Sleep and Alzheimer’s Disease

Cool Brain Nerds
Marine Delgrange, Neil Beluso, Mengqun Lyu (Monica), Alexis Pierce, Seo-Jin Yang (Joy), Lauren Ring
An overview

● Introduction
  ○ Alzheimer’s disease
  ○ The mechanisms of sleep
● How do sleep and Alzheimer’s Disease interact?
  ○ Sleep/Wake cycles
    ■ How AD leads to sleep disturbance
    ■ How sleep disturbance favorizes the development of AD
  ○ Circadian rhythm
  ○ The glymphatic system
● Implications for therapy and future research
● Conclusion
Introduction

I. Alzheimer’s disease - an overview
II. The mechanisms of sleep

Marine Delgrange
Alzheimer’s disease - an overview

CLINICAL FEATURES

❖ Neurodegenerative disorder
❖ Most common type of dementia (60%), generally occurs after 65 years old
❖ Slow, relentless, progressive features
❖ Total duration: 10-12 years average
Alzheimer’s disease - an overview

CLINICAL FEATURES

❖ Initial symptoms: forgetfulness and memory disturbances
❖ Progression to loss of higher functions (thinking and planning)
❖ Appearance of language deficits
❖ Loss of sense of location and surrounding environment
❖ Associated symptoms: depression, agitation, sleep disorders
Alzheimer’s disease - an overview

ANATOMIC FEATURES

Credits: Bella Vista International Foundation
Alzheimer’s disease - an overview

MOLECULAR FEATURES

Two main actors

❖ Amyloid β, forming Amyloid Plaques
❖ Tau protein, forming Neurofibrillary Tangles

Note that neurons also die because the **immune system** triggers their apoptosis!
Alzheimer’s disease - an overview

OUTSIDE OF CELLS: AMYLOID PLAQUES

APP: Amyloid precursor protein

Plaques: Focal, spherical collections of dilated, tortuous, dying neurons (dystrophic neuritis) surrounding a central amyloid core

What it does: interfere in communication between neurons
Alzheimer’s disease - an overview

INSIDE OF CELLS: NEUROFIBRILLARY TANGLES

**Neurofibrillary tangles**: Bundles of filaments in cytoplasm of neurons that displace or encircle the nucleus. Composed of paired helical filaments containing hyperphosphorylated Tau.

**Tau**: axonal microtubule associated protein (holds MTs stable)

**What it does**: blocks the passage of nutrients and NTs from nucleus to synapse because of microtubule disruption
Alzheimer’s disease - an overview

RISK FACTORS

❖ Older age
❖ Female sex
❖ Head trauma
❖ Genetics/family history

Age
Family history
Coexisting genetic diseases
Lack of education
Female gender
Diabetes
Environmental hazards
Head injury
Alzheimer’s disease - an overview

RISK FACTORS - GENETIC FACTORS

<table>
<thead>
<tr>
<th>Genetic factor</th>
<th>Chromosome</th>
<th>Onset age</th>
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<tbody>
<tr>
<td>Down’s syndrome</td>
<td>21</td>
<td>&gt; 35</td>
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<tr>
<td>APP mutation</td>
<td>21</td>
<td>45-66</td>
</tr>
<tr>
<td>PS1 mutation</td>
<td>14</td>
<td>28-62</td>
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<tr>
<td>PS2 mutation</td>
<td>1</td>
<td>40-85</td>
</tr>
<tr>
<td>APOE e4 variant</td>
<td>19</td>
<td>&gt; 60</td>
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**APOE**: Apolipoprotein E, fat-binding proteins which transports cholesterol to neurons. Enhances proteolytic breakdown of Aβ, avoiding the formation of plaques.

