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Aging Pathobiology and Therapeutics 2020; 2(2):xx-xx *xx*
DOI: 10.31491/APT.2020.06.xxx

A mouse model of sleep deprived neuropathology to study resilience to Alzheimer's disease

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Abstract

Resilience to Alzheimer's disease (AD) is a well-known clinical and pathological observation, but the mechanisms involved are not known. Adequate sleep is a potential factor in maintaining resilience to neurodegenerative conditions such as AD. It is well known that sleep deprivation is a major health concern in developed countries and is associated with increasing age. Normal aging produces sleep disturbances including sleep fragmentation and sleep loss in humans, which has recently been recognized as an important risk factor for AD. The idea of enhancing AD resilience by targeting sleep deprivation encompasses the concept of physical resilience to aging. We demonstrate the detrimental effects of sleep deprivation in aging mice and propose a mouse model of AD to test the concept. The model provides a means of testing therapeutics that could be investigated in clinical trials designed to prevent sleep deprivation and enhance resilience to aging and AD in the elderly.

Keywords: Mouse model of sleep deprivation, resilience to aging, resilience to Alzheimer's disease

The prevalence of neurodegenerative diseases such as Alzheimer's disease (AD) is expected to soar with the number of elderly individuals in both developed and developing countries now rising dramatically. Efforts to find disease-modifying treatments have been largely unsuccessful in part due to inability to assess early signs of disease and risk factors associated with increasing age, and the lack of predictable preclinical animal models. One approach to investigating risk factors for AD is to look at attributes that oppose risk, ie, resilience. Resilience is the ability of an organism to successfully respond and recover from physical stress. The occurrence of resilience to AD has been suggested based on the absence of clinical signs of cognitive impairment but presence of neuropathological lesions typical of AD at autopsy. The causes for this apparent paradox are not known, but resilience to physical stress could play a role. A good example of a type of stress that has neurological effects is sleep deprivation.

It is fairly well established that sleep disturbances increase the risk of dementia and AD and there is growing evidence that poor sleep leads to acceleration in the progression of neurodegenerative disorders and may play a role in pathogenesis. Clinical studies are well supported by animal studies showing that sleep deprivation induces learning and memory dysfunction and exacerbates AD-like pathologies in AD transgenic mice [1]. Therefore, sleep deprivation is a physical stressor that decreases resilience to healthy aging and increases the risk for AD (Figure 1). Prevention of the adverse effects of sleep deprivation would be a logical approach to enhance resilience to AD by enhancing resilience to aging.

Preclinical models for investigating resilience to aging and AD are not well described. We have developed an aging mouse model of short-term sleep deprivation that results in neurodegenerative changes and cognitive impairment [2]. We suspected that sleep deprivation would adversely impact synaptic function through mitochondrial disruption. Mitochondrial dysfunction leading to decreased ATP production and increased ROS resulting from impaired electron transport chain function appears prominently in both aging and AD [3-5]. We showed that sleep-deprived mice had significantly higher levels of mitochondrial ROS production and a significant decrease in ATP synthesis in the brain compared with non-sleep deprived mice [6]. Closely linked with mitochondrial dysfunction, our mouse model of short-term sleep deprivation showed that learning impairment was associated with mechanisms related

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Received: 31 May 2020 / Accepted: 06 June 2020

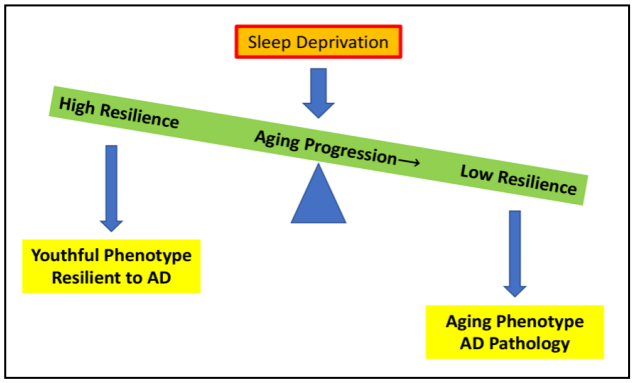

Figure 1. As aging progresses, the physical resilience of an individual towards aging and sleep deprivation decreases, tipping the scale and leading to an aging phenotype and the development of AD pathology. Some individuals continue to maintain or regain functions quickly following insults as age increases, producing a more youthful phenotype and resilience to AD.

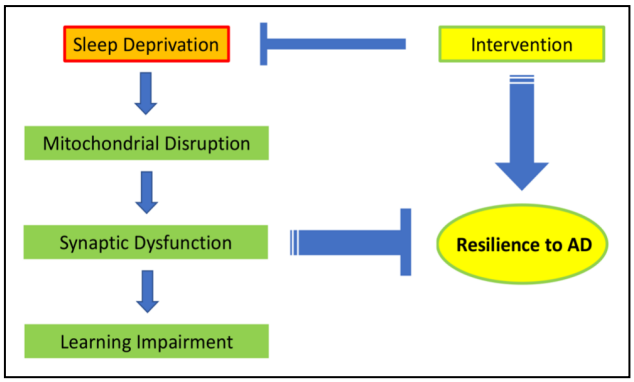

Figure 2. Short term sleep deprivation induces a cascade of molecular events starting with mitochondrial disruption to synaptic dysfunction and subsequent learning impairment. The neurological effects of sleep deprivation could intensify over time and decrease resilience to AD. Intervention strategies that prevent neuronal pathology induced by sleep deprivation in aging mice would have the potential to alleviate cognitive impairment and increase resilience to AD.

to synaptic plasticity in the hippocampus. N-methyl-D-aspartate receptor, a well-known synaptic glutamate receptor that regulates long-term potentiation and synaptic plasticity [7-8], and brain derived neurotropic factor, a supportive regulator of synaptic plasticity, were both significantly decreased. In addition, neuroinflammatory cytokine levels of MCP-1, TNF-α, and IL-6 were increased.

This aging mouse model of short-term sleep deprivation provides an excellent background for studying effects on pathogenesis of AD. Certainly it would be applicable to currently available transgenic AD mouse models. However, in most of the transgenic lines, a significant increase in APP production begins early in life possibly in utero, which may trigger consequences that alter aging and the rate of aging, and may not mimic the biochemical changes observed in AD. Most importantly, it is problematic to measure early events in the development of AD with increasing age in these models. Desirable features of a model system would allow for a precisely controlled challenge time and onset of disease in an aging background. We have shown that introduction of Aβ42/P301Ltau into the brains of older mice results in cognitive impairment and neuropathology including inflammation, neuronal degeneration, synaptic dysfunction, and vascular impairment (unpublished data). Effective use of this model does require access to aging mice, AAV vectors, and expertise in stereotactic injections into specific regions of the mouse brain [9]. Whatever the AD model, short-term sleep deprivation provides a highly informative and rapid model to investigate ways of enhancing resilience to aging and AD by preventing sleep deprived neuropathology with drugs or other intervention measures (Figure 2).

Declaration

Conflict of Interest: The authors declare that they have no conflict of interest.

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