into other proteopathies lend further credence to the revelations reported from the prion related research and bring us closer to understanding the disease mechanism behind both OSA and protein misfolding. The conglomeration of findings from studies into proteopathies clearly provides significant impetus into continuing research in proteopathies to improve our understanding of not only sleep disordered breathing but the enigma that is proteopathy. Potential discovery in one area promises to expand our knowledge into the other.

Disclaimer

The views expressed in this manuscript/abstract are those of the authors and do not reflect the official policy or position of the Department of the Army, Department of Defense, or the US Government.

Compliance with Ethical Standards

As a manuscript describing a technique, without any patient information or data, this manuscript is exempt from needing to be reviewed by the Tripler Army Medical Center Investigational Review Board.

Ethical Approval

This article does not contain any studies with human participants performed by any of the authors.

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