**PS1/PS2**: presenilin 1&2, proteins that are part of the gamma-secretase complex, which is involved in the cleavage of APP
The mechanisms of sleep

SLEEP CYCLES

- Stages defined by EEG characteristics
- REM (Rapid Eye Movement) vs non-REM sleep
- Cycles of typically 90 minutes
- 4-6 cycles per night in young adults
- REM density decreases with age, replaced by increased stage 2
The mechanisms of sleep

NON-REM SLEEP

Decreased muscle tone, regular and slow respiration

- **Stage 1**: loss of alpha rhythm, theta waves. Brief transition stage; hypnagogic hallucinations occur at that stage.
- **Stage 3**: delta waves. Hard to wake up. Also called slow-wave sleep.
The mechanisms of sleep

REM SLEEP

❖ “Paradoxical sleep” -> EEG similar to wakefulness
❖ Irregular respiration
❖ Loss of muscle tone
❖ Vivid dreams
The mechanisms of sleep

THE SLEEP-WAKE CYCLE

- Sleep and wake inhibit each other
- Synchronized with SCN oscillatory activity (circadian rhythm)
- Excitatory NTs: Ach, DA, NE, 5-HT, histamine. Inhibit the sleep system.
- Sleep system: GABA
OREXIN AND MELATONIN

- **Orexin**: wake-promoting NT, also intervenes in appetite and motivation
- Also called hypocretin
- Synthesized in lateral and posterior HP
- Orexin-producing neurons innervate arousal systems and cerebral cortex, inhibiting REM sleep
- Stabilizes sleep-wake transitions

- **Melatonin**: regulated by the circadian rhythm, mainly when it gets dark
Sleep/Wake cycles in Alzheimer’s Disease

Neil Beluso & Monica Lyu
Sleep disturbance in AD patients

- 25-66% of AD patients experience sleep disturbances or sleep disorders
  - One of the leading causes of AD institutionalization
  - Once considered a bi-product of neurodegeneration -> actually a bidirectional relationship
- Examples of sleep disturbances in Alzheimer’s
  - Excessive daytime sleepiness (EDS) and insomnia
    - Increased wakefulness at night, increased sleep during the day
  - Sleep architecture is less efficient
    - Decreased REM, NREM and slow-wave sleep
    - Increased latency to REM
    - Sleep fragmentation
Sleep disturbance may precede AD pathology

- **Lim et al. (2013):** “Cognitively normal older individuals with high sleep fragmentation had a 1.5-fold increased risk of developing AD and self-reported reduced sleep was associated with a 2-fold increased risk of AD development”

- **Sleep disturbance markers as biomarkers for AD:**
  - **Ju et al. (2013):** decreased sleep efficiency in amyloid-positive, cognitively-normal people than amyloid-negative = role of Aβ aggregation
  - **Petit et al. (2014):** rate of EEG slowing in wake & REM sleep increases with AD severity = slowing of EEG in REM as biomarker
Why do AD patients experience sleep disturbances?

- Most likely cause: pathology-induced neuronal breakdown in sleep-regulating brain areas and pathways.
Why do AD patients experience sleep disturbances?

- Most likely cause: pathology-induced neuronal breakdown in sleep-regulating brain areas and pathways
Ventrolateral Preoptic Nucleus of the Hypothalamus (VLPO)

- Also called the intermediate nucleus of the preoptic area
- Projects GABA & Galanin to inhibit arousal -> regulate sleep/wake

Lim et al. (2013): AD patients show fewer galanergic VLPO neurons

More galanin-immunoreactive VLPO neurons associated with less fragmented sleep in AD & non-AD individuals

- Galanin immunoreactivity as potential biomarker for sleep disturbance in AD

During sleep, projections from the VLPO nucleus in the hypothalamus (GABA, galanin) inhibit the main components of the arousal system
Amyloid & Tau in other sleep-regulating areas

- **Tau aggregation**
  - Locus coeruleus (NE for arousal)
  - Dorsal raphe (5-HT for sleep-wake)
  - Tuberomammillary nucleus (histamines for sleep-wake)
  - Parabrachial nucleus (glutaminergic neurons for wake)
  - Basal forebrain (ACH for wake and REM)

- **Amyloid deposition**
  - Hypothalamus (including VLPO)
  - Periaqueductal gray matter (PAG; projects to raphe nuclei -> 5-HT levels for sleep/wake)

- These occur before the appearance of amyloid plaques or cortical tau pathologies!
- Reversible by Aβ immunotherapy = **causative role of Aβ**
How does sleep dysregulation affect AD pathology?

