Neurobiological Foundations of Sleep – Why Do We Sleep?

Teofilo Lee-Chiong MD
Professor of Medicine
National Jewish Health
Professor of Medicine
University of Colorado
Chief Medical Liaison
Philips Respironics
Disclosure

Research funding: Philips Respironics

Consulting: Elsevier, CareCore National

Chief Medical Liaison: Philips Respironics


I will not be discussing off-label uses
Learning Objectives

1. Learn the phylogeny and ontogeny of sleep
2. Identify the physiologic changes that occur during sleep
3. Know the consequences of sleep deprivation
4. Understand the neural processes responsible for the generation and regulation of sleep and waking
5. Review the role of the glympathic system during sleep and waking
Why Do We Sleep

A *grand unified theory* explaining the function of sleep remains elusive

- It appears unlikely that sleep has no function at all (i.e., an evolutionary error) given its complexity
Function of Sleep

Any theory should take into account sleep’s function in several areas

- Across geologic history
- Across different species (phylogeny)
- Across the lifespan (ontogeny)
- In diverse geographic areas
- Specific sleep stages (NREM vs. REM)
- Components of specific sleep stages (dreaming, penile tumescence, rapid eye movement)
- Effects on organ systems and processes
Function of Sleep

Three basic approaches to understand the function of sleep

- Comparative physiology between sleep and wakefulness (vs. anesthesia)
- Effects of sleep deprivation (total or selective) on physiologic processes
- Effects of sleep enhancement
Historical Background

• Aristotle (384 - 322 BCE)
• “On Sleep and Sleeplessness”
Aristotle: On Sleep

- Sleep is the opposite of wakefulness and must exist together in the same animal.
  - Every creature is endowed by nature with the power to move, but cannot move always and continuously.
  - The purpose of sleep is conservation of energy.

- Sleep and wakefulness both originate in the heart, and is regulated by digestion of food.
  - As a general rule, persons who are dwarf-like, or have abnormally large heads, are addicted to sleep.
Historical Background

**Restorative and somatic growth theory**
- Anabolic processes
- Growth hormone release during N3 sleep

**Metabolic theory**
- Regulation of body temperature
- Energy conservation
- Removal of “toxins” generated during wakefulness
Historical Background

- Survival theory
  - Protective and adaptive behavior
  - Immune defense function

- Neural growth and processing
  - Neuronal synaptic plasticity
  - Brain development and restoration
  - Learning, and memory consolidation
Phylogeny of Sleep

Amphibian sleep
• Except for possibly bullfrogs, exhibit behavioral signs of sleep

Fish sleep
• Some species demonstrate behavioral sleep

Invertebrate sleep
• Sleep behavior has been described in fruit fly, crayfish, honey bees, cockroaches and scorpions
Phylogeny of Sleep

Avian sleep
- Birds exhibit both NREM and REM sleep
- The eye contralateral to the hemisphere with lower SWA is usually left open during NREM sleep
- Very short (< 10 sec) REM sleep

Reptilian sleep
- High-voltage EEG spikes associated with higher arousal thresholds have been described in crocodiles, lizards and turtles
- No REM sleep
Phylogeny of Sleep

Mammalian sleep

- NREM and REM sleep are present in all mammals with the possible exemption of cetaceans
- Some echidnas exhibit neocortical NREM-like and brainstem REM-like EEG activity
# Ontogeny of Sleep

## Age at which specific EEG features first develop

<table>
<thead>
<tr>
<th>Active sleep</th>
<th>Quiet sleep</th>
<th>EEG waveforms</th>
</tr>
</thead>
</table>
| • 28-30 weeks of gestation | • Trace’ discontineau – 32 weeks of gestation  
• Trace’ alternant – 36 weeks of gestation | • Sleep spindles – 1 month  
• Delta waves – 3 months  
• K complexes – 6 months |
# Ontogeny of Sleep

TST gradually decreases throughout childhood

<table>
<thead>
<tr>
<th>Age Group</th>
<th>TST (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 month</td>
<td>19</td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>15</td>
</tr>
<tr>
<td>1-3 years</td>
<td>12</td>
</tr>
<tr>
<td>3-5 years</td>
<td>10</td>
</tr>
<tr>
<td>&gt; 5 years</td>
<td>9</td>
</tr>
</tbody>
</table>
Ontogeny of Sleep

