How Sleep and Brain Waste Removal Protect Against Neurodegeneration

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Disclosures

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The views expressed in this talk do not reflect those of the US Government.
The long road to Alzheimer’s disease

Sequential progression of Alzheimer’s pathology and cognitive/functional impairment

Alzheimer’s disease pathology:
Amyloid plaques
Neurofibrillary tangles

Alzheimer’s pathology precedes cognitive impairment by decades.

Targeting processes “upstream” (to the left) of the development of pathology would permit primary prevention.

Jack et al. Lancet Neurol 2013
Sleep disruption and neurodegeneration. A two-way street?
The clinical association between poor sleep and cognitive impairment

In 614 participants 40-100 years of age evaluated over 10-20 years, short sleep duration (< 7hrs) or variable sleep were associated with incident cognitive impairment.
QUESTION 1
Short sleep duration is associated with increased Alzheimer’s pathology.

**Alzheimer’s disease pathology:**
- Amyloid plaques
- Neurofibrillary tangles

Spira et al. JAMA Neurology 2013
Levels of Alzheimer’s-related proteins in the brain are acutely regulated by sleep

Sleep-wake regulation of amyloid levels in humans

Kang et al. Science 2009
Brainwashing.  
The good kind
The human brain - 86 billion neurons - 125 trillion synapses - billions-trillions of action potentials per second

The brain is a high-performance machine

Brain waste clearance

From the Allen Brain Institute

National Cancer Institute
More than a cushion

CSF

Blood Vessels

Cortical Surface

60µm

120µm

180µm

Iliff et al. Sci Transl Med 2012
Perivascular exchange is regulated by sleep state

**Intracisternal Tracer Injection**
- 3kD Dextran

**Interstitial Tracer**
- $^{14}$C-Inulin (~5kD)
- $^{125}$I-Amyloid β$_{1-40}$

**Interstitial $^{125}$I-Amyloid β$_{1-40}$ clearance**

**Graphs**
- $^{125}$I-Amyloid β$_{1-40}$ recovery (%)
- Rate constant (min$^{-1}$)

* Xie et al. *Science* 2013
Glymphatic flow supports the clearance of wastes from the brain through sleep-active perivascular fluid transport.
QUESTION 2
More than mice?
Imaging glymphatic function in the human brain
Measuring glymphatic function in rats by MRI after contrast agent injection.

Time after contrast injection:
60 min
120 min
180 min

Roese, Pike, Iliff (unpublished)

Measuring glymphatic function in humans by MRI after contrast agent injection.

n = 8 reference subjects, 41.1 +/- 13.0 yrs

Scans at t = 0, 1, 3, 4.5 and 24 hrs

Ringstad et al. Brain 2017
Imaging glymphatic clearance in the human brain

Eide et al. Brain 2021
Sleep-active brain waste clearance occurs in the human brain.
Getting old is a dirty business. Does slowing brain waste clearance contribute to Alzheimer’s disease?
Slowed brain waste clearance promotes the development of Alzheimer’s-related pathology

In human populations, neurodegenerative conditions are…

…associated with aggregation of Aβ, tau, α synuclein.

In animal models, glymphatic function…

…contributes to the clearance of soluble Aβ, tau, α synuclein.

In animal models, impairment of glymphatic function…

…promotes Aβ pathology.

…promotes tau pathology.

…promotes α synuclein pathology.
Aquaporin-4 (AQP4) supports perivascular glymphatic exchange and amyloid β clearance.
Aqp4 gene deletion exacerbates Aβ pathology in mouse models of Alzheimer’s.

Pedersen et al. Neurobiol Dis 2023
Neurodegenerative conditions are associated with protein mis-aggregation.

...influenced by non-genetic risk factors:
- Aging
- Cerebrovascular disease
- Traumatic brain injury
- Chronic sleep disruption

Glymphatic dysfunction...promotes amyloid β, tau and synuclein pathology (in animal models).

...is impaired in animal models of:
- Aging
- Cerebrovascular injury
- Traumatic brain injury
- Acute sleep deprivation

Adapted from Jucker and Walker Nature 2013
Glymphatic function is impaired in the aging brain

Effect of aging on Aβ clearance

125I-Amyloid β

Kress et al. Annals Neurol 2014

Intracisternal CSF tracer injection
CSF Tracers
3 kD
45 kD

t = 30 min post-injection
Reduced perivascular AQP4 localization in the aging brain

**Mouse Model of Aging**

**Young (2-3 months)**

![Immunofluorescence images of AQP4 and GFA in young mice.](image1)

**Aged (18 months)**

![Immunofluorescence images of AQP4 and GFA in aged mice.](image2)

**Cognitively Normal**

![Immunofluorescence images of AQP4 polarization in cognitively normal mice.](image3)

**Mild Cognitive Impairment**

![Immunofluorescence images of AQP4 polarization in mild cognitive impairment mice.](image4)

**Alzheimer’s Disease**

![Immunofluorescence images of AQP4 polarization in Alzheimer’s disease mice.](image5)

**Statistical Analysis**

![Graph showing AQP4 polarization across different conditions.](image6)
Reduced perivascular AQP4 localization in the aging brain

*In cognitively-intact and MCI individuals
Conclusions

Perivascular glymphatic exchange supports the sleep-active clearance of aggregating proteins including Aβ, tau, and α synuclein in rodent models.

Sleep-active glymphatic exchange occurs in the human brain.

In animal models, glymphatic impairment is sufficient to promote the development of Aβ, tau, and α synuclein pathology.

Glymphatic function is impaired in animal models corresponding to non-genetic Alzheimer’s risk factors including aging, CV disease, sleep disruption, and TBI.

Initial clinical neuroimaging, histopathological, genetic and transcriptomic studies provide corollary data linking glymphatic dysfunction to Alzheimer’s pathology and progression in human populations.
Conclusions

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Work over the past 12 years suggests that impairment of brain waste clearance may contribute to the development of Alzheimer’s disease and other dementing disorders.

However, a clear causal role has not yet been demonstrated.
QUESTION 3
Sequential progression of Alzheimer’s pathology and cognitive/functional impairment

Alzheimer’s disease pathology:
Amyloid plaques
Neurofibrillary tangles

Jack et al. Lancet Neurol 2013
Detection of glymphatic impairment may enable the identification of patients at risk for the development of neurodegenerative disease during the long pre-clinical phase of disease.
Within these individuals, targeting glymphatic function therapeutically may enable primary prevention of these conditions.
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