- Sleep-wake disruption as a early symptoms of the Alzheimer’s Disease (AD)
  - Even precede the development of cognitive symptoms
- Accumulating evidence suggests the role of sleep and circadian disturbances in the pathogenesis of AD.
  - Sleep-wake cycle is associated with the level of pathogenic amyloid-beta (Aβ) peptide in the brain
- Implication in the treatment of AD
Sleep disturbances may predict dementia and Aβ Pathology

- Cognitively normal older adults who self-report poor sleep were more likely to have Aβ plaque in the precuneus
  - Precuneus atrophy in early-onset AD (Karas, et al, 2007)
- Rest fragmentation at night increases with age and is related to increased risk of developing dementia within 1-6 years.
  - Obtained through actigraphy
  - Appeared to exacerbate the effects of apolipoprotein E4 on dementia risk, amyloid plaque burden, and tau pathology.
Apolipoprotein E4 (APOE-4)

- APOE: class of proteins involved in the metabolism of fats in the body
- Produced by the liver in peripheral tissues; produced by astrocytes in the brain.
- APOE-4 as a well-established genetic risk factor for AD
  - Associated with increased prevalence of AD and lower onset age
  - Important role in Aβ metabolism
    - More likely to form senile plaques as the result of Aβ metabolism
Apolipoprotein E4 (APOE-4)
Apolipoprotein E4 (APOE-4)

- Longitudinal study with up to 6 years of follow-up (Lim et. al, 2013)
- Actigraphic recording to quantify the degree of sleep consolidation
- Better sleep consolidation attenuates the effect of APOE-4
  - ↓ Development of neurofibrillary tangle
  - ↓ Incident of AD
Control of Aβ levels by the sleep wake cycle - BIDIRECTIONAL RELATIONSHIP

- Brain Interstitial Fluid (ISF) Aβ levels fluctuation in mice (Kang et. al)
  - Highest when mice tend to be awake (dark phase)
  - Lowest when mice tend to be asleep (light phase)
  - ISF Aβ correlated with total awake time
  - Sleep deprivation delayed the dip in Aβ levels at the onset of light phase
Control of Aβ levels by the sleep wake cycle - BIDIRECTIONAL RELATIONSHIP

- Aβ levels may be associated with neuronal activity
  - Increased neuronal activity during the wake phase might mediate increased Aβ levels during the day
  - Slow wave sleep: neuronal hyperpolarization may be associated with decreased Aβ levels
  - Damped Aβ level during the day as plaque pathology advanced; restored when plaques were eliminated following Aβ immunotherapy
Sleep regulate the clearance of Aβ

- Xie et al.
  - Increase in extracellular fluid in the brain during sleep
    - Enhances the clearance of metabolites and proteins out of the brain via the glymphatic system (more on this later)
    - Faster clearance of endogenous injected Aβ in sleeping mice than waking ones
Sleep deprivation exacerbates Aβ pathology

- Kang et al.
  - APP/PS1 mutated mice
  - Develop Aβ plaque with age
  - Striking increase in Aβ plaque after forced sleep deprivation
  - Decrease in Aβ plaque after treatment with orexin antagonist almorexant (increase sleep)

- Similar result in human study
Sleep deprivation mediates neuronal injury independent of Aβ level

- Tau phosphorylation
- Synaptic injury
- Impaired learning and memory
Takeaway

- Sleep quality is crucial for the proper function of the brain
- Vicious Circle
  - Chronic sleep disturbances may facilitate Aβ deposition
  - Aβ pathology impairs sleep wake cycle
Circadian Rhythm Function in Alzheimer’s Disease

Alexis Pierce
What Are Circadian Rhythms?

- Roots: “Circa” = About; “Dia” = Day
- Also known as the “body clock”
- Cycle that regulates many of the body’s physiological body processes, as well as sleeping, waking, eating, etc.
- Coordinated with light-dark cycles
- Circadian rhythms are oscillations which happen over a 24 hour period of time
- Sleep-wake cycle (talked about previously) is only one of the many circadian rhythm cycles in the body
What Do Circadian Rhythms Look Like?

Image Courtesy of Liz Harrison, PhD (UCSD Center for Circadian Biology)
Pretty Much Everything Has a Circadian Rhythm!!

- Sleep-wake cycle (talked about previously) is only one of the many circadian rhythm cycles in the body.