Aging

<table>
<thead>
<tr>
<th>Stays the same</th>
<th>Increases</th>
<th>Decreases</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sleep requirements</td>
<td>• Nocturnal sleep disturbance</td>
<td>• N3 sleep</td>
</tr>
</tbody>
</table>
<pre><code>                                                                               | • Tolerance to sleep deprivation                                      | • Amplitude of circadian sleep-wake rhythms |
                                                                               |                                | • Homeostatic sleep drive       |
</code></pre>
Physiology during Sleep

**What Goes Down**
- Sympathetic activity
- PaO2 and SaO2
- Ventilatory responses
- HR, CO and BP
- Glomerular filtration

**What Goes Up**
- Parasympathetic activity
- PaCO2
- Renal water reabsorption
- Growth hormone
- Prolactin
Physiology of Sleep

• Thermoregulation
  – Peaks in the late afternoon and early evening: 6-8 pm
  – Falls at the onset of sleep
  – Nadir at 2 hours prior to usual wake time: 4-5 am

Baker FC et al 2001
<table>
<thead>
<tr>
<th></th>
<th>Maximum</th>
<th>Minimum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric acid secretion</td>
<td>Between 10 PM and 2 AM</td>
<td>Between 5 AM and 11 AM</td>
</tr>
<tr>
<td>Cortisol</td>
<td>8-9 AM</td>
<td>12 AM</td>
</tr>
<tr>
<td>Thyroid stimulating hormone</td>
<td>Between 9 PM and 6 AM</td>
<td>Between 10 AM and 7 PM</td>
</tr>
</tbody>
</table>
Sleep Deprivation

• Vulnerability to SD varies within individuals across time and between individuals (😊 ≠ 😞)

• Consequences of total SD appear to differ those of chronic sleep restriction (SD ≠ SR)
Sleep Deprivation

- Sympathetic activity
- Insulin resistance
- Metabolic rate
- Mortality

- Vigilance / cognition
- Seizure threshold
- Resistance to infection
Sleep Deprivation

Polysomnography

- Shortened sleep onset latency
- Increase in total sleep time
- Greater N3 sleep (1\textsuperscript{st} night after SD)
- Greater REM sleep (2\textsuperscript{nd} night after SD)

Waking EEG

- Shift to slower EEG frequencies (theta and delta waves)
# Systems Generating Wakefulness

<table>
<thead>
<tr>
<th>Transmitter</th>
<th>Neurons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>Ascending reticular formation</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Substantia nigra</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>Hypothalamus (perifornical)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Locus ceruleus</td>
</tr>
<tr>
<td>Serotonin</td>
<td>Raphe nuclei</td>
</tr>
<tr>
<td>Histamine</td>
<td>Tuberomammillary nucleus</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>Basal forebrain</td>
</tr>
</tbody>
</table>
Systems Generating Wakefulness

**Motor activation**
- Dopamine
- Acetylcholine

**Alertness and attention**
- Acetylcholine
- Norepinephrine
- Histamine

**Emotional arousal**
- Dopamine
- Norepinephrine
- Serotonin
# Systems Generating Sleep

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<tr>
<td>GABA</td>
<td>VLPO, hypothalamus and basal forebrain</td>
</tr>
<tr>
<td>Adenosine</td>
<td>Basal forebrain</td>
</tr>
<tr>
<td>Glycine</td>
<td>Spinal cord</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>PPT/LDT (pons) and basal forebrain</td>
</tr>
</tbody>
</table>
Wake-Sleep Switch

Wake

NE, 5HT, HA

Sleep

GABA (VLPO)
Bidirectional reciprocal inhibitory interactions between GABA (sleep) and N-S-H (wake)
Activation of GABA neurons produces coordinated inhibition of arousal systems.
Thalamocortical Circuit Switch

NREM

Wake/REM
Wake/REM sleep: Presence of excitatory inputs (Ach, etc.) $\Downarrow$ Depolarization (excitation) of thalamocortical neurons

NREM sleep: Removal of excitatory inputs by GABA) $\Downarrow$ Hyperpolarization (inhibition) of thalamocortical neurons
Wake/REM sleep:

