This is what really happens in your brain when you sleep.
Cleaning occurs during deep sleep.
“Furthermore, relatively short-term (3 weeks) sleep deprivation markedly accelerated amyloid plaque deposition in amyloid precursor protein transgenic mice.

Thus, sleep-wake behavior is linked to Aβ levels, and abnormal sleep may be linked to AD pathogenesis.”

BRAIN REMOVES TOXIC WASTE THROUGH THE GLYMPHATIC SYSTEM
Glympatic System

Throughout most of the body, a complex system of lymphatic vessels is responsible for cleansing the tissues of potentially harmful metabolic waste products, accumulations of soluble proteins and excess interstitial fluid. But astonishingly, the body’s most sensitive tissue – the central nervous system – lacks a lymphatic vasculature. What then accounts for the efficient waste clearance that must occur in order for the neural tissue of our brains to function properly?

This question has puzzled scientists for centuries. Our group believes that understanding how this process functions in the healthy nervous system holds the key to developing treatment options for a wide variety of neurological diseases, especially those characterized by the improper accumulation of misfolded proteins. The breakdown of the brain’s innate clearance system may in fact underlie the pathogenesis of neurodegenerative disorders such as Alzheimer’s, Parkinson’s, and Huntington’s disease, in addition to ALS and chronic traumatic encephalopathy. Past efforts to explain how the brain cleanses parenchymal tissue have suggested that solute and fluid exchange occurs between the interstitial fluid and the cerebrospinal fluid, and that this exchange is driven by diffusion. Yet as many have noted, the distances for diffusion in the brain are too great to explain the highly regulated interstitial environment.
NOTE:
GLYMPHATIC SYSTEM CLEARS WASTE BEST DURING DEEP SLEEP!
DAYTIME

NEURONS

DEEP SLEEP

NEURONS SHRINK 😞
Awake

Fluid

Neurons

Deep Sleep

Wash Debris Between Neurons

CSF: Cerebral Spinal Fluid

Neurons Shrink ↑!
Sleep Drives Metabolite Clearance from the Adult Brain

Lulu Xie, Hongyi Kang, Qiwu Xu, Michael J. Chen, Yonghong Liao, Meenakshisundaram Thiagarajan, John O’Donnell, Daniel J. Christensen, Charles Nicholson, Jeffrey J. Iliff, Takahiro Takano, Rashid Deane, Maiken Nedergaard

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance fluid. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.
Sleep disturbances may precede the onset of neurodegenerative diseases. In some cases, by decades!
Sleep changes are part of the normal aging process.
Sleep changes are part of the normal aging process.

1. increased sleep fragmentation
2. nighttime awakenings
3. increased daytime sleep
“The older you are, the worse you sleep.”
1st: Arousal System

THALAMUS

ACH = Acetylcholine
Cholinergic (ACH) neurons in the brainstem activate the thalamus.
THALAMUS ALERTS CORTEX TO INCOMING IMPORTANT INFORMATION

AROUSAL SYSTEM

THALAMUS

ACH

BIG IDEA: GATE TO ALERTNESS
These neurons

1. Fire fastest during wakefulness & REM sleep

2. Not so active during NREM
2nd:
Arousal System
These neurons:

1. Fire fastest when awake
2. Slow down during NREM
3. Stop during REM
Lesions in the arousal system ⇒ produce profound sleepiness &/or coma.
What drives sleepiness?
ventrolateral preoptic area

VLPO
What activates VLPO?

(what makes your brain sleepy?)
As you think & work, you need energy.

ATP $\Rightarrow$ ADP $\Rightarrow$ AMP $\Rightarrow$ ADENOSINE
When you have ↑↑ adenosine levels, you are tired!
ATP → ADP → AMP → ADENOSINE

When you have ↑↑ adenosine levels, you are tired!

* ADENOSINE SECRETION REFLECTS BRAIN ACTIVITY

* ADENOSINE LEVELS RISE DURING WAKEFULNESS
ATP $\rightarrow$ ADP $\rightarrow$ AMP $\rightarrow$ ADENOSINE

When you have ↑↑ adenosine levels you are tired!

ADENOSINE BINDS TO VLPO AREA $\rightarrow$ SLEEP

ADENOSINE LEVELS DECLINE DURING SLEEP
ATP $\rightarrow$ ADP $\rightarrow$ AMP $\rightarrow$ ADENOSINE

When you have ↑↑ adenosine levels, you are tired!

Note: COFFEE

✓ Caffeine interferes with adenosine binding
Lesion VLPO?

→ insomnia

• sleep for a few hours per day

↓ NREM & ↓ REM SLEEP

people are extremely tired

→ but find it difficult to sleep.
VLPO:

are active during
Sleep
VLPO inhibits arousal system during sleep.
VLPO:

x help control REM sleep states

* helps to transition to sleep via histamine neurons
VLPO
INHIBIT
norepinephrine
VLPO
AROUSAL SYSTEM
AROUSAL SYSTEM
FLUP-FLOP SWITCH

SLEEP INHIBITS AROUSAL

AROUSAL INHIBITS SLEEP

INHIBIT

INHIBIT
Alzheimer’s Disease characteristics

- Chronic neurodegeneration
- Dementia, most common
- Short-term memory loss
Amyloid-β Dynamics Are Regulated by Orexin and the Sleep-Wake Cycle

Jae-Eun Kang,¹ Miranda M. Lim,¹ Randall J. Bateman,¹,²,³ James J. Lee,¹ Liam P. Smyth,¹ John R. Cirrito,¹,² Nobuhiro Fujiki,⁴ Seiji Nishino,⁴ David M. Holtzman¹,²,³,⁵*

Amyloid-β (Aβ) accumulation in the brain extracellular space is a hallmark of Alzheimer’s disease. The factors regulating this process are only partly understood. Aβ aggregation is a concentration-dependent process that is likely responsive to changes in brain interstitial fluid (ISF) levels of Aβ. Using in vivo microdialysis in mice, we found that the amount of ISF Aβ correlated with wakefulness. The amount of ISF Aβ also significantly increased during acute sleep deprivation and during orexin infusion, but decreased with infusion of a dual orexin receptor antagonist. Chronic sleep restriction significantly increased, and a dual orexin receptor antagonist decreased, Aβ plaque formation in amyloid precursor protein transgenic mice. Thus, the sleep-wake cycle and orexin may play a role in the pathogenesis of Alzheimer’s disease.
The second hallmark of altered sleep as we age is fragmentation. The older we get, the more frequently we wake up throughout the night. Causes include body pain and a weakened bladder. Reducing fluid intake in the evening can help the latter, but it isn’t a cure-all.
Mechanisms linking circadian clocks, sleep, and neurodegeneration

Erik S. Musiek* and David M. Holtzman

Disruptions of normal circadian rhythms and sleep cycles are consequences of aging and can profoundly affect health. Accumulating evidence indicates that circadian and sleep disturbances, which have long been considered symptoms of many neurodegenerative conditions, may actually drive pathogenesis early in the course of these diseases. In this Review, we explore potential cellular and molecular mechanisms linking circadian dysfunction and sleep loss to neurodegenerative diseases, with a focus on Alzheimer’s disease. We examine the interplay between central and peripheral circadian rhythms, circadian clock gene function, and sleep in maintaining brain homeostasis, and discuss therapeutic implications. The circadian clock and sleep can influence a number of key processes involved in neurodegeneration, suggesting that these systems might be manipulated to promote healthy brain aging.
The Secret to Retaining a New Skill: Learn, Exercise, Sleep
Be Happy
Get enough Sleep!