Image Courtesy of Liz Harrison, PhD (UCSD Center for Circadian Biology)
How Are These Circadian Rhythms Controlled?

- Systemic circadian rhythms (Sleep-wake cycle, hormone secretion, and blood pressure) are all controlled by the hypothalamic suprachiasmatic nucleus.
Suprachiasmatic Nucleus

- SCN: Master body clock
- Takes the peripheral oscillations (different circadian rhythms) and light-dark cues and synchronizes them to form whole-body rhythms and that make sense
- Location: Tiny region of the brain in the hypothalamus, directly above the optic chiasm
SCN Function

- Sleep-wake cycle, hormone secretion, and blood pressure circadian rhythms
- Synchronize peripheral clocks
- SCN regulates the release of melatonin, which promotes onset of sleep → Lesions lead to loss of circadian rhythms and arrhythmic sleep
- BMAL1 and CLOCK → Transcriptional activators
- PERIOD (Per1-3) and CRYPOTCHROME (Cry1-2) → Transcriptional repressors
SCN Function (...continued)

- Aspects of the core clock SCN and all cells in the body and mediates 10-20% of all transcripts
- Whole-organism and cell autonomous rhythms may be separated and can continue to oscillate apart from the organism, without SCN input
- Arrhythmias can occur in organs, cells, etc., due to deletion of clock genes
- SCN lesions disrupt synchronization of whole-body rhythms, but allow individual cellular clocks to continue to function
So What Causes The Issue?- Looking At Mouse and Human Models

- Dysregulation of these systemic circadian rhythms (sleep-wake cycle, activity, and melatonin secretion) in AD (Mouse Model)
- Eventual disappearance of these circadian rhythms with AD (Mouse Model)
- Dysfunction/degeneration of SCN may be the main cause of the dysfunction of circadian rhythms in AD (Human Model)
- An issue that causes confusion and disorientation in AD individuals is when the light/dark does not match what time of day they think it is
Melatonin Secretion

- Melatonin: Produced in the pineal gland at night (in response to signals from the SCN throughout the day)
- Light is key component in regulating circadian rhythms (Sleep timing, blood pressure regulation, and seasonal reproduction)
- Chronic dysregulation of rhythms may result in daytime sleepiness and nighttime insomnia
- Regulates homeostasis through circadian rhythms (using MT1 and MT2 receptors)
What Came First: Circadian Rhythm Dysfunction or Alzheimer’s?

- While identified as one of the major symptoms of AD, it could be that the circadian rhythm dysfunction is what causes the Alzheimer’s (and not the other way around)
- Epidemiology study: Cognitively normal adults with impaired circadian rhythms (as seen through actigraphy) are actually at an increased risk for future development of AD
- 3 separate polymorphisms in the Clock gene, resulting in increased risk in the development of AD (3 small studies)
- Diurnal oscillations in Aβ could have a circadian rhythm and influenced by the circadian system
- Disruption of the main circadian clock in the brain may result in direct neurodegeneration
How Can Circadian Rhythms Injure the Brain? (Mice Study)

- Direct link between the disruption of the circadian rhythms and injury to the brain
- Deleted master clock gene *Bmall* in the hippocampus and the cortex
- SCN (controls circadian rhythms) was left intact
- What Did This Do?: Systemic circadian rhythms and sleep-wake cycle still functioning, but complete disruption of the circadian transcriptional regulation throughout the rest of the brain
- This resulted in normal rhythms of behavior (normal wheel-running) and sleep-wake cycle
- However, resulted in injury to the brain: severe cortical astrogliosis, oxidative damage, and synaptic degeneration (Due to impaired circadian transcription of several redox defense genes)
- Decreased BMAL1-mediated transcription enhanced degeneration of the brain
- More studies need to be done on these topics
Summary

- Sleep/wake cycles and circadian rhythms are closely related but they are their own separate entities that work interconnectedly.
- While Alzheimer’s displays symptoms including disrupted circadian rhythms, circadian rhythm disruption early in life may be a precursor for the disease.
- Understanding circadian rhythms and their role in behavior can allow for treatment and improved quality of life.
The Glymphatic System in Alzheimer’s Disease

Joy Yang & Lauren Ring
Terms (credits to Wikipedia and Google)