Presence of excitatory inputs (Ach, etc.)

\[ \downarrow \]

Depolarization (excitation) of thalamocortical neurons

NREM sleep:

Removal of excitatory inputs by GABA

\[ \downarrow \]

Hyperpolarization (inhibition) of thalamocortical neurons
REM-on/REM-off switch

“REM-on” neurons – acetylcholine
“REM-off” neurons – N-S-H
REM-on neurons are inhibited by REM-off neurons
REM sleep develops when the inhibitory input from REM-off neurons is reduced or ceases.
# Bottom Line: Neurotransmitters

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<tbody>
<tr>
<td>Acetylcholine</td>
<td>↑↑</td>
<td>X</td>
<td>↑</td>
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<td>↑</td>
<td>X</td>
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<td>Histamine</td>
<td>↑</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Hypocretin</td>
<td>↑</td>
<td>X</td>
<td>X</td>
</tr>
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**Bottom Line: Neurotransmitters**

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- **GABA** is shown to have an increased presence in both NREM and REM stages compared to the wake stage.
# Bottom Line: Neurotransmitters

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<td>↑↑</td>
<td>↑↑</td>
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≥ 9 transmitters to form the stages.
3 switches to control the changes.
One brain to rule them all.
   In the land of slumber where the shadows lie.
Neural Regulation of Waking

Ascending reticular formation in brainstem

- Serotonergic
- Noradrenergic
- Histaminergic
- Dopaminergic
- Cholinergic
RF: Ascending Pathways

Dorsal pathway

- Reticular formation
- Thalamus
- Cortex
RF: Ascending Pathways

Ventral pathway

Reticular formation → Hypothalamus and forebrain → Cortex
**FIGURE 1.**
Cortical Arousal

T=thalamus; Hy=hypothalamus; ACh=acetylcholine; HA=histamine; BF=basal forebrain; NE=norepinephrine; 5-HT=serotonin; M=muscarinic; H=histamine.

Hypocretin Neurons

• Active during waking

Cortex

Locus ceruleus, dorsal raphe and tuberomamillary nuclei
Neural Regulation of Sleep

- Ventrolateral preoptic neurons – GABA
- PPT/LDT – acetylcholine

- NREM
- REM
- REM
FIGURE 2.
Sleep-promoting GABA system

GABA=γ-aminobutyric acid; Hy=hypothalamus; BF=basal forebrain; LDT=laterodorsal tegmental; PPT=peduncolopontine tegmental; TMN=tubero-mamillary nucleus; VLPO=ventrolateral preoptic nucleus; LC=locus coeruleus; DRN=dorsal raphe nucleus.

Pontine LDT/PPT

- REM-on neurons

Ascending: produce EEG desynchrony

Descending: produce muscle atonia
The Brain Glympathic System

Sleep drives metabolite clearance from the adult brain.


Proteins linked to neurodegenerative diseases are present in the interstitial space surrounding cells of the brain

- β-amyloid, α-synuclein and tau

Glymphatic system

- CSF recirculates through the brain interchanging with interstitial fluid (ISF)
- CSF influx around arteries, whereas ISF exits along veins
- Removes interstitial waste products and proteins, including β-amyloid
Background

Interstitial concentration of β-amyloid is higher during waking than sleep

- Increased β-amyloid production during waking
- Increased β-amyloid clearance during sleep (upregulation of lymphatic clearance)?
• In vivo two-photon imaging to compare CSF influx into the cortex of awake, anesthetized, and sleeping mice
• Fluorescent tracers were infused into the subarachnoid CSF
• Electrocorticography (ECoG) and electromyography (EMG) were recorded
• Time-dependent CSF influx of CSF tracers in sleep versus awake
• Time-dependent influx of CSF tracers in awake versus ketamine/xylazine anesthesia
• Volume of cortical extracellular space
  – Real-time TMA iontophoretic quantification
• Volume of the extracellular space
  – TMA+ iontophoretic quantification
• Clearance of β-amyloid
  – Disappearance of $^{125}$I-Ab$_{1-40}$ after its injection into the frontal cortex
Summary

• No grand unified theory of the function of sleep
• Sleep and waking are components of the 24-hour continuum of life
• Sleep is a function of the brain and functions for the brain
Questions