- **Apolipoprotein E (ApoE)**: proteins involved in metabolism of fats in the body
- **Aquaporin 4 (AQP4)**: water channel protein encoded by the AQP4 gene (water transport channel); conducts water through the cell membrane
- **Brain Parenchyma**: functional tissue in the brain consisting of neurons and glial cells
- **Ependyma**: type of glial cells that line the CSF-filled ventricles in the brain and the central canal of the spinal cord
- **Interstitial Fluid (ISF) (a.k.a. Extracellular Fluid)**: fluid outside the cell
- **Lymphatic System**: network of tissues and organs that help to clean up toxins and other unwanted materials; transports lymph (fluid containing white blood cells) throughout the body
- **Perivascular Space (a.k.a. Virchow-Robin Space)**: gaps (space) containing interstitial fluid that span between blood vessels and the organ
  - Serves as extravascular channels through which solutes can pass
What is Glymphatic System? - Joy

- **Simple Definition:**
  - “Pseudo-lymphatic” function in the brain
  - Known to be waste clearance system in the CNS
  - Uses perivascular channels (Virchow-Robin channels)
  - Eliminates soluble proteins and metabolites from the CNS
  - Helps distribute non-waste compounds (i.e., glucose, lipids, amino acids and neurotransmitters)

*Lymphatic System*: network of tissues and organs that help to clean up toxins and other unwanted materials; transports lymph (fluid containing white blood cells) throughout the body

*Perivascular Space (a.k.a. Virchow-Robin Space)*: gaps (space) containing interstitial fluid that span between blood vessels and the organ
  - Serves as extravascular channels through which solutes can pass

*Perivascular Channels (Virchow-Robin Channels)*: channels within the perivascular (Virchow-Robin) space

*CNS* = Central Nervous System
Cerebrospinal Fluid (CSF)

- **What is CSF?**
  - Clear body fluid found in the brain and spinal cord
- **Produced by choroid plexus**
- **CSF volume ~150-160 mL in human**
- **Constantly produced and removed**
  - “Renewed” 4-12 times a day (24 hours)
- **Serves multiple purposes:**
  - Protection
  - Buoyancy
  - Waste products clearance
  - Transporting hormones
- **Virchow-Robin spaces filled with CSF**
Glymphatic System - How does it work?

- CSF and ISF continuously interchange
  - Facilitated by convective influx of CSF along the periarterial space
- CSF flows from 3rd ventricle $\rightarrow$ 4th ventricle $\rightarrow$ subarachnoid space
- Subarachnoid space $\rightarrow$ Virchow-Robin spaces
  - Driven by:
    - Arterial pulsatility
    - Respiration
- CSF transportation into brain parenchyma is facilitated by AQP4 water channels
  - Drives convective ISF fluxes within the tissue toward perivenous spaces surrounding the large deep veins

*Aquaporin 4 (AQP4):* water channel protein encoded by the AQP4 gene (water transport channel); conducts water through the cell membrane
*Brain Parenchyma: functional tissue in the brain consisting of neurons and glial cells
*Periarterial: relating to tissues surrounding the artery
*Perivenous: relating to tissues surrounding the vein
Iliff et al. 2012

- Used two-photon microscopy in mice
- Fluorescent tracers injected into the cisterna magna
  - Labeled CSF
- Found:
  1. CSF enters the brain along the cortical pial arteries
  2. Influx into Virchow-Robin spaces along penetrating arterioles
  3. CSF enters the parenchyma through periarterial pathway
  4. Exits the brain along central deep veins and lateral-ventral caudal rhinal veins
- The movement of CSF through the brain parenchyma facilitate clearance of interstitial solutes

*Arteriole*: small branch of an artery leading into capillaries

*Brain Parenchyma*: functional tissue in the brain consisting of neurons and glial cells

*Capillary*: any of the fine branching blood vessels that form a network between the arterioles and venules (small blood vessel) -smallest blood vessels in the body
Why does this matter?

- Interstitial solutes are cleared by the Glymphatic System
  - May play a role in clearing accumulated proteins that are toxic to the body
- Iliff et al. found that β-amyloid is cleared by the glymphatic pathway
- Lipid transportation
  - Apolipoprotein E
    - protein that mediate the clearance of excess hydroxylated cholesterol and β-amyloid
    - Allows delivery of lipids (i.e., cholesterol) to neurons
    - Shares production site and transport pathways with CSF within choroid plexus → suggests lipid transportation by glymphatic system
  - Many Alzheimer’s patients have the e4 variant (APOE4) → less effective in breaking down β-amyloid = gain of toxic function

*Allele*: alternate forms of a gene that arise by mutation (found on the same chromosome)
How is it related to Sleep?

- Glymphatic system activities enhanced during sleep state, and suppressed during wake state
  - Activities reduced by 90% during wake state
- Interstitial space expanded to 22-24% during sleep
  - Allow more flow of the fluid = more clearance of metabolites
- Norepinephrine (NE)
  - Major factor for arousal
  - Possible suppressor of glymphatic system during waking
  - Study shows:
    - NE receptor antagonists = increase in CSF influx
    - NE application = decrease in interstitial volume fraction
    - NE inhibits CSF production in choroid plexus
  - Fun Fact: NE high during stress = less glymphatic activities
Glymphatic System and Aging

- Highest risk factor identified for neurodegenerative diseases
- Decline in glymphatic CSF influx
- Decline in interstitial solute clearance (including Aβ)
- 80-90% reduction of function (old vs. young mice) (Jessen 2015)

Why is function reduced?
- Reduced penetrating arterial pulsatility
- Reactive gliosis
- Dysregulation of astroglial water transport
  - Loss of perivascular AQP4 polarization
- Decline in CSF production by 66% and CSF pressure by 27% percent
Glymphatic System and Type II Diabetes

- Enhanced glymphatic CSF influx
- Slowed interstitial solute clearance
- More mismatch = more cognitive decline
Glymphatic System and TBI

- TBI increases the risk of premature dementia and Alzheimer's disease
- Repeated trauma can lead to progressive neurodegeneration
- Induces β-amyloid and C-tau release
  - Hypothesis (Jessen 2015): tau increase leads to neurofibrillary tangles
- Reduction of glymphatic function occurs from day 1-28
  - Associated w/ glial scarring and mis-localization of AQP4
- Amount of tau in the tissue correlates with decrease in glymphatic clearance
- Degree of glymphatic function suppression after TBI is connected to outcome
- Short-term inhibition can be resolved
Glymphatic System and Alzheimer’s

- Aging -> Failure in adequate CSF bulk flow
  - β-amyloid accumulation
- Feed-forward relationship
  - How?
    - Periarterial accumulation of β-amyloid reduces CSF influx
    - Stagnation of CSF influx accelerates β-amyloid accumulation
- Enlarged perivascular space
  - Changes of perivascular space are likely to negatively impact glymphatic function
    - Ex. Vascular dementia
    - Still speculative
Peng et al. 2016

- **Mouse model: APP/PS1 mice**
  - APP - Amyloid Precursor Protein (overexpressed)
  - PS1 - Presenilin 1 (plays a role in amyloid-β generation with APP)
- **Aβ40**
  - Most common isoform of amyloid-β
  - Reduces cerebral blood flow by inducing vasoconstriction
- **Aβ42**
  - CSF biomarker of AD (reduced as disease progresses)
  - More prone to oligomerization
    - Soluble oligomers are neurotoxic
    - Data suggests they cause delocalization of AQP4
Intracisternal injection of CB-dextran (inert reference) and Aβ40 or Aβ42
- All were present in penetrating arteries, Aβ42 transport restricted in the parenchyma

Pre-infusion of Aβ
- Aβ40, but not Aβ42, reduced the glymphatic transport of the dextran into brain

Artificial CSF containing Aβ40 and C-inulin (reference) was injected intracisternally
- Inflow of Aβ and inulin was reduced with age
- Reduced in APP/PS1 mice compared to controls, more so w/ prominent amyloid-β deposits
  - 2x decrease for old mice w/ plaques, 1.5x decrease for young mice

CSF was microinjected into the frontal cortex
- APP/PS1 mice had reduced clearance
- Aβ40 adhering to amyloid-β plaques may promote accumulation
Peng et al. 2016
Highlights

1. Glympathic transport is suppressed prior to significant accumulation of amyloid-β.
2. CSF Aβ40 and Aβ42 circulate through the brain parenchyma.
3. CSF-derived Aβ is taken up by cells within the parenchyma, e.g., neurons.
4. CSF-derived Aβ may contribute to amyloid-β plaque formation.
5. Long-term exposure to Aβ40 in CSF suppresses glympathic transport.
So what?

- Therapeutic targets
- Early disease indication
Implications for Therapy and Future Research

Neil Beluso
Usual treatments for AD

- Cholinesterase inhibitors: donepezil, rivastigmine, tacrine
  - Sustain the communication between neurons by blocking the normal breakdown of ACh (typically depleted in AD)
- More recently: memantine
  - Acts on the glutamatergic system by blocking NMDA receptors -> improved neuronal communication, reduced AD symptoms
- Symptoms-specific treatments: NSAIDs (anti-inflammatory), vitamin E (antioxidants), anti-anxiety medication, sleep aids

No cure (yet)! These interventions just slow the progression of the disease or target specific symptoms.
Therapeutic interventions to target the sleep-wake cycle

- Target Aβ deposition
  - Aβ immunotherapy
- Target circadian clock synchronization & diurnal rhythm
  - Melatonin supplementation (levels decrease w/ age & preclinical AD)
  - Light therapy (alone vs. in conjunction w/ melatonin)
Pharmacological interventions to target the sleep-wake cycle

- **Target melatonin receptivity**
  - Ramelteon: M1/M2 receptor agonist -> treat insomnia
  - Tasimelteon: M1/M2 receptor agonist -> treat circadian disturbance in blind patients

- **Target genetics of circadian clocks**
  - Molecules to alter circadian gene expression
    - Small molecule agonists of the orphan nuclear receptors RevErba and -β

- **Target orexin system**
  - Suvorexant: first FDA-approved orexin receptor antagonist
  - Almorexant: orexin receptor antagonist
Future Research

- Sleep disturbances as a precursor/biomarker for AD
  - Implications for early disease indication
- Effectiveness of therapies targeting AD pathologies in sleep-regulating areas
- Effects of improved glymphatic system function

No isolated cause = multiple areas of future research
Alzheimer’s disease and sleep
Conclusion

Marine Delgrange
The sleep-wake cycle as a modulator of AD pathogenesis: a feed-forward cycle

- AD patients exhibit sleep disruption patterns, preceding the formation of amyloid plaques. This would be a result of Aβ deposition and tau aggregation.

- But sleep disturbances are not only a consequence of AD! They might precede the symptom onset and even drive the disease pathology.
The sleep-wake cycle as a modulator of AD pathogenesis: a feed-forward cycle

- Aβ levels correlate with awareness and neuronal activity
- Sleep deprivation:
  - Exacerbate the toxic effects of APOEe4
  - Is associated with increased Aβ
- Sleep (especially slow-wave sleep) limits amyloid beta production by:
  - Tempering neuronal activity
  - Removing amyloid beta via the glymphatic system
The glymphatic system in AD and sleep

- Waste clearance system of CNS, clears toxic proteins including Aβ
- Decline in glymphatic CSF influx with aging, favorizing Aβ accumulation
- Bi-directional relationship because Aβ accumulation reduces CSF influx
- Activity enhanced with sleep and reduced during wake state
- Less effective functioning of glymphatic system with APOEe4 variant
- NE (stress): suppressive effect on glymphatic system functioning
Circadian dysfunction in AD pathogenesis

- The disruption of circadian rhythms in AD patients seems to be precursory of the disease, and accelerate neurodegeneration
- It might be due to the degeneration of the SCN, which is the “master clock” of the body
- This could itself be accelerated by the decline in *Bmal1* and *Clock* expression, natural with age but more important in some polymorphisms that AD patients could have
- Drives the sleep-wake cycle and as such as the same bidirectional relationship with Aβ
So if you want to prevent Alzheimer’s...

❖ Sleep at regular times and for enough time, don’t fragment your sleep!
❖ Exercise your brain!

❖ But if there is one thing to remember: AD has many causes, and the most important factors are genetic!
Resources

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980916/
- https://academic.oup.com/brain/article/137/10/2847/2847696 - Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer’s disease